SOFT GELATIN CAPSULES

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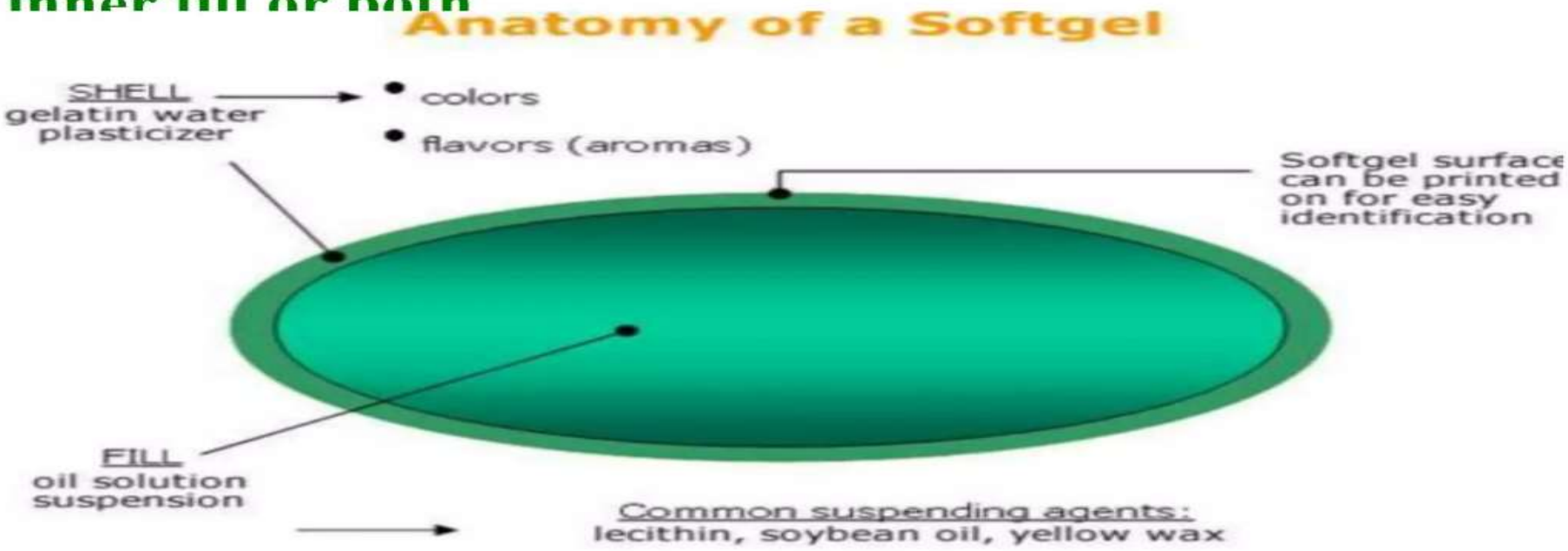
INTRODUCTION

Soft gelatin capsules, also called as softgels, are one piece solid capsule, hermetically sealed, soft gelatin shells (outer shell) containing a liquid, a suspension, or a semi – solid (inner fill). An active ingredient may be incorporated in the outer shell, inner fill or both



Advantages

- Easy to swallow, tasteless, available in different variety of shapes, colours, and sizes.
- Unit dose delivery system and tamper proof.
- Accuracy and uniformity of dosage, capsule to capsule and lot to lot, are predominant advantages.
- Permit liquid medications to become easily portable and increases the bioavailability.
- Low melting point drugs can also be easily incorporated.
- Safer handling of highly potent or cytotoxic drug compounds.
- Dissolution rate or disintegration time are better, so they show an advantage over other solid dosage formulations.

