

Pharmaceutical Incompatibility

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Incompatibilities:

- It is the result of **prescribing or mixing two or more substances** which are **antagonist in nature** and an **undesirable product** is formed which may affect the **safety, purpose or appearance** of the preparation.
- Incompatibilities are usually **unintentional**.
- It may occur in vitro between drugs & other components during **preparation, storage or administration**.
- Incompatibility may be :
 1. **Pharmaceutical /Physical Incompatibility**
 2. **Therapeutic Incompatibility**
 3. **Chemical Incompatibility**

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Physical Incompatibility:

- A **visible physical change** takes place .
- An **unacceptable, non-uniform, unpalatable product** is formed.
- **Difficult** to measure an **accurate dose**.
- Result of **insolubility & immiscibility, precipitation, liquefaction, Adsorption and complexation** of solid materials.
- Can be corrected by applying pharmaceutical skill.

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Correction (Physical incompatibilities):

By one or more methods:

1. Order of mixing
2. Alteration of solvents
3. Change in the form of ingredients
4. Alteration of volume
5. Emulsification and addition of suspending agent,
6. Addition, substitution or omission of therapeutically inactive substances.

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1. Immiscibility:

- It is the result of the mixture of two or more immiscible liquid or an immiscible solid with a liquid.
- Acceptable liquid product can be obtained by emulsification or solubilization.

Rx

Olive oil 30ml

Water up to 120ml

Make an emulsion

Use a suitable emulsifying agent

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2. Insolubility:

- Liquid preparation with indiffusible solids (e.g. Sulphamethoxazole, Phenacetin, Zinc oxide, calamine etc.)
- A suspending agent is required to uniform distribution of the solids in the liquid phase for sufficiently long time so as to facilitate accurate measurement of dose.

Rx

Sulphamethoxazole 4.0g

Trimethoprim 0.8g

Na- CMC 0.5g

Purified water qs to 100ml

Prepare a solution.

- Sulphamethoxazole & Trimethoprim are indiffusible in water.
- To make them diffusible a suspending agent is used.

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- Insoluble Powders such as Sulphur, certain corticosteroids and Antibiotic is not get wetted with water & non-distributed in vehicle & hence wetting agents such as Saponins & Polysorbates are added for uniform distribution of it in vehicle.

- Insoluble non-wetted drug powders + water + wetting Agent (polysorbates/saponins)

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3. Precipitation:

- A solubilised substance may precipitate from its solution if a non solvent for the substance is added to the solution.
 - Alcoholic solution of resins + water = precipitated resins
 - Aqueous dispersion of hydrophilic colloids (polysaccharide mucilage + high conc. of alcohol or salts = precipitated colloids)
- But significant amount are tolerated if well diluted and added in small amount with vigorous stirring.

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4. Liquefaction:

- Certain low melting point solids sometimes liquefy when mixed together due to the formation of eutectic mixture or liberation of water.
- E.g., if any 2 of the following medicaments are combined together, they form a eutectic mixture: Menthol, Thymol, Camphor, Phenol, Salol, Naphthol and chloral hydrate.

Correction:-

1. The eutectic forming ingredient may either be **dispensed separately**.
2. These may be **mixed separately** with enough quantity of **adsorbent powder** like magnesium carbonate or Kaolin to form free flowing product.
3. Alternately, if liquefaction has already occurred, the liquid may be adsorbed on a surface of sufficient quantity of powder, filled into capsule and dispensed.

Example:

Rx

Menthol	2.0g
Camphor	2.0g
Ammonium carbonate	20.0g

Make a powder.

- In this case, if the ingredients are mixed together, they shall liquefy due to formation of a eutectic mixture.
- Hence, to dispense them in the form of a powder, it is necessary to mix them separately with sufficient quantity of a suitable **adsorbent like magnesium carbonate**.
- The three mixture then mix together to obtain a powder.

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Chemical Incompatibilities:

- Chemical Incompatibilities is usually a **result of chemical interaction taking place among the ingredients of a prescription**.
- Such interactions may take place immediately upon compounding when these are termed as immediate incompatibilities and are evident as **effervescence, precipitation or colour change**.
- More often the interaction are not evident immediately on compounding but **take place over a period of time**. Such interaction are termed delayed incompatibilities.

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a) Tolerated:-

The reaction is **minimized** 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 of the preparation (substitution of caffeine citrate with caffeine in sodium salicylate and caffeine citrate mixture).

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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** proceed 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.

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Method A

- This is suitable for diffusible precipitates
1. Divide all or most of the vehicle into two portions
 2. Dissolve the reactants in separate portions
 3. 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.)

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Method B

It is used for bulky indiffusible precipitates.

