CAPSULE

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- The word ‘capsule’ is derived from the Latin *capsula*, meaning a small box. In pharmacy, the word is used to describe an edible package made from gelatin or other suitable material which is filled with drug(s) to produce a unit dosage, mainly for oral use.

- 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”.

ADVANTAGES OF CAPSULES

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

DISADVANTAGES OF CAPSULES

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

Components of Capsules Shell

1. Gelatin.
2. Plasticizer.
3. Colourants.
4. Water.
5. Opacifying agents.
6. Preservatives.
7. Other excipients.

Note: 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**:

- Shell is generally made from gelatin, but can be made from other polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), hypromellose.
- Gelatin is a colorless, almost tasteless, translucent proteinaceous substance that is brittle when dry and elastic when mixed with controlled amount of moisture. It is digested by proteolytic enzymes.
- It is produced by irreversible, partial hydrolysis of collagen, which is obtained from animal skin and bones.
- Gelatin is a translucent brittle solid substance, colorless or slightly yellow, nearly tasteless and odorless.
- There are two main types of gelatin: type A, which is produced by acid hydrolysis, and type B, which is produced by basic hydrolysis.

- Gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water. Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule. Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents.

➢ Gelatin 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:

1. It is non-toxic, widely used in foodstuffs and acceptable for use worldwide.
2. It is readily soluble in biological fluids at body temperature.
3. It is good film-forming material, producing a strong flexible film

4. 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.
- Normally, hard gelatin capsules contain 13% to 16% of moisture. However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape.

In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become brittle and crumble when handled. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.

- Alternative to hard gelatin capsules, hard capsule shells are also manufactured using non-gelatinous polymer such as HPMC & starch. They have more physical stability (i.e., do not become fragile and crack on exposure to low humidity) towards moisture than gelatinous capsules.

2- Plasticizer:

Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable.

Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatin.

3- Colourants:

Most frequently, hard gelatin capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product.

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.

Capsules are colored by the addition of colorants to the gelatin solution during the manufacturing stage.

Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.

4- Water:

Water usually accounts for 30-40% of the wet gel formulation and its presence is important both during the manufacturing process (to facilitate manufacture) and in the finished product to ensure that the capsule is flexible.

5- Opacifying agents:

Opacifiers (e.g., titanium dioxide) may be included to make clear gelatin opaque. Opaquse capsules may be employed to provide protection against light or to conceal the contents.

6- Preservatives:

Preservatives are added to prevent microbiological contamination during manufacture and storage.

- Examples of commonly used as preservatives include potassium sorbate, and methyl, ethyl, propyl hydroxybenzoate.
- 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.
- In the finished hard gelatin capsules, the moisture levels, 12–16% w/ v, are such that the water activity will not support bacterial growth because the moisture is too strongly bound to the gelatin molecule.

7- Other excipients:

- ✓ Other, infrequently, used excipients can include flavouring agents and sweeteners to improve palatability.
- ✓ 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.

Manufacture of Hard Gelatin Capsules

Hard gelatin capsules are manufactured using a dip- coating method and the various stages involved are as follows:

- 1- **Preparation of the gelatin solution (dipping solution):**

  A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water which has been heated to 60–70°C in jacketed pressure vessels. This solution contains 30 – 40% w/w of gelatin and is highly viscous, which causes bubbles as a result of air entrapment. The presence of these bubbles in the final solution would yield capsules of inconsistent weight. To remove the air bubbles, a vacuum is applied to the solution.

- Following the above steps, colourants and pigments are added to attain the desired final capsule appearance.

- At this stage, other processing aids may be added, such as sodium lauryl sulfate, to reduce surface tension. The solution viscosity is measured and adjusted as needed with hot demineralized water to achieve the target specification. This latter parameter is used to control the thickness of capsule shells during production: the higher the viscosity, the thicker the shell wall produced.
- The prepared mixes are then transferred to a heated holding hopper on the manufacturing machine

2- Dip-coating the gelatin solution on to metal pins (moulds), (Dipping):

Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan. Because the moulds are below the gelling temperature, the gelatin begins to form a thin gelatin layer or film on the moulds.