Disadvantages

- Need special type of equipments for the manufacture
- Not suitable to formulate water soluble compounds.
- Not suitable to formulate highly efflorescent drugs as they may cause leaking, or softening of shell.
- Not suitable to formulate deliquescent drugs as they may cause hardening of shell or production of brittle capsules.
- Higher manufacturing costs compared to tablets

Applications of Soft Gelatin Shell Capsules

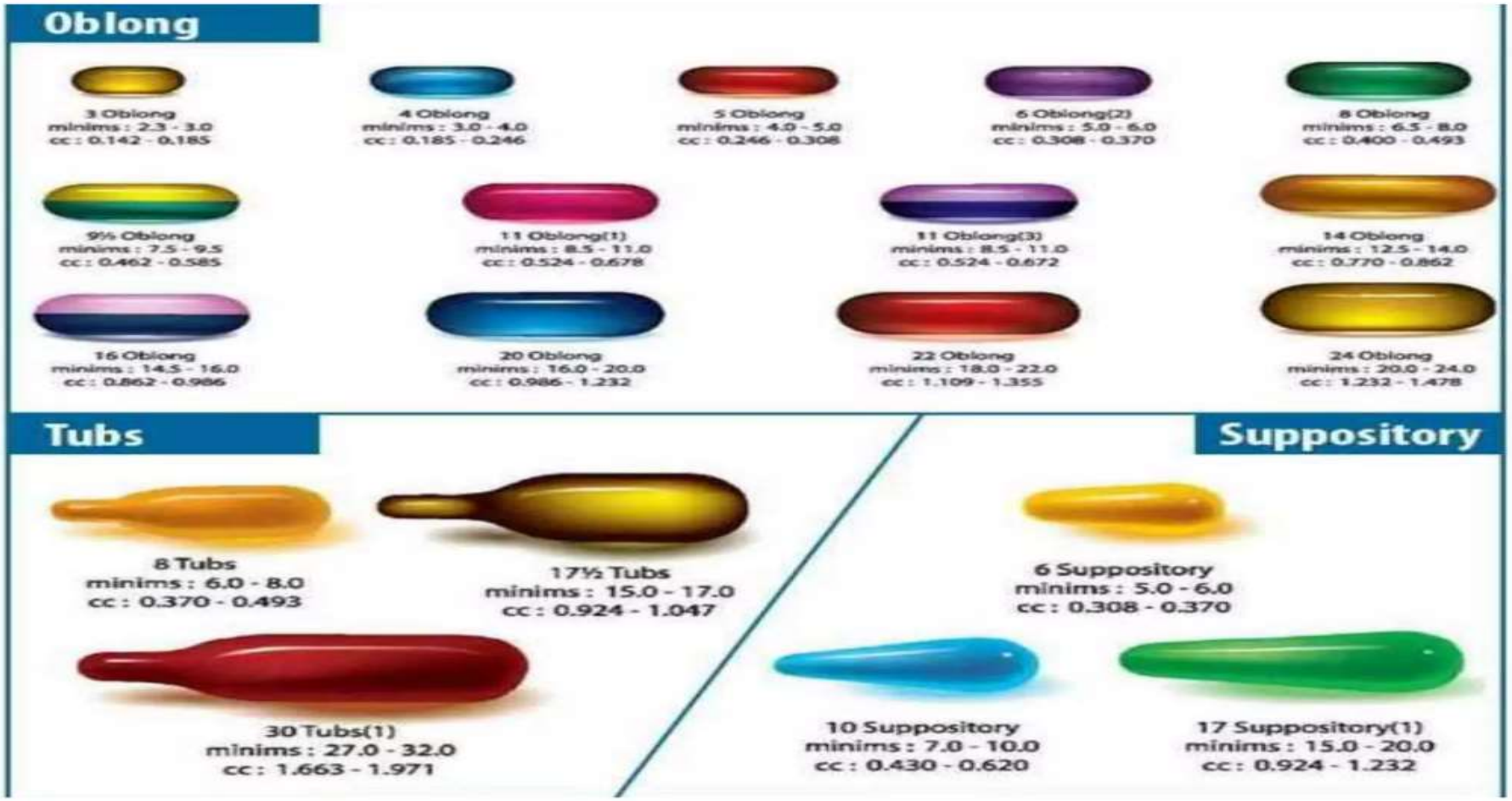
- As an oral dosage form for human or veterinary use.
- As a suppository dosage form for rectal or vaginal use
- As a speciality package in the tube shape, for human or veterinary use of topical, ophthalmic, otic (ear) preparations.
- In the cosmetic industry, these can be formulated as a speciality package for breath fresheners, perfumes, bath oils, various skin creams etc.

