NOTES ON
TABLETS, CAPSULES & PHARMACEUTICAL AEROSOLS

(FORMULATIVE PHARMACY)

FIFTH SEMESTER **B.PHARM**

(As per syllabus of PCI & **Kerala University of Health Sciences)**

Dr. Boby Johns G

M.Pharm, PhD, ARPharmS, MBA, M.Sc (Psych)

Professor & Head, Dept.of Pharmaceutics

St. Joseph's College of Pharmacy Cherthala, Kerala-688 524

www.sjpharmacycollege.com

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TABLETS

Tablets can be defined as solid pharmaceutical dosage forms containing drug substances, with or without suitable diluents, and prepared either by compression or molding method .They are the most important and most popular dosage form.

Advantages

1. They are tamperproof: No chance of adulteration and mixing
2. There is accuracy in dosage (or) Dose precision
3. Low cost dosage forms
4. Lightest and most compact of all dosage forms.
5. Ease in administration
6. Diversity of use.

Disadvantages

1. Some drugs cannot be compressed into tablets because of their amorphous nature.
2. Drugs with poor wetting, slow dissolution properties, or large dosage cannot be formulated into tablets.

Bitter tasting drugs, drugs with objectionable odour, oxygen sensitive drugs etc. need other processes before tabletting

Classification of tablets based on route of administration

Oral Tablets

a. Compressed tablets-Mainly the standard uncoated tablets manufactured by wet granulation, dry granulation and direct compression
b. Multiple compressed tablets- Layered tablets and compression coated tablets
c. Repeat action tablets-Release an initial dose and then maintenance dose through specialized coating
d. Delayed action tablets-delayed release of drug
e. Enteric coated tablets-Intact in stomach and release drug in the upper intestine. Cellulose acetate phthalate (CAP) is the prime polymer used here.
f. Sugar coated tablets-Using sugar syrup and water soluble polymers coating
g. Film coated tablets- Thin film or layer of polymeric materials on tablet surface.
h. Chewable tablets-For children, infants and elderly patients
i. Controlled release tablets-Continuous and consistent release of drug from a tablet

Tablets for oral cavity

a. Buccal tablets
b. Sublingual tablets
c. Lozenges
d. Dental cones

Tablets administered by other routes

a. Implants
b. Vaginal tablets

Tablets for solutions

1. Effervescent tablets
2. Dispensing tablets
3. Hypodermic tablets
4. Tablet triturates.

Pre formulation studies

It is essential to study various aspects of a product before its formulation into a particular dosage form. The important pre-formulation studies include,

I. Stability: (solid state) -Light, temperature etc.
II. Stability(solution): Excipient drug stability
III. Physico-mechanical properties: Particle size, bulk density, crystalline properties, compressibility, Melting point, taste, colour, appearance etc.
IV. Physico chemical properties: Solubility and pH
V. In vitro dissolution: Absorption, effect of excipients and surfactants.

Excipients

An excipient is a substance that serves as the vehicle or medium for a drug or other active substance. Examples are,

1. Diluents
2. Binders and adhesives
3. Lubricants, anti-adherents and glidants
4. Disintegrants
5. Colours
6. Flavours and sweeteners
7. Miscellaneous: Such as buffers and adsorbents

Diluents

Used to make up the required bulk of the tablet, when the drug quantity itself is not sufficient to produce the bulk

Ideal Characters of Diluents

1. They must be non-toxic
2. Must be available in acceptable grades
3. Low cost
4. Must not be contra- indicated Ex: Sucrose in diabetic patients

5. Must be physiologically inert
6. Should be physically and chemically stable; must be compatible with other ingredients in the solution.
7. No microbial contamination
8. Colour compatible
9. Should not affect bio availability of the drug
10. Must not be hygroscopic
11. Should possess sufficient degree of cohesiveness and compressibility.

Examples of excipients

1. **Lactose (Anhydrous) & Spray dried lactose**: They may show discoloration in presence of amines.
2. **Starch:** Diluent, disintegrant and binder
3. **Mannitol:** in chewable tablet
4. **Sorbitol:** Usually combined with equal weight of dialcium phospahate
5. **Sucrose:** Pick up moisture
6. **Microcrystalline Cellulose:** Avicel (P^H 101and P^H 102) : Directly compressible. Flow property is good. Act as a disintegrating agent also. But Expensive
7. Di calcium Phosphate (**DCP): (dehydrate)** Directly compressible diluent. Where the active ingredient occupies less than 40 to 50% of final tablet weight.

Binders

Binders are adhesives to obtain cohesiveness to the powders, thereby providing necessary bonding to form granules. Examples are acacia, tragacanth, Cellulose derivatives-Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Hydroxy Propyl Cellulose etc., Poly Vinyl Pyrrolidone (PVP), Starch, Sucrose-50 to 75%.

Miscellaneous Binders: Sodium alginate, Magnesium aluminium silicate, PEG etc.

An example of a typical granulation system is given below (table):

Binder	% of granulating system	% in the formula
Acacia	10-20	2-5
Cellulose derivatives	05-10	1-5
Gelatin	10-20	1-5
PVP	03-15	2-5
Starch Paste	05-10	1-5
Sucrose	50-85	2-25
Sorbitol	10-25	2-10
Sodium Alginate	03-05	2-5

Disintegrants

Disintegrants are Substances that are added to the tablet formula which facilitate break up of tablet after administration.

Disintegration agents may be added prior to granulation or during lubrication step, prior to compression or at both stages

1. Intragranular (inside the granules)
2. Intergranular (In between the granules)
3. Both together

Mechanism of disintegration

a. **By Swelling:** After absorption of water from the environment, the tablet swells and because of internal pressure it explodes and causes disintegration.
b. **By penetration of aqueous medium:** The aqueous fluid present in the G.I.T may penetrate the tablet and thus cause erosion or breaking up of tablet mass, thus releasing the contents.
c. **Liberation of gas by chemical Reaction**
d. **(Effervescence):** A tablet may contain ingredients which when come in contact with the aqueous environment of the G.I.T react and a gas usually CO2 is evolved. This evolution of gas can cause break of tablet causing disintegration.

Method of incorporation

- One part of disintegrant is added to the powdered material before granulation- which will help in the breakup of individual granules.
- Other part is added during lubrication before compression- Which will help in breakup of tablet to granules.

Material	Concentration (% w/w)
Starches	2-10
Gums	2-10
Algins	2-10
Clays	1-10
Cellulose	1-10
Wetting agents (SLS)	0.1-0.5

Super disintegrants

Traditionally starch has been the disintegrant of choice for tablet formulations, and is still widely used. In more recent years, several newer disintegrants have been developed often called as super disintegrants, which can be used at lower levels than starch. Because they can be a smaller part of the overall formulation than starch, any possible adverse effect on fluidity or

compatibility would be minimized. Super disintegrants can be classified into three categories based on their chemical structure.

Structural type(NF name)	Description	Trade name (mfgr.)
Modified starches (**Sodium starch glycolate NF)**	Sodium carboxymethyl starch; the carboxymethyl groups induces hydrophilicity and cros linking reduces solubility.	Explotab,Primogel,Tablo etc.
Modified Cellulose (**Croscarmellose NF)**	Sodium carboxymethylellulose which as bn cros linked to render the material insoluble.	AcDiSol,Nymcel,Primellose,Solutab
Cross linked poly vinyl prrolidone (**Cros povidone NF)**	Ross linked poly vinyl pyrrolidone;the high molecul weight and cross linking render the material insoluble in water.	CrospovidoneM,Kollidon CL, Polyplasdone XL

Lubricants, anti-adherents and glidants

1. **Lubricants**: To reduce friction between the granules and die wall during compression and ejection.
2. **Anti-adherents**: Prevent sticking to punch and to a less extent to the die wall.
3. **Glidants**: To improve flow properties of granules.

Mechanism of lubrication

1. **Fluid lubrication:** Liquid paraffin (Liquid hydrocarbon)
2. **Boundary lubrication**: Which results from the adherence of the polar portions of molecules with long carbon chains to the metal surface of the die wall?
   Magnesium stearate is a typical example.

1. Lubricants equalize the pressure distribution in compressed tablets.
2. When lubricants are added to the granulation, they form a coat around the individual particles (granules) which remain more or less intact during compression.

Lubricants are usually hydrophobic in nature, though water soluble types are also in use. Hydrophobic lubricants may cause an increase in disintegration time and reduce dissolution rates.

Water insoluble lubricants	Water soluble lubricants
Magnesium stearate	Boric acid
Calcium stearate	Sodium acetate
Sodium stearate	Sodium benzoate
Talc,	Sodium Chloride
Waxes	DL –leucine

Water soluble lubricants

Sodium Lauryl Sulfate
Mg Lauryl sulphate
PEG-600
Sodium oleate

Lubricants are generally added dry at homogenous condition and mixed for 2-5 minutes Over mixing may lead to poor DT and Dissolution rates. They can also be added in alcoholic solutions. Ex: PEGs. Powder lubricants are added prior to wet granulation

Water soluble lubricants are in general, used only when a tablet must be completely water soluble, as in the case of effervescent tablets

Anti-adherents & glidants

1. Talc
2. Magnesium stearate
3. Corn starch
4. Aerosil (Silicic acid) *
5. DL-Lucine*

* *Water soluble*

Colours

Reasons for adding colour:

1. Esthetic(beauty) value/marketing value
2. For identification of similar looking products
3. To minimize the possibility of mix-ups

Types of colours

FD&C, D& C DYES (solutions) AND LAKES

Dyes are water soluble materilas, while lakes are formed by the adsorption of water –soluble dye on inert material such as hydrous oxide (usually aluminium hydroxide.)

Methods of incorporation

1. Dissolution of water-soluble dyes in the granulating system or binder solution. This assure uniform distribution of colour
2. Adsorption of colours on to carriers such as starch, lactose,calcium sulphate, sugar etc.from aqueous or alcoholic solutions of the colour.
3. Lakes are usually blended with other dry excipients

Flavours and sweeteners

a. In chewable and tablets intended to dissolve in mouth.
b. Saccharin sodium, Sucrose, Mannitol, dextrose etc.

Apart from these, miscellaneous components like buffers and adsorbents are also used.

Ex: Silicon dioxide, TCP, Bentonite, Magnesium silicate etc.

Granulation

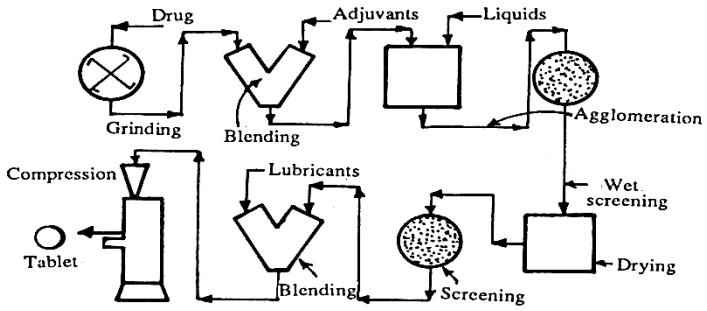
Depending upon the physical characteristics of the material, any one of the following methods can be applied for tabletting.

1. Wet/Moist Granulation
2. Dry Granulation
3. Direct Compression

Wet granulation- Most widely used method

Steps

1. Milling of drugs and excipients
2. Mixing of milled products
3. Mixing of binder solution with powder mixture to form wet mass
4. Coarse screening of wet mass using 6 to 12 mesh screen
5. Drying the moist granules
6. Screening of dry granules through 14 to 20 mesh screen
7. Mixing the screened dry granules with lubricants, disintegrants etc.



Wet granulation

Advantages

1. The cohesiveness and compressibility of powders are improved because of the formation of granules

2. High dose drugs having poor flow or compressibility properties can be prepared by wet granulation.
3. Uniform distribution of contents and colour
4. The dissolution rate of hydrophobic drugs may be improved by wet granulation method.

Disadvantages

1. Cost: It is an expensive process- labour, time, equipment,energy and space requirement
2. Cannot be used for moisture sensitive drugs.
3. The use of soluble dyes often lead to migration of dyes during drying stage
4. Any incompatibility or chemical reactions will be aggravated by moisture during granulation**.**

Important steps

1. Preparation of the powder mixture with screening and mixing
2. Addition of the binder solution and mixing with powder for proper wetting and we screening of the mass-4,6,8 or 12 mesh screen
3. Drying the solid-liquid blend (wet granules)-pass through 20 mesh screen
4. Milling the dry granulation to the desired size.
5. Addition of lubricant, glidant and or other excipients prior to compression

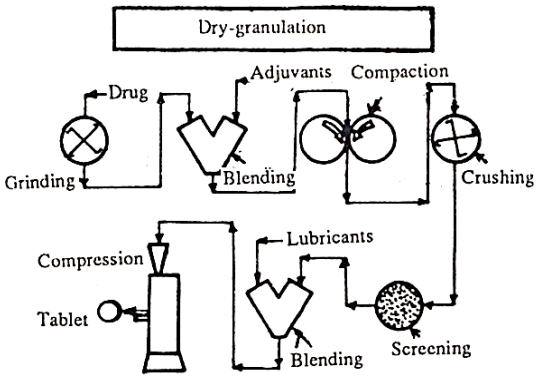
Machinery for wet granulation: Fluid bed spray Granulators

Dry granulation

Granulation of a powder mixture by compression (slugs) without use of heat and solvent can be termed as dry granulation. When wet granulation and direct compression is not possible, dry granulation is the only choice. Ex: granulation of aspirin and granulation of effervescent granules. Slugging is often referred as pre compression or double compression. Excipients used here are basically the same as in wet granulation. The active constituent will produce the bulk of the final product. Fillers used in dry granulation include lactose, dextrose, sucrose, micro crystalline cellulose,calcium sulphate, dicalcium phosphate, tri calcium phosphate and starch.

Important Steps

1. Milling of drugs and excipients
2. Mixing of milled products
3. Compression into large hard tablets to make slugs
4. Screening of slugs
5. Mixing lubricants and disintegrants
6. Tablet Compression



Dry granulation

Advantages of Dry Granulation

1. It uses less equipments and space
2. Binder solutions and mixing equipments can be avoided
3. Drying step can be avoided
4. It can be used for moisture sensitive materials
5. Can be used for heat sensitive materials
6. Tablets show improved disintegration since powder particles are not bonded together by a binder.
7. Improved solubility.

Disadvantages

1. For slugging, specialized heavy duty equipments are needed.
2. Colour distribution is not uniform as can e achieved with wet granulation.
3. More dust formation since the process is a dry one.

Oscillating granulator

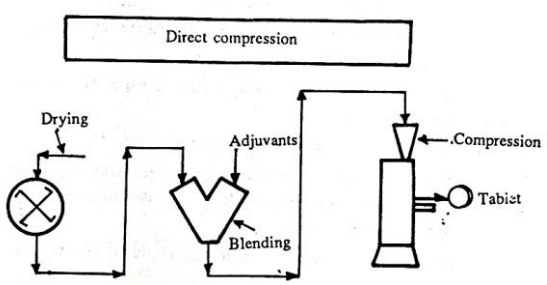
Direct compression

Until 1950, vast majority of tablet produced were manufactured by a process requiring granulation. The availability of new excipients, diluents and the invention of new machineries have allowed the compression of tablets by the much simpler process of direct compression. Few materials possess the flow, cohesion and lubricating properties under pressure to make such compression possible. Ex: Sodium chloride and potassium bromide.

