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# CAPSULE MANUFACTURING PROCESS

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## ❖ ABSTRACT:-

Capsules are solid preparations in which drug substance(s) and/or excipients are enclosed in either a soft or hard soluble shell. The sell is normally made from gelatin or other suitable polymeric material and results in a simple, tasteless, odourless, elegant, easy-to-swallow dosage form without the need for a secondary coating step. Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatin film while the hard capsule is composed oftwo pieces in the form of cylinders closed at one end; the shorter piece, called the „cap" and the longer piece, called the
„body". Capsules may be filled with a range of formulation types including dry powders, semisolids,nonaqueous liquids, and other dosage forms such as beads, mini-tablets, and even mini capsules most of whichare intended for oral administration. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories. Also, In the recent advancements, non-gelatin capsuleshave been discovered, which do not contain gelatin as it"s shell-forming agent. Under this category of capsulesare the HPMC, PVA and starch capsules. This review captures various categories of capsule types, formulation and filling of capsules, locking and sealing of capsules, and, quality control tests. The various packaging and storage method were also highlighted

## ❖ INTRODUCTION:-

### CAPSULE:

Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. 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 releasingthe

medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol canalso be used to make the capsule shells. There are mainly two types of capsules which are:
Hard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g.processes of extrusion or spheronization. These are made in two halves: a smaller- diameter "body" that is filled and then sealed using a larger-diameter "cap".
Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animal protein (mainly gelatin) or plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose). Other ingredients can be added to the gelling agent solution including plasticizers such as glycerin or sorbitol to decrease the capsule's hardness. [2]

**STR.- CAPSUL**

## ❖ ADVANTAGES OF CAPSULE:

1. Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
2. They are attractive in appearance
3. They are slippery when moist and, hence, easy to swallow with a draught of water.
4. As compared to tablets less adjuncts are required.
5. The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
6. They are economical
7. They are easy to handle and carry.
8. protection from light.
9. They are more elegant in appearance.
10. They are easy to transport.
11. They are tasteless and odourless shells
12. They are suitable for drugs possessing unpleasant taste and odour.
13. Provide ready bioavailability of drug because of minimal excipients and little pressureapplied duringmanufacturing.

## ❖ DISADVANTAGES OF CAPSULE:

1) The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are notsuitable for filling into capsules.
2) The concentrated solutions which require previous dilution are unsuitable for capsules because if administeredas such lead to irritation of stomach.
3) They are not suitable for extremely soluble materials, such as potassium chloride, potassium bromide and ammonium chloride, because sudden release of these drugs may irritate the gastric mucosa.
4) They are not suitable for efflourescent materials because they absorb moisture and causesoftening of capsules.
5) They are not suitable for aqueous or hydroalcoholic solutions.
6) Fillling process is laborious and time consuming, Therefore production rate is slower than tableting.

## ❖ TYPES OF CAPSULE:

**Generally capsules are of two types:**

1. **Hard Gelatin capsules**
2. **Soft Gelatin capsules**

### ➢ Hard Gelatin Capsule

Gelatin is a colorless, almost tasteless, translucent proteinaceous substance that is brittle when dry andelastic when mixed with controlled amount of moisture. It is produced by irreversible, partial hydrolysis of collagen, which is obtained from animal skin and bones. It forms a semisolid col-loid gel in the presence of water, which displays a temperature- dependent gel–sol transformation and viscoelastic flow. It has crystallites (microscopic crystals formed during the cooling phase of manufacture of capsule shells) that stabilize the three-dimensional gel network structure and are respon-sible for streaming birefringence in gelatin solutions.

A hard gelatin capsule shell consists of two pieces: a cap and a body. The body has slightly lower diameter than the cap and fits inside the cap. They are produced empty and are then filled in a separate operation.

During the capsule filling unit operation, the body is filled with the medicament, fol-lowed by the insertion of the cap over the body.
The shapes and interlocking arrangement of the body and the cap have evolved to meet the manufacturing and use requirements of hard gelatin capsules.

Schematic diagrams (a–c) of hard gelatin capsules illustrating their design features. The larger, narrower part of the capsules is the body and the smaller, wider part isthe cap.

Conventionally, the body and the cap had smooth edges with a diameter of the cap beingslightly higher than that of the body. The two components could slide over each other.
To minimize defects during the production process, the design of the edge of the body wastapered to allow smooth penetration into the cap with minimum defects during high-speed production operation.
The capsules were modified to have an encircling groove each on the cap and the body and/or a notch to allow firm locking of the cap on the body.
To accommodate the need for a firm seal in the case of liquid and semisolid- filled hard gelatin capsules, raised circular bands (dimples) were introduced on the body and the cap along the sealing zone.
For the use of hard gelatin capsules in double-blind clinical trials, it was necessary to have hard gelatin capsules that could not be reopened after closing. To meet this objective, capsules with the cap thatcovers most of the body were developed.
For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 (the largest, fill volume 1.37ml) to 5 (the smallest, fill volume 0.13ml), The powder-filling capacity of these capsules varies depending on the packed density of the formulation.