Size and Shape of Soft Gelatin Shell Capsules

Twist-off

Number:	6	14	16	20	22
Minimal:	5.0 - 6.0	12.5 - 14.0	14.0 - 16.0	16.0 - 20.0	18.0 - 22.0
CC's:	0.308 - 0.370	0.770 - 0.862	0.862 - 0.986	0.986 - 1.232	1.109 - 1.355

Special shapes


Oblong
3 Oblong
minims : 2.3 - 3.0
cc : 0.142 - 0.185
4 Oblong
minims : 3.0 - 4.0
cc : 0.185 - 0.246
5 Oblong
minims : 4.0 - 5.0
cc : 0.246 - 0.308
6 Oblong(2)
minims : 5.0 - 6.0
cc : 0.308 - 0.370
8 Oblong
minims : 6.5 - 8.0
cc : 0.400 - 0.493
9½ Oblong
minims : 7.5 - 9.5
cc : 0.462 - 0.585
11 Oblong(1)
minims : 8.5 - 11.0
cc : 0.524 - 0.678
11 Oblong(3)
minims : 8.5 - 11.0
cc : 0.524 - 0.672
14 Oblong
minims : 12.5 - 14.0
cc : 0.770 - 0.862
16 Oblong
minims : 14.5 - 16.0
cc : 0.862 - 0.986
20 Oblong
minims : 16.0 - 20.0
cc : 0.986 - 1.232
22 Oblong
minims : 18.0 - 22.0
cc : 1.109 - 1.355
24 Oblong
minims : 20.0 - 24.0
cc : 1.232 - 1.478
Tubs
8 Tubs
minims : 6.0 - 8.0
cc : 0.370 - 0.493
17½ Tubs
minims : 15.0 - 17.0
cc : 0.924 - 1.047
30 Tubs(1)
minims : 27.0 - 32.0
cc : 1.663 - 1.971
Suppository
6 Suppository
minims : 5.0 - 6.0
cc : 0.308 - 0.370
10 Suppository
minims : 7.0 - 10.0
cc : 0.430 - 0.620
17 Suppository(1)
minims : 15.0 - 20.0
cc : 0.924 - 1.232

PRODUCTION OF SOFT GELATIN CAPSULES

Originally, soft gelatin capsules are made using leather mold and later iron mold for shaping the capsules. As technology advanced, the individual iron molds gave way to multiple molding units, and theses led to sets of plates containing pockets.

