PROCESSING OF CAPSULES

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➢ 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 pieces” 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.

➢ Capsule Size

- Capsule shells are manufactured in various sizes, lengths, diameters, and capacities. For human use, capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available. Larger capsules are used in veterinary applications. Figure;1 shows relative sizes and Table;1 lists the capacities of hard gelatin capsules for human use. Figure:2 shows the relative sizes of hard gelatin capsules for veterinary use.

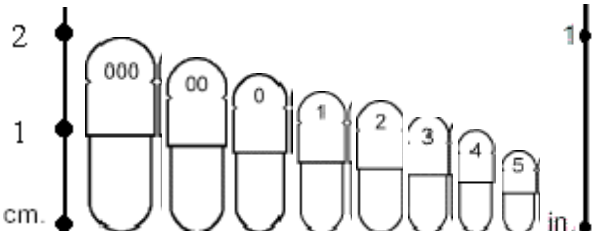
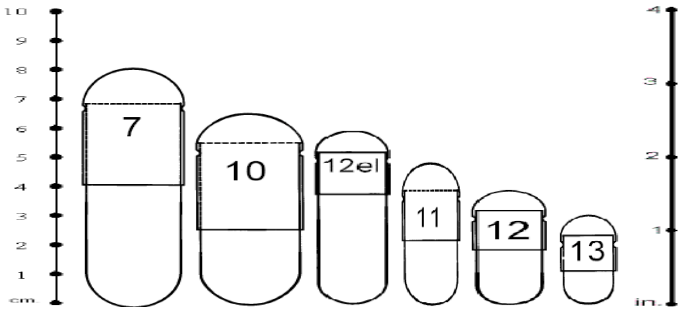


Fig:1

Table:1

Size	000	00	0	1	2	3	4	5
Weight (mg)	163 ± 10	118 ± 7	96 ± 6	76 ± 5	61 ± 4	48 ± 3	38 ± 3	28 ± 2
Volume (mL)	1.37	0.91	0.68	0.50	0.37	0.30	0.21	0.10
Length (mm)	26.1 ± 0.3	23.3 ± 0.3	21.7 ± 0.3	19.4 ± 0.3	18.0 ± 0.3	15.9 ± 0.3	14.3 ± 0.3	11.1 ± 0.4
Body OD (mm)*	9.55	8.18	7.34	6.63	6.07	5.57	5.05	4.68
Cap OD (mm)*	9.91	8.53	7.64	6.91	6.35	5.82	5.32	4.91
Powder Density		**Capsule Capacity (mg)**						
0.6 g/mL	822	546	408	300	222	180	126	78
0.8 g/mL	1096	728	544	400	296	240	168	104
1.0 g/mL	1370	910	680	500	370	300	210	130
1.2 g/mL	1644	1092	816	600	444	360	252	156

Fig:2 

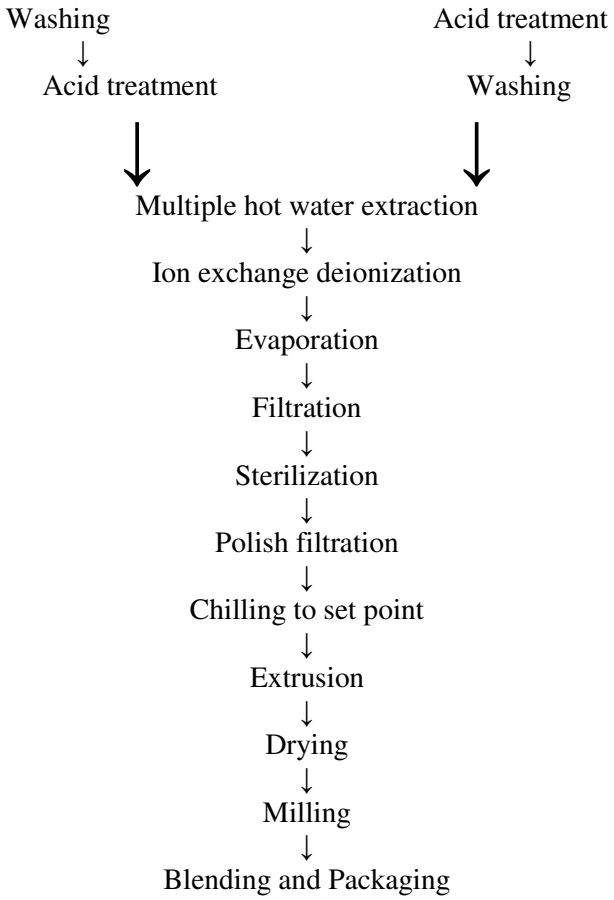
➢ RAW MATERIALS FOR CAPSULES:

- 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.
- **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 temperate 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.

Degreased dried crushed bone	Pig skins
↓	↓
Acid Treatment	Chopping
↓	↓
Lime treatment	Water wash
↓	↓



The flow chart for gelatin production has been shown.

