

## CAPSULES

Capsules are solid dosage forms in which the drug or a mixture of drugs with or without excipients is enclosed in Hard Gelatin Capsule Shells, in soft, soluble shells of gelatin, or in hard or soft shells of any other suitable material, of various shapes and capacities. They usually contain a single dose of active ingredient(s) and are intended for oral administration.

### ❖ Advantages:

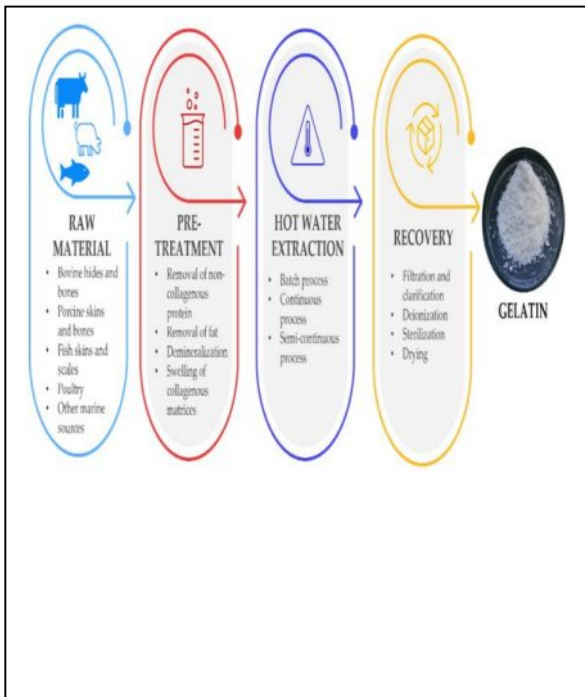
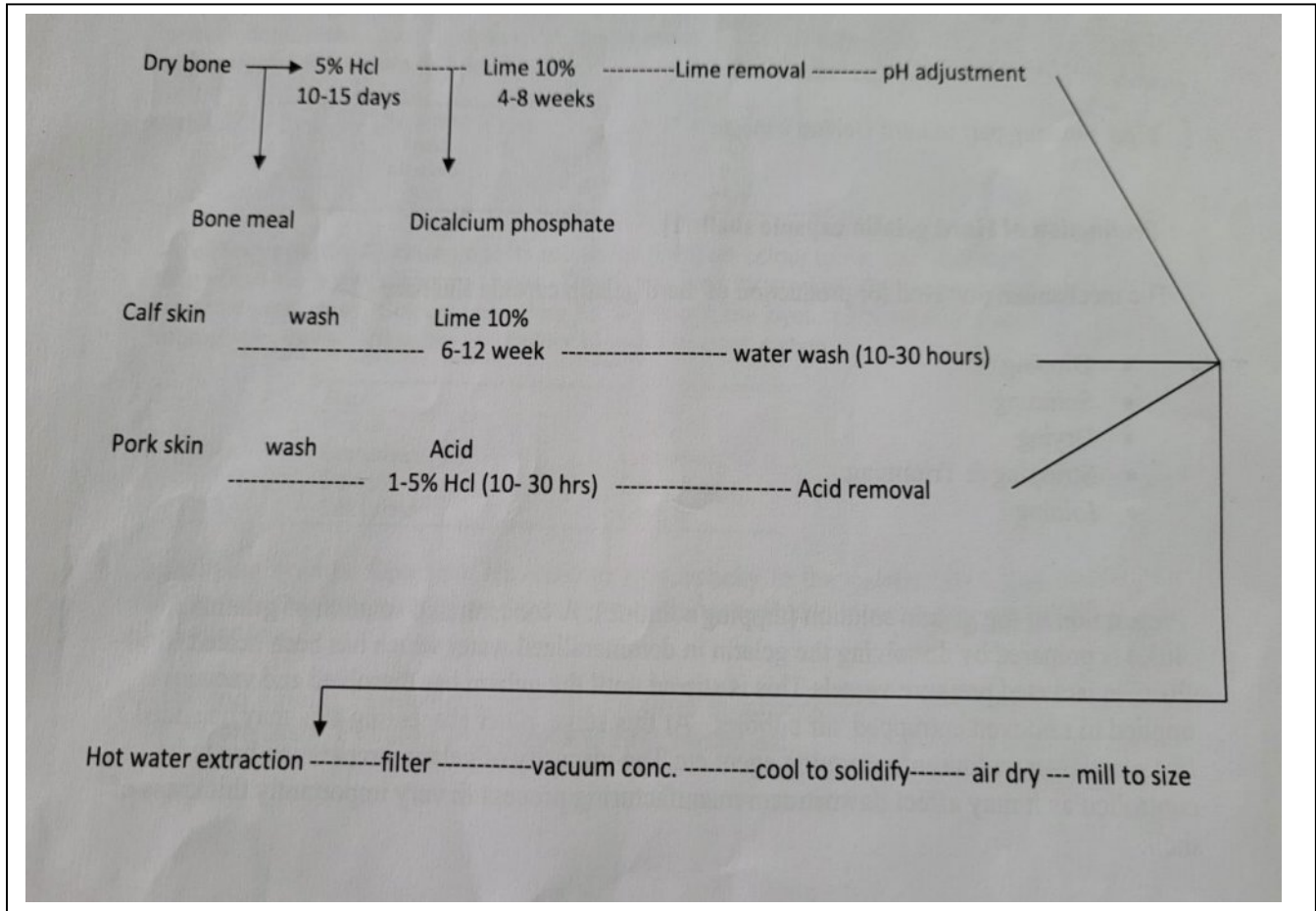
- The drugs having unpleasant odour and taste can be administered by enclosing them in a tasteless shell.
- They are smooth, become very slippery when moist and can be easily swallowed.
- They are economical
- They are easy to handle and carry.
- The capsules release the medicament as and when desired in gastro-intestinal tract.
- Capsules are made from gelatin and hence they are therapeutically inert.
- Capsules have elegant appearance so that it enhance patient acceptance.
- The drug in the form of solid, liquid & viscous form can be encapsulated in capsule shell.
- Capsule formulation provide better stability of drug as compare to uncoated tablet & liquid dosage form

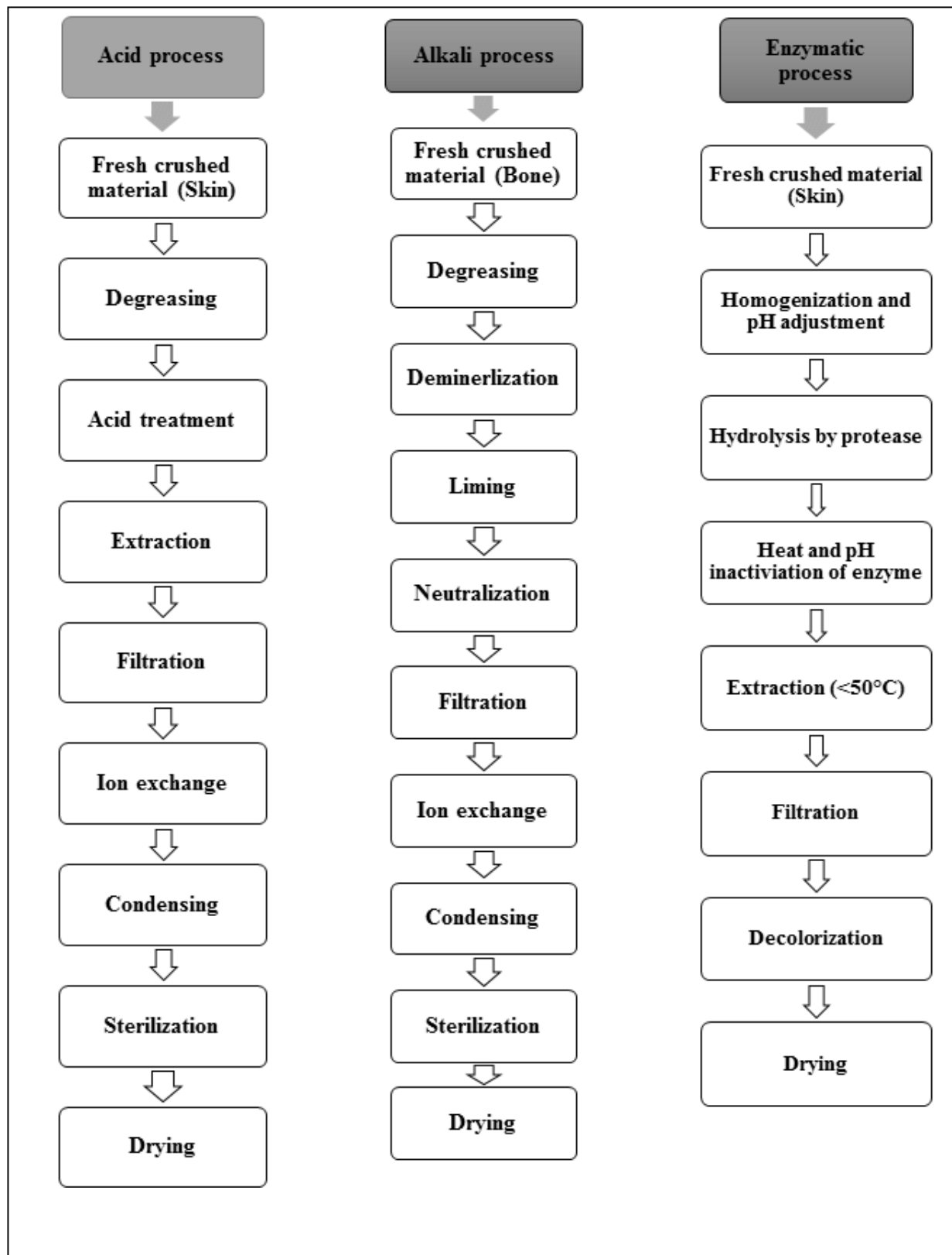
### ❖ Disadvantages:

- Capsules are not usually used for administration of extremely soluble materials such as potassium chloride, potassium bromide etc. since there is sudden release of such compound in stomach & causes irritation.
- Capsules should not be used for highly efflorescent material as material may cause the capsule to soften by losing water molecule to shell.
- Capsules should not be used for highly deliquescent powder as powder have tendency to absorb moisture from capsule shell & make it brittle.
- The capsule shells can absorb water from the environment and develop problems with drug stability and capsule shell can become tacky
- it is unsuitable for use with liquid formulations.

