Capsule

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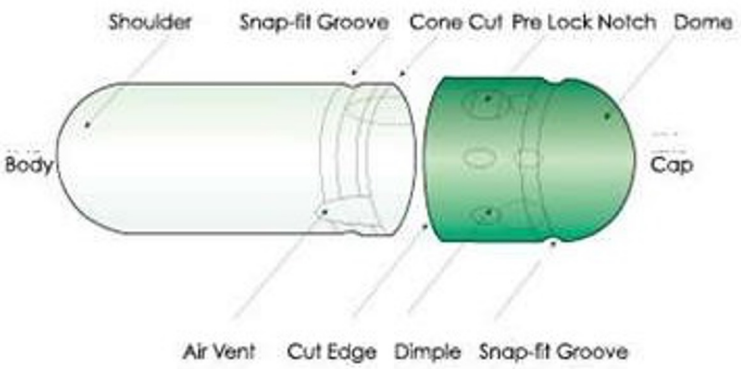
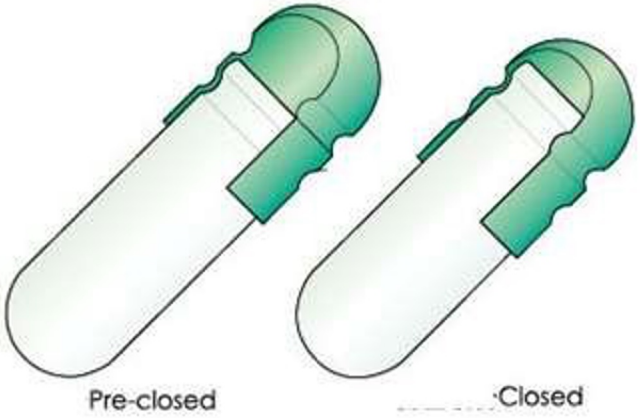




Locking Status of Capsule

INTRODUCTION:

CAPSULES:

Capsules are small containers made of gelatin that enclose medication in either a hard or soft shell. The name "capsule" comes from the Latin word capsula, which means small container. Medication in capsules can come in the form of a powder, liquid, or semisolid mass. Typically, capsules are meant to be taken orally by swallowing them whole, although in some cases they may be given rectally or vaginally.

HISTORY:

Capsules have a rich history in the field of pharmacy. In 1730, a Viennese pharmacist named De PAULI created oval-shaped capsules to conceal the bitter taste of pure turpentine used for treating gout. In 1834, a French pharmacist named JOSEPH DUPLANC was granted a patent for a method of producing single-piece, olive-shaped gelatin capsules. The method involved filling the capsule and then closing it with a drop of concentrated warm gelatin solution.

In 1846, a Frenchman named JULES LEHUBY was the first to suggest the use of two-piece capsules. These were made by dipping silver-coated metal pins into a gelatin solution and quickly drying them. Finally, in 1931, COLTON designed a machine that could manufacture both capsule bodies and caps and fit them together to create hard gelatin capsules.

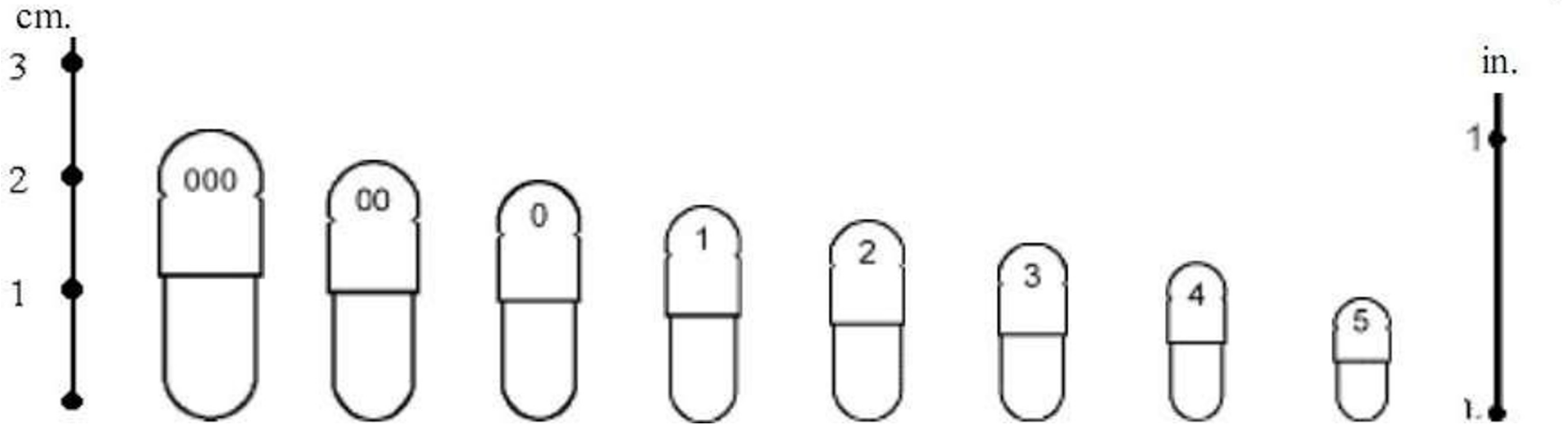
ADVANTAGES OF CAPSULES:

- Capsules offer several benefits, including being tasteless, odorless, and easy to administer.
- Capsules allow for the combination of different powders, providing more flexibility in medication formulations.
- Capsules are also visually appealing, which can be important for patient compliance.
- Enclosing drugs with unpleasant taste and odor in a tasteless shell helps improve patient experience.
- Capsules can be filled quickly and conveniently, making them a time-efficient dosage form.
- Capsules offer physicians the flexibility to adjust medication dose and combination according to patient requirements.
- Capsules are an economical option for medication delivery.
- Capsules are easy to handle and carry, making them a convenient option for patients on the go.
- The solubility of gelatin in gastric pH allows for rapid medication release in the stomach.
- Capsules are also cost-effective to package and ship, with less risk of breakage than liquid forms.

DISADVANTAGES OF CAPSULES:

- Capsules may not be suitable for administering liquid medications that can dissolve gelatin, such as aqueous or hydroalcoholic solutions.
- Concentrated solutions that require dilution beforehand may not be suitable for use in capsules, as they can cause irritation in the stomach if taken undiluted.
- Capsules may not be suitable for efflorescent or deliquescent materials. Efflorescent materials can cause capsules to soften, while deliquescent materials can dry out the capsule shell and make it brittle..

