Pharmaceutical Excipients of Granules and Tablets

Excipient

- Pharmacologically inactive ingredient which is added to a pharmaceutical compound
- In many cases, an "active" substance (such as acetylsalicylic acid) may not be easily administered and absorbed by the human body; in such cases the API may be dissolved into or mixed with an excipient

Requirements against the excipients

- Pharmacologically inert
- Stable for handling
- Cost effective
- No interaction with the drug and other components
- No taste, odour and colour

Note that some people may be allergic to some excipients - for example, many people are lactose-intolerant.

Excipient

Functions of excipients:

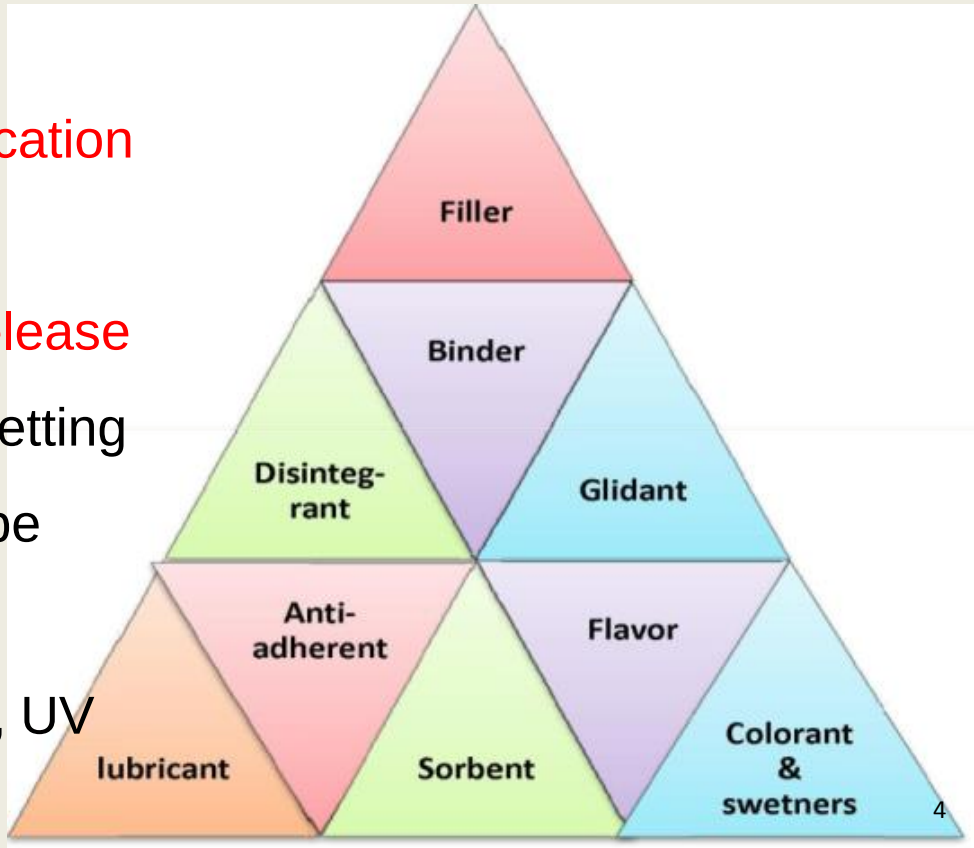
i) For providing essential manufacturing technology functions (binders, glidants, lubricants may be added),

