LECTURE 1

TABLET

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CONTENT.....

- Introduction
- General Properties
- Advantages
- Disadvantages
- Types of Tablets
- Tablet Additives

Introduction

- **Tablets**
- Solid dosage form comprises tablets and capsules constitute about 80% of all dosage forms.
- They are used to produce systemic action.
- ***A tablet is*** a unit dosage form of medication containing one or more drugs to which excipients are added and compressed as granules or powder to a definite shape.

Advantage of tablet as dosage forms

1. Are convenient to use and elegant dosage form.
2. Availability in a wide range of types which offer a range of drug release rates and duration of clinical effect.
3. Tablets may be formulated to release the drug at particular site within G.I.T. promoting the absorption at this site. This could not be done by other dosage forms.
4. Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
5. Accuracy of dose is maintained since tablet is a solid unit dosage form.

Advantage of tablet as dosage forms

6. Ease of masking bad taste by coating.
7. Tablets generally are non expensive.
8. Tablets are more stable chemically, physically or microbiologically than other dosage forms.
9. Formulation of tablets could contain more than one drug even if there is incompatibility between each drug.
10. All classes of therapeutic agent may be administered orally.

Disadvantage of tablet as dosage forms

1. The manufacture of tablets requires many steps of operation and in each step an increased product loss in manufacturing.
2. The drug absorption from tablets depends on physiological factors e.g. gastric emptying rate and show patient variation.
3. The compression of some drugs into dense compacts is poor owing to amorphous nature, low density character →may present problems in the manufacture.

Disadvantage of tablet as dosage forms

1. Drugs with poor wetting, slow dissolution properties, may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
2. Difficult to swallow in case of children, elderly peoples and unconscious patients.

- This problem is solved by using effervescent and chewable tablet.

General properties of tablet

- A tablet must be strong and hard to withstand mechanical shock during manufacturing, packing, shipping, dispensing and use.
- The drug content of the tablet must be bioavailable that is, the tablet must be able to release its content in a predictable and reproducible manner.
- Must have a chemical and physical stability over time (during manufacture, storage, and use) so as not to follow alteration of the medicinal agents
- The tablet should have elegant product identity which is free from any tablet defect (like chips, cracks, discoloration, and contamination).
- Tablets must be uniform in weight and in drug content.

Different Types of Tablets

I. Tablets ingested orally:
- Compressed tablet, e.g. Paracetamol tablet
- Multiple compressed tablet
- Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
- Sugar coated tablet, e.g. Multivitamin tablet
- Film coated tablet, e.g. Metronidazole tablet
- Chewable tablet, e.g. Antacid tablet

II. Tablets used in oral cavity:
- Buccal tablet, e.g. Vitamin-c tablet
- Sublingual tablet, e.g. Vicks Menthol tablet
- lozenges
- Dental cone

Different Types of Tablets

III. Tablets administered by other route:

- Implantation tablet
- Vaginal or Inserts, e.g. Clotrimazole tablet

IV. Tablets used to prepare solution:

- Effervescent tablet, e.g. Dispirin tablet (Aspirin)
- Hypodermic tablets: soft, readily soluble tablets (parental solutions)

Types of tablets

1- Conventional compressed tablets (C.T.)

- These tablets are designed to provide rapid disintegration and hence rapid drug release and represent a significant proportion of tablets clinically used.
- These tablets are manufactured by compressing granules or powders that containing the drug.
- On administration by the patient this tablet will disintegrate within G.I.T. allowing the drug to dissolve in the gastric fluid and absorbed.

Types of tablets

2- Multiple compressed tablets (M.C.T.)

- These are tablets composed of at least two layers
- These tablets are prepared by subjecting the fill material to more than one compression cycle.
- There are two designs;

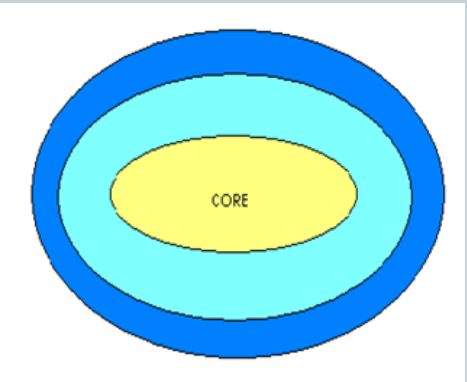
a- Multiple layered (tablet within tablet)

- tablets composed of two or more layers of ingredients
- In multiple layered tablets, the first layer is formed by light compression of granules containing the drug then a next layer of granules containing the drug is compressed on the first layer.

Types of tablets

b. – Compression coated (dry/press coated tablet)

- The first layer is prepared by light compression then removed and located in a second press machine (Manesty Drycota) to feed granules with drug around the formed layer (on the surface & edges) then compressed to form a coated layered tablet.
- The inner tablet being the core and the outer portion being the shell .



Manesty drycoat

- ✓ Manesty Drycoat Core and Coating Tablet Press. Consists of two rotating Tablet Presses (one used to produce the core, the other for the coating) connected by a transfer system.

➢ Operation

1. The tablet core is compressed in the first turret.
2. Tablet core pass over vacuum to remover the dust and any granules then transfer to the turret of the second press.
3. The tablet core is deposited in the coating die, coated then compressed.

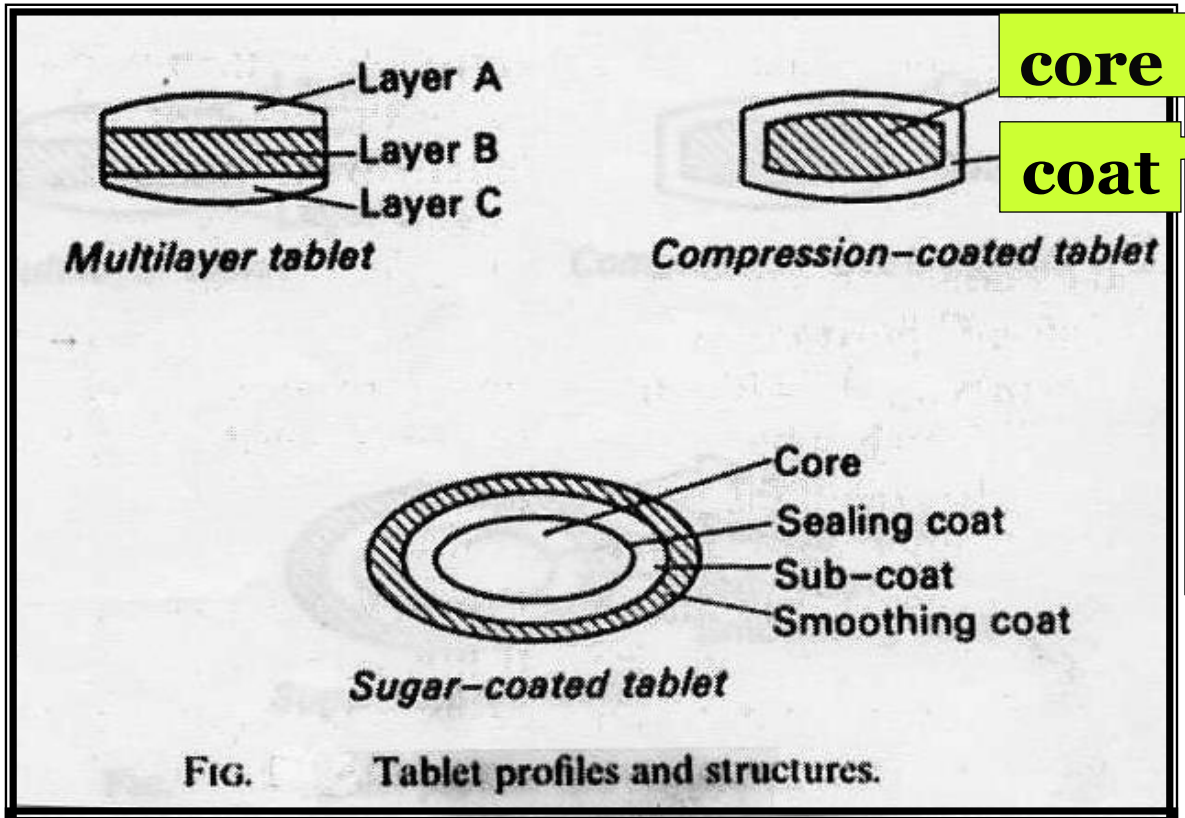


FIG. Tablet profiles and structures.

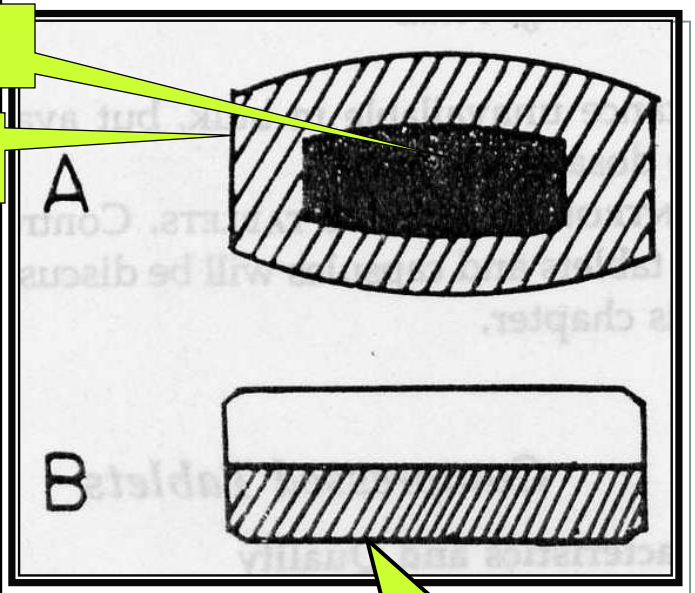


Fig. 7-24. Diagram of multiple-compressed tablets. A, having a core of one drug and a shell of another, and B, a multiple-layered tablet of two drugs.

Types of tablets

- **Application of using the multiple compressed tablets:**

1- Separation of incompatible drug in separate layered tablet.

2- The delivery of therapeutic agents at different rates or to different sites within G.I.T. from single tablet.

3- Production of coated tablets with an external layer that irritant to the stomach or unstable in acidic PH.

Types of tablets

3- Enteric coated tablets (E.C.T.)

- They are compressed tablets coated with a polymer that does not dissolve in acidic conditions (stomach) but dissolve in alkaline conditions of small intestine (pH 7.4)→ have delayed-release properties
- The polymers used for enteric coating inhibit the dissolution of the drug in the stomach or protect the drug (e.g. erythromycin) from degradation or protect the stomach mucosa from the irritation caused by some drugs (anti-rheumatics)

Types of tablets

- **Polymers used for enteric coating:**
  1. Cellulose acetate phthalate (CAP) or cellulose acetate butyrate, the dissolution of the polymer occurs in solution above pH 6.
  2. Hydroxyl propyl methyl cellulose succinate (HPMCS): this polymer dissolves in the intestinal secretions.
  3. Methacrylic acid co- polymers (Eudragits): it is characterized by presence of a wide range of functional groups which exhibit a range of solubility's.
     - Eudragits L100 which soluble in intestinal fluids from pH 5.5.
     - Eudragits S100 which is soluble in the intestinal fluids from pH 7.

Types of tablets

4- Sugar coated tablets (S.C.T.)

- They are conventional tablets coated with a concentrated sugar solution to improve the tablet appearance or to mask bitter taste of the drug.
- Now sugar coated tablets decreased in use for improved techniques of film coated tablets.

Types of tablets

5- Film coated tablets (F.C.T.)

- These are conventional tablets coated with a polymer or a mixture of polymers.
- Film coated with polymers that dissolve in stomach (non enteric) to enable tablet disintegration and dissolution such as:

  1- Hydroxyl propyl methyl cellulose (HPMC).

  2- Hydroxyl propyl cellulose (HPC).

  3- Eudragit E100.

Types of tablets

- If the film coating is employed to control the rate and duration of drug release in certain region of G.I.T, the drug release occurs by diffusion through the insoluble coating and subsequent partitioning into G.I.T fluids.
- Examples of polymers used for this purpose:

1- Ethyl cellulose (EC)

- It is insoluble in aqueous solutions at all pH values.
- 2- Eudragit RS and RL:
- Are methacrylate co- polymers that are insoluble in water. The RS differs from RL in the ratio of monomers.

Types of tablets

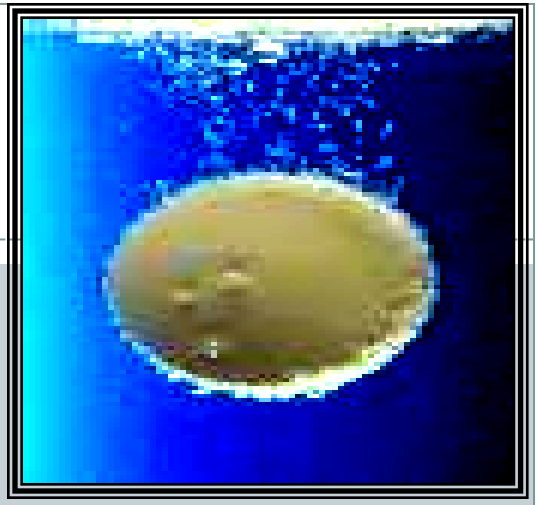
6- Chewable tablets

These are big sized tablets which are difficult to swallow and thus, are chewed within the buccal cavity prior to swallowing and applied mainly for:

- Administration to children and adults who have difficulty in swallowing conventional tablets.
- Antacid formulations in which the and the neutralization efficacy of the tablet is related to particle size within the stomach. e.g., magnesium trisilicate tablet

❑ If the drug taste is not acceptable, it is not recommended to be manufactured in chewable tablet.

Types of tablets



7- Effervescent tablets

- They are tablets when added to aqueous solutions → they will rapidly disintegrate with eff producing solution or suspension of the drug in aqueous medium.
- contain organic acids (such as tartaric or citric acid) and sodium bicarbonate in addition to the medicinal substance or API.
- The disintegration of the tablet is due to a chemical reaction occurs between two component in the presence of water, with the evolution of CO_2 which causes the disintegration.
- This type of tablets has the advantage of producing a solution ready for absorption in G.I.T.
- The main disadvantage is the need of a moisture impermeable package such as aluminum foil to inhibit the interaction between the acid and sodium bicarbonate.

Types of tablets

8- Buccal and sublingual tablets:

- Small, flat, oval tablets that are held within oral cavity and slowly dissolve.
- The drug is absorbed across the buccal mucosa to produce systemic effect.
- Buccal tablets are placed between the cheek (الخد) and the gingival (اللثة) while the sublingual tablets (glyceryl trinitrate) are placed under the tongue.
- These tablets are employed to achieve either rapid absorption & avoiding first pass metabolism or for drugs that are destroyed by the gastric juice and/or are poorly absorbed from the GIT.
- Buccal and sublingual tablets should be formulated to dissolve slowly *in vivo* and not disintegrate with retaining in the site of application.
- It should not contain components that stimulate the production of saliva.

Types of tablets

9- Lozenges tablets:

- These are disc-shaped solid preparations containing medicinal agents and generally a flavouring substance in a hard candy or sugar base.
- They are intended to be slowly dissolved in the oral cavity, usually for local effects.
- Example: Strepsils ® Dry Cough Lozenges

Types of tablets

10- Vaginal tablets

- These are uncoated ovoid shaped tablets that are inserted into the vagina using a special inserter.
- They are prepared by compression and are shaped to fit tightly on plastic inserter devices that accompany the product
- Following insertion → retention and slow dissolution of the tablet occur → release the therapeutic agent to provide local therapeutic effect, e.g. for the treatment of bacterial or fungal infection.

  Vaginal tablets may also be used to provide systemic absorption of the drug.
- It is essential that dissolution & not the disintegration of the tablet occurs in vivo.

Types of tablets

11. Implantation Tablets/ Implants

- These are long-acting sterile tablets designed to provide continuous release of drugs, often over a period of months or a year.
- They are placed subcutaneously for systemic or local delivery.
- Implants are mainly used for the administration of hormones for contraception.
- They usually contain rate-controlling excipients in addition to the active ingredient(s).

