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3. Capsule

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3.1 Definition:

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:

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

Disadvantages:

a. 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.
b. Capsule should not use for highly efflorescent material as material may cause the capsule to soften by losing water molecule to shell,
c. Capsule should not use for highly deliquescent powder as powder have tendency to absorb moisture from capsule shell & make it brittleness.
d. The capsule shells can absorb water from the environment and develop problems with drug stability and capsule shell can become tacky.
e. it unsuitable for use with liquid formulations

3.2 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.

A. Generally, two types of gelatins are used to manufacture capsule shell.

a. Type A Gelatin: it is derived from the acid treated precursor and exhibit isoelectric point in region of pH 9.
b. 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.

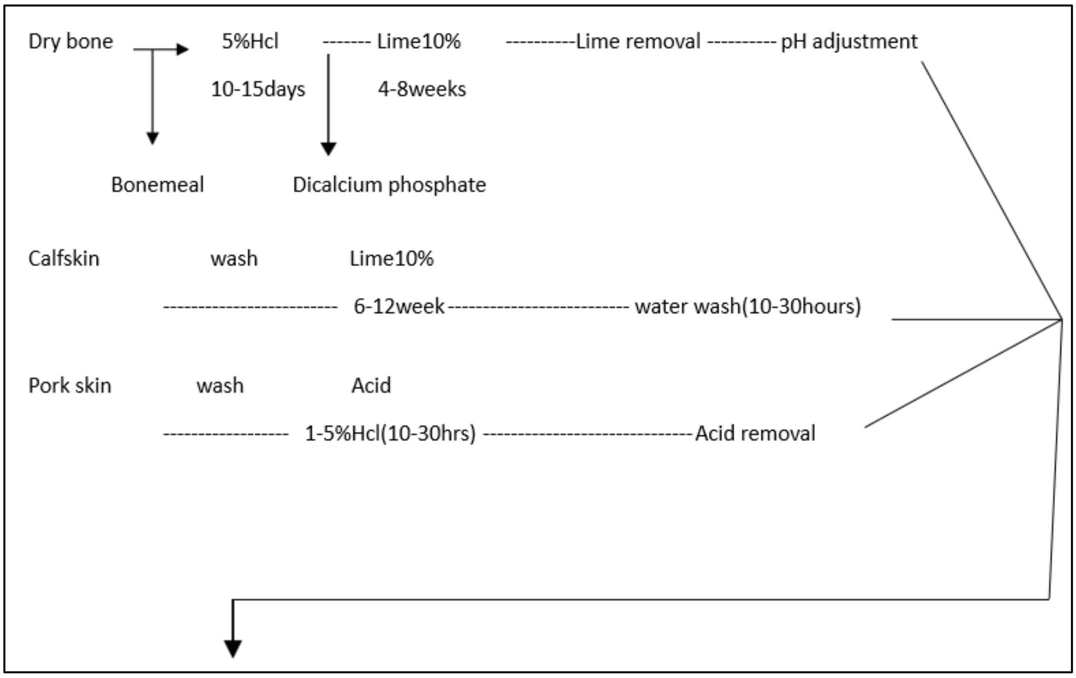

Figure 3.1: The Process of Manufacturing Gelatin

3.3 Type of Capsule (Based on Type of Shell):

- **Hard Gelatin capsule** [HGC]
- **Soft Gelatin capsule** [SGC]

3.3.1 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.

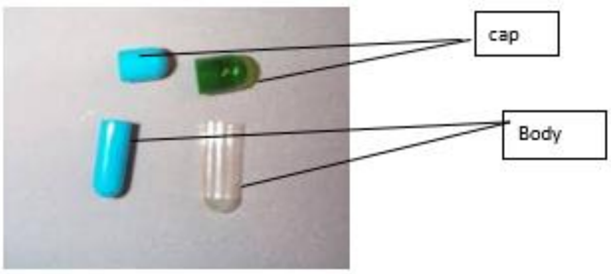

Figure 3.2: showing part of hard Gelatin capsule.

A. Production of Hard gelatin capsule shell:

The mechanism involved for production of hard gelatin capsule shell are

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

Preparation of the gelatin solution (dipping solution): 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 removed 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 as it may affect downstream manufacturing process & very importantly thickness of shell.

- **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.

