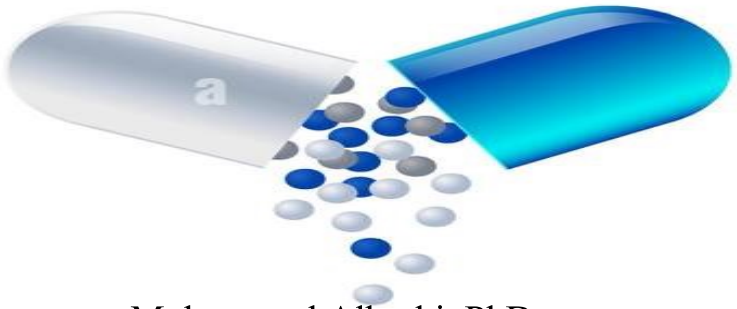
Lec. 2: Excipients

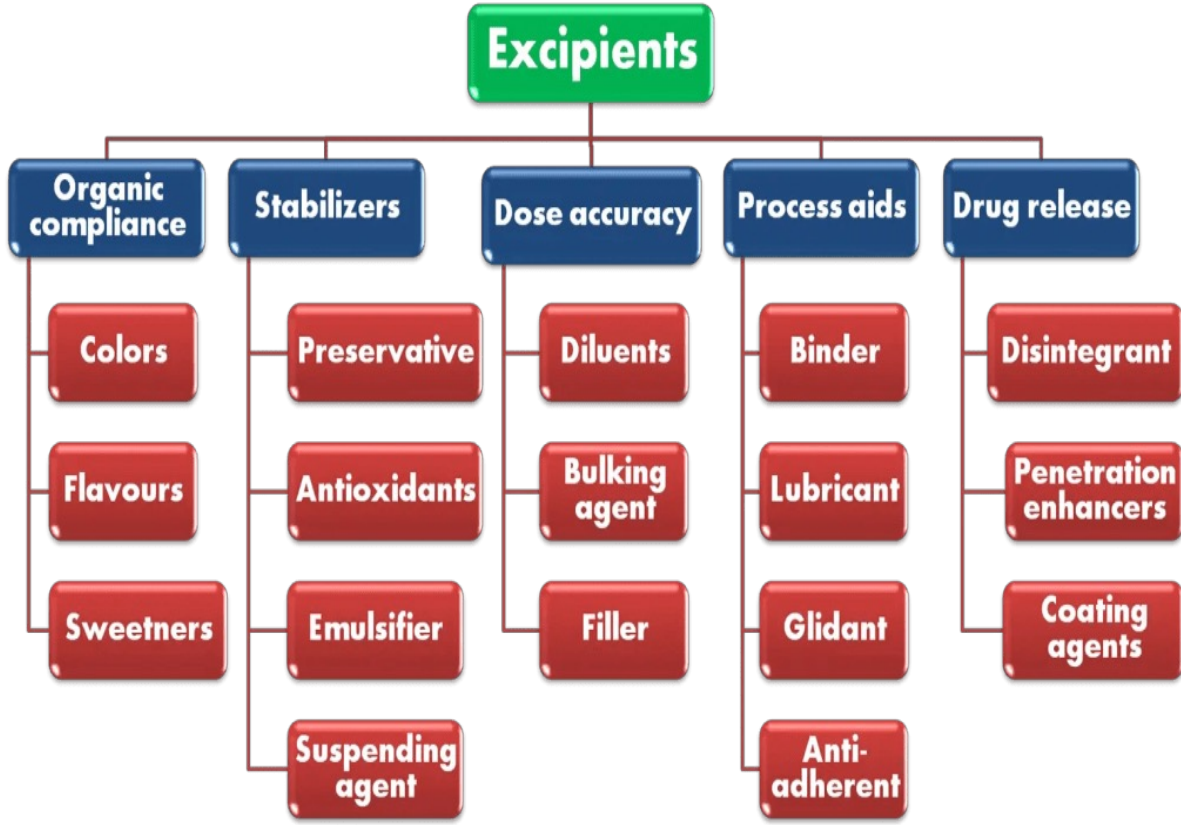


Mohammed Albarki, PhD

Tablet Excipients

- All "nondrug" materials of the formula are called **excipients**.
- Excipients are **necessary** for the following reasons:

