

PHARMACEUTICAL INCOMPATIBILITY

➤ **DEFINITION:** Incompatibility is the result of mixing two or more antagonistic substances as a result of which undesirable product or effect may be seen.

➤ **Ways of detecting Incompatibility**

It may be detected by:

- Physical change.
- Chemical change.
- Therapeutic change.

Importance Of Determining Incompatibility:

Incompatible products may effect:

- Safety of medicament.
- Efficacy of product.
- Appearance of a medicine.
- Purpose of medication.

Types Of Incompatibilities:

- Physical incompatibility.
- Chemical incompatibility.
- Therapeutic incompatibility.

PHYSICAL INCOMPATIBILITY:

- When two or more substances are combined together a physical change would take place leading to an incompatible product.

causes

- Immiscibility
- Insolubility
- Liquefaction

Consequences

Formation of unsighted product



Non uniform dosage form



Removal of Inaccurate dose



Improper Therapeutic effects

Immiscibility

- What is a miscible solution?
 - The components of an Ideal solution are miscible in all proportions for e.g. water and ethanol, propylene glycol and water, propylene glycol and acetone etc.

Examples:

- Oil and water .For e.g. Castor oil ,Olive oil.
- Concentrated Hydro alcoholic solutions of volatile oils (spirits and concentrated water)

Methods Of Rectifying Immiscibility:

Immiscibility can be overcome by:

- Vigorous shaking / stirring.
- Emulsification or solubilization for e.g. Fats soluble Vitamins, Certain antibiotics like Chloramphenicol, Amphotericin B, Analgesics like Aspirin, Acetanilide & phenacetin many alkaloids and glycosides etc are made soluble by the technique of solubilization.

Insolubility

- If the amount of the solute is not dissolved in a given amount of solvent.

Criteria for determining solubility

Condition	Amount Of Solvent Require to Dissolve 1 Part Of Solute
➤ Very soluble	less than 1 part
➤ Freely soluble	1 – 10 parts
➤ Soluble	10 – 30 parts
➤ Sparingly soluble	30 – 100 parts
➤ Slightly soluble	100 – 1000 parts
➤ Very slightly soluble	1000 – 10,000 parts
➤ Practically insoluble	More than 10,000 parts

Examples Of Insoluble Combinations:

- Some indiffusible solids such as Chalk, Aspirin, Phenobarbitone, Succinyl sulphathiazole etc
- Some Antibiotics like Cortisone Acetate, Hydrocortisone Acetate, Procaine benzyl penicillin.
- Constituents of alcoholic vegetable drugs may precipitate when the solvent is changed (On addition of water). For e.g. tinctures of Belladonna and hyoscyamus.
- Resinous tincture is precipitated when added to water. For e.g. Myrrh Tincture.

Methods Of Rectifying Insolubility:

- **Co solvency** : for e.g. we may use alcohol, propylene glycol, syrups.
- **Complexation**: for e.g. formation of tri iodide complex ,
complexation of caffeine with Sodium Benzoate.
- **Hydrotrophy**: for e.g. Hyoscamine with tween .
- **Solubilization**: for e.g. Fats soluble vitamins, certain antibiotics.

LIQUEFACTION

- It is the condition in which we mix the two powders of lower melting point so the mixture get liquefy due to the formation of eutectic mixture

Examples: Camphor , menthol, phenol, thymol , chloral hydrate, sodium salicylate, Aspirin , phenazone.

Methods Of Rectifying Liquefaction:

- By the use of absorbent like kaolin, light magnesium carbonate.

Techniques to Rectify:

- Order of mixing.
- Alteration of solvent.
- Change in the form of ingredients.
- Alteration of volume.
- Emulsification.
- Addition of suspending agents.
- Addition/Substitution/omission of therapeutically inactive substance.

Practical examples of prescriptions:

Rx

Olive oil 30 ml

Water up to 120 ml

Directions for Pharmacist:

Make an emulsion.

Comments:

Physical incompatibility.

Rx

- Menthol 5 gm
- Camphor 5 gm
- Ammonium chloride 30 gm
- Light magnesium carbonate 60 gm

Directions for Pharmacist:

Make an Insufflations. Send 40 gm.

Comments:

Correct prescription.

