Tablets Design and Formulation

Lecture 6

Industrial pharmacy

5th class

1st semester

Tablet Design and Formulation

All non-drug components of a formula are termed Excipients which are critical to the design of the tablet and play a major role in determining its quality and performance.

Conventional oral tablets for ingestion usually contain the same classes of components in addition to the active ingredients, which are one or more agents functioning as:

(1) Diluent

(2) Binder or an adhesive

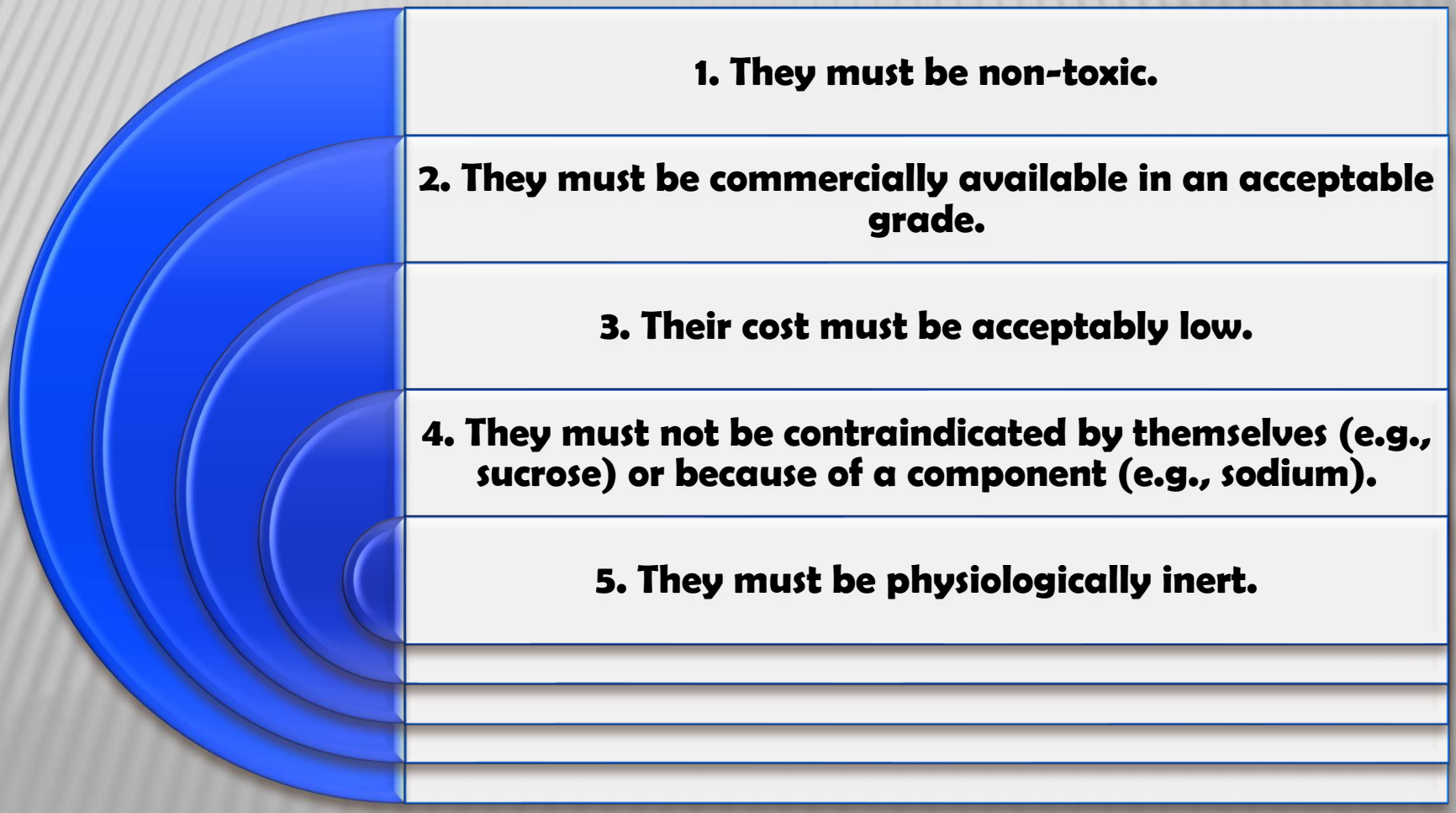
(3) Disintegrant

(4) Lubricant

Some tablet formulations may additionally require:

- **Flow promoters**
- **Colorants**
- and in chewable tablets: **flavors and sweeteners.**

Tablet excipients must meet certain criteria in the formulation. These include the following:



6. They must be physically and chemically stable themselves and in combination with the drug(s) and other tablet components.