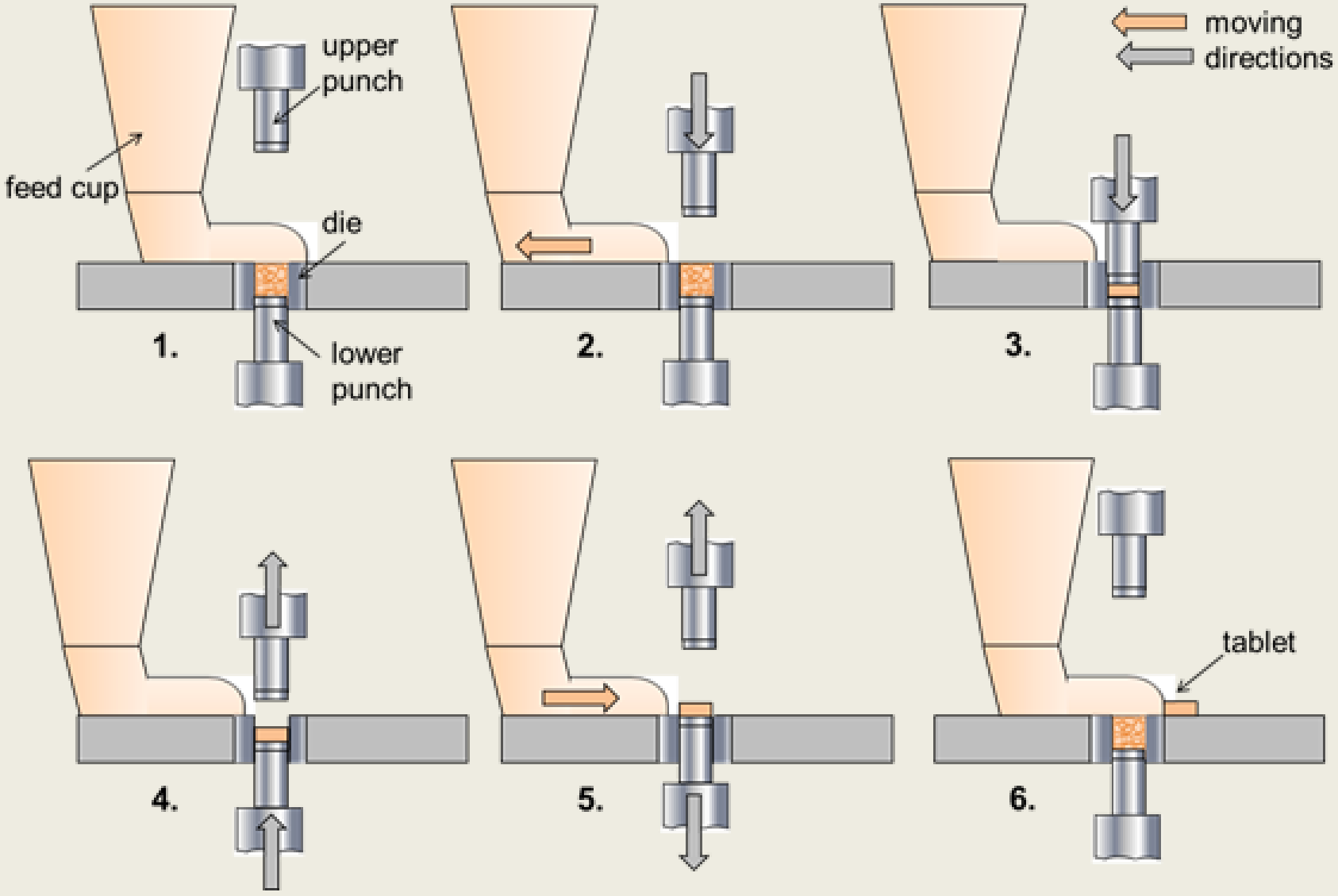
ii) For enhancing patient acceptance (flavors, colourants may be added),

iii) For providing aid in product identification (colourants may be added),

iv) For optimizing or modifying drug release (disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers may be added),

v) For enhancing stability (antioxidant, UV absorbers may be added

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Types of excipients

1. **Fillers**
2. **Diluents**
3. **Antiadherents**
4. **Binders**
5. **Coatings**
6. **Flavours**
7. **Colours**
8. **Lubricants**
9. **Glidants**
10. **Preservatives**
11. **Sorbents**
12. **Sweeteners**

1- Filler or diluent

use: to make required bulk of the tablet .
to provide better tablet properties such as to improve cohesion,
to permit use of direct compression manufacturing
to improve flowability

Most common fillers in tablets:

1. Lactose, sucrose, mannitol;
2. Dicalcium phosphate dihydrate
3. Starch
4. cellulose / microcrystalline cellolose

2- Binders and adhesives

Role: Ensure that granules and tablets can be formed with the required mechanical strength (**glue** that holds powders together to form granules).

- In dry powder form
- In solution

Examples:

starch paste 5-25%
gelatine solution 10-20%,
gum acacia, tragacantha, 10-25%
glucose syrup 50%,
cellulose derivative
polyvinylpyrrolidone 2% (PVP), PEG

3- Disintegrants

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion of tablets into smaller particles for quick dissolution when it comes in contact with water in the GIT.

Ideal properties of disintigrants:

- good hydration capacity,
- poor solubility,
- poor gel formation capacity.

