

Pharmaceutical Technology

Capsules

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Hard and soft capsules, liquid filled hard gelatin capsules, base adsorption, altered release capsules

Introduction

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin.

There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two piece” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatin capsule is also called as “one piece”. Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms.

Advantages of Capsules

- Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
- They are attractive in appearance
- They are slippery when moist and, hence, easy to swallow with a draught of water.
- As compared to tablets less adjuncts are required.
- The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
- They are economical
- They are easy to handle and carry.
- The shells can be opacified (with titanium dioxide) or colored, to give protection from light.

Disadvantages of Capsules

- The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are not suitable for filling into capsules.
- The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach.

Raw Materials for Capsules

The raw materials used in the manufacture of both hard and soft gelatin capsules are similar. Both contain gelatin, water, colorants and optional materials such as process aids and preservatives.

1. Gelatin – gelatin is the major component of the capsules and has been the material from which they have traditionally been made. Gelatin has been the raw material of choice because of

the ability of a solution to gel to form a solid at a temperature just above ambient temperature conditions, which enables a homogeneous film to be formed rapidly on a mould pin.

The reason for this is that gelatin possesses the following basic properties:

- It is non-toxic, widely used in foodstuffs and acceptable for use worldwide.
- It is readily soluble in biological fluids at body temperature.
- It is good film-forming material, producing a strong flexible film
- The gelatin films are homogeneous in structure, which gives them strength.

Some of the disadvantages with using gelatin for hard capsules include: it has a high moisture content, which is essential because this is the plasticizer for the film and, under International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conditions for accelerated storage testing, gelatin undergoes a cross linking reaction that reduces its solubility.

Gelatin is a translucent brittle solid substance, colorless or slightly yellow, nearly tasteless and odorless, which is created by prolonged boiling of animal skin connective tissue or bones.

Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly a mixture of both types is used considering availability and cost. Difference in the physical properties of finished capsules as a function of the type of gelatin used is slight.

Blends of bone and pork skin gelatins of relatively high strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing haze or cloudiness in the finished capsule.

Physical properties of gelatin: Gelatin is a protein product produced by partial hydrolysis of collagen extracted from skin, bones, cartilage, ligaments, etc. The natural molecular bonds between individual collagen strands are broken down into a form that rearranges more easily. Gelatin melts when heated and solidifies when cooled again. Together with water it forms a semi-solid colloidal gel.

Production of gelatin: On a commercial scale, gelatin is made from by-products of the meat and leather industry, mainly pork skins, pork and cattle bones, or split cattle hides. Contrary to popular belief, horns and hooves are not commonly used. The raw materials are prepared by different curing, acid, and alkali processes which are employed to extract the dried collagen hydrolysate. The entire process takes several weeks. The flow chart for gelatin production has been shown in figure 1.

2. Colorants – The color of pharmaceutical product plays an important role in their use. Color is used principally to identify a product in all stages of its manufacture and use. In the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products. The colorants that can be used in capsules are of two types: **water soluble dyes or insoluble pigments**. To make a range of colors dyes and pigments are mixed together as solutions or suspensions. Three most commonly used dyes are erythrosine, indigo carmine and quinolone yellow. The two types of pigments used are iron oxides- black, red and yellow and titanium dioxide which are white and used to make the capsule opaque. Capsules are colored by the addition of colorants to the gelatin solution during the manufacturing stage.

