**Capsules**

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

Gelatin capsule shells may be hard or soft, better adjectives would be ‘two-piece’ in place of ‘hard’ and ‘one-piece’ in place of ‘soft’ depending on their composition. These differ in both their mechanical properties and in capsule design.

Hard gelatin capsules are less flexible and are composed of two pieces, termed the capsule and the body, whereas soft gelatin capsules are more flexible and are composed of a one piece capsule shell. A wide range of formulation types may be included within the interior of the capsule. For example, powders, tablets, semisolids and non-aqueous liquids/gels may be filled into *hard* capsules, with powders being the most common formulation option. Soft gelatin capsules are usually filled with non-aqueous liquids containing the therapeutic agent either dispersed or dissolved within this carrier.

Most ﬁlled capsules are intended to be swallowed whole. However, it is fairly common 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.

**Advantages**

■ The use of capsules avoids many unit operations that are associated with the manufacture of tablets, e.g. compression, granulation, drying.

■ Capsules (generally soft gelatin capsules) may be formulated to increase the oral bioavailability of poorly soluble therapeutic agents. This is particularly the case when formulated as a liquid-filled hard gelatin or soft gelatin capsule.

■ Capsules are a convenient method by which liquids may be orally administered to patients as a unit dosage form.

■ The stability of therapeutic agents may be improved in a capsule formulation.

■ Capsules are a convenient means of formulating substances of abuse, e.g. temazepam

**Disadvantages**

■ the requirement for specialised manufacturing equipment

■ potential stability problems associated with capsules containing liquid fills

■ problems regarding the homogeneity of fill weight and content may be associated with capsule formulations.

**Materials and manufacture of capsules**

Capsules are primarily (but not exclusively) manufactured using gelatin; however, the suitability of other materials, e.g. hydroxyl propyl methyl cellulose (HPMC or Hypromellose) and starch, has been investigated as suitable replacements. Traditionally both contain gelatin, water, and colorants; in addition, soft capsules contain various plasticizers, such as glycerin and sorbitol.

Gelatin is a mixture of proteins that is extracted from animal collagen (derived from animal skins, and/or bovine bones) by either partial acid or partial alkaline hydrolysis. From these processes two types of gelatin are obtained, termed type A and type B. Type A is obtained by an acid treatment of pig skin at pH 1–3 for approximately 1 day) whereas type B is obtained using an alkaline treatment of demineralised bones for 1–3 months), following which gelatin is extracted using a series of hot-water washes. The gelatin solutions are then cooled to form a gel; subsequent evaporation of water results in the production of dried gelatin. The isoelectric points of type A and type B gelatin differ (between 7 and 9 and between 4.7 and 5.3, respectively), resulting in differing solubilities as a function of pH. Typically the molecular weight range for gelatin is 15 000–250 000.

The grade of gelatin is defined by the *bloom strength*, which is defined as the weight (in grams) required to depress a plunger (of defined diameter, 12.7 mm) to a defined depth (4 mm) within an aged gelatin gel (6.66% w/w in water). The gelatin used in hard capsule manufacture is of a higher Bloom strength (200–250g) than that used for soft capsules (150g) because a more rigid film is required for the manufacturing process. the viscosity of gelatin solution is also important as this regulates the thickness of the capsule (generally circa 100 lm). As the viscosity is lowered the capsule thickness will decrease.

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.

The use of gelatin as a capsule material is due to the excellent physicochemical and biological properties of it, including:

■ Non-toxic material that is used widely as a component of foods. More recently, the production of gelatin using bovine sources has received considerable attention due to the possible transmission of bovine spongiform encephalopathy (BSE). Therefore, if gelatin has been manufactured from bovine sources, it is important that this has been produced from countries in which the incidence of BSE is low.

■ Soluble in biological fluids at room temperature (note: gelatin capsules do not dissolve but swell when immersed in an aqueous solution 30C).

■ Excellent mechanical properties, most notably exhibiting good film, and hence capsule-forming properties.

■ Excellent rheological properties at elevated temperatures. At 50C, gelatin acts as a mobile liquid (termed a sol), thereby enabling the production of capsules by dip processing.

■ Undergoes a sol–gel transition at relatively low temperatures. Therefore, gelatin is readily converted to the rigid (gel) state by allowing warmed solutions of this material to cool.

**Hard Gelatin Capsules**

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. The empty capsule shells are made of gelatin, sugar, and water.

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.

**Manufacture of Hard Gelatin Capsules**

Metal molds at room temperature are dipped into a hot gelatin solution which gels to form a film. This is dried, cut to length, removed from the molds and the two parts are joined together. The required amounts of dye solutions and pigment suspensions added. The viscosity is measured and adjusted to a target value by the addition of hot water. This latter parameter is used to control the thickness of capsule shells during production: the higher the viscosity, the thicker the shell wall produced.

There are a limited number of specialist companies that manufacture empty capsule shells for supply to the pharmaceutical and health food industries, who fill them with their own products.

Hypromellose solutions can be converted into a gelling system by the addition of a gelling agent, such as carrageenan, and a co-gelling agent, such as potassium chloride, and used to manufacture capsules on standard unmodified machines.