7. They must be free of any unacceptable microbiologic “load”.

8. They must be color-compatible (not producing any off-color appearance)

9. If the drug product is classified as a food (certain vitamin products), the diluent and other excipients must be approved as direct food additives.

10. They must have no deleterious effect on the bioavailability of the drug(s) in the product.

DILUENTS

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk.

Note: The dose of some drugs is sufficiently high that no filler is required (e.g., aspirin and certain antibiotics).

- **Round tablets for ingestion are usually in a size range of 3/16 to ½ inch** (tablet weight range of perhaps 120 to 700 mg for standard density organic materials).
- Tablets below 3/16 inch may be difficult for the elderly to handle, and those larger than ½ inch become difficult to swallow.
- **Oval tablets, weighing up to 800 mg or more may be produced.**
- **A diluent may be added for secondary reasons such as:** improved cohesion to permit the use of direct compression manufacturing or to promote flow.

Cited Cases

Case 1: Pharmaceutical manufacturers actually producing products in which an excipient reduced the bioavailability of a drug, or in which chemical incompatibilities existed.

The former situation occurred with the marketing of an antibiotic that utilized a calcium salt as the diluent.

Ex: The tetracycline product made with a calcium phosphate filler had less than half the bioavailability of the standard product.

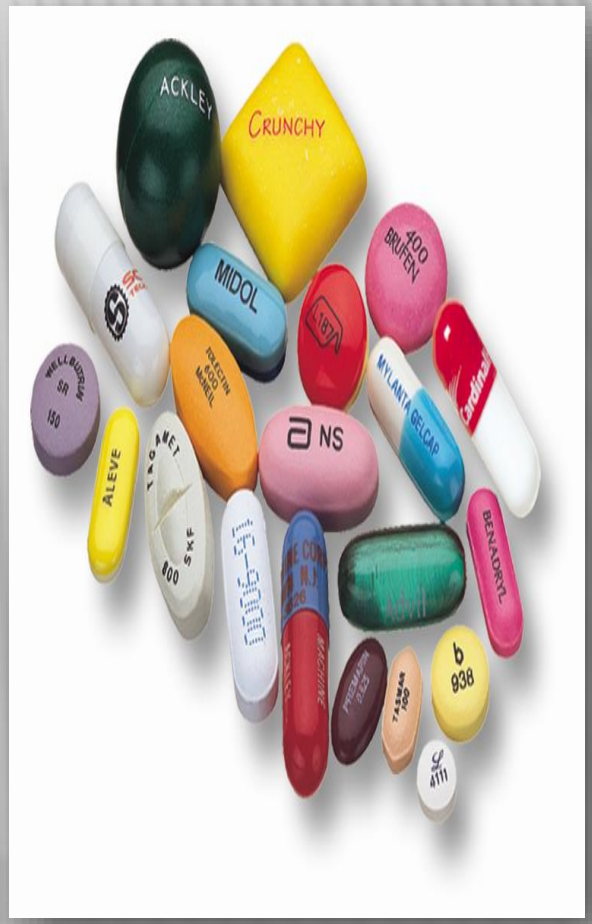
Mechansim: (Divalent and trivalent cations form insoluble complexes with a number of amphoteric or acid functionality antibiotics, which greatly reduces their absorption (which is also why should not be coadministered with these drugs).

Case 2: A classic case of a chemical incompatibility; interaction of certain amine drugs with the commonly used diluent lactose, in the presence of a metal stearate lubricant (such as magnesium stearate);

The resulting tablets were gradually discolored with time (Maillard reaction).

Important note: Physical and chemical interactions between formulation components may be promoted by the intimate contact between potential reactants that are tightly compressed together in a tablet compact.

Ex: materials that are capable of forming a eutectic mixture, may pose no problem when loosely packed as a powder in a capsule, while the same formulation when compressed in a tablet forms a compact that quickly soften and becomes unacceptable.



EXAMPLES OF DILUENTS

1. DIBASIC CALCIUM PHOSPHATE AND CALCIUM SULFATE

Advantage: possessing low concentrations of unbound moisture and having a low affinity for atmospheric moisture. These are required features for any excipient material to be combined with water-sensitive drug.