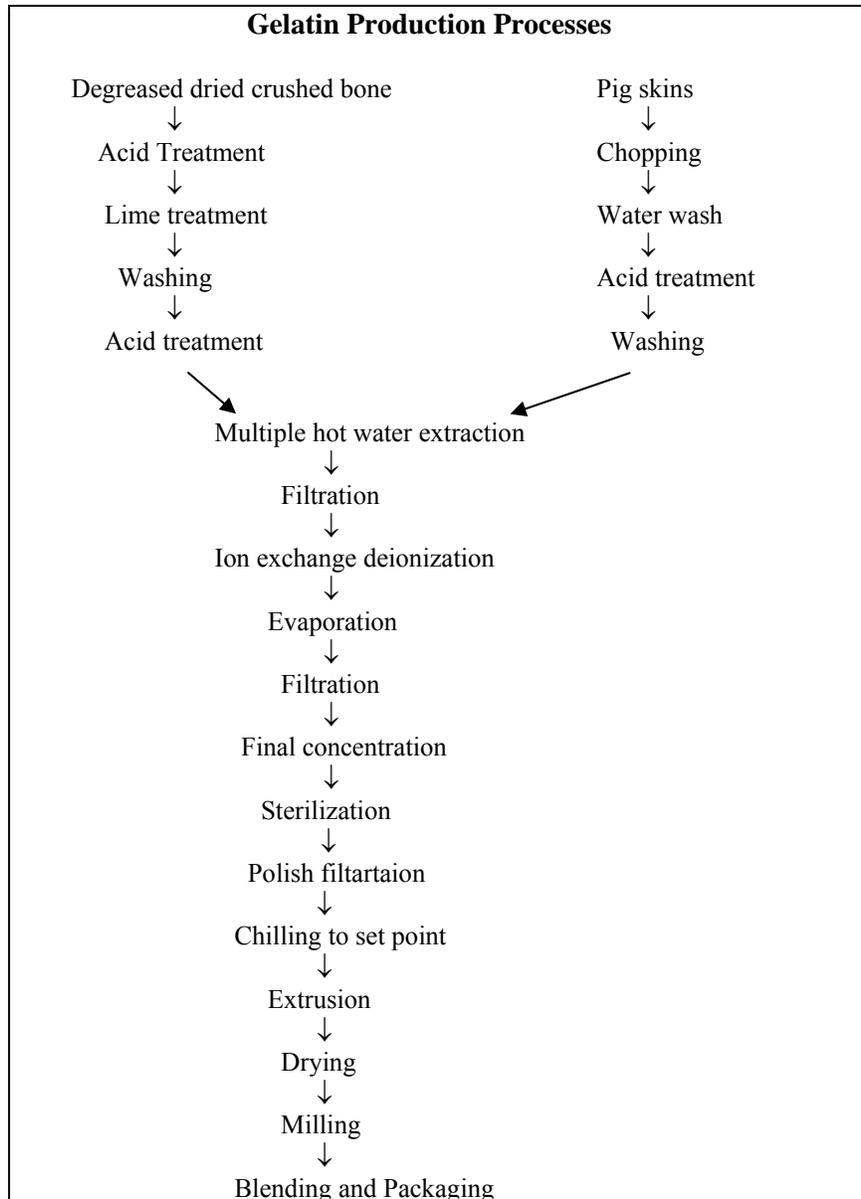


Figure 1: Flow chart for gelatin production process

3. Process aids – Preservatives and surfactants are added to the gelatin solution during capsule manufacture to aid in processing. Gelatin solutions are an ideal medium for bacterial growth at temperatures below 55° C. preservatives are added to the gelatin and colorant solutions to reduce the growth of microorganisms until the moisture content of the gelatin film is below 16% w/v. at moisture content below that value, the bacterial population will decline in numbers with time. The materials used as preservatives include: sulfur dioxide which is added as the sodium salts bisulfite or metabisulfite, sorbic acid or the methyl propyl esters of para hydroxy-benzoic acid, and the organic acids, benzoic and propanoic acids.

Some hard gelatin capsules may contain 0.15 % w/w of sodium lauryl sulphate which functions as wetting agent, to ensure that the lubricated metal moulds are uniformly covered when dipped into the gelatin solution. Capsules are available in many different sizes and shapes and can be used for the administration of powders, semisolids and liquids. Unpleasant tastes and odors of drugs are effectively masked by the practically tasteless capsule shell which dissolves or is digested in the stomach after about ten to twenty minutes. Capsules also can be used as a means of providing accurately measured doses for administration rectally or vaginally.

Hard Capsules

Hard capsules are usually made up of a base containing plasticizer and water. The base may also contain preservatives, colors, flavors and sugars.

Method of production of empty hard gelatin shells: Some of the major suppliers of empty gelatin capsules are: Eli Lilly and Company, Warner Lambert's Capsugel (formerly Park Davis) and R. P. Scherer Corporation.

The metal moulds 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 moulds and the two parts are joined together, these processes are carried out as a continuous process in large machines.

The completely automatic machine most commonly used for capsule production consists of mechanisms for automatically dipping, spinning, drying, stripping, trimming, and joining the capsules.

- Stainless steel pins are used on which the capsule is formed and controls some of the final critical dimensions of the capsule.
- One hundred and fifty pairs of these pins are dipped in to gelatin sol of carefully controlled viscosity to form caps and bodies simultaneously. The pins are usually rotated to distribute the gelatin uniformly, during which time the gelatin may be set or gelled by a blast of cool air.
- The pins are moved through a series of controlled air drying kilns for the gradual and precisely controlled removal of water. The capsules are stripped from the pins by bronze jaws and trimmed to length by stationary knives while the capsule halves are being spun in chucks or collets. After being trimmed to exact length, the cap and body sections are

joined and ejected from the machine. The entire cycle of the machine lasts approximately 45 min.

- Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and the speed and time of dipping. Mold pin dimensions, precise drying, and machine control relating to cut lengths are matters that are critical to the final dimensions. Precise control of drying conditions is essential to the ultimate quality of the cast film.

The in-process quality controls include periodic monitoring, and adjustment when required, of film thickness, cut lengths of both cap and body, color, and moisture content.

Inspection processes to remove imperfect capsules which were previously done visually, have recently been automated following the development and patenting of a practical electronic sorting mechanism by Eli Lilly and Company. This equipment mechanically orients the capsules and transports them past a series of optical scanners, at which time those having detectable visual imperfections are automatically rejected.

Properties of empty capsule – empty capsules contain a significant amount of water that acts as a plasticizer for the gelatin film and is essential for their function. The standard moisture content specification for hard gelatin capsules is between 13 % w/w and 16 % w/w. This value can vary depending upon the conditions to which they are exposed that is at low humidity's they will lose moisture and become brittle, and at high humidity's they will gain moisture and soften. The moisture content can be maintained within the correct specification by storing them in sealed containers at an even temperature.

Capsules are readily soluble in water at 37° C. When the temperature falls below this, their rate of solubility decreases. At below about 30° 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. Because of this most Pharmacopoeia have set a limit of 37° C ± 1° C for the media for carrying out these tests. Capsules made from have different solubility profile, being soluble at temperatures as low as 10° C.

Types of materials for filling into hard gelatin capsules:

Dry solids – powders, pellets, granules or tablets

Semisolids – suspensions or pastes

Liquids – non-aqueous liquids

A capsule size chart is shown in table 1.

