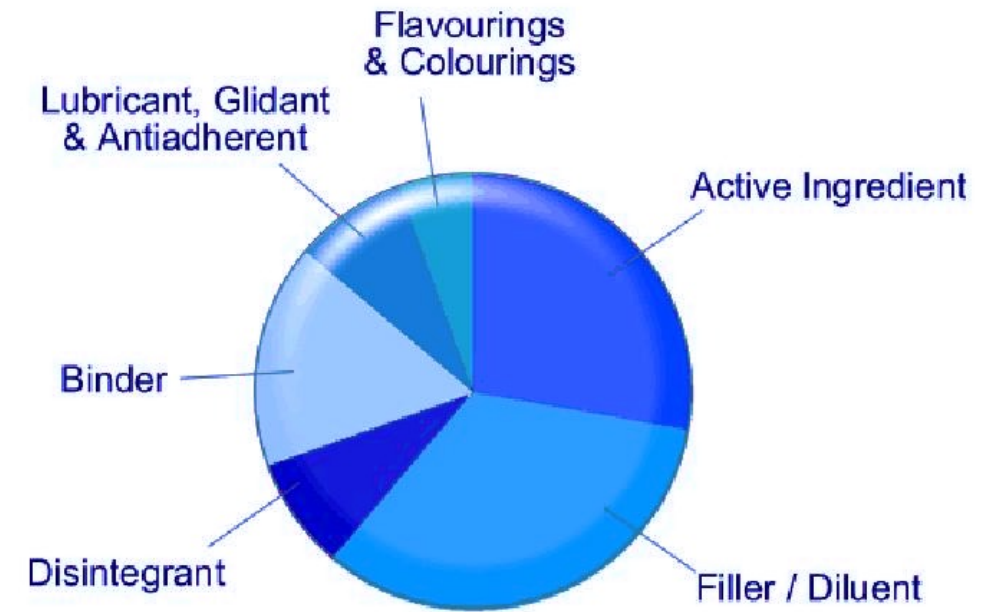




Tablet Excipients



- Tablets usually contain materials in addition to the active ingredient. All "nondrug" materials of the formula are called excipients.
- Excipients are necessary for the following reasons:
 1. Some drugs have small doses that cannot be compressed alone, e.g., Digoxin 0.25 mg.
 2. Some drugs have poor compressibility and flowability that cannot be compressed alone.
 3. If the tablets are compressed alone, they will not disintegrate **or** disintegrate very slowly.



Typical Tablet content

Ideal Excipient



- According to their function, excipients are classified into **diluents, binders, disintegrants, lubricants, glidants, colorants, flavors and sweeteners.**
1. Reasonable cost.
 2. They must not be troublesome by itself. e.g., sucrose and sodium salt.
 3. They must be physically, chemically and biologically stable.
 4. They must have no negative effect on the bioavailability of the active ingredient.
For example, tetracycline formulas made with calcium phosphate as a diluent had less than half the bioavailability of the other tetracycline products.
 5. They should be inert with no biological activity and non toxic.

Diluents (Fillers)



