UNIT 2: Tablets: Formulation of different types of tablets, tablet excipients, granulation techniques quality control and evaluation of tablets. Tablet coating, Type of coating, quality control tests for coated tablet.

TABLETS

DEFINITION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods.

This dosage form is mainly intended to be administered through oral route although special tablets like hypodermic, dispersible and dissolving tablets can be administered via other routes.

Definition according to Indian Pharmacopoeia

"Pharmaceutical tablets are flat or bi-convex discs prepared by compressing a drug or a mixture of drugs with or without suitable diluents."

Advantages of tablet dosage form over other oral drug delivery systems:

From patients stand point:

1. They are easy to carry.
2. They are easy to swallow.
3. They are attractive in appearance.
4. Unpleasant taste can be masked by sugar coating .
5. They do not require any measurement of dose. The strip or blister packing has further facilitated the process of taking the dose by the patient. Moreover, it provides a sealed covering which protects the tablets from atmospheric conditions like air, moisture and light etc.
6. Some of the tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage whenever a fractional dose is required.

From the standpoint of manufacturer:

7. An accurate amount of medicament, even if very small, can be incorporated.
8. Tablets provide prolonged stability to medicament. They have the best combined properties of chemical, mechanical and microbiological stability of all the oral dosage forms.
9. The incompatibilities of medicaments and their deterioration due to environmental factors are less in tablet forms.
10. Since they are generally produced on a large scale, therefore, their cost of production is relatively low, hence economical.
11. They are in general the easiest and cheapest to package and ship among all oral dosage forms.
12. Some specialized tablets like enteric coated tablet, sustained release tablets may be prepared for modified release profile of the drug.
13. Product identification is potentially the simplest and cheapest requiring no additional processing steps when employing an embossed or monogrammed punch face.

Disadvantages of tablet dosage forms:

(i) Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

(ii) Drugs with poor wetting, slow dissolution properties, intermediate to large dose, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate bioavailability.

(iii) Bitter tasting drugs, drugs with objectionable odour, or drugs sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression (if feasible of practical) or the tablets may require coating.

TYPES OF TABLETS

Tablets are classified according to their route of administration or function. The following are the four main classification groups:

(A) Tablets ingested orally:
(i) Compressed tablets
(ii) Multiple compressed tablets
(iii) Enteric coated tablets
(iv) Sugar coated tablets
(v) Film coated tablets
(vi) Chewable tablets

(B) Tablets used in the oral cavities:
(i) Buccal cavities
(ii) Sublingual tablets
(iii) Lozenges
(iv) Dental cone

(C) Tablets administered by other routes:
(i) Implantation tablets
(ii) Vaginal tablets

(D) Tablets used to prepare solutions:
(i) Effervescent tablets
(ii) Dispensing tablets
(iii) Hypodermic tablets
(iv) Tablet triturates

(A) TABLETS INGESTED ORALLY

These tablets are designed to be swallowed except the chewable tablets. The tablets covered in this category are:

Compressed tablets (C.T.)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with diluent, binders, disintegrants, lubricants, antiadherants and in many cases colorants.

These tablets contain water soluble drugs which after swallowing get disintegrated in the stomach and its drug contents are absorbed in the gastrointestinal tract and distributed in the whole body. e.g. Aspirin (,Dispirin) paracetamol tablets (Crocin)

Multiple compressed tablets:

These are compressed tablets made by more than one compression cycle:

Layered tablets

Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers. Special tablet presses are required to make layered tablets such as *Versa press.* (Stokes/Pennwalt)

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action or prolonged action products.

To avoid incompatibility , the ingredients of the formulation except the incompatible material are compressed into a tablet and then incompatible substance along with necessary excipients are compressed over the previously compressed tablet.

Sustained action tablets:

These are the tablets which after oral administration release the drug at a desired time and prolong the effect of the medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required to maintain the maximum effective concentration of the drug in the blood throughout the period of treatment.

e.g. Diclofenac SR tablets.

Enteric coated tablets:

These are compressed tablet meant for administration by swallowing and are designed to by-pass the stomach and get disintegrated in the intestine only.

These tablets are coated with materials resistant to acidic pH (like cellulose acetate phthalate, CAP) of the gastric fluid but get disintegrated in the alkaline pH of the intestine. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine, e.g. tablets containing anthelmintic and amoebicides.

Sugar coated tablets:
These are compressed tablets containing a sugar coating. Such coatings are done to mask the bitter and unpleasant odour and the taste of the medicament. The sugar coating makes the tablet elegant and it also safeguard the drug from atmospheric effects.
Film coated tablets:
The compressed tablets having a film coating of some polymer substance, such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose and ethyl cellulose. The film coating protects the medicament from atmospheric effects. Film coated tablets are generally tasteless, having little increase in the tablet weight and have less elegance than that of sugar coated tablets.

Chewable tablets:
These are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.
A number of antacid tablets and multivitamin tablets are prepared as chewable tablets.
For the preparation of chewable tablets mannitol is used as a sweetening base. Since mannitol is expensive other substances like sorbitol, lactose, chocolate powder, dextrose and glycerin can be substituted in place of mannitol. these tablets do not require any disintegrating agents to be present in the formulation.
These tablets should have very acceptable taste and flavour.
e.g. antacid tablets
Vitamin C chewable tablets e.g. CELIN - (Glaxo)

(B) TABLETS USED IN ORAL CAVITY
Buccal tablets:
These tablets are to be placed in the side of the cheek (buccal pouch) where they dissolve or erode slowly and are absorbed directly in the buccal cavity without passing into the alimentary canal.
therefore, they are formulated and compressed with sufficient pressure to give a hard tablet e.g. Progesterone tablets.
Sublingual tablets:
These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT e.g. tablets of nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate.
Lozenges tablets:
These tablets are designed to exert a local effect in the mouth or throat. These tablets are commonly used to treat sore throat to control coughing in common cold. They may contain local anaesthetics, antiseptics, antibacterial agents, astringents and antitussives.
These are prepared by compression at a high pressure by the moulding process and generally contain a sweetening agent, flavouring agent (e.g. peppermint, clove oil) and a substance which produces a cooling effect (e.g. mentha). e.g. Vicks lozenges.
Dental cones:
These are compressed tablets meant for placement in the empty sockets after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow-releasing antibacterial compounds or to reduce bleeding by containing the astringent.
These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride.
These cones generally get dissolved in 20 to 40 minutes time.

(C) TABLETS ADMINISTERED BY OTHER ROUTES
Implantation tablets:
These tablets are placed under the skin or inserted subcutaneously by means of minor surgical operation and are slowly absorbed. These may be made by heavy compression but are normally made by fusion. The implants must be sterile and should be packed individually in sterile condition.

Implants are mainly used for the administration of hormones such as testosterone steroids for contraception. These tablets are very usefully exploited for birth control purpose in human beings.
The disadvantages of implant tablets are their administration changing rate of release with change of surface area and possibility of tissue reactions.

Vaginal tablets:

These tablets are meant to dissolve slowly in the vaginal cavity. The tablets are typically ovoid or pear shaped for the ease of insertion. these tablets are used to release steroids or antimicrobial agents. the tablets are often buffered to promote a pH favorable to the action of a specified antimicrobial agent. The contains easily soluble components like lactose or sodium bicarbonate.

(D) TABLETS USED TO PREPARE SOLUTIONS

Effervescent tablets:

These tablets along with the active medicament contain ingredients like sodium bicarbonate, citric acid and tartaric acid which react in the presence of water liberating carbon dioxide and producing effervescence leading to disintegration of the tablet, thus hastens solution formation and increase the palatability.

Dispensing tablets:

These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. these tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as dosage form.
e.g. The drugs commonly incorporated are mild silver potentiate, bichloride of mercury merbromin an quarternary ammonium compounds.

Hypodermic tablets:

Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. These tablets are dissolved in sterile water or water for injection and administered by parenteral route. these tablets are not preferred now-a-days because the resulting solution is not always sterile.

Tablet triturates (Moulded tablets):

These are powders moulded into tablets. They are flat, circular discs, usually containing a potent substance mixed with lactose, lactose and sucrose, dextrose, or other suitable diluent.
Since they are intended to disintegrate very quickly in contact with moisture, water insoluble adjuncts are avoided. The name ‘tablet triturate’ is appropriate because they usually contain triturations (*trituration = dilution with an inert substance*).