Mechansim: this diluent exists in salt form as hydrates, containing bound water as water of crystallization, may nevertheless be excellent for very water-sensitive drugs, provided that the bound water is not released under any elevated storage condition to which the product might be exposed (but released in 80°C).

2. LACTOSE

Most widely used diluent in tablet formulation.

Properties:

1. It is an excipient that has no reaction with most drugs, whether it is used in the hydrous or anhydrous form.

2. Anhydrous lactose has advantage over lactose in that it does not undergo the Maillard reaction, (lead to browning and discoloration with certain drugs).

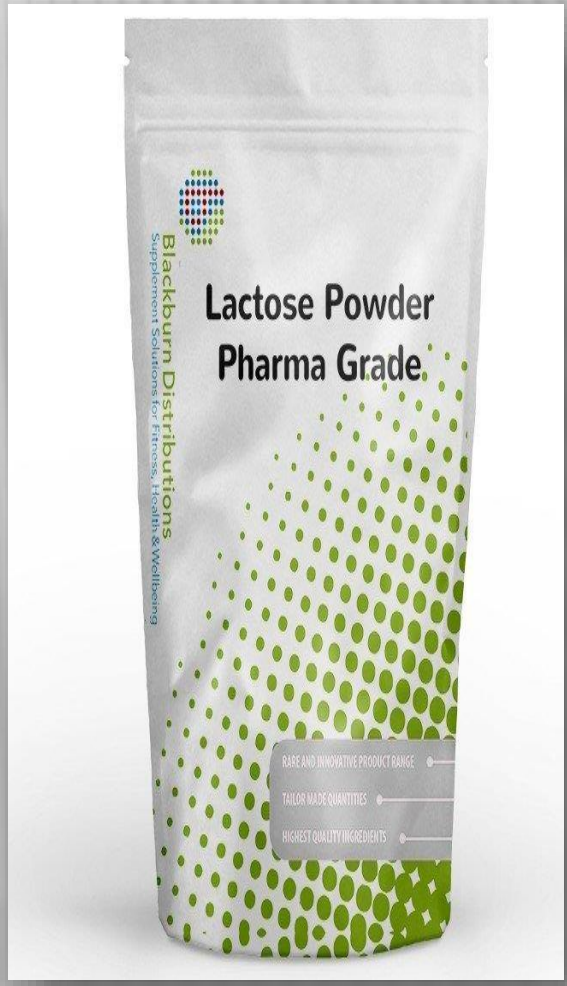
3. The anhydrous form, pick up moisture when exposed to elevated humidity. Such tablet may have to be carefully packaged to prevent moisture exposure.

4. When a wet granulation process is employed, the hydrous form of lactose should generally be used.

5. Two grades of lactose are available commercially: a 60-80 mesh (coarse) and an 80-100 (regular) grade.

6. Lactose formulations show good drug release rates, their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variation in tablet hardness.

7. Lactose is a low cost diluent but it may discolor in the presence of amine bases or salts of alkaline compounds.



3. STARCH

Starch, which may come from corn, wheat or potatoes used as a tablet diluent.

Types:

- **The USP grade of starch, possesses a high typical moisture content of between 11 and 14%.**

- **Specially dried types of starch** that have a standard **moisture level of 2 to 4%** are available, but at a premium price.
- **The use of such starches in wet granulation is wasteful since their moisture levels increase to 6 to 8% following moisture exposure.**

- **Directly compressible starches are now available commercially. Ex: Sta-Rx 1500**

