

Unit - III

SOFT GELATINE CAPSULE



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SOFT GELATIN CAPSULES

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












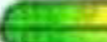

















CHARACTERISTICS

- They may be oblong, oval, or round.
- They Vary in sizes
- They may be single colored or two toned



Shapes of Capsules

ROUNDS						
						
Número:	2	3	4	5	6	7
Mínimo:	1.2 - 2.0	2.2 - 3.0	2.0 - 4.0	3.2 - 5.0	4.5 - 6.0	5.0 - 7.0
CC.	0.074 - 0.124	0.136 - 0.185	0.172 - 0.245	0.197 - 0.308	0.283 - 0.370	0.308 - 0.431
OBLONGS						
						
Número:	3	4	5	6	8	11
Mínimo:	2.3 - 3.0	3.0 - 4.0	4.0 - 5.0	6.0 - 6.0	5.5 - 8.0	6.5 - 11.0
CC.	0.142 - 0.185	0.165 - 0.246	0.246 - 0.308	0.308 - 0.370	0.400 - 0.493	0.524 - 0.679
OVALS						
						
Número:	2	3	4	5	6	7 1/2
Mínimo:	1.5 - 1.8	2.4 - 3.0	3.1 - 4.0	4.3 - 5.0	5.2 - 6.0	6.2 - 7.5
CC.	0.092 - 0.111	0.148 - 0.185	0.191 - 0.245	0.265 - 0.308	0.320 - 0.370	0.382 - 0.462
TUBES						
						
Número:	5	6	8	17 1/2	30	
Mínimo:	2.5 - 5.0	5.0 - 6.0	6.0 - 8.0	15.0 - 17.0	27.0 - 32.0	
CC.	0.164 - 0.308	0.308 - 0.370	0.370 - 0.493	0.924 - 1.047	1.645 - 1.971	
SUPPOSITORIES						
						
Número:	6	10	20	60		
Mínimo:	5.0 - 6.0	7.0 - 10.0	30.0 - 40.0	62.0 - 60.0		
CC.	0.308 - 0.370	0.430 - 0.620	1.950 - 2.460	3.819 - 4.928		

SEAMLESS ROUND SOFTGELS (DROPLETS)

PRODUCTION CAN BE ADAPTED TO PRODUCE SEAMLESS SOFTGELS AND THIS ONES CAN HAVE SIZES BETWEEN 5 mg AND 600mg. THE LIMITS CAN CHANGE DEPENDING ON THE



DESCRIPTION

- *Drug present in these capsules may be suspension, solution or emulsion*
- *Ingredients that are solid at room temperature can also be encapsulated in softgels if they are at least semisolids below 45degree.*
- *The softgels can be coated with enteric resistant or delayed release coating material.*

CAPSULE SHELL

The capsule shell is basically composed of Gelatin, a plasticizer & water it may contain additional ingredients such as preservative, coloring & opacifying agents, flavorings, sugars, acids & medicaments to achieve desired effects

1. Capsule shell WATER:

NOT MORE THAN 45% w/w the ratio by weight of water to dry gelatin can vary from 0.7 to 1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of the gelatin being used.

2. PLASTICIZER:

Used to make the soft gel shell elastic & pliable. Ratio used is between 0.3 to 1.8 for soft to hard shell on dry basis. E.g. glycerin, sorbitol

3.COLOUR:

Used in shell has to be darker than colour of encapsulating material colours may be natural or synthetic.

4.OPACIFIER:

Usually titanium dioxide, may be added to produce an opaque shell ,when the fill formulation is a suspension or to prevent photo degradation of light sensitive fill ingredients. Concentration of opacifier may be up to 0.5%

5.Chelating Agents:

Iron is always present in raw gelatin, & should not contain iron more than 15 ppm.

Additionally chelating agent may be used for preventing the reaction of iron with materials or colours.

"TYPICAL FORMULA FOR GELATIN SHEET"

A typical gel mass formula for making soft gelatin capsules would be:

- Gelatine 35-45%
- Plasticizer 15-25%
- Water ~40%
- Dye / Pigment as needed
- Opacifier as needed
- Other (flavor, sugar,) as needed

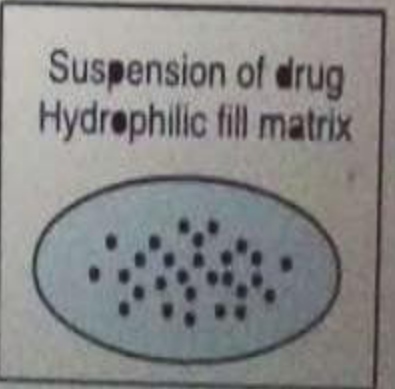
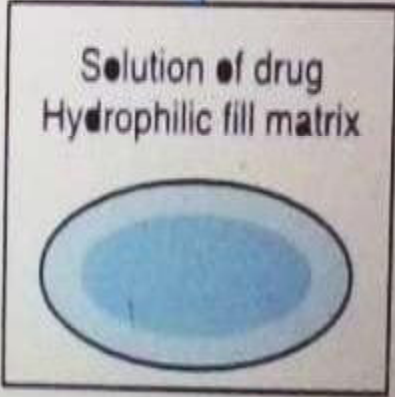
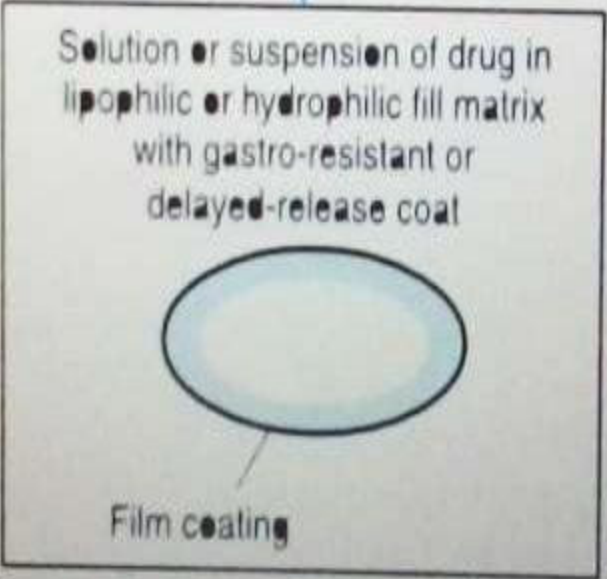
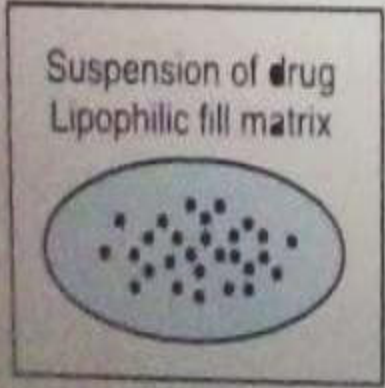
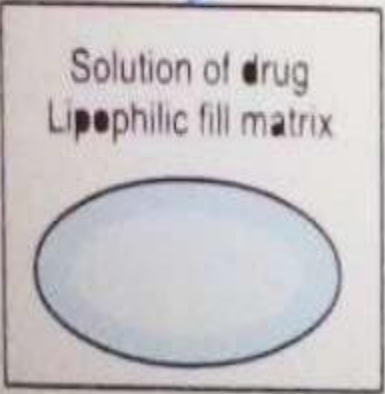
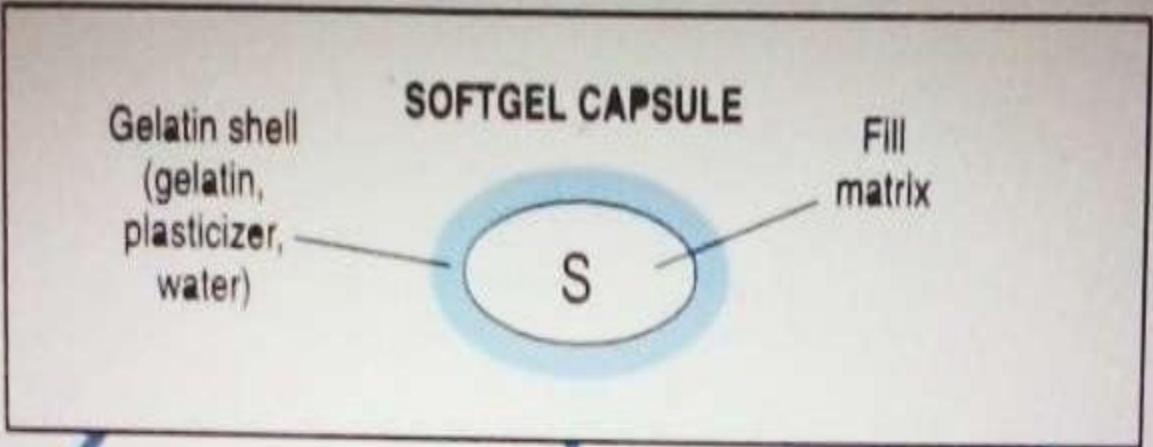
((1 part gelatin, 1 part water, 0.4-0.6 part plasticizer))

