Chapter 7 Capsules
ANSEL'S Pharmaceutical Dosage Forms and Drug Delivery Systems
Eleventh Edition

Objectives:
After reading this topic, the student will be able to:

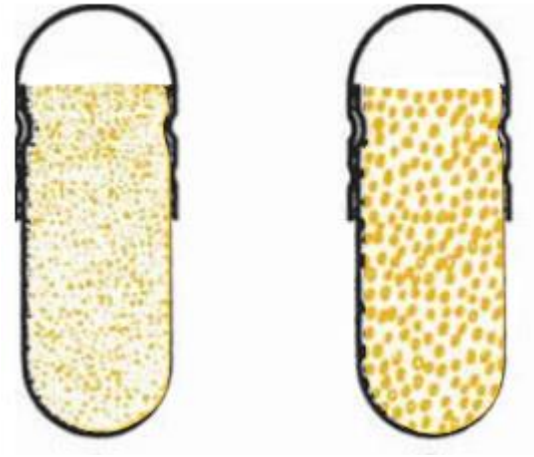
- Differentiate between hard and soft gelatin capsule.
- Understand the advantages and disadvantages of each type of capsule
- Identify the excipients used for both type of capsules
- Recognize the compendial requirement of capsules
- Understand the appropriate method for compounding and packaging and storage of capsules

Capsules

Capsules are solid dosage form in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin.

Gelatin capsule shells may be hard or soft, depending on their composition.

A capsule (from Latin capsula, "small box or chest"), or stadium of revolution, is a basic three-dimensional geometric shape consisting of a cylinder with hemispherical ends. Another name for this shape is sphero-cylinder.



Advantages of Capsule dosage form

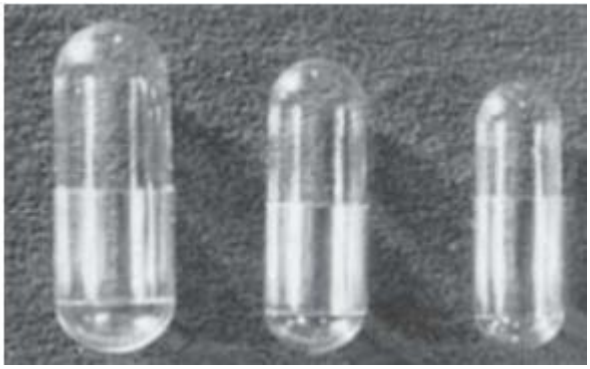
1. Elegant and conveniently carried, readily identified.
2. Easily swallowed, there is no need for spoons or other measuring devices,
3. Are tasteless and odourless when swallowed (mask the bitter taste and bad odour of medicinal agents)
4. Available for many medications in a variety of dosage strengths, providing flexibility to the prescriber and accurate individualized dosage for the patient.
5. They are packaged and shipped by manufacturers at lower cost and with less breakage than liquid dosage forms.
6. They are also more stable and have a longer shelf life than their liquid counterparts.

Hard Gelatin Capsule

Hard gelatin capsule shells are used in most commercial medicated capsules. They are also commonly employed in clinical drug trials to compare the effects of an investigational drug with those of another drug product or placebo. The community pharmacist also uses hard gelatin capsules in the extemporaneous compounding of prescriptions.

Composition of Hard gelatin capsule

- The empty capsule shells are made of gelatin, sugar, and water. As such, they can be clear, colorless, and essentially tasteless.
- They may be colored with various FD&C and D&C dyes and 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

- Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals.
- It is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.
- Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist. Normally, hard gelatin capsules contain 13% to 16% of moisture.
- 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 excessive humidity or dryness.

Effect of moisture on gelatin

- Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents 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 often used are dried silica gel, clay, and activated charcoal.

