HANDBOOK OF Pharmaceutical Manufacturing Formulations

Compressed Solid Products

VOLUME 1

Handbook of Pharmaceutical Manufacturing Formulations

Volume Series

Sarfaraz K. Niazi

Volume 1
Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

Volume 3
Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products

Volume 4
Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products

Volume 5
Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products

Volume 6
Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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Dedication

to the memory of Sidney Riegelman

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products even though they may easily fall into one of the other five categories is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations — "not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

Compressed solids present one of the greatest challenges to formulation scientists, as they offer remarkable marketing opportunities to marketers. A solid oral dosage form is easy to ingest, is relatively more stable than other dosage forms (longer shelf life), and with it, opportunities to design delivery profiles to meet specific therapeutic requirements are offered. As a result, almost two-thirds of all dosage forms fall into this category. The challenge in formulating these products includes finding an optimum medium of compromises that will ensure releases of an active drug at the most desired and consistent rate. The formulation components and process of manufacturing thus take pivotal importance. As a result, the formulations provided in this volume offer a rare opportunity for formulators to start with an optimal composition. Described in this volume are formulations for over 200 of the most widely used drugs for all types of release profiles.

The most significant issues in the formulation of compressed solids are related to bioequivalence. Over the past quarter of a century, the science of evaluating equivalence of products has taken a greater emphasis on testing in human subjects. Although they are expensive to conduct, such trials are now routine, requiring frequent evaluation during the development phases and before marketing new entities. Most frequently, trials are required when establishing generic equivalences. The U.S. FDA may require additional biostudies if there is a change in the manufacturing site or even a change in the specification of a raw material. This aspect of formulation development clearly differentiates the compressed solids category; as a result, Chapter 1 in the book deals with the guidelines for bioavailability and bioequivalence testing of pharmaceutical products. Noteworthy are the changes proposed in this guideline from what is the currently accepted methodology; for example, what was long considered necessary, the multiple-dose studies of modified release products, will yield to single-dose studies, which are considered more discriminating. The manufacturers are particularly reminded to understand the changes in the requirements of bioavailability and bioequivalence studies that are on the horizon.

The formulation of compressed solids involves a highly intricate series of events, from the characterization of the active pharmaceutical ingredient, to the choice of excipients, to the selection of processing, compression, and coating equipment and packaging systems appropriate for the specific drug and the dosage form. In Chapter 2 of this volume, we highlight what the manufacturers need to be aware of in establishing a manufacturing process based on the formulations presented.

In other volumes of this series, details are provided on various other issues that pertain to the manufacturing of compressed solids, including validation issues, compliance with cGMP, laboratory guidelines, etc. The reader is referred to the other volumes for further understanding of the subject matter.

Compressed solids or tablets are usually applied with coatings, mainly aqueous film coatings, for many reasons, from aesthetics to imparting higher physical–chemical stability. Coating technology is a separate science. Fortunately, the major suppliers of equipment, such as Accela-Cota® and Glatt® and coating materials such as Colorcon® and Röhm®, are very helpful in establishing coating parameters and choosing the right coating materials and formulations. A large number of coating formulations are listed in the Appendix, including sugar coating, film coating, and enteric coatings. With such a wide variety available, coating steps are omitted from all formulations where coating is recommended. Instead, the reader is referred to the Appendix to make an appropriate choice.

The formulations are presented with a scale for each unit, per tablet; and quantities are expressed for 1000 tablets. It is customary for manufacturers to scale formulas for a specific weight, such as 100 or 1000 Kgs, to match mixing vessel requirements. This can be done roughly by multiplying the weight of each tablet by the quantity desired to calculate the size of the batch. Remember that the actual yield may be different because of differences in the scale and quantity, due to differences in the chemical forms of the drugs used, excesses added, and losses of moisture during manufacturing. Further, the adjustment of quantity based on the potency of the raw material, where pertinent, changes the quantity requirements.

A distinctive feature of this volume is the identification and inclusion of the most popular prescription products. The 200 most widely prescribed drugs (by brand name) are marked with a bracketed number to indicate their rankings. These data are derived from over 3 billion prescriptions filled during 2002 in the U.S., comprising the majority of the U.S. prescription market. Because in some instances more than one brand name is prescribed, only the top brand is listed; therefore, the total number of chemical equivalents is less than 200. The compressed solids represent more than an 80% share of this list,

therefore expounding the need to elaborate this list in this particular volume. Obviously, for a generic manufacturer, it would be advantageous to enter the market with products that have a wide market, not necessarily the largest margin, and this list will further help in the selection of products. It is noteworthy that in the preparation of an ANDA (Abbreviated New Drug Application), it is important for both regulatory and scientific reasons to keep the selection of excipients as close as possible to the innovator's product. The listing provided here includes every excipient used in the innovator listing. Whereas, in most instances, sufficient details are provided to assist in the formulation of a generic equivalent with exact quantities of excipients and conditions appropriate for processing, the examples provided for other drugs of similar types should be sufficient for an astute formulator to quickly develop these formulations. However, should there be a need for assistance in finalizing the formulation, the reader is invited, without any obligation, to write to the author at niazi@pharmsci.com.

I am grateful to CRC Press for taking this lead in publishing what is possibility the largest such work in the field of pharmaceutical products. It has been a distinct privilege to have known Mr. Stephen Zollo, the senior editor at CRC Press, for many years. Stephen has done more than any editor can to encourage me to complete this work on a timely basis. The editorial assistance provided by the CRC Press staff was exemplary, particularly the help given by Erika Dery, Joette Lynch, and others at CRC Press. Though much care has gone into correcting errors, any errors remaining are altogether mine. I would appreciate it if the readers bring these errors to my attention so that they can be corrected in future editions of this volume (niazi@pharmsic.com).

This book is dedicated to Sidney Riegelman, who was born July 19, 1921, in Milwaukee, Wisconsin. He attended the University of Wisconsin, graduating with a Bachelor of Science degree in pharmacy in 1944 and a Ph.D. in pharmacy in 1948. Following his graduate work, Sid joined the faculty of the School of Pharmacy at the University of California at San Francisco. In 1958, Sid published a series of papers with graduate student Wilfred Crowell, which appeared in the scientific edition of the *Journal of the American Pharmaceutical Association* under the major heading of "The Kinetics of Rectal Absorption." For these studies, Sid was awarded the Ebert Prize in 1959, which recognized Sid's publications as the best work published in the journals of the American Pharmaceutical Association during the year 1958. Sid's contributions to pharmaceutical sciences, particularly in the field of pharmacokinetics, earned him a revered place in the profession. On April 4, 1981, Sid drowned while scuba diving with his wife at Salt Point, California, a coastal area just north of San Francisco. At the University of California, a plaque is dedicated to Sid "by his graduate students, who honor his scientific achievements and excellence, his inspirations and contagious enthusiasm in research and teaching. We shall always remember Sid as our mentor, scientific father and most importantly, as our beloved friend and confidant."

I had the distinct privilege, both during my graduate studies and later as a faculty member teaching biopharmaceutics and pharmacokinetics, to interact with Sid. When my book, *Textbook of Biopharmaceutics and Clinical Pharmcokinetics*, was published, Sid called to congratulate me. It was like receiving a call from God — that is how he was revered in the profession. I remember vividly how he would argue in seminars while appearing to be dozing off during the presentation. Sid was a giant: a scientist, a scholar, and, above all, a loving human being. When a professional crisis arose, I called Sid for advice. Instead of telling me what I should do, Sid told me a story about his childhood: "Sarf, my brother was much stronger than I and every time he would run into me, he would take a jab at me, and when I would return his jab, he would knock me down. I complained about this to my father, and my father advised me not to return the jabs. My brother became so frustrated, he started jabbing others." I have never forgotten his advice.

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About the Author

Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents and is licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from consumer products to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science of formulations and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com).

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Appendix Coating Solutions

I. INTRODUCTION

Solid dosage forms are frequently coated for varied purposes, including the following:

- Mask taste and smell
- Protect from environment
- Provide protection from gastric acid — enteric coating
- Make easy to swallow
- Provide identification
- Give aesthetic appeal
- Hide surface defects

Many types of coatings are available. Sugar coating used to be a choice coating method years ago. This was mostly replaced with film coatings, as new polymers with better film-forming properties and equipment for applying these coatings became available. Several proprietary coating formulations are also available, such as Eudragit® (http://www.roehm.com/en/rohmamerica.html), Colorcon® (http://www.roehm.com/en/rohmamerica.html), or Aquacoat® by Asahi Kasei. The advantages of using these prepacked formulations are: consistency in color matching and other considerations based on their ease of use. The basic components of a film-coating system are:

- Polymer
- Solvent
- Plasticizer
- Other ingredients
  - Antitack agent
  - Antifoam agent
  - Colorant
  - Filler/extender
  - Flavor
  - Surfactant

The following polymeric materials form the basis of the most currently available coating formulations:

- Cellulose-based
  - Cellulose acetate phthalate (CAP)
  - Hydroxypropylmethylcellulose (HPMC)
  - Hydroxypropylcellulose (HPC)
  - Hydroxypropylethylcellulose
  - Ethylcellulose
  - Methylcellulose
  - Microcrystalline cellulose and carageenan
- Methacrylic acid/methacrylate esters
  - Anionic and cationic polymers of methacrylic acid
  - Copolymers of methacrylates
  - Copolymers of acrylate and methacrylates
  - Copolymers of ethacrylate and methylmethacrylate
- Polyvinylacetatephthalate
- Shellac
- Polyvinylpyrrolidone

The choice of a coating formulation depends, to a great degree, on the purpose of the coating. For example, certain coatings from a clear coat to a multilayered coating will protect highly sensitive vitamins from oxidative degradation.

In this book, the author described several prototype formulations that can be readily adapted for the formulations provided here. The most significant aspect remains the choice of colors, which often determines the method of manufacturing the coating solutions. With a limited choice of dyes and lakes available for selection, manufacturers often use a combination of several colors and dyes, along with agents such as talc for opaqueness, to obtain the desired colors and protection levels.

Another choice often confronted by the manufacturer is whether to use an aqueous coating or an organic coating system. Both have advantages and disadvantages. Whereas organic coating provides greater protection against moisture uptake during the coating process (important for moisture-sensitive ingredients) and are easier to apply because of the fast evaporation of solvents, the problems related to environmental control of organic solvents going in the atmosphere, the need to perform solvent residue tests, and the need to have explosion-proof facilities often yields to these advantages of aqueous coating systems. In recent years, many developments in the formulation of aqueous coatings made them an almost universally accepted mode of application.

II. HYDROXYPROPYL METHYLCELLULOSE (METHOCEL, HPMC) AQUEOUS COATINGS

Methocel-based coatings in an aqueous base are the most popular coating options. Two methods of making solutions are possible. If a lake is used, then alcohol is also included (see, for example, Holberry Red).

A. Brite Rose

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.25	4	Dye Red D&C No. 30 Lake	2.50
2.00	5	Titanium dioxide, special coating grade	20.00
QS	6	Water, purified, QS to	1 l

MANUFACTURING DIRECTIONS

Charge 250 ml of water into a suitable container, and heat to 60 to 70°C. With gentle stirring, disperse the hydroxypropyl methylcellulose onto the hot water. When the cellulose has wetted, quickly add 250 ml of cold water. Stir until the dispersion is homogenous, although the solution of cellulose may not be complete. Dissolve polyethylene glycol 8000 in 50 ml of water, and then add to the step above. Add polyethylene glycol 400 to the basic solution above. Load a suitable sized ball jar with Dye Red No. 30 Lake and titanium dioxide. Add a sufficient amount of water to cover the pigment and balls. Mill overnight or for 12 h. Other pigment reduction methods may be used to yield a particle size not above 1 μm. Add milled pigments to the base solution from the step above, and make up the volume with cold water. Use within 7 days.

B. Cherry Red

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
1.80	4	Dye Red FD&C No. 3 Lake	18.00
0.10	5	Dye Red FD&C No. 2 Amaranth	1.00
2.10	6	Titanium dioxide, special coating grade	21.00
QS	7	Water, purified,, (deionized) QS to	1 l

C. Geranium Rose

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.24	4	Dye Red FD&C No. 3 Lake	2.00
QS	5	Water, purified	1 l

D. Gloss

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
3.33	1	Hydroxypropyl methylcellulose 2910 15 cps	33.33
1.66	2	Polyethylene glycol 400	16.66
QS	3	Water, purified, QS to	1 l

E. Red

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
2.50	4	Dye Red FD&C No. 3 Lake	25.00
0.50	5	Titanium dioxide	5.00
QS	6	Water, purified, QS to	1 l

F. Moderate Red

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.50	4	Dye Yellow FD&C No. 3 Aluminum Lake	5.00
2.50	5	Dye Red Ponceau 4R Lake	25.00
1.00	6	Titanium dioxide, special coating grade	10.00
QS	7	Water, purified, QS to	1 l

G. Clear

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
0.10	2	Acid sorbic NF	1.00
2.00 v/v	3	Alcohol SD 3A 200 proof[a]	20.00 ml
2.00	4	Polyethylene glycol 400	20.00
2.00	5	Polyethylene glycol 8000 (optional)	20.00
QS	6	Water, purified, QS to	1 l

[a] Increase the amount to 6.00 if Item 5 is not used.

MANUFACTURING DIRECTIONS

Charge approximately 500 ml of water into a suitable vessel. Heat the water to between 65 to 70°C. Add the polyethylene glycol 8000 to the hot water, and dissolve (if used). While maintaining gentle agitation, sprinkle the hydroxypropyl methylcellulose onto the surface of the hot water solution from the preceding step. Position the stirring head to avoid an excessive entrainment of air. When the cellulose disperses, add the polyethylene glycol 400. Continue to stir until the dispersion is homogenous, although the solution of cellulose may not be complete. Stop stirring, and allow the solution to stand until entrained air is removed. Dissolve acid sorbic in alcohol, and ensure that the solution is complete. When the solution from the step above is clear, add 250 ml of cold water, mix well, and then add the sorbic acid solution. Mix, and then make up to the volume by adding cold water. Store the coating solution in well-filled, well-closed containers. Use within 3 months.

H. Green

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.0000	1	Hydroxypropyl methylcellulose 2910 15 cps	60.000
0.1000	2	Acid sorbic	1.000
2.0000 v/v	3	Alcohol SD 3A 200 proof	20.000 ml
2.0000	4	Polyethylene glycol 400	20.000
2.0000	5	Polyethylene glycol 8000	20.000
1.0000	6	Titanium dioxide	10.000
0.0100	7	Dye Yellow E 104 Aluminum Lake	0.100
0.0032	8	Dye Blue FD&C No. 1 Lake 11 to 13%	0.032
QS	9	Water, purified, QS to	1 l

I. Holberry Red

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
0.10	2	Acid sorbic	1.00
2.00 v/v	3	Alcohol SD 3A 200 proof	20.00 ml
2.00	4	Polyethylene glycol 400	20.00
2.00	5	Polyethylene glycol 8000	20.00
1.00	6	Titanium dioxide	10.00
1.50	7	Dye Red FD&C No. 40 Lake 29%	15.00
0.50	8	Dye Blue FD&C No. 3 Lake	5.00
QS	9	Water, purified, QS to	1 l

J. Sun Orange

Bill of Materials			
Scale (%, w/v)	**Item**	**Material Name**	**Quantity/l**
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
0.17	2	Acid sorbic	1.70
2.00 v/v	3	Alcohol SD 3A 200 proof	20.00 ml
2.00	4	Polyethylene glycol 400	20.00
2.00	5	Polyethylene glycol 8000	20.00
2.38	6	Titanium dioxide	23.80
2.47	7	Dye Yellow FD&C No. 5	24.70
0.16	8	Dye Yellow FD&C No. 6	1.60
QS	9	Water, purified, QS to	1 l

K. Opadry Yellow (Caplets)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Caplets(g)**
10.00	1	Hydroxypropyl methylcellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	Polyethylene glycol (PEG 4000)	1.60
1.20	4	Titanium dioxide	1.20
0.30	5	FD&C Blue No. 1 (lake)	0.30
0.50	6	Dispersed FD&C Blue No. 2	0.50
0.75	7	Opadry-OY-S 29019 clear	0.75
QS	8	Purified water	225.00

MANUFACTURING DIRECTIONS

The formula for the coating solution is prepared to obtain a weight gain of 10 mg per caplet (around 600 mg in weight), considering the evaporation and loss during the coating operation. Disperse Item 1 in 175 g of Item 8 (70 to 80°C) while stirring. Keep overnight for complete dispersion. Disperse Items 2 and 3 in 25 g of Item 8 (25 to 30°C). Keep overnight for complete hydration. Add the step above. Homogenize using an homogenizer, with a gap setting of 1.5 mm. Homogenize Items 4, 5, and 6 in 50 g of hypromellose dispersion from the step above, twice using the homogenizer, at a gap setting of 1.5 mm. Pass the dispersion twice through a 90-µm sieve. (*Note:* This is a critical step. Follow this strictly to prevent foreign particles and spots.) To prepare the polishing solution, disperse Item 7 in 25 g of Item 8 under slow stirring. Make a vortex by slow stirring, and add the powder in such a way as to avoid foam formation.

L. Opadry Yellow (Tabs)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets(g)**
10.000	1	Hydroxypropyl methylcellulose (hypromellose)	10.000
4.000	2	Talc (fine powder)	4.000
1.600	3	Polyethylene glycol (PEG 4000)	1.600
1.340	4	Titanium dioxide	1.340
0.046	5	E110 (Sunset Yellow FCF)	0.046
1.340	6	D&C Yellow No. 10 (lake)	1.340
0.750	7	Opadry-OY-S 29019 clear	0.750
—	8	Purified water	225.000

M. Opadry Red

Bill of Materials			
Scale (mg/caplet)	**Item**	**Material Name**	**Quantity/1000 Caplets (g)**
10.00	1	Hydroxypropyl methylcellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	Polyethylene glycol (PEG 4000)	1.60
1.34	4	Titanium dioxide	1.34
0.15	5	Iron oxide red	0.15
0.75	6	Opadry-OY-S 29019 clear	0.75
—	7	Purified water	225.00

N. Opadry Green

Bill of Materials			
Scale (mg/caplet)	**Item**	**Material Name**	**Quantity/1000 Caplet (g)**
10.000	1	Hydroxypropyl methylcellulose (hypromellose)	10.000
4.000	2	Talc (fine powder)	4.000
1.600	3	Polyethylene glycol (PEG 4000)	1.600
2.125	4	Titanium dioxide	2.125
0.053	5	FD&C Blue No. 1 (lake)	0.053
0.150	6	D&C Yellow No. 10 (lake)	0.150
0.750	7	Opadry-OY-S 29019 clear	0.750
—	8	Purified water	225.000

MANUFACTURING DIRECTIONS

Disperse Item 1 in 175 g of Item 8 (70 to 80°C) while stirring. Keep overnight for complete dispersion. Disperse Items 2 and 3 in 25 g of Item 8 (25 to 30°C). Keep overnight for complete hydration. Add together, and homogenize using a homogenizer, with a gap setting of 1.5 mm. Homogenize Items 4, 5, and 6 in 50 g of hypromellose dispersion from the step above, twice using the homogenizer, with a gap setting of 1.5 mm. Pass the dispersion twice through a 90-µm sieve. (*Note:* This is a critical step. Follow this strictly to prevent foreign particles and spots.) Disperse Item 7 in 25 g of Item 8 under slow stirring. Make a vortex by slow stirring, and add the powder in such a way to avoid foam formation. Follow the parameters for coating in Accela Cota 48.

Caplet load	620 g
Pan speed	4 r/min
Drying air temperature	70 to 75°C
Exhaust temperature	50 to 55°C
Fluid pressure	15 to 20 psi
Valve upon spray gun	One revolution open
Atomizing pressure	55 psi
Nozzle orifice	1 mm
Nozzle distance to bed	250 to 280 mm
Difference of air pressure	–1.0 to –1.5 cm
Spray rate	200 to 225 gm/min
Coating time	3.0 to 3.5 h

Continuously stir the dispersion at a slow speed (6 to 10 r/min). Spray the polishing solution under same condition mentioned previously, adjusting the spray rate to 180 g/min. Check the caplet surface every 5 min for sticking. If sticking tends to appear, stop the coating immediately. When the spraying is over, roll the tablets in the pan for 10 min with cold air blowing to the caplets. Unload the film-coated caplets in stainless steel containers lined with polythene bags. The appearance will be as a light-green-colored, film-coated caplet that is smooth, with no sticking or chipping on the caplet surface. The weight gain per caplet is not less than 10 mg/tablet.

O. White Coating

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
22.75	1	Hyperomellose	2.73
4.54	2	Polyethylene glycol	0.59
12.50	3	Talc, fine powder	1.50
10.00	4	Titanium dioxide	1.20
1.30	5	D&C Yellow No.10 Lake	0.16
—	6	Purified water	24.00
—	7	Ethanol 95%	21.00

III. HYDROXYPROPYL METHYLCELLULOSE OPAQUE ORGANIC COATING

A. Brite Green

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.000	1	Titanium dioxide	10.000
50.000 v/v	2	Alcohol SD 3A 200 proof, approximate	397.000
1.690	3	Polyethylene glycol 400	16.900
0.020	4	Dye Yellow FD&C No. 5	0.200
0.0068	5	Dye Blue FD&C No. 1	0.068
4.000	6	Hydroxypropyl methylcellulose 2910 15 cps	40.000
QS	7	Methylene chloride, approximate	625.000

MANUFACTURING DIRECTIONS

Charge titanium dioxide and QS with alcohol into the Ball mill. Mill the material for 16 h. Charge 465 ml of alcohol into a suitable mixing tank. Start agitation. Slowly add polyethylene glycol 400 to the mixing tank. Mix for 5 min. Add dye yellow to the mixing tank with continued agitation. Rinse the bottle with alcohol tapped from the mixing tank. Return the rinse to the mixing tank. Add dye blue to the mixing tank, and rinse. Mix for 2 h. Tap approximately 10 ml of the solution from the mixing tank after 1/2, 1, and 1 1/2 h of mixing. Put the solution back into the mixing tank. *Note:* The trapping solution assures that dye is not trapped in a lower valve or pipeline. Rinse the Ball mill into two rinses with 11.6 ml alcohol each time. Reseal the Ball mill, and allow it to run 2 to 5 min between rinses. Empty the content of the Ball mill and rinses into the mixing tank. Slowly sprinkle hydroxypropyl methylcellulose into the mixing tank with constant agitation. Agitate for an additional 15 min. (*Note:* Prevent the development of lumps by slowly sprinkling hydroxypropyl methylcellulose into the alcohol.) After mixing 10 min, tap approximately 10 ml from the mixing tank, and put it back into the tank to recirculate. Add a sufficient amount of methylene chloride (approximately 474 ml) to bring up to volume. Continue agitation for 2 h. After 1/2, 1, and 1 1/2 h, tap approximately 10 ml of the solution from the mixing tank, and put it back into the mixing tank to recirculate. (*Note:* There should be no residue in the solution when tapped at 1 1/2 h. If there is, continue agitation, and tap every 15 min until no residue is present. Nitrogen pressure may be used to assist bottle filling.

CAUTION: Avoid contact with methylene chloride and vapors. They may have toxic effects when swallowed or inhaled.

Strain the mixing tank contents through two-ply cheesecloth, or a similar material, into suitably approved containers (1/2 the total number of the bottles). *Note:* Lumps may obstruct spray nozzle.

B. Red Mahogany

Bill of Materials			
Scale(%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
0.40	1	Titanium dioxide	4.00
45.00 v/v	2	Alcohol SD 3A 200 proof, ca	375.30
0.40	3	Vanillin crystals	4.00
1.00	4	Propylene glycol	10.00
1.50	5	Dye Red FD&C No. 40 Lake 29%	15.00
1.00	6	Dye brown lake	10.00
4.00	7	Hydroxypropyl methylcellulose 2910 15 cps	40.00
QS	8	Methylene chloride, ca	530.40

C. Sun Orange

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
3.00	1	Titanium dioxide	30.00
50.00 v/v	2	Alcohol SD 3A 200 proof, ca	397.00
2.11	3	Propylene glycol	21.10
3.11	4	Dye Yellow FD&C No. 5	31.10
0.20	5	Dye Yellow FD&C No. 6	2.00
4.00	6	Hydroxypropyl methylcellulose 2910 15 cps	40.00
QS	7	Methylene chloride, ca	625.00

D. Dark Red

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.0000	1	Titanium dioxide	10.000
20.0000 v/v	2	Alcohol SD 3A 200 proof, approximate	200.000 ml
2.0000	3	Polyethylene glycol 400	20.000
0.0200	4	Dye Red Ponceau 4R	20.000
0.0068	5	Dye Blue FD&C No. 1	0.068
2.9500	6	Hydroxypropyl methylcellulose 2910 15 cps	29.500
QS	7	Methylene chloride, QS to	1 l

E. Deep Yellow

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
2.00	1	Titanium dioxide	20.00
50.00 v/v	2	Alcohol SD 3A 200 proof, approximate	397.00
2.00	3	Polyethylene glycol 400	20.00
2.00	4	Dye Yellow FD&C No. 5 Lake	20.00
2.95	5	Hydroxypropyl methylcellulose 2910 15 cps	29.50
QS	6	Methylene chloride, QS to	1 l

F. Pale Yellow

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.50	1	Titanium dioxide	15.00
50.00 v/v	2	Alcohol SD 3A 200 proof, approximate	397.00
2.00	3	Polyethylene glycol 400	20.00
0.50	4	Dye Yellow FD&C No. 10 Aluminum Lake 14 to 17%	5.00
2.95	5	Hydroxypropyl methylcellulose 2910 15 cps	29.50
QS	6	Methylene chloride, QS to	1 l

G. Scarlet Red

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
2.00	1	Titanium dioxide	20.00
20.00 v/v	2	Alcohol SD 3A 200 proof, approximate	200.00
2.00	3	Polyethylene glycol 400	20.00
2.00	4	Dye Yellow FD&C No. 7 Lake	20.00
1.00	5	Dye Yellow FD&C No. 5 Lake	10.00
2.95	6	Hydroxypropyl methylcellulose 2910 15 cps	29.50
QS	7	Methylene chloride, QS to	1 l

IV. HYDROXYPROPYL METHYLCELLULOSE–HYDROXYPROPYL CELLULOSE (KLUCEL) COATING

A. White

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
2.00	1	Titanium dioxide	20.00
0.50	2	Hydroxypropyl cellulose NC	5.00
45.00 v/v	3	Alcohol SD 3A 200 proof, approximate	450.00
2.00	4	Propylene glycol	20.00
4.50	5	Hydroxypropyl methylcellulose 2910 15 cps	45.00
QS	6	Methylene chloride, QS to	1 l

MANUFACTURING DIRECTIONS

Into a suitable size Ball jar, place the titanium dioxide and sufficient methylene chloride to cover the balls. Mill the items for not less than 16 h. While mixing the alcohol, add and disperse the hydroxypropyl methylcellulose, the hydroxypropyl cellulose, and the propylene glycol, followed by 250 ml of methylene chloride. Continue mixing until the dissolution is complete. While mixing the solution from the second step, empty into it the contents of the Ball jar, rinse balls and jar with methylene chloride, and add the rinsing to the batch and mix. Complete the batch to volume with methylene chloride, and mix well until homogenous. Strain the batch through muslin into suitable, approved bottles, and seal and store.

V. HYDROXYPROPYL METHYLCELLULOSE–ETHYLCELLULOSE COATING

A. Reddish Orange Opaque

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.16	1	Titanium dioxide	11.60
45.00 v/v	2	Alcohol dehydrated 200 proof, ca	450.00
0.20	3	Vanillin	2.00
0.50	4	Albumen powder	5.00
2.00	5	Polyethylene glycol 400	20.00
1.30	6	Dye Red FD&C No. 3	13.00
0.05	7	Dye Red FD&C No. 2	0.50
0.20	8	Dye Yellow FD&C No. 6	2.00
2.95	9	Hydroxypropyl methylcellulose 2910 15 cps	29.50
QS	10	Methylene chloride, QS to	1 l

MANUFACTURING DIRECTIONS

Load the vanillin, albumen, titanium dioxide, dye Red FD&C No. 3, dye Red FD&C No. 2, and dye Yellow FD&C No. 6 into a suitably sized ball jar. Add a sufficient amount of methylene chloride to cover the pigments and balls. Mill for 24 h. Blend the hydroxypropyl methylcellulose and the ethylcellulose together. Measure 400 ml of alcohol into a suitable stainless steel container. Sprinkle the hydroxypropyl methylcellulose/ethylcellulose onto the surface of the alcohol while stirring vigorously. When the hydroxypropyl methylcellulose/ethylcellulose is wetted, quickly add 300 ml methylene chloride while stirring vigorously. Add the polyethylene glycol 400 to the solution from the fourth step, and rinse the container with the remaining alcohol, adding the rinsing to the bulk. Empty the contents of the ball jar from the first step into the coating solution from the fifth step, while stirring vigorously. Rinse the ball jar with methylene chloride; adding the rinsing to the bulk. Make up to volume by adding methylene chloride.

B. Subcoating Solution

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
45.00 v/v	1	Alcohol 190 proof	450.00 ml
0.50	2	Hydroxypropyl cellulose NF	5.00
4.50	3	Hydroxypropyl methylcellulose 2910 15 cps	45.00
QS	4	Methylene chloride, QS to	1 l

VI. HYDROXYMETHYL CELLULOSE AND HYDROXY CELLULOSE COATING

A. Blue

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.000	1	Hydroxymethyl cellulose	10.00
1.000	2	Hydroxyethyl cellulose 15 cps	10.00
0.312	3	Titanium dioxide	3.21
1.000	4	Dye Blue FD&C No. 1 Lake 12%	10.00
0.375	5	Oil castor	3.75
0.375	6	Sorbitan monooleate	3.75
50.000 v/v	7	Alcohol SD 3A 200 proof	500.00 ml
QS	8	Methylene chloride, QS to	1 l

MANUFACTURING DIRECTIONS

Premix hydroxypropyl methylcellulose USP 15 cps and hydroxypropyl cellulose, and add to 440 ml alcohol SD 3A 200 proof with rapid agitation. Mix for not less than 1 h. Charge dye Blue FD&C No. 1 Lake 12%, and titanium dioxide into Ball mill. Cover the balls and materials with 60 ml of alcohol, and mill for 16 h. Add the contents to the mixing tank, and add the castor oil and sorbitan monooleate. Rinse the Ball mill with methylene chloride, and add the rinsing to the mixing tank. Make up to a volume of 1 l with methylene chloride, and mix for at least 1 h.

B. Clear (50:50)

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.000	1	Hydroxymethyl cellulose	10.00
1.000	2	Hydroxyethyl cellulose 15 cps	10.00
0.375	3	Oil castor odorless	3.75
50.000 v/v	4	Alcohol SD 3A 200 proof	500.00 ml
QS	5	Methylene chloride, QS to	1 l

VII. HYDROXYMETHYL CELLULOSE AND ETHYL CELLULOSE COATING

A. Clear

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
1.000	1	Hydroxymethyl cellulose	10.00
1.000	2	Hydroxyethyl cellulose 15 cps	10.00
0.375	3	Oil castor odorless	3.75
50.000 v/v	4	Alcohol SD 3A 200 proof	500.00 ml
QS	5	Methylene chloride, QS to	1 l

MANUFACTURING DIRECTIONS

Charge all the alcohol into the mixing tank. Turn on the mixer to mixing speed; maintain mixing speed throughout the preparation of the coating solution. Charge the hydroxypropyl methylcellulose and the ethylcellulose into the mixing tank. Let mix for 1 h. Add methylene chloride (approximately 500 ml) to bring the final volume to 1 l. Mix 1 h. The solution does not need to be agitated at all times. Keep the tank tightly closed at all times. The rubber stopper on the bottles must be protected from methylene chloride with a polyethylene layer.

VIII. POLYVINYLPYRROLIDONE COATINGS

A. Subcoating

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
20.00	1	Povidone K 29-32[a]	200.00
80.00 v/v	2	Alcohol SD 3A 200 proof	800 ml

[a] May be substituted with Kollidon VA64 (polyvinylpyrrolidone/vinyl acetate copolymer) 10%; Item 2 can be replaced with isopropyl alcohol. Spray the solution onto the warm tablet cores (30 to 40°C) for a few minutes before continuing with the aqueous main coating procedure. The amount of 0.4 mg/cm^2 tablet surface is sufficient for a good subcoating protection. No plasticizer is needed in this formulation due to the plasticity of Kollidon VA 64.

B. Kollidon VA 64

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
5.00	1	Kollidon VA 64 (BASF)	50.00
4.00	2	Lutrol E 6000	40.00
0.50	3	Glycerin	5.00
1.50	4	Iron oxide or lake	15.00
3.00	5	Titanium dioxide	30.00
5.00	6	Talc	50.00
QS	7	Purified water, QS to	1 l

MANUFACTURING DIRECTIONS

The suspension is passed through a disk mill before use and is sprayed under the following conditions:

- Sugar-coating pan
  - Spray gun — Walther WAXV with 1-mm nozzle
  - Spraying time — 3 sec
  - Pause — 0.5 sec
  - Dry air — 6 sec
  - Pause — 3 sec
- Accela Cota (continuous spraying)
  - Spray gun — Walther WAXV with 0.8-mm nozzle
  - Temperature at inlet — 45°C
  - Temperature at outlet — 38°C
  - Spraying pressure — 2 bar
  - Spraying time — approximately 50 min

If the film is too sticky, a certain part of Kollidon VA 64 should be substituted by HPMC or sucrose.

C. Kollidon VA 64 and Polyvinyl Alcohol

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
5.00	1	Kollidon VA 64 (BASF)	50.00
4.00	2	Lutrol E 6000	40.00
6.00	3	Polyvinyl alcohol	76.00
68.00	4	Purified water	680.00
0.50	5	Glycerin	5.00
1.50	6	Iron oxide or lake	18.00
3.00	7	Titanium dioxide	37.00
5.00	8	Talc	50.00
QS	9	Purified water	168.00

MANUFACTURING DIRECTIONS

Dissolve Items 1 to 3 in Item 4. Add the polyvinyl alcohol, and stir the mixture for 45 min, avoiding the formation of too many air bubbles. Suspend the pigments and talc in 168 ml of water, and pass this mixture through a colloid mill. To obtain the final coating suspension, mix this solution with the first solution.

- Coating procedure (Accela Cota)
  - Tablet core loading — 5.0 kg
  - Amount of coating suspension — 1.26 kg
  - Inlet air temperature — 59°C
  - Outlet air temperature — 46°C
  - Nozzle — 1.0 mm
  - Rotation speed of the pan — 15 rpm
  - Spraying pressure — 2.0 bar
  - Spraying rate — 15 g/min
  - Spraying time (continuously) — 83 min
  - Final drying — 5 min
  - Quantity of film formerly applied about 3 mg/cm^2

D. Kollidon 30 and Shellac

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
2.0	1	Kollidon 25 or 30 (BASF)	20.00
17.7	2	Shellac	177.00
18.50	3	Titanium dioxide	185.00
6.50	4	Talc	65.00
1.50	5	Cetyl alcohol	15.00
3.00	6	Sorbitan trioleate	30.00
5.00	7	Color lake	50.00
QS	8	Isopropanol or alcohol	458.00

MANUFACTURING DIRECTIONS

Dissolve shellac and sorbitane oleate in the warm solvent, and then dissolve Kollidon and cetyl alcohol. Add titanium dioxide, talc, and the lake, and mix in the colloid mill. To apply the coating suspension, apply about 50 g of suspension to 1 kg of tablet cores in a conventional coating pan or in an Accela Cota pan (1- to 2-mg film formers/cm^2).

E. Kollidon VA 64 and Hydroxypropylmethyl Cellulose

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
4.00	1	Kollidon VA 64 (BASF)	53.00
1.00	2	Lutrol E 6000	12.00
6.00	3	Hydroxypropylmethyl cellulose	79.00
1.50	4	Iron oxide or lake	18.00
3.00	5	Titanium dioxide	37.00
4.00	6	Talc	50.00
QS	7	Purified water QS to	1 Kg

MANUFACTURING DIRECTIONS

Dissolve Lutrol E6000 and Kollidon VA 64 in a portion of water. Add HPMC, and stir 45 min, avoiding the formation of too many air bubbles. Suspend the pigments and talc in the portion of water, and pass this mixture through a colloid mill. Mix the two portions.

- Coating procedure (Accela Cota)
  - Tablet core loading — 5 kg
  - Core size — 9-mm biconvex
  - Amount of coating suspension applied — 1.2 kg
  - Inlet air temperature — 60°C
  - Outlet air temperature — 40°C
  - Nozzle — 1 mm
  - Rotation speed of the pan — 12 rpm
  - Spraying pressure — 2.0 bar
  - Spraying rate — 50 g/min
  - Spraying time (continuously) — 34 min
  - Final drying — 2 min
  - Drying after spraying — 5 min at 60°C
  - Quantity of film formerly applied — 3.14 mg/cm^2

F. Povidone, Ethylcellulose, and Talc

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
7.50	1	Povidone K 29-32 (BASF)	75.00
4.25	2	Ethylcellulose	42.50
0.50	3	Polyethylene glycol 400	5.00
5.00	4	Talc	50.00
45.00 v/v	5	Alcohol SD 3A 200 proof	450.00 ml
QS	6	Methylene chloride to	1 l

MANUFACTURING DIRECTIONS

Dissolve povidone in alcohol, and then add polyethylene glycol 400. Add ethylcellulose to the solution from Step 1. Mix until evenly dispersed, and then make up to the volume by adding methylene chloride with constant stirring. Add the talc to the solution from Step 2, and stir to ensure distribution. The solution should be freshly prepared and used within 10 days of manufacture. Thoroughly disperse talc before use. If the batch is more than 200 l, do not add talc. If the coating solution is manufactured without talc, then the solution should be used within 4 weeks.

IX. CELLULOSE ACETATE PHTHALATE AND CARBOWAX COATINGS

A. Brite Green

Bill of Materials			
Scale (%w/v)	**Item**	**Material Name**	**Quantity (g/l)**
6.000	1	Cellulose acetate phthalate	60.00
1.860	2	Propylene glycol	18.65
0.660	3	Sorbitan monooleate (Span 80)	6.00
0.125	4	Oil castor odorless	1.25
0.850	5	Dye Blue FD&C No.1	0.850
3.110	6	Dye Yellow DC No. 5 Lake	31.10
5.330	7	Titanium dioxide	53.30
21.580	8	Methylene chloride	215.00
QS	9	Acetone to	1 l

MANUFACTURING DIRECTIONS

Place the methylethyl ketone in a suitably sized mixing tank. While stirring, add the propylene glycol, Span 80, and the castor oil. Add the cellulose acetate phthalate, and allow to soak overnight. Load the dye Blue FD&C No. 1, dye Yellow FD&C No. 5 Lake, and the titanium dioxide into a suitably sized Ball jar. Add a sufficient amount of acetone to cover the raw materials and balls. Ball mill overnight. Melt the Carbowax with a portion of the acetone, using gentle heat. Add the melted Carbowax to the mixture. Empty the contents of the Ball jar mill into the mixture. Rinse the Ball jar with acetone and add the rinse. Add acetone to the volume, and mix well. If necessary, strain solution through a gauge before storage or use.

B. Cherry Red

In the formulation given above, use dye Red FD&C No. 3 (6.800 g), dye Red FD&C No. 2 amaranth (1.000 g), and dye Yellow FD&C (5.400 g).

C. Clear

Delete dyes.

D. Orange

Use Dye Yellow FD&C No. 6 (4.000 g) and Dye Yellow FD&C No. 5 (12.000 g).

E. Red Mahogany

Use Dye Red FD&C No. 40 Lake 29% (15.000 g) and Dye Brown Lake Blend No. 9022 (WJ) (20.800 g).

F. Orange

Use Dye Yellow FD&C No. 6 (4.000 g) and Dye Yellow FD&C No. 5 (12.000 g).

X. SUGAR COATINGS

A. Basic

Bill of Materials			
Scale(%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
4.00	1	Kollidon VA 64 (BASF)	40.00
16.00	2	Sucrose	160.00
2.40	3	Titanium dioxide	24.00
1.20	4	Color lake	12.00
3.20	5	Lutrol E 4000	32.00
4.00	6	Talc	40.00
QS	7	Purified water QS to	1 kg

MANUFACTURING DIRECTIONS

Dissolve the sucrose, Kollidon VA 64, and Lutrol E 4000 in the water, and suspend the other components. Pass through a colloid mill.

- Coating procedure (Accela Cota)
  - Tablet core loading — 5 kg
  - Amount of coating suspension — 1.2 kg
  - Inlet air temperature — 45°C
  - Outlet air temperature — 35°C
  - Nozzle — 0.8 mm
  - Rotation speed of the pan — 15 rpm
  - Spraying pressure — 2 bar
  - Spraying time (continuously) — 50 min
  - Quantity of film formerly applied — 4 mg/cm^2

B. Automatic

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
4.00	1	Kollidon 30 (BASF)	40.00
38.00	2	Sucrose	380.00
4.50	3	Titanium dioxide	45.00
QS	4	Color lake	QS
4.50	5	Calcium carbonate	45.00
14.50	6	Talc	145.00
QS	7	Purified water QS to	1 kg

(According to *Nürnberg Pharm. Ind.*, 28, 5, 221–304, 1996.)

MANUFACTURING DIRECTIONS

Dissolve the sucrose in the hot water, mix with glycerol, dissolve Kollidon 30, and suspend the other components.

- Coating procedure
  - 4 kg of tablet cores with a weight of 420 mg are sprayed with 2.5 kg of the preceding suspension in a conventional coating pan under the following conditions:
- Spray phase — 5 s
- Interval — 10 min
- Drying phase (warm air) — 10 min
- Total coating time — 16 h

C. Manual White

Bill of Materials			
Scale (%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
0.336	1	Kollidon 30 (BASF)	3.36
0.292	2	Carmellose sodium	2.92
0.214	3	Aerosil 200	2.14
QS	4	Color lake	QS
1.620	5	Talc	16.20
0.100	6	Polysorbate or Cremophor RH40	1.00
1.400	7	Titanium dioxide	14.00
62.700	8	Sucrose	627.00
33.400	9	Purified water	334.00

MANUFACTURING DIRECTIONS

Dissolve Kollidon, polysorbate, or Cremophor and sucrose in the water, and suspend the other components in this solution. Mix in a colloid mill. Start with formulation without the color, and then apply the color coat. The polishing can be done by means of a solution of beeswax or polyethylene glycol 6000.

XI. ENTERIC COATINGS

A. Kollicoat and Kollidon Enteric Film Coating

Bill of Materials			
Scale(%w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
0.50	1	Titanium dioxide	5.00
2.00	2	Talc	20.00
0.50	3	Iron oxide	5.00
0.50	4	Kollidon 25 or Kollidon 30	5.00
50.00	5	Kollicoat MAE 30 DP (methacrylic acid/ethyl acrylate copolymer [1:1])	500.00
1.50	6	Triethyl citrate	15.00
QS	7	Purified water QS to	1 kg

MANUFACTURING DIRECTIONS

- Tablet core loading — 5 kg
- Core size — 9 mm biconvex
- Quantity of suspension applied — 1890 g
- Quantity of solids/cm^2 — 9 mg
- Quantity of film-forming agent/cm^2 — 6 mg
- Speed of the coating pan — 12 r/min
- Spray nozzle — 0.8 mm
- Spraying pressure — 2.0 bar
- Type of spraying — continuous
- Inlet air temperature — 50°C
- Outlet air temperature — approximately 30°C
- Spraying time — approximately 60 min
- Spraying rate — approximately 30 g/min

B. Eudragit Enteric Aqueous

1. Brick Red

Bill of Materials			
Scale (% w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
46.66	1	Water, purified (distilled)	466.66
1.51	2	Talc,, powder	15.19
0.79	3	Titanium dioxide,, special coating grade	7.98
1.55	4	Iron oxide, red	15.50
0.42	5	Polysorbate 80, NF	4.26
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.15
47.60	7	Eudragit, use Eudragit L 30D-55	476.00
1.42	8	Triethyl citrate (Eudraflex)	14.25

MANUFACTURING DIRECTIONS

Weigh the quantity of water (Item 1) needed. Take approximately 21.5% of the total quantity of water (Item 1) in a suitable mixing container. Add the talc powder, and stir vigorously until well suspended (approximately 20 min). Add the following to the preceding suspension, and mix thoroughly: titanium dioxide, iron oxide red, Tween 80, and dimethyl polysiloxane emulsion (30%). *Note:* The pigments may require homogenizing with colloid, corrundum disc mill, or ball mill. Take the Eudragit L 30D-55 in a suitable mixing vessel, and add the following with continuous mixing: homogenized pigment mixture from Step 2, Eudraflex (i.e., triethyl citrate) and the remaining quantity of water (Item 1). *Note:* When PEG 8000 is used as a plasticizer, it should be incorporated as a 10% aqueous solution.

2. Yellow

Bill of Materials			
Scale (% w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
46.667	1	Water, purified	466.66
1.258	2	Talc	12.57
0.779	3	Titanium dioxide	7.79
1.836	4	Dye Yellow FD&C No. 10 Aluminum Lake 14 to 17%	18.36
0.428	5	Polysorbate 80	4.27
0.012	6	Dimethyl polysiloxane emulsion (30%)	0.12
47.600	7	Eudragit, use methacrylic acid copolymer (Eudragit L 30D-55)	476.00
1.421	8	Triethyl citrate (Eudraflex)	14.21

3. Brown

Bill of Materials			
Scale (% w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
46.667	1	Water, purified	466.66
0.476	2	Titanium dioxide	4.76
0.853	3	Iron oxide black	8.53
2.262	4	Iron oxide red	22.61
0.258	5	Iron oxide yellow	2.57
0.427	6	Polysorbate 80	4.26
0.010	7	Dimethyl polysiloxane emulsion	0.09
47.633	8	Eudragit, use Eudragit L 30D-55	476.33
1.429	9	Triethyl citrate (Eudraflex)	14.28

4. Dark Orange

Bill of Materials			
Scale (% w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
46.667	1	Water, purified	466.66
2.519	2	Talc	25.188
0.392	3	Titanium dioxide	3.92
0.932	4	Dye Yellow FD&C No. 6 Aluminium Lake	9.32
0.429	5	Polysorbate 80	4.29
0.014	6	Dimethyl polysiloxane emulsion (30%)	0.13
47.633	7	Eudragit, use Eudragit L 30D-55	476.33
1.428	8	Triethyl citrate (Eudraflex)	14.28

5. Orange

Bill of Materials			
Scale (% w/w)	**Item**	**Material Name**	**Quantity (g/kg)**
46.667	1	Water, purified	466.667
2.600	2	Talc	26.000
0.785	3	Titanium dioxide	7.847
0.466	4	Dye Yellow FD&C No. 6 Aluminum Lake	4.662
0.427	5	Polysorbate 80	4.273
0.012	6	Dimethyl polysiloxane emulsion (30%)	0.117
47.617	7	Eudragit, use Eudragit L 30D-55	476.166
1.429	8	Triethyl citrate (Eudraflex)	14.296

6. Dispersed Orange

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.92	1	Opagloss NA 7150	0.92
7.07	2	Methacrylic acid copolymer (Eudragit L 100-55)	7.07
0.09	3	Sodium hydroxide pellets (caustic soda)	0.09
0.73	4	Polyethylene glycol (PEG 6000)	0.73
2.50	5	Talc (fine powder)	2.50
0.10	6	Simethicone emulsion 30% (simethicone antifoam M30)	0.10
0.27	7	Povidone (PVP K25)	0.27
50.00	8	Sucrose	50.00
0.54	9	Povidone (PVP K25)	0.54
0.36	10	Titanium dioxide	0.36
0.36	11	D&C Yellow No. 10 (lake)	0.36
0.04	12	Dispersed orange[a]	0.04
1.07	13	Sucrose	1.07
0.38	14	Polishing emulsion	0.38
—	15	Purified water	65.41

[a] Dispersed orange: This material is the aluminum lake of sunset yellow FCF (E110).

C. Hydroxypropyl Methylcellulose Phthalate Enteric Coating

1. Clear Enteric

Bill of Materials			
Scale (% w/v)	**Item**	**Material Name**	**Quantity (g/kg)**
20.00 v/v	1	Acetone	200.00 ml
10.00 v/v	2	Water, purified	100.00 ml
4.00	3	Hydroxypropyl methylcellulose	40.00
0.30	4	Vanillin	3.00
0.40	5	Acetylated monoglycerides	4.00
QS	6	Alcohol SD 3A 200 proof QS to	1 l

MANUFACTURING DIRECTIONS

Charge acetone, purified water, and 470 ml of alcohol into a suitable mixing tank. Add the hydroxypropyl methylcellulose phthalate, vanillin (if used), and the distilled acetylated monoglycerides, and mix until a clear solution is obtained. Make up to 1 l with alcohol, and record the volume used. Mix for 1 h.

2. Orchid Pink Opaque

Bill of Materials			
Scale (% w/v)	**Item**	**Material Name**	**Quantity (g/kg)**
20.000 v/v	1	Acetone	200.00 ml
10.000 v/v	2	Water, purified	100.00 ml
8.000	3	Hydroxypropyl methylcellulose phthalate	80.00
0.800	4	Diacetylated monoglycerides	8.00
0.060	5	Dye Red D&C No. 30 Lake	0.60
0.006	6	Dye Blue FD&C No. 2 Aluminum Lake 14%	0.060
0.700	7	Titanium dioxide	7.00
QS	8	Alcohol SD 3A 200 proof, QS to	1 l

3. Light Apricot Orange

Bill of Materials			
Scale (% w/v)	**Item**	**Material Name**	**Quantity (g/kg)**
20.00 v/v	1	Acetone	200.00 ml
10.00 v/v	2	Water, purified	100.00 ml
8.00	3	Hydroxypropyl methylcellulose phthalate	80.00
0.80	4	Diacetylated monoglycerides	8.00
0.10	5	Dye Yellow FD&C No.10 Aluminum Lake 14 to 17%	1.00
0.06	6	Dye Red FD&C No. 3 Aluminum Lake 14%	0.60
0.70	7	Titanium dioxide	7.00
QS	8	Alcohol SD 3A 200 proof, QS to	1 l

Part I

Regulatory and Manufacturing Requirements in Compressed Solid Dosage Forms

1 Bioavailability and Bioequivalence Studies for Orally Administered Drug Products

I. INTRODUCTION

Demonstration of bioequivalence is a critical requirement for gaining marketing authorization of new drugs and generics. These requirements are specified in the Code of Federal Regulations, Title 21, Part 320 (21 CFR Part 320) as they apply to dosage forms intended for oral administration. Substantial changes to these guidelines have been contemplated. In the discussion that follows, an overview of the guidelines that will soon become effective is provided. Manufacturers contemplating the development of new drug products should pay close attention to the changes described in Sections II.B. and II.C. regarding bioavailability (BA) or bioequivalence (BE) studies.

II. BACKGROUND

A. General

Studies to measure BA and establish BE of a product are important elements in support of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their supplements. As part of INDs and NDAs for orally administered drug products, BA studies focus on determining the process by which a drug is released from the oral dosage form and moves to the site of action. BA data provide estimates of the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can generally be documented by a systemic exposure profile obtained by measuring drug or metabolite concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the IND period can serve as a benchmark for subsequent BE studies.

Studies to establish BE between two products are important when considering certain changes before approval for a pioneer product in NDA and ANDA submissions, and in the presence of certain postapproval changes in NDAs and ANDAs. In BE studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product should exhibit the same rate and extent of absorption as the reference drug product.

BA and BE studies are required by regulations, depending on the type of application being submitted. Under § 314.94, BE information is required to ensure therapeutic equivalence between a pharmaceutically equivalent test drug product and a reference listed drug. Regulatory requirements for documentation of BA and BE are provided in Part 320, which contains two subparts. Subpart A covers general provisions, while Subpart B contains 18 sections delineating the following general BA and BE requirements:

- Requirements for submission of BA and BE data (§ 320.21)
- Criteria for waiver of an *in vivo* BA or BE study (§ 320.22)
- Basis for demonstrating *in vivo* BA or BE (§ 320.23)
- Types of evidence to establish BA or BE (§ 320.24)
- Guidelines for conducting *in vivo* BA studies (§ 320.25)
- Guidelines for design of single-dose BA studies (§ 320.26)
- Guidelines for design of multiple-dose *in vivo* BA studies (§ 320.27)
- Correlations of BA with an acute pharmacological effect or clinical evidence (§ 320.28)
- Analytical methods for an *in vivo* BA study (§ 320.29)
- Inquiries regarding BA and BE requirements and review of protocols by the FDA (§ 320.30)
- Applicability of requirements regarding INDs (§ 320.31)
- Procedures for establishing and amending a BE requirement (§ 320.32)
- Criteria and evidence to assess actual or potential BE problems (§ 320.33)
- Requirements for batch testing and certification by the FDA (§ 320.34)

- Requirements for *in vitro* batch testing of each batch (§ 320.35)
- Requirements for maintenance of records of BE testing (§ 320.36)
- Retention of BA samples (§ 320.38)
- Retention of BE samples (§ 320.63)

B. Bioavailability

Bioavailability is defined in § 320.1 [21 CFR 320.1(a)] as:

> … the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action.

From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the BA data for a solution, suspension, or intravenous dosage form [21 CFR 320.25(d)(2) and (3)]. In addition, BA studies provide other useful pharmacokinetic information related to distribution, elimination, effects of nutrients on absorption of the drug, dose proportionality, linearity in pharmacokinetics of the active moieties, and, where appropriate, inactive moieties. BA data may also indirectly provide information about the properties of a drug substance before entry into the systemic circulation, such as permeability and the influence of presystemic enzymes and transporters (e.g., *p*-glycoprotein).

BA for orally administered drug products can be documented by developing a systemic exposure profile obtained from measuring the concentration of active ingredients or active moieties and, when appropriate, its active metabolites over time in samples collected from the systemic circulation. Systemic exposure patterns reflect release of the drug substance from the drug product and a series of possible presystemic and systemic actions on the drug substance after its release from the drug product. Additional comparative studies should be performed to understand the relative contribution of these processes to the systemic exposure pattern.

One regulatory objective is to assess, through appropriately designed BA studies, the performances of the formulations used in the clinical trials that provide evidence of safety and efficacy [21 CFR 320.25(d)(1)]. The performance of the clinical trial dosage form may be optimized, in the context of demonstrating safety and efficacy, before marketing a drug product. The systemic exposure profiles of clinical trial material can be used as a benchmark for subsequent formulation changes and may be useful as a reference for future BE studies.

C. Bioequivalence

Bioequivalence is defined in § 320.1 [21 CFR 320.1(e)] as:

> … the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

As noted in the statutory definitions, BE and product quality BA focus on the release of a drug substance from a drug product and subsequent absorption into the systemic circulation. For this reason, similar approaches to measuring BA in an NDA should generally be followed in demonstrating BE for an NDA or an ANDA. Establishing product quality BA is a benchmarking effort, with comparisons to an oral solution, an oral suspension, or an intravenous formulation. In contrast, demonstrating BE is usually a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits for such criteria.

1. INDs/NDAs

BE documentation may be useful during the IND or NDA period to establish links between the following:

- Early and late clinical trial formulations
- Formulations used in clinical trial and stability studies, if different
- Clinical trial formulations and to-be-marketed drug products
- Other comparisons, as appropriate

In each comparison, the new formulation or new method of manufacture is the test product, and the prior formulation or method of manufacture is the reference product. The determination to redocument BE during the IND period is generally left to the judgment of the sponsor, who may wish to use the principles of relevant guidances (see Section II.C.3. and Section II.C.4.) to determine when changes in components, composition, or method of manufacture suggest that further *in vitro* and *in vivo* studies should be performed.

A test product may fail to meet BE limits because the test product has higher or lower measures of rate and extent of absorption compared with the reference product, or because the performance of the test or reference product is more variable. In some cases, nondocumentation of BE

may arise because of inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability and not because of the high or low relative BA of the test product. Adequate design and execution of a BE study will facilitate an understanding of the causes of nondocumentation of BE.

Where the test product generates plasma levels substantially above those of the reference product, the regulatory concern is not therapeutic failure but the adequacy of the safety database from the test product. Where the test product has levels that are substantially below those of the reference product, the regulatory concern becomes therapeutic efficacy. When the variability of the test product rises, the regulatory concern relates to safety and efficacy because it may suggest that the test product does not perform as well as the reference product, and the test product may be too variable to be clinically useful.

Proper mapping of individual dose–response or concentration–response curves is useful in situations where the drug product has plasma levels that are either higher or lower than the reference product and are outside usual BE limits. In the absence of individual data, population dose–response or concentration–response data acquired over a range of doses, including doses above the recommended therapeutic doses, may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk. Similarly, population dose– or concentration–response relationships observed over a lower range of doses, including doses below the recommended therapeutic doses, may be able to demonstrate that reduced levels of the test product compared with the reference product are associated with adequate efficacy. In either event, the burden is on the sponsor to demonstrate the adequacy of the clinical trial dose– or concentration–response data to provide evidence of therapeutic equivalence. In the absence of this evidence, a failure to document BE may suggest that the product should be reformulated, the method of manufacture for the test product should be changed, or the BE study should be repeated.

2. ANDAs

BE studies are a critical component of ANDA submissions. The purpose of these studies is to demonstrate BE between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug [21 CFR 314.94 (a)(7)]. Together with the determination of pharmaceutical equivalence, establishing BE allows a regulatory conclusion of therapeutic equivalence to be drawn.

3. Postapproval Changes

Information on the types of *in vitro* dissolution and *in vivo* BE studies that should be conducted for immediate-release and modified-release drug products approved as NDAs or ANDAs in the presence of specified postapproval changes is provided in the FDA guidance for industry titled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls,* In Vitro *Dissolution Testing, and* In Vivo *Bioequivalence Documentation* (November 1995) and *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls,* In Vitro *Dissolution Testing, and* In Vivo *Bioequivalence Documentation* (September 1997). In the presence of certain major changes in components, composition, or methods of manufacture after approval, *in vivo* BE should be redemonstrated. For approved NDAs, the drug product after the change should be compared with the drug product before the change. For approved ANDAs, the drug product after the change should be compared with the reference listed drug. Under § 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC 356a(c)(2)(B)], postapproval changes requiring completion of studies in accordance with Part 320 must be submitted in a supplement and approved by the FDA before distributing a drug product made with the change.

III. METHODS TO DOCUMENT BA AND BE

As noted in § 320.24, several *in vivo* and *in vitro* methods can be used to measure product quality BA and establish BE. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and *in vitro* studies. These general approaches are discussed in the following sections of this guidance. Product quality BA and BE frequently rely on pharmacokinetic measures, such as AUC and C_{max}, that are reflective of systemic exposure.

A. Pharmacokinetic Studies

1. General Considerations

The statutory definitions of BA and BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety to the site of action, emphasize the use of pharmacokinetic measures in an accessible biological matrix, such as blood, plasma, or serum, to indicate release of the drug substance from the drug product into the systemic circulation. This approach rests on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible, and furthermore, that some relationship exists between the efficacy and safety and concentration of the active moiety and its important metabolite or metabolites in the systemic circulation. To measure product quality BA and establish BE, reliance on pharmacokinetic measurements may be viewed as a

bioassay that assesses release of the drug substance from the drug product into the systemic circulation. A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g., gastric emptying, motility, pH), are assumed to have less interoccasion variability compared with the variability arising from formulation performance. Therefore, differences between two products because of formulation factors can be determined.

2. Pilot Study

If the sponsor chooses, a pilot study among a small number of subjects can be carried out before proceeding with a full BE study. The study can be used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information. For example, for conventional immediate-release products, careful timing of initial samples may avoid a subsequent finding in a full-scale study that the first sample collection occurs after the plasma concentration peak. For modified-release products, a pilot study can help determine the sampling schedule with which to assess lag time and dose dumping. A pilot study that documents BE may be appropriate, provided its design and execution are suitable, and a sufficient number of subjects (e.g., 12) completed the study.

3. Pivotal Bioequivalence Studies

General recommendations for a standard BE study based on pharmacokinetic measurements are provided in the Appendix to this chapter.

4. Study Designs

Nonreplicate study designs are recommended for BE studies of immediate-release and modified-release dosage forms. However, sponsors and applicants have the option of using replicate designs for BE studies for these drug products. Replicate study designs offer several scientific advantages compared with nonreplicate designs. The advantages of replicate study designs are that they:

- Allow for comparisons of within-subject variances for the test and reference products
- Indicate whether a test product exhibits higher or lower within-subject variability in the bioavailability measures when compared with the reference product
- Provide more information about the intrinsic factors underlying formulation performance
- Reduce the number of subjects needed in the BE study

The recommended method for analysis of nonreplicate or replicate studies to establish BE is average bioequivalence, as discussed in Section IV. General recommendations for nonreplicate study designs are provided in the Appendix. Recommendations for replicate study designs can be found in the Guidance for Industry *Statistical Approaches to Establishing Bioequivalence* (January 2001) (http://www.fda.gov/cder/guidance/3616fnl.htm).

5. Study Population

Unless otherwise indicated by a specific guidance, subjects recruited for *in vivo* BE studies should be 18 years of age or older and capable of giving informed consent. This guidance recommends that *in vivo* BE studies be conducted in individuals who represent the general population, taking into account age, sex, and race. If the drug product is intended for use in both sexes, the sponsor should attempt to include similar proportions of males and females in the study. If the drug product is to be used predominantly in the elderly, the sponsor should attempt to include as many subjects who are 60 years old, or older, as possible. The total number of subjects in the study should provide adequate power for BE demonstration, but it is not expected that there will be sufficient power to draw conclusions for each subgroup. Statistical analysis of subgroups is not recommended. Restrictions on admission into the study should generally be based solely on safety considerations. In some instances, it may be useful to admit into BE studies patients for whom a drug product is intended. In this situation for the duration of the BE study, sponsors and applicants should attempt to enter patients who have a disease process that is stable. In accordance with § 320.31, for some products that will be submitted in ANDAs, an IND may be required for BE studies to ensure patient safety.

6. Single-Dose/Multiple-Dose Studies

Instances where multiple-dose studies may be useful are defined under § 320.27(a)(3). The new guidelines generally recommend single-dose pharmacokinetic studies for both immediate- and modified-release drug products to demonstrate BE because they are *generally* more sensitive in assessing the release of the drug substance from the drug product into the systemic circulation (see Section V). If a multiple-dose study design is important, appropriate dosage administration and sampling should be carried out to document the attainment of a steady state.

7. Bioanalytical Methodology

Bioanalytical methods for BA and BE studies should be accurate, precise, selective, sensitive, and reproducible. A separate FDA guidance titled *Bioanalytical Method*

Validation (May 2001) is available to assist sponsors in validating bioanalytical methods (http://www.fda.gov/cder/guidance/4252fnl.htm).

8. Pharmacokinetic Measures of Systemic Exposure

Direct (e.g., rate constant, rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residence time, C_{max} normalized to area under the curve [AUC]) pharmacokinetic measures are limited in their abilities to assess rate of absorption. This guideline, therefore, recommends a change in focus from these direct or indirect measures of absorption rate to measures of systemic exposure. The C_{max} and AUC values can continue to be used as measures for product quality BA and BE, but more in terms of their capacity to assess exposure than their capacity to reflect the rate and extent of absorption. Reliance on systemic exposure measures should reflect comparable rates and extents of absorption, which, in turn, should achieve the underlying statutory and regulatory objective of ensuring comparable therapeutic effects. Exposure measures are defined relative to early, peak, and total portions of the plasma, serum, or blood concentration–time profile, as described in Section III.A.8.a. through Section III.A.8.c.

a. Early Exposure

For orally administered immediate-release drug products, BE may generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be informative on the basis of appropriate clinical efficacy and safety trials or pharmacokinetic and pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of T_{max} values for the reference formulation. At least two quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.

b. Peak Exposure

Peak exposure should be assessed by measuring the peak drug concentration (C_{max}) obtained directly from the data without interpolation.

c. Total Exposure

For single-dose studies, the measurement of total exposure should be as follows:

- Area under the plasma/serum/blood concentration–time curve from time 0 to time t ($AUC_{0\text{-}t}$), where t is the last time point with measurable concentration for individual formulation
- Area under the plasma/serum/blood concentration–time curve from time 0 to time infinity ($AUC_{0\text{-}\infty}$), where $AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_t/\lambda_z$, C_t is the last measurable drug concentration, and λ_z is the terminal or elimination rate constant calculated according to an appropriate method; the terminal half-life ($t_{1/2}$) of the drug should also be reported.

For steady-state studies, the measurement of total exposure should be the area under the plasma, serum, or blood concentration–time curve from time 0 to time τ over a dosing interval at steady state ($AUC_{0\text{-}\tau}$), where τ is the length of the dosing interval.

B. Pharmacodynamic Studies

Pharmacodynamic studies are not recommended for orally administered drug products when the drug is absorbed into the systemic circulation, and a pharmacokinetic approach can be used to assess systemic exposure and establish BE. However, in those instances where a pharmacokinetic approach is not possible, suitably validated pharmacodynamic methods can be used to demonstrate BE.

C. Comparative Clinical Studies

Where no other means are available, well-controlled clinical trials in humans may be useful to provide supportive evidence of BA or BE. However, the use of comparative clinical trials as an approach to demonstrate BE is generally considered insensitive and should be avoided when possible (21 CFR 320.24). The use of BE studies with clinical trial end points may be appropriate to demonstrate BE for orally administered drug products, when measurement of the active ingredients or active moieties in an accessible biological fluid (pharmacokinetic approach) or pharmacodynamic approach is infeasible.

D. *In Vitro* Studies

Under certain circumstances, product quality BA and BE can be documented using *in vitro* approaches [21 CFR 320.24(b)(5) and 21 CFR 320.22(d)(3)]. For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an *in vitro* approach (dissolution studies) is appropriate based on the biopharmaceutics classification system. This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved NDAs and ANDAs. In addition, *in vitro* approaches to document BE for *nonbioproblem* drugs approved before 1962 remain acceptable (21 CFR 320.33).

