

SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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7

CAPSULES AND TABLETS

Chapter at a Glance

Capsules

Hard Gelatin Capsules

- The Manufacture of Hard Gelatin Capsule Shells
- Capsule Sizes
- Preparation of Filled Hard Gelatin Capsules
- Developing the Formulation and Selection of Capsule Size
- Filling Hard Capsule Shells
- Capsule Sealing
- Cleaning and Polishing Capsules

Soft Gelatin Capsules

- Preparation of Soft Gelatin Capsules
- Utilization of Soft Gelatin Capsules

Compendial Requirements for Capsules

- Added Substances
- Containers for Dispensing Capsules
- Disintegration Test for Capsules
- Dissolution Test for Capsules
- Weight Variation
- Content Uniformity
- Content Labeling Requirement
- Stability Testing
- Moisture Permeation Test

Official and Commercially Available Capsules

Inspecting, Counting, Packaging, and Storing Capsules

Tablets

Types of Tablets

- Compressed Tablets (C.T.)
- Multiple Compressed Tablets (M.C.T.)
- Sugar-Coated Tablets (S.C.T.)
- Film Coated Tablets (F.C.T.)
- Gelatin-Coated Tablets
- Enteric-Coated Tablets (E.C.T.)
- Buccal or Sublingual Tablets
- Chewable Tablets

Effervescent Tablets

- Molded Tablets (M.T.)
- Tablet Triturates (T.T.)
- Hypodermic Tablets (H.T.)
- Dispensing Tablets (D.T.)
- Immediate Release Tablets (I.R.)
- Instant Disintegrating/Dissolving Tablets
- Extended Release Tablets (E.R.)
- Vaginal Tablets

Compressed Tablets

- Quality Standards and Compendial Requirements
- Compressed Tablet Manufacture
- Wet Granulation
- All-in-One Granulation Methods
- Dry Granulation
- Tableting of Granulation
- Direct Compression Tableting
- Tablet Dedusting

Chewable Tablets

Molded Tablets

Tablet Coating

- Sugarcoating Tablets
- Film-coating Tablets
- Enteric Coating
- Fluid-Bed or Air Suspension Coating
- Compression Coating

Impact of Manufacturing Changes on Solid Dosage Forms

Official and Commercially Available Tablets

Packaging and Storing Tablets

Oral Administration of Solid Dosage Forms

Other Solid Dosage Forms for

Oral Administration

- Lozenges
- Pills

WHEN MEDICATIONS are to be administered orally to adults, capsules and tablets usually are preferred because they are conveniently carried, readily identified, and easily taken.

Consider the convenience of a patient carrying a day's, week's, or month's supply of capsules or tablets compared with equivalent doses of a liquid medication. With capsules and tablets as dosing units, there is no need for spoons or other measuring devices, which sometimes may be inconvenient and may result in less than accurate dosing. Also, most capsules and tablets are tasteless when swallowed, which is not the case with oral liquid medication.

The characteristic shapes and colors of capsules and tablets and the manufacturer's name and product code number commonly embossed or imprinted on their surface make them readily identified. This enhances communications between the patient and health care providers, assists patient compliance, and fosters safe and effective medication use.

Capsules and tablets are available for many medications in a variety of dosage strengths thereby providing prescribing flexibility to the prescriber and accurate individualized dosage for the patient. Some tablets are *scored*, or grooved, which allows them to be easily broken into two or more parts. This enables the patient to swallow smaller portions as may be desired, or when prescribed, it allows the tablet to be taken in reduced or divided dosage. Tablets that are not scored are not intended to be broken or cut by the patient since they may have special coatings and/or drug-release features that would be compromised by altering the tablet's physical integrity.

From a pharmaceutical standpoint, solid dosage forms are efficiently and productively manufactured; they are packaged and shipped by manufacturers at lower cost and with less breakage than comparable liquid forms; and are more stable and have a longer shelf-life than their liquid counterparts.

As discussed later in this chapter, empty hard gelatin capsules are often used by the pharmacist in the extemporaneous compounding of prescriptions. On occasion, a pharmacist may use commercially available capsules and tablets as the *source* of a medicinal agent when it is not otherwise available. In these instances, the pharmacist must take into account any excipients that are present in the commercial product to ensure compatibility with the other ingredients in the compounded prescription. Capsules and tablets designed to provide modified drug release are discussed in Chapter 8.

Capsules

Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed within a small shell of gelatin. Gelatin capsule shells may be *hard* or *soft* depending on their composition.

The vast majority of filled capsules are intended to be swallowed whole by the patient for the benefit of the medication contained therein. However, it is not unusual practice in hospitals and extended care facilities for a caregiver to open capsules or crush tablets to mix with food or drink, especially for children or other patients unable to swallow solid dosage forms. This should be done only with the concurrence of the pharmacist since the drug release characteristics of certain dosage forms could be altered and adversely affect the patient's welfare.

Dosage forms that must be left intact include: enteric coated tablets, designed to pass through the stomach for drug release and absorption in the intestine; extended-release dosage forms, designed to provide prolonged release of the medication; and sublingual or buccal tablets, formulated to dissolve under the tongue or in the oral cavity (1). In instances in which a patient is unable to swallow an intact solid dosage form, an alternative product, such as a chewable tablet, instant dissolving tablet, oral liquid, suppository or injection may be employed.

Hard Gelatin Capsules

Hard gelatin capsule shells are used to manufacture most of the commercially available medicated capsules. They are also commonly employed in clinical drug trials, to compare the effects of an investigational drug to another drug product or placebo. Hard gelatin capsules also are used by the community pharmacist in the extemporaneous compounding of prescriptions. The empty capsule shells are made from a mixture of gelatin, sugar and water. As such, they are clear, colorless, and essentially tasteless. They may be colored with various FD&C and D&C dyes and may be made opaque by adding agents such as titanium dioxide. Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors.

Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals. In commerce, it is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets (Fig. 7.1).

Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist.



Fig. 7.1 *Pork skin manufacture of gelatin (Beecham.)*

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Fig. 7.1 Pork skin gelatin used as raw material in the manufacture of gelatin capsules. (Courtesy of SmithKline Beecham.)

Normally, hard gelatin capsules contain between 13 and 16% of moisture (2). However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape. In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost and the capsules may become brittle and crumble when handled. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excess humidity or dryness.

Because moisture may be absorbed by gelatin capsules and affect hygroscopic agents contained within, many capsules are packaged along with a small packet of a desiccant material to protect against the absorption of atmospheric moisture. The desiccant materials most used are dried silica gel, clay, and activated carbon.

Prolonged exposure to high humidity can affect *in vitro* capsule dissolution. Such changes have been observed in capsules containing tetracycline, chloramphenicol, and nitrofurantoin (3). Because such changes could forewarn of possible changes in bioavailability, capsules subjected to such stress conditions must be evaluated on a case by case basis (3).