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

Gelatin administration

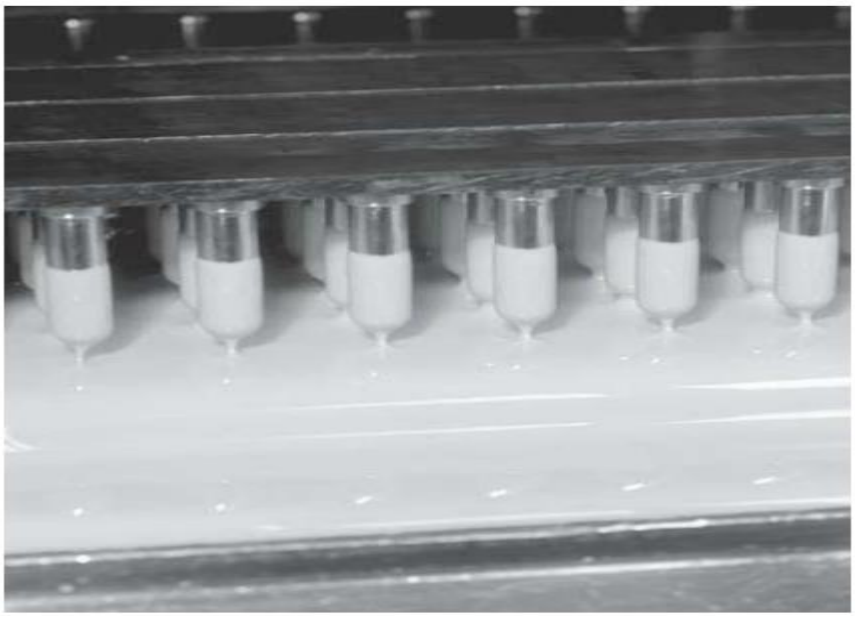
- Although gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water.
- Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule.
- Gelatin is soluble 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.

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.
- 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 is dried by a gentle flow of temperature- and humidity-controlled air.
- When dried, each capsule part is trimmed mechanically to the proper length and removed from the pegs, and the capsule bodies and caps are joined together.

Hard gelatin capsules manufacture consideration.

- 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.

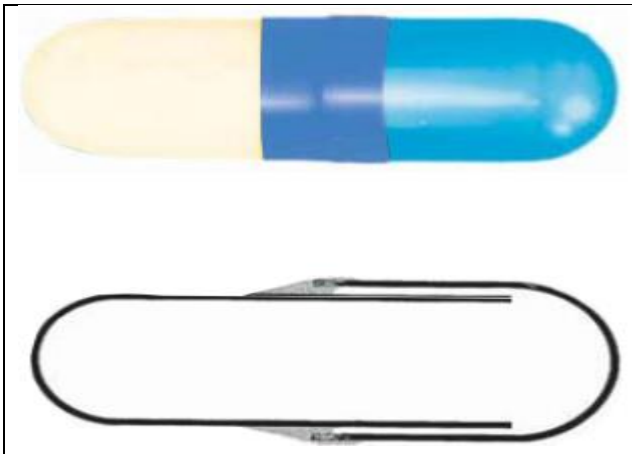
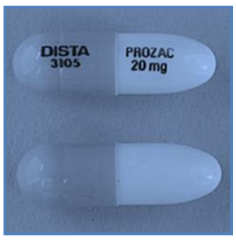
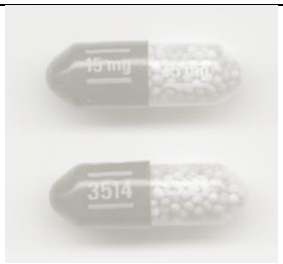


- In capsule shell production, there is a continuous dipping, drying, removing, and joining of capsules as the peg-containing plates rotate in and out of the gelatin bath.

Capsule shapes and designs

1. Conventional Hard Gelatin Capsule

Hard gelatin capsule is cylindrical with hemispherical ends. 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 uses capsules with the ends of both the bodies and caps highly tapered (Spansule Capsules, SmithKline Beecham).