Manufacture of tablets

- In this important section we will explain the following:

  1- Excipients used in the manufacture of tablets

  2- Methods used for the manufacture of tablets

1- Excipients used in the manufacture of tablets:

- The following excipients are used in the manufacturing of the conventional tablets:

  1- Diluents = fillers = bulking agents

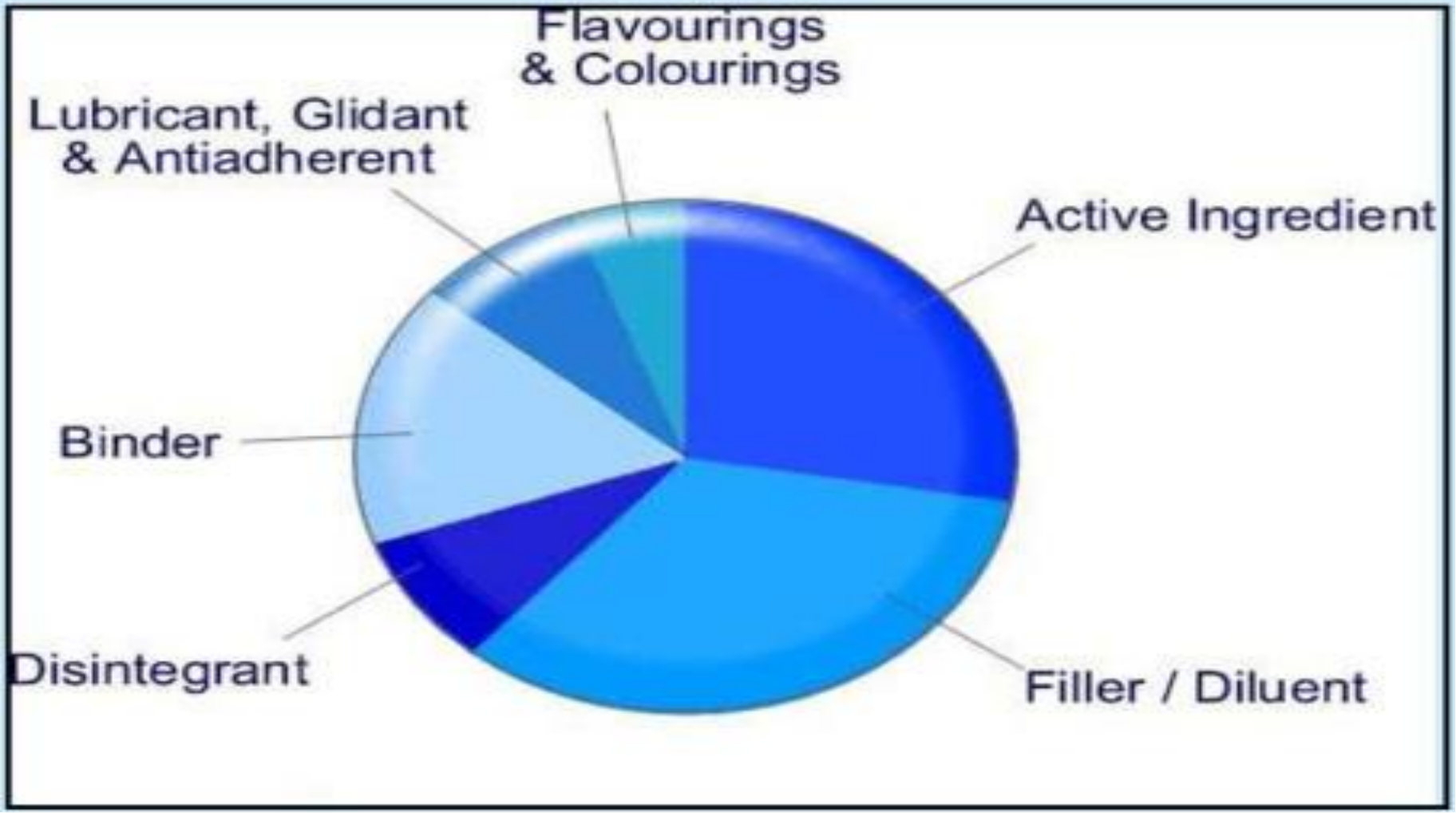
  2- Binders

  3- Disintegrants

  4- Lubricants *5- Glidants*

  6- Miscellaneous

A typical tablet contains



Excipients used in the manufacture of tablets:

Excipient	Role	Example
Diluents	Diluents increase the volume to a formulation to prepare tablets of the desired size. Widely used as fillers	• Lactose • Dextrin • MCC
Binders	Promote binding the particles of the formulation and make them cohesive during direct compression and ensure the tablet remaining intact after compression	• Starch • Gelatin • Na.Alg
Lubricants	Substance that preventing the adhesion of the tablet material to the dies and punches. It works by coating on the surface of particles.	• Glycerylmonostearate • Mg.Sterate
Glidants	Substance that is added to improve powder flowability.	• Talc • Starch
Disintegrant	Agents added to tablet formulations to promote it is breakup into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance	• Starch. • SAA • Alginic acid

Tablet Ingredients

1- Diluents = fillers = bulking agents

- They are employed in tablet formulation by any method to increase the size of the tablets to get a significant tablet weight that can be handled or compressed, thereby rendering the manufacturing process more reliable and reproducible.
- Tablets weigh normally at least 50 mg, therefore a low dose of a potent drugs requires addition of a filler to increase the bulk volume of the powder and hence the size of the tablet.
- Diluents must

1. exhibit good compression proprieties and not expensive
2. They should be physiologically and chemically inert,
3. non-hygroscopic, hydrophilic (water soluble)
4. Have an acceptable taste

1- Diluents = fillers = bulking agents

Lactose possesses many good filler properties:

- **Anhydrous lactose:**
  - Is available in a range of particle sizes & used mainly as diluents in wet granulation & dry granulation. It is a crystalline material.
- **Lactose monohydrate:**
  - It is available in a wide range of grades with different physical properties e.g.: particle size & bulk density.
- **Spray dried lactose:**

  It is a mixture of crystalline α-lactose monohydrate (80- 90 %) & 10-20% amorphous lactose. It is prepared by spray drying a suspension of α-lactose monohydrate. The specific use of spray dried lactose for the manufacture of tablets by direct compression method.

1- Diluents = fillers = bulking agents

Mannitol:

- It is a polyol used as diluents specially for chewable tablets due to its sweetness (imparts a cooling sensation when chewed). It has excellent flowability.

Starch:

- It is a polysaccharide composed of amylose & amylopectin used as diluent, binder & disintegrants.
- Pregelatinized grade is available in which the granules of starch physically & chemically modified to produce free flowing powder (granular starch)

1- Diluents = fillers = bulking agents

Microcrystalline cellulose (MCC): Avicel®

- It is crystalline powder prepared by controlled hydrolysis of cellulose. Different grades are present that differ in physical & chemical properties such as density, flow properties & particle size distribution. E.g.: Avicel PH- 101 (powder) & Avicel PH- 102 (granular).
- Also, used as dry binders and disintegrants

Dibasic calcium phosphate:

- It is available as different hydrate forms with range of particle sizes. It is a basic excipient & may react with acidic component in presence of moisture. It has an excellent flow & compression properties.

Selection of diluent

- Based on the experience of the manufacturer as well as on the cost of the diluent and its compatibility with the other tablet ingredients, the proper diluent could be chosen.

1. Calcium salts can not be used as fillers for Tetracycline products because calcium interferes with the absorption of Tetracycline from GIT.
2. When drug shows low water solubility, it is recommended that water soluble diluents be used to avoid possible bioavailability problems.
3. The combination of amine bases and salts with Lactose in presence of alkaline lubricant results in discoloration upon ageing.

2. Binders (Adhesive, granulators)

Role:

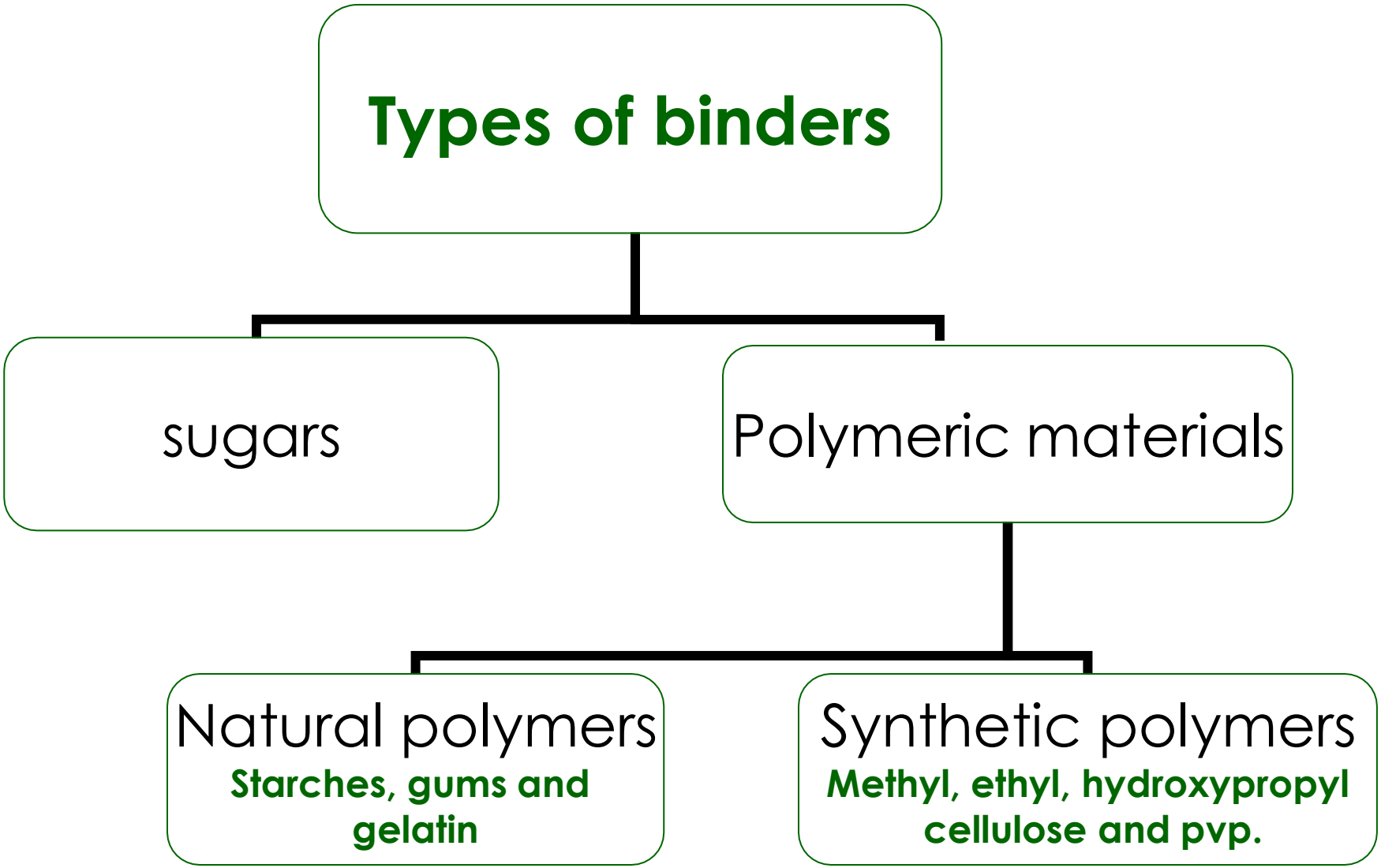
→impart cohesive qualities to powdered materials used in tablet manufacture →

- To bind powders together in the wet granulation process
- To bind granules together during compression

Example of commonly used binders:

1. Solution binders as **starch, sucrose and gelatin.**
2. Dry binders as **microcrystalline cellulose and cross linked PVP**

❑ The binding action is more effective when the binder is in a solution form than if it was dispersed in a dry form and moisten with the solvent.


Types of binders
sugars
Polymeric materials
Natural polymers
Starches, gums and gelatin
Synthetic polymers
Methyl, ethyl, hydroxypropyl cellulose and pvp.

- Different used binders

Name	Conc. used	Solvent
1. Starch	5-10%	Aqueous paste
2. Pregelatinized starch	5-10%	Added dry to powder
3. Gelatin	2-10%	Aqueous solution
4. Polyvinyl pyrrolidon	5-10%	Aqueous alcoholic solution
5. Methyl cellulose	2-10%	Aqueous solution
6. Sod. carboxy methyl cellulose	2-10%	Aqueous solution
7. Ethyl cellulose	5-10%	Alcohol or hydro alcoholic solution
8. Poly Vinyl alcohol	5-10%	Aqueous solution

Different Ways to add a Binder:

1. ***Solution binder***

- As a dry powder which is mixed with the other ingredients before wet granulation.
- **Mechanism of action:** During the granulation procedure the binder dissolves partly or completely in the liquid; as a solution which is used during wet agglomeration.

2. ***Dry binder***

As a dry powder which is mixed with other ingredients before compaction.

Both binders are included in the formulation at low concentrations, 2 – 10 %.

N.B. The use of excessive binder → will make a hard tablet that will not disintegrate easily when the tablet meets moisture and will also cause excessive wear of punches and dies.

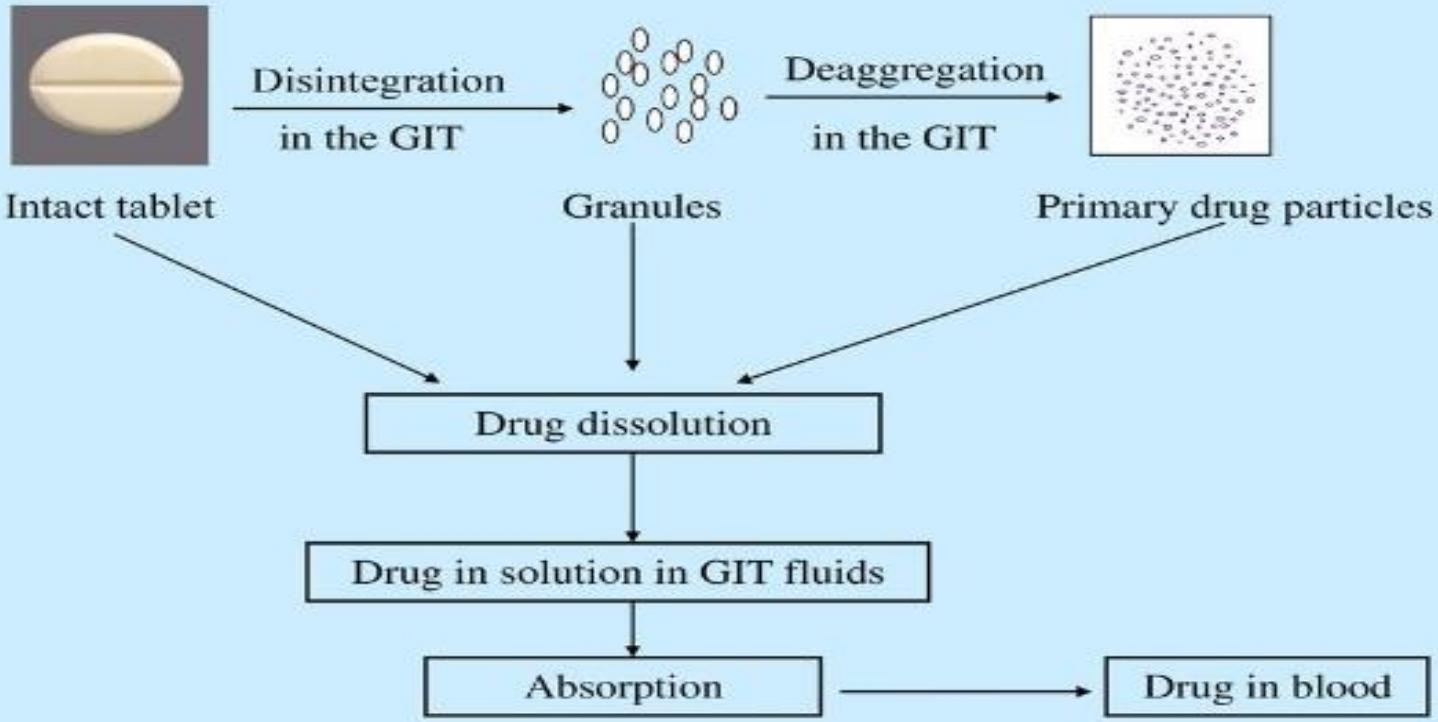
3- Disintegrants

- They are employed to overcome the cohesive strength imparted during compression → facilitate the breakdown of the tablet granules upon entry into the stomach.
- The disintegrant is essential in hydrophobic tablets with high compression force to enable disintegration within the pharmacopeia standards (15 minutes for conventional tablets)

Tablet disintegration

3- Disintegrants

Tablet disintegration may be critical to subsequent drug dissolution rate and to satisfactory bioavailability



3- Disintegrants

Mechanisms of disintegration:

1. Swelling:

- Croscarmellose sodium, swell in contact with gastric fluids and exert sufficient mechanical pressure within the tablet, the adhesiveness of other ingredients in a tablet is overcome → causing the tablet to break apart into small segments and thus hasten the absorption by increasing surface area of particles.

3- Disintegrants

Mechanisms of disintegration:

2. **Porosity and Capillary Action (Wicking):**

- Disintegrants may increasing the porosity and wettability of the compressed tablet matrix → provides pathways for the penetration of fluid into tablets → Liquid is drawn up into these pathways through capillary action and rupture the inter-particulate bonds causing the tablet to break apart.