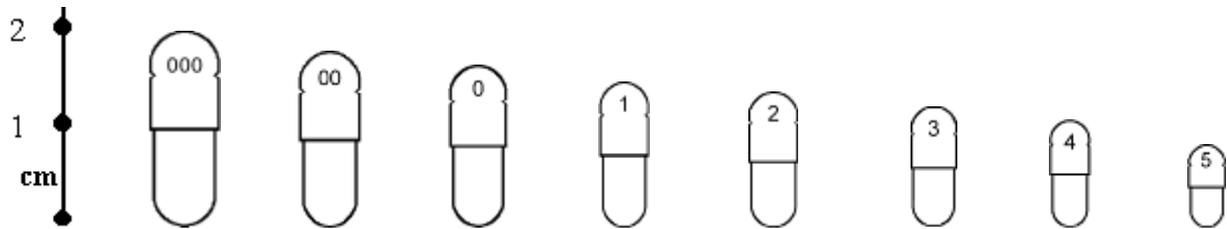
Capsule shell filling

Hand operated hard gelatin capsule filling machines – hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical.

A hand operated gelatin capsule filling machine consists of the following parts and is shown in figure 2.

1. A bed with 200-300 holes.
2. A capsule loading tray
3. A powder tray
4. A pin plate having 200 or 300 pins corresponding to the number of holes in the bed and capsule loading tray.
5. A lever
6. A handle
7. A plate fitted with rubber top.

Table 1: Size of hard gelatin capsules -Capsule size chart



Empty Hard Gelatin Capsule Physical Specifications				
Size	Outer Diameter (mm)	Height or Locked Length (mm)	Actual Volume (mL)	Typical Fill Weights (mg) 0.70 Powder Density
000	9.91	26.14	1.37	960
00	8.53	23.30	0.95	665
0	7.65	21.70	0.68	475
1	6.91	19.40	0.50	350
2	6.35	18.00	0.37	260
3	5.82	15.90	0.30	210

4	5.31	14.30	0.21	145
5	4.91	11.10	0.13	90

(Source - Remington – The Science and Practice of Pharmacy, 20th Edition, Volume – 1)

All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds, and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled



Figure 2: Hand operated hard gelatin capsule filling machine

(Source: Remington – The Science and Practice of Pharmacy, 20th Edition, Volume 1, courtesy – Park Davis)

Working: The empty capsules are filled into the loading tray which is then placed over the bed. By opening the handle, the bodies of the capsules are locked and caps separated in the loading tray itself which is then removed by operating the liver. The weighed amount of the drug to be filled in the capsules is placed in powder tray already kept in position over the bed. Spread the powder with the help of a powder spreader so as to fill the bodies of the capsules uniformly. Collect excess of the powder on the platform of the powder tray. Lower the pin plate and move it downward so as to press the powder in the bodies. Remove the powder tray and place the caps holding tray in position. Press the caps with the help of plate with rubber top and operate the lever to unlock the cap and body of the capsules. Remove the loading tray and collect the filled capsules in a tray. With 200 hole machine about 5000 capsules can be filled per hour and with 300 hole machine 7500 capsules can be filled per hour.

On large-scale manufacturing various types of semiautomatic and automatic machines are used. They operate on the same principle as manual filling, namely the caps are removed, powder filled in the bodies, caps replaced and filled capsules are ejected out. With automatic capsule

filling machines powders or granulated products can be filled into hard gelatin capsules. With accessory equipment, pellets or tablets along with powders can be filled into the capsules.

Capsule filling devices

A number of different manually operated capsule filling devices are commercially available for filling up to 50 or 100 capsules at a time. The method of using these machines requires a careful determination of the capsule formulation. The powder is blended as previously discussed. Empty gelatin capsules are placed into the device and, oriented so that the cap is on top. The machine is worked to separate the base from the cap and the portion of the machine holding the caps is removed and set aside.

The capsule bases are allowed to “drop” into place so that the tops are flush with the working surface. The powder mix is spread over the working surface. A plastic spatula can be used carefully to spread the powder uniformly and evenly into the capsule bases or the machine can be “tapped” to spread the powder and drop it down into the capsule bases. A small device consisting of several “pegs” on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is spread evenly over and into the capsule bases and tamped. These procedures are repeated until all of the powder is in the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged.

A process flow diagram for automated capsule filling is shown in figure 3.

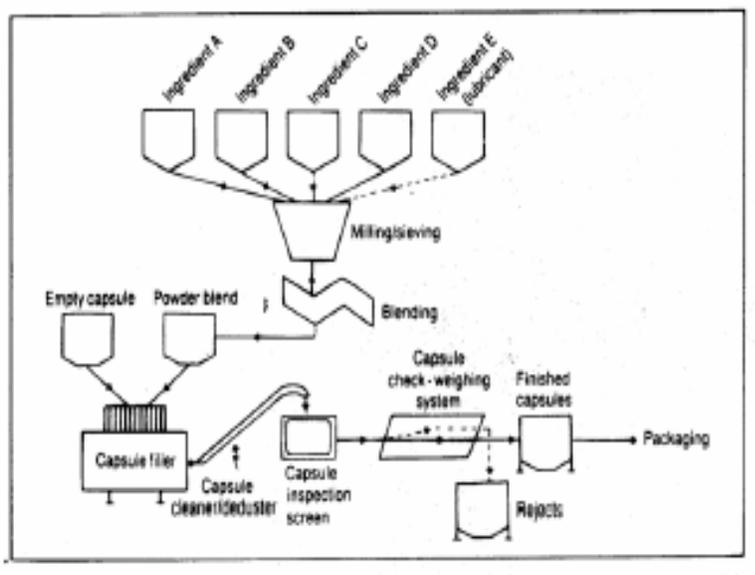


Figure 3: Process flow diagram for automated capsule filling
(Source – Textbook of Pharmaceutics by Bentley, 8th Edition)

Filling capsules with a semisolid mass: If the material to be placed into hard gelatin capsules is a semisolid, it can be encapsulated by either forming a pipe or pouring a melt.

