Tablet Ingredients/ Excipients

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

- Diluent / Filler
- Binder and adhesive
- Disintegrants
- Lubricants and glidants
- Colouring agents
- Flavouring agents
- Sweetening agents

Function of excipients

- Impart weight, accuracy, & volume.
- Improve solubility
- Increase stability
- Enhance bioavailability
- Modifying drug release
- Assist product identification
- Increase patient acceptability
- Facilitate dosage form design

Diluents

- Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk.
- Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow.

A diluent should have following properties:

- They must be non-toxic and low cost.
- They must be commercially available in acceptable grade
- They must be physiologically inert, physically & chemically stable by themselves & in combination with the drugs.
- They must be free from all microbial contamination.
- They do not alter the bioavailability of drug.
- They must be color compatible.

Cont.

Characteristics of an ideal diluents:

- They must be nontoxic and acceptable to the 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 and 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 color-compatible (should not produce any off-color appearance).
- They must have no negative effects on the bioavailability of the drug(s) in the product.

Cont.

Commonly used tablet diluents

- Lactose-anhydrous and spray dried lactose
- Directly compressed starch-Sta Rx 1500
- Hydrolyzed starch-Emdex and Celutab
- Microcrystalline cellulose-Avicel (PH 101and PH 102)
- Dibasic calcium phosphate dehydrate
- Calcium sulphate dihydrate
- Mannitol and Sorbitol
- Sucrose- Sugartab, DiPac, Nutab
- Dextrose

Cont.

- ***Lactose:*** Lactose is the 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) A 60 to 80 mesh – coarse

(ii) a 80 to 100 mesh – regular grade

Advantages:

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

Disadvantages:

- Lactose reacts with amine drug bases 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.

Cont.

- ***Calcium salts ((DCP/TCP):*** Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP) [$CaHPO_4$, $2H_2O$], Calcium sulfate dihydrate ($CaSO_4$, $2H_2O$).

Advantages:

- Diluents that exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization. This bound water of calcium sulfate is not released below 800C. They possess very low concentration of unbound moisture. Hence, these salts are excellent diluents for water-sensitive drugs. 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++) form insoluble complexes and salts with number of amphoteric or acidic functionality antibiotics, which generally reduces their absorption (which is also why milk should not be co administered with these drug).

Cont.

- ***Spray dried lactose:***

Advantages:

- It is used for direct compression (containing drug + diluent + disintegrant + lubricant).
- In addition to the direct compression properties, spray dried lactose also has good flow characteristics. It can usually be combined with as much as 20 to 25% of active ingredients without losing these advantageous features.

Disadvantages:

- 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.
- 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.

Cont.

- ***Starch:*** Starch may be obtained from corn, wheat or potatoes and rice. It is occasionally used as a tablet diluent. USP grade of starch is usually possesses moisture content between11 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. It is used as diluent, binder, disintegrant.
- Emdex and Celutab – are two hydrolyzed starches – contains dextrose 90–92% and maltose 3–5%
- free flowing and directly compressible and may be used in place or mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

Cont.

Dextrose (D–Glucose): 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 and has poor flow characteristics and usually require fairly high lubricant level.

Sorbitol

- It is an optical isomer of mannitol and is sometimes combined with mannitol formulations to reduce the diluent cost.

Disadvantages:- It is hygroscopic at humidities above 65%.

Cont.

Sucrose

- Some sucrose based diluents are:
- Sugar tab– 90 to 93% sucrose + 7 to 10% invert sugar
- Di Pac – 97% sucrose + 3% modified dextrins
- 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 and Adhesive

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

❑ They impart a cohesiveness to the tablet formulation (both direct compression and wet–granulation method) which insures the tablet remaining intact after compression.

❑ They improves the free-flowing qualities by the formation of granules of desired size and hardness.

How to add binder

Method-I

- Binders are used in dry form in the powder and then moistened with a solvent (of the binder) to form wet lumps.

Method-II

- Binders are often added in solution form. It requires lower concentration of binder.
- By Method-I the binder is not as effective in reaching and wetting each of the particles within the mass of the powder. Each of the particle 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-III

- In direct compression method MCC, microcrystalline dextrose, amylose and PVP are used – those have good flow property and cohesiveness as well.
- It has been postulated that MCC is a special form of cellulose fibril in which individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking intercrystallite bonds by the disintegrating medium.

Example of Binders

- ***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 other wise 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 (Polyvinylpyrollidone) Used as an aqueous or alcoholic solution. Concentration 2% and may vary.

Disintegrants

- A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after administration in the GIT. The active ingredients must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution.
- 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 and for rapid disintegration 10 – 15% w/w may be taken.

- ***Superdisintegrants***: Super disintegrants like Croscarmelose - cross linked cellulose, Crospovidone - cross linked polyvinyl pyrrolidone and Sodium starch glycolate- cross linked starch
- ***Mode of action***

❑ Croscarmelose 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***

❑ 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.

Lubricant and Glidants

Objectives:

- Prevents adhesion of the tablet material to the surface of dies and punches.
- Reduce inter-particular friction, improve the rate of flow of tablet granulation.
- Facilitate ejection of the tablets from the die cavity.

Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

- Example: Stearic acid, Stearic acid salt - Stearic acid, Magnesium stearate, Talc, PEG (Polyethylene glycols), Surfactants.

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.

- Example: Corn Starch – 5-10% conc., Talc-5% conc., Silica derivative - Colloidal silicas such as Cab-O- Sil, Syloid, Aerosil in 0.25-3% conc.

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.

Coloring agent

Objectives of using colors that

(i) It makes the tablet more esthetic in appearance and

(ii) Colour helps the manufacturer to identify the product during its preparation. Colorants areobtained 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 tablets or other tablets intended to dissolve in the mouth. 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).
- The use of ***sweeteners*** is primarily limited to chewable tablets. 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 and (ii) carcinogenic

- Cyclamate– either alone or with saccharin– it is banned
- Aspartame (Searle) – widely replacing saccharin

Disadvantage – lack of stability in presence of moisture