- These disintegrants are mainly hydrophilic polymers.
- Examples: The most traditional disintegrant in conventional tablet is Starch (10%)
- Super-disintegrants (1.5 %); e.g. Sodium Starch Glycolate that swells 7-12 fold in less than 30 sec. e.g. Croscaramelose that swells 4-8 fold in less than 10 sec

3- Disintegrants

Notes

- Disintegrants may be added intra- or, extra-granularly or both (which may be varied to achieve the best result).
- It does not always mean that the higher the concentration of disintegrants the faster the rate of disintegration.
- The concentration may have a direct relationship with the rate of disintegration until it gets to maximum after which disintegration rate decreases with increase in concentration of disintegrants.

4- Glidants

- Like lubricants, they act to enhance the flow properties of tablet granules or powders within the hopper by reducing friction between particles → is due to the ability of glidants particles to locate within the spaces between the powder particles/ granules.
- To achieve this effect the Glidants must be small in particle size and to be arranged on the surface of the granules.
- Their concentration must not exceed the recommended as it is hydrophobic & may affect the disintegration of the tablet and the dissolution of the drug.
- Examples:

1. Traditional glidant is Talc (0.5- 3 % w/w)
2. most common glidant today is Colloidal silicon dioxide (0.1 - 0.5 % w/w)

5- Lubricants

- Lubricants reduce the friction occurs between the walls of the tablets and the walls of the die cavity and punches during compression facilitate the ejection of the tablets from the die cavity.
- Insufficient lubricant will lead to tablet, with a pitted محفور surface
- where high conc. of lubricant → will lead to reduced disintegration and dissolution.
- In addition, the time of mixing of lubricant with granules as well as the particle size of the lubricant will affect the performance of the lubricant. → Over mixing may adversely affect tablet disintegration & drug dissolution.
- Lubricants should be added after disintegrants to avoid coating it or preferably at the final stage prior to compression to ensure mixing time is kept to a minimum

5- Lubricants

- Mixing of disintegrant & insoluble lubricant together should be avoided for this should form a film of lubricant on the disintegrant surface which reduce wettability of disintegrant
- There are 2 main categories of lubricants:

1- Insoluble lubricants:

- They are added to the final mixing stage before tablet compression.
- The efficacy of lubricant is enhanced if its area is increased (decrease the particle size).
- Examples of insoluble lubricant material:
  1. Magnesium stearate (0.25 - 0.5 % w/w)
  2. Stearic acid (1 – 3 % w/w)

5- Lubricants

2- Soluble lubricants:

- They are used to overcome the bad effects of insoluble lubricant on the tablet disintegration & drug dissolution, although the effect of insoluble lubricant is superior than the soluble lubricants. Examples:
- 1. PEG 4000, 6000 or 8000 grades.
- 2. Sodium lauryl sulfate 1- 2 % w/w.

6- Miscellaneous excipients

(1) Adsorbents

- They are included to be adsorbed a liquid or semisolid component (e.g., flavour) when incorporated within the tablet formulation.
- Examples: Magnesium oxide or carbonate and kaolin or bentonite.

(2) Sweetening agent / flavors

- They are incorporated to control the taste and tablet acceptability especially chewable tablets if the components have disagreeable taste.

6- Miscellaneous excipients

(3) Colors

- They are used to improve the tablet appearance or to identify the finished product.
- The color must be distributed well throughout the tablet by adding a water soluble color to the granulation liquid in wet granulation method.

(4) Surface active agents

- They are added to improve the wetting properties of hydrophobic tablets → increasing the rate of tablet disintegration.
- Also they are added to increase the solubility of poorly soluble drug in G.I.T hence increasing the rate of tablet dissolution e.g: Sodium lauryl sulfate.

Methods used for the manufacture of tablets

- Tablets are commonly manufactured by one of the following processes:

I. Wet granulation: wet method (Discuss In Granulation)

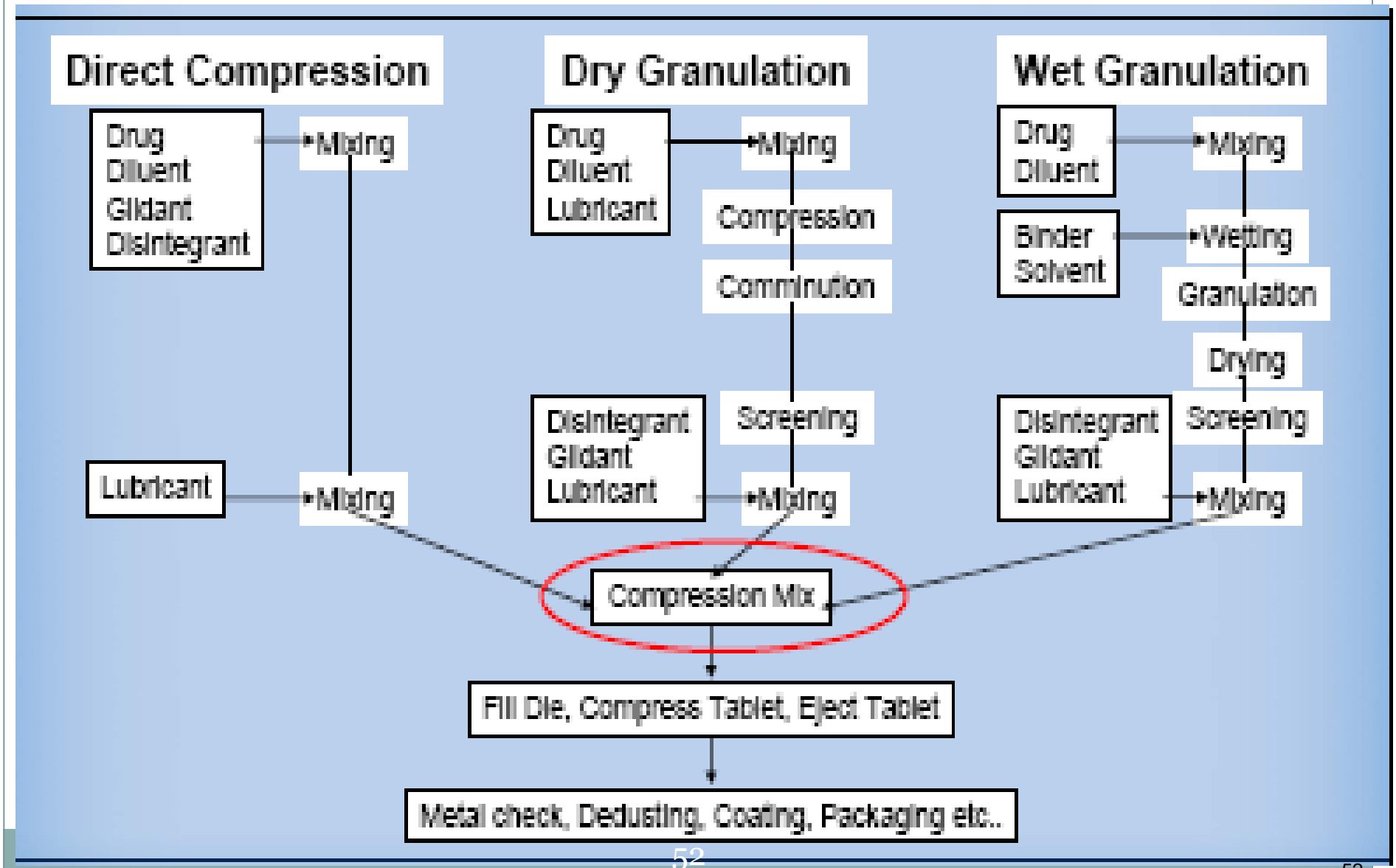
II. Dry granulation or slugging or roller compaction (Discuss In Granulation)

III. Direct compression

- The choice of manufacture method is dependent on these factors:

1. **Physical and chemical stability of the drug during manufacturing.**
2. **The availability of the necessary processing equipment.**
3. **The cost of manufacturing process.**
4. **The excipients used to formulate the product.**

Tableting methods



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Granulation

What is the granulation?

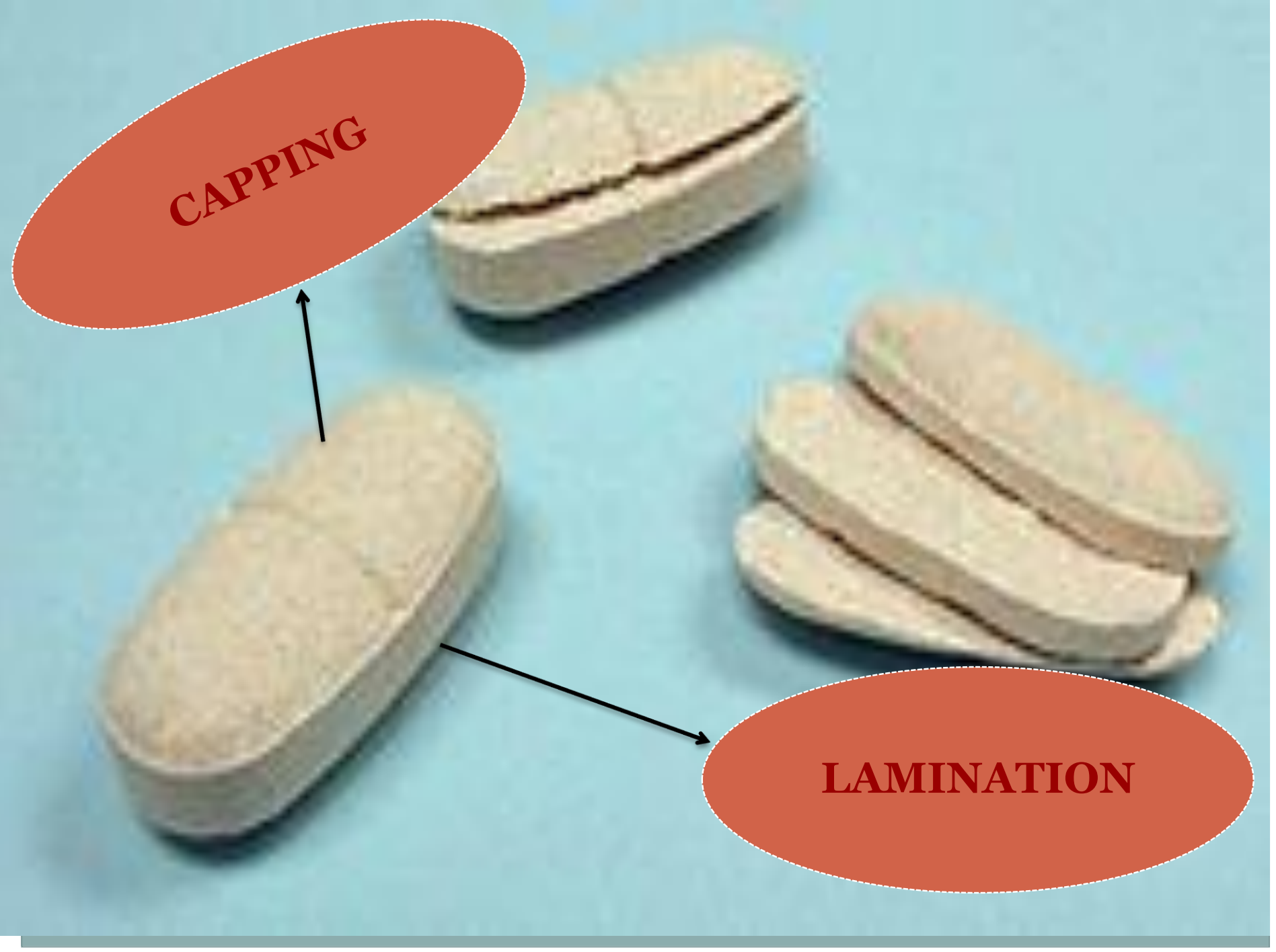
- It is defined as a size enlargement process whereby small primary powder particles are made to adhere to form larger, multiparticle entities called granules.

Why we prepare granules when we have powders….?

1. Powder not flow well in the hopper of the tablet machine.
2. Powder do not flow uniformly in the die, which leading to variation in tablet weight.
3. Air trapped in the powder, which causes lamination or capping of tablet when the pressure is released

CAPPING: It is partial or complete separation of the top or bottom of tablet.

LAMINATION: It is separation of tablet into two or more layers.


CAPPING
LAMINATION

Reasons for granulation

1. To prevent segregation of the constituents of the powder mix
2. To improve the flow properties of the mix
3. To improve the compaction characteristics of the mix
4. Other reasons

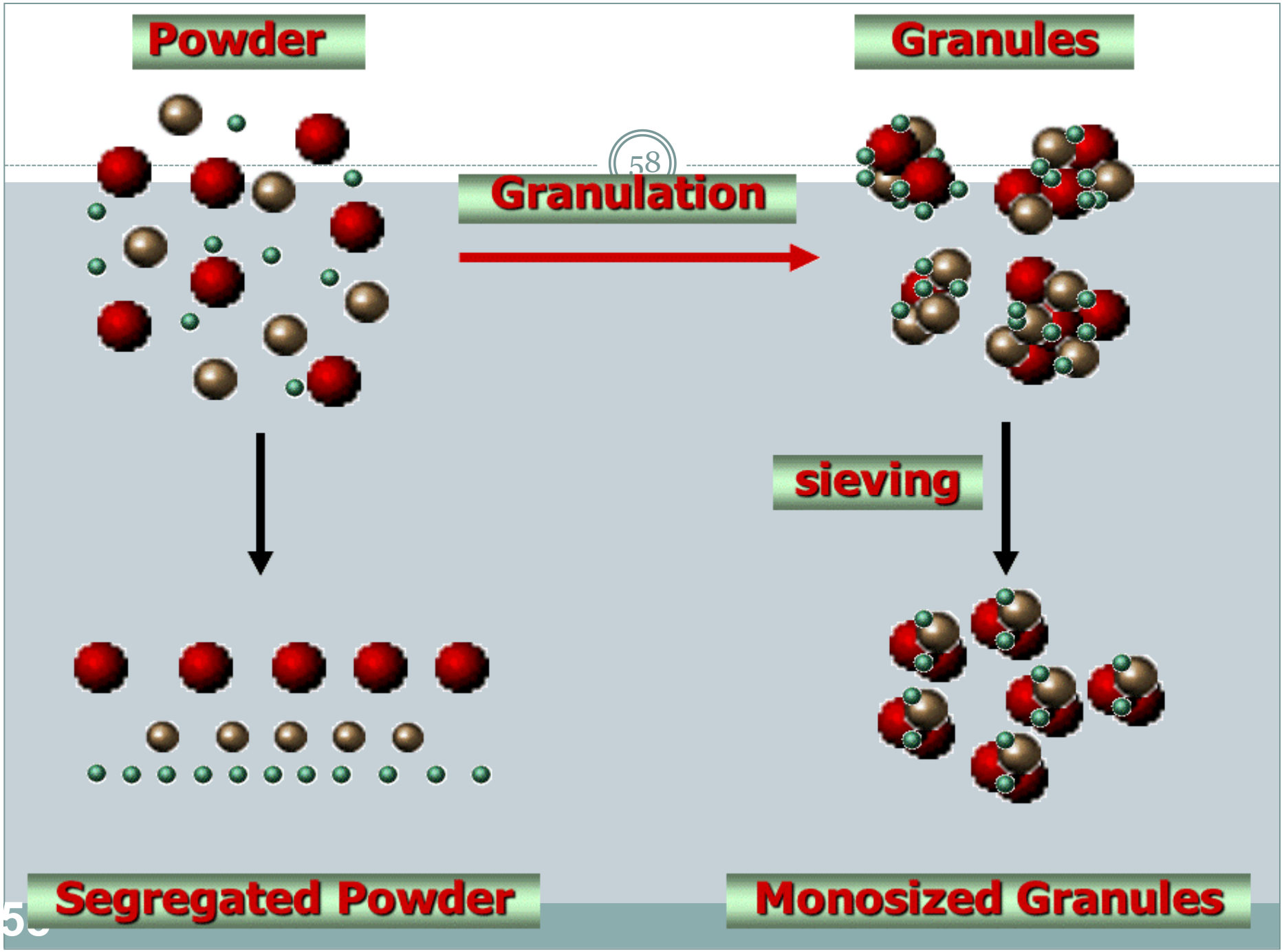
- Reduce the hazard of toxic dust powders (dust free formulations).
- Reduced caking and lump formation
- More convenient for storage.