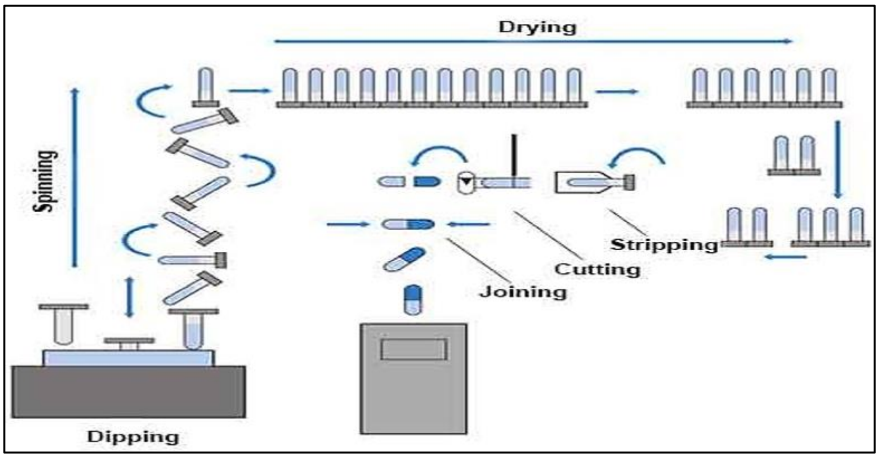

Figure.3.3: Sequence of two-piece hard gelatin capsule shell manufacture

Size of Capsule:

Table 3.1: capsule size & body fill volume

Size	Volume(mL)	Fill weight(g) at powder Density of 0.8/cm^3
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

B. Filling of Hard Gelatin Capsule:

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

a. Rectification: The empty capsules 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.

b. Separation of cap from bodies: This process depends on the difference in diameter between the cap and body. The rectified capsules 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.

c. Dosing of fill material: various method like Auger principle, vibratory fill principle, piston- Tamp principle are employed for filling

d. 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.

C. Filling Principles:

a. Auger fill principle: The empty hard gelatin capsule is taken from hopper to the rectifying unit. the rectifier descends 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 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 drives 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.

b. Vibratory fill principle: in this type of machine, 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.

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 types of machines.

- Dosing-disc type machine
- Dosator type machine

d. Vacuum fill principle: The machine consists 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.

D. Capsule Filling Methods:

a. Manual filling
b. Hand filling machine
c. semi-automatic machine
d. Fully automatic capsule filling machine

a. Manual Filling Method:

- This method is opted when number of capsules 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 capsules 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 over it with little pressure

b. Hand Filling Machine:

- It consists 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 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 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.

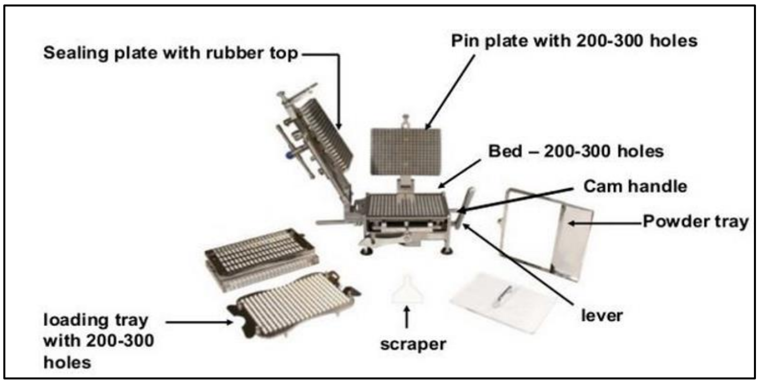

Figure 3. 4: Hand Filling Capsule Machine

c. 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:

- capsule feeding
- Aligning
- insertion into bores of holding ring
- vacuum is used for separating capsule cap and body in first station.
- 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 Iower 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.

d. 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, up to 100-fold less than that employed in typical tablet compression.

Often plugs are very soft compacts and not able to recovered intact from filled capsule. There are two main types of these fillers:

Dosator machine and dosing disc machine.