Dissolution testing is also used to assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release. Dissolution testing is also used to provide process control and quality assurance and assess whether further BE studies relative to minor postapproval changes should be conducted, where dissolution can function as a signal of bioinequivalence. Dissolution characterization *in vitro* is encouraged for all product formulations investigated (including prototype formulations), particularly if *in vivo* absorption characteristics are defined for the different product formulations. Such efforts may enable the establishment of an *in vitro–in vivo* correlation. When an *in vitro–in vivo* correlation or association is available [21 CFR 320.24(b)(1)(ii)], the *in vitro* test can serve not only as a quality control specification for the manufacturing process but also as an indicator of how the product will perform *in vivo*. The following guidances provide recommendations on the development of dissolution methodology, the setting of specifications, and the regulatory applications of dissolution testing: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997) and *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of* In Vitro/In Vivo *Correlations* (September 1997).

The following information should generally be included in the dissolution method development report for solid oral dosage forms.

For an NDA, the following should be included:

- The pH solubility profile of the drug substance
- Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 rpm for U.S. Pharmacopoeia [USP] Apparatus I [basket], and 50 to 100 rpm for USP Apparatus II [paddle])
- Dissolution profiles generated on all strengths in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer); water can be used as an additional medium; if the drug being considered is poorly soluble, appropriate concentrations of surfactants should be used

The agitation speed and medium that provide the best discriminating ability, taking into account all the available *in vitro* and *in vivo* data, will be selected.

For ANDAs, the following should be included:

- USP method
- If a USP method is not available, the FDA method for the reference listed drug should be used.
- If USP or FDA methods are not available, the dissolution method development report described previously should be submitted.

This guidance recommends that dissolution data from three batches, for NDAs and ANDAs, be used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms.

IV. COMPARISON OF BA MEASURES IN BE STUDIES

An equivalence approach was and continues to be recommended for BE comparisons. The recommended approach relies on:

1. Criterion to allow the comparison
2. Confidence interval for the criterion
3. BE limit; log transformation of exposure measures before statistical analysis is recommended

BE studies are performed as single-dose, crossover studies. To compare measures in these studies, data were analyzed using an average BE criterion. This guidance recommends continued use of an average BE criterion to compare BA measures for replicate and nonreplicate BE studies of immediate- and modified-release products.

V. DOCUMENTATION OF BA AND BE

An *in vivo* study is generally recommended for all solid oral dosage forms approved after 1962 and for *bioproblem* drug products approved before 1962. Waiver of *in vivo* studies for different strengths of a drug product may be granted under § 320.22(d)(2), when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer conducted an acceptable *in vivo* study; and (3) the new strength meets an appropriate *in vitro* dissolution test. This guidance defines *proportionally similar* in the following ways:

- All active and inactive ingredients are in the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).
- Active and inactive ingredients are not in exactly the same proportion between different strengths, as stated previously, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances (up to Level II).
- For high-potency drug substances, where the amount of the active drug substance in the

dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ±10% of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances (up to Level II).

Exceptions to these definitions may be possible, if adequate justification is provided.

A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, *in vivo* BA or BE can be waived [21 CFR 320.22(b)(3)(i)]. Generally, *in vivo* BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident, and that the solutions do not contain any excipient that significantly affects drug absorption [21 CFR 320.22(b)(3)(iii)]. However, certain excipients, such as sorbitol or mannitol, can reduce the bioavailability of drugs with low intestinal permeability in amounts sometimes used in oral liquid dosage forms.

B. Suspensions

BA and BE for a suspension should generally be established just as they are for immediate-release solid oral dosage forms, and both *in vivo* and *in vitro* studies are recommended.

C. Immediate-Release Products: Capsules and Tablets

1. General Recommendations

For product quality, BA and BE studies, where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study should be performed. The *in vivo* BE studies should be accompanied by *in vitro* dissolution profiles on all strengths of each product. For ANDAs, the BE study should be conducted between the test product and reference listed drug using the strength specified in *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*).

2. Waivers of *In Vivo* BE Studies (Biowaivers)

a. INDs, NDAs, and ANDAs: Preapproval

When the drug product is in the same dosage form but in a different strength and is proportionally similar in its active and inactive ingredients to the reference listed drug, an *in vivo* BE demonstration of one or more lower strengths can be waived to the reference listed drug based on dissolution tests and an *in vivo* study on the highest strength.

For an NDA, biowaivers of a higher strength will be determined to be appropriate based on clinical safety and efficacy studies, including data on the dose and the desirability of the higher strength; linear elimination kinetics over the therapeutic dose range; the higher strength being proportionally similar to the lower strength; and the same dissolution procedures being used for both strengths and similar dissolution results obtained. A dissolution profile should be generated for all strengths.

If an appropriate dissolution method was established (see Section III.D.), and the dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength, then dissolution profiles in one medium are usually sufficient to support waivers of *in vivo* testing. Otherwise, dissolution data in three media (pH 1.2, 4.5, and 6.8) are recommended.

The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile, such that further *in vivo* studies are not necessary. For an f_2 value < 50, further discussions with review staff from the U.S. FDA Center for Drug Evaluation and Research (CDER) may help to determine whether an *in vivo* study is necessary [21 CFR 320.22(d)(2)(ii)]. The f_2 approach is not suitable for rapidly dissolving drug products (e.g., ≥85% dissolved in 15 min or less).

For an ANDA, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety, subject to approval by the Division of Bioequivalence, Office of Generic Drugs, and provided that the following conditions are met:

- Linear elimination kinetics were shown over the entire therapeutic dose range.
- Higher strengths of the test and reference products are proportionally similar to their corresponding lower strengths.
- Comparative dissolution testing on the higher strength of the test and reference products was submitted and found to be appropriate.

b. NDAs and ANDAs: Postapproval

Information on the types of *in vitro* dissolution and *in vivo* BE studies for immediate-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry titled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls,* In Vitro *Dissolution Testing, and* In Vivo *Bioequivalence*

Documentation (November 1995). For postapproval changes, the *in vitro* comparison should be made between the prechange and postchange products. In instances where dissolution profile comparisons are recommended, an f_2 test should be used. An f_2 value of ≥ 50 suggests a sufficiently similar dissolution profile, and no further *in vivo* studies are needed. When *in vivo* BE studies are recommended, the comparison should be made for NDAs between the prechange and postchange products and for ANDAs between the postchange and reference listed drug products.

D. Modified-Release Products

Modified-release products include delayed-release products and extended-controlled-release products.

As defined in the USP, delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form passed through the acidic medium of the stomach. The *in vivo* tests for delayed-release drug products are similar to those for extended-release drug products. The *in vitro* dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8).

Extended-release drug products are dosage forms that allow a reduction in dosing frequency as compared with when the drug is present in an immediate-release dosage form. These drug products can also be developed to reduce fluctuations in plasma concentrations. Extended-release products can be capsules, tablets, granules, pellets, and suspensions. If any part of a drug product includes an extended-release component, the following recommendations apply.

1. NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity or for a new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity, formulated as a modified-release drug product. The first modified-release drug product for a previously approved immediate-release drug product should be submitted as an NDA. Subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product should be submitted as ANDAs. BA requirements for the NDA of an extended-release product are listed in 21 CFR 320.25(f). The purpose of an *in vivo* BA study for which a controlled-release claim is made is to determine if all the following conditions are met:

- The drug product meets the controlled-release claims made for it
- The BA profile established for the drug product rules out the occurrence of any dose dumping
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and is subject to an approved full NDA
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units

As noted in 21 CFR 320.25(f)(2), "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product," such as the following:

- Solution or suspension of the active drug ingredient or therapeutic moiety
- Currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling
- Currently marketed controlled-release drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted as an NDA:

- Single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules
- Single-dose, food-effect study on the highest strength
- Steady-state study on the highest strength

BE studies are recommended when substantial changes in the components or composition or method of manufacture for an extended-release drug product occur between the to-be-marketed NDA dosage form and the clinical trial material.

2. ANDAs: BE Studies

For modified-release products submitted as ANDAs, the following studies are recommended: a single-dose, nonreplicate, fasting study comparing the highest strength of

the test and reference listed drug product, unless the drug or drug product is highly variable, in which case a replicate design study is recommended; and a food-effect, nonreplicate study comparing the highest strength of the test and reference product (see Section VI.A.). Because single-dose studies are considered more sensitive in addressing the primary question of BE (i.e., release of the drug substance from the drug product into the systemic circulation), multiple-dose studies are generally not recommended, even in instances where nonlinear kinetics are present.

3. Waivers of *In Vivo* BE Studies (Biowaivers): NDAs and ANDAs

a. Beaded Capsules — Lower Strength

For modified-release beaded capsules, where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BE study should be carried out only on the highest strength, with waiver of *in vivo* studies for lower strengths based on dissolution profiles. A dissolution profile should be generated for each strength using the recommended dissolution method. The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed.

b. Tablets — Lower Strength

For modified-release tablets, when the drug product is in the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an *in vivo* BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an *in vivo* study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths, based on the f_2 test in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8). The dissolution profile should be generated on the test and reference products of all strengths.

4. Postapproval Changes

Information on the types of *in vitro* dissolution and *in vivo* BE studies for extended-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry titled *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls,* In Vitro *Dissolution Testing, and* In Vivo *Bioequivalence Documentation* (September 1997). For postapproval changes, the *in vitro* comparison should be made between the prechange and postchange products. In instances where dissolution profile comparisons are recommended, an f_2 test should be used. An f_2 value of ≥ 50 suggests a similar dissolution profile. A failure to demonstrate similar dissolution profiles may indicate that an *in vivo* BE study should be performed. When *in vivo* BE studies are conducted, the comparison should be made for NDAs between the prechange and postchange products and for ANDAs between the postchange product and the reference listed drug.

E. Miscellaneous Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and BE. Chewable tablets should also be evaluated for *in vivo* BA and BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because they might be swallowed by a patient without being properly chewed. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient or moiety. Infrequently, different test conditions or acceptance criteria may be indicated for chewable and nonchewable tablets, but these differences, if they exist, should be resolved with the appropriate review division.

VI. SPECIAL TOPICS

A. Food-Effect Studies

Coadministration of food with oral drug products may influence drug BA and BE. Food-effect BA studies focus on the effects of food on the release of the drug substance from the drug product as well as the absorption of the drug substance. BE studies with food focus on demonstrating comparable BA between test and reference products when coadministered with meals. Usually, a single-dose, two-period, two-treatment, two-sequence crossover study is recommended for food-effect BA and BE studies.

B. Moieties to Be Measured

1. Parent Drug vs. Metabolites

The moieties to be measured in biological fluids collected in BA and BE studies are either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolites [21 CFR 320.24(b)(1)(i)]. This guidance recommends the following approaches for BA and BE studies.

For BA studies (see Section II.B.), determination of moieties to be measured in biological fluids should take into account concentration and activity. *Concentration* refers to the relative quantity of the parent drug or one or more metabolites in a given volume of an accessible biological fluid, such as blood or plasma. *Activity* refers to

the relative contribution of the parent drug and its metabolite in the biological fluids to the clinical safety and efficacy of the drug. For BA studies, the parent drug and its major active metabolite should be measured, if analytically feasible.

For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration–time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are exceptions to this general approach:

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The metabolite data obtained from these studies should be subject to a confidence interval approach for BE demonstration. If there is clinical concern related to efficacy or safety for the parent drug, sponsors and applicants should contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.
- Metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and efficacy, it does not need to be measured. The parent drug measured in these BE studies should be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

2. Enantiomers vs. Racemates

For BA studies, the measurement of individual enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay. Measurement of individual enantiomers in BE studies is recommended only when all the following conditions are met:

- Enantiomers exhibit different pharmacodynamic characteristics.
- Enantiomers exhibit different pharmacokinetic characteristics.
- Primary efficacy and safety activity reside with the minor enantiomer.
- Nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with a change in the input rate of the drug) for at least one of the enantiomers.

In such cases, BE criteria should be applied to the enantiomers separately.

3. Drug Products with Complex Mixtures as the Active Ingredients

Certain drug products may contain complex drug substances (i.e., active moieties or active ingredients that are mixtures of multiple synthetic and natural source components). Some or all the components of these complex drug substances cannot be characterized with regard to chemical structure or biological activity. Quantification of all active or potentially active components in pharmacokinetic studies to document BA and BE is neither necessary nor desirable. Rather, BA and BE studies should be based on a small number of markers of rate and extent of absorption. Although necessarily a case-by-case determination, criteria for marker selection include the amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety relative to other moieties in the complex mixture. Where pharmacokinetic approaches are not feasible to assess the rate and extent of absorption of a drug substance from a drug product, *in vitro* approaches may be preferred. Pharmacodynamic or clinical approaches may be called for if no quantifiable moieties are available for *in vivo* pharmacokinetic or *in vitro* studies.

C. Long Half-Life Drugs

In a BA or pharmacokinetic study involving an oral product with a long half-life drug, adequate characterization of the half-life calls for blood sampling over a long period of time. For a BE determination of an oral product with a long half-life drug, a nonreplicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. The C_{max}, and a suitably truncated AUC, can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 h ($AUC_{0\text{-}72\,h}$) can be used in place of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$. For drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution. In such cases, sponsors and applicants should consult the appropriate review staff.

D. First Point C_{max}

The first point of a concentration–time curve in a BE study based on blood and plasma measurements is sometimes the highest point, which raises a question about the measurement of true C_{max} because of insufficient early sampling times. A carefully conducted pilot study may avoid this problem. Making collections at an early time point, between 5 and 15 min after dosing, followed by making additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient for assessing early peak concentrations. If this sampling approach is followed, data sets should be considered adequate, even when the highest observed concentration occurs at the first time point.

E. Orally Administered Drugs Intended for Local Action

Documentation of product quality BA for NDAs, where the drug substance produces its effects by local action in the gastrointestinal tract, can be achieved using clinical efficacy and safety studies or suitably designed and validated *in vitro* studies. Similarly, documentation of BE for ANDAs and for NDAs, as well as for ANDAs in the presence of certain postapproval changes, can be achieved by using BE studies with clinical efficacy and safety end points or suitably designed and validated *in vitro* studies, if the latter studies are reflective of important clinical effects or are more sensitive to changes in product performance compared with a clinical study. To ensure comparable safety, additional studies with and without food may help in understanding the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.

F. Narrow Therapeutic Range Drugs

The guidance defines *narrow therapeutic range* drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors and applicants should contact the appropriate review division at CDER to determine whether a drug should or should not be considered to have a narrow therapeutic range.

The guidance recommends that sponsors consider additional testing and controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. It is not designed to influence the practice of medicine or pharmacy.

Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80 to 125% for nonnarrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs.

Appendix 1A — General Pharmacokinetic Study Design and Data Handling

For replicate and nonreplicate *in vivo* pharmacokinetic BE studies, the following general approaches are recommended, recognizing that the elements may be adjusted for certain drug substances and drug products.

STUDY CONDUCT

- The test or reference products should be administered with about 8 oz (240 ml) of water to an appropriate number of subjects under fasting conditions, unless the study is a food-effect BA and BE study.
- Generally, the highest marketed strength should be administered as a single unit. If warranted for analytical reasons, multiple units of the highest strength can be administered, providing the total single-dose remains within the labeled dose range.
- An adequate washout period (e.g., more than 5 half-lives of the moieties to be measured) should separate each treatment.
- The lot numbers of both test and reference listed products and the expiration date for the reference product should be stated. The drug content of the test product should not differ from that of the reference listed product by more than 5%. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference listed products. In accordance with 21 CFR 320.38, samples of the test and reference listed product must be retained for 5 years.
- Before and during each study phase, subjects should be allowed water, as desired, except for 1 h before and after drug administration; be provided standard meals no less than 4 h after drug administration; and abstain from alcohol for 24 h before each study period and until after the last sample from each period is collected.

SAMPLE COLLECTION AND SAMPLING TIMES

- Under normal circumstances, blood, rather than urine or tissue, should be used. In most cases, drug or metabolites are measured in serum or plasma. However, in certain cases, whole blood may be more appropriate for analysis. Blood samples should be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, 12 to 18 samples, including a predose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half-lives of the drug. The exact timing for sample collection depends on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood (C_{max}) and terminal elimination rate constant (λ_z) can be estimated accurately. At least three to four samples should be obtained during the terminal log-linear phase in order to obtain an accurate estimate of λ_z from linear regression. The actual clock time when samples are drawn as well as the elapsed time related to drug administration should be recorded.

SUBJECTS WITH PREDOSE PLASMA CONCENTRATIONS

- If the predose concentration is less than or equal to 5% of the C_{max} value in that subject, the subject's data, without any adjustments, can be included in all pharmacokinetic measurements and calculations. If the predose value is greater than 5% of C_{max}, the subject should be dropped from all BE study evaluations.

DATA DELETION DUE TO VOMITING

- Data from subjects who experience emesis during the course of a BE study for immediate-release products should be deleted from statistical analysis if vomiting occurs at or before two times median T_{max}. In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted.

PHARMACOKINETIC INFORMATION RECOMMENDED FOR SUBMISSION

- Plasma concentrations and time points
- Subject, period, sequence, treatment
- AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, k_z, and $t_{1/2}$
- Intersubject, intrasubject, and total variability, if available
- C_{min} (concentration at the end of a dosing interval), C_{av} (average concentration during a dosing interval), degree of fluctuation $[(C_{max} - C_{min})/C_{av}]$, and swing $[(C_{max} - C_{min})/C_{min}]$, if steady-state studies are employed
- Partial AUC, requested only as discussed in Section III.A.9.a. of this chapter

STATISTICAL INFORMATION FOR AUC_{0-T}, $AUC_{0-\infty}$, AND C_{MAX}:

- Geometric mean
- Arithmetic mean
- Ratio of means
- Confidence intervals

BIOEQUIVALENCE DEMONSTRATION MEASURES

- Logarithmic transformation should be provided for measures used for BE demonstration.

CONFIDENCE INTERVAL VALUES

- Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80 to 125, the value should be at least 80.00 and not more than 125.00.

2 Guidance on Formulating Compressed Solids

The manufacturing of compressed solids is a complex process, requiring several steps to render powders compressible, yet easily dispersed, and with the active ingredient dissolved when placed at the site of administration. As a result, the formulations that deliver the drugs to the site of action, while maintaining an appropriate stability profile, are valuable. However, a formulation, as described in this volume, requires an understanding of the manufacturing environment conducive to manufacturing a compliant dosage form. The sections in this chapter highlight some of these considerations that would benefit formulators. The topics of interest are presented in alphabetical order for quick reference.

I. ABBREVIATED DIRECTIONS

Abbreviated directions are necessary, particularly where a direct compression involved is provided. However, these directions can be expanded based on examples given elsewhere. General working steps, such as sifting the material, the timing for blending lubricants, the use of stainless steel vessels, etc., are common to all.

II. API

The active pharmaceutical ingredient (API) ultimately controls the quality of a product. The generic manufacturer faces a serious problem when procuring supplies of APIs coming off patent. Whereas Title 35 USC, Section 112, Paragraph 1 for patentability of invention requires that the inventor fully disclose the invention, the fact is that "full disclosure" does not necessarily mean disclosing steps that do not appear material in the production of the raw material. For example, it is routine practice (though questionable) for inventors of new chemical entities not to describe every step needed to remove impurities, to obtain the correct crystal structure (of a polymorph), or to obtain the correct particle size in the manufacturing process. As a result, generic manufacturers face serious situations when trying to reproduce and replicate a branded product. The issue of impurities is serious, and the regulatory authorities are getting tougher. In most instances, an unidentified peak can result in the rejection of an application. If the manufacturer of an API is unable to control the impurity profile, serious problems can arise in the manufacturing of the products.

III. BIO VS. PRODUCTION BATCHES

It is important that the manufacturer compare the drug substance used to manufacture the stability batch, bioequivalence batch, or clinical batch and the drug substance used for commercial batches. Therefore, the specifications, analytical methods, and test results for the lots of the drug substance used to manufacture these batches should be written precisely. Because the safety of the drug may be based upon the types and levels of impurities, and different physical characteristics may affect dissolution or content uniformity, these data must be developed.

IV. CLEANING VALIDATION

Solid drug powders can reach into deep cavities of the equipment, making the equipment difficult to clean. It is of utmost GMP importance that all equipment be entirely disassembled and thoroughly cleaned prior to switching to the manufacture of another drug. Appropriate standards of practice (SOP) validating cleanliness of equipment are required to assure compliance with the GMP. Problems arise in the use of highly potent, water-insoluble drugs, which are difficult to remove.

V. COATINGS

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light; masking of unpleasant tastes and odors; improvement of appearance; and control of the site of drug release in the gastrointestinal tract. Classically, tablets were coated with sugar applied from aqueous suspensions containing insoluble powders, such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and aesthetic value, the outside coatings may be colored. The finished coated tablets are polished by applying dilute solutions of wax in solvents, such as chloroform or powdered mix. Water-protective coatings consisting of substances such as shellac or cellulose acetate phthalate are often applied out of nonaqueous solvents before the application of sugar coats. Excessive quantities should be avoided. The drawbacks of sugar coatings include a lengthy time necessary for application, the need for waterproofing, which adversely affects dissolution, and the increased bulk of the finished tablet.

These factors resulted in increased acceptance of film coatings. Film coatings consist of water-soluble or dispersible materials, such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, and mixtures of cellulose acetate phthalate and polyethylene glycols applied out of nonaqueous or aqueous solvents. The evaporation of the solvents leaves a thin film that adheres directly to the tablet and allows it to retain the original shape, including grooves or identification codes. Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet passes through the stomach.

VI. COMPLIANCE WITH REGULATORY REQUIREMENTS

Compliance with the current good manufacturing practices (cGMP) in the manufacturing of solid dosage forms comprises three phases of the validation process: product development, design of the validation protocol, and demonstration runs (validation) of the equipment and process in the manufacture of full-scale commercial production batches. In all preapproval and postapproval inspections, the primary purpose is to assure compliance with validated processes.

The U.S. FDA issued specific guidelines that define process validation as establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product, while meeting its predetermined specifications and quality attributes. The three components of this definition include documented evidence, consistency, and predetermined specifications. Documented evidence includes the experiments, data, and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process. With regard to consistency, several batches would have to be manufactured, using the full-scale batch size, to demonstrate that a process meets the consistency test. At least three batches are needed to demonstrate consistency.

VII. COMPRESSION PROCESS CONTROL

Compressed solids are subject to dissolution problems. As a result, compression parameters, such as hardness of tablets, are important. Generally, harder tablets are often difficult to eject and take longer to disintegrate. However, control of friability may require harder tablets. Newer compression equipment has built-in online monitoring of compressed culls. Where such systems are not available, continuous monitoring of compression is required to assure that the batch does not have highly diversified properties, including friability and hardness.

VIII. CONTENT UNIFORMITY

Control of the physical characteristics of the excipient is important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipient, for example, may affect content uniformity. Therefore, there is a need to test physical characteristics (particle size) for each batch of excipient. For many single-source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases. However, for some multisource excipients and where the dosage formulator expects to shift sources of supply, there may be differences in physical characteristics (particle size) that may affect dose uniformity and dissolution.

IX. CROSS-CONTAMINATION

Environmental controls for cross-contamination and protection of operators must be considered when creating an appropriate environment. Of prime importance are pressure differentials, relative humidity (often, total grains of moisture are measured), temperature, and air changes. The regulatory requirements for segregation of penicillin and cephalosporin are well established. Similar situations arise when hormones and oncolytics are manufactured. Highly active drugs pose another set of problems, wherein a low level of contamination can seriously affect the health of the operators and also create a cross-contamination situation. Remember, highly potent drugs can contaminate other products easily because there is always a threshold for preventing contamination. Generally, it is a good idea to manufacture potent drugs in separate areas.

X. DESEGREGATION OF POWDERS

Differences in particle sizes, particle shapes, hydrophilicities of powder surfaces, strengths of crystal lattice, polymorphic structures, environmental humidities, powder surface electrostatic charges, and the force and the nature of force applied all make a difference in how powders mix and de-mix. Segregation is a typical characteristic known from the example of separating chafe from hay by shaking the hay. The same process applies to mixing pharmaceutical ingredients in a mixer. The aim of mixing is to desegregate different powders, and it may require the use of some surfactants or other excipients to enhance the mixing or desegregation process. Overmixing, which increases electrostatic charges, can lead to segregation, particularly

after lubricants are added. Lubricants, by nature, are often hydrophobic (such as magnesium stearate) and readily develop electrostatic charge. The validation process develops a rationale for mixing times at all stages, from the initial mixing to mixing with binding solutions to blending with lubricants. To reduce charges, lubricants are not sifted through finer meshes. Segregation may also occur in a tablet machine hopper, causing serious problems of content uniformity.

XI. DISINTEGRATION TEST

A disintegration test is provided to determine compliance with the limits on disintegration stated in the individual monographs, except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms. Determine the type of units under testing from the labeling and from observation, and apply the appropriate procedure to six or more dosage units. Disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

The apparatus consists of a basket-rack assembly, a 1000 ml, low-form beaker, 138 to 155 mm in height, with an inside diameter of 97 to 110 mm for the immersion fluid; a thermostatic arrangement for heating the fluid between 35° and 39°; and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke, the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

A. Uncoated Tablets

Place one tablet in each of the six tubes of the basket, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid, unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all the tablets disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

B. Plain Coated Tablets

Apply the test for uncoated tablets, operating the apparatus for the time specified in the individual monograph.

C. Delayed-Release (Enteric-Coated) Tablets

Place one tablet in each of the six tubes of the basket, and if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 min. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 h of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

D. Buccal Tablets

Apply the test for uncoated tablets. After 4 h, lift the basket from the fluid, and observe the tablets: all the tablets disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

E. Sublingual Tablets

Apply the test for uncoated tablets. Observe the tablets within the time limit specified in the individual monograph: all the tablets disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

XII. DISSOLUTION

This test is provided to determine compliance with the dissolution requirements, where stated in the individual monograph, for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric coated, and a dissolution or disintegration test does not specifically state that it is to be applied to enteric-coated articles, the individual monograph should include how to handle it. For gelatin-coated tablets that do not conform to the dissolution specification,

repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the medium in the individual monograph, the same medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 ml. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 ml.

XIII. DISINTEGRATION AND DISSOLUTION

Disintegration is an essential attribute of tablets intended for administration by mouth, except for those intended to be chewed before swallowing and for some types of extended-release tablets. A disintegration test is provided, and limits on the times in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs. For drugs of limited water solubility, dissolution may be a more meaningful quality attribute than disintegration. A dissolution test is required in a number of monographs on tablets. In many cases, it is possible to correlate dissolution rates with biological availability of the active ingredient. However, such tests are useful mainly as a means of screening preliminary formulations and as a routine quality-control procedure.

XIV. DRUG SUBSTANCE CHARACTERIZATION

Characterization of the chemical and physical properties of a drug substance is one of the most important steps in the development of a solid dosage form. The identification of chemical properties, especially impurities, is very important. In addition, the physical properties of the API, such as solubility, polymorphism, hygroscopicity, particle size, density, etc., must be addressed. The literature and actual experience demonstrate that the physical quality (e.g., particle size of raw materials), can sometimes produce a significant impact on the availability and clinical effect of a dosage form drug. Therefore, it is appropriate that the physical characteristics of a drug substance be characterized, that the impact of the physical characteristics be determined, and that a specification for the bulk drug product be established, if necessary.

XV. DRYING PROCESS

Manufacturing formulas clearly specify how granules are to be dried. The temperature and length of drying are important, not only for losing a certain amount of moisture but also for achieving a specific granular structure. The end point of granulation is often described in terms of loss on drying (LOD), which is often characterized in terms of the Ohaus or Brabender index (e.g., LOD at 105°C for 1 h) or an equivalent. Fluid-bed dryers and the newer granulator-vacuum dryers offer different rates of moisture loss and may form granules of different characteristics. The scale-up process should validate any changes in the equipment used and the technique used to dry granules. The validation should include compression tests and stability evaluations.

XVI. DYES IN FORMULATIONS

Manufacturers choose to include dyes in formulations for several reasons: for aesthetics, for identification, and for hiding inevitable mottling. Dyes can be included in the cores or in coating solutions when used. The Appendix to this book includes several formulations for coating solutions. Certifiable color additives (FD&C Certified) are available for use in foods or pharmaceuticals as either "dyes" or "lakes." Dyes dissolve in water and are manufactured as powders, granules, liquids, or other special-purpose forms. Lakes are the water-insoluble forms of dyes. Lakes are more stable than dyes and are ideal for coloring products containing fats and oils or items lacking sufficient moisture to dissolve dyes. Typical uses include coated tablets, cake and doughnut mixes, hard candies, and chewing gums. It is imperative that the manufacturer seek clarification of the status of a particular dye or lake before using it, particularly if the product has to be shipped to other countries. Labeling requirements include identification of all color additives. (The PDR is a good source to use to learn which colors are used in a particular product. For generic manufacturers, this is a good starting point.)

XVII. EQUIPMENT

The formulations provided do not specify equipment, and the manufacturer is supposed to select appropriate equipment for the batch size required. The selection of equipment must be based on full knowledge of the limitations of the equipment. The following sections (A through D) briefly describe some issues associated with equipment.

A. Blenders

Many solid oral dosage forms are made by direct compression. Two types of mixers are generally used: low energy and high energy. The low-energy mixers represent the classic type of slow mixers, such as ribbon blenders, tumblers, and the planetary pony pan. The high-energy mixers include some basic features of the low-energy mixer but also contain some type of high-speed blade, commonly termed an intensifier bar or chopper.

1. Pony Pan

This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents, such as starch paste, could be added while mixing. Because it is usually open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems. The usefulness of these mixers is limited to wet granulating. With this type of mixer, there is good horizontal (side-to-side) blending. However, vertical (top-to-bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or demixing is also a recognized problem. To minimize this problem, some manufacturers empty the pan contents halfway through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To alleviate the problem of the lack of mixing along the sides or walls of the pan, manufacturers often utilize a handheld steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce. Thus, it would be difficult to validate.

The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products. Consequently, whenever such dry blending is encountered, the manufacturer should be alert to potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card along with the weight of the dosage unit to be manufactured are needed for calculations.

2. Ribbon

In the ribbon blender, powder is mixed horizontally and vertically. Loading operations can be dusty. However, during the actual blending, it is enclosed, thereby limiting the amount of dust generated to the environment.

The major and potentially the most serious problem with the ribbon blender is that there is a "dead-spot" or zone at the discharge valve in some of these blenders. To compensate for this dead-spot, manufacturers recycle the powder from this area at some point during the mixing process. Obviously, there should be adequate and specific directions and procedures for assuring that this critical step is performed. Another concern with this mixer is poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and as with other mixers, care must be taken not to overfill the mixer.

Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified. If manufacturers do not disassemble and clean the seals and packing between batches, they should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.

3. Tumbler

Common mixers of this type include the twin-shell and double cone. These mixers exert a gentle mixing action. Because of this mild action, lumps of powder will not be broken up and mixed. Powders may also clump due to static charges, and segregation can occur. Low humidity can contribute to this problem. Blending under very dry conditions was found to lead to charge buildup and segregation, while blending of some products under humid conditions led to lumping. More so than with other mixers, powder charge levels should not exceed 60 to 65% of the total volume of the mixer.

Fabricators of tumbler-type blenders identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.

4. High-Shear (High-Energy)

There are several fabricators of these mixers, including GRAL, Diosna, and Lodige or Littleford. These mixers are highly efficient and ideally suited for wet granulations. The end point of wet granulations can be determined by measurement on a gauge of the work needed to agitate the blend. The mixing vessel is enclosed, and dust only enters the environment when loading.

One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different.

These mixers are efficient. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substances may partially dissolve and recrystallize upon drying as a different physical form.

An intensifier bar in the center of the blender, which rotates at very high speeds, breaks down smaller and harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat that can sometimes result in the charring of some sugar-base granulations. It should be pointed out that these same comments are applicable to other high-energy mixers, which also rely on high-speed choppers to disperse powders. Also, between-product cleaning of the blender requires disassembly of the intensifier bar.

5. Plastic Bag

Any discussion of mixers would not be complete without addressing the plastic bag. Manufacturers resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product. In fact, it continues to be a popular method, as often mentioned in the formulations described in this treatise.

B. Dryers

Two basic types of dryers are used. One is the oven dryer, where the wet granulation is spread on trays and dried in an oven. The second dryer is the fluid-bed dryer, in which the wet granulation is "fluidized" or suspended in air. A third type recently introduced involves drying of granulations *in vacuo* while being mixed and processed. Generally, the fluid-bed dryer yields a more uniform granulation with spherical particles. However, this may result in compression problems that may require additional compression force to remedy these problems. It is not unusual to see manufacturers change from an oven dryer to a fluid-bed dryer. However, such a change should be validated for equivalency with conducted *in vitro* testing, such as hardness, disintegration, and comparative dissolution, and stability testing. Major changes in process details will require demonstration of bioequivalence.

Other issues of concern with drying include moisture uniformity and cross-contamination. Tray dryers present more moisture uniformity problems than fluid-bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to assure moisture uniformity in granulations at the end point of drying. With respect to fluid-bed dryers, moisture problems can occur if the granulation is not completely fluidized.

Regarding cross-contamination, oven dryers, particularly those in which air is recirculated, present cross-contamination problems because air recirculates through a common filter and duct. For fluid-bed dryers, the bag filters present cross-contamination problems. To minimize problems, manufacturers should use product dedicated bags.

C. Tablet Compression Equipment

Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require uniform granulation to function correctly. Setup of the microprocessor-controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will sound an alarm when a lower- or higher-weight tablet is compressed.

Different tablet compression equipment can cause dose uniformity, weight uniformity, and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. The speed of the machine can affect fill of the die and tablet weight. Therefore, as previously discussed, it is important to have specific operating directions.

Many unit operations now provide for blending in totes, with discharge of the tote directly into tablet compression equipment. Because of segregation problems at the end of discharge, tablets from the end of compression should be tested for content uniformity. The use of inserts in totes was shown to minimize segregation.

With regard to the newer computer-controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be in accordance with written methods. Reworking processes for culls must be validated.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations requires humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as the Lilly and Parke-Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled-up to high-speed encapsulation equipment, flow problems and poor weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug, which could impact dissolution.

D. Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate, and temperature can be controlled by some of the more highly automated operations. However, for many sugar-coated, enteric-coated, and delayed-release products, some portions of the coating process are not highly soluble and are performed manually. Generally, the shellac undercoat used for sugar-coated tablets presented disintegration and dissolution problems, particularly in aged samples.

With respect to poor disintegration, ferrous sulfate tablets probably represent the classical example. Over the years, there have been many recalls from many different manufacturers for poor disintegration of coated ferrous sulfate tablets. Likewise, there have been many problems with poor dissolution attributed to the coating process. Again, the shellac undercoat hardens, and even sometimes cracks, resulting in poor dissolution.

The numbers of applications of coats, volume of coating solution in a specific application, and temperature of the solution during applications are parameters that need to be addressed. For example, the temperature of the application and even heat during drying can cause dissolution failures in aged tablets. Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat. For example, it was shown that estrogen tablets are heat sensitive and exhibited stability problems. Thus, it is important to control this phase of the process.

There are a few products, such as some of the antihistamine tablets, in which the drug substance is applied during the coating process. Other products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process. For these products, it is particularly important to apply the drug in the coating solution in many controlled applications.

Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and to control the parameters of the coating process.

XVIII. EXCIPIENTS

Excipients are well defined in the official pharmacopoeia. No specific pharmaceutical grades are specified in this book, except where there is a specific reason to do so. However, it is known that different pharmacopoeia may have different specifications, such as particle size, impurities, moisture, etc. The harmonization of excipients, a global effort that is under way, would go a long way in making the choice of excipients. The manufacturer is referred to http://www.ipecamericas.org/index.html and the *Handbook of Pharmaceutical Excipients* for further advice. A large number of proprietary excipients are widely used, such as Ac-Di-Sol®, Explotab®, Aerosil®, Ludipress®, Avicel®, etc., and many of these are now part of pharmacopoeias. There is a significant advantage, though the cost is high, in using these ingredients because they offer additional benefits, often reducing processing time. Additionally, the suppliers of these ingredients are always willing to provide formulation support and have large databases, particularly pertaining to stability of drugs, that may be of great value to manufacturers. The following sections (A through F) list the most commonly used excipients in compressed solids.

A. Coating Agent

Carboxymethylcellulose, Sodium Cellacefate (formerly Cellulose Acetate Phthalate), Cellulose Acetate, Cellulose Acetate Phthalate (see Cellacefate), Ethylcellulose, Ethylcellulose Aqueous Dispersion Gelatin Glaze, Pharmaceutical Hydroxypropyl, Cellulose Hydroxypropyl Methylcellulose, Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate), Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate), Methacrylic Acid Copolymer, Methacrylic Acid Copolymer Dispersion, Methylcellulose Polyethylene Glycol, Polyvinyl Acetate, Phthalate Shellac Sucrose, Titanium Dioxide Wax, Carnauba Wax, Microcrystalline Zein

B. Glidant

Calcium Silicate, Magnesium Silicate, Silicon Dioxide, Colloidal Talc

C. Tablet Binder

Acacia Alginic Acid Carboxymethylcellulose, Sodium Cellulose, Microcrystalline Dextrin Ethylcellulose Gelatin Glucose, Liquid Guar Gum Hydroxypropyl Methylcellulose, Methylcellulose Polyethylene Oxide Povidone Starch, Pregelatinized Syrup

D. Diluent

Calcium Carbonate, Calcium Phosphate, Dibasic Calcium Phosphate, Tribasic Calcium Sulfate Cellulose, Microcrystalline Cellulose, Powdered Dextrates, Dextrin, Dextrose, Excipient, Fructose, Kaolin, Lactitol, Lactose, Mannitol, Sorbitol, Starch, Pregelatinized Sucrose, Sugar, Compressible Sugar, Confectioner's Sugar

E. Disintegrant

Alginic Acid Cellulose, Microcrystalline Croscarmellose Sodium, Crospovidone Polacrilin, Potassium, Sodium Starch, Glycolate Starch, Starch, Pregelatinized

F. Lubricant

Calcium Stearate, Glyceryl Behenate, Magnesium Stearate, Mineral Oil, Light Polyethylene Glycol, Sodium Stearyl Fumarate Stearic Acid, Stearic Acid, Purified Talc, Vegetable Oil, Hydrogenated Type I Zinc Stearate

The choice of excipients is made based on three distinct considerations:

- Compatability with the active drug — Many excipients have active functional groups that can interact with the active drug and enhance its degradation. Even the water of hydration or

moisture in the excipients can create difficulties in solid-state degradation of the active drug; so, it is not only the selection of the ingredient but also the grade (such as anhydrous or hydrous) that is important.

- Effect on efficacy — Excipients are known to alter the release patterns (e.g., a strong binder would delay break up of the tablet) and often bind the drug molecules in the gastrointestinal tract. The evaluation should be made in the full composition of ingredients because the presence of two ingredients may change their individual characteristics.
- Cost of formulation — Even though excipients contribute a small cost of the total formulation, the declining cost of APIs makes the selection of excipients based on cost an important consideration. This is particularly true when generic manufacturers are filing ANDAs knowing well that they will compete on a price basis. However, the total cost of formulation should not only be calculated on the basis of excipients. Often, the use of expensive excipients reduces process time, eliminates certain process steps, and even allows for the use of a cheaper packaging material. The manufacturer must, therefore, calculate the overall manufacturing cost. This aspect of formulation creates unique considerations by the multinational companies doing business worldwide; they are often forced to develop alternate formulations depending on the availability of excipients, manpower cost, and local environmental considerations.

The rule of thumb in the selection of excipients remains — keep it simple and at the bare minimum. The goal of excipients selection should be clearly defined — the dosage form yielding to a solution form at a predetermined rate (not necessarily the fastest in all instances).

The formulations described in this volume provide a quantitative listing of excipients recommended. An astute formulator would know the need to alter their quantity based on the type of equipment used to process them, the size of the batch processed at one time, and the quality of compressed product obtained. Therefore, all quantitative listings of excipients must be considered the best starting point, which can be adjusted and optimized, if necessary. In many instances, a range of excipients is allowed, such as in the case of a binder solution, to yield a suitable mass (as it is often described in the formulation of wet massing).

Where exact quantities of excipients are not available, but the excipients are identified for an innovator's product, this is still a better starting point than establishing the choice of excipients. Knowledge of the physicochemical characteristics of the API takes a more pivotal role when the information available is limited. Obviously, one can readily identify the role of the identified, but not quantified, excipients. Some experimentation is required. However, as provided throughout this volume, significant knowledge can be gained by benchmarking the formulation. Other similar drugs or excipients should provide a good clue of the starting quantities. It is noteworthy that in obtaining the copies of competitor NDAs, through the Freedom of Information Act, some quantities are often redacted, leaving the formulator to guess. However, this should not be a difficult step, as long as the quantities of excipients chosen provide a similar weight, thickness, and disintegration and dissolution characteristics.

A common practice by innovator companies, as the NCE gets closer to the patent term expiry, is to patent a variety of formulations; for example, in the case of Augmentin®, the innovator chose to patent a different combination of amoxicillin and clavulanic acid and developed a composition for pediatric therapy. The purpose of this exercise is to keep generic competition out; the generic product in some cases may be the same, but not exact. The patent-end changes may also include changes in specification, choice of solvent systems used, or other cosmetic changes. However, a generic manufacturer would do well by just following the original formulation (for obvious reasons of regulatory compliance) because this has withstood the test of time. The author recommends that no changes be made to an otherwise working formula, albeit this may improve processing, until such a time that the generic manufacturer has sufficient experience with the product. Most unusual things can happen when unsuspecting changes, appearing benign at the surface, are made to proven formulas. Given the cost of bioequivalence study requirements for compressed solids, changes in formulation should not be made unless essential and, even then, only for compliance purposes.

XIX. FILL WEIGHTS

Fill weights are provided in all formulations. These may not coincide with scale for many reasons, as described elsewhere: differences in the salt forms, hydrates, or overages added in manufacturing and also to provide the extra margin of variation in filling during fast compression operations.

XX. FINAL PACKAGING

A formulation design does not end with assuring that good tablets are formed; it must allow for handling during packaging, such as sliding into blister sheets or dropping into bottles. Actual fill runs must be conducted, and then the finished product must be subjected to simulated and, finally, the actual rigors of shipping before finalizing a

formulation. Know that during shipping, the product may be exposed to diverse and often harsh weather conditions. Silica gel is often placed in the finished packs, or cotton is inserted, mainly to provide moisture or absorb odor (in the case of cotton).

XXI. FINAL TESTING

Finished product testing, particularly assay, content uniformity, and dissolution, are required. In the review of dissolution test results, it is important to eventually see results close to 100% dissolution. In some cases, manufacturers profile the dissolution results only to the specification. However, if lower but still acceptable results are obtained (such as 85%), it is important to continue the test. This can be performed by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

XXII. FINES

Solids, when grinded to small particle sizes (as when passing through sieves or crushing granules), yield a distribution of various particle sizes. A certain amount of very fine particles, such as those passing #100 mesh, is required to fill in the gaps in a good compaction process; however, a large proportion of fines (as they are called) can create a problem in the flow or compaction of material. As a result, many Master Formulas require the reworking of fines back to granules. Any such recommendation should be carried out considering the type of processing and equipment used. These are mere suggestions; if a product compacts well, then it has the right proportion of fines.

XXIII. FORMULA EXCESSES

The difference between the scale and the quantity used for manufacturing is a result of either adjustment for the chemical form used (such as salt form for labeled base), hydrate forms (to compensate for additional water), potency variations (such as for antibiotics and biologicals), manufacturing excesses (for losses of drug during manufacturing), stability excesses (to compensate for loss during the shelf life; this is most important for vitamin products), and solvent/hydration loss (such as during manufacturing).

XXIV. GEOMETRIC DILUTION

In all instances where low-dose drugs are manufactured, the mixing of ingredients should be done in a geometric dilution process; for example, a tablet containing 100 µg per tablet will first require mixing the active drug with a smaller quantity of excipient and then building up the volume to make sure the API is properly distributed. Further consistency to the product is imparted during the mixing of the granulated mixture.

XXV. GRANULATION/MIX ANALYSIS

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender that have the greatest potential to be nonuniform can be sampled. This is particularly true of the ribbon-type blender and planetary or pony-type mixers.

In some cases, such as for large or tumbler-type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle, and bottom of each drum should be collected.

In most cases, sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.

Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes, such as 1 oz, will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis can yield misleading results.

The acceptance criteria for granulation dose uniformity testing needs to be continuously evaluated. Although many manufacturers evaluate dose uniformity using the compendia dose uniformity specifications (85 to 115% with an RSD of 6 to 7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases, compendia assay limits for the finished product (90 to 110% of label claim) are broad enough for this purpose, and most manufacturers should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used.

In addition to the analysis of blends for dose uniformity and potency, blends are tested for physical characteristics.

A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for comparison of the biobatch with production batches and should be repeated when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for the tablet made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet as well as its dissolution. For example, dissolution failure may be attributed to a change in the milling screen size, yielding a granulation with larger granules. When coated, larger pores permit increased penetration into the tablet by the coating solution, resulting in slower dissolution.

Another test typically performed on the granulation, particularly when the wet granulation process is used, is loss on drying (LOD) and moisture content. If organic solvents are employed, then residual solvent residues are also tested. In the validation of a drying process, LOD levels are determined before, during, and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase, with the validation phase used to confirm the adequacy of the process.

XXVI. INGREDIENT WARNING

Whereas many organic solvents are removed, traces may remain, and these may cause reactions, particularly in children; additionally, appropriate consideration should be given to the choice of using lactose for its intolerance in some of the use of sulfites or preservatives to which patients may be allergic.

XXVII. IN-PROCESS TESTING

In-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. For tablets, individual tablet weights, moisture, hardness (compression force), and disintegration are performed. Because hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate equivalency (comparability) and consistency.

Specifications required to control the manufacturing process must be established and justified. This will require granulation studies that would include blend uniformity, sieve analysis, and moisture. In the formulations provided in this book, the in-process milestones are not generally identified; the manufacturer is supposed to know this. Critical in-process testing stages for compressed solids are:

- Assuring cleanliness of equipment
- Checking and recording temperature where specified for dissolving or mixing ingredients, such as in the making of binder solutions or slurries
- Testing of granules for content uniformity, flow rate, tap density, moisture content (LOD), or other specific testing, as required
- Testing of tablets during compression for weight, thickness, friability, and disintegration
- Final testing of weight, friability, content uniformity, disintegration, and dissolution
- Assay and finished product release

With regard to moisture, some tablets set up (harden) upon aging as a result of poor moisture control and inadequate specifications. For example, this was shown to be a major problem with Carbamazepine tablets.

XXVIII. LOSS ON DRYING (LOD)

This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified. Mix and accurately weigh the substance to be tested, and, unless otherwise directed in the individual monograph, conduct the determination on 1 to 2 g. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Take a glass-stoppered, shallow weighing bottle that has been dried for 30 min under the same conditions to be employed in the determination. Put the test specimen in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, side-wise shaking, distribute the test specimen as evenly as practicable to a depth of about 5 mm and not more than 10 mm in the case of bulky materials. Place the loaded bottle in the drying chamber, remove the stopper, and leave it in the chamber. Dry the test specimen at the temperature and for the time specified in the monograph. (*Note:* The temperature specified in the monograph is to be regarded as being within the range of ± 2° of the stated figure.) Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than that specified for the determination of LOD, maintain the bottle with its contents for 1 to 2 h at a temperature 5 to 10° below the melting temperature, then dry at the specified temperature. Where the specimen under test is tablets, use powder from not less than four tablets ground to a fine powder. Where the individual monograph directs that the LOD should be determined by thermogravimetric analysis, a sensitive electrobalance must be used. Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, must be

used. When drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequently replacing. Where drying in a capillary-stoppered bottle in vacuum is directed in the individual monograph, use a bottle or tube fitted with a stopper having a 225 ± 25 µm diameter capillary, and maintain the heating chamber at a pressure of 5 mm or less of mercury. At the end of the heating period, admit dry air to the heating chamber, remove the bottle, and with the capillary stopper still in place, allow it to cool in a desiccator before weighing.

Many Pharmacopoeial articles are hydrates or contain water in adsorbed form. As a result, the determination of the water content is important in demonstrating compliance with the Pharmacopoeial standards. Generally, one of the methods given next is called for in the individual monograph, depending upon the nature of the article. In rare cases, a choice is allowed between two methods. When the article contains water of hydration, Method I (Titrimetric), Method II (Azeotropic), or Method III (Gravimetric) is employed, as directed in the individual monograph.

XXIX. MANUFACTURING YIELDS

The formulas provided here include scale as well as quantities for 1000 tablets; often in a scale-up, yields must be calculated to extrapolate exact quantities needed for a specific batch size; yields vary because of differences in the tablet weight (within the specified range), losses in equipment, and losses to the environment. The exhaust or vacuum can carry with it a lot of product at times.

XXX. MASTER FORMULA

This document must include specific manufacturing directions for the full-scale commercial process, including in-process and finished product specifications. The cGMP-compliant Master Formula will have room for direct entry onto the documents of all critical parameters, such as temperature, mixing times, LOD, etc., beside signatures of the persons responsible for complying with the specifications. No specific guidelines are provided for the formatting of this document. However, those skilled in assuring compliance with the GMP know the art of capturing most eventualities that may arise in the manufacturing of the product. The key is to assure that no individual discretions are allowed.

XXXI. MULTIPLE-ITEM ENTRIES

In the formulations provided in this book, an ingredient may appear in multiple places; this is necessary so as to identify the different quantities used at different stages and at different times for different purposes. For example, the dry form of starch may be mixed with the drug and then used in the making of a paste for granulation. Similarly, solvents are often listed in many places.

XXXII. MULTIPLE STRENGTHS OF FORMULATIONS

The formulations disclosed in this book handle multiple strengths in two ways: one to adjust the fill weight of tablets and the other to provide a different formulation. There are specific reasons for this. Where the quantity of API is high, a simple doubling of fill weight might not work, and an adjustment to the excipients will be required. On the other hand are products where the API is less than 1% of the total weight, in which case, the formulation remains the same, with one of the major components, such as lactose or dicalcium phosphate, providing compensation for the additional weight. Then, the tablet can be compressed at the same weight.

XXXIII. NOVEL DRUG DELIVERY SYSTEMS

From osmotically driven release of the API to wax matrices to plastic "ghosts" (e.g., Gradumet®), the compressed solid dosage forms offer a variety of possibilities for incorporating novel drug delivery systems. It should be noted that the compression force required to manufacture the dosage form can deform a structured component; on the other hand, the high compression force and the resultant rise in temperature that is inevitable can be used to create unique dosage form designs. One such example is the use of polyethylene glycol (PEG) 6000 or 8000 in direct compression formulations. The compression pressures in a typical tabletting machine or in a roller compactor are generally high enough to produce sufficient heat to melt the PEGs and then congeal to provide adequate binding without the need for wet massing. The author used this technique to formulate a myriad of drugs, particularly those subject to stability problems, such as vitamins. PEGs are compatible with most drugs, are cheap, and dissolve rapidly to release the drug. The author highly recommends using this technique to formulate directly compressible formulations instead of using the direct-compression-grade raw materials that are very expensive. Another technique that lends itself appropriately to solid compression is the use of solid solutions. Many drugs, when melted with water-soluble compounds, such as succinic acid, polyethylene glycol, etc., congeal in a molecular dispersion, which, when placed in the gastrointestinal environment, releases the drug rapidly — it is already in a solution state. Wax embedding is another process (such as used for diltiazem) for moderating the release of drugs.

Briefly, the formulator has many tools available with which to formulate novel drug delivery systems with compression of solids. These techniques have, however, not been exploited as widely as their potential offers. The young formulators not yet biased by the need to follow a traditional route of formulating are encouraged to experiment with a myriad of possibilities, using components that have well proven their utility but in a different role. Remember, a temperature rise during the compression process is a source of energy that can be put to use.

XXXIV. PARTICLE COATING

Even though solid-state compression excludes moisture, which is the primary starting point in chemical degradation, these dosage forms are not impervious to atmosphere; this protection is generally provided by coating the final compressed dosage form, such as by sealing with waxes. However, there are instances where it may be necessary to coat the particles of the drug before incorporating them into formulations. There can be several reasons for doing this, besides imparting greater stability. It is done to mask the taste, for example, in chewable tablets, to improve flow in tablets comprising a larger proportion of the active drug, to impart specific release characteristics, or to protect the gastrointestinal mucosa (such as in the case of particle-coated iron tablets). Coated particles should be treated as a specialized form of excipient, which must be properly tested for its specifications prior to incorporating in the final dosage form. Most of the particle-coating methods involve a fluid-bed system or coating on a nonpareil bead.

XXXV. PRESERVATIVES IN COMPRESSED SOLID DOSAGE FORMULATIONS

As a rule of thumb, good formulations include only essential components. Because compressed solids have low moisture content, microbiological stability generally does not pose a problem, with few exceptions. However, in the wet granulation process, slurries or pastes are made that are water-based and are often kept for a few hours before being used, requiring the use of preservatives, particularly when gelatin is also used with starch. Generally, a standard combination of propyl and methyl-parabens would do. Preservatives are also included in compressed solids, where the compositions may be highly hygroscopic, resulting in localized liquefaction of powders that might promote microbial growth.

XXXVI. PUNCH SIZE AND SHAPE

The choice of punch size is dependent on the amount of API, the quantity of excipients needed to make it compressible, and what can be reasonably administered. Tablets ranging in weight from less than 100 mg to over 1 g are compressed in 6- to 15-mm diameter punches. The size is also important because a proportion between thickness and diameter must be maintained. Thick tablets are difficult to eject from dyes, such as a long cylindrical product. Experienced machine operators know how well a tabletting mix compresses on one punch size and shape, and it becomes difficult to compress using other shapes and sizes. Whereas round tablets are the easiest to compress (from a technical viewpoint of design of punches to ejection), manufacturers use all different shapes, from Bugs Bunny-shaped vitamins to diamond-shaped Viagra® tablets.

The formulations provided in this book may have to be altered to meet the compaction requirements of different punch shapes and sizes other than those recommended here. Concave punches (giving convex tablets) are made to reduce the contact of compressed material with the wall of the die. This makes ejection of a tablet easier. However, because of the shape, there may be more picking of tablets. In several formulations described here, biplanar flat, round punches are recommended. The identification marks or logos on the tablets create additional problems in the picking of tablets. The polishing of punches remains an essential part of good tablet compressing. Often, punches wear out fast depending on the type of compression material used.

Regardless of what the supplier of a punch recommends, a punch must be replaced once it fails to provide the surface quality needed. Punches should ideally be replaced in groups and not individually (except to replace broken items).

XXXVII. REWORKING CULLS

During the setup of machines and through rejection, especially in automated rejection systems, there may be a substantial amount of culls available. In most instances, it would be prudent to just discard them; however, for expensive APIs, reworking can be done. An internal SOP should clearly define the proportion of rework allowed and how the calculations will be made to the BOM.

XXXVIII. SCALE-UP

Whereas the formulations given in this book are robust enough to be scaled-up to most sizes, manufacturers may find the need to modify these to comply with scaled-up performance. For example, the quantity of lubricants, the amount of moisture, the size of the granules, etc., are all pertinent.

XXXIV. SEGREGATION

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size, and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density, or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling. One of the most common reasons for postblending (after adding lubricants) segregation is overblending. Lubricants develop electric charge very quickly, making compression difficult and altering the dissolution profile. A critical specification in the manufacturing method is the length of blending. Follow this strictly.

XXXV. SIFTING INGREDIENTS AND GRANULES

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point-of-use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves before adding them to mixing or blending vessels. For most raw materials, sifting through a #60 sieve (250 μm) is desired. Know that passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a #8 (2.38-mm) sieve, and dried granules are passed through a #16 (1.19-mm) mesh sieve. Lubricants should be sieved through a #60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than that of a #35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) follows:

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
(continued)			

(continued)	Inches	Microns	Millimeters
	0.0232	595	0.595
	0.0197	500	0.500
	0.0165	400	0.400
	0.0138	354	0.354
	0.0117	297	0.297
	0.0098	250	0.250
	0.0083	210	0.210
	0.0070	177	0.177
	0.0059	149	0.149
	0.0049	125	0.125
	0.0041	105	0.105
	0.0035	88	0.088
	0.0029	74	0.074
	0.0024	63	0.063
	0.0021	53	0.053
	0.0017	44	0.044
	0.0015	37	0.037

XXXVI. SPECIFICATIONS

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full-scale manufacturing process require scientific judgment based on good scientific data. The in-process control and product specifications are established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications. Specifications, such as hardness and particle size, should be established before validation of the process; these specifications should be included in the validation protocol. The use of product development runs of the process to establish specifications and demonstrate that the system is validated often causes problems.

XXXVII. STABILITY TESTING

Even though compressed solids offer a major advantage over other dosage forms in being the most stable, both chemically and physically, complete stability profiles must be developed every time any change, albeit minor, is made in the formulation, the processing conditions, the equipment used, or even the manufacturing site used. This applies not just to drugs with known stability problems, but even to highly stable drugs, such as erythromycin. Subtle alternations in formulation can bring such major unsuspected changes as prolonged disintegration and dissolution. The stability profiles are developed over a span of time to establish not only the chemical stability (providing the labeled quantity), but also the *in vitro* release characteristics. Stability testing is also required to be conducted in the specific temperature zone areas as dictated

by compendia. This creates a significant problem for multinational companies selling products around the world, where different zone temperature stability requirements come into play. A universal formula is often difficult to design for this reason. Generic manufacturers must, therefore, take this aspect into consideration and mimic the formulations used by innovators in the world regions where these products are to be sold. Unfortunately, it is not as easy to obtain this information for formulations sold outside of the U.S. Some reverse engineering may be in order to accomplish this.

XXXVIII. STORAGE OF IN-PROCESS MATERIAL

At several stages during the manufacturing, the bulk material would have to be kept in quarantine, awaiting QC results, such as LOD measurement, content uniformity of tabletting mix, etc. The Master Formula should specify the conditions of storage and the length of a validated storage period. In some instances, silica gel is to be kept in the drums storing the product. Follow these instructions carefully. In most instances, the bulk should receive a final blending turnover before filling the compression hoppers; this is necessary in order to avoid any segregation of powders during storage or during transportation to and from the storage facility.

XXXIX. TABLET FRIABILITY

This friability determination of compressed, uncoated tablets is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet crushing strength. For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding to 6.5 g. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets, as before, and accurately weigh. If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the benchtop, and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned, and these tablets normally require special packaging. In the case of hygroscopic tablets, a humidity-controlled environment (relative humidity less than 40%) is required for testing.

XL. TABLET MANUFACTURING

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of wet and dry granulation is to improve flow of the mixture and to enhance its compressibility. Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of heat and moisture in the processing. Dry granulations can be produced by extruding powders between hydraulically operated rollers to produce thin cakes that are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances, such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct-compaction fillers are microcrystalline cellulose, anhydrous lactose, spray-dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression.

XLI. TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in the U.S. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are commonly referred to as caplets. Boluses are large tablets intended for veterinary use, usually for large animals. Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process and not upon the compaction force. Tablet triturates are small, usually cylindrical, molded or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used

today. Hypodermic tablets are molded tablets made from completely and readily water-soluble ingredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required, such as in the case of nitroglycerin tablets, sublingually. Buccal tablets are intended to be inserted in the buccal pouch, and sublingual tablets are intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones), there are a number of advantages. Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and should be labeled to indicate that they are not to be swallowed directly.

Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant-tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. These tablets have been used in tablet formulations for children, especially in multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste.

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as fillers. Where the amount of active ingredient is small, the overall tableting properties are, in large measure, determined by the filler. Because of problems encountered with the bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets. Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression. A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play roles in effectiveness. Lubricants reduce friction during the compression and ejection cycles. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such, tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required. Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas. Colorants are often added to tablet formulations for aesthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive, and they fade when exposed to light. The U.S. FDA regulates the colorants employed in drugs.

XLII. WATER-PURIFIED USP

As a general practice, the water used in wet granulation processes should be of at least the water-purified USP grade. Other grades are acceptable, provided their use can be validated, mainly for the reasons of microbiological quality and the presence of other dissolved solids.

XLIII. WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity, where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar coated. Thus, the pharmacopoeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit, pass a content uniformity test,

wherein individual tablets are assayed for actual drug content.

XLIV. WET GRANULATION VS. DRY GRANULATION OR DIRECT COMPRESSION

Drug powders are often not easily compressible. Even if they are compressible, the small quantity that needs to be dispensed requires the adding of excipients for bulking the product; however, the addition of these compatible bulking agents may render the mixture less compressible. Books were written on the physics of powder compression. In a nutshell, the compression of powders involves the breaking of a crystal lattice and the rebonding of lattices to yield a unit structure. Binders provide the bridging gap between and among the ingredients that would rather stay away (to put it simply). With compression machines, the requirement that powders fill the compression cavities as they are compressed no longer holds. The conundrum with powders is that they must flow easily — to fill the cavities. But, as the particle size gets smaller, the specific surface area increases, along with interparticulate friction that keeps the powder from flowing (angle of repose), subject to the individual characteristics of the chemical. Therefore, for the powders to easily flow into compression cavities, they must be present in granular form, rather than in the form of fine powder. Powders can be converted to granular form by wetting them and drying to form the bonds between particles, particularly in the presence of binding agents (the most popular being starch). The wet granulation process, therefore, involves mixing the powders with a paste of starch (generally about 30%) or using polyvinylpyrrolidone (PVP) in an organic solvent to make a wet mass. In most instances, the characteristic of the wet mass is judged by how well it forms a mass as tested. The wet mass is then passed through a coarse mesh, spread on trays, and dried at 50 to 60°C or directly placed in a fluid-bed dryer. The test of drying is that the LOD ranges from 1 to 3%. This is referred to as wet granulation. Dry granulation is a process where the active drug is mixed with ingredients that are inherently granular and compressible or are made by modifications through wet granulation, to impart good flowability and compressibility to the mix. Several APIs are also available in direct compressible grades, often coated to impart an additional element of chemical stability. Directly compressible aspirin or ascorbic acid are good examples. The cost of APIs rendered compressible is obviously higher; however, in the long run, it is cheaper to use directly compressible powders.

Part II

Compressed Solid Formulations

Acetaminophen, Ibuprofen, and Orphenadrine Tablets (250 mg/200 mg/200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Acetaminophen powder < 300 μm	250.00
200.00	2	Ibuprofen	200.00
200.00	3	Orphenadine hydrochloride	200.00
200.00	4	Ludipress	200.00
5.00	5	Magnesium stearate	5.00
5.00	6	Aerosil 200	5.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.5-mm sieve, mix, and press with high-compression force.
2. Compress 761 mg in 12-mm planar punches.

Acetaminophen, Norephedrine, and Phenyltoloxamine Tablets (300 mg/25 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Acetaminophen crystalline	300.00
25.00	2	Norephedrine hydrochloride	25.00
22.00	3	Phenyltoloxamine	22.00
200.00	4	Starch (maize)	200.00
25.00	5	Kollidon 30	25.00
—	6	Alcohol	QS
25.00	7	Kollidon CL	25.00
5.00	8	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 through 4 with a solution of Items 5 and 6. Dry, pass through a 0.8-mm sieve, add Items 7 and 8, and press with high-compression force.
2. Compress 601 mg in 12-mm biplanar punches.

Acetaminophen and Phenprobamat Tablets (200 mg/200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Acetaminophen powder < 0.5 mm	200.00
200.00	2	Phenprobamat	200.00
35.00	3	Microcrystalline cellulose (Avicel PH 101)	35.00
20.00	4	Kollidon VA 64	20.00
10.00	5	Kollidon CL	10.00
5.00	6	Magnesium stearate	5.00
6.00	7	Aerosil 200	6.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress 475 mg in 12-mm biplanar punches.

Acetaminophen and Orphenadrine Citrate Tablets (450 mg/35 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
450.00	1	Acetaminophen powder	450.00
35.00	2	Orphenadrine citrate, 5% excess	35.00
66.00	3	Starch (maize)	66.00
20.00	4	Microcrystalline cellulose (Avicel PH 102)	5.00
7.50	5	Aerosil 200	7.50
0.25	6	Dye yellow	0.25
16.00	7	PVP K30	16.00
5.00	8	Aerosil 200	5.00
7.50	9	Glycerine	7.50
10.00	10	Gelatin powder	10.00
25.00	11	Premojel	25.00
12.00	12	Avicel PH 102	12.00
2.00	13	Aerosil 200	2.00
2.00	14	Magnesium stearate	2.00
—	15	Water, purified, ca	464 ml

MANUFACTURING DIRECTIONS

1. Charge Items 7 and 6 into a mixer, add 50% of Item 15, and mix for 10 to 15 min at medium speed.
2. Add Item 5 into Step 1 slowly, while stirring at medium speed, and disperse well.
3. Add Item 9, and mix for 3 min.
4. In a separate vessel, add Item 10 and the balance of Item 15; mix for 5 min at medium speed.
5. Add Step 3 into Step 4, and mix for 2 to 3 min.
6. In a separate mixer, charge Items 1 to 5, and mix and chop for 3 min at slow speed.
7. Add the solution from Step 5 to Step 6, and mix for 2 to 3 min.
8. Dry the wet mass in a fluid-bed dryer at 60°C for 60 min until a loss on drying rate of 1.5 to 2.5% is reached.
9. Pass the dried granules through a 6-mm sieve followed by a 1.5-mm sieve in a granulator.
10. Add to the granules Items 11 to 13, previously sieved through a 500-μm sieve. Mix for 3 min.
11. Add Item 14, previously sieved through a 250-μm sieve, and blend for 1 min.
12. Compress using 12.7-mm round flat punches to a fill weight of 660 mg.

