Tablet excipients

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients.

Different excipients are:

1. Diluent.
2. Binder.
3. Disintegrents.
4. Lubricants and glidants.
5. Colouring agents.
6. Flavoring agents.
7. Sweetening agents.
8. Matrix former.

1- Filler (Diluent, bulking agent):

Fillers are used to arrive at a tablet of reasonable size when a drug forms a small portion of the formula.

Tablets normally weigh at least 50 mg. Therefore, a low dose of a potent drug requires the incorporation of a substance into the formulation to increase the bulk volume of the powder and hence the size of the tablet. This excipient, known as the filler or the diluent, is not necessary if the dose of the drug per tablet is high.

- Commonly used diluents are microcrystalline cellulose (MCC), lactose, mannitol, sorbitol, and dicalcium phosphate.
- Each excipient presents characteristics that define its preferred application:

✓ Mannitol has a negative heat of solution and, thus, provides a cooling sensation in the mouth. It is typically used for chewable and orally dissolving tablets.

The ideal filler should has a series of requirements, such as:

- ✓ Be chemically inert
- ✓ Be non-hygroscopic
- ✓ Be biocompatible
- ✓ Possess good biopharmaceutical properties (e.g. water soluble or hydrophilic)
- ✓ Have an acceptable taste.
- ✓ Be cheap.

➢As all these requirements cannot be fulfilled by a single substance, different substances have gained use as fillers in tablets, mainly carbohydrates but also some inorganic salts

➢Lactose :

Is the most common filler in tablets. It possesses a series of good filler properties, e.g. dissolves readily in water, has a pleasant taste, is non-hygroscopic, is fairly non-reactive and shows good compactability. Its main limitation is that some people have an intolerance to lactose.

• Lactose exists in both crystalline and amorphous forms.

➢ Amorphous lactose dissolves more rapidly than crystalline and shows better compactability. Its main use is therefore in the production of tablets by direct compaction. Amorphous lactose is, however, hygroscopic and physically unstable, i.e. it will spontaneously crystallize if crystallization conditions are met as a result of elevated temperature or high relative humidity.

Note:

- ✓ lactose generally is not preferred for use with drugs that have primary amine groups due to the propensity for Maillard reaction.
- ✓ Lactose is a fragile excipient that fragments to undergo brittle fracture during compression.

  Addition of lactose to powder blends can improve interparticle bonding during compression

- ➢ **Microcrystalline cellulose: i**s the most widely used direct compression excipient serving as a strong dry binder, tablet disintegrant, an absorbent, filler or diluent, a lubricant, and anti-adherent.

➢A final important example of a common filler is an inorganic substance, dicalcium phosphate dihydrate. This is insoluble in water and non-hygroscopic, but is hydrophilic, i.e. easily wetted by water.

2- Matrix former:

In order to affect or control the release of the drug from the tablet, i.e. to speed up or to slow down its release rate, the drug may be dispersed or embedded in a matrix formed by an excipient or a combination of excipients. This type of excipient may thus be referred to as a matrix former.

The matrix former is often a polymer or a lipid and may constitute a significant fraction of the total tablet weight. When the objective is to increase drug dissolution, the matrix former can be a water-soluble substance or a lipid and the drug is dissolved or suspended as fine particles in the matrix. An example of a water-soluble matrix former is poly ethylene glycol (PEG).

• When the objective is to prolong the drug release, the matrix former can be either an insoluble substance (a polymer or a lipid) or a substance that forms a gel in contact with water. The drug is normally dispersed in particulate form in the matrix .

A common gel-forming substance in tablets is hydroxy propyl methyl cellulose (HPMC).

3- Disintegrating Agents:

- Disintegrating agents are an important component of tablet dosage forms. They are added to a tablet formulation to break apart the compressed tablet (disintegrate) when placed in aqueous environments.

Disintegration of conventional compressed tablets must occur within 15 minutes.