- ✓ The term capsule is derived from the Latin word capsula, meaning a small container.
- ✓ Capsule occupy a significant position in the drug development.
- ✓ They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms.
- ✓ Gelatin has the property of disintegrating when it comes in contact with water, thereby releasing the medicament completely.
- ✓ Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells.
- ✓ 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.
- ✓ Gelatin as a component of capsule shell :
  - As the gelatin is the main source for production of capsule shell,we need to understand its source & process of manufacture.
  - Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen as it never occurs naturally.
  - The physical & chemical properties of gelatin are the function of parent collagen, method of extraction,pH value ,thermal degradation & electrolyte content.
  - The main source of collagen which are required for production of gelatin are animal bones and frozen pork skin.
  - Generally two type of gelatins are used to manufacture capsule shell.
  - Type A Gelatin: it is derived from the acid treated precursor and exhibit isoelectric point in region of pH 9.
  - Type B Gelatin: it is derived from an alkali treated precursor & exhibit isoelectric point in region of pH 4

[The isoelectric point is the pH at which a molecule carries no net electrical charge or is electrically neutral]





The process of manufacturing gelatin

Physicochemical properties of gelatin are expressed in

- Bloom strength
- Viscosity
- Iron content

**Bloom 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 gelatin.

It is determined by measuring the weight in grams required to move a plastic plunger 4mm into a gelatin gel that has been held at 10 ° c for 17 hrs.

Bloom may range between 150 to 250 g

**Viscosity**

25-45 mill poise

**Iron content**

Should not more than 15 ppm of iron

**Capsule types:** there exist various capsule types in scholarly articles,

They are; the soft gelatin and hard gelatin capsules, Hydroxypropylmethyl cellulose (HPMC) capsules, polyvinyl alcohol (PVA) capsules, starch capsules. These can be summarized as the gelatinous and non-gelatinous capsules.

**Gelatin capsules** this category of capsules is basically made from gelatin; they can either be soft or hard gelatin capsules.

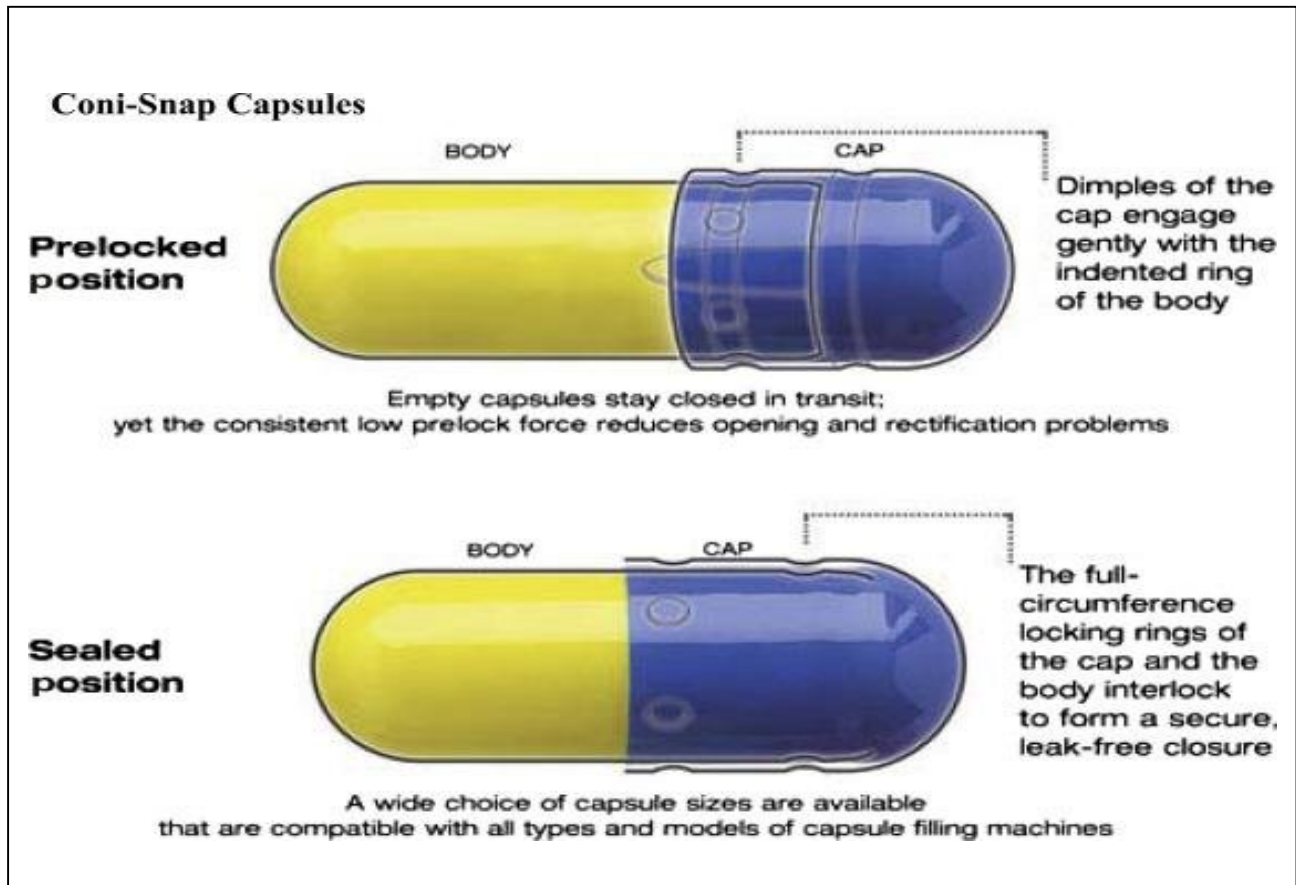
## Hard Gelatin capsule [HGC]:

Hard Gelatin capsule: it is the capsule in which medicament(s) with or without excipient in the dry powder form are enclosed in a shell which consist of cap & body.

Hard gelatin capsules General aspect:

- The majority of capsule products is made of hard gelatin capsules.
- Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits tightly over the open end of the capsule body.
- The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colorless, and essentially tasteless.
- Hard gelatin capsule shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation.
- During the capsule filling unit operation, the body is filled with the drug substances and the shell is closed by bringing the body and the cap together.





Basic component of hard gelatin capsules:

- Gelatin
- Plasticizer
- Colourants
- Opacifying agents
- Preservatives

Gelatin

- Gelatin is by far the most common and most well-known material used to produce hard capsule shells.
- It is a generic term for a mixture of purified protein fractions obtained from irreversible hydrolytic extraction of collagen obtained from the skin, white connective tissue, and bones of animals.

### Plasticizer

- Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerin and polyhydric alcohol.
- Water is also a good plasticizer and is naturally present in the gelatin.

### Colourants

- Most frequently, hard gelatin capsules are colored to enhance the aesthetic properties and also to act as a means of identifying the product.
- Colorants used must meet the regulatory requirements of those countries where the product will be sold.
- Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.

### Opacifying agents

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

### Preservatives

- Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture.
- Manufacturers operating their plants to Good Manufacturing Practice (GMP) guidelines no longer use them.
- In the finished 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.

A concentrated solution of gelatin (35- 40%) is prepared by dissolving the gelatin in demineralized water which has been heated to 60– 70°C in jacketed pressure vessels. This is stirred until the gelatin has dissolved and vacuum is applied to remove entrapped air bubbles. At this stage, other processing aids may be added like plasticizer, colourant, opaquing agent etc. The viscosity of gelatin preparation has to be controlled.



## Production of Hard gelatin capsule shell:

The mechanism involved for production of hard gelatin capsule shell are

- ✓ Dipping
- ✓ Spinning
- ✓ Drying
- ✓ Stripping & Trimming
- ✓ Joining

### 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.

### Spinning of the dip-coated pins:

After adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is rotated more times to evenly distribute the gelatin solution around the pins, as uniform gelatin distribution being critical for correct and precise capsule wall thickness.