1. Divide the vehicle into two equal portions as in A
2. Dissolve one reacting substance in one portion
3. Place the other portion in a mortar and incorporate a suitable amount of Tragacanth powder (2gm/100ml of the finished product) with constant trituration until a smooth mucilage is produced, then add and dissolve the other reacting substances.
4. Mix the two portions by slowly adding one portion to the other with rapid stirring.

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Alkaloidal Incompatibilities:

Incompatibility	Example	Reaction	Correction
Alkaloidal salt reacts with alkaline substances	Alkaloidal salt: Strychnine HCl, Atropine sulfate, Morphine HCl Alkaline substances: Aromatic spirit of ammonium bicarbonate, ammonium hydroxide	Free alkaloid is ppt. which is insoluble in water	1. Alkali may be omitted. 2. Alcohol may included if not affected. 3. Method A or B is applied.
Alkaloidal salt reacts with tannic acid	Preparation containing tannic acid: Tincture of catechu, tincture of galls, infusion of cloves	Alkaloidal tannate is ppt. which is insoluble in water	1. Before mixing ingredients, they are diluted 2. Method A
Alkaloidal salts reacts with iodides & bromides	Alkaloidal salts reacts with KI and KBr	Hydroiodide and Hydrobromide are ppt.	1. Method A
Alkaloidal reacts with Salicylates & Benzoates	A. Salts reacts with Na-Salicylates and Na-Benzoates	Salicylates and Benzoates are ppt.	1. Method B

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Incompatibilities of Iodides & Bromides:

Incompatibility	Example	Reaction	Correction
Iodides and Bromides with ferric salts	KI & KBr reacts with ferric salts	Iodine and Bromine will be liberated	1. Convert ion into iron oxide 2. One ingredient may be omitted
Iodides and Bromides with mercurous salts	KI & KBr reacts with mercurous salts	Mercurial salt is formed	1. Method A
Iodides and Bromides with Quinines sulphate, H ₂ SO ₄ , with water	KI reacts with Quinines sulphate, H ₂ SO ₄ , with water	Olive green crystals of iodosulphate of quinine is formed after 3 days	1. 3 days use: dispense together 2. Otherwise dispense separately

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Incompatibilities of Salicylates & Benzoates:

Incompatibility	Example	Reaction	Correction
Salicylates & Benzoates reacts with acids	Na- salicylates & Na- Benzoates react with H ₂ SO ₄ / HCL	Salicylic/Benzoic acid is ppt.	1. NaHCO ₃ is added 2. Method B 3. Replace acid
Salicylates & Benzoates Reacts with alkali	Na- salicylates & Na- Benzoates Reacts with NaHCO ₃	Dark brown color is formed	1. Add liquid extract of liquorice
Salicylates & Benzoates Reacts with ferric salt	Na- salicylates & Na- Benzoates Reacts with ferric salt	Ferric salicylate/benzoate is ppt.	1. Method A

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Incompatibilities causing evolution of CO₂:

Incompatibility	Reaction	Correction
NaHCO ₃ reacts with borax, glycerin & water	Carbon dioxide is evolved	They should be mixed with water in an open vessel until effervescence ceases
NaHCO ₃ reacts with Bismuth Subnitrate & water	---same---	Reaction must be accelerated by using hot water.
NaHCO ₃ reacts with Dil. H ₂ SO ₄ or Dil. HCl	---same---	They should be mixed with water in an open vessel until effervescence ceases
NaHCO ₃ reacts with Calcium chloride or MgCl ₂ & water	---same---	Reaction must be accelerated by using hot water.

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Miscellaneous Incompatibilities

Incompatibility	Example	Reaction	Correction
Iron salt reacts with tannic acid	Ferric chloride reacts with preparation containing tannic acid	Bluish black iron tannate is formed	Any one ingredient is omitted
Liquid extract of liquorice reacts with acid	Liquid extract of liquorice reacts with H ₂ SO ₄ or HCl	Sweetening principle is decomposed	Acid may be omitted

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- 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 a very **good water solubility** whereas their **corresponding unionized 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.

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Example I

Rx

Sodium salicylate 4g
Lemon syrup 20ml
Purified water to 100ml
make a mixture.

- Since Lemon syrup contains citric acid, it will acidify the solution and cause precipitation of the free acid (salicylic acid).
- In order to overcome this incompatibility, it is necessary to use other sweetening and flavouring agent instead of lemon syrup.

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Example II

Rx

Strychnine hydrochloride solution 5ml
Aromatic spirit of ammonia 3ml
purified water to 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. since the precipitate formed is diffusible, the incompatibility may be taken care by suitable formulation.
- In this case, 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 portion should be mixed slowly.