Acetaminophen Tablets, Chewable

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
89.90	1	Acetaminophen, use acetaminophen-coated particles (cellulose acetate — PVP)	89.90
246.00	2	Mannitol granular	246.00
30.00	3	Microcrystalline cellulose	30.00
9.00	4	Aspartame	9.00
1.27	5	Dyes	1.27
2.10	6	Citric acid	2.10
2.30	7	Flavor	2.30
4.40	8	Magnesium stearate	4.40

MANUFACTURING DIRECTIONS

1. Acetaminophen is coated with a layer of a taste-masking composition with a thickness of about 3 to 10 µm. The coating should be substantially free of cracks, holes, and other imperfections when examined under a scanning electron microscope at 100 to 500× magnification.
2. Charge Items 1 to 7 in a suitable blender, and mix for 20 min.
3. Add Item 8 to Step 2, and blend for 2 min.
4. Compress the appropriate quantity.

Acetaminophen, Dextropropoxyphen Hydrochloride Tablets (325 mg/32 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
325.00	1	Acetaminophen	325.000
32.00	2	Dextropropoxyphen hydrochloride	32.500
8.00	3	Povidone (K29-32)	8.000
7.50	4	Starch (maize)	7.500
QS	5	Water, purified	80.00 ml
10.00	6	Cellulose microcrystalline (Avicel PH 101)	10.000
5.00	7	Talc purified	5.000
2.00	8	Magnesium stearate	2.000
QS	9	Coating solution white opaque methocel-ethocel	160.000 ml

MANUFACTURING DIRECTIONS

1. Granulation
   a. Pass acetaminophen, dextropropoxyphen, and starch through a 595-µm aperture screen, transfer to a suitable mixer, and mix for 10 min.
   b. Warm the water, and dissolve the povidone.
   c. Slowly add the povidone solution to the mixer, and mix until a suitable-consistency mass is obtained. Add extra water if needed.
   d. Pass the mass through a 4-mm aperture screen on an oscillating granulator, and dry in a tray drier at 105°C until the LOD is below 2% (Brabender, 105°C, 1 h) or the equivalent.
   e. Pass the granules through a 1.59-mm aperture screen on a suitable comminuting mill, at medium speed, with knives forward into tared polyethylene-lined drums.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the cellulose microcrystalline, talc, and povidone through a 595-µm aperture screen, add to the blender, and blend for 5 min.
   c. Screen the magnesium stearate through a 400-µm aperture screen, and add it to the blender. Blend for 2 min.
   d. Discharge the granule into polyethylene-lined drums, seal, and weigh for yield.
3. Compression
   a. Compress using 14.5 × 7.5-mm capsule-shaped punches. Weight 10 table about 4.05 g, not more than 3% variation; thickness was 5.2 to 5.8 mm (range not more than ± 5%); hardness 8 kpa; and disintegration time not more than 15 min in water.
   b. Collect in clean, tared polyethylene-lined drums, and weigh for yield.
4. Coating
   a. *Pan spray:* Binks Bullow L450 spray gun or equivalent, fitted with a No. 63B material nozzle, a No. 66SF or 66SD atomizing nozzle, or a No. 39 needle.
      i. Divide tablets and solution.
      ii. Load into pan, and preheat for 3 h to 48°C.
      iii. Apply the solution at 10 to 21 psi, with a liquid pressure of 5 to 10 psi, to give a flow rate of 350 to 500 ml/min; pan speed of 20 to 25 rpm. Rotate pan, and commence spraying with continuous application of hot air at 46 to 49°C (damper fully open). Ensure that the tablet bed does not become too hot. Tablets should be put only just above room temperature. You must switch off hot air when a coating solution is not being sprayed. Continue applying the solution until the average tablet weight has increased by 8 mg. When this weight gain is achieved, roll the tablets until dry with the application of cool air. When completely dry, remove the tablets from the pan, and transfer to polyethylene-lined drums. Leave the drums open for at least 6 h in a dust-free area.
   b. *Accela Cota:* Airless high-pressure spray system with two guns. Nozzle type: 0.018-in. (0.45-mm) orifice diameter with a 65° spray angle, pan speed of 5 rpm, inlet temperature of 70°C, inlet airflow set at quarter to half available flow, and exhaust sufficient to maintain coating drum under negative pressure (set water gauge at 7 in.).
      i. Divide tablets and solution.

ii. Load tablets, rotate pan occasionally, and warm tablets until the exhaust temperature is 38 to 42°C. Do not rotate longer than is necessary to achieve even warming.
iii. Adjust the pump pressure to give an application rate of approximately 500 to 600 ml/min. Commence spraying with the coating solution. Adjust the pressure to maintain the exhaust temperature of 38 to 42°C.
iv. When the average weight gain of 8 mg is obtained, the tablets are dried: reduce pan speed to 7 rpm, and maintain the inlet temperature and exhaust settings for 5 min. If the exhaust temperature reaches 45°C, switch off heat and control rotation for another 10 min; occasionally rotate the pan to ensure even cooling. Remove tablets when the exhaust temperature is 28 to 32°C.
v. Ensure that tablets are thoroughly dry, and unload into polyethylene-lined drums — leave it unsealed for 1 h in a dust-free humidity-controlled area.

Acetaminophen and Codeine Tablets [34]

Acetaminophen, 4′-hydroxyacetanilide, is a nonopiate, nonsalicylate analgesic and antipyretic that occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. It has the following molecular formula: $C_8H_9NO_2$, with a molecular weight of 151.16.

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. It has the following molecular formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot {}^1/_2H_2O$, with a molecular weight of 406.37.

Tablets and elixir:
Each Tylenol with codeine tablet contains:
No. 2 codeine phosphate … 15 mg
Acetaminophen … 300 mg
No. 3 codeine phosphate … 30 mg
Acetaminophen … 300 mg
No. 4 codeine phosphate … 60 mg
Acetaminophen … 300 mg
Tylenol inactive ingredients:
Tablets: Powdered cellulose, magnesium stearate, sodium metabisulfite, pregelatinized starch, starch (corn).

Acetaminophen, Salicylamide, Caffeine, and Codeine Tablets (150 mg/200 mg/50 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Salicylamide	200.00
150.00	2	Acetaminophen powder	150.00
50.00	3	Caffeine anhydrous	50.00
10.00	4	Codeine phosphate	10.00
130.00	5	Starch (maize)	130.00
5.00	6	Gelatin powder	5.00
8.00	7	PVP K30	8.00
1.00	8	Aerosil 200	1.00
30.00	9	Starch (maize)	30.00
—	10	Water, purified	300 ml
10.00	11	Talc powder	10.00
19.00	12	Starch (maize), dried	19.00
1.00	13	Aerosil 200	1.00

MANUFACTURING DIRECTIONS

Note: The binding solution is prone to microbiological growth. Use freshly prepared and properly stored solution only.

1. Charge Item 6 and about 25 ml of Item 10 into a vessel to dissolve Item 6. Mix for 10 min.
2. In a separate vessel, add and dissolve Items 9 and 7 in about 12 ml of water.
3. Charge Item 5 into a vessel; add about 40 ml of cold Item 10 and 20 ml of hot (70 to 75°C) water, after first dissolving in cold.
4. In a separate vessel, charge Items 1 to 5 after passing them through a 630-µm sieve. Mix for 5 min at medium speed.
5. Add binding solution from Step 3, and mix at medium speed. Continue until a satisfactory mass is obtained.
6. Dry the wet mass in a fluid-bed dryer at 50°C for 45 min to 1.5 to 2.5% LOD.
7. Pass the dried granules through a 1.5-mm sieve.
8. Load granules in a cone blender, and mix for 5 min.
9. Add Items 11 to 13 (passed through a 500-µm sieve) to blender, and blend for 5 min.
10. Compress 634 mg in 12.7-mm flag bevel-edge punches.

Acyclovir Tablets [162]

Each 800-mg tablet of Zovirax contains 800 mg of acyclovir and the inactive ingredients FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. Each 400-mg tablet of Zovirax contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The chemical name of acyclovir sodium is 9-[(2-hydroxyethoxy) methyl]guanine.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
800.00	1	Acyclovir	800.00
240.00	2	Lactose	240.00
100.00	3	Microcrystalline cellulose (Avicel PH 101)	100.00
24.00	4	Povidone	24.00
32.00	5	Sodium starch glycolate	32.00
8.00	6	Magnesium stearate	8.00
—	7	Alcohol	48.00

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 3 through 250-µm mesh in a granulating vessel.
2. In a separate container, mix Items 4 and 5 in Item 6, and add the solution to Step 1. Pass the wet mass through #8 mesh, dry, and size the granules.
3. Compress 1204 mg.

Acyclovir Water-Dispersible Tablets (800 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
800.00	1	Acyclovir	800.00
100.00	2	Microcrystalline cellulose (Avicel PH 101)	100.00
53.00	3	Veegum F	53.00
42.00	4	Sodium starch glucolate 42.00	42.00
9.40	5	Magnesium stearate	9.40
—	6	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 4 through 250-µm mesh into a granulating vessel.
2. Add a sufficient quantity of Item 6 to make a wet mass. Pass it through a granulator, dry, and size through a #11 sieve.
3. Pass Item 5 through a 250-µm sieve, and add to Step 2.
4. Compress 1004 mg in a suitable punch.

Albendazole Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Albendazole	200.00
84.00	2	Starch (maize)	84.00
101.25	3	Lactose monohydrate	101.25
5.00	4	Sodium starch glycolate (Primojel)	5.00
13.00	5	Povidone (PVP K-30)	13.00
5.00	6	Saccharin sodium	5.00
1.00	7	Polysorbate 80 (Tween 80)	1.00
110.00	8	Microcrystalline cellulose (Avicel PH 102)	110.00
50.00	9	Sodium starch glycolate (Primojel)	50.00
5.00	10	Vanilla dry flavor	5.00
5.00	11	Blood orange dry flavor	5.00
4.00	12	Stearic acid	4.00
2.00	13	Magnesium stearate	2.00
2.75	14	Colloidal silicon dioxide (Aerosil 200)	2.75
2.00	15	Sodium lauryl sulfate	2.00
—	16	Alcohol (ethanol 95%)	105.00
—	17	Purified water	73.33

MANUFACTURING DIRECTIONS

Note: Avoid overmixing the lubricants, or otherwise, hardness will be reduced.

1. Dissolve Item 7 in Item 16 by spatula. Dissolve Items 5 and 6 in Item 17 by stirring with a stirrer. Add Item 7 (Tween-80) solution in Items 5 and 6 (PVP-saccharin) solutions, while mixing with a stirrer.
2. Sift Items 1, 2, 3, and 4 through a stainless steel sieve, 500 µm. Collect in a polyethylene bag.
3. Load the sifted powder into the mixer. Mix for 2 min at low speed.
4. Add the binding solution from Step 1 to Step 2, while mixing at low speed over a period of 2 min. Scrape the sides and blades of the mixer. Mix and chop at low speed for 2 min. Check the end point of granulation. If required, add Item 17 to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of granules.) Unload the wet mass on stainless steel trays to dry.
5. Dry the wet granules in the oven at 55°C for 10 h. After 2 h of drying, scrape the semidried granules to break the lumps for uniform drying.
6. Check the LOD. The limit is 1.0 to 1.5%.
7. Grind the dried granules through a 1.25-mm sieve using the granulator at medium speed.
8. Sift Items 8, 9, 10, and 11 through a 500-µm sieve. Add the sieved powder from Step 1. Mix manually for 2 min.
9. Mix Items 12, 13, 14, and 15 in a polyethylene bag. Sift through a stainless steel 250-µm sieve. Collect in a polyethylene bag. Add into Step 1. Mix manually for 1 min.
10. Compress to a weight of 10 tablets, 5.900 gm ± 2%; hardness 9 to 11 kp.
11. Coat using the hydroxypropylmethylcellulose (HPMC) system, and add a finishing coat. (See the Appendix.)

Alendronate Tablets [38]

Alendronate sodium is an aminobisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate. The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$, and its formula weight is 325.12. Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, slightly soluble in alcohol, and practically insoluble in chloroform. Fosamax tablets for oral administration contain either 6.53, 13.05, or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, and 40 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

Alendronate Tablets, Effervescent (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Alendronate, use alendronate sodium	13.05
650.00	2	Citric acid anhydrous	650.00
367.00	3	Sodium bicarbonate granular	367.00
40.00	4	Sodium carbonate anhydrous	40.00
25.00	5	Flavor	25.00
5.00	6	Color	5.00
7.50	7	Sodium benzoate	7.50
—	8	Water, purified	2.00

Note: For other strengths, adjust with lactose.

MANUFACTURING DIRECTIONS

1. Premix sodium benzoate with sodium bicarbonate and alendronate sodium. Mix the color with sodium carbonate. Place citric acid in a bowl of a suitable blender.
2. Add the 2 mg of water to the citric acid slowly, and mix thoroughly to form a moist blend. Add to the blend, in sequence, while mixing, the sodium bicarbonate mix and the sodium carbonate–color mix. Mix until uniformly distributed.
3. Compress tablets using suitably sized tooling. Cure the tablets, cool, and package in aluminum foil.

Alendronate Sodium Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Alendronate, use alendronate sodium	52.00
10.00	2	Polyvinyl pyrrolidone	10.00
100.00	3	Lactose anhydrous	100.00
1.50	4	Sodium stearyl fumarate	1.50
—	5	Water, purified	100.00

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 3 through a 500-μm sieve, and blend for 10 min.
2. Add Item 2, and mix it well with Item 5. Add to Step 1 to granulate, dry, size, and add Item 4.
3. Compress 163.50 mg in a suitable punch.

Allopurinol Tablets (100 mg) [84]

Allopurinol is known chemically as 1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one. It is a xanthine oxidase inhibitor that is administered orally and intravenously. Each scored white tablet contains 100 mg of allopurinol and the inactive ingredients lactose, magnesium stearate, potato starch, and povidone. Each scored peach tablet contains 300 mg of allopurinol and the inactive ingredients cornstarch, FD&C Yellow No. 6 Lake, lactose, magnesium stearate, and povidone.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Allopurinol	100.000
1.00	2	Sorbitan monooleate	1.000
73.00	3	Starch (maize)	73.000
100.00	4	Lactose	100.00
10.00	5	Starch (maize)	10.000
8.00	6	Sodium starch glycolate	8.000
QS	7	Purified water (deionized), approximately	65.00 ml
4.50	8	Talc purified	4.5000
1.50	9	Silicon dioxide	1.5000

MANUFACTURING DIRECTIONS

CAUTION: Wear gloves, mask, and protective glasses during all manufacturing operations.

1. Granulation
   a. Prescreen the allopurinol through a 75-µm aperture screen, and transfer it to a suitable mass mixer. Dissolve the sorbitan monoleate in 10 ml of water, and add the solution to the mixer. Mix until the allopurinol is wetted.
   b. Pass the wetted allopurinol through a 2.00-mm aperture screen on an oscillating granulator, and dry in a tray drier at 50°C until the LOD (Brabender 105°C, 1 h or equivalent) is less than 2%.
   c. Rescreen the dried allopurinol through a 75-µm aperture screen, and transfer it to the mass mixer. Add the starch (Item 3) and lactose, and mix for 15 min.
   d. Add the starch (Item 5) to about 15 ml of water, and mix until a smooth slurry, free from lumps, is formed.
   e. Heat 40 ml of water to boiling. Reduce the heat, and then, while mixing, add the slurry from Step 1d. Continue mixing well, until a smooth translucent paste is formed. Allow to cool to 50°C before using the next step.
   CAUTION: Control the heat to avoid charring of the paste.
   f. Add half of the starch paste from Step 1e to the blended powders in the mixer, and mix for 1 min. Stop mixing, and scrape the blades and sides of the mixer. Add the second half of the starch paste, and mix for another 1 min. Stop mixing, scrape the blades and sides of the mixer, and examine the mass.
   g. If necessary, add more water at 50°C, in small quantities, mixing for 1 min after each addition, until a good wet, holding mass is formed.
   CAUTION: Do not overwet or overmix the mass.
   h. Pass the mass through a 2.00-mm aperture screen on an oscillating granulator, and dry in a tray drier at 50°C until the LOD (Brabender 105°C, 1 h or equivalent) is in the range of 1 to 2%.
   i. Arrange for sample.
   j. Pass the granules through a 595-µm aperture screen on an oscillating granulator into tared, polyethylene-lined drums, seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the sodium starch glycolate, talc, magnesium stearate, and colloidal silicon dioxide through a 595-µm aperture screen. Add to the blender. Blend for 15 min.
   c. Discharge the granule into polyethylene-lined drums, seal, and weigh for yield.
3. Compression

a. Compress using 9.52-mm (0.375 in.) diameter concave punches with the bisect on the upper punch.
b. Compress to the following specifications:
   i. Weight of 10 tablets — 3.025 g
   ii. Weight variation — Average weight differs from theoretical weight by not more than 3%
   iii. Thickness — 3.5 to 4.3 mm (range: not more than 5%)
   iv. Hardness — NTL 8 kp
   v. Disintegration time – Not more than 15 min in water

Allopurinol Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Allopurinol	300.00
180.00	2	Lactose	180.00
20.00	3	Povidone (K 29)	20.00
50.00	4	Starch (maize)	50.00
QS	5	Water, purified (deionized)	65.00 ml
20.00	6	Croscarmellose sodium	20.00
30.00	7	Starch (maize), dried	30.00

MANUFACTURING DIRECTIONS

CAUTION: Wear gloves, mask, and protective glasses during all manufacturing operations.

1. Granulation
   a. Transfer the allopurinol, lactose, povidone, and starch (Item 4) to a suitable mass mixer. Mix for 15 min, and then pass through a 250-µm sieve aperture screen.
   b. Return the screened mix from Step 1 to the mixer, and add sufficient water until a good wet, holding mass is formed. Pass the mass through a 2.00-mm aperture screen on an oscillating granulator, and dry in a tray drier at 50°C until the LOD (Barbender 105°C, 1 h or equivalent) is in the range of 1 to 2%.
   c. Pass the granules through a 595-µm aperture screen on an oscillating granulator into tared, polyethylene-lined drums, then seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the croscarmellose sodium and dried starch through a 595-µm aperture screen, and add to the blender. Blend for 15 min.
   c. Discharge the granule into polyethylene-lined drums, then seal, and weigh for yield.
3. Compression
   a. Compress using 11.11-mm (0.4375 in.) diameter concave punches with the bisect on the upper punch. (Weight of 10 tablets — 6.00 g; weight variation — average weight differs from theoretical weight by not more than 3%.)

Alprazolam Tablets (0.25 mg/0.50 mg/1.0 mg)

Xanax tablets contain alprazolam, which is a triazolo analog of the 1,4-benzodiazepine class of central nervous system-active compounds. The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4H-*s*-triazolo [4,3-α][1,4] benzodiazepine. Alprazolam is a white crystalline powder that is soluble in methanol or ethanol, but it has no appreciable solubility in water at its physiological pH. Each Xanax tablet, for oral administration, contains 0.25, 0.5, 1, or 2 mg of alprazolam and the following inactive ingredients: cellulose, cornstarch, docusate sodium, lactose, magnesium stearate, silicon dioxide, and sodium benzoate. In addition, the 0.5-mg tablet contains FD&C Yellow No. 6, and the 1-mg tablet contains FD&C Blue No. 2.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 tablets (g)
0.25	1	Alprazolam, with excess	0.252
82.50	2	Dicalcium phosphate	82.50
2.25	3	Starch (maize)	2.25
2.25	4	Gelatin	2.25
33.50	5	Starch (maize)	33.50
0.082	6	Propyl paraben	0.082
0.082	7	Methyl paraben	0.082
1.00	8	Magnesium stearate	1.00
1.00	9	Sodium starch glycolate	1.00
0.30	10	Dye yellow	0.30
—	11	Water, purified, ca	100 ml

MANUFACTURING DIRECTIONS

1. Charge Items 2 and 5 in a suitable vessel after sifting through an 80-mesh sieve. Mix for 2 min.
2. Sift Item 1 through a 60-mesh sieve, and add to Step 1. *Note:* Because of the small quantity of Item 1, use a geometric dilution method to mix the entire amount.
3. Mix for 5 min.
4. In a separate vessel, sift (through 80 mesh) and charge Items 3, 4, 6, 7, and 10, and mix for 2 min. Add a sufficient quantity of Item 11 to form a suitable lump-free paste.
5. Add Step 4 into Step 3, and knead and chop to prepare a suitable mass without lumps.
6. Spread the wet mass from Step 5 on trays, and dry at 50°C for 12 h to an LOD of not more than 2%; dry for an additional hour, if necessary.
7. Pass dried granules through 20 mesh.
8. Sift Items 8 and 9 through a 250-μm sieve screen, and add to Step 7. Blend for 2 min.
9. Compress 125 mg using 6-mm punches. For 0.5-mg and 1.0-mg strengths, adjust with Item 2, and compress the same weight and size.

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic Acid Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, use monosodium trihydrate	6.55
110.45	2	Lactose anhydrous	110.45
80.00	3	Microcrystalline cellulose	80.00
1.00	4	Magnesium stearate	1.00
2.00	5	Croscarmellose sodium Type A	2.00

MANUFACTURING DIRECTIONS

1. The active ingredient (equivalent to 5 mg of anhydrous free acid per tablet) is premixed with one-third quantity of the microcrystalline cellulose and one-half the quantity of the anhydrous lactose in a ribbon blender for 5 min at 20 r/min.
2. To the premix is added the remaining two-thirds of the microcrystalline cellulose and the remaining one-half of the anhydrous lactose. Blend for 10 min at 20 r/min.
3. Add croscarmellose sodium to the blended powders in Step 2, and mix for 5 min at 20 r/min.
4. Add Item 4 to the mixture after passing it through a 90-mesh screen, and blend for an additional 5 min at 20 r/min.
5. Compress 192 mg in a suitable punch.

Aminophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Aminophylline	100.00
196.00	2	Starch (maize)	196.00
2.00	3	Talc	2.00
3.00	4	Magnesium stearate	3.00
QS	5	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Item 2 in a suitable vessel, and add a sufficient quantity of Item 5 to prepare a 30% smooth slurry.
2. Add Item 1 into Step 1, and mix well to form a suitable mass.
3. Pass the wet mass through a #6 sieve to granulate.
4. Dry the granules at 60°C for 10 h to an LOD of not more than 3%.
5. Pass the dried granules through 1.19-mm sieve, and transfer to a blending vessel.
6. Sift Items 3 and 4 through a 250-μm sieve, and add to Step 5. Blend for 2 min.
7. Compress 300 mg in 9-mm punches.

Amiodarone Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.000	1	Amiodarone hydrochloride	200.000
86.000	2	Lactose monohydrate	86.000
27.500	3	Starch (maize)	27.500
8.500	4	Povidone (PVP K-30)	8.500
25.000	5	Starch (maize)	25.000
2.000	6	Magnesium stearate	2.000
1.000	7	Colloidal silicon dioxide (Aerosil 200)	1.000
—	8	Purified water	116.67

MANUFACTURING DIRECTIONS

Note: Avoid over mixing lubricants because it reduces hardness.

1. Sieving and dry mixing
   a. Sift Items 1, 3, and 2 through a stainless steel sieve, 500 µm. Load into the mixer. Mix for 5 min at low speed.
2. Preparation of binder
   a. Dissolve Item 4 in 16.67 g of Item 8 by using a stirrer at a slow speed in a stainless steel container.
   b. Pass Item 5 through a 250-µm sieve.
   c. Make a homogeneous slurry of Item 5 in 25.0 g of Item 8 (30°C) in a stainless steel container. Check that it is free of lumps.
   d. Heat 75.0 g of Item 8 to 90°C in a stainless steel container. Add the slurry from Step 2. Stir until complete gelatinization occurs. Cool to 50°C.
   e. Add the solution from Step 2 into Step 3, and stir for 5 min.
   f. Check the quantity of the binder: theoretical weight, 150 g. Adjust the weight with purified water by mixing if required.
3. Kneading
   a. Knead the powder in a mixer (Diosna) with the binder, while mixing at low speed over a period of 2 min. Scrape the sides and the blades. Mix and chop at low speed for 2 min. Check the end point of granulation. If required, add more purified water to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of the granules.)
   b. Unload the wet granules in a stainless steel tray for drying.
4. Drying
   a. Dry the wet granules at 550°C for 5 h.
   b. Check the LOD: the limit is 1.0 to 1.5%. If required, dry further at 550°C for 1 h. Check the LOD.
   c. Transfer the dried granules to a polyethylene bag.
5. Grinding
   a. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in a polyethylene bag.
6. Lubrication
   a. Sift Items 6 and 7 through a 250-µm sieve in a stainless steel sieve. Collect in a polyethylene bag. Take approximately 66.67 g of granules from Step 5 into the polyethylene bag. Mix manually. Add into Step 5. Mix for 1 min.
   b. Store in a polyethylene bag.
7. Compression and specifications
   a. Compress the granules using a rotary tabletting machine, 10-mm round plain convex punch. (Weight of 10 tablets: 3.5 g ± 3%.)

Amlodipine Besylate Tablets [9]

Amlodipine besylate is a long-acting calcium channel blocker. Amlodipine besylate is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$. Amlodipine besylate (Norvasc) is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	(-) Amlodipine	0.50
183.00	2	Lactose anhydrous	183.00
15.00	3	Starch pregelatinized	15.00
1.50	4	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

1. Sieve the active ingredient, (-) amlodipine, through a suitable sieve, and blend with lactose and pregelatinized maize starch.
2. Add suitable volumes of purified water to granulate.
3. After drying, screen the granules, and blend with the magnesium stearate.
4. Compress using 7-mm diameter punches to a total weight of 200 mg. Adjust the formula for other strengths with lactose (2.5 and 5.0 mg).

Amitriptyline Tablets (50 mg) [42]

Amitriptyline HCl is 3-(10,11-dihydro-5*H*-dibenzo [a,*d*] cycloheptene-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride. Its empirical formula is $C_{20}H_{23}N \cdot HCl$.

Amitriptyline HCl, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, odorless, crystalline compound that is freely soluble in water.

Elavil® (amitriptyline HCl) is supplied as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150-mg tablets and as a sterile solution for intramuscular use. Inactive ingredients in the tablets are as follows: calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. The 10-mg amitriptyline HCl tablets also contain FD&C Blue No. 1. The 25-mg amitriptyline HCl tablets also contain D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Yellow No. 6. The 50-mg amitriptyline HCl tablets also contain D&C Yellow No. 10, FD&C Yellow No. 6, and iron oxide. The 75-mg amitriptyline HCl tablets also contain FD&C Yellow No. 6. The 100-mg amitriptyline HCl tablets also contain FD&C Blue No. 2 and FD&C Red No. 40. The 150-mg amitriptyline HCl tablets also contain FD&C Blue No. 2 and FD&C Yellow No. 6.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Amitriptyline	50.00
20.00	2	Starch (maize)	20.00
20.00	3	Lactose monohydrate	20.00
15.00	4	Dicalcium phosphate	15.00
2.00	5	Magnesium stearate	2.00
3.00	6	Talc	3.00
20.00	7	Starch (maize)	20.00
—	8	Water, purified, ca	100 ml

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through a 250-µm sieve, and charge in a suitable mixer.
2. In a separate vessel, charge Item 2, and add Item 8 at 80°C. Mix until a good paste is formed. Cool to 50°C.
3. Add Step 2 into Step 1, and knead and chop until granules are formed without lumps.
4. Spread the wet mass onto trays, and dry in an oven at 50°C for 15 h to an LOD of not more than 1.5%.
5. Pass the dried granules through No. 18 mesh, and transfer to a suitable blender.
6. Pass Item 5 though a 250-µm sieve and Item 7 through a 500-µm sieve; add to Step 5 and blend for 2 min.
7. Compress 130-mg tablets in a suitable punch.
8. Coat the tablet using an organic base coating. (See Appendix.)

Amoxicillin Tablets (250 mg/500 mg/1 g)

Amoxicillin is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically, it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$. The molecular weight is 419.45.

- Tablets — each tablet contains 500 mg or 875 mg of amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is embossed with AMOXIL, centered over 500 or 875, respectively. The 875-mg tablet is scored on the reverse side. The inactive ingredients are colloidal silicon dioxide, crospovidone, FD&C Red No. 30 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.
- Chewable tablets — each cherry-banana-peppermint-flavored tablet contains 125 mg, 200 mg, 250 mg, or 400 mg of amoxicillin as the trihydrate. The 125-mg and 250-mg pink oval tablets are imprinted with the product name AMOXIL on one side and 125 or 250 on the other side. The inactive ingredients are citric acid, cornstarch, FD&C Red No. 40, flavorings, glycine, mannitol, magnesium stearate, saccharin sodium, silica gel, and sucrose. Each 125-mg chewable tablet contains 0.0019 mEq (0.044 mg) of sodium; the 250-mg chewable tablet contains 0.0037 mEq (0.085 mg) of sodium. Each 200-mg chewable table contains 0.0005 mEq (0.0107 mg) of sodium; the 400-mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200-mg and 400-mg pale pink, round tablets are imprinted with the product name AMOXIL and 200 or 400 along the edge of one side. The inactive ingredients are aspartame, crospovidone, FD&C Red No. 40 Aluminum Lake, flavoring, magnesium stearate, and mannitol.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Amoxicillin (871 mcg/mg activity)[a]	287.00
28.50	2	Cellulose microcrystalline NC (Avicel PH 101)	28.50
20.00	3	Povidone K 29-32	20.00
QS	4	Alcohol 190 proof, approximately	70.00 ml
3.50	5	Magnesium stearate	3.50

[a] Adjust according to potency. Adjust the tablet size as given below to yield 1 g, 500 mg, and 250-mg tablets.

MANUFACTURING DIRECTIONS

CAUTION: Handle with extreme care. Protect face and hands because some individuals may be sensitive, and reactions may occur.

1. Granulation
   a. Pass amoxicillin through a 595-µm aperture screen using a Fitz mill, with knives forward, at medium speed.
   b. Charge the following ingredients in a suitable mixer: cellulose microcrystalline, sodium starch glycolate, and milled amoxicillin. Mix for 30 min.
   c. Add 100 g of alcohol and mix for an additional 15 min.
   d. Dissolve povidone in approximately 150 g of alcohol.
   e. Add povidone solution to the mixture from Step 3, with continuous mixing. Mix for 15 min, until a suitable granulating mass is obtained. If necessary, add more alcohol.
   f. Pass the wet mass through a 4.76-mm aperture screen.
   g. Spread the wet granulation onto trays. Oven dry at 38°C or until the LOD is 2 to 3.5% (vacuum 60°C, 3 h).
   h. Pass the dry granulation through a 1.2-mm aperture screen in an oscillating granulator.
2. Lubrication
   a. Charge half of the amount of dried granulation into a suitable mixer. Pass magnesium stearate through a 500-µm aperture screen, and add to the mixer. Mix for 10 min.
   b. Add the balance of granulation, and mix for an additional 5 min.

c. Charge into polyethylene-lined drums.

3. Compression
   a. Compress 1-g tablets using 20 × 9-mm bisected ovaloid punches (hardness not less than 15; thickness 9.6 to 10.6 mm).
   b. Compress 500-mg tablets using 18 × 8.5-mm ovaloid punches (thickness 6.5 to 6.7 mm; hardness 12 to 18).
   c. Compress 250-mg tablets using 10.3-mm diameter punches (thickness 5.1 to 5.3 mm; hardness 12).

Amoxicillin Trihydrate and Clavulanate Potassium Tablets (500 mg/125 mg)

Augmentin is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$. The molecular weight is 419.46. Chemically, amoxicillin is (*2S, 5R, 6R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins, and it possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$. The molecular weight is 237.25. Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Each Augmentin tablet contains 0.63 mEq of potassium.

Each 125-mg chewable tablet and each 5 ml of reconstituted Augmentin 125 mg/5 ml oral suspension contain 0.16 mEq of potassium. Each 250-mg chewable tablet and each 5 ml of reconstituted Augmentin 250 mg/5 ml oral suspension contain 0.32 mEq of potassium. Each 200-mg chewable tablet and each 5 ml of reconstituted Augmentin 200 mg/5 ml oral suspension contain 0.14 mEq of potassium. Each 400-mg chewable tablet and each 5 ml of reconstituted Augmentin 400 mg/5 ml oral suspension contain 0.29 mEq of potassium.

Inactive ingredients:

Chewable tablets — colloidal silicon dioxide, flavorings, magnesium stearate, mannitol, and one or more of the following: aspartame, D&C Yellow No. 10, FD&C Red No. 40, glycine, sodium saccharin, and succinic acid.

Tablets — colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Amoxicillin, use amoxicillin trihydrate compacted, with excess	587.50
125.00	2	Clavulanate, use clavulanate potassium with Avicel (1:1)	305.00
25.00	3	Sodium starch glycolate	25.00
30.00	4	Aerosil 200	30.00
10.00	5	Sodium carmellose	10.00
10.00	6	Talc	10.00
5.00	7	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Dry Item 1 at 45°C for 2 h.
2. Dry Items 6, 7, 5, and 3 at 80°C for 4 h.
3. Sift Items 1 to 7 through #40 mesh screen, charge in a drum mixer, and mix for 30 min.
4. Slug the mixture in Step 3 using 16-mm punches and a hardness of 6 to 7 kg/cm^2.
5. Break the slugs by passing through 2.5-mm mesh sieves on a mill.
6. Transfer the comminuted slugs to a blender, and add Items 6 and 7 for 15 min.
7. Compress using 19 × 9-mm punches.
8. Coat the tablets using HPMC organic coating. (See Appendix.)

Amoxicillin and Potassium Clavulanate Tablets (250 mg/62.5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Amoxicillin, use amoxicillin trihydrate	250.00
62.50	2	Clavulanic acid, use potassium clavulanate	62.50
23.00	3	Polyplasdone XL, dried	23.00
23.00	4	Syloid AL1	23.00
4.50	5	Magnesium stearate	4.50
450.00	6	Microcrystalline cellulose	450.00

MANUFACTURING DIRECTIONS

1. Polyplasdone XL, dried is present as a disintegrant. The Syloid AL1 is a desiccant used to prevent hydrolytic degradation of the actives. The magnesium stearate is present as a lubricant. The microcrystalline cellulose is a tablet binder and disintegrant.
2. Mill the amoxicillin trihydrate using a swing hammer mill at fast speed through a 0.063-in. screen, with knives forward.
3. Mix the milled amoxycillin trihydrate with the potassium clavulanate, polyplasdone, Syloid AL1, part of the magnesium stearate, and part of the microcrystalline cellulose.
4. Slug the blend from Step 3, or use a roller compacted.
5. Mill the compacts or flake from Step 4 through a swing hammer mill at medium speed, with knives forward, and fitted with a 0.063-in. screen.
6. Blend granules with remaining magnesium stearate and remaining microcrystalline cellulose.
7. Compress to a core weight of 450 mg and a hardness of 15 to 20 Kp.
8. Provide a film subcoating with an aqueous suspension of hydroxypropyl methyl cellulose, further coated with a Eudragit enteric coating, and finally, with a further overcoating of hydroxypropyl methyl cellulose. (See Appendix.)

Amphetamine Salts Tablets

This is a single-entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextroisomer of amphetamine saccharate, and 6, L-amphetamine aspartate.

Each Tablet Contains	5 mg	10 mg	20 mg	30 mg
Dextroamphetamine saccharate	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine aspartate	1.25 mg	2.5 mg	5 mg	7.5 mg
Dextroamphetamine sulfate	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine sulfate	1.25 mg	2.5 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	6.3 mg	12.6 mg	18.8 mg

Inactive ingredients:

Sucrose, lactose, cornstarch, acacia, and magnesium stearate.

Atenolol Tablets (50 mg/100 mg)

Atenolol, a synthetic, β_1-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4–{2′-hydroxy-3′-[(1-methylethyl)amino]propoxy}. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1*N* HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). Tenormin is available as 25, 50, and 100-mg tablets for oral administration. The inactive ingredients are magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Atenolol	50.00
87.50	2	Magneisum carbonate heavy	87.50
29.70	3	Starch (corn)	59.70
3.30	4	Sodium lauryl sulfate	3.30
30.00	5	Starch (corn)	30.00
2.00	6	Gelatin	2.00
5.00	7	Magnesium stearate	5.00
QS	8	Purified water	QS

Note: The above formula is used for both 50- and 100-mg strengths; see below for fill weights to obtain the correct strengths.

MANUFACTURING DIRECTIONS

1. Massing
   a. Mix starch (#5) with approximately 27.3 ml of purified water (#9) in a glass or stainless steel vessel, avoiding the formation of lumps.
   b. Boil the remaining 52.8 ml of purified water (#9), and add the mix from Step 1 with continuous stirring until a gel is formed. Further heat may be necessary. *Note:* A mix temperature greater than 95°C must be exceeded before a gel is formed.
   c. Pass gelatin through a 1.59-mm aperture, and add water at 50°C, dissolve, and add to Step 2.
   d. Add sodium lauryl sulfate to Step 3 without excessively mixing (to avoid foaming).
   e. Mill the Atenolol through a 1.59-mm aperture screen at medium speed with knives forward, then charge into a suitable mixer.
   f. Pass magnesium carbonate heavy, starch (corn) (#3) through a 1.00-mm aperture stainless screen, and add to the mixer. Mix at 60 r/min for 10 min.
   g. Pass the mixed powders from Step 4 through a 1-mm aperture stainless steel screen, and return to the mixer.
   h. Add, in one charge, the starch and gelatin and sodium lauryl sulfate gel from Step 4 at 70 to 80°C, and mix for 5 min at 60 r/min.
   i. Stop the mixer, and inspect the mass. Add the extra 6.88 ml of purified water (#9) at 50°C to complete the granulation while mixing. Mix for a further 5 min at 60 r/min.
2. Drying/granulation: Proceed to Step 1 or 2.
   a. Oven drying
      i. Pass the wet mass through a granulator fitted with a 4.76-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
      ii. Dry the granules in a hot air oven at 60°C (not more than 65°C). After 1 h drying, pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen. Collect the granules on paper-lined trays, and return to the hot air oven at 60°C.
   b. Fluid-bed drying
      i. Pass the wet mass through a granulator fitted with a 4.76-mm aperture stainless steel screen into the fluid-bed drier bowl.
      ii. Dry the granules in the fluid-bed drier at 60°C for 30 min, turning over after 15 min. Then pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen, and then return to the fluid-bed drier bowl with the air inlet and outlet fully open. Proceed to Step 3.
   c. Continue drying the granules until the LOD is between 1.5 and 2%.

d. Pass the dried granules through a granulator fitted with a 1-mm aperture stainless steel screen. Collect the granules in a polyethylene-lined drum, and close securely.

3. Lubrication
   a. Place the dried granules from Step 2 ("Drying/granulation") in a suitable blender.
   b. Add magnesium stearate and the remainder of the starch via a 0.6-mm aperture stainless steel screen, and mix for 25 min.
   c. Transfer to a polyethylene-lined drum, and close securely until ready for compression.
4. Compression
   a. Compress on a suitable tablet machine using round punches — weight of 10 tablets is 2.075 g for 50-mg strength and 4.15 g for 100-mg strength; hardness more than 5; disintegration time not more than 15 min.
5. Coating
   a. Use either organic coating or aqueous methocel as needed. Follow with a clear gloss.

Atorvastatin Tablets (10 mg/20 mg)

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin calcium is [*R*-(*R**,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4 [(phenylamino)carbonyl]-lH-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca{\cdot}3H_2O$, and its molecular weight is 1209.42.

Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, or 40 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hydroxypropylmethylcellulose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; and simethicone emulsion.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00 11.00	1	Atorvastatin, use atorvastatin calcium trihydrate	10.00 11.00
36.00	2	Calcium carbonate	36.00
65.00	3	Lactose monohydrate	65.00
30.00	4	Microcrystalline cellulose (Avicel PH 102)	30.00
3.00	5	Polyvinylpyrrolidone (Povidone K-30)	3.00
0.40	6	Polysorbate 80 (Tween 80)	0.40
4.00	7	Croscarmellose sodium (Ac-Di-Sol)	4.00
0.60	8	Magnesium stearate	0.60
—	9	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift atorvastatin calcium trihydrate, calcium carbonate, lactose monohydrate, and Avicel PH 102 through a 0.500-mm stainless steel sieve.
2. Dissolve PVP K-30 and Polysorbate-80 in purified water (50°C) by slow stirring until it becomes clear. Cool the solution to 30°C. This is the granulating solution.
3. Knead the powder mix with granulating solution to get the desired granules.
4. Dry the granules to a targeted LOD of 2%.
5. Pass the dried granules through #16 mesh.
6. Sift Ac-Di-Sol and magnesium stearate through 0.500 mm.
7. Load the ground granules from Step 5 and the powder mix from Step 6 into a suitable blender. Blend for 1 min.
8. Compress 150 mg into 12-mm punches. For 20-mg strength, compress 300 mg in 15-mm punches.
9. Prepare a hypromellose and polyethylene glycol 4000 solution in the mixture of purified water and ethanol 95%. Keep overnight for complete gelation. (See Appendix.)
10. Add talc and titanium dioxide into Step 10, and homogenize for a uniform coating dispersion.
11. Coat the tablets using the coating dispersion Accel Cota to a targeted weight.

Azithromycin Tablets (250 mg)

Zithromax (azithromycin tablets, azithromycin capsules, and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-*a*-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-*b*-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 785.0. Zithromax is supplied for oral administration as film-coated, modified capsule-shaped tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin, and D&C Red No. 30 Aluminum Lake.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Azithromycin, 5% excess	262.50
22.50	2	Microcrystalline cellulose	22.50
5.00	3	Sodium carmellose	5.00
10.00	4	Starch (maize)	10.00
3.50	5	Talc	3.50
3.50	6	Magnesium stearate	3.50
3.50	7	Aerosil 200	3.50
1.00	8	Sodium lauryl sulfate	1.00
32.50	9	Starch (maize)	32.50

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 3 through a 250-µm sieve, and charge in a mixer.
2. Mix for 15 min.
3. Charge Item 4 in a suitable vessel, add hot Item 10 (80°C), and mix; allow to cool to room temperature.
4. Add Step 3 to Step 2, and mix to make wet mass without lumps.
5. Spread wet mass on trays, and dry at 50°C for 12 h.
6. Pass dried granules through #20 mesh, and transfer to a tumble mixer.
7. Add Items 5 to 9 (sifted through a 250-µm sieve), and mix for 2 min.
8. Compress 340 mg in 16 × 6-mm punches.
9. Coat tablets using HPMC methylene chloride coating. (See Appendix.)

Benzafibrate Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Benzafibrate	200.00
84.00	2	Lactose monohydrate	84.00
25.00	3	Starch (maize)	25.00
5.800	4	Methocel E5	5.80
13.00	5	Gelatin	13.00
14.90	6	Microcrystalline cellulose (Avicel PH 102)	14.90
14.90	7	Premojel	14.90
6.90	8	Talc	6.90
5.80	9	Magnesium stearate	5.80
QS	10	Water, purified, ca	80 ml

MANUFACTURING DIRECTIONS

1. Dissolve Item 5 into 50% of Item 10 at 70 to 80°C by mixing at medium speed and avoiding foam formation.
2. Cool all to 50°C prior to use.
3. In a separate mixer, dry-mix Items 1 to 4 at medium speed for 5 min.
4. Add the gelatin solution from Step 2 slowly to the powder mix at slow speed; add more of Item 10, if necessary, to achieve a satisfactory mass, avoiding big lumps.
5. Spread the granules on stainless steel trays to a 10-mm thickness, and load in the oven for drying at 55°C for 12 h to an LOD of not more than 1%.
6. Grind the dried granules through a 1.25-mm sieve in a granulator, and transfer to a double-cone blender.
7. Pass Items 6 to 8 through a 250-μm sieve in a sifter, load the mixture in a double-cone blender (Step 6), and blend for 5 min.
8. Pass Item 9 through a 250-μm sieve sifter, and collect in a bag. Take a small amount of granules from Step 7, mix with Item 9 manually, and then add the mixture to the double-cone blender in Step 7.
9. Compress using 11-mm round concave punches, 370 mg per tablet.
10. Coat the tablets with hypermellose. (See Appendix.)

Benazepril Hydrochloride Tablets

Benazepril HCl is a white to off-white crystalline powder, soluble (>100 mg/ml) in water, in ethanol, and in methanol. Benazepril's chemical name is 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid monohydrochloride. Its empirical formula is $C_{24}H_{28}N_2O_5 \cdot HCl$, and its molecular weight is 460.96. Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group. Lotensin is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg of benazepril for oral administration. The inactive ingredients are cellulose compounds, colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-mg, 10-mg, and 20-mg tablets), iron oxides, lactose, magnesium stearate (40-mg tablets), polysorbate 80, propylene glycol (5-mg and 40-mg tablets), starch, talc, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Benazepril hydrochloride	20.00
32.90	2	Lactose monohydrate	32.90
5.00	3	Starch, pregelatinized	5.00
1.00	4	Silicon dioxide colloidal	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
—	8	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Mill Items 1 to 3, and blend together.
2. Add water to granulate the blend, screen wet granules, and oven dry.
3. Mill dried granules after mixing with Items 5 to 7.
4. Screen Item 4 and add to Step 3; blend for 1 min.
5. Compress.
6. Coat using HPMC 2910 3 cps (4.88 mg) and polysorbate 80 (0.119 mg) in aqueous dispersion; dust tables with talc.

Betamethasone Tablets (0.50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.50	1	Betamethasone base, 10% excess	0.55
20.00	2	Maize starch	20.00
85.90	3	Lactose monohydrate	85.95
3.00	4	Maize starch	3.00
0.50	5	Magnesium stearate	0.50
QS	6	Purified water	25.00

MANUFACTURING DIRECTIONS

1. Pass Item 2 through a 250-μm sieve, and make a homogenous slurry in cold purified water (5 kg) to assure it is free of lumps.
2. Add the slurry to a container with water (20 kg) at 80°C; stir until completely gelatinized; cool to 50°C.
3. Mix Item 1 gradually with Item 3, and pass through a 250-μm sieve; pass Item 4 through a similar sieve, and mix the powders for 15 min.
4. Add starch paste, and mix for 10 min; pass the wet mass through a Fitz mill sieve 24205 at medium speed.
5. Dry granules at 55°C for 10 h; do not exceed a moisture content of 2%; pass dried granules through a 1-mm sieve into a double-cone blender.
6. Pass Item 5 through a 250-μm sieve, mix with granules, and mix for 1 min.
7. Compressed average tablet weight is 1.10 g; hardness not less than 2.0 Kp.

BIRB 796 Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	BIRB 796	100.00
200.00	2	β-cyclodextrin	200.00
225.00	3	Microcrystalline cellulose	225.00
165.00	4	Lactose	165.00
7.50	5	Colloidal silicon dioxide	7.50
30.00	6	Starch, pregelatinized	30.00
15.00	7	Sodium starch glycolate	15.00
7.50	8	Magnesium stearate	7.50

Note: Item 2 can be replaced with Item 4 (a total of 365 mg of lactose).

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 7 in a suitable mixer after passing through a 250-μm sieve; mix for 10 min.
2. Add Item 8, and blend for 3 min.
3. Compress 750 mg in a 15-mm biplanar punch.

Bisoprolol Fumarate and Hydrochlorothiazide Tablets

Bisoprolol fumarate and hydrochlorothiazide (HCTZ) is indicated for the treatment of hypertension. It combines two antihypertensive agents in a once-daily dosage: a synthetic β_1-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide). Bisoprolol fumarate is chemically described as (±)-1-(4-((2-(1-methylethoxy)ethoxy)methyl) phenoxy)-3-((1-methylethyl)amino)-2-propanol (*E*)-2-butenedioate (2:1) (salt). It possesses an asymmetric carbon atom in its structure and is provided as a racemic mixture. The *S*(-) enantiomer is responsible for most of the beta-blocking activity. Its empirical formula is $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$, and it has a molecular weight of 766.97.

Bisoprolol fumarate is a white crystalline powder, approximately equally hydrophilic and lipophilic, and readily soluble in water, methanol, ethanol, and chloroform. HCTZ is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is a white, or almost white, almost odorless crystalline powder. It is slightly soluble in water, sparingly soluble in dilute sodium hydroxide solution, freely soluble in *n*-butylamine and dimethylformamide, soluble in methanol, and insoluble in ether, chloroform, and dilute mineral acids. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and it has a molecular weight of 297.73.

Each bisoprolol fumarate HCTZ 2.5-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 2.5 mg and hydrochlorothiazide 6.25 mg. Each bisoprolol fumarate HCTZ 5-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 5 mg and hydrochlorothiazide 6.25 mg. Each bisoprolol fumarate HCTZ 10-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 10 mg and hydrochlorothiazide 6.25 mg. Inactive ingredients include colloidal silicon dioxide, cornstarch, dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. The 5-mg/6.25-mg tablet also contains red and yellow iron oxide. The 2.5-mg/6.25-mg tablet also contains crospovidone, pregelatinized starch, and yellow iron oxide.

Bromazepam Tablets (3 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Bromazepam	3.00
0.23	2	Aluminum lake erythrosine (19.4%)[a]	0.23
1.80	3	Talc	1.80
100.00	4	Microcrystalline cellulose (Avicel PH 102)	100.00
94.37	5	Lactose crystalline	94.37
0.60	6	Magnesium stearate	0.60

[a] If a different dye is used, adjust the weight with lactose crystalline (Item 5).

MANUFACTURING DIRECTIONS

1. Charge Item 1 and 3% of Item 5 in a mixer, and mix for 10 min.
2. Pass the mixture through an oscillating granulator with a 0.5-mm screen.
3. Rinse the oscillator with 2% of Item 5, and add it to the mixture in Step 2.
4. In a separate mixer, add Item 2 (if used), Item 3, and 5% of Item 4, and mix for 3 min.
5. Pass the mixture in Step 4 through a mill at medium speed.
6. Transfer the mixture in Steps 5 and 3 into an oscillating granulator, add the balance of Item 5, add Item 3, pass through a 0.5-mm sieve, and mix for 1 h.
7. Transfer the mixture to a blender, add Item 6, and blend for 30 min.
8. Compress at 4- to 5-ton pressure, compress 200 mg using 9-mm × 2.5-mm cylindrical biplanar punches.

Bromhexine Tablets (8 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
8.00	1	Bromhexine hydrochloride	8.00
78.00	2	Lactose monohydrate	78.00
30.40	3	Starch (maize)	30.40
3.00	4	Gelatin	3.00
—	5	Water, purified, ca	120 ml
0.60	6	Magnesium stearate	0.60

MANUFACTURING DIRECTIONS

1. Charge Item 4 in a suitable vessel, add Item 5 at 70 to 80°C to dissolve Item 4; mix for 10 min.
2. Charge Items 1 to 3 in a suitable container after passing them through a 630-µm sieve. Mix and chop for 5 min.
3. Add binding solution from Step 1 to the mixer in Step 2, and mix for 5 min at high speed and then slow speed until a suitable mass is obtained (add more of Item 5 if needed).
4. Spread the wet mass on trays, and dry at 60°C for 10 h, turning granules over every 4 h until not more than 2% moisture remains.
5. Pass the dried granules through a 1.5-mm sieve and then a 1.0-mm sieve.
6. Pass Item 6 through a 250-µm sieve, add to Step 5, and blend for 2 min.
7. Compress using 7-mm flat punches and 120 mg per table.

Bromocriptine Tablets

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
6.00	1	Bromocriptine mesylate, with excess	6.10
205.50	2	Ludipress	205.50
2.20	3	Magnesium stearate	2.20

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress 214 mg in 9-mm biconvex punches.

Buflomedil Hydrochloride Tablets (150 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Buflomedil hydrochloride	300.00
74.00	2	Lactose	74.00
14.00	3	Povidone K 29-32	14.00
2.00	4	Magnesium stearate	2.00
QS	5	Water, purified	55.00 ml

Note: For 150-mg strength, adjust all components proportionally.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Dissolve the povidone in purified water using a glass or stainless steel vessel.
   b. Pass through a 500-µm aperture screen, and add the buflomedil hydrochloride and lactose. Charge into a suitable planetary or ribbon mixer. Mix at 15 to 30 r/min for 10 min.
   c. Granulate the mixed powders with the povidone solution, adding 20-ml aliquots every 2 to 3 min, with a mixer speed of 30 r/min.
   d. Stop the mixer, and inspect the mass. Additional purified water may be added to complete the granulation.
   e. Pass the wet mass through a suitable granulator fitted with a 2000-µm aperture stainless steel screen. Collect granules on paper-lined trays, and spread out evenly, 1/2 to 1 in. (1.0 to 2.5 cm) deep.
   f. Dry the granules in a hot air oven at 40°C for 3 h or until the LOD is between 0.7 to 2.8%.
2. Lubrication
   a. Pass the dry granules through a 100-µm aperture stainless steel screen, and charge into a cone or ribbon blender.
   b. Mix the magnesium stearate with one scoopful of granules from the previous step, and add to the bulk. Blend for 10 min at 20 to 30 r/min, and empty the blender into polyethylene-lined drums for compression.
3. Compression
   a. The tablet can be compressed using 9.5-mm or 11.11-mm punches: 385.40 mg per tablet. The weight of a 150-mg tablet is 246 mg.
4. Coating
   a. Use a clear CAP/Carbowax coating to control the release of the active ingredient. (See Appendix.)

Buflomedil Hydrochloride Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
600.00	1	Buflomedil hydrochloride	600.00
160.00	2	Sodium calcium alginate (Kelset)	160.00
30.00	3	Povidone K 29-32	30.00
QS	4	Water, purified, ca	300 ml
4.35	5	Magnesium stearate	4.35

MANUFACTURING DIRECTIONS

CAUTION: Wear a face mask and rubber gloves. When wetted, alginate materials result in slippery surfaces — exercise care.

1. Granulation (standard method using planetary or horizontal mixer) — *Note:* Water used should not exceed 30°C, so cool it if necessary.
   a. Pass any agglomerated materials through a 375-µm screen.
   b. Load buflomedil, sodium alginate, sodium-calcium alginate, and povidone into suitable mixing equipment. Blend for 10 min. Add while mixing 250 ml water (#5) over a period of 5 to 10 min, then mix for 5 min. Add additional water in small portions with mixing, until granulation is complete. Record the amount of water added. Stop mixing, and allow mixture to stand for approximately 5 min. (The granulation end point occurs when the mass is of a slightly wet but crumbly consistency. Avoid overwetting. The quantity of water and the mixing time must be sufficient to dissolve the povidone.)
   c. Load granules onto paper-lined oven trays, and dry at 50°C until the LOD is 3 to 5% (IR balance or similar at 100°C for 15 min). The drying time is 5 to 8 h depending on tray loading. Should the LOD be above 5% at the completion of the drying period, increase the temperature of the drying oven to 60°C and continue until the LOD is satisfactory. It is important that you do not increase the temperature until the initial drying period is complete.
   d. After drying, screen granules through an 840-µm screen fitted on the oscillating granulator. Pack into tightly sealed polyethylene-lined drums, and store in an air-conditioned area.
2. Lubrication
   a. Blend magnesium stearate with a portion of granules, and then screen through a 600-µm screen fitted to the oscillating granulator. Incorporate the remaining granules by serial dilution, mixing between additions. Do not overblend.
3. Compression
   a. Compress oval-shaped tablets.
4. Coating
   a. Coat using methocel coatings. (See Appendix.)

Bupropion Hydrochloride Tablets

Bupropion HCl, an antidepressant of the aminoketone class and a nonnicotine aid to smoking cessation, is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion HCl powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

- Immediate-release tablets — Wellbutrin is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients — *75-mg tablet:* D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; *100-mg tablet:* FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.
- Sustained-release tablets — *Wellbutrin SR:* Wellbutrin SR tablets are supplied for oral administration as 100-mg (blue) and 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients: carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake and polysorbate 80; the 150-mg tablet contains FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, and polysorbate 80. *Zyban:* Zyban (bupropion HCl for smoking cessation) is supplied for oral administration as 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients: carnauba wax, cysteine HCl, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Bupropion hydrochloride	100.00
68.50	2	Microcrystalline cellulose	68.50
6.90	3	Sodium starch glycolate	6.90
3.80	4	L-Cysteine hydrochloride	3.80
17.30	5	Talc	17.30
0.20	6	Silicon dioxide colloidal	0.20
—	7	Water, purified	8.00
—	8	Alcohol SD3A anhydrous	24.00

MANUFACTURING DIRECTIONS

1. Sift the bupropion hydrochloride, microcrystalline cellulose, and sodium starch glycolate through a 30-mesh Russell–Finex sifter.
2. Blend the sifted items in Step 1 for 15 min in a slant-cone blender.
3. In a separate container, dissolve the cysteine hydrochloride in purified water.
4. Add Item 8 to Step 3, and mix thoroughly.
5. Add to Step 1 in a granulating vessel: make a wet mass, dry granules in a fluid-bed dryer until the LOD is between 1 and 2%.
6. Sift dried granule through a 20-mesh Russell–Finex sifter.
7. Sift Items 4 and 6, and blend with Step 6.
8. Compress 172.6 mg in round 7.8-mm punches.

Buspirone Hydrochloride Tablets

Buspirone HCl is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative and anxiolytic drugs.

Buspirone hydrochloride is a white crystalline, water-soluble compound with a molecular weight of 422. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl) butyl)-8-azaspiro [4,5] decane-7,9-dione monohydrochloride. The empirical formula is $C_{21}H_{31}N_5O_2 \cdot HCl$.

BuSpar is supplied for oral administration in 5-mg and 10-mg, white, ovoid-rectangular, scored tablets. BuSpar tablets, 5 mg and 10 mg, contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Buspirone Hydrochloride Tablets, Controlled-Release (30 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
30.00	1	Buspirone hydrochloride	30.00
120.00	2	Polyvinyl chloride	120.00
11.00	3	Polyvinyl acetate C10-V7	11.00
1.60	4	Magnesium stearate	1.60
—	5	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Dry mix buspirone hydrochloride with polyvinyl chloride.
2. Granulate the powder mixture with a solution of polyvinyl acetate in ethanol.
3. Mill dried granules and compress into 7-mm round tablets (162.60 mg).

Captopril Tablets (25 mg)

CAPOTEN (captopril tablets) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

CAPOTEN is designated chemically as 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline; its molecular weight is 217.29. Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor. It is soluble in water (approximately 160 mg/ml), methanol, and ethanol, and is sparingly soluble in chloroform and ethyl acetate. CAPOTEN is available in potencies of 12.5 mg, 25 mg, 50 mg, and 100 mg as scored tablets for oral administration. Inactive ingredients include microcrystalline cellulose, cornstarch, lactose, and stearic acid.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Captopril	25.00
91.00	2	Ludipress	91.00
2.00	3	Kollidon CL	2.00
2.00	4	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force to meet the following specifications.
2. Compress 122-mg tablets in 8-mm biplanar punches.

Carbamazepine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.000	1	Carbamazepine[a]	208.00
25.880	2	Microcrystalline cellulose (Avicel PH 101)	25.880
9.000	3	Croscarmellose sodium (Ac-Di-Sol)	9.000
1.520	4	Carboxymethylcellulose sodium (CMC sodium)	1.520
1.500	5	Poloxyl 40 stearate	1.500
0.500	6	Colloidal silicon dioxide (Aerosil 200)	0.500
6.000	7	Sodium starch glycolate (Primojel)	6.000
7.000	8	Croscarmellose sodium (Ac-Di-Sol)	7.000
0.600	9	Magnesium stearate	0.600
—	10	Purified water	104.000

[a] Carbamazepine 8.0 mg/tablet added to compensate the assay (98.0–102.0%) and LOD of the material.

MANUFACTURING DIRECTIONS

Note: Avoid overmixing lubricants, otherwise hardness is reduced. *Critical note:* Hardness is critical for this product. Increasing or decreasing hardness from the specified limit will affect the dissolution.

1. Sieving and dry mixing
   a. Sift Items 1, 2, and 3 through a 630-µm stainless steel sieve in the sifter. Load into the mixer. Mix for 5 min at low speed.
2. Preparation of the binder
   a. Dissolve Item 5 in 104 g of Item 10 (55 to 65°C). Cool to 30°C. Dissolve Item 4 while stirring with a stirrer. Check the weight — theoretical weight: 107.02 g.
3. Kneading
   a. Knead the powder mix with the binding solution at a rate of 28 to 32 g/min while mixing at low speed. Scrape sides and blades. Mix and chop at low speed for 2 min. Check the end point of granulation, consisting of free-flowing granules with little lumps. If required, add more purified water to get to the end point.
   b. Sift the granules in the granulator through a 3.5-mm stainless steel sieve, and follow by sifting through a 1-mm stainless steel sieve.
   c. Unload the wet granules into stainless steel trays for drying.
4. Drying
   a. Dry the wet granules in an oven at 55°C for 8 h.
   b. Check the LOD — limit: 0.5 to 1%.
   c. If required, dry further at 55°C for 1 h.
5. Grinding and lubrication
   a. Grind the dried granules through a 1-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into a drum blender.
   b. Sift Items 6, 7, and 8 through a 500-µm sieve, using a sifter, and add it to the drum blender. Mix for 2 min.
   c. Sift Item 9 through a 250-µm sieve. Add 4- to 8-g granules from the bulk (Step 5a. in "Grinding and lubrication"). Mix in a polyethylene bag for 1 min. Add to blender. Blend for 1 min.
   d. Unload in stainless steel drums. Check and record the weight of the granules — theoretical weight: 260 g.
6. Compression
   a. Check temperature and humidity before starting compression.
   b. Limits are that the temperature should not exceed 27°C, and the recommended relative humidity is 55 to 60%.
   c. Compress the granules using a rotary tabletting machine. At 9 mm, the weight of 10 caplets is 2.6 gm ± 2%.

Carbamazepine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Carbamazepine	200.00
300.00	2	Ludipress	300.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 496 mg in 12-mm biplanar punches.

Carbidopa and Levodopa Tablets

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate.

Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3. Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. The inactive ingredients are cellulose, magnesium stearate, and starch. Tablets Sinemet 10-100 and 25-250 also contain FD&C Blue No. 2. Tablets Sinemet 25-100 also contain D&C Yellow No. 10 and FD&C Yellow. Sinemet CR (carbidopa–levodopa) is a sustained-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome. The inactive ingredients in Sinemet CR 50-200 are D&C Yellow No. 10, magnesium stearate, iron oxide, and other ingredients. Inactive ingredients in Sinemet CR 25-100 are magnesium stearate, red ferric oxide, and others. The Sinemet CR tablet is a polymeric-based drug delivery system that controls the release of carbidopa and levodopa as it slowly erodes. Sinemet CR 25-100 is available to facilitate titration and as an alternative to the half-tablet of Sinemet CR 50-200.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Carbidopa	25.00
100.00	2	Levodopa	100.00
224.00	3	Microcrystalline cellulose (Avicel PH 101)	224.00
15.00	4	Croscarmellose sodium	15.00
3.00	5	Silicon dioxide colloidal	3.00
3.00	6	Magnesium stearate	3.00
50.00	7	Carbidopa	50.00
200.00	8	Levodopa	200.00
80.00	9	Methocel E4M premium CR	80.00
61.00	10	Microcrystalline cellulose	61.00
2.00	11	Silicon dioxide colloidal	2.00
2.00	12	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. This is a bilayer or two-compartment tablet consisting of a core layer of sustained-release carbidopa–levodopa overcoated with a layer of immediate-release carbidopa–levodopa.
2. The core ingredients (Items 7 to 10) are blended separately (as are the outer layer [Items 1 to 4] ingredients), compressed to produce core tablets, and then overcoated with the compressed outer-layer blend using a suitable coating press.

Carisoprodol Tablets

Soma tablets are available as 350-mg round, white tablets. Chemically, carisoprodol is *N*-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate. Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water; freely soluble in alcohol, in chloroform, and in acetone; its solubility is practically independent of pH. Carisoprodol is present as a racemic mixture. The molecular formula is $C_{12}H_{24}N_2O_4$, with a molecular weight of 260.33. Other ingredients include alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic hydrogen phosphate.

Carvedilol Tablets

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (±)-1-(carbazol-4-yloxy)-3-[[2-(*O*-methoxyphenoxy) ethyl] aminol-2-propanol. It is a racemic mixture. Coreg (carvedilol) is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or 25 mg of carvedilol. The 6.25-mg, 12.5-mg, and 25-mg tablets are Tiltab® tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide. Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Carvedilol	25.00
25.00	2	Saccharose	25.00
28.00	3	Lactose monohydrate	28.00
1.78	4	Polyvinyl pyrrolidone 25 K	1.78
20.17	5	Polyvinyl pyrrolidone cross-linked	20.17
10.00	6	Microcrystalline cellulose	10.00
5.32	7	Silicon dioxide colloidal	5.32
2.17	8	Magnesium stearate	2.17
—	9	Purified water	115.00

MANUFACTURING DIRECTIONS

1. Charge the following in a mixing vessel: Item 3 sieved, Item 2 (half), and Item 4; add and mix Item 9, and then mix by stirring for 30 min.
2. Add Item 7 and Item 1, and stir for another 30 min until a homogenous suspension is obtained.
3. Pass the suspension in Step 2 through a colloid mill, and keep circulating.
4. Add Items 2 and 5 to a fluid-bed dryer, and then pour the suspension in Step 3 to obtain dry granules.
5. Sieve the granules through a 1.2-mm mesh sieve.
6. Lubricate granules, and compress.

Cefadroxil Dispersible Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Cefadroxil, use cefadroxin anhydrous	268.65
2.00	2	PVP potassium 30	2.00
—	3	Isopropyl alcohol	10.80
77.00	4	Lactose monohydrate	77.00
93.50	5	Starch (maize)	93.50
13.00	6	Aspartame	13.00
1.50	7	Aerosil 200	1.50
0.45	8	Methyl paraben	0.45
0.05	9	Propyl paraben	0.05
4.00	10	Starch (maize)	4.00
5.00	11	Magnesium stearate	5.00
5.00	12	Talc	5.00
QS	13	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 2 and 3, and prepare a binding solution.
2. Sift Item 1 through a 250-µm sieve.
3. Add Step 1 into Step 2, and prepare a wet mass.
4. Spread granules on trays, and dry in a dehumidified room.
5. Pass dried granules through a 595-µm sieve.
6. Prepare a paste of Item 5 using purified water.
7. Sift Items 4 and 6 into 9 through a 250-µm sieve. Mix for 15 min.
8. Add the paste from Step 6, and mix until a wet mass is obtained without lumps.
9. Dry the granules obtained in Step 8 in a fluid-bed dryer at 50°C for 2 h.
10. Mix granules from Step 5 and Step 9, and charge into a tumble mixer.
11. Sift Items 10 to 12 through a 250-µm sieve, add to Step 10, and blend for 2 min.
12. Compress 630 mg using 11.3-mm punches.