		
Conventional Hard Gelatin Capsule	Tapered capsule body	Tapered both the cap and body

During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule filling machines (more than 180,000 capsules per hour), splitting (telescoping) and/or denting of the capsule shell occur with the slightest contact between the two rims when they are joined.

To ensure reliable closing of the filled capsules, capsule shells with locking grooves (or indentations) have been prepared such as snap fit and coni snap fit capsules.

2. **Snap-fit.** Snap-Fit® has the concentric locking rings of the body and cap which prevent reopening after filling.
   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.

3. **Coni -snap and Coni – snap Supro hard gelation**
   The **Coni-Snap® capsule**, which is the improved form of Snap-Fit®, has the rim of the capsule body which is slightly tapered. These capsules have a rounded hemispherical end which are stronger and more resistant to deformation, this reduces the risk of the capsule rims touching on joining and essentially 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. This type of capsule 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.
   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.

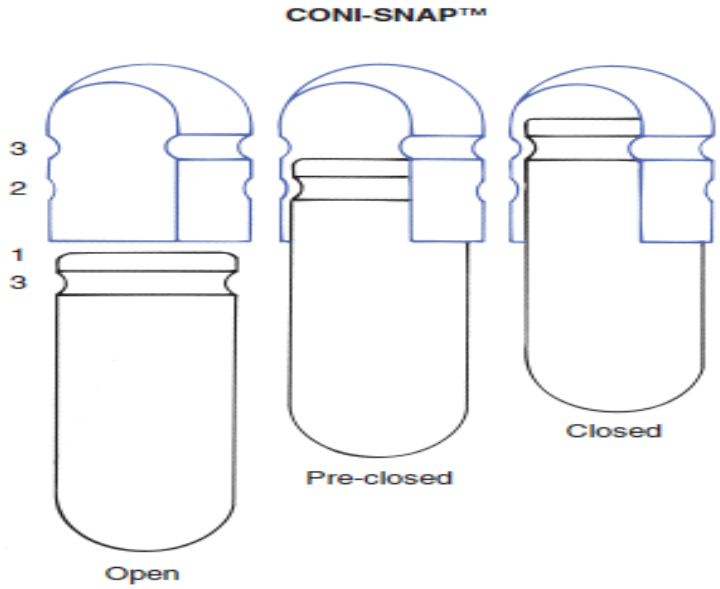
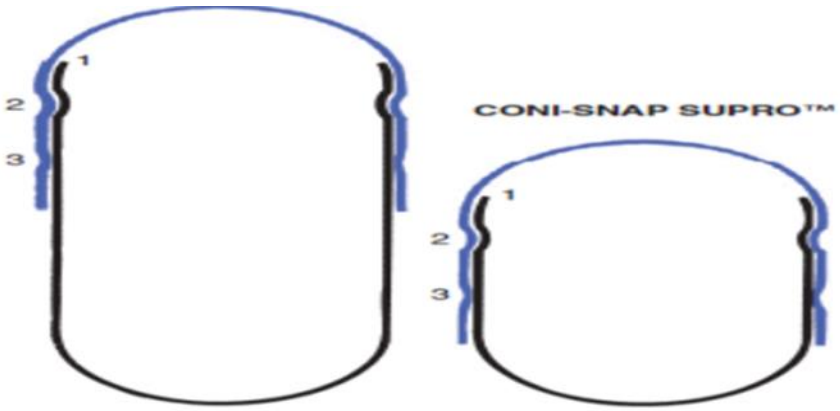


FIGURE 7.4 Line drawings of the CONI-SNAP capsule in open, preclosed, and closed positions. The tapered rims (*1*) avoid telescoping; the indentations (*2*) prevent premature opening; and the grooves (*3*) lock the two capsule parts together after the capsule is filled. (Courtesy of Capsugel Division,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



1. Tapered rim to avoid telescoping (CONI-SNAP™)
2. Grooves which lock the two halves together once the capsule has been filled (SNAP-FIT™ principle)
3. Indentations to prevent premature opening

FIGURE 7.5 Line drawings of the CONI-SNAP and CONI-SNAP SUPRO (*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.)

