INCOMPATABILITY

Definition:

When two or more ingredients of a prescription are mixed together, the undesired change that may take place in the physical, chemical or therapeutic properties of the medicament is termed as *incompatibility*. It may affect the safety, efficacy and appearance of a medicine.

TYPES

A. PHYSICAL INCOMPATIBILITY oR pharmaceutical

B.

A visible physical change takes place in this type of incompatibility. Usually, this is due to immiscibility or insolubility. It can cause unsightly, non-uniform products from which removal of an accurate dose is very difficult.

Physical incompatibilities are often called pharmaceutical incompatibilities and are evidenced by the failure of the drugs to combine properly.

How to prevent;

These types of incompatibilities can be corrected by one or more methods:

- *Alteration in the order of mixing*
- *alteration of solvents*
- *change in the form of ingredients*
- *alteration of volume*
- *Emulsification and addition of suspending agent,*
- *addition, substitution or omission of therapeutically inactive substances.*

***Classification*:**

(A) Immiscibility
(B) Insolubility
(C) Liquefaction

(A) Immiscibility

1) Oils are immiscible with water and hence combination of oily drugs with water produces a product possessing two separate layers.

***Remedy*:** This problem can be overcome by emulsification or solubilization (e.g. Emulsion and creams).

Example # 1:

℞

Olive oil 30ml

Water	up to 120ml

Remedy: Make an emulsion using a suitable emulsifying agent

2) Care must be taken when concentrated hydroalcoholic solutions of volatile oils such as spirits and concentrated waters, are used as adjuncts (e.g. as flavouring agents) in aqueous preparations. Large globules of oils may be separated.

Remedy: To prevent the formation of large globules, the hydroalcoholic solution should either be gradually diluted with the vehicle before admixture with the remaining ingredients or poured into the vehicle with constant stirring.

3) Addition of high concentrations of electrolytes to mixture in which the vehicle is a saturated aqueous solution of a volatile oil causes the oil to separate and collect as a surface layer.

e.g. This happens in *Potassium Citrate Mixture B.P.C.* in which large quantity of soluble solids salts out the lemon oil.

Remedy: To disperse the droplets evenly, quillaia tincture is added as a wetting agent.

(B) <u>Insolubility</u>

1) Liquid preparations containing indiffusible solids such as chalk, aromatic chalk powder, Sulphamethoxazole, Phenacitin, calamine and zinc oxide (in lotions) - a thickening agent is necessary to obtain a uniform product from which uniform doses can be removed.

Example # 1:

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Sulphamethoxazole	4.0g
Trimethoprim	0.8g
Na- CMC	0.5g
Purified water qs to make	100ml

Remedy: a uniform distribution of the solids in the liquid phase can be achieved with a thickening agent

2) Some insoluble powders such as sulphur and certain corticosteroids (*hydrocortisone acetate*) and antibiotics are difficult to wet with water.

Remedy: Wetting agents

e.g. *saponins* for sulphur containing lotions and *polysorbates* in parenteral suspensions of corticosteroids and antibiotics are used to distribute the powder and prevent formation of a slowly dispersing, solid stabilised foam on shaking.

3) Sometimes excess of surface active agent leading to deflocculation in a suspension may result claying.

Remedy: Reduce the concentration of surface active agent

4) When a resinous tincture is added to water the water insoluble resin agglomerate forming indiffusible clots.

Remedy: This is prevented by slowly adding the undiluted tincture, with vigorous stirring, to a diluted dispersion of protective colloid (*Tragacanth mucilage or compound tragacanth powder*). This will produce a stable preparation.

5) Aqueous dispersion of Hydrophillic colloids i.e., polysaccharide mucilage are precipitated by high conc. of Alcohol or salts.

Remedy: Well dilute and add small amounts with vigorous shaking.

5) High concentrations of electrolytes cause cracking of soap emulsions (ionic) by salting out the emulsifiers.

6) Some medicaments are soluble in organic solvents but water soluble adjuncts (inorganic salts) may be precipitated in such solvents.

C) <u>Liquefaction</u>

When certain low melting point solids are powdered together a liquid or soft mass is produced due to lowering of the melting point of the mixture to below room temperature. Thus an eutectic mixture is formed.

Any two of the following exhibits this type of behaviour, camphor, menthol, phenol, thymol and chloral hydrate, also sodium salicylate or Aspirin with phenazone.