No pretreatment of the powder blends of active ingredients is needed in direct compression. Occasionally potent drugs are sprayed in the form of solution onto one of the excipients. These vehicles possess fluidity and compressibility. The first such vehicle was spray dried lactose; micro crystalline cellulose.

Important Steps

1. Milling of drugs and excipients
2. Mixing of ingredients
3. Tablet compression



Direct compression

Advantages

1. Economy
2. Elimination of heat and moisture
3. Stability of formulation can be improved
4. Particle size uniformity

Disadvantages

1. Problems in the uniform distribution of low dose drugs
2. Drugs having high bulk volume, poor compressibility and poor fluidity are not suitable for direct compression.
3. Direct compression excipients are costly
4. Many active ingredients are not compressible I its crystalline or amorphous form
5. The lack of moisture content may lead to static charges which can lead to un blending
6. Non uniform distribution of colour.

Directly compressible excipients

a) Micro crystalline cellulose (Avicel)
b) Ethyl Cellulose
c) Methyl Cellulose
d) Cyclodextrins
e) Spray dried lactose

Tablet compression operation

Tablet compression machine (tablet press) consists of the following basic components

1. Hoppers for holding and feeding the materials to be compressed
2. Dies, which define the shape and size of the tablet
3. Punches, which compress the granules within the dies
4. Cam tracks for guiding the movement of the punches
5. A feeding mechanism, which moves granules or material to be compressed from hopper into dies.

Types of machines

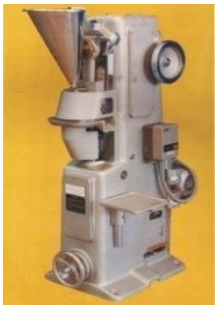
i. Single station or single punch press
ii. *Compression is applied by upper punch only*
iii. Multi station or rotary press - Compression *by compression wheels*

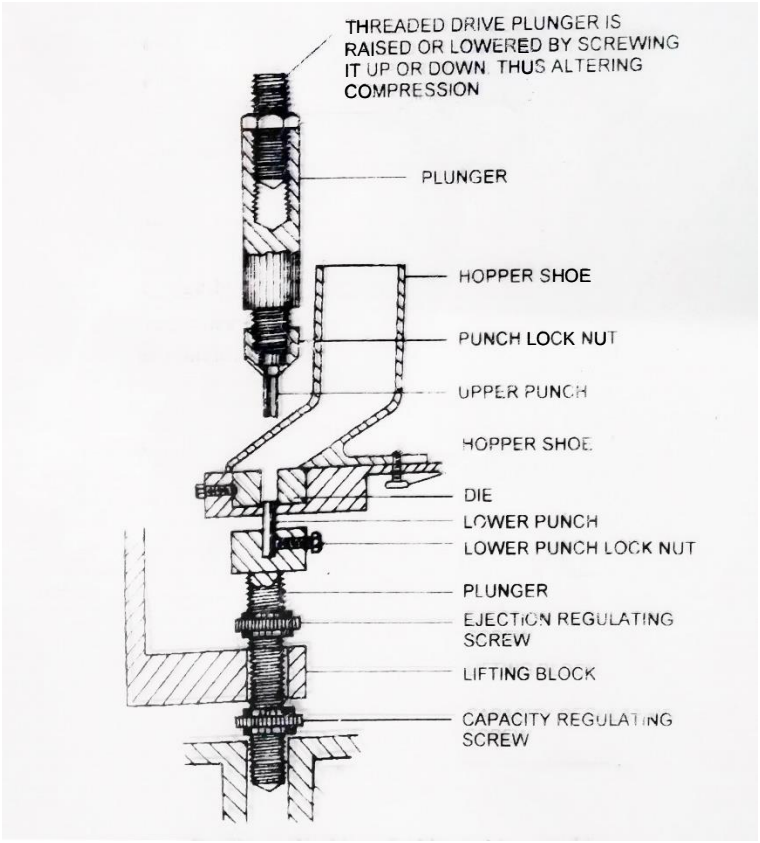
Single punch machine

1. Consists of a die and a set of punches-the lower punch and upper punch
2. The lower punch can move freely in the die cavity.
3. The horizontal metal platform holds the die firmly.

Important features of lower punch in single punch machines

1. We can vary the depth to which the lower punch falls or descend in the die cavity. Thus it can control the volume or weight of the material to be compressed.
2. Secondly the lower punch can be adjusted in such a way that at the top of the compression cycle, the lower punch is exactly at the same level as the upper surface of the die. The upper punch can be fixed in such a way that it enters the die cavity, corrects on its downward stroke. The depth in which the upper punch descends can be controlled through controlling the pressure applied on the material. Thus the upper punch can control the hardness of the compressed tablet.





Construction of a single punch tablet machine

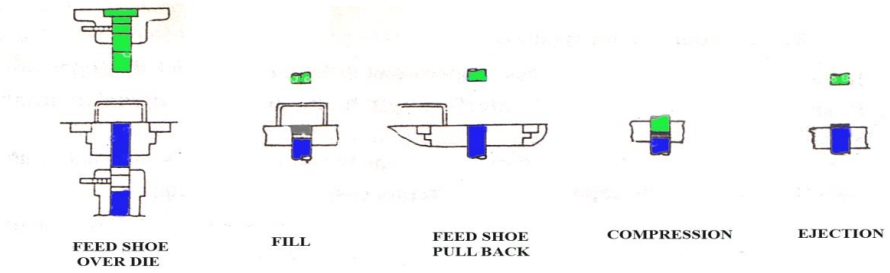
Compression cycle

1) The first stage is the filling during which the upper punch rises and the hopper containing the granules rotate till it is over the die. The lower punch is lowered to a particular position adjusted by a regulating screw to form a cavity in the die to provide a volume corresponding to the correct fill weight. Granules to be compressed are filled in the die.

2) The bottom punch remains stationary while the upper punch descends into the die, compressing the granules filled in the die cavity.

3) The upper punch now rises, the lower punch also rises flush with the surface of the die to eject the tablet to the surface

4) The feed shoe (hopper shoe) now rotates over the die cavity and knocks the finished tablets aside. The hopper now again fills the die cavity and the cycle is repeated.



COMPRESSION CYCLE

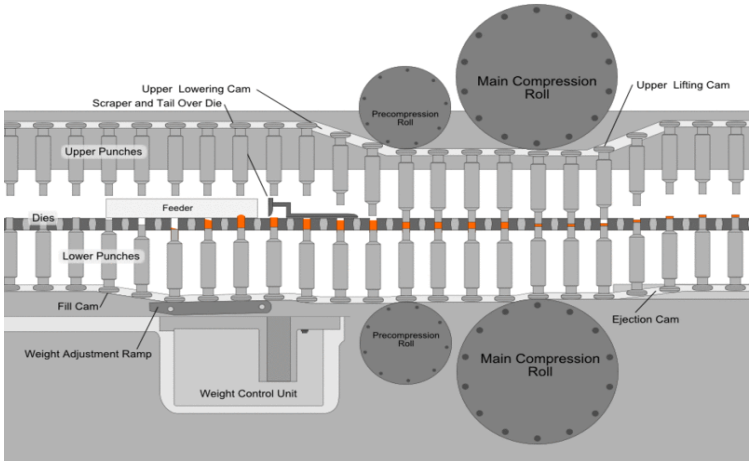
Rotary tablet presses

Turret

Rotary tablet compression cycle

1. The head of the tablet machine which holds the upper punches, dies and lower punches in place rotates.
2. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression and ejection.
   The portions of the head which hold the upper and lower punches are called the upper and lower turrets respectively. The portion holding the dies is called the die tablet
4. At the start of compression cycle, the granules stored in the hopper empties into the feed frame.
5. The feed frame compartments spread the granules over a wide area to provide enough time to fill the die to fill.
6. There are two sets of cams provided.
7. The pull down cam guides the lower punches to the bottom of their vertical travel, allowing the dies to over fall.

8. The lower punches then pass over a weight control cam which reduces the fill in the dies to the desired amount.
9. There is a wipe off blade at the end of the feed frame, which removes the excess granules and directs it around the turret and back into the front of the feed frame.
10. There are two compression rolls, the upper and lower.
11. The lower punches then travel over the lower compression roll while at the same time, the upper punches ride beneath the upper compression roll.
12. The upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granules within the dies.
13. In order to regulate the upward movement of lower punches, the height of the lower pressure roll is changed.
14. After compression, the upper punches are withdrawn (raised) slowly as they follow over the upper punch raising cam.
15. The lower punches ride up another cam which brings the tablet flush with the surface of the dies.
16. The exact position is determined by a threaded bolt called the ejector knob
17. The tablets formed then strike a sweep-off blade, which is affixed to the front of the frame.
18. The tablets then slide down through a chute into a receptacle
19. The lower punches re enter the pull down cam. The cycle is repeated.



Compression cycle

The process of compression

Compression is the process of applying pressure to a mateial.In Pharmaceutical tabletting, an appropriate volume of granules in die cavity is compressed between an upper punch and lower punch to consolidate the mass into a single solid matrix

Events in compression (physics of tablet compression)

a. Transitional re packing
b. Deformation at points of contact
c. Fragmentation and or deformation
d. Bonding
e. Deformation of the solid body
f. Decompression
g. Ejection

Transitionalrepacking (or) particle arrangement

The particle size distribution of the granulation and the shape of the granules determine the initial packing (bulk density) as the granules are delivered in to the die cavity. Initially, the punch and particle movement occur at low pressure. The granules flow with respect to each other, with the *finer particle entering the void between the larger particles, and thus the bulk density of the granulation is increased*. Spherical particles undergo less particle re arrangement than irregular particles as the spherical particles tend to assume a *close packing arrangement* initially.

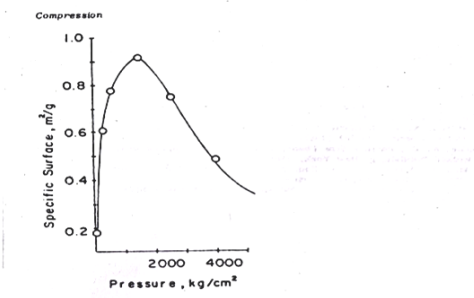
Deformation at point of contact

When a stress (force) is applied to a material, deformation(change of form) occurs. If the deformation disappears completely (returns to the original shape)upon release of the stress, it is an elastic deformation. A deformation that does not completely discover after release of the stress is called as plastic deformation. The force required to initiate a plastic deformation is known as yield stress. When the particles of a granulation are so closely packed that no further filling of the void can occur, a further increase in compressional forces causes deformation at the points of contact.

Deformation increases the area of true contact and the formation of potential binding areas.

Fragmentatiion and deformation

At higher pressure, fracture occurs when the stresses when the particles become great enough to propagate cracks. Fragmentation increases the number of particles and forms new clean surfaces that are potential bonding areas. The specific surface of the starch and sulfathiazole granulation was 0.18 m2/g; the tablet compressed at a pressure of 1600 kg/cm2 had specific surface of 0.9 m2/g



The effect of applied pressure on the specific surface of sulfathiasole tablets. (From Ref. 3, with permission of the copyright owner, The American Pharmaceutical Association.)

With some materials fragmentation does not occur because the stresses are relieved by plastic deformation. Plastic deformation may be thought of as a change in *particle shape* and as the sliding of groups of particles in an attempt to relieve stress. *(Visco elastic flow)* Such deformation produces new, clean surfaces that are potential binding areas.

Bonding

Several mechanisms of bonding in the compression process have been conceived. Three theories are the mechanical theory, the inter molecular theory and liquid surface film theory

Mechanical Theory

This theory proposes that under pressure, the individual particles undergo elastic, plastic or brittle deformation and that the edges of the particles intermesh, forming a mechanical bond. Mechanical interlocking is not a major mechanism of bonding ion pharmaceutical tablets.

Inter molecular forces Theory

Under pressure, the molecules at the point of true contact between new, clean surfaces of the granules are close enough so that van der Wal's forces interact to consolidate the particles. A micro crystalline cellulose tablet has been described as cellulose fibrils in which the crystals are compressed close enough together so that hydrogen bonding between them occurs. It appears that very little deformation or fusion occurs in the compression of micro crystalline cellulose.

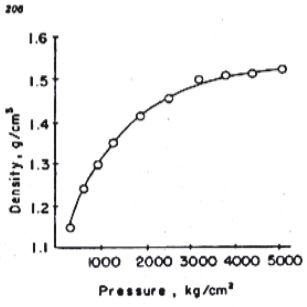
Liquid-surface film theory

This theory attributes bonding to the presence of a thin liquid film, which may be the consequence of fusion or solution, a surface of the particle induced by the energy of compression. During compression, an applied force is exerted on the granules, however, locally the force is applied to small area of true contact so that a very high pressure exists at the true contact surface. The local effect of the high pressure on the melting point and solubility of a material is essential for bonding

Granulations that are absolutely dry have poor compression characteristics. Water or saturated solutions of the material being compressed may form a film that acts as a lubricant, and if less force is lost to overcome friction, more force is utilized in compression and bonding and the ejection force is reduced. In formulations containing hydrophilic granulating agents there may be an optimum moisture content. It has been reported that the optimum moisture content for starch granulation of lactose is approximately 12% and of phenacetin is 3%

Deformation of the solid body

As the applied pressure is further increased, the bonded solid is consolidated toward a limiting density by plastic and or elastic deformation of the tablet within the die as shown in the figure.



The effect of applied pressure on the apparent density of tablets of sulfathiazole. (From Ref. 3, with permission of the copyright owner, The American Pharmaceutical Association.)

Decompression

The success or failure to produce an intact tablet depends on the stresses induced by elastic rebound and the associated deformation processes during decompression and ejection.

If only elastic deformation occurred, with the sudden removal of axial pressure the granules would return to their original form breaking any bonds that may have formed under pressure. Also the die wall pressure would be zero as the elastic material recovered axially and contracted radially. Actually under non isostatic pressure, pharmaceutical materials undergo sufficient plastic deformation to produce die wall pressure in excess of that that may be relieved by elastic recovery accompanying removal of upper punch. Stress relaxation of plastic deformation is time dependent. Materials with slow rates of stress relaxation crack in the die upon decompression. (Figure)

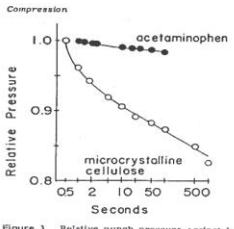


Figure 3 Relative punch pressure against logarithm of time. (From Ref. 12, with permission of the copyright owner, The American Pharmaceutical Association.)

Ejection

As the lower punch rises and pushes the tablet upward there is a continued residual die wall pressure and considerable energy may be expanded due to the die wall friction. As the tablet is removed from the die, the lateral pressure is relieved and the tablet undergoes elastic recovery with an increase in the volume of that portion of the tablet removed from the die.(2% to 10%).during ejection, that portion of the tablet within the die is under strain, and if the strain exceeds the shear strength of the tablet, the tablet caps adjacent to the region in which the strain had just been removed

What is tooling ?