"GELATIN MASS MANUFACTURE

- >The gel is prepared in a **300-litre** stainless steel vessel
- >Gelatin powder is mixed with water and glycerine. Heating. Stirring. The molten gelatin mass is formed
- >It is decanted into **200-kg** mobile vessels
- >Turbine mixing where colours and flavours can be added. It ensures consistency of gelatin mass
- >This mass is kept at a constant temperature until it is needed for the next stage of the process

"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, yellow wax



Types of softgels

- **Orally administered:** Solutions or suspensions that release contents in stomach.
- **Chewable softgels:** Highly flavored shell is chewed to release drug liquid fill matrix.
- **suckable softgels:** gelatin shell to be sucked & liquid matrix or just air inside capsule
- **Meltable softgels:** meltable softgels are used for pessaries or suppositories.



Hard Vs soft gelatin Capsules

Criteria	Hard Gelatin Capsules	Soft Gelatin Capsules
Shell	Not plasticized	Plasticized (glycerin, propylene glycol, sorbitol)
Moisture	12-16%	6-10%
Sizes and Shapes	Limited Two-piece	Many One-piece
Content	Usually dry solids (liquids/ semi-solid matrices possible)	Usually liquids or suspensions (dry solids possible)
Manufacture	Shells made in one operation and filled in a separate process	Formed/filled in one operation
Closure	Traditional friction-fit; mechanical interlock, banding and liquid sealing possible	Hermetically sealed (inherent)

Manufacture of softgels:

1.plate process:

- It involves pressing 2 sheets of wet gelatin together b/w 2 molds.
- Each die mold contained pockets into which gelatin sheet was pressed & into which medication was filled.
- Pressure b/w 2 plates enable each capsule to cut out from mold & capsules were subsequently dried.

2. ROTARY DIE PROCESS

*Robert P scherer in 1933 invented this method

*the material to be encapsulated flows by gravity

<<Principle>>

“Involves the formation of a heat seal b/w two gelatin ribbons, simultaneous with dosing of fill liquid into each capsule”

Before encapsulation, two processes are carried out:

1. Gell mass (providing softgel shell)
2. Fill matrix (for softgel contents)

GELL MASS

prepared by dissolving gelatin in water at approx, 80 degrees under vacuum and addition of plasticizers (glycerol)

** once gelatin is fully dissolved then other components are added (colorants, flavourants, preservatives)*

Rotary die process (contd.)

ENCAPSULATION:

molten gel is pumped to machine and two thin ribbons of gelatin formed.
thickness of each gel ribbon is controlled in range of 0.5-1.5mm

Ribbons pass over rollers and are fed between two rotating die cylinders that determine the size and shape of capsules, forming two halves of capsule

ribbons converge next to a fill injector

Here appropriate volume of fill material is measured and dispensed by a pump

die assembly rotates, filled capsule halves sealed together by heat and pressure application and ejected

ROTARY DIE PROCESS (CONTD.)

FINISHING:

drying in tumblers containing lint-free towels and large volume of forced air

Capsules transferred To trays and placed in low-humidity drying rooms, at room temp, to remove excess moisture

water content of the gelatin shell at start ---around 30%
water content of the gelatin shell when evaporation end -- 8 or 9%

The following should be monitored/controlled:

