

# Tablets Excipients

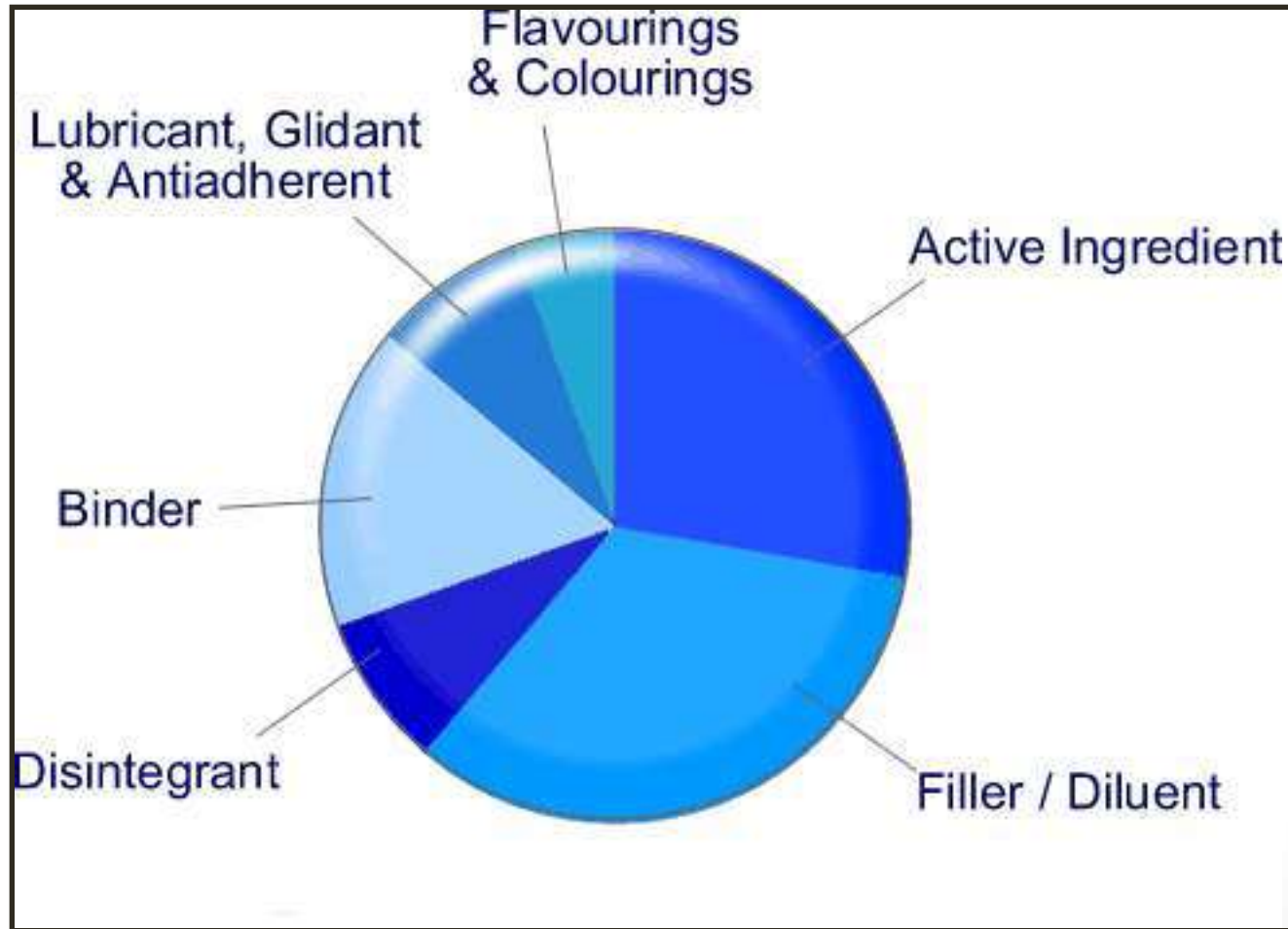
## **Their role:**

To ensure that tablets of specified quality are prepared.