A set of punches and dies are often referred to as tooling.
A *station of tools* consists of an upper punch,
Lower punch and die

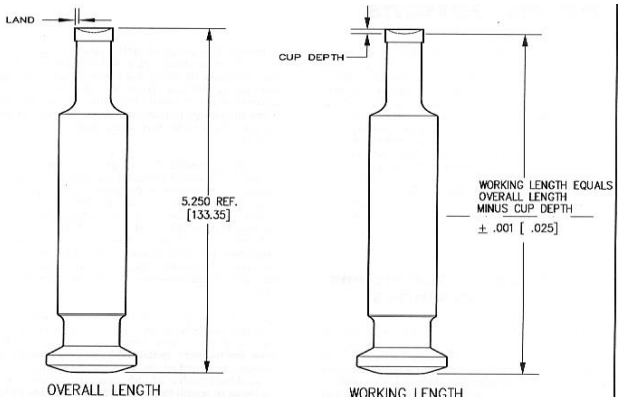
a. **BB** Tooling- Most common , 5.25 inches in length and nominal barrel diameter of 0.75 inches and 1 inch head diameter
b. **B** Tooling- Same as that of BB but lower punch is only 3 $^{9/16}$ inches long
c. **D** tooling- Most popular for large tablets having 1 inch barrel diameter, 1 ^{¼} inches head diameter and 5.25 inches length

Working Length

The most important dimension of the tooling is the working length variation within a set of punches. Working length is the distance from the bottom of the cup to the head flat. Working length is controlled to a very tight specification. Variations in this specification will result in weight, thickness and hardness variation.

Overall length

The distance from the Cup edge to the head flat is called the working length. This dimension is not critical to the success of the tablet.



Dwell time

Dwell time is the actual amount of time that the powder is under pressure. The key factors to controlling dwell time are **punch head flat diameter, number of compression points and rpm.** Slowing the machine down will provide more dwell time (Increased dwell time).

i. The output from a tablet compression machine is regulated by three basic characteristic designs
ii. Number of tooling sets- A set of punches and dies are often referred to as tooling. A station of tools consists of an upper punch, lower punch and die.
iii. Number of compression stations
iv. Rotational speed of the press.

Differences between single punch and rotary tablet machines

Single punch tablet machine	Rotary tablet machine
Compression of granules are abrupt	Gradual
Compression of granules are abrupt	Gradual
Pressure is exerted by lower and upper punches	By pressure rolls
During compression, the lower punch is stationary and the upper punch is moving	Both punches are moving
Weight of the tablet is adjusted before filling	After filling
Feed shoe is used for feeding the material	Feed frame is used
Fixed die plate which hold the die	Consists of a revolving turret, in which the dies are continuously revolving
Less economic and output is limited	More economic with high output due to multi stations.
More chances of tablet capping due to abrupt compression	Less chances of capping due to gradual compression

Double rotary machines

Machines which possess two pairs of compression rolls, two hoppers, two feed frames and sets of cams. Here each punch set makes two tablets per revolution of the turret. The output is greatly increased. Maintenance of these machines is comparatively high.

Drycota machines

Basically it consists of two rotary tablet presses joined by a single driving shaft and a transverse system. The tablet cores are made on the turret of one tablet press is transferred to a second turret. The coating is put on cores in the second rotary press. The cores are connected to

a vacuum system through flexible tubing. These machines usually have 33 compression stations. It can produce a maximum of 900 tablets per minute

Auxiliary equipments

- ✓ Manesty Granulation feeding device
- ✓ Thomas table Sentinel II

Tablet printer, Tablet counter, Compression pressure monitor etc.

Processing problems in tablets (Tablet defects)

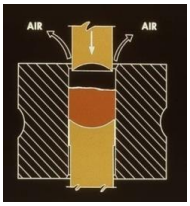
Improper formulation of tablets can be resulted due to difficulties in processing steps, incorrect tablet press settings, operation etc. The common defects are,

1. Capping and lamination
2. Picking and sticking
3. Mottling
4. Weight variation
5. Granule size and size distribution before compression
6. Poor flow
7. Punch variation
8. Hardness variation
9. Double impression

Capping and lamination

Capping is a term used to describe the partial or complete separation of the top or bottom crowns of a tablet from its main body.

Lamination means the separation of a tablet into two or more distinct layers.



Capping and lamination

Capping occur due to air entrapment in the die, during compression, as punches move together to apply pressure and then expands when the pressure is released. During compaction the particles undergo plastic deformation and then elastic recovery. *This is very common when the granule contains large amount of fines*

1. Often deep concave punches can develop capping
2. Tablet tooling also can cause capping
3. Incorrect setup of the machine can cause capping.

The causes and remedies of capping related to granulation

S. No.	Causes	Remedies
1.	Large amount of fines in the granulation	Remove some or all fines through 100 to 200 mesh screen
2.	Too dry or very low moisture content (leading to loss of proper binding action).	Moisten the granules suitably. Add hygroscopic substance e.g.: sorbitol, methyl- cellulose or PEG-4000
3.	Not thoroughly dried granules.	Dry the granules properly.
4.	Insufficient amount of binder or improper binder.	Increasing the amount of binder OR Adding dry binder such as pre-gelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar.
5.	Insufficient or improper lubricant.	Increase the amount of lubricant or change the type of lubricant.
6.	Granular mass too cold to compress firm.	Compress at room temperature.

The causes and remedies of capping related to 'machine' (dies, punches and tablet press)

S. No.	Causes	Remedies
1.	Poorly finished dies	Polish dies properly. investigate other steels or other materials.
2.	Deep concave punches or beveled-edge faces of punches.	Deep concave punches or beveled-edge faces of punches.
3.	Lower punch remains below the face of die during ejection.	Make proper setting of lower punch during ejection.
4.	Incorrect adjustment of sweep-off blade.	Adjust sweep-off blade correctly to facilitate proper ejection.
5.	High turret speed.	Reduce speed of turret (increase dwell time).

The causes and remedies of lamination related to machine (dies,punches and tablet press)

S. N.	Causes	Remedies
1.	Rapid relaxation of the peripheral regions of a tablet, on ejection from a die.	Use tapered dies, i.e. upper part of the die bore has an outward taper of 3° to 5°.
2	Rapid decompression	Reduce turret speed and reduce the final compression pressure.

Picking and sticking

Picking: It is a term used to describe the surface material from a tablet that is sticking to and being removed from the tablet's surface by the punch. It may happen due to punches with engraving or embossing. Small enclosed area such as those found in the letters A, B and O are difficult to manufacture cleanly.

Sticking: Refers to the tablet material adhering to the die wall. When sticking occurs, additional force is required to overcome the friction between the tablets and die wall.

Picking and sticking

The causes and remedies of sticking related to formulation (granulation

S. no.	Causes	Remedies
1.	Granules not dried properly.	Dry the granules properly. Make moisture analysis to determine limits.
2.	Too little or improper lubrication	Increase or change lubricant.
3.	Too much binder	Reduce the amount of binder or use a different type of binder.
4.	Hygroscopic granular material.	Modify granulation and compress under controlled humidity.
5.	Oily or way materials	Modify mixing process. Add an absorbent.
6.	Too soft or weak granules.	Optimize the amount of binder and granulation technique.

The causes and remedies of picking related to formulation (granulation)

S. No.	Causes	Remedies
1.	Concavity too deep for granulation.	Reduce concavity to optimum.
2.	Too little pressure.	Increase pressure.
3.	Compressing too fast.	Reduce speed

The causes and remedies of picking related to formulation (granulation)

S. No.	Causes	Remedies
1.	Excessive moisture in granules.	Dry properly the granules, determine optimum limit.
2.	Too little or improper lubrication.	Increase lubrication; use colloidal silica as a 'polishing agent', so that material does not cling to punch faces.
3.	Low melting point substances, may soften from the heat of compression and lead to picking.	Add high melting-point materials. Use high meting point lubricants.
4.	Low melting point medicament in high concentration.	Refrigerate granules and the entire tablet press.
5.	Too warm granules when compressing.	Compress at room temperature. Cool sufficiently before compression.
6.	Too much amount of binder.	Reduce the amount of binder, change the type or use dry binders.

The causes and remedies of picking related to machine (dies, punches and tablet press)

S. No.	Causes	Remedies
1.	Rough or scratched punch faces.	Polish faces to high luster.
2.	Embossing or engraving letters on punch faces such as B, A, O, R, P, Q, G.	Design lettering as large as possible. Plate the punch faces with chromium to produce a smooth and non-adherent face.
3.	Bevels or dividing lines too deep.	Reduce depths and sharpness.
4.	Pressure applied is not enough; too soft tablets.	Increase pressure to optimum.

Mottling

It is the un equal distribution of colour on a tablet, with light or dark areas standing out. The surface does not show uniform colour.

Mottling

Causes and remedies in mottling

S. No.	Causes	Remedies
1.	A coloured drug used along with colourless or white-coloured excipients.	Use appropriate colourants.
2.	A dye migrates to the surface of granulation while drying.	Change the solvent system, Change the binder, Reduce drying temperature and Use a smaller particle size.
3.	Improperly mixed dye, especially during ‘Direct Compression’.	Mix properly and reduce size if it is of a larger size to prevent segregation.
4.	Improper mixing of a coloured binder solution.	Incorporate dry colour additive during powder blending step, then add fine powdered adhesives such as acacia and tragacanth and mix well and finally add granulating liquid.

Weight variation

Anything that can vary the die filling process can affect the weight of the tablets. Ratios in the size of granules may also affect. The filling of the die is based upon uniform flow of granules. When uniform flow of granules is not there, dies may fill incompletely leading to off weight tablets. Excess machine speed also causes weight variation in tablets. Addition of glidants like talc or colloidal silica may be useful in this regard.

Hardness variation

It is a problem that has the same cause of weight variation. If the volume of the material or the distance between the punches varies, hardness is likely in consistent.

Granule size and size distribution before compression

Variations in the ratio of large to small granules influence how the void spaces between the particles are filled. If large granules are used to fill small die cavity, relatively few granules are required and the difference in these granules may affect the weight of the tablets

Poor flow

The die fill process is based upon uniform and continuous flow of granules from the hopper through the feed frame. When the granules do not flow readily, it tends move spasmodically through the feed frame so that some dies are incompletely filled. Similarly, excess machine speed also can cause filling problems. Devices intended to improve flow properties scan be a remedy for this.

Punch variation

When lower punches are of un equal lengths, the fill in each die may vary. A good punch and die control program (tooling) can rectify this problem.

Double impression

Happens with only punches with a monogram or other engraving on it. At the moment of compression, the tablet receives the imprint on it. During its travel, the lower punch may rotate and may make a new impression on the bottom surface of the tablet resulting in double impression. Advanced machines are equipped with an anti-turning device.

Double impression

In-process quality control

During compression of tablets, in process tests are routinely run to monitor the process, including tests for tablet weight, weight variation,hardness,thickness,

disintegartion,and evaluations of elegance. The in-process QC tests are done by QC personnel. her data formulated by the formulator usually employed by QC personnel to establish the test limits.

Evaluation of tablets

1. General Appearance
2 Size & shape
3. Unique identification Markings
4. Organoleptic Properties
5. Hardness and Friability

1. General Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

2. Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Unique identification marking: These marking utilize some form of embossing, engraving or printing. These markings include company name or symbol, product code, product name etc.

4. Organoleptic properties: Color distribution must be uniform with no mottling. For visual color comparison compare the color of sample against standard color

5. Hardness and Friability: Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength.

Hardness testers

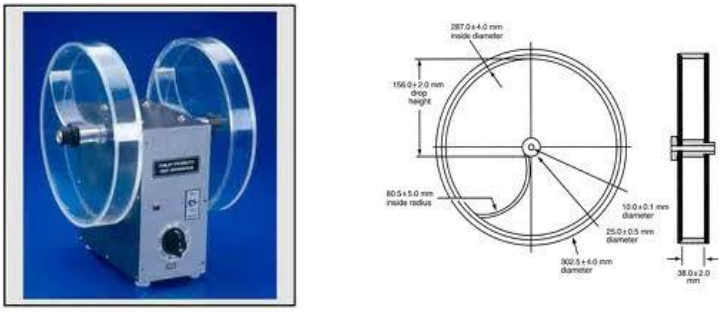
Pfizer type

Monsanto type

Miscellaneous type

6. Friability: Friability of a tablet can determine in laboratory by Roche friabilator. This consist of a plastic chamber that revolves at 25 rpm, dropping the tablets through a Distance of six inches

in the friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compressed tablet that lose less than 0.5 to 1.0 % of the Tablet weights are consider acceptable.



Friability testing apparatus

Drug Content and Release

(I) **Weight Variation test (U.S.P.): T**ake 20 tablet and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet passes the U.S.P. test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

(II) **Content Uniformity Test:** Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10^{th} tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablet assayed individually and none may fall outside of the 85 to 115% range

(III) **Disintegration Test (U.S.P.):** The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0 C such that the tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.

According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass.

Disintegration time: Uncoated tablet: 5-30 minutes

Coated tablet: 1-2 hours

Disintegration test apparatus

3. Dissolution Test (U.S.P.): Two set of apparatus:

Apparatus-1: A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 100 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37 ± 0.5^0C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions.

Apparatus-2: It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit.

Dissolution Test apparatus

TABLET COATING

Tablets are coated for the following reasons.

They may:

1. Mask the taste of unpalatable drugs,
2. Protect the drug from deterioration due to light, oxygen or moisture,
3. Separate incompatible ingredients,
4. Control the release of medicament in the gastrointestinal tract,
5. Provide an elegant or distinctive finish to the tablet.

Types of coating

a. Sugar coating
b. Film coating
c. Enteric coating
d. Compressive coating

Coating Materials

1. The materials used for coating may largely comprise sucrose (sugar coating),
2. Water-soluble film-forming polymers (film coating) or substances which are soluble in the intestinal secretions but not in those of the stomach (enteric coating).
3. The compression coating technique is suitable for sugar and enteric coatings, but not for film coating.

Coating Process

1. Pan Coating
2. Compression Coating
3. Air Suspension Coating
4. Dip Coating

Tablet Coating Pan

Sugar coating of tablets

Sugar coating is a multi-step process. Here esthetics is the main goal. It needs skilled man power. So sugar coating is considered as a protracted and tedious process. However Modern equipments and automation has reduced the processing time.

Steps in sugar coating process

1. Sealing
2. Sub coating
3. Smoothing
4. Colour coating
5. Polishing
6. Printing

1. Sealing

1. The sealing coat is applied directly to the tablet core for the purpose of *separating the tablet ingredients* (mainly the drug) and water which is the most important constituent of the coating solution.

2. It is used to *strengthen the tablet core*.

Sealing coats usually consist of alcoholic solutions (10-30% solids) of resins such as shellac, zein, cellulose acetate phthalate etc. Shellac has proven to be the most popular material although it may cause impaired bio availability due to a change in resin property upon long storage. This can be overcame by addition of Poly Vinyl Pyrrolidone (PVP)

Since most of the sealing coats develop a degree of tack (stickiness) at some time during the drying process, it is usual to apply a dusting powder like asbestos free talc. If an enteric coated product is required, additional quantities of seal coat solutions are applied. Synthetic polymers like CAP or Poly vinyl acetate phthalate etc. are used here.