Capsule sizes

- Empty gelatin capsules are manufactured in various lengths, diameters, and capacities.
- 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

- For estimation, a comparison may be made with powders of well known features and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material.
- However, the final determination may be largely the result of trial and error.
- For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available
- Larger capsules are available for veterinary use.
- For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide number of options for 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.

	Approximate capacity of empty gelatin capsules							
Drug substance (mg)[a]	**Capsule size**	**000**	**00**	**0**	**1**	**2**	**3**	**4**	**5**
	Volume (mL)	**1.40**	**0.95**	**0.68**	**0.5**	**0.37**	**0.3**	**0.21**	**0.13**
	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

[a] Amount may vary with the degree of pressure used in filling the capsules

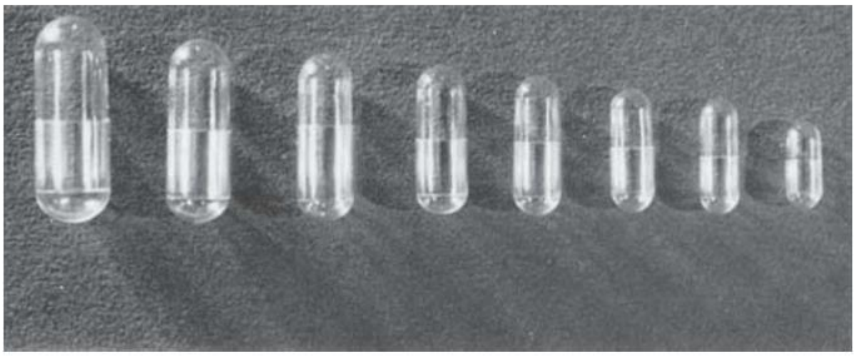


FIGURE 7.6. Actual sizes of hard gelatin capsules. From left to right, sizes 000, 00, 0, 1, 2, 3, 4, and 5.

Preparation of Filled Hard Gelatin Capsules and Selecting the capsule size

To determine the capsule size to be used

Capsule fill weight =tapped density of formulation X capsule volume

- Example
- Formulation of capsule has a fill weight of 450mg and tapped density of 0.8g/mL
- Volume occupied =0.45g/0.8g/ml=0.56mL
- So the size 0 capsule is appropriate (0.54mL)

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.

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

Developing the Capsule Formulation

In developing a capsule formulation, the goal is to prepare a capsule with;

1. Accurate dosage,
2. Good bioavailability,
3. Ease of filling and production,
4. Stability, and
5. Elegance.

- In dry formulations, the active and inactive components must be blended thoroughly to ensure a **uniform powder mix** for the fill.
- Care in blending is especially important for **low-dose drugs**, since lack of homogeneity in blending may result in significant therapeutic consequences.
- Preformulation studies are performed to determine whether all of the formulation's bulk powders may be effectively blended together as such or require **reduction of particle size** or any other processing to achieve homogeneity.

- To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar. This is particularly important when a drug of low dosage is blended with other drugs or nondrug fill.
- 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.

Excipients	Example	Function
Diluent or Filler	Lactose, Microcrystalline cellulose, Starch	Provide **bulk** to powder lend to produce the proper capsule fill volume often provide **cohesion** to the powders
Disintegrants	Pregelatinized starch, Croscarmellose, Sodium starch glycolate.	Assist the breakup and distribution of the capsule's contents in the stomach.
Lubricant or Glidant	Fumed silicon dioxide, Magnesium stearate, Calcium stearate, Stearic acid, or Talc (about 0.25% to 1%)	Enhances flow properties
Wetting agent	Sodium lauryl sulphate	Improve dissolution

- When magnesium stearate is used as the lubricant, the waterproofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption. A surface-active agent, such as sodium lauryl sulphate, is used to facilitate wetting by the gastrointestinal fluids to overcome the problem.