3- Disintegrants

The Method of Disintegrant Addition:

1. Mixed with other ingredients prior to granulation & thus incorporated within the granules **(intragranular addition)**.
2. Mixed with the dry granules before the complete powder mixture is compacted **(extragranular addition)**.
3. incorporated as **both** an intragranular and an extragranular portion.

Commonly Used Disintegrants:

1. Starch:
   - concentration up to 5-20% of tablet weight
   - swells in contact with water
2. Polyvinyl-pyrrolidone
3. Carboxymethyl-cellulose
4. Superdisintegrants (e.g. sodium starch glycolate, croscarmellose, crosspovidone = cross linked povidone)
   - Swells up to ten fold within 30 seconds when contact water.

4- Glidants

Role: Improve flowability of the powder

They are added during direct compaction and to granulation before tabletting **(they reduce interparticulate friction).**

Common Glidants:

1. Talc (concentration 1-2 %).
2. Colloidal silica (0.2 %).
3. Corn Starch 5-10%

5- Lubricants

Role: Lubricants

- prevent adherence of granule/powder to die wall and
- promote ejection from the die after compaction,
- reduce inter particle friction and
- improve the rate of flow of the tablet granulation

5- Lubricants

Disadvantages of lubricants

1. Lubricants tend to be hydrophobic, so their levels (typically 0.3 – 2%) need to be optimized:

–Under-lubricated blends tend to flow poorly and show compression sticking problems

–Over-lubricated blends can adversely affect tablet hardness and dissolution rate, as well as tablet strength.

5- Lubricants

Commonly used Lubricants

A. Water- insoluble (Fatty acids-based) lubricant

- Magnesium Stearate
- Calcium Stearate
- Stearic Acid, stearic acid salt
- Talc
- Silica derivative- colloidal silica such as Cab-O-Sil, Aerosil in 0.25-3% conc.
- liquid paraffin, propylene glycol (PG)

B. water-soluble lubricant

- PEG 6000; less effective
- Magnesium/sodium lauryl sulfate; good lubrication and surface wetting effect

6- Adsorbents

Adsorbents are the agents that can retain large quantities of liquids.

Therefore liquids (Vitamin E, essential oils, eutectics, hygroscopic agents) can be incorporated into tablets by addition of adsorbents.

Large surface-adsorbes the moisture
Water-absorbtion capacity: 44-99%

Generally the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formulation.

6- Adsorbents

Most commonly used adsorbents:

- anhydrous calcium phosphate,
- starch,
- silica colloidalis anhydrica (Aerosil)

7 – Antistatic agents

Reduces electrostatic charge developing during handling of the powder.

Most commonly used antistatic agent:

- silica colloidalis anhydrica (Aerosil)

8- Flavours

Use: give the tablet a more pleasant taste or to mask an unpleasant one. (Chewable tablet)

- Flavouring agents are often thermolabile and so cannot be added prior to an operation involving heat.
- They are often mixed with the granules as an alcohol solution.

Ex: citric acid, glycerol, orange oil, menthol, vanillin etc.

9- Sweeteners

They are used in **chewable tablet** to exclude or limit the use of sugar in the tablets.

Most commonly used sweetenrs:

- **Mannitol, lactose, sucrose, Dextrose** 72% as sweet as sucrose.
- **Saccharin,** 500 times sweeter than sucrose.

  Disadvantage: has a bitter aftertaste
- **Aspartame,** largely replace saccharin., 180 times sweeter than sucrose

  Disadvantage: lack of stability in the presence of moisture.

10 - Colorants

Uses: It is added to tablets to

- aid identification,
- improve patient compliance.
- mask of off color drug
- production of more elegant product.

All coloring agents must be approved and certified by FDA.

These dyes are applied as solution in the granulating agent.

10 - Colorants

Example:

Yellow 6- FD & C sunset yellow
yellow 5- FD & C Tartrazine
green 3- FD & C Fast Green
blue 1- FD & C Brilliant Blue
blue 2 – FD & C Indigotine
red 3- FD & C Erythrosine FD & C
red 22 – FD & C Eosin Y

It is added during coating.

- It can also be added prior to compaction. (can be added as an insoluble powder or dissolved in the granulation liquid)

11 - Buffers

Buffers are added to maintain a required pH since a change in pH may cause significant alteration in stability.

Most commonly used buffering agent in tablet formulation includes sodium bicarbonate, calcium carbonate, and sodium citrate.