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient(s), tablets contain a number of inert materials. The latter are known as **additives** or **excipients**.

They may be classified according to the part they play in the finished tablet.

Group-I: Contains those which help to impart satisfactory processing and compression characteristics to the formulation. This includes: *diluents, binders, glidants* and *lubricants*.

Group-II: Helps to give additional desirable physical characteristics to the finished tablet. This includes: *disintegrants, colours,* and in the case of chewable tablets, *flavors* and *sweetening agents*.

Group-III: In the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

DILUENTS

Objectives of incorporating diluents:

(i) Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression.

Compressed tablets of dexamethasone contains 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible.

The dose of some drugs is sufficiently high that no filler is required (e.g. aspirin and certain antibiotics).

Diluents used for this purpose include *dicalcium phosphate* (DCP), c*alcium sulfate, lactose, cellulose, kaolin, mannitol, dry starch* and *powdered sugar*.

(ii) Certain diluents, such as *mannitol, lactose, sorbitol, sucrose* and *inositol*, when present in sufficient quantity, can impart properties that will help in disintegration of the tablet in the mouth by chewing. Such tablets are commonly called **chewable tablets**.

(iii) Diluents used for direct compression formulas give the powder mixture necessary flowability and compressibility.

(iv) To delay or control the rate of release of drug from the tablet.

Characteristics of an ideal diluents:

1. They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
2. They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
3. They must be cheap compared to the active ingredients.
4. They must be physiologically inert.
5. They must be chemically stable alone and/or in combination with the drug(s) and/or other tablet components.
6. They must be free of any unacceptable "microbiological load".
7. They must be color-compatible (should not produce any off-color appearance).
8. They must have no negative effects on the bioavailability of the drug(s) in the product.

[N.B. e.g. Calcium phosphate as diluent, reduces the bioavailability of some antibiotics like tetracycline.]

Classification of diluents:

DILUENTS

Sugars	Polysaccharides	Inorganic compounds	Miscellaneous compounds
Dextrose	Starches	Calcium phosphate dihydrate	Bentonite
Lactose	Modified starch	Calcium sulfate dihydrate	Polyvinyl pyrrolidone
Sucrose	e.g. Sta-RX 1500, Celutab etc.	Calcium lactate trihydrate	Kaolin
Amylose	Cellulose	Calcium carbonate	Silicone derivatives
Mannitol	Cellulose derivatives	Magnesium carbonate	
Sorbitol	Microcrystalline cellulose	Magnesium oxide	
Inositol	(MCC)		

CALCIUM SALTS

Example: Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP) [$CaHPO_4$, 2 H_2O], Calcium sulfate dihydrate ($CaSO_4$, $2H_2O$).

Advantages:

- Diluents that exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization. This bound water of calcium sulfate is not released below 80^0C. They possess very low concentration of unbound moisture. Hence, these salts are excellent diluents for water-sensitive drugs. It is superior to anhydrous diluent, which has a moderate to high moisture demand.

Disadvantages:

- Tetracycline products made with calcium phosphate diluent had less than half the bioavailability of the standard product. Divalent cation (Ca^{++}) form insoluble complexes and salts with number of amphoteric or acidic functionality antibiotics, which generally reduces their absorption (*which is also why milk should not be co-administered with these drug*).

LACTOSE

Lactose is the most widely used diluent for tablet formulation.

- It is obtained in hydrous and anhydrous form. The anhydrous form, picks up moisture when exposed to elevated humidity. Such tablets should be packed in moisture proof packets or containers. When a wet granulation method is employed, the hydrous form of lactose should generally be used.
- Two grades of lactoses are commercially available:
  (i) A 60 to 80 mesh – coarse
  (ii) a 80 to 100 mesh – regular grade

Advantages:

1. Lactose has no reaction with most of the drugs, whether in hydrous or anhydrous form.
2. Lactose formulations show good release rates
3. Their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness.
4. It is a low cost diluent.

Disadvantages:

1. Lactose reacts with amine drug bases in presence of alkaline lubricants e.g. metal stearates (e.g. magnesium stearate) and gradually discolours (dark brown) with time due to the formation of furaldehyde. This reaction is called Maillard reaction.

SPRAY DRIED LACTOSE

Advantages:

1. It is used for direct compression (containing drug + diluent + disintegrant + lubricant)
2. In addition to the direct compression properties, spray dried lactose also has good flow characteristics. It can usually be combined with as much as 20 to 25% of active ingredients without losing these advantageous features.

Disadvantages:

1. If spray dried lactose is allowed to dry out and the moisture content falls below the usual 3% level, the material loses some of its direct compressional characteristics.
2. Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds owing to Maillard reactions. Hence, a neutral or acid lubricant should be used.

STARCH

Starch may be obtained from corn, wheat or potatoes. It is occasionally used as a tablet diluent

- USP grade of starch is usually possesses moisture content between 11 to 14%.
- Specially dried types of starch that have a standard moisture level of 2-4% are available, but are costly. Use of such starches in wet granulation is wasteful since their moisture level increase to 6-8% following moisture exposure.

DIRECTLY COMPRESSIBLE STARCHES

Sta–Rx 1500 – free flowing, directly compressible starch
– used as diluent, binder, disintegrant

Emdex and Celutab – are two hydrolyzed starches
– contains dextrose 90–92%
maltose 3–5%
– free flowing and directly compressible
– may be used in place or mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

DEXTROSE (D–Glucose)

Available in two forms: as hydrates and anhydrous forms.

Dextrose may sometimes be combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.

MANNITOL

Advantages

- Because of the negative heat of solution (cooling sensation in the mouth) its slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets.
- It is relatively non-hygroscopic and can be used in vitamin formulations.
- Low calorie content and non-carcinogenic.

Disadvantages

- Costly
- Mannitol has poor flow characteristics and usually require fairly high lubricant level.

SORBITOL

It is an optical isomer of mannitol and is sometimes combined with mannitol formulations to reduce the diluent cost.

Disadvantages: It is hygroscopic at humidities above 65%.

SUCROSE

Some sucrose based diluents are:

Sugar tab – 90 to 93% sucrose + 7 to 10% invert sugar
Di Pac – 97% sucrose + 3% modified dextrins
Nu Tab – 95% sucrose + 4% invert sugar + small amount of corn starch + Mg-stearate

Advantages: They are all used for direct compression.

Disadvantages: All are hygroscopic when exposed to elevated humidity.

MICROCRYSTALLINE CELLULOSE (MCC)

Trade Name : Avicel – is a directly compression material

Two grades are available PH 101 → powder
PH 102 → granules

Advantages: It acts as diluent and disintegrating agents.

BINDERS

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators.

Objective of incorporating binders

1. They impart a cohesiveness to the tablet formulation (both direct compression and wet–granulation method) which insures the tablet remaining intact after compression.
2. They improves the free-flowing qualities by the formation of granules of desired size and hardness.

Characteristics of binder

Method-I

Binders are used in dry form in the powder and then moistened with a solvent (of the binder) to form wet lumps.

Method-II

Binders are often added in solution form. It requires lower concentration of binder.

By Method-I the binder is not as effective in reaching and wetting each of the particles within the mass of the powder. Each of the particle in a powder blend has a coating of adsorbed air on its surface, and it is this film of air which must be penetrated before the powder can be wetted by the binder solution.

Method-III

In direct compression method MCC, microcrystalline dextrose, amylose and PVP are used – those have good flow property and cohesiveness as well.

It has been postulated that MCC is a special form of cellulose fibril in which individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking intercrystallite bonds by the disintegrating medium.

STARCH PASTE

Corn starch is often used in the concentration of 10–20%.

Method of preparation

Corn starch is dispersed in cold purified water to make a 5 to 10% w/w suspension and then warming in water both with continuous stirring until a translucent paste is formed.. (Actually hydrolysis of starch takes place.)

LIQUID GLUCOSE

50% solution in water is fairly common binding agent.

SUCROSE SOLUTION

50% to 74% sugar solution is used as binder. They produce hard but brittle granules. Their cost is low.

GELATIN SOLUTION

Concentration 10–20% aqueous solution

Should be prepared freshly and added in warm condition other wise it will become solid.