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b. Gas formation

- Gas may be evolved due to chemical reaction between the ingredients of a formulation.
- Example: carbonates or bicarbonates with an acid or acidic drug resulting in the evolution of carbon dioxide.
- Reaction of sodium bicarbonate, borax and glycerol

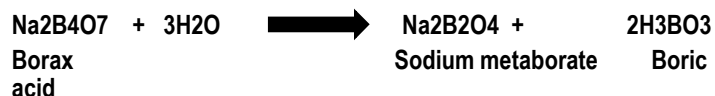
Rx

Sodium bicarbonate 1.5g
Borax 1.5g
Phenol 0.75g
glycerin 25 ml
water to 100ml
Prepare a spray

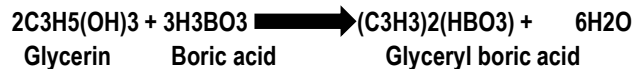
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□ Happenings:-

- In this case , borax decomposes in presence of glycerin to form sodium metaborate and boric acid



- Boric acid thus formed further reacts with glycerin to form Glyceryl boric acid



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Overcoming the incompatibility causing evolution of CO₂ gas

- For compounding of such preparation, 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 a chances of explosion.
- The reaction may be hastened by the use of hot water.

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Reaction of alkali bicarbonates with soluble calcium and magnesium salts...

- ❖ When alkali bicarbonate 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.

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c. Color 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 phenolphthalin (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.

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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.

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Rx

Sodium salicylate 4g
 Sodium biocarbonate 4g
 Peppermint water to 60ml
 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 metabisulphite.

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4. Ionic Reactions:

- The therapeutic or pharmaceutical properties of many organic compounds are usually associated with a large cation or anion. Interaction of such ions of opposing types may yield compounds which may totally lack the useful properties of the interacting molecules.
- For instances, Cream prepared using cationic emulgents may crack if mixed with a cream prepared using an anionic emulgents.
- Similarly an anionic solubilizers may lower the antimicrobial activity of a cationic medicament or preservative.

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5. Explosive Combination:

- Oxidizing agents are chemically incompatible with reducing agent and a combination of the two in a formulation may lead to an explosive reaction.
- For example, if Potassium chlorate is prescribed with an oxidisable substance like Sulphur, tannic acid, etc and the two are triturated or heated together, there is a fair chance of an explosive reaction taking place.
- In such case, it is better to dispense the components separately or if it is necessary to mix them together, the mixing should be done very lightly.

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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.

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1) Overdose :-

Rx

Codeine phosphate 0.5 gms
Make powders.
Send such 10 powders.

Overcome:-

- It is a unintentional incompatibility.
- This is the example of overdose medication.
- The prescription should be referred back to prescriber for necessary correction.

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2) Drug interaction:-

Rx

Tetracycline Hydrochloride 250 gms

Directions for Pharmacist:

Make Capsules.
Send 10 such capsules.

Label:

Take 10 capsules every six hours with milk.

- ❖ Overcome:- Avoid administration of tetracycline with milk to prevent the formation of insoluble complex.

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3) Synergism:-

- Aspirin & Paracetamol increases analgesic activity
- Penicillin & streptomycin increases antibacterial activity.

Rx

Amphetamine Sulphate 20 mg
Ephedrine Sulphate 100 mg
Simple syrup up to 100 ml.
Make a mixture.

Overcome:-

- Both are sympathomimetic drugs cause additive effect. Hence of individual drugs dose should be reduced to avoid the therapeutic incompatibility.
- Otherwise the prescription should be referred back to the prescriber for necessary correction.

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4) Antagonism:-

Rx

Aspirin

Probencid

Overcome:-

- Both are anti-gout agents. But upon prescribing them together there is a neutralization effect.
- Hence prescription should be referred back to the prescriber for necessary correction.

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5) Contraindicated Drugs:-

1. Penicillin & sulphonamides are not prescribed for those patients who are allergic to it.
2. Corticosteroids are never prescribed in peptic ulcer condition
3. The drugs which will excrete into milk are never prescribed in lactating mothers.
e.g. Phenytoin, Phenobarbitone, chloramphenicol etc.

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Question Bank:

2 Marks

1. Define therapeutic incompatibility.
2. Solve the following incompatibility

Rx

Sodium Salicylate – 5 gm.

Lemon syrup – 20ml

Purified water - 75 ml.

5 Marks

1. Write a note on reasons & remedies of physical incompatibility.
2. Short note- Physical incompatibility.**
3. Short note- Therapeutic incompatibility.

10 Marks

1. Define incompatibility. Discuss in detail chemical incompatibility.
2. What is incompatibility? Discuss the reasons why physical & therapeutic incompatibility occurs. Describe the methods to correct such incompatibility.

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Don't stop
when you are tired.
STOP
when you are
DONE!

My Dear Valentine

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