

## **TABLET COMPONENTS/ FORMULATION**

A tablet contains active ingredients as well as other substances known as excipients, which have specific functions.

Ingredients used in tablet formulation are:

1. Active Ingredient/Drug/API
  - a. Insoluble drug- exert local effect
  - b. Soluble drug- exert systemic effect
2. Excipients/Additives/Inactive Pharmaceutical ingredients/Nonactive ingredients
  - a. Diluents/Fillers
  - b. Binders/Adhesive
  - c. Disintegrants
  - d. Antifrictional agent
    - I. Lubricants
    - II. Glidants
    - III. Antiadherants
  - e. Organoleptic additives
    - I. Colors
    - II. Flavoring agent
    - III. Sweetener
  - f. Co-processed Excipients

### **Additives/Excipients:**

A pharmaceutical excipient is defined as an inactive ingredient or any component other than the active ingredient added intentionally to the medicinal formulation or everything in the formulation except the active drug.

Pharmaceutical excipients are also called additives, pharmaceutical ingredients, or inactive pharmaceutical ingredients.

### **Criteria for Selection of Additives/Excipients:**

- ✓ No harmful or toxicological effect and listed as GRAS (generally recognized as safe).
- ✓ Good stability with no drug – excipient incompatibility and by any impurities in the excipients.
- ✓ No interference in quality validation and analytical tests.

- ✓ Satisfaction of regulatory issues and guidelines in all countries where the product is to be marketed.
- ✓ No instability with primary packing materials.
- ✓ Ease of accessibility, distribution, and economical cost.
- ✓ Satisfaction for environmental issues.
- ✓ Be physiologically inert.
- ✓ Be physically and chemically compatible with the active substance and the other excipients in the formulation.
- ✓ No unacceptable microbiological burden.

## **DILUENTS/FILLERS**

Diluents are the inert substance added to increase the bulk of the tablet.

### **Objectives of incorporating diluents:**

- ✓ In order to produce tablets of reasonable size (i.e. minimum diameter of 3mm), it is necessary to add an inert material known as Diluent/ Filler.
- ✓ Diluent increase the bulk in order to make the tablet a practical size for compression.
- ✓ The dose of some drugs is sufficiently high that no filler is required (e.g. aspirin and certain antibiotics).
- ✓ Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties that will help in disintegration of the tablet in the mouth by chewing. Such tablets are commonly called **chewable tablets**.
- ✓ Diluents used for direct compression formulas give the powder mixture necessary flowability and compressibility.
- ✓ To delay or control the rate of release of drug from the tablet.

### **Characteristics of ideal diluents:**

- ✓ They must be nontoxic and acceptable to the drug-regulatory agencies in all countries where the product is to be marketed.
- ✓ They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
- ✓ They must be cheap compared to the active ingredients.
- ✓ They must be physiologically inert.
- ✓ They must be chemically stable alone and/or in combination with the drug(s) and/or other tablet components.
- ✓ They must be free of any unacceptable microbiologic "load".
- ✓ They must be color-compatible.
- ✓ They must have no negative effects on the bioavailability of the drug(s) in the product.

## CLASSIFICATION OF DILUENTS:

Sugars	Polysaccharides	Inorganic compounds	Miscellaneous compounds
Dextrose	Starches	Calcium phosphate dihydrate	
Lactose	Modified starch	Calcium sulfate dihydrate	Bentonite
Sucrose	e.g. Sta-RX 1500, Celutab etc.	Calcium lactate trihydrate	Polyvinyl Pyrrolidone (PVP)
Amylose	Cellulose	Calcium carbonate	Kaolin
Mannitol	Cellulose derivatives	Magnesium carbonate	Silicone derivatives
Sorbitol	Microcrystalline cellulose (MCC)	Magnesium oxide	
Inositol			

### CALCIUM SALTS

Example:

Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP)

Dibasic calcium sulfate dihydrate

#### Advantages:

- Possess very low concentration of unbound moisture.
- Low affinity for atmospheric moisture.
- Excellent diluents for water-sensitive drugs.
- Bound water of calcium sulfate is not released below 80°C.
- It is superior to anhydrous diluent, which has a moderate to high moisture demand.

#### Disadvantages:

- Tetracycline products made with calcium phosphate diluent had less than half the bioavailability of the standard product.
- Divalent cation (Ca<sup>++</sup>) form insoluble complexes and salts with number of amphoteric or acidic functionality antibiotics, which generally reduces their absorption.