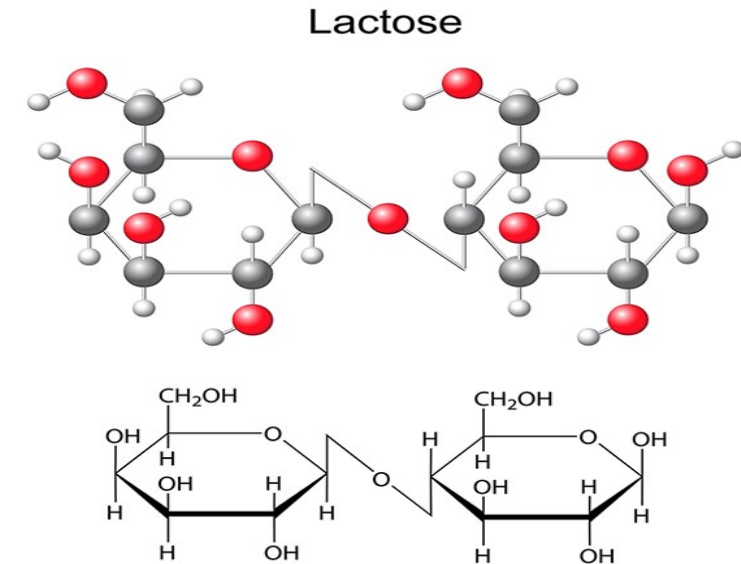
- Diluents are materials used to make up the required bulk of the tablet when the drug itself is inadequate to provide this bulk.
- Occasionally, the active ingredient has large dose and good compressibility so that it does not need diluent, e.g., aspirin and some antibiotics.
- Round tablets are usually in the size range of 5-13 mm. Tablets below 5mm may be difficult for elderly to handle and those larger than 13 mm become difficult to swallow.
- Diluents are therefore used to formulate the tablets within the desired size range.
- There are large numbers of diluents and the following are examples on them:
- Lactose, Starch, Dextrose, Mannitol, Sucrose, Microcrystalline Cellulose

Diluents

Lactose



- The most widely used diluent in tablet formulation that has no reaction with most drugs.
- There are three forms of lactose available which are anhydrous, hydrous and spray dried lactose.
- **Anhydrous** lactose has an advantage over the other two types; on aging, it does not undergo discoloration (brown discoloration) with amines and alkali compounds.
- It is worth to mention that **anhydrous** lactose may pick up water from the environment and converts to the hydrous form when exposed to elevated humidity.
- When wet granulation is used for the production of tablets, the **hydrous** form is usually used since it is cheaper and its less hygroscopic.



Lactose



- **Spray dried** lactose is used for direct compression due to its good compressibility and flowability.
- In general, all lactose types show:
 1. Good drug release.
 2. Its granulations are easily dried.
 3. The disintegration time of lactose containing tablets are not very sensitive to variation in tablet hardness.
 4. Low cost.

Diluents 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 expert.
 2. Amount used: it is used as **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 **diluent** when added in the **dry form** at the beginning of the procedure (mixing step), **binder** when used **as a paste** in the preparation of wet mass step and **disintegrant** when added finally after granulation **as a dry form** (to allow rapid water uptake, swelling and destruction of the tablet).

Diluents



Dextrose:

- It is available in two form: hydrous and anhydrous.
- Dextrose is sometimes used in the formulas to replace some of lactose to minimize the discoloration (when used with alkaline compounds).

Mannitol:

- It is widely used in the mouth tablets such as chewable and orodispersible tablets because of its sweet taste (sugar) and pleasant feeling in the mouth (due to the negative heat of solution).
- 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 required high lubricant level.

Diluents



Sucrose:

- It is used sometimes in tablet formulations. In general, sucrose and sucrose based diluents are avoided by some manufacturers due to their effect on diabetic patients.

Microcrystalline cellulose:

- It is often referred to by the trade name Avicel®.
- It is multipurpose excipient used as **diluent** and **disintegrant**. It is inert and can be used with alkaline or acidic substances, has high purity and low moisture content.
- Avicel is directly compressible diluent due to its **good compressibility** and **flowability**. Due to the above feature, it is commonly used diluent in tablet formulation.
- Avicel containing tablets characterized by short disintegration time, high hardness, low friability and low weight variation. (*Why?*)
- Different grades of Avicel are available such as PH 101 (powder) and PH 102 (granules).

Binders



- 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 D.C). Below are some examples:

Acacia and tragacanth:

- Natural gums. These materials are more effective as solution than if they are used as powders. The disadvantages of them are that they differ in composition and performance according to their origin and they also easily contaminated by bacteria.

Gelatin:

- Natural protein and is more preferred than acacia and tragacanth and also easier to prepare in solution than the two gums. However, bacterial growth is also a troublesome.

Binders



Starch:

- One of the most commonly used granulating agents (binder). It is prepared by dispersing starch into water which is then heated for certain time. A properly made paste is translucent rather than clear.