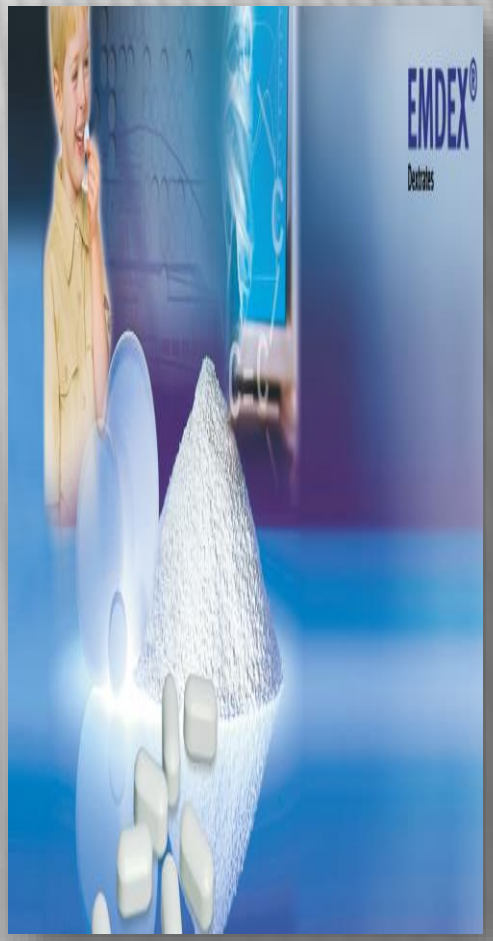
Properties:

1. **Free-flowing**
2. **Directly compressible**
3. **Used as a diluent, binder and /or disintegrating agent.**
4. **Used as self-lubricating, (it may be compressed alone, but when combined with drugs, it may require addition of a lubricant, and possibly a flow promoter such as 0.25% of a colloidal silicone dioxide).**
5. **Contains about 10% moisture and is prone to softening when combined with excessive amount (more than 0.5%) of magnesium stearate.**

- **Two hydrolyzed starches are Emdex and Celutab, which are basically 90 to 92% dextrose and about 3 to 5% maltose.**

Properties:

1. Free-flowing and directly compressible.
2. Can be used in place of mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.
3. Contain about 8 to 10% moisture and may increase in hardness after compression.



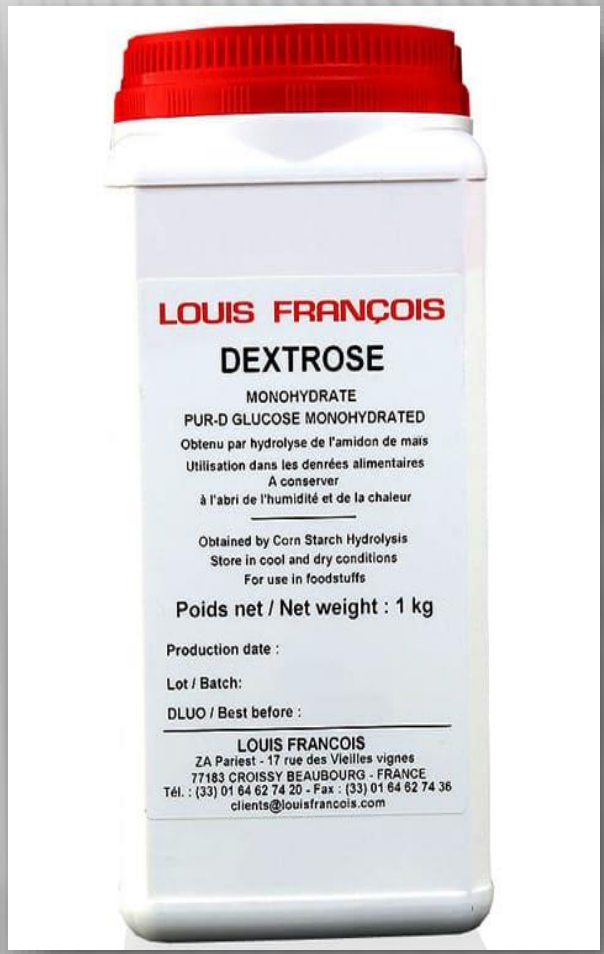
4. DEXTROSE

Used as a tablet diluent.

It is available under the name Cerelose

Types: hydrate, and in anhydrous form when low moisture contents are required.

Properties: combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.



5. MANNITOL

Most expensive sugar used as a tablet diluent.

Properties:

1. **Because of its negative heat of solution, slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets.**

2. **It is relatively non-hygroscopic and can be used in vitamin formulation, in which moisture sensitivity may be a problem.**

Disadvantage: Mannitol formulations typically have poor flow characteristics and usually require fairly high lubricant levels.

6. SORBITOL

Optical isomer of mannitol

Properties:

1. **Combined in mannitol formulations to reduce diluent cost.**
2. **Both sorbitol and mannitol have a low caloric content and are noncariogenic.**

Disadvantage: hygroscopic at humidities above 65%.

7. SUCROSE

Sucrose, or sugar, and various sucrose-based diluents are employed in tablet making.