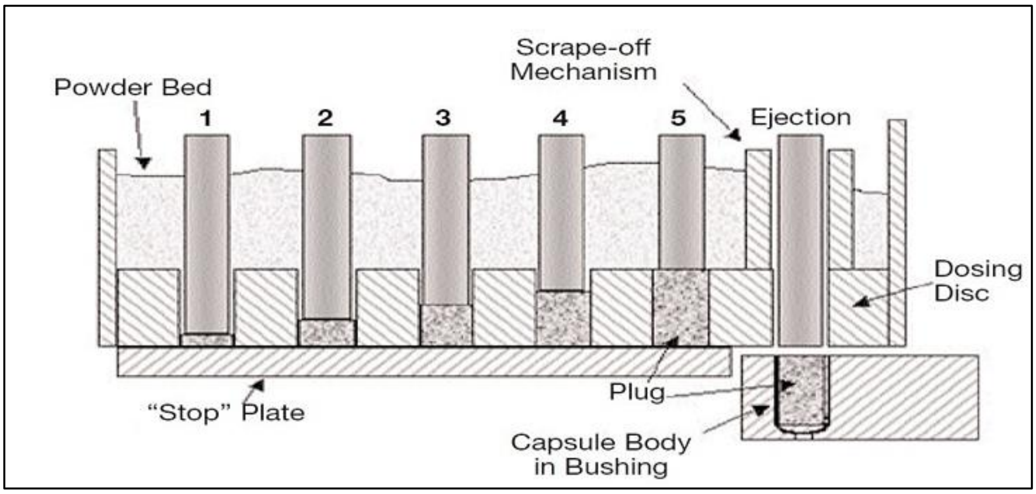

Figure 3.5: Dosing Disc Type Machine

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.

E. 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:

- Cloth dusting: it is manual method in which small number of capsules are rubbed with a cloth or gauze which may or may not contain inert oil.
- Polishing: special pan may be used for polishing the filled capsule. these pans lined with cheese or polyurethane cloth which remove the dust or other powder adhere to capsule.
- 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 is available e.g. – Roto sort.

Formulation Of Powder Need to Be Fill Capsule Shell:

Table 3.2: List of Excipients Used in Powder Formulation for Capsule Filling

Ingredients Type	Purpose	Example
API	Produce therapeutic effect	Amoxicillin
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
Hydrophilic agent	Improve the wettability of Poorly soluble drug	Methyl cellulose, hydroxyl Ethyl cellulose

F. Special technique of formulation used in hard gelatin capsule:

a. 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.
b. Solubility: For special purpose capsule attempt to retard solubility in some manner.
    - formalin treatment has been employed to modify the solubility of gelatin capsule. exposure to formalin vapour 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 in solubilization.
    - various coating has been used to provide similarity modified solubility character. These coating include salol, shellac, cellulose acetate phthalate.
c. Separation of incompatible material: it is involving two phases fill in the capsule. one phase consists 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 points during filling cycle.
d. 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.

G. Manufacturing defect of hard gelatin capsule:

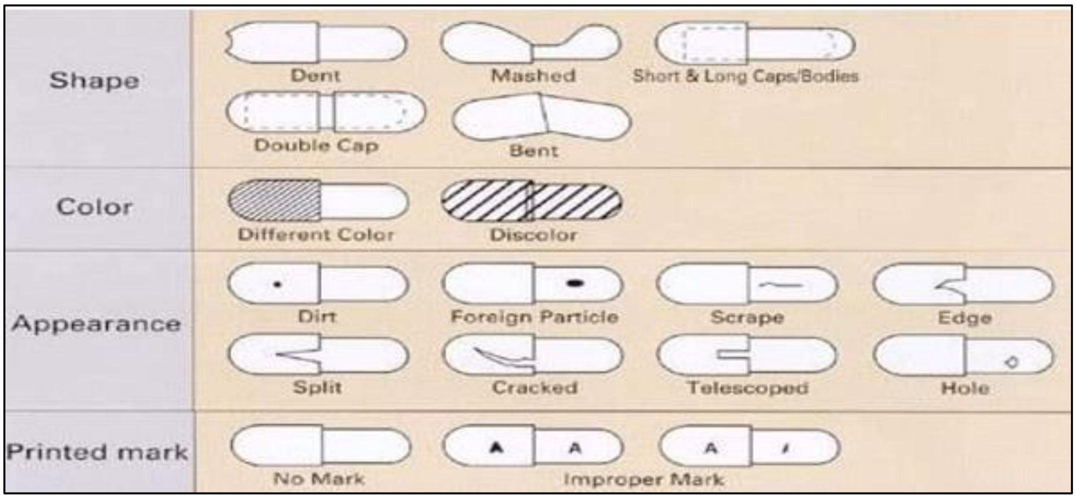

Figure 3.6: Manufacturing Defect of Hard Gelatin Capsule

a. 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
- Colour 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.