Although gelatin is insoluble in cold water, it does soften through the absorption of up to ten

times its weight of water. Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule. Gelatin is soluble in hot water and in warm gastric fluid a gelatin capsule rapidly dissolves and exposes its contents. Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.

A number of methods have been developed to track the passage of capsules and tablets through the gastrointestinal tract to map their transit time and drug-release patterns. Among these is gamma scintigraphy, a noninvasive procedure which involves use of a gamma ray-emitting radiotracer incorporated into the formulation with a gamma camera coupled to a data recording system (4-5). The quantity of material added to allow gamma scintigraphy is small and does not compromise the usual *in vivo* characteristics of the dosage form being studied. When scintigraphy is combined with pharmacokinetic studies, the resultant *pharmacoscintigraphic* evaluation provides information of the transit and drug release patterns of the dosage form as well as the rate of drug absorption from the various regions of the gastrointestinal tract (4). This method is particularly useful in: (a) identifying whether a correlation exists between *in vitro* and *in vivo* bioavailability for immediate-release products; (b) assessing the integrity and transit time of enteric coated tablets through the stomach enroute to the intestines; and (c) drug/dosage form evaluation in new product development (4-5). A separate technique, using a pH-sensitive, nondigestible, radiotelemetric device termed the Heidelberg capsule, the approximate size of a No. 0 gelatin capsule, has been used as a *nonradioactive* means to measure gastric pH, gastric residence time, and gastric emptying time of solid dosage forms in fasting and nonfasting human subjects (6).

As discussed in Chapter 4, drug absorption from the gastrointestinal tract depends on a number of factors, including the solubility characteristics of the drug substance, the type of product formulation (i.e., immediate-release, modified-release, enteric coated), the gastrointestinal contents and intersubject differences in physiologic character and response.

The Manufacture of Hard Gelatin Capsule Shells

Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap. The two parts overlap when joined, with the cap fitting snugly over the open end of the capsule body.

The shells are produced industrially by the mechanical dipping of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture (Figs. 7.2, 7.3). The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath, the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating. Then the plate and the pegs are slowly lifted from the bath and the gelatin dried by a gentle flow of temperature- and humidity-controlled air. When dried, each capsule part is trimmed mechanically to the proper length, removed from the pegs and the capsule bodies and caps are joined together. It is important that the thickness of the gelatin walls be strictly controlled so that the capsule's body and cap fit snugly to prevent disengagement. The pegs on which the caps are formed are slightly larger in diameter than the pegs on which the bodies are formed, allowing the telescoping of the caps over the bodies. In capsule shell production, there is a continuous dipping, drying, removing and joining of capsules as the peg-containing plates are rotated in and out of the gelatin bath. As noted earlier, capsule shells may be made distinctive by adding colorants and/or opaquants to the gelatin bath.

A manufacturer also may prepare distinctive-

looking capsules by altering the usual rounded shape of the capsule-making pegs. By tapering the end of the body-producing peg while leaving the cap-making peg rounded, one manufacturer prepares capsules differentiated from those of other manufacturers (PULVULES, Eli Lilly). Another manufacturer utilizes capsules with the ends of both the bodies and caps highly tapered (SPANSULE Capsules, SmithKline Beecham). Yet another innovation in capsule shell design is the SNAP-FIT, CONI-SNAP, and CONI-SNAP SUPRO hard gelatin capsules depicted in Figures 7.4 and 7.5. The original SNAP-FIT construction enables the two halves of the capsule shells to be positively joined through locking grooves in the shell walls. The two grooves fit into each other and thus ensure reliable closing of the filled capsule. During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule filling machines (over 180,000 capsules per hour), capsule splitting ("telescoping") and/or denting of the capsule shell occurs with the slightest contact between the two capsule-part rims when they are joined. This problem, which exists primarily with straight-walled capsule shells, led to the development of the CONI-SNAP capsule, in which the rim of the capsule body is not straight, but tapered slightly (Fig. 7.5). This reduces the risk of the capsule-rims touching on joining, and essentially



Fig. 7.2 Body of capsules and their caps are shown as they move through automated capsule-making machine. Each machine is capable of producing 30,000 capsules per hour. It takes a 40-minute cycle to produce a capsule. (Courtesy of SmithKline Beecham.)



Fig. 7.3 Capsule-making equipment.

eliminates the scale filling of capsules, the lower part of the capsule is difficult to grip. This increases the integrity of the capsule.

After filling capsules, the sealing technique is used later in this process. The imprinting of the manufacturer's (NDC) number and product identification is shown in Figure 7.6.

Capsule Size

Empty gelatin capsules come in various sizes, varying from size 00 to size 5. The size

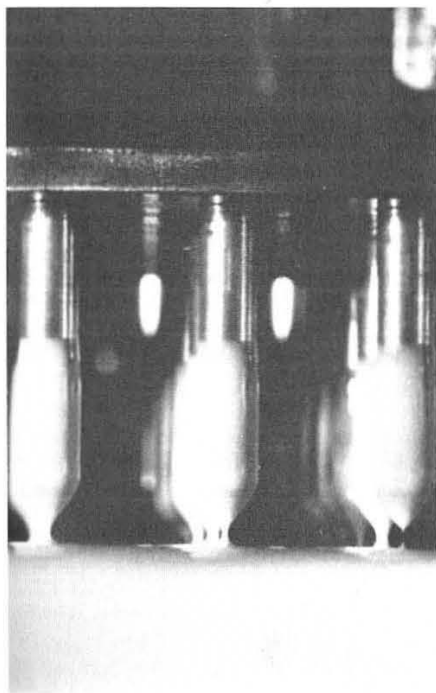


Fig. 7.3 Capsules being dipped for coloring on automated capsule-making equipment. (Courtesy of SmithKline Beecham.)

eliminates the problem of splitting during large-scale filling operations. In the CONI-SNAP SUPRO capsules, the upper capsule part extends so far over the lower part that only the rounded edge of the latter is visible (Fig. 7.5). Opening of such a filled capsule is difficult because the lower surface offers less gripping surface to pull the two halves apart. This increases the security of the contents and the integrity of the capsule.

After filling, some manufacturers render their capsules tamper-evident through various capsule sealing techniques. These methods are discussed later in this section. Capsules and tablets also may be imprinted with the names or monograms of the manufacturer, the assigned national drug code (NDC) number and other markings making the product identifiable and distinguishable from other products (Fig. 7.6).

Capsule Sizes

Empty gelatin capsules are manufactured in various sizes, varying in length, in diameter, and capacity. The size selected for use is determined by the

amount of fill material to be encapsulated. The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell (7). For estimation, a comparison may be made with powders of well-known features (Table 7.1) and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material. However, the final determination largely may be the result of trial. For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available (Fig. 7.7). Larger capsules are available for veterinary use.

