# INCOMPATIBILITY

1. Define and classify incompatibility with examples.

Incompatibility:

It is defined as mixing of 2 or more substances result in changes of physical, chemical or therapeutic effect.

It effects the safety, appearance, ~~effection~~ and over all stability of pharmaceutical preparation.

Interaction of drug with another drug or a drug with additive, dosage errors, ommition, packaging consideration etc., all fall under incompatibility.

It may occur in compounding and dispensing of prescription during formulation, manufacturing, packaging or administration of drugs.

The problem of incompatibility should be overcomed by the pharmacist with his sound knowledge on chemistry, pharmacology, pharmacy.

An understanding of solubility, chemical reactivity, drug stability and therapeutic efficacy is essential.

classification:

They are classified widely into 3 major groups

* physical incompatibility
* chemical incompatibility
* therapeutic incompatibility.

⇒ PHYSICAL INCOMPATIBILITY

It is classified into 3 types as

* Immescibility
* Insolubility
* Liquifaction.

* IMMESCIBILITY

Oils are immescible in $H_2O$.

e.g: Castor oil in $H_2O$,
Mineral oil in $H_2O$,
Arachis oil in $H_2O$.

The problem can be overcome by selecting a suitable emulsifier when concentrated hydro alcoholic solution like volatile oils, elixirs, spirits, aromatic $H_2O$. when mix with one another they result in separation of soluble constituents.

It can be overcome by mixing the aqueous phase slowly in portion to the alcoholic phase and gradually dil the concentrated with constant stirring.

Incorporation of high conc. of strong electrolytes to the mixture containing saturated aqueous solution containing volatile oil.

e.g: Cinnamon $H_2O$, anise $H_2O$, peppermint $H_2O$ etc, result in separation of oils.

* INSOLUBILITY

Liquid preparation containing indiffusible solids requires suspending agent for conversion of indiffusible solids to diffusible solids.

e.g: Chalk powder, sulphadimidine.

(20)

Solids like sulphur, certain antibiotics, cortico steroids are of insoluble in nature and difficult to wet with $H_2O$ requires a suitable wetting agent.

Excess conc. of surfactant acts as deflocculating agent may result in claying.

Preparation contain potent medicament as suspensions should require vigorous shakings before consuming.

Failure to shake or delay in removal of the dosage form leads to overdose at the end.

eg: Barbiturates, Alkaloids etc.,

Alcohols soluble constituents must be diluted with aqueous solution to prevent separation. Order of mixing should be followed strictly.

eg: Alcohols, Vegetable extracts, triturates, elixirs, volatile oils etc.,

Addition of precipitate yield substances to aqueous system lead to formation of diffusible solids.

eg: Resinous tinctures should be slowly added to the centre of the aqueous cream with constant stirring.

High concentration of electrolytes causes cracking of soap emulsion by salting out the emulgent.

* LIQUEFACTION

e.g: Eutectic mixtures

Certain solids when powdered together result in the formation of liquid or a soft mass is produced.

e.g: compounds like camphor, methanol etc.,

⇒ CHEMICAL INCOMPATIBILITY

This type of incompatibility occured due to pH change, oxidation, reduction, acid-base reaction, double-decomposition, complex formation.

They can be identified by the precipitate, effervescence, decomposition, colour change or explosion.

They are classified into

* ~~Air~~ tolerant incompatibility
* Adjusted incompatibility.

* ~~AIR~~ TOLERANT INCOMPATIBILITY / Tolerable.

The chemical changes can be minimized by changing the order of mixing or mixing the solution in dil. form without any alternation in the active ingredients of prescription.

* ADJUSTED INCOMPATIBILITY

Any addition or substitution that doesn't effect the medicinal activity. or the chemical interaction can be prevented by addition or substitution of any one of the ingredients with another substances which is having equal therapeutic value.

1) precipitate yielding interaction method (a)

Suitable for diffusible precipitate.