Encapsulation of different ingredients

1. Inserting tablets or small capsules into capsules is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules This may be done to separate chemically incompatible agents or to add premeasured amounts of potent drug substances. Rather than weighing a potent drug, a pharmacist may choose to insert a prefabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then be weighed and added.

2. On an industrial scale, coated pellets designed for modified-release drug delivery are also commonly placed in capsule shells.

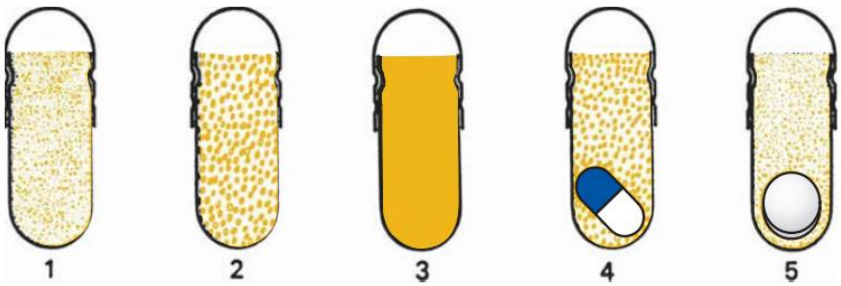


FIGURE 7.7. Examples of fill in hard gelatin capsules. *1*, powder or granulate; *2*, pellet mixture; *3*, paste; *4*, capsule; and *5*, tablet. (Courtesy of Capsugel Division, Warner-Lambert.)

Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet.

Liquid fill

- Gelatin capsules are unsuitable for aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents.
- However, some liquids, such as fixed or volatile oils, that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid.
- Rather than placing a liquid as such in a capsule, the liquid may be mixed with an inert powder to make a wet mass or paste, which may then be placed in capsules in the usual manner.
- Eutectic mixtures of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material that may form.

Extemporaneous compounding of prescriptions

1. Calculate for the preparation of one or two more capsules than required to fill the prescription, to compensate a slight loss of powder
2. Selection of the capsule size, If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added. A properly filled 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.

Filling Hard Capsule Shells

When filling a small number of capsules in the pharmacy, the pharmacist may use the **punch method**.

The pharmacist takes the precise number of empty capsules to be filled from the stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled,

1. the pharmacist guards against filling the wrong number of capsules and
2. avoids contaminating the stock container with drug powder.