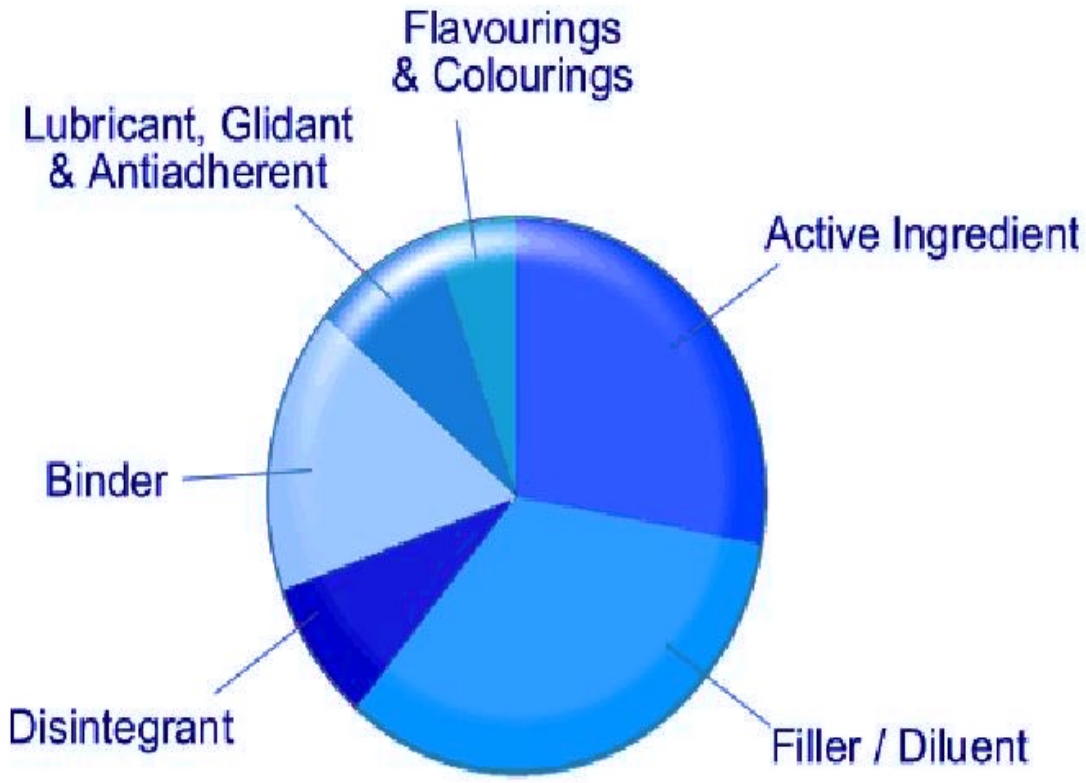
1. Improve **patient compliance** such as color, flavor, and sweeteners.
2. Increase **dosage form stability** such as antioxidants, and preservatives.
3. Increase **dose accuracy** such as diluent or fillers.
4. Act as a **process aid** such as binders and lubricants.
5. Improve and **control drug release**, such as disintegrant and coating agents.



Types of Excipients

- The main excipients used in tablet formulation are:

1. Diluents (fillers) such as lactose, starch, and microcrystalline cellulose.
2. Binders (granulating agents) such as starch, acacia, and gelatin.
3. Disintegrants such as starch, and super disintegrant.
4. Lubricant, Antiadherent, Glidants such as magnesium stearate and stearic acid.



Typical Tablet content

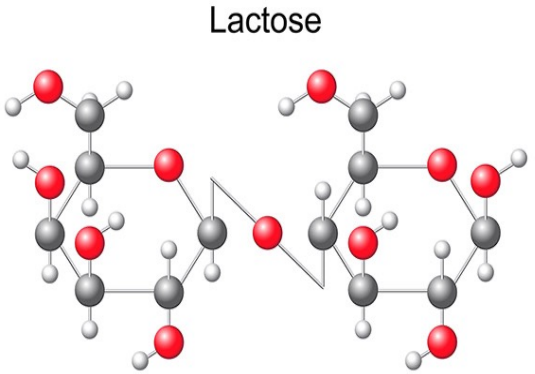
Diluents (Fillers)

- Diluents are materials used to **make up the required bulk** of the tablet when the drug itself is inadequate to provide this bulk.
- Occasionally, the active ingredient has a **large dose and good compressibility** so that it does not need diluent, e.g., aspirin and some antibiotics.
- However, **most** tablets need a diluent.
- Round tablets are usually in the size range of **5-13 mm**. Tablets below 5mm may be difficult for the elderly to handle and those larger than 13 mm become difficult to swallow.

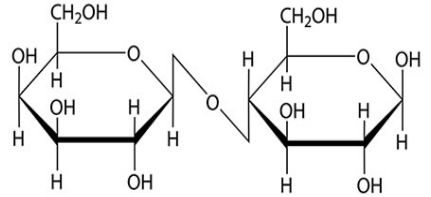
1. Diluents are therefore used to **formulate the tablets within the desired size range**.
2. The diluent can also provide better tablet properties such as improved **cohesion** or **promote flow.**

Lactose

- The **most widely used** diluent in tablet formulation **because** it does not react with most drugs.
- Three forms of lactose are available (anhydrous, hydrous, and spray-dried):



1. **Anhydrous** lactose has an advantage over the other two types; on aging, it does not undergo discoloration (brown discoloration, Maillard reaction) with **amines and alkali** compounds.



2. When exposed to elevated humidity, the anhydrous lactose may pick up moisture from the environment and convert to the hydrous form.
   - ➔These Tablets should be carefully packaged to prevent moisture exposure.
3. The **hydrous form** is usually used when **wet granulation** is used to produce tablets.

Lactose

- In general, all lactose types show the following **advantages:**

1. Good drug **release**.
2. In granulations, granules are **easily dried**.
3. The **disintegration time** of lactose-containing tablets is **not very sensitive** to variations in tablet hardness.
4. Low **cost**.
5. Has **no reaction** with most drugs.