Reasons for granulation

1. To prevent segregation of the constituents of the powder mix

A. **Segregation is due primarily to differences in the size or density of the components of the mix,**

- **The smaller and/or denser particles concentrating at the base of a container, while the larger and/or less dense ones above them.**
- **An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur (Fig. 1).**


Powder
Granules
Granulation
sieving
Segregated Powder
Monosized Granules

Reasons for granulation

B. Control the particle size distribution of the granules because if there is a wide size distribution the granules themselves may segregate.

If this occurs in the hoppers of sachet filling machines, capsule filling machines or tablet machines, products with large weight variations will result. This will lead to an unacceptable distribution of the drug content within the batch of finished product.

Reasons for granulation

2. To improve the flow properties of the mix

- Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well.
- Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc.

⟶ Granules produced from such a cohesive system will be larger and more iso-diametric, both factors contributing to improved flow properties.

Reasons for granulation

3. To improve the compaction characteristics of the mix

- Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets. This is associated with the distribution of the adhesive within the granule.

Other Reasons for granulation

i. **Reduce the hazard of toxic dust powders.**

- The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders.

ii. **Reduced caking and lump formation, as in the granulation of fertilizers.**

- Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

iii. **More convenient for storage.**

- Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of granulation

Granulation methods can be divided into two types:

1. **Wet methods, which use a liquid in the process, and**
2. **Dry methods in which no liquid is used.**

Dry Granulation

- Dry granulation converts primary powder particles into granules using the application of pressure without the intermediate use of a liquid.
- It therefore avoids heat-temperature combinations that might cause degradation of the product.

Two pieces of equipment are necessary for dry granulation:

- first, a machine for light compressing the dry powders blend into compacts or flakes, under low pressures
- secondly a mill for breaking up these intermediate products into granules.

Steps in Dry Granulation

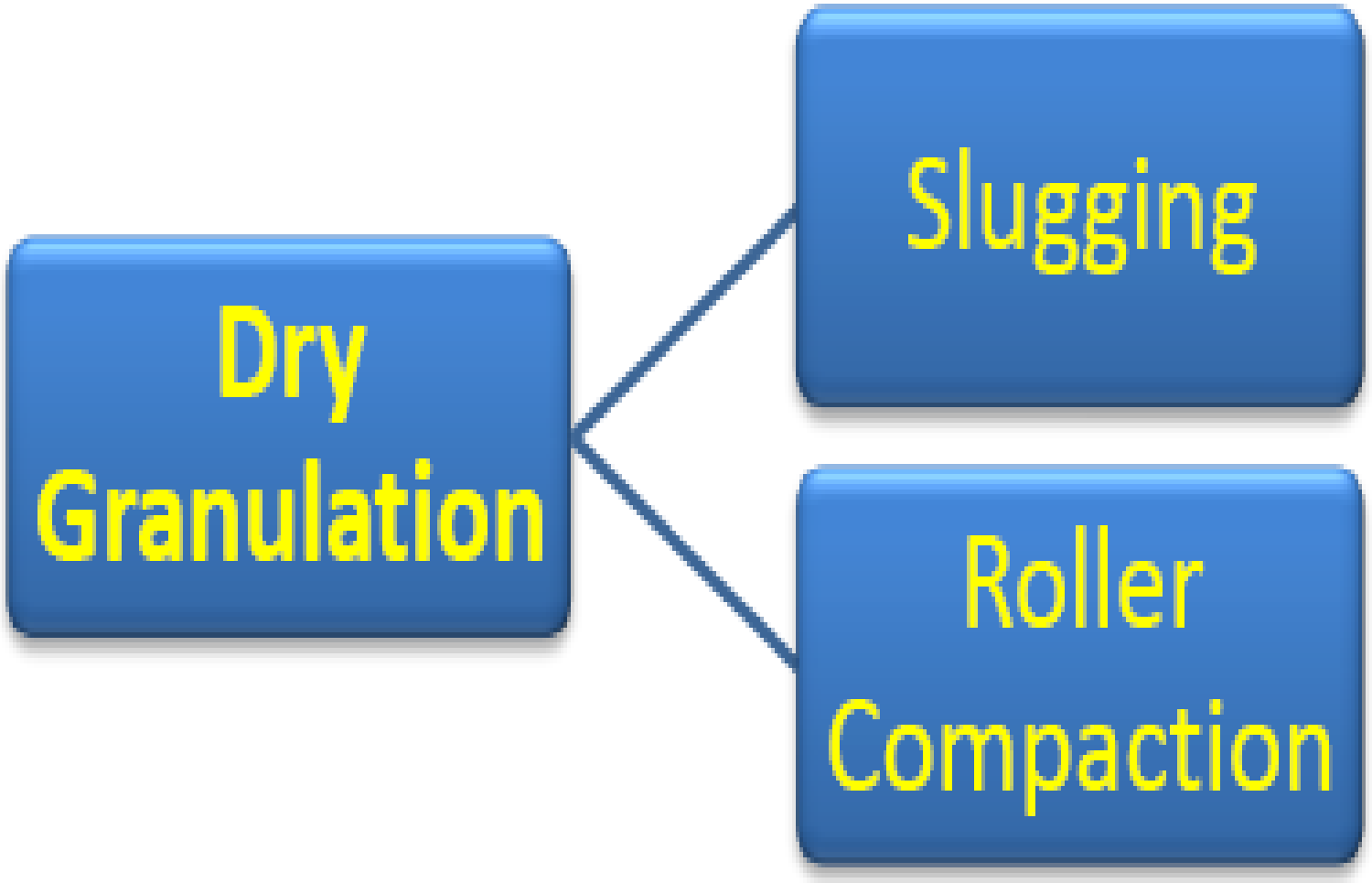
Compaction of powder

Milling

Screening

When To Choose DRY method?

- **Drug dose is too high.**
- **Do not compress well after wet granulation as calcium lactate**
- **Heat sensitive drugs.**
- **Moisture sensitive drugs.** **e.g. Aspirin , Vitamins**
- **For improved disintegration since powder particles are not bonded together by a binder.**


Dry Granulation
Slugging
Roller Compaction

Dry granulation

- In the dry methods of granulation, the primary powder particles are aggregated under high pressure.
- There are two main processes.

1. Either a large tablet (known as a *'slug')* is produced in a heavy-duty tabletting press (a process known as *'slugging')* or
2. The powder is squeezed between two rollers to produce a sheet of material *('roller compaction').*

- In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction.
- The unused fine material may be reworked to avoid waste.

1. Sluggers

Steps in dry granulation (Slugging) :

1. Compression of finely divided dry powders into large, hard tablets (slugs) using a conventional tablet machine or, more usually into the dies of a large capacity tablet press and compacting by means of flat faced punches.
2. Screening of slugs, a hammer mill is suitable for breaking the compacts.

- Slugs is typically 25 mm diameter by about 10-15 mm thick.
- The slugging process is still used today by only a few manufacturing firms that have old pharmaceutical formulation processes.

Disadvantage:

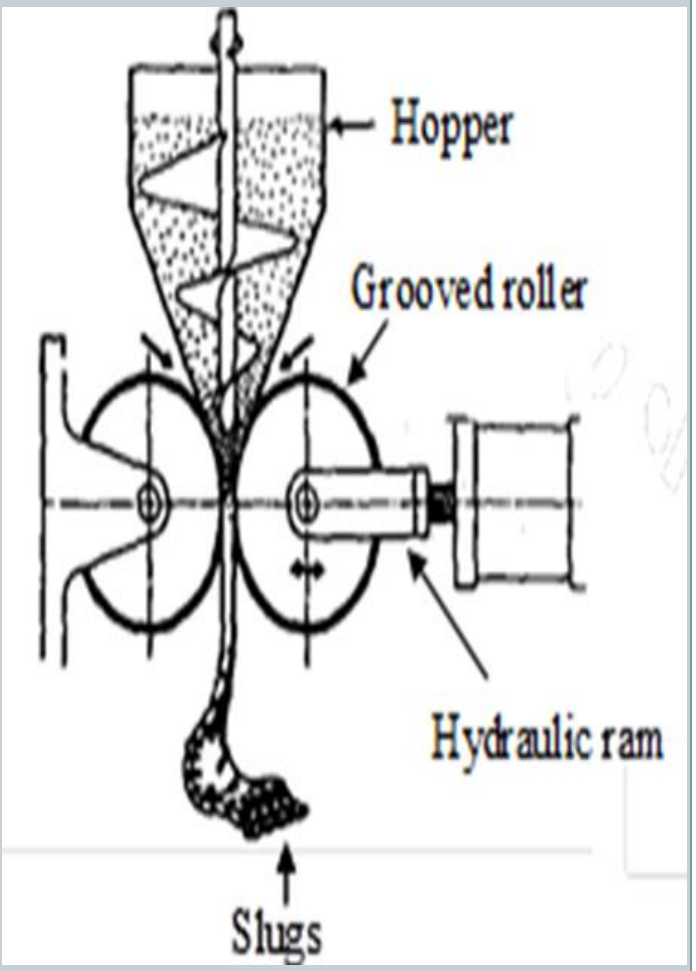
This method cause weight variation from one tablet (slug) to another due to a small particle size do not flow well into the die of a tablet pres

1. Sluggers

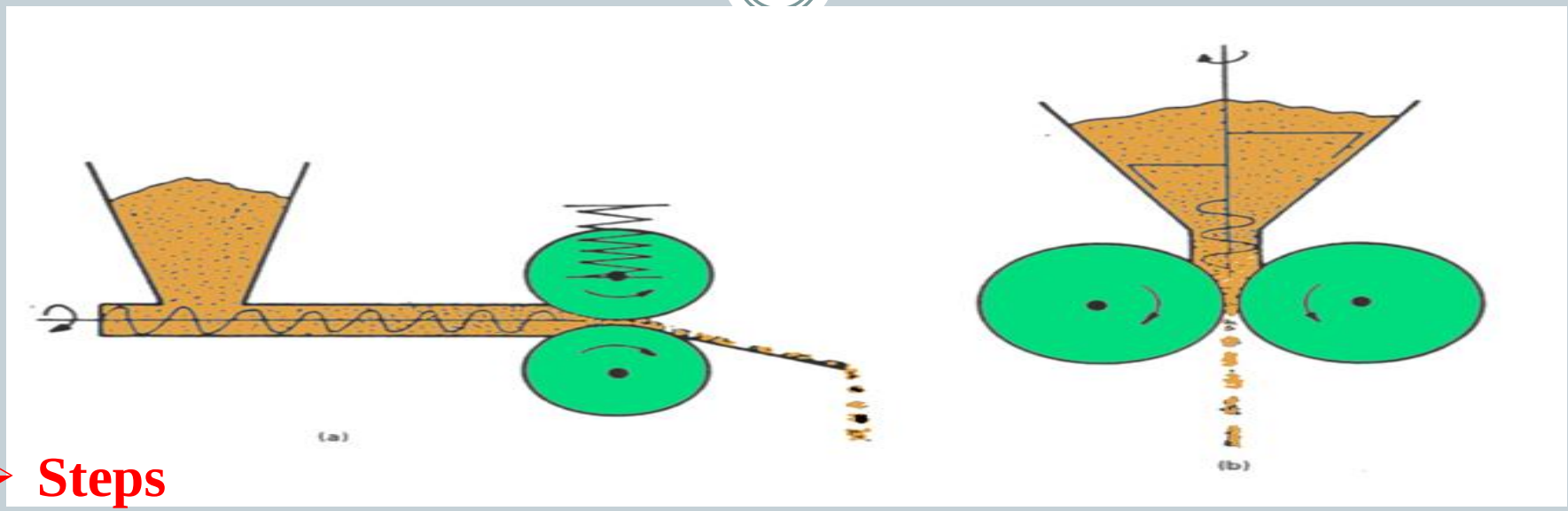
- These are heavy-duty tablet presses that are fitted with punches and dies of about 1 inch in diameter.
- Pressures up to 20.000 p.s.i. can be exerted.

2. Roller Compaction (Chilsonator)

- Roller compaction is an alternative gentler method, well suited for dry granulation in the area of modern development of active pharmaceutical ingredients
- The powder mix being squeezed between two rollers to form a compressed sheet (Fig. 2).
- The sheet normally is weak and brittle and breaks immediately into flakes.
- These flakes need gentler treatment to break them into granules, and this can usually be achieved by screening alone.
- It used for material that normally require slugging two or more times, so it can be granulated by passing single time through ***"chilsonator"***.



2. Roller Compaction (Chilsonator)



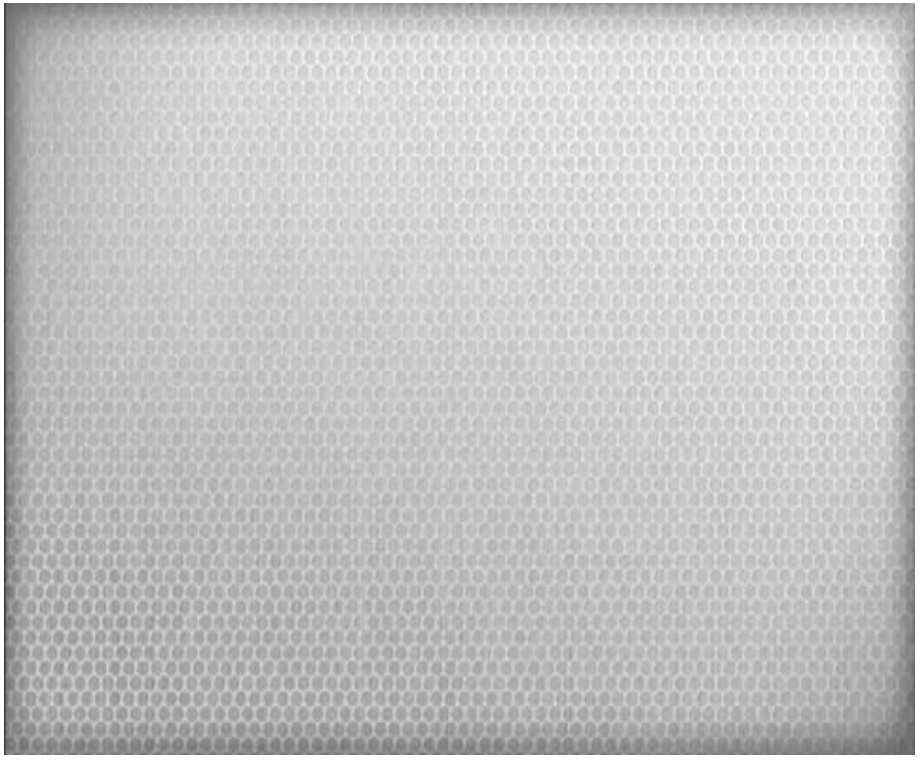
➢ **Steps**

1. **A feeding system**, powders are fed from a hopper *which contains a spiral screw*, → conveys the powder to the compaction area between the 2 rotating rollers.
2. **A compaction unit**, where powder is compacted between two rotating rolls to a ribbon by applying a force at a controlled rate and pressure regulate by hydraulic means.
3. **A size reduction unit**, the product obtained in the form of compressed sheets, which can be broken up in to granules of the desired particle size.

2. Roller Compaction (Chilsonator)

Notes:

- *The pressure between the rolls is regulated by hydraulic means.*
- *The screw serve to maintain a constant flow of the powder into the compaction rolls.*



2. Roller Compaction (Chilsonator)

Advantages chilsonator over slug processing

1. Increased production capacity
2. Greater control of compaction pressure, and
3. No need for lubrication of the powder.

Advantage and Disadvantage of Dry granulation

Advantages

- We used conventional grades of excipients.
- Less equipment & space
- Eliminate need of binder solution, heat or heavy mixing equipment and time consuming drying step required for wet granulation

Disadvantages

- *It requires a specialized heavy duty tablet press to form slug.*
- No uniform color distribution
- 2. Segregation may occur post mixing.
- The final tablet produced by dry granulation tends to be softer than these of wet granulation rendering them difficult for further process such as coating.
- Process create more dust, *increasing the potential contamination*

2. Wet Granulation

1. The granulating fluid contains a solvent which must be
- volatile so that it can be removed by drying, and be
- non-toxic.
- Typical liquids include water, ethanol and isopropanol, either alone or in combination.

2. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry.

- Natural Polymers: Starch, Pregelatinized Starch.
- synthetic binders: PVP, MC, HPMC, Maltrodextrin

Water is commonly used for economical and ecological reasons.

Disadvantages of water as a solvent are:

A. It may adversely affect drug stability, causing hydrolysis of susceptible products, and

B. It needs a longer drying time than do organic solvents.

This increases the length of the process and again may affect stability because of the extended exposure to heat

Advantage of water:

- It is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment are not needed.
- Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.
- In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried.

I. Wet granulation

- **Important steps involved in the wet granulation**

1. The active ingredient and excipients are weighed and mixed.
2. The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly
3. Screening the damp mass through a mesh to form pellets or granules
4. Drying the granules through conventional tray-dryer or fluid-bed dryer.
5. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size

Important steps involved in the wet granulation

Step 1

- Mixing the therapeutic agent with the powdered excipients (without lubricant)
- Using a mixer for a sufficient specified time and speed till become homogenous.