SHAPES OF CAPSULE:



*The largest size of the capsule is No: 000.
*The smallest size is No: 5.
*The standard shape of capsules is traditional, symmetrical bullet shape.

SIZE OF CAPSULE:

Size	Volume in ml	Size in mm
000	1.37	26.3
00	0.95	23.7
0	0.68	21.8
1	0.50	19.2
2	0.37	18.3
3	0.30	15.3
4	0.21	14.7
5	0.15	11.9

RAW MATERIALS:

1. Gelatin

2. FD & C and D & C colorant

3. Sugar

4.Water - 12 to 16 % (may vary depending on the storage condition)

5.Sulfur dioxide (15%) - prevent decomposition during manufacture

6. Colorants / Opacifying agent : There are two types

A) water soluble dyes – e.g. erythrosine

B) pigments – e.g. iron oxides, titanium dioxide

7. Preservatives: To prevent microbial growth during manufacture.

8. Diluents: lactose, mannitol, sorbitol, starch, etc

9. Lubricants and Glidants : talc, magnesium stearate & calcium stearate

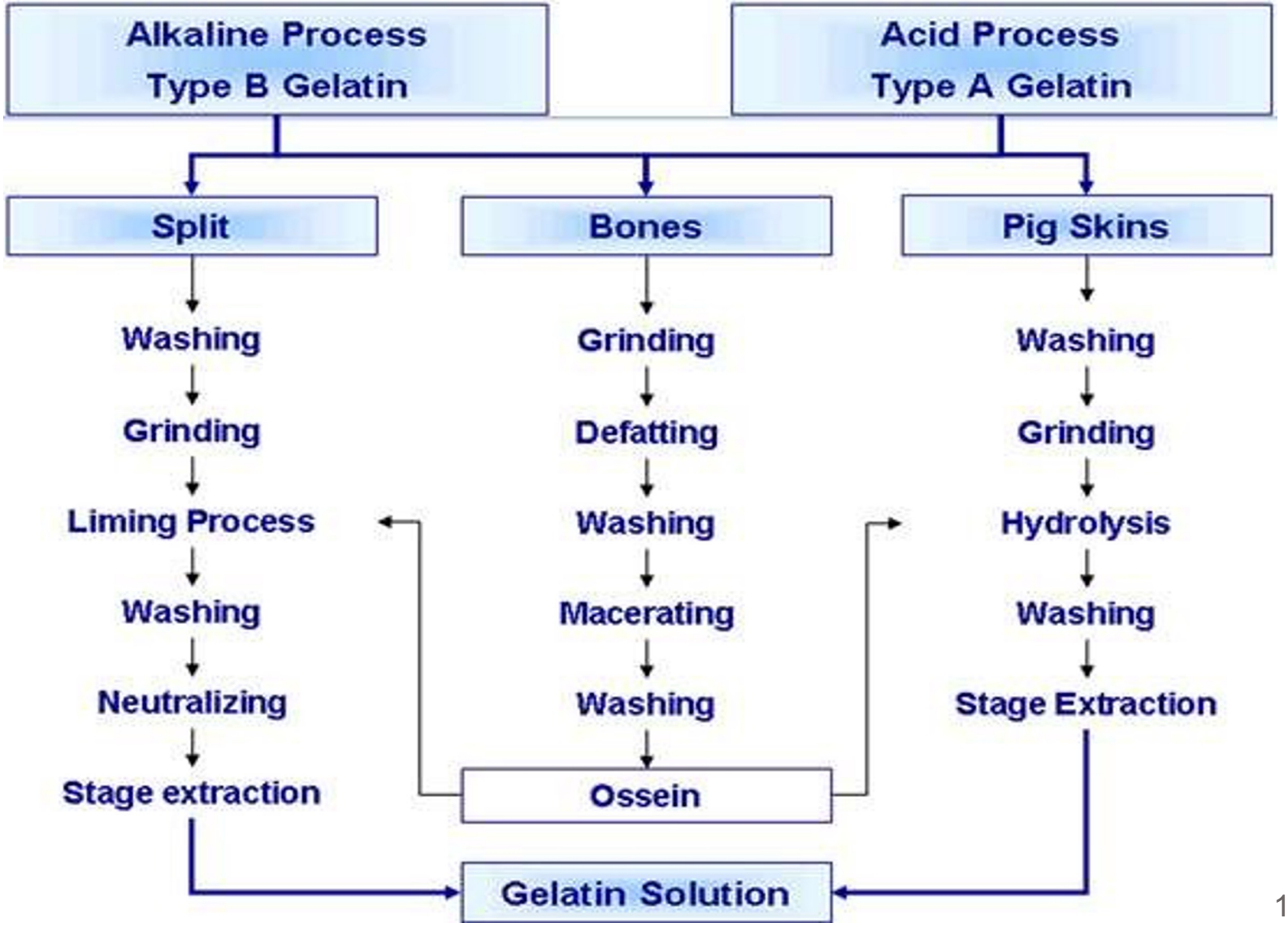
10. Wetting agents: sodium lauryl sulphate