Modified natural polymers:

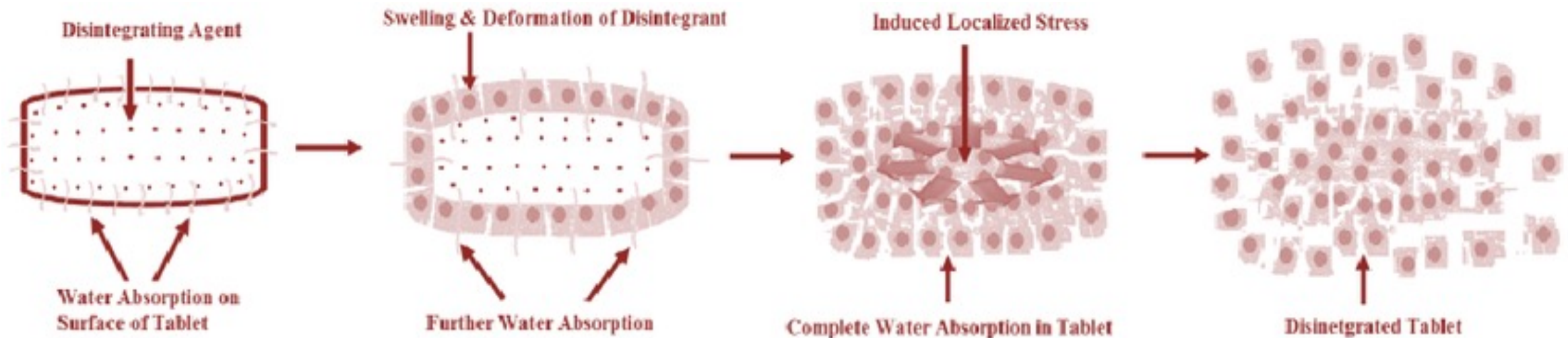
- Common and important binders. Alginates (e.g., **sodium alginates**) and cellulose derivatives (e.g., **methyl cellulose (MC)**, **ethyl cellulose (EC)**, **hydroxypropyl cellulose (HPC)** and **hydroxypropyl methyl cellulose (HPMC)**) are examples of these binders. Except EC, all of the cellulose derivatives can be used as dry powders (in D.C. and dry granulation) and as aqueous solution (in wet granulation). HPC can also be used as alcoholic solution, thus it is useful for water sensitive drugs.
- EC used only as alcoholic solution because it is insoluble in water, therefore it may retard tablet disintegration.

Polyvinyl pyrrolidone (PVP): is a synthetic binder and can be used as dry, aqueous and alcoholic solution. It is common binder especially in effervescent tablets.

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 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 subsequent dissolution of the drug and to achieve a satisfactory bioavailability.



Disintegrants



Starch

- The most commonly used disintegrants because of its 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 rupture of the tablet due to the increase in internal pressure.

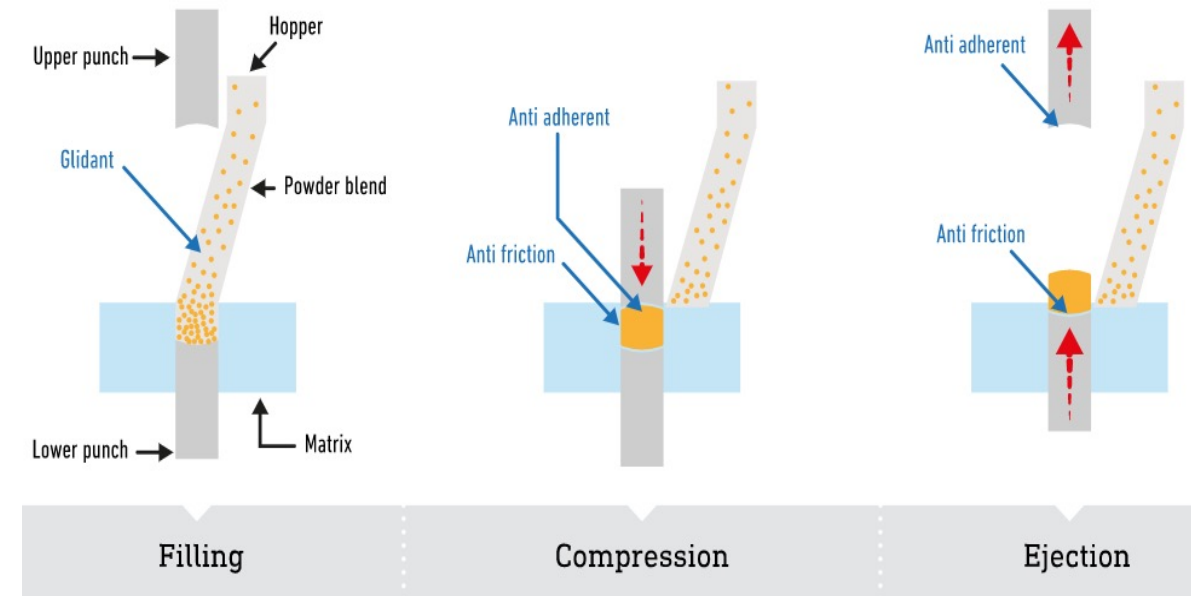
Super Disintegrant:

- They are so called due to their powerful disintegrating action. Examples on these materials are **sodium starch glycolate** (Explotab®), **croscarmellose sodium**.
- They are very potent if compared with the classic disintegrants. For example, croscarmellose sodium swells to 900% 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 and Glidants



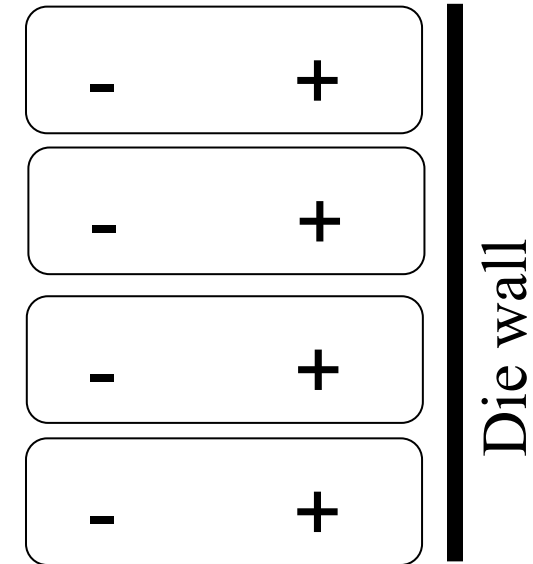
- **Lubricants** are materials used to reduce the friction during tablet ejection between the tablet and walls of the die.
- **Glidants** are used to promote the flow of granules or powders by reducing the friction between the particles themselves.
- Advantages of lubricants
 - 1. Facilitate tablets ejection and prevent their sticking in the die.
 - 2. Prolong the life of the die.
 - 3. Decrease the liberated heat (friction heat).



Lubricants and Glidants



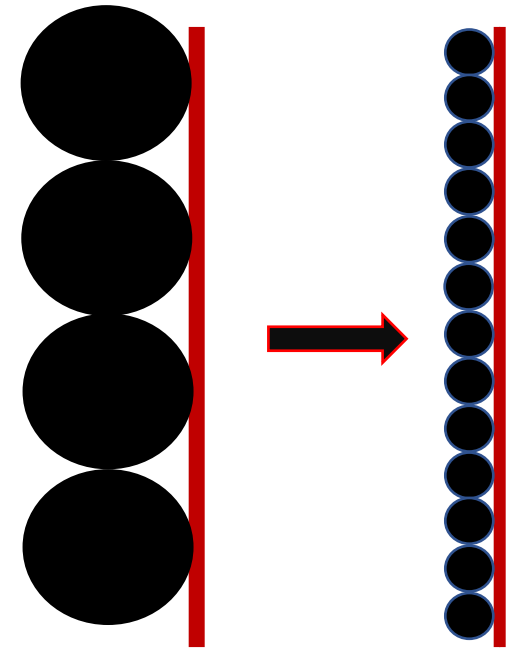
- **Mechanism of action of the lubricants**
 1. Fluid lubrication (Hydrodynamic (formation of thin film)): this mechanism is used for explain the action of *liquid* lubricants. In general, all liquids (especially oily ones) decrease the friction between two surfaces.
 2. Boundary lubrication: this mechanism is used for *solid* lubricants. In this type, the polar portion of the lubricant attached to the metal and prevent tablet sticking with the die.
- **Glidants** are thought to work by filling irregularities in granules making them more round and reduce friction between granules.