Step 2

- Wet granulation of the powder mix to make homogenous granules (0.2 - 4 mm diameter)

Important steps involved in the wet granulation

- ***Description of wet granulation***

1. To achieve cohesion between powders: we use a binder within the formulation either in the solid state within the powder mix or dissolved in the binding fluid (water, isopropanol or ethanol) the wetted mass is then passed into an oscillating granulator which forces the wet mass through a metal screen under the action of an oscillatory stress.

Important steps involved in the wet granulation

2. Achieving wet granulation using high speed mixer/ granulator:

- This is more recent as in this machine single operation is employed. e.g: high shear (speed) mixer

3. Using fluidized bed drier for granulation and drying. This system of operation includes 3 steps in one operation.

  - Mixing of powder ,
  - Spraying the binder solution within mixing ,
  - Applying hot air (controlled temperature) → the solvent will evaporate and the formed granules will be dried.

Important steps involved in the wet granulation

- ***Advantages of granulation step in tablet manufacture***

1. Prevention of segregation of powder component during manufacture process.
2. Enhancement of the flow properties from the tablet hopper to tablet dies in the machine to prevent the variability in tablet weight.
3. Enhancement of the compaction properties due to the presence of binder on the surface of granules leading to greater intergranule adhesive interactions.
4. Lower incidence of dust production.

Important steps involved in the wet granulation

Step 3

- Drying of the granules:

  The produced wet granules are dried in the shelf or tray drier which is similar to the design of conventional oven.

Step 4

- Milling of the granules: reduction of the granule size to:

  a) Controlling the particle size to improve the flow of granules into the tablet die and the fill of granules within the die.

  b)The choice of the granule size is determined by the size of the die & hence the final tablet size.

- The reduction of the granule size is performed by using:

  1. Oscillating granulator 2. Using Quadro-Co mill.

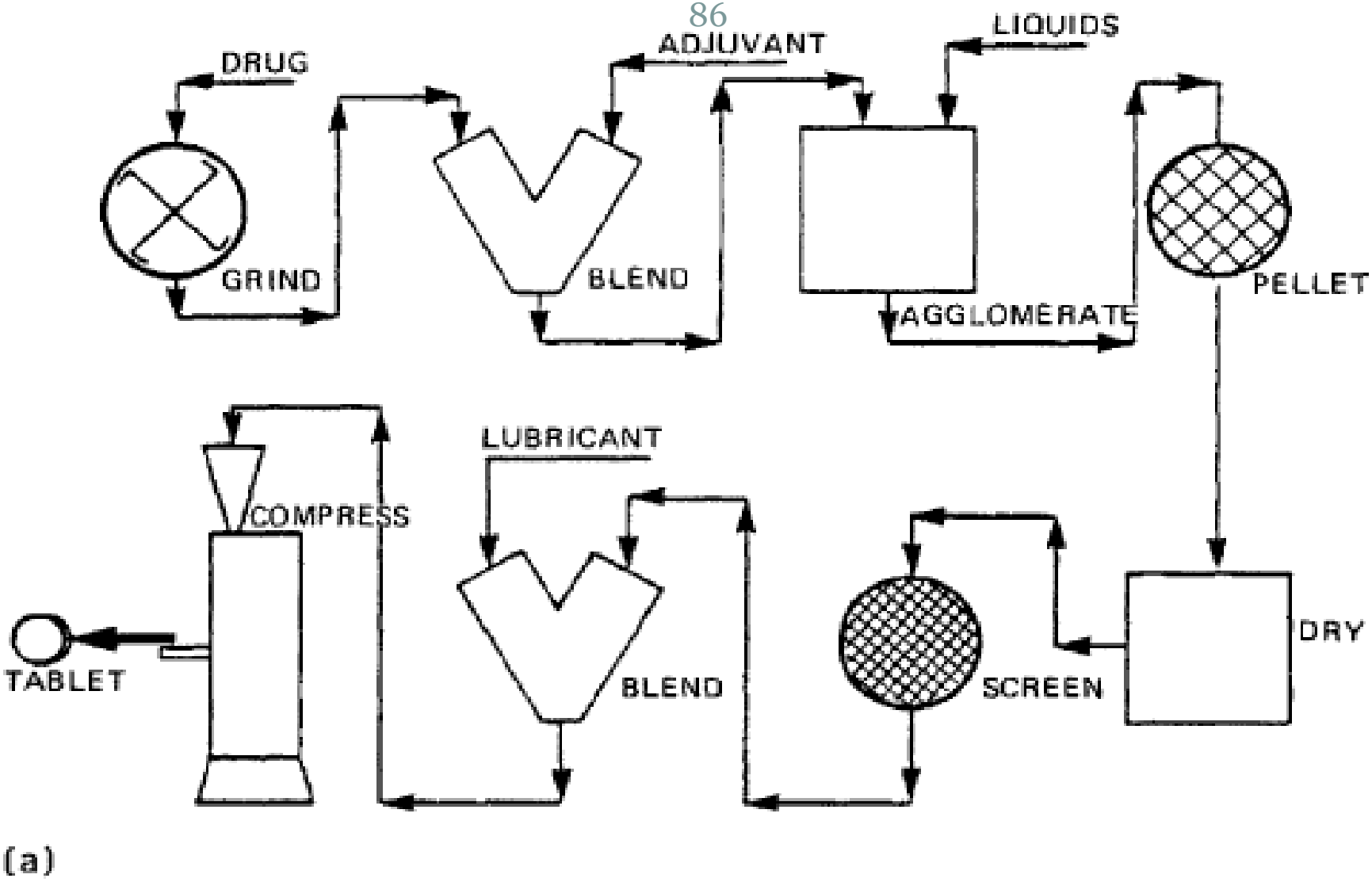
Important steps involved in the wet granulation

Step 5

- Mixing of granules with lubricant:

  Mix the dried and milled granules with the specified quantity of the lubricant before feeding to the tablet press hopper.

Wet granulation



Advantages and disadvantages of wet granulation method

- **Advantages:**

1. Reduced segregation of the component during processing.
2. Useful technique for the manufacture of tablets containing low concentration of therapeutic agents.
3. Employs conventional excipients i.e.not dependent on special excipients such as direct compression method.

Disadvantages:

1. Several proceeding steps are required increase the time , loss of material and effort.
2. It is not used with heat and/or moisture – sensitive material.
3. Solvents are required in this process; this may lead to different problems such as:

a. Drug degradation may occur in the presence of the solvent.

b. Drug may be soluble in the granulation fluid.

c. Heat is required to remove the solvent; → this could result degradation of the thermally labile therapeutic agents.

Disadvantages:

4. Cost is high because of long procedures and use number of expensive equipments.
5. It requires a large area with temperature and humidity control as it require many steps.

Compressed tablet manufacture

➢ Tablet manufacturing methods

Granulation

- **Wet granulation**: suitable for drugs that are stable to moisture and heat
- **Dry granulation**: suitable for drugs that are sensitive to moisture and heat

Direct compression

- **Powder compression** : suitable for drugs that are sensitive to moisture and heat, fill material possessing good flowability and compressibility
- **Crystal compression**： suitable for drugs with proper crystal form and good flowability

➢ Classification of tablet machine

- **Tablet machine:**

  a. single-punch Tablet machine

  b. multi-station rotary presses (rotary tablet)

1. single-punch tablet machine

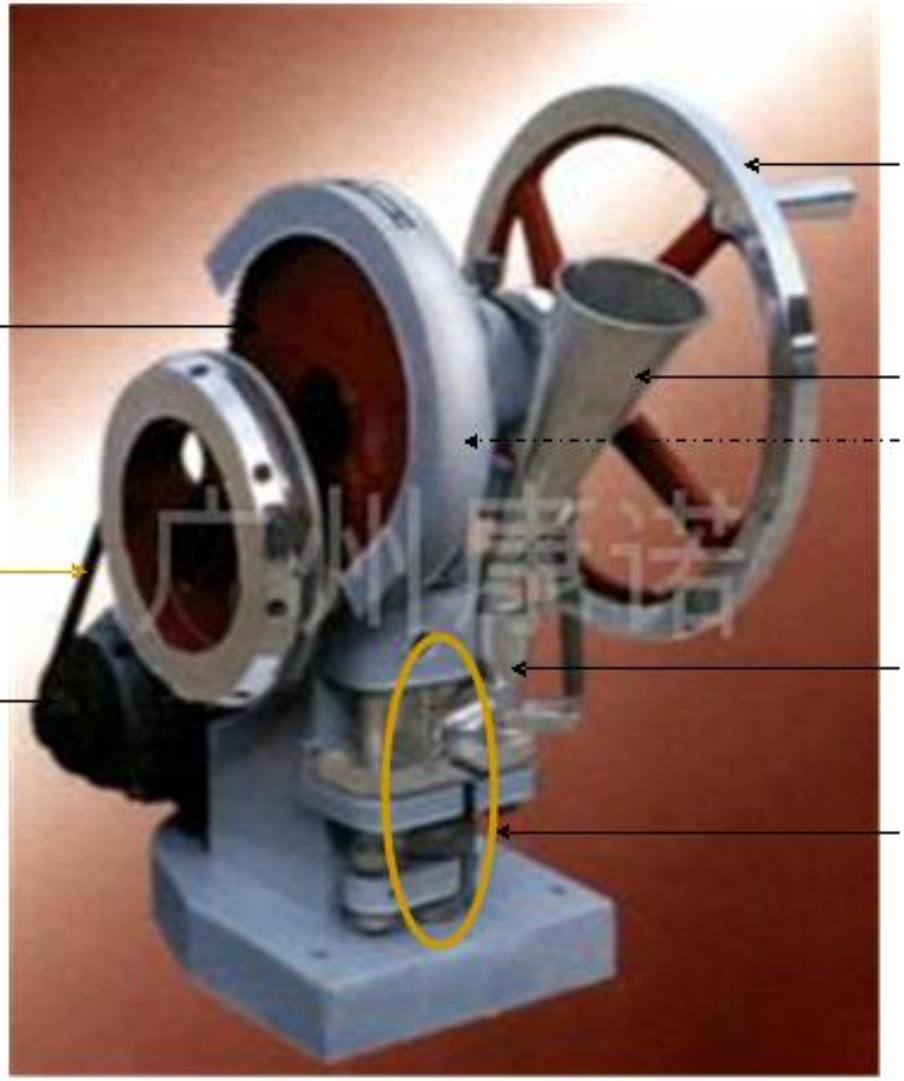
✓ **The basic mechanical parts of single-punch tablet machine:**

1. Stationary Die fitted with upper and lower punch.
   - Upper punch is out of the die, while the lower punch is at the lowest position of die.
2. Movable feed hopper
3. Feed shoe connected to the movable hopper

Main part and it is function

1	**Die**	The die cavity is where the powder granules are compressed into tablet by allowing the lower and upper punch to come close together to compress the material. The die determines; 1. The diameter of the tablet 2. The size and shape of the tablet 3. To some extent the thickness of the tablet.
2	**Upper punch**	Form the upper surface of the tablet
3	**Lower punch**	Form the lower surface of the tablet It control the weight of tablet by controlling the size of the die cavity
4	**Feed shoe**	Connect the hopper to the die
5	**Hopper**	This is connected to the feed shoe and it is used to hold the materials (drug or the drug with excipients/ granules) to be compressed and supply the material to the die and removes the tablet after its compression. It can be filled manually or by using mechanical equipment during subsequent tableting.

1. single-punch tablet machine



Single-punch tablet press

❑ The Compression cycle of a single Punch tablet machine

Filing

Position 1 – The upper punch is raised and lower punch drops to create a cavity in the die.
Position 2 – Feed shoe moves over the die cavity and granules fall into the die cavity under the influence of gravity from the hopper.

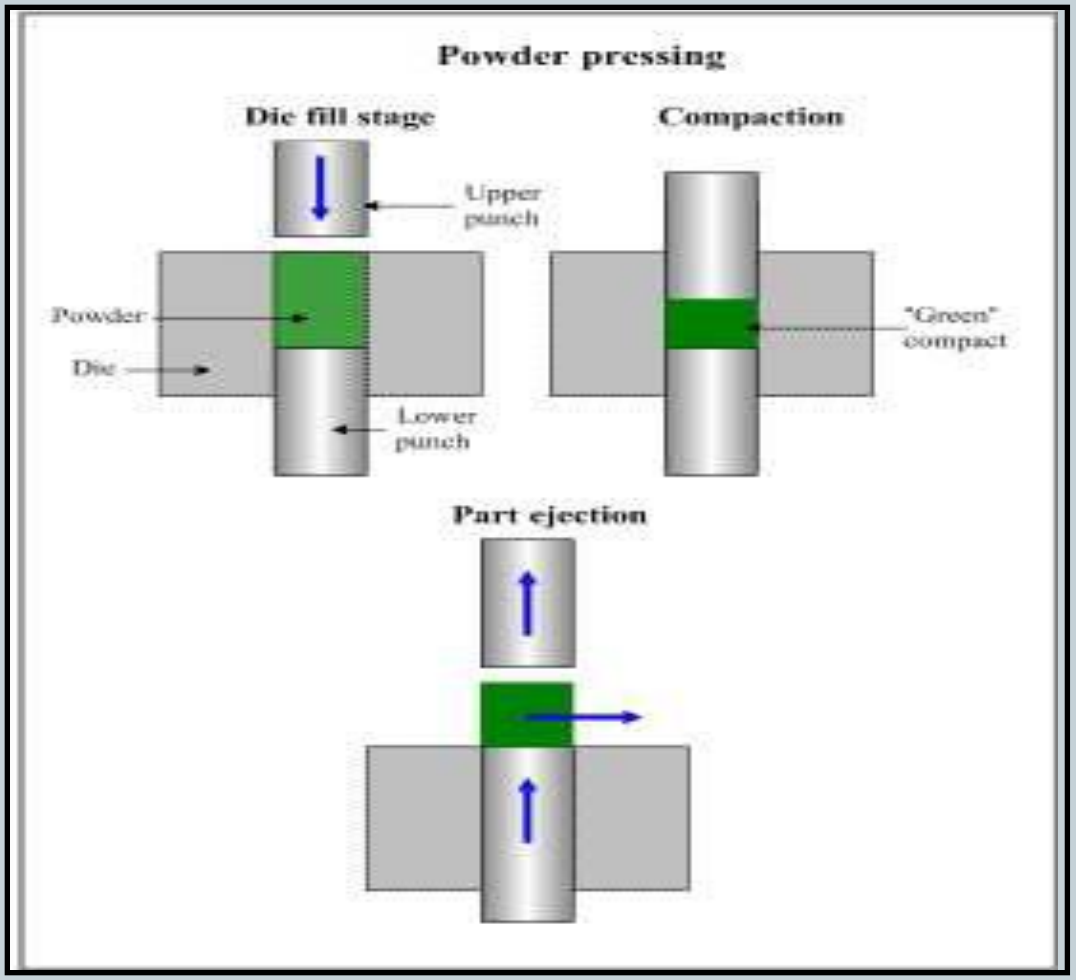
Compression

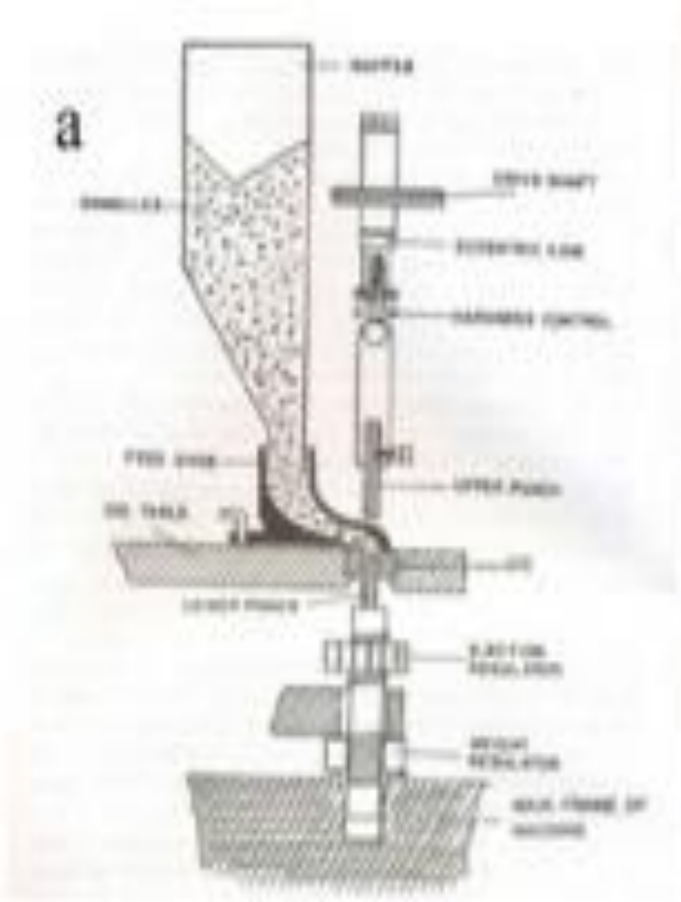
Position 3 – Feed shoe moves out of the way and the upper punch descends to compress the granules/powder mixture into tablets by progressive reduction of the porosity of the die content and forcing of the particles into close contact with one another.