Cefdinir Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Cefdinir bulk powder	306.80
29.20	2	Microcrystalline cellulose (Avicel PH 101)	29.20
29.20	3	L-HPC (LH-21, Shin-Etsu Chemical)	29.20
3.70	4	Polyvinylpyrrolidone (Kollidon 30)	3.70
0.90	5	Silicic acid light anhydorus (Aerosil 200)	0.90
4.40	6	Magnesium stearate	4.40
15.00	7	Saccharin sodium	15.00
5.60	8	Strawberry flavor	5.60

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 4 after passing through a 250-µm mesh into a mixing vessel. Mix for 10 min.
2. Add Items 5 to 8, one at a time, and blend for 1 min each time.
3. Compress 395 to 400 mg.

Cefixime Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Cefixime bulk powder	448.90
38.90	2	Microcrystalline cellulose (Avicel PH 101)	38.90
38.90	3	L-HPC (LH-21, Shin-Etsu Chemical)	38.90
4.90	4	Polyvinylpyrrolidone (Kollidon® 30)	4.90
1.20	5	Silicic acid light anhydrous (Aerosil 200)	1.20
5.90	6	Magnesium stearate	5.90
20.00	7	Saccharin sodium	20.00
7.50	8	Strawberry flavor	7.50

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 4 after passing through a 250-μm mesh into a mixing vessel. Mix for 10 min.
2. Add Items 5 to 8, one at a time, and blend for 1 min each time.
3. Compress 566 to 570 mg.

Cefprozil Tablets (250 mg)

Cefprozil is a semisynthetic broad-spectrum cephalosporin antibiotic. Cefprozil is a *cis* and *trans* isomeric mixture (≥ 90% *cis*). The chemical name for the monohydrate is (6*R*,7*R*)-7-((*R*)-2-amino-2-(*p*-hydroxy-phenyl)acetamido)-8-oxo-3-propenyl-5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid monohydrate. Cefprozil is a white to yellowish powder with a molecular formula for the monohydrate of $C_{18}H_{19}N_3O_5S{\cdot}H_2O$ and a molecular weight of 407.45. Cefzil® tablets contain cefprozil equivalent to 250 mg or 500 mg of anhydrous cefprozil. In addition, each tablet contains the following inactive ingredients: cellulose, hydroxypropylmethylcellulose, magnesium stearate, methylcellulose, simethicone, sodium starch glycolate, polyethylene glycol, polysorbate 80, sorbic acid, and titanium dioxide. The 250-mg tablets also contain FD&C Yellow No. 6.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Cefprozil	250.00
30.00	2	Starch (maize)	30.00
3.00	3	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Dry blend Items 1 and 2 for 20 min.
2. Sieve Item 3 through a 250-μm mesh, and blend with Step 1. Blend for 2 min.
3. Compress.

Celecoxib Tablets

Celebrex® (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38. Celebrex oral capsules contain 100 mg and 200 mg of celecoxib. The inactive ingredients in Celebrex capsules include croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Cephalexin Tablets

Keflex is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S{\cdot}H_2O$, and the molecular weight is 365.41. The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterions (i.e., the molecule contains both a basic and an acidic group). The isoelectric point of cephalexin in water is approximately 4.5 to 5. The available crystalline form of cephalexin is a monohydrate. It is a white crystalline solid with a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/ml may be dissolved readily, but higher concentrations are obtained with increasing difficulty. The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a D-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position. Each pulvule contains cephalexin monohydrate equivalent to 250 mg (720 mcmol) or 500 mg (1439 mcmol) of cephalexin. The pulvules also contain cellulose, FD&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients. Each tablet manufactured by Biocraft contains cephalexin monohydrate equivalent to 250 mg (720 mcmol) or 500 mg (1439 mcmol) of cephalexin. Inactive ingredients include hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 90, sodium starch glycolate, and titanium dioxide.

Cetirizine and Pseudoephedrine Delayed-Release Tablets (5 mg/120 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cetirizine dihydrochloride, excess	6.25
120.00	2	Pseudoephedrine hydrochloride	120.00
25.00	3	Hydroxypropyl methylcellulose (Methocel DE5)	25.00
110.00	4	Hydroxypropyl methylcellulose (Methocel F4N)	110.00
10.00	5	Hydroxypropyl methylcellulose (Methocel K5M)	10.00
174.00	6	Microcrystalline cellulose	174.00
1.00	7	Dye yellow	1.00
2.50	8	Aerosil 200	2.50
2.50	9	Magnesium stearate	2.50
5.00	10	Ethyl cellulose (7PPS)	5.00
0.001 ml	11	Propylene glycol	1.00 ml
0.06 ml	12	Dichloromethane	60.00
0.16 ml	13	Water, purified	16.60 ml

MANUFACTURING DIRECTIONS

1. Charge Items 2 to 6 and 8 in a suitable mixer. Mix for 5 min.
2. Compress the mixture in Step 1 at 445 mg per tablet.

Cetirizine Hydrochloride Tablets (10 mg)

Cetirizine HCl is an orally active and selective H_1-receptor antagonist. The chemical name is (±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. Cetirizine HCl is a racemic compound with an empirical formula of $C_{21}H_{25}C1N_2O_3{\cdot}2HCl$. The molecular weight is 461.82. Cetirizine HCl is a white, crystalline powder and is water soluble. Zyrtec tablets are formulated as white, film-coated, rounded-off rectangular-shaped tablets for oral administration and are available in 5- and 10-mg strengths. The inactive ingredients are as follows: lactose, magnesium stearate, povidone, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, and cornstarch.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Cetirizine hydrochloride	10.20
39.00	2	Maize starch	39.00
70.55	3	Lactose monohydrate	70.55
2.60	4	PVP K-30	2.60
7.00	5	Maize starch, dried	7.00
0.65	6	Magnesium stearate	0.65
QS	7	Purified water	30.00

MANUFACTURING DIRECTIONS

1. Prepare the binding solution by dissolving Item 4 in Item 7 at 25 to 30°C until the solution becomes clear.
2. Sift Item 1 through a 500-µm sieve in portions.
3. Add binding solution slowly, and granulate.
4. Add water if necessary. Dry granules at 55°C for 10 h.
5. Pass granules through a 1.25-mm sieve in a V-blender. Add Items 5 and 6, and mix for 1 min. Compress tablets of 130 mg with hardness 5 to 8 Kp.
6. Coat using the HPMC. (See Appendix.)

Chlorcyclizine Hydrochloride Tablets (50 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Chlorcyclizine hydrochloride	50.00
109.75	2	Lactose monohydrate	109.75
4.28	3	Povidone (K 29-32)	4.28
11.30	4	Alcohol ethanol 190 proof	11.30
QS	5	Water, purified	QS
95.71	6	Starch (corn)	95.71
6.21	7	Talc	6.21
2.60	8	Magnesium stearate	2.60

MANUFACTURING DIRECTIONS

1. Charge chlorcyclizine hydrochloride, lactose, and povidone into a mass mixer. Mix well.
2. Add alcohol (diluted with an equal weight of purified water) and QS to mass.
3. Granulate through a 15.88-mm aperture or similar.
4. Dry at 41°C to less than 1% LOD (1 h Brabender or equivalent at 105°C).
5. Sift and grind through a 1.19-mm aperture or similar screen.
6. Lubricate by adding cornstarch (#6), talc, and acid stearic (or magnesium stearate) sifted through a 600-µm aperture or similar.
7. Compress using 7.94-mm standard round convex punches with logo.
8. Coating is optional; use organic coatings, preferably.

Chlordiazepoxide and Clinidium Bromide Tablets (5 mg/2.5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.50	1	Clinidium bromide, 5% excess	2.625
5.00	2	Chlordiazepoxide, 5% excess	5.25
131.02	3	Lactose powder	131.02
8.50	4	Starch (maize)	8.50
2.30	5	Talc	2.30
0.30	6	Magnesium stearate	0.30
QS	7	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Prepare a paste with maize starch and water. Use this for separately granulating Items 1 and 2. Use a 1:4 starch and water mixture, and heat to 50°C with continuous stirring.
2. Knead, granulate, dry, and sieve Item 1 using Step 1 paste. Mix a 1:5 ratio of Item 1 to Item 3, and mix together for 5 min. Pass the mixture through an oscillating granulator using a 1-mm sieve. Add paste from Step 1, and mix for 5 min. Add Item 3 (part), and pass the wet mass through a 7-mm sieve. Dry at an humidity of 40 to 50%. Pass the dried granules through a 1.5-mm perforated sieve.
3. Knead, granulate, dry, and sieve Item 2 using Step 1 paste. Use a 1:3 ratio of Item 2 to lactose, and mix for 5 min. Then pass the mixture through a 1-mm oscillating granulator. Pass the wet mass through a 7-mm sieve, dry at 60°C overnight in a relative humidity of granules that is 34 to 43%. Pass the dried granules using a 1.5-mm perforated sieve.
4. Mix the granules from Steps 2 and 3, and tumble the mix for 1 h at low r/min.
5. Premix Items 5 and 6 for 5 min, and then blend this mixture with Step 4. Tumble the mix for a half hour at low r/min.
6. Compress 150 mg in 8-mm cylindrical biconvex punches at 4 to 5 tons of pressure.
7. Apply a sugar coating (see Appendix) to the final weight of 300 mg.

Chlordiazepoxide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Chlordiazepoxide	10.00
61.70	2	Lactose	61.70
6.17	3	Starch (maize)	6.17
0.60	3	Talc	0.60
0.30	4	Magnesium stearate	0.30
QS	5	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Mix Items 1 and 2 in a blender for 10 min at medium speed.
2. In a separate vessel, prepare a paste of Item 3 with Item 5, at 50°C, and maintain this temperature until fully gelatinized without lumps.
3. Transfer the hot paste to the blender in Step 1, and mix for 30 min. Then pass it through a granulator with a 10-mm perforated screen.
4. Dry the granules overnight at 45°C.
5. Sift the dry granules in an oscillating granulator with a 1-mm sieve.
6. Add Item 4, and mix in a tumbler for 10 min.
7. Compress 80 mg using 6 × 3-mm cylindrical biconvex punches.
8. Sugarcoat the tablets. (See Appendix.)

Chloroquine Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Chloroquine diphosphate	250.00
100.00	2	Dicalcium phosphate (Ditab)	100.00
10.00	3	Kollidon 30	10.00
—	4	Isopropyl alcohol	83.00
10.00	5	Kollidon CL	10.00
2.00	6	Aerosil 200	2.00
3.00	7	Talc	3.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4. Then dry, pass through a 0.8-mm sieve, add the mixture of Items 5 to 7, and press with low-compression force.
2. Compress 361 mg in 8-mm biplanar punches.

Choline Theophyllinate Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Choline theophylline	100.00
244.00	2	Ludipress	244.00
6.00	3	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.5-mm sieve. Mix and press with very low compression force.
2. Compress 350 mg in 8-mm biplanar punches.

Chymotrypsine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Chymotrypsin	27.50
71.50	2	Ludipress	71.50
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm screen, and press with low compression force.
2. Compress 100 mg in 8-mm biplanar punches.

Cilazapril Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.50	1	Cilazapril anhydrous	2.50
37.00	2	Lactose powder	37.00
2.87	3	Talc	2.87
57.43	4	Starch (maize)	57.43
7.65	5	Hydroxypropyl methylcellulose 2910/3C	7.65
1.91	6	Sodium stearyl fumarate	1.91
QS	7	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Disperse Item 5 in 50 ml of Item 7, and allow this to stand overnight.
2. In a tumble mixer, add Item 1 and 10 g of Item 2, and mix for 5 min.
3. Add the balance of Item 2 and 20 g of Item 4, and mix well.
4. Add the granulating solution from Step 1, and knead. Then pass through a 7-mm sieve in a granulator.
5. Spread on paper-lined trays, and dry at 45°C overnight.
6. Pass the dried granules through a 1.5-mm sieve at 20 to 25% RH.
7. In a tumble mixer, add the balance of Item 4, and then add Items 3 and 6. Mix for 6 min.
8. Compress 200 mg in a suitable punch.
9. Coat using the Opadry coating. (See Appendix.)

Cimetidine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Cimetidine[a]	202.00
48.89	2	Microcrystalline cellulose (Avicel PH 102)	48.89
6.00	3	Povidone (PVP K-30)	6.00
0.40	4	Sodium lauryl sulfate	0.40
0.26	5	Dispersed blue E132	0.26
0.26	6	Ferric oxide (iron oxide yellow)	0.26
13.11	7	Starch (maize)[b]	14.41
9.44	8	Sodium starch glycolate (Primojel)	9.44
1.40	9	Magnesium stearate	1.40
—	10	Purified water	77.78

Note: For higher strength (400- and 800-mg tablets), adjust formula and fill weights accordingly.

[a] Cimetidine 2.0 mg/tablet (1%) was added as an extra to compensate for the moisture.
[b] Maize starch 1.3 mg/tablet (10%) was added as an extra to compensate for the moisture.

MANUFACTURING DIRECTIONS

1. Prepare a slurry of Item 7 in 15.56 g of Item 10 (30 to 40°C). Then make a translucent paste by adding 44.44 g of Item 10 (90 to 95°C). Cool to 45 to 50°C.
2. Disperse Items 5 and 6 in 4.44 g of Item 10 (25 to 30°C) by homogenizing. Add the color dispersion to the starch paste at Step 1, and mix well.
3. Dissolve Item 3 in 13.33 g of Item 10. Stir until the solution is clear. Add Item 4 to the solution. Stir just to dissolve. Do not produce foam by stirring. Add this solution to the colored paste at Step 2, and mix for 5 min.
4. Pass Items 1 and 2 through a 1200-µm sieve using a sifter. Collect in an s.s. drum. Load to a mixer. Mix at a high speed for 10 min.
5. Add colored starch paste from Step 3 to the dry powder in the mixer. When the addition is over, mix at medium speed to get the satisfactory wet mass.
6. Add Item 10 if required. Record extra quantity if used.
7. Pass the wet mass through a Fitz mill using sieve 24250, knives forward, at medium speed.
8. Collect and spread the granules onto the trays, one-third the thickness of the tray, and dry the granules at 55°C for 16 h. After 4 h of drying, stir the granules in the trays, and change the positions of the trays for uniform drying. *Note:* Stirring is a very important step to avoid migration of color. Migration leads to mottling of the tablet.
9. Check the moisture of dried granules. The limit is not more than 1.5%. Dry further if required to get a moisture content of 1.5%.
10. Pass the granules through a 1.25-mm sieve using a granulator at medium speed. Do not fill the hopper completely. This increases excess fines.
11. Pass Item 8 through a 500-µm sieve using a sifter. Collect in a polyethylene bag, and add to the blender. Mix for 5 min
12. Pass Item 9 through a 250-µm sieve using a sifter. Collect in a polyethylene bag, and add 4.4 to 6.7 g powder from the bulk. Mix it, and then add it to the blender. Mix for 1 min.
13. Check temperature and humidity before starting compression. The limits are as follows: temperature 25 to 27°C; RH 45 to 55%.
14. Compress the granules using round concave punches. The weight of 10 tablets is 2.80 gm ± 2%.
15. Coat tablets. (See the details in the Appendix.)

Ciprofloxacin Tablets (500 mg)

Ciprofloxacin hydrochloride tablets and oral suspension are synthetic broad-spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluora-1, 4-dihydro-4-oxa-7-(1-piperazinyl)-3quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance, with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$, and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance.

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Cipro film-coated tablets are available in 100-mg, 250-mg, 500-mg, and 750-mg (ciprofloxacin equivalent) strengths. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and water.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00 582.19	1	Ciprofloxacin Ciprofloxacin $HCl \cdot H_2O$	 582.19
10.00	2	Crospovidone (Kollidon CL)	10.00
60.00	3	Sodium Starch glycolate (Primojel)	60.00
9.50	4	Povidone (PVP K-30)	9.50
54.37	5	Microcrystalline cellulose (Avicel PH 101)	54.37
20.00	6	Crospovidone (Kollidon CL)	20.00
20.00	7	Sodium starch glycolate (Primojel)	20.00
6.00	8	Magnesium stearate	6.00
3.46	9	Colloidal silicon dioxide (Aerosil 200)	3.46
—	10	Absolute alcohol (ethanol, dehydrated alcohol)	268.00

MANUFACTURING DIRECTIONS

Note: It is important to note the following:

- Avoid the overmixing of lubricants because this could reduce hardness.
- Process the products in an explosion-proof area. Relative humidity should not be more than 50%, and the temperature should be not more than 27°C.

1. Granulating solution
   a. Dissolve Item 4 in Item 10 under slow stirring by stirrer.
2. Dry powder mixing
   a. Sift Items 1, 3, and 2 through a stainless steel sieve (900-µm) in sifter. Load into a mixer. Mix and chop for 3 min at low speed.
3. Kneading
   a. Knead the mixed powder with granulating solution for 2 min while mixing at low speed. Then mix and chop at high speed for 2 min.
   b. If required, add more absolute alcohol, and mix and chop at low speed to get to the end point of granulation. Record the additional quantity of absolute alcohol. Unload the wet mass in a stainless steel tray for drying.
4. Drying
   a. Dry the wet mass in the oven. Start air circulation without the heater "on" for 2 h, keeping the door open. Then dry at 55°C for 5 h.
   b. Check the LOD. The limit is 1.5 to 2.0%.
   c. If required, continue drying at 55°C for another half an hour to get the desired LOD.
5. Grinding
   a. Pass the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums.
6. Lubrication
   a. Sift Items 5, 7, 6, and 9 through a 500-µm sieve, and add it to the dry granules in the drum.
   b. Pass Item 8 through a 250-µm sieve using a sifter. Add 40 to 60 g of granules from bulk. Mix in polyethylene bag for 1 min. Add to a drum blender and mix for 1 min.
7. Compression
   a. Compress the granules using a rotary tabletting machine with 18 × 8-mm oblong concave punches. Compress 770 mg per tablet.
8. Coating
   a. Coat using HPMC coating. (See Appendix.)

Ciprofloxacin Tablets (750 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
750.00 900.00	1	Ciprofloxacin Ciprofloxacin HCl·H_2O	 900.00
15.00	2	Crospovidone (Kollidon CL)	15.00
70.00	3	Sodium starch glycolate (Primojel)	70.00
11.00	4	Povidone (PVP K-30)	11.00
70.00	5	Microcrystalline cellulose (Avicel PH 101)	70.00
25.00	6	Crospovidone (Kollidon CL)	25.00
30.00	7	Sodium starch glycolate (Primojel)	30.00
7.50	8	Magnesium stearate	7.50
3.50	9	Colloidal silicon dioxide (Aerosil 200)	3.50
—	10	Absolute alcohol (ethanol, dehydrated alcohol)	400.00

MANUFACTURING DIRECTIONS

See the directions for the 500-mg tablet.

Cisapride Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Cisapride	5.20
80.90	2	Lactose monohydrate	80.90
10.80	3	Starch (maize)	10.80
3.00	4	Povidone (PVP K-30)	3.00
0.15	5	Polysorbate 20 (Tween 20)	0.15
19.40	6	Microcrystalline cellulose (Avicel PH 102)	19.40
0.60	7	Magnesium stearate	0.60
—	8	Purified water	18.00

MANUFACTURING DIRECTIONS

Note: Avoid overmixing lubricants, otherwise hardness can be reduced.

1. Preparation of binding solution
   a. Dissolve Item 4 in 16.0 g of Item 8 (30°C), while mixing at slow speed by stirrer.
   b. Add Item 5 to 2.0 g of Item 8 (60 to 70°C). Stir manually with a spatula to make a clear solution.
   c. Add the previous step into Step 1. Mix manually.
2. Sieving and mixing
   a. Sift Items 1, 2, and 3 through a 500-µm sifter. Load into a mixer, and mix for 5 min at low speed.
3. Kneading
   a. Add the binding solution to the dry powders, while mixing at Speed I for 2 min. After the binding solution is added, mix further for 1 min, using the mixer and chopper at low speed. Scrape sides and blade. Check for satisfactory granules with little or no lumps.
   b. If required, add extra purified water, and record.
   c. Unload the granules into a stainless steel tray for drying.
4. Drying
   a. Dry the granules in an oven at 55°C for 10 h. After 4 h of drying, scrape the semidried granules to break the lumps for uniform drying.
   b. Check the LOD. The limit is 0.7 to 1.0%.
   c. Transfer the dried granules into stainless steel drums.
5. Grinding
   a. Pass the dried granules through a 1-mm sieve at medium speed. Collect in stainless steel drums.
   b. Load granules into the drum blender.
6. Lubrication
   a. Sift Item 6 through a 500-µm sieve using a sifter. Add to Step 2, in a drum blender. Mix for 5 min.
   b. Sift Item 7 through a 500-µm stainless steel sieve in sifter. Add 4- to 6-g granules in a polyethylene bag to sieve item. Mix manually for 1 min. Add to drum blender, and blend for 1 min.
   c. Unload in stainless steel drums.
7. Compression
   a. Compress the granules using a rotary tabletting machine with 7-mm round punches and a compression weight of 120 mg.

Citalopram Hydrobromide Tablets

Celexa™ (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. The molecular formula is $C_{20}H_{22}BrFN_2O$, and its molecular weight is 405.35. Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol. Celexa is a film-coated, oval-scored tablet containing citalopram HBr in strengths equivalent to a 20-mg or 40-mg citalopram base. The inactive ingredients are: copolyvidone, cornstarch, croscarmellose sodium, glycerin, lactose, monohydrate, magnesium stearate, hydroxypropyl methyl cellulose, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and iron oxides are used as coloring agents in the pink 20-mg tablets.

Clarithromycin Tablets (250 mg/500 mg)

Clarithromycin is a semisynthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96.

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. Biaxin is available as tablets and granules for oral suspension. Each yellow oval film-coated Biaxin tablet contains 250 mg or 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin. The 250-mg tablet also contains pregelatinized starch.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Clarithromycin[a]	256.00
80.90	2	Microcrystalline cellulose (Avicel PH 102)	80.90
8.00	3	Croscarmellose sodium (Ac-Di-Sol)	8.00
9.00	4	Povidone (PVP K-30)	9.00
1.10	5	Polysorbate 80 (Tween 80)	1.10
51.50	6	Microcrystalline cellulose (Avicel PH 102)	51.50
10.00	7	Croscarmellose sodium (Ac-Di-Sol)	10.00
22.00	8	Pregelatinized starch (starch 1500)	22.00
2.25	9	Magnesium stearate	2.25
4.50	10	Talc (fine powder)	4.50
3.00	11	Stearic acid	3.00
1.75	12	Colloidal silicon dioxide (Aerosil 200)	1.75
—	13	Alcohol (ethanol 95%)	88.00

[a] Clarithromycin 6.0 mg/tablet was added as an excess to compensate for the water content and assay of the material. The weight of clarithromycin is factored based on potency. The weight of microcrystalline cellulose (Avicel PH 101) is then adjusted to compensate for the factored potency of clarithromycin. Adjust the fill weight and formula for a 500-mg tablet.

MANUFACTURING DIRECTIONS

Precautions: Avoid the overmixing of lubricants, otherwise hardness can be reduced. Process the products in an explosion-proof area, with relative humidity of not more than 50%, and a room temperature of not more than 27°C.

1. Screen, if necessary, through an approximately 710-µm screen, the following: clarithromycin, croscarmellose sodium, microcrystalline cellulose (Avicel PH 101), and silicon dioxide. Blend together in suitable massing equipment.
2. Dissolve povidone in approximately 240 ml of ethanol — a complete solution must be achieved.
3. While mixing the blended powders from Step 1, add the povidone solution from Step 2.
4. Continue mixing to ensure an even distribution of the solution, and then add extra ethanol until a characteristic granule mass is obtained.
5. If necessary, pass the wet mass through a 3- to 4-mm screen. Dry at approximately 50 to 55°C until the LOD is not more than 3%.
6. Sift dried granule over a 1.4-mm (approximately) screen. Pass the oversized granules through a 1.7-mm (approximately) screen, using a suitable mill. Alternate screening and milling systems may be used to yield suitable sized granules.
7. Load a portion of the granule from Step 6 into a suitable blender. Add microcrystalline cellulose (Avicel PH 102) and croscarmellose sodium, blend, add talc, purify, and blend until uniform.
8. Mix together stearic acid and magnesium stearate with a small portion of granule. If necessary, pass through a 0.5-mm (approximate) screen.
9. Add the steps above, mix, then add the balance of granule. Mix until uniform.
10. Compress tablets to the following parameters: tablet weight 8.5 g/10 tablets ± 3%.
11. Coat using an HPMC coating solution.

Clenbuterol Tablets (20 mcg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.02	1	Clenbuterol hydrochloride	0.02
99.00	2	Ludipress	99.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components in a Turbula mixer, and press to tablets with a compression force of 20 kN.
2. Compress 100 mg in 8-mm punches.
3. If the content uniformity does not meet the requirements, prepare a premix of clenbuterol hydrochloride with a small part of the Ludipress before mixing with the other components of the tabletting mixture.

Clindamycin Tablets (20 mg)

Clindamycin hydrochloride is the hydrated hydrochloride salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(*S*)-chloro-substitution of the 7(*R*)-hydroxyl group of the parent compound lincomycin. Clindamycin hydrochloride capsules contain clindamycin hydrochloride equivalent to 150 mg of clindamycin. The inactive ingredients are cornstarch, FD&C Blue No. 1, FD&C Yellow No. 5, gelatin, lactose, magnesium stearate, talc, and titanium dioxide.

The chemical name for clindamycin hydrochloride is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidine-carboxamido)-1-thio-L-threo-*a*-*o*-galacto-octopyranoside monohydrochloride.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Clindamycin, use clindamycin hydrochloride	22.70
265.00	2	Lactose dihydrate	265.00
33.33	4	Starch (maize)	33.30
2.00	5	Hydroxypropyl cellulose (Klucel EF)	2.00
30.00	6	Calcium lactate. 5H20	30.00
41.00	7	Lactic acid	41.00
128.00	8	Microcrystalline cellulose (Avicel PH 102)	128.00
12.00	9	Kollidon CL	12.00
7.00	10	Aerosil 200	7.00

MANUFACTURING DIRECTIONS

1. Clindamycin HCl, lactose, one-half of the cornstarch, HPC, calcium lactate, and lactic acid are granulated in a fluidized-bed granulator.
2. The resulting granules and the remainder of the cornstarch, Kollidon, microcrystalline cellulose, magnesium stearate, and Aerosil are passed through a forced sieve (1.25 mm) and homogenized in a container mixture.
3. The resulting mixture is tabletted on a rotary tabletting machine.

Clobazam Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Clobazam	10.00
135.00	2	Dicalcium phosphate	135.00
7.00	3	Kollidon VA64	7.00
7.00	4	Kollidon CL	7.00
1.50	5	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force (15 kN).
2. Compress 165 mg in 8-mm biplanar punches.

Clomifen Citrate Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Clomifen citrate	50.00
100.00	2	Ludipress	100.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, sieve, and press with low-compression force.
2. Compress 154 mg in 8-mm biplanar punches.

Clomipramine Hydrochloride Tablets, Effervescent (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Clomipramine hydrochloride	300.00
1985.00	2	Sodium bicarbonate	1985.00
1000	3	Citric acid	1000

MANUFACTURING DIRECTIONS

1. The components (i.e., clomipramine hydrochloride, sodium bicarbonate, and citric acid, as set forth in the preceding table) are thoroughly mixed.

An effervescent tablet is produced by placing the mixture in a die, following with compression with an appropriate punch. Relatively little compression force is used (e.g., about 3000 to about 20,000 pounds of force).

Clomipramine Hydrochloride Tablets, Buccal (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Clomipramine hydrochloride	10.00
90.00	2	Gelatin	90.00
20.00	3	Glycerin, anhydrous	20.00
10.00	4	Lactose, anhydrous	10.00
20.00	5	Mannitol	20.00

MANUFACTURING DIRECTIONS

1. Clomipramine hydrochloride (10 g) and 90 g of gelatin are mixed and pulverized in a mill.
2. After the mixing is complete, 20 g of glycerin, 10 g of lactose, and 20 g of mannitol are added, and the components are mixed until uniform.
3. Compress 150 mg to provide a buccal dosage unit. Each buccal unit contains 10 mg of clomipramine hydrochloride.

Clonazepam Tablets (1 mg/2 mg)

Klonopin, a benzodiazepine, is available as scored tablets with a K-shaped perforation containing 0.5 mgf and 1 mg or 2 mg of clonazepam, and unscored tablets with a K-shaped perforation containing 1 mg or 2 mg of clonazepam. Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose, and cornstarch, with the following colorants: *0.5 mg:* FD&C Yellow No. 6 Lake; *1 mg:* FD&C Blue No. 1 Lake, and FD&C Blue No. 2 Lake.

Chemically, clonazepam is 5-(*o*-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light-yellow crystalline powder. It has a molecular weight of 315.72. The molecular formula is $C_{15}H_{10}ClN_3O_3$.

Clonidine Tablets (0.1 mg/0.2 mg/0.3 mg)

Clonidine hydrochloride USP is a centrally acting antihypertensive agent available as tablets for oral administration in three dosage strengths: 0.1 mg, 0.2 mg, and 0.3 mg. The 0.1-mg tablet is equivalent to 0.087 mg of the free base. The inactive ingredients in Catapres are colloidal silicon dioxide, cornstarch, dibasic calcium phosphate, FD&C Yellow No. 6, gelatin, glycerin, lactose, magnesium stearate, methylparaben, and propylparaben. The Catapres 0.1-mg tablet also contains FD&C Blue No. 1 and FD&C Red No. 3. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. It has the following molecular formula: $C_9H_9CI_2N_3 \cdot HCl$, with a molecular weight of 266.56. Clonidine hydrochloride is an odorless, bitter, white, crystalline substance that is soluble in water and alcohol.

Clopidogrel Bisulfate Tablets (75 mg)

Plavix (clopidogrel bisulfate) is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation, acting by direct inhibition of ADP binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically, it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$, and its molecular weight is 419.9.

Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but is freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as pink, round, biconvex, engraved film-coated tablets containing 97.875 mg of clopidogrel bisulfate, which is the molar equivalent of 75 mg of clopidogrel base. Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000, and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000, and titanium dioxide. The tablets are polished with carnauba wax.

Codeine, Acetaminophen, and Pentobarbital Tablets (15 mg/300 mg/30 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Codeine phosphate, 2.5% excess	15.375
300.00	2	Acetaminophen	300.00
30.00	3	Pentobarbital sodium, use pentobarbital	27.50
40.00	4	Calcium carbonate, precipitated	40.00
58.66	5	Lactose monohydrate	58.66
20.00	6	Povidone K 29-32	20.00
20.00	7	Starch (corn)	20.00
2.00	8	Polyethylene glycol, milled	2.00
0.066	9	Red dye	0.066
0.054	10	Yellow dye	0.054
0.018	11	Scarlet dye	0.018
25.79	14	Polacrillin potassium (Amberlite IRP-88)	25.79
10.40	15	Magnesium steareate	10.40

MANUFACTURING DIRECTIONS

1. Mixing
   a. Add codeine phosphate to acetaminophen in the presence of an authorized person.
   b. Pass Step A through a micropulverizer fitted with a 6.35-mm aperture or similar screen at high speed, with the hammers forward if the acetaminophen has a bulk density above 0.4 g/cc. After micropulverizing, the bulk density should be checked and should not exceed 0.4 g/cc. Add this to the mixer.
   c. Pass pentobarbital and calcium carbonate through an 840-µm aperture screen, and then add to the mixer.
   d. Add lactose, povidone, cornstarch, and polyethylene G 8000 NF (milled) to the mixer, and mix for 5 min.
   e. Dissolve the dyes in water, and add alcohol.
   f. Add the dye solution to the powders in the mixer, and mix until the color is evenly dispersed.
   g. Screen the wet granulation through a 9.52-mm aperture screen.
   h. Oven dry for 2 to 3 h at 43°C, or use a fluid-bed dryer at room temperature for 12 min or until the LOD is 1 to 2% (1 h at 105°C on an Ohaus, Brabender, or equivalent balance).
   i. Mill the dried granulation through a 1.2-mm aperture screen (Fitz mill or similar, medium speed, knives forward), and then add to a suitable mixer (V or similar).
   j. Pass the amberlite and magnesium stearate through a 595-µm aperture screen on a suitable shaker (Russel or similar), and add to the mixer (V or similar).
   k. Blend for 30 min.
   l. Discharge the blended material into polyethylene-lined containers. Seal and deliver this to the compression area.
2. Compression
   a. Compress on an 11.90-mm standard concave punch.
   b. The weight of 10 tablets is 5.2 g.

Conjugated Estrogens (0.3–2.50 mg)

Conjugated estrogens are a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 α-dihydroequilin, together with smaller amounts of 17 α-estradiol, equilenin, and 17 α-dihydroequilenin as salts of their sulfate esters. Tablets are available in 0.3-mg, 0.625-mg, 0.9-mg, 1.25-mg, and 2.5-mg strengths of conjugated estrogens. Premarin tablets contain the following inactive ingredients: calcium phosphate tribasic, calcium sulfate anhydrous (white tablet), calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, talc, and titanium dioxide. The 0.3-mg tablets also contain D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6. The 0.625-mg tablets also contain FD&C Blue No. 2, D&C Red No. 27, and FD&C Red No. 40. The 0.9-mg tablets also contain: D&C Red No. 6, D&C Red No. 7. The 1.25-mg tablets contain black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6. The 2.5-mg tablets contain: FD&C Blue No. 2 and D&C Red No. 7.

Conjugated Estrogens and Medroxyprogesterone Tablets

Prempro therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg or 5 mg of medroxyprogesterone acetate (MPA) for oral administration. Premphase therapy consists of two separate tablets: a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on Days 1 through 14, and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of MPA that is taken orally on Days 15 through 28. The conjugated equine estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate. They contain, as concomitant components, sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

MPA is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air that melts between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53.

- Prempro 2.5 mg — Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and red ferric oxide.
- Prempro 5 mg — Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens, 5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and FD&C Blue No. 2.
- Premphase — Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1. Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and FD&C Blue No. 2.

Coumadin Tablets

Coumadin tablets also contain (all strengths) — lactose, starch, and magnesium stearate; *1 mg:* D&C Red No. 6; *2 mg:* FD&C Blue No. 2 and FD&C Red No. 40; *2-1/2 mg:* FD&C Blue No. 1, and D&C Yellow No. 10; *4 mg:* FD&C Blue No. 1 Lake; *5 mg:* FD&C Yellow No. 6; *7-1/2 mg:* D&C Yellow No. 10, and FD&C Yellow No. 6; *10 mg:* dye free.

Cyclobenzaprine Hydrochloride Tablets (10 mg) [64]

Cyclobenzaprine HCl is a white, crystalline tricyclic amine salt, with the empirical formula $C_{20}H_{21}N{\cdot}HCl$ and a molecular weight of 311.9. It has a melting point of 217°C and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(5*H*-dibenzo[*a,d*]cycloheptene-5-ylidene)-*N*,*N*-dimethyl-1-propanamine hydrochloride. Cyclobenzaprine HCl is supplied as 10-mg tablets for oral administration. The inactive ingredients are hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Cyclobenzaprine	10.00
74.00	2	Lactose anhydrous	74.00
35.00	3	Starch (maize)	35.00
1.00	4	Magnesium stearate	1.00
25.00	5	Starch (maize)	25.00
—	6	Water, purified	30.00 ml

MANUFACTURING DIRECTIONS

1. Charge the active ingredient (cyclobenzaprine) and lactose in a suitable mixer.
2. Blend until a uniform mix is obtained.
3. Add Item 5 to Item 6 to make a paste.
4. Add Step 3 into Step 2 to form a suitable mass.
5. Add Item 3 to Step 4, and mix until granules are formed.
6. Screen granules through a suitable milling machine, using a 1/4-in. stainless steel screen.
7. Dry the milled granules in a suitable drying oven until the desired moisture of less than 2% is obtained.
8. Mill the dried granules through a suitable milling machine using a 1/4-in. mesh stainless steel screen, and transfer to a blender.
9. Add the magnesium stearate to the blender after passing through a 250-μm sieve. Then blend for 3 min.
10. Compress the tablets.
11. Coat the tablets using an aqueous or nonaqueous coating. (See Appendix.) For example, 2.5 mg of hydroxypropymethylcellulose can be dissolved in 25 mg of deionized water. An aqueous (10 mg) suspension of 1.88 mg of talc, 0.5 mg of titanium dioxide, 0.1 mg of yellow iron oxide, and 0.02 mg of red iron oxide is stirred into this solution. The coating suspension is sprayed on the tablets. The coated tablets are dried overnight at 45°C.

Cyproheptadine Tablets (4 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Cyproheptadine	4.00
194.00	2	Ludipress	194.00
2.00	3	Magnesium stearate	12.00

MANUFACTURING DIRECTIONS

1. Pass all ingredients through an 0.8-mm sieve.
2. Mix and press with very low-compression force (4 kN).
3. Compress 202 mg in 8-mm biplanar punches. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Dapsone Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Dapsone	50.00
80.00	2	Starch (maize)	80.00
50.00	3	Dicalcium phosphate	50.00
20.00	4	Lactose monohydrate	20.00
8.00	5	Starch (maize)	8.00
0.12	6	Methyl paraben	0.12
0.02	7	Propyl paraben	0.03
1.50	8	Talc	1.50
1.00	9	Magnesium stearate	1.00
—	10	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 4 in a suitable vessel, after passing them through a #40 mesh screen. Mix at medium speed for 15 min.
2. In a separate vessel, take a sufficient quantity of Item 10, and heat it to 80°C; add Items 5 and 6, and dissolve. Allow the mixture to cool to 50°C, and then add Item 7. Stir and mix this to obtain a smooth paste.
3. Add the wet mass in Step 2 to Step 1, and mix well. Pass the wet mass through an 8-mm screen, and collect on paper-lined trays.
4. Dry the wet mass at 50°C overnight to an LOD of not more than 2%.
5. Pass dried granules through an 18-mm sieve, and collect them in a tumble mixer.
6. Pass Item 8 through a 500-µm and Item 9 through a 250-µm sieve screen, and add to Step 5. Blend for 1 min.
7. Compress 200 mg using 8-mm round punches.

Desloratidine Tablets (5 mg)

Desloratadine is a white to off-white powder that is slightly soluble in water and very soluble in ethanol and propylene glycol. It has an empirical formula of $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*benzo[5,6]cyclohepta[1,2-*b*] pyridine. Clarinex® (desloratadine) tablets are light blue, round, film-coated tablets containing 5 mg of desloratadine, an antihistamine, to be administered orally. It also contains the following excipients: dibasic calcium phosphate dihydrate USP, microcrystalline cellulose NF, cornstarch NF, talc USP, carnauba wax NF, white wax NF, coating material consisting of lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and FD&C Blue # 2 Aluminum Lake.

Desogestrel and Ethinyl Estradiol Tablets (0.15 mg/0.03 mg)

Ortho-Cept 21 and Ortho-Cept 28 tablets provide an oral contraceptive regimen of 21 orange, round tablets, each containing 0.15 mg of desogestrel (13-ethyl-11-methylene-18,19-dinor-17 α-pregn-4-en-20-yn-17-ol) and 0.03 mg of ethinyl estradiol (19-nor-17 α-pregna-1,3,5(10)-trien-20-yne-3,17,diol). Inactive ingredients include vitamin E, cornstarch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc, and ferric oxide. Ortho-Cept 28 also contains seven green tablets containing the following inactive ingredients: lactose, pregelatinized starch, magnesium stearate, FD&C Blue No. 1 Aluminum Lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc.

Diazepam Tablets (2 mg/5 mg/10 mg)

Diazepam is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, is insoluble in water, and has a molecular weight of 284.74.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Diazepam	10.00
70.00	2	Potato starch	70.00
150.00	3	Lactose	150.00
1.50	4	Potato starch, cold swelling	1.50
0.076	5	Polysorbate 80	0.076
48.00	6	Microcrystalline cellulose	48.00
0.75	7	Magnesium stearate	0.75
QS	8	Talc, QS	300.00

MANUFACTURING DIRECTIONS

1. Granulation
   a. Weigh and mix for 10 min the potato starch, lactose, potato starch (cold swelling), and diazepam in a suitable mixer.
   b. Pass the mixture through a Fitz mill at high-speed impact forward.
   c. Separately dissolve polysorbate 80 in purified water.
   d. Wet the mixture from "Granulation" Step 1b with the solution from Step 1c, adding more water if necessary.
   e. Pass the wet mass through a Fitz mill sieve #24192, and dry in a drying oven at 35°C for 20 h.
   f. Pass the dried granulation through a Fitz mill.
   g. Separately pass through a Fitz mill sieve (0.3-mm screen) the following: microcrystalline cellulose, magnesium stearate, and talc.
   h. Add the granules from Step 1f, and mix for 15 min.
2. Compression
   a. Compress using round, flat punches with beveled edges and a break line on one side. Theoretical weight of 300 mg (290 to 310 mg); thickness 3.2 mm (range: 3.1 to 3.3 mm); diameter 9.5 mm (range 9.3 to 9.7 mm).

For 2-mg and 5-mg tablets, adjust fill weight accordingly; for larger tablet size, adjust proportionally with lactose and starch.

Diclofenac Sodium Tablets (25 mg)

Diclofenac, as the sodium or potassium salt, is a benzene acetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzene acetic acid, monosodium or monopotassium salt.

Diclofenac, as the sodium or potassium salt, is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. Molecular weights of the sodium and potassium salts are 318.14 and 334.25, respectively. It is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water, while diclofenac potassium is soluble in water. The noctanol/water partition coefficient is, for both diclofenac salts, 13.4 at pH 7.4 and 1545 at pH 5.2. Both salts have a single dissociation constant (pKa) of 4.0 + 0.2 at 25°C in water.

Diclofenac potassium is available as Cataflam® immediate-release tablets of 50 mg for oral administration.

Cataflam inactive ingredients include calcium phosphate, colloidal silicon dioxide, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, starch, sucrose, talc, and titanium dioxide.

Diclofenac sodium is available as Voltaren delayed-release (enteric-coated) tablets of 25 mg, 50 mg, and 75 mg for oral administration, as well as Voltaren-XR extended-release tablets of 100 mg.

Voltaren inactive ingredients are hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide, D&C Yellow No. 10 Aluminum Lake (25-mg tablet only), and FD&C Blue No. 1 Aluminum Lake (50-mg tablet only).

Voltaren-XR inactive ingredients are cetyl alcohol, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, polysorbate, povidone, silicon dioxide, sucrose, talc, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diclofenac sodium	25.00
85.00	2	Lactose, monohydrate	85.00
10.00	3	Sodium starch glycolate (pH 5.5–7.5)	10.00
3.00	4	Povidone (K 29-32)	3.00
3.00	5	Starch (corn)	3.00
58.00 ml	6	Alcohol isopropyl, anhydrous	58.00 ml
5.00	7	Sodium starch glycolate (pH 5.5–7.5)	5.00
1.50	8	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

1. Granulation
   a. Dry mix together the diclofenac sodium, lactose, sodium starch glycolate, and starch in a suitable planetary mixer for 10 to 15 min.
   b. Dissolve the povidone in 44 ml of alcohol, and ensure complete solution.
   c. While mixing, add povidone solution to Step 1a, and add the remaining alcohol to obtain suitable mass. Add an extra quantity of alcohol if required.
   d. Pass the wet mass through a #4 mesh (4.8-mm aperture) screen, and spread on paper-lined oven trays.
   e. Dry the granules at 40°C to an LOD of not more than 2% (3 h at 60°C under vacuum).
   f. Request samples.

   Note: The balance of manufacturing in the "Granulation" section should be done at not more than 45% relative humidity and at a temperature not exceeding 26.5°C.
   g. Mill the dried granule through a Fitz mill fitted with a 1.19-mm aperture screen at slow speed and with knives forward.
   h. Store the material in clean, polyethylene-lined containers that are sealed.
2. Lubrication
   a. Charge one-half of the screened granule from "Granulation" Step 1h into a suitable blender. Add sodium starch glycolate and magnesium stearate to the blender, and then add the balance of screened granule from "Granulation" Step 1h. Blend for 15 to 20 min.
   b. Store in clean, tared polyethylene-lined containers, and seal and weigh for yield.

3. Compression
   a. Compress on a suitable tablet machine equipped with a dedusting unit, using 1/4-in. diameter concave punches with both sides plain.
   b. The theoretical weight of 10 tablets is 1.325 g (range 1.295 to 1.355 g), with a thickness of 3.7 to 4.1 mm.
4. Coating
   a. Use a subcoat, an enteric color coat, and a finishing coat. (See Appendix.)

Diclofenac Sodium Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Diclofenac sodium	50.00
85.00	2	Lactose, monohydrate	85.00
15.00	3	Sodium starch glycolate (pH 5.5–7.5)	15.00
5.00	4	Povidone (K 29-32)	5.00
4.00	5	Starch (corn)	5.00
0.073 ml	6	Alcohol isopropyl, anhydrous refined	73.00 ml
7.00	7	Sodium starch glycolate (pH 5.5–7.5)	7.00
2.00	8	Magnesium stearate impalpable powder	2.00

MANUFACTURING DIRECTIONS

1. Follow the directions in the previous formulation. The theoretical weight of 10 tablets is 1.68 g (range: 1.64 to 1.72), with a thickness of 4.60 to 5.0 mm. Apply an enteric coat. (See Appendix.)

Diclofenac Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Diclofenac sodium	100.00
15.00	2	Eudragit® RSPN, 5% (methyl methacrylate copolymer)	15.00
6.00	3	Dibutyl phthalate (2%)	6.00
176.00	4	Dicalcium phosphate dihydrate	176.00
3.00	5	Magnesium stearate	3.00
—	6	Isopropyl alcohol	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1, 2, and 4 in a planetary blender, and mix for 10 min.
2. In a separate container, add Item 3 and Item 6 until homogenous. Add to Step 1 slowly to form loose aggregates of blend.
3. Pass the aggregates through a #8 mesh sieve onto paper-lined trays.
4. Dry the granules in a room with low humidity.
5. Pass the dried granules through a #20 mesh screen into a blending vessel.
6. Add Item 5 after passing through a 250-µm sieve to Step 5, and blend for 2 min.
7. Compress 300 mg in a suitable punch.
8. Coat using an enteric coating. (See Appendix.)

Didanosine Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Didanosine	50.00
17.00	2	Microcrystalline cellulose	17.00
2.10	3	Sodium starch glycolate	2.10
0.60	3	Magnesium stearate (for compaction)	0.60
0.40	4	Magnesium stearate (for tabletting)	0.30

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through a 250-µm mesh, mix well, and dry compress.
2. Pass granules through a large mesh and blend with Item 4. Finally, compress 70 mg in 8-mm punches.
3. Coat using Eudragit L-30D-55 coating solution. (See Appendix.)

Diethylcarbamazine Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Diethylcarbamazine citrate	102.00
100.00	2	Dicalcium phosphate	100.00
3.50	3	Gelatin	3.50
130.00	4	Lactose monohydrate	130.00
35.00	5	Starch (maize)	35.00
10.00	6	Talc	10.00
3.50	7	Magnesium stearate	3.50
—	8	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1, 2, and 4 through a 500-µm sieve, and charge them in a suitable blender. Blend for 5 min.
2. In a separate vessel, charge Items 3 and 5; add sufficient hot Item 8 to dissolve and disperse into a smooth slurry.
3. Add Step 2 into Step 1, make a suitable wet mass, and pass through a 2.38-mm sieve onto paper-lined trays. Dry overnight at 60°C to an LOD of not more than 2.5%.
4. Pass the dried granules through a #16 mesh sieve into a blending vessel.
5. Sift Items 6 and 7 through a 250-µm sieve, add to Step 4, and blend for 1 min.
6. Compress 350 mg into 9.7-mm punches.

Difenoxin and Atropine Tablets (0.5 mg/0.025 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.50	1	Difenoxin hydrochloride	0.50
0.025	2	Atropine sulfate	0.025
88.00	3	Lactose monohydrate	88.00
23.00	4	Starch (corn)	23.00
2.50	5	Starch (corn)	2.50
5.00	6	Talc	5.00
1.00	7	Magnesium stearate	1.00
—	8	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Blending
   a. Prepare a blend of lactose, starch (Item 4), and talc.
   b. Blend difenoxin hydrochloride and atropine sulfate with a small quantity of blend from Step 1a.
   c. Blend this premix with the remainder of Step 1. Pass through a #40 mesh (420-µm aperture or similar) screen.
   d. Slurry the starch (Item 5) in 5 ml of cold purified water. Add the slurry to 20 ml of boiling purified water.
   e. Mass blend with starch paste from Step 1d, adding more hot purified water, if necessary.
   f. Pass the mass through a #8 mesh (2.38-mm aperture or similar) screen.
   g. Dry the granules at 35°C (95°F) until the LOD is not greater than 5%.
   h. Screen the dried granules through a #20 mesh (840-µm aperture or similar) screen, and lubricate with magnesium stearate.
2. Compression
   a. Compress on a rotary tablet machine using 6.35-mm circular punches.

Digoxin Tablets (0.125 mg/0.25 mg) [92]

Digoxin is one of the cardiac (or digitalis) glycosides — a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence, "glycosides"). Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1,4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1,4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95. Digoxin exists as odorless, white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

Tablets — lanoxin is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin and the following inactive ingredients: corn and potato starches, lactose, and magnesium stearate. In addition, the dyes used in the 125-mcg (0.125-mg) tablets are D&C Yellow No. 10 and FD&C Yellow No. 6.

Diltiazem Hydrochloride Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
60.00	1	Diltiazem hydrochloride	60.00
100.00	2	Lactose monohydrates	100.00
66.00	3	Oil castor hydrogenated (Cutina HR)	66.00
20.00	4	Polyethylene glycol 8000, milled	20.00
0.06 ml	5	Alcohol isopropyl anhydrous	60.00 ml
4.00	6	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

1. Mill the castor oil hydrogenated through a #120 mesh (125-μm aperture) screen at medium speed with knives forward.
2. Charge milled castor oil hydrogenated from Step 1, lactose (Item 2), and diltiazem hydrochloride into a suitable planetary mixer and dry blend for 10 to 15 min.
3. Dissolve the polyethylene glycol in the isopropyl alcohol (warm to 40 to 45°C, if necessary).
4. Gradually add the warm solution from above Step 3 to powder blend, and mix until a suitable mass is obtained.
5. Pass the mass through a #4 mesh (4.8-mm aperture) screen, and spread on paper-lined oven trays.
6. Dry the granules at 45 to 50°C to an LOD of not more than 1% (at 60°C under vacuum for 3 h). Allow to cool.
7. Mill the dried granule through a #16 mesh (1.19-mm aperture) screen, with knives forward at medium speed. As an alternative, pass the dried granule through a 1.19-mm aperture screen fitted to an oscillating granulator.
8. Charge the screened granule into a suitable blender, add magnesium stearate, and blend for 5 to 10 min.
9. Compress on a suitable rotary machine, using 3/8-in. standard concave punches. The theoretical weight of 10 tablets is 250 mg/tablet, with hardness not less than 4 kPa.

Diltiazem Tablets 60 mg [95]

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem HCl is 1,5-benzothiazepin-4(5*H*)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-*cis*-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. *Cardizem direct-compression tablets:* Each tablet contains 30 mg, 60 mg, 90 mg, or 120 mg of diltiazem HCl. It also contains D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake (60 mg and 120 mg), or FD&C Blue No. 1 Aluminum Lake (30 mg and 90 mg), hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, microcrystalline cellulose, silicon dioxide, and other ingredients.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Diltiazem	60.00
141.00	2	Ludipress	141.00
5.00	3	Polyethylene glycol 6000 powder	5.00
1.00	4	Aerosil 200	1.00
1.00	5	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress 215 mg using 8-mm biplanar punches.

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets (2.5 mg/0.025 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Diphenoxylate hydrochloride	2.50
0.025	2	Atropine sulfate	0.025
11.40	3	Starch (maize)	11.40
54.00	4	Lactose monohydrate	54.00
2.50	5	Starch (maize)	2.50
0.60	6	Magnesium stearate	0.60
QS	7	Water, purified, ca	11.00

MANUFACTURING DIRECTIONS

1. Sieve Item 5 and disperse into 2.50 g of cold Item 7. Then add the balance of Item 7 at 70°C and heat to 80°C until completely gelatinized. Prepare a smooth slurry without lumps.
2. Leave the starch paste to cool to 40 to 50°C.
3. Sieve Item 4 and Item 3 through a 250-µm sieve. Load Items 1 and 2 into the mixer, and mix the items for 5 min at medium speed.
4. Add a starch paste cooled to 40 to 50°C, and mix for 3 min at slow speed until a satisfactory mass is obtained. Add extra Item 7 if required.
5. Spread the wet granules onto trays, and dry at 55°C for 12 h.
6. Pass the dried granules through a 1-mm sieve.
7. Sieve Item 6 through a 250-µm sieve, add to granules, and mix for 1 min.
8. Compress 71 mg in 5.5-mm punches.

Divalproate Sodium Tablets (125 mg) [121]

Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with a 0.5 equivalent of sodium hydroxide. Chemically, it is designated as sodium hydrogen *bis*(2-propylpentanoate).

Divalproex sodium occurs as a white powder with a characteristic odor.

Depakote tablets

Depakote tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg, or 500 mg of valproic acid. The inactive ingredients are cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains cornstarch), silica gel, talc, titanium dioxide, and vanillin.

In addition, individual tablets contain the following: *125-mg tablets:* FD&C Blue No. 1 and FD&C Red No. 40; *250-mg tablets:* FD&C Yellow No. 6 and iron oxide; and *500-mg tablets*: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.25	1	Povidone K 29-32	6.25
125.00	2	Valproic acid, use divalproex sodium	134.55
25.00	3	Cornstarch	25.00
6.25	4	Povidone K 29-32	6.25
35.00	5	Silicon dioxide	35.00
QS	6	Alcohol SD 3A 200 proof, ca	38 ml
7.50	7	Silicon dioxide	7.50

MANUFACTURING DIRECTIONS

CAUTION: Avoid inhaling or making skin contact with sodium hydrogen divalproate. Wear dust respirator and eye protection during the processing of granulating, lubricating, and compressing sections.

1. Granulation
   a. Dissolve the povidone (Item 1) in approximately 33 ml of alcohol.
   CAUTION: Sodium divalproate melts under excessive shear. Ensure adequate lubrication during the milling step.
   b. Cross-feed sodium hydrogen divalproate, pregelatinized starch, povidone (Item 4), and approximately one-half of the silicon dioxide (Item 5) through a comminuting mill, fitted with a 686-µm aperture screen at high speed, hammers forward. *Note:* To permit easy milling, it is advantageous to premix the sodium hydrogen divalproate with one-third of the silicon dioxide (Item 5) for 5 min in a suitable mixer before passing through the comminuting mill.
   c. Charge the milled materials from Step 2 and the remaining silicon dioxide (Item 5) into a suitable mixer. Blend for 5 to 10 min. Add povidone solution (Step 1a) to the contents of the mixer to obtain a suitable mass. The materials do not wet easily, but they overmass rapidly. If necessary, add extra alcohol, up to 15 ml. Another method, if using high-shear mixers is to charge the milled materials from Step 2 and the remaining silicon dioxide into the mixer bowl. Blend at fast mixer/fast chopper conditions for 2 min. Add the povidone solution (Step 1) over a period of 20 to 30 sec using fast mixer/fast chopper conditions. Discharge from the mixer at a motor current of 35 to 40 amps. If necessary, add extra alcohol, portion wise, up to 8 ml, allowing for sufficient time between additions to ensure that the motor current does not exceed 40 amps.
   d. Pass the wet mass through an oscillating granulator fitted with a 4.0-mm aperture screen and spread on paper-lined oven trays. As an alternative, pass the wet mass through a 9.53-mm aperture screen fitted to a comminuting mill, at slow speed, with knives forward, and spread on paper-lined oven trays. Dry at 49°C to an LOD of not more than 2% (3 h, 60°C, vacuum). *Note:* The balance of manufacturing in the "Granulation" section should be done at not more than 45% relative humidity and at temperatures of not more than 30°C.

e. Pass the dried granule through a 1.18-mm or 1.40-mm aperture screen fitted to an oscillating granulator, or screen the dry granules on a 1.4-mm aperture screen fitted to a suitable sieve shaker. Pass coarse granule through either a 1.18-mm or 1.40-mm aperture screen fitted to an oscillating granulator.

2. Lubrication
   Note: The balance of manufacturing in the "Lubrication" stage should be done at not more than 40% relative humidity and at not more than 30°C.
   a. Charge one-half of the screened granule from Granulation Step 1d into a suitable blender. Add the silicon dioxide (Item 7) via a 1.7-mm aperture screen to the blender followed by the balance of the screened granule from Granulation Step 1d.
   b. Blend for 20 min, ensuring that no pockets or agglomerations of lubricant silicon dioxide remain.
   c. Discharge into tared polythene-lined drums.
3. Compression
   Note: The balance of manufacturing in the "Compression" stage must be done at not more than 40% relative humidity and at not more than 26.5°C.
   a. Compress 215 mg per tablet using 6.24 × 11.90-mm punches. For higher-strength 250- and 500-mg tablets, use proportional amounts and larger-sized punches.
4. Coating
   a. Apply a PVP subcoat, an enteric opaque methocel coating, and a finishing coat. (See Appendix for details.)

Divalproex Sodium Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Valproic acid, use divalproex sodium, milled	538.20
80.00	2	Hydroxypropyl methylcellulose (Methocel K 15M), CR	80.00
180.00	3	Methyl cellulose (Methocel K100L), CR	180.00
121.80	4	Lactose, anhydrous	121.80
50.00	5	Microcrystalline cellulose (Avicel PH 101)	50.00
30.00	6	Colloidal silicon dioxide	30.00

Note: Item 3 can be replaced by Item 4. Note that this is a once-daily use formulation.

MANUFACTURING DIRECTIONS

1. Pass Item 1 through a #40-mesh sieve (0.42 mm nominal mesh opening, and charge in a suitable mixing vessel).
2. Pass Items 2 to 5 through a 250-μm mesh, add to Step 1, and mix for 20 min.
3. Add Item 6 to Step 2, and blend for an additional 5 min.
4. Compress 1000 mg in a suitable punch.

Doxazosin Mesylate Tablets (1 mg/2 mg/4 mg/8 mg) [112]

Doxazosin mesylate is a quinazoline compound that is a selective inhibitor of the α_1 subtype of α-adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$, and the molecular weight is 547.6. Cardura is freely soluble in dimethylsulfoxide; soluble in dimethylformamide; slightly soluble in methanol, ethanol, and water (0.8% at 25°C); and very slightly soluble in acetone and methylene chloride. Doxazosin mesylate is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange), and 8 mg (green) of doxazosin as the free base.

The inactive ingredients for all tablets are microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate, and sodium lauryl sulfate. The 2-mg tablet contains FD&C Yellow No. 10 and FD&C Yellow No. 6; the 4-mg tablet contains FD&C Yellow No. 6; the 8-mg tablet contains FD&C Blue No. 10 and FD&C Yellow No. 10.

Doxycycline Hydrochloride Tablets (100 mg) [91]

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. It is available as doxycycline monohydrate; doxycycline hyclate; doxycycline hydrochloride hemiethanolate hemihydrate; and doxycycline calcium for oral administration. It is also available as doxycycline hyclate for intravenous use as well as in coated hyclate pellets.

The molecular formula of doxycycline monohydrate is $C_{22}H_{24}N_2O_8 \cdot H_2O$, and it has a molecular weight of 462.46. The chemical designation for doxycycline is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$, and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients for the tablet formulation are ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, talc, titanium dioxide, and FD&C Yellow No. 6 Lake.

Inert ingredients for the coated pellets are lactose, NF; microcrystalline cellulose, NF; and povidone, USP. Each shell and band contains FD&C Blue No. 1; FD&C Yellow No. 6, D&C Yellow No. 10; gelatin, NF; silicon dioxide; sodium laurel sulfate, NF; and titanium dioxide, USP.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Doxycycline hydrochloride	100.00
40.00	2	Microcrystalline cellulose PH102	40.00
3.00	3	Aerosil 200	3.00
13.00	4	Sodium starch glycolate	13.00
1.75	5	Magnesium stearate	1.75
2.00	6	Talc	2.00

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 6 in a suitable blender after passing them through a #60 sieve.
2. Mix the items for 10 min.
3. Compress 160 mg in 12 × 5-mm punches.
4. Coat using HPMC coating. (See Appendix.)

Enalapril Maleate Tablets (2.5 mg/5 mg/10 mg/20 mg) [66]

Vasotec is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$. Enalapril maleate is a white to off-white crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol. Enalapril is a prodrug — following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin-converting enzyme inhibitor. Enalapril maleate is supplied as 2.5-mg, 5-mg, 10-mg, and 20-mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: lactose, magnesium stearate, starch, and other ingredients. The 2.5-mg, 10-mg, and 20-mg tablets also contain iron oxides.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Enalapril maleate	20.00
10.00	2	Sodium carbonate powder	10.00
146.72	3	Lactose hydrous powder	146.72
22.00	4	Starch (corn)	22.00
1.10	5	Magnesium stearate	1.10
0.050	6	Iron oxide red	0.050
0.130	7	Iron oxide yellow	0.130

MANUFACTURING DIRECTIONS

Note: Use goggles, and wear dust protection. Also, process under low-humidity conditions.

1. Granulation
   a. Mix the ingredients with the excipients in a planetary mixer. Pass through a Fitz mill equipped with a stainless steel screen, and remix in the planetary mixer. Wet the granulate with starch paste. Pass the wet mass through Fitz mill. Dry the granules in hot air, and pass the dried granules through a Fitz mill. Collect in polyethylene-lined containers.
2. Lubrication
   a. Transfer the dried, milled granules into the planetary mixer, and magnesium stearate, and mix. Collect in polyethylene-lined drums.
3. Compression
   a. Compress 200 mg in round punches.

Enalapril Maleate Tablets (10 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Enalapril maleate	20.00
5.00	2	Sodium carbonate powder	5.00
160.50	3	Lactose hydrous powder	160.50
22.00	4	Starch (corn)	22.00
1.10	5	Magnesium stearate	1.10
0.050	6	Iron oxide red	0.050

MANUFACTURING DIRECTIONS

Follow the instructions listed for the 20-mg strength.

Enoxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Enoxacin, use enoxacin sesquihydrate	434.00
80.00	2	Calcium carboxymethyl cellulose	80.00
6.00	3	Hydroxypropylmethyl cellulose	6.00
60.00	4	Cellulose microcrystalline (Avicel PH 101)	60.00
6.00	5	Silicon dioxide colloidal	6.00
14.00	6	Magnesium stearate	14.00
QS	7	Water, purified, ca	200 ml

MANUFACTURING DIRECTIONS

1. Granulation
   a. If necessary, mill the enoxacin using a comminuting mill fitted with a 3-mm screen, or sift through a 425-µm (40-mesh) screen.
   b. Load the Enoxacin and calcium carboxymethylcellulose into a suitable mixer, and blend for 10 min.
   c. Dissolve the hydroxypropyl cellulose in 200 ml of hot (80°C) water and allow to cool to below 40°C.
   d. Add the solution from Step 3 to the powder blend from Step 2. Mix to produce a satisfactory mass. If necessary, add more purified water.
   e. If necessary, pass the wet mass through a 4-mm screen, and load onto paper-lined trays.
   f. Dry at 55°C to give an LOD of 6.5 to 7.5% (140°C, 2 h).
   g. Pass the dried granulation through a 1.00-mm screen using a suitable granulator, adding the Avicel, silicon dioxide, colloidal, and magnesium stearate, simultaneously.
   h. Blend for 5 min in a suitable mixer.
2. Compression
   a. Compress using 16.00 × 8.00-mm ovaloid punches.
3. Coating
   a. Coat by using aqueous Methocel* coating. (See Appendix.)

Erythromycin Ethylsuccinate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Erythromycin, use erythromycin ethylsuccinate, citrate, washed[a]	470.58
200.00	2	Sucrose	200.00
200.00	3	Sodium citrate	200.00
50.00	4	Starch (maize)	50.00
2.50	5	Dye (optional)	2.50
—	6	Water, purified, ca	90.00
40.00	7	Polarcillin potassium (Amberlite IRP-88)	40.00
6.00	8	Magnesium stearate	6.00

[a] Adjust for potency; taken as 850 mcg/g for the amount given.

MANUFACTURING DIRECTIONS

CAUTION: Protect face and hands; relative humidity in the working area should not exceed 50%.

1. Granulation
   a. Pass the following items through a 0.5-mm aperture stainless steel screen: erythromycin ethylsuccinate, sucrose, sodium citrate, starch (maize), and dye (if used). Transfer the screened items to a suitable planetary mixer, and mix for 10 min.
   b. While mixing, add the purified water to the powders from Step 1 until a suitable mass is formed. If necessary, add more purified water to complete the granulation.
   c. Pass the wet mass from Granulation Step 1b through a suitable granulator fitted with a 2.0-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
   d. Dry the granules in an oven at 50°C until the LOD content is in the range of 1 to 1.5%.
   e. Pass the dried granules through a suitable granulator fitted with a 1.0-mm aperture screen. Collect the granules, and store in securely closed, double polyethylene-lined drums.
2. Lubrication
   a. Place into a suitable blender the dried, screened granules from Granulation Step 6.
   b. Pass the amberlite and magnesium stearate through a 0.5-mm aperture stainless steel screen. Add the screened powders to the blender.
   c. Blend for 10 min.
   d. Discharge the blended granules into double polyethylene-lined drums. Close securely, and store until ready for compression.
3. Compression
   a. Compress using 9×19-mm ovaloid punches. Compress 967 mg. If using dye, compress 969 mg per tablet.
4. Coating
   a. Apply a Methocel*, opaque methocel, and Celar glass Methocel* coatings. (See Appendix.)