Notes About Lubricants



- 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.
- The **particle size** of the lubricants is very important; they should be 200 mesh in size or finer. As a general rule, as the particle size of the lubricants increase, their efficacy decrease.
- The **amount** of the lubricant in the formula should not exceed 1% (for most lubricants) since 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.
- In addition, adding excess lubricants will result that hydrocarbon portion cover the whole surface of the tablet and the interaction between particle will be replaced by interaction of hydrocarbons which is **weaker** and thus the tablet structure is weakened



Lubricants and Glidants



- The **mixing time** of the lubricant with the formula should be 2-5 min.
- Over mixing decrease the lubricant efficacy because it causes the penetration of the lubricant from the surface to the core of the formula.
- The **mixing rate** is also important; high mixing rate causes the penetration of the lubricant inside the core of the formula and thus, decreases the lubricant efficacy.
- Examples on the commonly used lubricants are listed below:
- **Mineral oils** such as **liquid paraffin** have been applied on the granules as **fine spray**. The problem with using this type of lubricants is the production of **spots** on the produced tablets. Other problem, is that the particle surface will be hydrophobic and may slower the dissolution rate and may alter bioavailability.

Lubricants and Glidants



- **Magnesium** and **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 property and small particle size. It is used effectively in direct compression.
- **Talc** may also be used as lubricant. **Problem:** it does contain trace amount of iron, so it should be applied carefully in any formulation containing drug whose breakdown is catalyzed by the presence of iron.
- **Poly ethylene glycols** (PEG) with molecular weight of 400-600 are used as lubricants in cases when water solubility is important. PEG are water soluble, but **less effective** than stearate group. They may be used as powder or solution to be sprayed on the formula.
- **Regarding the glidants**, they are less commonly used than the lubricants. Examples on these materials are **talc** and **Aerosil®**.

Colorant



- These materials are used for the following reasons:
 - 1. Product identification.
 - 2. The production of more elegant product.
 - 3. To hide undesirable properties. For example, vitamin C undergoes oxidation that causes brown discoloration, therefore vitamin C tablets are usually colored with yellow or red color.
- **Types of colorants**
 - 1. **Natural colorants:** are **not** preferred because they are limited (few colors are available) and unstable.
 - 2. **Dyes:** are synthetic colorants applied as *solution*. They are dissolved in the granulating solution. When using water soluble dyes, care should be taken to prevent their migration during the drying process.
 - 3. **Lakes:** they are *powders* insoluble in water mixed with the formula (as powder) and compressed with the tablet to give the desired color.



Flavors



- They are used only in mouth tablets to mask the undesirable taste. There are different types of flavors:
 1. **Water soluble flavors:** they are not preferred due to their poor stability.
 2. **Oily flavors:** they dissolved in suitable solvent and mixed with the binder solution. It is important that such flavors should tolerate the subsequent drying. The maximum allowed oily flavors is 0.5-0.75%.
 3. **Dry flavors:** these are dry powders blended with the formula.

Sweeteners



- They also used in mouth tablets.
- **Sucrose** not used commonly due to its effect on diabetics.
- **Mannitol** which is about 72% as sweet as sucrose can be used.
- Synthetic sugars such as **saccharine** are also used. This material is about 500 times sweeter than sucrose. However, it has disadvantage of bitter after taste and it is reported to be carcinogenic on large doses.
- **Aspartame** is another synthetic sugar and is more preferred than saccharine. Its disadvantage is that it has poor stability in the presence of moisture.