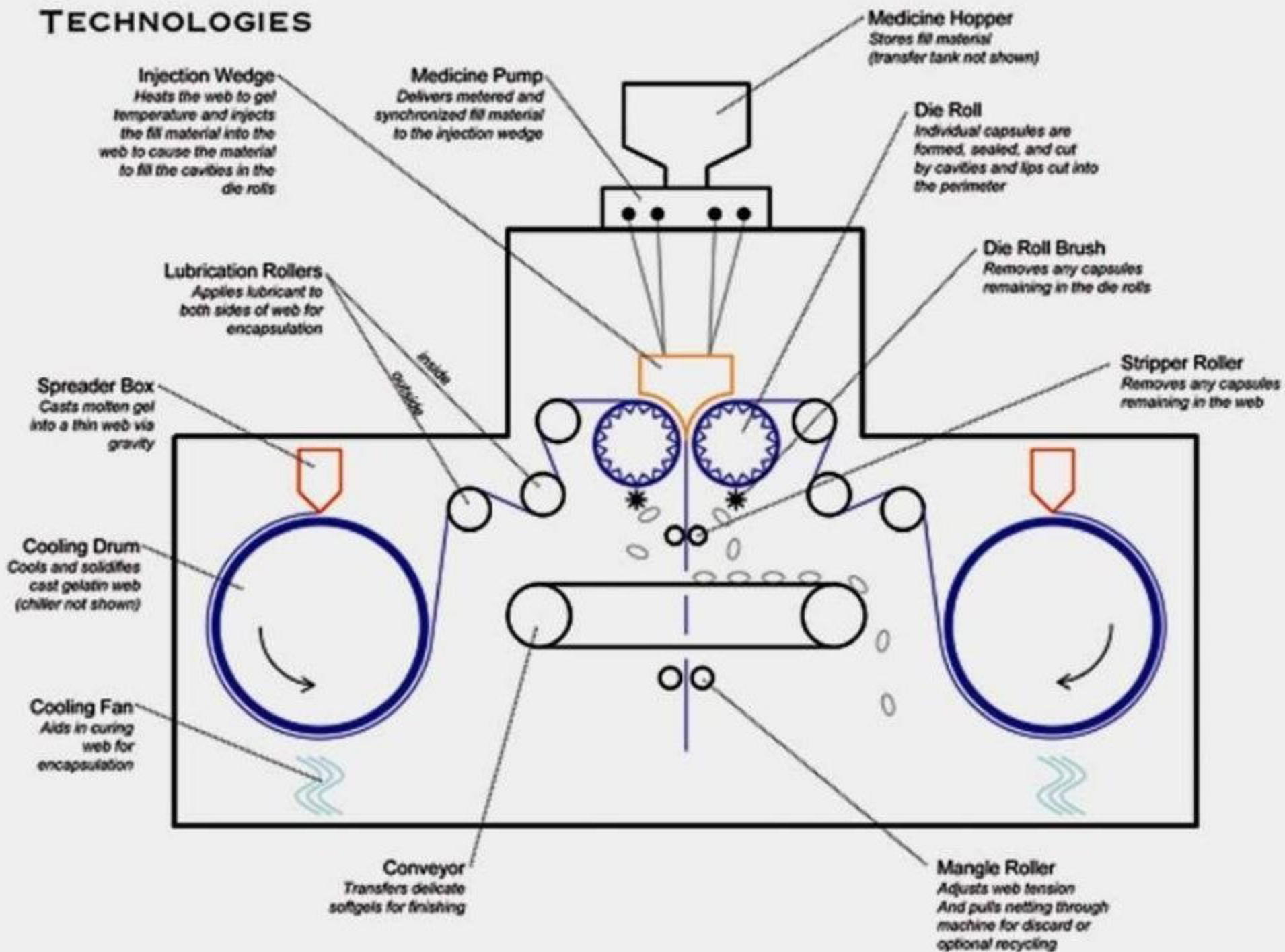
- *Gelatin temperature*
- *Fill temperature*
- *Ribbon thickness*
- *Seal or seam width*
- *Fill quantity*
- *pressure (b/w rotary dies, controls softgel shape and final cut out from gel ribbon*



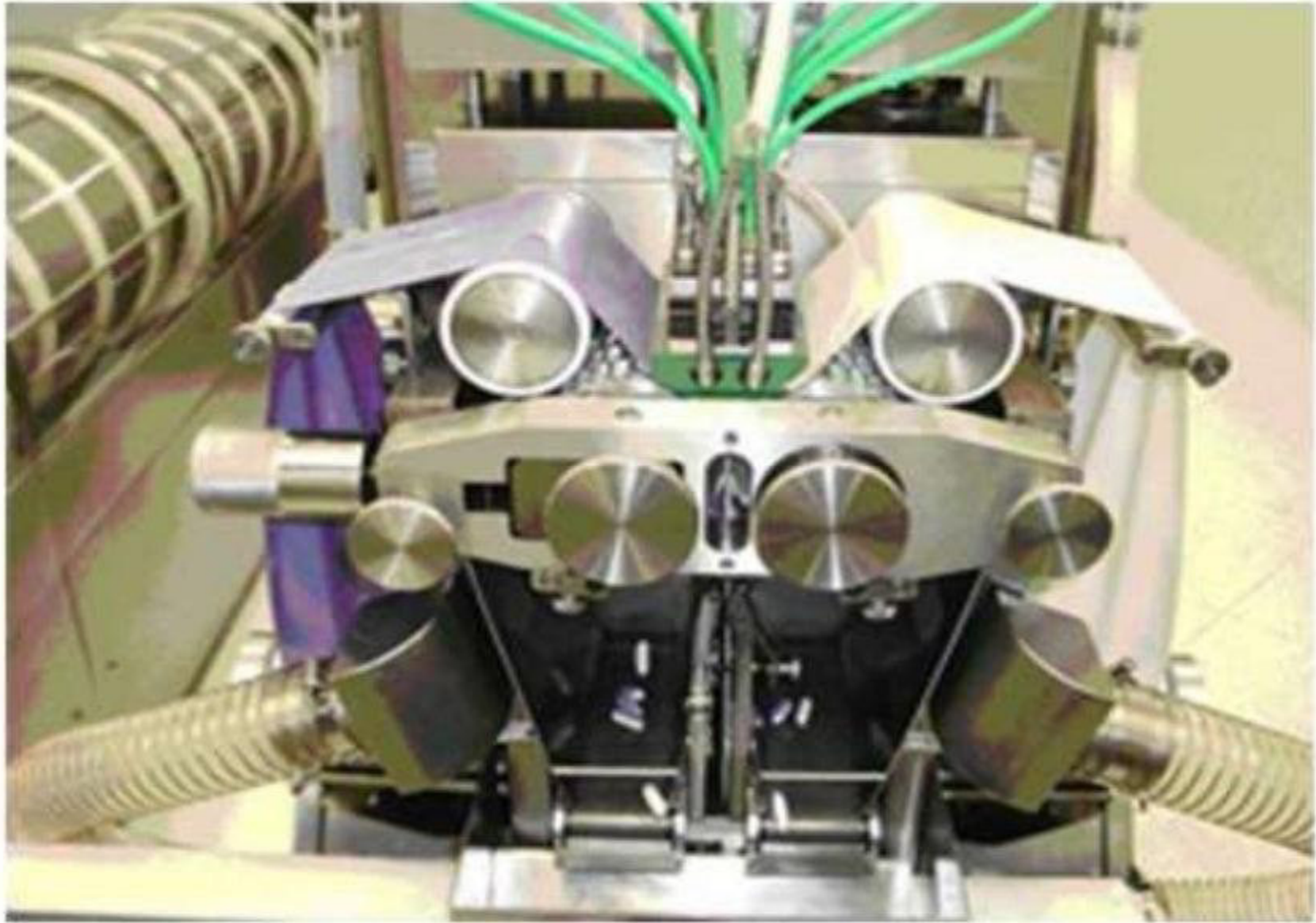
Typical Parts Of Machine

- 1.Spreader Box
- 2.Cooling Drum
3. Oil Lubrication Roller
4. Gelatin Ribbon Guide Roller
- 5.Die Roll
- 6.Injection Wedge
- 7.Capsule Stripper
- 8.Conveyor
- 9.Medicine Filling Hopper
- 10.Medicine Filling Pump