The rows of pins are arranged so that caps are formed on one side of the machine while bodies are simultaneously formed on the opposite side of the machine.

3- Rotation of the dip-coated pins, (Spinning) :

Following adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is removed and rotated several times to evenly distribute the solution around the pins, correct gelatin distribution being critical to uniform and precise capsule wall thickness and dome strength.

4- Drying of the gelatin-coated pins, (Drying):

Once the gelatin is evenly distributed on the mould, a blast of cool air is used to set the gelatin on the mould.

At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

5- Stripping and trimming:

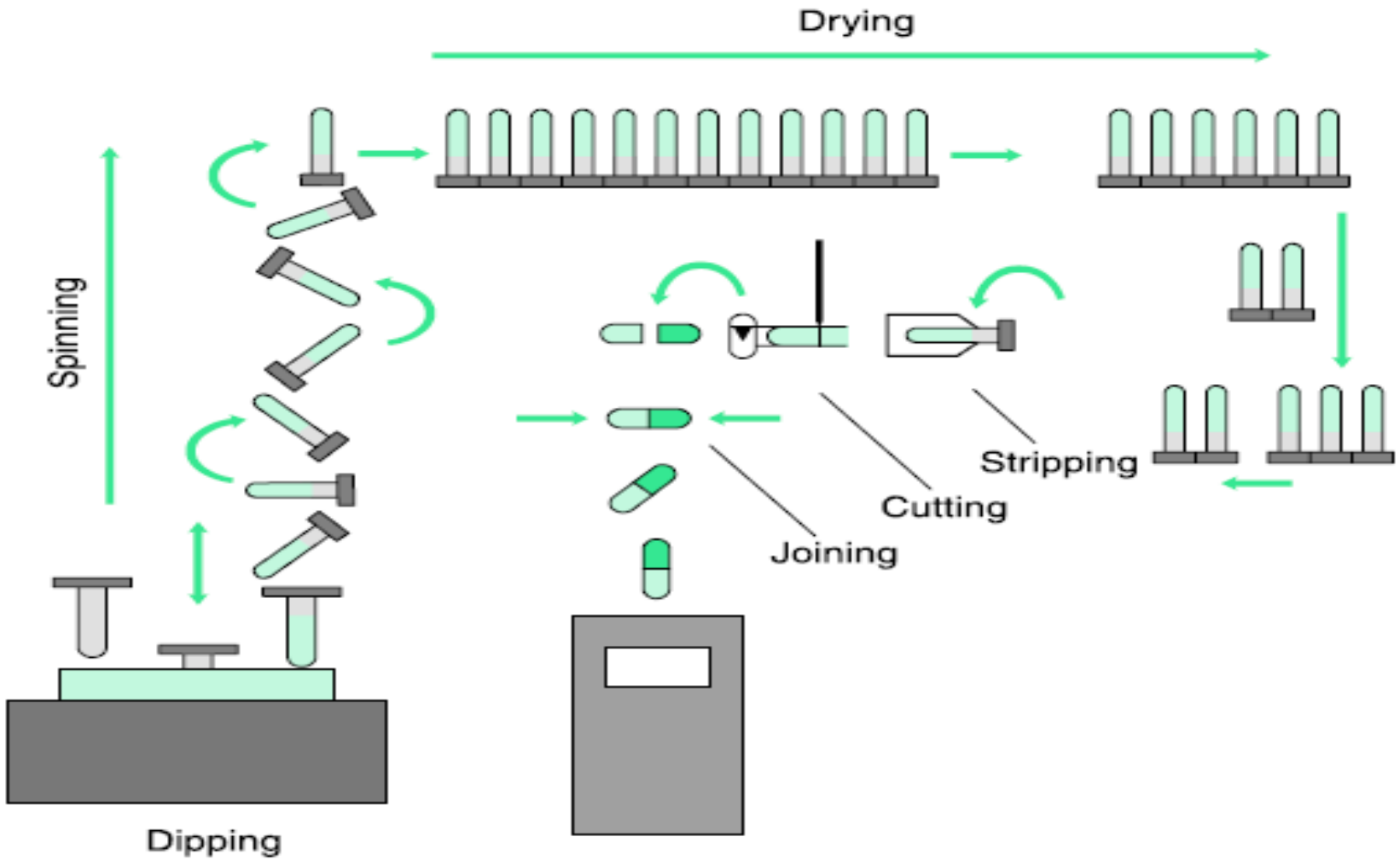
After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length.