## LACTOSE

- Most widely used diluent for tablet formulation.
- It is obtained in hydrous and anhydrous form.
- The anhydrous form picks up moisture when exposed to elevated humidity. Such tablets should be packed in moisture proof packets or containers.
- When a wet granulation method is employed, the hydrous form of lactose should generally be used.
- Two grades of lactoses are commercially available:
  - (i) 60 to 80 mesh – coarse grade
  - (ii) 80 to 100 mesh – regular grade

### Advantages:

1. Lactose has no reaction with most of the drugs, whether in hydrous or anhydrous form.
2. Lactose formulations show good release rates
3. Their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness.
4. It is a low cost diluent.

### Disadvantages:

1. Lactose reacts with amine drug (aminophylline and amphetamine) in presence of alkaline lubricants e.g. metal stearates (e.g. magnesium stearate) and gradually discolours (dark brown) with time due to the formation of furaldehyde. This reaction is called **Maillard reaction**.

## SPRAY DRIED LACTOSE

### Advantages:

1. It is used for direct compression (containing drug + diluent + disintegrant + lubricant).
2. Spray dried lactose also has good flow characteristics.
3. It can usually be combined with as much as 20 to 25% of active ingredients without losing these advantageous features.

### Disadvantages:

1. If spray dried lactose is allowed to dry out and the moisture content falls below the usual 3% level, the material loses some of its direct compressional characteristics.
2. Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds owing to Maillard reactions. Hence, a neutral or acid lubricant should be used.

## STARCH

- Starch may be obtained from corn, wheat or potatoes.
- Occasionally used as a tablet diluent

- USP grade of starch is usually possesses moisture content between 11 to 14%.
- Specially dried types of starch that have a standard moisture level of 2-4% are available, but are costly.
- Use of such starches in wet granulation is wasteful since their moisture level increase to 6-8% following moisture exposure.

#### DIRECTLY COMPRESSIBLE STARCHES

Sta-Rx 1500 – free flowing, directly compressible starch

– used as diluent, binder, disintegrant

Emdex and Celutab – are two hydrolyzed starches

– contains dextrose 90–92%

maltose 3–5%

– free flowing and directly compressible

– may be used in place of mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

#### DEXTROSE (D–Glucose)

- Available under the name Cerelose
- Available in two forms: as hydrates and anhydrous forms.
- Dextrose may sometimes be combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.

#### MANNITOL

##### Advantages

- Because of the negative heat of solution (cooling sensation in the mouth), its slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets.
- It is relatively non-hygroscopic and can be used in vitamin formulations.
- Low calorie content and non-carcinogenic.

##### Disadvantages

- Costly
- Mannitol has poor flow characteristics and usually requires fairly high lubricant level.

#### SORBITOL

- It is an optical isomer of mannitol.
- Sometimes combined with mannitol formulations to reduce the diluent cost.
- Low caloric content & Noncariogenic.

Disadvantages: It is hygroscopic at humidities above 65%.

## SUCROSE

- Some sucrose based diluents are:
  - Sugar tab– 90 to 93% sucrose + 7 to 10% invert sugar
  - Di Pac – 97% sucrose + 3% modified dextrans
  - Nu Tab– 95% sucrose + 4% invert sugar + small amount of corn starch + Mg-stearate

Advantages: They are all used for direct compression.

Disadvantages: All are hygroscopic when exposed to elevated humidity.

## MICROCRYSTALLINE CELLULOSE (MCC)

- Trade Name: Avicel – is a directly compression material
- Two grades are available PH 101 → powder  
PH 102 → granules

Advantages: It acts as diluent and disintegrating agents.

## BINDERS

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators.

### Objective of incorporating binders

1. They impart cohesiveness to the tablet formulation (both direct compression and wet-granulation method) which insures the tablet remaining intact after compression.
2. They improve the free-flowing qualities by the formation of granules of desired size and hardness.

### Characteristics of binder

*Method-I*

1. Binders are used in dry form in the powder and then moistened with a solvent (of the binder) to form wet lumps.
2. By this Method, the binder is not as effective in reaching and wetting each of the particles within the mass of the powder. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film of air which must be penetrated before the powder can be wetted by the binder solution.

*Method-II*

Binders are often added in solution form. It requires lower concentration of binder.