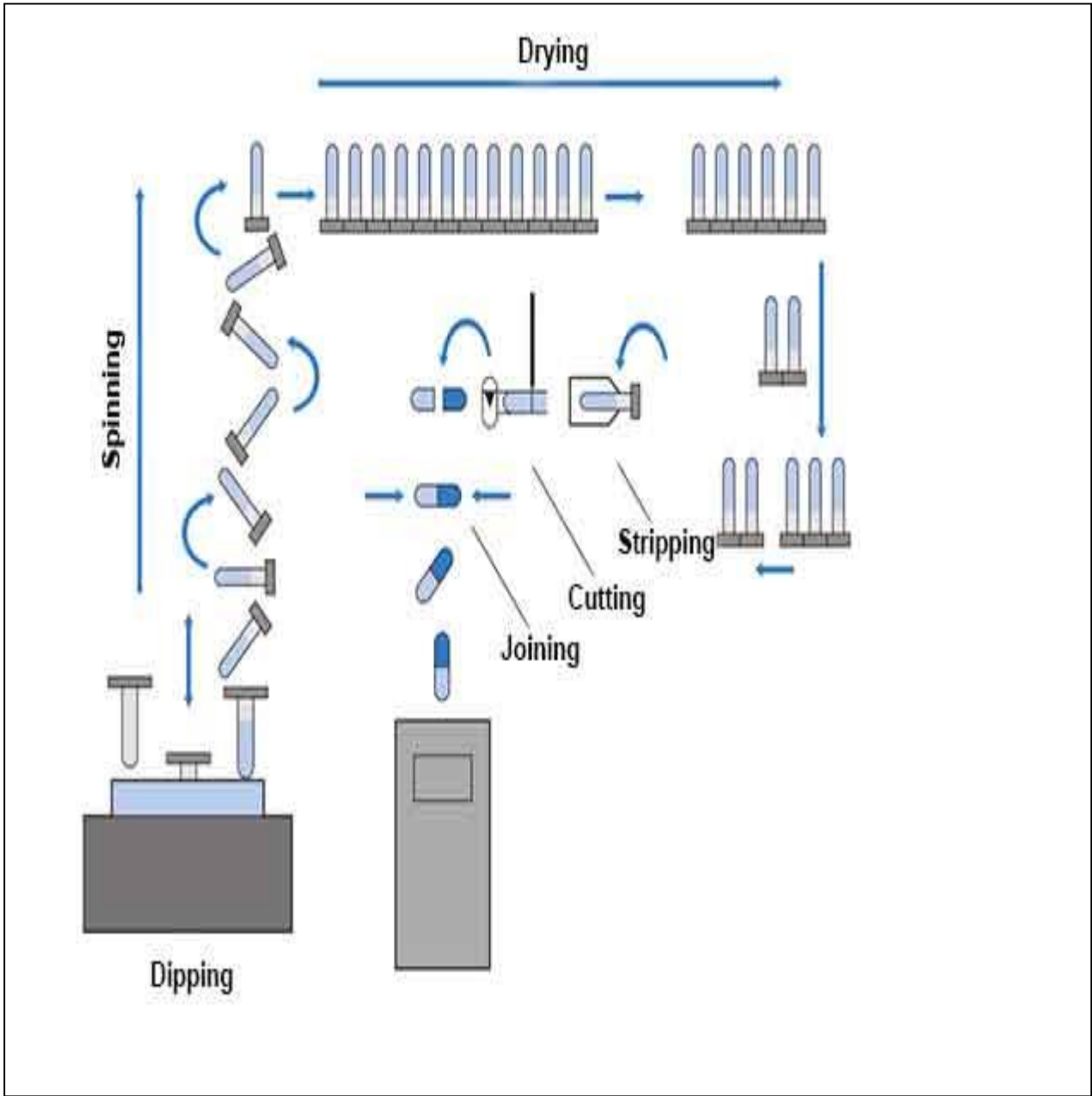
### Drying of the gelatin-coated pins:

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.

**Stripping & Trimming:** After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length

### 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



Size	Volume (ml)	Locked length (mm)	External diameter (mm)
5	0.13	11.1	4.91
4	0.20	14.3	5.31
3	0.27	15.9	5.82
2	0.37	18	6.35
1	0.48	19.4	6.91
0	0.67	21.7	7.65
0E	0.7	23.1	7.65
00	0.95	23.3	8.53
000	1.36	26.14	9.91
13	3.2	30	15.3
12	5	40.5	15.3
12el	7.5	57	15.5
11	10	47.5	20.9
10	18	64	23.4
7	24	78	23.4
Su07	28	88.5	23.4

Filling of Hard Gelatin capsule:

The several type of filling machine in use in the pharmaceutical industry have in common the following operation.

- ✚ Rectification
- ✚ Separation of cap from bodies:
- ✚ Dosing of fill material
- ✚ Replacement of cap and ejection of filled capsule

#### Rectification:

- The empty capsule are oriented so that all point the same direction, i.e body end downward.
- The capsule pass one at a time through a channel just wide enough to provide a frictional grip at cap end.
- Capsule will always be aligned body end downwards regardless of which end entered the channel first.

#### Separation of cap from bodies:

- This process depend on the difference in diameter between the cap and body.
- The rectified capsule are delivered body end first into the upper portion of split brushing .
- A vacuum applied below pull the bodies down into the lower portion.
- The diameter of cap is too large to allow them to bodies into the lower portion

#### Dosing of fill material:

- Various method like
  - Auger principle
  - Vibratory fill principle
  - piston- Tamp principle are employed for filling 4

#### Replacement of cap and ejection of filled capsule:

- The cap & body bushing portion are rejoined.
- Pins are used to push the filled bodies up into the caps for closure and to push the closed capsule out of the bushing.
- Compressed air also used to eject the capsules.

Filling principles:

**a) Auger fill principle:**

The empty hard gelatin capsule are taken from hopper to the rectifying unit.

The rectifier descend the capsule such that caps are turned up and bodies are down.

When vacuum is applied capsule from rectifying unit are placed one by one in the filling ring kept on rotating mode.

The ring consists of upper and lower ring having cavities for for placing capsule.

When all the cavities of ring filled, the upper ring is lifted which causes separation of bodies from caps.

The lower ring is rotate with constant speed and the hopper containing powder is held over the ring.

The auger drive the powdered drug into the capsule bodies.

After bodies are completely filled, the hopper is set aside & rotating ring is stopped.

Now ring holding caps are placed over ring holding the bodies which are then joined together.



○ Eg: Perry Accofil machine

## b) Vibratory fill principle:

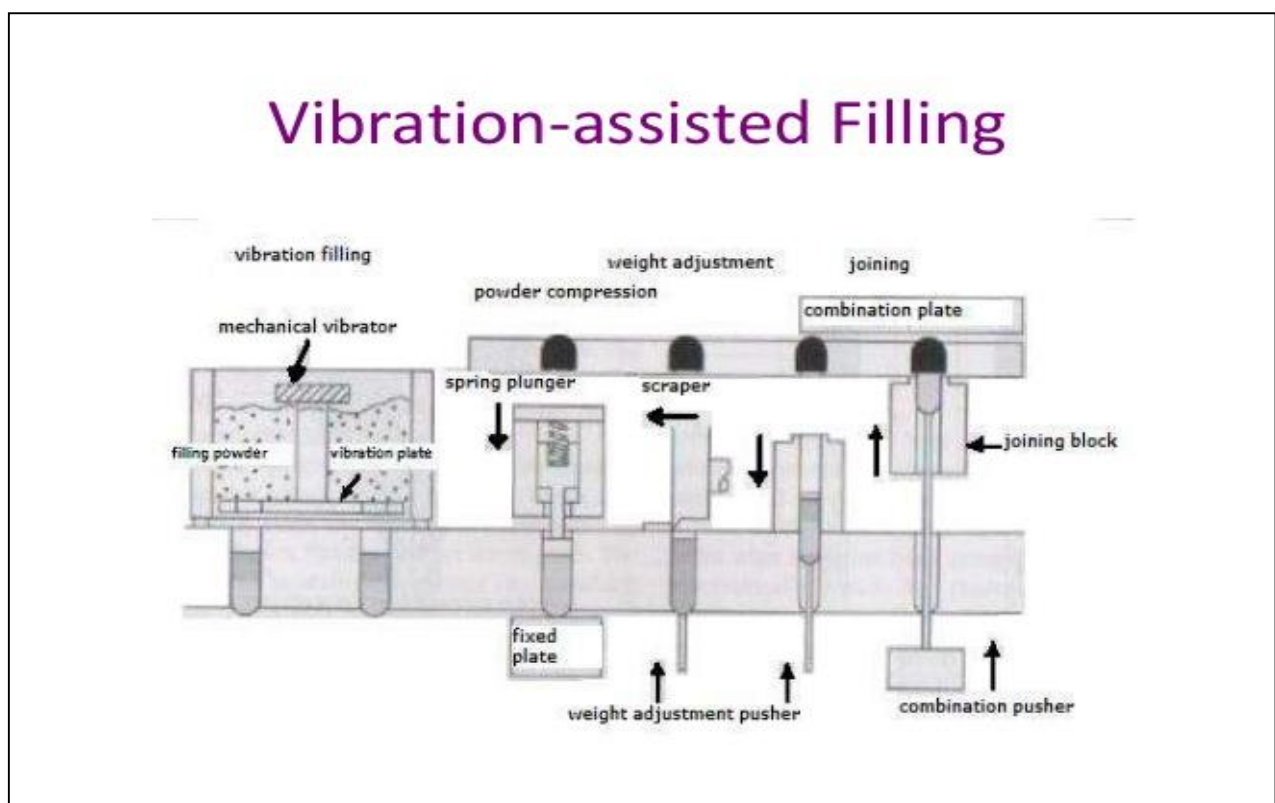
In this type the feed is placed in the feed hopper & capsule bodies are pass under it.