Example # 1:

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Camphor	2 gm
Menthol	2 gm
Talc q.s to make	100 gm

Make powder.

Comments: If these ingredients are triturated together, they will form an eutectic mixture.

<u>Remedy</u>

<u>Method-I</u>:

When all the ingredients are triturated and an eutectic mixture (liquid) is formed, the liquid is then triturated with enough absorbent powder e.g. light kaolin, light magnesium carbonate or Talc, to give a free flowing powder.

<u>Method-II</u>:

Each ingredient is triturated separately with small amount of adsorbent or diluent and then these powders are lightly mixed by tumbling action and packed.

The diluent largely prevents contact between the ingredients and adsorbs any liquid that may be produced.

Example # 2:

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Aminopyrine	0.3 g
Acetyl salicylic acid	0.2 g

Codeine sulphate	0.015 g
Belladonna extract	0.010 g

Prepare capsules.

Comment: In this prescription aminopyrine and acetyl salicylic acid form eutectic mixture and wetting of belladonna extract give green colour.

Remedy: Light magnesium oxide (approximately 65 mg) may be added. The half quantity of magnesium oxide is mixed with aminopyrine and the other half with acetyl salicylic acid separately. The two are mixed gently and then other ingredients are added and mixed gently.

C. CHEMICAL INCOMPATIBILITY

Chemical incompatibility occurs when a reaction between two or more substances lead to a change in chemical properties of pharmaceutical dosage form.

Chemically incompatibility is generally caused by pH change, a double decomposition reaction or complex formation.

Provided the product is harmless the interaction falls into:

a. Tolerated-: the reaction is minimised by applying some suitable order of mixing or mixing the solution in dilute form but no alteration is made in the active ingredients of the preparation.

b. Adjusted-: the reaction is prevented by addition or substitution of one of the reacting substances with another of equal therapeutic value but does not affect the medicinal activity of the preparation (substitution of caffeine citrate with caffeine in sodium salicylate and caffeine citrate mixture).

Precipitate yielding combination

Generally reaction between strong solutions proceed at a faster rate and the precipitates formed are thick and do not diffuse readily. Reaction between the dilute solutions proceeds at a slow rate and the precipitates formed are light and diffuse readily in the solution. Hence the reacting substances should be diluted as much as possible before mixing. The preparation should contain a thickening agent if the precipitate is non-diffusible.

Method A

This is suitable for diffusible precipitates

- Divide all or most of the vehicle into two portions
- Dissolve the reactants in separate portions
- Mix the two portions by slowly adding one to the other with stirring rapidly.

(Sometimes a small volume must be reserved for dissolving other ingredients, rinsing measures, and adjusting to volume.)

Method B

It is used for bulky indiffusible precipitates.

- Divide the vehicle into two equal portions as in A
- Dissolve one reacting substance in one portion
- Place the other portion in a morter and Incorporate a suitable amount of Tragacanth powder (2gm/100ml of the finished product) with constant trituration untill a smooth mucilage is produced, then add and dissolve the other reacting substances.

Mix the two portions by slowly adding one portion to the other with rapid stirring.

pH effects

Modern medicaments are often salts of weak acids and bases. These salts are usually soluble in water while most of the unionized acids and bases are practically insoluble. Consequently if a salt of weakly basic drug is made alkaline, the free base may be precipitated, while precipitation of free acid may occur if a solution of a weakly acidic drug is acidified.

Whether precipitation occurs or not depends on

a) The solubility of the unionized acid or base.

b) The pH of the solution.

c) The dissociation exponent (pKa) of the acid or base

Solubility of the Unionized Acid or Base

Alkaloids

Most of salts are soluble in water but alkaloidal bases practically insoluble in water and are freely soluble in organic solvents. When an alkaline substance like aromatic spirit of ammonia, solution of ammonia, ammonium bicarbonate, Sodium bicarbonate, Borax, etc., is added to an alkaloidal salt solution the free alkaloid may be precipitated. However they are not always precipitated, because all alkaloids are slightly soluble in water. e.g., Strychnine, morphine, cocaine etc.

