UNIT 2: CAPSULES

Syllabus: Production and filling of hard gelatin capsules, Raw material for shell, finishing, quality control tests for capsules. Production and filling of soft gelatin capsules, quality control tests for soft gelatin capsules

DEFINITION

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin.

Advantages of capsule dosage forms

1. They obscure the taste and odour of unpleasant drugs.
2. They are attractive in appearance.
3. They are slippery when moist and, hence, easy to swallow with a draught of water.
4. If properly stored, the shells contain 12-15% of moisture which gives flexibility and, consequently very considerable resistance to mechanical stresses (cf. cachets).
5. Less adjuncts are necessary than tablets.
6. The contents are usually in fine powder which combined with adjuncts, provides rapid and uniform release of medicament in the GIT.
7. The shells can be opacified with TiO_2 or coloured to give protection from light.
8. The shells are physiologically inert and easily and quickly digested in the GIT.
9. Presentation of a drug in capsules, rather than in tablets, allows quicker submission of anew drug for clinical trials, because fewer development problems are involved. Also it is easier to vary the dose.

Disadvantages of capsule dosage forms

1. Capsules are not used for administering extremely soluble materials such as potassium chloride, potassium bromide, or ammonium chloride since sudden release of such compounds in the stomach could result in irritation.
2. Capsules should not be used for highly efflorescent or deliquescent materials.
   Efflorescent materials may cause the capsules to soften.
   Deliquescent materials may dry the capsule shell to excessive brittleness.

MATERIALS

Capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opaquing agents, plasticizers and preservatives.

To modify the solubility of the capsules (e.g. to impart enteric property) methyl cellulose, polyvinyl alcohols and denatured gelatin are used.

GELATIN

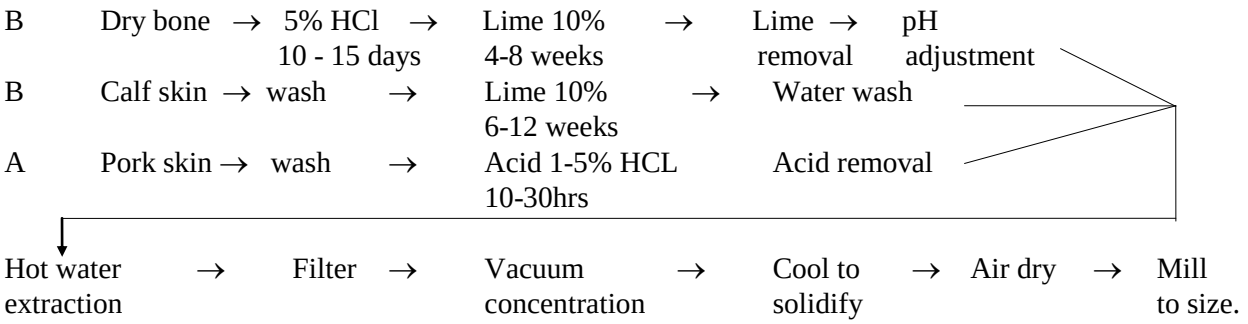
Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen (obtained from animal skin and bone).

Common sources of collagen are animal bones, hide portions, and frozen pork skin.

There are mainly two types of gelatin commercially available:

Type A: Gelatin is derived mainly from pork skin by acid treatment. This gelatin has an isoelectric point in the region of pH 9.

Type B: Gelatin is derived from bones and animal skins by alkaline processing (pH 4 – 5).



Blends of Gelatin A and Gelatin B are used.

- Bone gelatin produces a tough, firm film, but tends to be hazy and brittle.

- Pork skin gelatin contributes plasticity and clarity to the blend, hence bone gelatin and pork skin gelatin are generally used in blends.

Method of production of empty hard gelatin capsule shells

1. Hundred and fifty (150) pairs of stainless mold pins (on which capsule is formed) are dipped into a gelatin sol (melted gelatin) of carefully controlled viscosity to form the caps and bodies simultaneously.
2. 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.
3. The pins are moved through a series of controlled air drying kilns for the gradually and precontrolled removal of water.
4. 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.
5. 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 minutes.

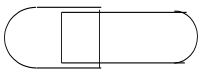
CAPSULE SHAPE

1. Simple telescoping hard gelatin capsules

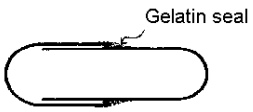
Body moves easily inside the cap

Disadvantages

(a) Body can come out of the cap easily spilling over the powder inside.
(b) In high speed capsule filling machines capsules may split and/or denting of the capsule shell may occur.