b. In process Quality control (IPQC) for capsules:

- Mfg. of Gelatin Shell.
- Drying of shells in controlled humidity.
- Mfg. of granules.
- Filling of Shells.
- Packaging & Labelling.

c. IPQC Checks During Gelatin Shell Manufacturing:

- % purity of gelatin
- Viscosity of gelatin solution 25-45 milli poise
- Bloom strength of gelatin solution 150-250 gm
- Iron content NMT 15 ppm

- Film Thickness
- Colour, surface, appearance of empty shells
- Temperature of hot air, for drying of shells
- Length of Capsule & Body of the shell
- Moisture content 12-15%

d. Inspection of defects like:

- Hardening of shells
- Softening of shells
- Swelling of shells
- Cracking of shells
- Discoloration of shells
- Misprinting of logo on shells

H. Finished product quality control test of capsule:

a. 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.

b. 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 from 000 (the largest) to 5 (the smallest) are commercially available. inspection must be done for size and shape.

c. Unique Identification Markings: Capsule surfaces may bear symbols or other unique identification markings for better identification.

d. 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. 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.

Table 3.3: Percentage Deviation for Capsule Weight

Average weight of capsule Contents	Percentage deviation
Less than300mg	10
300m or more	7.5

e. 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.

f. 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.

- **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.
- **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.
- **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.

g. 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 ±15% and the drug content of none of the capsule fall outside the average drug content ±25%. If 1-3 capsules fall outside the average drug content ±15%, the remaining 20 are assayed. The drug content of at least 27 out of 30 assayed should be within the average drug content ±15% limits. and the drug content of none of the capsules falls outside the average drug content ±25% limits. The test is prescribed for capsules when active ingredient is<10 mg or 10% of fill weight.

h. 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 370 c +-0.50c by means of a constant temperature suitable water bath. The stirrer speed and type of dissolution medium are specified in the individual monograph.

Table. 3.4: Acceptance Criteria for Dissolution Study

Stage	Number of capsules tested	Acceptance criteria
S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units (S1+S2) is equal to or greater than Q and no unit is less than Q – 15%.
S3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and No unit is less than Q – 25%.

The quantity Q, is the specified amount of dissolved active substance, expressed as a percentage of the labelled content.

3.3.2 Soft Gelatin Capsule (SGP):

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

A. 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 enhances patient compliance due to its elegant appearance.
- Suitable for medicaments like semisolid, oils, liquid forms.
- Soft gelatin capsules increase the bioavailability of API.

B. Disadvantages:

- Few fillings 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:

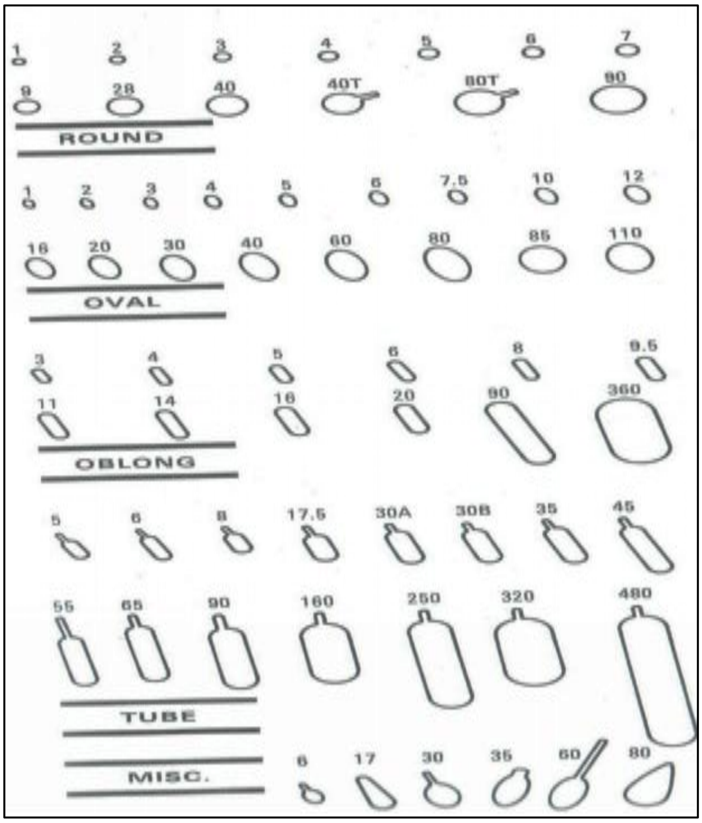

Figure.3.6 Size and shape of soft gelatin capsules. number represents the normal capacity in minims.