- Super disintegrants are the substances which facilitate faster disintegration with smaller quantity in contrast to disintegrants due to its combined effect of swelling and water absorption and hence promotes wettability and dispersibility of the system thus enhancing the disintegration and dissolution. E.g: Sodium starch glycolate & Crosslinked cellulose

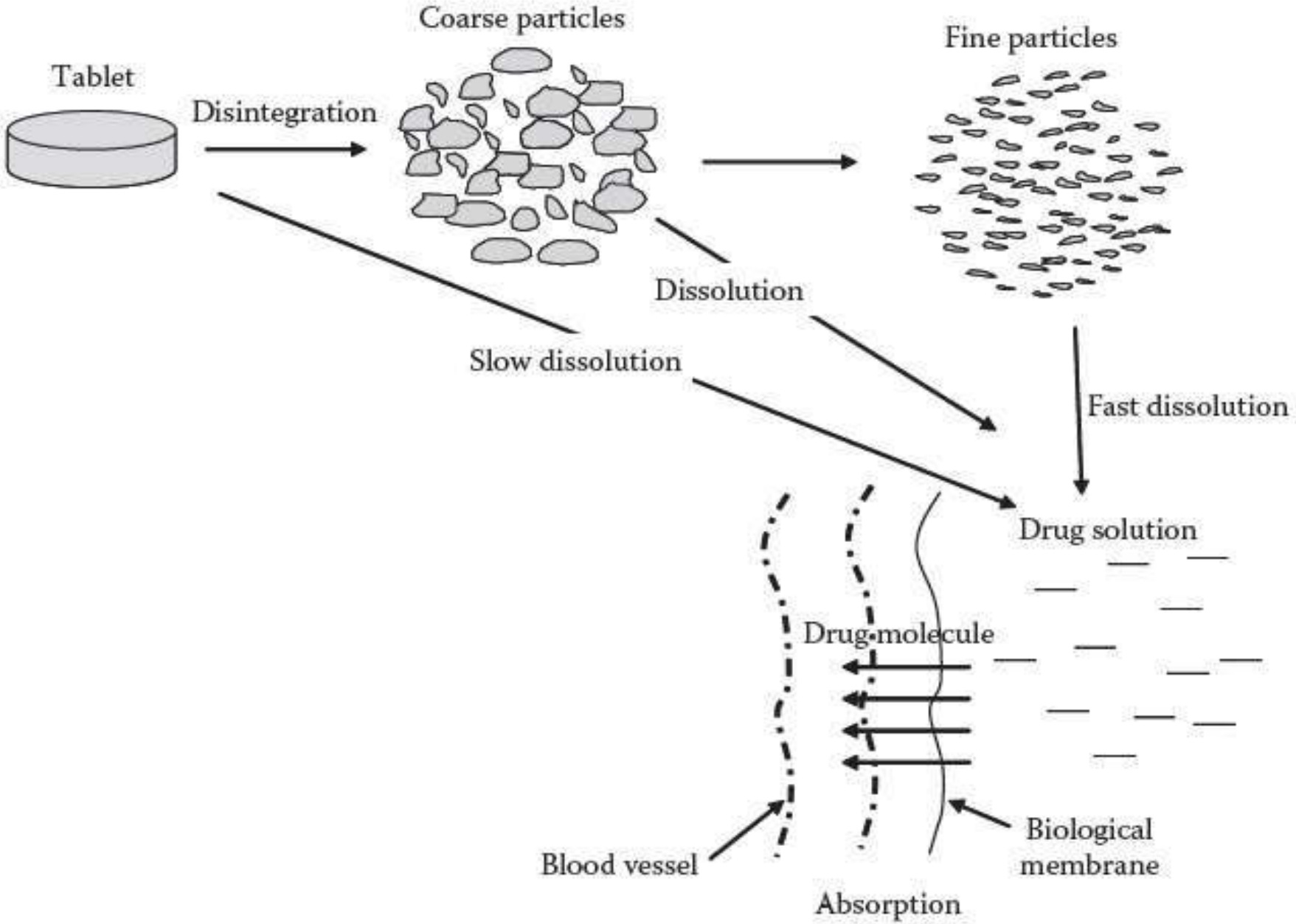


FIGURE 17.4 Relationship between disintegration, dissolution, and drug absorption from an intact tablet.

Disintegrants may work by one of the following mechanisms:

- Disintegrants can increase the porosity and wettability of compressed tablets. In doing so, they enhance the penetration and uptake of GI fluids into the tablet matrix and disintegrate. Starch and microcrystalline cellulose act by this mechanism.

- Disintegration can happen due to the effervescence properties of granules, which can break the tablets very quickly when they come into contact with water.

- Swelling of the disintegrant in the presence of water can increase the internal pressure of the tablet matrix and cause eventual disintegration of the tablet.