Method of preparation

The gelatin is dispersed in cold water and allowed to stand until hydrated. The hydrated mass is warmed in water bath to dissolve.

CELLULOSIC SOLUTIONS

HPMC (Hydroxy propyl methyl cellulose) Soluble in cold water.

Method of preparation: HPMC is dispersed in hot water, under agitation. The mixture is cooled as quickly as possible and as low as possible

HEC (Hydroxy ethyl cellulose), HPC (Hydroxy propyl cellulose) are other successful binders.

PVP (Polyvinylpyrollidone) Used as an aqueous or alcoholic solution. Concentration 2% and may vary.

LUBRICANTS

Objectives:

1. Prevents adhesion of the tablet material to the surface of dies and punches.
2. Reduce inter-particular friction, improve the rate of flow of tablet granulation.
3. Facilitate ejection of the tablets from the die cavity.

Examples:

Talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycols (PEG).

Method of addition of lubricants:

1. The lubricant is divided finely by passing it through a 60 to 100 mesh nylon cloth on to the granulation. In production this is called 'bolting the lubricant'.
2. After addition the granulation is tumbled or mixed gently to distribute the lubricant without coating all the particles too well.
   * Complete coating will produce dissolution problem.
   * Prolonged mixing will produce excessive fines by breaking the granules.

Soluble lubricants

Examples: Sodium benzoate – includes a mixture of sodium benzoate and sodium acetate
Sodium chloride, leucine and carbowax 4000.

Magnesium stearate

Though it is a widely used lubricant it retards disintegration and dissolution. To overcome this some time surfactants like sodium lauryl sulfate are included.

Lubricants are included to reduce the friction during tablet ejection between the walls of the tablet and the wall of the die in which the tablet was formed.

Antiadherents are used for the purpose of reducing the sticking or adhesion of any of the tablet ingredients or powder to the faces of the punches or to the die wall.

Glidants are intended to promote flow of the tablet granulation or powder materials by reducing the friction between the particles.

An ingredient used for lubrication purpose may possess other two properties as well.

Relative properties of some tablet lubricants:

Material	Usual percent	Glidant properties	Antiadherent properties	Lubricant properties
1. Calcium or Magnesium stearate	1 or less	Poor	Good	Excellent
2. Talc	1 – 5	Good	Excellent	Poor
3. Stearic acid	1 – 5	None	Poor	Good
4. High melting waxes	3 – 5	None	Poor	Excellent
5. Corn starch	5 – 10	Excellent	Excellent	Poor

Water soluble tablet lubricants

Lubricant	Percentage
Boric acid	1
Sodium chloride	5
Sodium benzoate	5
Sodium acetate	5
Sodium oleate	5
PEG 4000, 600	1 – 4
dl-leucine	1 – 5

DISINTEGRANTS

Definition

A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after administration in the GIT.

The active ingredients must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution.

Disintegrants can be classified chemically as:

Starches, clays, celluloses, alginates, gums and cross-linked polymers.

Starch

Corn starch, potato starch

For their disintegrating effect starches are added to the powder blends in dry state.

Mode of action:

Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.

Others have suggested that the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action.

Normally 5% w/w is suggested.

For rapid disintegration 10 – 15% w/w may be taken.

Super disintegrants

Croscarmelose - cross linked cellulose
Crospovidone - cross linked polyvinyl pyrrolidone
Sodium starch glycolate - cross linked starch

Mode of action

Croscarmelose swells 4 to 8 fold in less than 10 seconds

Crospovidone acts by wicking or capillary action.

Sodium starch glycolate swells 7 to 12 folds in less than 30 seconds.

Other materials

VeegumHV, Methyl cellulose, Agar, Bentonite, Cellulose, Alginic acid, Guargum, and Carboxymethyl cellulose.

* Sodium lauryl sulfate is a surfactant. It increases the rate of wetting of the tablet, thus decreases the disintegrating time.

Method of blending with powder

The disintegrants are usually mixed with active ingredients and diluents prior to granulation.

Starch may be divided into two portions:

One part – added prior to granulation
remainder – added prior to compression.

While disintegration the portion of the starch added prior to compression rapidly breaks down the tablet to granules, and the starch mixed prior to granulation disintegrates the granules into smaller particles.

COLOURING AGENT

Objectives of using colors

(i) It makes the tablet more esthetic in appearance.

(ii) Colour helps the manufacturer to identify the product during its preparation.

All colorants used in pharmaceuticals *must be approved and certified by the FDA (food & Drug Administration*). Dyes are generally listed as FD&C (food, Drug & Cosmetic Dyes) dyes and D&C (Drug & Cosmetic Dyes).

Colour	Other Names	Color Index (CI, 1971)
D&C Red 22	Eosin Y	45380
FD&C Yellow 5	Tartrazine	15985
FD&C Yellow 6	Sunset Yellow FCF Yellow Orange 5	19140
FD&C Blue 1	Brilliant Blue FCF	42090
FD&C Blue 2	Indigocarmine	73015
FD&C Green 3	Fast Green FCF	42035
Caramel	Burnt sugar	
Titanium dioxide	–	77891

Colorants are obtained in two forms **dyes** and **lakes**.

- Dyes are dissolved in the binding solution prior to the granulating process. However, during drying their color may migrate to the surface and may produce mottling of the tablet.
- So another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with other ingredients.
- Color lakes are dyes which are adsorbed onto a hydrous oxide of a heavy metal (like aluminium) resulting in an insoluble form of the dye.

FLAVOURS AND SWEETENERS

Flavours are usually limited to chewable tablets or other tablets intended to dissolve in the mouth.

Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder).

N.B. Usually, the maximum amount of oil that can be incorporated to a granulation without influencing its tableting characteristics is 0.5 to 0.75% w/v.

The use of sweeteners is primarily limited to chewable tablets.

e.g. Sugar

Mannitol – 72% as sweet as sugar, cooling & mouth filling effect

Saccharin – Artificial sweetener
500 times sweeter than sucrose
Disadvantages (i) it has a bitter after taste
(ii) carcinogenic

Cyclamate – either alone or with saccharin
– it is banned

Aspartame (Searle) – widely replacing saccharin
– *Disadvantage* – lack of stability in presence of moisture

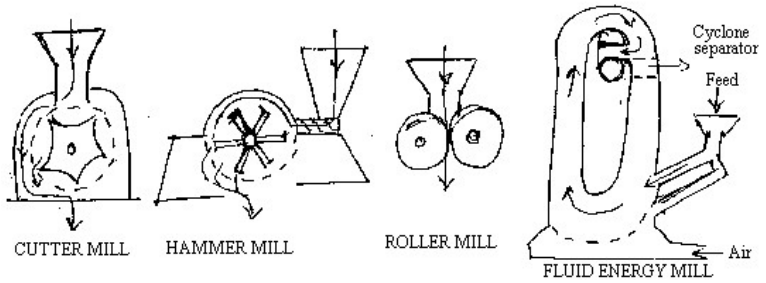
MANUFACTURE OF TABLETS

Manufacture of tablets involves certain well defined *steps*: namely,

Pulverization and mixing Granulation Compression Coating (if required)

PULVERIZATION AND MIXING

In this step the different solid / powder ingredients are reduced to the same particle size since particles of different sizes will segregate while mixing.

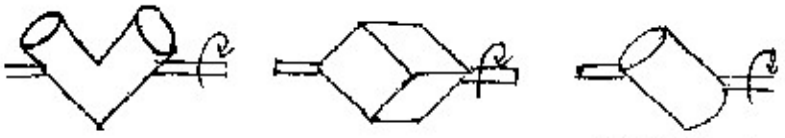


Instruments used for milling or size reduction:

General characteristics of various types of mills

Types of Mill	Action	used for	Not used for
Cutter	Cutting	fibrous, crude animal and vegetable drugs	friable material
Revolving	Action and impact	fine grinding of abrasive materials	soft material
Hammer	impact	almost all drugs	abrasive materials
Roller	Pressure	soft material	abrasive material
Attrition	Attrition	soft and fibrous material	abrasive material
Fluid energy mill	attrition and impact	moderately hard and friable material	soft and sticky material

For mixing dry powders following mixers are used:



Twin shell blender Cubic blender Cylindric blender

GRANULATION

Objectives:

Simple powder may not have the desired flow property because there are may types of forces acting between solid particles:

1. Frictional forces,
2. surface tension forces,
3. mechanical forces caused by interlocking of particles of irregular shapes
4. electrostatic forces and
5. cohesive or van der Waals forces.