THERAPEUTIC INCOMPATIBILITY

- It may be the result of prescribing certain drugs to the patient with the intention to produce a specific degree of action but the nature or the intensity of the action produced is different from that intended by the prescriber.

CAUSES:

It may be due to the administration of :

- Overdose or improper dose of a single drug.
- Improper Dosage form.
- Contraindicated drug.
- Synergistic and antagonistic drugs.

Mechanisms of therapeutic incompatibility

- They are divided into two groups:
- **Pharmacokinetics:**
 - involve the effect of a drug on another from the point of view that includes absorption ,distribution , metabolism and excretion.
- **Pharmacodynamics:**
 - are related to the pharmacological activity of the interacting drugs e.g. synergism. antagonism, altered cellular transport, effect on the receptor site.

Pharmacokinetic interactions:

- **Altered GIT absorption**

- Altered pH
- Altered bacterial flora
- Formation of drug chelates or complexes
- Drug induced mucosal damage and altered GIT motility

- **Displaced protein binding**

- It depends on the affinity of the drug to plasma protein. The most likely bound drugs is capable to displace others. The free drug is increased by displacement by another drug with higher affinity

- **Altered metabolism**

- The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC, skin, lung, and GIT.

- **Altered renal excretion:**

- Inhibition of renal tubular secretion:

- It occurs in the proximal tubules (a portion of renal tubules). The drug combines with a specific protein to pass through the proximal tubules.

- When a drug has a competitive reactivity to the protein that is responsible for active transport of another drug. This will reduce such a drug excretion increasing its concentration and hence its toxicity.

- E.g., *Probenecid* *Decreases tubular secretion of methotrexate*

Complexation or chelation:

EX1., **Tetracycline** interacts with **iron** preparations

or

Milk (Ca^{2+}) → **Unabsorbable complex**

Ex2., **Antacid** (aluminum or magnesium) hydroxide

**Decrease absorption of
ciprofloxacin by 85%
due to chelation**

Pharmacodynamic interactions

- It means alteration of the drug action without change in its serum concentration by pharmacokinetic factors.
 - a. **Additive effect**-occurs when two or more drugs having the same effect are combined and the result is the sum of the individual effects relative to the doses used. This additive effect may be beneficial or harmful to the client.
 - b. **Synergistic effect**- occurs when two or more drugs, with or without the same overt effect, are used together to yield a combined effect that has an outcome greater than the sum of the single drugs active components alone

- c. **Potentiation**-describes a particular type of synergistic effect-a drug interaction in which only one of two drugs exerts the action that is made greater by the presence of the second drug.
- d. **Antagonistic**-reactions have the opposite effect of synergism and result in a combined effect that is less than either active component alone. (e.g. Protamine administered as an antidote to anticoagulant action of heparin)

Rx

Tetracycline Hydrochloride

250 gms

Directions for Pharmacist:

Make Capsules.

Send 10 such capsules.

Label:

Take 10 capsules every six hours with milk.

Comments:

Therapeutic incompatibility.

Chemical Incompatibility

- Def.: Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form.
- Types of chemical changes:
 - Oxidation
 - Hydrolysis
 - Polymerization
 - Isomerization
 - Decarboxylation
 - Absorption of CO_2
 - Formation of insoluble complexes

- **Oxidation:**

Def.: Oxidation is defined as loss of electrons or gain of oxygen

- Auto-oxidation: It is a reaction with oxygen of air which occur spontaneously without other factors.
- Pre-oxidants: are substances catalyze oxidation process i.e. metals, some impurities.

- **Hydrolysis:**

- A chemical reaction in which water is used to break down a compound; this is achieved by breaking a covalent bond in the compound by inserting a water molecule across the bond.

- **Polymerization:**

- In polymerization, small repeating units called monomers are bonded to form a long chain polymer.

- **Isomerization:**

- **CO₂ – absorption:**

- When some pharmaceutical dosage forms contain CO₂, precipitate is formed:
- Ex: $\text{Ca(OH)}_2 + \text{CO}_2 \rightarrow \text{CaCO}_3$

ASSIGNMENT

- Hair cosmetics , Skin cosmetics, Deodorants and antiperspirants: **G1**
- Oral care products, Nail products , Eye cosmetics , Lip products : **G2**
- Veterinary dosage forms: **G3**