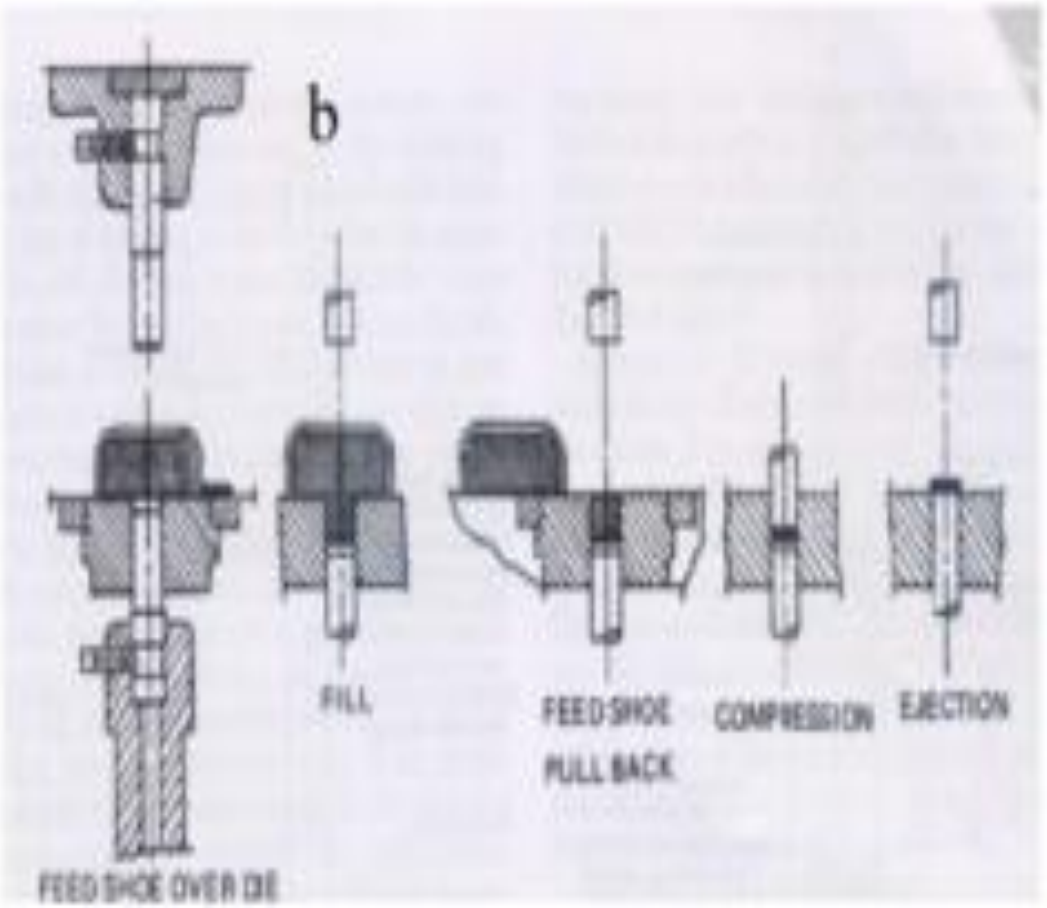
Ejection

Position 4 – The upper punch retracts and the lower punch moves upwards too to form the lower surface of the tablet then the feed shoe eject the compressed tablet. The whole events repeat over and over again unit the feed material is exhausted.

Stages of tablet formation







- The high to which the lower punch rises is adjustable because of:
- ✓ If too low ----------> the feed shoe would split or cap the tablet during ejection.
- ✓ If too high ----------> feed shoe strike the lower punch with mutual damage

❑ Advantages of Single Punch Tablet Press

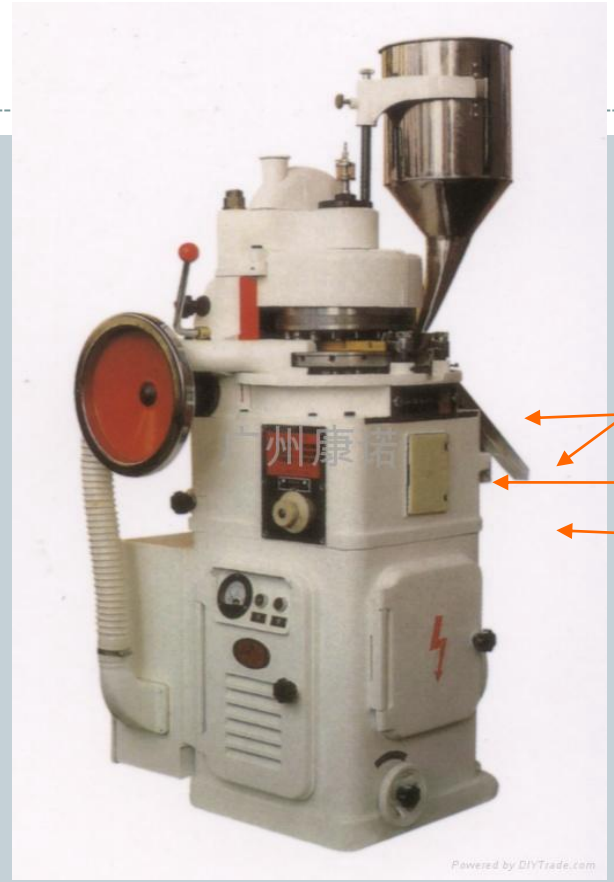
1. The single punch structure is rational and small.
2. Easy to operate and it operates at a high utilization ratio.
3. The compression time is very short.
4. It can manufacture odd shaped products with a diameter of up to 20 mm.
5. It is ideal for development of tablets and small batch production (100 tab/ min).
6. Single punch tablet press utilizes a high amount of pressure to reduce weight variations between tablets while maintaining a low noise level at the same time.

2. Rotary tablet machine

- Rotary tablet machine (Multi-station press) is a mechanical device that unlike the single punch tablet press has movable die and stationary feed hopper
- Multi-station press are also referred to as rotary tablet press because it is about circular rotating head carrying an :

- the upper punches in the upper part
- The dies (≥ 60 dies) in central part with the feed frame placed over it.
- The lower punches in lower part.

- Rotary press employs the principle of compression.
- This tableting machine was developed to increase the output of tablets (up to 10000 tablet / minute).



hopper

feed-frame

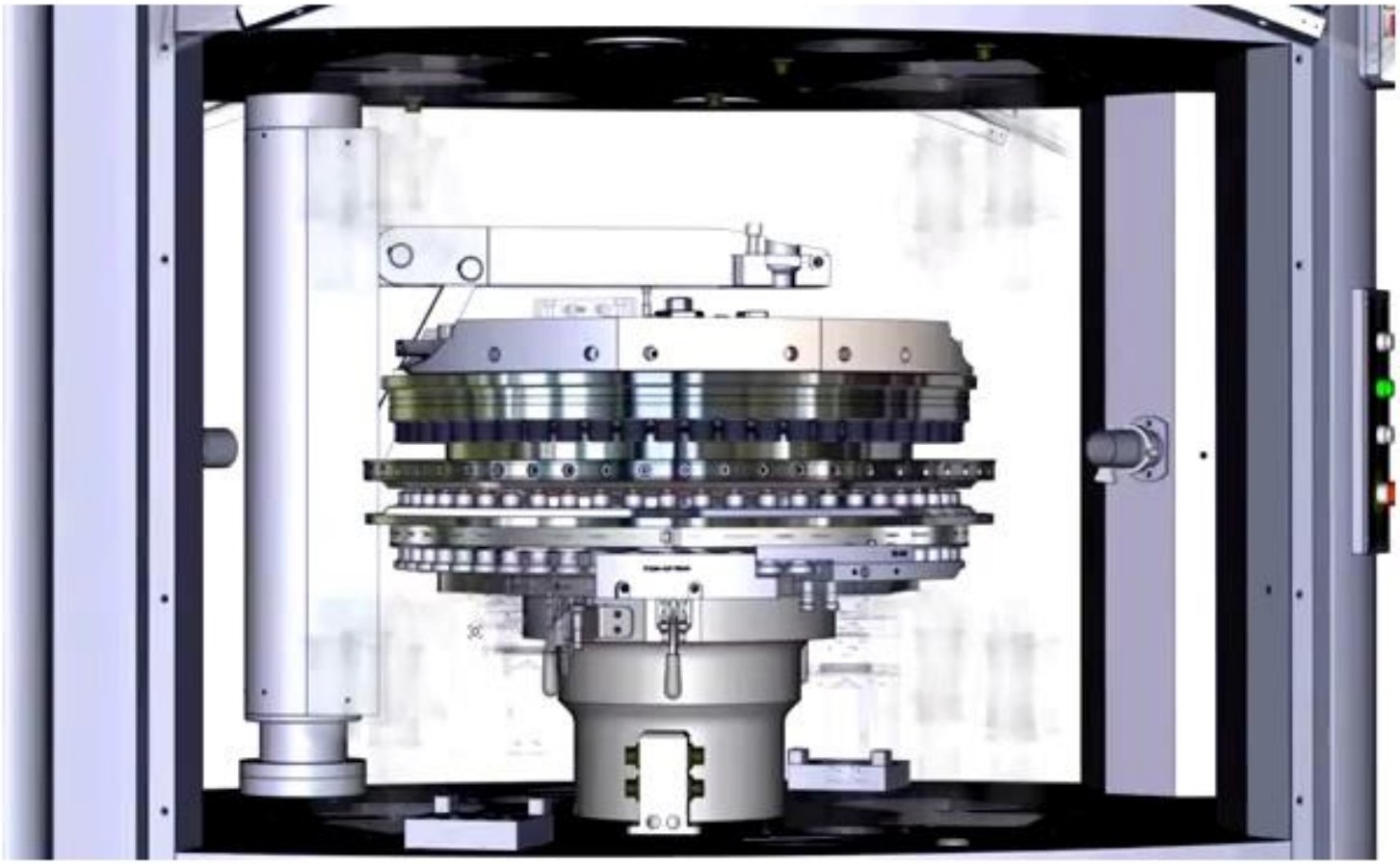
head: upper turret, lower turret, die table

upper turret

die table

lower turret

MULTI-STATION TABLET PRESS



❑ The Compression cycle of a rotary tablet machine

Filing

- The head revolve, the die come under the feed frame and filed with granules.

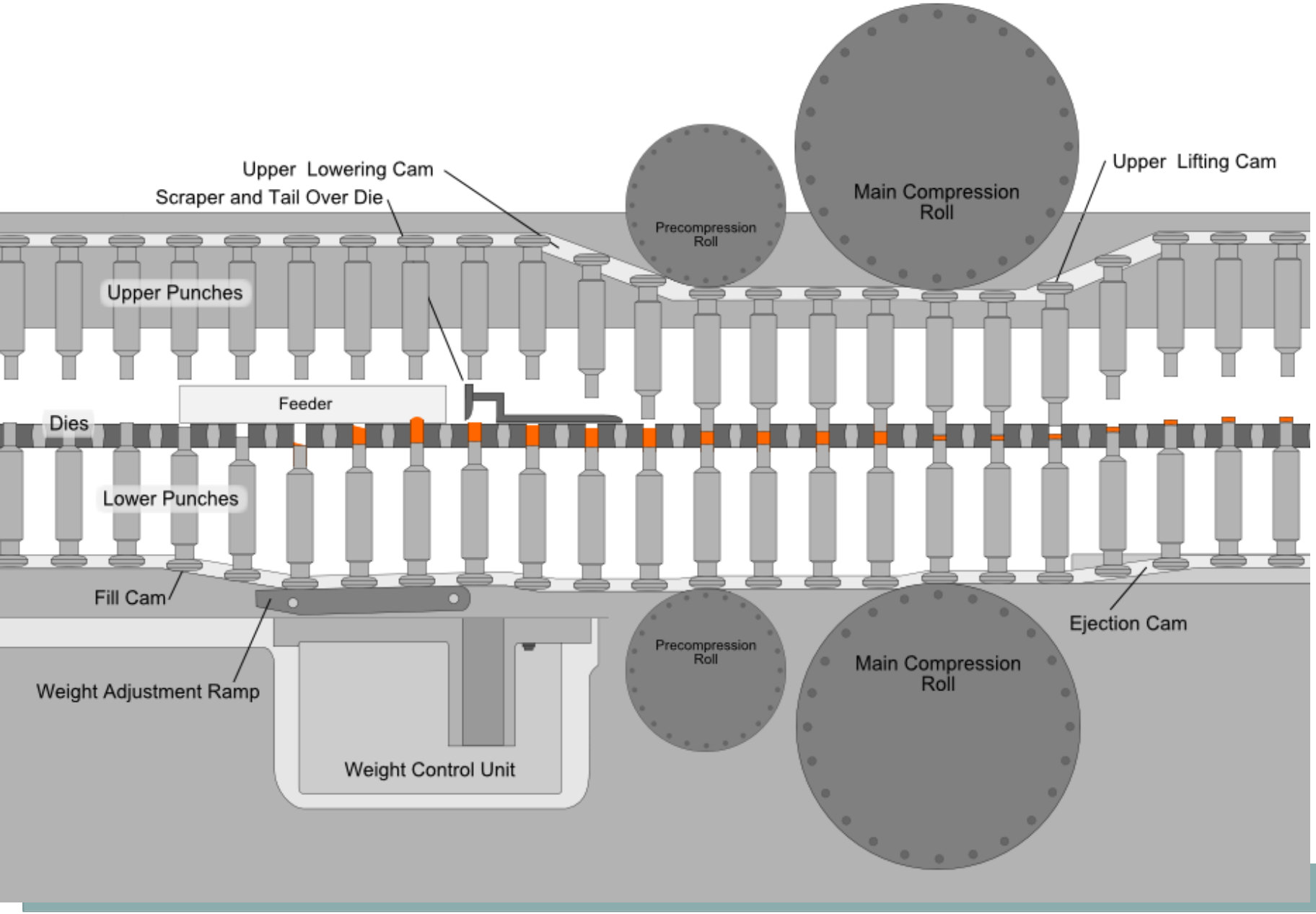
Compression

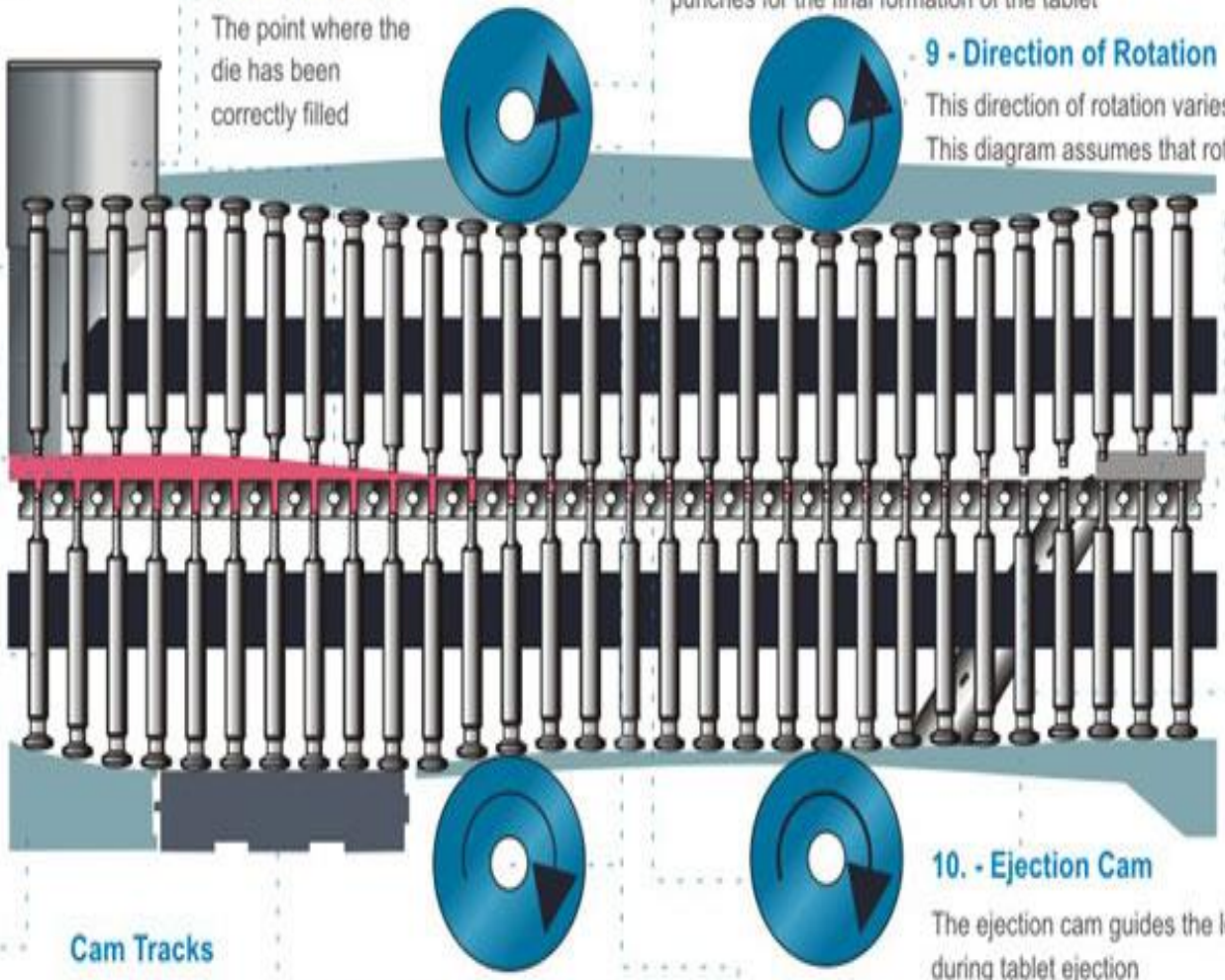
- The upper and lower punch pass between rollers and compress the granules as follow:
  - The upper punch is in raised position and lower punch drop to the lowest position
  - The upper punch descend to enter the die cavity and lower punch pass between roller then compress the tablet.