Though bulk density and shape of the particles are important but two of the most common experiments done to get some idea about the flow property are

(i) angle of repose and (ii) hopper flow rate measurement.

Values for angle of repose $\leq 30^0$ usually indicate a free-flowing material and values of angle of repose $\geq 40^0$ suggests a poorly flowing material.

Hopper flow rates have been used as a method to assess flowability of the powder mass. In this method the flow of powder from a conical hopper is continually monitored by the flow of material out of the hopper on to a recording balance device.

Question: *"Mostly the materials, intended for compression into tablets are converted into granules" – Why?*

Ans: Materials intended for compaction into tablets must possess two characteristics:

(1) fluidity and (2) compressibility.

Good flow properties are essential for the transport of the material through the hopper, into and through the feed frame into the dies. Tablet materials should therefore be in a physical form that flows uniformly and smoothly. The ideal physical form is sphere, since spheres offers minimum contact surface between themselves and with the walls of the machine parts.

Unfortunately, most materials do not easily form spheres; however shapes approaching spheres improve flowability. hence flow properties of powder materials are improved by forming sphere like regular shaped aggregates called granules.

WET GRANULATION

Step-I Milling of the drug and excipients

- Milling of the active ingredients, excipients etc. are milled to obtain a homogeneity in the final granulation.
- If the drug is given in solution then during drying it will come up to the surface. To avoid this problem drug is mixed with other excipients in fine state.

Step-II Weighing

- Weighing should be done in clean area with provision of air flow system.
- In the weighing area all the ingredients must not be brought at a time to avoid cross-contamination.

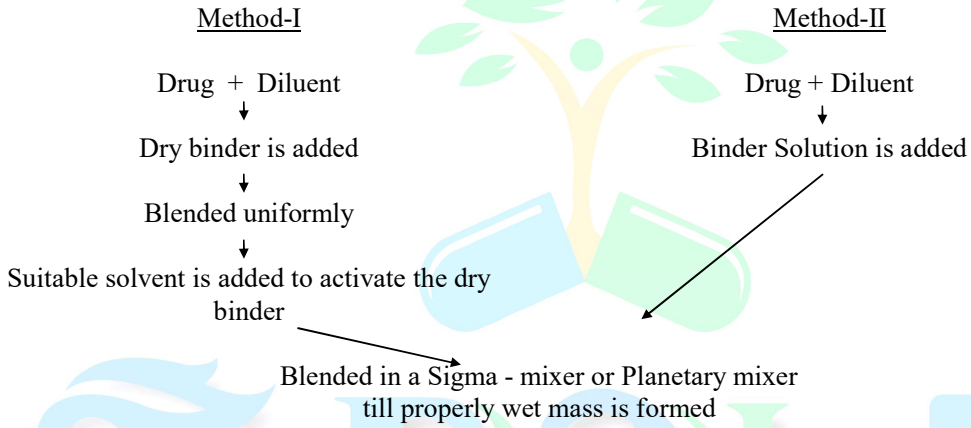
Step-III Mixing

Commonly used blenders are: (a) Double cone blender
(b) V – blender
(c) Ribbon blender
(d) Planetary mixer

Any one of the blender may be used to mix dry powder mass.

Step-IV Wet Massing

Wet granulation forms the granules by binding the powders together with an adhesive.
Binder solutions can be added in two methods:



- The powder must be moist and not paste.
- Blending may take 30 mins to 1 hour.

N.B.

- To determine the proper moistening, the moist mass is balled in a palm, pressed by two fingers, if fragments of granules are formed and not powder then the blending is stopped.
- Since, in general, the mass should be moist rather than wet or paste, there is a limit to the amount of solvent that may be incorporated.

Therefore, when
(i) a small quantity of solvent is permissible, method-I is adopted and
(ii) a large quantity of solvent is required method-II is adopted.

- However, method-II will give more cohesiveness than method-I if the amount of binder remains constant.
- If granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance.
- If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

Step-V Wet Screening

Wet screening process involves converting the moist mass into coarse, granular aggregates by
(i) passage through a hand screen (in small scale production) or,
(ii) passage through an oscillatory granulator of hammer mill equipped with screens having large perforations (# 6 – 8 mesh screen).

Purpose (i) Increase particle contact point
(ii) Increase surface area to facilitate drying.

Step-VI Drying

- Drying is usually carried out at **60^0C.** Depending on the thermolabile nature of the drug the temperature can be optimized.
- Drying is required in all wet granulation procedures to remove the solvent, but is not dried absolutely because it will pose problems later on. Hence, certain amount of moisture (1 – 4 %) is left within the granules – known as the *residual moisture*.

Methods: Drying can be carried out

1. *Tray dryers* – it may take 24 hrs of drying
2. *Truck dryers* – the whole cabinet can be taken out of the dryer
3. *Fluid-bed dryer* – dried for 30 mins.

The total surface of the granules are dried uniformly but in tray dryer the lower surface of the granules may not be dried uniformly. *Case hardening* may sometime occur in tray dried products.

N.B. In case hardening the outer surface of the lumps of the wet powder will be dried quickly and become hard (forming a hard crust), while the inner part will remain wet. This phenomenon is called case hardening.

Step-VII Dry Screening

After drying, the granule size is reduced by passing through smaller mesh screen.

- For drying granules the screen size to be selected depends on the diameters of the punch. The following sizes are suggested:

Tablet diameter upto	Mesh Size
3/16 ”	# 20
3.5 / 16 – 5/16”	# 16
5.5/16 – 6.5/16”	# 14
7.0/16 or larger	# 12

Step-VIII Lubrication of granules

- After dry granulation, the lubricant is added as a fine powder. It usually, is screened onto the granulation through 60 or 100 mesh nylon cloth to eliminate small lumps as well as increase the covering capacity of the lubricant.
- The lubricant is blended very gently using tumbling action to maintain the uniform granule size.
- Too much fine powder is not desirable because fine powder may not feed into the die uniformly causing variation in weight and density.
- Since, the very nature of lubricant produce hydrophobic surface on the particle hence over blending prevents the inter granule bonding that takes place during compression.

Example of wet granulation formulae:-

Ferrous sulfate tablets

Ingredients	Quantity / tablet	Remarks
Ferrous sulfate	300 mg	Active ingredient
(dried)	60 mg	Diluent
Corn Starch	q.s.	Binder
20% sugar solution	45 mg	Disintegrant
Explotab	30 mg	Superdisintegrant
Talc	4 mg	Lubricant
Magnesium stearate		

Method of preparation

FeSO4 + Corn Starch
↓ *Mix*
↓ *Moistened with sugar solution*
↓ *Passed through #12*
Wet granules
↓ *Dried on tray dryer (Temp: 60 – 65^{0}C, over night)*
↓ *Dry Screened through #18*
Dry granules ← Explotab + talc + Mg-stearate
↓ *Compression*
TABLET

DRY GRANULATION

Dry granulation is followed in situations where
(i) the effective dose of a drug is too high for direct compaction,
(ii) if the drug is sensitive to heat, moisture or both, which precludes wet granulation.
e.g. many aspirin and vitamin formulations are prepared for tableting by compression granulation.

Steps of granulations

Milling → Weighing → Screening → Blending → Slugging → Granulation (Dry) → Lubrication
↓
Compaction

Slug:
Slug may described as poorly formed tablets or, may be described as compacted mass of powdered material.
Purpose: To impart cohesiveness to the ingredients, so as to form tablets of desired properties.
Method: It is done either by (i) by high capacity heavy duty tablet press
(ii) by Chilsonator roller compactor.

(i) By *high capacity tablet press* large tablets are made because
(a) fine powders flow better into large cavities, and
(b) large slugs reduces production time

- The punches are flat faced
- Sufficient pressure should be applied.
- Powdered materials contains a considerable amount of air; under pressure this air is expelled and fairly dense piece is formed. More time is allowed for this air to escape.
- The compressed slugs are comminuted in desired mesh screen.
- Lubricant is added twice : i.e.
  1. During blending with other powders and
  2. added to the granulations
- The lubricant is blended gently with the granulation and is compressed into tablets

(ii) *Chilsonator roller compactor*

- Chilsonator consists of two grooved rollers. Powder is flowed into the grooves and compressed mass is produced as the rollers rotates.
- Distance between two rollers can be adjusted.
- By the impeller always the air is removed from the powder mass.
- By using oscillatory granulator granules are prepared and lubricant is blended with the granules and compressed into tablets.

