Pharmaceutical Additives

- **Definition:**

  "Any substance other than the active drug or prodrug that is included in the manufacturing process or is contained in a finished pharmaceutical dosage form."

- Excipients are not inactive and have impact on the manufacture, safety, and efficacy of the drug substance in dosage form.

- **Purposes served by excipients:**
  - Provide bulk to the formulation.
  - Facilitate drug absorption or solubility and other pharmacokinetic considerations.
  - Aid in handling of "API" during manufacturing.
  - Provide stability and prevent from denaturation etc.

- **Pharmaceutical additives must:**

1. Be safe in the amount used in the drug.
2. Be Non-allergic. Some people may be allergic to some excipients .

   e.g., Many people are lactose-intolerant.
3. Not affect the bioavailability and performance of the drug.
4. Be manufactured in accordance with good standards

3

Roles of Excipients in Pharmaceuticals:

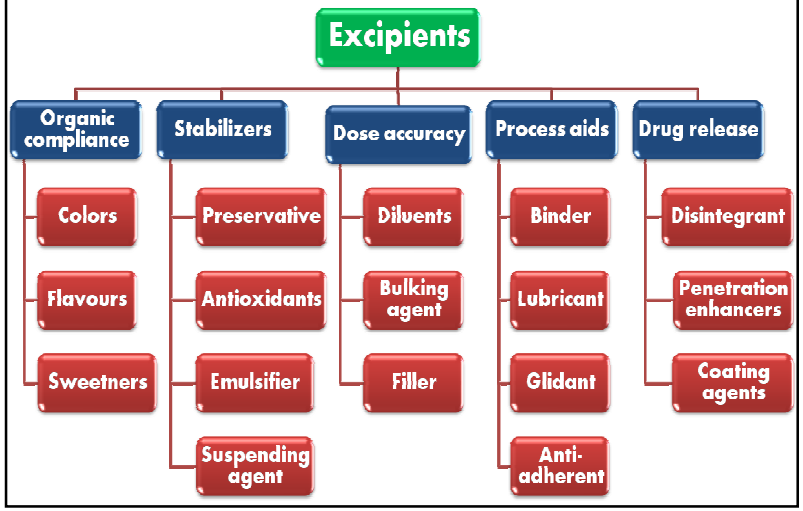
1. **Modulating solubility & bioavailability of the drug**
2. **Enhancing stability of the drug in its dosage forms**
3. **Helping drug to maintain a suitable polymorphic form**
4. **Maintaining pH & osmolarity of liquid products**
5. **Acting as antioxidants, suspending agents, emulsifier, aerosol propellants, base, tablet diluents**
6. **Preventing aggregation or dissociation**
7. **Modulating the immunogenic response of drug**

4

Ideal Properties of Excipients:

5

Classification of Excipients Based on Objective of Addition in Dosage Forms:



A list of pharmaceutical excipients used in pharmaceutical preparations usually:

1. **Fillers.**
2. **Binders.**
3. **Disintegrants.**
4. **Coatings.**
5. **Sorbents.**
6. **Antiadherent.**
7. **Lubricants.**
8. **Glidants.**
9. **Preservatives.**
10. **Antioxidants.**
11. **Flavoring Agents.**
12. **Sweeting Agents.**
13. **Coloring Agents.**
14. **Solvent & Co-solvent.**
15. **Buffering Agents.**
16. **Chelating Agents.**
17. **Viscosity imparting Agents.**
18. **Surface Active Agents.**
19. **Humectants .**

Fillers:

- Fillers typically **also fill out the size of a tablet or capsule**, making it practical to produce and convenient for the consumer to use.
- **Function of fillers:**
  Fillers **add volume and/or mass to a drug substance**, thereby facilitating precise metering and handling thereof in the preparation of dosage forms. Used in tablets and capsules.
- **Typical features of fillers:**
  A good filler should typically **be inert, compatible with the other components of the formulation, non-hygroscopic, relatively cheap, compatible, and preferably tasteless or pleasant tasting.**
- **Examples:**
  Plant cellulose and dibasic calcium phosphate are used popularly as fillers. A range of vegetable fats and oils can be used in soft gelatin capsules. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate.

Binders:

- Binders **hold the ingredients in a tablet together**. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.
- **Typical features of binders:**

  A binder **should be compatible** with other products of formulation and **add sufficient cohesion** to the powders .
- **Classification and examples:**

Binders are classified according to their application,

- **Solution binders** are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol.
- **Dry binders** are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone and polyethylene glycol.

Disintigrants:

Disintegrants are substances or mixture of substances added to the drug formulations, which **facilitate dispersion or breakup of tablets and contents of capsules 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.
- **Examples:**

  Polyvinylpyrrolidone, Carboxymethyl Cellulose, Sodium Starch Glycolate etc.

Coating Agent:

Coating is a process by which an essentially dry, outer layer of coating material is **applied to the surface of a dosage form** and agents which are used in this coating process is called coating agents.