Sodium starch glycolate, croscarmellose, and pregelatinized starch work according to this mechanism.

Disintegrants can be added to formulations before compression by three different methods:

- Internal addition (Intragranular addition): The disintegrant is mixed with other powders before granulation.
- External addition (Extragranular addition): The disintegrant is added to the granules before compression (mixing prior to compression).
- Combination method: Both internal and external additions of disintegrants are used.
- The most efficient way of adding a disintegrant to a tablet formulation before compression.

4- Absorption enhancer

For drugs with poor absorption properties, the absorption can be affected by using substances in the formulation that affect the permeability of the intestinal cell membrane and thus increase the rate at which the drug passes though the intestinal membrane. An additive that modulates the permeability of the intestine is often referred to as an absorption enhancer.

5- Dissolution enhancer:

For drugs of low aqueous solubility, the dissolution of the drug may be the rate-limiting step in the overall drug release and absorption processes.

Agents found in the composition of a tablet with the role to speed up the drug dissolution process by temporarily increasing the solubility of the drug during drug dissolution.

An important example of a dissolution enhancer is the incorporation into the formulation of a substance that forms a salt with the drug during dissolution, e.g. increasing the dissolution rate of aspirin by using magnesium oxide in the formulation.

6- Binder

A binder (also sometimes called an adhesive) is added to a drug- filler mixture to ensure that granules and tablets can be formed with the required mechanical strength.

Binding agents (adhesives) are added in either dry or liquid form to promote formation of cohesive agglomerate (granule) or to promote cohesive compacts during direct compression.

Binders can be added to a powder in different ways:

- As a solution which is used as agglomeration liquid during wet agglomeration. The binder is here often referred to as a solution binder
- As a dry powder which is mixed with the other ingredients before compaction (slugging or tableting). The binder is here often referred to as a dry binder.

• Both solution binders and dry binders are included in the formulation at relatively low concentrations, typically 2–10% by weight.

➢More commonly used binders today, with improved adhesive properties, are polymers such as polyvinylpyrrolidone and cellulose derivatives (in particular hydroxypropyl methylcellulose).

➢Common traditional solution binders are starch, sucrose and gelatin.

➢Examples of dry binders are microcrystalline cellulose and crosslinked polyvinylpyrrolidone.

- The type and concentration of binder affect the granule strength, friability, and the granule growth rate during the wet-granulation process. Densification of granules can affect the rate of drug release. For example, higher molecular weight HPC or PVP binders produce larger and denser granules.

7- Glidant:

The role of the glidant is to improve the flowability of the powder by reducing interparticulate friction.

Glidants are used in formulations for direct compaction but are often also added to granules before tableting to ensure that sufficient flowability of the tablet mass is achieved for high production speeds.

These glidants are very small size powder particles that occupy surface ridges and irregularities in coarse powder particles, thus increasing the sphericity and reducing the tendency to adhere to surfaces.

The commonly used glidants are fumed (colloidal) silica, starch, and talc.

•Magnesium stearate, normally used as a lubricant, can also promote powder flow at low concentrations (<1% by weight).

8- Lubricants:

•Lubricants have a number of functions in tablet manufacture: they prevent adherence of the tablet material to the surfaces of the punch faces and dies, reduce inter-particle friction, and facilitate the smooth ejection of the tablet from the die cavity. Many lubricants also enhance the flow properties of the granules.

- Commonly used lubricants are magnesium stearate, stearic acid, and sodium stearyl fumarate.
- These lubricants are small hydrophobic particles that tend to coat the surface of larger powder particles by spreading out under the mild shear during mixing. Hydrophobic surface coating reduces noncovalent hydrophilic interparticle and particleequipment forces that are generally responsible for adhesion and sticking.

➢Among these, magnesium stearate is the most popular lubricant, as it is effective as both a die and punch lubricant. However, for many drugs, magnesium stearate is chemically incompatible (e.g., aspirin) and therefore talc or stearic acid is often used.

- Most lubricants, with exception of talc, are used in concentration ≤1% w/w.
- **Over lubrication**, due to the use of high concentration, mixing, or shearing of the lubricant, can result in reduced compactibility of the blend and/or rate of drug release from the tablets.
- Sodium stearyl fumarate is the only water soluble or hydrophilic lubricant and is used in formulations that are highly sensitive to hydrophobic lubricants

9- Sorbent:

• Sorbents are substances that **are capable of sorbing some quantities of fluids in an apparently dry state**.