For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide prescribing latitude by the physician. The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient.

Preparation of Filled Hard Gelatin Capsules

The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

CONI-SNAP[®]

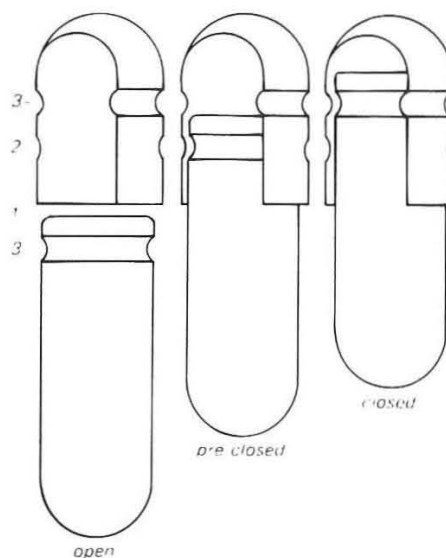


Fig. 7.4 Line drawings of the CONI-SNAP capsule in open, pre-closed, and closed positions. The tapered rims 1) avoid telescoping; the indentations 2) prevent premature opening, and the grooves 3) lock the two capsule parts together after the capsule has been filled. (Courtesy of Capsugel Division, Warner-Lambert Co.)

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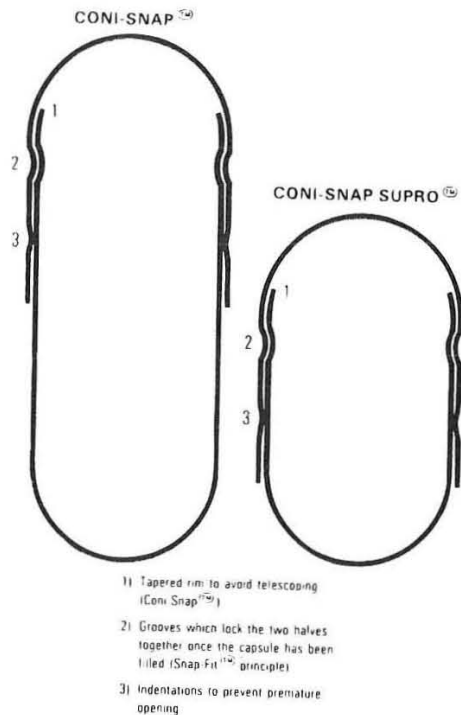


Fig. 7.5 Line drawings of the CONI-SNAP and CONI-SNAP SUPRO (on right) capsules. The latter is designed to be smaller and to have the lower portion of the capsule shell concealed except for the rounded end. This makes separation of the two parts more difficult and contributes to capsule integrity. (Courtesy of Capsugel Division, Warner-Lambert Co.)

1. Developing and preparing the formulation and selecting the size capsule.
2. Filling the capsule shells.
3. Capsule sealing (optional).
4. Cleaning and polishing the filled capsules.

Developing the Formulation and Selection of Capsule Size

In developing a capsule formulation, the goal is to prepare a capsule with accurate dosage, good bioavailability, ease of filling and production, stability, and elegance.

In dry formulations, the active and inactive components must be blended thoroughly to ensure a uniform powder mix for the capsule fill. Care in blending is especially critical for low-dose drugs since lack of homogeneity could result in significant therapeutic consequences. Preformulation studies

are performed to determine if all of the formulation's bulk powders may be effectively blended together as such or if they require reduction of particle size or other processing to achieve homogeneity.

A diluent or filler may be added to the formulation to produce the proper capsule fill volume. Lactose, microcrystalline cellulose and starch are commonly used for this purpose. In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells (2). Disintegrants are frequently included in a capsule formulation to assist the break-up and distribution of the capsule contents in the stomach. Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate.

To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar. This is par-



Fig. 7.6 Examples of tablets and capsules marked with a letter-number code to facilitate identification. (Courtesy of Eli Lilly and Company.)

Table 7.1. Ap

Drug Substance	Volume (mL)
Quinine Sulfate	
Sodium Bicarbonate	
Aspirin	

*Amount may

ticularly important for drugs that are blended with other ingredients. If necessary, particles may be produced in the micron range. Milling is particularly effective for uniform mixing when the particle size is in the (8). For drugs that are capsules are required depending on the granulation process. 1 to 20 microns.

In preparing capsules, high-speed automatic machines or granules may be used for the passage of the capsules through the encapsulation shells. The addition of fumed silicon dioxide, stearate, stearic acid, and powder mix end.

When magnesia is used, the water-soluble components of the gastrointestinal agents, as sodium

Table 7.1. Approximate Capacity of Empty Gelatin Capsules

Volume (mL)	Capsule Size							
	1.40	0.95	0.68	0.50	0.37	0.30	0.21	0.13
<i>Drug Substance (mg)*</i>								
Quinine Sulfate	650	390	325	227	195	130	97	65
Sodium Bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

*Amount may vary according to the degree of pressure used in filling the capsules.

ticularly important when a drug of low dosage is blended with other drugs or nondrug fill (8). When necessary, particle size may be reduced by *milling* to produce particles ranging from about 50 to 1000 microns. Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is 10 mg or greater (8). For drugs of lower dose or when smaller particles are required, *micronization* is employed. Depending on the materials and equipment used, micronization produces particles ranging from about 1 to 20 microns in size.

In preparing capsules on an industrial scale using high-speed automated equipment, the powder mix or granules must be free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells. The addition of a *lubricant* or *glidant* such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25–1%) to the powder mix enhances flow properties (2).

When magnesium stearate is used as the lubricant, the water-proofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption. The addition of surface active agents, as sodium lauryl sulfate, to capsule and

tablet formulations is used to facilitate wetting by the gastrointestinal fluids to overcome the problem (9). Even in instances in which a water-insoluble lubricant is not used, after the gelatin capsule shell dissolves, gastrointestinal fluids must displace the air that surrounds the dry powder and penetrate the drug before it can be dispersed and dissolved. Powders of poorly soluble drugs have a tendency to resist such penetration. Disintegration agents included in a capsule formulation facilitate the break up and distribution of the capsule's contents.

Whether it be the presence of a lubricant, surfactant, disintegrating agent, or some other pharmaceutical excipient, formulation can influence the bioavailability of a drug substance and can account for differences in drug effects, which may be encountered between two capsule products of the same medicinal substance. Pharmacists must be aware of this possibility when product-interchange is considered.