Disadvantage:

a) Some manufacturers avoid their use in products that would subject a diabetic to multiple gram quantities of sugar.

b) Pick up moisture when exposed to elevated humidity.

Types:

1. Sugartab (90 to 93% sucrose plus 7 to 10% invert sugar).
2. diPac (97% sucrose plus 3% modified dextrins).
3. Nu tab (95% sucrose and 4% invert sugar with a small amount of corn starch and magnesium stearate).

Properties:

i. Available for direct compression

ii. Employed with or without mannitol in chewable tablets

8. MICROCRYSTALLINE CELLULOSE

Referred to by the trade name Avicel, It is a commonly employed direct compression excipient.

Types:

1. PH 101 (powder)
2. PH 102 (granules).

Properties:

a) The flow properties are good.
b) Direct compression are excellent.
c) Producing cohesive compacts.
d) Acts as a disintegrating agent (added to tablet formulation for several possible function).

Disadvantage: a relatively expensive material when used as a diluent in high concentration and is thus typically combined with other materials.

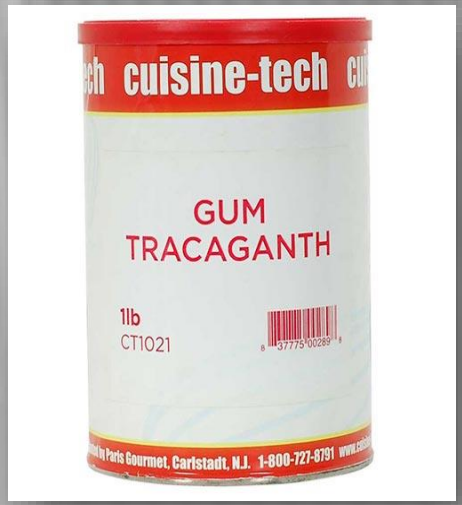
BINDERS AND ADHESIVES

The reason behind adding these materials :

1. Dry or in liquid form during wet granulation to form granules.
2. Promote cohesive compacts for directly compressed tablets.

1. Acacia and tragacanth

Natural gums, and are employed in solutions ranging from 10 to 25% concentration, alone or in combination.



Properties: These materials are much more effective when they are added as solution in the preparation of granulations than when they are added dry to a direct compression formula.

Disadvantages:

1. Variable in their composition and performance based on their natural origin.
2. Fairly heavily contaminated with bacteria.

Ex: wet granulation masses should be quickly dried at a temperature above 37°C to reduce microbial proliferation.

2. GELATIN

natural protein and is sometimes used in combination with acacia.

Properties:

1. More consistent material than the two natural gums.
2. Easier to prepare in solution form.
3. Forms tablets equally as hard as acacia or tragacanth.

3. STARCH PASTE

One of the most common granulating agents.

Preparation: dispersing starch into water, which is then heated for some prescribed time.

During heating

The starch undergoes hydrolysis to dextrin and to glucose.

A properly made paste is translucent rather than clear (which would indicate virtually complete conversion to glucose) and produces cohesive tablets that readily disintegrate when properly formulated.

4. MODIFIED NATURAL POLYMERS

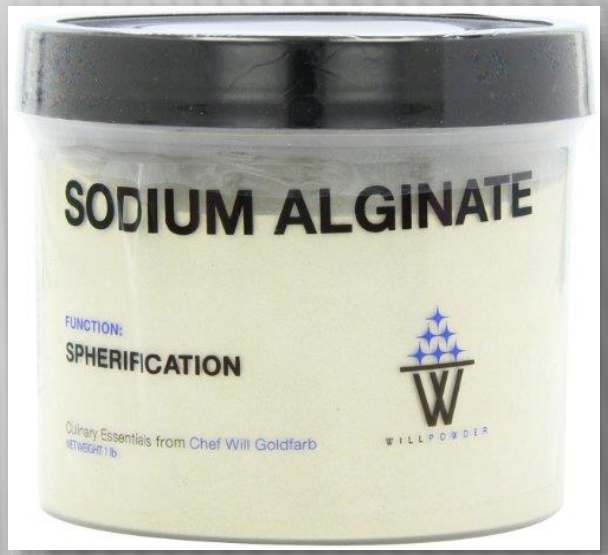
- **As the alginates and cellulose derivatives (methylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose), are common binders and adhesives.**