Sorbents are materials that soak up oil from the water.

Sorbent are used for tablet/capsule moisture-proofing by limited fluid sorbing (taking up of a liquid or a gas either by adsorption or by adsorption) in a dry state.

Ex. Microcrystalline cellulose and silica are examples of sorbing substances used in tablets.

10- Flavour:

• Flavouring agents are incorporated into a formulation **to give the tablet a more pleasant taste or to mask an unpleasant one**. The latter **can also be achieved by coating the tablet or the drug particles.**

• Flavouring agents are often thermolabile and so cannot be added prior to an operation involving heat. They are often mixed with the granules as an alcohol solution.

11- Colourant:

- Colourants are added to tablets to aid identification and patient compliance.
- Colouring is often accomplished during coating but a colourant can also be included in the formulation prior to compaction.
- In the latter case, the colourant can be added as an insoluble powder or dissolved in the granulation liquid.
- The latter procedure may lead to a colour variation in the tablet caused by migration of the soluble dye during the drying stage.

Functional Excipients Used in Tablets

Functional Role	Examples	Description and Functionality
Filler	• Microcrystalline cellulose (MCC) • Lactose monohydrate or anhydrous • Mannitol • Sorbitol	• Add bulk to the dosage form • May contribute to dissolution and disintegration characteristics
Binder	• Polyvinyl pyrrolidone (PVP) • Hydroxypropyl cellulose (HPC) • Starch	• Bind the powder ingredients to form granules for processing
Disintegrant	• Croscarmellose sodium (CCS) • Crospovidone (xPVP) • Sodium starch glycolate (SSG) • Starch	• Disintegration of the tablet to granules and powders upon coming in contact with water
Glidant	• Colloidal silicon dioxide	• Aid the flow of granules/blend
Lubricant	Magnesium stearate • Stearic acid • Sodium stearyl fumarate	• Aid the flow of granules/blend and ejection of tablets in the tablet press

Coating material	• Polymers such as hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), polyvinyl alcohol (PVA) • Plasticizer (e.g., polyethylene glycol) • Opacifier (e.g., titanium dioxide); • Glidant (e.g., talc); and • Colorant (e.g., iron oxide red and/or yellow)	• Provide a physical barrier coating on the surface of the compressed core tablets
Coloring agent	• Iron oxide red and/or yellow • FD&C Blue #6	• Visual appeal of color
Stabilizer	• Antioxidants such as ascorbic acid, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT), α-tocopherol	• Stabilization of the drug in the dosage form from stresses such as oxidation
Sweetener	• Aspartame, saccharin sodium, sucralose, acesulfame potassium	• Sweetening to overcome drug taste and/or improve palatability for some types of tablets
Flavoring agent	• Proprietary flavors (orange, pineapple, etc.)	• Flavoring to overcome drug taste and/or improve palatability for some types of tablets