1. Pipe: If the material is sufficiently plastic, it can be rolled into a pipe with a diameter slightly less than that of the inner diameter of the capsule in which it will be enclosed. The desired quantity of material is cut using a spatula or knife, the length determining the weight of the material enclosed. The pieces may be dusted with corn starch (check patient allergies) prior to individual insertion into the capsules.

If a material is too fluid to be worked as described, it may be necessary to add cornstarch or some similar material to yield a more firm consistency. The quantity to be added can be determined empirically.

2. Semisolid pour: If the material is too firm to roll into a pipe but its melting point is satisfactory, it can be melted and poured into the capsule bases, cooled, and the caps replaced. A stand to hold the capsule bodies may be fashioned from a block of wood into which a series of holes the diameter of the capsule caps is drilled. When capsule caps are glued into these holes, capsule bases may be inserted for filling without scratching or marking by the wood.

This method also can be used to enhance the bioavailability of drugs, which are poorly soluble and exhibit bioavailability problems. For this purpose, the drug is added to a melt of a material such as polyethylene glycol (PEG). The mixture is heated and stirred until the powder is either melted or thoroughly mixed in the PEG. The melt is cooled to just above the melting point of the PEG and poured into the capsule shells as described. When this method is used, the desired quantities can be measured using a pipet, syringe, or calibrated dropper to deliver the volume to the individual capsules.

Liquids in Hard Gelatin Capsules

Liquids can be prepared in hard gelatin capsules if the gelatin is not soluble in the liquid to be encapsulated; alcoholic solutions and fixed and volatile oils work well. It may be necessary to determine the solubility of gelatin in the liquid by experimentation. The liquid can be measured accurately using a pipette (micropipet) or a calibrated dropper and dropped into the gelatin base, taking care not to touch the opening. The gelatin caps can be touched, open end down, on a moist towel to soften the gelatin at the opening of the caps or a cotton swab dipped in warm water can be rubbed around the edge of the capsule cap to soften. The cap is placed over the base containing the liquid with a slight twist and the softened edge of the cap should form a seal with the base to prevent leakage. Prior to packaging, these capsules should be placed on a clean, dry sheet of paper and observed for leakage. Another method of sealing makes use of a warm gelatin solution that is painted around the capsules and the inside of the caps prior to placing on the base.

Industrial scale filling – the machines for industrial -scale filling of hard gelatin capsules come in great variety of shapes and sizes, varying from semi- to fully automatic and ranging in output from 5000 to 15000 per hour. Automatic machines can be either continuous in motion, like a rotary tablet press, or intermittent, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsules. The capsule filling process is illustrated in figure 4.

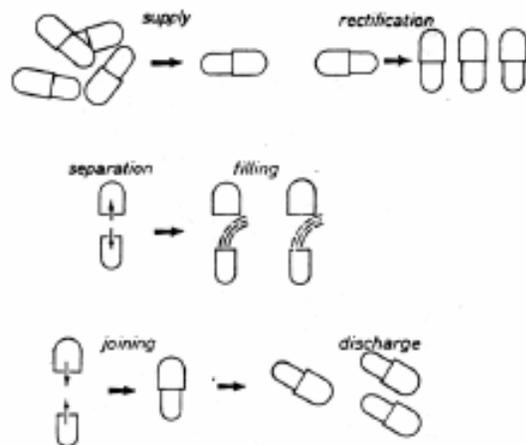


Figure 4: The capsule filling process

The dosing systems can be divided into two groups:

Dependent – dosing systems that use the capsule body directly to measure the powder. Uniformity of fill weight can only be achieved if the capsule is filled completely eg. Auger filling.

Independent - dosing systems where the powder is measured independently of the body in a special measuring device. Weight uniformity is not dependent on filling the body completely. With this system the capsules can be part filled eg. Dosator. An illustration of dosator principle is shown in figure 5.

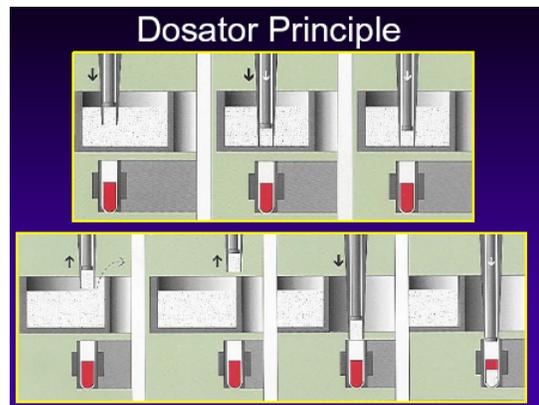


Figure 5: Dosator principle of filling capsule

(Source - Modern Pharmaceutics by Gilbert S. Bankers, 4th Edition, Dekker series)

Types of excipients used in powder-filled capsules

- **Diluents** – diluents are the excipients that are usually present in the greatest concentration in a formulation and they make up the necessary bulk when the quantity of the active ingredient is insufficient to make up the required bulk eg. Lactose, maize starch, calcium sulfate etc.

- **Lubricants and Glidants** – which reduce powder to metal adhesion and promote flow properties eg. Magnesium stearate, talc.
- **Wetting agents** – which improve water penetration for poorly soluble drugs eg. Sodium lauryl sulfate
- **Disintegrants** – which produce disruption of the powder mass crospovidone, sodium starch glycolate.