Standard Softgel Machine



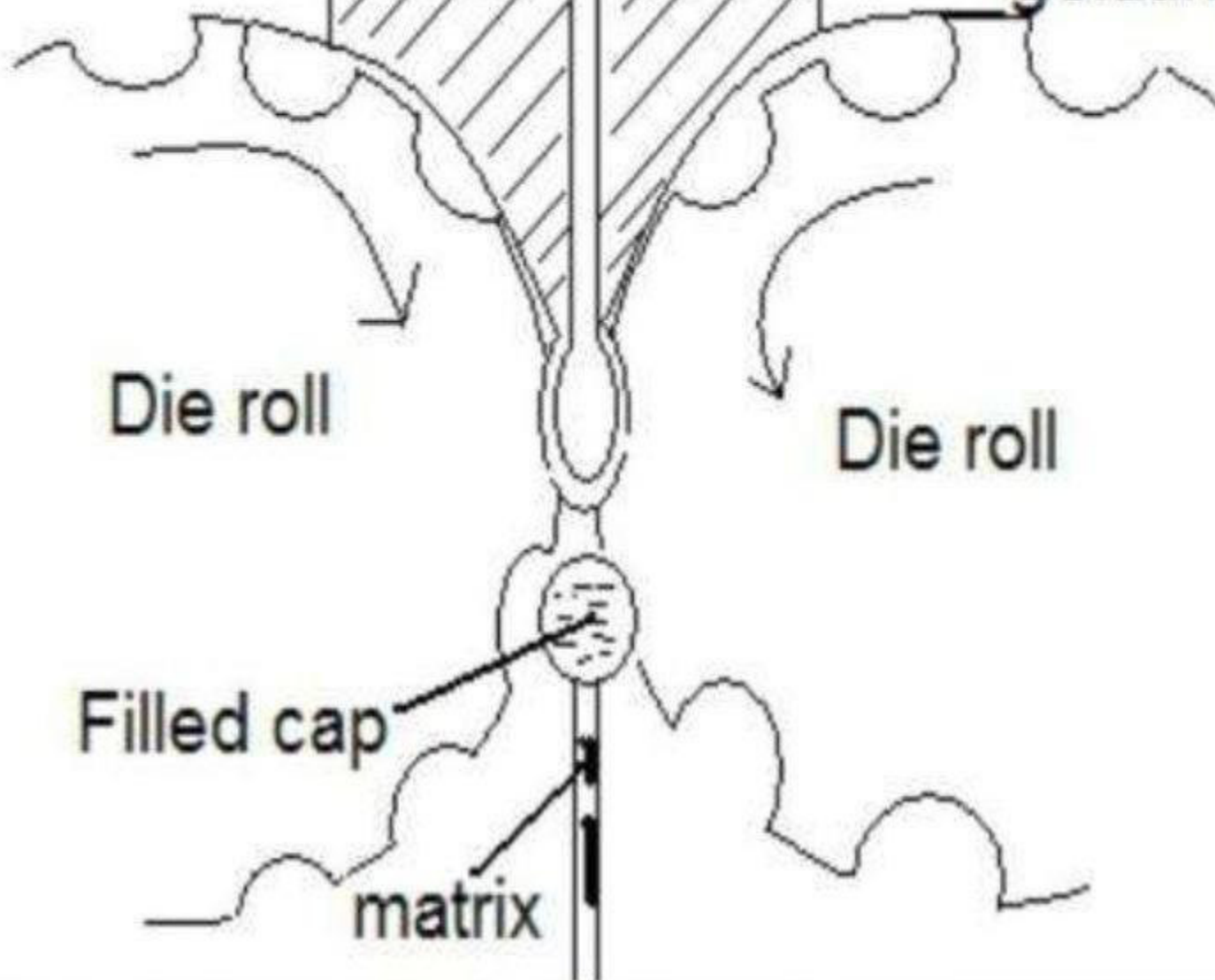
Rotary die encapsulation machine



Metered volume
of product

filling wedge

(warmed to softened
gelatin ribbon)