- **Disadvantages**: Hydrous form undergoes discoloration when used with alkali or amine-containing compounds

Starch

- It may be derived from different sources such as corn, wheat, or potatoes.
- Great care should be taken when using starch in the formula **because** it can be used as **diluent**, **binder,** or **disintegrant** depending on:

1. **Type of starch**: the useful type for a particular formula can be known by experts.
2. **The amount used**: it is used as a **diluent** in the ratio of 50-60%, **binder** in the ratio of 2-10%, and **disintegrant** in the ratio of 5-20%.
3. **Stage of addition**:
   - it is used as a **diluent** when added in the **dry form** at the beginning of the procedure (mixing step),
   - a **binder** when used **as a paste** in the preparation of the wet mass step,
   - and **disintegrant** when added finally after granulation **as a dry form**.

Other Diluents

Dextrose:

It is available in two forms: **hydrous** and **anhydrous**.

- Dextrose is sometimes used in the formulas to replace some of the lactose to **minimize the discoloration** (when used with alkaline compounds).

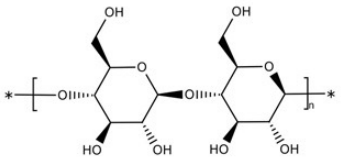
Mannitol:

- It is widely used in chewable and orodispersible tablets because of its **sweet taste** (sugar) **pleasant feeling** in the mouth (due to the negative heat of solution), and **slow solubility**.
- It is **non-hygroscopic** so can be used safely in water-sensitive formulations like vitamin formulations.
- However, it is somewhat **expensive**, has **poor flow,** and **requires a high lubricant** level.

Diluents

Microcrystalline cellulose:

AVICEL PH
Microcrystalline cellulose



- It is often referred to by the trade name **Avicel®**.
- It is a multipurpose excipient used as a **diluent** and **disintegrant**.

Advantages:

- It is **inert** and can be used with alkaline or acidic substances (**No discoloration**).
- Has high purity and low moisture content.
- Avicel is a directly compressible diluent due to its **good compressibility** and **flowability**.

- Avicel-containing tablets are **characterized by** short disintegration time, high hardness, low friability, and low weight variation. (*Why?*)

Binders (Granulating agent)

- They are substances that **bind the particles together** to form granules (in wet and dry granulation) or to promote the formation of cohesive compacts (in Direct compression).
- Below are some examples:

Acacia and tragacanth:

- Natural gums. These materials are more effective when added as a solution than if they are used as powders.

Disadvantages:

- They are variable in their composition (**why?**) and performance according to their origin.
- They are also easily contaminated by bacteria.

Gelatin:

- **Synthetic protein** is preferred over acacia and tragacanth and is also easier to prepare in solution than the two gums. However, bacterial growth is also troublesome.

Binders

Starch:

- One of the most commonly used granulating agents (binder) and used as a paste.
- It is prepared by dispersing starch into water which is then **heated** for a certain time to induce **starch hydrolysis into dextrin and glucose**.
- A properly made paste is **translucent** rather than clear (which indicates complete conversion to glucose).

Binders

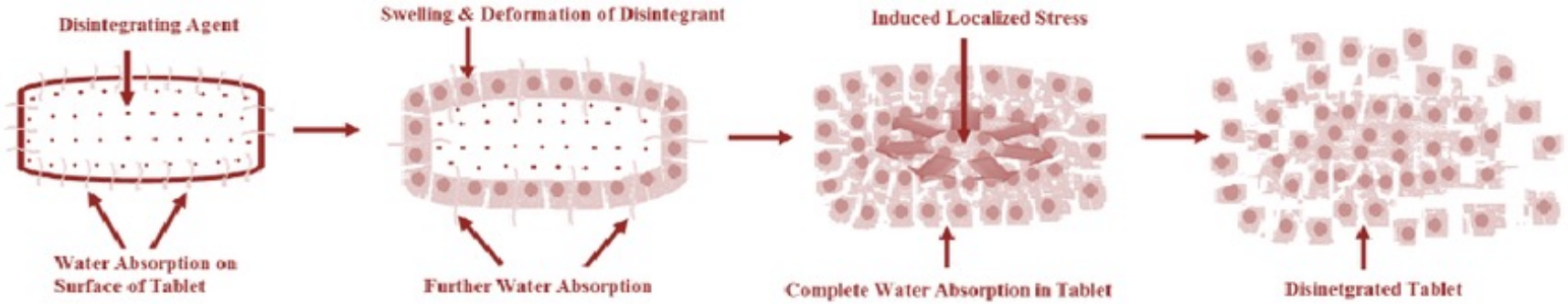
Modified Natural Polymers:

- Common and important binders. Alginates (e.g., **sodium alginates**) and cellulose derivatives (e.g., **methylcellulose** (MC), **ethyl cellulose** (EC), **hydroxypropyl cellulose** (HPC) and **hydroxypropyl methylcellulose** (HPMC)) are examples of these binders.

- Except for EC, all of the cellulose derivatives can be used as dry powders (in Direct compression and dry granulation) and as an aqueous solution (in wet granulation).
- HPC can also be used as an **alcoholic solution**, thus it is useful for water-sensitive drugs.
- EC is used **only** as an alcoholic solution because it is insoluble in water, therefore it may **retard** tablet disintegration.

Disintegrants

- A disintegrant is a substance that **facilitates the breakdown** of the tablet into smaller fragments upon contact with GI fluids. (https://youtu.be/s5aGmUQIzSs)
- The function of the disintegrant is to **oppose the effect of the tablet binder** and the **physical force** that is applied during the compression process.
- The disintegrants **act by** drawing water into the tablet, swelling and rupturing the tablet.
  - This tablet fragmentation is critical to the **drug's subsequent dissolution and achieving satisfactory bioavailability**.
- Disintegrants may added at **two stages**: during the formation of granules (to give intragranular action) and at the second mixing stage during compaction of granules into tablets (extragranular).