## ❖ MANUFACTURE OF HARD GELATIN CAPSULE:

Hard gelatin capsules are manufactured using a dip-coating method and the various stagesinvolved are as follows

### ▪ Step 1: Preparation of the gelatin solution (dipping solution)

A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water which has beenheated to 60–70℃ in jacketed pressure vessels. This solution contains 30 – 40% w/w of gelatin and is highly viscous, which causes bubbles as a result of air entrapment. The presence of these bubbles in the final solution would yield capsules of inconsistent weight and would also become problematic during capsule filling and upon storage. To remove the air bubbles, a vacuum is applied to the solution; the duration of this process varieswith batch size.
Following the above steps, colourants and pigments are added to attain the desired final capsule appearance. At this stage, other processing aids may be added, such as sodium lauryl sulfate, to reduce surface tension. Thesolution viscosity is measured and adjusted as needed with hot demineralized water to achieve the target specification.

### ▪ Step 2: Dip-coating the gelatin solution on to metal pins (moulds)

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. Because the

moulds are below the gelling temperature, the gelatin begins to form a thin gelatin layer or film on the moulds.
The rows of pins are arranged so that caps are formed on one side of the machine while bodies aresimultaneously formed on the opposite side of the machine.

### ▪ Step 3: Rotation of the dip-coated pins

Following adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is removedand rotated several times to evenly distribute the solution around the pins, correct gelatin distribution being critical to uniform and precise capsule wall thickness and dome strength.

### ▪ Step 4: 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 gelatinon 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

### ▪ Step 5: Stripping and trimming

After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length.

### ▪ Step 6: 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.

- **Step 7: Printing**

After formation, the capsule shells can be printed to improve identification. Printing canbe achieved usingone or two colours, containing information such as product name or code number, manufacture‟s name or logo and dosage details.
Printing reduces the risk of product confusion by the numerous handlers and users of theproduct includingmanufacturers, pharmacists, nurses, doctors, caregivers, and patien.

## ❖ Quality Control Test:

### Disintegration Test:

According to B.P., which applies to both hard and soft capsules:

- Introduce one capsule in each tube and suspend the apparatus in a beaker containing 60ml water at 37C.
- If hard capsules float on surface of water, then disc may be added.
- Operate the apparatus for 30 minutes. Remove the assembly from the liquid.
- The capsules pass the test, if no residue remains on the screen of apparatus.

### Weight variation:

- Weigh 20 capsules individually and determine average weight.
- The individual wt should be within limit of 90-110% of average weight.
- If not all of capsule fall within the limit, weigh, weigh 20 capsule individually again.
- Remove the net content of each capsule with the aid of small brush.
- Weight the empty shell individually.
- Net weight of contents individually = Weight of shell − Gross weight.
- Determine the average net content from the sum of individual net weight.
- Then determine the differences between each individual net content and average net content.

### Moisture Permeation Test:

- The degree and rate of moisture penetration is determined by packaging the dosage unittogether with a coloris revealing desiccant pellet.
- Expose the packed unit to known relative humidity over a specified time.
- Observe the desiccant pellet for colour change.
- Any change in colour indicates absorption of moisture.
- By measuring pre-test weight and protest weight of pellet, amount can be calculated.

### Bloom Strength of Gelatin:

- Gelatin is weighed into water to typically create a 6.67% solution in standard bloom bottles.
- The mix is then stirred and kept for 3 hours at room temp.
- Bottles are placed in 65oC bath for 20 minutes,
- Allow the bloom jars to cool for 15 minutes at room temperature
- They are then conditioned for 16 hrs in 10oC water bath.

➢ **SOFT GELATIN CAPSUL**

## Introduction:

Soft capsules are formed in a single piece and are more suitable for oils e.g. Fish oils, or drugs that needto be dissolved in oils or other liquids to aid the drug to be absorbed in the stomach. In soft capsules the drug iscombined with an appropriate solvent in the centre of the capsule and the capsule shell melts within minutes in the stomach. Unpleasant drug tastes and odors are masked by the tasteless gelatin shell. The softgel as a dosageform has remained largely unchanged over the years. Banner has developed new softgel variants that not only offer specific benefits over the standard softgel, but also provide additional patent protection tothe compoundsthey deliver. Softgels‟ ability to enhance bioavailability not only makes them the preferred dosage form for newchemical entities with poor oral bioavailability, they can alsobe used for reformulation of existing drugs, with the purpose of life-cycle extension.

## ❖ Manufacturing of soft gelatin:

## Capsule:

Following methods are used:

1. **Plate process**
2. **Rotary die process**
3. **Reciprocating die process**
4. **Accogel process**
5. **Seamless gelatin capsules**

## 1. Plate process:

In this process a warmed sheet of gelatin sheet is placed over a die plate having a number of depression ormoulds or numerous die pockets. The sheet is drawn into these depressions or pockets by applying vacuum. A measured quantity of liquid medicament is pour over it. Over this another plate of the mould is placed and the pressure is then applied to the combine plate. The capsules are then simultaneously shaped, filled, sealed and cut into individual units. This method is uses for small scale preparation of soft gelatin capsules. It has 20-40% of net moisture content.