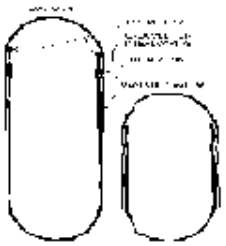


2. Gelatin seal fuses the two capsule halves to create a one-piece capsule that is tamper proof.



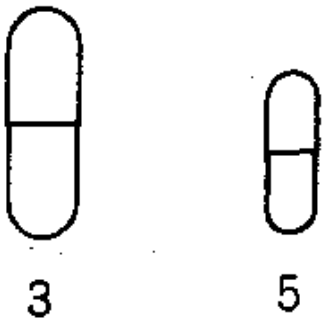
3. In the body:-

(a) Tapered rim is provided to prevent splitting / denting.
(b) Grooves which interlock the two halves together once the capsule has been filled.
(c) Indentations to prevent premature opening.



CAPSULE SIZE

Empty gelatin capsules are manufactured in various sizes, varying in length, in diameter, and capacity.
Their capacities vary with the bulk-density of the contents and the pressure applied during filling.
For human use, empty capsules ranging in size from 000, the largest, to 5, the smallest are commercially available.



Capsule No.	000	00	0	1	2	3	4	5
Approx. vol (ml)	1.50	0.90	0.75	0.55	0.40	0.30	0.25	0.15

CAPSULE FILLING EQUIPMENT

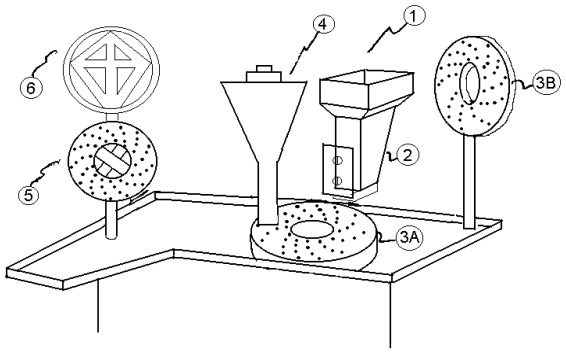
There are several equipment available in the market but they may be classified into two classes depending on the mode of operation.

- **Lily**, Parke-Davis, Höfliger and Karg, Osaka and Perry
- **Zanasi**, Macofar, Farmatic and mG2 equipment

LILY TYPE CAPSULE FILLING EQUIPMENT

Number of operators required = 1

Number of capsule output = 200,000 capsules / day



(a) The empty capsules are fed from the storage hopper (1) and through the rectifying unit (2), into the two-piece filling ring (3A and 3B). Rectification is based on dimensional differences between the outside diameters of the cap and body portions of the capsule.

(b) As the ring (3A and 3B) is rotated, a vacuum is applied on its underside. The vacuum sucks the bodies into the lower half of the ring, while the caps are retained in the upper portion. The two pieces of the ring are separated, and the cap-containing portion is placed aside.

(c) The body containing portion of the ring is placed on a variable speed turntable and is mechanically rotated under the powder hopper (4), which contains an auger for the forced delivery of the powder.

(d) After one (or more) complete rotations of the rings, the powder hopper (4) is removed, and the two segments of the ring (3A and 3B) are rejoined.

(e) The intact ring is positioned in front of the peg ring (5) and the closing plate (6) is pivoted to a positioned approximately 180^0 from the position showed in the figure. Pneumatic pressure is applied to the peg ring (5), which forces the caps in position.

(f) After opening the closing plate 96) the capsules are ejected through the portion of the ring by giving slight hand pressure against the peg ring.

(g) The filled capsules are collected through the chute (7) into a collection chamber.

- Highest turntable speed: minimum total fill weights
  maximum weight variation
- Lowest turntable speed: maximum total fill weights
  minimum weight variation

ZANASI CAPSULE FILLING MACHINE

No. of operators required = 0 (automatic)

No. of capsules output = 4000 to 150,000 capsules / hr.

In this type of equipment the empty capsule shells come down from hopper through individual tubes and rectified. The capsule shells are seated in a holder with the body downward. Vacuum assists its placement.

Another vacuum is applied over the top of the holder to separate the cap from the body of the capsule.

The cap containing half is moved aside. The lower part of the holder is exposed for filling.

The powder is continuously mixed within the powder hopper and is maintained at a constant level prior to change.

A set of volumetric dosing nozzles, each of which picks up the product from the constant level container, first compressing and then ejecting the powder into the capsule bodies.

The cap holder half is repositioned over the block and closing is accompanied by both upper and lower closing pins.