Advantages of chilsonator over tablet press

1. Very high production rate
2. Pressure can be controlled
3. Lubrication is not required in the primary stage.

Using a tablet press	Using a chilsonator
Powder + Lubricant	Powders
↓	↓
Slugs	Slugs
↓	↓
Granules	Granules
↓	↓
Lubricated	Lubricated
↓	↓
Compressed	Compressed

Hence, in a chilsonator only once lubricant is used. Since lubricants, such as talc, magnesium stearate etc. are hydrophobic in nature they will

(i) impart problem in in-vitro disintegration

(ii) compaction will not be efficient due to the decrease in inter-particular cohesive force.

Advantages of dry granulation over wet granulation

1. No application of moisture (required in wet granulation) and heat (for drying). So the drugs susceptible to either moisture or heat or both can be made by dry granulation. e.g. calcium lactate cannot be used by wet granulation. (Aspirin, Vitamin C)
2. Dry granulation involves less steps and hence less time is required than that of wet granulation.
3. Less steps requires less working space and energy.

Since popularity of wet granulation is more that dry granulation because former will meet all the physical requirement for the compression of good tablets.

Example of dry granulation

Preparation of Aspirin tablets

Ingredients	Quantity required per tablet	Remarks
Aspirin (#20 mesh)	325.0 mg	Active ingredient
Starch (dried)	32.5 mg	Diluent / Disintegrant
Cab-o-sil	0.1 mg	Lubricant

Method:

Aspirin + Starch + Cab-o-sil

10 mins ↓ Mixed in twin-shell blender for 10 mins

Powder blend

↓ Compressed into slugs of 1 inch diameter flat-face punch

Slugs

↓ Size reduction by Oscillatory granulator

Granulation (# 16 mesh)

↓

Compressed

N.B. All operations are carried out in a dehumidified area at a relative humidity less than 30% at 70^0F (21.1^0C).

DIRECT COMPRESSION

Steps:

Milling
↓
Weighing
↓
Sieving
↓
Blending
↓
Compression

Advantages: (i) It is much more quicker than any of the previous process
(ii) Minimum number of steps are required.

Modified diluents, binders etc. are available in the market which assure spherical shape of the granules to modify flow property. However, they are not used extensively.

1. If active medicament is less in amount then there will be no problem but in case of high dose large amount of active ingredient is to be replaced by specially treated vehicles to improve flow property or compressibility.
2. These specially treated materials are costly.

Example **Vitamin B1 tablets**

Ingredients	Quantity for each tablet	Remarks
Thiamine hydrochloride	100 mg	Active ingredient
Avicel PH 102	83.35 mg	Glidant
Lactose (anhydrous)	141.65 mg	Diluent
Mg-stearate	6.65 mg	Lubricant
Cab-o-sil	1.65 mg	Lubricant

Method:

Vitamin B1 + Avicel + Lactose + Cab-o-sil
↓
Mg-stearate + Mixture
↓ Mixed for 5 minutes
Compressed

N.B. Anhydrous lactose can be replaced with Fast Flo lactose which will reduce the requirement of glidant (Avicel).

PROBLEMS FACED IN TABLETING

1. CAPPING AND LAMINATION

Capping is the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet.

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

Usually these problems are apparent immediately after compression, or even hour or days later.

Detection: Subjecting tablets to the friability test is the quickest way to reveal such problems.

(a) **Reason:** Entrapment of excess air in the granules during compression. If the granules are light and fluffy this type of problems are encountered frequently.

Remedies: Increasing the density of granules by adding more binder or changing the solvent of binder.

(b) **Reason:** New set of punches and dies are very tightly fitted; i.e. the clearance is very negligible hence air cannot come out.
Remedy: In that case punch diameter should be reduced by 0.005" (i.e. 5 thou)
(c) **Reason:** Granules should not be completely dried. if over dried or under dried then capping may take place.
Remedy: So moisture content should be kept within 1 – 2%.
(d) **Reason:** Concave punches, used for longer period of time will form claw-shaped curve – this forms capping.
Remedy: Punches are changed.

2. PICKING AND STICKING

Picking and sticking are the removal of surface materials from a tablet by sticking to the punch faces.
Picking: When some portion of the surface of the tablet is removed – it is termed as picking.
Cause: When punch tips have engraving or embossing, usually of letters B, A, O are difficult to manufacture cleanly. These may produce picking.
Remedy: (i) Lettering should be designed as large as possible, particularly on punches of small diameter.
(ii) Plating of the punch faces with chromium produces smooth, non-adherent face.
(iii) Colloidal Silica (Cab-o-sil) is added as polishing agent that makes the punch faces smooth; so that material does not cling to them.

Sticking: Sticking refers to tablet materials adhering to the die wall.
Disadvantages:

1. When sticking occurs, additional force is required to overcome the friction between tablet and the die wall during ejection.
2. Serious sticking at ejection can cause chipping of a tablet's edges and can produce a rough edge.
3. Also, a sticking problem does not allow the lower punches free movement and therefore can place unusual stresses on the cam tracks and punch heads, resulting in their damage.
4. Sticking can also cause build-up of material on punch faces.

Causes:

1. Excessive moisture may be responsible for sticking.
   Remedy: Further drying of the granulation is then required.
2. During compression heat is generated and
   (a) low m.p. lubricants e.g. stearic acid may produce sticking.
   Remedy: Low melting point lubricant are replaced with high melting point lubricants (e.g. Poly ethylene glycol)
   (b) Low m.p. substances, either active ingredients or additives may soften sufficiently form the heat of compression to cause sticking.
   Remedies:
   - Dilution of active ingredient with additional high m.p. diluents.
   - Increase in the size of tablet.
   - If a low m.p. medicament is present in high concentration then refrigeration of the granules and then compressing may be the order.

3. MOTTLING

Mottling is an unequal distribution of color on a tablet, with light or dark patches in an otherwise uniform surface.

Cause: Migration of water soluble dyes to the surface while drying.

Remedies:

- Change the solvent system.
- Change the binder system
- Reduce the drying temperature
- Grind to a smaller particle size.
- *** Use lakes instead of water soluble dyes.

QUALITY CONTROL OF COMPRESSED TABLET

Quality control of compressed tablet can be done by

(i) Official methods and

(ii) Unofficial methods.

1. WEIGHT VARIATION (Official)

This test is based on the fact that, if the weight variation is not much then it can be said that *the amount of medicament will not vary considerably*. Conversely, if the weight variation is larger then it can be concluded that the active medicament will also vary considerably.

Sources of weight variation

Weight variation is solely dependent on the poor flow property of granules and filling of die cavity.

Poor flow properties arise from: (a) improper lubrication
(b) size of granules
(c) adjustment of lower punch.

Weight variation test

The U.S.P. weight variation test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP 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.*"

N.B.

Say 20 tablets weighed separately
Percentage limit is ± 10%.
Say the average weight was 100 mg.
Then the sample of tablets will pass the USP weight variation test if
18 tablets remain within 90 mg to 110 mg and
2 tablets remain within 80 mg to 120 mg.

The weight variation tolerance for uncoated tablets differ on average tablet weight.

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	± 10
130 to 324	± 7.5
More than 324	± 5

N.B. Weight of tablets: $w_1, w_2, w_3, ..w_n..,w_{20}$.

Average weight of the tablets = $\overline{w}$

So the weight variation of n^{th} tablet = $\frac{\left(\left|\overline{w} - w_n\right|\right)}{\overline{w}} \times 100\%$

2. CONTENT UNIFORMITY TEST

N.B. Weight variation test is applicable when the amount of medicament in the tablet is high. in potent drug the medicament is less in amount in comparison to the other excipients. The weight variation may meet the pharmacopoeial limitation but this will not ensure the correct variation of potency. hence, in this case the weight variation test is followed by content uniformity test.

Content uniformity test

In this test 30 tablets are randomly selected for sample, and at least 10 of them are assayed individually according to the official assay method.