Die roll

Die roll

Filled cap

matrix

2

The rotary or reciprocating die

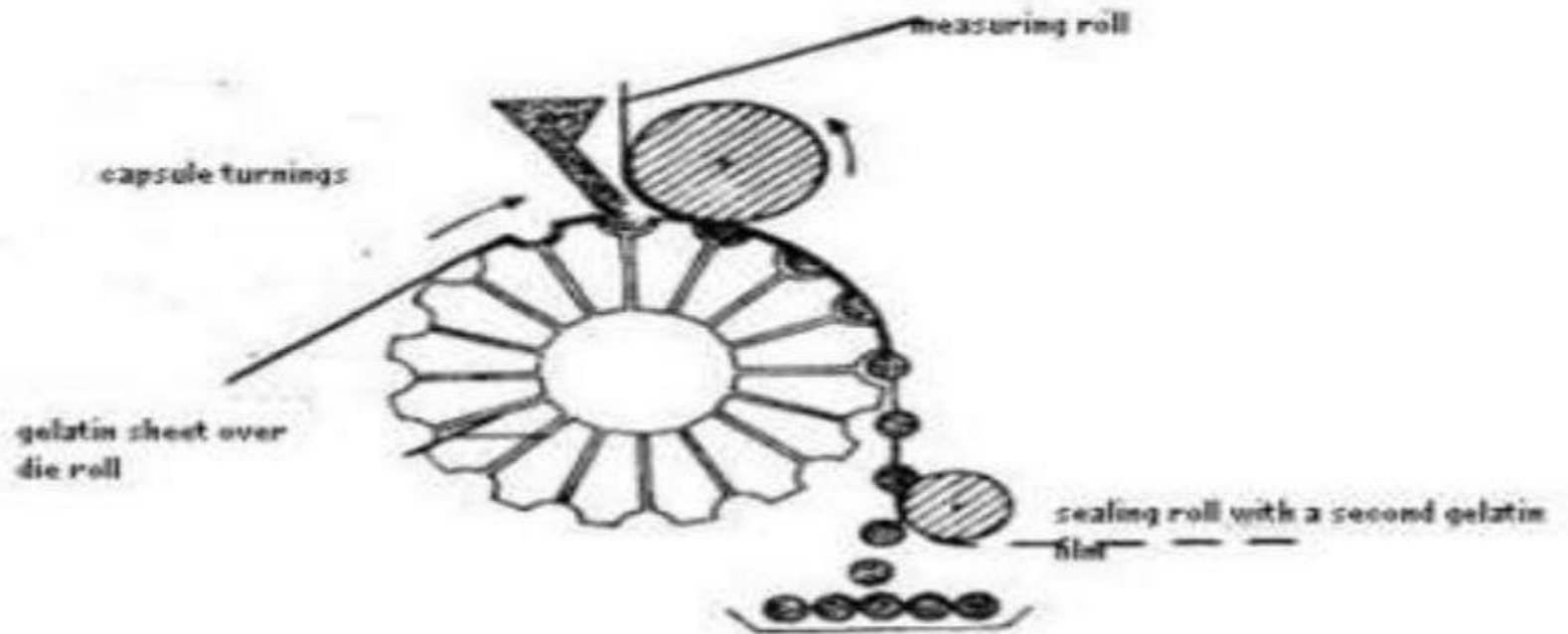


"Accogel Capsule Machine"

Or Stern machine, uses a system of rotary dies but is unique in that it is only machine that can successfully fill dry powder into a soft gelatin capsule.

- Measuring roll rotates directly over the die roll, and the pockets in the 2 rolls are aligned each other.
- Measuring roll-powder or granular fill material under vacuum.
- Die roll-plasticized sheet under vacuum Sealing roll-second gelatin sheet applied to form other half of capsule Pressure developed between die roll and sealing roll seals and cuts out the capsules

Schematic representation of Accogel process



**<<<PRODUCT QUALITY
CONSIDERATIONS>>>**

>>>> **GENERAL OFFICIAL Q.C. TESTS TO BE PERFORMED ON ALL TYPES OF CAPSULES** <<<<
((ACCORDING TO B.P.))



1. Uniformity of dosage unit
2. uniformity of content
3. uniformity of mass
4. dissolution
5. Storage
6. labelling

** IN PROCESS TESTS

1. gel ribbon thickness and uniformity across the ribbon
2. seal thickness
3. weight of capsule fill and its variation from capsule to capsule
4. weight of capsule shell and its variation from capsule to capsule
5. moisture level of the capsule shell before and after drying

**** FINISHED PRODUCT TESTS**

1. *Permeability and sealing*
2. *potency and impurity content*
3. *average weight and weight variation*
4. *uniformity of content*
5. *disintegration*
6. *dissolution*
7. *moisture content*
8. *microbial content*

1. permeability and sealing:

capsules are tested for physical integrity, by visual inspection like, absence of breakage or open cap and body

2. POTENCY AND IMPURITY CONTENT:

All capsules are tested for drug contents, as well as impurities and other substances must meet pre-defined specifications for a batch to be acceptable

3. Weight variation test

FOR HARD CAPSULES:

20 capsules are individually weighed Test



complies if individual capsule falls within 90-110% of average weight



FOR SOFT CAPSULES

proceed as directed under hard capsules, but determine the net wt of the contents of individual capsules as follows:

weigh the capsules individually then cut and open the capsules

remove the contents by washing with the suitable solvent

allow the solvents to evaporate from the shells at room temp

weigh the individual shells

Calculate the net contents



CONTENT UNIFORMITY

10 capsules are taken and subjected to assay



9 of 10 capsules should be in the range of $\pm 15\%$ (85-115%)



And 10th capsule are beyond $\pm 15\%$ range then 20 capsules are assayed



All capsules with in range of $\pm 25\%$ (75-125%)

MOISTURE PERMEATION TEST

The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour 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 post test weight of pellet, amount can be calculated.

6. microbial content:

- ❑ capsules are tested to ensure lack of growth of bacteria and mold by microbiological testing.
- ❑ test is carried out by incubating the capsule contents in growth medium and counting colonies formed after pre-defined period of time.

DISINTERATION TEST-

- The disintegration test determines the whether capsules disintegrated with a prescribed time when placed in a liquid medium under the prescribed integral conditions .

METHOD-

- According to B.P and which applies to both hard and soft capsules
 - 1.introduce one capsule in each tube and suspend the apparatus in a beaker containing 60ml water at 37⁰ C,
 - if hard capsules float on surface of water, the disc may be added.
 - 2.Operate the apparatus for 30 min, remove the assembly from the liquid.

3.the capsule pass the test if

- No residue remains on the screen of the apparatus or,
- If the residue remains, it consists of fragments shells ,
- If a soft mass with no palpable core ,
- If the disc is used any residue is remaining on its lower surface should only consists of fragments of shells.



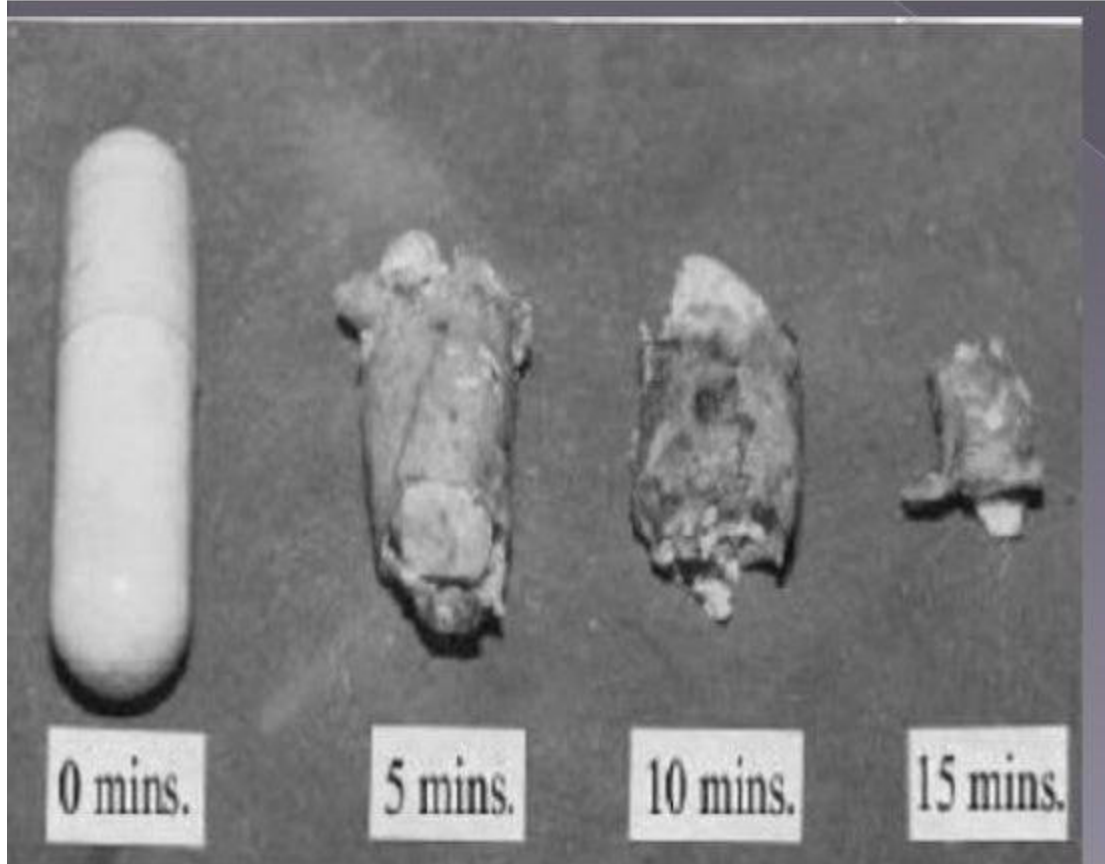
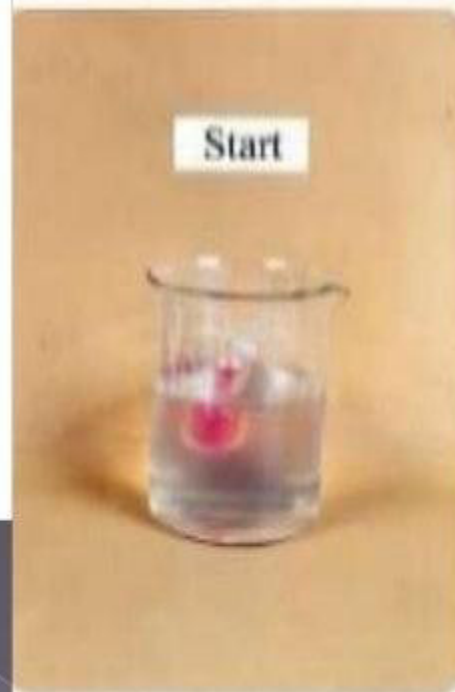