A perforated resin plate (connected to vibrator) is placed in feed hooper.

Due to vibration of resin plate the powder flows freely through the pores into the capsule bodies.

Pins are present below the capsule bodies for support.

Capsule bodies are filled when the pins are pulled down. but when there is overfilling, The capsule bodies are pushed up to reach the level of disc plate and excess the powder is forced out by scrapping



Eg: Osaka model R-180

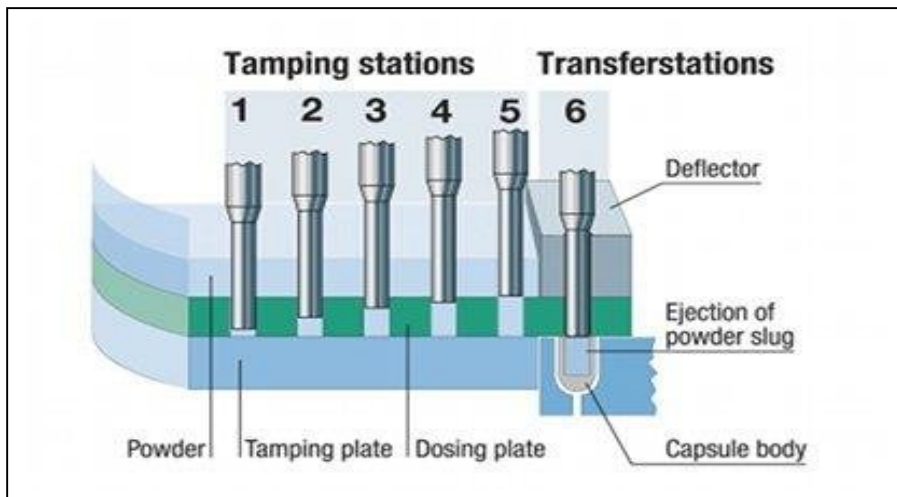
### C) Piston-tamp principle:

Automatic capsule filling machines work on piston-Tamp principle by using piston or Tamping pins.

The piston tamps alter the shape of powder by compressing the powder to form plugs (slugs).

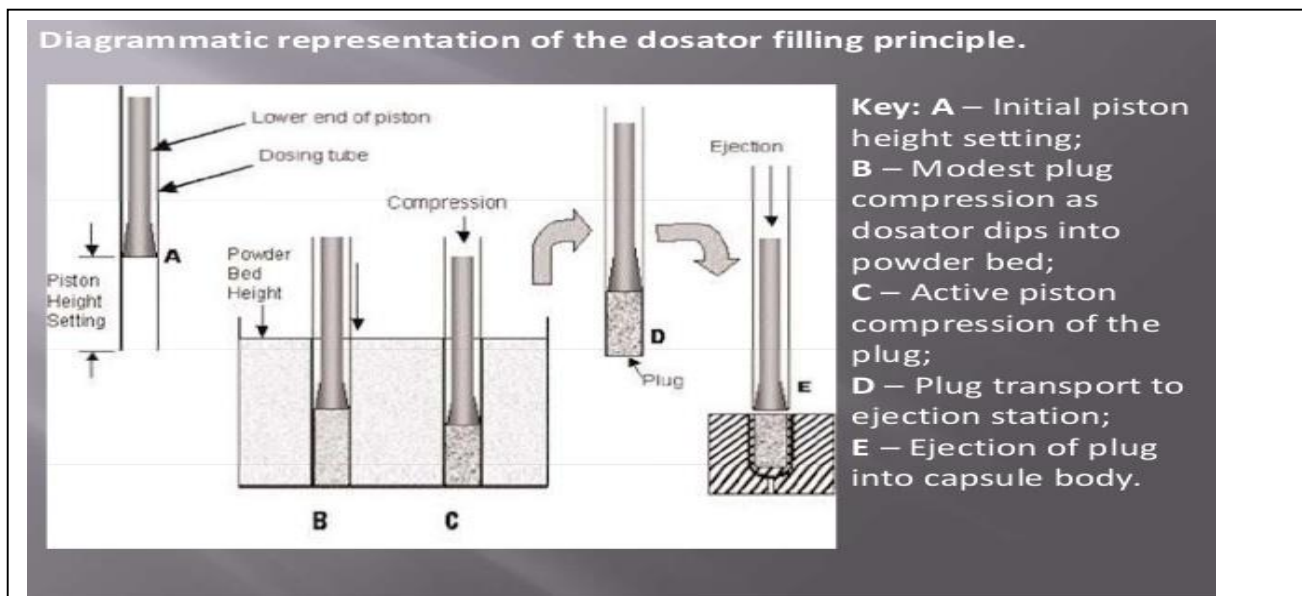
These plugs are transferred into empty capsule shell with the application of little pressure.

This piston pump principle can be explained by two type of machine



### Dosing disc machines

Eg: HOFLIGER-KARG GFK MODEL, SHIONOGI QUALICAPS F-80



### Dosator machines

Eg: ZANASI, PEDINI, MATIC, MG2

#### **d) Vacuum fill principle:**

The machine consist of an open ended cylinder. The upper end of this cylinder is fitted with piston.

The lower end (open end) is placed in bulk powder. Vacuum is applied and the piston is moved upward by sucking the specific amount of powder, this result in filling of the cylinder, the powder is filled up to the piston height and the vacuum is held until the piston is positioned over empty capsule body. Now the vacuum and pressure in the form of compressed air is applied over the piston to transfer the powder into the capsule body.

#### **Capsule filling methods:**

1. Manual filling
2. Hand filling machine
3. Semi-automatic machine
4. Fully automatic capsule filling machine

##### **Manual filling method:**

This method is opted when number of capsule to be filled is less

Initially the ingredients to be filled are triturated & make is uniform mixing.then put it on clean paper

Now the required number of empty capsule are taken and caps are separated from body.

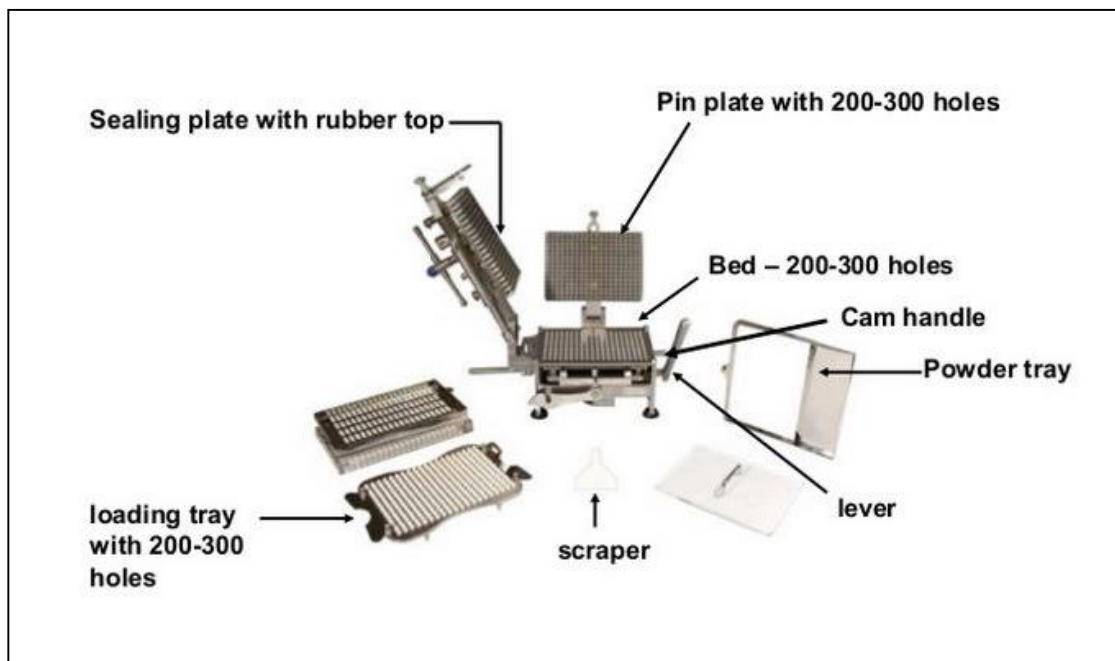
Then individually powder has to be filled with the help of spatula to the capsule body. Then cap has to be fitted ovet it with little pressure.