Ejection is accomplished by compressed air.

PREPARATION OF FILLED HARD GELATIN CAPSULES

The preparation of filled hard gelatin capsules may be divided into the following steps.

1. Developing and preparing the formulation and selecting the size of the capsule.
2. Filling the capsules shells.
3. Cleaning and polishing the filled capsules.

CAPSULE FORMULATION

In developing a capsule formulation, the goal is to prepare a formulation that results in accurate dosage, good bioavailability characteristics, and ease of capsule filling during production.

(a) To achieve uniform drug distribution throughout the powder mix the density and particle size of the drug and excipients should be similar.

If required the particle size may be reduced by milling.

Then the drug and excipients are blended thoroughly to get a uniform powder mix.

(b) The powder mix must provide the type of flow characteristics required by the equipment.

- In case of **Lily** type equipment powder must be *free flowing* e.g. with acetyl salicylic acid flowable *corn starch* is used.
- In case of **Zanasi** type equipment powder must have sufficient cohesiveness to retain its slug form during delivery to the capsules. e.g. with acetyl salicylic acid compactible excipients such microcrystalline cellulose are required.
- Lubricant such as, magnesium stearate can be used in Lily type and binders like mineral oil can be used in Zanasi type capsule filling equipments.

(c) **Selection of capsule size.**

(i) When the dose of the drug is large and the diluent is not required or negligible in quantity, the size may be selected after the development and preparation of the formulation.

(ii) When the capsule is meant for young or elderly patients the capsule size (smaller size) is selected first and then formulation is prepared. If required the dose may be divided into two capsules.

(iii) A properly filled capsule should have its body filled with the drug mixture and its cap fully extended down the body – a capsule size should be selected to meet this requirement.

FILLING THE CAPSULE SHELLS

(a) **Manual punch method**

For filling a small number of capsules in a dispensary pharmacists generally use punch method.

- Precise number of empty hard gelatin capsule shells are taken.
- The powder is taken on a clean sheet of paper or glass or porcelain plate. With a spatula a cake is formed with the powder having a height of approximately 1/4 to 1/3 the length of the capsule body.
- Then the empty capsule body is held between thumb and forefinger and "punched" vertically into the powder cake repeatedly until filled. The capsule bodies are capped.
- After capping the capsules are weighed to ensure accurate filling.

(b) Filling can be done by hand-operated capsule filling machine, Lily and Zanasi type capsule filling machines. Lily is semi-automatic and Zanasi is fully automatic.

[For details see the equipment - how they are filled]

CAPSULE SEALING

To make the capsules "tamper evident" (previously the term was "tamper resistant") two types of sealing processes are there

(i) *Banding*: The two capsule parts are sealed with a gelatin or polymer band at the seam of the cap and body.

(ii) The contact areas of the cap and body are wetted with a mixture of water and ethanol and then thermally bonded at 40 to 45^0C.

Capsule sealing equipment may be linked with capsule filling equipment to maintain production levels of upto 150,000 capsules per hour per unit.

CLEANING AND POLISHING

After filling some powder formulation may adhere to the outside of the capsules. This powder

- may be bitter or unpalatable,
- may reduce the appearance of the capsule.

Methods of cleaning

1. *Pan polishing*

The Accela-Cota tablet coating pan may be used to clean and polish capsules. A *polyurethane* or *cheese cloth* liner is placed in the pan, and the liner is used to trap the removed dust as well as to impart a gloss to the capsules.

2. *Cloth dusting*

In this method, the bulk filled capsules are rubbed with a cloth that may not be impregnated with an inert oil. Though it is a hand operation but by this method

(a) large volume of capsules can be polished,
(b) powders too resistant to remove by other methods can be removed easily by this method.
(c) it imparts a somewhat improved gloss to the capsules.

3. *Brushing*

In this procedure, capsules are fed under rotating soft brushes, which serve to remove the dust from the capsule shell. This operation is accompanied by a vacuum for dust removal.

e.g. ROTOSORT– it removes loose powder,
removes unfilled joined capsules
removes capsules with loose caps
Erweka KEA – dedusting and polishing
Scidenader PM60 – for cleaning and polishing

SOFT GELATIN CAPSULES

Advantages of soft gelatin capsules:

(i) Soft gelatin capsules are useful when it is desirable to seal the medication within the capsule.
(ii) The capsules are especially important to contain liquid drugs or drug solutions.
(iii) Also, volatile drug substances or drug materials especially susceptible to deterioration in the presence of air may be better suited to a soft gelatin capsule than hard gelatin capsules.
(iv) Soft gelatin capsules are elegant and are easily swallowed by the patients.