## 2. Rotary Die Process:

Before encapsulation process takes place, there are two basic processes.

### Production of gel mass which provide the soft gel shell:

The gel mass is prepared by dissolving the gelatin in water approximately at 80ºC and under vacuum, followed by addition of plasticizer. Once the gelatin is fully dissolved other components such as color, opacifier, flavours and preservatives may be added. The color is compared with the standard. Then the temperature maintained at 57-60ºC in melting tank. The hot gel mass is then supplied to the encapsulation machine throughheated transfer pipes by a casting method that forms two separate gelatin ribbons. The gelatin mass is fed by gravity to a metering device which controls the flow of mass on to air heated (13-14ºC) rotating drums. Duringthe casting process the gelatin pass through the sol gel transformer and the thickness of each ribbon is controlled to ±0.1 mm. The thickness is checked regularly during the process. The two gel ribbons are then carried throughrollers (at which a small quantity of vegetable oil lubricant is applied) and onwards to the rotatory die encapsulation. Each ribbon provides one- half of the softgel.

### Fill Matrix:

The liquid fill matrix containing the active drug substance is manufactured separately from preparation of molten gel. Manufacture of the active fill matrix involves dispersing or dissolving the drug substances in the non aqueous liquid vehicle using conventional mixer homogenizers. They also break up the agglomerates of solids. Oxygen sensitive drugs are protected by mixing under vacuum and or inert gas or by addition of antioxidant

### Rotatory Die:

This machine has two, side-by-side cylinders in each of which half-moulds are cut. These cylinders, like the rollers ofa mangle, rotate in contrary direction and as they are mirror images the moulds come together precisely during rotation. These rotary machines are capable of producing between 25000 and 30000 capsules an hour with an accuracy of dosage of approximately ±1percent.

### Encapsulation:

Liquid gelatin flowing from an overhead tank is forward into continuous ribbon by the rotating drum and brought together between twin rotating dies. The injection of liquid between the ribbons, force the gel to expend and into the packets of dies, which govern the size n shape of the softgels. The sealing of the
capsules is done by mechanical pressure on the die rolls and the heating of ribbons by the wedge. After manufacture, it is subjected to IR drying and then they are separated on the tray and stacked in funnel drier thatsupplies air at 20% relative humidity.

## 3. Reciprocating Die Process:

This is similar to rotary process, but is differ in the actual encapsulating process. The gelatin ribbons arefed between a set of vertical dies that continuously open and close to form the rows of the pockets in the gelatinribbons. These pockets are filled with the medication and are sealed, shaped and cut out of the film as they progress through the machinery.

## 4. Accogel Process (Stern Machine):

This is another rotary process involving the measuring roll, a die roll and a sealing roll. The measuring roll rotates directly over the die , and the pockets in the two rolls are aligned with each other. The powder or granular fill material is held in the pockets of the measuring roll under vacuum. A plasticized sheet is drawn in to the die pockets of the die roll under vacuum. As the measuring roll and the die roll rotate, the measured dosesare transferred to the gelatin lined pockets of the die roll. The continue rotation of the filled die converges with the rotating sealing roll where second gelatin sheet is applied to form the other half of capsule. The pressure developed between the both rolls seals and cut out of the capsules

## 5. Seamless gelatin capsules:

It is a modern method for making soft gelatin capsules takes advantage of the phenomenon of drop formation. The essential part of the apparatus consists of two concentric tubes. Through the inner tube flows themedicament and, through the surrounding outer tube, the gelatin solution. The medicament, therefore, issues from the tube surrounded by gelatin and forming a spherical drop. This is ensured by allowing the drop to formin liquid paraffin in which the gelatin is insoluble. Regular induced pulsations cause drops of the correct size tobe formed, and a temperature of 4°C ensures that the gelatin shell is rapidly congealed. The capsules are subsequently degreased and dried.

## ❖ CONCLUSION:

From the above premises, capsules are solid preparations in which drug substance(s) and/or excipients are enclosed in either a soft or hard soluble shell. The shell is normally made from gelatin or other suitable polymericmaterial and results in a simple, tasteless, odourless, elegant,easy-to-swallow dosage form without the need fora secondary coating step.

Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatin film. The shells may be composed of two pieces in the form of cylinders closed at one end; the shorter piece, called the „cap" and the longer piece, called the „body", or they may be composed of a single piece. The two-piece capsules and one-piece capsules are commonly referred to as hard-shell capsules and soft-shell capsules respectively.

Capsules may be filled with a range of formulation types including dry powders, semisolids, nonaqueous liquids, and other dosage forms such as beads, mini-tablets, and even mini capsules most of which are intended for oral administration. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories.

Also, In the recent advancements, non-gelatin capsules have been discovered, which do not contain gelatin as it"s shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.

Regardless of the type of capsule, the basic components of these capsules include but not limited to; gelatin, plasticizer, colourants, opacifying agents, preservatives, water, thickening agents, flavouring agents, sweeteningagents, etc.

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