C. Nature of capsule shell:

- The capsule shell is basically composed of gelatin, plasticizer & water. Additionally, it may contain preservative, colouring agent, opacifying agent, flavour, sweetening agent to achieve desired effect.
- The gelatin is USP grade with additional specification required by the capsule manufacture. The additional specification concerns 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 milli poise.

- 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.

Table .3.5: Typical Shell Hardness Ratios and Their Uses

Hardness	**Ratio Dry glycerin / Dry gelatin**	**Usage**
Hard	0.4/1	Oral, oil based or shell softening product, designed for hot, humidity areas
Medium	0.6/1	Oral, water miscible based, shell hardening product and designed for temperate areas
Soft	0.8/1	Tube, vaginal, water miscible based or shell hardening product and destined for cold, dry areas

D. 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 falls in this category.
- Similarly, gelatin plasticizer such as glycerine 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.

E. Formulation of filling material of SGC:

The various liquid phase filling matrices used in soft gelatin capsule are selected considering following criteria:

a. Compatibility with capsule shell
b. Ability to dissolve the drug.
c. Rate of dispersion in the GI fluid after shell disintegration in the GIT
d. Ability to optimize the bioavailability of drug.

F. Types of filling/Bases:

a. Hydrophilic Liquids: like PEG 400 having high mol weight are frequently used.
b. Lipophilic liquid: soya bean oil commonly used. the drug like steroid, vitamin D are mixed with this oil.
c. Microemulsion system: it consists of oil-surfactant-water system. blend of oil and surfactant together with the active ingredient is filled into the capsule.
d. Emulsifying oil: mixture of pharmaceutical oil & non-ionic surfactant like polyoxyethylene sorbitan mono oleate serve as self-emulsifying oil matrix.
e. Suspension: the drugs which are insoluble in liquid matrices of capsule & which are poorly soluble in GI fluid can be formulated as suspension.

G. 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 tools is Base adsorption of solid(s) to be suspended.
- Base adsorption is expressed as the number of grams 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 (40g 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 450 angle above the mixture.

Base adsorption = weight of base/weight of solid

H. Minim per gram factor(M/g):

- The base adsorptions used to determine the “minim per gram” factor (M/g) of the solid(s).
- 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 centimetre or 16.23 minims (V).

♣ (BA+S) x 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.

I. Manufacture of soft gelatin capsule:

a. Plate process
b. Rotary die process
c. Reciprocating die process
d. Accogel capsule filling machine

J. 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.

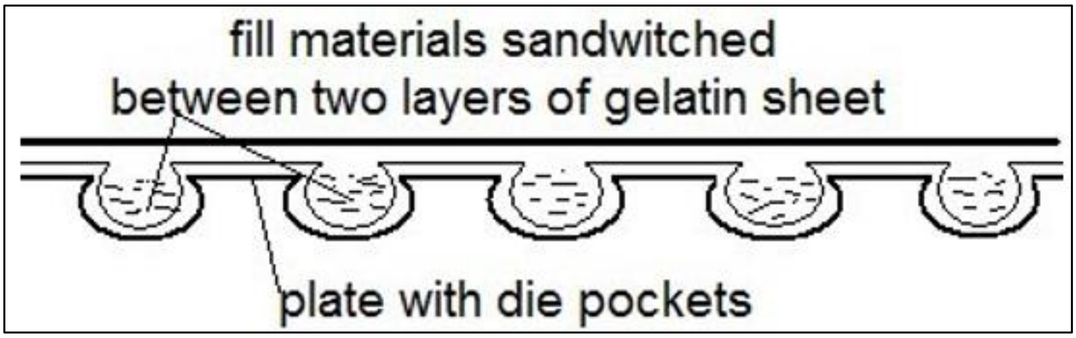

Figure .3.8: Plate Process

K. 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 another 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.
- 4)This half shell of the capsule is formed.
- At this stage the measured quantity of the medicament is filled into 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.