- **Types:**

  Three types of coating agents are used pharmaceutically,
  - ✓ **Film coating**.
  - ✓ **Sugar coating**.
  - ✓ **Compression coating**.
- **Function of coating agents:**

  Protection, masking, elegance, ease of swallowing, identification etc..
- **Examples:**

  HPMC, MC, HPC etc..

Sorbents:

Sorbents are materials that **soak up oil from the water.**

- **Types and examples of sorbents:**
- Natural sorbents- peat moss, sawdust, feathers, and anything else natural that contains carbon.
- Synthetic sorbents- polyethylene and nylon etc..

- **Functions of sorbents:**

Sorbent are **used for tablet/capsule moisture-proofing** by limited fluid sorbing (taking up of a liquid or a gas either by adsorption or by adsorption) in a dry state.

Antiadherents:

Antiaderents or anti-sticking agents **prevent adhesion of the tablet surface to the die walls and the punches** and as a consequence counter the picking or sticking of tablet.

- **Examples:**

Water insoluble lubricants such as magnesium stearate can be used as antiadherents, as can talc and starch.

Lubricants:

Lubricants **prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine**. Lubricants also **ensure that tablet formation and ejection can occur with low friction between the solid and die wall.**

Types:

- Hydrophilic- Generally poor lubricants, no glidant or anti-adherent properties.
- Hydrophobic-Most widely used lubricants in use today are of the hydrophobic category. Examples include magnesium stearate.

- **Roles of lubricants:**

1. **True Lubricant Role:**

   To **decrease friction** at the interface **between a tablet's surface and the die wall during ejection** and reduce wear on punches & dies.

2. **Anti-adherent Role:**

   Prevent sticking to punch faces or in the case of encapsulation, lubricants. Prevent sticking to machine dosators, tamping pins, etc.

3. **Glidant Role:**

   Enhance product flow by reducing interparticulate friction

- **Examples of lubricants:**

Polyethylene glycol, Magnesium stearate, Stearic acid and it's derivatives.

Glidants:

A substance (as colloidal silica) that **enhances the flow of a granular mixture by reducing inter-particle friction** and that is used in the pharmaceutical production of tablets and capsule.

- **Functions of glidants:**

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.

- **Examples:**

Fumed silica, talc, and magnesium carbonate.

Preservatives:

Preservatives are substances that commonly added to various foods and pharmaceutical products **in order to prolong their shelf life.**

- **Ideal properties of preservatives:**

1. Exert a **wide spectrum of antimicrobial activity** at low inclusion levels.
2. Maintain **activity throughout** product manufacture, **shelf life** and usage.
3. **Not compromise the quality or performance** of product, pack or delivery system.
4. **Not adversely affect patient safety** or tolerance of the product.

- **Examples:**

Methyl & Ethyl parabens, Propyl paraben, Benzoic acid and its salts, Sorbic acid and its salts.

Antioxidants:

An antioxidant is a molecule **that inhibits the oxidation of other molecules**. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent.

- **Ideal Properties of Antioxidants:**
  1. Effective at a low, nontoxic concentration
  2. Stable and effective under normal conditions of use, over a wide pH and temperature range
  3. Soluble at the required concentration
  4. Compatible with a wide variety of drugs and pharmaceutical excipients
  5. Free from objectionable odor, objectionable taste
  6. Colorless in both the original and oxidized form
- **Examples:**

BHT (Butylated Hydroxy Toluene), BHA (Butylated Hydroxy Anisol), Sodium sulfite, Ascorbic acid etc..

Sweetening Agents:

Sweetening agents are employed in liquid formulations designed for oral administration specifically **to increase the palatability of the therapeutic agent.**

Example:

Sucrouse, Saccarine, Aspertame, Sorbitol etc.

Uses of sweetening agent:

The main sweetening agents employed in oral preparations are **sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium and aspartame. Aspartame is an artificial sweetening agent.** The use of artificial sweetening agents in formulations is increasing . The use of sugars in oral formulations for children and patients with diabetes mellitus is to be avoided.

Flavoring Agents:

Flavouring agents are added to **increase patient acceptance**. The four basic taste sensations are **salty, sweet, bitter and sour**. It has been proposed that certain flavours should be used **to mask these specific taste sensations.**

Example:

Clove oil, citric and syrup, glycerin, rose oil, orange oil, menthol etc..

Coloring Agents:

Coloring agents are pharmaceutical ingredients that **impart the preferred color to the formulation.**

There are two types of coloring agents

1.Natural and

2.synthetic

Example:

1. White: Titanium dioxide
2. Blue: Brilliant blue, Indigo carmine
3. Red: Amaranth Carmine
4. Yellow: Saffron 5. Green 6. Brown: caramel

Solvents:

A solvent is a substance that **can dissolve a solute (a chemically different liquid, solid or gas) resulting in solution**. A solvent is usually a liquid but it can also be solid or a gas. A solvent never changes its state forming a solution.