6- Joining of the trimmed capsule shell:

Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

7- Printing:

The capsule shells can be printed to improve identification



The sequence of two-piece hard gelatin capsule shell manufacture.

- **Types of materials for filling into hard gelatin capsules:**

Dry solids – powders, pellets, granules or tablets

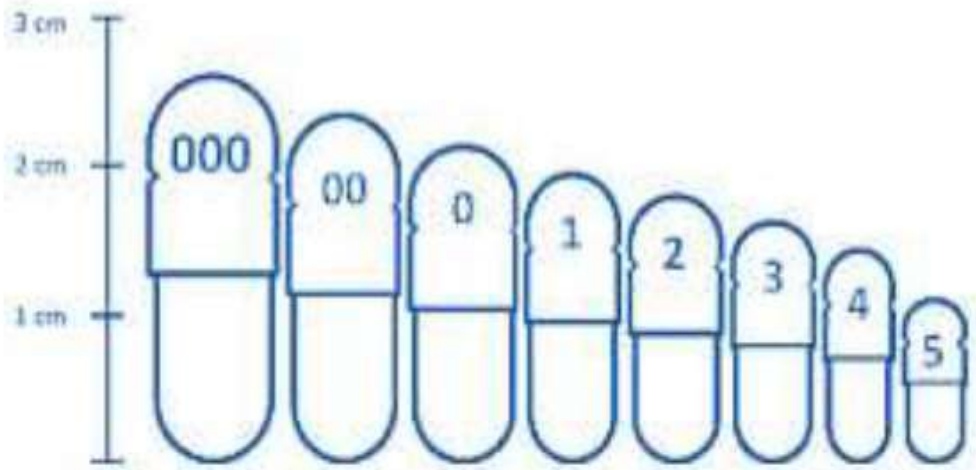
Semisolids – suspensions or pastes

Liquids – non-aqueous liquids

Capsule size:

- For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 (the largest, fill volume 1.37ml) to 5 (the smallest, fill volume 0.13ml).
- Larger capsules are available for veterinary use.
- **The selection of the capsule size** for a commercial product is done during product development. The choice is determined by requirements of the formulation, including the dose of the active ingredient and the density and compaction characteristics of the drug and other components.

- If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added.



Capsule No.	000	00	0	1	2	3	4	5
Content (mg)	950	650	450	300	250	200	150	100

Size designation	*Fill volume (mL)*
000	1.37
00	0.95
0	0.68
1	0.50
2	0.37
3	0.30
4	0.21
5	0.13

FILLING THE CAPSULE SHELLS:

- MANUAL FILLING METHOD (PUNCH METHOD).
- HAND OPERATED METHOD.
- AUTOMATIC OPERATED FILLING MACHINES.

MANUAL FILLING METHOD (PUNCH METHOD)

✓Used for filling a small number of capsules in the pharmacy, at the prescription counter.

✓The ingredients are triturated to fine & uniform powder.

✓The powder is placed on a powder paper or ointment slab and smoothed with a spatula to a height approximately half the length of the capsule body

✓The base of the capsule is held vertically and the open end is repeatedly pushed or "punched" into the powder until the capsule is filled;

✓The cap is then replaced to close the capsule. Each filled capsule is weighed using an empty capsule as a counterweight.