Ejection

- The upper punch to it is raised position and lower punch rises to completely eject the compressed tablet. The whole events repeat over and over again unit the feed material is exhausted.

Rotary tablet press





1. Hopper

Contains the granules that are to be compresses into tablets

Upper Punch

The upper punch moves vertically in and out of the die bore

2 - Feeder Housing

Hopper feeds material into the rotating die via the feeder housing

3 - Feed Paddles

Helps force feed the granules into dies especially during faster rotation

Lower Punch

The lower punch remains within the bore of the die during the entire cycle

4 - Lower Cam Track

The lower cam track guides the lower punch during the filling stage so that the die bore is over filled to allow accurate adjustment

Cam Tracks

These lift and lower both upper and lower punches as

6 - Fill Station

The point where the die has been correctly filled

8 - Main Compression Rollers

This rollers apply compression force to the punches for the final formation of the tablet

9 - Direction of Rotation

This direction of rotation varies from machine to machine
This diagram assumes that rotation is from left to right

11. Take - off Blade

Fitted in front of the feeder housing this deflects the tablet down the discharge chute

Die

Punch move within the die bore to compress the granules into tablets

12 - Discharge Chute

The Chute which the tablet passes through for collection

10. - Ejection Cam

The ejection cam guides the lower punch upwards during tablet ejection

5 - Depth of Fill (Weight Control)

The lower punch track during the later part of the fill stage, adjustable to ensure that as the punch rises the correct quantity of granule, remains within the die, and therefore the tablet weight is correct

7 - Pre - Compression Rollers

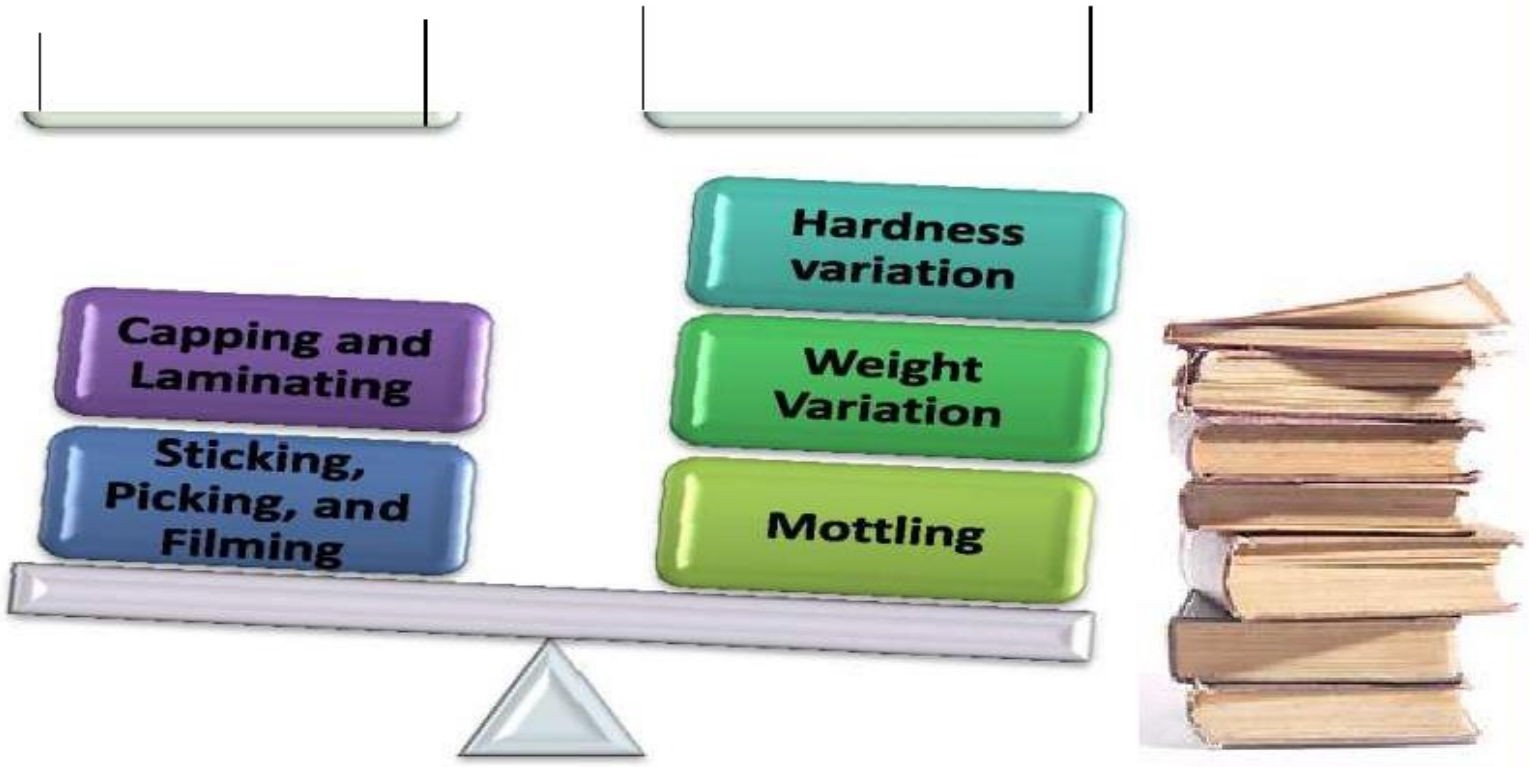
This roller gives the granule an initial compression force to remove excess air that might be entraped

❑ Advantages of Rotary Tablet machine

1. High productivity can be gained with a minimal number of labor while saving money.
2. Rotary press has an output of between 9000 – 234000 tab/hour thus saves time and meets up with the high demand of tablet dosage form.
3. The powder filled cavity can be automatically managed by a moving feeder.
4. Rotary press decreases waste of valuable formulation in non-specific tablets.
5. The machine allows independent control of both weight and hardness.

Quality Control Tests of pharmaceutical dosage forms

Manufacturing problems



1. Binding:

- **It is the adhesion of the granules to the die wall** and this cause the resistance of the tablet to eject from the die,
- it is usually due to **insufficient lubrication**, which produce tablets with rough and vertical score marks on the edges.

- **Solution:**

1. Increasing ***lubrication***.
2. Improve ***lubricant distribution***.
3. Increasing **the *moisture content*** of the granulation.

2. Sticking, Picking & Filming:

Adhesion of the material to the punch faces.

❑ Sticking : (whole adhesion)

- Is usually due to improperly (incorrectly) dried or lubricated granulation causing the whole tablet surface to stick to the punch faces → **dull, scratched, or rough tablet faces**.

❑ Picking : (localized adhesion)

- Is a form of sticking in which a small portion of granulation sticks to the punch face & a portion of the tablet surface is missed.

2. Sticking, Picking & Filming:

- **Filming:** is a slow form of sticking and is largely due to excess moisture in the granulation, high humidity, high temperature, or loss of highly polished punch faces due to wear.

These may be overcome by:

1. Decreasing the moisture content of the granulation.
2. Polishing the punch faces.
3. Cleaning and coating the punch faces with light mineral oil

3. Capping & Laminating:

- These two defects occur during the ejection stage of the manufacturing process.
- **Capping** occurs when the upper segment of the tablet separates from the main portion of the tablet & comes off as a cap.
- It is usually due to air entrapped in the granulation that is compressed in the die during the compression & then expands when the pressure is released.

- **Reasons of capping :**

1. large amount of fines in the granulation &/or the lack of sufficient clearance between the punch and the die wall.
2. In new punches and dies that are tight fitting.
3. Too much or too little lubricant or excessive moisture

3. Capping & Laminating:

- **Lamination** is due to the same causes as capping except that the tablet splits at the sides into two or more parts.
- If tablets laminate only at certain stations, the tooling is usually the cause.

Solutions for capping & laminating:

1. Increasing the binder.
2. Adding dry binder such as gum acacia, PVP or powdered sugar.
3. Decreasing or changing lubrication.
4. Decreasing the upper punch diameter

4. Mottling:

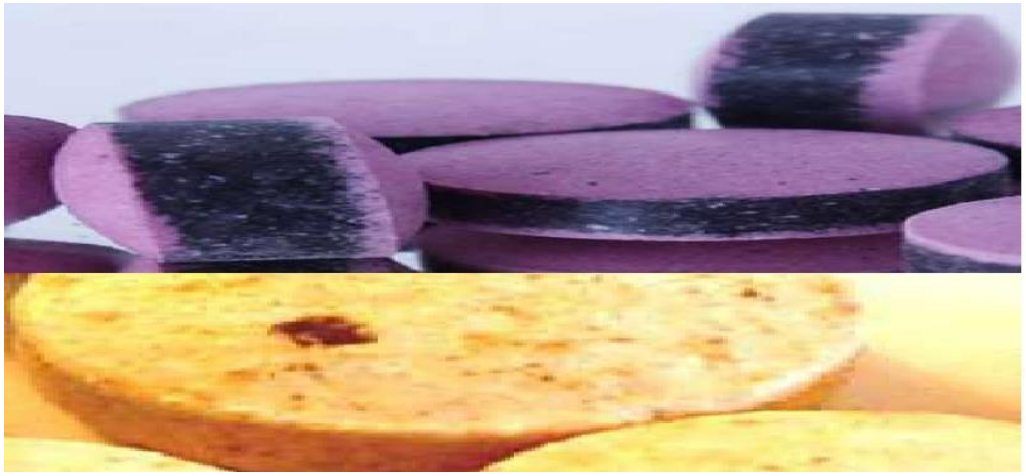
- It is an unequal distribution of color on the surface of the tablet with light or dark areas standing out in an otherwise uniform surface.

- **Reasons of Mottling :**

1. A drug is differs in color from its excipients or whose degradation products are highly colored.
2. Migration of a dye during drying of a granulation.

To overcome this difficulty,

- The formulator may change the solvent system, reduce the drying temperature, or grind to a smaller particle size.



5. Chipping and Cracking:

- **Chipping:** Breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

- **Reasons of Chipping**

1. Incorrect machine settings, specially mis-set ejection take-off.

2. These problems are similar to those of capping and laminating, and are annoying and time consuming.

- **Cracked** tablets are usually cracked in the upper and lower central surface of the tablets or very rarely on the side wall.
- different from capping.


Cracking

Causes:

- It often occurs where deep concave punches are used.
- Large size of granules
- Too dry granules
- - tablets expanding

Solutions for Chipping & Cracked :

1. Polishing punch faces.
2. Replacing nicked or chipped punches.
3. Reducing fines.
4. Adding dry binder such as pregelatinized starch, gum acacia, PVP,

Tablets evaluation

Evaluation of tablets includes:

1- General appearance
2- Weight variation
3- Friability
4- Disintegration test
5- Dissolution rate
6- Hardness
7- Content uniformity
8- Thickness

1- General appearance

Size, shape, and thickness:

This is important to facilitate packaging and to decide which tablet compressing machine to use.

-Organoleptic properties:

which include color, taste and odor of the tablets

2. Weight variation

- To ensure that the tablet formulation is uniform in weight.
- Weight variation test is applicable when the tablets containing **50 mg or more** of drug substance or when the drug substance represents **50% or more** (by weight) of the dosage form unit.

1. Twenty tablets are dusted and weighed.
2. The average weight (Mean) is calculated **(X)**.
3. Each tablet is then weighed individually .
4. Calculate the % of deviation for each tablet according to the Formula.

- % Deviation = [(weight of tablet – mean) / mean] X 100

Weight variation:

- According to USP, B.P The batch accepted when :

- **Not more than 2 tablets** are permitted to deviate from the average weight by greater than the permissible deviation listed.
- **No tablet** is permitted to deviate from the average weight by more than double deviation

Notes :

- The test not carried out for coated tablets due to the content of coating materials are not calculated.
- The test indicates the uniformity of drug content if the drug content is more than 50 mg

USP 32

Average weight mg	% Deviation
120 mg or less	± 10
>120 mg to < 300 mg	± 7.5
300 mg or more	± 5

B.P

Average weight mg	% Deviation
130 mg or less	± 10
>130 mg to < 324 mg	± 7.5
324 mg or more	± 5

- *Limit:*
- Upper limit = average weight + (average weight * %error)
- Lower limit = average weight - (average weight * %error)
- The individual weights are compared with the upper and lower limits.

>>Not more than two of the tablets differ from the average weight by more than the % error listed, and no tablet differs by more than double that percentage.

Tablets that are coated are exempt from these requirements but must conform to the test for content uniformity if it is applicable.

Problem 1

Solve the following

- The tablet below provides the weight of each of 20 tablets sampled during drug production for in-process weight variation test (tablet specified weight is 300 mg). Guided by the USP, state whether this given batch will be accepted or rejected.
- Justify your answer.

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	286	305	311	300	307	290	310	314	311	304
Tablet	11	12	13	14	15	16	17	18	19	20
Weight (mg)	301	299	309	289	295	301	287	313	291	307

Solution

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	286	305	311	300	307	290	310	314	311	304
Tablet	11	12	13	14	15	16	17	18	19	20
Weight (mg)	301	299	309	289	295	301	287	313	291	307

Average weight	Percentage of deviation	Lower limit of deviation	Upper limit of deviation
300 mg	5 %	285	315

Double limit of deviation	Double lower limit of deviation	Double upper limit of deviation
10%	270	330

No. of tablets within limit	No. of tablets without limit	Approval of batch
20	0	Accepted

Problem 2

- Solve the following
- The table below provides the weight of each of 20 ibuprofen tablets sampled during drug production for in-process weight variation test (tablet specified weight is 200 mg). Guided by the USP, state whether this given batch will be accepted or rejected.
- Justify your answer.

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	187	204	255	200	200	190	210	215	190	204
Tablet	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Weight (mg)	201	198	189	202	197	201	199	213	191	208

Solution

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	187	204	255	200	200	190	210	215	190	204
Tablet	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Weight (mg)	201	198	189	202	197	201	199	213	191	208

Average weight	Percentage of deviation	Lower limit of deviation	Upper limit of deviation
200 mg	**7.5 %**	**185**	**215**

Double limit of deviation	Double lower limit of deviation	Double upper limit of deviation
15%	**170**	**230**

No. of tablets within limit	No. of tablets without limit	Approval of batch
19	**1(no.3 without double limit of deviation)**	**Rejected**

Problem 3

- Solve the following

The table below provides the weight of each of 20 tablets sampled during drug production for in-process weight variation test (tablet specified weight is 90 mg). Guided by the USP, state whether this given batch will be accepted or rejected.

Justify your answer.