Solvent classification:

Solvents can be broadly classified into two groups:

- Polar
- Non polar

Normally solvation of a solvent depends upon its classification. Generally polar solvent dissolves polar compound best and non polar solvent dissolves non polar compound best.

Example and uses of solvent:

- The first choice for a solvent is water in which a drug is freely soluble.
- Water–miscible solvent such as Chlordiazepoxide hydrochloride can be used to improve solubility and stability.
- Oils are used as emulsion, intramuscular injections and liquid fill oral preparation.
- Aqueous methanol is widely used in HPLC and is the standard solvent in sample extraction.
- Other acceptable non-aqueous solvents are glycerol, propylene glycol, ethanol and are used generally for a lipophilic drug.

Co-solvents:

Co-solvents are defined **as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility** of poorly water soluble substances or to enhance the chemical stability of a drug.

Properties of co-solvent:

- Co-solvent increases the solubility of a drug.
- An ideal co-solvent should possess values of dielectric constant between 25 and 80.
- The most widely used system that will cover this range is a water/ethanol blend.
- It should not cause toxicity or irritancy when administrated for oral or parental use
- Other co-solvents are sorbitol, glycerol, propylene glycol and syrup..

Chelating Agents:

Chelating agents are molecules that are **capable of forming complexes with the drug involving more than one bond** it's a complex compound contains one or more ring in its structure.
For example: EDTA

Example and uses of chelating agent:

- EDTA: Ethylene Diamine Tetra Acetate is used for the estimation of metals ions .
- EDTAH4: Ethylene Diamin Tetraacetic Acid is used for softening water.
- Calcium Disodium Edetate: it is used in the treatment of heavy metal poisoning mostly caused by lead.
- Disodium Edetate: it is used in hypercalcemic states. It is also useful ion the treatment of cardiac arrhythmias.

Buffering Agent:

These are materials which, when dissolved in solvent will enable the solution **to resist any change in pH.** The choice of suitable buffer depends on the pH and buffering capacity required.

Features of buffering agent:

It should have a low toxicity, it should be buffered at the range of 7.4 as the pH of the body is 7.4, it should be non-irritant.

Examples of buffering agent:

Most of the buffering system are based on carbonate, citrates, gluconates ,lactates, phosphates, or tartrates etc.

Viscosity Imparting Agents:

- These agents are used when it is desirable **to increase or decrease the viscosity of a liquid** either to serve as adjacent for palatability or to improve pour ability. **They are also called thickening agents.**

- **Most commonly used viscosity imparting agents are:**
  - Hydroxyethylcellulose
  - Hydroxypropylmethylcellulose
  - Methylcellulose
  - Polyvinyl alcohol
  - Polyvinylpyrrolidone

Humectants:

- A humectants attracts and **retains the moisture** in the nearby air via absorption, drawing the water vapor into and/or beneath the organism/object's surface.
- **Humectants absorb water vapors from atmosphere** till a certain degree of dilution is attained. Aqueous solutions of humectants can reduce the rate of loss of moisture.

- **Ideal properties of humectants:**
  - It must absorb moisture from atmosphere and retain the same under the normal conditions of atmospheric humidity.
  - It should be colorless or not of too intense color.
  - It should have good odor and taste.
  - It should be nontoxic and nonirritant.
  - It should be noncorrosive to packaging materials
  - It should not solidify under normal conditions.
  - It should not be too costly.

- **Classification of humectants with examples:**
- There are **three** types of humectants such as inorganic humectants, metal organic humectants and organic humectants.
  - **Inorganic humectants:** Calcium chloride
  - **Metal organic humectants:** Sodium lactate.
  - **Organic humectants:** The most commonly used organic humectants are glycerol, ethylene glycol, polyethylene glycol (PEG), diethylene glycol, tri-ethylene glycol, propylene glycol, dipropylene glycol, glycerin, sorbitol, mannitol, glucose.

Surfactants:

- Surfactants are compounds **that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid and increase the solubility**. They are also known as surface active agents.
- **Properties of surfactants:** A surfactant must fulfill two structural requirements:
  A surfactant must contain a lipophilic region.
  A surfactant must contain a hydrophilic region.
- **Types of surfactants:**
  There are of **four** types of surfactants based on the charge of the hydrophilic region :
  1. **Anionic surfactant:** (here the hydrophilic region is negatively charged i.e. an anion)
     Sodium lauryl sulphate - It is used as an excipient on some dissolvable aspirins and other fiber therapy caplets.

2. Cationic surfactant: (here hydrophilic region is positively charged i.e. a cation)
Cetyl trimethyl ammonium bromide (cetrimide) - is an effective antiseptic agent against bacteria and fungi.

3. Non-ionic surfactants :

Tween 80 (polyoxyethylene sorbitol monooleate)- Polysorbate 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration

Span (sorbitan ester of lauric acid)

4. Amphoteric surfactant :

Lecithin- it acts as a wetting, stabilizing agent and a choline enrichment carrier, helps in emulsifications and encapsulation, and is a good dispersing agent.

N-dodecyl alanine.