##### **Hand filling machine :**

- It consist of a bed having 200-300 hole, a loading tray having 200-300 holes, a powder tray, a pin plate having 200-300 pins, a sealing plate having a rubber top, a lever, a cam handle.
- The empty capsules are filled in the loading tray and it is palced over the bed. The cam handle is operated to separate the capsule caps from their bodies.
- The powder tray is placed in a proper position and filled with an accurate quantity of powder with scraper.



- The excess of the powder is collected on the platform of the powder tray. The pin plate is lowered and the filled powder is pressed by moving the pin downwards.
- After pressing the pin plate is raised and the remaining powder is filled into the bodies of the capsules.
- The powdered tray is removed after its complete filling. The cap holding tray is again placed in position.
- The plate with the rubber top is lowered and the lever is operated to lock the caps and bodies. The loading tray is then removed and filled capsules are collected.



Hand filling machine

Semi-automatic machine:

There are 3 stations in this semi-automatic capsule filling machine

- ✓ Orientation of capsule
- ✓ Powder filling
- ✓ Capsule closing

The functions of first station include:

1. Capsule feeding
2. Aligning
3. Insertion into bores of holding ring

4. Vacuum is used for separating capsule cap and body in first station.

5. After orientation of capsule, capsule cap can stay in upper holding ring and capsule body can stay in lower holding ring.

**Powder filling:** Separate the holding ring, put the lower (body) holding ring on the rotary table, pull the powder hopper over the lower (body) holding ring, then auger inside powder hopper starts to run and fill powder into the capsule body.

While lower holding ring turns one circle, push powder hopper to its original position.

**Capsule closing:**

- Put upper holding ring and lower holding ring together, then position intact holding ring in front of peg ring .closing plate is pivoted to a position approximately 180 degrees
- Pneumatic pressure is applied to peg ring which finally push capsules inside the bores of holding ring the finished capsules will be collected into the container.

**Fully automatic capsule filling machine:**

- Most automatic filling machines employs piston or tamping pin that lightly compress the powder into plugs, (sometimes referred as slugs) and eject the plugs into the empty capsule bodies.
- The compression forces are low, often range from 50-150N, upto 100 fold less than that employed in typical tablet compression.
- Often plugs are very soft compacts and not able to recover intact from filled capsule. There are two main type of these fillers: Dosator machine and dosing disc machine.
- The tamping pin type capsule filling process involves a number of stages. In this case, the machine has 5 stage tamping technology.
- This pan rotates continuously in a circular manner depending on the preset speed. Normally, as the dosing plate rotates below the powder bed, the filler material flows into each hole.
- The pins, which are in the tamping stations compress the powder to a controlled depth. That is, as the filler material flows into the first hole in the disc, tamping pin 1 compresses it to a predetermined depth.
- After this first step, the hole moves to the next stage where the powder again flows into the hole and tamping pin 2 compresses it to a predetermined depth.

- The force these tamping pins exert on the powder is just enough to compact it. That is, it may range from 50N to 150N.
- This process continues until the holes with the powder reaches the last tamping pin (no. 5), where the machine ejects a compacted powder through the dosing plate into the capsule.
- After filling the capsule shell, it moves to the next stage (sealing/covering the capsule). This is a continuous process and the production speed will depend on the preset machine conditions.

**Finishing of capsule:** in order to make capsule more elegant, they undergo the process of finishing, the commonly used step for producing finished capsule are as follows:

1. Cloth dusting: it is manual method in which small number of capsule are rubbed with a cloth or gauze which may or may not contain inert oil.
2. Polishing: special pan may be used for polishing the the filled capsule. these pan lined with cheese or polyurethane cloth which remove the dust or other powder adhere to capsule
3. Brushing: in this method capsule are projected under soft rotating brushes which remove the dust from capsule shell. This process is assisted under vacuum.

Sorting: This operation is needed to separate the imperfect & damaged capsule. although in large scale it done manually, some automatic equipment are available e.g-Rotosort.

Formulation of powder need to be fill capsule shell:

Ingredients type	purpose	Example
API	Produce therapeutic effect	Amoxycilin
Fillers	To increase bulk volume of formulation	Starch ,lactose
Lubricant	Reduce powder to metal adhesion	Magnesium stearate
Glidant	Improve powder flow	Colloidal silica
Surfactant	Increase the wetting of powder mass	SLS,sodium docusate
Super Disintegrant	Disruption of powder mass	Crospovidone,Croscarmellose sodium
Hydrophylic agent	Improve the wettability of poorly soluble drug	Methyl cellulose,hydroxyl ethyl cellulose

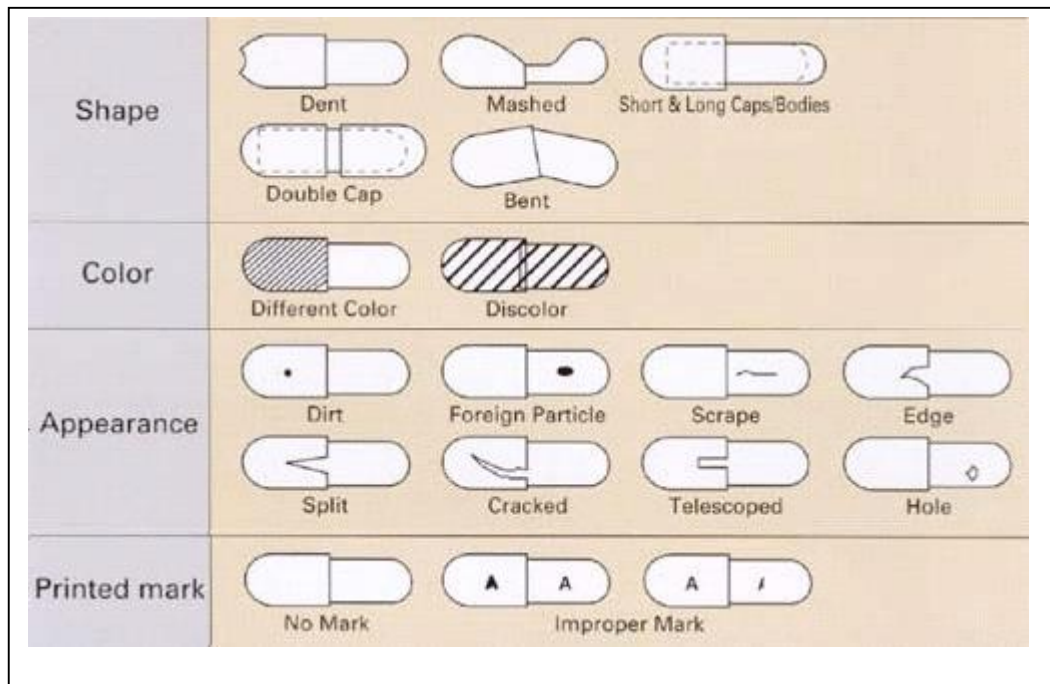
Special technique of formulation used in hard gelatin capsule:

1. Imprinting; is a convenient method by which company and/or product identification information can be placed upon each capsule. The imprinting operation is best performed on empty capsule although filled capsule can be printed.
2. Solubility: For special purpose capsule attempt to retard solubility in some manner.
  - a) Formalin treatment has been employed to modify the solubility of gelatin capsule. exposure to formalin vapor or treatment with aq formalin produce unpredictable decrease in solubility of the gelatin film. This result may be noted if product being filled contain aldehyde materials of aldehyde flavor.it is difficult to control degree of insolubilization.
  - b) Various coating have been used to provide similarity modified solubility character. These coating include salol, shellac, and cellulose acetate phthalate
3. Separation of incompatible material: it involving two phase fill in the capsule. One phase consist of either a soft capsule, a pill or suitably coated tablet that is filled into the capsule. In second phase a powder fill is added in usual manner. These changes include, at minimum the necessary changes in machine operation to allow material to be loaded at two point during filling cycle.
4. Filling of conventional two piece gelatin capsule with liquid & semisolid. the formulation used for filling are usually semisolid at ambient temperature, which are melted to allow filling or they are thixotropic formulation in which the shear developed in filling allows pumping but whose high viscosity when shear is absent prevent leakage after filling.

**Several defects that include;**

- Shell surfaces not smooth
- Opacify not proper
- Empty capsules after the filling stage
- The foreign matter inside the capsules
- Capsules fitting not uniform during filling
- Capsules are not of the specified type
- Color variation and non-uniformity of appearance

- Surface spots and embedded particles on the capsules
- Capsule may have cracks, breaks, pinholes or splits, losing its integrity.