The common types of tablet's excipients are described in the figure.

- **Fillers and Diluents**
- **Binders**
- **Coatings**
- **Disintegrants**
- **Coloring Agents**
- **Antiadherents**
- **Glidants**
- **Lubricants**
- **Sorbents**
- **Sweeteners**

# A typical tablet contains



## I-Diluent (filler or bulking agent):

Diluent adds bulk to make the tablet with practical size for compression and to be easily handled during manufacture and to achieve targeted content uniformity.

Tablets weigh normally at least 50 mg, therefore a low dose of a potent drug requires addition of a filler to increase the bulk volume of the powder and hence the size of the tablet.

Examples for potent drugs are:



Corticosteroid drugs such as;  
Dexamethasone (0.5 mg/Tablet)



Drugs used to replace thyroid hormone  
Levothyroid Tablet (0.05 mg/Tablet)

- Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk.
- Usually the range of diluent may be vary from **5-80%**.
- **Secondary reason** is to provide better tablet properties such as
  - improve cohesion,
  - to permit use of direct compression manufacturing
  - to promote flow
  - To adjust weight of tablet as per die capacity.

## A diluent should have following properties:

1. They must be non toxic
2. They must be commercially available in acceptable grade
3. Their cost must be low
4. They must be physiologically inert
5. They must be physically & chemically stable by themselves & in combination with the drugs.
6. They must be free from all microbial contamination.
7. They do not alter the **bioavailability of drug**.
8. They must be color compatible.

- Tablets diluents can be classified on the basis of their solubility in water into

<b>INSOLUBLE TABLET FILLERS OR DILUENTS</b>	<b>SOLUBLE TABLET FILLERS OR DILUENTS</b>
Starch Powdered cellulose Microcrystalline cellulose Calcium phosphates, etc.	Lactose Sucrose Mannitol Sorbitol, etc.

Tablet diluents may be divided into:

1- Organic materials: carbohydrate and modified carbohydrate **such materials exhibit binding properties in wet granulation.**

2- Inorganic materials: calcium phosphate and others.(not function as binder in wet granulation and direct compression)

3- co-processed diluents

- Filler is not necessary if the dose of the drug is high.
- One or more diluents may be used in one tablet preparation



# 1- Organic Carbohydrate diluents

## A- Sugar and sugar alcohols:

$\alpha$ -lactose monohydrate	Spray dried lactose	Anhydrous lactose
Not directly compressible ( suitable for wet granulation) Poor flow properties	Directly compressible Free flowing characteristic	Directly compressible <b>Not</b> exhibit free flowing
It contain app. 5% moisture which consider potential source of instability with moisture sensitive drugs.	Its compressibility is adversely affected if dried below 3% moisture	can pick up moisture at elevated humidity changing tablet dimension
Usually <b>unreactive, except discoloration</b> when combined with amine and alkaline (maillard reaction)	<b>More prone to darkening</b> in presence of excess moisture, amine due to furaldehyde Usually <b>neutral or acidic</b> lubricant should be used	<b>Not</b> undergo maillard reaction as spray dried lactose. Although may occur to slight degree in some cases
Inexpensive. Water soluble , not affect drug release rate	Expensive High dilution effect	Inexpensive

## Sucrose (Sugar)

## Mannitol

## Sorbitol

- Water soluble
- Has good binding properties used in direct compression
- Inexpensive
- Slightly hygroscopic, pick up moisture at high humidity
- Produce gritty mouth feel
- Calorie contributor and carcinogenic

- Sugar alcohol, it is optical isomer of sorbitol, water soluble
- Poor flowability and **required high lubricant levels**
- Most expensive sugar
- Non hygroscopic and can be used in vitamins formulations
- Widely used in chewable tablets bec. of its negative heat of solution, its slow solubility and its mild cooling sensation in mouth
- Low calorie value and is non carcinogenic

- Optical isomer of mannitol, water soluble
- Highly compressible
- Combined with mannitol formulation to reduce diluent cost
- Hygroscopic in nature at humidity's above 65%
- Has good mouth feel and sweet cooling taste
- Low calorie value and is non carcinogenic

## **B- Cellulose**

### **Powdered cellulose**

- Consist of finely divided amorphous and crystalline  $\alpha$ - cellulose particles.
- May be used alone or together with other filler.
- Has **poor compressibility** and **poor flow** properties.
- Has **poor binding properties** and **low dilution potential**.
- It is water insoluble.
- It is inexpensive.
- Posses some degree of inherent lubricity.

