Pilot Plant scale-up techniques for Capsule

By -
Gnyana Ranjan Parida
Assistant Professor
SPLS,CUTM

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- Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft soluble container or shell of a suitable form of gelatin.
- Steps in capsule production

1. Mixing of ingredient
2. Granulation and lubrication
3. Making of capsules
4. Filling of capsules
5. Uniformity testing
6. Packing and labeling

- The manufacturing process for capsulated products often same to that tablets.
- Both tablets & capsules are produced from ingredients that may be either dry blended or wet granulated to produce a dry powder or granule mix with uniformly dispersed active ingredients.
- To produce capsules on high speed equipment ,the powder blend must have the uniform particle size distribution, bulk density & compressibility required to promote good flow properties & result in the formation of compact of the right size and sufficient cohesiveness to be filled in to capsule shells.

Manufacture of Hard Gelatin Capsules

1.Raw Materials:

- *Materials are handled by mechanical means of lifting and tilting of drums.*
- *If the same systems are used to transfer materials for more than one product , steps must be taken to prevent cross contamination. A*
- *pproved and validated active constituents and excipients are used for formulation.*

Manufacture of Hard Gelatin Capsules

- ***Shell composition :***

➢Gelatin :Prepared by the hydrolysis of collagen.

➢Gelatin in its chemical and physical properties, depending upon the source of the collagen and extraction.

➢There are two basic types of gelatin:

Type – A and Type – B.

➢The two types can be differentiated by their isoelectric points (7.0 – 9.0 for type A and 4.8 – 5.0 for type B) and by their viscosity and film forming characteristics.

- Combination of pork skin and bone gelatin are often used to optimize shell characteristics.
- The physicochemical properties of gelatin of most interest to shell manufactures are the bloom strength and viscosity.

- Colorants :

- Various soluble synthetic dyes (“coal tar dyes”) and insoluble pigments are used.
- Not only play a role in identifying the product, but also may play a role in improving patient compliance.

E.g., white, analgesia; lavender, hallucinogenic effects; orange or yellow, stimulants and antidepressants.

- Opaquing agents :
  - Titanium dioxide may be included to render the shell opaque.
  - Opaque capsules may be employed to provide protection against light or to conceal the contents.

- Preservatives :
  - When preservatives are employed, parabens are often selected.

2) Shell manufacture :

I. Dipping :

- Pairs of the stainless steel pins are dipped into the dipping solution to simultaneously form the caps and bodies.
- The pins are at ambient temperature; whereas the dipping solution is maintained at a temperature of about 50^0C in a heated, jacketed dipping pan.
- The length of time to cast the film has been reported to be about 12 sec.

II. Rotation :

- After dipping, pins are elevated and rotated 2-1/2 times until they are facing upward.
- This rotation helps to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.

III. Drying :

- The racks of gelatin coated pins then pass into a series of four drying oven.
- Drying is mainly done by dehumidification.
- A temperature elevation of only a less degrees is permissible to prevent film melting.
- Under drying will leave the films too sticky for subsequent operation.

IV. Stripping :

- A series of bronze jaws strip the cap and body portions of the capsules from the pins.

V. Trimming :

- The stripped cap and body portions are delivered to collects in which they are firmly held.
- As the collects rotate, knives are brought against the shells to trim them to the required length.

VI. Joining :

- The cap and body portions are aligned concentrically in channels and the two portions are slowly pushed together.

3) Sorting :

- The moisture content of the capsules as they are from the machine will be in the range of 15 – 18% w/w.
- During sorting, the capsules passing on a lighted moving conveyor are examined visually by inspectors.
- Defects are generally classified according to their nature and potential to cause problems in use.

4) Printing :

- In general, capsules are printed before filling.
- Generally, printing is done on offset rotary presses having throughput capabilities as high as three-quarter million capsules per hour.

5) Sizes and shapes :

- For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 to 5.
- Capsule capacities in table:

Size	Volume	Fill weight(g) at 0.8 g/cm^3 powder density
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

6) Sealing :

- Capsules are sealed and somewhat reshaped in the Etaseal process.
- This thermal welding process forms an indented ring around the waist of the capsule where the cap overlaps the body.