Other weak bases

Certain other organic bases (e.g., local anesthetics, methadone etc.) of low solubility may precipitate under alkaline conditions

Barbiturates

Barbiturates i.e., Phenobarbitone, pentobarbitone etc. are insoluble in water but there salts are soluble in water. There salts make the solution alkaline and hence are incompatible with acids, acidic salts (ammonium bromide) and acidic syrups (Lemon syrup), which may precipitate the corresponding insoluble barbiturate.

Other weak acids

Certain other organic acids (e.g., sulphonamides) of low solubility may precipitate under acidic conditions

Generally Chemical incompatibilities results from:

1. ACID - BASE REACTIONS:

Acid base reactions often result into precipitation, gas formation, breaking of structure of disperse systems or colour change.

a. Precipitation

Most medicaments in use are often salts of weak acids or bases. These salts have very good water solubility whereas their corresponding unionised acids or bases are practically insoluble in water. If a solution of a salt of a weakly acidic drug is acidified, the free acid may be precipitated. Similarly, precipitation of free base may occur if a solution of a salt of weakly basic drug is made alkaline.

Example # 1:

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Sodium salicylate	4 g
Lemon syrup	20 ml
Purified water q.s to make	100 ml

Make a mixture

Since Lemon syrup contains citric acid, it will acidify the solution and cause precipitation of the free acid (salicylic acid).

Remedy: Use other sweetening and flavouring agent instead of lemon syrup.

Example # 2:

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Strychnine hydrochloride solution	5ml
Aromatic spirit of ammonia	3ml
Purified water q.s to make	100 ml

Make a mixture

Strychnine HCl used in the mixture is an alkaloidal salt, whereas aromatic spirit of ammonia is an alkaline substance. On reaction between the two, insoluble strychnine is precipitated.

Remedy: Strychnine HCl solution should be dissolved in half the required quantity of water while aromatic spirit of ammonia should dissolved in the remaining portion of water. The two portions should be mixed slowly.

b. Gas formation

Gas (e.g. CO_2) may be evolved due to chemical reaction between the ingredients of a formulation. For compounding such preparations, the ingredients should be allowed to react in an open vessel and only when the reaction is complete, should the preparation be transferred to the final container, otherwise there may be chances of explosion. The reaction may be hastened by the use of hot water. Example: carbonates or bicarbonates with an acid or acidic drug resulting in the evolution of carbon dioxide.

Example # 1:

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Sodium bicarbonate	1.5g
Borax	1.5g
Phenol	0.75g
glycerin	25 ml
water q.s to make	100ml

Prepare a spray

In this case, borax decomposes in presence of glycerin to form sodium metaborate and boric acid. The resultant boric acid reacts with glycerin to form Glyceryl boric acid which upon reaction with bicarbonates yield CO_2

Example # 2:

Reaction of alkali bicarbonates with soluble calcium and magnesium salts

When alkali bicarbonates are combined with soluble calcium and magnesium salts, double decomposition reaction occurs resulting in the formation of corresponding insoluble carbonate and carbon dioxide. Since the reaction proceeds slowly at room temperature, it should be accelerated by using a hot vehicle and the resulting mixture should not be pocked until reaction is complete.

3. Breaking of structure of disperse system

Gelling agent such as carbomers, sodium carboxymethyl cellulose etc. very rapidly lose viscosity by change in pH outside an optimum range.

- Carbomer dispersion liquify by decreasing their pH below 5 or increasing it above 10.
- alginic acid is precipitated from dispersion of sodium alginate at pH below 3.0
- Carboxy methyl cellulose is precipitated from its sodium derivatives at pH below 3.0.

Emulsion prepared using soap as emulsifying agent are liable to break in presence of mineral acids which destroy the emulsifying activity of soap by precipitating the acids.

When a dispersion system e.g., cream is diluted with another of different pH, precipitation and or degradation of active ingredients may occur.

4. Colour change

The colour of most of the dyes used in formulations is influenced by their ionization which in turn depends on the PH of the solution, Thus crystal violet which is also used as antiseptic is a purple coloured compound but changes colour through green to yellow on acidification. Similarly phenolphthelin (used as laxative) is colourless in acidic solution but becomes pink in alkaline media. Colour change due to change in PH can be prevented by properly buffering the vehicle or by preventing reaction that cause formation of free acid or base in the medium.