### **Microcrystalline cellulose (MCC)**

- Is **highly compressible** and perhaps the most widely used **direct compression tablet diluent**.
- **Hard tablet**, at low pressure are usually obtained when MCC is used.
- It undergo plastic deformation on compression and hence it is more sensitive to lubricants

- It exhibit **fair flowability**,
- They are biocompatible, chemically inert and they have good tablet forming and disintegration properties.
- They are also used as **dry binders** and **disintegrants** in tablet manufacture.
- Trade names for MCC are Avicel<sup>®</sup> PH 101 & 102 , Ambicel<sup>®</sup> and Flocel<sup>®</sup>.

## Starch and modified starch

- Sta-Rx 1500 <sup>®</sup> is direct compressible, freely flowable and self - lubricant.
- it is function as **diluent, disintegrant** and **binder**.
- Celutab <sup>®</sup> and Emedex <sup>®</sup> (dextrose +maltose)  
Used in chewable tablets bec. of sweetness and smooth mouth feel.

As an alternative to **mannitol**

## 2- Inorganic salts as fillers:

- An important example is **Calcium phosphate dihydrate**; it is **water insoluble, non-hygroscopic**, but hydrophilic i.e. easily wetted by water.

Hard tablets are produced when calcium phosphates are used as - diluent. They exhibit **good flow properties**.

- They are commonly used both as **wet granulation and direct compression diluent** in tablet formulation.

- it is inexpensive

- Calcium phosphates are **highly alkaline** and thus be **incompatible** with drug sensitive to alkaline conditions.

- They are abrasive in nature and hence cause wear of tablet tooling.

- **High bulk density** than organic fillers. They are used extensively in vitamins and mineral preparation.

### 3- Co-processed excipients

are a combination of two or more excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change.

These excipients have high functionalities as compared to individual excipients like better flow property, compressibility, reduced lubricant sensitivity.

## 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 after considering **its properties** such as compatibility, flowability, solubility, disintegration qualities, hygroscopicity, lubricity and stability.

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.

# POP QUIZ

In chewable tablet formulation, ----- can added as diluent to give palatable taste.

- A- Sucrose
- B- Emedex<sup>®</sup>
- C- Avecil<sup>®</sup>
- D- Starch





# POP QUIZ

To prepare an alkaline drug having poor compressibility and slightly soluble in water by direct compression method. So better to use ----- as diluent in its formulation.

- A- Spray dried lactose
- B- Calcium phosphate
- C- Cellulose
- D- Sorbitol



## II- Binder (adhesive):

Binder is added to drug-filler mixture.

- To promote **cohesive compacts** during direct compression and ensure the tablet remaining intact after compression.
- To promote **granulation** (i.e. as granulator) to ensure free flowing properties of the particles.
- Binders are used either in a **solution** or in a **dry form** depending on other materials in the formulation & the method of preparation.
- 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.

# Examples for binders

Common traditional solution binders are:

- Natural gums: acacia , tragacanth solution 10-25% conc.
- 25-50% solution of glucose
- Cellulose derivatives: methylcellulose, Hydroxypropylcellulose
- Polyvinylpyrrolidone (PVP) 2%
- 10-20% solution of gelatin, freshly prepared and used while warm.
- **Ethylcellulose 5% solution (insoluble in water but dissolved in alcohol or as dry binder), it is widely used as a binder for moisture sensitive materials.**

## **-Starch paste**

It is prepared by dispersing corn starch in cold purified water to make a 10-20% w/w solution, followed by warming in a water bath with continuous stirring until a translucent paste is formed. Starch paste is not only useful as a binder, but also as a disintegrant; as during paste formation, not all the starch is hydrolyzed.