7) Storage :

- Finished capsules normally contain an equilibrium moisture content of 13-16%.
- To maintain a relative humidity of 40-60% when handling and storing capsules.

Filling of hard gelatin capsules

- Hard gelatin capsules are produced using high speed equipments. The process is largely understood as two step :

  1.Formation of compacts or plugs

  2.Filling the compacts in to the capsule shell.

  Selection of equipments depends on properties of powder blend.

  Critical parameters that should be taken in to consideration are

  a. Fill time
  b. Loading rate
  c. Dwell time

Filling of hard gelatin capsules

- Equipment used in capsule filling operations involves one often of two types of filling systems.
- **Zanasi or Martelli encapsulator/ Dosator type-Piston and barrel type**

➢ Forms slugs in a dosatar which is a hollow tube with a
- plunger to eject capsule plug.

Hofliger-Karg machine/ Dosing disc type- Tamping pins

➢ Formation of compacts in a die plate using tamping pins to form a compact.

ZANASI AUTOMATIC
CAPSULE FILLING MACHINE

HOFLIGER KARG AUTOMATIC
CAPSULE FILLING MACHINE

- In this both system, the scale-up process involve bulk density, powder flow, compressibility, and lubricant distribution.
- Overly lubricated granules are responsible for delaying capsule disintegration and dissolution.
- Both types share the common steps. All encapsulation machine have same operation ,rectification, separation of caps and body and ejection of filled capsules. The functioning of two types of plug forming machines require proper attention.

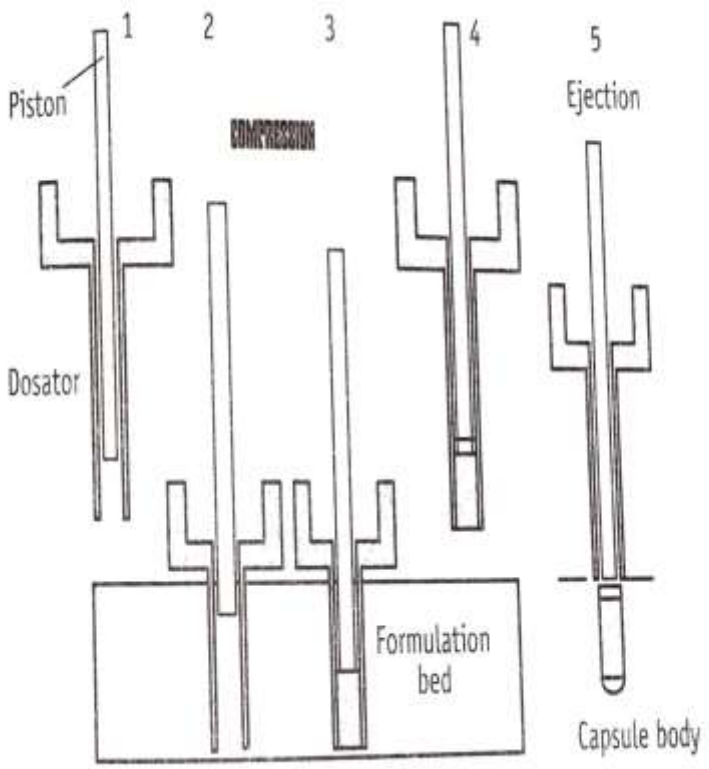
OSAKA MODEL R-180
SEMI AUTOMATIC CAPSULE FILLING MACHINE

Dosator Machine

The dosator machine can be viewed as a hollow barrel containing a moveable piston.

In the operation following steps are involved:

1. At a particular preset height ,the volume between piston head and open end of dosator would represent the appropriate mass of formulation (dose).
2. The open end of the dosator is plunged downward in to the formulation bed. The formulation enters through the open end, rises up until it reaches the stationary piston and forms a plug.



3. The machine provides additional compression through compression knob (or cam mechanism) on the piston. The plug is further compressed and consolidated.
4. Then the dosator along with the plug is lifted out the powder bed.
5. The dosator is positioned over an open capsule body. The piston is depressed via an ejection knob and pushes the plug in to the capsule body.