Divide the vehicle into two equal halves. Dissolve one of the reactant substances in one half another substances in another half. Mix the two portions slowly adding one to the other with rapid and constant stirring.

Method (b)

Suitable for ~~un~~diffusible precipitate.

Divide the vehicle into two portions. Dissolve the ingredients in one portion. place the second portion of the vehicle to a mortor and incorporate suitable amount of suspending agent with constant trituration until a smooth mucilage is formed. Add the other reactants substances to the mucilage. Mix the solution of the 1st reactants to the mucilage with rapid stirring.

2) Oxidation and reduction

this type of incompatibility Rx mixture are exposed to air excessive-storage, temperature, light, over dilution, alternation of pH or presence of catalyst.

They can be prevented by using anti-oxidants such as ascorbic acid, sodium bisulphite, sodium meta bisulphite etc.,

Oxidation of iron metals can be overcome by choosing suitable complexing agent like EDTA, editic acid, edetate sodium etc., Auto oxidation of oils, fats, aldehydes, phenoid substances etc, can

be controlled by agents like propyl gallol, BHA, BHT, Hydroquinones etc.,

Reduction of metals like silver, gold, mercury etc., can be reduced by prevention of exposing them to light. These are less common.

℞
Sodium salicylate
Sodium bicarbonate
peppermint water q.s. to.

Make a mixture. The solution becomes darken on standing due to alkaline catalysed oxidation of salicylate due to quinonoid form. Therefore 0.1% sodium bisulphate is used as an anti-oxidant to prevent the odour, colour change.

℞
potassium chlorate
Ferric iodide syrup
purified water q.s. to
Make a mixture.

Ferric ~~oxide~~ iodide undergoes oxidation with potassium chlorate. The mixture remains clear and fresh on standing. The crystals of iodine undergoes deposition and result in suspension.

$KClO_3 + FeI_3 \longrightarrow Fe(OI)_3 + I + KCl$

The two reacting substances are dispensed separately with instruction to mix before administration.

3) Acid-base reaction

This incompatibility can be identified by effervescence, precipitation, colour change.

a) precipitation

Soluble inorganic salts reacts with hydroxide and result in water insoluble compounds.

Soluble salts of phenols, carboxylic acids, barbituric acid etc., yields free acids when added to strong acids.

Soluble salts of amine drugs liberates free bases in presence of strong bases.

℞

Cocaine hydrochloride
Boric acid
Sodium benzoate
purified water q.s. to

Cocaine hydrochloride is completely soluble in $H_2O$. Addition of sodium benzoate imparts alkalinity to the preparation which leads separation of water soluble cocaine hydrochloride. This can be overcome by removal of sodium benzoate from the prescription.

b) Effervescence.

It leads to evolution of gas due to the chemical reaction between two compounds.

℞

sodium carbonate
Borax
Phenol
Glycerine
purified water q.s. to

· Make a spray.

Glycerine reacts with boric acid to form glyceroboric acid which result in effervescence. It can be overcome by performing the reaction in open vessels until effervescence ceases.

c) Colour change

The colour of dye compound are influenced by their ionisation which incase depends on the pH of the solution. The change in colour can be prevented by the incorporation of standard buffer solution or by changing the vehicle in order to prevent the formation of acid or base.

eg: phenopthalein is colourless in acid and red in alkaline.

Gention is a purple compound, on addition of acids the colour changes through green to yellow.

4) Hydrolysis

Many compounds are hydrolysed by $H_2O$ and the reaction is enhanced by heat, catalyst, hydroxyl and hydrogen ion. This can be prevented by addition of any one of the species formed as a result of the hydrolysis or it can be prevented by reverse of ionic hydrolysis.

eg: 1. Esters, amides, metals like zinc, iron etc.,
2. Soluble salts of barbituric acid result in formation of insoluble free acids.
3. Sulphoamides are hydrolysed in presence of

$H_2O$.

4. phenol salicylate hydrolysed in presence of base to form salicyclic acid and phenol.