DISSOLUTION TEST-

- The dissolution test is carried out using the dissolution apparatus official in both the U.S.P and I.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 $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ by means of a constant temperature suitable water bath .
- The stirrer speed and type of dissolution medium are specified in the individual monograph .

RESULT -

- Six capsules are tested and are accepted if each of them is not less than monograph specified i.e., $p \pm 5\%$
- If it fails then additional six capsules are tested the result is accepted if the avg. of 12 capsules is greater than or equal to p and none of them is less than $p - 15\%$.
- If the capsule still fails the test the additional 12 capsules are tested and are accepted if the avg. of 24 is greater than to p , if not more than two less than $p - 15\%$ and none of them is less than $p - 25\%$



0 mins.

5 mins.

10 mins.

15 mins.

FACTORS AFFECTING DRUG DISSOLUTION FROM HARD GELATIN CAPSULES

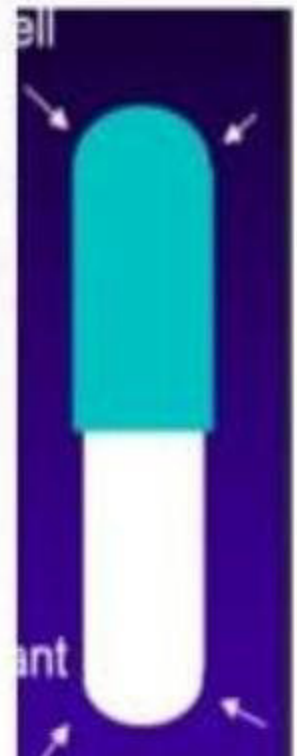
Overall Dissolution Rate is a Function of:

- Dissolution Rate of the Shell
 - Rate of Penetration of Dissolution Medium
 - Rate of Deaggregation of Powder Mass
 - Nature of Primary Drug Particles
- 

- Normally, shell ruptures and dissolves within about 4 minutes.

- Rupture occurs first at the shoulders where shell wall is thinnest.

- Ends fall away and as liquid penetrates and deaggregation occurs, formulation tend to spill out of the two ends.