2. Sub coating

1. It is a critical step which decides the weight of the final tablet. Sub coating is the stage where most of the buildup occurs (50-100%)

2. Sub coating is achieved by gum based solution to the sealed cores and once this has been distributed uniformly throughout the tablet mass, it is followed by a liberal dusting powder which reduces the tackiness. The sub coating is like a sandwich of alternate layers of gum and powder.

Typical suspension sub coating formulation

TYPICAL SUSPENSION SUBCATING FORULATION	
	% w/w
Distilled water	25.0
Sucrose	40.0
Calcium carbonate	20.0
Talc-asbestos free	12.
Gum acacia powdered	2.0
Titanium dioxide	1.0

BINDER SOLUTION FORMULATIONS FOR SUB CAOTRING		
	A % w/w	B% w/w
Gelatin	3.3	6.0
Powdered gum acacia powder	8.7	8.0
Sucrose	55.3	45.0
Water	To 100.00	To 100.00

DUSTING POWDRE FORMULATIONS FOR SUB COATING		
	A % w/w	B% w/w
Calcium	40.0	-
Titanium	5.0	1.0
Talc-	25.0	61.0
Powdered	28.0	38.0
Gum acacia	2.0	-

3. **Smoothing**

Smoothing of the tablet surface.

Smoothing depend upon how successfully the sub coat was applied, it may be necessary to smooth out the tablet surface further prior to application of colour coating. Smoothing usually can be accomplished by the application of a simple syrup solution (60 to 70%)

Smoothing syrups contain a low percentage of titanium dioxide (1-5%) as opacifier, particularly when water soluble dyes are used in the formulation.

4.**Colour coating**

1. Most critical stage in sugar coating.
2. This involves multiple applications of syrup solution (60 – 70%) containing the requisite colouring matter.
3. Dyes or pigments can be used depend upon their solubility in the coat solution.
4. Usually water soluble dyes produces the most elegant sugar coated tablets, since it is possible to obtain a cleaner, brighter final colour.
5. Water soluble dyes can migrate during drying stage and hence great care should be taken at this stage.
6. Lakes when used with an opacifier like titanium dioxide will result in excellent colour coating.

Polishing

1. To achieve a final gloss, the sugar coated tablets need polishing
2. Polishing is achieved by applying mixtures of waxes like bees wax, carnauba wax, candelila wax or hard paraffin wax to the tablets in the polishing pan.
3. These waxes are applied as powders or organic solutions.

Polishing Pan

Printing

1. This can be done either before or after polishing.
2. Pharmaceutical grade inks are used for this purpose.
3. The process of printing is generally done by a process called as offset rotogravure

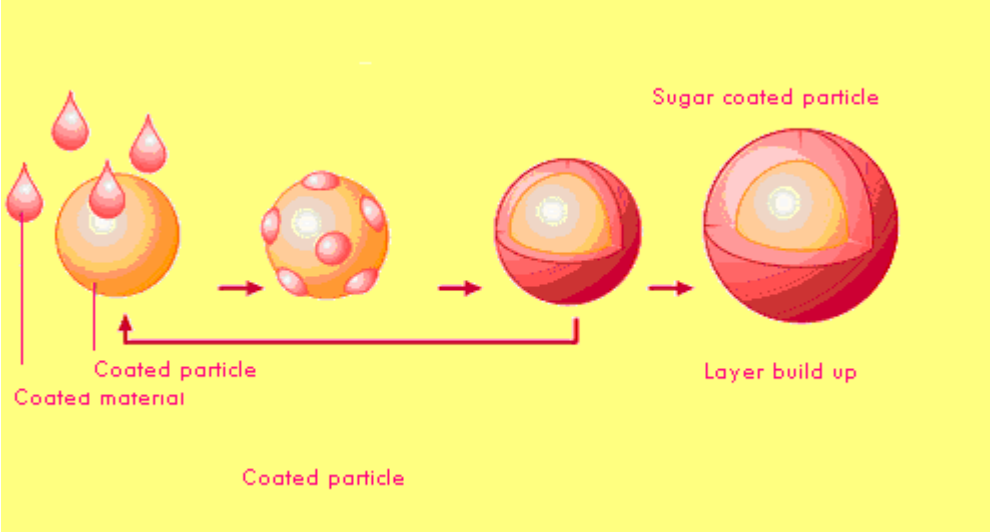
Printing

Formulations of coating solution: The constituents of coating solutions used for sugar coating are given below:

Seal coating	Sub coating	Syrup coating	Polishing soln.
Zein/Shellac	Gelatin	Colorant	Carnauba wax
Oleic acid	Acacia	Sub coating powder	(yellow)
Propylene glycol	Sugar cane powder	Cal. Carbonate	Bees wax
PEG 4000	Corn syrup	Cane sugar powder	(white)
Methylene chloride	Syrup	Corn starch	Paraffin wax
Alcohol	Distilled water	Syrup	Naphtha
		Distilled water	

Enteric coating polymers: Cellulose acetate phthalate, Acrylate polymers, Hydroxypropyl methyl cellulose phthalate, Polyvinyl acetate phthalate

Solvents used for coating: Ethanol, Methanol, Isopropanol, Chloroform, Acetone, Methylene chloride, Methylene ethyl ketone



Simplified representation of sugar coating process

Film coating

Reasons for film coating include,

1. Appearance or change the color
2. Ffor branding purposes or other aesthetic reasons
3. Stability
4. To protect the active ingredient from moisture, light, and/or the acidic environment of the stomach
5. Taste/odor Masking to provide an easy to swallow tablet without the bitter taste of many active ingredients

6. To obtain Release characteristics- Many film coating materials have functional properties which enable the creation of sustained or delayed (enteric) release dosage forms

P**rocesses**

1.**Pan-pour methods**

Pan pour methods have been used for many years in film coating, but they have been supplanted by newer coating techniques. The method utilized alternate solution application, mixing and drying steps similar to pan pour sugar coating. This method was relatively slow and relied on high skill

2.**Pan-spray methods**

Spraying equipment is used here to improve the efficiency of coating process. Automated control of liquid application is used here. Different spray patterns can be selected by using different nozzles.

Fluidized bed process also have been successfully used for rapid coating of tablets, granules and capsules

Process variables

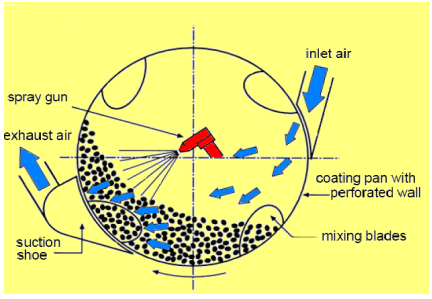
1. Pan variables like pan design,/baffling, Speed and Load
2. Process air: Quality of air, Temperature and air flow rate/volume/balance
3. Spray Variables: Spray rate, Degree of automization, Spray Pattern, Nozzle to bed distance

Modern film coating processes are Single stage process, which involves spraying a coating solution containing the following;

1. Polymer 2. Solvent
3. Plasticizer 4. Colourant

The solution is sprayed onto a rotating tablet bed followed by drying, which facilitates the removal of the solvent leaving behind the deposition of thin film of coating materials around each tablet.

Accela Cota



The vast majority of film coated tablets are produced by a process which involves spraying of the coating material on to a bed of tablets. Accela Cota is one example of equipment used for film coating.

Advantages

Produce tablets in a single step process in relatively short period of time. Process enables functional coatings to be incorporated into the dosage form.

Disadvantages

There are environmental and safety implications of using organic solvents as well as their financial expense.

Why is film coating favoured over sugar coating?

	Tablet appearance	Process
Film Coating	Retains shape of original core	Easy training operation
	Small weight increase of 2-3% due to coating material	Single stage process
	logo or 'break lines' possible	Easily adaptable for controlled release allows for functional coatings
Sugar Coating	Rounded with high degree of polish	Difficult to automated e.g. traditional coating pan
	Larger weight increase 30-50% due to coating material	Considerable training operation required
	Logo or 'break lines' are possible	Multistage process
		Not able to be used for controlled release apart From enteric coating.

Polymer used in film coating

Examples:

- Cellulose derivatives
- Methacrylate amino ester copolymers.

Plasticizer used in film coating

Examples:

- Polyols - Polyethylene glycol 400
- Organic esters - diethyl phthalate
- Oils/glycerides - fractional coconut oil

Colourants used in film coating

Examples:

- Iron oxide pigments
- Titanium dioxide
- Aluminium lakes.

Water insoluble pigments are more favourable than water soluble colours for the following reasons:

1. Better chemically stability in light
2. Optimised impermeability to water vapour
3. Better opacity
4. Better covering ability

Environmental Factors to be considered

Venting of untreated organic solvent vapour into the atmosphere is ecologically unacceptable but removal of gaseous effluent is expensive.

Safety Factors to be considered

Organic solvents possess safety hazard, such that they are Toxic, Explosive and inflammable

Financial

The hazards associated with organic solvents necessitate the need for building flame- and explosive- proof facilities. In addition, the cost of their storage and ingredients are relatively expensive.

Solvent residues

For a given process the amount of residual organic solvent in the film must be investigated. Thus, stringent regulatory controls exist.

Traditionally, organic solvents had been used to dissolve the polymer but modern techniques rely on water because of significant drawbacks. Below lists some of the problems associated with organic solvents.

Water vapour permeability and film tensile strength should be evaluated using appropriate instruments before proceeding for film coating of tablets.

Functional coatings

Functional coatings are coatings, which perform a pharmaceutical function. The most important one is Enteric coating and the other one is Controlled release coating

Enteric coating

The technique involved in enteric coating is protection of the tablet core from disintegration in the acidic environment of the stomach by employing pH sensitive polymer, which swell or solubilize in response to an increase in pH to release the drug.

Aims of Enteric protection:

1. To mask taste or odour
2. Protection of active ingredients, from the acidic environment of the stomach.
3. Protection from local irritation of the stomach mucosa.

4. Release of active ingredient in specific target area within gastrointestinal tract.

Examples of enteric coated OTC products

- Enteric coated aspirin E.g. Micropirin® 75mg EC tablets
- Enteric coated peppermint oil E.g. Colpermin®

The pH status of enteric coated polymers in the stomach

The polymers used for enteric coatings remain unionized at low pH, and therefore remain insoluble. As the pH increases in the gastrointestinal tract the acidic functional groups are capable of ionization, and the polymer swells or becomes soluble in the intestinal fluid.
Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine, where the drug is then released for absorption through the intestinal mucosa into the human body where it can exert its pharmacologic effects.

The ideal properties of enteric coated material

1. Permeable to intestinal fluid
2. Compatibility with coating solution and drug
3. Formation of continuous film
4. Nontoxic
5. Cheap and ease of application
6. Ability to be readily printed
7. Resistance to gastric fluids

Summary of Polymers used in pharmaceutical formulations as coating materials.

Polymer	Trade name	Application
Shellac	EmCoat 120 N Marcoat 125	Enteric Coatings Taste/Odor Masking

Cellulose acetate	Aquacoat CPD® Sepifilm™ LP Klucel® Aquacoat® ECD Metolose®	Enteric Coatings Taste masking Sustained release coating Sub coat moisture and barrier sealant pellet coating
Polyvinylacetate phthalate	Sureteric®	Enteric Coatings
Methacrylate	Eudragit®	Enteric Coatings Sustained Release Coatings Taste Masking Moisture protection Rapidly disintegrating Films

Shellac

1. Material of natural origin- purified resinous secretion of the insect Laccifer lacca.
2. Oldest known material used for enteric coatings.
3. Suited for drug targeting in the distal small intestine as soluble at pH 7.0
4. Its use is now less popular in commercial pharmaceutical applications for enteric coatings. Due to poor batch to batch reproducibility, which is a crucial requirement.

Cellulose acetate phthalate (CAP)

1. Chemical name: Cellulose acetate phthalate
2. Trade name: CAP, Aquateric
3. Application form: organic or aqueous dispersion
4. Functional groups: acetyl, phthalyl
5. Soluble above pH: 6
6. Additional remarks: sensitive to hydrolysis, 5-30% plasticizer required.

Polyvinyl acetate phthalate (PVAP)

1. Chemical name: polyvinyl acetate phthalate (CAP)
2. Trade name: Opadry enteric (aqueous), Coloron
3. Application form: organic solution, aqueous dispersion.

4. Functional groups: acetyl, phthalate, vinylacetat :crotonic acid ratio 90:10.
5. Soluble above pH: 5
6. Additional remarks: Plasticizer is required.

Acrylic polymers

1. Chemical name: Methacrylic
2. Trade name: Eudragit®
3. Application form: organic solution or aqueous dispersion.
4. Functional groups: methyacrylic acid
5. Soluble above pH: 5 * depends on co- polymers used.

Polymer dissolution

Factors affecting the release of a drug from a polymer:

1. Thickness of the coating material
2. Other excipients
3. Ionic state

Thickness of a coating material

- ***How much polymer is required for enteric protection?***

To achieve enteric protection of the core 3-4 mg/cm2 of the polymer is required to be applied to the dosage form.

- ***Do different polymers require different amounts for application?***

Meth acrylic acid copolymers require a lower amount of polymer compared to cellulose derivatives which usually require higher amounts of polymer to achieve the same core protection as the former.

- ***What effect does increasing polymer layers have on dissolution?***

The more polymer layers that are applied, the greater the rate of dissolution of the drug.

pH

Dissolution of polymers intended for enteric targeting is dependent upon the dissolution medium. This is influenced by the composition of the polymer, the monomers, or the type and degree of substitution

Ionic state

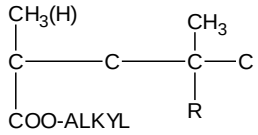
The rate of polymer dissolution is dependent upon the type of ions present in the dissolution medium.

It was shown that sodium chloride prevented dissolution of some polymers

Other excipients

 Influence the dissolution of polymer.

 Plasticizers may decrease or increase dissolution rate, depending on the nature of the plasticizer, whether it is lipophilic or hydrophilic.



General structure of Eudragit® Polymers

Changing the R group gives rise to polymers with different physiochemical properties.

Functional Group

Methacrylic Copolymer

E.g. Anionic -COOH

Applications: Gastro resistance, Delivery to the colon

Aminoalkyl methacrylate copolymer

E.g. -COOH-CH2-CH2N(CH3)2

Applications: Taste, odour and moisture protection, Dissolves in the stomach

Methacrylate copolymer

E.g. neutral -COOCH3 or COOC4H9

Applications

Delayed and sustained release (insoluble)

Delayed release: The drug is not released immediately after administration but at a later time.

Sustained release: An initial release of the drug soon after administration, followed by gradual release over an extended period

Aminoalkyl methacrylate copolymer

E.g. -COO-CH2-CH2N+(CH3)3 3CL-

Applications: Delayed and sustained release

Depending on the desired function of a coating, the following values are figures for the amount of polymer required:

Polymer Quantities

Enteric coatings:

4 – 6 mg for round tablets

5 – 10 mg for oblong-shaped tablets

5 – 20 mg for gelatin or HPMC capsules

Taste-masking coatings:

1 – 2 mg for round tablet

1 – 4 mg for oblong-shaped tablets

Moisture protection:

1 – 6 mg for round tablets

2 – 10 mg for oblong-shaped tablets

5 – 10 mg for gelatin or HPMC capsules

 Eudragit® is the trade name for the class of polymers known as the methacrylates.