**Commonly Used Granulating (Binding) Agents**

<b>Granulating Agent</b>	<b>Normal Concentration (%)</b>
Starch Paste	5 – 25
Pregelatinized starch	0.1-0.5
Acacia	1-5
Polyvinylpyrrolidone (PVP)	2-8
Hydroxypropyl methylcellulose (HPMC)	2-8
Methylcellulose (MC)	1-5
Gelatin	10-20

**STARCH PASTE**

Corn starch is often used in the concentration of 10–20%.

Method of preparation

Corn starch is dispersed in cold purified water to make a 5 to 10% w/w suspension and then warming in water both with continuous stirring until a translucent paste is formed.. (Actually hydrolysis of starch takes place.)

**LIQUID GLUCOSE**

50% solution in water is fairly common binding agent.

## SUCROSE SOLUTION

50% to 74% sugar solution is used as binder. They produce hard but brittle granules. Their cost is low.

## GELATIN SOLUTION

Concentration 10–20% aqueous solution

Should be prepared freshly and added in warm condition otherwise it will become solid.

### Method of preparation

The gelatin is dispersed in cold water and allowed to stand until hydrated. The hydrated mass is warmed in water bath to dissolve.

## CELLULOSIC SOLUTIONS

HPMC (Hydroxy propyl methyl cellulose) Soluble in cold water.

Method of preparation: HPMC is dispersed in hot water, under agitation. The mixture is cooled as quickly as possible and as low as possible

HEC (Hydroxy ethyl cellulose), HPC (Hydroxy propyl cellulose) are other successful binders.

PVP (Polyvinylpyrrolidone) Used as an aqueous or alcoholic solution. Concentration 2% and may vary.

## LUBRICANTS

### **Objectives:**

1. Prevents adhesion of the tablet material to the surface of dies and punches.
2. Reduce inter-particle friction; improve the rate of flow of tablet granulation.
3. Facilitate ejection of the tablets from the die cavity.

### **Examples:**

Talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycols (PEG).



### Method of addition of lubricants:

1. The lubricant is divided finely by passing it through a 60 to 100 mesh nylon cloth on to the granulation. In production this is called 'bolting the lubricant'.
2. After addition the granulation is tumbled or mixed gently to distribute the lubricant without coating all the particles too well.
  - \* Complete coating will produce dissolution problem.
  - \* Prolonged mixing will produce excessive fines by breaking the granules.

### Soluble lubricants

Examples: Sodium benzoate – includes a mixture of sodium benzoate and sodium acetate

Sodium chloride, leucine and carbowax 4000.

### Magnesium stearate

Though it is a widely used lubricant it retards disintegration and dissolution. To overcome this sometime surfactants like sodium lauryl sulfate are included.

**Lubricants** are included to reduce the friction during tablet ejection between the walls of the tablet and the wall of the die in which the tablet was formed.

**Antiadherents** are used for the purpose of reducing the sticking or adhesion of any of the tablet ingredients or powder to the faces of the punches or to the die wall.

**Glidants** are intended to promote flow of the tablet granulation or powder materials by reducing the friction between the particles.

An ingredient used for lubrication purpose may possess other two properties as well.

Relative properties of some tablet lubricants:

Material	Usual Percent	Glidant properties	Antiadherent properties	Lubricant properties
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1. Calcium or Magnesium stearate	1 or less	Poor	Good	Excellent
2. Talc	1 – 5	Good	Excellent	Poor
3. Stearic acid	1 – 5	None	Poor	Good
4. High melting waxes	3 – 5	None	Poor	Excellent
5. Corn starch	5 – 10	Excellent	Excellent	Poor

### Water soluble lubricants

Lubricant	Percentage
Boric acid	1
Sodium chloride	5
Sodium benzoate	5
Sodium acetate	5
Sodium oleate	5
PEG 4000, 600	1 – 4
dl-leucine	1 – 5

### Water Insoluble lubricants

Lubricant	Percentage
Stearates (Mg, Ca & Na)	0.25-2
Stearic acid	0.25-2
Sterotex	0.25-2
Talc	1-5
Wax	1-5

Sterowet	1-5
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### Antiadherent

Materials	Usual range (%)
Talc	1-5
Corn starch	3-10
Cab-O-Sil	0.1-0.5
Syloid	0.1-0.5
DL-leucine	3-10
Sodium Lauryl sulphate	< 1
Metallic stearates	< 1

### Glidant

Materials	Usual range (%)
Talc	5
Corn starch	5-10
Cab-O-Sil	0.1-0.5
Syloid	0.1-0.5
Aerosil	1-3

### DISINTEGRANTS

Purpose of a disintegrant is to facilitate the breakup of a tablet after administration in the GIT.