Empty gelatin capsules contain a significant amount of water that acts as a plasticizer for the film and is essential for their function. During industrial filling and packaging operations, they are subjected to mechanical handling and because the gelatin walls can flex, these forces can be absorbed without any adverse effect. The standard moisture content specification for hard gelatin capsules is between 13% and 16% w/w. The standard moisture content for hypromellose capsules is 3% to 6% and when they lose moisture they do not become brittle. Gelatin capsules are readily soluble in water at 37 °C. Their rate of dissolution decreases when the temperature falls below this. Below about 26 °C they are insoluble and simply absorb water, swell and distort. This is an important factor to take into account during disintegration and dissolution testing. Capsules made from hypromellose have a different solubility profile, being soluble at temperatures as low as 10 °C.

The shape of the capsule has remained virtually unchanged since its invention more than 160 years ago, except for the development of the self-locking capsule during the 1960s, when automatic filling and packaging machines were introduced. Filled capsules were subjected to vibration during this process, causing some to come apart and spill their contents. To overcome this, modern capsule shells have a series of indentations on the inside of the cap and on the external surface of the body which, when the capsule is closed after filling, form an interference fit sufficiently strong to hold them together during mechanical handling.

**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 size of capsule to be used determines the free space inside the capsule that is available to the formulator. The easier active compounds to formulate are low-dose potent ones, which in the final formulation occupy only a small percentage of the total volume (< 20%) and so the properties of the mixture will be governed by the excipients chosen. Those compounds with a high unit dose, e.g. 500 mg of an antibiotic, leave little free space within the capsule and the excipients chosen must exert their effect at low concentrations (< 5%) and the properties of the mixture will be governed by that of the active ingredient.

**Capsule Shell Filling**

 Hard capsules can be filled with a large variety of materials of different physicochemical properties. Gelatin and hypromellose are relatively inert materials. The substances to be avoided are those which are known to react with gelatin, e.g. formaldehyde, which causes a crosslinking reaction that makes the capsule insoluble, or those that interfere with the integrity of the shells, e.g. substances containing free water, which can be absorbed by the gelatin or hypromellose, causing them to soften and distort. There is also a limitation on the size of capsule that can be easily swallowed, and thus large doses of low-density formulations cannot be used.

**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

**1- DEVELOPING THE FORMULATION AND SELECTING THE 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 ﬁll. Care in blending is especially important for low-dose drugs, since lack of homogeneity in blending may result in signiﬁcant therapeutic consequences.

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 (i.e. improve flow properties), which is beneﬁcial in the transfer of the powder blend into capsule shells.

Disintegrants are frequently included in a capsule formulation to assist the breakup and distribution of the capsule’s 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 excipients are similar and this is particularly important when a drug of low dosage is formulated.

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 to the powder mix enhances ﬂow properties.

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 sulfate, is used to facilitate wetting by the gastrointestinal ﬂuids to overcome the problem. Powders of poorly soluble drugs have a tendency to resist water penetration. Disintegration agents in a capsule formulation facilitate the breakup and distribution of the capsule’s contents.

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

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.



**2- FILLING HARD CAPSULE SHELLS**: - When ﬁlling a small number of capsules in the pharmacy, the pharmacist use the punch method (explained in detail in the practical pharmaceutics lab). Pharmacists who prepare capsules on a regular or extensive basis may use a hand- operated ﬁlling machine. The various types of machines have capacities ranging from 24 to 300 capsules and, when efﬁciently operated, are capable of producing about 200 to 2,000 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 up to 165,000 capsules per hour.

**3- CAPSULE SEALING: -**

Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One method is to make distinctive-looking capsules by sealing them with a colored band of gelatin. 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.

Although it is difﬁcult and tedious, extemporaneously prepared 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.

**4- 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. 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.

**Soft Gelatin Capsules**

Soft gelatin capsules' shell consists of gelatin, water and a plasticizer. The shell may be transparent or opaque and can be colored and flavored if desired. 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.

The softgel can be coated with enteric-resistant or delayed-release coating materials.

Softgels can be formulated and manufactured to produce a number of different drug delivery systems:

• **Orally administered softgels** containing solutions or suspensions that release their contents in the stomach in an easy-to-swallow, convenient unit dose form

• **Chewable softgels**, where a highly flavored shell is chewed to release the drug liquid fill matrix. The drug(s) may be present in both the shell and fill matrix

• **Suckable softgels**, which consist of a gelatin shell containing the flavored medicament to be sucked and a liquid matrix or just air inside the capsule

• **Twist-off softgels**, which are designed with a tag to be twisted or snipped off, thereby allowing access to the fill material. This type of softgel can be used for unit dosing of topical medication, inhalations or for oral dosing of a paediatric product.

• **Meltable softgels** designed for use as pessaries or suppositories.