Inserting tablets or small capsules within capsules is sometimes a useful technique in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules (Fig. 7.8). This may be done to separate chemically incompatible agents or to add premeasured (as tablets) amounts of potent drug substances. Rather

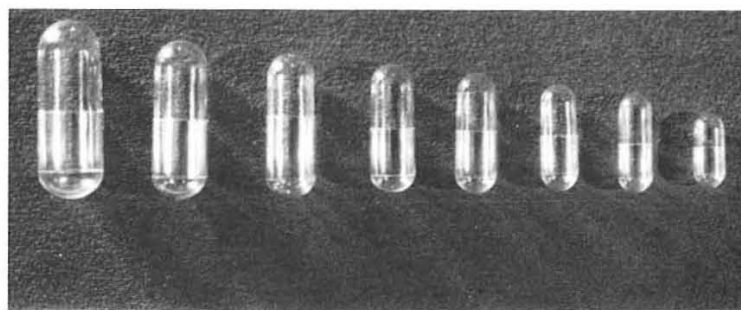


Fig. 7.7 Actual sizes of hard gelatin capsules. From left to right, sizes 000, 00, 0, 1, 2, 3, 4, and 5.

capsule should have its body filled with the drug mixture, not the cap. The cap is intended to fit snugly over the body to retain the contents.

The following examples demonstrate the drug and nondrug contents of a few commercially available capsules.

Tetracycline Capsules

Active ingredient: Tetracycline hydrochloride, 250 mg
 Filler: Lactose
 Lubricant/glidant: Magnesium stearate
 Capsule colorants: FD&C Yellow No. 6, D&C Yellow No. 10, D&C Red No. 28, FD&C Blue No. 1
 Capsule opaquant: Titanium dioxide

Acetaminophen with Codeine Capsules

Active ingredients: Acetaminophen, 325 mg
 Codeine phosphate, 30 mg
 Disintegrant: Sodium starch glycolate
 Lubricant/glidants: Magnesium stearate, stearic acid
 Capsule colorants: D&C Yellow No. 10, Edible Ink, FD&C Blue No. 1 (FD&C Green No. 3 and FD&C Red No. 40)

Diphenhydramine Hydrochloride Capsules

Active ingredient: Diphenhydramine HCl, 50 mg
 Filler: Confectioner's sugar
 Lubricants/glidants: Talc, colloidal silicon dioxide
 Wetting agent: Sodium lauryl sulfate
 Capsule colorants: FD&C Blue No. 1, FD&C Red No. 3
 Capsule opaquant: Titanium dioxide

Filling Hard Capsule Shells

When filling a small number of capsules in the pharmacy, the pharmacist uses the "punch" method. In this method, the pharmacist takes the precise number of empty capsules to be filled from his stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled, the pharmacist guards against filling an erroneous number of capsules and avoids contaminating the stock container with drug powder. The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body. Then an empty capsule body is held between the thumb

and forefinger and "punched" vertically into the powder cake repeatedly until filled. Some pharmacists wear surgical gloves or latex finger cots to avoid handling the capsules with bare fingers. Because the amount of powder packed into a capsule depends upon the degree of compression, the pharmacist should punch each capsule in the same manner and after capping weigh the product. When nonpotent materials are placed in capsules, the first filled capsule should be weighed (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, the other capsules should be prepared and weighed periodically to check the uniformity of the process. When potent drugs are being used, each capsule should be weighed after filling to ensure accuracy. Such weighings protect against the uneven filling of capsules and the premature exhaustion or underutilization of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed gently to distribute some powder to the cap-end to give the capsule a full appearance.

Granular material that does not lend itself to the "punch" method of filling capsules may be poured into each capsule individually from the powder paper on which it is weighed.

Pharmacists who prepare capsules on a regular or extensive basis may use hand-operated capsule filling machines (Fig. 7.9). The various types of available machines have capacities ranging from 24 to 300 capsules and when efficiently operated are capable of producing from about 200 to 2000 capsules per hour.

Machines developed for industrial use automatically separate the caps from empty capsules, fill the bodies, scrape off the excess powder, replace the caps, seal the capsules as desired, and clean the outside of the filled capsules at a rate of up to 165,000 capsules per hour (Fig. 7.10). The formulation must be such that the filled body contains the accurate drug dosage. This is verified through the use of automated in-process sampling and analysis equipment and processes (Figs. 7.11, 7.12).

As described later, the USP requires adherence to standards for *content uniformity* and *weight variation* for capsules to assure the accuracy of dosage units.

Capsule Sealing

As mentioned previously, some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer

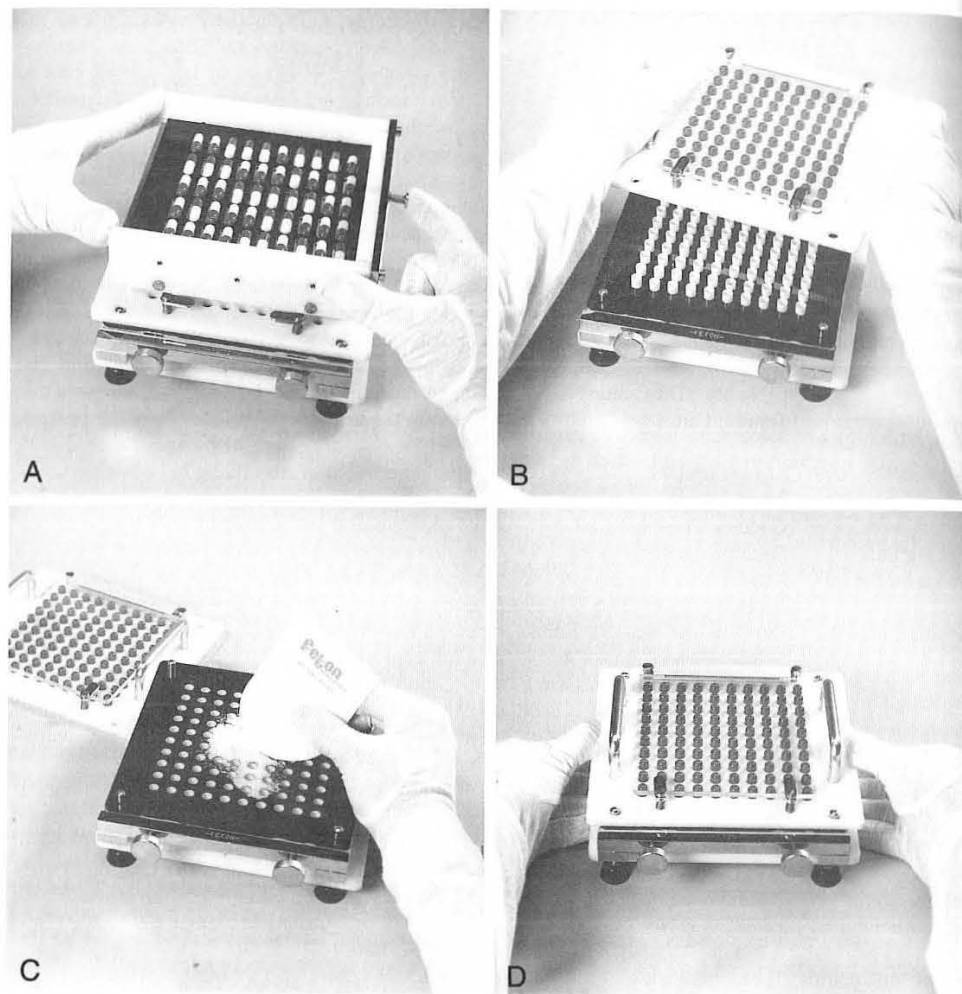


Fig. 7.9 The Fetton capsule filling machine. A, with empty capsules in the loader tray, the tray placed on top of the filler unit; B, the loader inserts the capsules into the filling unit and is removed and the top plate is lifted to separate the caps from the bodies; C, the powder is placed on the unit and the capsule bodies filled; D, the top plate then is returned to the unit and the caps placed on filled capsule bodies. (Courtesy of Chemical and Pharmaceutical Industry Company)

makes distinctive-looking capsules by sealing them with a colored band of gelatin (KAPSEALS, Parke-Davis). If removed, the band cannot be restored without expert resealing with gelatin. Capsules may also be sealed through a heat welding process that fuses the capsule cap to the body through the double wall thickness at their juncture (10). The process results in a distinctive "ring" around the capsule where heat welded. Still another process

utilizes a melting-point-lowering liquid wetting agent in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40–45°C) (11). Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin banded, heat welded, or thermally coupled capsules per hour (12). Figure 7.13 depicts a sealed hard gelatin capsule. Although difficult and tedious, extemporaneously prepared

Fig. 7.10 Osa Sharples-Stokes

capsules may surface of the immediately pr body.

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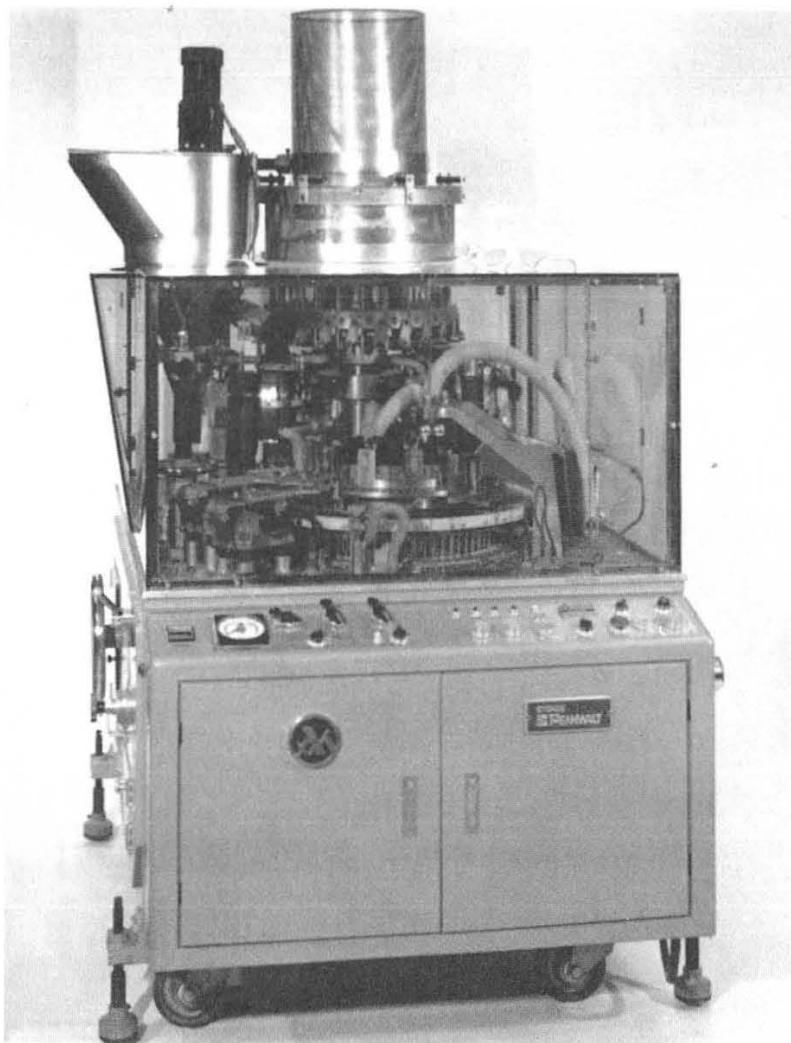


Fig. 7.10 Osaka Automatic Capsule Filler (Model R-180), capable of filling up to 165,000 capsules per hour. (Courtesy of Sharples-Stokes Div., Stokes-Merrill, Penncolt Corporation.)

capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to placement on the filled capsule body.

Cleaning and Polishing Capsules

Small amounts of powder may adhere to the outside of capsules after filling. The powder may be bitter or otherwise unpalatable and should be re-

moved before packaging or dispensing. On a small scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth. On a large scale, many capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment. Figure 7.14 shows the industrial cleaning and polishing of hard filled capsules using the Accela-Cota apparatus.