In process Quality control (IPQC) for capsules :

1. Mfg of Gelatin Shell.
  2. Drying of shells in controlled humidity.
  3. Mfg of granules.
  4. Filling of Shells.
  5. Packaging & Labeling.
- IPQC Checks During Gelatin Shell Manufacturing:
    - % purity of gelatin
    - Viscosity of gelatin solution 25-45 millipoise
    - Bloom strength of gelatin solution 150-250 gm
    - Iron content NMT 15 ppm
    - Film Thickness

- Color, surface, appearance of empty shells
- Temperature of hot air, for drying of shells
- Length of Capsule & Body of the shell
- Moisture content 12-15% Inspection of defects like:- Hardening of shells Softening of shells Swelling of shells Cracking of shells Discoloration of shells Misprinting of logo on shells

### **Finished product quality control test of capsule:**

1. Appearance: Capsules produced on a small or a large scale should be uniform in appearance. Visual or electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsule
2. Size and Shape: Hard capsules are made in a range of sizes, the standard industrial ones in use today for human medicines range from size 000 (the largest) to 5 (the smallest) are commercially available. Inspection must be done for size and shape.
3. Unique Identification Markings: Capsule surfaces may bear symbols or other unique identification markings for better identification.
4. Uniformity of weight: Weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible. To remove the contents of a soft capsule the shell may be washed with ether or other suitable solvent and the shell allowed to stand until the odour of the solvent is no longer detectable. Weigh the shell. The weight of the contents is the difference between the weighing's. Repeat the procedure with a further 19 capsules. Determine the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in below and none deviates by more than twice that percentage.
5. Uniformity of content. This test is applicable to capsules that contain less than 10 mg or less than 10 per cent w/w of active ingredient. Determine the content of active ingredient in each of 10 capsules taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision. The capsules comply with the test if not more than one of the individual values thus obtained is outside the limits 85 to 115 per cent of the average value and none is outside the limits 75 to 125 per cent. If two or three individual values are outside the limits 85 to 115 per cent of the average value repeats the determination using another 20 capsules. The capsules comply with the test if in the total sample of 30 capsules not more than three individual values are

outside the limits 85 to 115 per cent and none is outside the limits 75 to 125 per cent of the average value

6. Disintegration. The disintegration test is not applicable to Modified-release Capsules. For those Hard Capsules and Soft Capsules for which the dissolution test is included in the individual monograph, the test for Disintegration is not required..

a) Hard Capsules. Comply with the disintegration test in monograph, unless otherwise directed in the individual monograph use water as the medium. If the capsules float on the surface of the medium, a disc may be added. If the capsules adhere to the discs, attach a removable piece of stainless steel woven gauze with mesh aperture of 2.00 mm to the upper plate of the basket rack assembly and carry out the test omitting the discs. Operate the apparatus for 30 minutes unless otherwise directed

b) Soft Capsules. Comply with the disintegration test unless otherwise directed in the individual monograph use water as the medium and add a disc to each tube. Operate the apparatus for 60 minutes unless otherwise directed

c) Enteric Capsules. Use the apparatus described under disintegration test (2.5.1), using one capsule in each tube. Operate the apparatus for 2 hours without the discs in 0.1 M hydrochloric acid. No capsule shows signs of disintegration or of rupture permitting the escape of the contents. Replace the medium in the vessel with mixed phosphate buffer pH 6.8, add a disc to each tube and operate the apparatus for a further 60 minutes. Remove the apparatus from the medium and examine the capsules. They pass the test if no residue remains on the screen or on the underside of the discs, or, if a residue remains, it consists of fragments of shell or of a soft mass with no palpable, unmoistened core.

7. Content uniformity of drug: A sample of 30 capsule is taken and 10 are assayed individually. The drug content of a capsule should be within the limits of average drug content  $\pm 15\%$  and the drug content of none of the capsule fall outside the average drug content  $\pm 25\%$ . If 1-3 capsules falls outside the average drug content  $\pm 15\%$ , the remaining 20 are assayed. The drug content of at least 27 out of 30 assayed should be within the average drug content  $\pm 15\%$  limits. And the drug content of none of the capsules falls outside the average drug content  $\pm 25\%$  limits.

8. Dissolution test: The dissolution test is carried out using the dissolution apparatus as per U.S.P.

The capsule is placed in a basket, and the basket is immersed in the dissolution medium and caused to rotate at a specified speed. The dissolution medium is held in a covered 1000ml glass vessel and maintained at  $37.0 \text{ C} \pm 0.50 \text{ C}$  by means of a constant temperature suitable water bath. The stirrer speed and type of dissolution medium are specified in the individual monograph

## **SOFT GELATIN CAPSULE (SGP):**

Soft gelatin capsules are one piece , hermetically sealed , and are made up of gelatin in which glycerin or polyhydric alcohol (sorbitol) are added , containing liquid , suspension or semisolid enclosed in it.



### ❖ Advantages:

- Soft gelatin capsules are in sealed form so they protect the inner fill from oxidation and degradation.
- Opaque soft gelatin capsules also protect the inner fill from UV radiation and photo sensitive products.
- It enhance patient compliance due to its elegant appearance.
- Suitable for medicaments like semisolid, oils, liquid forms.
- Soft gelatin capsules increase the bioavailability of API.

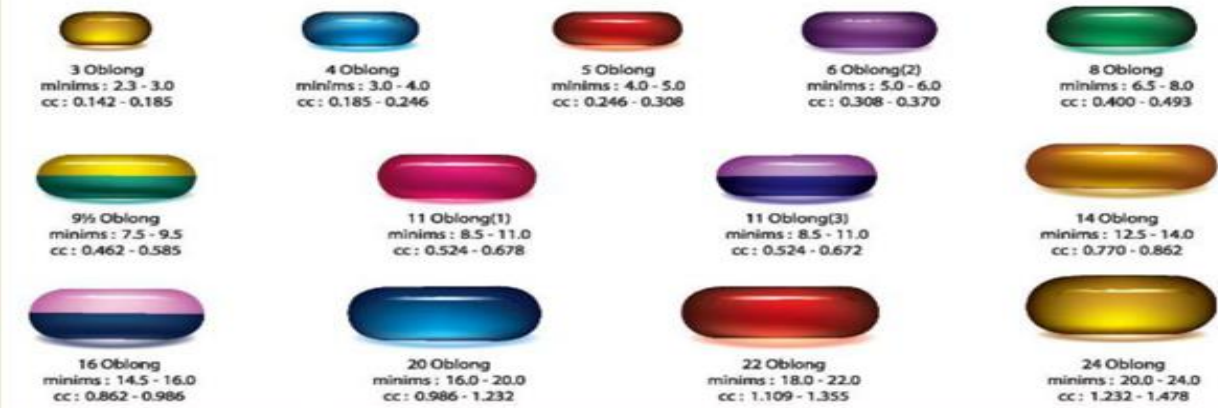
### ❖ Disadvantages:

- Few filling equipment available
- Manufacturing expensive
- Drugs from oily vehicle may pass into the shell
- Soft gelatin capsules having difficulties in dealing with water soluble materials.
- Soft gelatin capsules are highly sensitive to moisture.
- Soft gelatin capsules having difficulties in dealing with efflorescent materials.
- Soft gelatin capsules having difficulties in dealing with deliquescent material



## Shape of capsule shell:

### Oblong



### Round



### Oval



Round  
0.05-6 ml.



Oval  
0.05-6.5 ml.



Oblong  
0.15-25 ml.



Tube  
0.15-30 ml.

### **Nature of capsule shell:**

- The capsule shell is basically composed of gelatin, plasticizer & water. Additionally it may contain preservative, coloring agent, Opacifying agent, flavor, sweetening agent to achieve desired effect.
- The gelatin is USP grade with additional specification required by the capsule manufacture. The additional specification concern the bloom strength, viscosity, iron content of gelatin used.
- Bloom or gel strength: is a measure of cohesive strength of cross linking that occurs between gelatin molecule and is proportional to the molecular weight of gelatin. Bloom is determined by measuring the weight in gram required to move a plastic plunger that is 0.5 inches in diameter 4mm into a 6 2/3 % gelatin gel that has been held at 10oc for 17 hours. Bloom may vary from 150-250g.
- Viscosity: viscosity of gelatin determined on a 6 2/3 % conc of gelatin in water at 600 c, is a measure of molecular chain length and determines the manufacturing characteristics of gelatin. The viscosity for gelatin can ranges from 25 to 45 millipoise.
- Iron is always present in the raw gelatin and its concentration usually depend on the iron content of the large quantities of water used in its manufacture. Gelatin used in manufacture of soft gelatin capsule should not contain more than 15 PPM of this element.

### **Capsule content:**

- Content may be liquid, or a combination of miscible liquids, Solution of a solid(s) in a liquid(s) or Suspension of a solid(s) in a liquid. It can be a liquid like a volatile oil composition E.g. Vegetable oils like arachis oil or aromatic or aliphatic hydrocarbons, ethers, esters, or alcohols.
- Solids that are not Sufficiently soluble in liquids or in combination of liquids are capsulated as Suspension. Suspending agents used are Lecithin, Soyabean oil
- Liquids are important part of capsule content. only those liquid that are both water miscible & volatile cannot be included as major constituent of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface .water, ethyl alcohol fall inthis category.
- Similarly gelatin plasticizer such as glycerin and propylene glycol cannot be major constituent of capsule content owing to their softening effect on gelatin shell.
- Preparation for encapsulation should have a pH between 2.5 and 7.5, since preparation that are more acidic can cause hydrolysis and leakage of shell and preparation that are more alkaline can tan the gelatin and affect the solubility of shell.

- The maximum capsule size and shape for convenient oral use in human is the 20 minim oblong, the 16 minim oval, 9 minim round.