11. Disintegrants

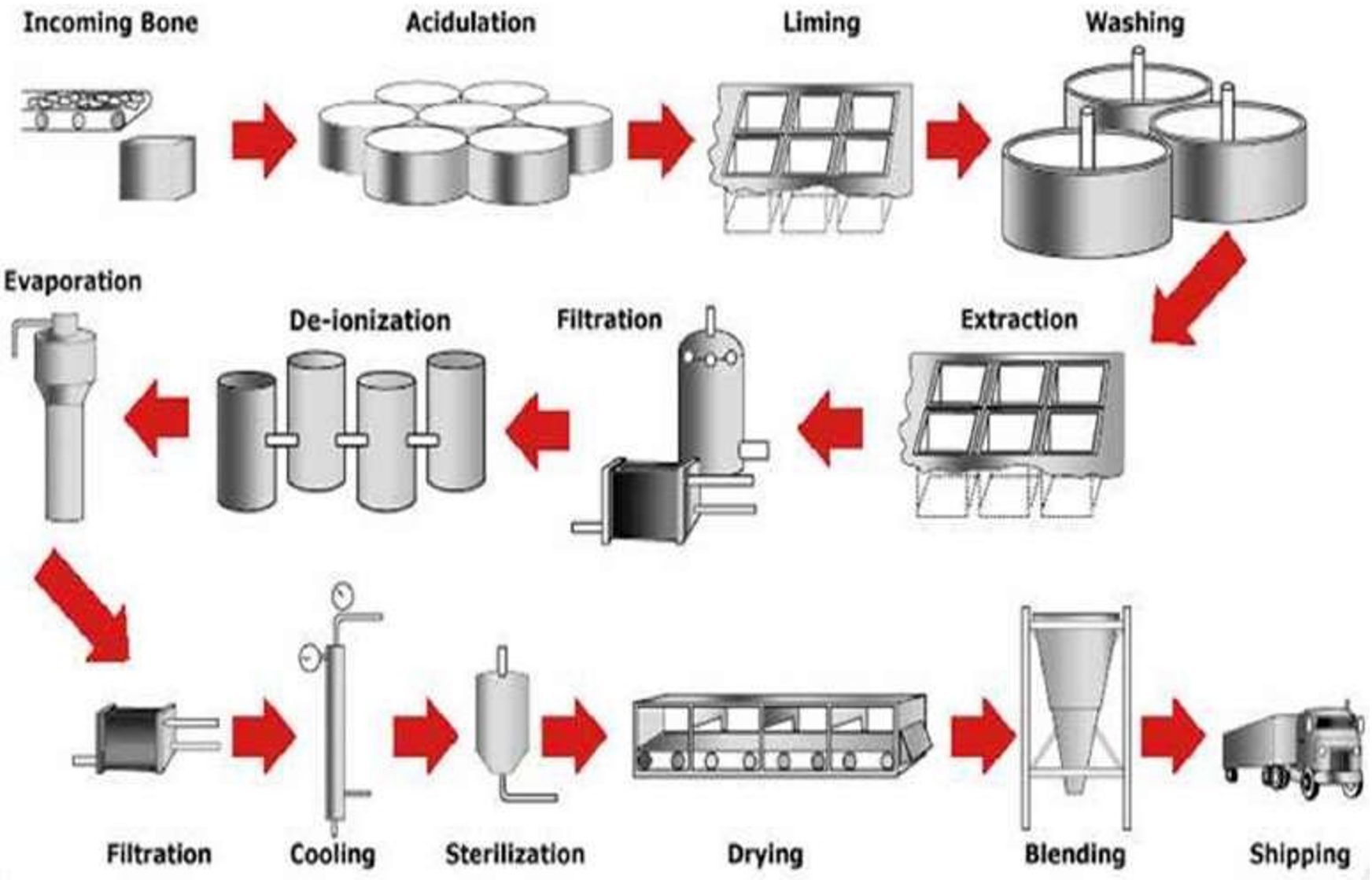
GELATIN:

Gelatin is a heterogeneous substance that is extracted through the hydrolysis of animal collagen. The primary sources of gelatin are animal bones, hide portions, and frozen pork skin. It is a crucial component in the production of capsules due to its unique properties. Gelatin is non-toxic, soluble in biological fluids at body temperature, and is an excellent film-forming material. Additionally, solutions with a high concentration of gelatin (40% w/v) are mobile at 50°C. Gelatin solutions also transform from a sol to a gel at temperatures only a few degrees above ambient. These five properties make gelatin an ideal material for use in capsule production.

Preparation of Gelatin:



Gelatin Manufacturing Process



TYPES OF GELATIN:

There are two basic types of gelatin

1. Type - A
2. Type - B

TYPE - A

This substance is derived from an acid-treated precursor that has an isoelectric point at pH-9. The primary source of this substance is pork skin, which is used to manufacture it.

TYPE - B

This substance is derived from an alkali-treated precursor that has an isoelectric point at pH-4.7. It is primarily manufactured using a process that involves the treatment of certain raw materials.

GENERAL CHARACTERISTICS OF GELATIN:

1 Bloom value;

- Bloom strength is a measure of the gelling power and strength of the resulting gel of a gelatin solution.
- Typically, gelatin products have a bloom strength that ranges from 50 to 300.

1 Gelling power;

- The primary function of gelatin is to act as a gelling agent in food products, pharmaceuticals, and other applications.
- The gelling power of gelatin can vary depending on the grade of the product. Higher quality gelatin tends to have a stronger gelling power than lower quality gelatin.
- The strength of a gelatin solution is measured in terms of its bloom value, which is an indication of its ability to form gels. The higher the bloom value, the greater the ability of the gelatin to form strong and stable gels.

3. Viscosity;

- In general, higher bloom strength gelatin products tend to have greater viscosity than those with lower bloom strength.
- Gelatin products made from beef bones typically have higher viscosity than those made from other sources.
- Viscosity is determined by measuring the flow time of a 6.67% solution of gelatin through a U-tube viscometer at a temperature of 60°C. The measurement of viscosity is expressed in millipoise (mps) units and can range from 20 to 70 mps.

4. Foamability;

- solutions, which can lead to a grainy texture in the final product. When using gelatin in pigskin grades, it can help create a light and airy texture in products like marshmallows or whipped toppings.
- Additionally, pigskin grades tend to have a higher collagen content than other grades of gelatin, which can also contribute to their foaming properties. Collagen is a protein that can form strong, stable films and can help trap air bubbles within a foam.
- It's worth noting that the foaming properties of gelatin can also be affected by factors such as temperature, pH, and the presence of other ingredients. But in general, pigskin grades of gelatin are often preferred for applications where a light, stable foam is desired.

5. Melting point;

- Lower bloom grade gelatins have weaker gel strength and lower melting points, which means they dissolve more easily and quickly in the mouth. This allows for the flavors to be released faster, resulting in a more immediate taste sensation. In contrast, higher bloom grade gelatins have stronger gel strength and higher melting points, which means they dissolve more slowly and can provide a longer-lasting texture and flavor release. The choice of gelatin type and bloom grade depends on the specific application and desired texture and sensory experience of the final product.

6. Color and odor;

- Gelatin should be clear and odorless. Clarity is measured with a turbidimeter.

7. Conductivity;

- High-purity gelatin with minimal or no conductivity is crucial in photography. De-ionized grades are advantageous due to low conductivity.

8. pH;

- pH of 1% gelatin solution is measured using a pH meter.