Nine of the 10 tablets must have potency within ± 15 % of the labeled drug content. Only one tablet may be within ± 25%.

if this conditions are not met then the tablets remaining from the 30 must be assayed individually and none may fall outside ± 15% of the labeled content.

N.B. For example:

30 tablets are taken at random

10 tablets are assayed individually

In which 8 tablets remained within ± 15%

and 2 tablets remained within ± 15 % and ± 25 %.

So the test has to be carried out with rest of the 20 tablets.

And those 20 tablets must remain within ± 15%.

Conclusion: Out of the 30 tablets the potency of only 2 tablets may remain within 15 to 25 % rest of all the tablets should remain within ±15%.

3. TABLET HARDNESS

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

Method:

A tablet is taken between the 2nd and 3rd finger and pressing it with the thumb as fulcrum. If the tablet breaks with a "sharp snap", yet, it does not break when it falls on the floor – is said to possess proper hardness.

Instruments used:

1. Monsanto Hardness Tester
2. Strong Cobb Hardness Tester — Manual mode of operation are more or less similar
3. Pfizer Hardness Tester
4. Schleuniger Apparatus – Operates without manual involvement.

Hardness of a tablet:

The hardness at which the tablet crushes is the hardness of the tablet.

Unit of hardness: Kg/sq.in. or lb/ sq.in

Limit : Generally maximum 5 kg/sq.in. hardness is required.

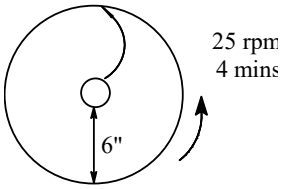
N.B.

- If the tablets are too hard then it may not meet tablet disintegration test.
- If the tablets are too soft then it may not with stand the handling, packaging and shipping operations.

4. FRIABILITY

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets may produce chipping, capping and lamination problems. Therefore another measure of tablet strength i.e. friability is often measured, i.e. the friability.

Instrument: ROCHE FRIABILATOR



Roche Friabilator

Objective of friability test:

This apparatus is designed to evaluate the ability of the tablet to withstand abrasion, in handling, packaging and shipping operation.

Method:

Few tablets, previously weighed are taken in the plastic chamber of the laboratory friability tester. In the plastic chamber the tablets are subjected to abrasion and shock by rotating the plastic chamber at 25 rpm for 4 mins (i.e. total 100 revolutions). The tablets are dusted and reweighed.

Limit

For conventional compressed tablet the weight loss should be within 0.5 to 1.0 %.

5. DISINTEGRATION TEST OF TABLETS (Official)

For most tablets, the first important step toward solution is breakdown of the tablet into smaller particles or granules – this process is known as disintegration .

- The time a tablet takes to disintegrate is the disintegration time.

USP disintegration test apparatus

The USP device to test disintegration uses glass tubes with the following dimensions:

number of tubes= 6
length = 3 inches
Upper end open, lower end closed with #10 mesh screen.

To test the disintegration time one tablet is placed in each tube, and the basket rack assembly is positioned in a 1-litre beaker of water, simulated gastric fluid or simulated intestinal fluid, at $37^0C \pm 2^0C$, such that the tablet remain 2.5 cm from the bottom of the beaker.

A standard motor moves the basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cpm (cycles per minute).

Perforated plastic discs may also be placed on top of the tablets to impart an abrasive action to the tablets. They are useful for tablets that float.

- USP disintegration test will be passed if all the tablets disintegrate and the particles passed through the #10 mesh screen within the specified time. If any residue remains, it must have a soft mass with no palpable firm core.
- Disintegration time is suggested for 5 minutes for uncoated Aspirin tablets. Majority of the uncoated tablets have maximum disintegration time (DT) of 30 minutes.
- Enteric coated tablets shows no evidence of disintegration after 1 hr in simulated gastric fluid. The same tablets are then tested in simulated intestinal fluid and are to disintegrate in 2 hrs plus the time specified in the monograph.

6. DISSOLUTION TEST

Why is it required?

1. Disintegration test simply identifies the time required for the tablet to break up under the condition of the test but it does not ensure the drug release in the bulk of the fluid.
2. Rate of dissolution is directly related to the efficacy of the drug.
3. Rate of dissolution is a good index for comparing the bioavailability of two tablet products of the same drug.

USP XX / NF XV, Supplement 3 specifies two apparatus for dissolution test.

1. Apparatus - I

In general, a single tablet is placed in a small wire mesh basket and immersed in the dissolution medium (as specified in the monograph) contained in a 1000 ml flask at $37^0 \pm 0.5^0C$. Generally it is rotated at 50 rpm unless otherwise specified.

2. Apparatus 2

The same equipment is used. Instead of basket a paddle is introduced as the stirring element. The tablet is allowed to sink at the bottom of the flask before stirring.
Limit: A value of $t_{90\%}$ (i.e 90% drug release) within 30 minutes is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is not less than 75% dissolved in 45 minutes.

TABLET COATING

Reasons behind coating of tablets:
The reasons behind coating of tablets are as follows:
1. To mask the taste, odour or colour of the drug. Improving the product appearance, particularly where there are visible differences in tablet core ingredients from batch to batch.
2. Provide physical protection, facilitates handling, particularly in high speed packaging / filling lines.
3. To provide chemical protection from its surrounding environment (particularly air, moisture and light).
4. To control the release of drug from the tablet e.g. sustained release tablets, repeat action tablets.
5. To protect the drug from the gastric environment of the stomach with an acid resistant enteric coating.

Tablet properties (or Core properties)
Tablets that are to be coated are called core. This core must possess the proper physical characteristics.
1. In pan coating process the core tablets roll in the pan or cascade in the air stream in air suspension coating. To endure the intense attrition between tablets or wall of the pan the tablets must have enough hardness.
2. Sugar coating can mask the imperfection on the surface but film coating cannot, hence, for film coating the core surface must be smooth.
3. The tablets must be in constant motion during the early drying phase or tablet agglomeration may occur. The ideal shape for coating is a sphere; the worst shape is a square flat-faced tablet and in practice rounded, convex shaped tablet cores are taken.
4. For coating materials to adhere to the tablet the coating composition must wet the surface of the core. e.g. hydrophobic tablet surfaces are difficult to coat with aqueous-based coating.

TYPES OF TABLET COATING PROCESSES
Two types of tablet coating are popular –
(i) Sugar coating and
(ii) Film coating
   a. Enteric coating
   b. Modified release coating

SUGAR COATING OF COMPRESSED TABLETS
The sugar coating process can be subdivided into six main steps:
1. Sealing
2. Subcoating
3. Smoothing (Syruping)
4. Color coating
5. Polishing and
6. Printing

1. Sealing

Objectives (i) To prevent moisture penetration into the tablet core, a seal coat is applied.
(ii) To strengthen the tablet core without a seal coat, the over wetted tablets would absorb excess moisture, leading to tablet softening, and may affect the physical

and chemical stability.

Ingredients
- Alcoholic solutions of Shellac (10 – 30% solid) or
- alcoholic solution of zein,
- alcoholic solution of cellulose acetate phthalate (CAP) or
- alcoholic solution of polyvinyl acetate phthalate.

N.B.
- With aging the disintegration and dissolution time is found to increase with shellac due to polymerization
- Zein is an alcohol soluble protein derivative obtained from corn (maize).

2. Subcoating

Objectives To round the edges and build up the tablet size. Sugar coating can increase the tablet weight by 50 to 100% at this step.

Method The subcoating step consists of alternately applying a sticky binder solution to the tablets followed by a dusting of subcoating powders and then drying.

Subsequent coatings are applied in the same manner until the tablet edges have been covered and the desired thickness is achieved.

Ingredients
- Binder solution formulations for subcoating:-

Gelatin	3.3%(w/w)
Gum acacia (powder)	8.7%(w/w)
Sucrose	55.3%(w/w)
Water to	100%(w/w)

- Dusting powder formulation

Calcium carbonate	40.0%(w/w)
Titanium dioxide	5.0%(w/w)
Talc (asbestos free)	25.0%(w/w)
Sucrose powder	28.0%(w/w)
Gum acacia powder	2.0%(w/w)

3. Smoothing or syruping

Objectives To cover and fill in the imperfections in the tablet surface caused by the subcoating step.