Cleaning and Packaging

It is imperative that every precaution to minimize traces of moisture or body oils on capsules be taken to reduce powders sticking to the surface, which would create disagreeable appearance and taste. Cleaning capsules is difficult if they have become moist or sticky. The capsules should be handled so that they retain their dryness and shiny appearance. Use of gloves provides a more hygienic environment and helps preserve the dry, shiny capsule appearance. An old method, where gloves are unavailable, is:

(1) Wash and dry hands thoroughly,

(2) Keep the fingers dry by the friction of a towel that is stripped through the tightly clenched fingers until a clearly perceptible heat is generated,

(3) Four or five capsules may be prepared before there will be a need to repeat the process. If the capsules have been kept dry, clinging surface powder can be removed by rolling between folds of a cloth or by shaking in a cloth formed into a bag or hammock. Another method of cleaning capsules is to place them in a container that is filled with sodium bicarbonate, sugar or salt then gently to roll the container. The contents then can be poured into a 10 mesh sieve and the “cleaning salt” allowed to pass through the screen, which collects the capsules. It must be emphasized that these cleaning methods are only effective if the capsules have been kept clean and dry. Once capsules become soiled and dull, they cannot be cleaned effectively.

ROTOSORT is a new filled capsule-sorting machine sold by Eli Lilly and Company. It is a mechanical sorting device that removes loose powder, unfilled joined capsules, filled or unfilled bodies, and loose caps. It can handle up to 150,000 capsules per hour, and it can run directly off a filling machine or be used separately.

Difficulties in filling capsules

1. **Deliquescent or Hygroscopic powders** – a gelatin capsule contain water which is extracted or taken up by a hygroscopic drug and renders the capsule very brittle which leads to cracking of the capsule. The addition of an adsorbent like magnesium carbonate, heavy magnesium oxide or light magnesium oxide overcomes this difficulty provided the capsules are packed in tightly closed glass capsule vials.
2. **Eutectic mixtures** – certain substances when mixed together tend to liquefy and form a pasty mass due to the formation of a mixture which has a lower melting point than room temperature. For filling these types of substances each troublesome ingredient is mixed with an absorbent separately then mixed together and filled in capsules. The absorbents

used are magnesium oxide and kaolin. Another method in dealing with such type of difficulty is that the substances are mixed together so as to form a eutectic mixture, then an absorbent like magnesium carbonate or kaolin is added.

3. **Addition of inert powders** – when the quantity of the drug to be filled in capsules is very small and it is not possible to fill this much small amount in capsules then inert substance or a diluent is added so as to increase the bulk of the powder, which can be filled easily in capsules.
4. **Use of two capsules** – some of the manufacturers separate the incompatible ingredients of the formulation by placing one of the ingredients in smaller capsule, and then placing this smaller capsule in a larger capsule containing the other ingredients of the formulation.
5. **Filling of granular powder** – some powders which lack adhesiveness and most granular powders are difficult to fill in the capsules by punch method because they are not compressible and flow out of the capsule as soon as they are lifted from the pile of powder into which they are punched. To overcome this difficulty the non-adhesive powders should be moistened with alcohol and the granular powders should be reduced to powder before filling into capsules.

Alternative material for Hard-shell capsules

Several materials have been examined as a substitute for the gelatin in two-piece hard capsules. Hydroxypropylmethyl cellulose (HPMC) has become a successful alternative material for two-piece capsules and is actually on the market in the world. HPMC capsules have been developed for both pharmaceutical products and dietary supplements. QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

Soft gelatin capsules

A soft gel (a soft gelatin capsule) is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner fill), as shown in figure 6. An active ingredient can be incorporated into the outer shell, the inner fill, or both.



Figure 6: Soft gel capsule in the form of cod liver oil capsules

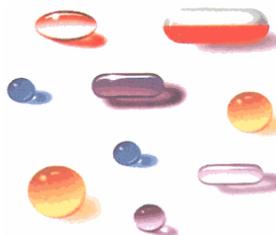


Figure 7. Different shapes of soft gel capsules

The formulation of drugs into soft gelatin capsules has gained popularity throughout the past decade due to the many advantages of this dosage form. The bioavailability of hydrophobic drugs can be significantly increased when formulated into soft gelatin capsules. Many problems associated with tableting, including poor compaction and lack of content or weight uniformity, can be eliminated when a drug is incorporated into this dosage form. Improved stability of drugs that are highly susceptible to oxidation can be achieved when formulated into a soft gelatin capsule.

Gelatin soft capsules are made from gelatin and water but with the addition of a polyhydric alcohol, such as glycerol or sorbitol, to make them flexible. Sorbitol is less hygroscopic than glycerol. They usually contain a preservative, such as beta-naphthol. They are available in variety of shapes and sizes as shown in figure 7.

- Spherical – 0.05 -5 ml
- Ovoid – 0.05 - 7 ml
- Cylindrical – 0.15- 25 ml
- Tubes – 0.5 - 0 ml
- Pear shaped – 0.3 - 5ml

They are most suitable for liquids and semisolids and are widely used, in spherical and ovoid forms for vitamin preparations such as cod liver oil, vitamins A and D and multiple vitamins.