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

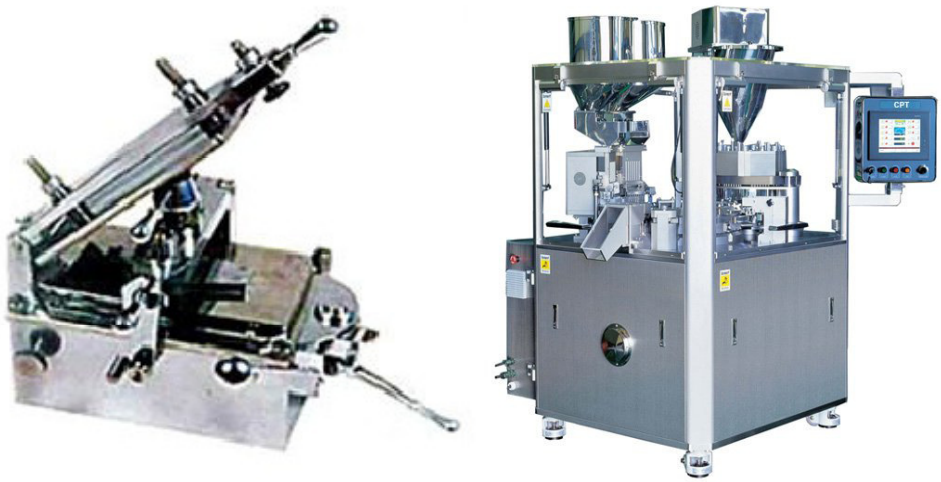
solution. Capsules are available in many different sizes and shapes and can be used for the administration of powders, semisolids and liquids. Unpleasant tastes and odors of drugs are effectively masked by the practically tasteless capsule shell which dissolves or is digested in the stomach after about ten to twenty minutes. Capsules also can be used as a means of providing accurately measured doses for administration rectally or vaginally.

➢ HARD GELATIN CAPSULES:

- Hard capsules are usually made up of a base containing plasticizer and water. The base may also contain preservatives, colors, flavors and sugars.
- **Types of materials for filling into hard gelatin capsules:**
  - **Dry solids –** powders, pellets, granules or tablets.
  - **Semisolids** – suspensions or pastes.
  - **Liquids** – non-aqueous liquids.
- **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 below:

  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.



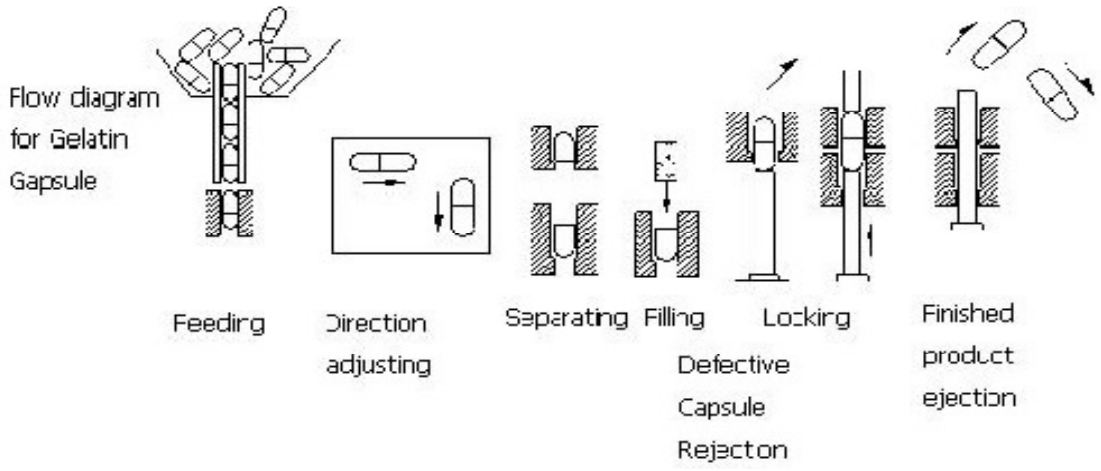
Hand operated capsule filling machine & automated capsule filling

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.

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.



The capsule filling process

➢ `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 3. An active ingredient can be incorporated into the outer shell, the inner fill, or both.
- 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 4.

- 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. Content of a soft gel 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.

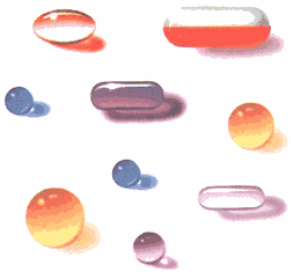


Figure 3 and 4: Cod liver oil capsules and Different shapes of soft gel capsules

- **Large-scale manufacture of soft gelatin capsules:**
  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 if figure 5.

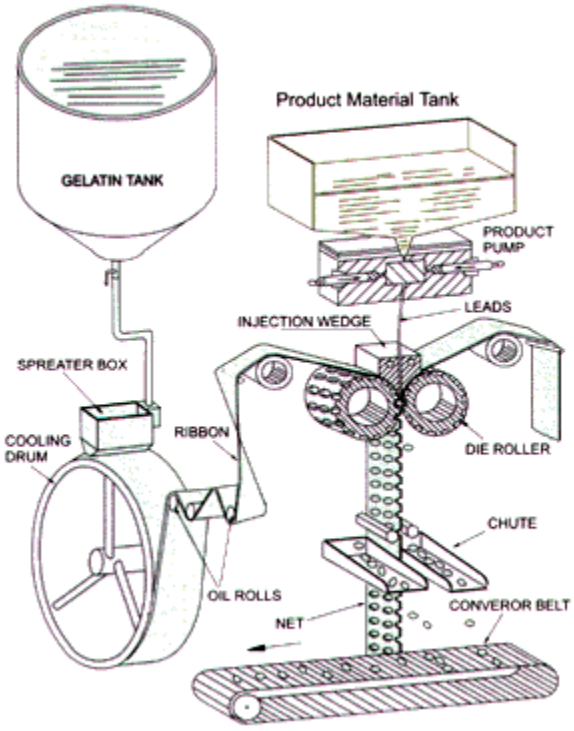


Figure 5: Automatic Soft Gelatin Encapsulation Machine

➢ QUALITY CONTROL TESTS 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.

➢ 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 day's 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.

➢ SPECIAL APPLICATIONS OF CAPSULES:

- Enteric coated capsules.
- Sustained Release capsules.
- Rectal capsules.
- Capsules containing ophthalmic ointments.