### III- Disintegrant:

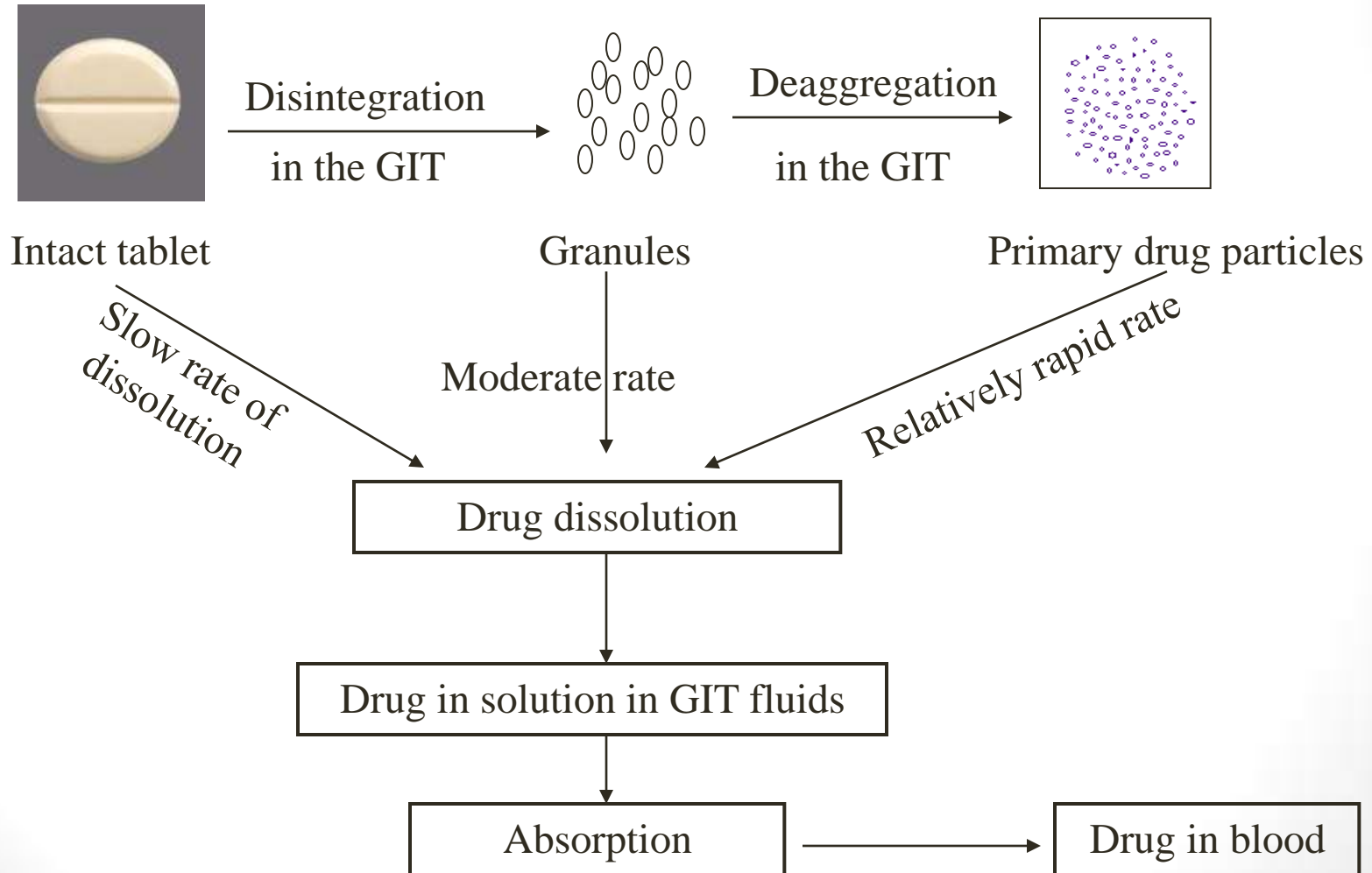
Disintegrant is added to tablet formulation:

- To facilitate tablet disintegration (break up) when it contacts the fluids in GIT and thus promotes rapid drug dissolution.