℞

Sodium salicylate
phenol barbitol sodium
Vitamin-D complex
Make a Elixir.

the alkalinity of salts causes deteriation of Vitamin-D complex which leads to precipitation of acid and salts. This can be prevented by supplying alkali salts seperately.

5. Racemation

It consists of conversation of a optical active form to a optical inactive form without a change in chemical structure but reduction in pharmalogical activity.

eg: Adrenaline, Epinephrine, nor-epinephrine.

6. Explosive combination

the combination of substances causing explosion while mixing both the mixtures.

⇒ THERAPEUTIC INCOMPATIBILITY.

It is defined as the change in response to one or more drug differ from the intended response or action. These incompatibilities can be overcomed by the interest of physician or pharmacist.

The pharmacist will sometime, return with prescription or may consult prescriber before dispensing.

Types of Therapeutic incompatibility

1. Dosage errors.
2. Wrong drug or dosage form.
3. Contra indicated drug.
4. Synergistics & antagonistic drug.
5. Drug interaction.

1. DOSAGE ERRORS

This type of errors occurs on overdose of medication. The pharmacist should take utmost care to overcome such type of errors in prescription.

℞

Atropine sulphate - 0.006g
phenobarbitol - 0.015g
Aspirin - 0.300g

Make a capsule.

Direction

1 capsule 3 times a day

The dose of atropine sulphate is more than, maximum recommended dose. Therefore, the prescription should be return back to the prescriber.

2. WRONG DOSE OR DOSAGE FORM

Certain drugs are having similar names and leads to damag danger of dispensing of drug

or dosage form
e.g: prednisdone & prednisone
Digoxin and digitoxin.

In some cases, drugs are available in different dosage form. If the dosage form is not clearly mentioned in the prescription, pharmacist must clarify it with prescriber.

## 3) CONTRA INDICATED DRUGS

Certain drugs may be contra indicated in a particular disease or to a particular patient who is allergic to it.

e.g: Corticosteroids are contra-indicated in peptic ulcer patients.

penicillin and sulpha drugs are contra-indicated with one another.

Amine containing foods should not be taken by patients consuming MADIS MAOI's Monoamine oxidase inhibitors

℞

| | |
|---|---|
| Sulphadiazene | 250 mg |
| Sulphamerazene | 250 mg |
| Ammonium chloride | 500 mg |

Make a capsule.

Ammonium chloride is an urinary acidifier it causes deposition of sulphur drugs like crystals in kidney. Hence, the prescription should be referred back to prescriber.

## 4) SYNERGISTICS AND ANTAGONISTIC DRUGS

Synergistics may sometime intentional by the prescriber to increase the therapeutic activity of drugs.

eg: paracetemol and aspirin combination increases the analgesic activity.

penicillin and streptomycin combination increases antibiotic activity.

Incases of undesirable consequences, the prescription should be referred back to prescriber

℞

Amphetamine 20 mg
ephedrine sulphate 100 mg
Simple syrup 100 ml
q.s. to

Make a mixture.

The combination of two sympathomimetic drugs gives an adequate effect so, there is a need to reduce the dose of each drug. prescription should be referred back.

When two or more drugs produces an opposite pharmalogical effect, antagonism occurs

℞

Aspirin 600 mg
probenicid 500 mg

Make a capsule.

Both these drugs are used in treatment of gout. The combination leads to neutralisation. Hence it should be referred back.

(30)

## DRUG INTERACTIONS

The effects of drugs is altered by The addition of prior or simultaneously administration of another drug. The drug interaction can be corrected by the proper adjustments of dose or removal of dosage if suspected interaction detected.

℞

Acetophenitidine 150 mg
Aspirin 200 mg
Caffine 30 mg
Make a capsule.

Acetophenitidine and aspirin are analgesics. Acetophenitidine depresses the CNS and side effect is undesirable. Caffine is CNS stimulant. It neutralises the side effect of acetophenitidine. Therefore the ~~un~~ incompatibility is intentional and dispensed as such.

℞

Tetracyclin 250 mg
Make a capsule.