TYPES OF CAPSULES:

- Capsules are available in two types:

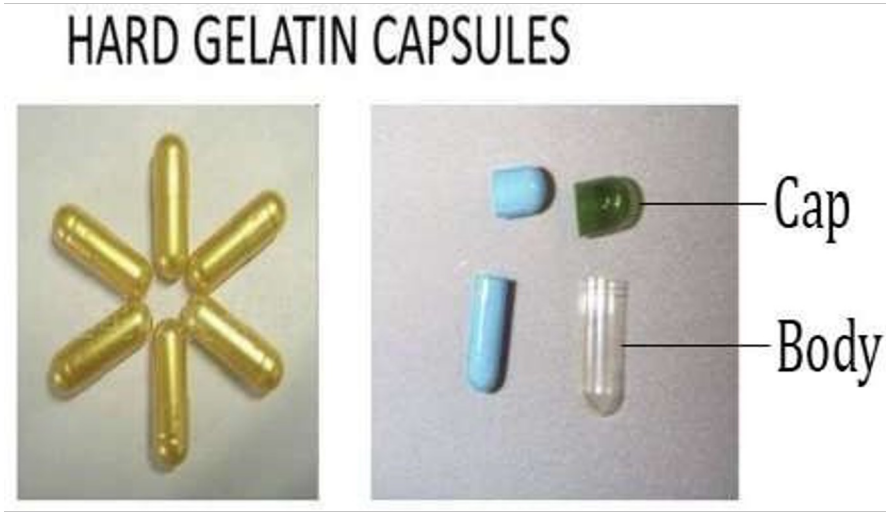
1. Hard gelatin capsules
2. Soft gelatin capsules.

1.Hard gelatin capsule

2.Soft gelatin capsule

1.HARD GELATIN CAPSULES:

- Hard gelatin capsules have two pieces: a cap and a body that fit together to enclose the drug substance.



Manufacturing of Hard gelatin capsules

Optical fiber manufacturing involves

six key steps

1. Dipping
2. Spinning
3. Drying
4. Stripping
5. Trimming and Joining
6. Polishing

1.DIPPING:

- ❖Stainless steel pins are dipped into a solution to simultaneously form capsule bodies and caps
- ❖The dipping solution is heated and maintained at around 50°C.

2.SPINNING:

To prevent the formation of a bead at the ends of the capsule, the pins are rotated to ensure even distribution of gelatin.

3.DRYING :

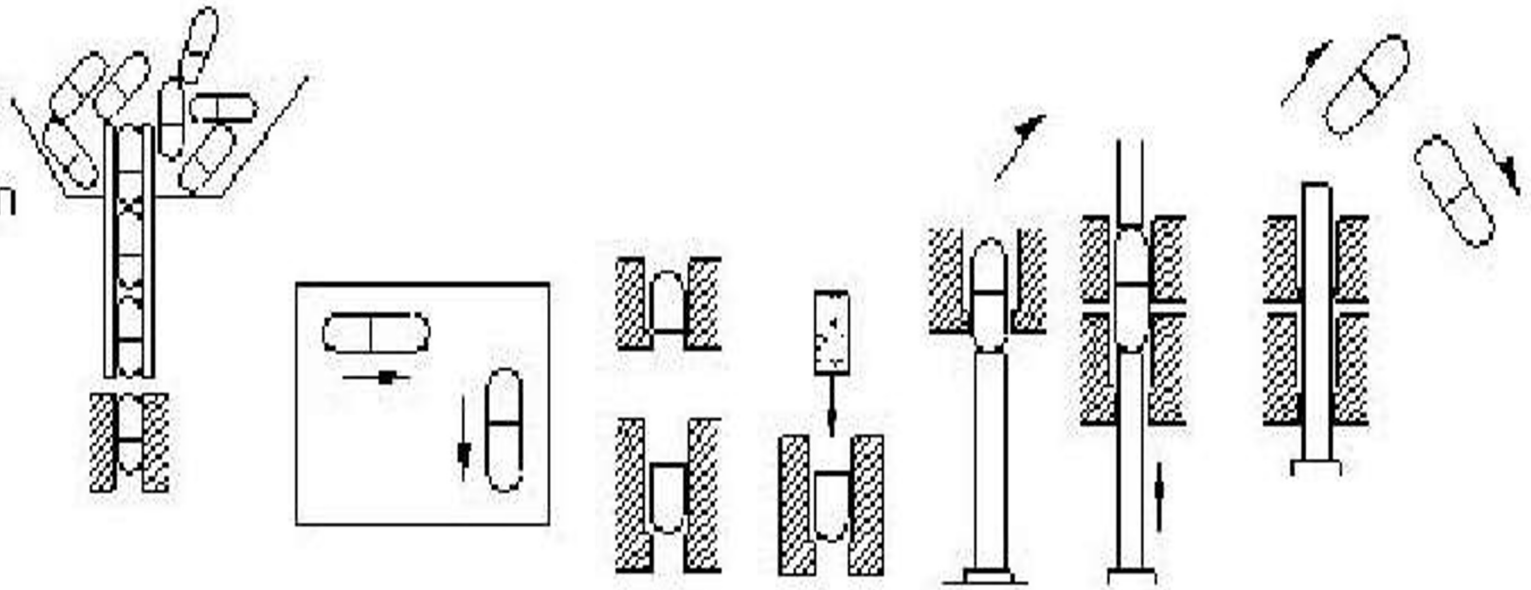
- Air drying is used to remove water and create hard shells from the gelatin. This is accomplished by blasting cool air or passing the capsules through a series of drying kilns.

4.STRIPPING :

- Bronze jaws are used to strip the cap and body portions of the capsules from the pins.

5.TRIMMING AND JOINING: Following stripping, the cap and body portions are trimmed precisely to length using stationary knives. Once trimmed, the cap and body are joined and quality is monitored throughout production, including size, moisture content, single wall thickness, and color. Finished capsules are sorted, visually inspected, and imprinted with the client logo before being pushed onto a conveyor belt for packaging.

Flow diagram for Gelatin Gapsule



6.POLISHING :

a) Pan Polishing : Acela-cota pan is used to and polish. dust

b)Cloth Dusting : Capsule are rubbed with cloth.