 Mostly commonly used polymer for enteric coating.

Eudragit® Polymers

Advantages:

 Pharmacologically inactive

 Excreted unchanged

 These are copolymers derived from esters of acrylic and methacrylic acid in, which properties are determined by the R group.

 Different grades of polymers are obtained by mixing monomers in different ratios.

Ex: Acid –neutral- alkaline

They contain –COOH as a functional group. They dissolve at ranges from pH 5.5 to pH 7.

General structure of Eudragit®

These are copolymers derived from esters of acrylic and methacrylic acid in, which properties are determined by the R group.

Changing the R group gives rise to polymers with different physiochemical properties.

The grades for enteric coatings are based on anionic polymers of methacrylic acid and methacrylates.

The different products are available as aqueous dispersions, powders and organic solvents

Coated tablets evaluation

The basic evaluation involves,

1. Adhesion tests with tensile strength testers (force required to peel the film from tablet surface)
2. Diametric crushing strength of coated tablets can be determined with a tablets hardness tester. The relative increase in crushing strength provided by the film can be studied from this.
3. Disintegration and or dissolution of coated tablets.
4. Stability studies –Ex: in different temperatures and humidity.
5. Surface hardness, roughness, uniformity in colour etc.

Film defects

1. **Sticking & Picking**

Reasons:

1. Poor formulation
2. Over wetting and excessive film tackiness causes tablets to stick to each other or to the coating pan.
3. On drying, apiece of film may remain adhered to the Pan or to another tablet giving a picked appearance to the tablet surface.

Remedy: A reduction in the application rate or increase in the drying air temperature can solve this.

2. **Roughness**

Reasons: Some of the droplets may dry too rapidly before reaching the tablet bed resulting in rough deposits on the spray dried particles instead of finely divided droplets of coating solution.

Remedy: Moving the nozzle closer to the tablet bed or reducing the degree of atomization can decrease

3. **Orange Peel Effects**

Reasons: Inadequate spreading of the coating solution before drying causes a bumpy or orange peel effect on the coating.

Remedy: Thinning the solution with additional solvents may solve this problem

4.**Bridging and Filling**

Reasons: During drying, the film may shrink and pull away from the sharp corners of the bisect resulting in bridging. Similarly, too much application of solution can cause "Filling" also.

Remedy: Monitoring fluid application and through mixing of tablets in pan prevent filling.

5.**Blistering**

Reasons: Too rapids evaporation of the solvent from the tablet core can cause blistering.

Remedy: Milder drying conditions

6.**Hazing/Dull Film(bloom)**- This is more evident when using cellulose polymers are used

Reasons: High processing temperature

Remedy: Monitoring temperature and humidity

7.**Colour variation**

Reasons: Improper mixing, un even spray pattern and insufficient coating may cause variation in color of the coat in the form of mottled or spotted appearance.

Remedy: Reformulation with different plasticizers and other additives during drying process. The use of lake dyes eliminates dye migration.

8.Cracking

Reasons: Internal stress in the film exceeds the tensile strength of the film.

Remedy: Increase tensile strength of the film can be increased by using higher molecular weight polymers or polymer blends.

Adjusting plasticizer concentration.

Specialized Coatings

Press Coating

Press coating process involves compaction of coating material around a preformed core. The technique differs from sugar and film coating process.

Advantages

This coating process enables incompatible materials to be formulated together, such that one chemical or more is placed in the core and the other (s) in the coating material.

Disadvantages

Formulation and processing of the coating layer requires some care and relative complexities of the mechanism used in the compressing equipment.

Other coating methods are Electrostatic coating, Dip coating, Vacuum film coating etc.

CAPSULE

Capsules are solid dosage forms in which medicinal agents are enclosed within hard or soft soluble shell. The shells are generally formed from gelatin. Capsules are regarded as container drug delivery systems that provide a tasteless/ odorless dosage form without need for secondary coating step.

Capsule are classified depending on nature of shell

1. Hard gelatin
2. Soft gelatin capsules, also called as soft gels

The basic raw material of capsule shell is Gelatin. In addition to this, the shell is consisting a plasticizer & water, it may contain additional ingredients such as preservative, coloring & opacifying agents, flavorings, sugars, acids & medicaments to achieve desired effects.

Types of capsules

1. Oral
2. Rectal
3. Vaginal
4. ophthalmic ointments

Advantages of capsules for oral administration

1. Convenience in carrying
2. Readily identifiable
3. Swallowing is easy for most patients.
4. Aesthetically pleasing
5. Prescribing flexibility
6. Efficiently and productively manufactured
7. Packaged and shipping at lower cost and with less breakage
8. More stable and have a longer shelf-life
9. Empty hard gelatin capsules are often used in the extemporaneous compounding of prescriptions
10. Taste and odor masking

Gelatin

Gelatin is obtained from partial hydrolysis of collagen derived from the skin, connective tissue & Bones of animals. Some of the major gelatin Manufacturers include Eli Lilly, Capsugel (both multinational) and Rallis India Limited (in India)

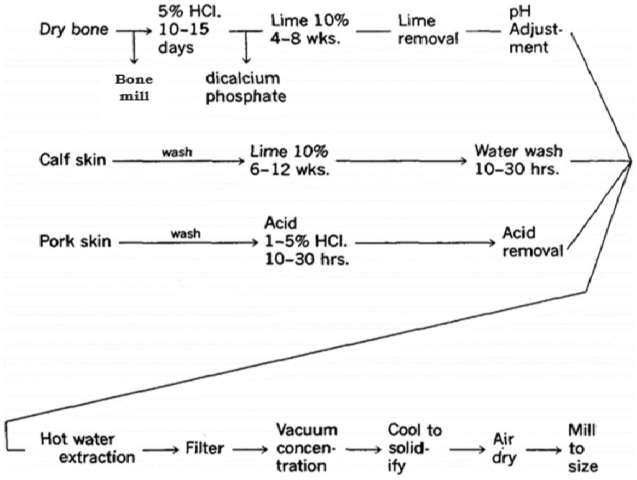
The capsule shell is basically composed of Gelatin, a plasticizer & water; it may contain additional ingredients such as preservative, coloring & pacifying agents, flavorings, sugars, acids & medicaments to achieve desired effects.

Types of Gelatin

TYPE A - Derived from acid treated precursor that exhibits an iso electric point at pH-9. It is manufactured mainly from pork skin. (Porcine)

TYPE B - Derived from alkali treated precursor that exhibits an iso electric point at pH-4.7. It is manufactured mainly from animal bones (Bovine)

** Bone gelatin contributes firmness, whereas pork skin gelatin contributes plasticity clarity



Gelatin Manufacture

Properties of soft gelatin

1. **The solubility property of gelatin**

Insoluble in cold water, soften through the absorption of up to ten times its weight of water; soluble in hot water and in warm gastric fluid. Gelatin, being a protein, is digested by proteolytic enzymes.

2. Bloom Strength

 Bloom strength is an empirical gel strength measure, which give an indication of the firmness of gel

 It is measured by a bloom gelometer

 It determines the weight in grams required to depress a standard plunger a fixed distance into the surface of 6 2/3 % w/w gel under standard conditions

 Bloom strength in the range of 150-280 g are considered suitable for capsules

3.Viscosity

 The viscosity of gelatin solution is vital to the control of the cast film.
 Viscosity is measured on a standard 6 2/3 % w/w solutions at 60 degree C in capillary pipette and generally the range of 30-60 millpoise is suitable
 Low viscosity(25-32mp)&high bloom(180-250gms) are used for hygroscopic vehicles or solids

Other shell materials

1. HPMC: Hydroxyl propyl methyl cellulose
2. HPMC capsules can be made by dipping technology
3. HPMC capsules generally have lower Equilibrium Moisture Content (EMC) than gelatin capsules and may show better physical stability on exposure to extremely low humidity

HARD GELATIN CAPSULES

The hard gelatin capsules are,

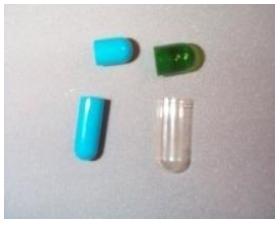
a. used to manufacture most medicated agents, about 10 fold in comparison to soft gels
b. employed in clinical trials
c. used in extemporaneous compounding

Manufacturing of hard gelatin capsule shells

1. The empty capsule shells consist of gelatin, sugar, water, colorants (various dyes), and opaquants (titanium dioxide).
2. The shell consists of two parts, the capsule body and the capsule cap.
3. The process of capsule shell production with the peg/pin method:

Dipping→ drying → stripping→ trimming→ joining

The thickness of the gelatin walls must be strictly controlled.

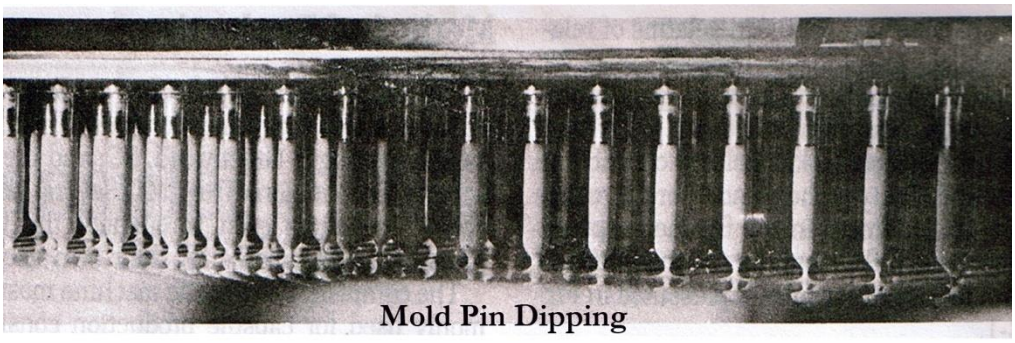


Parts of Capsule

The cap is slightly larger in diameter than the body

Dipping

1. Pairs of stainless steel pins (about 150 pins) lubricated, are dipped into the dipping solution to form caps and bodies simultaneously
2. The pins are at ambient temperature, 22^{o}C whereas the dipping solution is at 50^{o}C in jacketed heating pan.
3. The dipping time to cast the film is about 12 secs



Mold Pin Dipping

Rotation

1. After dipping, the pins are withdrawn from dipping solution. They are elevated and rotated until they are facing upward.
2. This helps distribution of the gelatin over the pins uniformly and to avoid the formation of bead at the capsule ends
3. After rotation they are given a blast of cool air to set the film.

Drying

1. The racks of gelatin coated pins then pass into a series of four drying ovens
2. Drying is mainly done by dehumidification by passing large volumes of dry air over the pins
3. Temperature elevation of few degrees are permissible to prevent film melting
4. Drying also must be too rapid to prevent case hardening
5. Under drying leave film sticky for subsequent operations
6. Over drying must be avoided as this could cause the films to split on the pins due to shrinkage or at least make them brittle for later trimming step

Stripping

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

Trimming

1. The stripped caps and bodies are delivered to collets(Chucks) in which they are firmly held
2. As the collets rotate the knives are brought against the shells to trim them to the required length

Joining

1. The cap and body portions are aligned concentrically in channels, and the two portions are slowly pushed together
2. The entire cycle takes about 45 minutes, about 2/3 of which is required for the drying step alone
3. Sorting
4. The moisture content of capsules as they are ejected from machine will be in the range of 15-18% w/w
5. During sorting, the capsules passing on a lighted moving conveyor are observed visually by inspector
6. Any defective capsules spotted are thus manually removed
7. The moisture content of capsules as they are ejected from machine will be in the range of 15-18% w/w
8. During sorting, the capsules passing on a lighted moving conveyor are observed visually by inspector
9. Any defective capsules spotted are thus manually removed.
10. The defects may cause serious problems like
11. Stoppage of a filling machine due to imperfect cuts, dented capsules, or capsule with holes
12. Some defects may cause usage problems
    Ex. Capsules with splits, long bodies etc.

Cosmetic faults like small bubbles, specks in film, marks on cut edge detract from appearance

Printing

1. In general, capsules are printed prior to filling as they are easy to handle
2. Generally printing is done on offset rotary presses having through capabilities as high as ¾ million capsules per hour
3. Available equipment can print axially along the length or radially around the circumference of capsules

***Rallis India Limited, Mumbai is a major Raw material supplier Associated capsule private Limited, Mumbai is a major shell supplier in India.*

Capsule sizes

How to select capsule size?

Based upon,

1) The amount of fill material to be encapsulated
2) The density and compressibility of the fill
3) The final determination largely may be the result of trial.

The sizes of empty capsules

- For human use: 000 (the largest) to size 5 (the smallest)
- For veterinary use: No.10,11 and 12 having capacities of 30, 15 and 7.5 g, respectively

Filling Capacity of Empty Capsules

Capsule Size	Approx. Volume (ml)	Quinine Sulfate (g)	Sodium Bicarbonate (g)	Acetyl-salicylic Acid (g)	Bismuth Subnitrate(g)
0	0.75	0.33	0.68	0.55	0.8
1	0.55	0.23	0.55	0.33	0.65
2	0.4	0.2	0.4	0.25	0.55
3	0.3	0.12	0.33	0.2	0.4
4	0.25	0.1	0.25	0.15	0.25
5	0.15	0.07	0.12	0.1	0.12

Sealing and self-locking closures

1. Hard gelatin capsules are made self locking by forming indentations (divided or edged with a zigzag line or grooves on the inside of the cap and body portions
2. When they are fully engaged, a positive interlock is created between the cap and body portions
3. Indentation formed further down on the cap provide a pre lock, thus preventing accidental separation
4. Hard gelatin capsules may made hermetically sealed by the technique of banding wherein a film of gelatin, often distinctly colored, is laid down around the seam of the cap and body
5. In the thermal method of spot welding, two hot metal jaws are brought into contact with the area where the cap overlaps the filled body
6. *Capsugel has proposed low temperature thermal method of hermetically (complete and airtight) sealing the hard gelatin capsules *a pharma Company in the U.S
7. This process involved immersion of the capsules for a fraction of second in hydro alcoholic solvent, followed by rapid removal excess solvent, leaving traces in the overlapping area of cap and body. Finally, the capsules are dried with warm air

8. A more recent approach is spraying of mist of hydro-alcoholic solution on to the inner cap surface immediately prior to the closure in filling machine
9. Storage, packaging, and stability
10. Finished capsules normally contain an EMC of 13-16%.
11. < 12% MC, the capsule shells become brittle
12. >18% make them too soft

Preparation of filled hard gelatin capsules

The general steps of preparation:

1) Developing and preparing the formulation and selecting the size of capsule.
2) Filling the capsule shells.
3) Capsule sealing.
4) Cleansing and polishing the filled capsules.