12 - Antioxidants

Antioxidants are added in tablet formulation: to protect drug from undergoing oxidation.

Chelators may also act as antioxidant.

Most commonly used antioxidants include

- ascorbic acid and their esters
- alpha-tocopherol
- ethylene diamine
- tetra acetic acid
- sodium metabisulfite
- sodium bisulfite
- citric acid
- tartaric acid

13. Chelating agents

tend to form complexes with trace amount of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments.

Most commonly used chelators:

- Ethylenediamine tetracetic acid and its salts
- Dihydroxy Ethyl Glycine
- Citric Acid
- Tartaric Acid are

14. Dissolution Enhancers

They are the agents that alter the molecular forces between ingredients to enhance the dissolution of solute in the solvent.

Fructose, Povidone, Surfactants are used as dissolution enhancer.

15. Dissolution Retardants

Dissolution retardants are incorporated into tablet formulation only when controlled release of drug is required.

Waxy materials like stearic acid and their esters can be used as dissolution retardants.

16. Wetting agents (surfactants)

in tablet formulation aid water uptake and thereby enhancing disintegration and assisting in drug dissolution.
Decrease the surface tension between two liquids or between liquid and solid, thus increase the solubility.

Anionic:
Sodium lauryl sulphate (SLS):

Cationic:
Cetrimid (antiseptic agent as well)

Nonionic:
Tweens, Spans

Question of splitting

1

- **API**
- Mannitol
- Sodium bicarbonate
- Anhydrous citric acid
- Ascorbic acid
- Cola flavour
- Orange flavour
- Aspartame

2

- **API**
- Ethylcellulose
- Silicon dioxide anhydrous
- Hypromellose 6cPS
- Mannitol
- Aspartame (15 mg)
- **Croscarmellose-sodium (superdisintegrant)**
- Magnesium-stearate
- Lemon flavour

3

- **API**
- Red iron oxide (E 172)
- Magnesium-steareate
- Hypromellose
- Poliethylene-oxide
- Sodium chloride
- Macrogol 3350
- Cellulose-acetate
- "Opadry White YS-2-7063”
- Titanium-dioxidide (E171)
- "Black Ink S-1-17823" (Black iron-oxide)

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- **API**
- **Core:** magnesium-stearate, povidone K30, purified water, microcrystalline cellulose, **sodium-alginate**.
- **Coating:** Montan-glycol wax, macrogol 6000, macrogol 400, titanium-dioxideE 171, talc