Capsule sizes and shapes

Shape	**Diagram**	**Size range (number represents the nominal capacity in minims (1 cc = 16.23 minim)**
Round		1,2,3,4,5,6,7,9,28,40,90,
		40T,80T
Oval		1,2,3,4,5,6,7.5,10,.12,16,20,30,40,60,80,85,110.
Oblong		3,4,5,6,8,9.5,11,14,16,20,90,360
Tube		55,65,90,160,250,320,480

MATERIALS

The capsule shell is basically composed of gelatin, a plasticizer and water. It may contain additional ingredients such as preservatives, coloring and opacifying agents, flavours, sugars, acids and medicaments to achieve desired effects.

GELATIN

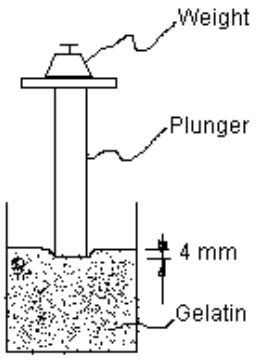
The gelatin should be of USP grade and it should have some additional specifications, namely, bloom strength, viscosity and iron content of the gelatin used.

Bloom or gel strength

It is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin.

Determination

6 2/3 % gelatin gel kept at 10^0C for 17 hours
A plastic plunger having diameter 0.5 inch.
Bloom strength = the weight (in gram) required to move the plastic plunger in the gelatin mass upto 4 mm.



- Normally for soft-gelatin capsules the bloom strength of gelatin required ranges from 150 to 250 g.

In general with all the other factors being equal, the higher the Bloom strength of the gelatin used, the more physically stable is the capsule shell.

- Cost is, in general, proportional to Bloom strength; hence, higher Bloom strength gelatins are only used when necessary to improve the physical stability of the product or large capsules (over 50 minims).

Viscosity of gelatin

Viscosity of a 6 2/3 % gelatin in water solution at 60^0C is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film.
General range of viscosity 25 to 45 millipoise, it may be within narrow range 38 ± 2 millipoise.

Iron content

Iron is always present in new gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture.
Limit: Gelatin used for soft gelatin capsules should not contain more than 15 ppm of iron.
Disadvantages:
(i) Iron may react with the certified dyes.
(ii) It may react with organic compounds to produce color (e.g. with phenolic compounds).

PLASTICISERS
Very few plasticisers are used for soft gelatin capsules
(i) Glycerin USP
(ii) Sorbitol USP or
(iii) a combination of glycerin and sorbitol
The ration by weight of dry plasticiser : dry gelatin determines the 'hardness' of the gelatin shell.
Typical shell hardness and their uses.

Hardness	**Ratio of Dry glycerin / Dry gelatin**	**Usage**
Hard	0.4 / 1	Oral, oil-based, or shell-softening products and those destined primarily for hot humid areas.
Medium	0.6 / 1	Oral, tube, vaginal Oil-base, water-miscible-base, or shell hardening products and those destined for temperate areas (hot & humid areas)
Soft	0.8 / 1	Tube, vaginal Water-miscible base or shell hardening products and those destined primarily for cold, dry areas.

Additional components of the gelatin mass

Ingredients	Concentration	Purpose
Category-I		
Methyl paraben ┐ Propyl paraben ┘ (4 : 1)	0.2 %	Preservative
FD&C and D&C water-soluble dyes, certified lakes, pigments, vegetable colours	q.s.	Colorants
Titanium di-oxide	0.2 to 1.2 %	Opacifier
Ethyl vanillin	0.1 %	Flavor
Essential oils	2 %	Flavor
Category-II		
Sugar (sucrose)	to 5 %	To produce chewable shell and taste
Fumaric acid	to 1 %	Aids solubility reduces aldehydic tanning of gelatin

NATURE OF THE CAPSULE CONTENT

Soft gelatin capsules can be used to dispense a variety of liquids,
solids,
combination of miscible liquids,
suspension of solids in liquids.

Selection of capsule size

The maximum capsules size and shape for convenient oral use in humans is the
20 minims oblong,
16 minims oval or
9 minims round

Types of liquids for encapsulation in soft gelatin capsules

1. Water, ethanol, emulsion – these are water miscible or volatile components and they cannot be included as major constituents of capsule since they can migrate into the hydrophilic gelatin shell and volatile from the surface.
2. Gelatin plasticizers like glycerin, propylene glycol cannot be major constituents of capsules owing to their softening effect on the gelatin shell.
3. Upto 10% glycerin and / or propylene glycol can be used as co-solvents with PEG or other liquids that have a shell-hardening effect when capsulated alone.

