Large scale production

**Rotary capsule machine:** This machine has two, side-by-side cylinders in each of which half-moulds are cut. These cylinders, like the rollers of a mangle, rotate in contrary direction and as they are mirror images the moulds come together precisely during rotation. Two ribbons of gelatin are fed between the rollers and, just before the opposing rollers meet, jets of medicament press the gelatin ribbon into the moulds, filling each half.

The moment of pressure follows, immediately sealing the two halves together to form a capsule. These rotary machines are capable of producing between 25000 and 30000 capsules an hour.
Seamless gelatin capsules
Another method of making soft capsules takes advantage of the phenomenon of drop formation. The essential part of the apparatus consists of two concentric tubes. Through the inner tube flows the medicament and, through the surrounding outer tube, the gelatin solution. The medicament, therefore, issues from the tube surrounded by gelatin and forming a spherical drop. This is ensured by allowing the drop to form in liquid paraffin in which the gelatin is insoluble. Regular induced pulsations cause drops of the correct size to be formed, and a temperature of 4°C ensures that the gelatin shell is rapidly congealed. The capsules are subsequently degreased and dried.

Formulation of soft gelatin capsules

Gelatin shell formulation: Typical soft gels are made up of gelatin, plasticizer, and materials that impart the desired appearance (colorants and/or opacifiers), and sometimes flavors.
Plasticizers: These are used to make the softgel shell elastic and pliable. They usually account for 20-30%. The most common plasticizers used in softgels is glycerol, although sorbitol and propylene glycol are used frequently often in combination with glycerol. The amount and choice of the plasticizer contribute to the hardness of the final product and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. Plasticizers are selected on the basis of their compatibility with the fill formulation, ease of processing, and the desired properties of the final soft gel, including hardness, appearance, handling characteristics and physical stability. 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 soft gel 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 soft gel 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 gels the equilibrium water content is typically in the range 5-8% w/w, which represents the proportion of water that is bound to the gelatin in the soft gel shell. This level of water is important for good physical stability, because in harsh storage conditions softgels will become either too soft and fuse together, or too hard and embrittled.

Colorants/opacifiers: Colorants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used in the wet gel formulation. Colorants can be either synthetic or natural, and are used to impart the 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. Titanium dioxide can either be used alone to produce a white opaque shell or in combination with pigments to produce a colored opaque shell.

Special types of hard gelatin and soft gelatin capsules

Modified Release: The rate of release of capsule contents can be varied according to the nature of the drug and the capsule excipients.
If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution.

If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release.

A very rapid release of the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide.

About 0.1 to 1% of sodium lauryl sulfate may be added to enhance the penetration of water into the capsule and speed dissolution.

If slower release of the active drug is desired, it can be mixed with various excipients, such as cellulose polymers (methylcellulose) or sodium alginate. In general, the rate of release is delayed as the proportion of polymer or alginate is increased relative to water soluble ingredients, such as lactose.

It should be mentioned that it is difficult to predict the exact release profile for a drug and to obtain consistent results from batch to batch. Further, reliable, consistent blood levels and duration of action can only be proved with controlled bioequivalence studies. In addition, many medications exhibit narrow therapeutic indices as the toxic and therapeutic doses are very close. Therefore, extemporaneous attempts to alter release rates to this extent should be avoided.

Coating capsules: Coatings have been applied extemporaneously to enhance appearance and conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coating of capsules requires considerable formulation skill and quality control equipment found in manufacturing facilities.

Capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract. Materials found suitable include stearic acid, shellac, casein, cellulose acetate.
phthalate and natural and synthetic waxes; the basis of their use is their acid insolubility but alkaline solubility.

Many of the newer coating materials are time: erosion-dependent rather than acid:base-dependent, i.e. they erode over time on exposure to gastrointestinal contents rather than over a pH gradient. There are, in addition, a number of newer materials with predictable pH solubility profiles.

a. Enteric-coated capsules

Enteric-coated capsules resist disintegration in the stomach but break up in the intestine. They have largely been superseded by enteric-coated tablets. Types of coating used commercially include cellulose acetate phthalate and mixtures of waxes and fatty acids and/or their esters. Enteric coating may be given to following categories of drugs:

For substances that irritate the gastric mucosa or are destroyed by the gastric juice, and for medicaments, such as amoebicides and anthelmintics that are intended to act in the intestine.

Which interfere with digestion e.g. tannins, silver nitrate and other salts of heavy metals.

Which are required to produce delayed action of the drug.

Several coating methods may be used and are described as follows:

1. Beaker-flask coating - Place a very small quantity of the coating material in the flask and gently heat until it has melted. Add a few capsules, remove from the heat and rotate the flask to start application of the coating. Periodically add a few more drops of melted coating material with continued rotation. The addition of very small quantities is all that is required to keep the capsules from sticking together and clumping.
2. **Dipping** - Heat the coating material in a beaker at the lowest feasible temperature. Individual capsules can be dipped using tweezers, allowing the coating to cool and repeating the process until a sufficient layer has been developed.