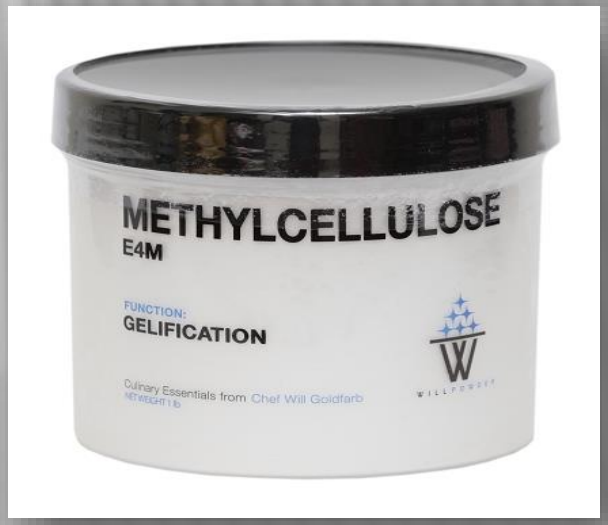
Uses:

1. Dry for direct compression (have some binder capabilities)
2. Aqueous solutions (have adhesive properties).

- **Hydroxypropyl cellulose (HPC)**

Used as an alcohol solution to provide an anhydrous adhesive.



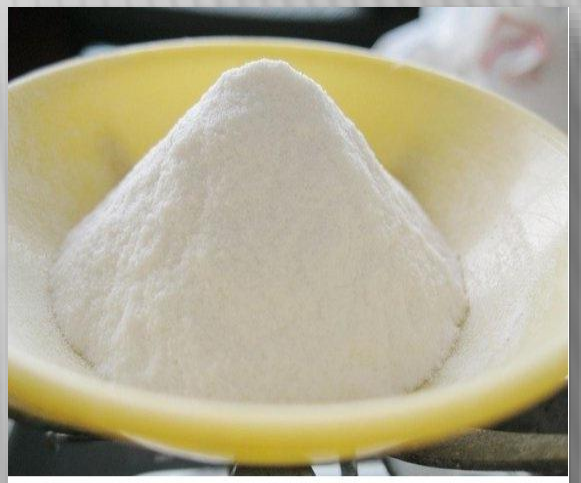


- **Ethylcellulose**

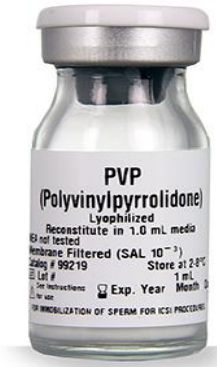
used only as an alcoholic solution (expected to retard disintegration and dissolution time of drugs in the resulting tablets when wet granulation is employed).

- **Polyvinylpyrrolidone (PVP)** is a synthetic polymer

(Used as an adhesive in either an aqueous solution or alcohol. It also has some capabilities as a dry binder).