Developing the formulation and selection of capsule size

The pharmaceutical processing in the preparation of filled hard gelatin capsules is,

1) *Blending*: To obtain uniform powder mix and uniform drug distribution
2) *Comminution/Milling*: To reduce particle size. For example, 50-100 micron size is suitable for a drug of low dose (10mg or greater)
3) *Micronization*: To reduce particle size up to 10-20 microns

Excipients used in the formulation

The pharmaceutical excipients in the preparation of filled hard gelatin capsules is,

1. Diluents/Fillers: To produce the proper capsules fill volume; to provide cohesion to the powders,
2. Ex. Lactose, microcrystalline cellulose and starch
3. Disintegrants/Disintegration agents: to assist the break-up and distribution of the capsule contents
4. Ex. Pre gelatinized starch
5. Lubricant or Glidant: to enhance the flow properties of the powder mix. Ex. Fumed silicon dioxide
6. Wetting agents: to facilitate wetting of the dry powder. Ex. Surfactant like SLS

Formulation aspects

1. De mixing should not occur during powder handling in filling equipment
2. Physical incompatibilities between active ingredients,diluents,capsule shell etc. should be evaluated
3. The powder mix should show god flow characteristics
4. The choice of exepients should be made as per FDA regulations (In USA)

5. Serious consideration should be given to suitable control measures for filling operations. -Ex: 100% weight checking after filling

***Rotoweigh is a high speed capsule weighing machine supplied by Eli Lilly and Company*.

Filling of hard gelatin capsules

The "punch" method

Placing the powder on paper, forming the powder mix into a cake and punching the empty capsule body into the powder cake (Obsolete Method)

The Pouring method

Pouring the required dose into the shell. This method is suitable for filling a small number of capsules in the pharmacy especially for granular material

Machineries

Hand-operated capsule filling machines

Consist of a couple of plates. The machine is made up of good quality steel and provided with a filling tray, fitting exactly on a die having the desired number of holes. A powder dispenser and scoop is provided with the machine to fill the hole with drug material. The capacity of die depends on the number f capsules produced at a time. (150 to 300)Different sets of dies and pin sets are provided along with the machine, to fill various sizes of capsule. Pin sets are used to press the contents of the capsules to accommodate the desired volume.

Hand-operated capsule filling machine

Operation

1. Fill the die with desired size of empty capsules, with the caps on upper side.
2. Operate the cam handle to separate the capsule cap from body
3. Place a powder tray on the die and pour a calculated amount of medicament into the tray.

4. Using the scrapper, distribute the powder completely in the capsules.
5. Operate the pin plate to compress the material in the capsule shells and re fill medicaments if any spaces remain.
6. Operate the liver to lock the capsule caps on the body of the capsules
7. Remove the loading tray and capsules filled.
8. Clean the capsules suitably and transfer to containers.

About 40,000 to 60,000 capsules can be filled on a single machine, in one shift of eight hours. *Semi-automatic capsule filling machines are also available.*

Automatic capsule filling/Rotary machines

Electrically operated computerized machines can be used for large scale production of capsules. They offer a very high rate of filling (MT 25000 capsules per hour), depending on the machine capacity.

Ex: Lilly Rotofil, Farmatic, H &K model 602, 2400, Macofar, Osaka, Zanasi, Perry etc. globally and Cadmach, Karnavati in India.

Working of Automatic Capsule Filling Machine

The process of working:

1. Rectification
2. Separating the caps from empty capsules
3. Filling the bodies
4. Replacing the caps
5. Sealing /and or locking the capsules
6. Finishing/Cleaning the outside of the filled capsules

Rectification

1. The empty capsules are oriented so that all point the same direction in the hopper. i.e. body end downwards
2. In general, capsule pass one at a time through a channel just wide enough to provide grip at cap end
3. The capsules will always be aligned body end downwards, regardless of which end entered the channel first with the help of specially designated blades
4. Separation of caps from body
5. The rectified capsules are delivered body end first into the upper portion of split bushings or split filling rings
6. A vacuum applied from below pulls the body down into the lower portion of the split bushing
7. The diameter of the bush is too large to allow them to follow body
8. The split bushings are separated to expose the bodies for filling

Filling

Auger fill

The auger (a tool resembling a large corkscrew, for boring holes) mounted in the hopper rotates at a constant rate, the rate of delivery of the powder to the capsules tend to be constant. *Two types of augers are used.*

1. Flat blade auger
2. Screw auger

Vibratory fill

1. In the powder, a perforated resin plate is positioned and connected to a vibrator
2. The powder blend tends to be fluidized by the vibration of plate and assists the powder to flow into the body of capsules through the holes in resin plate. Piston tamp (a disc or short cylinder fitting closely within a tube in which it moves up and down against a liquid or gas, used in a pump to impart motion).

In this, pistons or tamping pins lightly compress the individual doses of the powders into plugs (also called as slugs) and eject the plugs into empty capsule bodies. Two types include,

1.DOSING DISCS: a solid 'stop' brass plate is sliding down the dosing disc to close off the hole. Five sets of pistons compress the powder into cavities to form plugs

2.DOSATOR: it consists of cylindrical dosing tube fitted with movable piston. The position of the piston is preset to a particular height to define a volume. Powder enters the open end of dosator and is slightly compressed against the piston into a plug

Replacing the caps / Sealing and locking the capsules

Sealing of the caps on to the bodies is possible by moistening the upper part of the body and slipping the cap on. However, many manufacturers seal capsule by means of a coloured band of gelatin placed at the junction of the body and cap. More recently some configurations have been developed in the bodies and caps which enable their mechanical locking. For instance, Snap Fit capsules, marketed by Parke Davis, have matching interlocking rings on the body and in the cap. Another method suggested is to bring a hot needle like structure against the cap where it overlies the body to form a sort of spot weld.

Finishing/Cleaning and polishing capsules

Small amount of powder may adhere to the outside of capsules after filling.

1) Pan Polishing (salt polishing)-Uses sodium chloride granules and the granule are separated by screening.

2) Cloth Polishing -Individual Capsules are rubbed with cloth.

3) Brushing – Soft projected brushes are used which remove all dust

Inspection: This process sis desirable to pick up imperfect and damaged capsules. Automatic equipments are also available.

SOFT GELATIN CAPSULES

Soft Gelatin capsules are one piece, hermetically sealed, soft gelatin shells containing a liquid, a suspension, or a semisolid.

1. The Nomenclature for this dosage form has now been changed to soft gel. They have long been preferred dosage form for those, taking Health & Nutritional supplements.
2. Soft gelatin capsules (referred to as soft elastic gelatin capsules, liquid gels or soft gels) are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard gelatin capsules and liquids
3. However due to economic, technical and patent constraints there are relatively a few manufacturers of soft gels in the world
4. The soft gel consists of two major components, the gelatin shell and the fill. In the finished product gelatin shell is primarily composed of gelatin, plasticizer and water.
5. The fill material can include a wide variety of vehicles and can either be a solution or a suspension. Soft gels may be coated with suitable exterior coating agents such as Cellulose acetate phthalate (CAP) to obtain enteric release of encapsulated material.
6. Soft gelatin capsules generally contain the drug in a non aqueous solution or suspension.
7. The vehicle may be water immiscible liquid, such as PEG, and non ionic surface active agent, such as Polysorbate 80.
8. Hydrophobic drugs dissolved in a lipophilic solvent such as vegetable oil would generally demonstrate poor bioavailability compared to the same drug given as a powdered solid, suspension or hard gelatin capsules.

9. However, a drug dissolved or dispersed in a water miscible solvent may have better bioavailability than a compressed tablet of the same drug.

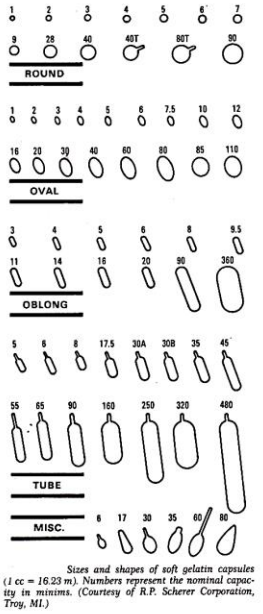
The pharmaceutical applications of soft gelatin capsules are:

a. as an oral dosage form
b. as a suppository dosage form
c. as a specialty package in tube form, for human and veterinary applications

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.

Gelatin



Sizes and shapes of soft gelatin capsules (1 cc = 16.23 m). Numbers represent the nominal capacity in minims. (Courtesy of R.P. Scherer Corporation, Troy, MI.)

It is a protein obtained from partial hydrolysis of collagen derived from the skin, connective tissue & Bones of animals.

 Bloom or gel strength: a measure of the cohesive strength of cross-linking that occurs between gelatin molecules & is proportional to the mw of the gelatin
 Higher the bloom strength, more physically stable the capsule shell.
 Bloom range:150-250 gm
Viscosity of gelatin: it is a measure of the chain length& manufacturing characteristics of gelatin film
 Low viscosity (25-32mp) &high bloom(180-250gms) are used for hygroscopic vehicles or solids
 Water: The ratio by weight of water to dry gelatin can vary from 0.7 to1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of the gelatin being used.
 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. The ratio by weight of dry plasticizers to dry gelatin determines “hardness” of the gelatin shell.

Hardness: ratio dry glycerin\dry gelatin

Hard	0.4\1
Medium	0.6\1
Soft	0.8\1

 Colour: used in shell has to be darker than color of encapsulating material colors may be natural or synthetic

 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. Conc.

 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 colors

 Flavoring Agents: Ethyl vanillin-0.15; essential oils -2%

 Sugars: 5% to produce chewable swell& taste

 Fumaric acid: 1%. aids solubility; reduces aldehyde tanning of gelatin

Typical Formula for Gelatin Sheet Manufacture

Glycerin IP	52.0 Kg
Propyl Paraben IP	0.512Kg
Methyl Paraben IP	0.128Kg
Gelatin 120 Bloom IP	152.000Kg
Brilliant Blue Ponceau 4R IP	0.300Kg
Sunset Yellow IP	0.300Kg
Titanium dioxide IP	16.000Kg
Water	120.00 L
Sorbitol Liq. IP	16.00Kg

Gelatin sheet is the basic requirement for soft gelatin shell manufacture.

Method of Gelatin Sheet Manufacture

1. The gel is prepared in a 300-litre stainless steel vessel.
2. Gelatin powder is mixed with water and glycerin.
3. Heating and Stirring, the molten gelatin mass is formed. It is decanted into 200-kg mobile vessels.
4. Turbine mixing where colors and flavors can be added. It ensures consistency of gelatin mass.
5. This mass is kept at a constant temperature until it is needed for the next stage of the process

Capsule content

1. Capsule content may be liquid, or a combination of miscible liquids.
2. A solution of a solid(s) in a liquid(s) or a suspension of a solid(s) in a liquid(s).
3. It can be a liquid like a volatile oil composition e.g. Pudin hara.

4. Vegetable oils like arachis oil or aromatic or aliphatic hydrocarbons, ethers, esters, or alcohols.
5. Solids that are not sufficiently soluble in liquids or in combination of liquids are capsulated as Suspension.
6. Suspending agents used are Lecithin, Soya bean oil, yellow wax.

Base adsorption (BA)

Base adsorption factor is the number of grams of the liquid base required to produce a capsulatable mix with one gram of the solid.

The value of B/A depends on particle size, shape, density, moisture content, hydrophilicity or hydrophobicity of the solid.

Weight of base/Weight of solid=Base adsorption

(B/A+S) x V/ D= M/G

Where B/A is the base adsorption factor,S stands for 1 g of solid, V represents the unit volume in cubic centimeters and D is the weight of the mixture per cubic centimeter.

M/g- minim per gram factor

Use

To predict the minim per gram factor (M/g) of solids. Lower base adsorption of solids means higher density of mixture and the capsule size will be small.

BA and M/g Factors of Some Typical Solids

Ingredient	*Base**	*BA*	*M/g*
Acetaminophen	Veg. oil	0.76	25.97
Acetaminophen	PEG 400	0.75	23.07
Ascorbic acid	Veg. oil	0.60	20.60
Ascorbic acid	Polysorbate 80	1.10	26.92
$Al(OH)_3$—$MgCO_3$ (FMA 11)	Veg. oil	1.90	41.30
$Al(OH)_3$—$MgCO_3$ (FMA 11)	PEG 400	2.44	42.10
Danthron	Veg. oil	1.30	33.75
Danthron	Glyceryl monooleate	1.39	33.94
Danthron	Polysorbate 80	1.38	31.28
Danthron	PEG 400	1.60	33.62
Danthron	Triacetin	1.83	36.02
Ephedrine SO_4	Veg. oil	1.30	36.80
Ferrous SO_4 exsiccated	Veg. oil	0.30	10.60
Ferrous SO_4 exsiccated	Polysorbate 80	0.47	12.90
Guaifenesin	Veg. oil	1.28	34.68
Lactose	Veg. oil	0.75	23.87
Desiccated liver	Veg. oil	0.80	25.70
Mephenesin	Veg. oil	2.50	57.38
Mephenesin	PEG 400	2.13	44.77
Meprobamate	Veg. oil	1.59	42.55
Meprobamate	PEG 400	1.30	32.52
Niacinamide	Veg. oil	0.80	25.63
Neomycin sulfate	Veg. oil	0.60	20.66
Phenobarbital	Veg. oil	1.20	33.60
Procaine penicillin G	Veg. oil	0.91	28.63
Sodium ascorbate	Veg. oil	0.76	22.40
Salicylamide	Veg. oil	0.80	25.80
Sulfathiazole	Veg. oil	0.43	17.90
Sulfanilamide	Veg. oil	1.03	28.55
Tetracycline (amphoteric)	Veg. oil	0.61	21.63

*Vegetable oil bases contain 3% soy lecithin.

Base adsorption

Manufacture of soft gelatin capsules

Ideal for soft gelatin capsule manufacturing – Relative humidity: NMT 45% Temp: 21 to 24 degree C.

I. Composition of the shell

1. The basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
2. 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
3. Up to 5% sugar may be included to give a "chewable" quality to the shell
4. The residual shell moisture content of finished capsules will be in the range of 6-10%.

II. Formulation

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

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 350C or less.
- The sealing temperature of gelatin films is 37-400C

III. Manufacture process (Encapsulation)

A. Plate process

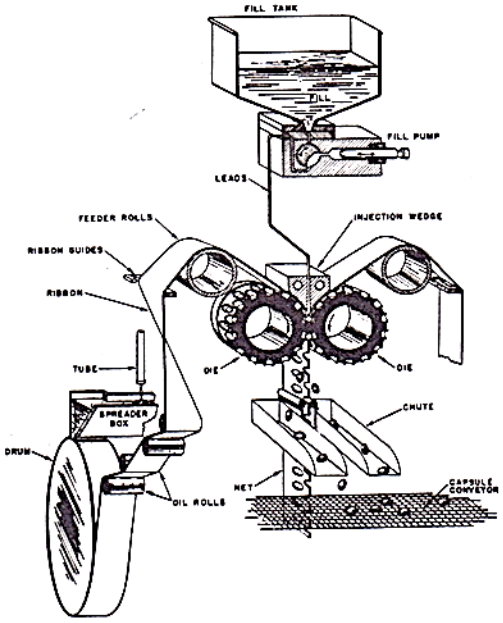
The process involves,

1. Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets,
2. Application of vacuum to draw the sheet in to the die pockets,
3. Filling the pockets with liquor or paste,
4. Folding the lower half of gelatin sheet back over the filled pockets, and

5. Inserting the "sandwich" under a die press where the capsules are formed and cut out

B. Rotary die press (Most widely used in Industries)

1. In this process, the die cavities are machined in to the outer surface of the two rollers.
2. 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.
3. Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism.
4. As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.



Schematic drawing of rotary die process.
(Courtesy of R.P. Scherer Corporation, Troy, MI.)