Tablet disintegration

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



# Mechanisms of action of disintegrants:

All disintegrants are hygroscopic and draw fluids into the matrix

Two main mechanisms:

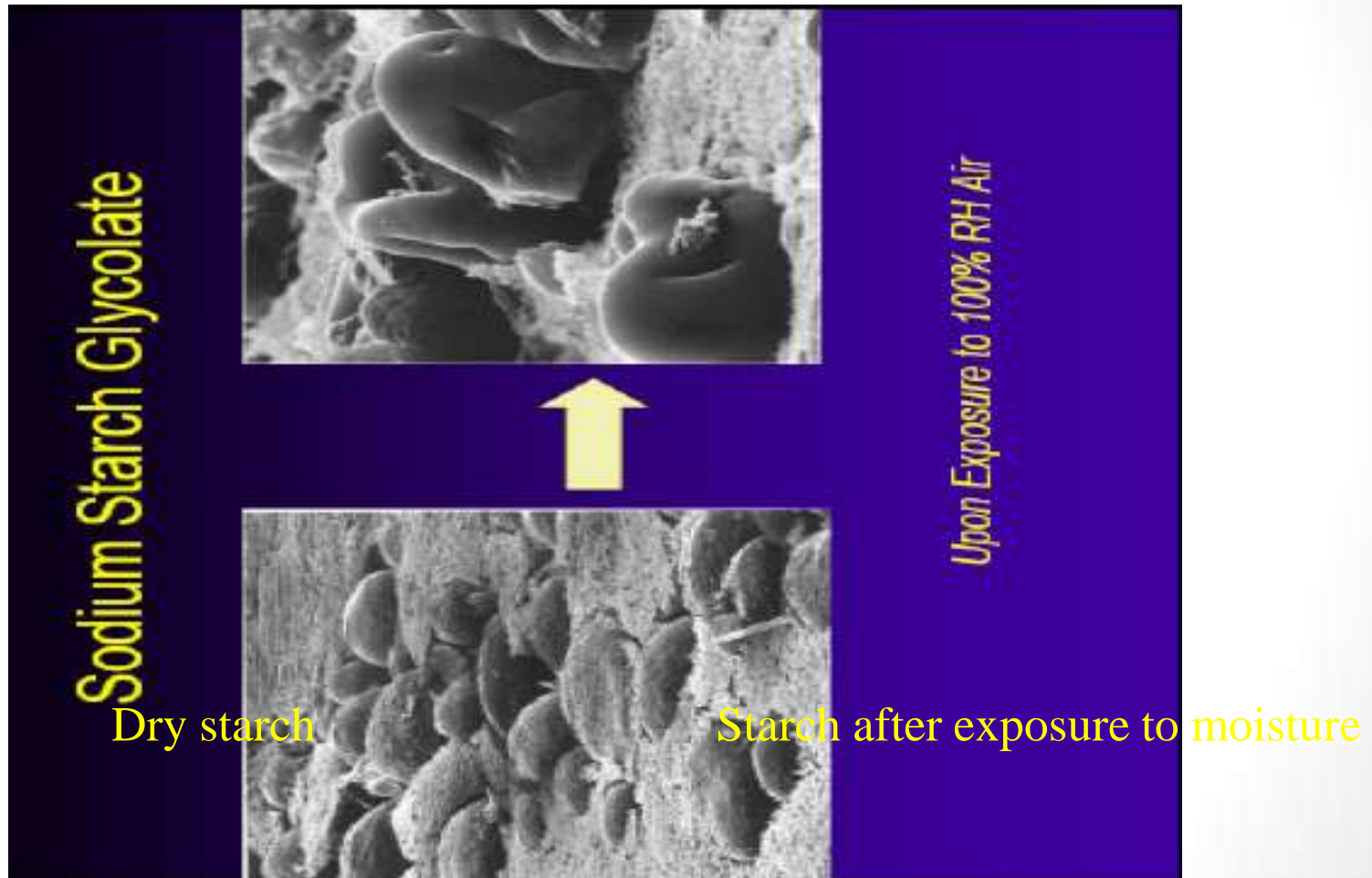
## 1- Facilitate water uptake:

✦ They act by facilitating the transport or drawing water into the tablet pores, and causing the tablet to burst and break into fragments,

e.g. starch may promote fluid penetration by capillary forces to suck water into the tablet; the spherical shape of the starch grains increases the porosity of the tablet, thus promoting the capillary action.