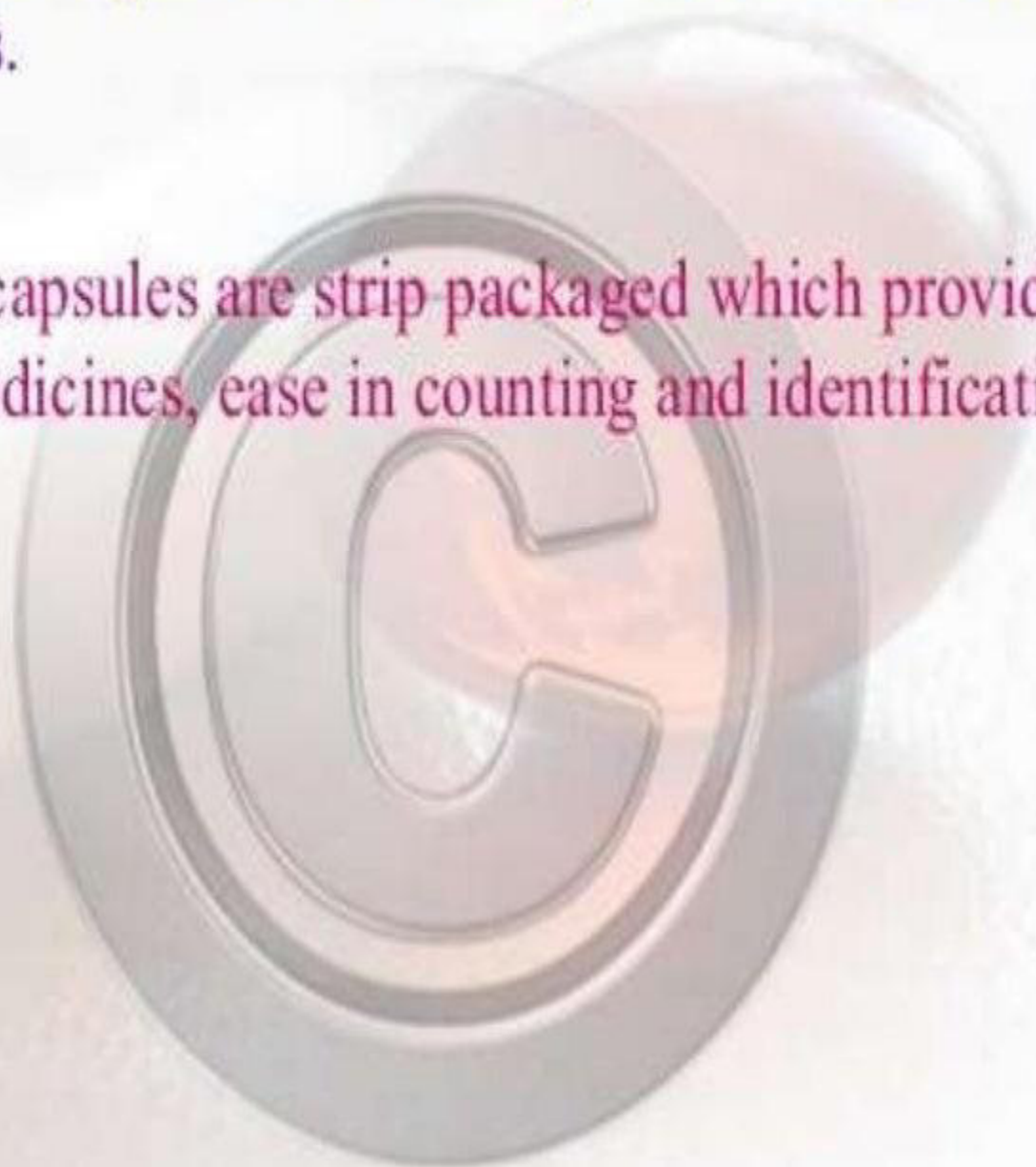
PACKAGING AND STORAGE OF CAPSULES

Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place.

- These type of containers have advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust.
- To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials.
- In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride

may be placed to prevent the absorption of excessive moisture by the capsules.

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



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



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



- Blister pack (heat sealed blister on a cardboard)



- Plastic pail/bucket(economical bulk package)



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



REFERENCE

- Pharmaceutical Dosage Forms and Drug Delivery, Second Edition By Ram I. Mahato
- http://www.pharmacopeia.cn/v29240/usp29nf24s0_c711.html
- <http://www.authorstream.com/Presentation/aSGuest89715-887369-soft-gelatin-capsules/>
- <http://www.slideshare.net/Ramyapriya7/quality-control-of-capsules>

HARD GELATIN CAPSULE



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INTRODUCTION :

○ Defination :

-Capsule are the solid dosage form in which drug substance are enclosed within hard or soft soluble shell. These shell are formed from gelatin.

-Capsule are of two type : 1. Hard Gelatin Capsule.

2. Soft Gelatin Capsule.

-These capsule are made up of gelatin blends , small amount of certified dye , opaquenets , preservative & plasticizer.

○ Gelatin :

-Gelatin is a heterogeneous product derived from hydrolytic extraction of animal collagen .

-Types of gelatin :

Type A : - Derived from acid treated precursor that exhibit an isoelectric point pH – 9. It is manufactured from pork skin .

Type B : - Derived from acid treated precursor that exhibit an isoelectric point pH – 4.7. It is manufactured from animal bones.

ADVANTAGES :

- Tasteless, odorless and can easily be administered.
- Combination of powders we can use.
- These are attractive in appearance.
- The drugs having un-pleasant odor and taste are enclosed in a tasteless shell.
- They can be filled quickly and conveniently.
- Physician can change the dose and combination of drug according to patient requirement.
- They are economical.
- They are easy to handle and carry



DISADVANTAGES

- Hydroscopic drug is not suitable for filling into the capsule. Because they will absorb water present in the capsule shell and cause brittle shell and also ultimately breakdown in two pieces.
- Extremely soluble materials like potassium chloride, potassium bromide or ammonium chloride are sudden release such compound in the stomach cause irritation.
- Efflorescent substance may cause to capsule too soft.
- Deliquescent material may dry to the capsule shell to excessive.



HARD GELATIN CAPSULE

- The hard gelatin capsule consists of two pieces in the form of cylinders closed at one end. The shorter piece is called the cap. This cap fits over the open end of longer piece called body.
- Hard gelatin capsules are also known as dry-filled capsules or two piece capsules. Hard gelatin capsules consists of two parts known as capsule body (longer part) and the capsule cap(the shorter part) The drug substance is placed in the body and the caps are slided over it, hence enclosing the drug substance.



PRODUCTION OF HARD GELATIN CAPSULE SHELL

○ Steps :

1. Dipping
2. Spinning
3. Drying
4. Stripping
5. Trimming & joining
6. Polishing

Dipping : Pairs of stainless steel pins are dipped into the dipping solution to form caps & bodies. The dipping solution is maintained at the temp about 50°C in a heated jacketed dipping pan.

Spinning : The pins are rotated to distribute the gelatin over the pins uniformly & to avoid the formation of beads at the capsule ends.

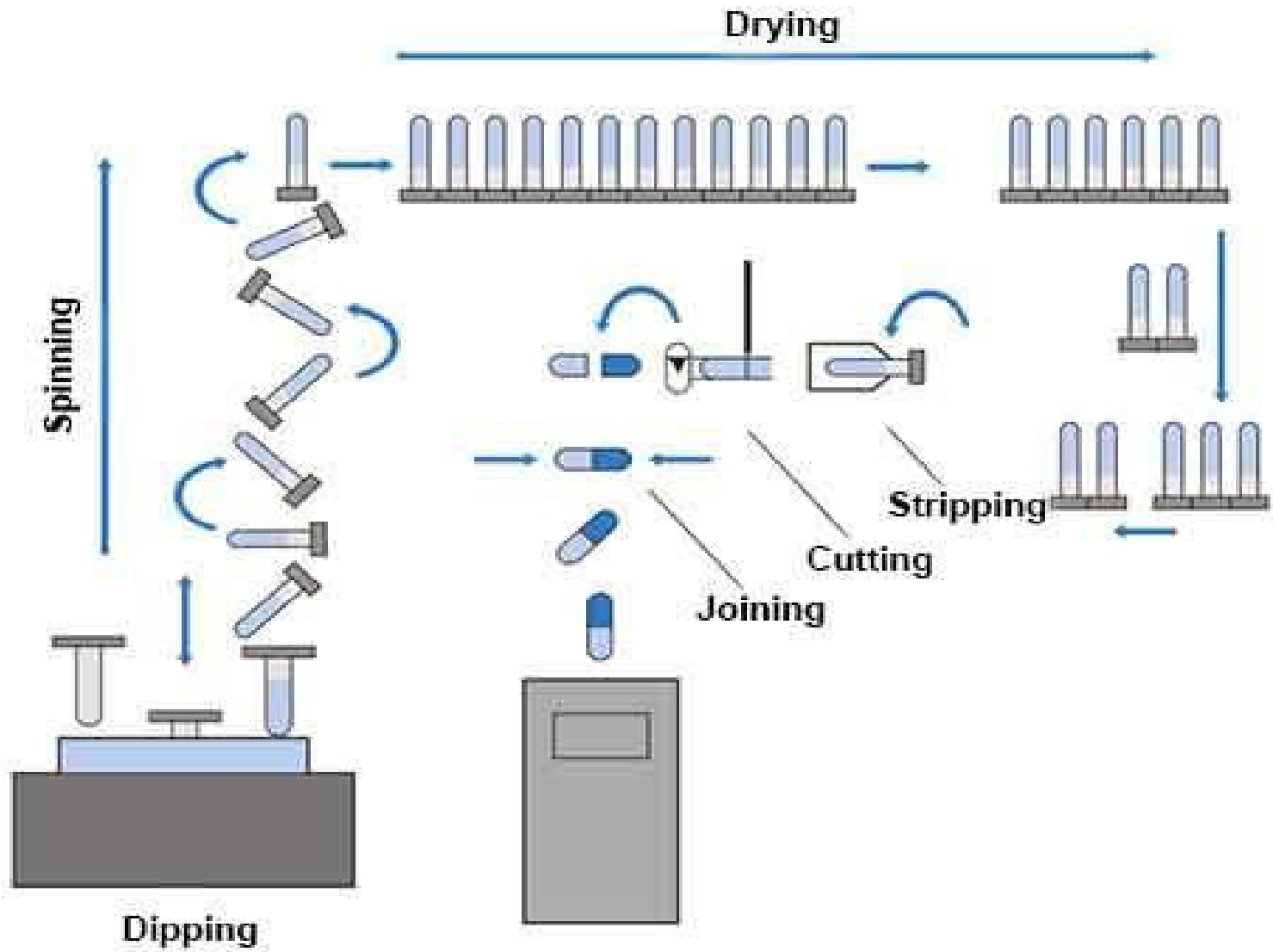
- **Drying :** The gelatin is dried at the blast of cool air to form the hard shell , the pins are moved through the series of air drying kilns to remove the water .
- **Stripping:** The series of bronze jaws strip the cap & body portion of the capsules from the pins.
- **Trimming & joining:** The stripped cap & body portion are trimmed to the required length by stationary knives.
- After trimming to the right length , the caps & body portion are joined from the machine.
- **Polishing :**