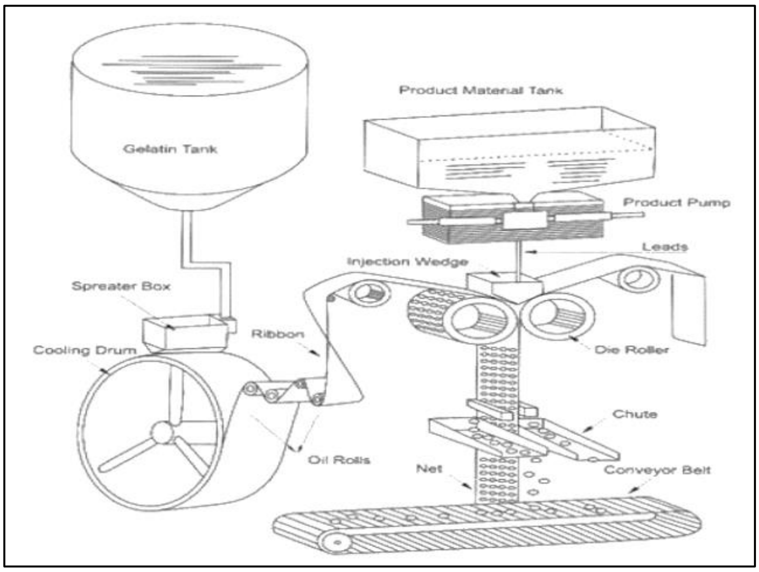

Figure 3.9: Rotary Die Process

a. 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.

b. 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 is transferred to the gelatin lined pockets of the die roll.

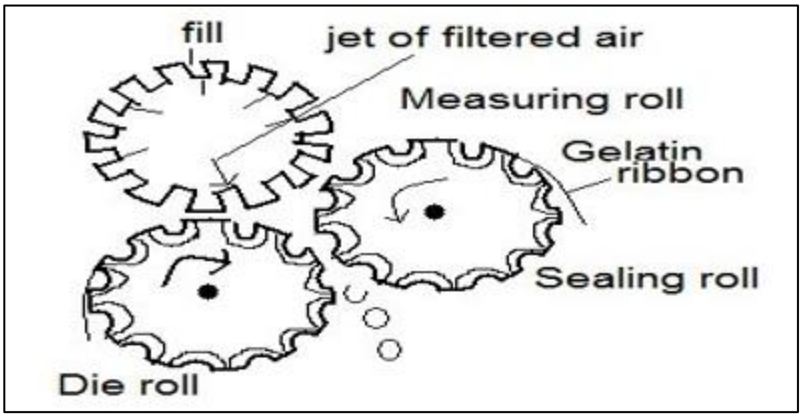

Figure 3.10: Accogel Capsule Filling Machine

c. 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.

d. 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.

L. 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 technologies 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 requires proper maintenance of temp & humidity

Table 3.6: Storage Condition of Capsule

Storage condition	**Relative humidity (%)**	**Temp (^{0}c)**
Minimum	35	15
Best possible	50	20
Maximum	65	25

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.

M. 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 glycerine 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 pickup 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 600 c.
- As the humidity increases the moisture content pickup of capsules increases.
- ex- at 30%RH at room temp shows that gelatin retain about12% (48 mg) of water and glycerine 7% (14 mg) of water. at 60%RH the moisture content should be 17.4%.
- High humidity (>60%RH at 21-240 c) produces 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 conducing at test conditions like

- 1.80%RH at room temp in an open container
- 2.400 c in open container
- 400 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:

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

Table 3.7: Effect Of Temp, Humidity on Capsule Shell

Temp	Humidity	Effect on capsule shell
21-24^{0}C	60%	Capsule become softer, tackier & bloated
>24^{0}C	>45%	More rapid & pronounced. effect-unprotected capsule melt & fuse together

N. Application of soft gelatin capsule:

- They permit liquid medications to become easily portable.
- 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.
- the physiologic availability of drug is often improved since these capsules contain the drug in liquid form.
- the biopharmaceutical characteristics of such formulations can alter and adjusted more easily than those of other solid dosage form.
- 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.

3.4 References:

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