INDUSTRIAL PHARMACY-I

UNIT II-TABLETS AND LIQUID ORALS

CLASS 9

Topic :Excipients, Formulation of tablets

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

1. Diluent
2. Binder and adhesive
3. Disintegrents
4. Lubricants and glidants
5. Colouring agents
6. Flavoring agents
7. Sweetening agents

Excipients-functions

- Impart weight, accuracy, & volume(its allow acccuracy of dose)
- Improve solubility
- Increase stability
- Enhance bioavailability
- Modifying drug release
- Assist product identification
- Increase patient acceptability
- Facilitate dosage form design

DILUENTS:

- **Diluent:** 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.
- If the dose of the drug is high no diluents is required(ex:Asprin and certain antibiotics)
- Round tablets for ingestion are usually in a size range of 3/16 to ½ inch
- Size below 3/16 difficule for elders to handle above ½ inch difficult to swallow
- This provides a standard range of perhaps 120 to 700mg for standard density organic materials

A Diluent should have following properties:

- They must be non toxic
- They must be commercially available in acceptable grade
- There cost must be low
- They must be physiologically inert
- They must be 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.

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
- Sorbitol
- Sucrose- Sugartab, DiPac, Nutab
- Dextrose

LACTOSE

- most widely used diluent for tablet formulation
- obtained in hydrous and anhydrous form
- 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:
- 60 to 80 mesh– coarse
- 80-100 mesh –regular
- Lactose formulations show
- good drug release rates
- Granulations are readily dried
- Disintegration times not readily sensitive to hardness
- Low cost diluent

But discolor in the presence of amine drug bases or salta of alkaline compounds

Spray dried lactose

- Directly compressable vehicle
- Good flow characterstics
- Prone to darkening in presence of excess moisture ,amines and other compounds due to presence of furaldehyde

A neutral or acid lubricant should be used

CALCIUM SALTS

- Example:Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP)[$CaHPO_4$,2 H_2O],
- Calcium sulfate dihydrate ($CaSO_4$, $2H_2O$)

Advantages:

- Diluents -exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization.
- bound water of calcium sulfate is not released below 80^0C.
- possess very low concentration of unbound moisture.
- salts are excellent diluents for water-sensitive drugs.
- 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 (*whichis also why milk should not be co-administered with these drug*).

Starch

- obtained from corn, wheat or potatoes
- used as a tablet diluent
- USP grade of starch is usually possesses moisture content between 11 to 14%.

DIRECTLY COMPRESSIBLE STARCHES

Sta–Rx 1500 – free flowing, directly compressible starch

- – used as diluent, binder, disintegrant
- Requires addition of lubricant and 0.25%colloidal silicon dioxide as flow promoter

Emdex and Celutab

- are two hydrolyzed starches
- contains Dextrose 90–92%,Maltose 3–5%
- free flowing and directly compressible
- may be used in place or mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

DEXTROSE (D–Glucose)

- Available in two forms: as hydrates and anhydrous forms.
- available under the name of **cerelose**

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)
- slow solubility,
- pleasant feeling in the mouth

widely used in chewable tablets.

- relatively non-hygroscopic
- can be used in vitamin formulations.
- Low calorie content and non-carcinogenic.

Disadvantages

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

SORBITOL

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

Disadvantages: 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 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: acts as diluent and disintegrating agents.

Dis advantages: relatively expensive

BINDERS

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

Objective of incorporating binders

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

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.(during heating hydrolysis of starch takes place)

- Starch-----dextrin------glucose

LIQUID GLUCOSE

- 50% solution in water is fairly common binding agent.

SUCROSE SOLUTION

- 50% to 74% sugar solution is used as binder.
- produce hard but brittle granules.
- 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.

CELLULOSE DERIVATIVES

DRY-DIRECT COMPRESSION,AQUEOUS FORMS –ADHESIVE PROPERTIES

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

Method of preparation: HPMC is dispersed in hot water, under agitation.

- 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 ADHESIVE either aqueous or alcoholic solution.