Erythromycin Particle-Coated Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
150.00	1	Cellulose microcrystalline (Avicel PH 101)	150.00
12.00	2	Sodium starch glycolate	12.00
12.00	3	Hydroxypropyl cellulose	12.00
150.00	4	Lactose monohydrate powder	150.00
QS	5	Alcohol SD 3A 200 proof, ca	200 ml
333.00	6	Erythromycin, use erythromycin particle coated*	530.25
1.25	7	Stearic acid	1.25
1.25	8	Wax hydrogenated vegetable (Sterotex K)	1.25
1.25	9	Magnesium stearate powder	1.25
1.25	10	Silicon dioxide	1.25

Note: Adjust weight of erythromycin-coated particles to allow for variable potency: (333 × 1000)/potency = G required for 1000 tablets. Adjust the weight of cellulose and microcrystalline NF (7) to compensate for variable potency of erythromycin. The amount required is 770.75; the factor weight of Item 6 is G, required for 1000 tablets.

MANUFACTURING DIRECTIONS

CAUTION: Protect face and hands from erythromycin because some individuals may be sensitive, and reactions may occur. Take a shower after excessive exposure during manufacture.

1. Granulating
   a. Charge cellulose microcrystalline (Item 1), sodium starch glycolate, hydroxypropyl cellulose, and lactose into a suitable mixer. Mix for approximately 20 min.
   b. Granulate by adding approximately 200 ml of alcohol while mixing.
   c. Pass wet granulation through a 5/8-in. band in rotary granulator or a similar granulator.
   d. Spread on paper-lined trays, and dry at 49°C until reaching an LOD of not more than 2% (60°C, 3 h vacuum).
   e. Pass dried granulation through 1.2-mm aperture screen. Mill oversize material through a 1.2-mm screen, knives forward, medium speed using a Fitz mill.
   f. Charge into polyethylene-lined drums.
2. Lubricating
   a. Charge granulation from Granulation Step 1f into the blender.
   b. Add erythromycin-coated particles.
   c. Mix and mill approximately 12.5 g of cellulose microcrystalline (Item 7), stearic acid, hydrogenated vegetable oil wax, magnesium stearate, and colloidal silicon dioxide through 595-µm aperture screen, knives forward, at high speed, using a Fitz mill into a blender.
   d. Charge the balance of the cellulose microcrystalline (Item 7) into the blender, and blend for 10 min.
   e. Discharge into polyethylene-lined drums.
3. Compression
   a. Compress the product using ovaloid 8.6 × 18.9-mm punches.
   b. Do not grind tablets or rework culls. Use a compressing machine with a force feeder.
   c. The weight of 10 tablets was 11 g, the thickness was 7.7 to 8.6 mm, and the hardness was 18 to 25.
4. Coating
   a. Use the HPMC clear coating solution. (See Appendix.)

Erythromycin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Erythromycin, use erythromycin stearate (600 mcg/mg[a])	166.667
91.18	2	Sodium citrate dihydrate powder	91.180
3.287	3	Povidone K 29-32	3.287
11.51	4	Sodium carboxymethylcellulose, high viscosity	11.518
—	5	Alcohol denatured 200 proof	50.800 ml
8.68	6	Pollarcillin potassium (Amberlite IRP-88)	8.684

[a] Adjust for potency.

MANUFACTURING DIRECTIONS

See below.

Erythromycin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Erythromycin, use erythromycin stearate (600 mcg/mg[a])	166.66
100.00	2	Sodium citrate dihydrate powder	100.00
12.80	3	Povidone K 29-32	12.80
14.20	4	Sodium carboxymethylcellulose, high viscosity	14.20
—	5	Alcohol denatured 200 proof	50.80 ml

[a] Adjust for potency.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Sift the sodium citrate through a 600-µm aperture or similar screen.
   b. Charge the erythromycin stearate, sodium citrate, povidone, starch, and sodium carboxymethylcellulose into the mixer, and mix for 15 min.
   c. Gradually add sufficient alcohol, while mixing, to produce a suitable mass.
   d. Dry the granulation at 49°C to less than 1.5% LOD or 7% moisture by Karl Fisher.
   e. Sift the dried granulation through a 1.19-mm aperture screen, or similar, and mill the oversized material through a no. 2 (1.59-mm aperture, or similar) band on the Hammer mill (Fitz mill), or similar, at medium speed, knives forward, for 0 to 30 min.
   f. Load the granulation into the blender, add Amberlite IRP-88, if used, and blend for 20 to 30 min.
   g. Unload the contents of the blender into polyethylene-lined drums, and deliver to the compressing area.
2. Compression
   a. Compress using 9.5-mm standard concave punches. Fill to appropriate amount.

Erythromycin Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Erythromycin, use erythromycin stearate (630 mcg/mg[a])	794.00
146.00	2	Starch (corn)	146.00
16.00	3	Povidone K 29-32	16.00
104.00	4	Magnesium hydroxide	104.00
—	5	Alcohol SD 3A 200 proof	210–250 ml
26.00	6	Polacrillin potassium (Amberlite IRP-88)	26.00

Note: During the drying step of granulation, starch has a water loss equivalent to approximately 6.2% of its weight. This enables a theoretical reduction in tablet weight of 9 mg. This may, however, be offset by a loss of active ingredient during the manufacturing process.

[a] Do not use erythromycin stearate with a potency less than 610 mcg/mg. Calculate the actual quantity of erythromycin stearate. Do not factor in any ingredient to compensate for erythromycin stearate potency change.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Load the povidone, cornstarch, magnesium hydroxide, and approximately one-half of the erythromycin stearate into a suitable blender, and blend for 10 min. Add the balance of the erythromycin stearate, and blend for 15 min. *Note:* Proceed to Step 1d if only one wet granulation step is necessary.
   b. Empty the blender into tared, polyethylene-lined drums, and weigh for yield.
   c. Divide the blended powder into equal portions for massing. (The size of a massing "part" is predetermined from considering the capacity of the massing equipment.)
   d. Load preblended materials from Step 1b into the mixer.
   e. Wet granulation, conventional method:
      i. Add 210 ml of alcohol slowly over a period of 10 min, then mix for 5 min. If necessary, add additional alcohol (20 to 40 ml), and mix until a satisfactory mass is obtained. Do not overmix. Usually, 5 min of mixing after the final addition of alcohol is sufficient. Record the total amount of alcohol used. Proceed to dry as in Step 1g.
   f. Wet granulation, high-speed mixer method:
      i. Load preblended materials from Step 1c into the mixer, or if preblending is not required, load the povidone, cornstarch, magnesium hydroxide, and erythromycin stearate into the high-speed mixer, and mix for 3 min with the agitator at slow speed and the granulator at fast speed.
      ii. Add 150 ml of alcohol while mixing with the agitator at a slow speed and the granulator at a fast speed over a period of 2 min. Continue to mix for another 4 min, adding additional alcohol, if necessary, to obtain a satisfactory granulation.
   g. Spread the wet mass onto paper-lined trays. Commence the drying setup immediately after this step has been completed. Do not air dry.
   h. Load trays of granulation into a suitable drying oven, and dry at 50°C to 2 to 3.5% LOD, 3 h in vacuum oven at 60°C, under 5-mm Hg vacuum. Under no circumstances must the Karl Fischer test method be used. Other LOD tests may be used for process control, provided equivalence can be demonstrated to the quoted vacuum oven method.
   i. Alternative fluid-bed drying method:
      i. Charge granulate into fluid-bed dryer and dry at 40 to 45°C. *Note:* It is important not to dry the granulation below 2%. This loss is obtained after approximately 4 h drying for oven loads from 70 to 130 kg, dependent upon the amount loaded onto trays and the number of trays.
   j. Repeat Steps d through h if there is more than one part of blended powder from Step 1b.
   k. Allow the dried granule to cool, then screen through an 840-µm aperture screen using an oscillating granulator or through a 1.8-mm aperture screen using a comminuting mill with cutters forward at medium speed. Record the total weight of granulation.
   l. Request samples.
   m. Proceed to "Blending and Lubrication."

2. Lubrication
   a. If Amberlite is lumpy, screen through a 600-μm aperture screen before preblending.
   b. Preblend Amberlite with a small portion of the granule and the blend with approximately one-half of the bulk granule for 5 min.
   c. Add the balance of granule, and blend for a further 10 min.
   d. Empty the blender into tared, polyethylene-lined drums. Weigh.
3. Slugging (if required)
   a. Use a suitable compressing machine with either 19- or 12-mm flat punches.
      i. Compress the material into slugs having the following specifications: For 19 mm, weight 1.7 to 1.75 g and hardness 16 to 17; for 12 mm, weight 0.8 to 0.85 g and hardness 14 to 15.
      ii. The slugs should show no signs of lamination, capping, or surface melting and should break with a distinct snap.
      iii. Reduce slugs by passing slowly through a 0.107-in. (2.7-mm) perforated screen using cutters at medium speed.
      iv. After reduction, lubricate as above.
4. Compression
   Note: Precompression may be used to meet hardness specifications.
5. Coating
   a. Aqueous methocel. (See Appendix.)

Estazolam Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
1.00	1	Estazolam	1.00
120.65	2	Lactose monohydrate	120.65
8.37	3	Starch (maize)	8.37
3.78	4	Starch (maize)	3.78
QS	5	Water, purified	19.00 ml
1.20	6	Stearic acid	1.20

MANUFACTURING DIRECTIONS

CAUTION: Use a respirator and gloves throughout; shower after exposure.

1. Granulation
   a. Mix starch (Item 5) together with approximately 10 ml water in a glass or stainless steel vessel; avoid formation of lumps.
   b. Boil the remaining 18 ml of water, and add it to the mix from Step 1a, with continuous stirring until a gel is formed. Further heat may be necessary. A mix temperature of 95°C must be achieved before a gel is formed.
   c. Pass estazolam through a 0.7-mm aperture stainless steel screen.
   d. Pass through a 1.19-mm aperture stainless steel screen the lactose, starch (Item 3), and hydroxypropylcellulose into a suitable planetary mixer. Add screened estazolam, and mix for 10 min.
   e. Add the starch gel from Step 1b, and mix for 20 min or until a suitable mass is formed.
   f. Pass the wet mass through an oscillating granulator or similar, fitted with a 2.38-mm aperture stainless steel screen. Collect granules on paper-lined trays.
   g. Dry in an oven at 50°C until the LOD is less than 7%.
   h. Pass the dried granules through an oscillating granulator or a similar granulator, fitted with a 1.4-mm aperture stainless steel screen. Collect in a polyethylene-lined drum, and close securely.
2. Lubrication
   a. Place the dried granules into a suitable planetary or ribbon filter.
   b. Pass the starch (Item 7) and magnesium stearate through a 0.25-mm stainless steel screen and mix. Add this blend to the granules, and mix for 5 min. Transfer to polyethylene-lined drums.
3. Compression
   a. Compress in a suitable rotary machine using a 7-mm diameter beveled edged, with weight of 10 tablets at 1.2 g (1.17 to 1.23 G) and thickness of 2.35 mm ± 0.12 mm.

Estazolam Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.00	1	Estazolam	2.00
79.30	2	Lactose	79.30
24.30	3	Starch (maize), dried	27.10
2.40	4	Hydroxypropylcellulose	2.40
5.00	5	Starch (maize)	5.00
QS	6	Water, purified	28.00 ml
5.70	7	Starch (maize)	5.70
0.30	8	Magnesium stearate	0.30

MANUFACTURING DIRECTIONS

See directions for estazolam 1-mg formulation.

Estradiol Tablets (0.5 mg/1 mg/2 mg) [85]

Estrace tablets for oral administration contain 0.5, 1, or 2 mg of micronized estradiol per tablet. Estradiol (17β-estradiol) is a white, crystalline solid that is chemically described as estra-1,3,5(10)-triene-3,17β-diol. Its molecular formula is $C_{18}H_{24}O_2$, and its molecular weight is 272.39. Estrace 0.5-mg tablets contain the following inactive ingredients: acacia, dibasic calcium phosphate, lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc. Estrace 1-mg tablets contain the following inactive ingredients: acacia, D&C Red No. 27 Aluminum Lake, dibasic calcium phosphate, FD&C Blue No. 1 Aluminum Lake, lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc. Estrace 2-mg tablets contain the following inactive ingredients: acacia, dibasic calcium phosphate, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 (tartrazine) (Aluminum Lake), lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc.

Estropipate Tablets (0.626 mg/1.25 mg/2.25 mg/5 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.626	1	Estropipate, 25% excess	0.769
157.02	2	Lactose monohydrate	157.02
1.00	3	Yellow dye	1.00
0.007	4	Yellow dye	0.007
1.00	5	Dibasic potassium phosphate, anhydrous	1.00
1.20	6	TRIS (tromethamine)	1.20
7.00	7	Hydroxypropyl cellulose	7.00
10.00	8	Sodium starch glycolate	10.00
40.00	9	Cellulose microcrystalline	40.00
QS	10	Water, purified	QS
QS	11	Alcohol SD 3A 200 proof	QS
0.50	12	Colloidal silicon dioxide	0.50
1.25	13	Magnesium stearate	1.25
1.25	14	Wax, hydrogenated vegetable oil (Sterotex K)	1.5

Note: For 1.25-mg, 2.25-mg, and 5.0-mg tablets, adjust with Item 2 and modify dyes.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Charge lactose cellulose microcrystalline, hydroxypropyl cellulose, dyes, or dye into mixer, and blend powders. If necessary, screen or mill powders to break up agglomerates. A portion of the cellulose microcrystalline may be added at the lubrication step.
   b. Dissolve the dibasic potassium phosphate in purified water. Use this solution to granulate powders in, Step 1a.
   c. Size wet granulation and dry, pass through screen and mill.
   d. Dissolve tromethamine and estropipate in water or alcohol.
   e. Charge granulation from Step 1c and sodium starch glycolate into mixer, and mass with Step 1d. Size wet granulation and dry. Pass the dried granulation through screen and mill.
2. Lubrication
   a. Charge the portion of the dried granulation into the blender.
   b. Screen colloidal silicon dioxide, magnesium stearate, and hydrogenated vegetable oil wax, and charge into blender.
   c. Charge remainder of dried granulation into blender, and blend.
3. Compression
   a. Compress using a rotary machine using oval tooling. The theoretical weight is 221 mg.

Ethambutol Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Ethambutol hydrochloride	400.000
5.60	2	Silicon dioxide colloidal	5.600
68.00	3	Starch (corn) NF[a]	76.800
33.50	4	Mannitol	33.600
22.40	5	Starch (corn)	22.400
11.20	6	Corn oil hydrogenated	11.200
8.00	7	Magnesium stearate	8.000
11.20	8	Talc powder	11.200
QS	9	Water, purified	80.000

[a] The quantity of starch (corn) is based on a moisture content of 13% w/w. If the moisture content varies outside this range of 12.5 to 13.5%, then the amount used should be factored accordingly.

MANUFACTURING DIRECTIONS

1. Massing
   a. Mix starch (Item 5) with approximately 27.3 ml of purified water (Item 9) in a glass or stainless steel vessel, avoiding the formation of lumps.
   b. Boil the remaining 52.8 ml of purified water (Item 9), and add the mix from Step 1a with continuous stirring until a gel is formed. Further heat may be necessary. *Note:* A mix temperature greater than 95°C must be exceeded before a gel is formed.
   c. Mill the ethambutol through a 1.59-mm aperture screen at medium speed with knives forward, then charge into a suitable mixer.
   d. Pass silicon dioxide, starch (corn) (Item 3), and mannitol through a 1.00-mm aperture stainless steel screen, and add to the mixer. Mix at 60 r/min for 10 min.
   e. Pass the mixed powders from Step 1d through a 1-mm aperture stainless steel screen, and return to the mixer.
   f. Add, in one charge, the starch gel from Step 1b at 70 to 80°C, and mix for 5 min at 60 r/min.
   g. Stop the mixer, and inspect the mass. Add the extra 6.88 ml of purified water (Item 10) at 50°C to complete the granulation while mixing. Mix for a further 5 min at 60 r/min.
2. Drying/granulation: Proceed to Step 2a or 2b.
   a. Oven drying
      i. Pass the wet mass through an A granulator fitted with a 4.76-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
      ii. Dry the granules in a hot-air oven at 50°C, turning over the granules every half hour. After 1 h of drying, pass the granules through an A granulator fitted with a 2.38-mm aperture stainless steel screen. Collect the granules on paper-lined trays, and return to the hot-air oven at 50°C.
   b. Fluid-bed drying
      i. Pass the wet mass through an A granulator fitted with a 4.76-mm aperture stainless steel screen into the fluid-bed drier bowl.
      ii. Dry the granules in the fluid-bed drier at 50°C for 30 min, turning over after 15 min. Then, pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen, and return to the fluid-bed drier bowl with the air inlet and outlet fully open. Proceed to Step 3.
   c. Continue drying the granules while turning them over every 30 min until the LOD is between 1.5 to 2%.
   d. Pass the dried granules through an A granulator fitted with a 1-mm aperture stainless steel screen. Collect the granules in a polyethylene-lined drum, and close securely.
   e. Request samples.
3. Lubrication
   a. Place the dried granules from "Drying/granulation" Step 2d in a suitable blender.
   b. Add oil castor hydrogenated, magnesium stearate, and talc via a 0.6-mm aperture stainless steel screen, and mix for 25 min.
   c. Transfer to a polyethylene-lined drum, and close securely until ready for compression.

4. Compression
   a. Compress on a suitable tablet machine using ovaloid punches that are 15.5 × 7.7 mm or 14.6 × 7.8 mm, where the weight of 10 tablets is 5.6 g, hardness is more than 5, and the disintegration time is not more than 15 min. If using a coating, move to the next step.
5. Coating
   a. Use an HPMC methylene chloride coating. (See Appendix.)

Ethambutol Tablets (800 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
800.00	1	Ethambutol	800.00
200.00	2	Dicalcium phosphate (Di-Tab)	100.00
30.00	3	Kollidon 30	30.00
—	4	Isopropyl alcohol	QS
50.00	5	Kollidon CL	50.00
15.00	6	Magnesium stearate	15.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4. Dry, pass through a 0.8-mm sieve, add Items 5 and 6, and press with high-compression force.
2. Compress 1.112 g in 20-mm oblong punches.

Etophylline and Theophylline Tablets (100 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Etophylline powder (Knoll)	101.00
22.00	2	Theophylline, anhydrous	23.00
53.00	3	Ludipress	53.00
1.00	4	Magnesium stearate	1.00
2.00	5	Aerosil 200	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press into tablets with low-compression force.
2. Compress 175 mg in 8-mm biplanar punches. To enhance the flowability of the tabletting mixture, the amount of Aerosil 200 can be increased.

Etophylline and Theophylline Tablets (100 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Etophylline powder (Knoll)	100.00
22.00	2	Theophylline, anhydrous	23.00
50.00	3	Starch (maize)	50.00
3.00	4	Kollidon VA 64	3.00
4.00	5	Kollidon VA 64	4.00
—	6	Water, purified, ca	35.00
1.00	7	Magnesium stearate	1.00
5.00	8	Talc	5.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 to 4 with solution of Items 5 and 6. Pass through a 0.8-mm sieve, dry, mix with Items 7 and 8, pass through a 0.5-mm sieve, and press with medium-compression force.
2. Compress 183 mg in 8-mm biplanar punches.

Famciclovir Tablets (125 mg/250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
125.00	1	Famciclovir	125.00
165.00	2	Microcrystalline cellulose (Avicel) QS	165.00
4.00	3	Sodium starch glycolate (Primojel®)	4.00
0.50	4	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

1. Sift Famciclovir, Avicel, and sodium starch glycolate through a 250-µm sieve into a mixer. Mix for 5 min.
2. Sift magnesium stearate through a 250-µm sieve, and add to Step 1. Blend for 3 min.
3. Compress 295 mg in a suitable punch. For 250-mg strength, compress 590 mg.
4. Coat using a hypermellose coating. (See Appendix.)

Famotidine Tablets (20 mg) [146]

The active ingredient in Pepcid® is an histamine H2-receptor antagonist. Famotidine is N′-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$. Its molecular weight is 337.43.

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine. The inactive ingredients are hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide.

Each Pepcid RPD orally disintegrating tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: aspartame, mint flavor, gelatin, mannitol, red ferric oxide, and xanthan gum.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Famotidine	20.00
80.00	2	Microcrystalline cellulose (Avicel PH 102)	80.00
67.60	3	Pregelatinized starch (Starch 1500)	67.60
2.00	4	Povidone (PVP K-25)	2.00
—	5	Alcohol (ethanol 95%)	36.67
22.80	6	Microcrystalline cellulose (Avicel PH 102)	22.80
8.16	7	Pregelatinized starch (starch 1500)	8.16
2.00	8	Glyceryl behenate	2.00
2.41	9	Talc (fine powder)	2.41

MANUFACTURING DIRECTIONS

1. Preparation of binding solution
   a. Dissolve Item 4 in Item 5 to make a clear solution by using a stirrer at medium speed in a stainless steel container.
2. Dry mixing
   a. Load Items 1, 2, and 3 into a mixer. Mix for 5 min with a mixer and chopper at low speed.
3. Wet massing
   a. Add the binding solution at a rate of 8.3 g/min to the dry powder in the mixer, while mixing at low speed. Mix and chop for a further 2 to 3 min at low speed.
   b. Check for a satisfactory wet mass. Add additional ethanol 95% if required to get a satisfactory wet mass.
4. Drying
   a. Spread the granules onto stainless steel trays to a thickness of one-quarter of the tray thickness. Load the trays on the trolley.
   b. Load the trolleys to the oven. Keep the doors open. Start the air circulation, heaters off, for 2 h.
   c. Start the heaters of the dryer. Close the doors. Set the temperature at 55°C for 6 h.
   d. Check the moisture contents of the dried granules (limit: not more than 3.5%). Dry further, if required, to get a moisture content of 3.5%.
5. Grinding
   a. Pass the dried granules through a sifter using a 1250-µm sieve. Pass the retained granules through a granulater equipped with a 1.0-mm sieve.
6. Lubrication
   a. Pass Items 6 and 7 through a 500-µm sieve using a sifter. Collect in a stainless steel container.
   b. Load the sized granules from Step 5a, along with sieved powder from Lubrication, Step 6a, into the blender. Blend for 3 min.
   c. Mix Items 8 and 9 in a polythene bag for 1 min. Pass this mixture through a 250-µm sieve into the sifter. Collect in a polythene bag. Add 3 to 5 g granules from Lubrication, Step 6b to it, and mix manually for 1 min. Add this mixture to Lubrication, Step 6b, and mix for 1 min.
   d. Unload in stainless steel drums.
7. Compression
   a. Compress the granules using a rotary tabletting machine. The dimension is 7.1 mm ± 0.1 mm concave plain. The weight of 10 tablets is 2.05 gm ± 2%,
8. Tablet coating
   a. Coat the tablet using an HPMC coating. (See Appendix)

Famotidine Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
40.00	1	Famotidine	40.00
70.50	2	Microcrystalline cellulose (Avicel PH 102)	70.50
67.60	3	Pregelatinized starch (Starch 1500)	67.60
0.09	4	Ferric oxide (iron oxide red)	0.09
2.50	5	Povidone (PVP K-25)	2.50
—	6	Alcohol (ethanol 95%)	36.67
11.16	7	Microcrystalline cellulose (Avicel PH 102)	11.16
8.66	8	Pregelatinized starch (Starch 1500)	8.66
2.00	9	Glyceryl behenate	2.00
2.41	10	Talc (Fine powder)	2.41

MANUFACTURING DIRECTIONS

See the directions for the 20-mg formulation.

Fexofenadine Tablets (30 mg/60 mg/180 mg) [26]

Fexofenadine HCl is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-l-piperidinyl]butyl]-α,α-dimethyl benzeneacetic acid hydrochloride. The molecular weight is 538.13, and the empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$. Fexofenadine HCl is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine HCl is a racemate and exists as a zwitterion in aqueous media at a physiological pH.

Each tablet contains 30, 60, or 180 mg of fexofenadine hydrochloride (depending on the dosage strength) and the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The aqueous tablet film coating is made from hydroxypropyl methylcellulose, iron oxide blends, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide.

Fexofenadine and Pseudoephedrine Tablets (10 mg/240 mg) [111]

Allegra-D® (fexofenadine HCl and pseudoephedrine HCl) extended-release tablets for oral administration contain 60 mg of fexofenadine HCl for immediate release and 120 mg of pseudoephedrine HCl for extended release. Tablets also contain the following excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, carnauba wax, stearic acid, silicon dioxide, hydroxypropyl methylcellulose, and polyethylene glycol. Fexofenadine HCl is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride. The molecular weight is 538.13. The empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$. Fexofenadine HCl is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine HCl is a racemate and exists as a zwitterion in aqueous media at physiological pH. Pseudoephedrine HCl is an adrenergic (vasoconstrictor) agent with the chemical name [*S*-(*R**,*R**)]-α-[1-(methylamino)ethyl]-benzenemethanol HCl. The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO \cdot HCl$. Pseudoephedrine HCl occurs as fine, white to off-white crystals or powder, having a faint, characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
240.00	1	Pseudoephedrine sulfate	240.00
15.00	2	Microcrystalline cellulose (Avicel PH 101)	15.00
200.00	3	Xanthan gum Keltrol TF	200.00
80.00	4	Sodium alginate keltone HVCR	80.00
53.00	5	Calcium carbonate	53.00
6.00	6	Magnesium stearate	6.00
6.00	7	Aerosil 200	6.00
10.00	8	Fexofenadine	10.00
95.00	9	Lactose monohydrate	95.00
66.50	10	Microcrystalline cellulose (Avicel PH 101)	66.50
1.00	11	Yellow FD&C No. 10	1.00
20.00	12	Starch (maize)	20.00
6.00	13	Starch (maize)	6.00
1.50	14	Magnesium stearate	1.50
—	15	Water, purified	60.00

MANUFACTURING DIRECTIONS

1. Charge pseudoephedrine sulfate, microcrystalline cellulose, xanthan gum, sodium alginate, calcium carbonate, and one-half of the lubricants in a suitable mixer, after sieving through a #44 sieve.
2. Pass the blend through a roll-compactor.
3. Sieve the compact through a #22 sieve to obtain granules.
4. Mix the granules with the remaining lubricants (Items 6 and 7), and compress into tablets (600 mg) to form the first tablet layer.
5. Charge Items 8 to 12 after passing through a #100 sieve in a suitable mixer. Blend for 10 min.
6. Charge Item 13 in a separate vessel, and make a paste (10%) using Item 14.
7. Add Step 6 into Step 5, and granulate.
8. Dry the granules, and blend the sifted Item 14.
9. Compress 200 mg in tablets (the second layer).
10. Use appropriate tabletting equipment for bilayer tabletting or core tabletting.

Finasteride Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Finasteride	5.00
56.70	2	Lactose monohydrate	56.70
5.00	3	Starch 1500 (pregelatinized starch)	5.00
20.00	4	Avicel PH 102 (microcrystalline cellulose)	20.00
27.00	5	Maize starch	27.00
5.50	6	Primojel (sodium starch glycolate)	5.50
0.60	7	Magnesium stearate	0.60
3.50	8	Hypromellose (hydroxypropyl methylcellulose)	3.50
0.60	9	Talc, fine powder, extra pure	0.60
0.60	10	Titanium dioxide	0.60
—	11	Purified water	QS
0.20	12	Disperse blue E132	0.20
0.10	13	Triacetin	0.10
—	14	Ethanol 95%	QS
—	15	Purified water	QS

MANUFACTURING DIRECTIONS

1. Make a slurry of starch paste in purified water.
2. Mix finasteride, maize starch, and Primojel.
3. Add lactose monohydrate with Step 2, and pass through a 0.5-mm sieve.
4. Knead the mixed powder from Steps 2 and 3 with starch paste to make a suitable wet mass. Pass the wet mass through a #8 sieve onto drying trays.
5. Dry the granules for approximately 3.5 h at 55°C to get the desired LOD of 2.5%.
6. Grind the dried granules from Step 5, and blend with magnesium stearate, previously sieved (250 μm) in a drum blender. Blend for 2 min.
7. Lubricate the granules.
8. Compress 120 mg in a suitable punch.
9. Disperse hypromellose and triacetin in purified water and ethanol. Keep it overnight. Disperse talc, titanium dioxide, and colorant, and homogenize.
10. Coat the core tablets with the coating dispersion in Step 9. (See Appendix.)

Fluconazole Tablets (50 mg/100 mg/200 mg) [75]

Diflucan (fluconazole), the first of a new subclass of synthetic triazole antifungal agents, is available in tablet form for oral administration, as powder form for oral suspension, and in a sterile solution form for intravenous use, in glass, and in Viaflex® Plus plastic containers.

Fluconazole is designated chemically as 2,4-difluoro-α,α¹-*bis*(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and a molecular weight of 306.3.

Fluconazole is a white crystalline solid that is slightly soluble in water and saline.

Diflucan tablets: These tablets contain 50, 100, or 200 mg of fluconazole and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone, croscarmellose sodium, FD&C Red No. 40 Aluminum Lake dye, and magnesium stearate.

Fluvoxamine Maleate Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Fluvoxamine maleate	50.00
96.00	2	Mannitol	96.00
39.00	3	Maize starch	39.00
12.00	4	Pregelatinized starch (Starch 1500)	12.00
0.60	5	Colloidal silicone dioxide (Aerosil 200)	0.60
1.50	6	Sodium stearyl fumarate	1.50
QS	7	Purified water	QS

MANUFACTURING DIRECTIONS

1. Make s slurry of starch paste in purified water.
2. Sift mannitol, fluvoxamine maleate, and the remaining part of maize starch through a 0.5-mm stainless steel sieve.
3. Knead the powder mix from Step 2 with starch paste to get the desired wet mass. Then pass the mass through a #8 mesh to drying trays.
4. Dry at 50°C for 24 h to reach an LOD of not more than 2%.
5. Pass the dried granules through a #16 mesh into a blending vessel.
6. Pass Starch 1500, Aerosil 200, and sodium stearyl fumarate through a 0.25-mm sieve into Step 5. Blend for 2 min.
7. Compress 200 mg in 12-mm punches.
8. Apply Eudragit L 100-55 coating. (See Appendix.)

Fluoxetine Hydrochloride Tablets (10 mg/20 mg/40 mg) [33]

Fluoxetine HCl is an antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated as (±)-*N*-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)-oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/ml in water. Each Prozac® pulvule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 mcmol), 20 mg (64.7 mcmol), or 40 mg (129.3 μmol) of fluoxetine. The pulvules also contain starch, gelatin, silicone, titanium dioxide, iron dioxide, and other inactive ingredients. The 10-mg and 20-mg pulvules also contain FD&C Blue No. 1, and the 40-mg pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

Each Prozac tablet contains fluoxetine HCl equivalent to 10 mg (32.3 μmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the preceding ingredients, the 10-mg tablet contains FD&C Blue No. 1 Aluminum Lake and polysorbate 80.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Fluoxetine, use paroxetine hydrochloride	11.45
20.00	2	Microcrystalline cellulose	20.00
64.05	3	Lactose	64.05
4.00	4	Sodium starch glycolate	4.00
0.50	5	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

1. Charge Items 1–4 in a suitable blender, after passing through a 250-μm sieve.
2. Mix for 20 min.
3. Add Item 5 after passing through a 250-μm mesh, and blend for 1 min.
4. Compress.
5. Coat using HPMC coating, adding 6 to 10% tablet weight.
6. For a controlled-release formulation, use 5 to 12% of tablet core weight)%w/w of Eudragit RS 100 and 86.0; dibutyl phthalate 10.0; talc 4.0; FD&C Yellow No. 6 0.01; and triacetin 10.

Fluoxetine Hydrochloride Tablets (12.5 mg/25.0 mg) Controlled-Release Bilayer

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Fluoxetine, use paroxetine hydrochloride	28.59
15.00	2	Methocel K4M	15.00
62.00	3	Lactose monohydrate	62.00
3.00	4	Polyvinyl pyrrolidone	3.00
1.00	5	Magnesium stearate	1.00
1.00	6	Syloid 244	1.00
15.04	7	Compritol 888	15.04
29.32	8	Lactose monohydrate	29.32
4.00	9	Polyvinyl pyrrolidone	4.00
1.52	10	Magnesium stearate	1.52
—	11	Water, purified	QS
29.32	12	Methocel E5	29.32
0.08	13	Iron oxide	0.08

MANUFACTURING DIRECTIONS

1. Two layers are made (Items 1 to 6 and Items 7 to 10, using Item 11 as necessary for wet granulation).
2. Compress tablets on a Manesty triple-layer press.
3. Coat using Items 12 and 13 on a Manesty triple-layer press.
4. Adjust Item 3 for 12.5-mg strength.

Fosinopril Tablets (20 mg) [133]

Fosinopril sodium is the sodium salt of fosinopril, the ester prodrug of an angiotensin-converting enzyme (ACE) inhibitor, fosinoprilat. It contains a phosphinate group capable of specific binding to the active site of the ACE. Fosinopril sodium is designated chemically as L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxyl](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, *trans*-. Fosinopril sodium is a white to off-white crystalline powder. It is soluble in water (100 mg/ml), methanol, and ethanol, and is slightly soluble in hexane. Its empirical formula is $C_{30}H_{45}NNaO_7P$, and its molecular weight is 585.65. Monopril is available for oral administration as 10-mg, 20-mg, and 40-mg tablets. Inactive ingredients include lactose, microcrystalline cellulose, crospovidone, povidone, and sodium stearyl fumarate.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Fosinopril sodium	20.00
134.50	2	Lactose monohydrate	134.50
40.00	3	Microcrystalline cellulose (Avicel PH 102)	40.00
7.00	4	Crospovidone	7.00
4.50	5	Povidone	4.50
4.00	6	Sodium stearyl fumarate	4.00
—	7	Alcohol	QS

Note: For 10- and 40-mg strength, adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 2 in a suitable mixer, after sifting, and mix for 20 min.
2. In a separate vessel, charge Item 5 with a suitable quantity of Item 7, and make a binder solution.
3. Add Step 2 into Step 1 to make a wet mass.
4. Dry the mass at 45 to 70°C in a tray oven or a fluid-bed dryer, until the LOD is less than 3%.
5. Pass the dried granules through a hammer mill fitted with 0.03 to 0.07 in screen.
6. Transfer screened granules into a suitable blender, add Items 3 and 4, and blend for 1 to 3 min.
7. Compress into 200-mg tablets.

Fucidine Tablets (125 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
125.00	1	Fucidine	125.00
63.00	2	Dicalcium phosphate (Di-Tab)	63.00
2.50	3	Kollidon 90 C	2.50
—	4	Isopropyl alcohol	30 ml
6.20	5	Kollidon CL	6.20
1.30	6	Aerosil 200	1.30
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4. Dry, and then pass the mixture through a 0.8-mm sieve.
2. Add the mixture of Items 5 and 6, and press with low-compression force.
3. Compress 200 mg using 9-mm punches. To accelerate the disintegration, the amount of Kollidon 90 F should be reduced, and Kollidon CL should be applied in intra- and extragranular forms.

Furazolidone Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Furazolidone	104.00
40.00	2	Lactose monohydrate	40.00
40.00	3	Dicalcium phosphate	30.00
2.00	4	Gelatin	2.00
2.00	5	Talc	2.00
2.00	6	Magnesium stearate	2.00
20.00	7	Starch (maize)	10.00
QS	9	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 3 through a 250-µm sieve, and charge into a suitable mixing vessel. Mix the items for 5 min.
2. Separately, charge a sufficient quantity of Item 9. Add Item 4, and dissolve it at 50°C. Add Item 7, and mix until a smooth slurry is formed.
3. Add Step 2 into Step 1, and mix to form a wet mass suitable for granulation. Pass the mass through the sieve onto paper-lined trays, and dry at 60°C overnight to reach an LOD of not more than 2%.
4. Pass the dried granules through 1.19-mm mesh into a suitable blending vessel.
5. Sift Items 5 and 6 through a 500-µm sieve, and blend for 2 min.
6. Compress 200 mg in 8.3-mm punches.

Furosemide Tablets (40 mg) [7]

Lasix is a diuretic that is an anthranilic acid derivative. Lasix for oral administration contains furosemide as the active ingredient. It also contains the following inactive ingredients: lactose, magnesium stearate, starch, and talc. Chemically, it is 4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid. Furosemide is available as white tablets for oral administration in dosage strengths of 20, 40, and 80 mg. Furosemide is a white to off-white odorless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions, and insoluble in dilute acids.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
40.00	1	Furosemide	40.00
158.00	2	Ludipress	158.00
2.00	3	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 205 mg in 8-mm biplanar punches.

Furosemide Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
40.00	1	Furosemide	40.00
83.10	2	Starch (maize)	83.10
30.00	3	Lactose monohydrate	30.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
14.00	5	Starch (maize)	14.00
2.00	6	Talc (fine powder)	2.00
20.00	7	Starch 1500 (pregelatinized starch)	20.00
1.60	8	Stearic acid	1.60
8.00	9	Starch (maize, dried)	8.00
0.30	10	Magnesium stearate	0.30
—	11	Purified water	70.00

MANUFACTURING DIRECTIONS

Note: Avoid overmixing lubricants, otherwise hardness can be reduced.

1. Preparating starch paste
   a. Make a smooth slurry of Item 5 in 14 g of Item 11 (25 to 30°C). Transfer the slurry into 56 g of Item 11 (80 to 90°C) preheated in a steam jacket vessel under continuous stirring to get a translucent paste. Cool to 45 to 50°C.
2. Sieving and dry mixing
   a. Sift Items 1, 3, 2, and 4 through a stainless steel 630-µm sieve in sifter. Load into mixer. Mix for 5 min at low speed.
3. Kneading
   a. Knead the powder mix in the mixer with starch paste at low mixer speed for 3 min. Scrape sides and blades. Mix and chop at low speed for 3 min. Check the end point of granulation. If required, add more purified water to separate the granules, freeing big lumps.
4. Drying
   a. Unload the wet mass in stainless steel trays for drying. Dry the wet mass in an oven at 55°C for 10 h. After 2 h of drying, scrape the semidried granules to break lumps for uniform drying.
   b. Check the LOD. The LOD limit is 2 to 2.5%.
   c. If required, dry further at 55°C to meet the LOD limit.
   d. Transfer the dried granules to stainless steel drums.
5. Grinding and lubricating
   a. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into the blender.
   b. Sift Items 7 and 9 through a 500-µm sieve, using a sifter, and add it into the blender. Mix for 2 min.
   c. Sift Items 6, 8, and 10 through a 500-µm sieve. Add 2 to 4 g of granules from bulk (Grinding and Lubricating, Step 5a).
   d. Mix in a polythene bag for 1 min, and add to blender. Blend the mixture for 1 min.
   e. Unload in stainless steel drums.
6. Compression
   a. Check temperature and humidity before starting compression. As a limit, the temperature should not exceed 27°C, and the recommended relative humidity is 55 to 60%. Compress the granules using a rotary tabletting machine. The diameter should be 8.0-mm round punches.

Furosemide Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Furosemide	200.00
388.00	2	Ludipress	388.00
6.00	3	Magnesium stearate	6.00
6.00	4	Aerosil 200	6.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 618 mg in 12-mm biplanar punches.

Gabapentin Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
600.00	1	Gabapentin (10–125 μm)	600.00
24.00	2	Hydroxypropyl cellulose 75–150 cps (Klucel LF)	24.00
39.00	3	Corpovidone sodium (polyplasdone XL)	39.00
12.00	4	Calcium stearate	12.00
—	5	Alcohol	QS

Note: Compress 675 mg; for 800 mg, compress 900 mg.

MANUFACTURING DIRECTIONS

1. Prepare a 7.5% solution of Item 2 in Item 5 by slowly adding Item 2 to Item 5 and mixing for 60 min at room temperature, until a clear homogenous solution is obtained
2. Charge Item 1 in a fluid-bed dryer, and apply the solution in Step 1 to granulate.
3. The process air volume is set to 100 cfm, and gabapentin is fluidized. When the product temperature reaches about 25 to 28°C, the binder solution is applied. This solution is introduced through a pneumatically atomized nozzle positioned in the expansion chamber of the fluid-bed processor. The fluidized gabapentin particles are thus coated with the binder solution. While spraying, the process air volume is increased until the product temperature is stabilized between 12 to 25°C. Once all the binder solution is applied, the process air volume is set to 150 cfm and the temperature to about 35°C to dry the coated particles. Drying is complete when the LOD, determined by a Computerized Moisture Analyzer Balance, is not more than 0.75%.
4. Pass the spray-coated particles through a comminuting mill.
5. Charge the sized particles in a V-blender with Items 3 and 4. Blend these materials for 5 min.
6. Compress at a pressure of 12 to 14 kN. The hardness range of the 600-mg tablets was 13.3 to 14.9 kp, with an average hardness of 14.2 kp.
7. Optionally, coat the tablets with an aqueous dispersion such as an Opadry. (See Appendix.)

Galanthamine Hydrobromide Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
1.00	1	Galanthamine hydrobromide	1.00
32.00	2	Calcium phosphate	3.20
5.00	3	Lactose	5.00
15.00	4	Microcrystalline cellulose	15.00
0.70	5	Talc	0.70
0.70	6	Magnesium stearate	0.70

Note: For 5-mg strength, fill a proportionate amount or adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 4 through a 250-μm sieve, and charge in a blending vessel. Mix the materials for 10 min.
2. Pass Items 5 and 6 through a 250-μm sieve, and add to Step 1. Blend this mixture for 1 min.
3. Compress.

Gemfibrozil Tablets (600 mg) [114]

Gemfibrozil is a lipid regulating agent. It is available in tablet form for oral administration. Each tablet contains 600 mg of gemfibrozil. Each tablet also contains calcium stearate; candelilla wax FCC; microcrystalline cellulose; hydroxypropyl cellulose; hydroxypropyl methylcellulose, USP; methylparaben, NF; Opaspray white; polyethylene glycol; polysorbate 80; propylparaben; colloidal silicon dioxide; and pregelatinized starch. The chemical name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid. The empirical formula is $C_{15}H_{22}O_3$, and the molecular weight is 250.35. The solubility in water and acid is 0.0019%, and in dilute base it is greater than 1%. The melting point is 58 to 61°C. Gemfibrozil is a white solid that is stable under ordinary conditions.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Gemfibrozil	600.00
120.00	2	Microcrystalline cellulose (Avicel PH 101)	120.00
40.00	3	Gelatin	40.00
2.00	4	Diotilan	2.00
16.00	5	Calcium stearate	16.00
54.00	6	Sodium carboxymethyl starch	54.00
24.00	7	Talc	24.00
8.00	8	Silicon dioxide colloidal	8.00
9.50	9	Hydroxypropylmethyl cellulose	9.50
4.00	10	Polyethylene glycol 4000	4.00
0.50	11	Simethicone	0.50
2.00	12	Titanium dioxide	2.00
—	13	Water, purified	QS
—	14	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Charge the gemfibrozil and microcrystalline cellulose in a suitable whirlpool mixer, and homogenize.
2. Prepare an aqueous solution of Item 3, and add to Step 1.
3. Prepare an ethanolic solution of Item 4, add to Step 1, and granulate.
4. Dry the granules. Screen the granules through a 0.8-mm sieve screen, return to the mixer, and homogenize with the components of the external layer (calcium stearate, sodium carboxymethyl starch, talc, colloidal silicic acid).
5. Compress the homogenized mixture into oval biconvex tablets weighing 864 mg.
6. Coat the tablets to a final weight of 880 mg, using Items 9 to 12. (See Appendix for details.)

Glibenclamide Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.50	1	Glibenclamide, micro (4.8% excess)	2.62
80.88	2	Lactose monohydrate	80.88
50.00	3	Starch (maize)	50.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
11.00	5	Starch (maize)	11.00
10.00	6	Starch (maize, dried)	10.00
3.00	7	Talc (fine powder)	3.00
0.50	8	Magnesium stearate	0.50
1.00	9	Colloidal silicon dioxide (Aerosil 200)	1.00
—	10	Purified water	55.00

MANUFACTURING DIRECTIONS

Note: Glibenclamide is an oral hypoglycemic agent. During the processing of the batch, the person involved may take a glass full of 5% glucose solution, if required.

1. Preparing the binder
   a. Make a slurry of Item 5 in 15 g of Item 10 (40 to 45°) in a stainless steel container. Check that it is free of lumps.
   b. Charge this slurry into 40 g of Item 10 heated to 95°C into the vessel. Stir until there is complete gelatinization.
   c. Cool to 50°C.
2. Dry mixing
   a. Load Items 1, 2, 3, and 4 into the mixer (Diosna P 250). Mix and chop for 5 min at high speed.
3. Kneading
   a. Add starch paste to the mixer. Mix for 2 min, with the mixer at low speed and the chopper at high speed.
   b. Scrape the sides and blades. Mix and chop at low speed for 2 min. If required, add Item 10.
   c. If required for breaking bigger lumps, pass the wet mass through a Fitz mill, using sieve #24205 at medium speed, with knives forward.
4. Drying
   a. Spread the wet granules onto the trays. Load the trolleys onto the dryer. Dry the granules at 55°C for 10 h or up to the moisture content limit. Scoop the granules after 4 h of drying. Then rotate the trays — put the upper trays down and the down trays up — for uniform drying.
   b. Check the moisture content. Limit: not more than 2.5%.
5. Grinding
   a. Pass the dried granules through a 1-mm sieve. Collect in a stainless steel drum and load in a blender.
6. Lubricating
   a. Mix Items 6, 7, and 9 in a polythene bag. Pass through a 250-μm sieve, using a sifter. Collect in a polythene bag. Add to the granules in the blender (Step 5a). Mix this mixture for 5 min.
7. Pass Item 8 through a 250-μm sieve. Collect in a polythene bag. Mix 2 g of granules with this, and add it to the blender in Step 5a. Mix for 1 min. Unload lubricated granules in a stainless steel drum.
8. Compressing
   a. Compress the granules using a rotary tabletting machine. Toolings should be of length 10 mm × 5 mm. The weight of 10 tablets should be 1.6 gm ± 3%.

Glibenclamide Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Glibenclamide, micro	5.00
78.50	2	Lactose monohydrate	78.50
50.00	3	Starch (maize)	50.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
10.00	5	Starch (maize)	10.00
11.00	6	Starch (maize, dried)[a]	11.00
3.00	7	Talc (fine powder)	3.00
0.50	8	Magnesium stearate	0.50
1.00	9	Colloidal silicon dioxide (Aerosil 200)	1.00
—	10	Purified water	55.00

[a] LOD: Not more than 4.5% when dried at 120°C for 4 h.

MANUFACTURING DIRECTIONS

Follow the directions provided in the previous formulation.

Gliclazide Tablets (80 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
80.00	1	Gliclazide[a]	80.00
30.00	2	Starch (maize)	30.00
40.00	3	Lactose monohydrate	40.00
23.00	4	Dicalcium phosphate	23.00
4.00	5	Starch maize	40.00
1.80	6	Gelatin	1.80
0.06	7	Propyl paraben	0.06
0.06	8	Methyl paraben	0.06
1.00	9	Talc	1.00
1.00	10	Magnesium stearate	1.00
1.00	11	Sodium croscarmellose	1.00
1.00	12	Aerosil 200	1.00
1.00	13	Sodium starch glycolate	1.00
—	14	Water, purified, ca	50 ml

[a] Untapped bulk density of 0.69 to 0.70.

MANUFACTURING DIRECTIONS

1. Screen Items 1 to 4 through a 250-µm sieve.
2. Charge Items 1 to 4 in a suitable vessel, and mix for 30 min.
3. In a separate vessel, heat Item 14 to boiling, and add to it Items 7 and 8 at 90°C to dissolve. Add Item 6, and stir and mix to dissolve completely. Then allow the mixture to cool to room temperature.
4. Add Item 5 to Step 3, and stir and mix to obtain a lump-free slurry. Stop heating, and mix for another 5 min.
5. Add the slurry in Step 4 to Step 2. Stir at a high speed for 30 min to obtain a uniform wet mass.
6. Pass the wet mass through an 8-mm size sieve, and dry the mass in a fluid-bed dryer for 50 min at 50°C.
7. Pass the dried granules through #20 mesh (grind larger size), and transfer to a tumbler.
8. Sift Items 11 to 13 through a 500-µm sieve, and sift Item 10 through a 250-µm sieve. Then add these items to Step 7, and blend for 10 min.
9. Compress 180 mg in 3-mm punches.

Glimepiride Tablets (1 mg/2 mg) [129]

Glimepiride tablets are oral blood-glucose-lowering drugs of the sulfonylurea class. Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder formulated into tablets of 1-mg, 2-mg, and 4-mg strengths for oral administration. Amaryl® tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose (hydrous), sodium starch glycolate, povidone, microcrystalline cellulose, and magnesium stearate. In addition, Amaryl 1-mg tablets contain ferric oxide red. Amaryl 2-mg tablets contain ferric oxide yellow and FD&C Blue No. 2 Aluminum Lake. Amaryl 4-mg tablets contain FD&C Blue No. 2 Aluminum Lake. Chemically, glimepiride is identified as 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea. The molecular formula for glimepiride is $C_{24}H_{34}N_4O_5S$. The molecular weight is 490.62. Glimepiride is practically insoluble in water.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Glimepiride	2.00
109.90	2	Lactose monohydrate	109.90
35.00	3	Avicel PH 102 (microcrystalline cellulose PH 102)	35.00
8.00	4	Primojel (sodium starch glycolate)	8.00
0.75	5	Iron oxide yellow	0.75
0.85	6	Dispersed FD&C Blue No. 2	0.85
3.00	7	Polyvinyl pyrrolidone K-30 (PVP K-30)	3.00
0.50	8	Magnesium stearate	0.50
QS	9	Purified water	QS

MANUFACTURING DIRECTIONS

1. Dissolve color in water, and homogenize it, finally make a binding solution with PVP K-30.
2. Mix glimepiride with Primojel, iron oxide yellow, and dispersed blue E 132 (FD&C Blue No. 2), and pass through a 0.710-mm sieve.
3. Mix Avicel PH 102 with powder from Step 2, and pass through a 0.710-mm sieve.
4. Mix lactose monohydrate with powder from Step 3, and pass through a 0.710-mm sieve.
5. Knead the powder with binding solution to get the desired granules.
6. Dry the granules at 60°C for 12 h to obtain an LOD of not more than 3%.
7. Pass the dried granules in a Frewitt granulator using a 1.25-mm sieve.
8. Compress 160 mg granules in 12-mm punches. For 1-mg and 3-mg strengths, compress the same weight and adjust with lactose.

Glipizide Tablets (5 mg) [71]

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class. The chemical abstracts name of glipizide is 1-cyclohexyl-3-[[*p*-(2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$. The molecular weight is 445.55. Glipizide is a whitish, odorless powder with a pK_a of 5.9. It is insoluble in water and alcohols, but is soluble in 0.1*N* NaOH. It is freely soluble in dimethylformamide.

- Immediate-release tablets — Each immediate-release tablet for oral administration contains glipizide, 5 mg or 10 mg, and the following inactive ingredients: cornstarch, anhydrous lactose, microcrystalline cellulose, colloidal silicon dioxide, and stearic acid.
- Extended-release tablets — Inert ingredients in the formulations are as follows: polyethylene oxide, hydroxypropyl methylcellulose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, and Opadry white and black ink. Glucotrol XL extended-release tablets are similar in appearance to conventional tablets. Each tablet, however, consists of an osmotically active drug core surrounded by a semipermeable membrane. The core is divided into two layers: an "active" layer containing the drug and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet. The Glucotrol XL extended-release tablet is designed to provide a controlled rate of delivery of glipizide into the GI lumen, which is independent of pH or GI motility. The function of the Glucotrol XL extended-release tablet depends upon the existence of an osmotic gradient between the contents of the bilayer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant and then gradually falls to zero. The biologically inert components of the tablet remain intact during drug GI transit and are eliminated in the feces as an insoluble shell.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Glipizide, 10% excess	6.00
43.00	2	Starch (maize)	43.00
50.00	3	Lactose monohydrate	50.00
28.00	4	Dicalcium phosphate	28.00
2.00	5	Gelatin	2.00
0.075	6	Propyl paraben	0.075
0.075	7	Methyl paraben	0.075
2.00	8	Magnesium stearate	2.00
2.00	9	Sodium starch glycolate	2.00
—	10	Water, purified, ca	50 ml

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 4 through a 250-µm sieve, and charge in a suitable blender. Mix these items for 30 min.
2. In a separate vessel, charge Item 10 and bring to boil by heating. Add Items 6 and 7, and stir to dissolve at 90°C. Allow to cool to 50°C.
3. Add Items 4 and 5 to Step 2. Stir and mix vigorously at 50°C to obtain a smooth paste without lumps. Allow the mixture to cool to room temperature.
4. Transfer Step 3 to Step 1, and mix to obtain a wet mass.
5. Transfer the wet mass onto trays, and dry in an oven at 60°C overnight to an LOD of not more than 2.5%.
6. Pass dried granules through #20 mesh, and collect in a tumble blender.
7. Pass Item 9 through a 500-µm sieve and Item 8 through a 250-µm sieve. Add to Step 8. Blend for 2 min.
8. Compress 120 mg in 6-mm punches.

Glipizide Tablets CR (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Xanthan gum	20.00
30.00	2	Locust bean gum	30.00
108.00	3	Dextrose	108.00
8.30	4	Surelease®	8.30
—	5	Water, purified	—
5.00	6	Glipizide	5.00
3.30	7	Sodium stearyl fumarate	3.30
43.70	8	Dextrose powder, anhydrous	43.70

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a mixer, and mix at high speed for 3 min using a chopper blade.
2. In a separate vessel, add and mix Item 4 with Item 5, and spray the mixture gradually into Step 1 while mixing at high speed to provide even distribution and to produce a suitable wet mass.
3. Dry the wet mass in a fluid-bed dryer to an LOD of less than 10% (preferably less than 5%).
4. Pass the dried granules through a 20-mesh screen, and transfer them to a mixing vessel (V blender). Blend for 10 min.
5. Add Items 6 and 8 to Step 4 after passing through a 250-µm sieve. Blend the mixture for 15 min.
6. Add Item 7, and blend for 3 min.
7. Compress 220 mg in a suitable punch at 5-Kg hardness.

Glyburide and Metformin Tablets (250 mg/500 mg; 1.25 mg/2.50 mg) [124]

Glucovance® (glyburide and metformin HCl tablets) contains two oral antihyperglycemic drugs used in the management of Type 2 diabetes — glyburide and metformin hydrochloride. Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl] sulfonyl]-3-cyclohexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The glyburide used in Glucovance has a particle size distribution of 25%, with an undersize value not more than 6 µm, a 50% undersize value not more than 7 to 10 µm, and a 75% undersize value not more than 21 µm.

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of Type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or (α)-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of an aqueous solution of metformin hydrochloride is 6.68.

Glucovance is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Metformin hydrochloride	250.00
1.25	2	Glyburide	1.25
7.00	3	Croscarmellose sodium	7.00
10.00	4	Povidone	10.00
28.25	5	Microcrystalline cellulose (Avicel PH 101)	28.25
2.25	6	Magnesium stearate	2.25
—	7	Water, purified	QS

Note: For 2.5/500 strength, increase the fill volume to double.

MANUFACTURING DIRECTIONS

1. Charge croscarmellose sodium and glyburide in a suitable blender, and blend for 10 min.
2. In a separate vessel, charge metformin hydrochloride and magnesium stearate (99.5%:0.5% w/w) using high shear force.
3. In a separate container, add Item 4 and an appropriate quantity of Item 7 (1:10 ratio) to make paste.
4. Add the paste in Step 3 to Steps 1 and 2 combined and mixed prior to the addition of the paste.
5. Granulate using a high-shear mixer. Dry the granules in a fluid-bed dryer at approximately 60°C to achieve a moisture content of not more than 2%.
6. Size the dried granules with a screening mill, and mix with the microcrystalline cellulose using a tumble mixer.
7. Incorporate magnesium stearate as a lubricant, using a tumble mixer (Step 6) to produce the final compression blend.
8. Compress 300 mg for 250/1.25 and 600 mg for 500/2.5 tablets.
9. Coat the tablets using an HPMC-based film-coating system, until the required amount of film coat is applied. The typical level of a film coat applied to the tablets is 2% w/w. See Appendix for details.

Glyburide Tablets (5 mg) [81]

The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]-sulfonyl]-3-cyclohexylurea. The molecular weight is 493.99.

Micronase® tablets (standard glyburide) — µmase tablets contain glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as µmase tablets of 1.25-, 2.5-, and 5-mg strengths for oral administration. The inactive ingredients of the compound are colloidal silicon dioxide, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, sodium alginate, and talc. In addition, the 2.5-mg tablet contains aluminum oxide and FD&C Red No. 40. The 5-mg tablet contains aluminum oxide and FD&C Blue No. 1.

Glynase® PresTab® tablets (micronized glyburide) — Glynase PresTab tablets contain micronized (smaller particle size) glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as Glynase PresTab tablets of 1.5-, 3-, and 6-mg strengths for oral administration. The inactive ingredients of the compound are colloidal silicon dioxide, cornstarch, lactose, and magnesium stearate. In addition, the 3-mg strength contains FD&C Blue No. 1 Aluminum Lake, and the 6-mg tablet contains D&C Yellow No. 10 Aluminum Lake.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Glyburide, micronized (ca 5m^2/g)	5.25
140.00	2	Lactose spray dried (foremost spray-dried lactose #315 or #316)	140.00
28.60	3	Starch (maize)	28.60
0.75	4	Magnesium stearate	0.75

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a suitable mixing vessel. Mix for 20 min, until a homogenous mixture is reached.
2. Sift Item 4 through a 250-µm mesh, and add to Step 1. Blend slowly for 2 min.
3. Compress ca 175 mg in a suitable punch.

Griseofulvin Tablets (125 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
125.00	1	Griseofulvin, micronized	125.00
250.00	2	Ludipress	250.00
10.00	3	Polyethylene glycol 6000 powder	10.00
19.00	4	Aerosil 200	19.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.5-mm sieve, mix, and press with low-compression force, applying a vibrating hopper.
2. Compress 367 mg in 12-mm biplanar punches. The flowability of the tabletting mixture can be increased by adding higher amounts of Ludipress and Aerosil 200.

Griseofulvin Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Griseofulvin	500.00
100.00	2	Kollidon VA 64	100.00
—	3	Dimethylformamide	7500.00
75.00	4	Kollidon CL	75.00
75.00	5	Lactose monohydrate	75.00
5.00	6	Magnesium stearate	5.00
5.00	7	Aerosil 200	5.00

MANUFACTURING DIRECTIONS

Dissolve the mixture of Items 1 and 2 in Item 3, and evaporate to dryness. Pass the obtained coprecipitate through a 0.5-mm sieve. Then mix with Items 4 to 7 and press with low-compression force. Compress 751 mg in 12-mm biplanar punches.

Hydrochlorothiazide and Potassium Chloride (50 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Hydrochlorothiazide	50.00
300.00	2	Potassium chloride	300.00
15.00	3	Kollidon CL	15.00
2.00	4	Aerosil 200	2.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve. Mix the components, and press.
2. Compress 369 mg in 9-mm punches.

Hydrochlorothiazide Tablets (50 mg) [10]

Hydrochlorothiazide is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$. It is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water and freely soluble in sodium hydroxide solution. Hydrochlorothiazide is supplied as 25-mg, 50-mg, and 100-mg tablets for oral use. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, starch, and talc.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Hydrochlorothiazide	50.00
280.00	2	Ludipress	280.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components. Pass through a 0.8-mm sieve.
2. Compress with a low-compression force. Compress 328 mg in 8-mm punches.

Hydrochlorothiazide Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Hydrochlorothiazide	50.00
422.00	2	Lactose monohydrate	422.00
8.00	3	Kollidon 90 F	8.00
—	4	2-Propanol	38 ml
15.00	5	Kollidon Cl	15.00
2.00	6	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with Item 2, Pass through a 0.8-mm sieve, add Items 5 and 6, and press with low-compression force.
2. Compress 495 mg in 12-mm biplanar punches.

Hydrocodone and Acetaminophen Tablets (5.0 mg/500 mg; 7.50 mg/750 mg)

Each tablet contains hydrocodone bitartrate (5 mg) and acetaminophen (500 mg). Other ingredients include colloidal silicon dioxide, cornstarch, croscarmelllose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid.

Each extra-strength tablet contains hydrocodone bitartrate (7.5 mg) and acetaminophen (750 mg). Other ingredients include colloidal silicon dioxide, cornstarch, croscarmellose sodium, magnesium stearate, povidone, and stearic acid. Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Acetaminophen, 4′-hydroxyacetanilide is a nonopiate nonsalicylate analgesic and antipyretic that occurs as a white odorless crystalline powder possessing a slightly bitter taste.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
750.00	1	Acetaminophen powder	750.00
7.50	2	Hydrocodone bitartrate	7.50
12.00	3	Colloidal silicon dioxide	12.00
154.40	4	Microcrystalline cellulose	154.40
64.00	5	Croscarmellose sodium	64.00
26.00	6	Hydroxypropyl methylcellulose	26.00
124.80	7	Starch (maize)	124.80
4.00	8	Magnesium stearate	4.00
—	9	Water, purified	QS

Note: For 500 mg Item 1 and 5.0 mg Item 2 formulation, adjust fill volume.

MANUFACTURING DIRECTIONS

1. Pass hydrocodone bitartrate through a #20 mesh. Pass acetaminophen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum at speed setting 5 (approximately 1030 r/min).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbo Sieve at the same settings as in Step 1. Charge the screened powders into a Lodige MGT-600 mixer, and mix for 5 min with the plow speed at approximately 103 r/min and no choppers.
3. Add water to the mixer over a 10-min period, using a stainless steel transfer container with a valve, while mixing with the plows at about 103 r/min and the choppers at slow speed.
4. Mix the wet mass for another 15 min, until a wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material. Preheat a Glatt fluid-bed dryer by running it for 2.5 min at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 min, and the filter shaking duration for 5 sec. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 min. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a Fitz mill using a #20 mesh wire screen with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a Frewitt SG Turbo Sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum. The speed setting is at approximately 1030 r/min.
8. Add magnesium stearate, and mix for 3 min.
9. Compress using a 13/32-in. round tooling.

Hydrocodone and Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Ibuprofen	400.00
15.00	2	Hydrocodone bitartrate	15.00
12.00	3	Colloidal silicon dioxide	12.00
154.40	4	Microcrystalline cellulose	154.40
64.00	5	Croscarmellose sodium	64.00
26.00	6	Hydroxypropyl methylcellulose	26.00
124.80	7	Starch (maize)	124.80
4.00	8	Magnesium stearate	4.00
—	9	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Pass hydrocodone bitartrate through a #20 mesh. Pass ibuprofen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum at speed setting 5 (approximately 1030 r/min).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbo Sieve at the same settings as in Step 1. Charge screened powders into a Lodige MGT-600 mixer, and mix for 5 min with the plow speed at approximately 103 r/min and no choppers.
3. Add water to the mixer over a 10-min period, using a stainless steel transfer container with a valve while mixing with the plows at about 103 r/min and the choppers at slow speed.
4. Mix the wet mass for another 15 min until a wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material using a preheated Glatt fluid-bed dryer; preheat by running the dryer for 2.5 min at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 min, and the filter shaking duration for 5 sec. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 min. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a Fitz mill using a #20 mesh wire screen, with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a Frewitt SG Turbo Sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum. The speed setting is at approximately 1030 r/min.
8. Add magnesium stearate, and mix for 3 min.
9. Compress using a 13/32-in. round tooling.

Hydroxyzine Tablets [132]

Hydroxyzine hydrochloride is designated chemically as 1-(*p*-chlorobenzhydryl) 4-[2-(2 hydroxyethoxy)-ethyl] piperazine dihydrochloride. Inert ingredients for the tablets are acacia, carnauba wax, dibasic calcium phosphate, gelatin, lactose, magnesium stearate, precipitated calcium carbonate, shellac, sucrose, talc, and white wax. The 10-mg tablets also contain sodium hydroxide, starch, titanium dioxide, and FD&C Yellow No. 6 Lake. The 25-mg tablets also contain starch and velo dark green. The 50-mg tablets also contain starch and velo yellow. The 100-mg tablets also contain alginic acid, FD&C Blue No. 1, polyethylene glycol, and FD&C Red No. 3.

Hyoscine Butyl Bromide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.000	1	Hyoscine butyl bromide	10.000
16.500	2	Lactose monohydrate	16.500
28.000	3	Lactose monohydrate, dense	28.000
17.930	4	Starch (maize)	19.720
2.240	5	Povidone (PVP K-30)	2.240
—	6	Purified water	5.080
0.400	7	Magnesium stearate	0.400
2.740	8	Pregelatinized starch (Starch 1500)	2.740

MANUFACTURING DIRECTIONS

CAUTION: Hyoscine butyl bromide is a potent smooth muscle relaxant. Inhalation can produce toxic effects. Strictly adhere to the usage of mask, gloves, and goggles.

1. Preparation of binding solution
   a. Dissolve Item 5 in Item 6 by stirring to make a clear solution. Use the stirrer at medium speed in a stainless steel container.
2. Dry mixing
   a. Check to see if hyoscine butyl bromide is in fine powder form. If not, pass through a 630-µm sieve using a sifter. Load Items 1, 2, 4, and 3 into the mixer, and mix for 5 min with the mixer and chopper at low speed.
3. Wet massing
   a. Add the binding solution to the dry powder in the mixer while mixing at low speed. When the addition is over, mix and chop for a further 2 min at high speed.
   b. Scrape the lid and blade, and check for a satisfactory wet mass. Add more Item 6 if required to get a satisfactory wet mass.
4. Drying
   a. Spread the granules onto stainless steel trays to a thickness of one-third of the tray thickness, and load the trays on the trolley.
   b. Load the trolleys into the oven. Dry at 60°C for 16 h. Turn the granules after 3 to 4 h so as to ensure uniform drying of the granules.
   c. Check the moisture content of the dried granules, keeping in mind the limit of 1.0 to 1.5%.
5. Grinding
   a. Pass the dried granules through a granulator equipped with a 1.0-mm sieve.
6. Lubricating
   a. Mix Items 7 and 8 in a polythene bag, and pass through a 250-µm sieve using a sifter. Collect the material in a stainless steel container.
   b. Load the sized granules from Grinding, Step 5a, along with sieved powder from Lubricating, Step 6a, into the drum mixer. Mix these items for 3 min.
   c. Unload into stainless steel drums.
7. Compression
   a. Compress the granules using a rotary tabletting machine (with dies and punches: 6 mm, concave, plain punches with fill weights of 780 mg).
8. Coating
   a. Sugar coat the tablets. (See Appendix.)