Ethyl cellulose

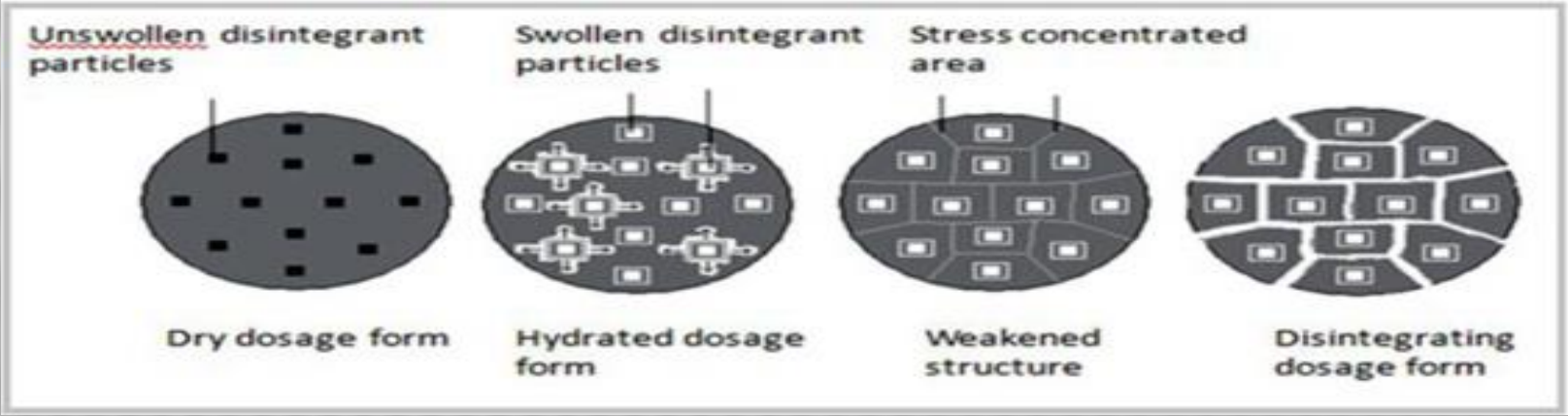


DISINTEGRANTS

A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when it contacts water in the gastrointestinal tract.

Mechanism

Disintegrants may function by drawing water into the tablet, swelling, and causing the tablet to burst apart.



1. STARCH USP AND VARIOUS STARCH DERIVATIVES

Properties:

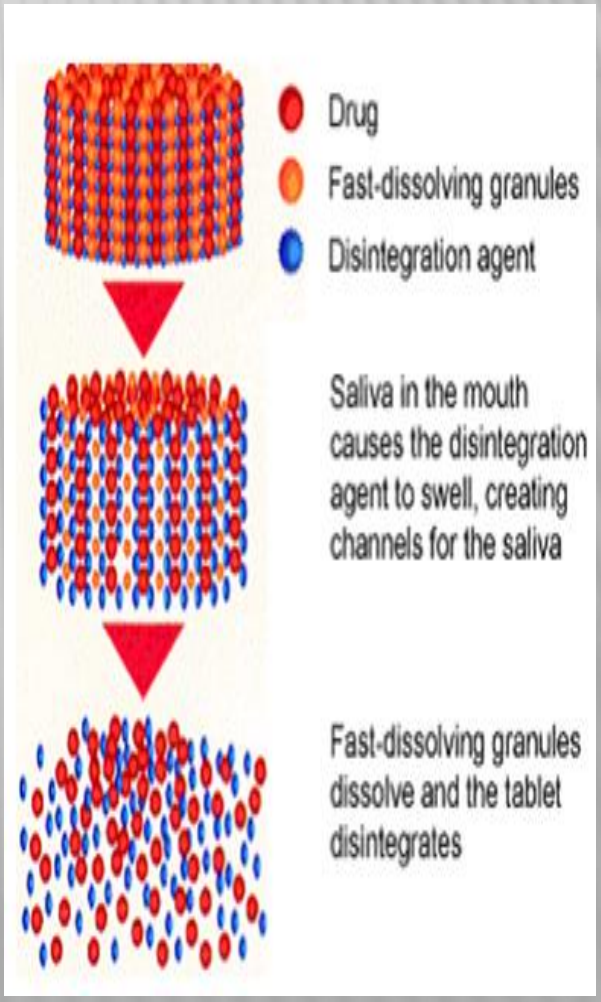
1. Most common disintegrating agents.
2. Lowest cost.

Types:

i. Starch is typically used in a conc. range of 5-20% of tablet weight.

ii. Modified starches (sodium starch glycolate) as Primogel and Explotab, are used in lower conc. (1 to 8%, with 4% usually reported as optimum).

iii. Various pregelatinized starches are also employed as disintegrants, usually in a 5% conc.



2. CLAYS SUCH AS VEEGUM HV AND BENTONITE

used as disintegrants at about a 10% level.

Disadavantages:

The use of such materials is limited unless the tablets are colored

1. Produce off-white appearance
2. Less effective as disintegrant

3. AC-DI-SOL

New material (Croscarmellose sodium) known as Ac-Di-Sol or Solutab is now available and is effective in low concentration levels (0.5-5%).

LUBRICANTS, ANTIADHERENTS, AND GLIDANTS

These three classes of materials are typically described together because they have overlapping functions.