Disintegrants

Starch

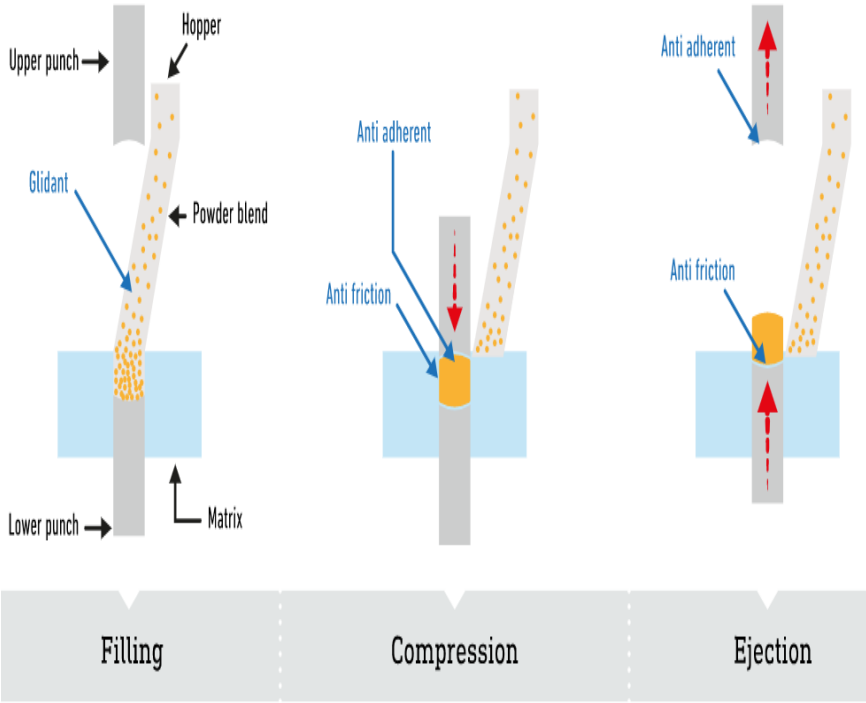
- The most commonly used disintegrants because of their **low cost**. It is used in the ratio of 5-20% of the tablet weight.
- Starch has the property of **rapid water uptake and swelling** that leads to the rupture of the tablet due to the increase in internal pressure.

Super Disintegrant:

- They are so-called due to their powerful disintegrating action. Examples of these materials are **sodium starch glycolate** (Explotab®), **croscarmellose sodium, and crospovidone** (Kollidon CL).
- They are **very potent** if compared with the classic disintegrants. For example, croscarmellose sodium swells to **900% of its original** volume in acidic media while starch swells to 25% only in the same media. They are used when rapid disintegration is required such as in orodispersible tablets.

Lubricants, Antiadherent, and Glidants

- **Lubricants:**
  - **They** are materials used to **reduce the friction** during tablet ejection between the tablet and the walls of the die cavity in which the tablet was formed.
- **Antiadherents**:
  - Reduce sticking of tablet granules to the **faces of the bunches** or to the die wall
- **Glidants:**
  - **They** are used to **promote the flow** of granules or powders by reducing the friction between the particles themselves.
  - Glidants are thought to work by **filling irregularities** in granules making them more round and reducing friction between granules.



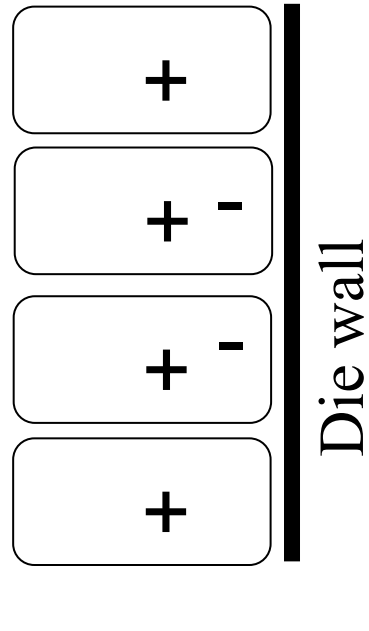
Lubricants

- **Advantages** of lubricants

1. **Facilitate** tablets' ejection and prevent their sticking in the die.
2. **Prolong** the life of the die.
3. **Decrease** the liberated heat (friction heat).