### **Basic components of soft gelatin capsule shell**

The various components of the soft gelatin capsule shell are as follows:

#### a. Gelatin

- Similar to hard gelatin capsule shells, the basic component of soft gelatin capsule shell is gelatin. A large number of different gelatin shell formulations are available depending on the nature of the liquid fill matrix.
- Most commonly, the gelatin is alkali- (or base-) processed (type B) gelatin and it normally constitutes 40% of the wet molten gel mass. Type A acid-processed gelatin can also be used.
- The properties of gelatin shells are controlled by the choice of gelatin grade and by adjusting the concentration of plasticizer in the shell.

#### b. Plasticising agents

- Plasticizing agents are added in a soft gelatin capsule formulation to ensure adequate flexibility. They interact with gelatin chains to reduce the glass transition temperature ( $T_g$ ) of the gelatin shell and/or promotes the retention of moisture (hygroscopicity).
- The most common plasticizer used for soft gelatin capsules is glycerol. Sorbitol, mannitol, and polypropylene glycol can also be used in combination with glycerol.

#### c. 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.
- The desirable water content of the gelatin solution used to produce a soft gelatin capsule shell depends on the viscosity of the specific grade of gelatin used.
- It usually ranges between 0.7 and 1.3 parts of water to each part of dry gelatin.

d. Preservatives

- Preservatives are often added to prevent the growth of bacteria and mould in the gelatin solution during storage.
- Examples of commonly used as preservatives include potassium sorbate, and methyl, ethyl, and propyl hydroxybenzoate.

e. Colorant and/or opacifier

- A colourant (soluble dyes, or insoluble pigments or lakes) and/or opacifier (e.g., titanium dioxide) may be added to the shell for visual appeal and/or reducing the penetration of light for the encapsulation of a photosensitive drug.
- The colour of the capsule shell is generally chosen to be darker than that of its contents.

f. Other excipients

- Other, infrequently, used excipients can include flavouring agents and sweeteners to improve palatability.
- Acid-resistant polymers are used to impart enteric release characteristics. They can also be used to formulate chewable soft gelatin capsules.
- A chelating agent, such as ethylene diamine tetracetic acid (EDTA), can be added to prevent chemical degradation of oxidation sensitive drugs catalyzed by free metals in gelatin, such as iron.

**Formulation of filling material of SGC:**

- The various liquid phase filling matrices used in soft gelatin capsule are selected considering following criteria:
- Compatibility with capsule shell Ability to dissolve the drug Rate of dispersion in the GI fluid after shell disintegration in the GIT Ability to optimize the bioavailability of drug Types of filling/Bases:
  1. Hydrophilic Liquids: like PEG 400 having high mol weight are frequently used
  2. Lipophilic liquid: soya bean oil commonly used. the drug like steroid, vitamin D are mixed with these oil

3. Microemulsion system: it consist of oil-surfactant-water system. blend of oil and surfactant together with the active ingredient is filled into the capsule

4. Emulsifying oil: mixture of pharmaceutical oil & non ionic surfactant like polyoxyethylene sorbitan mono oleate serve as self emulsifying oil matrix

5. Suspension: the drugs which are insoluble in liquid matrices of capsule & which are poorly soluble in GI fluid can be formulated as suspension.

### **Base adsorption:**

- In the formulation of suspension for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size. so one of such tool is Base adsorption of solid(s) to be suspended.
- Base adsorption is expressed as the number of gram of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s). The Base adsorption of solid influenced by
  - Particle size & shape
  - Its physical state (amorphous or crystalline)
  - Density, moisture content, its oleophylic & hydrophilic nature

### **Determination of Base adsorption:**

- weigh a definite amount( 40 g is convenient) of solid into 150 ml tared beaker.
- In a separate 150ml tared beaker , place about 100g of the liquid base.
- Add small increment of base to the solid and using the spatula ,stir the base into the solid after each addition until the solid is completely wetted & uniformly coated with 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° angle above the mixture.
- $\text{Base adsorption} = \frac{\text{weight of base}}{\text{weight of solid}}$  Minim per gram factor(M/g): T
- The base adsorptions used to determine the “minim per gram” factor (M/g) of the solid(s).

### Minim per gram factor (M/g):

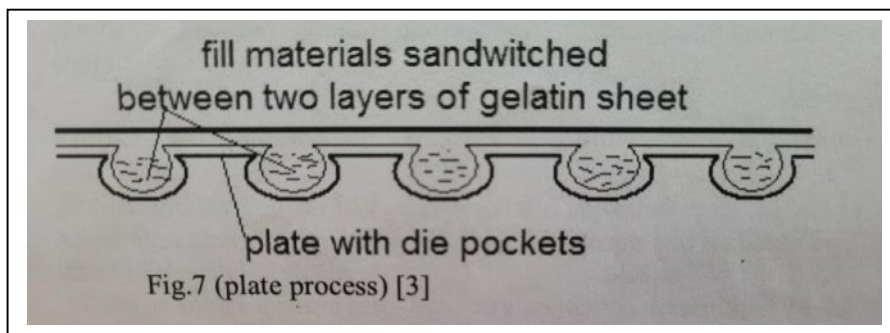
- The minim per gram factor is the volume in minims that is occupied by one gram of the solid plus the weight of the liquid base(BA) required to make capsulatable mixture.
- The minim per gram factor is calculated by dividing the weight of the base plus the gram of solid base (BA+S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V).
- ♣  $(BA+S) \times V/W = M/g$
- Thus lower the base absorption of the solids and higher the density of the mixture, the smaller the capsule will be.

### Manufacture of soft gelatin capsule:

- Plate process
- Rotary die process
- Reciprocating die process
- Accogel capsule filling machine

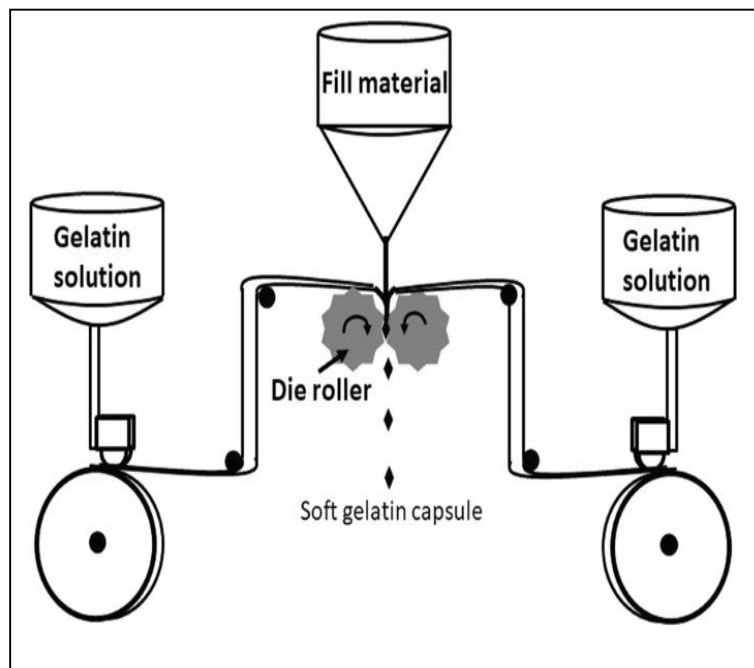
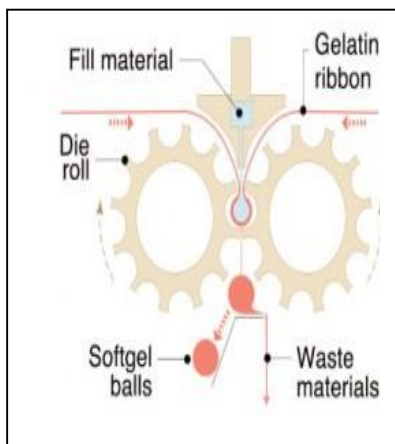
#### Plate process:

- Place the gelatin sheet over a die plate containing numerous die pockets.
- Application of vacuum to draw the sheet in to the die pockets.
- Fill the pockets with liquid or paste.
- Place another gelatin sheet over the filled pockets, and
- Sandwich under a die press where the capsules are formed and cut out.