Advantages of soft gel capsules:

1. Ease of use - easy to swallow, no taste, unit dose delivery, temper proof.
2. Versatile
 - i. Accommodates a wide variety of compounds filled as a semisolid, liquid, gel or paste.
 - ii. Wide variety of colors, shapes and sizes
 - iii. Immediate or delayed drug delivery-can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media

Disadvantages of soft gel capsules:

1. Requires special manufacturing equipment
2. Stability concerns with highly water soluble compounds, and compounds susceptible to hydrolysis
3. Limited choices of excipients/carriers compatible with the gelatin

Content of a softgel capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in a liquid(s) or a suspension of a solid(s) in a liquid(s).

Liquids are an essential part of the capsule content. Only those liquids that are both water miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface. Water, ethyl alcohol and emulsions fall into this category.

There are a large number of liquids that do not fall into the above category and thus can function as active ingredients, solvents or vehicles for suspension type formulations. These liquids include aromatic and aliphatic hydrocarbons, high molecular weight alcohols, esters or organic acids. The mostly widely used liquids for human use are oily active ingredients such as vegetable oils (soybean oil), mineral oil, non-ionic surface active agents (polysorbate 80) and PEG (400 and 600) either alone or in combination.

There are three primary types of inner fill materials:

1) Neat Substance, especially oily liquids

eg. Cod liver oil capsules

2) Solution Fills: Active dissolved in a carrier

- Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids)
- Polyethylene Glycols: especially PEG 400 -600
- Other solvents: Any other solvent, which does not degrade or solubilize the gelatin shell, i.e., dimethyl isosorbide, surfactants, diethylene glycol monoethyl ether.

Optional Ingredients for solution fills:

1. Water or alcohol: up to 10% w/w (if needed for solubility).
2. Glycerin: 1 to 4% w/w (to retard the migration of the glycerin out of the shell into the fill).
3. Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG (can increase drug solubility, and also improve stability by inhibiting drug recrystallization).

3) Suspension Fills: Active dispersed in a carrier.

- ❖ Suspensions can accommodate about 30% solids before viscosity and filling become a problem
- ❖ Suspensions can be heated up to 35°C to decrease viscosity during the filling process
- ❖ Suspended solids must be smaller than 80 mesh -- mill or homogenize before filling to prevent needles from clogging during filling.

Solids that are not sufficiently soluble in liquids or in combinations of liquids are capsulated as suspensions. Most organic and inorganic solids or compounds may be capsulated. Such materials must be 80 mesh or finer in particle size, owing to certain close tolerances of the capsulation equipment and for the maximum homogeneity of the suspension. Many compounds cannot be capsulated, owing to their solubility in water and thus their ability to affect the gelatin shell, unless they are minor constituents of a formula or are combined with a type of carrier (liquid or solid) that reduces their effect on the shell. Examples of such solids are strong acids (citric), strong alkalis (sodium salts of weak acids), salts of strong acids and bases (sodium chloride) and ammonium salts. Also, any substance that is unstable in the presence of moisture (eg. Aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

The capsulation of suspensions is the basis for the existence of a large group of products. Again, the design of suspension type formulations and the choice of the suspending medium are directed toward producing the smallest size capsule having the characteristics previously described, i.e. maximum production capacity consistent with maximum physical and ingredient stability and therapeutic efficacy.

The formulation of suspensions for capsulation follows the basic concepts of suspension technology. Formulation techniques, however, can vary depending on the drug substance, the desired flow characteristics, the physical or ingredient stability problems, or the biopharmaceutical properties desired. In most instances, these techniques must be developed through the ingenuity of the formulating chemist, however, in the formulation of suspensions for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size.

Base Adsorption of solids to be suspended in soft gelatin capsules – base adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s). The base adsorption of a solid is influenced by such factors such as the solids particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature.

In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and nonionic type bases, the addition of a wetting agent is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2 to 3 % by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for good drug use. Increasing the concentration above 3 % appears to have no added advantage.

A practical procedure for determining base adsorption and for judging the adequate fluidity of a mixture is as follows:

Weigh a definite amount of the solid (40g is convenient) into a 150 ml tared beaker. In a separate 150 ml beaker tared beaker, place about 100 g of the solid base. Add small increments of the liquid base to the solid, and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture.

The base adsorption is obtained by means of the following formula –

$$\text{Weight of the base/ Weight of the solid} = \text{Base Adsorption}$$

The base adsorption is used to determine the “minim per gram” factor (M/g) of the solid(s). the minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of the liquid base (BA) required to make a capsulatable mixture. The minim per gram

factor is calculated by dividing the weight of the base plus the gram of solid base (BA+ S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V).

a convenient formula is-

$$(BA + S) \times V / W = M/g$$

Thus lower the base adsorption of the solid (s) and higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can affect its base adsorption.

The final formulation of a suspension invariably requires a suspending agent to prevent the settling of the solids and to maintain homogeneity prior to, during, and after capsulation. The nature and the concentration of the suspending agent vary. In all instances the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been pre-heated to 40 degrees prior to the addition of any solids. The solids are then added, one by one, with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing order to prevent interaction prior to complete wetting by the base.

Example of suspension fills include drug suspended in the following carriers:

1. Oily mixtures:

- a) Soybean Oil with beeswax (4-10% w/w) and lecithin (2-4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.

- b) **Gelified Oil** (e.g. Geloil® SC), a ready to use system composed of soybean oil, a suspending agent, and a wetting agent.

2. Polyethylene glycol

- PEG 800 -1000 for semi-solid fills
- PEG 10,000 -100,000 for solid fills
- Or mixtures of the above. (Heat up to 35°C to make fluid enough for filling)

Optional Ingredients that can be added in the suspension fill:

- Surfactant: sorbitan derivatives such as polysorbate 80 or lecithin.
- For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB 10 will increase the dispersibility of the product in aqueous fluids and also may improve bioavailability.