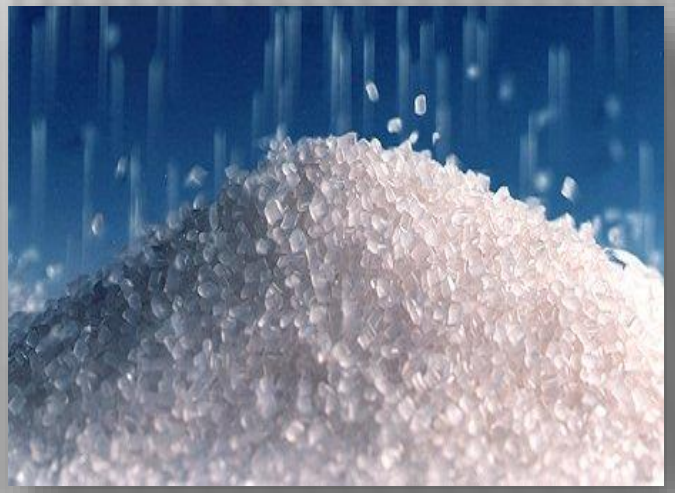
- A material that is primarily described as an antiadherent is typically also a lubricant, with some glidant properties as well.

- **The differentiation between these terms is as follows:**

1. **Lubricants:** intended to reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity in which the tablet was formed.

2. **Antiadherents**: have the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches and to the die wall.

3. **Glidants:** promote flow of the tablet granulation or powder materials by reducing friction between the particles.



EXAMPLES OF LUBRICANT

1. **The most widely used lubricants have been stearic acid salts and derivatives (Calcium stearate 0.5-2% and magnesium stearate o.25-5%).**

Note: Stearic acid is a less effective lubricant than those salts and also has a lower melting point.

2. **Talc the second most commonly used tablet lubricant (1-10%).**

Note: Most talc samples are found to contain trace quantities of iron, and talc should be considered carefully in any formulation containing a drug whose breakdown is catalysed by the presence of iron.

EXAMPLES OF LUBRICANT

3. **The higher molecular weight polyethylene glycols and certain polymeric surfactants have been used as water-soluble lubricants** (These materials are much less effective as lubricants).

Note: **Since lubrication is basically a coating process, the finer the particle size of the lubricant**

the more effective the lubricant action is likely to be.

EXAMPLES OF ANTIADHERENT AND GLIDANT

- **Most of the** materials listed as lubricants, also function as Antiadherents (Talc, magnesium stearate, starch derivatives and various colloidal silicas).

- **Materials used as glidants, or flow promoters**

Typically, talc at a 5% concentration, corn starch at a 5 to 10% concentration, or colloidal silicas (silicon dioxide, SiO_2) such as Cab-O-Sil, or Aerosil in 0.05 to 0.5% concentration. Colloidal silica has the added advantage of acting as a moisture scavenger, thereby providing a drier environment.

(COLORS, FLAVORS AND SWEETENERS)
COLORS

The use of colors and dyes in tablet making has served three purposes:

1. **Disguising of (mask) off-color drugs.**
2. **Product identification.**
3. **Production of a more elegant product.**

- The availability of natural vegetable colors is limited, and these colors are often unstable.

Types of dye:

1. **FD&C and D&C dyes:** applied as solutions, typically in the granulation agent.
2. **Lake forms of the dyes:** that have been absorbed on a hydrous oxide and are employed as dry powders for coloring.

Several precautions should be concerned when colors are employed:

i. When using water-soluble dyes, pastel shades usually show the least mottling from uneven distribution in the final tablet.

ii. When wet granulation is employed, care should be taken to prevent color migration during drying.

iii. In any colored tablet, the formulation should be checked for resistance to color changes on exposure to light.

FLAVORS

Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth.

Types of flavors:

A. Water-soluble have little acceptance in tablet making because of their poor stability.

B. Flavor oils are added to tablet granulations in solvents, (dispersed on clays and other absorbents, or are emulsified in aqueous granulating agents).

(The maximum amount of oil that can be added to a granulation without influencing its tabletting characteristics is 0.5 to 0.75%).

C. Various dry flavors for use in pharmaceutical products are also available from flavor suppliers.

SWEETENERS

The use of sweeteners is primarily limited to chewable tablets to exclude or limit the use of sugar in the tablets.

Examples:

1. **Mannitol** is about 72% as sweet as sucrose.

2. Until recently, **Saccharin** was the only artificial sweetener available (500 times sweeter than sucrose).

Disadvantages: bitter after taste and reported to be carcinogenic.

3. **Aspartame:** new artificial sweetener that is expected to largely replace saccharin.

Disadvantage: lack of stability in the presence of moisture. When used in a chewable tablet with hygroscopic components

It will be necessary to determine its stability under conditions in which the product can adsorb atmospheric moisture.