This mechanism is the most widely used and small pilot scale machines follow the principle.

Yielding capacity- 1,20,000 capsules per hour.

Dosing disc machine

This machine contains a number of tamping pins. In operation , following steps are involved.

a. A dosing disc contains a set of cavities arranged in equally spaced locations around the periphery. The size of cavities is smaller than the internal diameter of the capsule. Five of these locations serve as plug tamping stations and sixth one is the plug ejection station.

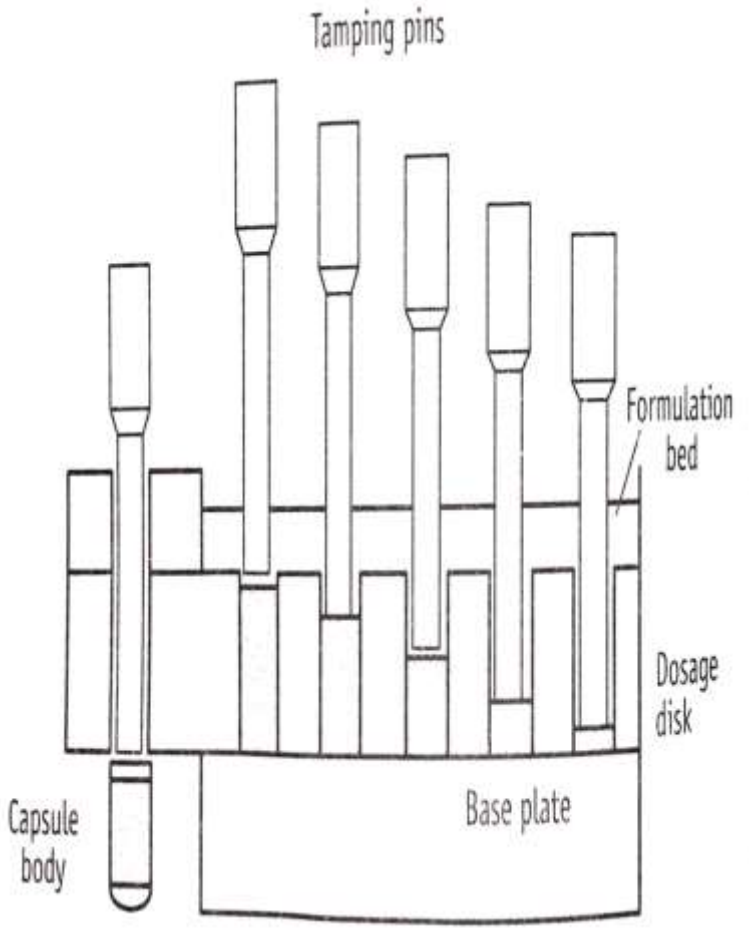
b. The powder formulation bed is maintained at a relatively constant level over the dosing disc. The powder bed level is sensed by a capacitance and feed mechanism gets activated, if the powder bed level falls below the level of the sensor.

c. The powder falls in to the holes by gravity. At each station , the pin tamps the drug powder to form a soft plug. This procedure is repeated several times until the cavity is full.

d. The excess powder is scraped off from the cavity by a deflector plate.

e. The cavity is then positioned over the capsule body . The plugs are ejected.

Lubrication of formulation is important to prevent build up of materials on the tamping pins and also for smooth ejection. Flow properties are important for obtaining uniform weight of the plug.



Processing conditions

1. **Mixing load, mixing speed , mixing time-** As per CGMP , blending /mixing is an important process, which ensures the drug content uniformity in capsule.
2. **Moisture content-** It is critical factor for granules to become compact as well as to maintain physical stability (sticking and picking) and chemical stability(degradation).
3. **Plug formation-** The tamping pressure affects dissolution rate. Hence minimum tamping pressure is required in case of dosing disc machine. In case of dosator machine a stable powder arch is needed to prevent loss of material , ejection and quantitative transfer of powder in to the capsule shell. A few factors need to be identified.

a. Plug height to diameter ratio> 1(as high as 5:1)

b. Compression force range : 50-200N.

c. Piston or tamping pin compression speed range : 100-500min/sec.