Direction:
Take 1 capsule every 6 hours with milk.

Tetracyclin is inactivated by calcium salts present in milk. It should not be taken with milk. The incompatibility is unconditional and should be refused back.

2. Explain in brief the various physical incompatibility and their remedies with examples.

## PHYSICAL INCOMPATIBILITY

It is defined as mixing of two or more substances result in changes of physical effect It effects the safety, appearance, effection, overall stability of pharmaceutical

## CLASSIFICATION

It is classified into three types as

* Immescibility
* Insolubility
* Liquifaction.

### * IMMESCIBILITY

Oils are immescible in $H_2O$.

e.g: Castor oil in water
Mineral oil in water
Arachis oil in water.

Remedy

The problem can overcome by selecting a suitable emulsifier.

When concentrated hydro alcoholic solution like volatile oils, elixirs, spirits, aromatic water. when mix with one another, they result in separation of soluble constituents. It can be overcome by mixing the aqueous phase slowly in portion to the alcoholic phase and gradually dilute the concentration with constant stirring.

Incorporation of high concentration of strong electrolytes to the mixture containing saturated.

Aqueous containing volatile oil.

e.g: Cinnamon oil water, anise water, peppermint water etc., result in separation of oils.

e.g: potassium citrate mixture BPC.

Incorporation of large concentration of electrolytes leads to salting of the lemon oil. This can be overcome by replacing the lemon tincture with quillia tincture in the prescription.

* INSOLUBILITY

Liquid preparation containing indiffusible solid requires suspending agent for conversion of indiffusible solids to diffusible solids.

e.g: chalk powder
Sulphadimidine.

Solids like sulphur, certain antibiotics, cortico steroids are of insoluble in nature and difficult to wet with water requires a suitable wetting agent.

Excess concentration of surfactant acts as deflocculating agent may result in p caking.

preparation contain potent medicament as suspensions should require vigorous shakings before consuming. The failure to shape or delay in removal of the dosage form leads to overdose at the end.

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Alcohols soluble constituents must be diluted with aqueous solution to prevent separation. Order of mixing should be followed strictly.

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e.g: Resinous tinctures should be slowly added to the centre of the aqueous cream with constant stirring.

High concentration of electrolytes causes cracking of soap emulsion by salting out the emulgent.

## * LIQUIFACTION

e.g: Eutectic mixtures.

compounds like camphor, methanol etc.,

The powder contains eutectic substances like camphor and methanol which acts as corminative. when two or more eutectic powders are mixed together they undergo liquifaction due to formation of a new compound having lower melting point than the original compound.

Remedy

The problem can be rectified by using kaolin as an adsorbant. Kaolin makes the mixtures

dry and free particles which dissolve in small portions of alcohol. when alcohol evaporates, the camphor converts into free particles.

3. Write a note on therapeutic incompatibilities and their remedies with examples.

## THERAPEUTIC INCOMPATIBILITIES

It is defined as change in response to one or more drugs differ from the intended action or response. these incompatibilities can be overcomed by the interest of physician or pharmacist.

The pharmacist will sometime return the prescription or may consult the prescriber before dispensing.

## TYPES OF THERAPEUTIC INCOMPATIBILITIES

1. Dosage errors
2. Wrong drug or dosage form.
3. Contra indicated drug.
4. Synergistics and antagonistic drug
5. Drug interactions.

### 1. DOSAGE ERRORS

This type of errors occurs on overdose of medication. the pharmacist should take utmost care to overcome such type of erras in prescription.

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| phenobarbitol | 0.015 g |
| Aspirin | 0.300 g |

Make a capsule.

Direction

1 capsule 3 times a day.

The dose of atropine sulphate is more than, maximum recommended dose. Therefore, the prescription should be returned back to the prescriber.

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Certain drugs are having similiar names and leads to danger of dispensing of drug or dosage form.

eg: prednisolone and prednisone.
Digoxin and Digitoxin.