Ingredients Simple syrup solution (approximately 60 – 70%(w/w)).
Often the smoothing syrups contain a low percentage of titanium dioxide (1 – 5%) as an opacifier. This gives a very bright and reflective background for the subsequent coloring step.

4. Colour coating

Objective To impart an elegant and uniform colour.

Ingredient Syrup (60 – 70% sucrose) containing the desired color.

Method Syrup solutions containing the dyes are coated upto 60 individual applications until the desired color is achieved. After each application of color the coatings are dried.

In the finishing step a few clear coats of syrup may be applied.

5. Polishing

Objective To produce the desired luster on the surface of the tablet.

Ingredients Mixtures of waxes (like beeswax, carnauba wax, candella wax or hard paraffin).

Method Either this mixtures of waxes are applied as powder or as dispersions in various organic solvents in a polishing pan (canvas line pan).

6. Printing

In order to identify sugar-coated tablets often it is necessary to print them, using pharmaceutical grade ink, by means of a process of offset rotogravure.

FILM COATING

Film coating adds 2 to 5% to the tablet weight.

Film coating can be done by the following three methods.

(i) **Pan-pour method:**

Viscous coating materials are directly added from some container into the rotating pan moving with the tablet bed. Tablets are subjected to alternate solution application, mixing and then drying.

Disadvantages:

- The method is relatively slow.
- It relies heavily on the skill of the operator.
- Tablets always require additional drying to remove the latent solvent.
- Aqueous film coating are not suitable for this method because localized over wetting will produce physicochemical instability.

(ii) **Pan-spray method:**

Coating material is sprayed over the tablet bed from nozzles and hot air is passed through the tablet bed to dry it.

The variables to be controlled is pan-spray film coating process are:

(a) Pan variables:

Uniform mixing is essential to deposit the same quantity of film on each tablet.

1. *Pan design or baffling*:

Some tablet shapes mixes freely while other shapes may require a specific baffling arrangement to ensure adequate mixing.

Disadvantages: Baffles may produce chipping and breakage if not selected properly.

(b) Pan speed

Pan speed affects mixing and the velocity at which the tablet pass under the spray.

- Too slow speed cause localized over-wetting resulting in tablets sticking to each other or to the pan.
- Too high speeds may not allow enough time for drying before the same tablets are reintroduced to the spray. This results in a rough coating appearance on the tablets.
- Optimum pan speed: 10 – 15 rpm for nonaqueous film coating
  3 – 10 rpm for aqueous film coating.

(c) Spray variables

1. Rate of liquid application
2. Spray pattern
3. Degree of atomization

These three spray variables are interdependent.

For spraying two types of systems are there:

(a) High-pressure, airless system and

(b) low-pressure, air atomization system.

- The proper rate of liquid application depends on the mixing and drying efficiency of the system and the coating formula.
- A band of spray should be spread evenly over the tablet mass. In larger pans, more nozzles must be added to cover the tablet bed width.

A spray pattern that is too wide will apply coating on the pan.

A spray pattern that is too narrow will produce localized over-wetting.

Spray width can be adjusted by moving the nozzles closer or further away from the tablet bed.

- Atomization is the process where by the liquid stream is finely subdivided into droplets. The degree of atomization (i.e. the size and size-distribution of the droplets). Too fine atomization causes some droplets to dry before reaching the tablet surface, resulting in roughness on the tablet surface and excess dust in the pan. Too large atomization causes localized over-wetting – leads to sticking, picking or a rough "**orange peel**" effect.

(d) Process air variables (temperature, volume, rate) are required for optimum drying of the coating by evaporation of the solvent.

The balance between the supply and exhaust air flow should be such that all the dust and solvent are confined within the coating system.

(iii) **Fluidized bed process** (air suspension coating)

This process have been successfully used for rapid coating of tablets, granules and capsules. Process variables are as follows:

(a) Chamber design and air flow rate controls the fluidization pattern.
(b) Tablet shape, size and density.
(c) Volume and rate of air flow
- – too high rate produce attrition and breakage of tablets
- – too low rate → mass does not move fast enough through the spray region → over-wetting occurs.

(d) Inlet and exhaust air temperature.

DEVELOPMENT OF FILM COATING

Before coating a tablet the coating formula is first cast on either a glass, teflon or aluminium foil surface. Glass is preferred for cast films. The coating is done by spreading with a glass rod. After drying, the cast films are assessed for the following properties:

(i) Physical appearance – potential colorant or opaquant separation is noted.
(ii) lack of color uniformity
(iii) insoluble additives have been properly suspended or not.
(iv) water vapor permeability
(v) film tensile strength

MATERIAL USED FOR FILM COATING

Film formers

Nonenteric materials : e.g.	Hydroxypropyl methylcellulose (HPMC) Methylhydroxy ethyl cellulose (MHEC) Ethylcellulose (EC) Hydroxypropyl cellulose (HPC) Polyvinyl pyrrolidone (PVP) Sodium carboxymethyl cellulose (Sod. CMC) Polyethylene glycols (PEG) Acrylate polymers e.g. Eudragit E
Enteric materials: e.g.	Cellulose acetate phthalate (CAP) Acrylate polymers (Eudragit L, S) Hydroxypropyl methylcellulose phthalate (HPMCP) Polyvinyl acetate phthalate (PVAP)

Solvents

Criteria

1. It should either dissolve or disperse the polymer system.
2. It should easily disperse other coating solution components into the solvent system.
3. Small concentration of polymers (2 to 10%) should not result in an extremely viscous solution system (> 300 cps), creating process problems.
4. It should be colorless, tasteless, odourless, inexpensive, non-toxic, inert and non-inflammable.
5. It should have no environmental impact.

Colorants: Same as tablet.

Opaquant extenders:

Very fine inorganic powders e.g.

		titanium dioxide (TiO_2)
silicates	like	talc, aluminium silicate
carbonates	like	magnesium carbonate
sulfates	like	calcium sulfate
oxides	like	magnesium oxide and
hydroxides	like	aluminium hydroxides.

Miscellaneous coating solution components

Flavors and sweeteners
Surfactants are used to solubilize immiscible or insoluble ingredients
Antioxidants
Antimicrobial agents.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products to modify drug release. The USP describes two types of modified release dosage forms, namely those that are *delayed release* and those that are *extended release*. Delayed-release products often are designed to prevent drug release in the upper part of the gastrointestinal (GI) tract. Film coatings used to prepare this type of dosage form are commonly called *enteric coatings*, while film coatings that are required to extend drug release over a long period of time (from 6 to 24 hours) are commonly called *sustained-* or *controlled-release* film coatings.

Enteric Coatings

Enteric coatings generally remain intact in the stomach but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs that are inactivated by the stomach contents, (e.g., pancreatin, erythromycin, and substituted benzimidazole compounds, such as proton pump inhibitors) or may cause nausea or bleeding by irritating the gastric mucosa (e.g., aspirin, and many nonsteroidal anti-inflammatory drug substances).

In addition, such coatings can be used to give a simple repeat-action; in this case, a tablet core containing part of the dose is enteric coated, and then additional API is applied to the surface of the enteric coated tablet, with the result that the outer-most layer of API will be released immediately on ingestion, while the remainder of the dose will only be released once the enteric coating has dissolved. The functionality of enteric coatings stems from the way the polymers react to differences in composition of the respective gastric and intestinal environments, especially with regard to pH and enzyme content. Although there have been repeated attempts to produce coatings that are susceptible to enzymatic breakdown, this approach is not popular because such breakdown of the coating can be relatively slow. Thus, most currently used enteric coatings are weak acids that remain undissociated and thus insoluble in the low pH environment of the stomach but readily ionize and dissolve when the pH rises to above 5.