c) Brushing : Capsule are feed under soft rotating brush

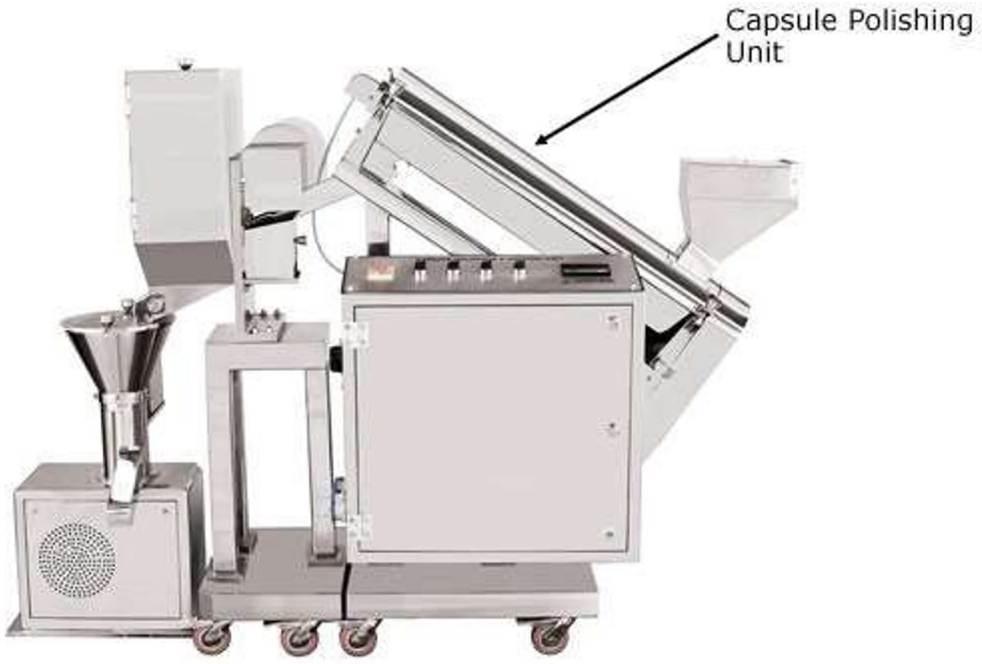


Fig : Capsule polishing machine

STORAGE :

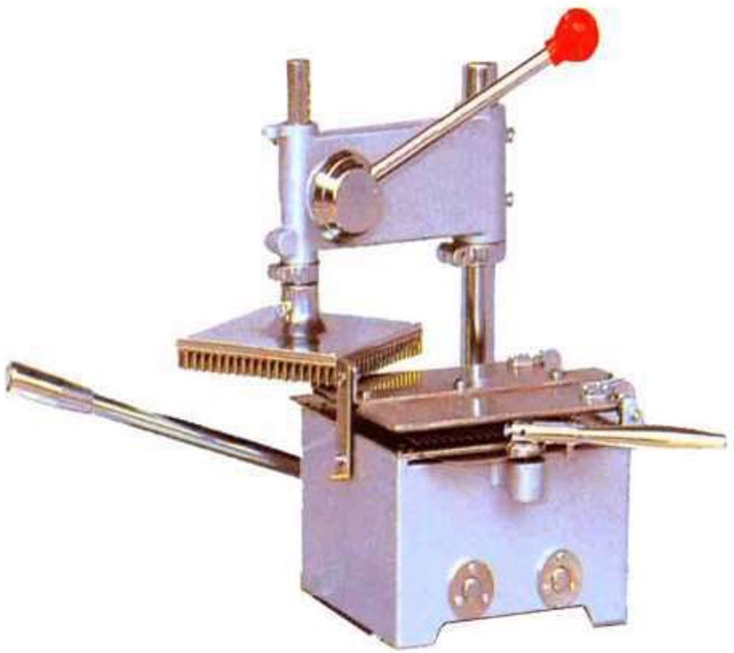
Finished capsules typically have an equilibrium moisture content of 13-16%. When handling and storing capsules, it is important to maintain a relative humidity of 40-60%."

FILLING OF HARD GELATIN CAPSULES :

❖There are three types of capsule filling devices: hand-operated/semi-automatic, punch/manual, and automatic machines.

ex: osaka capsule filling machine ,macofar capsule filling machine

- ***HAND OPE***
  - ***HAND OPE***
    M



- ***It consists of:***

1.A bed having 200-300 holes

2.A loading tray having 200-

30 holes

3.A powder tray

4.A pin plate having a rubber to

5.A lever

6. A cam handle.

The empty capsules are filled in the loading tray .

↓

and it is placed 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 powder is collected on the plat for of the powder tray

↓

The pin plate is lowered and the filled powder is pressed by moving

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 a

↓

The loading tray is then remo
and the filled capsules are co

PUNCH METHOD:

- To fill a capsule, form a cake of powder on a clean paper or porcelain plate using a spatula. The cake should be one-fourth to one-third the length of the capsule body.
- To fill the capsule, hold the empty body between your thumb and forefinger and punch it vertically into the powder cake repeatedly until filled.

FILLING OF HARD CAPSULE SHELL

The process of working:

- Rectification
- Separating the caps from empty capsules
- Filling the bodies
- Scraping the excess powder
- Replacing the caps
- Sealing the capsules
- Cleaning the outside of the filled cap
- 160,000 capsules per 8hour shift

Fig : OSAKA MODEL R-180 SEMI AUTOMATIC CAPSULE FILLING MACHINE

Rectification ;

To ensure proper orientation, empty capsules are aligned with the body end downwards. They pass through a channel that provides grip at the cap end and special blades align the capsules even if they entered the channel in reverse.

Separation of caps from body ;

Rectified capsules are loaded body end first into split bushings or split filling rings. A vacuum from below pulls the body down into the lower part of the bushing. The bush diameter is too large to allow the caps to pass through.

Principles of capsule Filling:

Auger Fill principle:

The rectifier unit orients the empty capsules with the caps turned up and bodies down. They are then placed one by one in a rotating filling ring where the powdered drug is driven into the bodies by an auger.

Vibratory Fill Principle:

The feed hopper contains a perforated resin plate through which the powder feed flows freely into the capsule bodies due to the vibrations of the plate.

Piston – Tamp principle:

Piston tamps compress the powder to form slugs, which are transferred into empty capsule bodies with slight pressure. The compression force ranges from 50-200N. The bodies are then ejected from the machine.

a)Dosator machine b) Dosing Disc

Vacuum Fill principle:

The vacuum powder filler is an open-ended cylinder with a piston at the top. To fill the cylinder with a predetermined amount of powder, the open end is placed in the bulk powder and a vacuum is applied, causing the piston to move upward and suck in the powder.

HOFLIGER KARG
AUTOMATIC CAPSULE
FILLING MACHINE

ZANASI AUTOMATIC
CAPSULE FILLING MACHINE

Various Filling Machine Available…

- Eli-lily
- Farmatic
- Hofliger and Karg
- Zanasi Nigris
- Parke-Davis
- Osaka
- Macofar SAS

(These machine differ in there design and output)

Locking and Sealing of Capsules :

Banding – Gelatin color bands are placed at the meeting point of capsule caps and bodies.

Moistening - the inner surface of caps with lukewarm gelatin solution.

Spot - welding the joints leaves a ring-like appearance at the seal point.

Wetting - solution lowers melting point at meeting points for thermal sealing at 40-45ºC.

Coni-snap - capsules use grooves to lock caps with bodies.

FINISHING OF CAPSULES:

Cloth dusting: Capsule are rubbed with cloth.