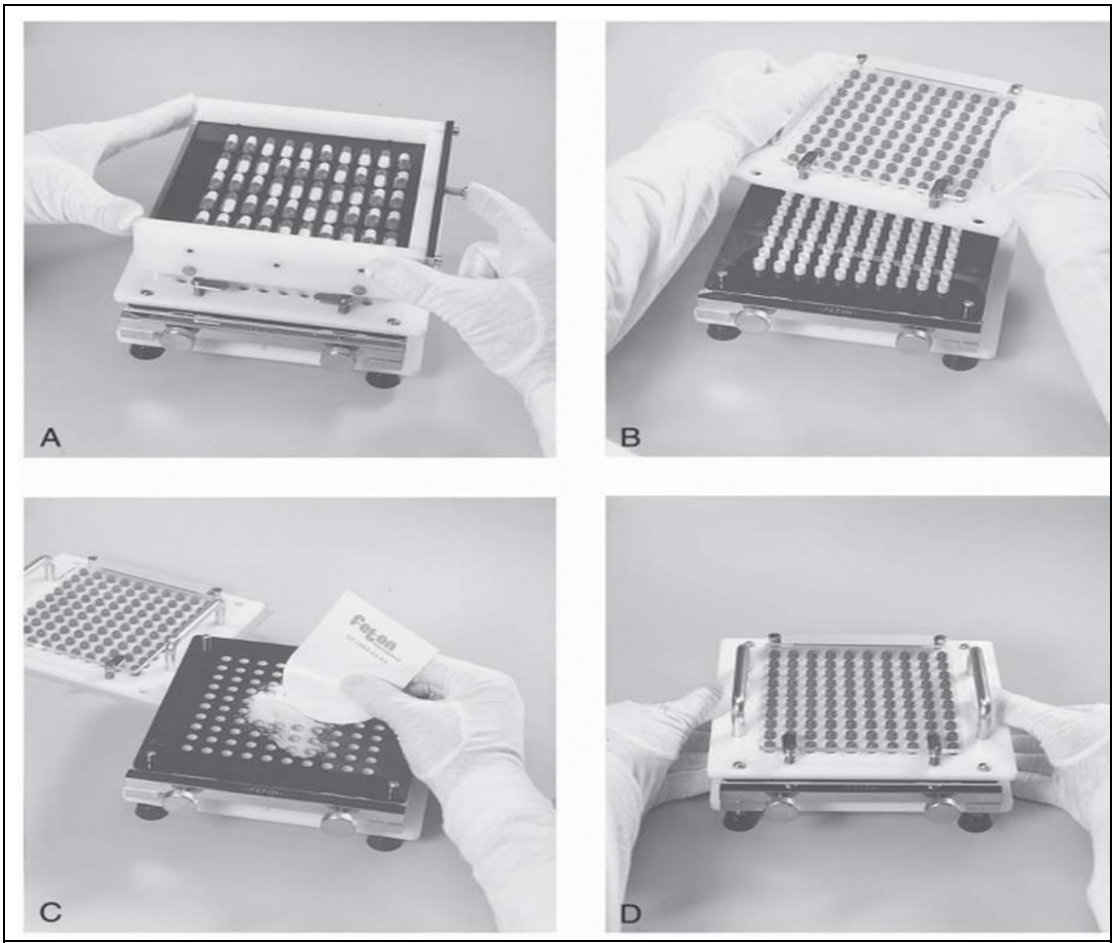
The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

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 on the degree of compression, the pharmacist should punch each capsule in the same manner and weigh the product after capping.

When **non-potent** 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 weighing protects against uneven filling of capsules and premature exhaustion or underuse of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.

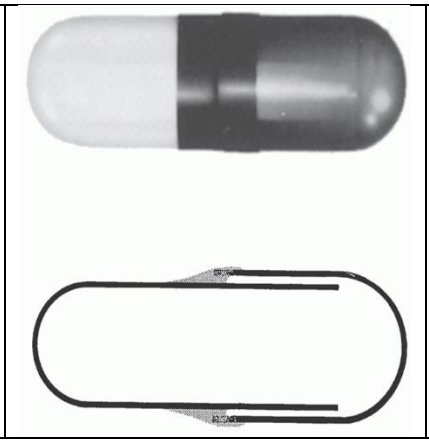
Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper on which it is weighed.



The Feton capsule-filling machine.
With empty capsules in the loader tray, the tray placed on top of the filler unit.
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.
The powder is placed on the unit and the capsule bodies are filled.
The top plate is returned to the unit and the caps are placed on filled capsule bodies.

Capsule sealing

- Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer 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. The process results in a distinctive ring around the capsule where heat welded. Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C-45°C) . Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour



Capsule identification

Capsules and tablets also may be imprinted with the names or monograms of the manufacturer, the assigned national drug code number, and other markings making the product identifiable and distinguishable from other products.

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 removed 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.

Soft gelatin capsules

- Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added.
- Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative, such as methylparaben and/or propylparaben, to retard microbial growth.
- Soft gelatin capsules may be oblong, oval, or round.
- They may be single colored or two-toned and may be imprinted with identifying markings. As with hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic features to the capsule shell.

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

FIGURE 7.13. Examples of soft gelatin capsules. (Courtesy of Carlos Restrepo/Shutterstock.)

Uses of soft gelatin capsules

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

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, such as polysorbate 80.
3. Water-miscible and relatively nonvolatile compounds such as propylene glycol and isopropyl alcohol, depending on factors such as concentration used and packaging conditions.

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

Soft gelatin capsule contents contraindication

- Liquids that can easily migrate through the capsule shell are not suitable for 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.