## 2- Rupture the tablet:

Tablet rupturing can be caused by swelling of the disintegrant particles during absorption of fluids (in the GIT).



# Theories of disintegration

The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

- A. By Porosity and Capillary Action ( wicking)
- B. By swelling
- C. Because of heat of wetting ( air expansion)
- D. Due to disintegrating particle/particle repulsive forces
- E. Due to deformation
- F. Due to release of gases
- G. By enzymatic action



# Examples for disintegrants

Common disintegrants include:

- Starch and its derivatives (Sodium Starch Glycolate).
- Cellulose and its derivatives (MCC, Sod CMC and Croscarmellose)
- Clays (Veegum, bentonite)
- Alginates
- Cation exchange resin

1- The most **traditional disintegrant** in conventional tablet is Starch (e.g. potato, maize and corn starch).

Its concentration as disintegrant is up to 10%. They swell in water causing tablet rupturing. Starch in combination with SLS is an effective disintegrant.

2- **Super-disintegrants**; they can swell dramatically upon exposure to water and thus quickly and effectively break the tablet. They are included in the formulation at relatively low concentration 1-5% by weight. Examples are:

- modified starch (e.g. **Sodium Starch Glycolate** that swells **7-12** fold in less than **30 sec**).
- modified cellulose (e.g. **Croscarmellose** that swells **4-8** fold in less than **10 sec**).
- **Crosspovidone** ( cross-linking povidone polymer)

Type of disintegrant	Examples	comments
Traditional disintegrants	<b>starch</b>	Swell in water causing tablet rupture
Super disintegrants	Modified starch-Sodium starch glycolate ( <b>Explotab</b> )	Swell dramatically upon expose to water
Enzymes as disintegrants	<b>Cellulases</b> with cellulose derivative binders. <b>Amylases</b> with starch binders	Act directly on the binder used in the wet granulation process
Special type of disintegrants	Bicarbonate or carbonate salts in combination with citric or tartaric acid	Evolve of carbon dioxide Used in effervescent tablets

# How is disintegrant added during the tablet manufacturing?

Extragranular addition	Intragranular addition	Both Intragranular and Extragranular addition
<p>- It is more common for the disintegrant to be mixed with the dry granules before tablet compression</p> <p>-This procedure will contribute to an effective disintegration of the tablet into small fragments</p>	<p>-Disintegrant can be mixed with other ingredients prior to granulation and thus incorporated into the granules</p>	<p>- Disintegrant may also be added in two steps: A portion is added to drug diluent mixture (Intragranular addition) and the other portion is mixed with the dry granules before compression (Extragranular addition). Double disintegration of tablet.</p>

- **Other factors than the presence of disintegrants can affect significantly the disintegration time of compressed tablets:**

1- The binder

5-porosity

2- Tablet hardness

3- Lubricant.

4- Evolution of carbon dioxide. As in effervescent tablets

# Lubricant

- Lubricant functions in tablet manufacture.
- Prevent adhesion of the tablet material to the surface of the dies and punches.
- Reduce inter particles friction.
- Facilitate the ejection of the tablets from the die cavity.
- May improve the rate of flow of the tablet granulation.
  
- Commonly used lubricants include: talc, magnesium stearate, calcium stearate ,stearic acid, hydrogenated vegetable oils and (PEG).
  
- Most lubricants, with the exception of talc, are used in concentrations less than 1%. When used alone, talc may require concentrations as high as 5%.

## IV- Glidants, antiadherents and lubricants

They have overlapping functions:

**A- Glidants** promote the flow of the tablet granules or powder by reducing friction between particles, e.g. colloidal silica.