Polishing

Pan Polishing : Acela-cota pan is used to dust and polish which is lined with cheese or a polyurethane cloth.

Brushing : Capsule are feed under soft rotating brush

SORTING:

Storage, packaging, and stability:

- Finished capsules normally contain an EMC of 13-16%.
  - < 12% MC, the capsule shells become brittle.
  - >18% make them too soft.
- Maintain 40-60% relative humidity when handling and storing capsules.
- QUALI-V is the first HPMC capsule by Shionogi Qualicaps for use in pharmaceutical products.

SOFT GELATIN CAPSULE:

Definition:-

- Soft gelatin capsules are hermetically sealed, one-piece shells made of soft gelatin and containing a liquid, suspension, or semisolid.
- Soft gelatin mainly contains gelatin, plasticizers, preservatives, coloring and opacifying agents, flavorings, and sugars.

APPLICATION OF SOFT GELATIN CAPSULE:

The pharmaceutical applications of soft gelatin capsules are:

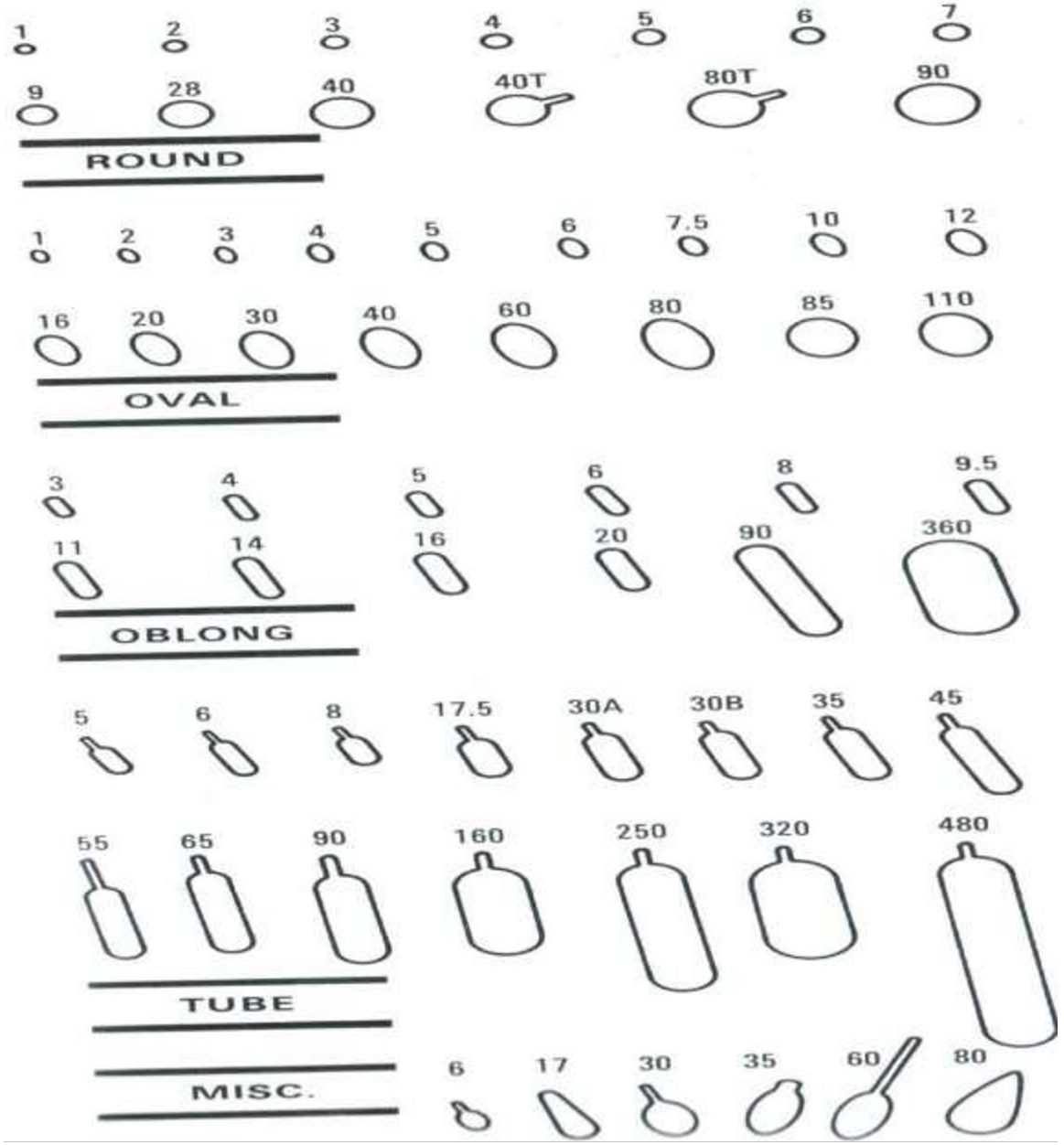
- As an oral dosage form
- As a suppository dosage form
- As a specialty package in tube form, for human

Soft gelatin capsules offer the following advantages:

- Easy administration
- Easy manufacturing
- Ability to encapsulate non-water-soluble liquids
- Availability in small to large sizes
- Elegant appearance
- Portability
- Faster drug action due to ready availability
- Masking of odor and taste
- Ability to create specialized dosage forms (e.g. chewable, extended release, captabs)
- Usability for ophthalmic, vaginal, and rectal suppositories (e.g. aplicaps)

SHAPE OF CAPSULE:

The shape of soft gelatin capsule are round, oval, oblong, tube.



soft gelatin capsules composition:

- A typical gel mass formula for making soft gelatin capsules would be:
  - Gelatin 35-45%
  - Plasticizer 15-25% (glycerin or sorbitol)
  - Water ~40%
  - Dye / Pigment as needed
  - Opacifier as needed
  - Other (flavour, sugar,) as needed

Formulation :

Soft gelatin capsule formulation is based on liquid technology rather than powder. The aim is to achieve maximum stability, therapeutic effectiveness and manufacturing efficiency while keeping the capsule size as small as possible. Only liquids that are compatible with the gelatin shell are used in the formulation.

Vehicles used in soft gelatin capsules:

Two main groups:

1. Water-immiscible liquids, including volatile ones such as vegetable oils, mineral oils, medium-chain triglycerides, and acetylated glycerin, are commonly used in soft gelatin capsule formulations.

2. Water-miscible and non-volatile liquids like low molecular weight PEG have gained popularity in soft gelatin capsule formulation due to their capability of easy mixing with water and enhancing the dissolution of dissolved or suspended drugs.