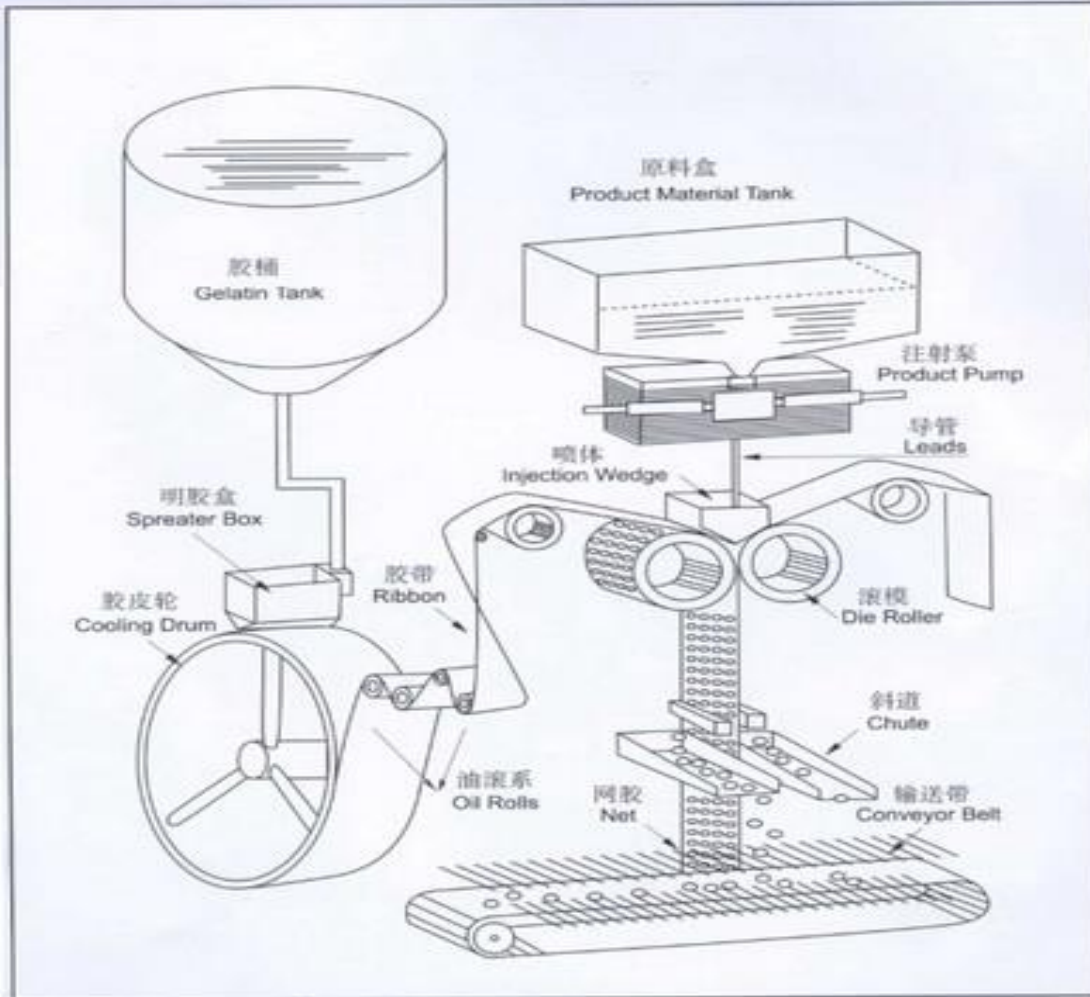


### Rotary die process:

- In this machine the soft gelatin capsules are prepared & then filled immediately with liquid medicaments it is having two hoppers & two rotating dies
- Liquid mixture is placed in one hopper & the liquid medicament in other Hooper.
- The two rotating dies rotate in opposite directions when the fluid gelatin mixture enters the machine from the hopper it produces two continuous ribbons.
- These half shell of the capsule is formed.
- At this stage the measured quantity of the medicament is filled in to it with the stroke of a pump with the subsequent movement of the dies the other half capsule is formed.
- The two halves' of the capsules are sealed together by the heat & pressure of the rotating dies
- As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules



# ROTARY DIE ENCAPSULATING MACHINE FOR SOFT GELATIN CAPSULE



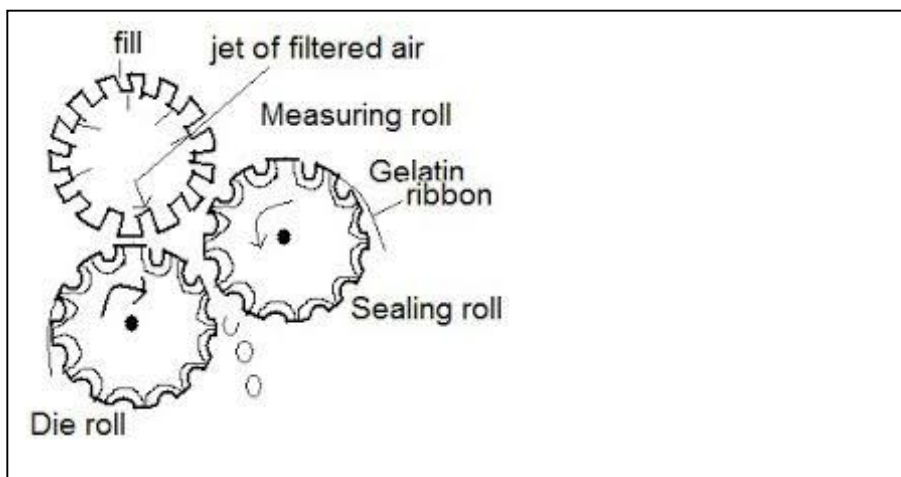


Reciprocating die process:

- This machine produces capsule completely automatically by leading two films of gelatin between a set of vertical dies.
- Rows after rows of pockets are formed across the gelatin film, filled with medicaments and as they process through the dies, are sealed, shaped and cut out of the film as capsules which drop into a cooled solvent bath

Accogel capsule filling machine:

- This is another rotary process involving a measuring roll, a die roll and a sealing roll.
- The measuring roll rotates directly over the die roll, and the pockets in the two rolls are aligned with each other.
- The powder or granular fill material is held in the pockets of measuring roll under vacuum.
- A plasticized gelatin sheet is drawn into the die pockets of the die roll under vacuum.
- As the measuring roll and die roll rotates, the measured dose are transferred to the gelatin lined pockets of the die roll.



In-process testing:

- During the encapsulation process the four most important tests are:-
- .The gel ribbon thickness;
- Soft gel seal thickness at the time of encapsulation;
- Fill matrix weight & capsule shell weight;
- Soft gel shell moisture level and soft gel hardness at the end of the drying stage.

For the determination of the fill weight each capsule is weighed and the contents removed by cutting open the capsule.

The shell is then washed with petroleum ether, and the empty shell is reweighed.

If necessary, adjustment can be made to obtain the proper fill weight.

#### **Finished product testing:**

Test parameter almost same as hard capsule Special quality control test on soft gelatin capsules:-

- Seal thickness:-Is measured under a microscope and it should one half to two third of the ribbon thickness.

- Total or shell moisture test:-Moisture content is determined by the toluene distillation method. Collecting the distillate over a period of one hour.

- Capsule fragility or rupture test:-Force required to rupture the capsule is determined.

- Determination of freezing and high temperature effect:-(>450 c for 30 days) These are performed similarly to the shell integrity test.

#### **Packaging & store of capsule:**

The main aim of packaging of filled capsule is to prevent contamination & loss or gain of moisture during long term storage.

Many plastic container & various packaging technology such as blister packaging, strip packaging are used for it.

In some container dehydrating powder(desiccants) is placed which retard the excessive moisture absorption by capsule.

Storage: storage of hard gelatin capsule shell for long time period require proper maintenance of temp & humidity

Very high humidity: capsules soften, stick together and lose shape

Very low humidity: capsules contract in size and become fragile

High or fluctuated temperatures: capsule forms lumps & condensation is seen on the surface of container.

### **Capsule physical stability:**

- Unprotected soft gelatin capsules rapidly reach equilibrium with the atmospheric conditions under which they are stored.
- This inherent characteristic warrants a brief discussion of the effects of temp and humidity on the products.
- General statements relative to the effects of temp 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 0.5-1 and water to dry gelatin ratio of 1-1 and that is dried to equilibrium with 20-30% RH and 21-24o 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 controlled capsule should have satisfactory physical stability at temp ranging from just above freezing to as high as 60o c.
- As the humidity increases the moisture content pickup of capsules increases .
- ex- at 30%RH at room temp shows that gelatin retain about 12% (48 mg) of water and glycerin 7% (14 mg) of water. at 60%RH the moisture content should be 17.4%.
- High humidity (>60%RH at 21-24o c )produce more lasting effects on the capsule shell Since as moisture is absorbed, the capsules become softer, tackier and bloated.
- The capsule manufacturer routinely conducts accelerated stability tests on new product as an integral part of the production development program.
- The successful results are obtained by conducting at test conditions like 1.80%RH at room temp in an open container 2.40o c in open container 3. 40o c in closed container (glass bottle with tight screw

cap) chemists conducting the physical stability test in their own lab should keep two important points in mind:

1. prior to testing ,the capsule should be equilibrated to known atm conditions, preferably 20-30%RH at 21-240 c.
2. Evaluation of the results of the previously described heat test should be made only after the capsules have returned to equilibrium to room temp

Effect of Temp,humidity on capsule shell

Temp	Humidity	Effect on capsule shell
21-24°C	60%	Capsule become softer,tackier & bloated
> 24°C	45%	More rapid & pronounced effect-unprotected capsule melt & fuse together

Application of soft gelatin capsule:

1. They permit liquid medications to become easily portable.
2. Accuracy and uniformity of dosage, capsule to capsule and lot to lot predominant advantage
3. The pharmaceutical availability of drugs formulated for this dosage form, as measured by disintegration time or by dissolution rate often shows an advantage over other solid dosage form
4. The physiologic availability of drug is often improved since these capsule contain the drug in liquid form
5. The biopharmaceutical characteristics of such formulations can altered and adjusted more easily than those of other solid dosage form
6. Orally administered drug, particularly if used chronically, can be irritating to the stomach .the dosage form of such drug can affect gastric tolerance indicated by study.