**B- Antiadherents** reduce sticking or adhesion of the tablet granules or powders to the faces of the punches or the die walls, e.g. Mg stearate, talc and starch.

**C- Lubricants** reduce the friction occurs between the walls of the tablets and the walls of the die cavity when the tablet is ejected, e.g. Mg stearate, waxes and talc.

## A.Glidants:

- They are used in the formulation for direct compression.
- They are also added to the granules before tableting to ensure **proper flowability of the tablet mass for high production speed.**

## Examples for glidants:

- Traditional glidant is *Talc powder*
- The most common glidant today is *colloidal silica (Aerosil<sup>®</sup>)* 0.2% by weight.
- Silica particles are very fine so they adhere to the surfaces of other ingredients and improve the flow by **reducing interparticulate friction.**
- Mg stearate** is mainly used as lubricant but also can be used as glidant (< 1%).

## **B. Antiadherents:**

-Many powders are prone to adhere to the punches "sticking" or "picking", which is affected by the moisture content of the powder. So antiadherents **reduce sticking or adhesion** of the tablet granules or powder to the face of the punches or the die walls.

- **Such adherence specially occurred if the tablet punches have markings or symbols.**



## **Examples of antiadherents:**

-Mg stearate

-Talc

-Starch



## **C. Lubricants:**

Lubricants are included in all tablet preparations. High friction during tableting can cause serious problems; inadequate tablet quality (tablet fragmentation during ejection) and may even stop production.

The lubricant should be finely divided by passing through a 100-mesh nylon cloth onto the granulation.

## **Examples for lubricants**

- Stearic acid and its salts.
- Mg stearate is the most commonly used lubricant owing to its superior lubricant property (<1% by weight).
- Talc 5% concentration.
- Waxes and hydrogenated vegetable oils.

# Problems due to lubricants

- 1- They may reduce tablet strength (HOW?) due to their interference with the bonding between the particles during compression. {and thus may counteract the role of the binder }.
- 2- They may retard tablet disintegration and dissolution such as magnesium stearate (WHY?) because most lubricants are hydrophobic (counteract the role of disintegrant). To overcome these waterproofing characteristics, sodium lauryl sulfate is sometimes included.
- 3- Alkaline metal stearates (aluminum stearate) and talc are incompatible with some drugs e.g. aspirin and ascorbic acid. It is preferable to use hydrogenated vegetable oil or stearic acid with aspirin.

## How to avoid this negative effect?

- 1- Minimum amount of lubricant is to be used.
- 2- More hydrophilic substances are suggested as alternatives e.g. surfactants and polyethylene glycol (PEG).
- 3- Combination hydrophobic and hydrophilic substances may be also useful.
- 4- Lubricants are added to granules before compression in a finely divided form.

# POP QUIZ

The substances that prevent sticking of tablets to the tools of tablet machine during compression so they facilitate removal of tablets from the die, is known-----

- A- diluents
- B- disintegrants
- C- lubricants
- D- binders



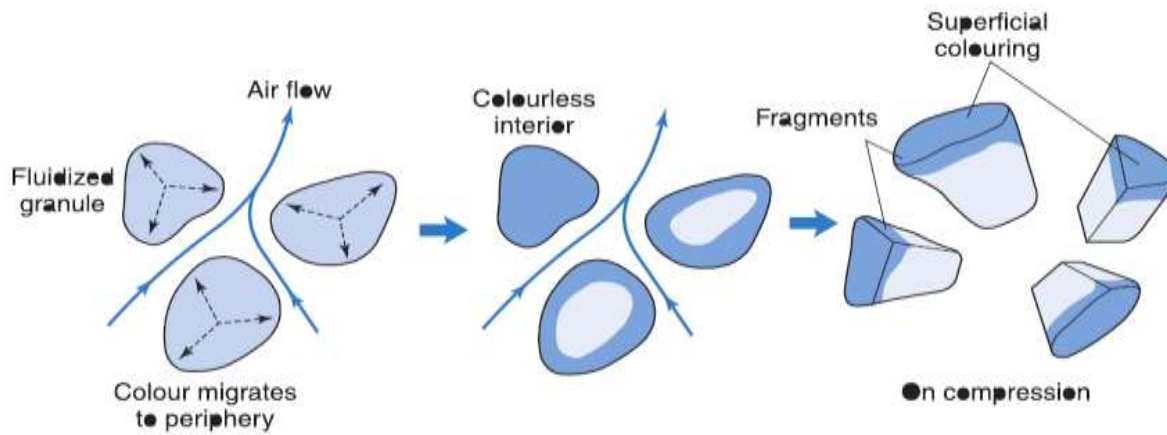
## V- Coloring agents (Colorants):