The most effective enteric polymers are polyacids having a pKa of about 5. Coatings that respond to enzymatic breakdown are now being considered as protective coatings suitable for the colonic delivery of polypeptide drugs. Historically, the earliest enteric coatings used formalin-treated gelatin, but this approach was unreliable because the polymerization of gelatin could not be controlled accurately and often resulted in failure to release the drug, even in the lower intestinal tract. Another early candidate was shellac, but again the main disadvantage resulted from further polymerization that occurred on storage, often resulting in failure to release the active contents. Pharmaceutical formulators now prefer to use synthetic polymers to prepare more effective enteric coatings. One of the oldest synthetic polymers used for enteric coating is cellulose acetate phthalate (CAP). However, a pH greater than 6 usually is required to allow the coating to dissolve, and thus a significant delay in drug release may ensue. It also is relatively permeable to moisture and gastric fluid compared to other enteric polymers, and it is very susceptible to hydrolytic decomposition (where phthalic and acetic acids are split off from the polymer chains), resulting in a change in

polymer properties, and thus enteric coating performance. Other useful enteric-coating polymers include polyvinyl acetate phthalate (PVAP, which is less permeable to moisture and gastric fluid, more stable to hydrolysis, and able to ionize at a lower pH); hydroxypropyl methylcellulose phthalate (HPMCP, which has properties similar to PVAP); acrylic copolymers, such as methacrylic acid–methacrylic acid ester copolymers (some of which have a high dissociation constant); cellulose acetate trimellitate (CAT, which has properties similar to CAP); carboxymethyl ethylcellulose (CMEC); and hydroxypropyl methylcellulose acetate succinate (HPMCAS). Today, acrylic copolymers are often preferred (in terms of performance and global acceptability) for designing enteric coating formulations.

Since enteric coating polymers are, by nature, insoluble in water (except at a pH >5), their use in aqueous coating systems is predicated by the use of either liquid polymer dispersions (sometimes called latices or pseudolatices) or dry powder coating systems that can readily be dispersed in water prior to use.

Sustained-Release Coatings

The concept of sustained-release formulations was developed to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs that need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects (e.g., the ulceration that occurs when potassium chloride is released rapidly into the milieu of the gastrointestinal tract). Formulation methods used to obtain the desired drug release rate from sustained-action dosage forms include

1. Increasing the particle size of the drug.
2. Embedding the drug in a matrix.
3. Coating the drug or dosage form containing the drug.
4. Forming complexes of the drug with materials such as ion-exchange resins.

Materials that have been found suitable for producing sustained- release coatings include:

1. Mixtures of waxes (beeswax, carnauba wax, etc.) with glyceryl monostearate, stearic acid, palmitic acid, glyceryl monopalmitate, and cetyl alcohol. These provide coatings that dissolve slowly or are broken down by other means in the GI tract.
2. Shellac and zein. These polymers remain intact until the pH of gastrointestinal contents becomes less acidic.
3. Ethylcellulose, which provides a membrane around the dosage form and remains intact throughout the gastrointestinal tract. However, it does permit water to permeate the film, dissolve the drug, and diffuse out with the dissolved drug.
4. Acrylic resins, which behave similarly to ethylcellulose as a diffusion-controlled drug-release coating material.
5. Cellulose acetate (diacetate and triacetate), which can function as semi-permeable membranes.
6. Silicone elastomers.
7. Polyvinyl acetate.

As with enteric coatings, many of the synthetic polymers suitable for sustained-release film-coating applications are available as aqueous polymer dispersions that can be used in aqueous coating processes.

Various methods have been used to prepare sustained- release products using film-coating techniques. Examples include the application of suitable film coatings to:

1. Dried granules (either irregular or spheronized)
2. Drug-loaded beads (or nonpareils)
3. Drug crystals
4. Drug/ion-exchange-resin complexes
5. Tablets, including mini tablets

In the first four examples, the final coated particles can be either filled into two-piece hard-gelatin capsules or compacted into tablets. Additionally, coated drug/ion-exchange-resin complexes may be dispersed in viscous liquids to create liquid suspensions. An interesting application of the film-coated, sustained release tablet is the osmotic pump concept as described by Wong *et al*. In this

device, a tablet core (formulated to contain osmotically active ingredients) is film coated with a semi-permeable membrane. This membrane is subsequently *pierced* with a laser to create a delivery orifice. Once such a device is ingested, the infusion of water generates an osmotic pressure within the coated tablet that *pumps* the drug out through the orifice.

With sustained-release products, one must remain aware constantly of the fact that the final dosage forms typically contain drug loadings that are sufficiently high to cause problems if the entire dose is released quickly. This phenomenon, commonly called *dose-dumping*, can be avoided only if:

1. The film coating is mechanically sound and will resist rupture on ingestion of the dosage form.
2. Sufficient coating is applied uniformly across the surface of the material that is to be coated.
3. The dosage form is not chewed or crushed prior to ingestion.

FILM DEFECTS

Variations in formulation and processing conditions may result in unacceptable quality in the film coating. Some of the problems are as follows:

Picking

Overwetting or excessive film tackiness or when the drying system is inefficient – tablets stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a "**picked**" appearance to the tablet surface and resulting in a small exposed area of the core tablet.

Remedy:

- A reduction in the liquid application rate or,
- increase in the drying air temperature and air volume usually solve this problem.
- If excessive tackiness is there then the formulation is changed.

Roughness

A rough or gritty surface is a defect often observed when the coating is applied by spray. Some of the droplets may dry too rapidly before reaching the tablet bed, resulting in droplets on the tablet of "spray dried" particles instead of finely divided droplets of coating solution.

Roughness also increases with pigment concentration and polymer concentration.

Remedy

- Moving the nozzle closer to the tablet bed
- Reducing the viscosity of coating solution.

Bridging and filling

During drying, the film may shrink and pull away from the sharp corners of a bisect, resulting in "bridging" of the surface depression.

This defect may be so severe that the monogram or the bisect is completely obscured.

This is a problem in the formulation.

Remedy

- Increasing the plasticizer amount in the formulation
- Changing the plasticizer can decrease the incidence of bridging.

Filling: If the solution is applied too fast, over-wetting may cause the liquid to quickly fill and be retained in the monogram – this is called filling.

Remedy

- Judicious monitoring of the fluid application rate, and
- thorough mixing of the tablets in the pan prevent filling.

Blistering

When coated tablets require further drying in ovens, too rapid evaporation of the solvent from the core and the effect of high temperature on the strength, elasticity and adhesion of the film may result in blistering.

Remedy Milder drying conditions are adopted.

Hazing / Dull film (Bloom)

It can occur when too high a processing temperature is used for a particular formulation. It is particularly evident when cellulosic polymers are applied out of aqueous media at high processing temperatures.

It can also occur if the coated tablets are exposed to high humidity conditions and solution of film results.

Color variation

- Improper mixing, uneven spray pattern.
- Insufficient coating may result in color variation.
- The migration of soluble dyes, plasticizers, and other additives during drying may give the coating a mottled or spotted appearance.

Remedy

- Use of lake instead of dye.
- Changing the plasticizer and additives.

Cracking

Cracking occurs if the internal stresses in the film exceed the tensile strength of the film. The tensile strength of the film can be increased by using higher molecular weight polymers or polymer blends.

Internal stresses in the film can be minimized by adjusting the plasticizer type and concentration, and the pigment type and concentration.

Plasticizers

These are used to impart flexibility to the film.

e.g. castor oil, propylene glycol, glycerin, polyethyleneglycol (PEG) 200 and 400, surfactants e.g. polysorbates (Tweens), Sorbitan esters (Spans) and organic esters.

Quality Control of Coated Tablets

The most important aspects of coated tablets that must be assessed from a quality-control standpoint are appearance characteristics and drug availability. From the appearance standpoint, coated tablets must be shown to conform, where applicable, to some color standard, otherwise the dispenser and the consumer may assume that differences have occurred from previous lots, signifying a changed or substandard product.

In addition, because of the physical abuse that tablets, both in their uncoated and coated forms, receive during the coating process, it is essential to check for defects such as chipped edges and picking, and ensure that they do not exceed predetermined limits.

Often, to identify the products, coated tablets may be imprinted (particularly with sugar-coated tablets) or bear a monogram (commonly seen with tablets that are film-coated). The clarity and quality of such identifying features must be assessed. The failure of a batch of coated tablets to comply with such preset standards may result in 100% inspection being required or the need for the batch to be reworked.

Batch-to-batch reproducibility for drug availability is of paramount importance; consequently each batch of product should be submitted to some meaningful test such as a dissolution test. Depending on the characteristics of the tablet core to be coated, tablet coatings can modify the drug release profile, even when not intended (unlike the case of enteric- or controlled-release products). Since this behavior may vary with each batch coated (being dependent, for example, on differences in processing conditions or variability in raw materials used), it is essential that this parameter be assessed, particularly in products that are typically borderline.

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