MANUFACTURE OF SOFT GELATIN CAPSULE:

Is manufactured by four methods,

1)Plate process

2)Rotary die process

3)Rotary accurate process

4)die machine

1.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.

•Sandwich under a die press where the capsules are formed and cut out.

2.ROTARY DIE PROCESS

1)This machine is used to prepare soft gelatin capsules and fill them with liquid medication. It has two hoppers and two rotating dies.

2)One hopper is used for the liquid gelatin mixture, while the other is for the liquid medication.

3)The two rotating dies move in opposite directions, forming two continuous ribbons when the gelatin mixture enters the machine from the hopper.

4)Half of the capsule shell is formed at this stage.

5)A measured quantity of the medication is then filled into the shell with a pump stroke, and the other half of the capsule is formed with the subsequent movement of the dies.

6)The two halves of the capsule are sealed together by the heat and pressure of the rotating dies.

7)As the dies rotate, the matching pockets converge to seal and cut out the filled capsules.

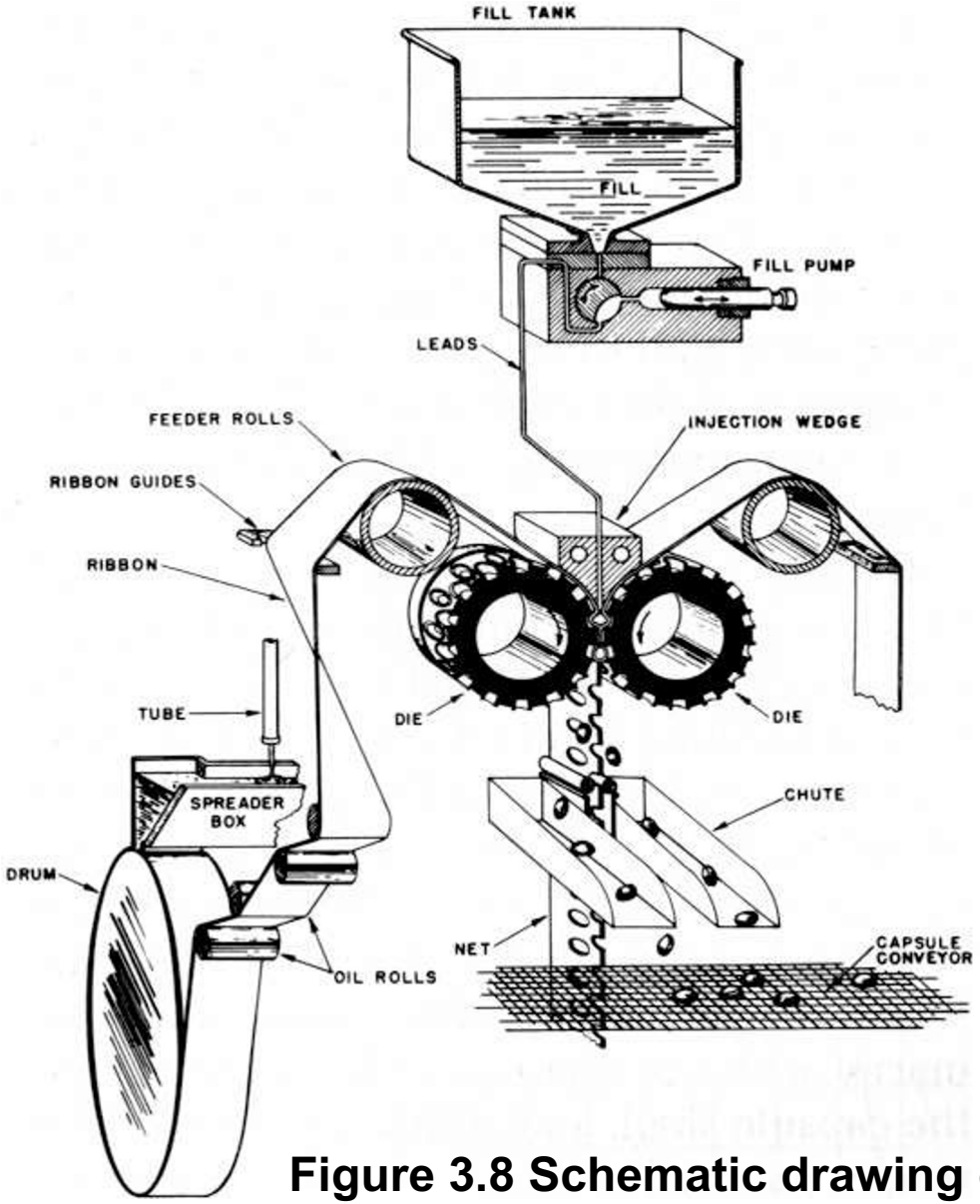


Figure 3.8 Schematic drawing of a rotary-die soft gelatin capsule filler (R.P. Scherer: Detroit, MI).

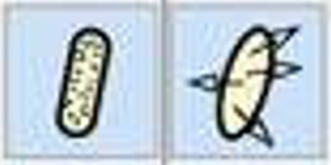
3.ACCOGEL CAPSULE MACHINE:

It consists of mainly 3 parts:

- Measuring roll
- Die roll
- Sealing roll

- This process involves the rotation of a measuring roll and die rolls to transfer measured doses into gelatin-linked pockets of the die roll. The filled die then rotates and converges with a sealing roll, where a second gelatin sheet is applied to form the other half of the capsule. Pressure between the two rolls seals and cuts out the capsules.

DIFFERENCE BETWEEN HARD GELATIN CAPSULES AND SOFT GELATIN CAPSULES

Advantages of hard gelatine capsules		over soft gelatine capsules
Contain 4-5 times less gelatine than soft gelatine capsules		Require 4-5 times more gelatine than the hard gelatine capsules
Require no other additives. Consists of water and gelatine only		Require addition of glycerin for softening purposes
Allow step-by-step filling of 2 different formulations (i.e. 2-stage-release)		Have to be sealed immediately after filling one substance (filling and sealing are one and the same process)
Heat resistant : allow filling of thermo-stable substances up to 75°C		Filling temperature limited to about 35°C : filling of solid substances with higher melting points impossible
Are stable in hot climates		Tend to stick together and become gluey
Will disintegrate faster due to the capsule wall being five times thinner than the walls of soft gelatine capsules		Will disintegrate slower due to the thickness of its gelatine/glycerin wall
Less product migration into the shell, less diffusion of odours		Glycerin acts as a plasticiser by disrupting the gelatine structure - consequently, higher diffusion into and through the walls
Constant external dimensions (easier blistering/packaging)		Dimensions vary according to filling weight and vary throughout a batch

CAPSULE SHELL:

This statement describes the composition of a soft gelatin capsule shell, which is made primarily of gelatin, a plasticizer, and water. Other ingredients may also be added to achieve certain effects, such as preservatives, coloring and opacifying agents, flavorings, sugars, acids, and even medicaments.