Large-scale manufacture

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 with an accuracy of dosage of approximately ± 1 percent. An automated soft gelatin encapsulation machine is shown in figure 8.

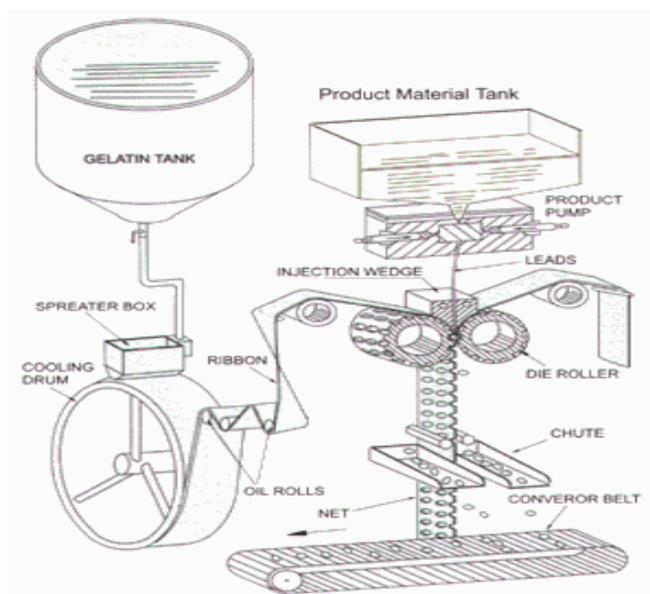


Figure 8: Automatic Soft Gelatin Encapsulation Machine
(Source - Encyclopedia of Pharmaceutical Technology, Volume – 2)

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 aspect 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.

Quality control of capsules

Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection must be made as they roll off the capsule machine onto a conveyor belt regarding uniformity in shape, size, color and filling. As the capsules moves in front of the inspectors the visibly defective or suspected of being less than the perfect are picked out.

The hard and soft gelatin capsules should be subjected to following tests for their standardization.

1. Shape and size
2. Color
3. Thickness of capsule shell
4. Leaking test for semi-solid and liquid ingredients from soft capsules
5. Disintegration tests
6. Weight variation test

7. Percentage of medicament test

In official books the following quality control tests are recommended for capsules:

Disintegration test: For performing disintegration test on capsules the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. One capsule is placed in each tube which are then suspended in the beakers to move up and down for 30 minutes, unless otherwise stated in the monograph. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.

Weight variation test: 20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weight. If this requirement is not met, then the weight of the contents for each individual capsule is determined and compared with the average weight of the contents. The contents from the shells can be removed just by emptying or with the help of small brush. From soft gelatin capsules the contents are removed by squeezing the shells which has been carefully cut. The remainder contents are removed by washing with a suitable solvent. After drying the shells, they are weighed and the content weights of the individual capsules are calculated. The requirements are met if (1) not more than 2 of the differences are greater than 10 % of the average net content and (2) in no case the difference is greater than 25 %.

Content uniformity test: This test is applicable to all capsules which are meant for oral administration. For this test a sample of the contents is assayed as described in individual monographs and the values calculated which must comply with the prescribed standards.

Capsule stability: Unprotected soft capsules (i.e., capsules that can breathe) rapidly reach equilibrium with the atmospheric conditions under which they are stored. This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on these products, and points to the necessity of proper storage and packaging conditions and to the necessity of choosing an appropriate retail package. The variety of materials capsulated, which may have an effect on the gelatin shell, together with the many gelatin formulations that can be used, makes it imperative that physical standards are established for each product.

General statements relative to the effects of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil, with a gelatin shell having a dry glycerin to dry gelatin ratio of about 0.5 to 1 and a water to dry gelatin ratio of 1 to 1, and that is dried to equilibrium with 20 to 30 % RH at 21 to 24 ° C, the physical stability of soft gelatin capsules is associated primarily with the pick-up or loss of water by the capsule shell. If these are prevented by proper packaging, the above control capsule should have satisfactory physical stability at temperature ranging from just above freezing to as high as 60° C, for the unprotected control capsule, low humidities (less than 20 % RH), low temperature (less than 2° C) and high temperatures (greater than 38° C) or combinations of these conditions have only transient effects. The capsule returns to normal when returned to optimum storage conditions. As the humidity is

increased, with in a reasonable temperature range, the shell of the unprotected control capsule should pick up moisture in proportion to its glycerin and gelatin content.

The total moisture content of the capsule shell, at equilibrium with any given relative humidity within a reasonable temperature range, should closely approximate the sum of the moisture content of the glycerin and the gelatin when held separately at the stated conditions.

The effect of temperature and humidity on capsule shell has been illustrated in Table 2.

Table 2: Effect of Temperature and Humidity on Capsule shell

Temperature	Humidity	Effect on Capsule shell
21-24°C	60%	Capsules become softer, tackier and bloated
Greater than 24°C	Greater than 45%	More rapid and pronounced effects – unprotected capsules melt and fuse together

Capsules containing water-soluble or miscible liquid bases may be affected to a greater extent than oil-based capsules, owing to the residual moisture in the capsule content and to the dynamic relationship existing between capsule shell and capsule fill during the drying process.