Disintegrating agent may be added:-

- Prior to granulation

- During the lubrication step prior to compression.
- At both processing steps

Disintegrants can be classified chemically as Starches, clays, celluloses, alginates, gums and cross-linked polymers.

### Starch

Corn starch, potato starch

For their disintegrating effect starches are added to the powder blends in dry state.

#### *Mode of action:*

Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.

Others have suggested that the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action.

Normally 5% w/w is suggested. For rapid disintegration 10 – 15% w/w may be taken.

#### Starch Disintegrants

Materials	Range (%)
Natural starch (Corn, Potato)	1-20
Sodium starch Glycolate	1-20
Pregelatinized starch	5-10
Modified corn starch	3-8

### Super disintegrants

- Crosscarmellose - cross linked cellulose
- Crospovidone - cross linked polyvinyl pyrrolidone
- Sodium starch glycolate - cross linked starch

#### *Mode of action*

Crosscarmellose swells 4 to 8 fold in less than 10 seconds

Crospovidone acts by wicking or capillary action.

Sodium starch glycolate swells 7 to 12 folds in less than 30 seconds.

## Other materials

VeegumHV, Methyl cellulose, Agar, Bentonite, Cellulose, Alginic acid, Guargum and Carboxymethyl cellulose.

\* Sodium lauryl sulfate is a surfactant. It increases the rate of wetting of the tablet, thus decreases the disintegrating time.

## COLOURING AGENT

### Objectives of using colors

- i. Agent impart colour to the tablets
  - ii. It makes the tablet more esthetic in appearance.
  - iii. Colour helps the manufacturer to identify the product during its preparation.
- All colorants used in pharmaceuticals *must be approved and certified by the FDA (food & Drug Administration)*. Dyes are generally listed as FD&C (food, Drug & Cosmetic Dyes) dyes and D&C (Drug & Cosmetic Dyes).

Colour	Other Names	Color Index (CI, 1971)
D&C Red 22	Eosin Y	45380
FD&C Yellow 5	Tartrazine	15985
FD&C Yellow 6	Sunset Yellow FCF Yellow Orange 5	19140
FD&C Blue 1	Brilliant Blue FCF	42090
FD&C Blue 2	Indigocarmine	73015
FD&C Green 3	Fast Green FCF	42035
Caramel	Burnt sugar	
Titanium dioxide	–	77891

Colorants are obtained in two forms **dyes** and **lakes**.

- Dyes are dissolved in the binding solution prior to the granulating process. However, during drying their color may migrate to the surface and may produce mottling of the tablet.
- So another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with other ingredients.
- Color lakes are dyes which are adsorbed onto a hydrous oxide of a heavy metal (like aluminium) resulting in an insoluble form of the dye.

## FLAVOURS AND SWEETENERS

**Flavours** are usually limited to chewable & effervescent tablets or other tablets intended to dissolve in the mouth.

Improve acceptability among pediatric and geriatrics.

Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder).

Should be used only in the concentration range of 0.5 to 0.75% w/v.

e.g. Citrus oil, Cardamom tincture etc

**Sweeteners:** - Mainly used in chewable, effervescent & mouth dissolving tablets for improvement of taste.

e.g. Sugar

Mannitol – 72% as sweet as sugar, cooling & mouth filling effect

Saccharin – Artificial sweetener

500 times sweeter than sucrose

*Disadvantages* (i) it has a bitter after taste

(ii) carcinogenic

Cyclamate – either alone or with saccharin

– it is banned

Aspartame (Searle) – widely replacing saccharin & approved by FDA.

– *Disadvantage* – lack of stability in presence of moisture & discoloration in presence of ascorbic acid & tartaric acid.

## Co-processed Excipients

- ✓ These are the mixture of one or more excipients used in combination to improve their characteristics.
- ✓ Reduces the number of excipients in a formulation.
- ✓ Reduces the overall cost and time for processing.

<b>Co-processed excipients</b>	<b>Brand Name</b>
Cellulose and Lactose	Cellactose
Lactose and MCC	Microcelac 100
Lactose and Maize starch	Starlac
Lactose and PVP	Ludipress
MCC and Sodium CMC	Avicel CL-611