C. Accogel process

1. In general, this is another rotary process involving a measuring roll, a die roll, and a sealing roll.
2. As the measuring roll and die rolls rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll.
3. The continued rotation of the filled die converges (come together from different directions so as eventually to meet) with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule.
4. Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

D. Bubble method

1. A concentric tube dispenser simultaneously discharges the molten gelatin from the outer annulus and the liquid content from the tube.
2. By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consist of a liquid medicament core within a molten gelatin envelop.
3. The droplets assume a spherical shape under surface tension forces and the gelatin congeals on cooling.
4. The finished capsules must be degreased and dried
5. Degreasing can be done by washing the capsules with nontoxic organic solvents.

Capsule drying and finishing

1. **Tumble Drying**: Dry, sterile air is forced across the tumbler and removes the moisture from the outer surface of the capsules.
2. **Supplemental Drying** (curing): After the tumbler dryers, the soft capsules are placed on special trays for final drying in the drying room. For a period up to 48 hrs

- Automatic capsule sizing machine eliminates undersized and oversized capsules.
- **Inspection**: Includes visual inspection to check malformed, damaged or improperly filled capsules.
  - **Counting**
  - **counting tray**
  - **counting and filling machines**

Counting apparatus

Packing

Capsule may be packaged in glass or plastic containers or may be strip or blister -packaged, so long as such packaging involves tight closures & plastics having a low moisture vapor transfer rate

Product quality considerations

1. Ingredient specifications

1. All ingredients of a soft gel are controlled and tested to ensure compliance with pharmacopoeial specifications.

2. Ex: Impurities such as aldehydes & peroxides which may be present in polyethylene glycols. Presence of high levels of these impurities gives rise to cross-linking of the gelatin polymer, leading to insolubilization through further polymerization.

2. In-process testing

1. In-process testing During the encapsulation process the four most important tests are:-
2. The gel ribbon thickness;
3. Soft gel seal thickness at the time of encapsulation;
4. Fill matrix weight & capsule shell weight;
5. Soft gel shell moisture level and soft gel hardness at the end of the drying stage

3. Finished product testing

1. Finished product testing These normally includes
2. Capsule appearance,
3. Active ingredient assay & related substances assay
4. Fill weight, Content uniformity and Microbiological testing.

Vegicaps soft capsules

 Vegicaps Soft capsules are an alternative animal free capsule. The shell is made from seaweed extract and gluten free starch, and contains no modified sugars or artificial ingredients.
 The shell can be clear or colored and there is a wide range of shapes, sizes and colors available.
 An alternative to gelatin for those who prefer an animal free product
 Those with a level of concern about animal-derived products Vegetarians
 Those with religious or cultural restrictions Consumers looking for the most natural alternative

Benefits of Vegicaps Soft capsules

 Free of all animal derivatives – no pork or beef content.
 Easy to swallow
 Soft
 Natural
 Perception of a healthier product
 Plant based shell
 Low shell odor.

New soft gel variants

 Enteric soft gel
 Controlled soft gel
 Chewable soft gel
 Gelatin free soft gel

Applications

1. As an oral dosage form of ethical or proprietary human or veterinary use.
2. As a suppository dosage form for rectal use for a vaginal use. Rectal dosage frms are becoming more acceptable for pediatric &geriatric use.
3. As a specially package in tube form, for human& veterinary single dose applications of topical, ophthalmic, & optic preparations, &rectal ointments.
4. In cosmetic industry these capsules used as specially package for breath fresheners, perfumes, bath oils, suntan oils& various skin creams.

Evaluation of capsules

1.**Weight variation**

This test is done by weighing 20 capsules individually and determines the average weight of each capsule and finding out the weight variations of each capsule against the average value. +/- 10% variation is permitted. If the variations are beyond this limit, net weight of contents of each capsule should be determined and compared with average net weight. As per standards of some pharmacopoeias, the net weight of not more than two capsules should differ by more than +/- 10%from the average net weight and no capsule should differ by more than +/- 25% ,net weights of 40 more capsules should be detrmined.In a total of 60 capsules, not more than six should deviate from average by more than +/- 10% and none by more than +/- 25%

Wcapsule – Wemptied shell = Wcontent 10 capsules

Labeled amount or average amount, ±10%

2. **Disintegration and Dissolution time**

Capsules are not normally tested for disintegration since their shells are known to dissolve rapidly in the gastric fluids. However, capsules which are enteric coated or shells treated with formaldehyde should be tested thus to ensure that they do not disintegrate in simulated gastric juice under simulated conditions. Dissolution tests run on the lines of compressed tablets. Any of the standard apparatus available for dissolution tests can be employed. The determination of dissolution time is important since absorption of drugs depends upon their dissolution times

3. **Drug Content uniformity**

Pharmacopoeias specify 30 capsules out of which 10 should be assayed in the first instance. Out of this, at least 9 should be within +/- 15% of average and none should be beyond +/- 25%.If 1 to 3 capsules out of the 10 assayed originally fall outside +/- 15% the remaining 20 should be assayed. Out of the total of 30 capsules, at least 27 should be within +/- 15% and no capsule should be beyond +/- 25%

The amount of active ingredient should be within the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label claim.

PHARMACEUTICAL AEROSOLS

Packaging of therapeutic active ingredients in a pressurized system can be called as aerosols. They deliver a fine dispersion of liquid or solid particles and their size is usually less than 50 mcm in diameter, as a *smoke* or *mist Aerosols* depends on the power of compressed or liquefied gas to expel the contents from containers

Categories

1. Topical Preparations
2. Local Analgesics
3. Antiseptic and skin sterilizers
4. Skin dressings
5. Fungicidal Agents
6. Anti-Parasitic Agents
7. Antibiotics
8. AI Agents
9. ENT Preparations
10. Oral Inhalations for Lungs
11. Veterinary Products

Advantages

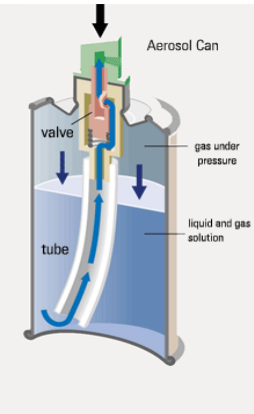
1. Convenience, Ease and speed of application
2. Minimized manual contact with drug
3. Efficient dispersion
4. Immediate local application
5. High concentration of drug over local area
6. Application without manual contact with patient
7. Rapid response to treatment
8. Controlled and uniform dosage by metered valves
9. Spray characteristics can be varied by using special valves
10. Sterility of the product can be maintained

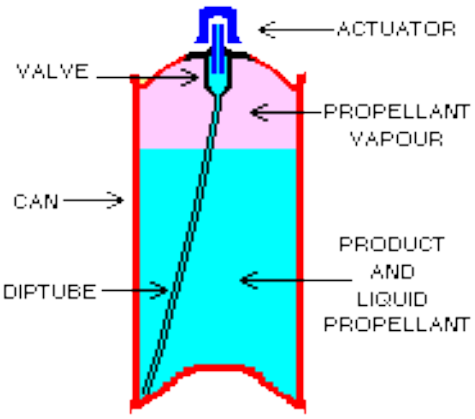
Label warnings

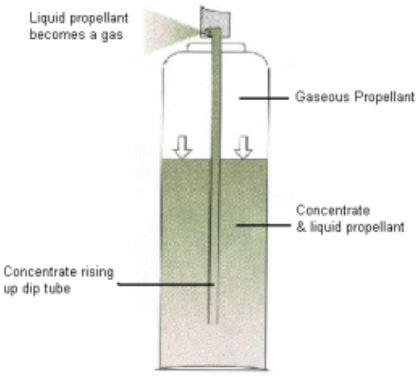
Disadvantages

1. Cost
2. Difficulty in disposal
3. Cannot be subjected to heat
4. Difficulty in formulation
5. Refrigerant effect of highly volatile propellants can cause discomfort .
6. Q.C testing complicated

Aerosol technology







Basic components

1. Propellant
2. Valve & Actuator
3. Container
4. Product Concentrate(drug)

Propellant

It is responsible for developing the power pressure with in the container and also expel the product when the valve is opened and in the atomization or foam production of the product. *Each propellant has its own vapour pressure*

For oral and inhalation

Fluorinated hydrocarbons Dichlorodifluromethane (propellant 12) Dichlorotetrafluromethane (propellent 114)

Topical preparation Propane Butane Isobutene

Compound gases Nitrogen Carbon di oxide Nitrous oxide

Fluorinated hydrocarbons

Name	Formula	Designation
Trichlorofluromethane	CCl_3F	Propellant 11
Dichloridifluromethane	CCl_2F_2	Propellant 12
Dichlorotetrafluro ethane symmetrical	$C.Cl_2F_2C.Cl_2F_2$	Propellant 114
Dichlorotetrafluro ethane assymmetrical	$C.Cl_2FCF_3$	Propellant 114a

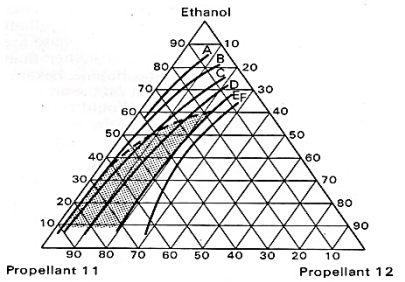
Ozone depletion of CFCS

Traditionally most pharmaceutical aerosols have been propelled with chlorofluorocarbons (CFCs), but current global regulations require pharmaceutical aerosols to be reformulated to contain non-ozone-depleting propellants. In the process of reformulation for this transition, there is the opportunity to improve today's pulmonary delivery technology and to create new systems to treat a wide array of Infirmities and afflictions.

Alternatives to CFCs

The two current alternatives to CFC propellants for pharmaceutical aerosols are hydrofluorocarbon(HFC) 134a (also known as hydrofluoroalkane (HFA) 134a or 1,1,1,2-tetrafluoroethane), and HFC-227ea (HFA-227ea or 1,1,1,2,3,3,3-heptafluoropropane)

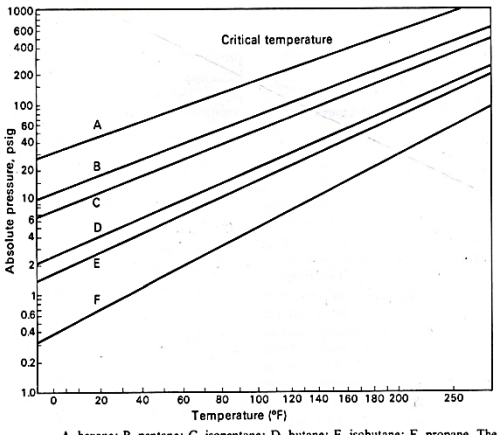
Ternary systems



Ternary system, propellants 11, 12 and ethanol.

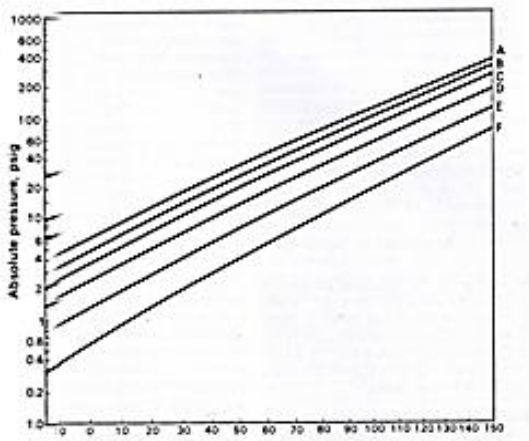
Vapour pressure contour	psig	kg/cm²
A	5	1.38
B	10	1.74
C	15	2.09
D	20	2.44
E	25	2.79
F	30	3.14

Vapour pressure-temperature relationship



A, hexane; B, pentane; C, isopentane; D, butane; E, isobutane; F, propane. The vapour pressure-temperature relationships of hydrocarbon propellants (adapted from Pressurized Packaging (Aerosols), Herzka and Pickthall, Butterworths Scientific Publications).

Effect of temperature on absolute pressure



The effect of temperature on the absolute pressure (in psig for kg/cm² conversion see 270308) of mixtures of propellants 12 and 114. A, 100 per cent propellant 12. B, 20 per cent propellant 12, C, 60 per cent propellant 12, D, 40 per cent propellant 12, E, 20 per cent propellant 12, F, 100 per cent propellant 114 (for gauge pressure subtract 14.7).

They must with stand pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 1300 F.

A. Metals

1. Tinplated steel (a) Side-seam (three pieces) (b) Two-piece or drawn (c) Tin free steel
2. Aluminium (a) Two-piece (b) One-piece(extruded)
3. Stainless steel
4. Glass
    1. Uncoated glass 2. Plastic coated glass

Tin plate containers - Sheet of steel plate that has been electroplated on both sides with tin. Welded side seam are done using two processes: ***Soudoronic*** and ***Conoweld*** **Aluminum containers** -Greater resistance to corrosion Light weight, not fragile Good for light sensitive drugs

Stainless steel containers- Limited for smaller size, extremely strong and resistant to most materials

Glass containers -Available with plastic or without plastic coating Compatible with many additives No corrosion problems. Can have various shape because of molding. Fragile and Not suitable for light sensitive drugs

Glass containers

<u>Physiochemical properties of propellants -Vapour pressure, boiling points & liquid density</u>

Vapor pressure of mixture of propellants is calculated by Dalton's low which states that total Pressure in any system is equal to the sum of individual or partial pressure of various compounds. Raoult's low regards lowering of the vapor pressure of a liquid by the addition of another substance, States that the dispersion of the vapor pressure of solvent upon the addition of solute is proportion to the mole fraction of solute molecules in solution. The relationship can be shown mathematically: $p_a = na/na+nb\ pAo = NAPAo$ Where, *Pa* = partial vapour pressure of propellant *A, pAo* = vapour pressure of pure propellant A

na = moles of propellant A,
nb = moles of propellant B
N_A = moles fraction of component A

To calculate the partial pressure of propellant *B: pb = nb/nb+na Pbo*
The total vapor pressure of system is then obtained as: *P = pa + pb*

Where, P = total vapor pressure of system

Valves

Valves are expected to deliver a given amount of medication in the desired form. The materials used for the manufacture of valves should be approved by the FDA.

Valves

Types

Continuous spray valve - High speed production technique.

Metering valves - Dispersing of potent medication at proper dispersion/ spray approximately 50 to 150 mg ±10 % of liquid materials at one time use of same valve.

Metered dose inhalers (MDI)

Valve which will deliver a pre determined amount of drug are called as metered dose inhalers(MDIs) They minimize the number of administration error and to improve the drug delivery of aerosols particles into the drug delivery system of the nasal passageways and respiratory tract. They contain a reservoir in the valve system which is pre calibrated.

Types of Metered valves

Metered valves are of two types

1. Depression of valve button may ***release the contents of the reservoir*** which refills on release of the button
2. Depression of the valve button may ***fill the reservoir***, the contents of which are ejected on release of the button.