- **Mechanism of action of the lubricants**

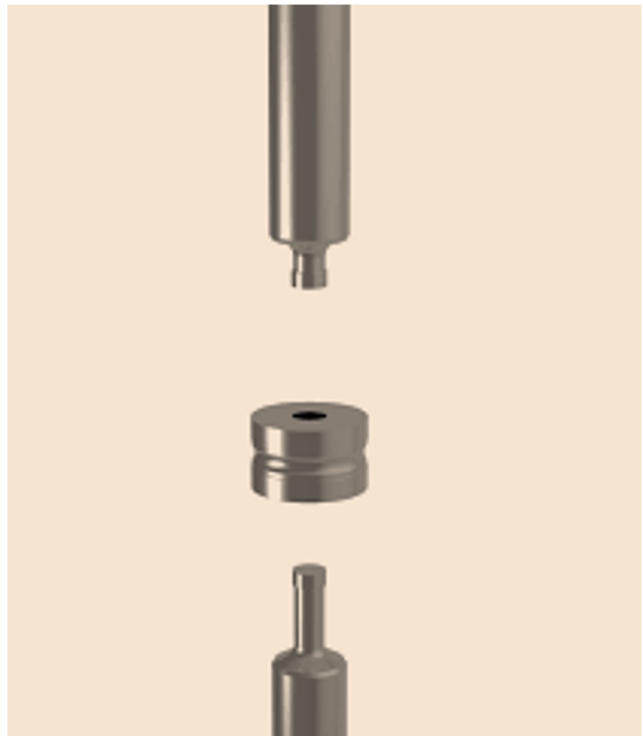
1. **Fluid lubrication** (Hydrodynamic (formation of thin film)): this mechanism is used to explain the action of *liquid* lubricants.
   - In general, all liquids (especially oily ones) decrease the friction between two surfaces.



- **Example: Mineral oils** such as **liquid paraffin** have been applied on the granules as a **fine spray**.
  - However, the **problem** with using this type of lubricant is the production of **oil spots**.
  - Another problem is that the particle surface will be hydrophobic and the tablet may have a slower dissolution rate ➔ may alter bioavailability.

- **Mechanisms of lubricants (continue):**

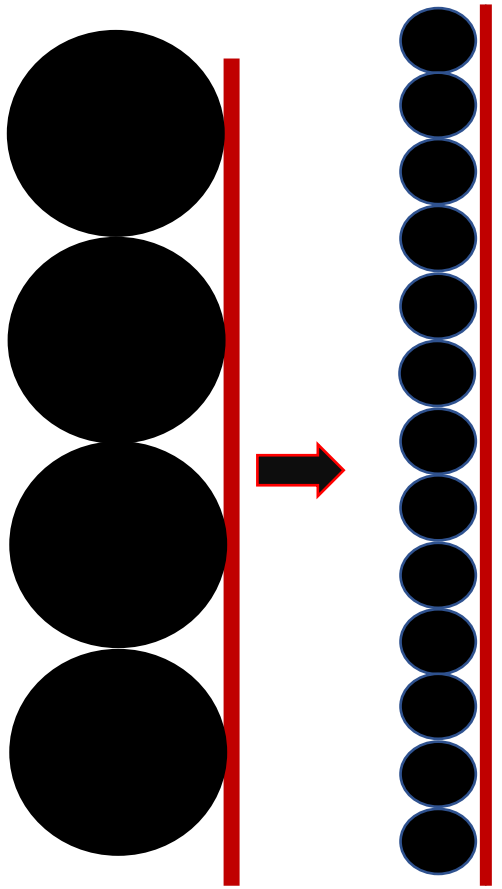
2. **Boundary lubrication**: this mechanism is used for ***solid*** lubricants.
   - In this type, the **polar portion** (such as –OH, $–NH_2$) of the lubricant is attached to the metal and prevents the tablet from sticking to the die.



- The lubricants should be added in the **last step** (just before compression) since they must be **present on the surface** of the granules and not between them.

Notes About Lubricants

1. The **particle size** of the lubricants is crucial; they should be 200 mesh in size or finer.
   - As a general rule, as the particle size of the lubricants **increases**, their efficacy **decreases**.
2. The **amount** of the lubricant in the formula should not exceed 1% (for most lubricants) and this is due to the following problems that can happen with increasing lubricant amount:
   - These materials are **water-insoluble** and present on the surface of the granules, thus retard water penetration and **decrease dissolution** rate and **may** alter bioavailability.



Lubricants

3. The **mixing time** of the lubricant with the formula should be 2-5 min.
   - **Over-mixing** decreases the lubricant efficacy because it causes the penetration of the lubricant from the surface to the core of the formula.
4. The **mixing rate** is also important; a high mixing rate causes the penetration of the lubricant inside the core of the formula and thus, decreases the lubricant's efficacy.

Lubricants and Glidants

Examples of the commonly used lubricants:

- **Magnesium or calcium stearate** are the most widely used lubricants due to their efficacy. These lubricants should **not** be used with acidic drugs like aspirin (due to pH-induced hydrolysis).
- **Stearic acid** is less effective than its magnesium and calcium salts. It should **not** be used with alkaline drugs.
- **Zinc stearate** is inert with good lubricating properties and **small particle size**. It is used effectively in **direct compression**.
- **Talc** may also be used as a lubricant. **Problem**: it does contain a trace amount **of iron**, so it should be applied carefully in any formulation containing a drug whose breakdown is catalyzed by the presence of iron.