2. OXIDATION - REDUCTION REACTION

Certain prescription mixtures may oxidize on exposure to air, heat, light or due to change in pH or reaction with trace metal ions. Use of antioxidants like ascorbic acid, Sodium metabisulphite etc, is often helpful in each cases.

Oxidation due to trace metal ions can be prevented by the use of chelating agents like Disodium EDTA.

Example # 1:

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Potassium Chlorate	4g
Ferric iodide syrup	10 ml
Purified water q.s to make	60 ml
Make a mixture	

In this case potassium chlorate react with ferric iodide. Initially the mixture is quite clear but on standing, crystals of iodine are deposited. It is therefore essential to dispense the two compounds separately with instructions to mix the two before administration.

Example # 2:

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Sodium salicylate	4g
Sodium biocarbonate	4g
Peppermint water	to 60mi
make a mixture	

Sodium salicylate gets oxidized in presence of sodium biocarbonate and the mixture darkens on storage. This alkaline catalyzed oxidation may however be prevented by the use of a suitable antioxidants like 0.1% sodium metabisulphate.

3. COMPLEXATION

Many macromolecular adjuncts used in formulation form complexes in which medicaments and preservatives are bound to the macromolecules or trapped within micelles. This behavior is most common with non-ionic macromolecules. Because these complexes are too large to penetrate cell membranes, the activity of the medicament or preservatives may be greatly reduced. A number of medicaments and excipients like suspending agent (polysaccharides), emulgents (macrogol esters and ethers) and solubilisers (polysorbates) exhibit this phenomenon.

Complexation may sometimes be useful especially when it is reversible. In such case a large amount of drug is available in the unbound form and when this drug is utilized, it is replaced

Example: anticancer drugs i.e., Vincristine, cyclophosphamide inhibit absorption of certain other drugs. i.e., digoxin.

c. Altered motility

Example: Metoclopromide (antiemetic) delay stomach emptying and increase absorption of certain other drugs. i.e., cyclosporine

2. Altered protein binding (Distribution)

Certain high affinity drugs displace other plasma protein bound drugs and thereby increases its concentration.

Example: Phenytoin (90% bound) and warfarrin (99% bound) are displaced by Aspirin and sulfonamides.

3. Altered metabolism

Majority of drugs are metabolized by CYP450 family. Certain drugs either induce or inhibit these enzymes and thereby affecting the metabolism of co-prescribed drugs (substrates).

a. Enzyme induction

Example: Phenytoin increases hepatic metabolism of theophylline leading to its decreased levels and reduced action.

b. Enzyme inhibition

Example: Verapamil inhibits carbamazepine metabolism and increases its concentrations.

Omeprazole Inhibits oxidative metabolism of diazepam

4. Altered renal excretion

a. Inhibition of renal tubular secretion

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.

Example: Probenecid….. Decreases tubular secretion of methotrexate.

b. Alteration of urine pH

Ionized drugs are reabsorbed lower than non-ionized ones. Making the pH of urine acidic will make weakly basic drugs ionized and hence enhance their excretion.

These are useful in some clinical situations such as poisoning treatment. For example, amphetamine poisoning can be reversed by enhancing its excretion via urine acidification.

Pharmacodynamic interaction

1. Synergistic (or additive) combination

When certain drugs having the same pharmacologic action are prescribed together, the combined action they produce is greater than the sum of their individual actions. Such combinations should be in reduced amount. The synergistic action will sometimes be desired to decrease toxicity or reduce cost of prescription.

Examples

Neomycin – erythromycin combination has a broader spectrum than either antibiotic alone.

Aspirin – codeine combination reduces the amount of expensive codeine required.

Sulphonamides - trimethoprim combination (broader spectrum).

2. Antagonistic combinations

When two or more drugs having opposite pharmacological action are prescribed together, their actions cancel each other and the resulting prescription will have no therapeutic action.

- Stimulants with sedatives (hypnotics) e.g. caffeine with chloral hydrate.
- Purgatives with antidiarrheals e.g. $MgSo_4$ with tannins
- Acidifiers with alkalinizers e.g. aspirin with $AL(OH)_3$.
- β-adrenoceptor antagonists i.e., Propranolol diminishes the effectiveness of β-receptor agonists, i.e., salbutamol or terbutaline.

Sometime this antagonistic affect is desirable e.g., Protamine is administered as an antidote to anticoagulant action of heparin (toxicity).