Compendial Requirements for Capsules Added Substances

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

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
4. Do not interfere with requisite compendial assays and tests

Enteric coated capsules

Capsules that have been coated or otherwise treated to resist dissolution in gastric fluids but release their contents in the intestine are said to be enteric.

Enteric coating is a useful strategy for oral delivery for:

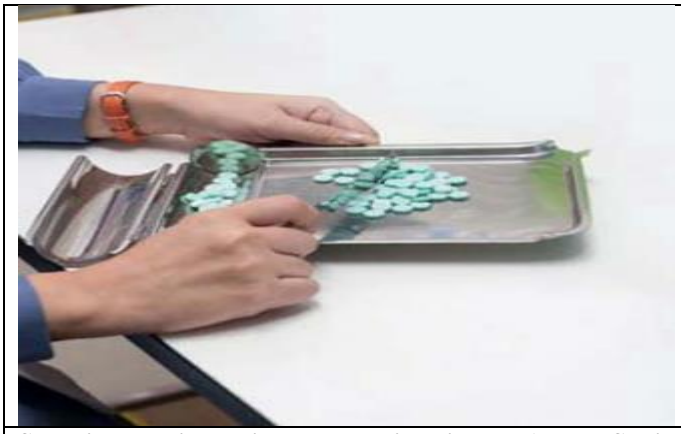
- Maintaining the stability of medications that are unstable in acidic conditions of the stomach such as erythromycin, pancreatin, and proton pump inhibitors such as omeprazole
- Such delayed release of medication may be desired if the drug is inactivated in gastric fluids or if the drug is irritating to the gastric mucosa. Minimizing the side effects (e.g. nausea and gastric irritation and bleeding) that can occur with drugs non-steroidal inflammatory drugs , garlic and fish oil (omega 3) which cause nausea
- Delayed action: the drug is given at night and permit effective blood levels of the medication prior to waking.
- Facilitate colonic drug delivery, a high local concentration of the drug may be especially desirable in the intestine, as in the case of anthelmintics.

Typical of materials used for enteric coating are shellac, cellulose acetate phthalate, and fatty waxy materials such as bees wax, carnauba wax and stearic acid. But these materials have a high potential to be hydrolysed when exposed to elevated temperature and humidity, thus replaced with poly vinyl acetate phthalate, hydroxy propyl methyl cellulose phthalate

The recent method of enteric coating involves polymers with poly-acidic groups that are unionized in the acidic media, and dissolve in water above the pKa of the acidic groups around pH 6 such as Eudragit L (poly methacrylic acid : methyl methacrylate 1:1) applied in non-aqueous solvent

Counting capsules

- In the pharmacy, capsules may be counted manually or by automated equipment. Specially designed trays are used for counting small numbers of solid dosage units.
- 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.
- With 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 uncoated tablets, may remain



Steps in counting solid dosage units with the Abbott Sanitary Counting Tray.
1. Transferring units from stock package to tray.
2. Counting and transferring units to trough.
3. Returning excess units to stock container.
4. Placing the counted units in prescription container.

Examples of some capsules

Official capsule	Type of capsules	Strength (mg)	Category
Amoxicillin	Hard gelatin cap	250, 500	Antibiotic
Erythromycin Estolate	Enteric coated hard gelatin capsule	250 mg	Antibiotic
Fluoxetine HCI Prozac® Pfizer	Tapered capsule body hard gelatin capsule	10, 20, 40	Antidepressant
Indomethacin	Enteric coated hard gelatin capsule	25, 50	Anti-inflammatory, analgesic
Pancreatin Creon® Abbot	Enteric coated micropellets capsules	150, 300	Digestive enzymes
Omeprazole	Enteric coated hard	20, 40	Proton pump inhibitor
Omega 3	Soft gelatin capsule	1000	Nutrient
Vitamin D3	Soft gelatin capsule	1000, 2000, 5000, 10000 IU	Nutrient