Composition of the capsule shell:

- The main constituent of soft gelatin shell is gelatin, which is plasticized to achieve the desired texture. The hardness of the shell is determined by the ratio of dry plasticizer to dry gelatin, with a range from 0.3-1.0 for very hard shells to 1.0-1.8 for very soft shells. Additionally, up to 5% sugar may be added to make the shell chewable. The residual moisture content of finished capsules typically falls within the range of 6-10%.

Constituents of Capsule Shell:

Constituents	Examples	Function
Gelatin	Type A, Type B	
Plasticizers	Glycerine USP, glycerol (85% & 98%)	Imparts softness, Elasticity & hardness
Preservatives	Methyl paraben, Sorbic acid (0.2%)	Retard growth of microorganisms
Solvents	Oils	Elegance
Opacifying agents	Tio2(0.2-1.2%)	Minimize transparency
Colours	Veg. colours,FD&C D&C water soluble dyes, certified lakes	Gives pleasant appearance to the shells.
Flavours	Ethyl vanillin(0.1-2%)	Good flavour
Sugars	Sucrose(up to 5%)	Sweet taste
Acids	Fumaric acid(up to 1%)	Lessen aldehydic tanning of gelatin
Thickening agents	Methyl cellulose	Adjust viscosity of gelatin
Water		

QUALITY CONTROL OF CAPSULES:

Irrespective of the scale of production, all soft gelatin capsules must undergo quality control testing to ensure the quality of the final product.

Quality control tests are divided into;

- ***PHYSICAL TEST***
  - Disintegration test
  - Weight variation
- ***CHEMICAL TEST***
  - Dissolution test
  - Assay
  - Content uniformity
  - Stability testing
  - Moisture permeation test

EVALUATION OF CAPSULES:

- Weight variation test
- Moisture permeation test
- Content uniformity
- Dissolution test
- Disintegration test

Weight variation test:

To ensure the quality of the finished product, soft gelatin capsules are subject to quality control tests. One such test involves randomly selecting 20 capsules and weighing them to determine the average weight. Each individual capsule is then weighed, and the weight is recorded. The capsules are considered to pass the test if the weight of each individual capsule falls within 90-110% of the average weight.

Moisture permeation test:

As per the U.S.P, soft gelatin capsules are packaged with desiccant pellets that change color in the presence of moisture, serving as an indicator. To test the quality of the capsules, the weight of the test capsule is compared with the weight of the other capsules in the batch. If the weight of the test capsule falls within 90-110% of the average weight of the batch, the capsules pass the quality control test.

Content Uniformity Test:

- The content of capsules meant for oral administration must comply with prescribed standards. To ensure compliance, a sample of the contents is assayed as described in individual monographs. The values obtained from the assay are compared to the prescribed standards. This test is applicable to all such capsules.

Content uniformity:

- The content uniformity test is applicable to all oral capsules. A sample of 30 capsules is selected and 10 of these are assayed individually. At least 9 of these capsules must contain between 85-115% of the drug, and none must contain less than 75-125% of the drug. If 1 to 3 capsules fall outside of the 85-115% limits, the remaining 20 capsules are individually assayed. The requirements are met if no fewer than 27 capsules contain between 85-115% of the drug and none contain less than 75-125% of the drug.

- ***Dissolution test procedure includes the following steps:***
  - ❖Add 1000 ml of air-free water with a temperature of 36.5ºC to 37.5ºC.
  - ❖Place the specified number of capsules into each basket.
  - ❖Start the motor and set the speed to 100 rpm according to the monograph.
  - ❖After 45 minutes or as specified in the monograph, withdraw the required volume of solution.
  - ❖Filter and weigh the active ingredient amount by the method specified in the monograph.
  - ❖Repeat the process four times.
  - ❖The test is considered to have passed if the active ingredient amount is not less than 70% of the stated amount given in the monograph.

- ***The Disintegration Test for capsules involves the following steps:***
  - Place one capsule in each basket and set the water temperature to 37 +/- 2 degrees Celsius.
  - Use the appropriate disc for the type of capsule being tested (HGC or SGC) to prevent floating.
  - Operate the apparatus for 30 minutes for HGC and 60 minutes for SGC.
  - The test is considered successful if no residue is left on the apparatus screen.
  - If one or two capsules fail to disintegrate, repeat the test for 12 capsules.
  - The test is considered successful if at least 16 out of 18 capsules disintegrate.

PACKING & STORAGE OF CAPSULES:

- Packing and storage are important factors in preserving the quality of capsules. To prevent moisture and other contaminants from affecting the capsules, they should be tightly packed in glass or plastic containers and stored in a cool and dry place, with a temperature not exceeding 30ºC.
- For additional protection, capsules can be individually wrapped in strip or blister packaging. In strip packaging, each capsule is hermetically sealed in a strip made of aluminum or plastic film. In blister packaging, the capsule is pressed through the backing strip by applying pressure to the blister.
- It is worth noting that the shelf life of capsules may vary depending on the type of packaging. Unopened glass bottles can preserve capsules for a longer period of time compared to strip packs. However, this may not hold true for opened containers, as exposure to air and moisture can reduce the shelf life of the capsules.

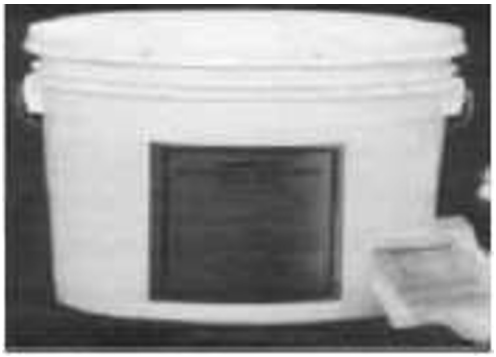
- Now a days capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification.

- Plastic bottle with screw cap . (*most popular package in USA*)

- Clam shell blister *(one piece plastic that folds over and locks itself; no heating required)*

- Blister pack *(heat sealed blister on a*

- Plastic pail/bucket*(economical bulk package)*



- Plastic pouch zip locked *(for sale via retail stores or route trucks must be packed in outer case for shipping)*

Reference

Prabakaran B.pharm.Vinnayaka vission’s collage of pharmacy