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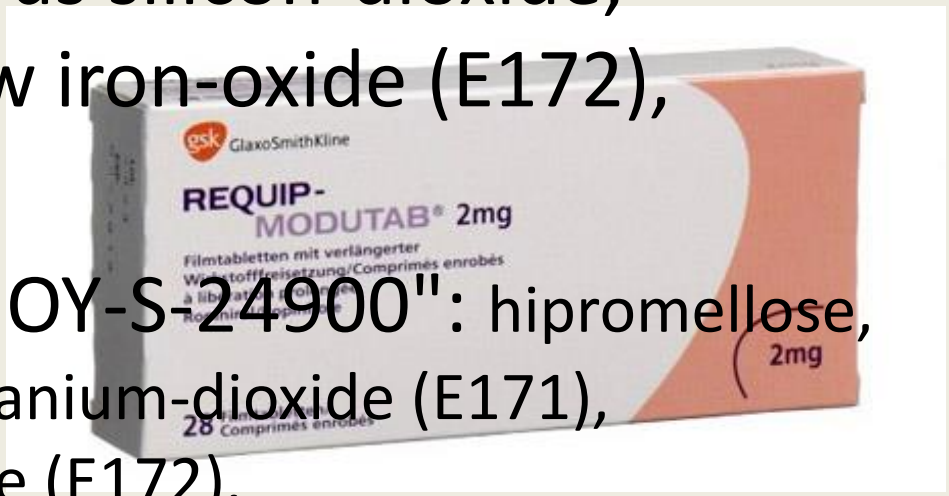
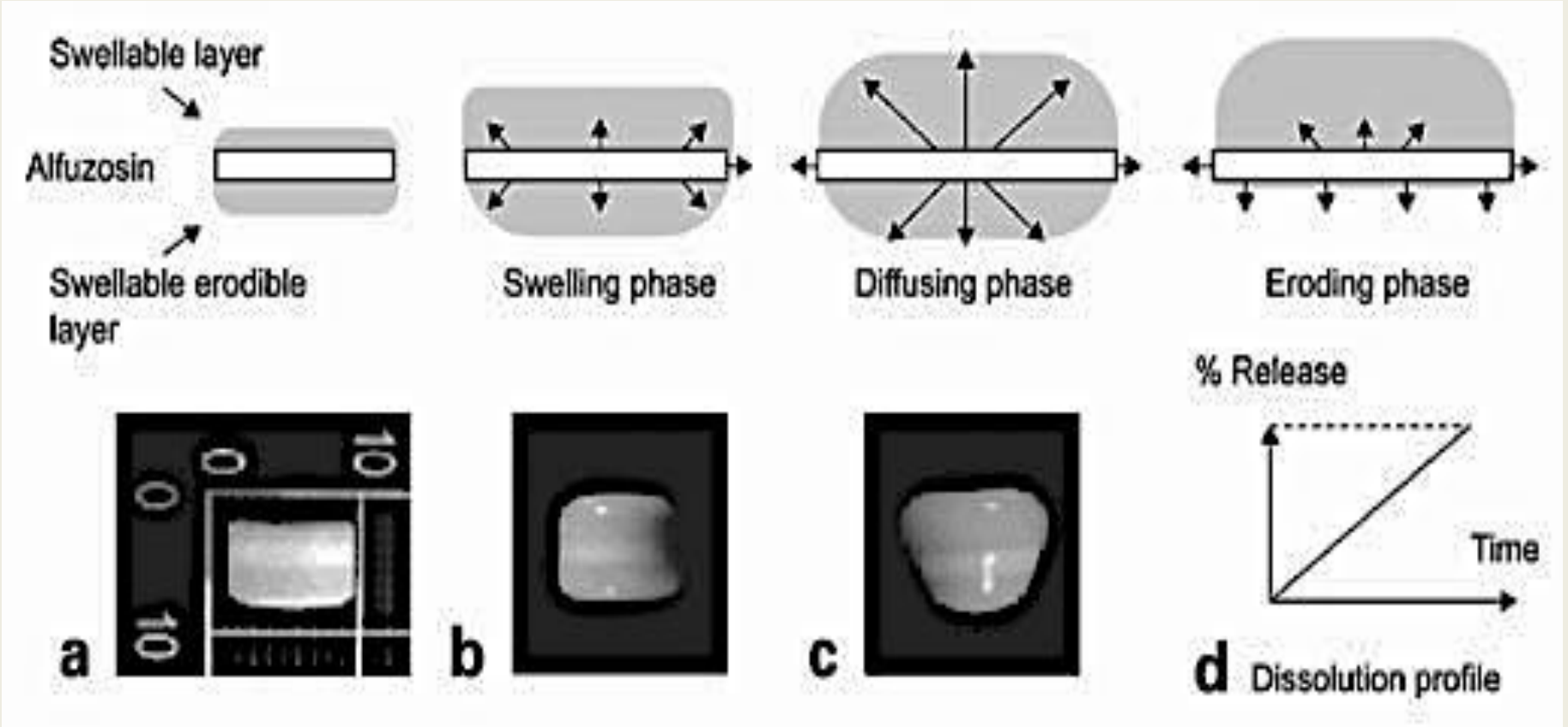
- **API**
- **Core:** hypromellose2208, hydrogenated castor oil, carmellose-sodium, povidone (K29-32), maltodextrine, magnesium-stearate, lactose-monohydrate, anhydrous silicon-dioxide, mannitol (E421), yellow iron-oxide (E172), glycerol-dibehenate.
- **Coating:** "Opadry pink OY-S-24900": hipromellose, yellow iron-oxide (E172), titanium-dioxide (E171), macrogol 400, red iron-oxide (E172).