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	93	105	83	92	89	93	89	94	97	87
Tablet	11	12	13	14	15	16	17	18	19	20
Weight (mg)	96	98	99	84	81	83	90	92	88	94

Solution

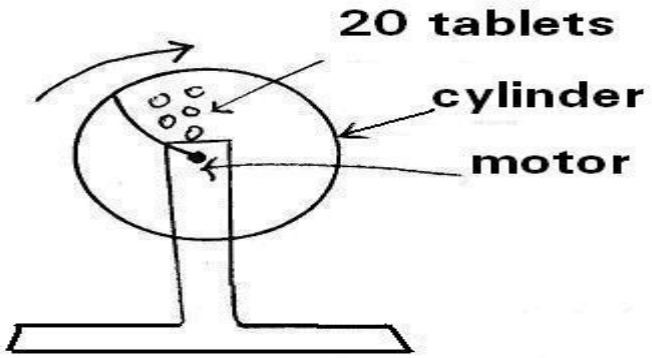
Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)	93	105	83	92	89	93	89	94	97	87
Tablet	11	12	13	14	15	16	17	18	19	20
Weight (mg)	96	98	99	84	81	83	90	92	88	94

Double limit of deviation	Double lower limit of deviation	Double upper limit of deviation
20%	72	108

No. of tablets within limit	No. of tablets without limit	Approval of batch
19	1(no.2)	Accepted

4. Tablet friability (official in USP)

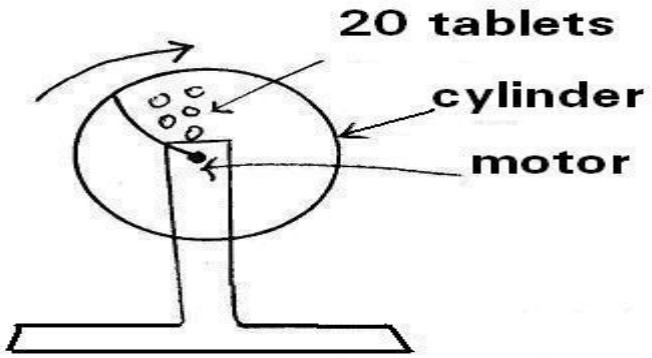
- To determine the ability of the tablets to withstand abrasion during packaging, handling and shipping.
- Friability is a property related to the hardness of the tablet.
- Ten tablets are dusted, weighed then placed in the drum of the friabilator which is allowed to rotate for 4 minutes or for 100 revolutions.
- During each revolution, the tablets fall from a distance of 6 inches to undergo repeated shocks.
- The tablets are then re-dusted and re-weighed (only the intact ones) .



Roche Friabilator

$$\%\ Friability = \frac{Initial\ weight - Final\ weight\ after\ rotation\ 4\text{min.}}{Initial\ weight} \times 100$$

- Friability (% loss) =It must be less than or equal to1% but
- Some chewable tablets and most effervescent tablets are highly friable and require special unit packaging.



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FTV2 - Tablet Friability Tester.FLV

The % loss in weight is calculated to indicate the friability. According to USP, The weight loss should not be more than 0.8%

Roche Friabilator

4- Disintegration test

- It is the time required for the tablet to break into particles, the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will **pass** through **10 mesh screen**.

Generally the disintegration time is as follow:

1. For uncoated tablets is 30 minutes.
2. For coated tablets is 1 hour.
3. For soluble tablets and effervescent tablets should disintegrate within 3 minutes.
4. Enteric-coated tablet should not disintegrate in simulated gastric fluid (2 hour), but should disintegrate in simulated intestinal fluid in 2 hours.
5. Chewable tablets are not subjected to the disintegration test.

4- Disintegration test

- Consists of a **rack holding 6 glass or plastic tubes** each having a **10-mesh screen** at its bottom.

- The tubes are raised and lowered at a fixed rate (30 cycle/ min.) in the fluid maintained at **37 ± 2°C (body temp) by a water bath.**

- **Six tablets** are placed one in each tube along with a **plastic disk** over each tablet (to prevent tablet floating and impart a slight pressure on the tablet to force any soft mass through the screen).

Liquids used in disintegration

- Water,
- simulated gastric fluid (PH = 1.2 HCl),
- or Simulated intestinal fluid

Six tubes opened at the upper end and closed by a screen at the lower

Disintegration test

Automatic High-End Tablet Disintegration Tester -.FLV

disintegrator.avi

5- Dissolution rate

- Dissolution is the process by which a solid enters a solution .
- **The dissolution rate** is defined as **the amount of drug substance that goes into solution per time** under standardized conditions of liquid / solid interface, temperature, and solvent composition .
- Dissolution is one of most important **quality control tests** and consider as tool for **predicating bioavailability** , in some cases, replacing clinical studies to determine bioequivalence.
- In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred as in vitro- in vivo correlation, IVIVC.

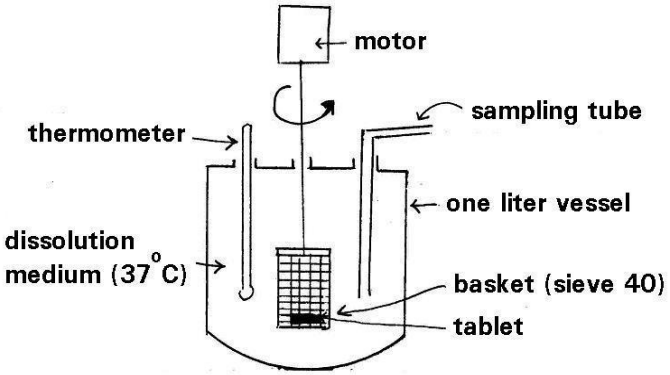
5- Dissolution rate

The batch will be accepted if not less than 70% of the labeled drug content of each tablet from 6 tablets tested have released (dissolved) within 45 minutes.

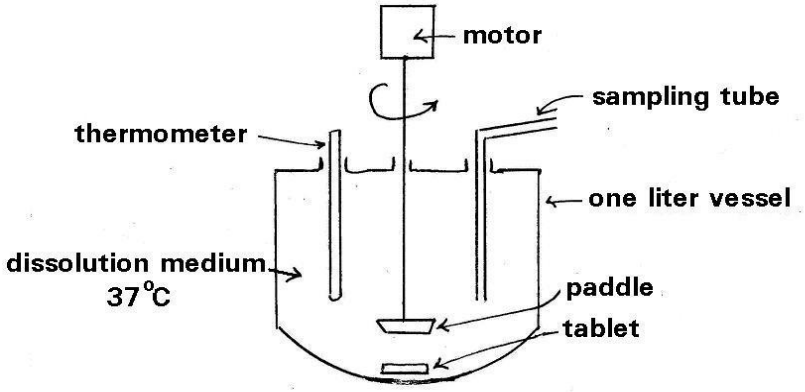
- If 1 or 2 tablets fail the test, 6 more tablets are tested. At least 10 of the 12 tablets must meet the requirements.

-The dissolution results are plotted as concentration versus time.

6. Dissolution test



"Dissolution apparatus"
"Apparaus1"
"Rotating basket apparatus"



"Dissolution apparatus"
"apparatus 2"
"rotating paddle apparatus"

dissolution 2 (paddle).mp4

Automated Dissolution Basket Test - YouTube.FLV

6- Hardness

- Tablet hardness, or tablet crushing strength is the force required to break a tablet. Hardness of 4-6 Kg is considered satisfactory to the tablet.

<u>To change Newton (force) to kilogram (mass), use the following equation:</u>

1 Newton = 1 kilogram X 9.8 meter second^{-2}

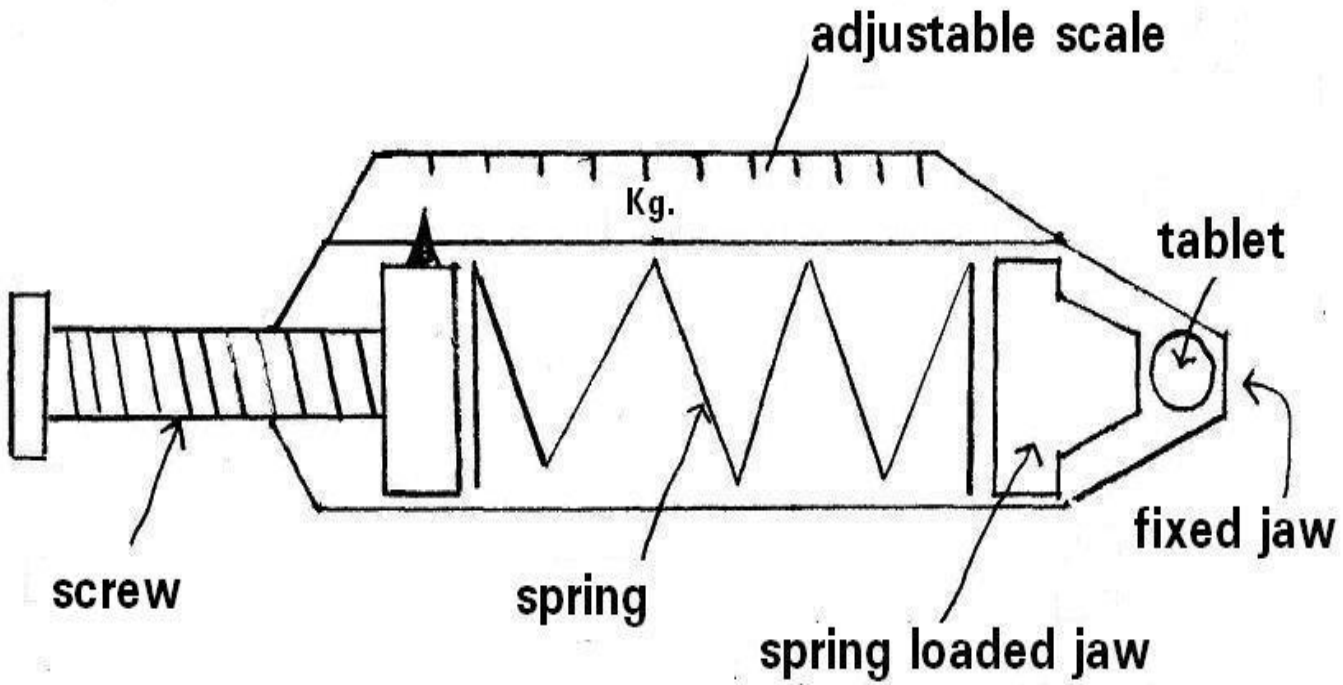
N.B.

- Acceleration = 9.8 m s^{-2}
- Force = mass X acceleration

  Newton = kilogram X meter second^{-2}
- e.g. 40 Newton = 40/9.8 = 4.08 K
- e.g. 6 K = 6 X 9.8 = 58.8 Newton

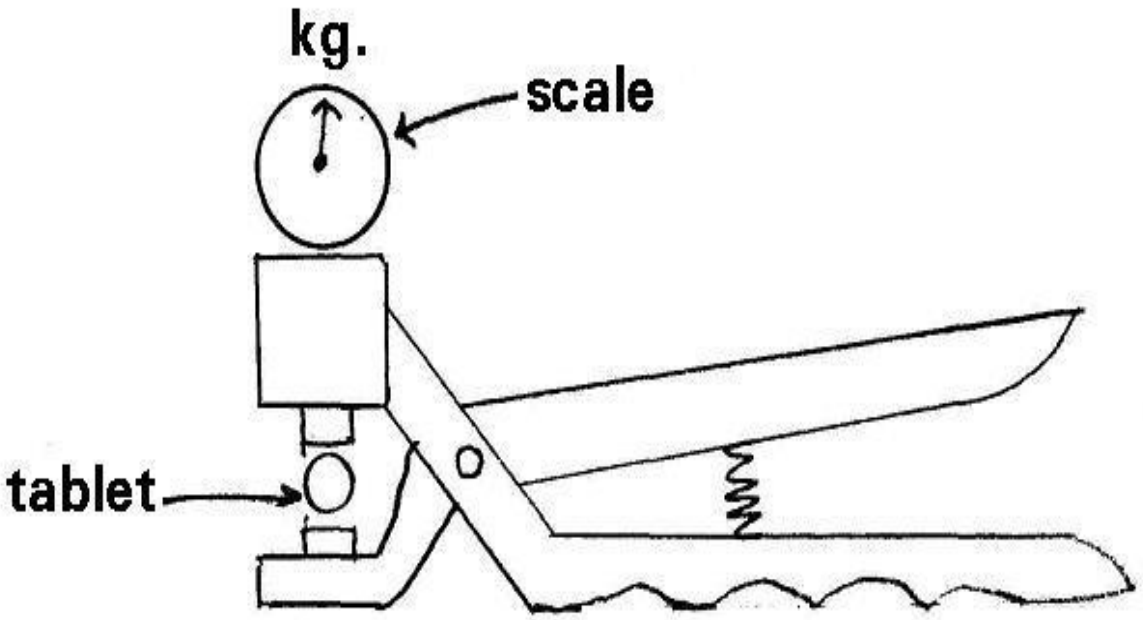
Tablet hardness devices:

1- Monsanto or stokes hardness tester:



"Monsanto hardness tester"

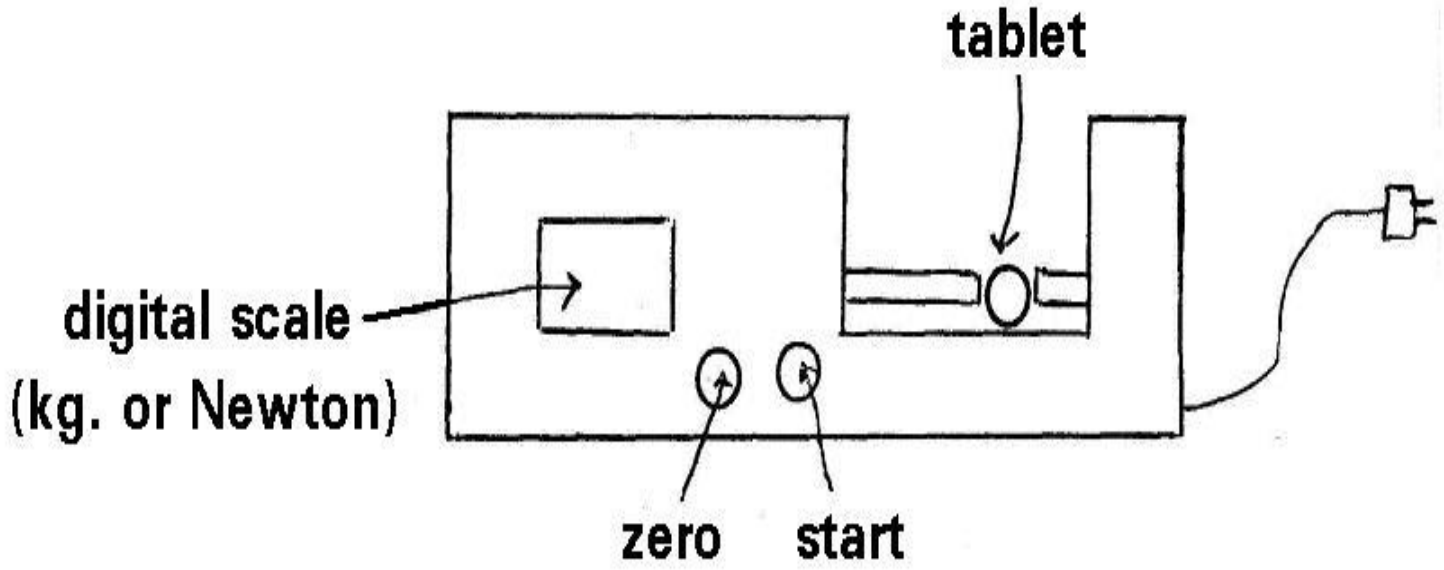
2- Pfizer hardness tester:



Pfizer hardness tester"

3- Electrical instrument:

It is digital instrument in which the force is applied electrically. It gives more reproducible results e.g. "Erweka" and "Pharma test" hardness testers.



Electrical hardness instrument

7- Content uniformity

This test to ensure that every tablet contains the labeled amount of the drug within the prescribed limits (generally ±15%).

B.P Method:

1. Take 20 tablets randomly, mill and assay the content according to the procedures in pharmacopeia.

2. Calculate the concentration of drug in 20 tablets and in each tablet by dividing over 20.

. % Recovery = (content x 100)/labeled amount.

The B.P permit ± 10% , i.e. the amount of active ingredient must be 90% - 110%.

The batch rejected if one tablet deviate from limits.

- **USP method :**

1. Take 10 tablets from random samples of 30 tablets and assay. If only one tablet deviate from USP limits ± 15 % (85%-115%)
2. select another 30 tablets and assay individually .

The batch are accepted, if Not less than 29 tablets obey the limits.

Factors affecting content uniformity:

1. Non uniform distribution of the drug in powder mixture or granulation.
2. Segregation of the powder mixture or granulation during manufacture processes.
3. Weight variation of the tablets.

8- Thickness

Tablet thickness is determined with a micrometer. The allowed limit of thickness variation is ±5% of the size of the tablet.
Variation in tablet thickness leads to counting and packaging problems.
Thickness of the tablet depends on the density of granulation, the pressure applied to the tablet and the speed of tablet compression.

Thank you