4.Flow properties and lubrication- Bulk density and flow properties are also critical for compressibility. These decides the flow and provide cohesiveness , so that filling (in to capsule shell) becomes easy. In this way , weight variation problems will be reduced.

- Over –lubrication may result in weight variation and form soft plugs, which may not permit complete transfer.
- Under- lubrication makes the plugs to stick to the plunger surface. Hence lubrication is critical.

Environment conditions

The storage of empty capsule shell or filled capsules and processing environment of capsules is closely controlled and monitored. Humidity has a significant effect on moisture content of the empty gelatin shell.

a. For empty gelatin shell- 15-20º C, 35-65%RH
b. For processing area – 25-30º C, 45-55%RH

Manufacture of Soft Gelatin Capsules

I. Composition of the shell:

- Similar to hard gelatin shells, the basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
- The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3-1.0 for very hard shell to 1.0-1.8 for very soft shell.
- Up to 5% sugar may be included to give a "chewable" quality to the shell.
- The residual shell moisture content of finished capsules will be in the range of 6-10%.

II. Formulation :

- Formulation for soft gelatin capsules involves liquid, rather than powder technology.
- Materials are generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic effectiveness and manufacture efficiency.
- The liquids are limited to those that do not have an adverse effect on gelatin walls.
- The pH of the lipid can be between 2.5 and 7.5.
- Emulsion can not be filled because water will be released that will affect the shell.

- The types of vehicles used in soft gelatin capsules fall in to two main groups:
  1. Water immiscible, volatile or more likely more volatile liquids such as vegetable oils, mineral oils, medium-chain triglycerides and acetylated glycerides.
  2. Water miscible, nonvolatile liquids such as low molecular weight PEG have come in to use more recently because of their ability to mix with water readily and accelerate dissolution of dissolved or suspended drugs.
- All liquids used for filling must flow by gravity at a temperature of 35^0c or less.
- The sealing temperature of gelatin films is 37-40^0C.

III. Manufacture process :

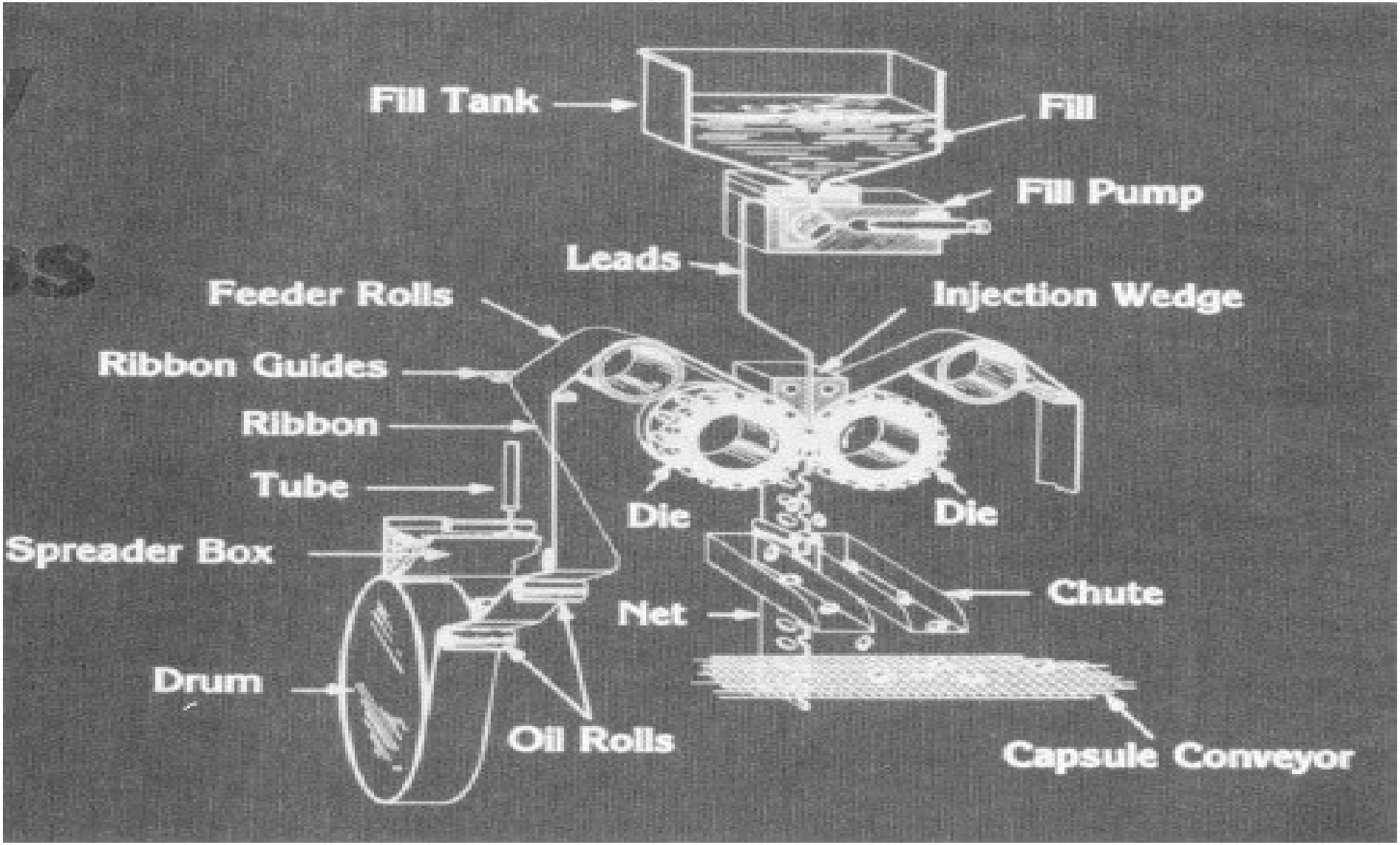
A. Plate process :