Valve Assembly

Valve components

Valve components

1. Ferrule or mounting cup
2. Valve body or housing
3. Stem
4. Gasket
5. Spring
6. Dip tube

Actuator

1. Actuator to ensure that aerosol product is delivered in the proper and desired form.
2. Different types of actuators
3. Spray actuators
4. Foam actuators
5. Solid steam actuators
6. Special actuators: These are specially designed button placed on the valve system which helps in easy opening and closing of the valve. It helps in deliver the product in the desired form. There are different type of actuators are used.
7. Spray Actuators
8. Foam Actuators
9. Solid Stream Actuators
10. Special Actuators

Actuators

Ferrule/ mounting cup

It is used to attach the valve in proper position to the container. Made from tin-plate steel although aluminium also can be used. To increase resistance to corrosion a single or double epoxy or vinyl coating can be added. Valve body / housing The part of the valve which holds the stem, gasket and spring in place and to which the dip tube is attached. It is made of nylon/delrin and contains an opening at the point of attachment of the dip tube which ranges from 0.013 to 0.080 inch. The housing may or may not contain another opening – vapour tap Produce fine particle size Prevents valve clogging with products containing insoluble materials Reduce the chilling effect of propellant on skin

Mounting Cup

Stem, Gasket, Spring & Dip tube

Stem: It is made of nylon /delrin/stainless steel. It contains one or more orifice (0.013 to 0.030) **Gasket**: It is made of Buna –N, Neoprene rubber **Spring**: It is used to hold the gasket in a place and when actuator is depressed and released, it returns the valve to its closed position It is made of stainless steel.

Dip tube: It is made up of poly propylene material / poly ethylene Inside diameter (0.120 – 0.125 inch) for capillary tubes -0.050 inch and Viscous product - 0.195

Types of aerosol system

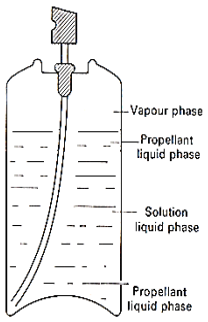
1. Two phase system (Solution system)
2. Three phase system (Water based system)
3. Suspension or Dispersion system
4. Foam system

Solution system / Two phase system Consists of two phases:

1. Liquid phase – Liquefied propellant + Product concentrate
2. Vapor phase

Two phase system

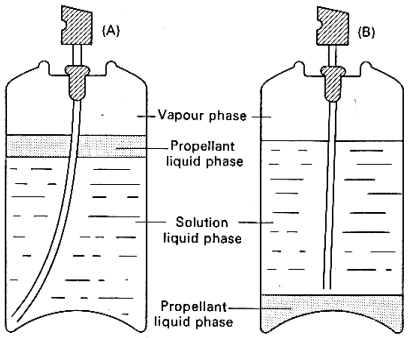
If Active ingredients are soluble in the propellant, no other co-solvent required. Generally used propellant may consist of: Propellant 12 – Fine spray Mixture of propellant 12 and other propellant – Coarse spray. As the amount of propellant 12 is increased, the pressure increases. The pressure of these systems necessitates packaging the contents in a metal container. Active ingredients to 10 -15 % Propellant 12/11(50:50) to 100%



Two phase system

Three phase system

Water based system / Three phase system Consist of large amount of water, usually to replace all or a portion of non aqueous solvents. Three phase system consists of: A layer of water-immiscible liquid propellant A layer of highly aqueous product concentrate and a vapour phase. The formulation must consist of a dispersion of active ingredients and other solvents in an emulsion system in which the propellant is in the external phase. Ethanol is used as co solvent in these systems. Surfactants (0.5-2%) are added for homogenous dispersion.



Aerosol three-phase systems A and B.

Dispersion system

Suspension or Dispersion system It is prepared by dispersion active ingredients in the propellant or a mixture of propellants by using suspending agent. Developed primarily for oral inhalation aerosols. Eg. Ephedrine bitartarate aerosol The physical stability of suspension can be increased by: Control of moisture content- must be below 300ppm Use of derivatives of AI having minimum solubility in propellant. Reduction of initial particle size to less than 5microns Adjustment of density difference Use of surfactants (HLB < 10 0.01 – 1 %)

Foam system

Foam system Consist of an aqueous or non aqueous vehicle, surfactant and propellant. Dispensed as stable or quick-breaking foam. Stable foam Liquefied propellant is emulsified and is found in

internal phase. Both hydrocarbons and compressed gas propellants may be used. Quick breaking foam Liquefied propellant is in the external phase

Different types of foam systems

1. Aqueous stable foams 2. No aqueous stable foams
3. Quick-breaking foams 4. Thermal foams intranasal aerosols

Types of System-Parameters to be considered

1. Physical, chemical and pharmacological properties of active ingredients.
2. Site of application

Manufacturing/filling of aerosols

Instruments used

A. Pressure filling apparatus
B. Cold filling apparatus
C. Compressed gas filling apparatus

Pressure filling

Advantages: It is the preferred method for solutions, emulsions and suspension. Less chances for contamination of product with the moisture. Less propellant is lost No refrigeration is required, can be carried out at room temperature.

Pressure filling apparatus

Cold filling process

The principle of cold filling method requires the chilling of all components including concentrate and propellant to a temperature of -30 to -40 º F. This temperature is necessary to liquefy the propellant gas. The cooling system may be a mixture of dry ice and acetone or refrigeration system. First, the product concentrate is chilled and filled into already chilled container followed by the chilled liquefied propellant.

Cold filling apparatus

Advantage

Easy process

Disadvantages

Aqueous products, emulsions and those products adversely affected by cold temperature cannot be filled by this method. For non aqueous systems, some moisture usually appear in the final product due to condensation of atmospheric pressure

Compressed filling

Compressed gases are present under high pressure in cylinders. These cylinders are fitted with a pressure reducing valve and a delivery gauge. The concentrate is placed in the container The valve is crimped in place Air is evacuated by means of vacuum pump The filling head is inserted into the valve opening, valve depressed and gas is allowed to flow into the container For those products requiring an increased amount of gas or those in which the solubility of gas in the product is necessary, carbon dioxide and nitrous oxide can be used. To obtain maximum solubility of the gas in the product, the container is shaken manually during and after the filling operation by mechanical shakers.

Large scale equipments

1. Concentrate filler
2. Valve placer
3. Purger and vacuum crimper
4. Pressure filler
5. Leak test tank

Evaluation of pharmaceutical aerosols

A. Leakage Test

B. Flammability and combustibility - Flame extension/projection/ ***Flash point***

C. Physiochemical characteristics -Vapour pressure, density, moisture content, identification of propellant(s)

D. Performance of aerosol valve discharge rate- Spray ***pattern*** dosage with metered valves, net contents, foam stability, particle size determination.

E. Biologic characteristics

F. Therapeutic activity

Leakage test

Individual container is completely immersed through a bath of hot water so that the contents reach a temperature of 54.4 degree centigrade, and examined for leakage. The bath is illuminated for easy inspection and covered with a grill for safety. The points examined are,

1. Valve
2. Valve cup & top
3. Bottom and side seams

Leakage testing

Flame /extension /projection test

This test indicates the effect of an aerosol formulation on the extension of an open flame. Product is sprayed for 4 sec. into flame. Depending on the nature of formulation, the flame is extended, and exact length was measured with ruler.

Flash point

Determined by using standard Tag open cap apparatus.

Procedure

Aerosol product is chilled to temperature of - 25^0F and transferred to the test apparatus. Temperature of test liquid is increased slowly, and the temperature at which the vapors ignite is taken a flash point, Calculated for flammable component, which in case of topical hydrocarbons

Measurement of vapour pressure

To determine pressure variation from container to container. Determined by pressure gauge or Can puncturing device. Variation in pressure indicates the presence of air in headspace.

Measurement of density

Determined by Hydrometer or a Pycnometer

Procedure: A pressure tube is fitted with metal fingers and hoke valve, which allow for the introduction of liquids under pressure. The hydrometer is placed in to the glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise half way up the length of the tube. The density can be read directly.

Moisture content

Karl Fischer method & Gas Chromatography.

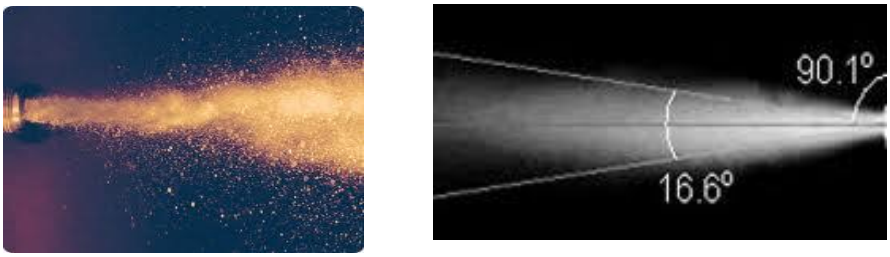
Identification of propellants gas chromatography I.R spectrophotometry

Aerosol valve discharge rate

Expressed as **gram per seconds**. Determined by taking an aerosol known weight and discharging the contents for given time using standard apparatus. By reweighing the container after time limit has expired, the change in weight per time dispensed is discharge rate.

Spray pattern

Spray the product on the coated (dye +talc) paper. Depending upon the nature of aerosol water /oil soluble dye is used. (Roots method) Another method is **Dixon's method**



Spray pattern

Dosage with metered valves

Reproducibility of dosage each time the valve is depressed. Amount of medication actually received by the patient. Reproducibility has been determined by assay technique, another method is that, involves accurate weighing of filled container fallowed by dispersing of several doses, container can have reweighed, and difference in weight divided by No. of dose, gives the average dosage.

Net content

Weight of empty container = gm Weight of the filled container = gm net content

Foam stability

Visual evaluation Time for a given mass to penetrate the foam by using a Rotational viscometer

Particle size

Cascade impactor Operates on the principle that in a stream of particles projected through a series of nozzles and glass slides at high velocity, larger particles became impacted first on the lower stages and the smaller particles pass on and are collected at higher stages.

Porush, Thiel and *Young* used ***light scattering method*** to determine particle size. As aerosols settle in turbulent condition, the change in light intensity of tyndall beam is measured. *Sciarra* and *Cutie* developed this method based on particle size distribution.

Flash point

Flash point Determined by using standard Tag Open Cap Apparatus.

Steps involved in Flash Point

Aerosol product is chilled to temperature of - 25^0F and transferred to the test apparatus. Temperature of test liquid increased slowly, and the temperature at which the vapors ignite is taken a flash point. Calculated for flammable component, which in case of topical hydrocarbons.

- **Biologic Testing-** Limited number of tests are used to find out the efficiencies: anti bacterial products
- **Therapeutic activity-** Topical preparations are applied to the test areas and adsorption is determined.
- **Toxicity**- Evaluating the topical and inhalation effect. These are carried out on test animals.

References

1. The theory and practice of industrial pharmacy fourth edition Leon Lachman (1991)
2. Remington: The science and practice of pharmacy vol. I and II 20th edition (2000)
3. Bentley's textbook of Pharmaceutics Eighth edition (2005)
4. Pharmaceutical dosage forms Tablets First edition by Herbert.A. Lieberman, Leon Lachman et al. Volume 1(1989)

KERALA UNIVERSITY OF HEALTH SCIENCES

SYLLABUS
(2017-18 Academic year onwards)

Formulative Pharmacy

BP 502 T. FORMULATIVE PHARMACY (Theory) **45 Hours**

Scope: Course enables the student to understand and appreciate the influence of pharmaceutical additives and various pharmaceutical dosage forms on the performance of the drug product.

Objectives: Upon completion of the course the student shall be able to

1. Know the various pharmaceutical dosage forms and their manufacturing techniques.
2. Know various considerations in development of pharmaceutical dosage forms
3. Formulate solid, liquid and semisolid dosage forms and evaluate them for their quality

Course content: **3 hours/ week**

UNIT-I **07 Hours**

Preformulation Studies: Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substances.

a. Physical properties: Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism

b. Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization BCS classification of drugs

Application of preformulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.

UNIT-II **10 Hours**

Tablets:

a. Introduction, ideal characteristics of tablets, classification of tablets. Excipients, Formulation of tablets, granulation methods, compression and processing problems. Equipments and tablet tooling.

b. Tablet coating: Types of coating, coating materials, formulation of coating composition, methods of coating, equipment employed and defects in coating.

c. Quality control tests: In process and finished product tests

UNIT-III **08 Hours**

Capsules:

a. **Hard gelatin capsules:** Introduction, Extraction of gelatin and production of hard gelatin capsule shells. size of capsules, Filling, finishing and special techniques of formulation of hard gelatin capsules. In process and final product quality control tests for capsules.

b. **Soft gelatin capsules:** Nature of shell and capsule content, size of capsules,importance of base adsorption and minimum/gram factors, production, in process and final product quality control tests. Packing, storage and stability testing of soft gelatin capsules

Pellets: Introduction, formulation requirements, pelletization process, equipments for manufacture of pellets

UNIT-IV **10 Hours**

Parenteral Products:

a. Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity

b. Production procedure, production facilities and controls.

c. Formulation of injections, sterile powders, emulsions, suspensions, large volume parenterals and lyophilized products, Sterilization.

d. Containers and closures selection, filling and sealing of ampoules, vials and infusion fluids. Quality control tests.

Ophthalmic Preparations: Introduction, formulation considerations; formulation of eye drops, eye ointments and eye lotions; methods of preparation; labeling, containers; evaluation of ophthalmic preparations

UNIT-V **10 Hours**

Cosmetics: Formulation and preparation of the following cosmetic preparations: lipsticks, shampoos, cold cream and vanishing cream, tooth pastes, hair dyes and sunscreens.

Pharmaceutical Aerosols: Definition, propellants, containers, valves, types of aerosol systems; formulation and manufacture of aerosols; Evaluation of aerosols; Quality control and stability studies.

Packaging Materials Science: Materials used for packaging of pharmaceutical products, factors influencing choice of containers, legal and official requirements for containers, stability aspects of packaging materials, quality control tests.

BP 506 P. FORMULATIVEPHARMACY (Practical) **4Hours/week**

1. Preformulation study for prepared granules
2. Preparation and evaluation of Paracetamol tablets
3. Preparation and evaluation of Aspirin tablets
4. Coating of tablets
5. Preparation and evaluation of Tetracycline capsules
6. Preparation of Calcium Gluconate injection
7. Preparation of Ascorbic Acid injection
8. Preparation of Paracetamol Syrup
9. Preparation of Eye drops
10. Preparation of Pellets by extrusion spheronization technique
11. Preparation of Creams (cold / vanishing cream)
12. Evaluation of Glass containers

Recommended Books: (Latest Editions)

1. Pharmaceutical dosage forms − Tablets, volume 1 −3 by H.A. Liberman, Leon Lachman &J.B.Schwartz
2. Pharmaceutical dosage form − Parenteral medication vol− 1&2 by Liberman & Lachman
3. Pharmaceutical dosage form disperse system VOL−1 by Liberman & Lachman
4. Modern Pharmaceutics by Gilbert S. Banker & C.T. Rhodes, 3rd Edition Remington: The Science and Practice of Pharmacy, 20th edition Pharmaceutical Science (RPS)
5. Theory and Practice of Industrial Pharmacy by Liberman & Lachman
6. Pharmaceutics− The science of dosage form design by M.E.Aulton, Churchill livingstone, Latest edition
7. Introduction to Pharmaceutical Dosage Forms by H. C.Ansel, Lea &Febiger, Philadelphia, 5th edition, 2005
8. Drug stability − Principles and practice by Cartensen & C.J. Rhodes, 3rd Edition, Marcel Dekker Series, Vol 107.