✓Powder is added or removed until the correct weight has been placed in the capsule.

✓The filled capsule is tapped so that no air spaces are visible within the contents.

Punch Method

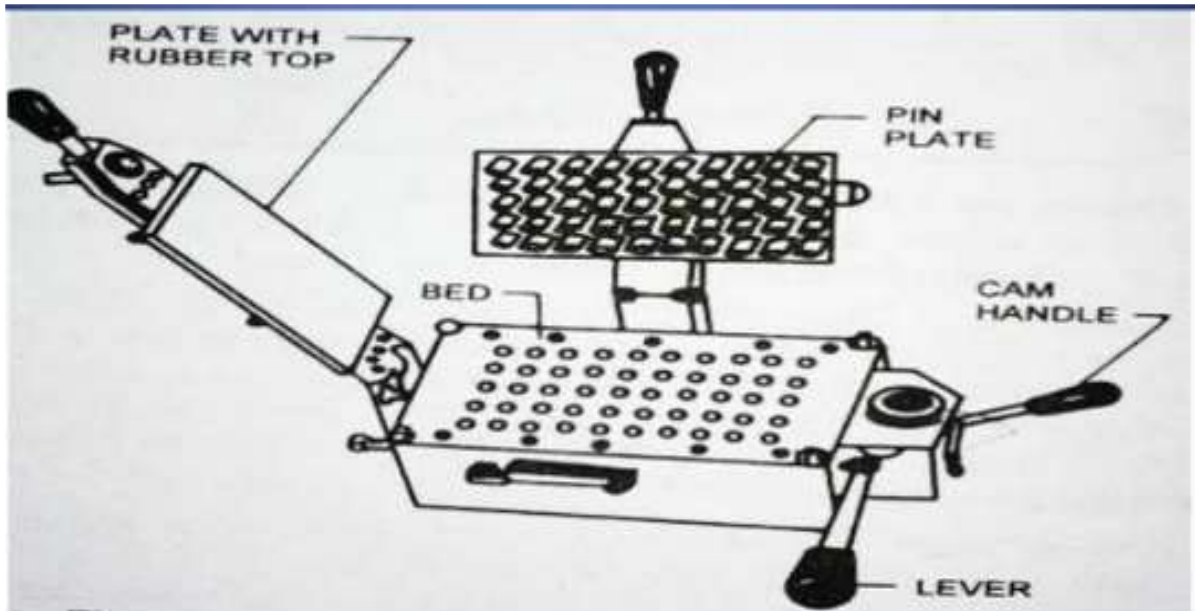
Used when filling a small number of capsules.

HAND OPERATED METHOD:

✓Pharmacists that prepare capsules on a regular or extensive basis may use hand-operated capsule machines.

✓ These machines are available in capacities of 24, 96, 100, and 144 capsules.

✓ Machine is the tray used to hold the fill over the empty capsules, the spreader and roller used to distribute the fill material in the tray and permit it to enter the capsules uniformly, and the packer used to compact the fill in the capsules



AUTOMATIC OPERATED FILLING MACHINES

Machines developed for industrial use can automatically remove the caps from empty capsules, fill the capsules, replace the caps, and clean the outside of the capsules at a rate of up to **1,65,000** capsules and greater per hour.

locking and sealing of hard gelatin capsules:

For the capsules filled by manual or hand filling machines, locking and sealing is done to prevent the detachment of caps from the bodies during packaging, carrying or storing. Locking and sealing also prevents the exudation of the capsule contents.