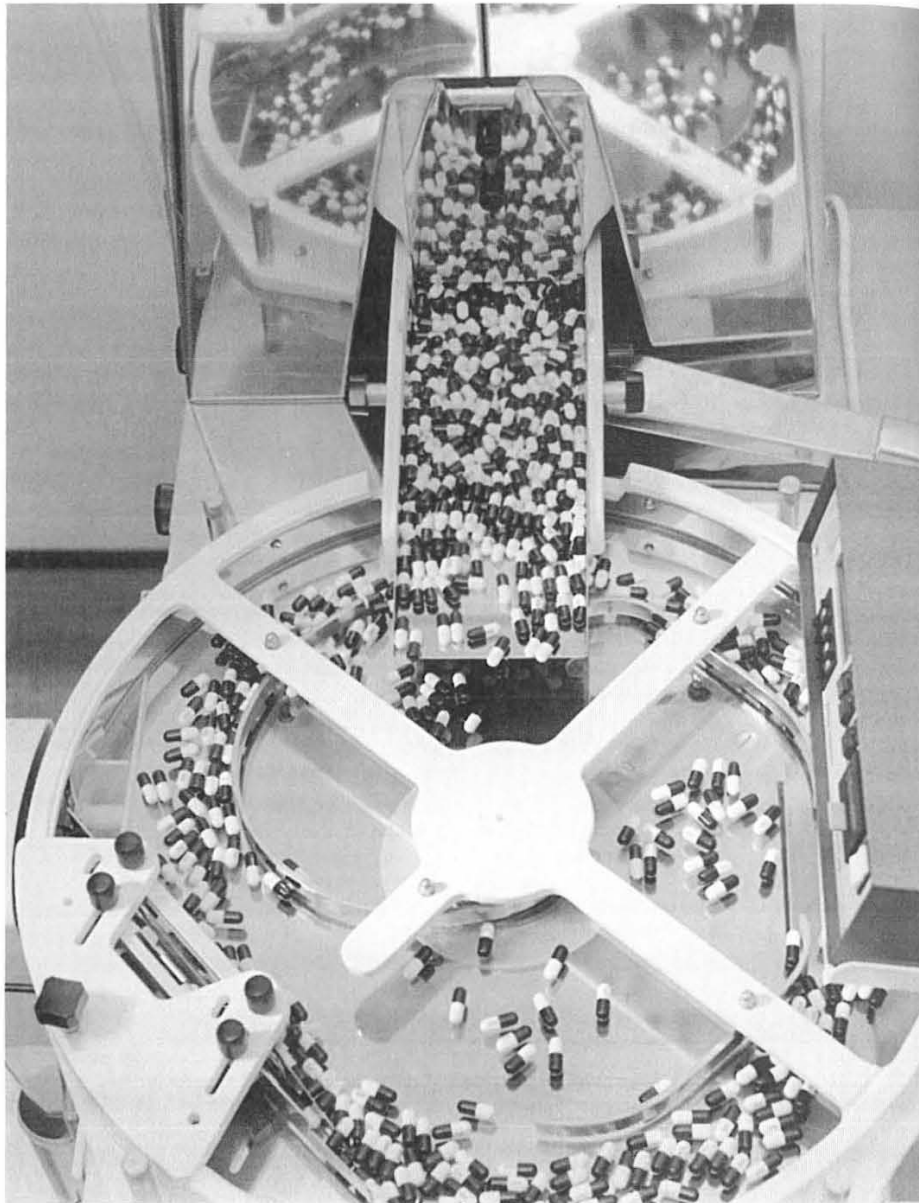


Fig. 7.11 Automatic capsule weighing apparatus, Vericap 1800 A Checkweigher, which rejects capsules not having the precise weight. (Courtesy of Elan Corporation)

Soft Gelatin Capsules

Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added to render the gelatin elastic or plastic-

like. Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative added as methylparaben and/or propylparaben to retard microbial growth. Soft gelatin capsules may be manufactured to be oblong, oval or round

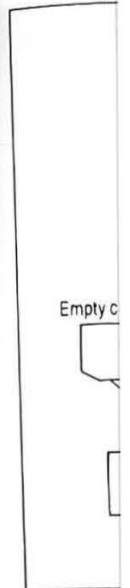


Fig. 7.12 Process automation for li

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Soft gelatin seal and enc materials, dry Soft gelatin c and are easily



Fig. 7.13 Z-1 halves together evident. (Cour

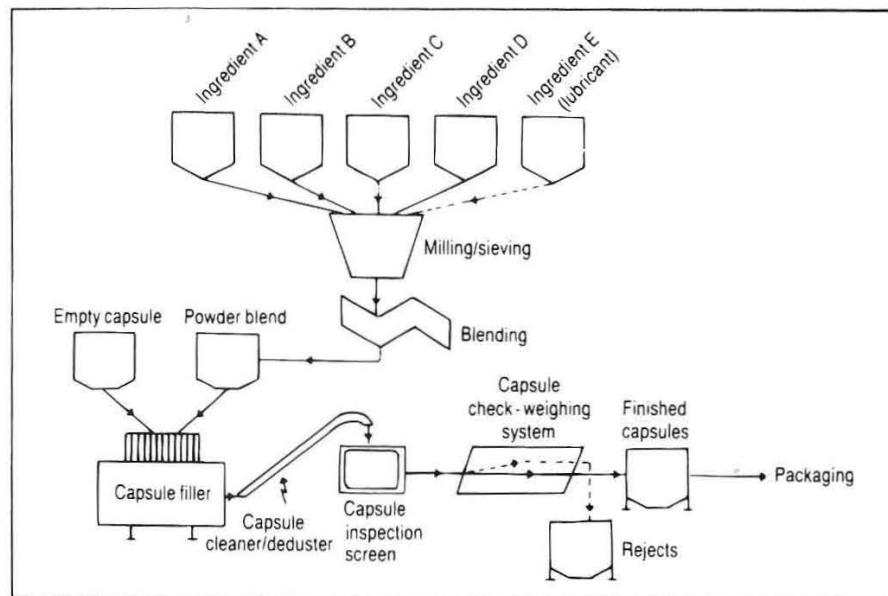


Fig. 7.12 Process flow diagram for automated capsule filling. (Reprinted with permission from Yelvoig M. Principles of process automation for liquid and solid dosage forms. Pharm Technol, 8:47, 1984.)

in shape. They may be prepared of a single or two-tone color and may be imprinted with identifying markings. As hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic feature to the capsule shell.

Soft gelatin capsules are used to hermetically seal and encapsulate liquids, suspensions, pasty materials, dry powders and even preformed tablets. Soft gelatin capsules are pharmaceutically elegant and are easily swallowed by the patient.

Preparation of Soft Gelatin Capsules (13)

They may be prepared by the plate process, using a set of molds to form the capsules, or by the more efficient and productive rotary or reciprocating die processes by which they are produced, filled, and sealed in a continuous operation (Fig. 7.15).

By the plate process, a warm sheet of plain or colored gelatin is placed on the bottom plate of the



Fig. 7.13 Z-Weld's gelatin seal fuses the two capsule halves together to create a one-piece capsule that is tamper-evident. (Courtesy of Raymond Automation Co.)



Fig. 7.14 Cleaning and polishing hard filled capsules using the Accela-Cota apparatus. (Courtesy of Eli Lilly and Company.)