Ibuprofen Tablets (400 mg) [19]

Motrin tablets and ibuprofen children's suspension contain the active ingredient ibuprofen, which is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74 to 77°C, is very slightly soluble in water (< 1 mg/ml,) and readily soluble in organic solvents, such as ethanol and acetone. Ibuprofen, a nonsteroidal antiinflammatory agent, is available in 400-mg, 600-mg, and 800-mg tablets for oral administration. The inactive ingredients are carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
115.00	1	Lactose	115.00
11.30	2	Povidone	11.30
QS	3	Water, purified	QS
23.00	4	Starch (maize)	23.00
40.00	5	Starch pregelatinized	40.00
11.00	6	French chalk	11.30
1.10	7	Magnesium stearate	1.10
6.80	8	Explotab	6.80
400.00	9	Ibuprofen	400.00

MANUFACTURING DIRECTIONS

1. Granulation
   a. Charge the following into a planetary mixer: ibuprofen, starch pregelatinized, and polyvinylpyrrolidone. Mix all for 15 min.
   b. Pass the powder through a #40 mesh screen.
   c. Add a sufficient quantity of purified water to form a desirable mass.
   d. Pass the mass through #40 mesh on a dryer tray.
   e. Dry the granules in a fluid-bed dryer or use a fan-forced oven at 50 to 60°C for 24 h to dry granules to an LOD of not more than 1%.
   f. Pass the granules through a #40 sieve mesh.
2. Blending
   a. Charge the granules in a planetary mixer. Add maize starch, French chalk (Item 6), magnesium stearate, and Explotab, and mix for 20 min.
3. Compressing
   a. Compress using a rotary press in round punches. The average weight is 610 mg (± 5%).
4. Coating
   a. Apply a sugar coating. (See Appendix.)

Ibuprofen Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Ibuprofen	400.00
43.70	2	Starch (maize)	48.45
18.00	3	Povidone (PVP K-30)	18.00
105.00	4	Starch (maize)	108.13
40.00	5	Starch (maize, dried)	40.00
4.00	6	Colloidal silicon dioxide (Aerosil 200)	4.00
3.45	7	Colloidal silicon dioxide (Aerosil 200)	3.45
1.50	8	Stearic acid	1.50
4.50	9	Magnesium stearate	4.50
—	10	Purified water	163.97

MANUFACTURING DIRECTIONS

1. Preparing the paste
   a. Pass Item 2 through a sifter using a 630-µm sieve. Prepare a slurry of Item 2, with 51.78 g of Item 10 (30°C). Pour the slurry into a vessel containing 112.19 g of Item 10 (70°C). Heat to 80 to 90°C, and mix until the material swells and becomes translucent.
   b. Cool to 50°C. Check the weight. The theoretical weight is 212.43 g.
   c. If required, adjust with Item 10 (70°C). Record the quantity of extra water added.
2. Mixing
   a. Load Items 1, 4, and 3 to the mixer. Mix for 5 min at high speed.
3. Wet massing
   a. Add two-thirds of the starch paste quantity (Preparing the paste, Step 1b) to the dry powder in the mixer (Diosna). Mix for 4 min at low speed. Scrape the sides and blades.
   b. Add the remaining quantity, and mix for 3 min at low speed. Scrape the sides and blades.
   c. Mix and chop for a further 2 min. Check for a satisfactory wet mass. If required, add additional purified water to obtain a satisfactory wet mass.
4. Drying
   a. Dry the granules in a fluid-bed dryer at 55°C for 3 h. Keep just enough air pressure in order to bounce the granules. After 1 h of drying, scrape the semidried granules to break the lumps for uniform drying. Unload in a stainless steel drum. Keep overnight for curing.
   b. Check the moisture content of the dried granules. The limit is not more than 2.5%
5. Grinding
   a. Pass the granules through a 1.25-mm sieve using a granulator. Collect the granules in a stainless steel drum, and add to the blender.
6. Lubricating
   a. Mix Items 6 and 8 in a stainless steel drum, and pass through a 500-µm sieve using a sifter. Collect in a stainless steel drum, and add to the blender.
   b. Pass Items 5 and 9 through a 250-µm sieve in a sifter. Collect the sieved items in a stainless steel drum, and add to the blender. Mix the materials for 2 min.
   c. Unload the result in stainless steel drums.
7. Compressing
   a. Compress the tablets after slugging.
   b. Check the temperature and humidity before starting slugging and compression.
   c. The recommended relative humidity is 45 to 55% at temperatures 25 to 27°C.
8. Slugging
   a. Slug the granules using a rotary tabletting machine with 16-mm punches.
9. Grinding
   a. Grind the slugs through a 6.0-mm sieve followed by a 1.25-mm sieve. Keep 5.40 g of the granules aside. Load the rest of the ground granules in a blender.
10. Sift 5.4 g of the ground granules from Step 9 through a 630-µm sieve using a sifter. Add the retained granules to the blender.
11. Add Item 7 into the sieved granules from Step 10. Mix in a polythene bag. Sift through a 630-µm sieve using a sifter. Add to the blender, and mix for 2 min.
12. Compress the granules using a rotary tabletting machine (12.7-mm concave punches; compress 620 mg).
13. Tablet coating
   a. Coat using Opadry and HPMC coatings. (See Appendix.)

Ibuprofen Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
600.00	1	Ibuprofen	600.00
129.80	2	Starch (maize)	144.22
1.15	3	Colloidal silicon dioxide (Aerosil 200)	1.15
70.00	4	Starch (maize)	70.00
5.00	5	Colloidal silicon dioxide (Aerosil 200)	5.00
8.07	6	Stearic acid	8.07
41.15	7	Pregelatinized starch (Starch 1500)	41.15
10.00	8	Magnesium stearate	10.00
—	9	Purified water	469.00

MANUFACTURING DIRECTIONS

See the directions for 400-mg strength.

Imipramine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Imipramine hydrochloride	26.00
1.40	2	Polyvinyl pyrroidone	1.40
1.40	3	Magnesium stearate	1.40
1.40	4	Talc	1.40
50.00	5	Lactose monohydrate	50.00
50.00	6	Dicalcium phosphate	50.00
14.00	7	Starch (maize)	14.00
—	8	Isopropyl alcohol, ca	20 ml

MANUFACTURING DIRECTIONS

1. Sift through a 250-µm sieve, and charge Items 1 and 5 to 7 in a suitable mixing vessel. Mix the items for 10 min.
2. In a separate vessel, charge Item 2 and a suitable quantity of Item 8 to dissolve it.
3. Add Step 2 into Step 1, and make a suitable wet mass; pass through a 2.38-mm sieve, and dry in a dehumidified room overnight.
4. Pass the dried granules through #18 mesh into a blending vessel.
5. Sift Items 3 and 4 through a 250-µm sieve, and add to Step 4. Blend for 1 min.
6. Compress 140 mg in 7.2-mm punches.

Irbesartan Tablets (75 mg/150 mg/300 mg) [149]

Avapro® (irbesartan) is an Angiotensin II receptor (AT 1 subtype) antagonist. Irbesartan is a nonpeptide compound, chemically described as 2-butyl-3-[[29-(1*H*-tetrazol-5-yl) [1,19-biphenyl]-4-yl] methyl]1,3-diazaspiro[4,4] non-1-en-4-one. Its empirical formula is $C_{25}H_{28}N_6O$. Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at a pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water. Avapro is available for oral administration in unscored tablets containing 75 mg, 150 mg, or 300 mg of irbesartan. Inactive ingredients include lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide, and magnesium stearate.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Irbesartan[a]	75.00
15.38	2	Lactose monohydrate	15.38
22.50	3	Microcrystalline cellulose (Avicel PH 101)	22.50
22.50	4	Pregelatinized starch	22.50
7.50	5	Croscarmellose sodium	7.50
4.50	6	Poloxamer 188 (Pluronic F 68)	4.50
1.12	7	Silicon dioxide colloidal	1.12
1.50	8	Magnesium stearate	1.50
—	9	Water, purified[b]	QS

[a] Use different fill weights for 150-mg and 300-mg strength tablets.

[b] The tablets are prepared by a wet granulation process wherein the total amount of water employed (by weight) is up to 50% of the total solids weight.

MANUFACTURING DIRECTIONS

1. Charge the irbesartan, lactose, pregelatinized starch, and a portion (one-half) of the croscarmellose sodium in a mixer. Mix the materials for 20 min.
2. Pass the powder blend in Step 1 through sizing equipment (cone mill or oscillator), and mix in a mixer.
3. Dissolve the poloxamer 188 in purified water (25% of the weight of total solids), and use it to wet granulate (with the further addition of water in an amount up to 25% of the weight of total solids, as needed) the mixed powder in Step 2.
4. Dry the granules (tray or fluid-bed dryer) until the LOD is 2% or less.
5. Pass the dried granules through a screen, or mill them to obtain the proper size (1 to 3 mm).
6. Mix the sized granules with the silicon dioxide, the microcrystalline cellulose, and the remaining croscarmellose sodium in a mixer.
7. Add and mix for 1 min the magnesium stearate.
8. Compress 150 mg for 75-mg strength, 300 mg for 150-mg strength, and 600 mg for 300-mg strength.

Isoniazid Tablets (100 mg)

Bill of Materials			
Scale (mg/Tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Isoniazid	105.00
2.00	2	Starch maize	2.00
1.25	3	Gelatin	1.25
1.25	4	Magnesium stearate	1.25
1.25	5	Talc	1.25
—	6	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Item 1 through a 250-µm sieve into a blending vessel.
2. In a separate vessel, charge Item 3 and a suitable quantity of Item 6, heat to 50°C, and dissolve Item 3. Then add Item 2 into Step 1, and form a smooth slurry.
3. Add Step 2 and form a suitable wet mass.
4. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays, and dry at 60°C for 8 h to an LOD of not more than 2.5%. Transfer the wet mass to a suitable blending vessel.
5. Sift Items 4 and 5 through a 500-µm sieve, and add to Step 4. Blend these materials for 1 min.
6. Compress 125 mg in 7.3-mm punches.

Isosorbide Dinitrate Tablets (5 mg) [68]

Isosorbide mononitrate, an organic nitrate and the major biologically active metabolite of isosorbide dinitrate, is a vasodilator that affects both arteries and veins.

The chemical name for isosorbide mononitrate is 1,4:3,6-dianhydro-,D-glucitol 5-nitrate.

Isosorbide mononitrate is a white, crystalline, odorless compound that is stable in air and in solution, has a melting point of about 90°C, and has an optical rotation of +144° (2% in water, 20°C).

Isosorbide mononitrate is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate, and dichloromethane.

Each Ismo tablet contains 20 mg of isosorbide mononitrate. The inactive ingredients in each tablet are D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 20, povidone, silicon dioxide, sodium starch glycolate, titanium dioxide, and hydroxypropyl cellulose.

Imdur tablets contain 30 mg, 60 mg, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of ethanol.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Isosorbide dinitrate (40% in Lactose)	13.15
25.00	2	Microcrystalline Cellulose (Avicel PH 102)	25.00
58.60	3	Lactose (Spray Dried)	58.60
0.75	4	Magnesium Stearate	0.75
2.50	5	Starch (Maize, dried)	2.50

MANUFACTURING DIRECTIONS

Note: Protect the product from heat and moisture. Heat and moisture affect the potency of isosorbide.

1. Dry Mixing and Sieving
   a. Mix items 1, 2, and 3 in a suitable stainless steel drum. Pass these materials through a 630-µm sieve using a sifter. Collect in a stainless steel drum.
   b. Load the powders into the drum blender.
2. Mixing
   a. Mix Items 4 and 5 in a bag. Pass the material through 250-µm sieve. Collect in a bag.
   b. Take about 1.25 g powder from Step 1b and add to Step 2a. Mix manually, and transfer to Step 1b.
3. Mix for 5 min using a drum blender.
4. Check and record the weight of the granules. The theoretical weight of the granules is 100.0 g.
5. Compression
   a. Compress 100 mg of the granules using a rotary tabletting machine with 6-mm punches.

Isosorbide Dinitrate Tablets (10 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Isosorbide dinitrate (40% in lactose)	26.30
50.00	2	Microcrystalline Cellulose (Avicel PH 102)	50.00
117.20	3	Lactose (spray dried)	117.20
1.50	4	Magnesium Stearate	1.50
5.00	5	Starch (maize, dried)	5.00

MANUFACTURING DIRECTIONS

See directions for the 5-mg formulation.

Ketotifen Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
1.00	1	Ketotifen, use ketotifen fumarate DC	1.38
1.90	2	Magnesium stearate	1.90
32.50	3	Maize starch	32.50
154.20	4	Calcium hydrogen phosphate anhydrous	154.20
QS	5	Water purified	QS

MANUFACTURING DIRECTIONS

1. Granulation
   a. Make a 10% paste with maize starch using a sufficient quantity of purified water and one-half the quantity of maize starch.
   b. Add calcium hydrogen phosphate anhydrous with one-half the quantity of the starch paste.
   c. Add one-half the quantity of maize starch with ketotifen; mix in a planetary mixer.
   d. Add mixture from Step 1b to 1c, and mix for 5 min. Add the balance of the maize starch powder, and mix for another 10 min.
   e. Pass the wet mass through a #20 mesh screen over lined trays and dry at 95°C until an LOD of not more than 3% is achieved.
2. Lubrication
   a. Mix dry granules with magnesium stearate for 3 min.
3. Compression
   a. Compress using round, flat, beveled edge, scored punch with the logo on one side; diameter is 7 mm, weight is 190 mg.

Lamotrigine Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Lamotrigine, 3% excess	103.00
48.00	2	Avicel PH 102	48.00
111.00	3	Lactose monohydrate	111.00
7.00	4	Primojel	7.00
7.00	5	PVP K30	7.00
1.00	6	Iron oxide yellow	1.00
12.00	7	Avicel PH 102	12.00
8.00	8	Primojel	8.00
1.50	9	Magnesium stearate	1.50
1.50	10	Iron oxide yellow	1.50
—	11	Water purified, ca	75 ml

MANUFACTURING DIRECTIONS

1. Charge Items 1–4 after sifting through a 500-µm sieve into a suitable mixer.
2. In a separate vessel, charge Items 5, 6 and 11; dissolve and homogenize for 5 min at medium speed.
3. Add Step 2 to Step 1, and knead for 1–2 min; mix until a suitable mass is obtained.
4. Dry granules on trays at 55°C for 12 h to and LOD of 0.8%.
5. Grind the dried granules through 1.25-mm sieve.
6. Transfer Step 5 to a blender, and add Items 7–9 after passing them through a 500-µm sieve. Blend for 2 min.
7. Compress 300 mg in 9.5-mm round punches.

Lansoprazole Tablets (10 mg or 20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Lansoprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Lansoprazole Tablets (10 mg or 20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Lansoprazole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Lansoprazole Tablets Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Lansoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose, anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

MANUFACTURING DIRECTIONS

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress 672 mg in 15-mm biplanar punches. For 20-mg tablets, increase the quantity of Item 1, and compress an additional 10 mg.

Lansoprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Lansoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Levamisole Hydrochloride Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
40.00	1	Levamisole hydrochloride, with excess	47.40
10.00	2	Starch (maize)	10.00
20.00	3	Lactose monohydrate	20.00
10.00	4	Sodium starch glycolate	10.00
30.60	5	Starch (maize)	30.60
1.00	6	Magnesium stearate	1.00
5.00	7	Talc	5.00
1.00	8	Aerosil 200	1.00
—	9	Water, purified, ca	50 ml

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through a 250-µm sieve, and charge in a suitable mixer. Mix the items for 15 min.
2. In a separate vessel, charge Item 5, mix with hot Item 9, and form a smooth slurry.
3. Add Step 2 into Step 1, and mix the items to achieve a lump-free mass.
4. Pass the wet mass through a #8 sieve onto paper-lined trays.
5. Dry the granules at 50°C overnight to reach an LOD of no more than 2%. Transfer to a blender.
6. Pass Items 6 to 8 through a 250-µm sieve, add to Step 5, and blend for 2 min.
7. Compress 125 mg in 7-mm punches.
8. Coat tablets with an HPMC methylene chloride coating. (See Appendix.)

Levamisole Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
150.00	1	Levamisole hydrochloride	150.00
300.00	2	Ludipress	300.00
4.00	3	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass the mixture through a 0.8-mm sieve, and press with low-compression force.
2. Compress 458 mg in 12-mm biplanar punches.

Levofloxacin Tablets (250 mg) [69]

Levofloxacin is a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(*S*)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Its empirical formula is $C_{18}H_{20}FN_3O_4 \cdot {}^1/_2H_2O$, and its molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/ml). Levofloxacin is considered soluble to freely soluble in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/ml) and is considered freely soluble in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/ml) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This *in vitro* chelation potential has the following formation order: $Al^{+3} > Cu^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2}$.

Levaquin tablets are available as film-coated tablets and contain the following active ingredients: *250 mg (as expressed in the anhydrous form):* hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red iron oxide; *500 mg (as expressed in the anhydrous form):* hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red and yellow iron oxides.

Levothyroxine Tablets [4]

Levothyroxine sodium tablets contain synthetic crystalline L-3,3′,5, 5′-tetraiodothyronine sodium salt (levothyroxine [T_4] sodium). Synthetic T_4 is identical to that produced in the human thyroid gland. T_4 sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \times H_2O$ and a molecular weight of 798.86 (anhydrous). The inactive ingredients in synthroid tablets are acacia, confectioner's sugar (contains cornstarch), lactose, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength: *25 mcg:* FD&C Yellow No. 6; *50 mcg:* none; *75 mcg:* FD&C Red No. 40 and FD&C Blue No. 2; *88 mcg:* FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; *100 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6; *112 mcg:* D&C Red No. 27 and 30; *125 mcg:* FD&C Yellow No. 6, FD&C Red No. 40, FD&C Blue No. 1; *150 mcg:* FD&C Blue No. 2; *175 mcg:* FD&C Blue No. 1, D&C Red No. 27 and 30; *200 mcg:* FD&C Red No. 40, *300 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6, and FD&C Blue No. 1.

Levothyroxine Tablets (50 mcg) [25]

Levothyroxine sodium tablets and injections contain synthetic crystalline L-3,3′,5,5′-tetraiodothyronine sodium salt (levothyroxine [T_4] sodium). Synthetic T_4 is identical to that produced in the human thyroid gland. T_4 sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \times H_2O$, and a molecular weight of 798.86 (anhydrous).

The inactive ingredients in synthroid tablets are as follows: acacia, confectioner's sugar (contains cornstarch), lactose, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength: *25 mcg:* FD&C Yellow No. 6; *50 mcg:* none; *75 mcg:* FD&C Red No. 40 and FD&C Blue No. 2; *88 mcg:* FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; *100 mcg:* D&C Yellow No.10, FD&C Yellow No. 6; *112 mcg:* D&C Red No. 27 and 30; *125 mcg:* FD&C Yellow No. 6, FD&C Red No. 40, and FD&C Blue No. 1; *150 mcg:* FD&C Blue No. 2; *175 mcg:* FD&C Blue No. 1 and D&C Red No. 27 and 30; *200 mcg:* FD&C Red No. 40; and *300 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6, and FD&C Blue No. 1.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.05	1	Levothyroxine sodium	0.05
10.00	2	Citric acid anhydrous	10.00
1.00	3	Magnesium citrate	1.00
89.00	4	Ludipress	89.00

MANUFACTURING DIRECTIONS

1. Prepare a premix of Items 1 and 2. Add Items 3 and 4, and pass the mixture through a 0.8-mm sieve.
2. Mix and press with low-compression force.
3. Compress 101 mg in 6-mm biplanar punches. Item 2 may be omitted and compensated with Item 4. If the content uniformity of formulation No. 1 does not meet the requirements, add a small part of the Ludipress and Item 3 mixture, and the mixture of Items 1 and 2. The function of citric acid in formulation No. 2 is to stabilize the active ingredient.

Levothyroxine Tablets (0.025 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.025	1	Levothyroxine	0.025
11.42	2	Prosolv SMCC 50	11.42
104.29	3	Prosolv SMCC 90	104.29
6.14	4	Sodium starch glycolate	6.14
0.86	5	Magnesium stearate	0.86
0.28	6	FD&C Yellow No. 6	0.28

MANUFACTURING DIRECTIONS

1. Add Items 1 and 2 in a suitable blender. Blend the items for 10 min, and pass through #60 mesh.
2. In a separate container, take 50% of Item 3 and Item 6, and blend for 10 min.
3. Add the balance of Item 3 to Step 1, and blend for 1 min.
4. Add Step 3 into Step 1, and mix.
5. Add Items 4 and 5, one at a time, and blend.
6. Compress 123 mg.

Linezolid Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Linezolid	400.00
40.00	2	Starch (maize)	40.00
78.40	3	Microcrystalline cellulose PH 101	78.40
8.00	4	Hydroxypropyl cellulose	8.00
28.00	5	Sodium starch glycolate	28.00
5.60	6	Magnesium stearate	5.60

MANUFACTURING DIRECTIONS

Mix all ingredients, and compress 560 mg in 12-mm biplanar punches.

Lisinopril Tablets (10 mg) [52]

Lisinopril is an oral long-acting angiotensin-converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically described as (*S*)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$.

Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol.

Zestril is supplied as 2.5-mg, 5-mg, 10-mg, 20 mg, and 40-mg tablets for oral administration. The inactive ingredients are as follows: *2.5-mg tablets:* calcium phosphate, magnesium stearate, mannitol, and starch; *5-, 10-, and 20-mg tablets:* calcium phosphate, magnesium stearate, mannitol, red ferric oxide, and starch; *40-mg tablets:* calcium phosphate, magnesium stearate, mannitol, starch, and yellow ferric oxide.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Lisinopril	10.00
139.00	2	Ludipress	139.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low-compaction force (10 kN).
2. Compress 152 mg in 8-mm biplanar punches.

Lomefloxacin Hydrochloride Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Lomefloxacin, use lomefloxacin hydrochloride	442.00
123.00	2	Microcrystalline cellulose	123.00
13.50	3	Croscarmellose sodium Type A	13.50
1.80	4	Hydroxy propyl cellulose	1.80
3.50	5	Silicon dioxide, colloidal	3.50
2.70	6	Polyoxyl 40 stearate	2.70
81.00	7	Starch (maize)	81.00
7.50	8	Magnesium stearate	7.50
—	9	Water, purified, ca	65 ml
QS	10	Ethanol, ca	90 ml

MANUFACTURING DIRECTIONS

1. If necessary, mill all items to remove any lumps.
2. Mix in a suitable mixer (double-cone or Y). Before this, sieve Items 1 to 3 and Item 7 through a 60 mesh (0.25 mm). Then mix at medium speed for 15 min.
3. In a suitable container, mix disperse Items 4 and 6 and add Items 9 and 10. Mix until dissolved. Allow to stand overnight.
4. Add the binder solution from Step 3 to the mix obtained in Step 2, and pass the wet mass through a 20-mesh sieve to obtain granules.
5. Dry the granules at 55°C for 15 h to get a moisture content of not more than 2.5% (determined at 80°C for 4 h).
6. Blend the granules with Item 5 for over 5 min, then add Item 8, and mix again for 3 min.
7. Compress tablets with a target weight of 675 mg.
8. Coat, using an HPMC coating. (See Appendix.)

Loperamide Hydrochloride Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.00	1	Loperamide hydrochloride	2.00
68.00	2	Starch (maize)	68.00
46.00	3	Lactose monohydrate	46.00
3.00	4	Starch (maize)	3.00
56.00	5	Dicalcium phosphate	56.00
2.00	6	Talc	2.00
2.00	7	Magnesium stearate	2.00
—	8	Water, purified, ca	60 ml

MANUFACTURING DIRECTIONS

1. Sift Items 2, 3, and 5 through a 250-µm sieve, and sift Item 1 through #40 mesh. Charge them in a suitable mixing vessel by a geometric dilution process for Item 1, then mix for 30 min (this step is critical to content uniformity).
2. Charge Item 3 in a suitable vessel, and add Item 8. Heat it and mix to prepare a smooth slurry.
3. Add Step 2 to Step 1 slowly, and mix to obtain a lump-free mass.
4. Pass the wet mass through #6 mesh onto paper-lined trays.
5. Dry the granules in a fluid-bed drier at 50°C for 1 h to LOD of not more than 2.5%. Transfer to a blender.
6. Pass Item 6 through a 500-µm sieve and Item 7 through a 250-µm sieve, and add to Step 6; blend for 2 min.
7. Compress 170 mg in 8-mm punches.

Loratadine and Pseudoephedrine Sulfate Tablets (10 mg/240 mg) [127]

Claritin-D® 12-h extended-release tablets — These tablets contain 5 mg of loratadine in the tablet coating for immediate release, and 120 mg of pseudoephedrine sulfate, which is equally distributed between the tablet coating for immediate release and the barrier-coated extended-release core. The inactive ingredients are acacia, butylparaben, calcium sulfate, carnauba wax, cornstarch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein.

Claritin-D 24-h extended-release tablets — These tablets contain 10 mg of loratadine in the tablet film coating for immediate release, and 240 mg pseudoephedrine sulfate in the tablet core, which is released slowly, allowing for once-daily administration. The inactive ingredients for oval, biconvex Claritin-D 24-h extended-release tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax.

Loratadine is a long-acting antihistamine having the empirical formula $C_{22}H_{23}ClN_2O_2$ and the chemical name ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate. The molecular weight of loratadine is 382.89. It is a white to off-white powder that is not soluble in water but is very soluble in acetone, alcohol, and chloroform.

Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine, and it is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is α-[1-(methyl-amino)ethyl]-[*S*-(*R**,*R**)]-benzenemethanol sulfate (2:1)(salt).

The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol, and sparingly soluble in chloroform.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
240.00	1	Pseudoephedrine sulfate	240.00
15.00	2	Microcrystalline cellulose (Avicel PH 101)	15.00
200.00	3	Xanthan gum Keltrol TF	200.00
80.00	4	Sodium alginate keltone HVCR	80.00
53.00	5	Calcium carbonate	53.00
6.00	6	Magnesium stearate	6.00
6.00	7	Aerosil 200	6.00
10.00	8	Loratadine	10.00
95.00	9	Lactose monohydrate	95.00
66.50	10	Microcrystalline cellulose (Avicel PH 101)	66.50
1.00	11	FD&C Yellow No. 10	1.00
20.00	12	Starch (maize)	20.00
6.00	13	Starch (maize)	6.00
1.50	14	Magnesium stearate	1.50
—	15	Water, purified	60.00

MANUFACTURING DIRECTIONS

1. Charge pseudoephedrine sulfate, microcrystalline cellulose, xanthan gum, sodium alginate, calcium carbonate, and one-half of the lubricants in a suitable mixer after sieving through a #44 sieve.
2. Pass the blend through a roll-compactor.
3. Sieve the compact through a #22 sieve to obtain granules.
4. Mix the granules with the remaining lubricants (Items 6 and 7), and compress into tablets (600 mg) to form the first tablet layer.
5. Charge Items 8 to 12 after passing through a #100 sieve in a suitable mixer. Blend these items for 10 min.
6. Charge Item 13 in a separate vessel, and make a paste (10%) using Item 14.
7. Add Step 6 into Step 5, and granulate.
8. Dry the granules and blend or sift Item 14.
9. Compress 200 mg in tablets (the second layer).
10. Use appropriate tabletting equipment for bilayer tabletting or core tabletting.

Loratadine Tablets (10 mg) [32]

Loratadine is a white to off-white powder not soluble in water but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89 and an empirical formula of $C_{22}H_{23}ClN_2O_2$. Its chemical name is ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate.

Claritin® tablets contain 10 mg of micronized loratadine, an antihistamine, to be administered orally. They also contain the following inactive ingredients: cornstarch, lactose, and magnesium stearate.

Claritin Reditabs (rapidly disintegrating tablets) contain 10 mg of micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. Claritin Reditabs also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratadine	10.00
67.30	2	Lactose monohydrate	67.30
22.00	3	Starch (maize)	22.00
10.00	4	Starch (maize)	10.00
5.00	5	Starch (maize, dried)	5.00
0.70	6	Magnesium stearate	0.70
—	7	Purified water	40.00

MANUFACTURING DIRECTIONS

Note: Avoid overmixing the lubricants, otherwise hardness is reduced.

1. Sieving and dry mixing
   a. Sift Items 1, 2, and 3 through a stainless steel 630-µm sieve in a sifter. Load into mixer. Mix for 5 min at low speed.
2. Preparing the binder
   a. Prepare a slurry of Item 4 in 10 g of Item 7 (30 to 40°C). Then make a translucent paste in a Guisti steam jacked vessel, using 30 g of Item 7 (90 to 95°C). Cool to 45 to 50°C. Check the unity of the paste. The theoretical weight is 50 g.
3. Kneading
   a. Knead the powder with starch paste, while mixing at low speed over a period of 2 min.
   b. Scrape sides and backs. Mix and chop at Speed 1 for 2 min. Check the end point of granulation. If required, add additional purified water to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of the granules.)
   c. Unload the wet granules into a stainless steel tray for drying.
4. Drying and LOD
   a. Dry the wet granules in an oven at 55°C for 8 h. After 2 h of drying, scrape the semidried granules to break any lumps (for uniform drying).
   b. Check the LOD, with a limit of 2 to 3%.
   c. If required, dry further at 55°C for 1 h. Check the LOD.
   d. Transfer the dried granules into stainless steel drums.
5. Grinding and lubricating
   a. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into a drum blender.
   b. Sift Items 5 and 6 through a 500-µm sieve using a sifter, and add it into a drum blender. Mix for 2 min.
   c. Unload into stainless steel drums.
6. Compressing
   a. Compress the granules using a rotary tabletting machine with a 7-mm flat, bevel-edge punches to 115 mg per tablet.

Lorazepam Tablets (0.50 mg/1 mg/2 mg) [37]

Lorazepam, an antianxiety agent, has the chemical formula 7-chloro-5-(*0*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzo-diazepin-2-one. The active ingredient is a nearly white powder, almost insoluble in water. Each Ativan tablet, to be taken orally, contains 0.5 mg, 1 mg, or 2 mg of lorazepam. The inactive ingredients present are lactose and other ingredients.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.50	1	Lorazepam	0.50
50.00	2	Lactose	50.00
20.00	3	Starch (maize)	20.00
2.00	4	Methyl cellulose	2.00
25.00	5	Microcrystalline cellulose (Avicel PH 101)	25.00
1.00	6	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix lorazepam, lactose, starch, and one-half of the microcrystalline cellulose in a suitable mixer.
2. Granulate with a solution of the methyl cellulose in water.
3. Dry the granules. Mix in the rest of the microcrystalline cellulose and the magnesium stearate. Compress. Adjust the 1- and 2-mg strengths with lactose.

Losartan and Hydrochlorothiazide Tablets (50 mg/12.5 mg) [118]

Hyzaar (losartan potassium-hydrochlorothiazide) combines an Angiotensin II receptor (Type AT_1) antagonist and a diuretic, hydrochlorothiazide. Losartan potassium, a nonpeptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$.

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan. Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$. Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Hyzaar is available for oral administration, containing 50 mg of losartan potassium, 12.5 mg of hydrochlorothiazide, and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, and D&C Yellow No. 10 Aluminum Lake. Hyzaar contains 4.24 mg (0.108 mEq) of potassium.

Losartan Potassium Tablets (50 mg) [93]

Losartan potassium, the first of a new class of antihypertensives, is an Angiotensin II receptor (Type AT_1) antagonist. Losartan potassium, a nonpeptide molecule, is chemically described as 2-butyl-4-chloro-1[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$. Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan. Cozaar is available for oral administration, containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C Yellow No. 10 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake. Cozaar 25-mg and 50-mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Losartan potassium	50.00
46.00	2	Microcrystalline cellulose	46.00
75.50	3	Lactose, spray dried	75.50
7.50	4	Starch 1500	7.50
1.00	5	Magnesium stearate	1.00
3.00	6	Hypromellose	3.00
0.75	7	Talc, fine powder	0.75
0.75	8	Titanium dioxide	0.75
0.50	9	Polyethylene glycol	0.50
—	10	Ethanol	QS
—	11	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift losartan potassium, lactose spray dried, and microcrystalline cellulose through a stainless steel 500-µm sieve.
2. Load sifted powder into a blender, and blend well.
3. Sift magnesium stearate and Starch 1500 through a stainless steel 250-µm sieve.
4. Load Step 3 into the blender (Step 2), and blend well.
5. Compress 185 mg into 12-mm punches.
6. Coat the tablet using Eudragit L-100 coating. (See Appendix.)

Mebendazol Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Mebendazol	100.00
196.00	2	Ludipress	196.00
4.00	3	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 294 mg in 12-mm biplanar punches.

Meclizine Hydrochloride Tablets (25 mg) [135]

Meclizine hydrochloride, an oral antiemetic, is a white, slightly yellowish, crystalline powder that has a slight odor and is tasteless. The chemical name is 1-(ρ-chloro-α-phenylbenzyl)-4-(*m*-methyl-benzyl)-piperazine dihydrochloride monohydrate. Meclizine hydrochloride tablets are multiple-layered tablets (MLT) available in 12.5-mg, 25-mg, and 50-mg strengths for oral administration. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, starch, stearic acid, and other ingredients. In addition, the 12.5-mg tablet contains FD&C Blue No. 1; the 25-mg tablet contains D&C Yellow No. 10 and FD&C Yellow No. 5; and the 50-mg tablet contains D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Yellow No. 5.

Medroxyprogesterone Acetate Tablets (2.5 mg/5 mg/10 mg) [89]

Medroxyprogesterone acetate is a derivative of progesterone and is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6α)-. *Tablets:* Each Provera tablet for oral administration contains 2.5 mg, 5 mg, or 10 mg of medroxyprogesterone acetate. The inactive ingredients are calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, sucrose, and talc. The 2.5-mg tablet contains FD&C Yellow No. 6.

Mefanamic Acid and Dicyclomine Hydrochloride Tablets (250 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Mefanamic acid	250.00
10.00	2	Dicyclomine hydrochloride	10.00
30.00	3	Lactose monohydrate	30.00
16.00	4	Starch (maize)	16.00
4.80	5	Gelatin	4.80
3.20	6	Polyvinylpyrrolidone potassium 30	3.20
6.00	7	Talc	6.00
6.00	8	Magnesium stearate	6.00
6.00	9	Sodium starch glycolate	6.00
4.00	10	Aerosil 200	4.00
0.80	11	Methyl paraben	0.80
0.08	12	Propyl paraben	0.08
—	13	Water, purified, ca	75 ml

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a suitable mixer after passing them through a 250-µm sieve. Mix the items for 10 min.
2. In a separate vessel, bring to boil Item 13, and add Items 11 and 12 at 90°C to dissolve. Add Items 4 to 6 to the hot solution, and stir to disperse into a smooth slurry. Cool to 50°C.
3. Add Step 2 into Step 1, and mix thoroughly to obtain a lump-free wet mass. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays. Dry the granules at 50°C overnight until an LOD of not more than 2% is reached.
4. Pass the dried granules through a 1.19-mm mesh screen into a suitable tumbler.
5. Sift Items 9 and 10 through a 500-µm sieve and Item 8 through a 250-µm sieve into Step 4, and blend for 3 min.
6. Compress 335 mg using 9.5-mm punches.

Mefenamic Acid Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Mefenamic acid	250.00
40.00	2	Starch (maize)	40.00
5.00	3	Kollidon 90 F	50.00
—	4	Isopropyl alcohol	QS
12.00	5	Kollidon CL	12.00
85.00	6	Microcrystalline cellulose (Avicel PH 101)	85.00
5.00	7	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 and 2 with the solution of Items 3 and 4, sieve, dry, and add a mixture of Items 5 to 7.
2. Compress with medium-compression force. Compress 404 mg in 12-mm punches.

Mefloquine Hydrochloride Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00 275.00	1	Mefloquine, use mefloquine hydrochloride	250.00 275.00
50.00	2	Lactose monohydrate	50.00
65.00	3	Maize (starch)	65.00
3.00	4	Polyoxyl 40 stearate	3.00
10.00	5	Polyvinyl pyrrolidone (PVP K-30)	10.00
65.00	6	Microcrystalline cellulose (Avicel PH 102)	65.00
25.00	7	Crospovidone (Kollidone CL)	25.00
2.00	8	Magnesium stearate	2.00
5.00	9	Talc, fine powder	5.00
QS	10	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift mefloquine hydrochloride, lactose monohydrate, and maize starch through a 0.500-mm stainless steel sieve.
2. Dissolve polyoxyl 40 stearate and PVP K-30 in purified water (70 to 80°C) by slow stirring, until it becomes clear. Cool the solution to 25 to 30°C. This is the granulating solution.
3. Knead the powder mix with granulating solution to get the desired wet mass.
4. Pass the wet mass through #8 mesh onto drying trays.
5. Dry the granules to a targeted LOD of 2%.
6. Pass the dried granules through #16 mesh.
7. Sift Avicel PH 102 and Kollidone CL through a 0.500-mm stainless steel sieve.
8. Load the ground granules from Step 5 and the powder mix from Step 6 into a suitable blender. Blend for 2 min to get a homogeneous mixture.
9. Sift magnesium stearate and talc fine powder through a stainless steel 500-µm sieve. Add the powder mix in Step 7. Blend these items for 1 min.
10. Compress 500 mg in 15-mm suitable punches.
11. Coat using a hypermellose coating. (See Appendix.)

Meprobamate and Phenobarbital Tablets (400 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Meprobamate	400.00
30.00	2	Phenobarbital	30.00
76.00	3	Microcrystalline cellulose (Avicel PH 101)	76.00
13.00	4	Kollidon VA 64	13.00
21.00	5	Kollidon CL	21.00
8.00	6	Talc	8.00
1.00	7	Aerosil 200	1.00
1.00	8	Calcium arachinate	1.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix, and press with low-compression force.
2. Compress 551 mg in 12-mm biplanar punches.

Meprobamate and Phenobarbital Tablets (400 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Meprobamate	400.00
30.00	2	Phenobarbital	30.00
13.00	3	Kollidon VA 64	13.00
—	4	Isopropyl alcohol	QS
21.00	5	Kollidon CL	21.00
50.00	6	Starch (maize)	50.00
8.00	7	Talc	8.00
1.00	8	Aerosil 200	1.00
1.00	9	Calcium arachinate	1.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 and 2 with a solution of Items 3 and 4. Dry, pass through a 0.8-mm sieve, mix with Items 5 to 9, and press with low-compression force.
2. Compress 559 mg in 12-mm biplanar punches.

Meprobamate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Meprobamate	400.00
80.00	2	Microcrystalline cellulose (Avicel PH 101)	80.00
30.00	3	Starch (maize)	30.00
20.00	4	Kollidon VA 64	20.00
20.00	5	Kollidon CL	20.00
7.00	6	Talc	7.00
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (20 kN).
2. Compress 560 mg in 12-mm biplanar punches.

Meprobamate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Meprobamate	400.00
100.00	2	Starch (maize)	100.00
15.00	3	Kollidon 25 or Kollidon VA 64	15.00
4.50	4	Lutrol E 400[a]	4.50
—	5	Isopropyl alcohol	QS
2.00	6	Talc	2.00
0.20	7	Aerosil 200	0.20
0.30	8	Calcium arachinate	0.30

[a] Use only if selecting Kollidon 25 as Item 3.

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 to 5. Pass through a 0.8-mm sieve, add Items 6–8, and press.
2. Compress 520 mg (515 mg if deleting Item 4) in 12-mm biplanar punches.

Metamizol Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metamizol sodium (dipyrone)	500.00
100.00	2	Ludipress	100.00
10.00	3	Kollidon CL	10.00
10.00	4	Magnesium stearate	10.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.5-mm sieve, and press with low-compression force.
2. Compress 625 mg in 12-mm biplanar punches.

Metamizol Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metamizol sodium (dipyrone)	500.00
100.00	2	Microcrystalline cellulose (Avicel PH 101)	100.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
1.00	5	Aerosil 200	1.00
8.00	6	Talc	8.00
1.00	7	Calcium arachinate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.5-mm sieve, and press with low-compression force.
2. Compress 654 mg in 12-mm biplanar punches.

Metformin Hydrochloride Tablets, Extended Release (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metformin hydrochloride	500.00
240.00	2	Lactose anhydrous	240.00
250.00	3	Hydroxypropyl cellulose	250.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 4 through a 250-μm mesh, and charge in a suitable blender. Mix these materials for 15 min.
2. Add Item 5, and mix for 3 to 7 min.
3. Compress 1000 mg to a hardness of 16 to 20 kp in a suitable 15-mm punch. Adjust the weight and punch size for lower or higher strength.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metformin hydrochloride	500.00
190.00	2	Lactose anhydrous	190.00
300.00	3	Polyethylene oxide	300.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

4. Compress 1000 mg; adjust the weight for higher or lower strength.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metformin hydrochloride	500.00
160.00	2	Lactose anhydrous	160.00
330.00	3	Hydroxypropyl cellulose	330.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

5. Compress 1000 mg; adjust the weight for lower or higher strength.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metformin hydrochloride	500.00
45.90	2	Dibasic calcium phosphate	45.90
329.60	3	Hydroxypropyl cellulose	329.60
92.70	4	Ethyl cellulose	92.70
51.50	5	Povidone	51.50
5.15	6	Colloidal silicon dioxide	5.15
5.15	7	Magnesium stearate	5.15

6. Compress 1030 mg; adjust the weight for higher or lower strength.

Metformin Tablets (500 mg) [40]

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of noninsulin-dependent diabetes mellitus (NIDDM). Metformin HCl (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to the oral sulfonylureas.

Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68.

Metformin HCl tablets contain 500 mg and 850 mg of metformin HCl. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate, and hydroxypropyl methylcellulose (hypromellose) coating.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
100.00	2	Dicalcium phosphate	100.00
15.00	3	Kollidon 90 F	15.00
8.00	4	Kollidon 90 F	8.00
—	5	Isopropyl alcohol	90.00
5.00	6	Kollidon CL	5.00
15.00	7	Polyethylene glycol 6000 powder	15.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 to 3 with the solution of Items 4 and 5. Mix these granules with Items 6 and 7, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress 650 mg using 12-mm biplanar punches. If hardness is the problem, reduce the amount of Kollidon 90 F.

Metformin Tablets, Extended Release (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metformin	500.00
240.00	2	Lactose monohydrate	240.00
250.00	3	Hydroxypropyl cellulose	250.00
5.00	4	Silicon dioxide colloidal	5.00
5.00	5	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a suitable blending vessel, after passing through a 250-μm sieve.
2. Sift Items 4 and 5 through a 250-μm sieve, and add to Step 1.
3. Blend for 3 to 5 min.
4. Compress 1000 mg at 18 to 20 kp.

Methenamine Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Methenamine powder	500.00
0.50	2	Gelatin powder	0.50
4.50	3	Magnesium stearate	4.50

MANUFACTURING DIRECTIONS

1. Accurately weigh methenamine, gelatin, and magnesium stearate.
2. Mix methenamine and gelatin in a suitable blender for 15 min. Add magnesium stearate, and mix for additional 5 min.
3. Compress 505 mg in 3/8-in. round punch at 5 kg of pressure.

Methyclothiazide and Deserpidine Tablets (5 mg/0.25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Methyclothiazide	5.00
0.25	2	Deserpidine	0.25
7.80	3	Starch (corn)	7.80
166.80	4	Lactose monohydrate	166.80
6.80	5	Starch (corn)	6.80
QS	6	Water, purified, ca	30 ml
6.80	7	Talc	6.80
1.50	8	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

CAUTION: This is an expensive preparation — keep losses to a minimum. Deserpidine is poisonous — handle carefully. Maintain a low relative humidity during processing and storing.

1. Granulation
   a. Load methyclothiazide, deserpidine, and starch (Item 3) together with an equal quantity of lactose into a mixer, and blend for 30 min. Cover the mixing bowl during this operation.
   b. Pass blended materials from Step 1 through a 250-µm sieve aperture screen at high speed (hammers forward using an Apex mill or similar mill).
   c. Load the milled ingredients from Step 2 into the mixer, add the balance of the lactose, and dry blend for 30 min.
   d. Mix starch (Item 5) with 30 ml of cold purified water, and heat to make a paste.
   e. Add the hot starch paste to the blended powders in the mixer, and mass for 1 to 3 min. *Note:* Overmixing and overwetting will prolong tablet disintegration time.
   f. Pass the wet mass through a 4.76-mm aperture screen, and spread onto trays.
   g. Load trays of wet granulation into the oven, and dry for 4 h at 49°C. *Note:* It is essential to use a full oven load of trays.
   h. Remove the dried granulation from the oven, and pass through an 840-µm aperture screen, or pass mill-dried granulation through a 600-µm aperture screen using a Fitz mill, impact forward, high speed into polyethylene-lined drums. Tie liners tightly. *Note:* The Fitz mill method may improve dissolution.
2. Lubrication
   a. Load approximately 20% of granulation into blender.
   b. Mix talc and magnesium stearate, while milling through a 600-µm aperture screen, impact forward, high speed on a Fitz mill or similar mill, and load into the blender.
   c. Charge the remaining granulation into blender, and *blend for 14 min only. Note:* If lumps are present after several minutes of blending, it may be necessary to put the entire granulation through a 1.19-mm aperture, and then continue blending to the required time. *Note:* Overblending results in increased tablet disintegration time.
   d. Discharge into polyethylene-lined drums. Seal containers well.
3. Compression
   a. Compress using standard 7-mm concave square punches.

Methyclothiazide Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.20	1	Starch (corn)	5.20
QS	2	Dyes	QS
5.00	3	Methyclothiazide	5.00
9.40	4	Starch (corn)	9.40
166.40	6	Lactose monohydrate	166.40
QS	7	Water, purified, ca	25 ml
6.80	8	Talc	6.80
2.00	9	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Granulation and lubrication
   a. Make starch paste, using cornstarch (Item 1) and purified water.
   b. Mix dyes with Item 3, cornstarch (Item 4), and an equal amount of lactose, and mill through a comminuting mill using a 177-µm aperture screen, impact forward, high speed. Charge into the mixer. Add the balance of lactose to the mixer (mill through a 420-µm aperture screen, impact forward, high speed, if lumpy), and dry mix for 10 min.
   c. Add hot starch paste from Step 1 to the mixer. Mix until granular but not longer than 5 min. If necessary, 1.8 ml of purified water may be added to wet the mass during mixing. *Note:* Over mixing and over wetting will prolong the tablet disintegration time.
   d. Granulate the wet mass through a comminuting mill, using a 15.88-mm aperture band, and spread on trays.
   e. Dry at 60°C until the LOD is 1%, or less, when tested for 60 min in a Brabender (or equivalent) set at 105°C.
   f. Sift the dried granulation through a 1.19-mm aperture screen, and mill the coarse material through a comminuting mill fitted with a 1.59-mm aperture band, knives forward, at medium speed.
   g. Charge one-half of the granulation into the blender. Mix talc and magnesium stearate, while milling through a 600-µm aperture screen, impact forward, high speed, and charge into the blender. Charge the remaining half of the granulation into the blender, and *blend for 4 min only.*
   h. Discharge a portion of the granulation from the blender, and check for white lumps. If present, discharge the entire granulation from the blender through a 1.19-mm aperture screen to break lumps, and then return to the blender. Charge the remaining granulation into the blender, and *blend for 10 min only*. *Note:* Over blending results in increased tablet disintegration time.
   i. Discharge the blender into tared, polyethylene-lined drums. Seal, weigh, and deliver the drums to the storage area.
2. Compress in concave 7.1-mm punches; weight is 195 mg (to be determined based on amount of dyes used).

Methylergotamine Malate Tablets (0.5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.50	1	Methylergotamine malate, 10% excess	0.55
0.15	2	Maleic acid	0.15
5.25	3	Starch (maize)	5.25
47.08	4	Lactose monohydrate	47.08
1.00	5	Starch (maize)	1.00
0.50	6	Stearic acid	0.50
2.30	7	Talc	2.30
2.30	8	Magnesium stearate	2.30
	9	Water, purified, ca	60 ml

MANUFACTURING DIRECTIONS

1. Sift Items 2, 4, and 5 though a 250-µm sieve in a suitable mixing vessel. Mix the items for 5 min.
2. In a separate vessel, charge Item 5 and add a sufficient amount of hot Item 9 to make a paste.
3. Add Step 2 into Step 1, and make a suitable wet mass. Pass the wet mass through a 2.38-mm sieve onto drying trays.
4. Dry the granules at 50°C overnight to an LOD of not more than 3%.
5. Pass the granules through a #20-mesh sieve into a blending vessel.
6. Pass Item 1 through a 250-µm sieve, and, using a geometric dilution with granules in Step 5, add and mix Item 1 into Step 5.
7. Pass Items 6 and 7 through a 500-µm sieve and Item 8 through a 250-µm sieve, and add all three items to Step 6. Blend for 2 min. (Do not over blend.)
8. Compress 58 mg using 3-mm punches.
9. Provide a sugar coating to a final weight of 100 mg per tablet and a diameter of 5 mm. (See Appendix for sugar coating formulations.)

Methylphenidate Hydrochloride Tablets Extended Release (18 mg/36 mg) [122]

Concerta™ (methylphenidate HCl; available in extended-release tablets CII) is a central nervous system (CNS) stimulant. Concerta™ is available in two tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18 or 36 mg of methylphenidate HCl USP and is designed to have a 12-h duration of effect. Chemically, methylphenidate HCl is *d,l* (racemic) methyl *a*-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \cdot HCl$.

Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Concerta also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl methylcellulose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

Concerta uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients and a push layer containing osmotically active components. There is a precision-laser-drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within 1 h, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, that, in turn, controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

Methylprednisolone Tablets (2 mg/4 mg/8 mg/16 mg/24 mg/32 mg) [99]

Methylprednisolone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol; slightly soluble in acetone and in chloroform; and very slightly soluble in ether. It is practically insoluble in water. The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-6-methyl-,(6α, 11β)-, and the molecular weight is 374.48.

Each Medrol tablet for oral administration contains 2 mg, 4 mg, 8 mg, 16 mg, 24 mg, or 32 mg of methylprednisolone. The inactive ingredients found in Medrol are as follows: *2 mg:* calcium stearate, cornstarch, erythrosine sodium, lactose, mineral oil, sorbic acid, and sucrose; *4 and 16 mg:* calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, and sucrose; *8 and 32 mg:* calcium stearate, cornstarch, FD&C Yellow No. 6, lactose, mineral oil, sorbic acid, and sucrose; *24 mg:* calcium stearate, cornstarch, FD&C Yellow No. 5, lactose, mineral oil, sorbic acid, and sucrose.

Metoclopramide Tablets (10 mg) [138]

Metoclopramide hydrochloride is a white, crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. The molecular weight is 354.3.

Reglan tablets (metoclopramide tablets, USP), 10 mg, are white, scored, capsule-shaped tablets engraved with "Reglan" on one side and "AHR 10" on the opposite side. Each tablet contains 10 mg of metoclopramide base (as the monohydrochloride monohydrate). The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose, and stearic acid.

Reglan tablets, 5 mg, are green, elliptical-shaped tablets engraved with "Reglan 5" on one side and "AHR" on the opposite side. Each tablet contains 5 mg of metoclopramide base (as the monohydrochloride monohydrate). The inactive ingredients are cornstarch, D&C Yellow No. 10 Lake, FD&C Blue No. 1 Aluminum Lake, lactose, microcrystalline cellulose, silicon dioxide, and stearic acid.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Metoclopramide hydrochloride	10.00
89.50	2	Ludipress	89.50
0.50	3	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress 100 mg in 6-mm biplanar punches.

Metoclopramide Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Metoclopramide hydrochloride anhydrous, use metoclopramide hydrochloride	10.54
7.00	2	Starch (maize), dried	7.00
1.00	3	Silicon dioxide colloidal	1.00
0.76	4	Magnesium stearate	0.76
5.00	5	Starch pregelatinized	5.00
101.24	6	Lactose	101.24
—	7	Water purified (deionized)	15.00 ml

MANUFACTURING DIRECTIONS

1. Granulation
   Note: Dried cornstarch must be used for lubrication. Dry the starch at 80°C for 36 h before its use in manufacturing. Check the LOD of the starch. The LOD must be less than 2% (1 h on Brabender at 105°C or equivalent).
   a. Pass the lactose, starch pregelatinized, and metoclopramide hydrochloride through a 1.25-mm aperture screen, transfer to a suitable mass mixer, and mix for 5 min.
   b. Add the water slowly to the mixer, and mix for 30 min or until a suitable consistency is obtained. Add extra water if required.
   c. Pass the mass through a 4.8-mm aperture screen or an oscillating granulator (or by hand), and dry in a tray dryer or fluid-bed dryer at 50°C until the moisture content is below 5.5%.
   d. Arrange for samples.
   e. Pass the granule through an 875-µm aperture screen on an oscillating granulator (or comminuting mill at medium speed, knives forward) into tared polyethylene-lined drums. Then seal the drums and weigh.
2. Lubrication
   Note: Carry out at a relative humidity below 50% and temperature below 26°C.
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the starch (Item 2), magnesium stearate, and silicon dioxide through a 250-µm sieve aperture screen on a sieve shaker, and add to the blender. Blend for 10 min.
   c. Discharge the granules into polyethylene-lined drums, seal, and weigh for yield.
3. Compressing
   Note: Carry out at a relative humidity below 50% and at temperature below 26°C.
   a. Compress using 7.14-mm round, standard concave punches or 6.35-mm round, standard concave punches.
   b. Compress to the following specifications: weight of 10 tablets = 1.255 g ± 3%.

Metoprolol Succinate Tablets (95 mg) [21]

Toprol-XL, metoprolol succinate, is a β_1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. Toprol-XL was formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5 mg, 95 mg, and 190 mg of metoprolol succinate equivalent to 50, 100, and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt). Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; and practically insoluble in ethyl-acetate, acetone, diethylether, and heptane. The inactive ingredients are silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, and paraffin.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Metoprolol succinate	95.00
25.00	2	Polyoxol 40 hydrogenated	25.00
230.00	3	Hydroxypropyl methyl cellulose	230.00
94.00	4	Aluminum silicate	94.00
—	5	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Mix metroprolol with polyoxyl 40 hydrogenated castor oil, and then carefully mix it with the carrier materials, HPMC and aluminium silicate.
2. Granulate the mixture with ethanol, and dry the granules.
3. Add lubricant, and compress.

Metoprolol Tartrate Tablets [36]

Metoprolol tartrate is a selective β_1-adrenoreceptor blocking agent, available as 50- and 100-mg tablets for oral administration and in 5-ml ampules for intravenous administration. Each ampule contains a sterile solution of metoprolol tartrate, 5 mg, and sodium chloride, 45 mg. Metoprolol tartrate is (±)-1-(isopropylamino)-3-(*p*-(2-(methoxyethyl)phenoxy)-2-propanol (2:1) *dextro*-tartrate salt.

Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

The Lopressor tablets contain the following inactive ingredients: cellulose compounds, colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (50-mg tablets), FD&C Blue No. 2 Aluminum Lake (100-mg tablets), lactose, magnesium stearate, polyethylene glycol, propylene glycol, povidone, sodium starch glycolate, talc, and titanium dioxide.

Metronidazole Effervescent Vaginal Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Materials Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metronidazole	500.00
600.00	2	Sodium bicarbonate	600.00
30.00	3	Kollidon 30	30.00
10.00	4	Kollidon 30	10.00
—	5	Isopropyl alcohol	150 ml
500.00	6	Tartaric acid	500.00
50.00	7	Polyethylene glycol 6000 powder	50.00

MANUFACTURING DIRECTIONS

1. Granulate Items 1 and 2 with the solution of Items 3 and 4. Pass through a 0.8-mm sieve, mix with Items 6 and 7, and press.
2. Compress 1700 mg in 16-mm biplanar punches.

Metronidazole, Furazolidone, and Loperamide Tablets (200 mg/25 mg/2 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Metronidazole	200.00
25.00	2	Furazolidone	25.00
2.00	3	Loperamide	2.00
200.00	4	Starch (maize)	200.00
175.00	5	Dicalcium phosphate	175.00
5.00	6	Gelatin	5.00
110.00	7	Starch (maize)	110.00
1.16	8	Yellow dye	1.16
4.00	9	Magnesium stearate	4.00
2.00	10	Talc	2.00
—	11	Water, purified, ca	500 ml

MANUFACTURING DIRECTIONS

1. Sift Items 1, 2, 4, and 5 through a #40 mesh sieve into a mixing vessel.
2. Mix for 10 min, and use this mix to dilute Item 1 into the same vessel.
3. In a separate vessel, heat Item 11 to 90°C, and add Items 6 to 8. Stir to make a smooth slurry containing 30% starch.
4. Add the slurry in Step 3 into Step 2, and mix until a suitable mass for granulation is obtained. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays.
5. Dry the granules at 50°C overnight to meet an LOD of not more than 2.5%.
6. Pass the dried granules through a 1.19-mm mesh into a blending vessel.
7. Pass Item 9 though a 250-µm sieve and Item 10 through a 500-µm sieve into Step 6. Blend for 2 min.
8. Compress 680 mg in 13-mm punches.

Metronidazole Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Metronidazole	200.00
200.00	2	Avicel PH 101	200.00
6.00	3	Kollidon 30	6.00
10.00	4	Kollidon CL	10.00
5.00	5	Aerosil 200	5.00
5.00	6	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25 to 30 kN).
2. Compress 426 mg in 12-mm biplanar punches.

Metronidazole Tablets (200 mg/400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Metronidazole	400.00
150.00	2	Lactose monohydrate	150.00
37.50	3	Starch (corn)	37.50
30.00	4	Povidone K 29-32	30.00
37.50	5	Starch (corn)	37.50
QS	6	Water, purified	121.00 ml
13.00	7	Starch (corn)	13.00
1.25	8	Magnesium stearate	1.25

Note: For 200-mg strength, scale down the BOM proportionally, as given above, and compress using a 9.5-mm round, standard concave punch. The thickness should be 4.3 to 4.9 mm (range: *not more than* ± 5%); hardness: NTL 7 to 17; disintegration time: *not more than* 15 min in water.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Make a starch paste using starch (corn) (Item 3) and purified water (distilled) (Item 6) in a stainless steel container.
   b. Pass the following items through a 595-µm aperture screen, and transfer to a suitable mixer: metronidazole, lactose, and starch (corn) (Item 5).
   c. Add the povidone to the mixer, and mix for 5 min.
   d. Add the starch paste from Step 1 to the mixer, and mix until a suitable consistency mass is obtained. Add extra water if required.
   e. Pass the wet mass through a 2.36-mm screen on a suitable granulator.
   f. Spread the granules on paper-lined trays, and dry in an oven at 50°C until the moisture content is not more than 5.5%.
   g. Request samples for moisture content.
   h. Pass the dried granules through a 1.59-mm aperture screen on a suitable comminuting mill, at medium speed, with knives forward, into tared, polyethylene-lined drums. Then seal the drums and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the following items through a 595-µm aperture screen, and add the following to the blender: starch (corn) (Item 7) and magnesium stearate. Blend for 5 min.
   c. Discharge the granule into polyethylene-lined drums, seal, and weigh for yield.
3. Compression
   a. Compress using 12.7-mm round, standard concave punches.
4. Coating
   a. Coat using a methocel coating. (See Appendix.)

Metronidazole Tablets (400 mg) [147]

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole. Metronidazole tablets contain 250 mg or 500 mg of metronidazole. Inactive ingredients include cellulose, FD&C Blue No. 2 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, stearic acid, and titanium dioxide.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Materials Name**	**Quantity/1000 Tablets (g)**
400.00	1	Metronidazole	400.00
150.00	2	Avicel PH 102	150.00
25.00	3	Kollidon VA 64	25.00
15.00	4	Kollidon CL	15.00
5.00	5	Aerosil 200	5.00
50.00	6	Polyethylene glycol 6000, powder	50.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25 to 30 kN).
2. Compress 645 mg in 12-mm biconvex punches.

Metronidazole Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Metronidazole	500.00
220.00	2	Sorbitol, crystalline	220.00
10.00	3	Kollidon 90 F	10.00
—	4	Ethanol 96%, ca	75.00
20.00	5	Kollidon CL	20.00
4.00	6	Talc	4.00
0.50	7	Aerosil 200	0.50
0.50	8	Calcium arachinate	0.50

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with the solution of Items 3 and 4. Pass the mixture through a 0.8-mm sieve, dry it, mix it with Items 5 to 7, and press it with medium-compression force.
2. Compress 755 mg in 16-mm biplanar punches.

Mirtazapine Tablets [145]

Remeron® (mirtazapine) tablets are an antidepressant for oral administration. Mirtazapine has a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors (SSRIs), tricyclics, or monoamine oxidase inhibitors (MAOIs). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated as 1,2,3,4,10,14*b*-hexahydro-2-methylpyrazino[2,1-*a*] pyrido [2,3-*c*] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36.

Mirtazapine is a white to creamy white crystalline powder that is slightly soluble in water. Remeron is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine and unscored film-coated tablets containing 45 mg of mirtazapine. Each tablet also contains cornstarch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose, and other inactive ingredients.

Montelukast Sodium Tablets (5 mg) [54]

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor. Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt. The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18.

Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water; and it is practically insoluble in acetonitrile.

Each 10-mg film-coated Singulair tablet contains 10.4 mg of montelukast sodium, which is the molar equivalent to 10 mg of free acid, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red iron oxide, yellow iron oxide, and carnauba wax.

Each 5-mg chewable Singulair tablet contains 5.2 mg of montelukast sodium, which is the molar equivalent to 5 mg of free acid, and the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Nalidixic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Nalidixic acid	500.00
20.00	2	Lactose monohydrate	20.00
25.00	3	Starch (maize)	25.00
30.00	4	Starch (maize)	30.00
0.10	5	Propyl paraben	0.10
0.40	6	Methyl paraben	0.40
0.80	7	Sodium starch glycolate	0.80
2.50	8	Magnesium stearate	2.50
1.00	9	Talc	1.00
0.20	10	Aerosil 200	0.20
2.00	11	Starch (maize), dried	3.00
—	12	Water, purified, ca	400 ml

MANUFACTURING DIRECTIONS

1. Sift Items 1 and 2 through a #40 mesh sieve into a suitable blending vessel.
2. Sift Item 3 through #80 mesh sieve, add to Step 1, and mix for 10 min.
3. In a separate vessel, sift Item 4 through #80 mesh, add Items 5 and 6, and mix for 5 min. Add Item 12 at 80°C to prepare a 30% starch paste that is smooth and lump-free.
4. Add Step 3 into Step 2, and make a wet mass suitable for granulation.
5. Pass the wet mass through a 10-mm sieve in a mill, and dry in a fluid-bed dryer at 50°C for 1 h to an LOD of not more than 3%. Transfer to a blending vessel.
6. Sift Items 7 to 11 through a 250-µm sieve screen, and add to Step 5. Blend for 1 min only.
7. Compress 575-mg tablets in 13-mm punches.

Nalidixic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Nalidixic acid	500.00
15.00	2	Kollidon 30	15.00
—	3	Water, purified	125.00
25.00	4	Kollidon CL	25.00
5.00	5	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Granulate Item 1 with the solution of Item 2 in Item 3. Dry, and pass through a 0.8-mm sieve. Add the mixture of Items 4 and 5, mix during 10 min, pass again through a 0.8-mm sieve, and press with low-compression force (10 kN).
2. Compress 545 mg in 12-mm biplanar punches.

Naproxen Tablets (250 mg) [58]

Naproxen tablets for oral administration each contain 250 mg, 375 mg, or 500 mg of naproxen. Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical name for naproxen is 2-naphthaleneacetic acid, 5 methoxy-α-methyl-,(+). Naproxen is an odorless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH, and is freely soluble in water at high pH.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Naproxen	250.00
6.00	2	Kollidon 90 F	6.00
4.00	3	Kollidon 90 F	4.00
4.00	4	Cremophor RH40	4.00
—	5	Water	41.00
150.00	6	Tablettose	150.00
1.00	7	Stearic acid	1.00
10.00	8	Ac-Di-Sol	10.00
1.00	9	Magnesium stearate	1.00
10.00	10	Polyethylene glycol 6000 powder	10.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 to 5, dry, pass through a 0.8-mm sieve, add Items 6 to 9, and press with low-compression force.
2. Compress 441 mg in 12-mm biplanar punches.

Naproxen Tablets (250 mg/500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Naproxen	250.00
78.40	2	Lactose monohydrate	78.40
7.00	3	Starch (corn)	7.00
4.00	4	Sodium starch glycolate	4.00
0.60	5	Yellow dye	0.60
5.00	6	Povidone K 29-32	5.00
5.00	7	Polysorbate 80	5.00
QS	8	Isopropyl alcohol, ca	200.00 ml
3.70	9	Talc	3.70
3.30	10	Magnesium stearate	3.30

Note: For 500-mg strength, use the same formula with higher fill weight.

MANUFACTURING DIRECTIONS

1. Granulation
   a. Pass naproxen and lactose through a 16-mesh (1.2-mm aperture) screen into a planetary mixer (or something similar). Mix these items for 10 min.
   b. To a suitable blender, add starch (corn), sodium starch glycolate, and yellow dye. Blend these items for 10 min.
   c. Incorporate the blended powders from Granulation, Step 1b, into the blend in Granulation, Step 1a. Mix for 10 min.
   d. Dissolve povidone and polysorbate 80 in alcohol isopropyl. The solution must be complete.
   e. While mixing the blended powders from Granulation, Step 1c, add the solution from Granulation, Step 1d. When all the solution is added, continue mixing for 2 min, until a characteristic mass is obtained. Add more alcohol isopropyl, if required. Record the additional amount of alcohol isopropyl.
   f. Pass the wet mass through an 8-mesh (2.38-mm aperture) screen by hand. Load the granular mass onto paper-lined trays, and oven dry at 49°C until the LOD is between 1.5 and 2.5%.
   g. Pass the dried granules through a Fitz mill fitted with a 2A band (knives forward, medium speed) into tared, polyethylene-lined drums.
2. Lubrication
   a. Transfer the dried granules from Granulation, Step 1g to a suitable blender.
   b. Screen talc and magnesium stearate through a 30-mesh (595-µm aperture) screen, and add this to the blender. Blend this mixture for 10 min.
   c. Discharge the granules into clean, tared, polyethylene-lined drums. Then seal the drums, and weigh for yield.
3. Compression
   a. Compress on a suitable compression machine using 9.5-mm round, standard concave punches — tablet weight: 352 mg.