Pan Polishing : Acela – cota pan is used to dust & polish .

Cloth dusting : capsules are rubbed with the cloth.

Brushing : Capsules are filled under the soft rotating brush.





Capsule Size :

Size	Actual volume	Size in mm
000	1.37	26.3
00	.95	23.7
0	0.68	21.8
1	0.50	19.2
2	0.37	18.3
3	0.30	15.3
4	0.21	14.7
5	0.15	11.9



Developing and preparing the formulation

- Diluents and fillers: lactose, microcrystalline cellulose, starch.
- Disintegrants: sodium starch glycolate ,pregelatinised starch
- Gligants and lubricants: silicon dioxide,magnesium stearte,calcium stearate
- Wetting agents: SLS

HAND OPERATED CAPSULE FILLING MACHINE

It is having following parts:-

- a) Bed having 200-300 holes.
- b) Loading tray having 200-300 holes.
- c) Powder tray.
- d) Pin Plate having 200-300 pins.
- e) Sealing plate having rubber top.
- f) Lever
- g) Cam handel



Adinath International
Email: info@adinath.co.in



SEMI AUTOMATIC MACHINE

FILLING OF CAPSULES :

Steps :

1. Rectification: - Empty capsules are oriented so that all points in same direction. i.e. body ends downward.
2. separation of Body & caps : - Vacuum applied body pull down into lower portion of split bushing or split filling rings .
3. Dosing & fill material
4. Joining & Ejection : capsules are joined by peg rings. It forces the capsules body against the closing plates . Filled capsules are ejected via compressed air.
5. Collection : Filled capsules are collected through chute.



Filling of Capsules



POWDERS w/ capseal



GRANULES



BEADS



TABLETS

QUALITY CONTROL OF CAPSULES:

- Whether capsules are produced on a small scale or large scale all of them are required to pass through certain tests i.e., quality control tests to test the quality of the finished product
- Disintegration test
- Weight variation
- Dissolution test
- Assay
- Content uniformity
- Stability testing
- Moisture permeation test



1. Disintegration Test-

The disintegration test determines the whether capsules disintegrated with a prescribed time when placed in a liquid medium under the prescribed integral conditions .

○ METHOD-

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

1.introduce one capsule in each tube and suspend the apparatus in a beaker containing 60ml water at 37^o C,

– if hard capsules float on surface of water, the disc may be added.

2.Operate the apparatus for 30 min, remove the assembly from the liquid.

3.the capsule pass the test if

- No residue remains on the screen of the apparatus or,
- If the residue remains, it consists of fragments shells ,
- If a soft mass with no palpable core ,
- If the disc is used any residue is remaining on its lower surface should only consists of fragments of shells.

Disintegration apparatus



2. Weight Variation-

Weigh 20 capsules individually and determine the avg weight



The individual wts should be with in limit of 90-110% of avg wt



If not all of capsules fall with in the limits, Weigh 20 capsules individually.



Remove the net content of each capsule with the aid of a small brush



Weigh the empty shells individually



Wt Of Contents Individually = The Wt Of Shell-Gross Wt



Determine the avg net content from the sum of individual net wt



Then determine the difference b/w each individual net content and avg net content.



3. Dissolution Test-

The dissolution test is carried out using the dissolution apparatus official in both the U.S.P and I.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 37.0 ± 0.5 C by means of a constant temperature suitable water bath .

A) Apparatus -1 (rotating basket dissolution apparatus)

Small wire mesh size basket – 22

Temp – 37 ± 5 °C

Rotated speed- 25-150 rpm

Dissolution medium hight from the bottom of the vessel : 23 – 27mm

B) Apparatus -2 (rotating paddle dissolution apparatus)

Small wire mesh size – 22

Dissolution medium hight from the bottom of the vessel – 23 – 27 mm .



Dissolution apparatus



- Temperature – $37 \pm 5^\circ \text{C}$
- Rotated speed- 25 – 150 rpm

4. Content Uniformity :

- This test is applicable to all capsule which are meant for oral administration . For this test a sample of the content is assayed as described in individual monographs & the values calculated which must comply with the prescribed standards.
- -Content uniformity :
- - 30 capsules are selected & 10 of these are assayed individually.
- - At least 9 of these contain 85 – 115 % of drug & none contain below 75 – 125 % of drug.
- - If 1 to 3 of them fall outside of 85 – 115 % limits , the remaining 20 capsules are individually assayed & the requirements are met if no few than 27 contain 85 – 115 % of drug & none contain less than 75 – 125 % of drug.



5. Moisture Permeation Test :

- The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour 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 post test weight of pellet, amount can be calculated.



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