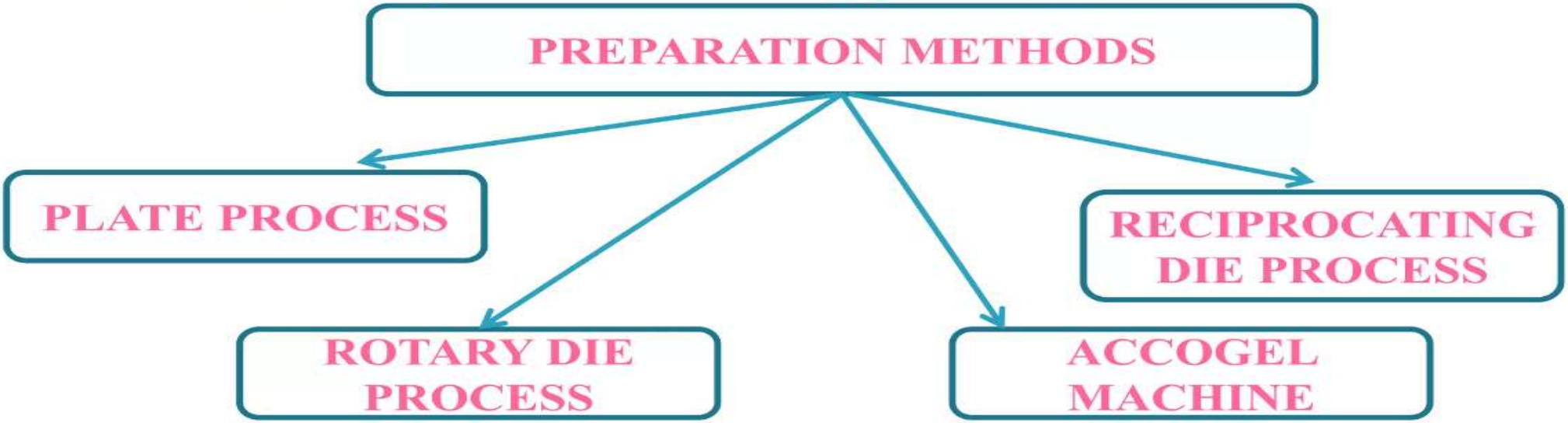


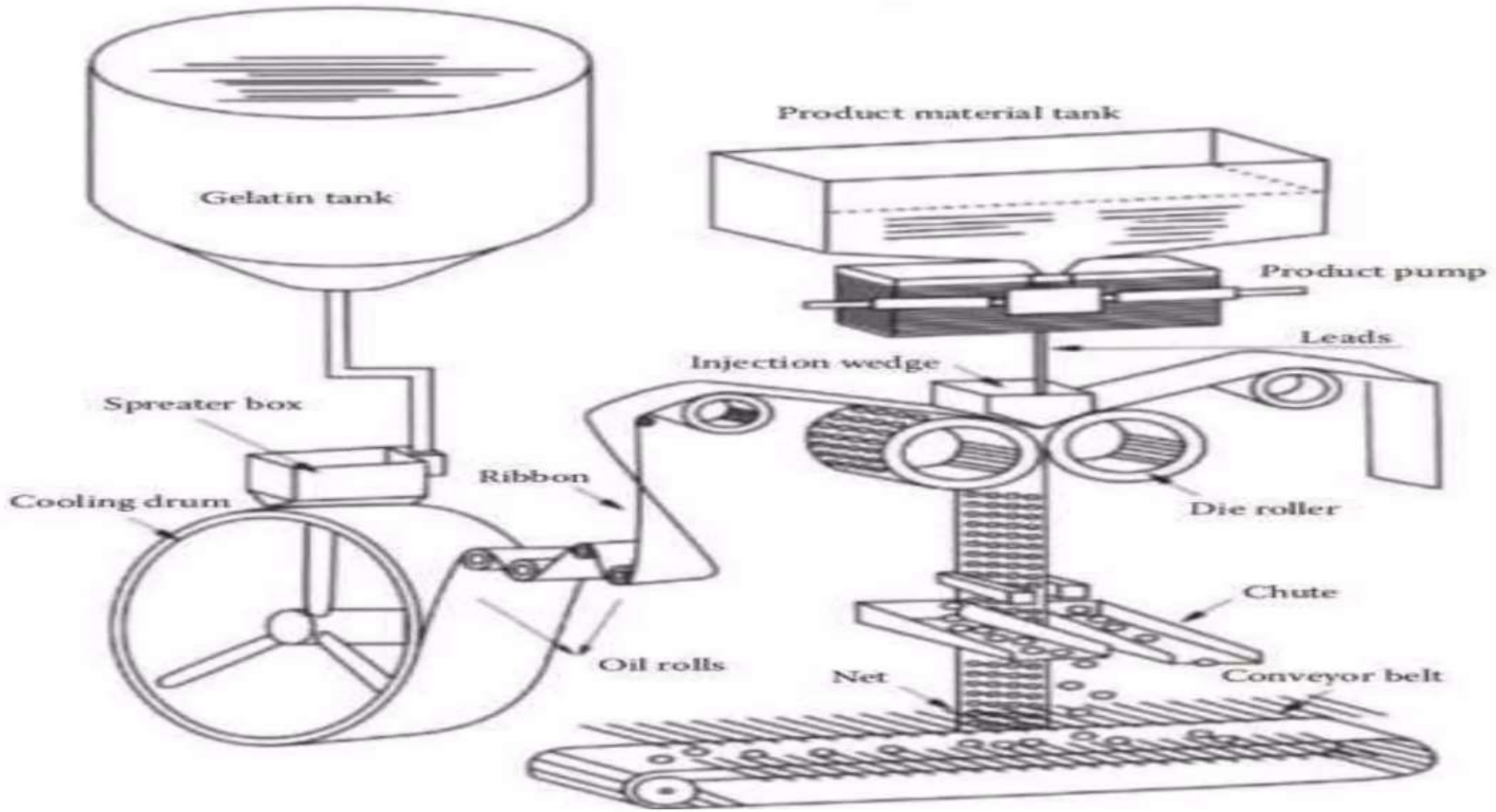
Plate Process

- Oldest commercial method of manufacture.
- Involves pressing two sheets of wet gelatin together between two molds provided with die pockets.
- One of the gelatin sheet is placed over the first mold and application of vacuum produce depressions in the gelatin sheet into which the active fill is placed.
- A second gelatin sheet is laid over the first gelatin sheet, and both the gelatin sheet were pressed together with the fill material sandwiched in between.