- Different manufacturers adopt different methods for locking and sealing the capsules

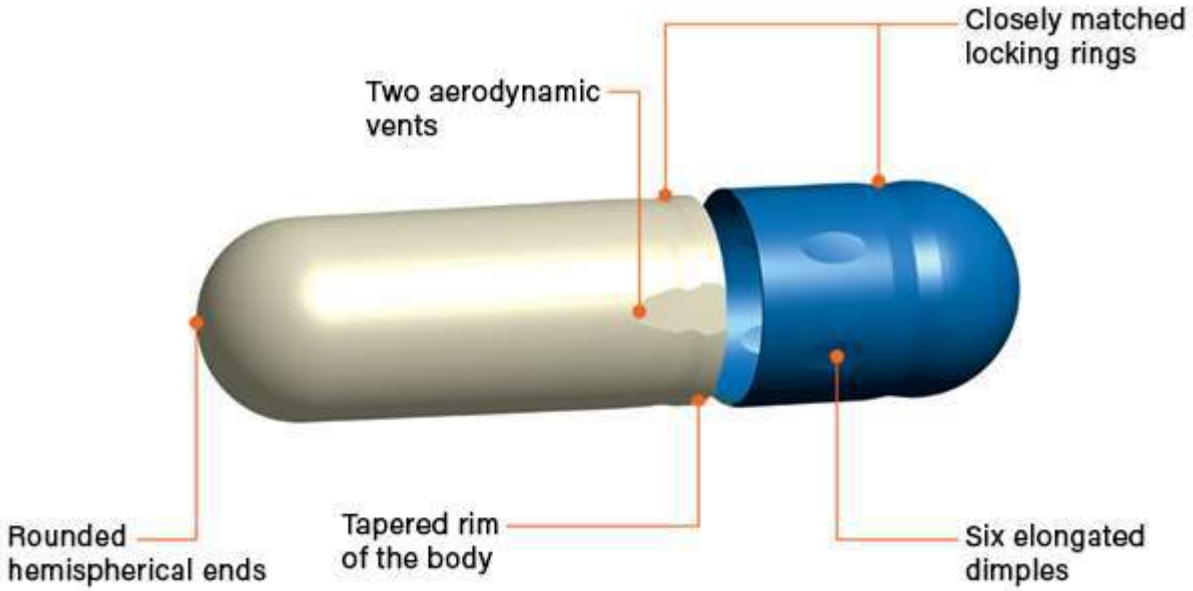
  1- Banding method: placing gelatin color bands at meeting point of caps and the bodies

  2- Moistening method: moistening the inner surface of caps with luke warm gelatin solution

  3- Spot welding method: spot welding the joints which leaves a ring like appearance at the point of sealing.

- 4- Thermal welding method: applying wetting solution. At the meeting point which causes lowering of melting point at applied area. Finally they are sealed at a temp. 40-45.

  5- By using coni-snap capsules: grooves help to lock the caps with the bodies.



SOFT GELATIN CAPSULE

- **Soft gelatin** capsules (also known as softgels) are made from a relatively more flexible, plasticized gelatin film than hard gelatin capsules.
- The softgel capsule shell consists of gelatin, water and a plasticizer. The shell may be transparent or opaque and can be coloured and flavoured if desired.
- Preservatives are not normally required owing to the low water activity in the finished product.
- The softgel can be coated with enteric-resistant or delayed-release coating materials. Although virtually any shape of softgel can be made, oval or oblong shapes are usually selected for oral administration

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

- Orally administered softgels: containing solutions or suspensions that release their contents in the stomach in an easy-to-swallow, convenient unit dose form.
- Chewable softgels: where a highly flavoured shell is chewed to release the drug liquid fill matrix. The drug(s) may be present in both the shell and the fill matrix.
- Suckable softgels: which consist of a gelatin shell containing the flavoured medicament to be sucked and a liquid matrix or just air inside the capsule.
- Twist-off softgels: which are designed with a tag to be twisted or snipped off, thereby allowing access to the fill material. This type of softgel can be used for unit dosing of topical medication, inhalations or oral dosing of a paediatric product

- Meltable softgels: designed for use as pessaries or suppositories.

Fig. 34.2 • Swallowable softgel capsules.

Fig. 34.3 • Twist-off softgel capsules.