Naproxen Tablets (450 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
450.00	1	Naproxen	457.50
10.00	2	Kollidon CL	10.00
25.00	3	Kollidon 30	25.00
—	4	Water, purified	90.00
2.50	5	Magnesium stearate	2.50

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4, pass through a 0.8-mm sieve, add Item 5, and press to tablets with low-compression force.
2. Compress 496 mg in 12-mm biplanar punches.

Neomycin Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Neomycin sulfate	250.00
334.00	2	Ludipress	334.00
6.00	3	Magnesium stearate	6.00
10.00	4	Aerosil 200	10.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with low-compression force.
2. Compress 600 mg in 12-mm biplanar punches.

Nifedipine Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Nifedipine	5.00
60.00	2	Starch (maize)	60.00
40.00	3	Lactose monohydrate	40.00
40.00	4	Dicalcium phosphate	40.00
4.00	5	Polyvinylpyrrolidone K30	4.00
0.04	6	Isopropyl alcohol	40 ml
2.00	7	Magnesium stearate	2.00
1.00	8	Talc	1.00

MANUFACTURING DIRECTIONS

1. Sift Item 1 through #40 mesh into a suitable mixing vessel. Sift Items 2 to 4 through a 250-µm sieve into the same vessel, portion by portion, mixing with Item 1 to achieve geometric dilution. Dry the mix for 15 min.
2. In a separate vessel, prepare the binding solution by dissolving Item 5 and Item 6.
3. Add the binding solution from Step 2 into Step 1 slowly, and mix until a suitable mass is obtained.
4. Pass the wet mass through a #6 sieve onto trays, and dry it overnight in a dehumidified room.
5. Pass dried granules through a #18 mesh sieve. Load into a blending vessel.
6. Sift Items 7 and 8 through a 250-µm sieve, and add to Step 5. Blend for 1 min.
7. Compress 150 mg in 7-mm punches.
8. Coat with an HPMC organic coating. (See Appendix.)

Nifedipine Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Nifedipine	10.00
40.00	2	Kollidon 25	40.00
—	3	Methylene chloride	180.00
105.00	4	Microcrystalline cellulose (Avicel PH 102)	105.00
20.00	5	Starch (maize)	20.00
25.00	6	Kollidon CL	25.00
0.40	7	Magnesium stearate	0.40

MANUFACTURING DIRECTIONS

1. Dissolve a mixture of Items 1 and 2 in Item 3. Granulate the mixture of Items 4 to 6 with the solution prepared previously, then sieve, dry the obtained coprecipitate, add Item 7, and press with low- to medium-compression force.
2. Compress 223 mg in 8-mm punches.

Nimesulide Dispersible Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Nimesulide	100.00
120.00	2	Lactose monohydrate	120.00
100.00	3	Starch (maize)	100.00
0.40	4	Sodium metabisulfite	0.40
0.40	5	Propyl paraben	0.40
30.00	6	Starch (maize)	30.00
5.00	7	Talc	5.00
1.50	8	Magnesium stearate	1.50
2.50	9	Flavor	2.50
11.20	10	Sodium starch glycolate	11.20
—	11	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 3 through a #40 mesh sieve into a suitable mixer, and mix for 15 min.
2. In a separate vessel, prepare the binding paste by taking an appropriate quantity of Item 11, heating it to 90°C, adding Item 5, and dissolving. Add Item 4 and dissolve. Finally, add Item 6, and make a smooth slurry (30% starch).
3. Add Step 2 into Step 1, and form a lump-free mass.
4. Pass the wet mass through an 8-mm sieve, and load onto trays. Dry the mass at 50°C, overnight, to less than 2% moisture.
5. Pass the dried granules through a #18 mesh sieve into a blending vessel.
6. Sift Items 7 to 10 through a 250-μm sieve into Step 4, and blend for 1 min.
7. Compress 358 mm in 40-mm punches.

Nitrendipine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Nitrendipine	26.00
53.00	2	Ludipress	53.00
1.50	3	Kollidon CL	1.50
0.50	4	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.5-mm sieve, mix, and press with low-compression force.
2. Compress 82 mg in 6-mm biplanar punches.

Nitrofurantoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Nitrofurantoin	100.00
20.00	2	Starch (maize)	20.00
38.00	3	Lactose monohydrate	38.00
10.00	4	Kollidon 30	10.00
—	5	Water, purified	QS
5.00	6	Kollidon CL	5.00
8.00	7	Starch (maize)	8.00
4.00	8	Talc	4.00
1.00	9	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 to 3 with a solution of Items 4 and 5, dry, sieve, mix with Items 6 to 9, and press.
2. Compress 180 mg in 8-mm punches.

Nitrofurantoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Nitrofurantoin	100.00
200.00	2	Ludipress	200.00
2.00	3	Magnesium stearate	2.00
3.00	4	Aerosil 200	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 307 mg in 12-mm punches.

Nitroglycerine Tablets (0.3 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.30	1	Nitroglycerin, use 1.95% mixture (diluted nitroglycerin)[a]	15.38
0.61	2	Glyceryl monostearate	0.61
16.37	3	Lactose monohydrate	16.37
0.065	4	Silicon dioxide colloidal	0.065
2.10	5	Pregelatinized starch	2.10
0.10	6	Calcium stearate	0.105

[a] Adjust quantity based on assay with Item 3. Do not add any excess.

MANUFACTURING DIRECTIONS

1. Mill glyceryl monostearate (Myvaplex 600P) and lactose monohydrate in a suitable mixing vessel equipped with an intensifier bar.
2. Separately mill silicon dioxide and lactose monohydrate together.
3. Add diluted nitroglycerin USP to Step 1. Blend for 10 min, with the intensifier bar set to "on."
4. Add Step 2 into Step 3, and mix for 3 min.
5. Add Item 5 after passing through a 250-µm sieve to Step 4, and mix for another 5 min, with the intensifier bar set to "on."
6. Add calcium stearate to the blend in Step 5, and blend for 5 min.
7. Compress a suitable quantity into tablets.

Noramidopyrine Methansulfonate and Dicyclomine Hydrochloride Tablets (500 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Noramidopyrine methansulfonate	500.00
10.00	2	Dicyclomine hydrochloride	10.00
4.00	3	Lactose monohydrate	4.00
12.50	4	Starch (maize)	12.50
1.50	5	Gelatin	1.50
1.50	6	Magnesium stearate	1.50
1.50	7	Talc	1.50
1.50	8	Methyl carboxycellulose	1.50
1.50	9	Aerosil 200	1.50
1.50	10	Sodium metabisulfite	1.50
0.22	11	Methyl paraben	0.22
0.02	12	Propyl paraben	0.02
—	13	Isopropyl alcohol	QS
—	14	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 3 in a suitable mixing vessel, and 7 g of Item 4, and mix for 5 min.
2. In a separate vessel, take a sufficient quantity of Item 14, bring it to a boil, and dissolve in it Items 11 and 12. Allow the mixture to cool to 50°C, add Items 5 and 10, and dissolve. Add the balance of Item 4, and mix well to prepare a smooth paste.
3. Add Step 2 into Step 1, and form a smooth wet mass. Pass the mass through a 2.38-mm sieve screen over paper-lined trays, and dry at 60°C, overnight, to an LOD of not more than 3%.
4. Pass the dried granules through a #16 mesh into a blending vessel.
5. Granulate Item 2 with a sufficient quantity of Item 13 (optionally containing a dye).
6. Dry the granules in Step 4 in a dehumidified room.
7. Add Step 6 into Step 5, and mix for 5 min.
8. Sift Items 6 to 9 through a 500-μm screen, and blend for 2 min.
9. Compress 625 mg in a suitable punch.

Norethindrone and Ethinyl Estradiol Tablets (0.75 mg/0.035 mg; 0.50 mg/0.035 mg; 1.0 mg/0.035 mg) [131]

The chemical name for norethindrone is 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one, for ethinyl estradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol and for mestranol is 3-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol.

Each of the following products is a combination oral contraceptive containing the progestational compound norethindrone and the estrogenic compound ethinyl estradiol:

- Ortho-Novum 7/7/7 — Each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each light peach tablet contains 0.75 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each peach tablet contains 1 mg of norethindrone and 0.035 of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Ortho-Novum 7/7/7 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.
- Ortho-Novum 10/11 — Each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each peach tablet contains 1 mg of norethindrone and 0.035 of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Ortho-Novum 10/11 28 package contains only inert ingredients, as listed under the green tablets in the Ortho-Novum 7/7/7 28 package.
- Ortho-Novum 1/35 — Each peach tablet contains 1 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Ortho-Novum 1/35 28 package contains only inert ingredients, as listed under green tablets in the Ortho-Novum 7/7/7 28 package.
- Modicon — each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Modicon 28 package contains only inert ingredients, as listed under the green tablets in the Ortho-Novum 7/7/7 28 package.

Norfloxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Norfloxacin	400.00
90.00	2	Microcrystalline cellulose (Avicel PH 112)	90.00
26.00	3	Croscarmellose sodium (Ac-Di-Sol)	26.00
4.00	4	Magnesium stearate	4.00
—	5	Absolute alcohol (ethanol, dehydrated alcohol)	60.00

MANUFACTURING DIRECTIONS

Note: Avoid the overmixing of lubricants, or hardness may be reduced.

1. Sieving and kneading
   a. Sift Item 1 through a 900-μm sieve. Load it into the mixer.
   b. Add Item 5 to Step 1, while mixing at low speed. Scrape sides and blades. Mix and chop at low speed for 2 min. Check the end point of granulation. If required, add additional absolute alcohol to get the end point. (The end point of the granulation is the point where there are little or no lumps in the granulation.)
2. Drying
   a. Dry the wet granules in an oven at 55°C for 6 h. After 2 h of drying, scrape the semidried granules to break the lumps for uniform drying.
3. Check the LOD. The limit is 0.7 to 1%. If required, dry further at 55°C for 1 h. Check the LOD.
4. Transfer the dried granules to stainless steel drums.
5. Grinding
   a. Grind the dried granules through a 1.25-mm sieve, using a granulator at medium speed. Collect the granules in stainless steel drums. Load the granules into the blender.
6. Lubrication
   a. Sift Items 2 and 3 through a 500-μm sieve, and add it to the blender. Mix the blend for 2 min.
   b. Sift Item 4 through a 250-μm sieve. Add 5 to 100 g granules from bulk (see the previous step). Mix in a polythene bag for 1 min. Then, add to the blender. Blend for 1 min.
   c. Unload in stainless steel drums.
7. Compression
   a. Check the temperature and humidity before starting compression. The limits are that the temperature cannot exceed 25°C, and the relative humidity should be between 45 to 50%.
   b. Compress the granules using a rotary tabletting machine (diameter: 16.2 × 8.3 mm, compression weight: 520 mg).
8. Tablet coating
   a. Coat with an HPMC solution. (See Appendix.)

Norgestimate and Ethinyl Estradiol Tablets (0.18 mg/0.035 mg; 0.215 mg/0.035; 0.25 mg/0.035 mg) [27]

Each of the following products is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

- Ortho Tri-Cyclen® 21 Tablets and Ortho Tri-Cyclen® 28 Tablets
  - Each white tablet contains 0.180 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include lactose, magnesium stearate, and pregelatinized starch.
  - Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
  - Each blue tablet contains 0.250 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4- en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
  - Each green tablet in the Ortho Tri-Cyclen 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.
- Ortho-Cyclen 21 Tablets and Ortho-Cyclen 28 Tablets
  - Each blue tablet contains 0.25 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4- en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
  - Each green tablet in the Ortho-Cyclen 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

Nystatin Tablets (50 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Nystatin	55.00
110.00	2	Ludipress	110.00
1.00	3	Aerosil 200	1.00
1.30	4	Magnesium stearate	1.30

MANUFACTURING DIRECTIONS

1. Mix the components, pass through a 0.8-mm sieve, and press with very low-compression force.
2. Compress 175 mg in 8-mm punches. For 100-mg strength, compress 350 mg in 10-mm punches.

Nystatin Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Nystatin	200.00
51.00	2	Lactose monohydrate	51.00
—	3	Isopropyl alcohol	40 ml
10.00	4	Kollidon CL	10.00
3.00	5	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 and 2 with a solution of Items 3 and 4. Dry, pass through a 0.8-mm sieve, add Item 5, and press with medium-compression force.
2. Compress 270 mg in 9-mm punches.

Olanzapine Tablets [110]

Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-l *OH*-thieno[2,3-*b*] [1,5] benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. Olanzapine is a Yellow crystalline solid, which is practically insoluble in water.

Olanzapine tablets are intended for oral administration only. Each Zyprexa® tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), or 10 mg (32 μmol). The inactive ingredients are carnauba wax, color mixture white, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Olanzapine	10.00
200.00	2	Pregelatinized starch	200.00
25.00	3	Microcrystalline cellulose (Avicel PH 101)	25.00
15.00	4	Povidone	15.00
10.00	5	Croscamellose	10.00
3.75	6	Magnesium stearate	3.75
2.50	7	FD&C Yellow No. 2 Lake	2.50
—	8	Water, purified, ca	5 ml

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3, 5, and 7 in a suitable blender, and mix them.
2. In a separate vessel, prepare a binding solution using Items 4 and 8.
3. Add to Step 1, and granulate. Dry granules in trays at 40°C under vacuum.
4. Pass the dried granules through 60 mesh.
5. Add and blend Item 6, and compress.

Omeprazole and Ibuprofen Tablets (10 mg/400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Omeprazole, use magnesium omeprazole	12.00
12.00	2	Nonpareil cores	12.00
1.80	3	Hydroxypropyl methyl cellulose	1.80
—	4	Water, purified	35.40
23.50	5	Hydroxypropyl cellulose	2.35
4.03	6	Talc	4.03
—	7	Water, purified	48.00
38.70	8	Methacrylic acid copolymer (30% suspension)	38.70
3.48	9	Triethyl citrate	3.48
0.58	10	Mono- and diglycerides	0.58
0.06	11	Polysorbate 80	0.06
—	12	Purified water	22.68
400.00	13	Ibuprofen	400.00
273.60	14	Microcrystalline cellulose	273.60
100.40	15	Polyvinylpyrrolidone cross-linked	100.40
33.30	16	Polyvinylpyrrolidone K-25	33.30
26.70	17	Sodium lauryl sulfate	26.70
—	18	Water, purified	297.00
4.0	19	Sodium stearyl fumarate	4.00

MANUFACTURING DIRECTIONS

Note: The formulation and directions given here can be used to formulate combinations of omeprazole with other NSAIDs, such as naproxen (250 mg) or piroxicam (20 mg). Omeprazole can be replaced with pantoprazole or lansoprazole.

1. Prepare a solution of Items 1 and 3 in Item 4, and spray onto Item 2 to prepare nonpareil cores in a fluid-bed drier.
2. Prepare a solution of Items 5 to 7 and 8 to 12 separately. Alternate application of these solutions on Step 1 to provide enteric properties to the cores.
3. Pass the enteric-coated cores through a sieve.
4. Prepare a granulating solution using Items 16 to 18.
5. Dry blend Items 13, 15 (one-tenth), and 16, and add Step 4 to this step to granulate. Add more of Item 18 to the mass. Pass granules through #8 mesh, and dry at 60°C for 6 h. Pass dried granules through a 0.8-mm sieve.
6. Add Step 3 and the balance of Item 15, and blend for 10 min.
7. Compress 886 mg in 15-mm punches. There is a disintegration time of less than 1 min in simulated gastric juice (USP without enzymes).

Omeprazole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Omeprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Omeprazole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Omeprazole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Omeprazole Tablets, Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Omeprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

MANUFACTURING DIRECTIONS

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress 672 mg in 15-mm biplanar punches. For 20-mg tablets, increase the quantity of Item 1 and compress an additional 10 mg.

Omeprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Omeprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Oxybutynin Chloride Tablets (5 mg/10 mg) [194]

Ditropan® XL (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each Ditropan XL extended-release tablet contains 5 mg or 10 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of *R*- and *S*-enantiomers.

Chemically, oxybutynin chloride is *d*,*l* (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HC_1$.

Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids but relatively insoluble in alkalis.

Ditropan XL also contains the following inert ingredients: cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

Ditropan XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 h. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser-drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, that in turn, controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of Ditropan XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Because the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Oxybutynin hydrochloride	10.00
15.00	2	Polyvinyl pyrrolidone	15.00
3.00	3	Silicon dioxide colloidal	3.00
100.00	4	Lactose	100.00
30.00	5	Fumaric acid	30.00
1.50	6	Sodium stearyl fumarate	1.50
—	7	Water, purified	85.00

MANUFACTURING DIRECTIONS

1. Charge the oxybutynin hydrochloride, fumaric acid, and lactose in fluidized-bed equipment.
2. Prepare in a separate container an aqueous PVP solution (in 85 g of water).
3. Spray the solution in Step 2 into Step 1 to form granules at a typical setting using a fluid bed dryer: Airflow (m^3/h) 100 to 110 m^3/h; liquid flow (g/min): 6 to 7 g/min; inlet temperature: 65; and spraying pressure: 2.8 bar.
4. Pass dried granules through a sieve (1-mm mesh). Sodium stearyl fumarate is weighed, added, and blended in a drum mixer.
5. Compress using 7-mm punches at 164 mg.
6. Coat the tablets using the following formula per tablet: ethylcellulose (ethocel) 10.10; polyvinylpyrrolidone (povidone) 5.50; stearic acid 2.40; and the total (dry weight of coated tablet) is 182.50.

Oxycodone Hydrochloride and Acetaminophen Tablets (5 mg/325 mg) [90]

Acetaminophen, 4′-hydroxyacetanilide, is a nonopiate, nonsalicylate analgesic and antipyretic that occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its molecular formula is $C_8H_9NO_2$. The molecular weight is 151.17. The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine. Its molecular formula is $C_{18}H_{21}NO_4 \cdot HCl$. The molecular weight is 351.83. Each tablet of Percocet contains: *acetaminophen:* 325 mg; *oxycodone HCl:* 5 mg (5 mg oxycodone HCl is equivalent to 4.4815 mg oxycodone.) The inactive ingredients are microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and other ingredients.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetaminophen powder	325.00
4.48	2	Oxycodone, use oxycodone hydrochloride	5.00
6.00	3	Colloidal silicon dioxide	6.00
77.00	4	Microcrystalline cellulose	77.00
32.00	5	Croscarmellose sodium	32.00
13.00	6	Hydroxypropyl methylcellulose	13.00
62.00	7	Starch (maize)	62.00
2.00	8	Magnesium stearate	2.00
—	9	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Pass hydrocodone bitartrate through a #20 mesh, acetaminophen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-line collecting drum at speed setting 5 (approximately 1030 r/min).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbosieve at the same settings as in Step 2. Charge screened powders into a Lodige MGT-600 mixer, and mix for 5 min with the plow speed at approximately 103 rpm and no choppers.
3. Add water to the mixer over a 10 min period, using a stainless steel transfer container with a valve, while mixing with the plows at about 103 r/min and the choppers at slow speed.
4. Mix the wet mass for another 15 min until a wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material. Preheat a Glatt fluid-bed dryer by running it for 2.5 min at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 min and the filter shaked the duration of 5 sec. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 min. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a Fitz mill using a #20 mesh wire screen, with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum.
8. Add magnesium stearate, and mix for 3 min.
9. Compress using a 13/32± round tooling.

Oxycodone Hydrochloride Tablets (5 mg) [119]

Oxycodone is 14-hydroxydihydrocodeinone, a white odorless crystalline powder derived from the opium alkaloid, thebaine. Each tablet contains oxycodone hydrochloride, 5 mg. The tablets also contain microcrystalline cellulose and stearic acid. The oral solution contains alcohol, FD&C Red No. 40, flavoring, glycol, sorbitol, water, and other ingredients.

Oxytetracycline Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Oxytetracycline hydrochloride	250.00
230.00	2	Ludipress	230.00
6.00	3	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with very low-compression force.
2. Compress 495 mg in 12-mm biplanar punches.

Pantoprazole Tablets [77]

The active ingredient in Protonix® (pantoprazole sodium) delayed-release tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S \cdot 1.5\ H_2O$, with a molecular weight of 432.4. The structural formula is:

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder that is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in *n*-hexane.

The stability of the compound in aqueous solution is pH dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 h at pH 5 and approximately 220 h at pH 7.8.

Protonix is supplied as a delayed-release tablet for oral administration, available in two strengths. Each delayed-release tablet contains 45.1 mg or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg of pantoprazole, respectively), with the following inactive ingredients: calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Pantoprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Pantoprozole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Pantoprozole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Pantoprazole Tablets, Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Pantoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

MANUFACTURING DIRECTIONS

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress 672 mg in 15-mm biplanar punches. For 20-mg tablets, increase the quantity of Item 1, and compress an additional 10 mg.

Pantoprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Pantoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Para Amino Salicylic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Calcium para amino salicylic acid	500.00
280.00	2	Ludipress	280.00
35.00	3	Kollidon 35	35.00
—	4	Isopropyl alcohol	QS
5.00	5	Magnesium stearate	5.00
5.00	6	Talc	5.00

MANUFACTURING DIRECTIONS

1. Granulate Items 1 and 2 with a solution of Items 3 and 4. Dry the granules, and lubricate with Items 5 and 6.
2. Compress 825 mg in 16-mm biplanar punches.

Paroxetine Hydrochloride Tablets (10 mg/20 mg/30 mg/40 mg) [15]

Paroxetine HCl is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors (SSRIs) or to tricyclic, tetracyclic, or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4′-fluorophenyl)-3*S*-[(3′,4′-methylenedioxyphenoxy)methyl] piperidine hydrochloride hemihydrate (immediate-release tablets and oral suspension); and (-) - (3*S*,4*R*)-4-[(*p*-fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine hydrochloride hemihydrate (controlled-release tablets). The empirical formula is $C_{19}H_{20}FNO_3 \cdot HCl \cdot {}^1/_2H_2O$. The molecular weight is 374.8 (329.4 as free base). Paroxetine HCl is an odorless, off-white powder, with a melting point range of 120 to 138°C, and a solubility of 5.4 mg/ml in water.

- Immediate-release tablets — Each film-coated Paxil® tablet contains paroxetine HCl equivalent to paroxetine as follows: *10 mg:* yellow; *20 mg:* pink (scored); 30 mg: blue; and *40 mg:* green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, and FD&C Yellow No. 6.
- Controlled-release tablets — Each enteric, film-coated, bilayer, controlled-release Paxil tablet contains paroxetine HCl equivalent to paroxetine as follows: 12.5 mg and 25 mg. One layer of the tablet consists of a degradable barrier layer, and the other contains the active material in a hydrophilic matrix. The barrier layer is pale yellow and pink for the 12.5-mg and 25-mg strength tablets, respectively; the active layer is white. Inactive ingredients consist of hydroxypropyl methylcellulose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer Type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: yellow ferric oxide or red ferric oxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Paroxetine, use paroxetine hydrochloride hemihydrate	22.67
83.34	2	Dicalcium phosphate (Ditab)	83.84
50.67	3	Microcrystalline cellulose (Avicel PH 102)	50.67
8.34	4	Sodium starch glycolate (Explotab)	8.34
1.67	5	Magnesium stearate	1.67

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Paroxetine, use paroxetine hydrochloride hemihydrate	34.00
125.00	2	Dicalcium phosphate (Ditab)	125.00
76.00	3	Microcrystalline cellulose (Avicel PH 102)	76.00
12.50	4	Sodium starch glycolate (Explotab)	12.50
2.50	5	Magnesium stearate	2.50

MANUFACTURING DIRECTIONS

1. Pass Item 2 through a screen, and weigh it into a planetary mixer.
2. Add 30-mesh paroxetine to the bowl.
3. Add 20-mesh Avicel and Explotab, and mix all the powders for 10 min.
4. Add magnesium stearate, and mix for 5 min.
5. Compress into pentagonal tablets using 9.5-mm punches for 30-mg tablets and 8.25 mg for 20-mg tablets. Compress 250 and 166.7 mg, respectively.

Penicillin Chewable Tablets (125 mg) [103]

Penicillin V potassium is the potassium salt of Penicillin V. This chemically improved form combines acid stability with immediate solubility and rapid absorption. It is designated as 4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, monopotassium salt, [2*S*-(2α,5α,6β)]-. The empirical formula is $C_{16}H_{17}KN_2O_5S$, and the molecular weight is 388.48. Each tablet contains Penicillin V potassium equivalent to 250 mg (400,000 units) or 500 mg (800,000 units) Penicillin V. The tablets also contain lactose, magnesium stearate, povidone, starch, stearic acid, and other inactive ingredients.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
277.16	1	Mannitol	277.16
53.00	2	Sugar	53.00
21.20	3	Sodium cyclamate	21.20
2.30	4	Saccharin sodium	2.30
125.00	5	Penicillin, use benzathine Penicillin V, 3% excess	172.83
—	6	Water, purified, ca	96.00 ml
5.50	7	Raspberry flavor	5.50
4.40	8	Polarcillin potassium (Amberlite IRP-88)	4.40
11.60	9	Talc	11.60
35.00	10	Magnesium stearate	35.00

Note: Adjust the weight of penicillin for potency, and alter the weight of mannitol to compensate. The weight of sodium citrate is 450 minus the weight of penicillin.

MANUFACTURING DIRECTIONS

Note: Allergic reactions sometimes occur with penicillin. Avoid contact as much as possible, and use equipment dedicated to penicillin or cephalosporin products. The LOD limits are low, so use an air-conditioned area.

1. Granulation
   a. Mill the mannitol, sugar, sodium cyclamate, and sodium saccharin through a 2.38-mm aperture screen using a suitable comminuting mill, with knives forward, at medium speed.
   b. Add the milled materials from Step 1 to the mixer, and then add the penicillin. Mix for 10 min. Add the water slowly, cleaning the sides of the mixer as necessary. Mix for 10 min after the water is added. The final mass should have a sandy appearance.
   c. Transfer the wet granulation to the bowl of a fluid-bed dryer through a 6.7-mm aperture screen. Dry at 30°C for 20 min. Stir, then pass the granulation by hand through a 5.5-mm aperture screen. After that, transfer the granulation to the bowl of the fluid-bed dryer.
   d. Continue drying at 60°C, turning over after each 30 min, until the LOD is no more than 0.8% (drying time is approximately 60 min).
   e. Screen the dried granules through an 840-µm aperture screen on a suitable sieve shaker, and pass the coarse material through a 1.6-mm aperture screen on a comminuting mill, at low speed, with knives forward.
   f. Screen the flavor, polarcillin potassium, magnesium stearate, and talc through a 595-µm screen on a sieve shaker. Charge the screened powders into a suitable blender.
   g. Charge the screened and milled granules from Step 5 into the blender, and blend for 30 min.
   h. Discharge the granulation into tared polyethylene-lined drums, and seal the bags. Weigh them for yield.
   i. Compress on 9.53-mm square punches. Note the weight according to the adjustments made (hardness 10 to 12 diagonally, 15 to 21 flat).

Perfloxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Perfloxacin, use perfloxacin mesylate	592.00
63.00	2	Lactose monohydrate	63.00
42.00	3	Dicalcium phosphate	42.00
52.00	4	Starch (maize)	52.00
22.00	5	Starch (maize)	22.00
1.00	6	Gelatin	1.00
15.60	7	Sodium starch glycolate	15.60
10.00	8	Talc	10.00
5.00	9	Magnesium stearate	5.00
3.00	10	Sodium starch glycolate	3.00
10.00	11	Starch (maize)	10.00
—	12	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through a 250-μm sieve, and charge into a suitable vessel; mix it for 10 min.
2. In a separate vessel, charge Items 5 to 7, and add hot Item 12 to make a 30% starch paste.
3. Add the paste in Step 2 to Step 1, and form a wet mass suitable for granulating.
4. Pass the wet mass through a #8 sieve, and spread it on paper-lined trays.
5. Dry the granules at 50°C overnight until an LOD of not more than 3% is reached.
6. Pass the dried granules through a 1.19-mm sieve screen into a blending vessel.
7. Sift Items 8 to 11 through a 250-μm sieve, and add to Step 6. Blend for 2 min.
8. Compress 815 mg in an 18.8×8.8-mm punch.
9. Coat the material with an HPMC methylene chloride coating. (See Appendix.)

Phendimetrazin Tablets (35 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
35.00	1	Phendimetrazin	35.00
281.00	2	Ludipress	281.00
281.00	3	Starch (maize)	281.00
3.00	4	Magnesium stearate	3.00
3.00	5	Aerosil 200	3.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress 604 mg in 12-mm biplanar punches. The amount of Ludipress and cornstarch may be reduced to obtain better disintegration times.

Phenindion Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Phenindion	50.00
165.00	2	Ludipress	165.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 230 mg in 8-mm biplanar punches.

Phenoxymethyl Penicillin Potassium Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
58.10	1	Sodium citrate powder	68.10
250.00	2	Penicillin V acid, use phenoxymethyl potassium[a]	277.20
29.50	3	Povidone K 29-32	29.40
—	4	Alcohol SD 3A 200 proof, ca	100 ml
16.00	5	Starch (maize)	16.00
16.00	6	Talc	16.00
6.10	7	Magnesium stearate	6.10

[a] Adjust the quantity based on the factored potency and adjusted by sodium citrate. Starch must be dried. The amount of sodium citrate is 345.30-weight of Item 2.

MANUFACTURING DIRECTIONS

Note: Allergic reactions sometimes occur with penicillin. Avoid contact as much as possible, and use equipment dedicated to penicillin or cephalosporin products. The LOD limits are low, so use an air-conditioned area.

1. Granulation
   Note: Dried cornstarch must be used for lubrication. Dry the starch at 80°C for 36 h prior to its use in manufacturing. Check the LOD of starch. The LOD must be less than 2%.
   a. Mill separately the sodium citrate through a 595-µm aperture screen using a suitable comminuting mill, at medium speed, with impact forward, and the penicillin through a 595-µm aperture screen with knives forward, at high speed. In a suitable mixer, mix them for 5 min.
   b. Dissolve the povidone in 100 ml of alcohol in a dry stainless steel bucket.
   c. Add the PVP-alcohol slowly to the mixer, and mix for 30 min or until balls form in the sandy mixture. Add and record extra alcohol if required.
   d. Pass the mass through a 9.52-mm aperture screen, place into a fluid-bed dryer bowl, and dry at 50°C for 1 h. Turn over as necessary. The LOD should not be more than 0.7%.
   e. Mill the granules through a 1.59-mm aperture screen using a suitable comminuting mill, with knives forward, at medium speed. Put the granules into tared polyethylene-lined drums, then seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the dried starch and talcum through a 595-µm aperture screen on a sieve shaker, and add to the blender. Blend this mixture for 30 min.
   c. Screen the magnesium stearate through a 595-µm aperture screen on a sieve shaker, and add it to the blender. Blend this for 30 min.
   d. Discharge the granules into polyethylene-lined drums. Then, seal and weigh for yield.
3. Compression
   a. Compress using 10.32-mm round, standard concave punches.
   b. Compress to calculated weight after adjustments, with a variation not more than 3%; thickness between 4.4 to 4.6 mm (range not more than ± 5%); hardness between 10 to 14, and disintegration time no more than 15 minutes in water.
4. Coating
   a. Coat by a methocel subcoat, color coat, and polishing coat. (See Appendix.)

Phenylbutazone Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Phenylbutazone	100.00
3.33	2	Lactose monohydrate	3.33
3.33	3	Mannitol	3.33
162.00	4	Starch (maize)	162.00
10.00	5	Starch (maize)	10.00
0.66	6	Polyvinylpyrrolidone potassium 30	0.66
0.28	7	Propyl paraben	0.28
0.28	8	Methyl paraben	0.28
5.00	9	Talc	5.00
3.00	10	Magnesium stearate	3.00
7.00	11	Sodium starch glycolate	7.00
—	12	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through #40 mesh into a suitable mixing vessel. Mix for 10 min.
2. In a separate vessel, heat Item 12 to boiling, and add and dissolve Items 7 and 8. Allow this blend to cool to 60°C, then add Item 6, and dissolve. Finally, add Item 5, and stir well to make a smooth paste of 30% starch.
3. Add the starch paste from Step 2 into Step 1, and mix to form a suitable wet mass.
4. Pass the wet mass in Step 3 through #18 mesh onto trays. Then, dry at 60°C overnight to an LOD of not more than 2.8%. Transfer to a blending vessel.
5. Sift Items 9 to 11 through a 250-µm sieve. Add to Step 4, and blend for 1 min.
6. Compress 280 mg in a 5-mm punch.
7. Coat the tablets with a sealing coat and a color coat (HPMC). (See Appendix.)

Phenylpropanolamine Hydrochloride Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
60.00	1	Phenylpropanolamine hydrochloride	60.00
180.00	2	Calcium sulfate dihydrate	180.00
QS	3	Starch paste (10%)	QS
12.00	4	Starch 1500 (StaRx)	12.00
6.00	5	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

1. Starch paste
   a. Add starch with a 1:10 ratio to cold water. Heat to a boil, with constant stirring, until a thick, translucent white paste is formed. Keep it for use in "Granulation," Step 2.
2. Granulation
   a. Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a sigma blade mixer for 15 min.
   b. Add starch paste from "Starch paste," Step 1, in sufficient quantity to form a wet mass suitable of desirable consistency.
   c. Allow to mix for 30 min.
   d. Pass the wet mass through a #14 screen and distribute on drying trays.
   e. Dry in a forced-air oven at 120 to 130°F or in a fluid-bed dryer.
   f. Pass the dried granules through a #18 mesh screen.
3. Lubrication
   a. Transfer granules to a twin-sell blender, add the Starch 1500 and the magnesium stearate, and blend for 6 to 8 min.
4. Compression
   a. Compress the granulation in a rotary press using 9.5-mm standard punches. The tablet weight should be 260 mg.

Phenytoin Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Phenytoin sodium	100.00
235.00	2	Ludipress	235.00
10.00	3	Magnesium stearate	10.00
8.00	4	Kollidon CL	8.00
5.00	5	Aerosil 200	5.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 346 mg in 12-mm biplanar punches.

Phenytoin Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Phenytoin sodium	100.00
50.00	2	Dicalcium phosphate	50.00
45.00	3	Sucrose crystalline	45.00
10.00	4	Kollidon 25	10.00
—	5	Isopropyl alcohol + ethanol (1:1)	30.00
5.00	6	Kollidon CL	5.00
2.00	7	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 to 3 with a solution of Items 4 and 5; dry. Pass through a 0.8-mm sieve, mix with Items 6 and 7, and press with high-compression force.
2. Compress 209 mg in 8-mm biplanar punches.

Phenytoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Phenytoin base	100.00
235.00	2	Ludipress	235.00
2.00	3	Magnesium stearate	2.00
2.00	4	Stearic acid	2.00
8.00	5	Kollidon CL	8.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 351 mg in 12-mm biplanar punches.

Pioglitazone Hydrochloride Tablets (15 mg/30 mg/45 mg) [87]

Actos (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Actos is used in the management of Type 2 diabetes mellitus (also known as noninsulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that Actos improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Actos improves glycemic control, while reducing circulating insulin levels. Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers.

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$ and a molecular weight of 392.90 daltons. It is soluble in *N*,*N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether. Actos is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

Pipemidic Acid Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Pipemidic acid, use pipemidic acid trihydrate	236.00
16.00	2	Calcium carboxymethyl cellulose	16.00
4.00	3	Hydroxypropyl cellulose	4.00
8.00	4	Cellulose microcrystalline	8.00
2.40	5	Silicon dioxide colloidal	2.40
5.60	6	Magnesium stearate	5.60
QS	7	Water, purified, ca	80.00 ml

MANUFACTURING DIRECTIONS

CAUTION: Wear a mask and gloves during all operations.

1. Granulation
   a. Pass pipemidic acid (Item 1) and calcium carboxymethyl cellulose (Item 2) through a 24-mesh (0.6-mm) screen attached to an oscillating granulator. Charge into a planetary mixer, and blend for 10 min.
   b. Dissolve the hydroxypropyl cellulose (Item 3) in 80 ml of water, using continuous mechanical stirring.
   c. Add the binder solution to the mixed powder from Step 1, and blend for 10 min to form a suitable mass. More water should be added, if necessary, to complete granulation and densification.
   d. The granules should then be screened through an 8-mesh (2-mm) screen.
   e. Spread the moist granules on trays, and dry at 50°C (122°F) for 16 h or until moisture level is within the range of 11 to 16%.
2. Lubrication
   a. Using an oscillating granulator, pass the dried granules through a 12-mesh (1.4-mm) screen.
   b. Pass the cellulose microcrystalline (Item 4), maize starch (Item 5), silicon dioxide colloidal (Item 6), and magnesium stearate (Item 7) through a 12-mesh (1.4 mm) screen.
   c. Charge the items from Lubrication, Step 2b, into planetary blender. Add half of the dried granule from Lubrication, Step 2a, and blend for 5 min. Then add the remainder of the dried granule, and blend for an additional 15 min at a nominal speed of 30 rpm.
   d. Load the lubricated granule into tared, polyethylene-lined drums, and weigh for yield.
3. Compression
   a. Compress on a suitable machine using ovaloid tooling, 12.5 mm × 6.5 mm; the compression weight is 280 mg. For 400-mg strength, 9.1 × 15.5-mm punches and 560-mg weight.
4. Coating
   a. Coat using a methocel/ethocel coating. (See Appendix.)

Pipobroman Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Pipobroman	25.00
100.00	2	Lactose monohydrate powder	100.00
5.00	3	Povidone K 29-32	5.00
QS	4	Water, purified, ca	12 ml
2.00	5	Starch (corn)	2.00
1.10	6	Magnesium stearate	1.10

MANUFACTURING DIRECTIONS

1. Granulation
   a. Pass pipobroman, lactose, and povidone through an 840-µm aperture screen using a Fitz mill or something similar, with impact forward and high speed.
   b. Charge milled granulation into a mixer. Mix for approximately 5 min, and then add 12 ml of purified water to the mass. Pass granulation through a Fitz mill or a similar method using a no. 5 (12.7-mm) band, with knives forward and at slow speed.
   c. Pass granulation thinly on paper-lined trays, set the oven at 50°C, and dry overnight, or until the LOD is less than 2% (1 h Brabender at 105°C).
   d. Sift dried granulation through an 840-µm aperture screen and Fitz mill the coarse granules through a 1-mm aperture screen, with knives forward, at a slow speed.
2. Lubrication
   a. Charge one-half of the base granulation into a Glen mixer or a similar mixing method.
   b. Mix cornstarch and magnesium stearate. Screen this mixture through a 595-µm aperture screen into a mixer.
   c. Charge the remaining granulation into the mixer. Blend for approximately 5 min.
   d. Discharge into polyethylene-lined drums. The theoretical lubricated weight is 133.1 g.
3. Compression
   a. Compress using 9/32-in. standard concave punches, with a compression weight of 133 mg.

Potassium Chloride Tablets (30 mg) [56, 137]

Potassium chloride extended-release capsules, USP, are a solid oral dosage form of potassium chloride containing 10 mEq (750 mg) of potassium chloride (equivalent to 10 mEq [390 mg] of potassium and 10 mEq [360 mg] of chloride) in a microencapsulated capsule. This formulation is intended to release potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.

Potassium chloride extended-release capsules are electrolyte replenishers. The chemical name is potassium chloride, and the structural formula is KCl. Potassium chloride, USP, occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol. The inactive ingredients are calcium stearate, gelatin, pharmaceutical glaze, povidone, sugar spheres, and talc.

Klor-Con extended-release tablets, USP, are a solid oral dosage form of potassium chloride. Each contains 600 or 750 mg of potassium chloride equivalent to 8 mEq or 10 mEq of potassium in a wax matrix tablet.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Potassium chloride	30.00
150.00	2	Gelatin powder	150.00
2.00	3	Croscarmellose sodium	2.00
5.00	4	Talc	5.00
3.00	5	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Accurately weigh potassium chloride, gelatin, croscarmellose sodium, talc, and magnesium stearate.
2. Add potassium chloride, gelatin, and croscarmellose sodium, one item at a time, in a suitable blender, and mix for 15 min. Add talc and magnesium stearate, and mix for an additional 5 min.
3. Compress 200 mg in 6-mm punches.

Pravastatin Sodium Tablets (10 to 40 mg) [48]

Pravastatin sodium is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis and conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β, δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt,[1*S*-[1α(β*S**,δ*S**),2α,6α,8β(*R**),8aα]]-. The formula for pravastatin sodium is $C_{23}H_{35}NaO_7$, and its molecular weight is 446.52.

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7. It is soluble in methanol and water (> 300 mg/ml); slightly soluble in isopropanol; and practically insoluble in acetone, acetonitrile, chloroform, and ether. Pravachol is available for oral administration as 10-mg, 20-mg, and 40-mg tablets. Inactive ingredients include croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10-mg tablet also contains red ferric oxide; the 20-mg tablet also contains yellow ferric oxide; and the 40-mg tablet also contains green lake blend (mixture of D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake).

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pravastatin sodium	10.00
12.00	2	Crospovidone	12.00
77.00	3	Lactose, spray dried	77.00
1.00	4	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Charge pravastatin sodium and polyplasdone in a blender after passing through a 250-μm sieve.
2. Add Item 3, and mix for 20 min at moderate speed.
3. Add Item 4, and blend for 5 min at low speed.
4. Compress in a suitable punch, 100 mg for 10-mg strength, and proportionally for strengths up to 40 mg.

Prazosin Tablets (5 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Prazosin hydrochloride, anhydrous[a]	5.00
94.00	2	Ludipress	94.00
1.00	3	Magnesium stearate	1.00

[a] If using polyhydrate, increase the amount to 6.00, and adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress 109 mg in 8-mm biplanar punches.

Prednisolone Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Prednisolone	5.00
60.00	2	Lactose monohydrate	60.00
32.50	3	Starch (maize)	32.50
6.00	4	Starch (maize)	6.00
4.00	5	Starch (maize, dried)[a]	4.00
2.00	6	Talc (fine powder)	2.00
0.50	7	Magnesium stearate	0.50
—	8	Purified water	18.00

[a] LOD: not more than 4.5% when dried at 120°C for 4 h.

MANUFACTURING DIRECTIONS

Precautions: The binding solution contains maize starch, and, therefore, it is possible to have microbiological growth. Thus, prepare the solution directly before the granulation process. Prednisolone is a potent corticosteroid, therefore, use a mask, gloves, and goggles during the whole process.

1. Preparation of binding solution
   a. Prepare an homogeneous slurry of Item 4 using 8 g of Item 8 (25 to 30°C). Check that it is free of lumps.
   b. Charge this slurry into 10 g of Item 8 heated to 90°C in the vessel (Giusti). Stir until there is complete gelatinization.
   c. Check the weight. The theoretical weight is 24 g.
   d. Leave the starch paste to cool to 40 to 50°C. *Note:* Compensate any loss of weight due to vaporization by adding Item 8.
2. Dry mixing
   a. Pass Items 1, 2, and 3 through a 630-µm sieve using a sifter. Load this powder to the mixer, and mix for 15 min at high speed.
3. Wet massing
   a. Add starch paste cooled to 40 to 50°C from "Preparation of binding solution," Step 1d. Mix for 10 min at high speed. Add purified water if required.
4. Pass the wet granules through sieve 24205 using the Fitz mill.
5. Drying
   a. Spread the wet granules onto the trays. Load the trolleys to the dryer. Dry the granules at 60°C for 14 h.
6. Grinding
   a. Pass the dried granules through a 1-mm sieve using a granulator.
7. Lubrication
   a. Pass Items 5 and 6 through a 250-µm sieve using a sifter. Collect the material in a stainless steel drum.
   b. Load the sieved material from Step 6 into the blender.
   c. Load the sieved lubricant powders from "Lubrication," Step 7a, into the blender.
   d. Blend the powders for 5 min.
8. Blending
   a. Pass Item 7 through a 250-µm sieve using a sifter. Load the sieved powder into the blender. Mix the powder for 1 min.
   b. Unload the lubricated granules in stainless steel drums.
9. Check and record the weight of the granules.
10. Compression
    a. Compress 110 mg of the granules using a rotary tabletting machine in 7.1-mm punches.

Prednisolone Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Prednisolone, use as prednisolone micronized	10.50
49.50	2	Microcrystalline cellulose (Avicel PH 102)	49.50
7.50	3	Sodium starch glycolate (Primojel)	7.50
105.00	4	Lactose (spray dried)	105.00
25.00	5	Starch (maize), dried	25.00
1.00	6	Colloidal silicon dioxide (Aerosil 200)	1.00
1.50	7	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

See the preceding directions for the 5-mg strength.

Prednisolone Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Prednisolone micronized	21.00
60.00	2	Microcrystalline cellulose (Avicel PH 102)	60.00
9.00	3	Sodium starch glycolate (Primojel)	9.00
127.00	4	Lactose (spray dried)	127.00
30.00	5	Starch (maize, dried)	30.00
1.00	6	Colloidal silicon dioxide (Aerosil 200)	1.00
2.00	7	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

See the previous directions for the 5-mg strength.

Prednisolone Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Prednisolone	20.00
155.00	2	Lactose monohydrate	155.00
10.00	3	Kollidon VA 64	10.00
8.00	4	Kollidon CL	8.00
5.00	5	Magnesium stearate	5.00
2.00	6	Aerosil 200	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 212 mg in 8-mm biplanar punches.

Prednisone Tablets (10 mg)

Deltasone tablets contain prednisone, which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, that are readily absorbed from the gastrointestinal tract. Prednisone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water and slightly soluble in alcohol, in chloroform, in dioxane, and in methanol. The chemical name for prednisone is pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-. Its molecular weight is 358.43.

Deltasone tablets are available in five strengths: 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg. The inactive ingredients are: *2.5 mg:* calcium stearate, cornstarch, erythrosine sodium, lactose, mineral oil, sorbic acid, and sucrose; *5 mg:* calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, and sucrose; *10 mg:* calcium stearate, cornstarch, lactose, sorbic acid, and sucrose; *20 mg:* calcium stearate, cornstarch, FD&C Yellow No. 6, lactose, sorbic acid, and sucrose; *50 mg:* cornstarch, lactose, magnesium stearate, sorbic acid, sucrose, and talc.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Prednisone	10.00
208.00	2	Ludipress	208.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress 223 mg in 8-mm biplanar punches.

Probenecid Tablets (500 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Probenecid	500.00
130.00	2	Starch (maize)	130.00
10.00	3	Kollidon 30	10.00
—	4	Alcohol	70.00 ml
25.00	5	Kollidon CL	25.00
3.00	6	Aerosil 200	3.00
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 and 2 with a solution of Items 3 and 4. Pass this mixture through a 0.8-mm sieve. Add Items 5 to 7, and press with low-compression force.
2. Compress 674 mg in 12-mm biplanar punches.

Promethazine Hydrochloride Tablets (10 mg) [107]

Promethazine hydrochloride is a racemic compound. The empirical formula is $C_{17}H_{20}N_2S \cdot HCl$, and its molecular weight is 320.88. Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as *N*,*N*,α-trimethyl-10*H*-phenothiazine-10-ethanamine monohydrochloride. Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder that slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

Each tablet of phenergan contains 12.5 mg, 25 mg, or 50 mg of promethazine hydrochloride. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength also contains the following: *12.5 mg* —FD&C Yellow No. 6 and saccharin sodium; *25 mg* —saccharin sodium; and *50 mg* —FD&C Red No. 40.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Promethazine HCl[a]	10.50
41.95	2	Lactose monohydrate	41.95
20.00	3	Starch (maize)	20.00
0.05	4	Sodium metabisulfite (sodium disulfite)	0.05
2.00	5	Povidone (PVP K-30)	2.00
5.00	6	Starch (maize), dried[b]	5.00
0.50	7	Magnesium stearate	0.50
—	8	Alcohol (ethanol 95%)	6.07
—	9	Purified water	8.67

[a] 0.5-mg promethazine HCl/tablet added extra, considering the assay and LOD of the material (assay 97 to 101.5%, calculated on the dried basis LOD NMT 0.5%).

[b] LOD: NMT 4.5% when dried at 120°C for 4 h.

MANUFACTURING DIRECTIONS

1. Avoid over mixing lubricants, or hardness may be reduced.
2. Mix Items 9 and 8 in a stainless steel container.
3. Dissolve Items 4 and 5 by slow stirring with a stirrer until the mixture becomes clear.
4. Sift Items 1, 2, and 3 through a stainless steel 500-µm sieve in a sifter. Load into a mixer, and mix for 5 min at low speed.
5. Add a binding solution 5 to 7 g/min to the dry powders while mixing at low speed. After addition is over, scrape sides and blades. Mix an additional 2 min using a mixer and chopper at low speed. Scrape sides and blades.
6. Check for the end point of granulation. The end point is the point of granulation that consists of little or no lumps. If required, add purified water.
7. Dry the wet granules with the air circulation heater off, to expel alcohol for 2 h. Then dry at 55°C for 14 h. After 4 h of drying, scrape the semidried granules to break the lumps for uniform drying.
8. Check the LOD. The limit is 1 to 1.5%. If required, dry further at 55°C for 2 h.
9. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect the granules in stainless steel drums.
10. Load the granules into the blender. Sift the Item 6 material through a 500-µm sieve using a sifter, and add it into the blender. Mix the blend for 3 min.
11. Sift Item 7 through a 500-µm sieve. Add 1 to 2 g granules from Step 10. Mix in a polythene bag for 1 min. Add to the blender. Mix for 30 sec.
12. Compress 0.80 G. Coat using one of the HPMC coatings. (See Appendix.)

Promethazine Hydrochloride Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Promethazine HCl	26.00
103.75	2	Lactose monohydrate	103.75
50.00	3	Starch (maize)	52.50
1.50	4	Sodium metabisulfite (sodium disulfite)	1.50
5.00	5	Povidone (PVP K-30)	5.00
12.50	6	Starch (maize), dried	12.50
1.25	7	Magnesium stearate	1.25
—	8	Alcohol (ethanol 95%)	15.00
—	9	Purified water	21.67

Propranolol Hydrochloride Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Propranolol hydrochloride	10.00
490.00	2	Ludipress	490.00
2.50	3	Magnesium stearate	2.50

Note: For 50-mg and 100-mg strengths, adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 514 mg for 10-mg, 496 mg for 50-mg, and 505 mg for 100-mg strengths, using 12-mm biplanar punches.

Propranolol Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
40.00	1	Propranolol	40.00
108.00	2	Ludipress	108.00
0.30	3	Magnesium stearate	0.30
0.40	4	Stearic acid	0.40

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress 150 mg in 8-mm biconvex punches.

Propranolol Hydrochloride Tablets (10 mg) [141]

Propranolol hydrochloride is a synthetic β-adrenergic receptor blocking agent chemically described as 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Propranolol HCl is a stable, white, crystalline solid that is readily soluble in water and ethanol. Its molecular weight is 295.81.

Propranolol HCl is available as 10-mg, 20-mg, 40-mg, 60-mg, and 80-mg tablets. The inactive ingredients contained in propranolol HCl tablets are lactose, magnesium stearate, microcrystalline cellulose, and stearic acid. In addition, propranolol HCl 10-mg and 80-mg tablets contain FD&C Yellow No. 6 and D&C Yellow No. 10; propranolol HCl 20-mg tablets contain FD&C Blue No. 1; propranolol HCl 40-mg tablets contain FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; and propranolol HCl 60-mg tablets contain D&C Red No. 30.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (Kg)
10.00	1	Propranolol hydrochloride	10.00
2.00	2	Maize starch	2.00
4.00	3	Lactose	4.00
0.20	4	Soluble starch	0.20
15.00	5	Purified water	15.00
3.00	6	Primojel	3.00
9.00	7	Microcrystalline cellulose	9.00
0.50	8	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 3 through a Fitz mill sieve 24228 at medium speed, and mix for 15 min.
2. Bring to boil 1.25 Kg of purified water (Item 5), and dissolve in it Item 4. Add the remaining water and allow boiling for a few minutes, allowing the mixture to cool to room temperature.
3. Make a uniform mass of Step 2 with Step 1 solution, and pass it through a Fitz mill sieve 24183, adding water if necessary.
4. Dry granules at 35°C for 14 h. Pass the granules through a Fitz mill sieve 24228 at low speed.
5. Pass Items 6 to 8 through a Fitz mill sieve 24228 and at medium speed.
6. Compress.
7. Coat in a pan at 25 to 30°C under a flow of warm air using the Opaspary coating. (See Appendix.) After coating, polish the film-coated tablet.

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Pyrazinamide	500.00
134.50	2	Ludipress	134.50
12.00	3	Kollidon CL	12.00
3.50	4	Aerosil 200	3.50

MANUFACTURING DIRECTIONS

1. Mix all components, sieve through a 0.8-mm screen, and press with medium-compression force.
2. Compress 652 mg in 12-mm biplanar punches.

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Pyrazinamide	500.00
50.00	2	Starch (maize)	50.00
20.00	3	Kollidon 30	20.00
—	4	Alcohol, ca	200 ml
5.00	5	Kollidon CL	5.00
6.00	6	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

1. Granulate mixture Items 1 and 2 with a solution of Items 3 and 4. Pass through a 0.8-mm sieve, mix with Items 5 and 6, and press with low-compression force.
2. Compress 605 mg in 12-mm biplanar punches.
3. The quantity of Items 5 can be increased to 10 mg if there is a problem in compressing tablets.

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Pyrazinamide	500.00
125.00	2	Mannitol	125.00
—	3	Water, purified	50.00 ml
25.00	4	Starch (maize)	35.00
QS	5	Water, purified	150 ml
10.00	6	Talc	10.00
6.00	7	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

Note: Carry out all operations subsequent to drying at a relative humidity below 50% and temperature below 26°C.

1. Granulation
   a. Pass the pyrazinamide and mannitol through a 1.2-mm aperture stainless steel screen on a sieve shaker, transfer them to a suitable mass mixer, and mix for 5 min.
   b. Add the starch to the water (Item 3) and mix until a smooth slurry, free from lumps, is formed.
   c. Heat the water (Item 5) to boiling. Reduce the heat, then, while mixing, add the slurry from Step 1b. Continue mixing well, until a smooth translucent paste is formed. Allow this paste to cool to 50°C before using it in Step 1d.
   d. Add one-half of the starch paste from Step 1c to the blended powders in the mixer, and mix for 1 min. Stop mixing, and scrape the blades and sides of the mixer. Add the second half of the starch paste and mix for another 1 min. Stop mixing, scrape the blades and sides of the mixer, and examine the mass.
   e. If necessary, add more water at 50°C in small quantities, mixing for 1 min after each addition, until a good, wet, holding mass is formed. Record extra water used.

   Note: Do not overwet or overmix the mass.
   a. Pass the wet mass through a 4.76-mm aperture stainless steel screen by hand, spread on paper-lined trays, and dry in a hot-air oven at 50°C, turning the granules every 20 min, to an LOD of 1 to 1.5% (3 h at 60°C under maximum vacuum).
2. Lubrication
   a. Pass the granules through a 1.2-mm aperture stainless steel screen on a sieve shaker, and transfer the fines to a blender.
   b. Pass the coarse granules through an 840-µm aperture stainless steel screen on an oscillating granulator, and then transfer the granules to the blender.
   c. Screen the talc and sodium starch glycolate through a 595-µm aperture stainless steel screen on a sieve shaker, and add the mixture to the blender. Blend it for 15 min.
   d. Screen the magnesium stearate through a 595-µm aperture stainless steel screen on a siever shaker, and add to the blender. Blend for 2 min only.
   e. Discharge into polyethylene-lined drums, and then seal and weigh.
3. Compression
   a. Compress using 12.5-mm round, concave bisected punches; disintegration time is not more than 15 min in water.

Pyridostigmine Bromide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Pyridostigmine bromide	10.00
96.00	2	Starch (maize)	96.00
8.50	3	Silicic acid (Aerosil 200)	8.50
1.50	4	Prejel PA5	1.50
30.00	5	Lactose powder anhydrous	30.00
3.70	6	Talc	3.70
0.23	7	Magnesium stearate	0.23
QS	8	Water, purified, ca	39.70 ml

MANUFACTURING DIRECTIONS

1. Mix 5% of Item 2 and equal amounts of Item 8 in a suitable vessel, at boiling. Mix and allow the paste to cool to 40°C.
2. Mix Item 1 into the paste in Step 1, in portions, and then add Items 4 and 3, avoiding large lumps; mix to homogenous mix.
3. Add the following to Item 5 (passed through a sieve), the balance of Item 8 (at 40°C), and Item 2, and mix to obtain a good mass; add more Item 8 if necessary.
4. Pass the through a 10-mm screen in a granulator.
5. Dry the granules at 50°C until the relative humidity over the granules is 30 to 40%.
6. Crush granules in an oscillating granulator with 1-mm perforation place.
7. Blend the granules with Items 6 and 7, and pass through a 1-mm sieve.
8. Blend for 10 min.
9. Compress to 150-mg weight.

Quetiapine Fumarate Tablets (25 mg/100 mg/200 mg) [161]

Seroquel (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$, and it has a molecular weight of 883.11 (fumarate salt). Quetiapine fumarate is a white to off-white crystalline powder that is moderately soluble in water. Seroquel is supplied for oral administration as 25-mg (peach), 100-mg (yellow), and 200-mg (white) tablets. The inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide. The 25-mg tablets contain red ferric oxide and yellow ferric oxide, and the 100-mg tablets contain only yellow ferric oxide.

Quinapril Hydrochloride Tablets (5 mg/10 mg/20 mg/40 mg) [51]

Quinapril hydrochloride is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat. Quinapril hydrochloride is chemically described as (3*S*-(2(*R**(*R**)),3*R**))-2-(2-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-1-oxopropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its empirical formula is $C_{25}H_{30}N_2O_5 \cdot HCl$. Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents. Accupril tablets contain 5 mg, 10 mg, 20 mg, or 40 mg of quinapril for oral administration. Each tablet also contains candelilla wax, crospovidone, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Quinapril, use quinapril hydrochloride	22.00
108.00	2	Lactose monohydrate	108.00
55.00	3	Magnesium carbonate	55.00
10.50	4	Crospovidone	10.50
4.00	5	Povidone K-30	4.00
0.50	6	Magnesium stearate	0.50
QS	7	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift the quinapril hydrochloride, lactose monohydrate, magnesium carbonate, and crospovidone through a 0.9-mm sieve.
2. Load sifted powder from Step 1 to a mixer granulator and mix for 5 min.
3. Dissolve povidone K-30 in purified water under slow stirring until the solution becomes clear.
4. Add the binding solution from Step 3 to Step 2, and mix for a few minutes until the proper granules are formed.
5. Unload the granules, and dry at 55°C in an oven to get the desired LOD of 2.5%.
6. Grind the dried granules to get granules of the desired particle size of #16 mesh.
7. Add crospovidone and magnesium stearate to ground granules in a blender, and blend for 3 min.
8. Compress 200 mg of the lubricated granules into tablets (12 mm).
9. Use appropriate coating materials (HPMC). (See Appendix.)

Quinine Sulfate Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Quinine sulfate	300.00
20.00	2	Starch (maize)	20.00
25.00	3	Lactose monohydrate	25.00
5.00	4	Sodium starch glycolate	5.00
0.80	5	Methyl paraben	0.80
0.10	6	Propyl paraben	0.10
2.00	7	Gelatin	2.00
20.00	8	Starch (maize)	20.00
3.00	9	Talc	3.00
1.50	10	Aerosil 200	1.50
2.00	11	Magnesium stearate	2.00
—	12	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1 to 4 through a 250-µm sieve into a suitable mixing vessel.
2. In a separate vessel, take the appropriate quantity of Item 12, and heat it to a boil. Add and dissolve Items 5 and 6. Cool to 50°C, and add Items 7 and 8. Then mix to form a 30% starch paste.
3. Add the paste from Step 2 into Step 1, and mix the paste to form a suitable mass for granulation.
4. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays; dry at 60°C overnight.
5. Pass the dried granules through #18 mesh into a blending vessel. Sift Items 9 to 11 through a 250-µm sieve, and the pieces add to Step 5, and blend for 2 min. Compress 375 mg in 9.5-mm punches.
6. Coat the tablets using HPMC and methylene chloride. (See Appendix.)

Quinolone Antibiotic Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Quinolone antibiotic*	100.00
23.50	2	Microcrystalline cellulose	23.50
15.00	3	Starch (maize)	15.00
6.50	4	L-Hydroxypropylcellulose	6.50
3.50	5	Magnesium stearate	3.50
1.50	6	Colloidal anhydrous silica (Aerosil 200)	1.50

* Applicable to most quinolone antibiotics.

MANUFACTURING DIRECTIONS

1. The manufacturing process described is for the 100-mg tablet. Adjust the weights of all components based on the quantity used. When calculating, factor in for salt form, moisture, and activity.
2. Sift Items 1 to 4.
3. Mix these (use two-thirds of Item 4) at this stage in a blender. Add screened Item 6, and mix at a slow speed.
4. Run the mixture through a compacting mill, and collect graded granules in a blender.
5. Add screened Item 6 and the balance of Item 4, and blend. Add the screened magnesium stearate in the rotating-shell blender. Mix at 6 r/min for 5 min. The final mixture is obtained.
6. Compress 8-mm tablets or 10-mm tablets (for 200-mg tablets).
7. Coat using an HPMC coating. (See Appendix.)

Rabeprazole Sodium Tablets (20 mg) [109]

The active ingredient in Aciphex™ delayed-release tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol; freely soluble in ethanol, chloroform, and ethyl acetate; and insoluble in ether and *n*-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media and is more stable under alkaline conditions. Aciphex is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. The inactive ingredients are mannitol, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxypropyl methylcellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide, carnauba wax, and ferric oxide (yellow) as a coloring agent.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Rabeprazole	20.00
50.00	2	Precipitated calcium carbonate	50.00
40.00	3	Starch (maize)	40.00
73.40	4	Lactose monohydrate	73.40
6.00	5	Hydroxypropyl cellulose	6.00
2.00	6	Magnesium stearate	2.00
—	7	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Mix *R*(+) rabeprazole, precipitated calcium carbonate, cornstarch, lactose, and hydroxypropyl-cellulose together.
2. Add water, and knead the mixture. Then dry in vacuum at 40°C for 16 h.
3. Pass the granules through a 16-mesh sieve to give granules.
4. Add Item 6, and blend.
5. Compress.

Raloxifene Tablets (60 mg) [100]

Evista (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy] phenyl]-, hydrochloride. Raloxifene HCl has the empirical formula $C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight of 510.05. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water. Evista is supplied in a tablet dosage form for oral administration. Each Evista tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Raloxifene HCl	60.00
156.00	2	Lactose anhydrous	156.00
7.20	3	Polyvinyl pyrrolidone	7.20
7.20	4	Polysorbate 80	7.20
7.20	5	Cross-linked polyvinyl pyrrolidone	7.20
2.40	6	Magnesium stearate	2.40

MANUFACTURING DIRECTIONS

1. Granulate the mixture of raloxifene HCl, lactose anhydrous, and cross-linked polyvinylpyrrolidone with an aqueous solution of polyvinylpyrrolidone and polysorbate 80.
2. Dry the granules, and reduce to a suitable size.
3. Mix and blend magnesium stearate.
4. Compress 240-mg tablets.

Ranitidine Hydrochloride Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
150.00	1	Ranitidine, use ranitidine hydrochloride	167.68
129.75	2	Microcrystalline cellulose	129.75
9.00	3	Hydroxypropyl methyl cellulose 2910	9.00

MANUFACTURING DIRECTIONS

1. Granulation
   a. Pass ranitidine and microcrystalline cellulose through a 595-µm aperture screen, transfer to a suitable mixer, and mix for 10 min.
2. Lubrication
   a. Screen the magnesium stearate through a 400-µm aperture screen and add to the blender. Blend for 2 min.
   b. Discharge the granule into polyethylene-lined drums. Seal the drums, and weigh for yield.
3. Compression
   a. Compress using slightly convex round punches. The weight of 10 tablets should be about 2.07 g, with not more than 3% variation. Disintegration time is not more than 15 min in water.
4. Coating
   a. Use opaque methocel–ethocel coating. (See Appendix.)

Ranitidine Tablets (75 mg)

Bill of Materials			
Scale(mg/tablet)	**Item**	**Material Name**	**Quantity/1,000Tabs (g)**
75.00	1	Ranitidine, use ranitidine HCl[a]	85.00
95.00	2	Microcrystalline cellulose (Avicel PH 102)	95.00
7.00	3	Croscarmellose sodium (Ac-Di-Sol)	7.00
6.60	4	Microcrystalline cellulose (Avicel PH 102)	6.60
1.40	5	Magnesium stearate	1.40

[a] Ranitidine HCl 1.5% was added as an extra to compensate LOD and process loss.

MANUFACTURING DIRECTIONS

1. Process the product in an area where the RH is between 40 and 45%, and the temperature does not exceed 25°C. Store the bulk tablets in polythene-lined stainless steel containers at a controlled RH 45 to 50% and a temperature not exceeding 25°C.
2. Pass Items 2, 3, and 1 through a sifter using a 900-µm sieve.
3. Load into blender, and mix for 3 min. Mix Items 4 and 5 in a polythene bag manually for 1 min. Pass through a sifter using a 500-µm sieve.
4. Collect in a polythene bag. Add to the blender, and blend for 1 min.
5. Check temperature and humidity before starting to get sluggish. (Temperature not exceeding 25°C, RH 40 to 45%.)
6. Slug 240.0 g of mixed powder in a rotary tabletting machine. Grind the slugs in the granulator, using a 3-mm sieve followed by a 1-mm sieve.
7. Compress 195 mg using oblong biconvex punches. Check the temperature and humidity before starting the compression. The limitation is that the temperature should not exceed 25°C, and the RH should be 40 to 45%.
8. Coat using a hydroalcoholic HPMC coating.