Rotary Die Process

- Gelatin mass is fed in to air cooled rotating drums. Gelatin ribbons of controlled thickness are formed from the rotating drums. Thicker shells are used on products requiring greater gelatin strength. The cost of the product is directly proportional to the shell thickness.
- Gelatin ribbons are then passed through a mineral oil bath over oil rolls, and then down between the wedge and the die rolls with die pockets.
- Material to be capsulated flows by gravity into a pump that accurately meters the material through the wedge into the gelatin ribbon between the die rolls. Bottom of the wedge contains small orifices lined up with the die pockets.

- Filled capsules shaped, hermetically sealed, and cut from the gelatin ribbons. Capsule sealing is achieved by using pressure and heat.
- Immediately after manufacture, capsules are automatically conveyed through a naptha wash unit to remove the mineral oil lubricant. The washed capsules are subjected to drying.
- The capsules are then spread on a tray and allowed to come to equilibrium with forced air conditions :– 20-30% RH and temperature of 21-24°C.


Gelatin tank
Product material tank
Product pump
Leads
Injection wedge
Spreater box
Ribbon
Cooling drum
Die roller
Chute
Oil rolls
Net
Conveyor belt

Reciprocating Die Process

- Similar to Rotary Die Process.
- Gelatin ribbons are fed into die rolls that continuously open and close to form rows and pockets in the gelatin ribbon.
- Pockets are filled with medication, and are sealed, shaped, and cut out of the film as they progress through the machine.
- As the capsules are cut from the ribbon, they fall in to refrigerated tanks which prevent the capsules from adhering to one another.

Accogel Machine

- This is the only machine that formulates dry powder in to soft gelatin capsule.
- Rest of the features are same as rotary die machine.

NATURE OF CAPSULE SHELL

Capsule shell is composed of gelatin, plasticizers, water, preservatives, opacifiers, colouring agent, flavours, sugars, and active ingredient.

- **Gelatin :-** 150-200 bloom strength, 2.8-4.5 millipoise at 60°C.
- **Plasticizers :-** added to make the shell elastic, and flexible and to minimise brittleness and cracking. E.g., polyethylene glycol, glycerine and sorbitol.
- **Water :-** demineralised water is used as solvent. Ratio of water to gelatin is about 0.7-1.3 (water) : 1.0 (gelatin), depending on the viscosity of gelatin used.
- **Preservatives :-** added in concentration of 0.2%. Eg. methyl paraben and propyl paraben.
- **Opacifying agent :-** titanium oxide used in 0.2 – 1.2%
- **Flavouring agent :-** used in concentration of 0.1-2%. Eg. ethyl vanillin.

NATURE OF CAPSULE CONTENT

Capsule content is individually developed to fulfil the specifications and requirements of the product. The content of a soft gelatin capsule can be **a liquid, a combination of miscible liquids, a solution or suspension of solid in a liquid.**

All such materials are formulated for capsulation to produce the smallest possible capsule with maximum ingredient and physical stability, therapeutic effectiveness and production efficiency. **The maximum capsule size for convenient oral use in humans is 20 minim oblong, 16 minim oval, 9 minim round.**

Liquids that are **water miscible and volatile** cannot be formulated as a major constituent of the capsule content since they can migrate into the hydrophilic shell and volatalize from its surface. Eg. water, ethyl alcohol etc. but they can be used as co – solvents in the preparation of solutions.

Liquids like aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, esters, organic acids can be formulated as active ingredient. The most widely used liquids for human use are oily active ingredients, vegetable oils, mineral oils, no ionic surfactants and polyethylene glycols.

All liquid solutions, suspensions, for capsulation should be homogenous and air free, should flow by gravity at room temperature. Preparations for encapsulation should have a pH between 2.5 -7.5, since preparations that are more acidic can cause hydrolysis, and leakage of gelatin shell, and preparations that are more alkaline can tan the gelatin and thus affect the solubility of the shell.