Most widely used liquids for human comsumptions are

- Oil active ingredients e.g. clofibrate
- Vegetable oils e.g. soybean oil
- Mineral oil, non-ionic surfactants e.g. polysorbate 80 and PEG (400 and 600) either alone or in combination
- Fish oils in vitamin capsules.

Other conditions for manufacturing soft gelatin capsules

1. The suspension products must be homogeneous, air free and preferably should flow by gravity at room temperature but not a temperature above 35^0C because the sealing temperature of gelatin films is usually 37 to 40^0C.
2. pH should be in between 2.5 and 7.5, since preparations that are more acidic can cause hydrolysis and leakage of the gelatin shell, and preparations those are more alkaline can tan the gelatin and thus affect the solubility of the shell.

CAPSULE MANUFACTURING

Plate process: It is the oldest process, contains sets of plates containing die packets.

Rotary die process

Reciprocating die process

Accogel machine is unique in that it is the only equipment that accurately fills **powdered dry solids** into soft gelatin capsules.

PROCESS

Gelatin preparation department

(i) Weighing of gelatin
Weighing of other liquids → chilled at 7^0C → Mixed in Pony mixer

(ii) The resultant fluffy mixture transferred to melting tanks and melted under vacuum at 93^0C

(iii) A sample of the resulting fluid mass is visually compared with a color standard, and additional colorants are added if required.

(iv) The mass is then maintained at 57 to 60^0C before and during capsulation process.

Material preparation department

(i) *Blending* → milling or homogenization

Equipments: Homoloid mill
Stone mill
Hopper mill
Urschel comitrol

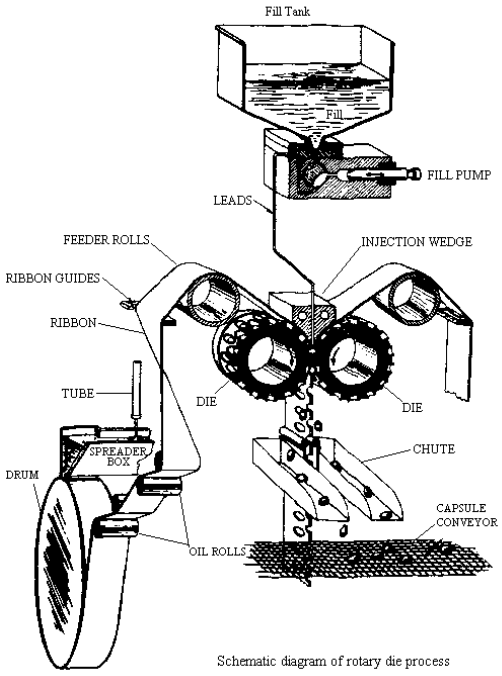
(ii) *Deaeration* →all mixtures are subjected to deaeration by
to achieve uniform capsule fill weight
and it reduces oxidation of the product.

Most liquids and suspensions may be deaerated by means of equipment designed to expose thin layers of the material continuously to a vacuum (29.5 mm Hg).

(iii) After deaeration the volatile ingredients are added and blended.

Material filling by rotary die process

- The gelatin mass is fed by gravity to a metering device (spreader box), which control the flow of the mass onto air cooled (13 to 14^0C) rotating drums. Gelatin ribbons of controlled thickness are formed. The wet film thickness may vary from 0.022 to 0.045 inch.
- The ribbons are fed through mineral oil lubricating bath, over guide rolls, and then down between the wedge and the die rolls.
- The materials to be encapsulated flows by gravity into a positive displacement pump. The pump accurately meters the material through the leads and wedges and into the gelatin ribbons between the die rolls. The bottom of the wedge contains small orifices lined up with the die pockets of the die rolls.
- The capsule is about half sealed when the pressure of the pumped material forces the gelatin into the die pockets, where the capsules are simultaneously filled, shaped, hermetically sealed, and cut from the gelatin ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating (37 to 40^0C) of the ribbons by the wedge.



Schematic diagram of rotary die process

- Immediately after the manufacture, the capsules are automatically conveyed through a naphtha wash unit to remove the mineral lubricating oil.
- The washed capsules may be automatically subjected to a preliminary infrared drying step which removes 60 to 70% of the water that is to be lost, or may be manually spread directly on trays. All the capsules are allowed to come to equilibrium with forced air conditions of 20 to 30 % relative humidity at 21 to 24^0C.