The process involved

- Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets,
- Application of vacuum to draw the sheet in to the die pockets,
- Filling the pockets with liquor or paste,
- Folding the lower half of gelatin sheet back over the filled pockets, and
- Inserting the " sandwich" under a die press where the capsules are formed and cut out.

B. Rotary die press:

- In this process, the die cavities are machined in to the outer surface of the two rollers.
- The die pockets on the left hand roller form the left side of the capsule and the die pockets on the right hand roller form the right side of the capsule.
- Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism.
- As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.


Fill Tank
Fill
Fill Pump
Leads
Feeder Rolls
Injection Wedge
Ribbon Guides
Ribbon
Tube
Die
Die
Spreader Box
Chute
Net
Drum
Oil Rolls
Capsule Conveyor

C. Accogel process:

- In general, this is another rotary process involving
  - A measuring roll,
  - A die roll, and
  - A sealing roll.
- As the measuring roll and die rolls rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll.
- The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule.
- Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

4. *Bubble method:*

- The Globex Mark II capsulator produces truly seamless, one-piece soft gelatin capsules by a “bubble method”.

- A concentric tube dispenser simultaneously discharges the molten gelatin from the outer annulus and the liquid content from the tube.
- By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consists of a liquid medicament core within a molten gelatin envelop.
- The droplets assume a spherical shape under surface tension forces and the gelatin congeals on cooling.
- The finished capsules must be degreased and dried.

IV. Soft/Liquid-filled hard gelatin capsules:

- Important reason: the standard for liquid filled capsules was inability to prevent leakage from hard gelatin capsules.
- As banding and of self-locking hard gelatin capsules, together with the development of high-resting state viscosity fills, has now made liquid/semisolid-filled hard gelatin capsules.
- As with soft gelatin capsules, any materials filled into hard capsules must not dissolve, alter or otherwise adversely affect the integrity of the shell.
- Generally, the fill material must be pumpable.

- Three formulation strategies based on having a high resting viscosity after filling have been described.
    1. Thixotropic formulations,
    2. Thermal-setting formulations,
    3. Mixed thermal-Thixotropic systems.
- The more lipophilic contents, the slower the release rate.
- Thus, by selecting excipients with varying HLB balance, varying release rate may be achieved.

CAPSULE POLISHING MACHINE

AUTO MATIC CAPSULE ARRANGEMNT


Thank
You!