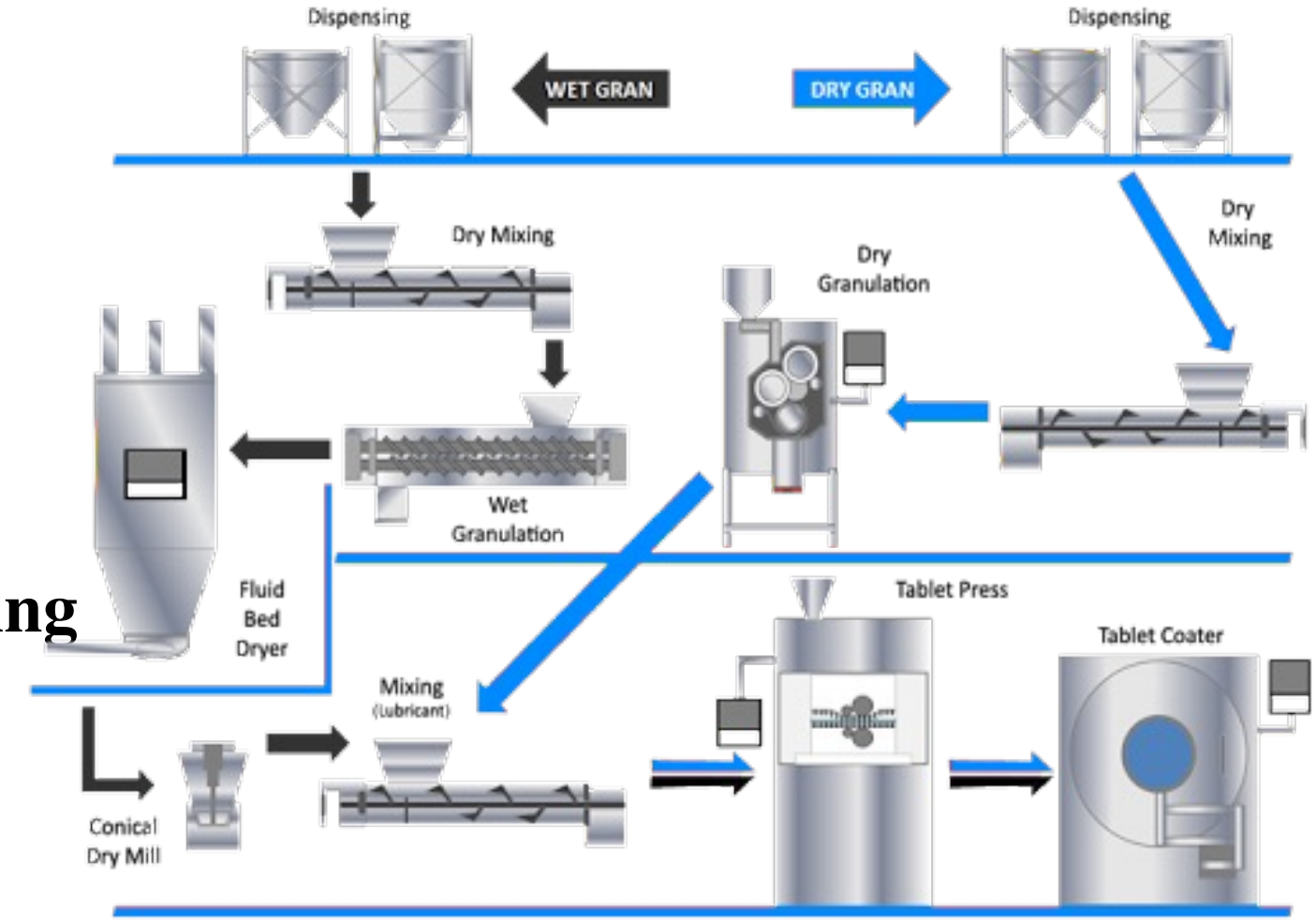
Tablet Design and Formulation

- Generally, tablet formulation consists of the following main processes:

1. Weighing.
2. Granulation.
3. Milling and mixing.
4. Compression.

- **Three types of tablet manufacturing process:**

1. Wet Granulation.
2. Dry Granulation.
3. Direct compression.



Mixing

- A crucial step in the formulation of the pharmaceutical dosage form.
  1. Mixing allows **uniform distribution** of tablet constituents throughout the formulation
  2. Allows for **adequate distribution** of lubricants around tablet granules.
- Undermixing will probably lead to impaired **content uniformity** of tablet formulation and **poor flow** properties
- Over-mixing will lead to other tablet manufacturing problems such as **poor flow** properties due to lubricants entering into the tablet granules instead of staying on the surface.