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**Advantages of Softgels**

1. Improved drug absorption: Improved rate and extent of absorption mainly for poorly water-soluble drugs.
2. Patient compliance and consumer preference: Easy to swallow. Absence of poor taste or other sensory problem. Convenient administration of a liquid-drug dosage form.
3. Safety – potent and cytotoxic drugs: Avoids dust-handling problems during dosage form manufacture; better operator safety and environmental controls
4. Oils and low melting point drugs: Overcomes problems with manufacture as compressed tablet or hard-shell capsules.
5. Dose uniformity for low-dose drugs: Liquid flow during dosage form manufacture is more precise than powder flow. Drug solutions provide better homogeneity than powder or granule mixtures.
6. Product stability: Drugs are protected against oxidative degradation by lipid vehicles and softgel capsule shells.

**PREPARATION OF SOFT GELATIN CAPSULES**

Most soft gelatin capsules are prepared by the rotary die process, a method developed in 1933. 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. 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 the ribbon. Use of ribbons of two different colors results in bicolored capsules.

**Gelatin shell formulation**

**Gelatin:** different gelatin shell formulations are available depending on the nature of the liquid fill matrix. Most commonly, the gelatin is alkali- (or base-) processed (type B) gelatin and it normally constitutes 40% of the wet molten gel mass.

**Plasticizers:** are used to make the softgel shell elastic and pliable. They usually account for 20–30% of the wet gel formulation. The most common plasticizer used in softgels is glycerol, although sorbitol and propylene glycol are also frequently used, often in combination with glycerol.

One of the most important aspects of softgel formulation is to ensure that there is minimum interaction or migration between the liquid fill matrix and the softgel shell. The choice of plasticizer type and concentration is important in ensuring optimum compatibility of the shell with the liquid fill matrix.

**Water:** The other essential component of the softgel shell is water. Water usually accounts for 30–40% of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and softgel encapsulation. Following encapsulation, excess water is removed from the softgels through controlled drying. In dry softgels, the equilibrium water content is typically in the range of 5–8% w/w which represents the proportion of water that is bound to the gelatin in the softgel shell.

**Colorants/opacifiers:** Colorants (soluble dyes or insoluble pigments or lakes) and opacifiers are typically used at low concentrations in the wet gel formulation. Colorants used to impart desired shell color for product identification. An opacifier, usually titanium dioxide, may be added to produce an opaque shell when the fill formulation is a suspension or to prevent photo-degradation of light-sensitive fill ingredients.

**Softgel Quality Control (Finished Product Testing)**

Finished softgels are subjected to a number of tests in accordance with standardized requirements for unit dose capsule products. These normally include capsule appearance, active ingredient assay, fill weight, content uniformity, microbiological and dissolution testing.

The disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus as described for uncoated tablets.

The dissolution test for capsules uses the same apparatus, dissolution medium, and test as that for uncoated and plain-coated tablets

The uniformity of dosage units may be demonstrated by determining weight variation and/or content uniformity. Unless otherwise stated, the amount of active ingredient, determined by assay, is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed, with no unit outside the range of 70% to 125% of the label claim.

**ORAL ADMINISTRATION OF SOLID DOSAGE FORMS**

Solid dosage forms (capsules and tablets) for oral administration are best taken by placing the dose upon the tongue and swallowing it with a glassful of water or beverage, e.g., milk, coffee, juice, tea. Ingesting solid dosage forms with adequate amounts of ﬂuid is important. Some patients attempt to swallow a tablet or capsule without water, but this can be dangerous because of the possibility that it will lodge in the esophagus. Esophageal ulceration can occur with dry ingestion of tablets and capsules, particularly taken just before bedtime. Among the drugs of greatest concern in this regard are alendronate sodium, aspirin, ferrous sulfate, any non-steroidal anti-inﬂammatory drug, potassium chloride, and tetracycline antibiotics.

The proper administration of alendronate sodium tablets (Fosamax®), for example, calls for the tablets to be taken with a full 6- or 8-ounce glass of plain water upon rising in the morning and at least half an hour before taking any food, beverage, or other medication to prevent local irritation of the esophagus and other upper gastrointestinal mucosa. The patient is also instructed not to recline for at least 30 minutes and until after the ﬁrst food of the day is eaten because of the possibility that the drug will reﬂux into the esophagus. In general, patients with gastro-esophageal reﬂux disease must take their medications with adequate amounts of water and avoid reclining for at least an hour to avoid reﬂux.

The administration of oral medication in relation to meals is very important because the bioavailability and efﬁcacy of certain drugs may be severely affected by food and certain drinks. For example, atorvastatin should not be administered with grapefruit juice because the juice inhibits the CYP 3A4 isoenzyme resulting in a higher plasma concentration of atorvastatin. The pharmacist should know about such instances and counsel patients accordingly.

As mentioned earlier, oral dosage forms with special coatings (e.g., enteric) or that are designed to provide controlled drug release, to preserve their drug release features, must not be chewed, broken, or crushed. When an ordinary tablet is crushed or a capsule opened to facilitate ease of administration, any unpleasant drug taste may be partially masked by mixing with custard, yogurt, rice pudding, other soft food, or fruit juice. The patient should be advised to consume the entire drug– food mixture to obtain the full dose, and to maintain stability, the drug should not be premixed and allowed to set.

 If a patient cannot swallow a solid dosage form, the pharmacist can suggest a chewable or liquid form of the drug. If these are not available, an extemporaneously compounded liquid form may be prepared.