Ranitidine Tablets (150 mg) [41]

Ranitidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is *N*[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N′*-methyl-2-nitro-1,1-ethenediamine, hydrochloride. The empirical formula is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, representing a molecular weight of 350.87.

Ranitidine HCl is a white to pale yellow granular substance that is soluble in water. It has a slightly bitter taste and sulfurlike odor. Each Zantac 150 tablet for oral administration contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine. Each tablet also contains the inactive ingredients FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Each Zantac 300 tablet for oral administration contains 336 mg of ranitidine HCl equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

Zantac 150 EFFERdose tablets and Zantac 150 EFFERdose granules for oral administration are effervescent formulations of ranitidine that must be dissolved in water before use. Each individual tablet or the contents of a packet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 183.12 mg (7.96 mEq) per 150 mg of ranitidine, and the total sodium content of each packet of granules is 173.54 mg (7.55 mEq) per 150 mg of ranitidine.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Ranitidine	150.00
147.00	2	Ludipress	147.00
3.00	3	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm screen, and press with low-compression force.
2. Compress 305 mg in 8-mm biconvex punches.
3. If the flowability of the tabletting mixture is not sufficient, add about 1% Aerosil 200. For 300-mg strength, use proportion weight, and increase fill weight; the use of 1% Aerosil 200 is required.

Ranitidine Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
300.00	1	Ranitidine use as ranitidine HCl*	340.00
110.00	2	Microcrystalline cellulose (Avicel PH 102)	110.00
10.00	3	Croscarmellose sodium (Ac-Di-Sol)	10.00
16.00	4	Microcrystalline cellulose (Avicel PH 102)	16.00
4.00	5	Magnesium stearate	4.00

* Anhydrous; adjust for moisture.

MANUFACTURING DIRECTIONS

Precautions: Process the product in an area where the relative humidity is between 40 and 45%, and the temperature should not exceed 25°C. Store the bulk tablets in polythene-lined stainless steel containers at a controlled relative humidity of 45–50% and at temperatures not exceeding 25°C.

1. Dry powder sieving and mixing
   a. Pass Items 2, 3, and 1 through a sifter, using a 900-µm sieve. Load into the blender, and mix for 3 min.
2. Lubrication
   a. Mix Items 4 and 5 in a polythene bag manually for 1 min. Pass through a sifter using a 500-µm sieve. Collect in a polythene bag. Add to the blender (Step 1), and blend for 1 min.
   b. Unload in stainless steel drums. Check and record the weight of powder mix.
3. Slugging
   a. Check the temperature and humidity before the start of slugging. Limits: temperature not exceeding 25°C; relative humidity of 40–45%.
   b. Slug 240.0 g of the mixed powder in a rotary tabletting machine using the following parameters. Keep the rest of the quantity in a stainless steel drum.
4. Grinding
   a. Grind the slugs in a granulator using a 3-mm sieve followed by a 1-mm sieve.
5. Mixing
   a. Ground granules, 240 g, from Step 2, and 240 g of the lubricated granules from Step 3a. Load into blender and mix for 1/2 min.
6. Compression
   a. Check the temperature and humidity before starting compression. Limits: temperature not exceeding 25°C; relative humidity of 40–45%. Compress the granules using a rotary tabletting machine. Compress 480 mg in 015.5 mm × 7 mm.

Rifampicin, Isoniazid, Ethambutol, and Pyridoxine Tablets (300 mg/200 mg/25 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
—	1	Alcohol SD 3A, 200 proof	150.00 ml
3.00	2	Alcohol cetostearyl	3.00
300.00	3	Rifampicin powder	300.00
12.00	4	Hydroxypropyl methyl cellulose 2910, 50 cps	2.00
—	5	Alcohol SD 3A, 200 proof	QS
200.00	6	Isoniazid zisonicotinylhydrazine, 10% excess	220.00
25.00	7	Pyridoxine hydrochloride	25.00
400.00	8	Ethambutol hydrochloride	400.00
20.00	9	Povidone K 29-32	20.00
—	10	Water, purified	50.00 ml
—	11	Water, purified	QS
20.00	12	Talc	20.00
40.00	13	Sodium starch glycolate	40.00
10.00	14	Magnesium stearate	10.00

MANUFACTURING DIRECTIONS

Note: Rifampicin and ethambutol hydrochloride are expensive raw materials, therefore, handle with care. The product should be manufactured in a separate, closed area, and all manufacturing equipment should be covered to minimize dust contamination.

1. Granulation I
   a. Charge the alcohol (Item 1) into a container, and while stirring, gradually add the alcohol cetostearyl. Continue mixing until it all dissolves.
   b. Charge the rifampicin into the mixer (preferably a planetary mixer), followed by the hydroxypropyl methylcellulose. Mix together for 5 min.
   c. While mixing the blended powders from "Granulation I," pour in the alcoholic solution from this step. (Do not add too slowly or excessive evaporation will occur.) When all the solution is added, continue mixing for 1 min.
   d. Stop the mixer, scrape the blades, walls, and bottom of the mixer, and then restart the mixer.
   e. While mixing, add extra alcohol (Item 5) in portions, mixing for 30 sec between each addition. Continue adding alcohol and mixing until the mass changes to a uniform dark reddish-brown color that exhibits good adhesion when squeezed and contains no dry powder. Stop mixing.
   f. Quickly scrape the blades, walls, and bottom of the mixer. Then pass the mass through a 4.76-mm aperture screen, spread on lined trays, and dry in a hot-air oven at 50°C to an LOD (60°C for 3 h under vacuum) of not more than 2.5%.
   g. Sift the dried granules through a 1.2-mm screen on a sieve shaker.
   h. Pass the coarse granules from Step 1g through a 1.7-mm screen.
   i. Transfer the siftings from Step 1g and the granules from Step 1h to a suitable blender.
2. Granulation II
   a. Pass successively, through a 1.2-mm aperture screen on a sieve shaker, the isoniazid followed by the pyridoxine hydrochloride. Charge the screened powders into a suitable mixer, and mix for 5 min.
   b. Pass the ethambutol hydrochloride through a 1.2-mm aperture screen, and transfer to the mixer. Blend all the powders together for 5 min.
   c. Add the water (Item 10) to a stainless steel container, and add, while mixing, the povidone. Continue mixing until it all dissolves.
   d. While mixing the powders from Granulation II, Step 2b, add the aqueous solution from Granulation II, Step 2c, in a slow stream. When all the solution is added, continue mixing for 1 min.
   e. Stop the mixer, and scrape the blades, wall, and bottom of the mixer. Start mixing again.
   f. Gradually add extra water until granulation is achieved with the formation of balls.

g. Pass the mass through a 4.76-mm aperture screen, and spread on lined trays. Dry in a hot-air oven at 50°C for 4 h, pass the granules through a 2.38-mm aperture screen, return to the oven, and continue drying to an LOD of less than 1% (60°C for 3 h under vacuum).
h. Sieve the dried granules through an 840-µm aperture screen on a suitable sieve shaker.
i. Pass the coarse granules from Granulation II, Step 2h, through an 840-µm aperture screen.
j. Transfer the fines from Granulation II, Step 2h, and the granules from Step 2i, to the blender (see Granulation I, Step 1i).

3. Lubrication
   a. Pass the talc and sodium starch glycolate through a 595-µm aperture screen on a sieve shaker, and then transfer to the blender with Granulations I and II.
   b. Blend all the items together for 15 min, then stop the blender.
   c. Pass the magnesium stearate through a 595-µm aperture screen on a sieve shaker, then transfer to the blender.
   d. Blend the batch for 3 to 4 min, then stop the blender.
   e. Discharge the contents of the blender into polyethylene-lined drums, and weigh.
4. Compression
   a. Compress 1.05 g using ovaloid punches (18.6 × 8.7 mm), with a disintegration time of not more than 20 min in water and a thickness of 8.4 to 8.8 mm.
5. Coating
   a. Apply an organic methocel coating. (See Appendix.)

Rifampicin Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
—	1	Alcohol SD 3A, 200 proof	150.00 ml
3.00	2	Alcohol cetostearyl	3.00
300.00	3	Rifampicin powder	300.00
12.00	4	Hydroxypropyl methylcellulose 2910 50 cps	12.00
—	5	Alcohol SD 3A, 200 proof	QS
8.00	6	Talc	8.00
16.00	7	Sodium starch glycollate powder	16.00
7.50	8	Magnesium stearate	7.50

MANUFACTURING DIRECTIONS

CAUTION: (1) Rifampicin is an expensive raw material; handle with care. (2) The product should be manufactured in a separate closed area, and all manufacturing equipment should be covered so as to minimize dust contamination. (3) Wash the manufacturing area and equipment thoroughly after use, with water and detergent. Personnel are to take a cleansing shower after exposure during manufacturing.

1. Granulation
   Do not over fill the mixer, because this retards penetration of the alcohol to the bottom of the bowl, leading to excessive evaporation and inadequate massing.
   a. Charge the alcohol (Item 1) into a container, and while stirring gradually, add the alcohol cetostearyl. Continue mixing until all has dissolved.
   b. Charge the rifampicin into the mixer (preferably a planetary mixer), followed by the hydroxypropyl methylcellulose. Mix together for 5 min.
   c. While mixing the blended powders from Step 1b, pour in the alcoholic solution from Step 1a. (Do not add too slowly or excessive evaporation will occur.) When all the solution is added, continue mixing for 1 min.
   d. Stop the mixer; scrape the blades, walls, and bottom of the mixer well, and then restart the mixer.
   e. While mixing, add extra alcohol (Item 5) in portions, mixing for 30 sec between each addition. Continue adding alcohol and mixing until the mass changes to a uniform dark reddish-brown color that exhibits good adhesion when squeezed and contains no dry powder. Stop mixing.
   f. Quickly scrape the blades, walls, and bottom of the mixer, and then pass the mass through a 4.76-mm aperture screen; spread on lined trays, and then dry in a hot-air oven at 50°C to an LOD not more than 2.5% (60°C for 3 h under vacuum). Request samples.
   g. Sift the dried granules through a 1.2-mm screen on a sieve shaker.
   h. Pass the coarse granules from Step g through a 1.7-mm screen on a granulator or something similar.
   i. Transfer the siftings from "Granulation," Steps g and h through a 1.7-mm screen on a granulator.
2. Lubrication
   a. Pass the talc and sodium starch glycolate through a 595-μm aperture screen on a sieve shaker, and then transfer to the blender.
3. Blend all the items together for 15 min, then stop the blender.
   a. Pass the magnesium stearate through a 595-μm aperture screen on a sieve shaker, then transfer to the blender.
   b. Blend the batch for 3 to 4 min, and then stop the blender.
   c. Discharge the contents of the blender into polyethylene-lined drums, and weigh. Record the batch weight.
4. Compression
   a. Compress the tablets on a suitable rotary tabletting machine, using round punches of 10.32 mm. The tablet weight for 10 tablets is as follows: (3.465 × 100)/(100% LOD). Hardness is 6 to 8; disintegration time should be more than 15 min in water; and thickness should be 5.15 to 5.25 mm.
      i. For other strengths of rifampicin, 450 and 600 mg, scale up the formula. For 450-mg tablets, use ovaloid punches of 15.2 × 7.77 mm. The tablet weight for

10 tablets is (5.145 × 100)/(100% LOD); hardness is 9 to 15; the disintegration time is not more than 15 min in water; and the thickness is 6.55 to 6.65 mm. The coating solution will be 200 ml — optionally add coating solution gloss methocel, 90.00 ml. (See Appendix.)

ii. For 600-mg tablets, use ovaloid punches of 18.6 × 7.8 mm. The tablet weight for 10 tablets is (6.930 × 100)/(100% LOD); hardness is 9 to 15; the disintegration time is not more than 15 min in water; and the thickness is 6.35 to 6.45 mm. Use a coating solution of 250 ml. Optionally add coating solution gloss methocel, 90.00 ml. (See Appendix.)

Rifampicin Tablets (450 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
450.00	1	Rifampicin	450.00
58.00	2	Starch maize	58.00
9.00	3	Kollidon 90 F	9.00
—	4	Isopropyl alcohol or alcohol, ca	50 ml
15.00	5	Kollidon CL	15.00
10.00	6	Stearic acid	10.00
2.00	7	Magnesium stearate	2.00
2.00	8	Aerosil 200	2.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4. Dry, sieve, and mix with Items 5 to 8, and press with low-compression force to tablets.
2. Compress 550 mg in 12-mm biplanar punches.

Risedronate Sodium Tablets (5 mg/30 mg) [188]

Actonel (risedronate sodium tablets) is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Actonel tablet for oral administration contains the equivalent of 5 or 30 mg of anhydrous risedronate sodium in the form of the hemipentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemipentahydrate is $C_7H_{10}NO_7P_2Na$ 2.5 H_2O. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]*bis*[phosphonic acid] monosodium salt. Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and is essentially insoluble in common organic solvents. The inactive ingredients are crospovidone, ferric oxide yellow (5-mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Risedronate sodium[a]	30.00
156.00	2	Lactose anhydrous	156.00
60.50	3	Microcrystalline cellulose	60.50
7.40	4	Crospovidone	7.40
1.10	5	Magnesium stearate	1.10

[a] This quantity of risedronate sodium is determined by assay and then adjusted to provide the designed dosage level of risedronate sodium on an anhydrous basis.

MANUFACTURING DIRECTIONS

1. Charge the risedronate active ingredient with the microcrystalline cellulose in a twin-shell blender. Blend for 20 min.
2. Pass the blend through an oscillator equipped with a 60-mesh screen.
3. Return the milled blend to the shell blender, along with the lactose and crospovidone, and mix until uniform.
4. Add the magnesium stearate, and mix until adequate lubrication is achieved.
5. Compress 250 mg.
6. Coat. (See Appendix.)

Risperidone Tablets (4 mg) [1050]

Risperidone is an antipsychotic agent belonging to a new chemical class known as the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1 -piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$, and its molecular weight is 410.49.

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 *N* HCl. Risperdal tablets are available in 0.25-mg (dark yellow), 0.5-mg (red-brown), 1-mg (white), 2-mg (orange), 3-mg (yellow), and 4-mg (green) strengths. The inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25-mg tablets contain yellow iron oxide; the 0.5-mg tablets contain red iron oxide; the 2-mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3-mg and 4-mg tablets contain D&C Yellow No. 10; and the 4-mg tablets contain FD&C Blue No. 2 Aluminum Lake.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Risperidone	4.00
140.00	2	Lactose monohydrate	140.00
105.00	3	Microcrystalline cellulose (Avicel PH 102)	105.00
81.00	4	Maize starch	81.00
18.00	5	Maize starch, dried	18.00
1.00	6	Colloidal silicone dioxide (Aerosil 200)	1.00
1.00	7	Magnesium stearate	1.00
QS	8	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift risperidone, lactose monohydrate, Avicel PH 102, and a part of the maize starch through a stainless steel 500-µm sieve.
2. Load the sifted powder into a mixer, and mix for 5 min.
3. Make a paste with the remaining part of the maize starch in purified water (80 to 90°C).
4. Knead the powder mix with the starch paste to get the desired granules.
5. Dry the granules in an air-circulating oven to a targeted LOD of not more than 2.5%.
6. Pass the dried granules through a 250-µm sieve into a blending vessel.
7. Lubricate with Aerosil 200, maize starch dried, and magnesium stearate previously sieved through a stainless steel 250-µm sieve. Blend for 1 min.
8. Compress into tablets to get the labeled amount of risperidone per tablet using specified tools.
9. Coat the tablets using a hypermellose coating. (See Appendix.)

Rofecoxib Tablets (12.5 mg/25 mg/50 mg) [31]

Vioxx (rofecoxib) is described chemically as 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2(5*H*)-furanone. Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36. Each tablet of Vioxx for oral administration contains 12.5, 25, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

Rosiglitazone Maleate Tablets (2 mg/4 mg/8 mg) [86]

Avandia (rosiglitazone maleate) is an oral antidiabetic agent that acts primarily by increasing insulin sensitivity. Avandia is used in the management of Type 2 diabetes mellitus (also known as noninsulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Avandia improves glycemic control while reducing circulating insulin levels.

Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the α-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione,(*Z*)-2-butenedioate (1:1), with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable.

The molecular formula is $C_{18}H_{19}N_3O_3S{\cdot}C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122 to 123°C. The pK_a values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3. Solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated Tiltab® tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and one or more of the following: synthetic red and yellow iron oxides and talc.

Roxithromycin Dispersible Tablets (200 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Roxithromycin	200.00
30.00	2	Ethylcellulose	30.00
12.80	3	Sodium croscarmellose	12.80
0.27	4	Isopropyl alcohol	270.00 ml
130.00	5	Dicalcium phosphate	130.00
4.40	6	Sodium lauryl sulfate	4.40
320.00	7	Starch (maize)	320.00
4.00	8	Magnesium stearate	4.00
4.00	9	Talc	4.00
28.00	10	Sodium starch glycolate	28.00
8.00	11	Aerosil 200	8.00
24.00	12	Aspartame	24.00
24.00	13	Flavor	24.00
—	14	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1, 3, and 5 through a 250-µm sieve into a suitable mixing vessel.
2. In a separate vessel, add and mix Items 2 and 4.
3. Add the binding solution in Step 2 to Step 1, and mix until a suitable mass is formed.
4. Pass the wet mass through a 2.38-mm sieve, and dry the granules in a dehumidified room.
5. Pass the dried granules through a 595-µm sieve into a blending vessel.
6. Pass Items 6 and 7 through a 250-µm sieve into a blender, and mix for 15 min.
7. Prepare the paste with a portion of Item 7 in hot water, and add to Step 6. Mix until a proper mass is formed.
8. Dry the granules at 50°C overnight, and pass the dried granules through 595-µm sieve.
9. Lubricate the two granules mixed together with Items 8 to 13.
10. Compress 150 mg in 8-mm punches.
11. Coat using HPMC coating. (See Appendix.)

Salbutamol Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
2.00	1	Salbutamol, use as salbutamol sulfate	2.40
80.00	2	Lactose monohydrate	80.00
33.60	3	Starch (maize)	33.60
3.30	4	Starch (maize)	3.30
0.10	5	FD&C Yellow No. 6	0.10
0.60	6	Magnesium stearate	0.60
—	7	Purified water	28.00

MANUFACTURING DIRECTIONS

Note: The binding solution is susceptible to microbial growth, so prepare the solution directly before use.

1. Sift Item 4 through a 250-µm sieve using a sifter.
2. Manually make a homogeneous slurry of Item 4 in 4 g of cold Item 7 (25 to 30°C) in a stainless steel container. Check that it is free of lumps.
3. Add Item 5 and the slurry of the starch paste (from Step 2) into 24 g of Item 7, heated to 85°C into a Giusti vessel. Stir until there is complete gelatinization. Cool to 50°C.
4. Sift Items 1, 3, and 2 through a 630-µm sieve using a sifter. Collect in a stainless steel container.
5. Load sieved powders in the mixer. Mix for 15 min at high speed.
6. Add starch paste from Step 4 to the mixer. Mix this for 10 min.
7. Pass the wet mass through a Fitz mill using sieve no. 24205 at medium speed, knives forward.
8. Spread the wet granules onto the trays. Load the trolleys into the oven. Dry the granules at 55°C for 10 h. Scoop the granules after 4 h of drying, then put the upper trays to the down position and the down trays to the upper position for uniform drying. Check the moisture content — as a limit, there should not be more than 2.5%.
9. Grind the dried granules through a 1-mm sieve using a granulator. Collect in a stainless steel drum, and load to the blender. Sift Item 6 through a 250-µm sieve using a sifter. Collect in a polythene bag. Mix 2 g of granules with this, and add to the blender. Mix this for 1 min.
10. Compress the granules. The weight of 10 tablets is 1.20 gm ± 3%; hardness is not less than 2 kp.

Salbutamol Tablets (4 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
4.00	1	Salbutamol, use as salbutamol sulfate	4.80
80.00	2	Lactose monohydrate	80.00
31.28	3	Starch (maize)	31.28
3.30	4	Starch (maize)	3.30
0.02	5	Red FD&C No. 3	0.02
0.60	6	Magnesium stearate	0.60
—	7	Purified water	28.00

MANUFACTURING DIRECTIONS

See the directions for the 2.0-mg strength.

Serratiopeptidase Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Serratiopeptidase	10.00
228.00	2	Ludipress	228.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low-compaction force (6 kN).
2. Compress 238 mg in 8-mm biplanar punches.

Serratiopeptidase Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
10.00	1	Serratiopeptidase, 40% excess	14.00
70.00	2	Lactose monohydrate	70.00
50.00	3	Microcrystalline cellulose potassium	50.00
80.00	4	Starch (maize)	80.00
—	5	Isopropyl alcohol	100 ml
2.50	6	Magnesium stearate	2.50
5.00	7	Talc	5.00

MANUFACTURING DIRECTIONS

1. Charge Items 2 to 4 in a suitable vessel. Mix these items for 5 min.
2. Add Item 5, and granulate the mass. Pass it through a 2.38-mm sieve onto paper-lined trays.
3. Dry the granules in a dehumidified area overnight.
4. Pass the granules through #18 mesh into a blending vessel.
5. Add Item 1 to Step 4, and mix well.
6. Sift Items 6 and 7 through a 250-μm sieve, and add to Step 5.
7. Compress 225 mg in 7-mm punches.
8. Coat with HPMC organic coating. (See Appendix.)

Sertraline Hydrochloride Tablets (25 mg/50 mg/100 mg) [14]

Sertraline HCl is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-*1*-naphthalenamine hydrochloride. The empirical formula is $C_{17}H_{17}NCl_2 \cdot HCl$. Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol. Zoloft is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50, and 100 mg and the following inactive ingredients: dibasic calcium phosphate dihydrate, D&C Yellow No. 10 Aluminum Lake (in the 25-mg tablet), FD&C Blue No. 1 Aluminum Lake (in the 25-mg tablet), FD&C Red No. 40 Aluminum Lake (in the 25-mg tablet), FD&C Blue No. 2 Aluminum Lake (in the 50-mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic Yellow iron oxide (in the 100-mg tablet), and titanium dioxide.

Sildenafil Tablets (25 mg/50 mg/100 mg) [43]

Viagra®, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase Type 5 (PDE5). Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/ml in water and a molecular weight of 666.7. Viagra is formulated as blue, film-coated, rounded-diamond-shaped tablets equivalent to 25 mg, 50 mg, and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD&C Blue No. 2 Aluminum Lake.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Sildenafil, use sildenafil citrate	70.50
100.00	2	Avicel PH 102	100.00
131.00	3	Dibasic calcium phosphate anhydrous	131.00
9.00	4	Ac-Di-Sol	9.00
1.00	5	Aerosil 200	1.00
1.50	6	Magnesium stearate	3.50

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 2 in a suitable blender or plastic bag after sifting through a 500-µm sieve. Mix them for 5 min.
2. Add Item 3 to Step 1 after sifting through a 500-µm sieve. Mix for 5 min.
3. Add Items 4 to 6 after sifting them through a 500-µm sieve (Item 6 through a 250-µm sieve). Blend this for 1 min.
4. Compress 315 mg using diamond-shaped 13.2×8.2-mm punches.
5. Coat using an HPMC coating. (See Appendix). Use dispersed Blue E, 132 1.4 mg/tab, to match the color of Viagra. Following is a proposed formulation of coating solution:

Bill of Materials

Scale (mg/tablet)	Item	Material Name
4.00	1	Hypermellose
0.80	2	Triacetin
1.22	3	Talc
2.60	4	Titanium dioxide
0.46	5	Lactose monohydrate
1.41	6	Dispersed blue E112
0.40	7	Opadry OY-LS 29019 clear
QS	8	Water, purified

Silimarin Tablets (35 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
35.00	1	Silimarin	35.50
410.50	2	Ludipress	410.50
4.50	3	Magnesium stearate	4.50

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force (about 10 kN).
2. Compress 458 mg in 12-mm biplanar punches.

Simvastatin Tablets (10 mg) [17]

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S**-[1α,3α,7β,8β(2*S**,4*S*),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$, and its molecular weight is 418.57. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol, and ethanol.

Zocor® tablets for oral administration contain 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide, and other ingredients. Butylated hydroxyanisole is added as a preservative.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Simvastatin	10.10
55.23	2	Lactose monohydrate	55.23
15.000	3	Pregelatinized starch (Starch 1500)	15.00
0.02	4	Butylated hydroxy anisole	0.02
2.50	5	Ascorbic acid	2.50
1.25	6	Citric acid	1.25
15.00	7	Microcrystalline cellulose (Avicel PH 102)	15.00
0.60	8	Magnesium stearate	0.60
0.30	9	Colloidal silicon dioxide (Aerosil 200)	0.30
—	10	Purified water	12.00
—	11	Absolute alcohol (ethanol, dehydrated alcohol)	5.00

MANUFACTURING DIRECTIONS

Note: Avoid overmixing lubricants, or hardness may be reduced.

1. Preparation of granulating solution
   a. Make a clear solution of Item 4 in Item 11 by slow stirring.
   b. Dissolve Items 5 and 6 in Item 10 under slow stirring by a stirrer.
2. Dry powder mixing
   a. Sift Items 1, 2, and 3 through a stainless steel 500-μm sieve in a sifter. Load into the mixer, and mix for 3 min at low speed.
3. Kneading
   a. Add a binding solution, 25 to 31 g/min, to the dry powders while mixing at low speed. After the addition is over, scrape the sides and blades. Mix further for 2 min using a mixer and chopper at low speed. Scrape sides and blades. Check for the end point of granulation. (End point of the granulation is the point when the wet mass consists of little or no lumps of granule.)
   b. If required, add purified water. Record the extra quantity of purified water added. Unload the wet granules onto stainless steel trays for drying.
4. Drying
   a. Dry the wet granules in an oven at 55°C for 6 h. After 3 h of drying, scrape the semidried granules to break the lumps for uniform drying.
   b. Check the LOD, with a limit of 1.0 to 1.5%.
   c. If required, dry further at 55°C for 1 h. Check the LOD. Transfer the dried granules in a stainless steel drum.
5. Grinding
   a. Grind the dried granules through a 1.25-mm sieve. Collect in a polyethylene bag.
6. Lubrication
   a. Sift Items 7 and 9 through a 500-μm sieve, and add this to the double polyethylene bag used in Step 5a. Mix manually for 1 min.

b. Sift Item 8 through a 500-μm sieve. Add 6 to 12 g granules from bulk (Step 5). Mix in a polythene bag for 1 min. Add this mixture to the polyethylene bag in Step 5. Mix manually for 30 sec. Add the two loads in the polyethylene bag, and mix manually for 15 sec.
c. Unload into stainless steel drums.

7. Compression
   a. Compress the granules using a rotary tabletting machine. The dimension should be 8.5 mm × 5-mm oval punches; 100 mg per tablet should be compressed.
8. Coating
   a. Coat the tablets using an HPMC coating. (See Appendix.)

Simvastatin Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Simvastatin	20.200
110.460	2	Lactose monohydrate	110.460
30.000	3	Pregelatinized starch (Starch 1500)	30.000
0.040	4	Butylated hydroxy anisol	0.040
5.000	5	Ascorbic acid	5.000
2.500	6	Citric acid	2.500
30.000	7	Microcrystalline cellulose (Avicel PH 102)	30.000
1.200	8	Magnesium stearate	1.200
0.600	9	Colloidal silicon dioxide (Aerosil 200)	0.600
—	10	Purified water	24.000
—	11	Absolute alcohol (ethanol, dehydrated alcohol)	10.000

Spironolactone Tablets (25 mg/50 mg/100 mg)) [130]

Aldactone oral tablets contain 25 mg, 50 mg, or 100 mg of the aldosterone antagonist spironolactone, 17-hydroxy-7-α-mercapto-3-oxo-17-α-pregn-4-ene-21-carboxylic acid γ-lactone acetate. Spironolactone is practically insoluble in water, soluble in alcohol, and freely soluble in benzene and in chloroform. Inactive ingredients include calcium sulfate, cornstarch, flavor, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide.

Bill of Materials			
Scale(mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	Spironolactone	25.00
175.00	2	Ludipress	175.00
1.50	3	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

1. Mix all components. Pass the mixture through a sieve, and press with medium-compression force.
2. Compress 197 mg in 8-mm biplanar punches.

Stalol Hydrochloride Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Sotalol hydrochloride	500.00
100.00	2	Microcrystalline cellulose or lactose anhydrous	100.00
80.00	3	Starch maize	80.00
30.00	4	Sodium starch glycolate	30.00
4.00	5	Magnesium stearate	4.00
4.00	6	Silicon dioxide colloidal	4.00
QS	7	Dyes	QS
—	8	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a granulating bowl, and mix for 20 min. (*Note:* For Item 2, a choice of using cellulose or lactose, or a combination thereof, is available.)
2. Add a sufficient quantity of Item 8 to form a wet mass.
3. Pass the wet mass in Step 2 through #8 mesh onto paper-lined trays. Dry at 60°C for 12 h to achieve an LOD of less than 5%.
4. Pass the dried granules through 16 or 20 mesh, and transfer to a blending vessel.
5. Add Items 4 to 7, and blend for 5 min.
6. Compress an appropriate amount in a suitable punch.

Sulfadimidine Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
500.00	1	Sulfadimidine	500.00
100.00	2	Lactose monohydrate	100.00
15.00	3	Kollidon 30	15.00
—	4	Water, purified, ca	200.00
25.00	5	Kollidon CL	25.00
2.40	6	Talc	2.40
0.30	7	Aerosil 200	0.30
0.30	8	Calcium arachinate	0.30

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with the solution of Items 3 and 4. Dry, pass through a 0.8-mm sieve, mix with Items 5 to 8, and press.
2. Compress 610 mg in 12-mm biplanar punches.

Sulfamethoxazole and Trimethoprim Tablets (400 mg/80 mg; 800 mg/160 mg; 100 mg/20 mg)) [106]

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.32 and a molecular formula of $C_{14}H_{18}N_4O_3$.

Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl) sulfanilamide. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28 and a molecular formula of $C_{10}H_{11}N_3O_3S$. Sulfamethoxazole–trimethoprim is a synthetic antibacterial combination product available in DS (double-strength) tablets, tablets, and suspensions for oral administration. Each DS tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole plus magnesium stearate, pregelatinized starch, and sodium starch glycolate. Each tablet contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole, plus magnesium stearate, pregelatinized starch, sodium starch glycolate, FD&C Blue No. 1 Lake, FD&C Yellow No. 6 Lake, and D&C Yellow No. 10 Lake. Each teaspoonful (5 ml) of the pediatric suspension or suspension contains 40 mg of trimethoprim and 200 mg of sulfamethoxazole in a vehicle containing 0.3% alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C Yellow No. 6, FD&C Red No. 40, flavors, and water.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Sulfamethoxazole	800.00
160.00	2	Trimethoprim	160.00
70.00	3	Starch (corn)	70.00
5.00	4	Alginic acid	5.00
—	5	Water, purified, ca	320.00 ml
5.00	6	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Granulation
   a. Pass the following ingredients through a 595-µm aperture screen: sulfamethoxazole, trimethoprim, and starch (corn), and charge into a suitable blender. Blend for approximately 20 min.
   b. Add and dissolve alginic acid (60°C) and purified water. Cool the solution to 35°C.
   c. Add the solution from Step 1b to blended powders, and blend until a suitable granulating mass is obtained. Add more purified water if needed.
   d. Pass the granulating mass through a 2.38-mm aperture screen.
   e. Oven dry the wet granules at 45°C for 16 h until the LOD is not more than 0.9% (105°C for 1 h).
2. Lubrication
   a. Pass the dried granulate through a 1.2-mm aperture screen on an oscillating granulator, and charge into a suitable blender.
   b. Add magnesium stearate, and mix well for approximately 10 min.
3. Compression
   a. Compress using a 19-mm caplet punch. The weight of 10 tablets is 10.4 g; the thickness is 7.4 to 8.2 mm; and the hardness is 14 to 22 units.
   b. For 400/80 tablets, use an 11.5-mm diameter flat, beveled edge punch. The weight of 10 tablets is 5.20 g; the thickness is 4.2 to 4.6 mm; and the hardness is 13 to 24.
   c. For 100/20 tablets, use 7.5-mm diameter beveled edge punch. The weight of 10 tablets is 1.2 g; the thickness is 2.4 to 2.7 mm; and the hardness is 6 to 12.

Sulfamethoxazole and Trimethoprim Tablets (400 mg/80 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
400.00	1	Sulfamethoxazole	400.00
80.00	2	Trimethoprim	80.00
15.00	3	Kollidon 30	15.00
—	4	Isopropyl alcohol	QS
24.00	5	Kollidon CL	24.00
2.00	6	Talc	2.00
8.00	7	Magnesium stearate	8.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 and 2 with a solution of Items 3 and 4. Pass this through a 0.8-mm sieve, dry, add Items 5 to 7, and press with low-compression force.
2. Compress 546 mg in 12-mm biplanar punches.

Sulfamethoxazole and Trimethoprim Tablets (800 mg/160 mg; 400 mg/80 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/500,000 Tablets (Kg)**
800.00	1	Sulfamethoxazole	800.00
160.00	2	Trimethoprim	160.00
20.00	3	Povidone K30	20.00
24.20	4	Primojel (sodium carboxymethyl starch)	24.20
5.00	5	Magnesium stearate	5.00
0.20	6	Dioctyl sodium sulfosuccinate	0.20

MANUFACTURING DIRECTIONS

1. First prepare the PVP solution sufficient for the above batch divided into four lots.
2. In a suitable stainless steel container, take 30 kg of deionized water, heat it to 70°C, and add to it while stirring Item 4 gradually.
3. After complete dissolution, continue to stir, and add 140 kg of deionized water, Item 3. Stir until completely dissolved.
4. Let stand overnight.
5. In a separate container, take one-fourth of Items 1 and 2, and mix. Then add, in small portions, the PVP solution made in Step 1, 45.1 kg each, until a moist mass with granular lumps is obtained. Pass the granules through a centrifugal granulator using a 10-mm sieve.
6. Spread the granules on trays, and dry at 60°C for 28 h. The relative humidity should be 15 to 20%.
7. Pass the granules through an oscillating granulator with 2-mm perforations at a rate of 2 to 2.5 kg/min.
8. Charge the granules in a V-type blender from each of the four lots, mix for 5 min, and transfer to a drum. Then add Item 5 and the balance of Primojel (12.1 kg). Mix in a tumble mixer for 10 min.
9. Charge the mixture in a V-blender, and mix for 1 h. The relative humidity should be 20 to 25%.
10. Compress at 4- to 5-ton pressure. The weight of one tablet is 1.010 mg. This is the formula for a double-strength tablet. Adjust quantities and fill the weight for 400/80 strength.

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Sulfamethoxazole and Trimethoprim Tablets, Dispersible (800 mg/160 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
800.00	1	Sulfamethoxazole powder	800.00
160.00	2	Trimethoprim micronized	160.00
80.00	3	Starch (maize)	90.00
3.00	4	Sodium lauryl sulfate	3.00
15.00	5	Gelatin	15.00
25.00	6	Starch (maize)	25.00
8.00	7	Magnesium stearate	8.00
9.00	8	Guar gum	9.00
—	9	Purified water	300.00

MANUFACTURING DIRECTIONS

Note: The binding solution is liable to microbiological growth, so prepare the solution fresh, before the granulation process.

1. Preparation of starch paste: Manually make a slurry of Item 6 in 40 g of Item 9 (40°C). Then add 110 g of Item 9 into the vessel, and heat to 80°C. Add the slurry of Item 6 to it, and mix until it swells and is translucent.
2. Add Item 5 slowly to 150 g of Item 9 (70°C) using a stirrer. Avoid lumps and excessive foam formation. Add the gelatin solution to the starch paste in Step 1, and mix for 10 min.
3. Dry powder mixing: Load Items 1, 2, 3, and 4 in the mixer. Mix and chop at high speed for 6 min.
4. Wet massing: Add starch paste from Step 2 to the dry powders in the mixer, while mixing and chopping at low speed. When the addition is over, mix further for 5 min or until a satisfactory mass is obtained. *Note:* Avoid lumps or a ball formation that is too big.
5. Drying
   a. Dry the granules in a fluid-bed dryer at 55°C for 1 h.
   b. Check the moisture content. The limit is 1 to 1.5%. *Note:* Moisture control is a very important step. It affects the microbial quality of this product.
6. Grinding: Grind the dried granules through a 1.5-mm sieve first, and then through a 1.25-mm sieve fitted on a dry granulator. Collect the granules in a stainless steel drum. Load the granules to the blender.
7. Lubrication
   a. Mix Items 7 and 8 in a polythene bag. Pass the mix through a 250-µm sieve using a sifter. Collect in a polythene bag. Add 10 g granules from Step 6. Mix for 1 to 2 min, add to the blender, and mix for 2 min.
   b. Unload into stainless steel drums.
8. Compression: Compress the granules using a rotary tabletting machine with 19 × 8.8-mm oblong punches. Each tablet will be 1,100 mg.

Sulfathiazole Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Sulfathiazole	250.00
237.00	2	Lactose monohydrate or dicalcium phosphate	237.00
12.00	3	Kollidon 30	12.00
—	4	Water, purified	QS
12.00	5	Kollidon CL	12.00
2.00	6	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1 to 3 with Item 4, pass through a 0.8-mm sieve, dry, add Items 5 and 6, and press with low-compression force.
2. Compress 504 mg (512 mg if using dicalcium phosphate) in 12-mm biplanar punches.

Sumatriptan Succinate Tablets (25 mg/50 mg) [125]

Imitrex is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-*N*-methyl-indole-5-methanesulfonamide succinate (1:1).

The empirical formula is $C_{14}H_{21}N_3O_2S{\cdot}C_4H_6O_4$, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

Each Imitrex tablet for oral administration contains 35 or 70 mg of sumatriptan succinate equivalent to 25 or 50 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and titanium dioxide dye.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
140.00	1	Sumatriptan, use*	140.00
154.00	2	Lactose monohydrate	154.00
17.00	3	Microcrystalline cellulose	17.00
3.30	4	Sodium croscarmellose	3.30
1.70	5	Magnesium stearate	1.70
—	6	Water, purified, ca	12.50 ml

* For 25 mg strength, use 35 mg sumatriptan succinate.

MANUFACTURING DIRECTIONS

1. Sift Items 1 and 2 through a 0.6-mm mesh sieve screen into a fluid-bed granulator.
2. Granulate by spraying Item 6 with an inlet temperature of 75°C; allow granules to dry.
3. Pass granules through a granulator fitted with a 0.8-mm mesh screen.
4. Transfer granules to a blender, add Item 5, and mix for 5 min.
5. Compress about 320 mg in a suitable punch.

Tamoxifen Tablets (10 mg/20 mg) [191]

Tamoxifen citrate tablets, a nonsteroidal antiestrogen, are for oral administration. Nolvadex tablets are available as follows: *10-mg tablets:* each 10-mg tablet contains 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen; *20-mg tablets:* each 20-mg tablet contains 30.4 mg of tamoxifen citrate, which is equivalent to 20 mg of tamoxifen. The inactive ingredients are carboxymethylcellulose calcium, magnesium stearate, mannitol, and starch.

Chemically, tamoxifen is the *trans*-isomer of a triphenylethylene derivative. The chemical name is (*Z*)2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Tamoxifen citrate has a molecular weight of 563.62. The pK_a' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/ml, and in 0.02 *N* HCl at 37°C, it is 0.2 mg/ml.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Tamoxifen, use tamoxifen citrate	15.30
114.50	2	Lactose monohydrate	114.50
38.00	3	Starch (maize)	38.00
3.50	4	PVP K30	3.50
0.75	5	Magnesium stearate	0.75
3.00	6	Ac-Di-Sol	3.00
—	7	Water, purified, ca	30 ml

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 after sifting them through a 500-µm sieve in a suitable mixer. Mix this for 5 min at low speed.
2. In a separate vessel, add and dissolve Item 4 in Item 7 at a slow speed.
3. Add Step 2 into Step 1, and knead and mix for 5 min, and then again, long enough to achieve a suitable wet mass.
4. Dry the wet mass on trays at 55°C for 5 h to an LOD of not more than 1 to 1.5%. If required, dry for another hour.
5. Pass the dried granules through a 1.25-mm sieve, and transfer to a blender.
6. Add Items 5 and 6 (sifted through a 500-µm sieve) to Step 5, and blend for 1 min.
7. Compress 175 mg in 8-mm round, plain concave punches. For 20-mg tablet, use appropriate fill weight in 10-mm punches.

Temafloxacin Hydrochloride Tablets (200 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Temafloxacin hydrochloride, excess 10%	220.00
112.50	2	Lactose monohydrate	112.50
40.00	3	Sodium starch glycolate	40.00
12.50	4	Hydroxy propylcellulose	12.50
100.00	5	Cellulose microcrystalline	100.00
5.00	6	Magnesium stearate	5.00
10.00	7	Talc	10.00
QS	8	Water, purified, ca	186.00 ml

MANUFACTURING DIRECTIONS

1. Granulation
   a. Dissolve hydroxypropylcellulose in two-thirds volume of purified water (Item 8).
   b. Pass lactose, temafloxacin hydrochloride, and the sodium starch glycolate through an approximately 765-µm aperture screen, if necessary, and charge into a mixer and mix. Add hydroxypropylcellulose solution from Step 1a, mix, and granulate. Add more water, if needed, until a granule mass is formed.
   c. Pass the wet mass through an approximate 4.8-mm aperture screen, and dry in a dryer at 45 to 52°C to an LOD of not more than 1.5%. Pass the dried granules through an approximately 1.18-mm screen. If necessary, screen the microcrystalline cellulose (and crospovidone for 400- and 600-mg tablets) through an approximate 500-µm aperture screen. Add to the dried granules, and blend for 10 min.
   d. Pass the magnesium stearate and talc through a 500-µm aperture screen. Add to the bulk from Step 1c, and blend for 5 to 10 min.
   e. Compress as follows: *200 mg:* 7.32 × 15.19 mm; *500 mg and 300 mg:* 8.5 × 17.5 mm; *750 mg.*
   f. Coat the compressed tablets by spraying with a color coat and then apply gloss. (See Appendix.)

Tenoxicam Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Tenoxicam	20.00
90.00	2	Lactose monohydrate	90.00
84.00	3	Maize starch	84.00
4.00	4	Talc	4.00
2.00	5	Magnesium stearate	2.00
—	6	Water, purified, ca	50.00 ml

MANUFACTURING DIRECTIONS

1. Charge Item 6 and Item 3 (20%) in a mixer heated to 40°C, and mix for 10 min. Heat at 70 to 80°C until a homogenous paste is formed. Cool to 50°C.
2. In a separate vessel, charge Item 2, the balance of Item 3, and Item 1. Mix well.
3. Add the paste from Step 1 into Step 2, and mix for 15 min until a loose, moist mass is obtained.
4. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
5. Spread over paper-lined trays, and dry at 45°C overnight (the relative humidity over the granules should be 20 to 35%).
6. Pass the dried granules through a 1.5-mm sieve granulator.
7. Transfer the granules to a tumbler, add Item 4 and then Item 5, and mix for 20 min.
8. Compress 200 mg in a suitable punch (11.5 × 6.0 mm).

Terazosin Tablets (1 mg–10 mg) [126]

Terazosin hydrochloride, an α^1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name and structural formula: (*RS*)-piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate.

Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline, with a molecular weight of 459.93. Hytrin capsules (terazosin hydrochloride capsules) for oral ingestion are supplied in four dosage strengths, containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin. Hytrin inactive ingredients: *1-mg capsules:* gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; *2-mg capsules:* D&C Yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; *5-mg capsules:* D&C Red No. 28, FD&C Red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; *10-mg capsules:* FD&C Blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
1.00	1	Terazosin hydrochloride	1.10
98.00	2	Ludipress	98.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low-compression force (10 kN).
2. Compress 98.1 mg for 1 mg and 97.6 mg for 5-mg strength in 6-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.
4. For 5-mg strength, adjust with Item 2.

Terazosin Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
128.560	1	Lactose	128.530
1.000	2	Terazosin, use terazosin monohydrate	1.187
7.500	3	Starch (maize)	7.500
6.000	4	Starch (maize)	6.000
—	5	Water, purified, ca	25 ml
6.000	6	Talc	6.000
1.123	7	Magnesium stearate	1.120

MANUFACTURING DIRECTIONS

1. Granulation
   a. Mix the terazosin and a portion of lactose. Mill the mixture through a 425-µm (or similar) aperture screen using a comminuting mill, with impact forward, at high speed.
   b. If necessary, mill the remainder of lactose.
   c. Add the powders (Step 1a and 1b) and starch (Item 3) to the mixer. and blend for 20 min.
   d. Disperse starch (Item 4) in purified water, and heat to make a paste.
   e. Add starch paste to powder blend, and blend for 5 to 7 min, adding extra purified water. Record any additional volume.
   f. If necessary, pass the granule through a 4.76-mm aperture on an oscillating granulator or a 12.7-mm aperture screen on a comminuting mill, with knives forward, at slow speed.
   g. Dry at 49°C to an LOD of not more than 2% (105°C for 1 h).
   h. Pass granules through a 1.18-mm aperture screen on an oscillating granulator.
   i. Add one-half of the granules to a suitable blender.
   j. Blend the magnesium stearate and talc with a portion of the granules. Pass through a 1.18-mm aperture screen, and add to the bulk.
   k. Add the remainder of granule, and blend for 10 min.
2. Compression: Use 7.14-mm or other similar size punches.
   a. For 2-mg, 5-mg, and 10-mg strengths, adjust with Item 1 and any dye added to differentiate tablets.

Terbinafine Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Terbinafine (used as terbinafine hydrochloride)	250.00
10.00	2	Hypromellose (hydroxy propyl methyl cellulose)	10.00
105.00	3	Avicel PH 102 (microcrystalline cellulose)	105.00
2.50	4	Ac-Di-Sol (croscarmellose sodium)	2.50
1.50	5	Magnesium stearate	1.50
QS	6	Purified water	QS

MANUFACTURING DIRECTIONS

1. Sift terbinafine hydrochloride and Avicel through a 250-µm sieve.
2. Dissolve hydroxy propyl methyl cellulose in purified water to make a granulating solution.
3. Knead the powder mix in Step 1 with the granulation solution to get the desired wet mass. Pass the mass through a #8 sieve onto drying trays.
4. Dry granules at 60°C for 12 h to an LOD of not more than 2%.
5. Pass the granules through #16 mesh into the blending vessel.
6. Pass croscarmellose sodium and magnesium stearate through a 250-µm sieve, and add to Step 5. Blend for 3 min.
7. Compress 400 mg in a suitable punch.

Terfenadine Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
60.00	1	Terfenadine	60.00
235.00	2	Ludipress	235.00
6.00	3	Kollidon CL	6.00
1.00	4	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with very low-compressive force.
2. Compress 301 mg in 8-mm biplanar punches.

Tetracycline Tablets (125 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
125.00	1	Tetracycline hydrochloride	125.00
100.00	2	Ludipress	100.00
42.00	3	Microcrystalline cellulose (Avicel PH 101)	42.00
3.00	4	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with very low-compression force.
2. Compress 278 mg in 8-mm biplanar punches.

Tetracycline Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.00	1	Tetracycline hydrochloride	250.00
175.00	2	Lactose monohydrate	175.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
28.00	5	Talc	28.00
3.50	6	Aerosil 200	3.50
3.50	7	Calcium arachinate	3.50

MANUFACTURING DIRECTIONS

1. Pass Items 1 to 4 through a 0.5-mm sieve, add the mixture of Items 6 and 7, and press with low-compression force.
2. Compress 505 mg in 12-mm biplanar punches.

Tetrazepam Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Tetrazepam	50.00
113.00	2	Microcrystalline cellulose (Avicel PH 101)	113.00
30.00	3	Starch 1500 (Colorcon)	30.00
5.00	4	Kollidon VA 64	5.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Pass the components through a 0.5-mm sieve, and press with low-compression force.
2. Compress 208 mg in 8-mm biplanar punches.

Theophylline and Ephedrine Tablets (130 mg/15 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
130.00	1	Theophylline (0.1 to 0.4 mm)	130.00
15.00	2	Ephedrine hydrochloride	15.00
150.00	3	Ludipress	150.00
2.00	4	Aerosil 200	2.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with very low-compression force.
2. Compress 302 mg in 8-mm biplanar punches.

Theophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Theophylline (0.1 to 0.4 mm)	100.00
147.00	2	Ludipress	147.00
3.00	3	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress 247 mg in 8-mm biplanar punches.

Theophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Theophylline	100.00
137.10	2	Lactose anhydrous	137.10
60.00	3	Carbopol® 971P	60.00
1.50	4	Cab-o-Sil®	1.50
1.50	5	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

1. Pass all items through a 250-µm mesh, and charge Items 1 to 3 in a suitable blender. (Item 3 can be used granulated in a fluid-bed.)
2. Add Items 4 and 5, and blend for 3 min.
3. Compress 300 mg in a suitable punch.

Theophylline Tablets CR (200 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
200.00	1	Theophylline powder	200.00
2.00	2	Sodium lauryl sulfate	2.00
2.00	3	Calcium stearate	2.00
35.00	4	Ethyl cellulose	35.00
3.60	5	Cetanol	3.60
1.60	6	Sodium lauryl sulfate	1.60
148.00	7	Triethyl citrate	148.00
—	8	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 to 3 in a suitable mixer, and mix for 10 min.
2. Granulate Step 1 by passing the items through a compactor or dry granulator.
3. Pass the compact material from Step 2 through #16 to #32 mesh.
4. In a separate vessel, add Items 4 to 7, and make a solution with Item 8 to 200 g.
5. Transfer Step 3 into a fluid-bed granulator, and apply the solution in Step 4 to coat the granules.
6. Compress.

Tibolone Tablets (0.3 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
0.30	1	Tibolone (Org GD 14)	0.30
1.95	2	Hydroxypropyl cellulose	1.95
32.50	3	Starch (maize)	32.50
0.32	4	Magnesium stearate	0.32
29.93	5	Lactose anhydrous	29.33
—	6	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 3 and 5 in a suitable blender, and mix for 1 min after passing them through a 250-µm sieve.
2. In a separate vessel, charge Items 1 and 2; add a sufficient amount of Item 6 to make a uniform solution.
3. Add Step 2 into Step 1 gradually, and granulate for 2 min.
4. Pass the wet mass through #8 mesh, and dry at 40°C for 4 h.
5. Screen the granules through a 710-µm sieve into a blender.
6. Add Item 4, and blend for 1 min.
7. Compress 65 mg in a suitable punch.

Ticlopidine Hydrochloride Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
250.0	1	Ticlopidine HCl	250.0
72.0	2	Starch, maize	72.0
68.8	3	Microcrystalline cellulose (Avicel)	68.8
6.0	4	Polyvinylpyrrolidone (PVP K30)	6.0
1.2	5	Colloidal silicon dioxide (Aerosil 200)	1.2
2.0	6	Magnesium stearate	2.0
—	7	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Blend ticlopidine HCl, maize starch, Avicel, and PVP K-30 after passing through a 350-µm sieve.
2. Charge Item 3 in a separate vessel, and prepare a paste using Item 7.
3. Add Step 2 into Step 1. Knead to make a suitable wet mass.
4. Pass the wet mass through #8 mesh onto drying trays. Dry at 60°C for 12 h. The LOD should not be more than 2.5%.
5. Pass the dried granules through #16 mesh into a blending vessel.
6. Blend with Avicel, Aerosil, and magnesium stearate previously sieved through a 500-µm sieve.
7. Compress 400 mg in 15-mm punches.
8. Coat the tablets with hypermellose solution. (See Appendix.)

Tolterodine Tablets (1 mg/2 mg) [171]

Detrol® tablets contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (*R*)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is 475.6. Tolterodine tartrate is a white, crystalline powder. It is soluble at 12 mg/ml in water at room temperature and is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. Detrol tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hydroxypropyl methylcellulose, magnesium stearate, sodium starch glycolate (pH 3.0 to 5.0), stearic acid, and titanium dioxide.

Topiramate Tablets (100 mg/200 mg) [189]

Topamax® (topiramate) is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. It is available as 25-mg, 100-mg, and 200-mg round tablets for oral administration. Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/ml. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5-*bis*-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate.

Topamax (topiramate) tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100- and 200-mg tablets), and polysorbate 80.

Tosufloxacin Tosylate Tablets (75 mg)

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Tosufloxacin tosylate monohydrate	75.00
37.40	2	L-Aspartic acid	37.50
21.45	3	Cellulose, crystalline	21.45
34.50	4	Starch (maize)	34.50
7.50	5	Silicon dioxide, hydrated	7.50
2.25	6	Hydroxypropyl cellulose	2.25
1.80	7	Magnesium stearate	1.80

MANUFACTURING DIRECTIONS

1. Pass Items 1 and 2 through a 790-µm sieve into a suitable blender.
2. Blend for 2 min.
3. Add Items 3 to 6, passing each item through a 500-µm sieve.
4. Blend for 5 min.
5. Pass Item 7 through #100 mesh into Step 4.
6. Blend for 1 min.
7. Compress 180 mg in 8-mm punches.

Trazodone Hydrochloride Tablets (100 mg) [61]

Trazodone HCl is an antidepressant that is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated as 2-[3-{4-(*m*-chlorophenyl)-1-piperazinyl]propyl]*s*-triazol[4,3-*a*]-pyridine-3(2*H*)-one monohydrochloride. Trazodone HCl is a white to off-white crystalline powder that is sparingly soluble in chloroform and water. Its molecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O{\cdot}HCl$.

Trazodone HCl is supplied for oral administration in 50-mg, 100-mg, 150-mg, and 300-mg tablets.Trazodone HCl tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 Aluminum Lake, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Trazodone HCl tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Trazodone HCl tablets, 150 mg, contain the following in active ingredients: microcrystalline cellulose, FD&C Yellow No. 6 Aluminum Lake, magnesium stearate, pregelatinized starch, and stearic acid.

Trazodone HCl tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, yellow ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, and stearic acid.

Triamcinolone Tablets (4 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
4.00	1	Triamcinolone	4.00
191.00	2	Ludipress	191.00
2.00	3	Kollidon CL	2.00
2.00	4	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress 206 mg in 8-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Trifluoperazine Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
5.00	1	Trifluoperazine hydrochloride	5.00
194.00	2	Ludipress	194.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a sieve, and press with very low-compression force.
2. Compress 204 mg in 8-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Tulobuterol Hydrochloride Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
1.00	1	Tulobuterol hydrochloride	1.00
44.96	2	Lactose monohydrate	44.96
40.00	3	Blue dye	40.00
28.00	4	Starch (maize)	28.00
2.00	5	Acacia	2.00
3.00	6	Calcium carboxymethyl cellulose	3.00
—	7	Water, purified, ca	20 ml
1.00	8	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

CAUTION: Tulobuterol is a low-dose bronchodilator. Operators should wear a mask and gloves during all stages of manufacture.

1. Blending
   a. Cross feed tulobuterol, blue dye, and lactose through a comminutng mill fitted with a 790-µm screen, with high speed knives.
   b. Blend the maize starch, acacia, and calcium carboxymethyl cellulose. Put the tulobuterol blend in a suitable mixer/blender for 20 min, and disintegrate.
2. Granulation
   a. Load the blended ingredients from Blend A or B into a suitable planetary mixer. While mixing, add water in a slow steady stream. Continue massing for 5 min after all the water is added. Proceed to the drying step.
3. Drying
   a. Pass the wet mass through a 4-mm aperture screen onto paper-lined trays. Dry at 50 to 55°C. The final LOD should be between 1.5 and 5% (105°C for 1 h).
   b. Pass the dried granule through an oscillating granulator fitted with a 720-µm aperture screen.
4. Lubrication
   a. Load the dried granules into a suitable blender. Pass the magnesium stearate and an equal portion of dried granule through a 600-µm aperture screen. Add to a blender, and blend for 5 min.
5. Compression
   a. Compress using a rotary machine fitted with 7/32-in. flat bevel-edged punches. The weight should be 80 mg ± 3%.
   b. For a 2-mg dose, adjust with lactose.

Valacyclovir Hydrochloride Tablets (500 mg/1 g) [144]

Valtrex® (valacyclovir hydrochloride) is the hydrochloride salt of L-valyl ester of the antiviral drug acyclovir (Zovirax® Brand, GlaxoSmithKline Inc.).Valtrex caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 g of valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

The chemical name of valacyclovir hydrochloride is L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl) methoxy] ethyl ester, monohydrochloride. Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4 \cdot HCl$ and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/ml. The pK_a values for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

Valdecoxib Tablet (10 mg/20 mg) [148]

Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isox-azolyl) benzenesulfonamide and is a diaryl-substituted isoxazole. The empirical formula for valdecoxib is $C_{16}H_{14}N_2O_3S$, and the molecular weight is 314.36. Valdecoxib is a white crystalline powder that is relatively insoluble in water (10 µg/ml) at 25°C and pH 7, is soluble in methanol and ethanol, and is freely soluble in organic solvents and alkaline (pH = 12) aqueous solutions.

Bextra tablets for oral administration contain 10 or 20 mg of valdecoxib. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

Valproate Sodium Tablets (500 mg) [121]

Also see "Divalporoate Sodium." Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with a 0.5 equivalent of sodium hydroxide. Chemically, it is designated as sodium hydrogen *bis*(2-propylpentanoate).

Divalproex sodium occurs as a white powder with a characteristic odor. Depakote tablets and Sprinkle capsules are antiepileptics for oral administration.

Depakote tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg, or 500 mg of valproic acid. The inactive ingredients are cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains cornstarch), silica gel, talc, titanium dioxide, and vanillin. In addition, individual tablets contain the following: *125-mg tablets:* FD&C Blue No. 1 and FD&C Red No. 40; *250-mg tablets:* FD&C Yellow No. 6 and iron oxide; *500-mg tablets:* D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Valproate sodium	500.00
80.00	2	Starch (maize)	80.00
20.00	3	Kollidon 30	20.00
—	4	Isopropyl alcohol, ca	60 ml
5.00	5	Kollidon CL	5.00
5.00	6	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

1. Granulate the mixture of Items 1 and 2 with a solution of Items 3 and 4. Pass through a sieve, mix the dry granules with Items 5 and 6, and press with low-compression force.
2. Compress 607 mg in 12-mm biplanar punches. *Note:* The powder mixture easily develops electric charge.

Valsartan and Hydrochlorothiazide Tablets (80 mg/12.5 mg; 160 mg/25 mg) [108]

Diovan HCT® (valsartan and hydrochlorothiazide, USP) is a combination of valsartan, an orally active, specific angiotensin II antagonist acting on the AT1 receptor subtype, and hydrochlorothiazide, a diuretic. Valsartan, a nonpeptide molecule, is chemically described as *N*-(1-oxopentyl)-*N*-[[2-(1*H*-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, and its molecular weight is 435.5. Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water. Hydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its molecular weight is 297.73. Diovan HCT tablets are formulated for oral administration to contain valsartan and hydrochlorothiazide, USP 80/12.5 mg, 160/12.5 mg, and 160/25 mg. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
80.00	1	Valsartan	80.00
12.50	2	Hydrochlorothiazide	12.50
1.50	3	Colloidal silica anhydrous (Aerosil 200)	1.50
31.50	4	Microcrystalline cellulose (Avicel PH 102)	31.50
20.00	5	Polyvinyl pyrrolidone crospovidone	20.00
4.50	6	Magnesium stearate	4.50

MANUFACTURING DIRECTIONS

1. Blend all components (use only 50% of magnesium stearate) in a container mixer.
2. Sieve the blended material, and mix again.
3. Compact using a roller compactor such as Bepex Pharmapaktor L 200/50 P, Hosokawa Micron Group by applying a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 r/min.
4. Sieve the compacted material and the remaining portion of the magnesium stearate, and blend again for 2 min.
5. Compress 150 mg.

Venlafaxine Hydrochloride Tablets (25 mg/37.5 mg/50 mg) [53]

Venlafaxine hydrochloride is a structurally novel antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (*R*/*S*)-1-[2-(dimethylamino)-1-(4 methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α [(dimethylamino)methyl] *p*-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2HCl$. Its molecular weight is 313.87.

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/ml in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol–water (0.2 M sodium chloride) partition coefficient is 0.43.

Compressed tablets of Effexor® contain venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg of venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg of venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hydroxypropyl methylcellulose, iron oxide, and titanium dioxide.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Venlafaxine	25.00
90.00	2	Microcrystalline cellulose	90.00
100.30	3	Pregelatinized starch	100.30
7.00	4	Croscarmellose	7.00
0.20	5	Magnesium stearate	0.20

MANUFACTURING DIRECTIONS

1. Sieve the active ingredient through a suitable sieve, and blend with the excipients until a uniform blend is formed.
2. Screen the dry blend, and blend with the magnesium stearate.
3. Compress and adjust weight for different strengths.

Verapamil Tablets (120 mg) [65]

Verapamil® hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil is administered as a racemic mixture of the *R* and *S* enantiomers. Verapamil HCl is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil HCl is not chemically related to other cardioactive drugs. It has the following molecular formula: $C_{27}H_{38}N_2O_4 \cdot HCl$. The molecular weight of verapamil HCl is 491.08. Its chemical name is benzenacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)monohydrochloride.

Calan is available for oral administration in film-coated tablets containing 40 mg, 80 mg, or 120 mg of verapamil HCl. The inactive ingredients are microcrystalline cellulose, cornstarch, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide colorant, lactose, magnesium stearate, polyethylene glycol, talc, and titanium dioxide. Sustained-release/extended-release tablets are designed for sustained release of the drug in the gastrointestinal tract. Sustained-release characteristics are not altered when the tablet is divided in half.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Verapamil hydrochloride	120.00
270.00	2	Ludipress	270.00
3.00	3	Magnesium stearate	3.00
3.00	4	Aerosil 200	3.00

MANUFACTURING DIRECTIONS

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress 400 mg in 12-mm biplanar punches.

Warfarin Tablets (1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg) [59]

Crystalline warfarin sodium is an anticoagulant that acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the *R* and *S* enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium. Its empirical formula is $C_{19}H_{15}NaO_4$.

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light, and it is very soluble in water, freely soluble in alcohol, and very slightly soluble in chloroform and in ether.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
11.470	1	Starch (maize)	11.470
0.215	2	Dye	0.215
0.119	3	Dye	0.119
3.020	4	Starch (maize)	3.020
—	5	Water, purified, ca	9.000
37.000	6	Cellulose microcrystalline	37.000
126.310	7	Lactose monohydrate	126.310
1.000	8	Warfarin sodium anhydrous[a]	1.000
0.930	9	Magnesium stearate	0.930
0.930	10	Amberlite (RP-88) ion exchange resin	0.930

[a] Factored quantity; adjust with lactose. Dyes are selected to color-code different strengths for safety.

MANUFACTURING DIRECTIONS

CAUTION: Warfarin is poisonous. Wear a dust mask when handling. Send a 5-g sample to redetermine factor before granulating.

1. Granulation
   a. Roughly blend cornstarch (Item 1) with dyes, and mill through a #80-mesh (117-µm aperture or similar) screen.
   b. Rough blend 200 mg of colored starch mixture from Step A with cornstarch (Item 4).
   c. Make a starch paste using the colored starch mixture from Step 1b and approximately 18 ml purified water.
      Note: Starch paste should be smooth and thin. A thick starch paste will cause dye spots.
   d. Rough blend the remaining colored starch mixture from Step 1a with the following items: cellulose microcrystalline, lactose, and warfarin sodium, and mill through a 30-mesh (600-µm aperture or similar) screen.
   e. Charge the milled material into a day mixer (or similar) and blend for 10 min. Mass with hot starch paste. The addition of starch paste should be finished in 2 min. Mass for another 15 min using additional purified water, if necessary. Record the amount of purified water added. *Note:* Do not over wet or mass for too long.
   f. Granulate through a 5/8-in. (15.88-mm aperture or similar) band.
   g. Dry overnight at 49°C to not more than a 1.5% LOD at 105°C.
      Note: Protect the granules from moisture from this step on. Make sure that the relative humidity is not greater than 40% at 24°C (54 grains).
   h. Sift and grind through a #30-mesh (600-µm aperture or similar) screen.
   i. Or, sift the dried granulation through a #20-mesh (840-µm aperture or similar) screen, and mill the coarse material through a #20-mesh (840-µm aperture or similar) screen using Fitz mill (or similar), with knives forward, at medium speed.
2. Lubrication
   a. Charge the granulation into the blender.
   b. Sift magnesium stearate and amberlite through a #30-mesh (600-µm aperture, or similar) screen into a partial drum of granulation. Mix by hand, and charge into a blender.
   c. Add the remaining granulation to a blender, and blend for 10 min.
   d. Discharge the blender into polyethylene-lined drums.
3. Compression
   a. Compress using an 8-mm round flat, beveled-edged punch. The weight of 10 tablets is 1.85 g; thickness is 2.7 to 2.9 mm. Different dyes and different strengths of warfarin sodium can be adjusted with lactose.

Zolpidem Tartrate Tablets (5 mg/10 mg) [35]

Zolpidem tartrate is a nonbenzodiazepine hypnotic of the imidazopyridine class and is available in 5-mg and 10-mg strength tablets for oral administration. Chemically, zolpidem is *N*,*N*,6-trimethyl-2-*p*-toyl-imidazo(1,2,-*a*)pyridine-3-acetamide L-(+)-tartrate (2:1).

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Each Ambien® tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5-mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

Bill of Materials

Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Zolpidem hemitartrate	10.00
91.00	2	Lactose monohydrate	91.00
12.00	3	Microcrystalline cellulose	12.00
2.52	4	Hydroxypropyl methyl cellulose	2.52
3.84	5	Sodium carboxymethyl cellulose	3.84
0.72	6	Magnesium stearate	0.72
—	7	Water, purified	QS

MANUFACTURING DIRECTIONS

1. Mix Items 1 to 4, and blend for 10 min.
2. Add Item 7 to granulate, dry, and sieve granules.
3. Mix granules with Items 5 and 6, and compress 120 mg.