Combination of miscible liquids often are used to produce desired physiological actions (increased or more rapid absorption of active ingredient) or physiochemical actions (improved solubility and flow property).

Except for Accogel process (where solids are formulated as dry powders), **solids** are filled into soft gelatin capsules in the form of solution or suspension. Solids should be 80 mesh size or finer particles. A **solution** is more easily capsulated and exhibits better uniformity, stability and biopharmaceutical properties than a suspension.

In formulation of a **suspension,** minimum capsule size should be determined. The final formulation also requires a suspending agent to prevent the settling of solids and to maintain homogeneity. Suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly with the stirring in to the bulk portion of the liquid base.

Two important factors that affect the calculation of the minimum capsule size are :-

- **Base Adsorption Factor**
- **Minim / Gram Factor**

BASE ADSORPTION FACTOR (BA)

Base adsorption is defined as the number of grams of liquid base required to produce the capsulated mixture when mixed with 1 gm of solid(s). BA of a solid is influenced by its particle size and shape, its physical state (fibrous, amorphous or crystalline), its density, its moisture content, and its oleophilic or hyrophilic nature.

In determination of a BA factor, the solid must be wetted thoroughly by the liquid base, and in case of solids that are not easily done, a wetting agent is required.

Procedure :-

Two 150 ml beakers are taken. Weigh a definite amount of solid (40gm) into one beaker, and 100g of the liquid base in the other. Add small increments of the liquid base to the solid, and using a spatula, stir the base into the solid, until the solid is thoroughly wetted and uniformly coated with the base. This produces a mixture that has a soft ointment like consistency.

Continue to add liquid and stir until the mixture flows steadily from the spatula when held at a 45^{o} angle. As the mixture tends to stop flowing, note down the weight of the added liquid base.

Formula of finding BA Factor :-

BA = weight of the liquid base added / weight of the solid

Lower the BA of the solid, higher the density of the mixture, smaller the capsule size.

MINIM / GRAM FACTOR (M/G)

BA factor is used to determine the minim/ gram factor of the solid.

M/G factor is the volume in minims that is occupied by one gram of solid plus the weight of the liquid base required to make the capsulated mixture.

M/G factor is calculated by the following formula,

$$M/G = \{(BA + S) \times V \} / W$$

S = gram of solid

W = weight of the mixture

V = minim

Problem :-

A soft gelatin capsule (4gm mixture) of drug (1gm) by using vegetable oil (liquid base) is to be prepared. If BA = 0.75 gm and M/G = 25, then find the volume to be capsulated.

Solution :-

$$M/G = \{(BA + S) \times V \} / W$$

$$25 = \{(0.75 + 1) \times V \} / 4$$

$$V = 3.52 \text{ ml or } 57.14 \text{ minims}$$

(1 minim = 0.062 ml)