3. **Spraying** - An alcoholic or ethereal solution of the coating material is prepared and placed in a small sprayer. The capsules are placed on a screen in a well-ventilated area. The solution of coating material is applied in very thin coats with sufficient time allowed for drying between coats (A hair dryer may be used cautiously for this step). The process is repeated until a sufficient layer has been developed.

**Sustained release capsules (spansule)**

The traditional method of taking a dose three or four times a day leads to periods of excess and deficiency in blood concentration of the medicament. One way of correcting this and, at the same time, reducing the number of doses per day, is to administer a capsule containing numerous coated pellets that release the drug successively over a long period.

- The finely powdered drug is first converted into pellets, usually by attaching it to sugar granules with an adhesive.
- The pellets are then treated with protective coatings that delay release of the drug, each batch receiving a different thickness.
- The batches are mixed thoroughly and suitable doses are filled into capsules. For example, a mixture might contain 30 percent of uncoated pellets, for immediate release of drug, 30 percent each of coated pellets that release at 4 hours and 8 hours, and 10 percent of neutral pellets, used solely to fill the capsule. Each batch may be colored differently to simplify identification and facilitate control of mixing.
Liquid filled hard gelatin capsules

It is generally accepted that many of today’s NCE’s (New Chemical Entities) are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising strategies to deliver these insoluble compounds is using dissolved systems like using lipids, liquids or semi-solids to formulate new products. Two piece hard shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations.

The empty hard gelatin capsule and comparison to soft gelatin capsules

The hard gelatin capsule for liquid filling is identical in composition to the capsule used for filling powders and comprises gelatin, water, colouring and opacifying agents. For an efficient sealing process, however, it is important that the fill material does not penetrate into the zone between the body and cap before the sealing operation.

In contrast to the hard gelatin capsule the soft gelatin capsule contains a plasticizer in addition to gelatin and water. Usually glycerol at a level of approx. 30% is used. The moisture uptake of soft gelatin capsules plasticized with glycerol is considerably higher than that for hard gelatin capsules. Another effect of the plasticizer is migration of a drug into the shell of a soft gelatin capsule can occur which may result in drug degradation and difficulties in assay.

One basic difference exists between the hard and soft gelatin encapsulation processes. In the hard gelatin capsule process, the capsule is pre-fabricated and supplied empty, whereas in the soft gelatin capsule process the encapsulation and filling take place simultaneously.

Rectal capsules

Soft gelatin capsules may be used as substitutes for rectal and vaginal suppositories. Various shapes and sizes are used for this purpose. They are generally wider at one end which is inserted first; the movement of
the sphincter muscles forces the capsules forward into the rectum. Liquids or solids can be filled into rectal capsules but the base in which the medicaments have been incorporated must be non-toxic, non-irritant and compatible with the capsule shell.

**Capsules for packing of ophthalmic ointments**

It is very important that the ophthalmic ointments should be sterile and free from irritant effect. Therefore they must be packed in such a manner that the product remains sterile until whole of it is used up. The best method to keep the preparation free from contamination during use is to pack it in single dose containers. Now a days soft gelatin capsules are very commonly used for filling ophthalmic ointments. These capsules are meant for single application to the eye. Just before application, the capsule is punctured with a sterile needle, the contents instilled into the eye and the shell discarded.

**Recent updates in Capsule technology**

**New products by Capsugel:**

A. **Oceancaps capsules**, these capsules made from all natural fish gelatin derived from farm-raised fish, they have the same characteristics as traditional gelatin capsules, including appearance, machinability, mechanical properties, hygroscopic and oxygen properties, chemical stability, and versatility. Plus, they are odorless and tasteless.
**B. Licaps** new 000 size capsules are ideal for maximizing liquid dosage with a fill capacity of 1000mg to 1400mg depending on the density of the liquid fill material. This two-piece capsules has been specially designed to be sealed for secure containment of liquids and semi-solids without banding. Available in both gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules they are available in a variety of colors to meet your specific needs.

**C. Coni-Snap® Sprinkle Capsules**

A new generation of consumer-centric capsules specifically designed to meet the needs of a rapidly growing population that have difficulty swallowing.

**D. Press-Fit® & XPress-Fit® Gelcaps**

Capsugel’s proprietary Press-Fit® and XPress-Fit® gelcap technology is difficult to mimic and enables brands to create a new look for their product with minimal effort and without having to reformulate. Flexible gelcaps are stretched around a caplet of specified shape and dimension.

- XPress-Fit technology achieves a faster disintegration time by leaving an exposed center portion of the caplet. This patented technology allows for rapid-release by allowing gastric fluid to enter the exposed center portion and accelerate gelcap disintegration.
E. DPI Capsules

Dry powder inhalation (DPI) technology offers a favorable drug development opportunity for respiratory or systemic drug delivery. Delivering a uniform dose in a portable, easy-to-use system, capsule-based DPI is a simple and cost-effective way to deliver inhalable medication. Capsugel’s customized capsules, in both gelatin and hypromellose, are optimized to provide superior performance and compatibility between the capsule/device and capsule/formulation.

Caplet

A caplet is a smooth, coated, oval-shaped medicinal tablet in the general shape of a capsule. Many caplets have an indentation running down the middle so they may be split in half easier.