V- Shape Mixer

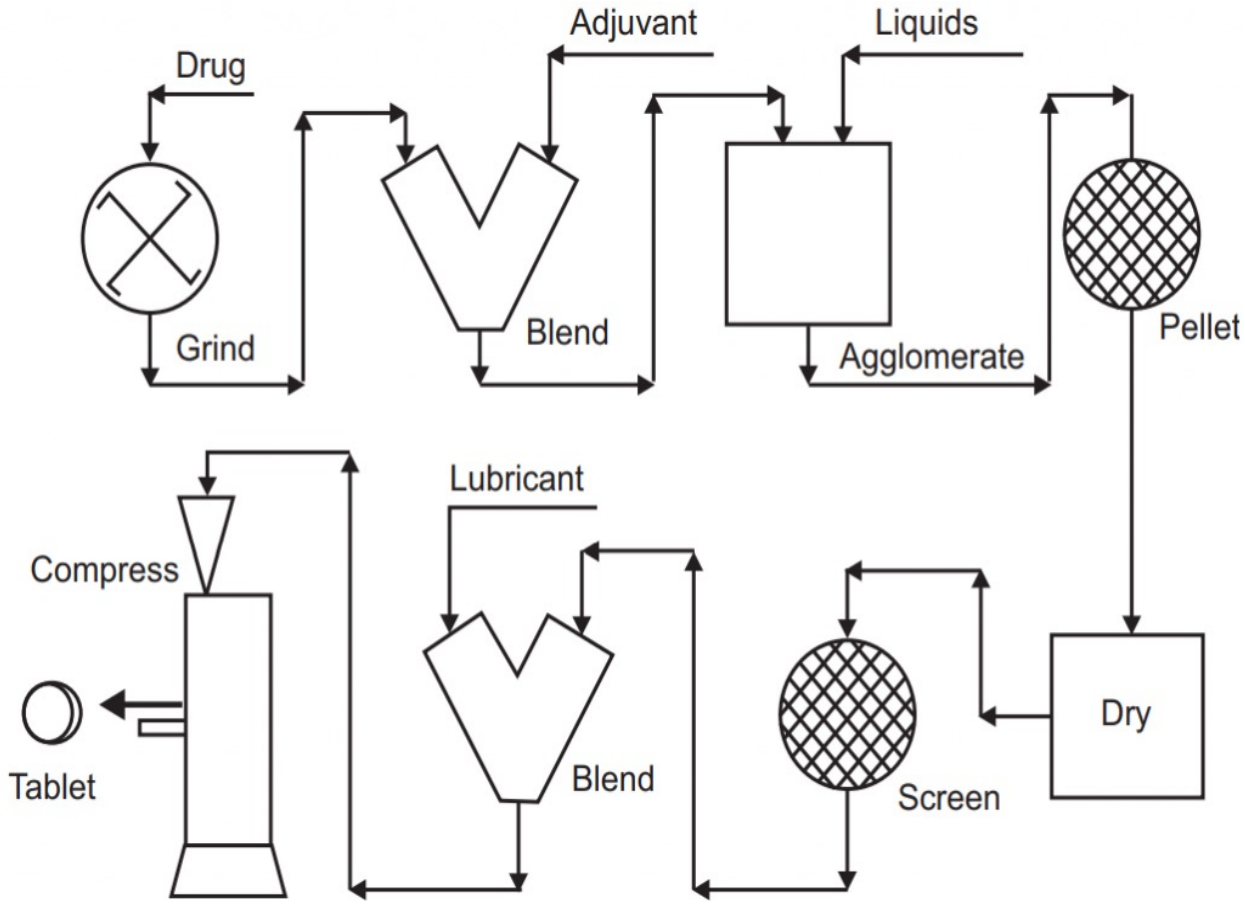
Granulation

- Fine powder drug mostly has poor flow properties.
- Granules have:

1. Better **flowability** than individual ingredients
2. Better **compressibility** than individual ingredients.
3. It ensures the **consistent spread** of API in the formulation.

Wet Granulation (used liquid binder)

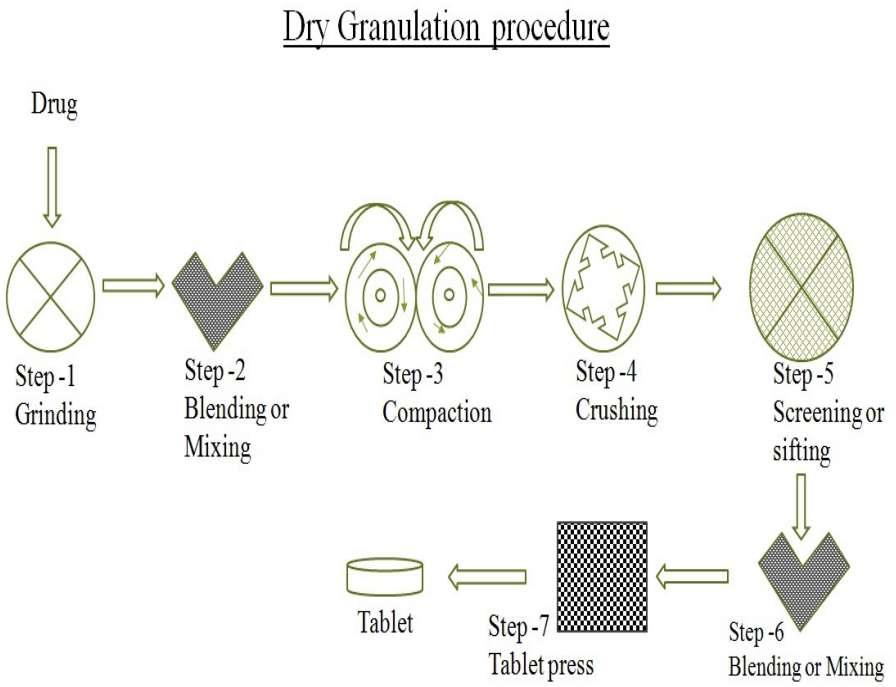
- Most common; Contains more steps but is relatively easier to control and compress.
- Active ingredients plus excipients are mixed together then a binder (binding **liquid**) is added to a rapid mixer granulator (machine)
- Granules are then dried and milled to the required size range
- Then mix with lubricant and compress



Dry Granulation

1. Used when there is a limitation for using a granulating solution such as the **interaction** between the active ingredient and the solution
2. Also in cases when the drug is **sensitive to heat**.