Examples of immediate release tablet compositions

A. Acetaminophen tablets

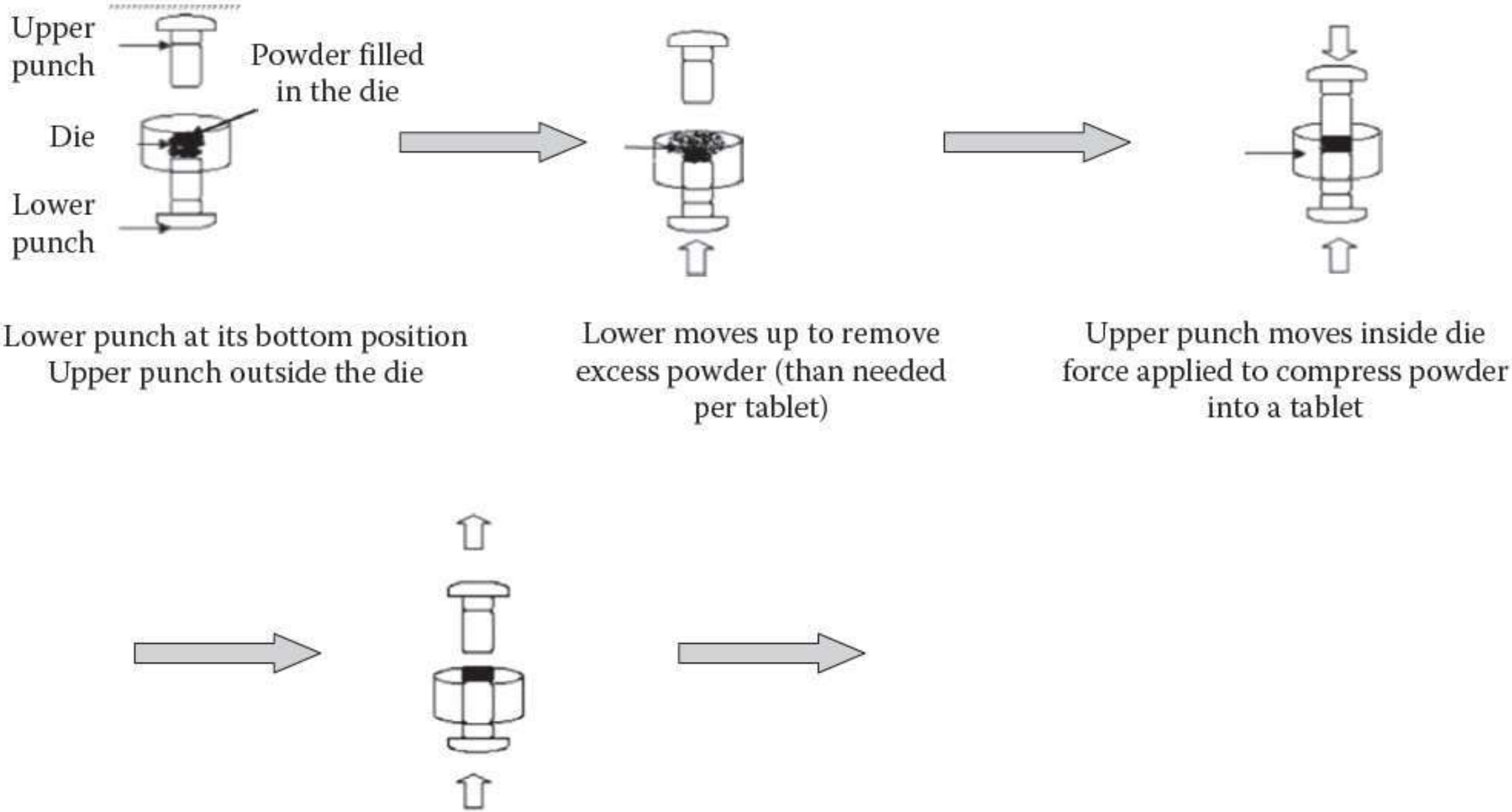
Ingredient	Quantity per tablet	Use
Acetaminophen	325 mg	Drug
Sucrose	60 mg	Filler
PVP 10% in alcohol	q.s.	Binder
Stearic acid	6 mg	Lubricant
Talc	15 mg	Lubricant, glidant
Corn starch	30 mg	Disintegrant
Alginic acid	20 mg	Disintegrant

TABLET MANUFACTURING

❖Requirements for tableting :

Tableting involves compression of a powder blend in a die cavity between the upper and the lower punches.

Several punches and dies are arranged on three rotary turrets on a high speed rotary tablet press that moves in a circular motion as the tablets are made. The powder is fed into the dies at one port through a hopper and the tablets are collected at another port .


Upper punch
Powder filled in the die
Die
Lower punch
Lower punch at its bottom position
Upper punch outside the die
Lower moves up to remove excess powder (than needed per tablet)
Upper punch moves inside die force applied to compress powder into a tablet
Upper punch moves outside die
Lower punch moves up eject tablet

This process requires :

- Uniform flow of blend into the die cavity through a hopper.
- Nonsegregation of powder blend in the hopper and during loading in the die cavity.
- Compactibility of the powder in the die cavity during compression.
- Nonsticking of the powder blend to walls of dies and surfaces of punches .
- Adequate cohesion of the powder blend to form a strong tablet.