Concentration 2% and may be used as dry binder

Ethyl cellulose -alcoholic solution

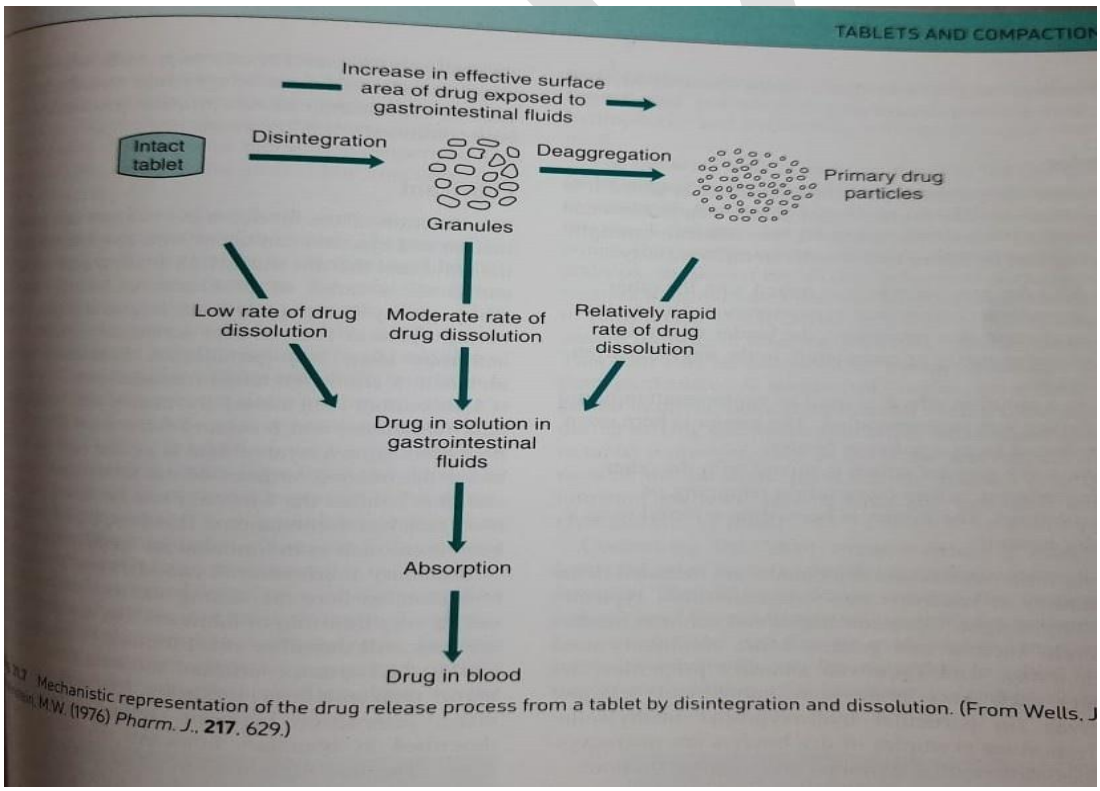
Retard disintegration and dissolution time

Disintegrants

Definition

- A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after administration in the GIT.
- 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.
- 

Mechanistic representation of the drug release process from a tablet by disintegration and dissolution. (From Wells, J ... M.W. (1976) *Pharm. J.*, **217**, 629.)

Method of blending with powder

The disintegrants are usually mixed with active ingredients and diluents prior to granulation. Starch may be divided into two portions:

- *One part* – added during the formation of granules prior to wetting with the granulating fluid

- *remainder* – added at the second mixing stage during compaction of granules into tablets –extra granular disintegrants cause the tablet –disintegrate quickly into granules
- Intragranular disintegrants break down the granules giving a finer product

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, facilitating the rupture of the tablet matrix.
- 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.
- Primogel and explotab are low substituted carboxy methyl starches (1 to 8% optimum 4%)

Super disintegrants- markedely reduce disintegration time

Superdisintegrants have improved efficiency and facilitate faster disintegration with smaller quantity, compared to regular disintegrants. Commonly used superdisintegrants are highly efficient at low concentration levels (2-5%w/w).

- Croscarmelose- cross linked cellulose
- Crospovidone - cross linked polyvinyl pyrrolidone
- 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**

- 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.

Lubricants/glidant/antiadhesives

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.

Examples:

Talc,

magnesium stearate,

calcium stearate,

stearic acid,

hydrogenated vegetable oils and

polyethylene glycols (PEG).

Lubricants/glidant/antiadhesives

- **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.

Method of addition of lubricants

- 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'.

After addition the granulation is tumbled or mixed gently to distribute the lubricant without coating all the particles too well

Soluble lubricants

- ExamplesSodium benzoate – includes a mixture of sodium benzoate
- sodium acetate Sodium chloride,
- leucine

carbowax 4000.

Magnesium stearate

- Though it is a widely used lubricant it retards disintegration and dissolution.

To overcome this some time surfactants like sodium lauryl sulfate are included

Anti adherents

- Talc
- Magnesium stearate
- Starch
- Starch derivatives
- Colloidal silicas

Glidants

- Talc 5%
- Corn starch 5 to 10%
- Colloidal silica Cab-O-sil

Syloid or aerosil in 0.25 to 3% concentration

- Act by lodging in the surface irregularities of the granule
- Reduce the interparticular friction
- Colloidal silica –advantage acts as a moisture scavenger provides drying facilities

Coloring agent

- **Coloring agent**: The use of colors and dyes in a tablet has three purposes:

(1) Masking of off color drugs

(2) Product Identification

(3) Production of more elegant product q

- All coloring agents must be approved and certified by FDA.
- Two forms of colors are used in tablet preparation – FD &C and D & C dyes.
- These dyes are applied as solution in the granulating agent or Lake form of these dyes.
- Lakes are dyes absorbed on hydrous oxide and employed as dry powder coloring. Example: FD & C yellow 6-sunset yellow,
- FD & C yellow 5- Tartrazine ,FD & C green 3- Fast Green,

FD & C blue 1- Brilliant Blue ,FD & C blue 2 - Indigo carmine

Flavoring agents/ Sweetening agents

- **Flavoring agents**: For chewable tablet- flavor oil are used 0.5 to 0.75%
- **Sweetening agents**: For chewable tablets: Sugar, mannitol.
- **Saccharine (artificial):** 500 time's sweeter than sucrose

Disadvantage: Bitter aftertaste and carcinogenic

Aspartame (artificial)

- Disadvantage: Lack of stability in presence of moisture.