Geomatrix® technology



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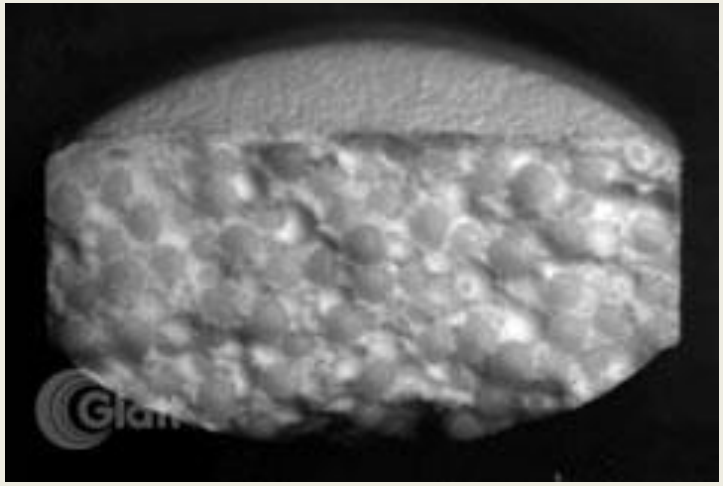
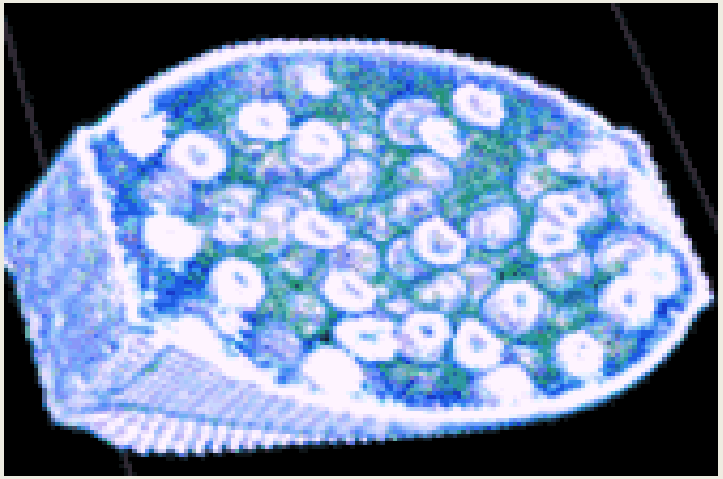
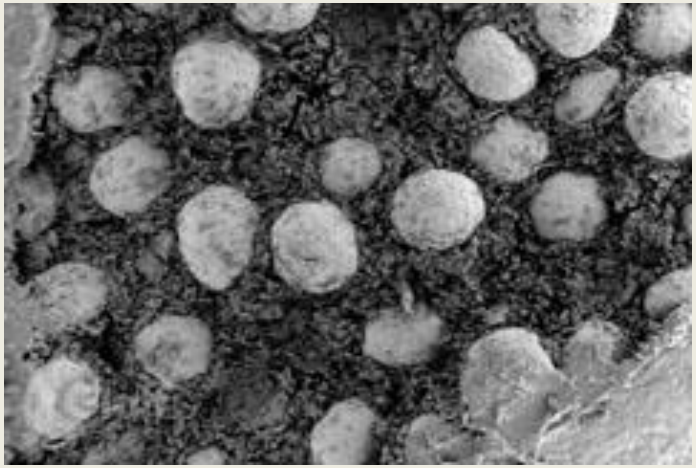
- **API**
- Diethyl-phtalate, Eudragit L100, Eudragit NE30D, Eudragit L30D, talc, shellac, inert sucrose and corn starch microgranules
- **Shell:**
  eritrosine (E 127), titanium-dioxide (E 171), gelatine

Multiple Unit Pellet System (MUPS)







Thank you
for your attention!

Excipients	Function
Diluent	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size
Binder	Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet.
Disintegrants	A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment

Antifrictional Agents	Function
Lubricant	Lubricants are intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.
Antiadherants	Antiadherents are added to reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall
Glidants	Glidants are intended to promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.

MISCELLANEOUS	Function
Wetting agent	Wetting agents are added to tablet formulation to aid water uptake during disintegration and assist drug dissolution.
Dissolution retardant	Dissolution retardants as the name suggest, retards the dissolution of active pharmaceutical ingredient(s).
Dissolution enhancer	Dissolution enhancers as the name suggest, enhance the dissolution rate of active pharmaceutical ingredient(s).
buffers	Buffers are added to provide suitable micro environmental pH to get improved stability and / or bioavailability.
Adsorbents	Adsorbents are capable of retaining large quantities of liquids without becoming wet; this property of

Excipients	Function
Antioxidants	Antioxidants are added to maintain product stability, they act by being preferentially oxidized and gradually c.onsumed over shelf life of the product
Chelating agents	Chelating agents are added to protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.
Colours	Colours are added to tablet formulation for following purposes: to disguise off colour drugs, product identification and for production of more elegant product.
Flavours	Flavours are added to tablet formulation in order to make them palatable enough in case of chewable tablet by improving the taste.