TABLETING METHODS

• There are three methods by which tablets are manufactured:

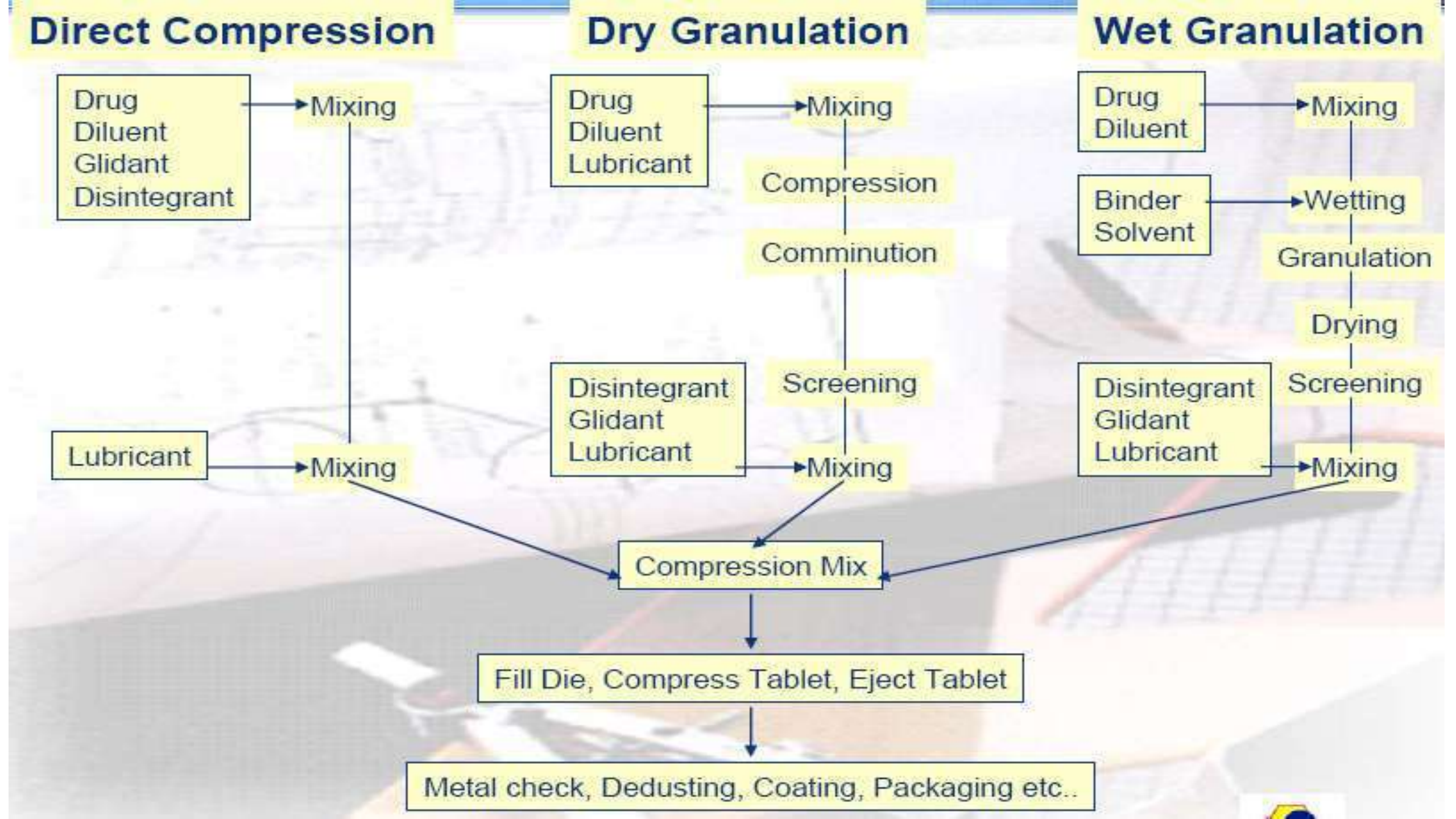
1. Wet granulation

2. Dry granulation

3. Direct compression

➢Manufacturing process is dependent on several factors, including the compression properties of the therapeutic agents, the particle size of the therapeutic agent, excipients and the chemical stability of the therapeutic agent during the manufacturing process.

- The purpose of both wet and dry granulation is to improve the flow of the mixture and to enhance its compression properties by increasing particle size, density, and sphericity. The selection among these processes is based on the physicomechanical properties of the API and the raw material blend (API with excipients).
- For example, stability of the API to other ingredients used for preparing granulation blends and processing conditions (e.g., use of water during wet granulation) is critical. For example, dry granulation may be preferred for moisture and/or heat sensitive APIs.