They are added to the tablet formulation to **mask off color drug**, to **provide product identification** and **acceptable appearance** which is more elegant .



- All colorants used in pharmaceuticals must be approved and certified by the FDA. Two forms of colors are used in tablet preparation – FD&C and D&C dyes.
- Colorants are often accomplished **during coating**, but can be also included in the formulation **prior to compaction**. In the latter case, the colorant can be added as a **soluble dye** (wet granulation process) or **insoluble lakes** (direct compression).

**Soluble dyes** when added to granulation liquid may lead to color variation (tablets mottling) that caused by intra-granular **migration** of soluble dye during **drying stage** which may give rise to dry granules with highly colored outer zone and a colorless interior. During compaction granules are fractured and colorless interior is exposed resulting in mottled tablet.



**Mottled tablet**

9.12 • Diagram of mottling caused by intragranular migration.

Using **Insoluble aluminum “Lake” colorant** as dry insoluble powder (in which soluble dye strongly adsorbed onto insoluble Alumina particles) in preference to soluble dye. The production of small granules which do not fracture so readily are preferable to avoid tablet mottling.

## VI- Flavoring agents & sweeteners:

- They are usually limited to chewable tablets or tablets that are intended to dissolve in mouth, to impart pleasant taste to mask unpleasant taste.

### Flavoring agents:

- Water-soluble flavours usually have poor stability. For this reason flavour oils or dry powders are typically used.
- Oil flavors may be added to tablet granules **just before compression** (WHY?) because they are sensitive to moisture and volatilization upon heating (during drying process).
- Since oils interfere with flowability and compressibility of the granules, minimum amount of the flavouring agent (0.5% of the granulation) is used to avoid their negative effect on the tablet characteristics.

## Sweetening agents:

- Some sweeteners may come from the diluent (e.g. lactose and mannitol).
- Artificial sweeteners such as Saccharine and Aspartame may be also included.
- Saccharine has an unpleasant after taste.
- Aspartame is unstable in presence of moisture and heat.

## **Examples of Sweeteners :**

Saccharin is about 400 times sweeter than sucrose but it has bitter after taste , which can be minimized by the addition of 1% of sod. Chloride .

Aspartame is about 180 times sweeter than sucrose .



- **Compaction**, an essential manufacturing step in the manufacture of tablets, includes:
- **compression** (i.e., volume reduction and particle rearrangement),
- **consolidation** (i.e., interparticulate bond formation).

# POP QUIZ

Which of the following excipients of tableting are superdisintegrants ?

- 1) Cross-binding PVP
- 2) Carboxymethyl cellulose
- 3) Sodium starch glycolate
- 4) Cellulose acetate phthalate

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**Note** Superdisintegrant is preferred in analgesic tablet formulations, why????



# POP QUIZ

The flavor and sweetener are usually recommended to be added in the formulation of -----

- A- Enteric coated tablets
- B- Implanted tablets
- C- Sublingual tablets
- D- Effervescent tablets





**Thank  
You!!!**



**Q1- Enumerate four different mechanism of disintegration with an example for each ?**

**Q2- Name the excipients type according to their function in the tablets for the following : ( arrange your answer in a table)**

**Calcium stearate**

**Crosspovidone**

**Silicone dioxide**

**Celutab**

**Starch**

**Sorbitol**

**Polyvinylpyrrolidone**

**Microcrystalline cellulose**

**Glucose solution**

**Aspartame**