The capsule manufacturers routinely conduct accelerated physical stability tests on all new capsule products as an integral part of the product development program. The following tests have proved adequate for determining the effect of the capsule shell content on the gelatin shell. The tests are strictly relevant to the integrity of the gelatin shell and should not be confused as stability tests for the active ingredients in the capsule content. The results of such tests are used as a guide for the reformulation of the capsule content or the capsule shell, or for the selection of the proper retail package. The test conditions for such accelerated physical stability tests are shown in table 3.

The capsules at these stations are observed periodically for 2 weeks. Both gross and subtle effects of the storage conditions on the capsule shell are noted and recorded. The control capsule should not be affected except at the 80 % RH station, where the capsule would react as described under the effects of high humidity.

Table 3 Test conditions for accelerated physical stability tests for capsule dosage forms

Test conditions	Observation
80 % RH at room temperature in an open container.	Capsules are observed periodically for 2 weeks, both gross and subtle effects of the storage conditions are noted and recorded. The control capsule should not be affected
40° C in an open container.	

40° C in a closed container (glass bottle with tight screw-cap).	except at the 80% RH station.
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Packaging and storage of capsules

Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place. These type of containers have advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust. To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials. In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride may be placed to prevent the absorption of excessive moisture by the capsules. Now a days capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification.

Empty gelatin capsules should be stored at room temperature at constant humidity. High humidity may cause softening of the capsules and low humidity may cause drying and cracking of the capsules. Storage of capsules in glass containers will provide protection not only from extreme humidity but also from dust.

Storage of filled capsules is dependent on the characteristics of the drugs they contain. Semisolid filled hard gelatin capsules should be stored away from excessive heat, which may cause a softening or melting of the contents.

Capsule Administration

Capsules of the size No. 5 to No. 0 generally are not too difficult to swallow. Many patients may have difficulty swallowing the No. 00 and No. 000 capsules. If this occurs, the patient may be advised to place the capsule on the back of the tongue before drinking a liquid, or to place the capsule in warm water for a few seconds prior to taking to make it slide over mucous membranes easily. The pharmacist may suggest an alternative dosage form, *e.g.* smaller capsules or a liquid or rectal preparation.

Special types of hard gelatin and soft gelatin capsules

Altered 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.

In general, the application of a coating requires skill and additional equipment. A general coating can be applied but should probably only be used in medications that would not be of a critical nature. In many cases, experience must be developed for specific formulations depending upon the requests of the physicians and the needs of the individual patients.

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 (a model airplane paint sprayer works well). 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 – 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 new technology of packaging liquids in hard gelatin capsules is considered a major breakthrough. It can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulations when only small quantities of drug substance is available. The process can be scaled-up and also kept in-house similar to the operations of tableting or powder/pellet filling of hard gelatin capsules.

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. As described by Bauer et al, the moisture uptake of soft gelatin capsules plasticized with glycerol is considerably higher than that for hard gelatin capsules. Another effect of the plasticizer has been reported by Armstrong et al, they found that 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. The moisture content of the gelatin/plasticizer mass at this stage can be around 50%, the equilibrium moisture level only being reached after several days storage on trays. It is conceivable that this is the most critical period during which migration and degradation of moisture sensitive drugs, which are readily soluble in glycerol, can occur.

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

A) New products by Capsugel:

1. **Capsugel has introduced 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
2. **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.

B) New product by Natco Pharma

1. Hyderabad based NATCO Pharma Limited has launched LUKATRET - a medicine used in the treatment of a rare form of leukemia.

LUKATRET (Tretinoin - all trans retinoic acid) available in the form of 10 mg. capsules (in a pack of 100 capsules) is used in the treatment of Acute Promyelocytic Leukemia (APL). LUKATRET is a treatment option for remission induction in newly diagnosed, relapsed and / or refractory, chemotherapy non-responsive patients and for patients where anthracycline based chemotherapy is contraindicated. Use of Lukatret results in differentiation and clinical remission.

C) New products by Banner Pharmacaps Inc.

Banner Pharmcaps has developed an Enteric Softgel called Entericare, with enteric properties built into the shell matrix of the capsules for delivering very potent (small quantities) as well as drugs that require larger quantities and provide sustained delivery for more than an 8- to 12-hour period.

D) New product by Shionogi Qualicaps

QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

References

1. Pharmaceutics – The Science of Dosage form Design by M.E. Aulton, 2nd Edition.
2. Remington – The Science and Practice of Pharmacy, 20th Edition, Volume – 1.
3. The Theory and Practice of Industrial Pharmacy by Leon Lachman.
4. Encyclopdia of Pharmaceutical Technology, Volume – 2.
5. Textbook of Pharmaceutics by Bentley, 8th Edition.
6. Modern Pharmaceutics by Gilbert S. Bankers, 4th Edition, Dekker series.
7. Website – www.capsugel.com
8. Website – www.liquidcapsules.com
9. Ogura T, Furuya Y, Matuura S. HPMC capsules: an alternative to gelatin. Pharm Tech Europe. 1998; 10(11): 32-42.
10. Gelatin. Gelatin Manufacturer's Institute of America.
11. Hard Gelatin and Hypromellose (HPMC) Capsules: Estimation of Rupture Time by Real-time Dissolution Spectroscopy: Yasser El-Malah; Sami Nazzal; Carey B. Bottom. Published in: Drug Development and Industrial Pharmacy, Volume 33, Issue 1 January 2007 , pages 27 - 34
12. Pharmabiz.com: Hard gelatin packs for liquids, May 12, 2005.

Suggested Reading

Leon Lachman. The Theory and Practice of Industrial Pharmacy