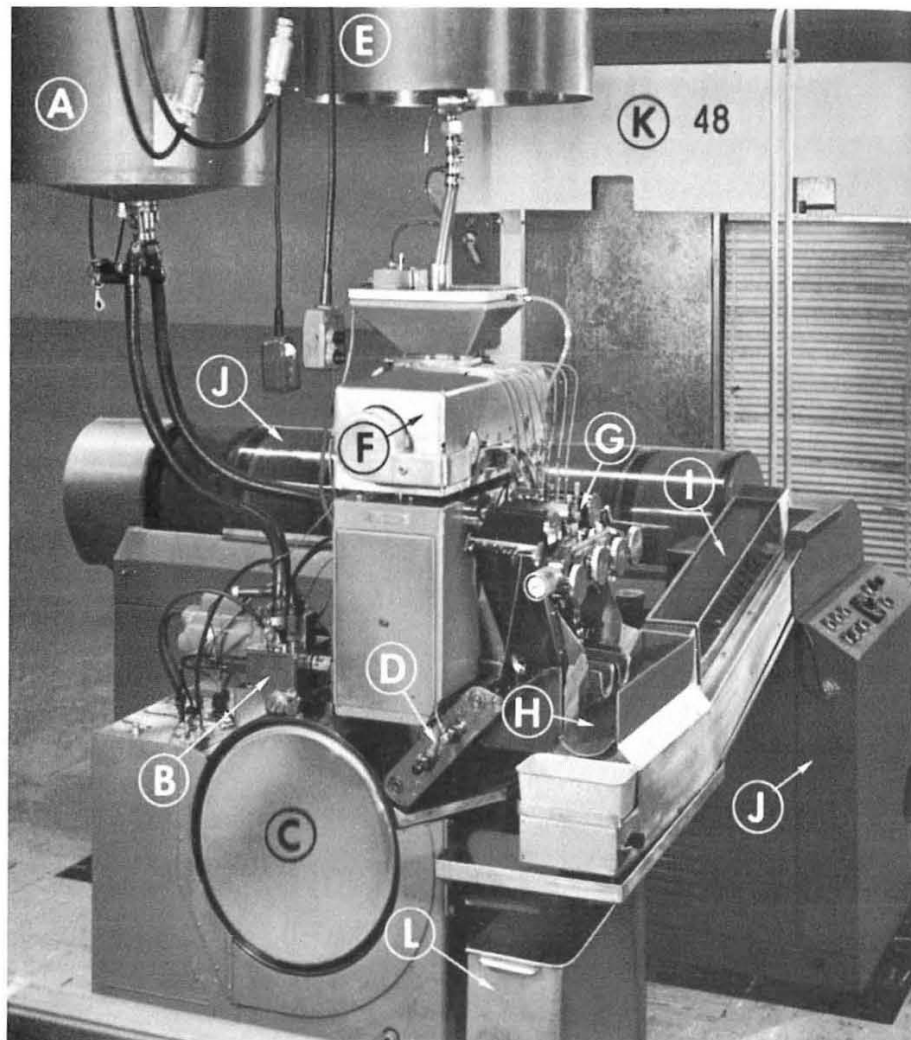


Fig. 7.15 Rotary die process equipment. A, Gelatin tank; B, spreader box; C, gelatin ribbon casting drum; D, mineral oil lubricant bath; E, medicine tank; F, filling pump; G, encapsulating mechanism; H, capsule conveyor; I, capsule washer; J, infrared dryer; K, capsule drying tunnel; L, gelatin net receiver. (Courtesy of R.P. Scherer Corporation.)

mold and the liquid-containing medication is evenly poured on it. Then a second sheet of gelatin is carefully placed on top of the medication and the top plate of the mold is put into place. Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously. The capsules are removed and washed with a solvent harmless to the capsules.

Most soft gelatin capsules are prepared by the rotary die process, a method developed in 1933 by

Robert P. Scherer. By this method, liquid gelatin flowing from an overhead tank is formed into two continuous ribbons by the rotary die machine and brought together between twin rotating dies (Fig. 7.16). At the same time, metered fill material is injected between the ribbons precisely at the moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are sealed by pressure and heat and then severed from

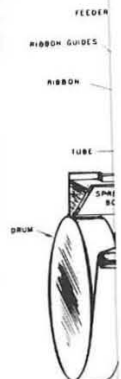


Fig. 7.16 Schematic of R.P. Scherer's rotary die process.

the ribbon. The results in big

The reciprocating process and used to actual encapsulation are fed between gelatin ribbons medication the film as the capsules refrigerated adhering to

Utilization

Soft gelatin variety of liquid may be encapsulated the following

1. Water-insoluble liquids such as organic acids, hydrocarbons, and

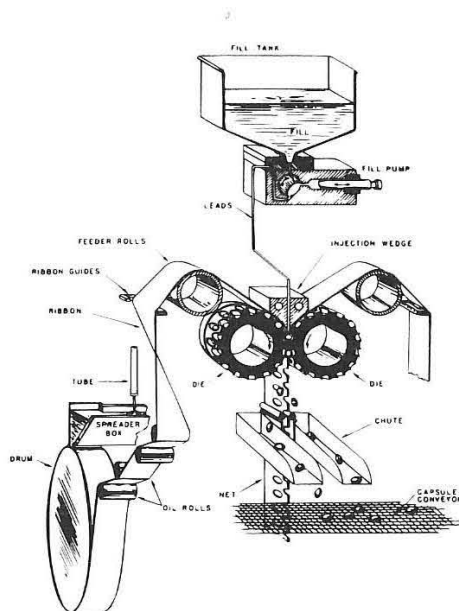


Fig. 7.16 Schematic drawing of rotary die process. (Courtesy of R.P. Scherer Corporation.)

the ribbon. Use of ribbons of two different colors results in bicolored capsules.

The reciprocating die process is similar to the rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into refrigerated tanks which prevent the capsules from adhering to one another.

Utilization of Soft Gelatin Capsules

Soft gelatin capsules are prepared to contain a variety of liquid, pasty, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following (13):

1. Water-immiscible volatile and nonvolatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols and organic acids.

2. Water-miscible, nonvolatile liquids, such as polyethylene glycols, and nonionic surface active agents as polysorbate 80.
3. Water-miscible and relatively nonvolatile compounds, as propylene glycol and isopropyl alcohol, depending on factors as concentration used and packaging conditions.

Liquids that can easily migrate through the capsule shell cannot be encapsulated into soft gelatin capsules. These materials include water above 5%, and low molecular weight water-soluble and volatile organic compounds such as alcohols, ketones, acids, amines, and esters.

Solids may be encapsulated into soft gelatin capsules as solutions in a suitable liquid solvent, suspensions, dry powders, granules, pellets, or small tablets.

Compendial Requirements for Capsules

Added Substances

Substances added to official preparations, including capsules, to enhance their stability, usefulness, elegance, or to facilitate their manufacture, may be used only if they (14):

1. are harmless in the quantities used;
2. do not exceed the minimum amounts required to provide their intended effect;
3. do not impair the product's bioavailability, therapeutic efficacy or safety, and
4. do not interfere with requisite compendial assays and tests.

Containers for Dispensing Capsules

There are specifications listed in the USP prescribing the type of container suitable for the repackaging or dispensing of each official capsule and tablet. Depending on the item, the container might be required to be *tight, well-closed and light resistant*.