- Drug powder and inactive ingredients are mixed together and passed through a powder **roller compactor** machine to produce **slugs.**
- **This process is called slugging**
  - Slugs undergo milling and screening to get the desired particle size
- Examples are vitamin formulations



Direct Compression

- A special case of tablet formulation.
- **No** granulation step; only mixing ingredients and excipients and compressing directly.
- It requires certain properties of the active ingredients to be able to produce a good tablet:
  1. **Crystalline** in nature.
  2. **Components are easy to compress.**
- Sodium chloride, potassium salts of iodide, or chloride tablets can be done using this method.
- **Limitation**: Most materials have weak intermolecular interaction attraction that tends to hinder compaction.

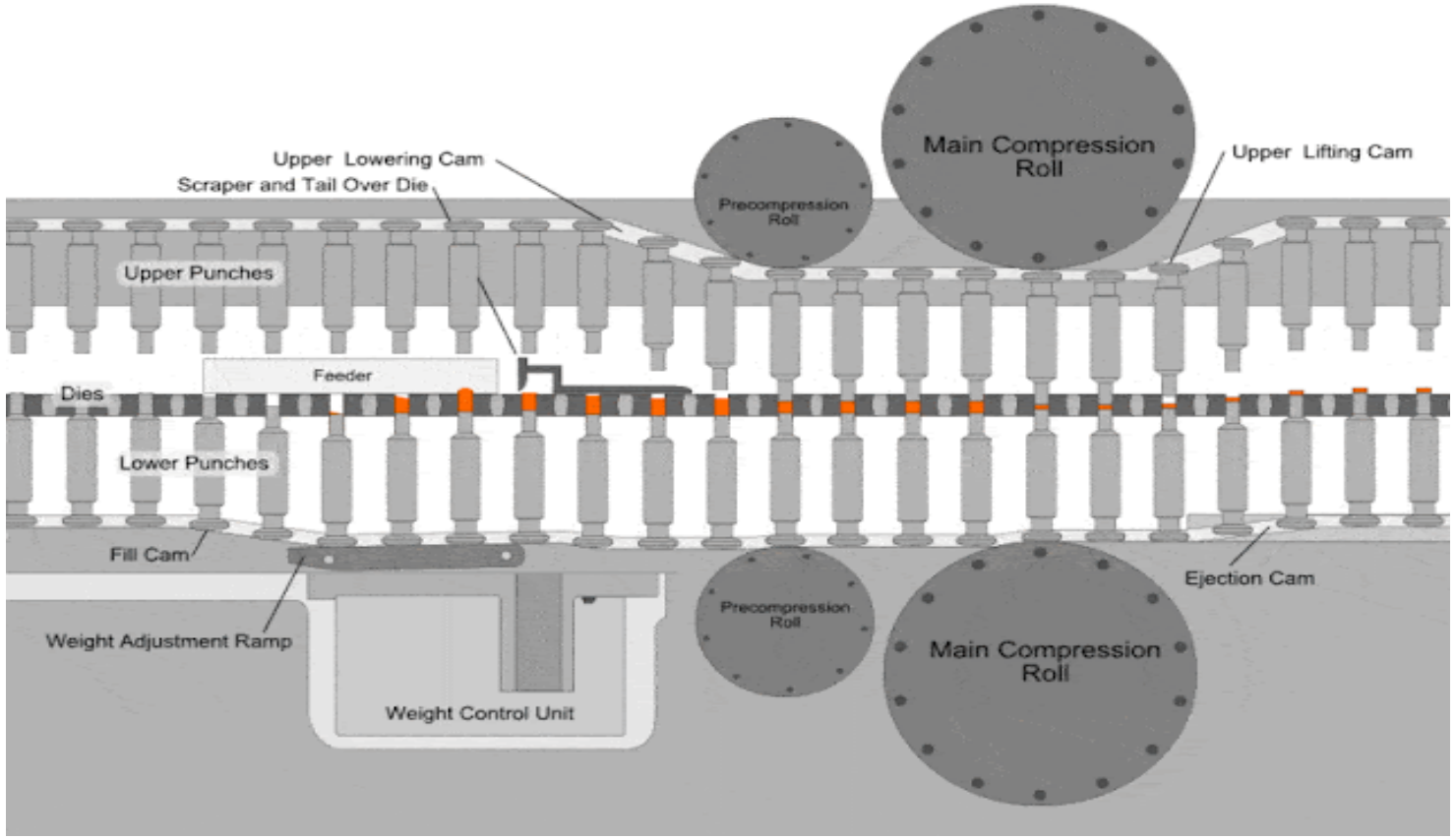
Direct Compression

- **Advantages of Direct Compression:**

1. Simple, low labor input and hence **economic**.
2. Being a **dry process**, the risk of deterioration of the active ingredient is decreased.
3. Tablets will **disintegrate onto their primary** particles rather than granular aggregates → the resultant increase in surface area available for dissolution should result in faster drug release.

Compression

- The final step is tablet formulation.
- Required a set of variables to be evaluated which are beyond the scope of this class.



Tablet Compression Machine

1. Hopper(s) for holding and feeding tablet components.
2. Dies that define the size and shape of the tablet.
3. Punches for compressing the granulation within the dies.
4. Cam tracks to guide the movement of the punches.

- **Note:** there are various auxiliary equipment designed to aid in tablet production such as automatic feeders, deduster (beyond the scope of this class)