Direct Compression
Drug
Diluent
Glidant
Disintegrant
Mixing
Lubricant
Mixing
Dry Granulation
Drug
Diluent
Lubricant
Mixing
Compression
Comminution
Screening
Disintegrant
Glidant
Lubricant
Mixing
Wet Granulation
Drug
Diluent
Mixing
Binder
Solvent
Wetting
Granulation
Drying
Screening
Disintegrant
Glidant
Lubricant
Mixing
Compression Mix
Fill Die, Compress Tablet, Eject Tablet
Metal check, Dedusting, Coating, Packaging etc..

Wet Granulation

Wet granulation is a widely employed method for the production of compressed tablets.

The steps required are:

(a) Weighing and blending the ingredients.

(b) Preparing a dampened powder or a damp mass,

(c) Screening the dampened powder or damp mass into pellets or granules.

(d) Drying the granulation.

(e) Sizing the granulation by dry screening.

(f) Adding lubricant and blending.

(g) Forming tablets by compression.

1- Weighing and Blending:

Specified quantities of active ingredient, diluent or filler, and disintegrating agent are mixed by mechanical powder blender or mixer until uniform.

2- Preparing the Damp Mass:

•A liquid binder is added to the powder mixture to facilitate adhesion of the powder particles.

•A damp mass resembling dough is formed and used to prepare the granulation.

•A good binder results in appropriate tablet hardness and does not hinder the release of the drug from the tablet.

3- Screening the Damp Mass into Pellets or Granules:

The dampened powder granules are screened, or the wet mass is pressed through a screen (usually 6 or 8 meshes) to prepare the granules

4- Drying the Granulation:

Granules may be dried in thermostatically controlled ovens that constantly record the time, temperature, and humidity

5- Sizing the Granulation by Dry Screening:

•After drying, the granules are passed through a screen of a smaller mesh than that used to prepare the original granulation.

•The degree to which the granules are reduced depends on the size of the punches to be used. In general, the smaller the tablet to be produced, the smaller the granules. Screens of 12- to 20-mesh size are generally used for this purpose.

•Sizing of the granules is necessary so that the die cavities for tablet compression may be completely and rapidly filled by the free-flowing granulation.

•Voids or air spaces left by too large a granulation result in the production of uneven tablets.

6- Adding Lubricant and Blending:

After dry screening, a dry lubricant is dusted over the spread-out granulation through a fine-mesh screen.

Dry Granulation

- By the dry granulation method, the powder mixture is compacted in large pieces and subsequently broken down or sized into granules. For this method, either the active ingredient or the diluent must have cohesive properties.
- Dry granulation is especially applicable to materials that cannot be prepared by wet granulation because they degrade in moisture or the elevated temperatures required for drying the granules.

➢ ***Slugging.***

➢ ***Roller Compaction.***

Direct Compression

• Tablets are compressed directly from powder blends of the active ingredient and suitable excipients.

• No pretreatment of the powder blends by wet or dry granulation procedures is necessary.

• Some granular chemicals like potassium chloride possess free flowing as well as cohesive properties that enable them to be compressed directly in a tablet machine with out need of either wet or dry granulation .

• In the direct compression method the tablet excipients used must be materials with properties of fluidity and compressibility .

- Direct compression: Direct compression is the preferred method if powder blend has adequate flow, compactibility, and cohesion with low segregation potential. This is the simplest process that involves the least extent of material handling. Direct compression involves simply mixing the required ingredients and compressing them into tablets on the press.
- Direct compression has been used mainly for two types of drug, firstly, relatively soluble drugs which can be processed as coarse particles and, secondly, relatively potent drugs which are present in a few milligrams in each tablet and can be mixed with relatively coarse excipient particles.

Advantages & Disadvantages of Direct Compression

Advantages:

1. There are fewer processing steps and therefore the method is potentially more cost effective than other methods.
2. Direct compression does not require the use of water or other solvents. Therefore negates potential problems regarding the stability of therapeutic agents in the presence of the solvents. In addition heating is not required in direct compression.
3. Lubrication is performed in the same vessel as powder mixing, thereby reducing both transfer losses and contamination of equipment.

Disadvantages:

1. Special grade excipients are required.
2. The quality and uniformity of the final dosage form depends on the excipients.
3. There may be issues regarding powder flow into the tableting machine.
4. The final tablets produced by direct compression tend to be softer than those produced by wet granulation, rendering them more difficult to process using post tableting techniques, eg: film coating
5. It is not used if a colourent is required in the formulation due to the mottled appearance of the resulting dosage form.