Disintegration Test for Capsules

The compendial disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described later in this chapter for uncoated tablets. The capsules are placed in the basket-rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To fully satisfy the test, the capsules disinte-

mineral oil lubricant, infrared dryer;

liquid gelatin med into two machine and ting dies (Fig. material is in- ly at the mo- he gelatin rib- ng gelatin are severed from

Table 7.2. Examples of Some Official Capsules

Official Capsule	Some Representative Commercial Capsules	Capsule Strengths	Category
Amoxicillin	Wymox (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Ampicillin	Omnipen (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Cephalexin	Keflex (Dista)	250 and 500 mg	Antibacterial
Diphenhydramine HCl	Benadryl HCl (Parke-Davis)	25 and 50 mg	Antihistaminic
Doxycycline Hyclate	Vibramycin (Pfizer)	50 and 100 mg	Antibacterial
Erythromycin Estolate	Ilosone (Dista)	125 and 250 mg	Antibacterial
Fluoxetine HCl	Prozac (Dista)	10 and 20 mg	Antidepressant
Flurazepam HCl	Dalmane (Roche)	15 and 30 mg	Hypnotic
Gemfibrozil	Lopid (Parke-Davis)	300 mg	Antihyperlipidemic
Griseofulvin	Grisactin (Wyeth-Ayerst)	125 and 250 mg	Antifungal
Indomethacin	Indocin (Merck)	25 and 50 mg	Antiinflammatory; antipyretic; analgesic
Levodopa	Larodopa (Roche)	100, 250, and 500 mg	Antiparkinsonian
Loperamide HCl	Imodium (Janssen)	2 mg	Antidiarrheal
Oxazepam	Serax (Wyeth-Ayerst)	10, 15 and 30 mg	Antianxiety
Propoxyphene HCl	Darvon (Lilly)	32 and 65 mg	Analgesic
Tetracycline HCl	Achromycin V (Lederle)	250 and 500 mg	Antimicrobial

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signed trays are used, as the type depicted in Figure 7.17. In using this tray, the pharmacist pours a supply of capsules or tablets from the bulk source onto the clean tray, and using the spatula counts and sweeps the dosage units into the trough until the desired number is reached. Then the pharmacist closes the trough cover, picks up the tray, returns the uncounted dosage units to the bulk container by means of the lip at the back of the tray, places the prescription container at the opening of the trough, and carefully transfers the capsules or tablets into the container. By this method, the dosage units remain untouched by the pharmacist. To prevent batch-to-batch contamination, the tray must be wiped clean after each use because powder, particularly from counting uncoated tablets, may remain.

In some community and hospital pharmacy settings, small automated counting and filling machines may be used as shown in Figure 7.18.

On the industrial scale, solid dosage forms are counted by large automated pieces of equipment that count and transfer the desired number of dosage units into bulk containers. The containers are then mechanically capped, inspected visually or electronically, labeled, and inspected once more. Some filled containers are then placed into outer packaging cartons. An industrial counting and filling machine is shown in Figure 7.19. Capsules are packaged in glass or in plastic containers, some containing packets of a desiccant to prevent the absorption of excessive moisture.

The unit dose and strip packaging of solid dosage

Table 7.3. Examples of Medications Commercially Prepared into Soft Gelatin Capsules

Drug Substance	Trade Name and Manufacture	Contents and Comments*
Acetazolamide	Diamox Sequels (Lederle)	Acetazolamide is a powder which is very slightly soluble in water. The capsules contain coated pellets of the drug with sustained release features. Acetazolamide is a carbonic anhydrase inhibitor.
Cyclosporine	Sandimmune (Novartis)	Cyclosporine is a slightly water soluble crystalline powder. The capsule also contains corn oil and polyoxyethylated glycolized glycerides. Cyclosporine is an immunosuppressive agent.
	Neoral (Novartis)	The capsule contains cyclosporine, dehydrated alcohol, corn oil-mono-ditriglycerides, polyoxyl 40 hydrogenated castor oil. The formulation forms a microemulsion in contact with aqueous fluids for enhanced bioavailability.
Digoxin	Lanoxicaps (Glaxo Wellcome)	Digoxin is a practically water-insoluble powder. The drug is dissolved in a solvent of polyethylene glycol 400, ethyl alcohol, propylene glycol and water. Digoxin is a cardiac glycoside.
Ethchlorvynol	Placidyl (Abbott)	Ethchlorvynol is a liquid immiscible in water. It is a hypnotic. The capsules also contain polyethylene glycol and sorbitol.
Ethosuximide	Zarontin (Parke-Davis)	Ethosuximide is a water soluble powder. The capsule also contains polyethylene glycol 400. Ethosuximide is an anticonvulsant.
Ranitidine HCl	Zantac GELdose (Glaxo Wellcome)	Ranitidine HCl is a water soluble granular powder. The drug is in a nonaqueous matrix of synthetic coconut oil and triglycerides. Ranitidine is a histamine H_2 -receptor inhibitor.

*Only a partial listing of the capsule contents is given. The soft capsule shells may also contain colorants, opaquants, preservatives, and other agents.

forms, particularly by pharmacies that service nursing homes and hospitals, provides sanitary handling of the medications, ease of identification, and security in accountability for medications. Typical small scale strip packaging equipment and commercial unit-dose packages of capsules and tablets are presented in Figures 7.20 and 7.21, respectively. Capsules should be stored in tightly capped containers in a cool, dry place.

Tablets

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics, and in other aspects, depending upon their intended use and method of manufacture. The ma-

jority of tablets are used in the oral administration of drugs. Many of these are prepared with colorants and coatings of various types. Other tablets, as those administered sublingually, buccally or vaginally are prepared to have features most applicable to their particular route of administration. Advantages of tablets for oral administration were presented at the outset of this chapter.

Tablets are prepared primarily by compression with a limited number prepared by molding. Compressed tablets are manufactured with tablet machines capable of exerting great pressure in compacting the powdered or granulated tableting material (Fig. 7.22). Their shape and dimensions are determined by use of various shaped punches and dies (Fig. 7.23). Molded tablets are prepared on a large-scale by tablet machinery or on a small-scale by manually forcing dampened powder material

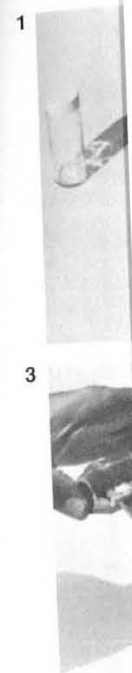


Fig. 7.17 Step 1: Capsule placed onto tray, 2) Capsule filled with powder, 3) Capsule placed into mold.

into a mold for ejection and a

The various types of tablets, with their different shapes and sizes, are used for different purposes.

Compressed Tablets

In addition to the various types of tablets, there are also compressed tablets. These are prepared by compression and are used for the same purposes as the other types of tablets. They are usually prepared in large quantities and are used for the same purposes as the other types of tablets.