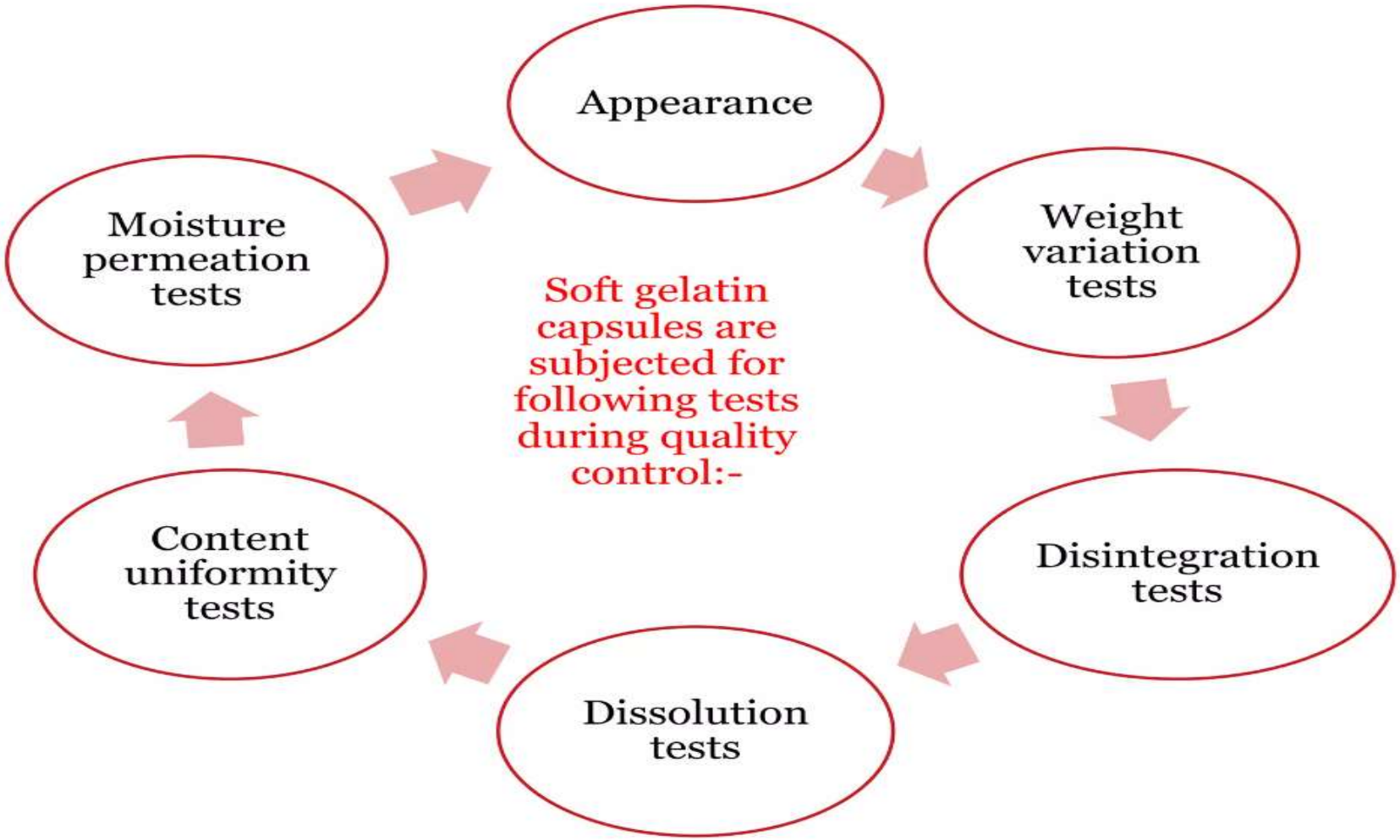
IN PROCESS AND FINAL PRODUCT QUALITY CONTROL TESTS

During the process, capsules are taken periodically for checking :-

- Seal thickness
- Fill weight check
- Capsule diameter sorter
- Capsule colour sorter
- Capsule counting

- **Seal thickness :-** is measured under a microscope and changes in gelatin ribbon thickness, heat or pressure are made if necessary. Acceptable seal thickness is ½ - 2/3 of the ribbon thickness.
- **Fill weight check :-** are made by weighing the whole fresh capsule, slitting it open, and the contents are removed. The shell is then washed in a suitable solvent, and the empty shell is reweighed. If there is weight variation, then necessary changes are made in the pump that measure the weight of the material to be filled.
- **Capsule diameter sorter :-** allows to sort and check the capsules are within the range of ± 0.020 inch of the theoretical diameter of the capsules. Overfills, underfills, or foreign capsules are discarded.

- **Capsule colour sorter :-** capsules are fed into the colour sorter automatically from the diameter sorter. Any capsule whose colour does not conform to the standard for that particular product is discarded, while other capsules that pass the test are accepted.
- **Capsule counting :-** here the capsules are counted, and about 8000 capsules can be counted per minute. They are then, moved to further quality control tests of the finished product.


Soft gelatin capsules are subjected for following tests during quality control:-
Appearance
Weight variation tests
Disintegration tests
Dissolution tests
Content uniformity tests
Moisture permeation tests

Weight variation testing conditions

Average net weight	Deviation (%)	No. of Capsules
Less than 300 mg	±10	Min 18
	±20	Max 2
300mg and more	±7.5	Min 18
	±15	Max 2

Disintegration testing condition and interpretation

Type of capsule	Disintegration medium	Temperature	Limit
Hard gelatin capsule	Water/ buffer	37 °C ± 2°C	30 min
Soft gelatin capsule	Water	37 °C ± 2°C	60 min
Enteric coated capsule	0.1 M HCl mixed phosphate buffer pH 6.8	37 °C ± 2°C	2 hr in HCl – no disintegation 1 hr in buffer - disintegrate

Difference between Hard and Soft Gelatin Capsule

Hard gelatin capsules	Soft gelatin capsules
Cylindrical in shape	Round, oval and tube like shapes
Two piece :- body and cap	One piece
Plasticizer to gelatin ratio :- 0.4:1	Plasticizer to gelatin ratio :- 0.8:1
Boundary wall firm and rigid	Boundary wall soft and flexible
Volatile drug substance is not suitable for filling	Volatile drug substance is suitable for filling
Preservative less	Preservative more than hard capsules
Amount of plasticizer is less	Amount of plasticizer is more than hard capsules

STABILITY TESTING

Stability testing of capsules is performed to determine the physicochemical stability of the drug substance in the finished drug product under specified package and recommended storage conditions and the influence of environmental factors.

Unprotected capsules rapidly reach equilibrium with atmospheric conditions under which they are stored. Due to this property, effect of humidity and temperature, storage and packing conditions, effect of capsule content on the gelatin shell should be studied and the standards should be established.

Stability studies should be conducted by comparing test capsules and control capsule (capsule with just mineral oil). The capsules must be set to an equilibrium conditions with 20 – 30% RH at 21 -24°C before starting a stability study. The physical stability of soft gelatin capsules is associated primarily with the pick up or loss of water by the capsule shell.

If the capsules have protected packaging, the capsules should have satisfactory physical stability at temperatures ranging from the freezing point to as high as 60°C.

For unprotected capsules, stability test should be conducted as the following :-

Condition 1	Observation
RH lower than 20%, temperature lower than 2°C and greater than 38°C . Such a condition has only transient effects.	The transient effects are brittleness, susceptibility to mechanical shock. The capsule can return to normal when optimum storage conditions are provided. On returning to normal, capsule can become dull or may stick together.

Condition 2	Observation
RH greater than 45%, and temperature greater than 24°C	Capsule melts and fuse together
Condition 3	**Observation**
RH greater than 60%, and a reasonable temperature 21-24°C	Capsule shell picks up moisture. The capsule becomes softer, tackier, and bloated. The capsules do not leak unless any ingredient in the capsule attacks the gelatin under the influence of the moisture picked.

Manufacturer also conducts accelerated physical stability study. The results of the study are then taken as a guide for reformulation of capsule content or capsule shell or for selection of retail package. The tests are done in the following conditions for two weeks :-

Tests conditions	Observation
Condition 1 :- 80% RH at room temperature in an open container	The results show a change in :- disintegration, leakage, unusual brittleness or softening of the capsule shell, loss of volatile ingredients from the capsule, widening of the corners of the capsule etc.
Condition 2 :- 40°C in an open container	
Condition 3 :- 40°C in a closed container (glass bottle with tight screw cap)	

- Such defects observed in the results can be further corrected by changing the capsule content, gelatin content, colorants used, or the machine speed or machine dies.
- The control capsule should not undergo any changes other than **Condition 1,** as in such condition capsules have the effect of high humidity, and undergo picking up of moisture in the capsule shell.
- **The stability studies and accelerated studies should be further conducted with capsules in its retail package.**

PACKAGING & STORAGE OF CAPSULES

When **bulk shipments** of capsules are made by the manufacturer, they are temporarily protected from the normal changes in humidity by a suitable barrier such as 0.003 inch polyethylene bag within a standard fibre board carton. The bulk capsules should be stored in an air conditioned area in which the humidity does not exceed 45% RH at 21-24°C.

Retail packaging of capsules in the bulk shipment should be done in the similar conditions as soon as the shipments are opened, for the maximum physical and chemical stability of the product.

Capsules should be stored in glass or plastic containers or maybe strip or blister packaged, and stored at temperature not exceeding 30°C.

If the content in the capsules in glass or plastic container, are hygroscopic in nature, a packet of dessicant (eg. silica gel) is added to absorb any excess moisture present.

In strip packaging, capsules are tight sealed in aluminum or plastic film. In blister packaging, capsules are pushed out of the package, by a force given on any blister in the package.