In some cases, drugs are available in different dosage form. If the dosage form is not clearly mentioned in the prescription. pharmacist must clarify it with prescriber.

3) CONTRA INDICATED DRUGS

Certain drugs may be contra indicated in a particular diseases or to a particular patient who is allergic to it.

eg: Cortico steroids are contra indicated in peptic ulcer patients.

pencillin and sulphur drugs are contra indicated with one another.

@mine containing foods should not be taken by patients consuming MAOI'S.

@spirin preparation should be avoided by patients under treatments with anti-coagulants, oral anti-diabetes, anti neurotransmitors.

℞

Sulphadiazene 250mg
Sulphamerazene 250mg
@mmonium chloride 500mg

Make a capsule.

@mmonium chloride is an urinary acidifier it causes deposition of sulphur drugs are crystals in kidney. Hence, the prescription should be referred back to the prescriber.

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| Amphetamine | 20 mg |
| Ephedrine sulphate | 100 mg |
| Simple syrup q.s to | 100 ml |

Make a mixture.

The combination of two sympathomimetic drugs gives an adequate effect. So, there is a need to reduce the dose of each drug. Prescription should be referred back.

When two or more drugs produces an opposite pharmacological effect, antagonism occurs.

℞

| | |
|---|---|
| Allopurinol | 600 mg |
| Probenecid | 500 mg |

Make a capsule.

Both these drugs are used in treatment of gout. The combination leads to neutralisation. Hence, it should be referred back.

5) DRUG INTERACTIONS

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be corrected by the proper adjustments of dose or removal of dosage if suspected interaction is detected.

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Make a capsule.

Acetophenitidine and aspirin are analgesics. Acetophenitidine depresses the CNS and side effect is undesirable. Caffeine is CNS stimulant. It neutralises the side effect of acetophenitidine. Therefore the incompatibility is intentional used and dispensed as such.

℞

Tetracycline 250 mg

Make a capsule.

Direction

Take 1 capsule every 6 hours with milk.

Tetracycline is inactivated by calcium salts present in milk. It should not be taken with milk. The incompatibility is uncondition and should be returned back.

5. How will you dispense the following.

℞

| | |
|---|---|
| Quinine sulphate | 1.6g |
| Dilute sulphuric acid | 4ml |
| potassium iodide | 8g |
| water q.s.To | 180 mL |

℞

| | |
|---|---|
| Quinine sulphate | 1.6g |
| Dilute sulphuric acid | 4ml |
| potassium iodide | 8g |
| water q.s.to | 180ml. |

This prescription shows chemical incompatibility. That is in this preparation dilute sulphuric acid is used to dissolve Quinone sulphate because it is not freely soluble in water. when this preparation is freshly prepared, a clear solution will be formed. But after keeping it more than three days, the following reaction takes place.

$$H_2SO_4 + KI_2 \xrightarrow{\text{oxidation}} HI \text{ (Hydroiodic acid)}$$

$$\text{Hydroiodic acid} \xrightarrow[\text{by dil. } H_2SO_4]{\text{partially oxidised}} \text{free iodine}$$

In the mixture, Quinine sulphate + Iodine + Hydroiodic acid ⟶ Iodo sulphite of Quinine (Herapathite)

(4)

(It is identified by bronze or olive green scales).

a) Dil. sulphuric acid reacts with potassium iodide and liberates hydroiodic acid.

b) This hydroiodic acid is partially oxidised by remaining amount of dil. $H_2SO_4$ and free iodine will be liberated.

c) In this mixture, when Quinine sulphite, iodine, hydroiodic acid are combined together a new compound called as Herapathite or Iodo sulphite of Quinine is formed. The reaction is called as "Herapathite reaction".

d) The formed herapathite deposits as bronze or olive green scales inside the bottle, which is undesirable and non elegant in nature.

There are two methods to avoid incompatibility.

1) The mixture should be dispensed to the patient in such a way that all the doses of preparation should be finished within three days. No alteration required.

2) If the preparation is to be dispensed for more than 3 days, then supply potassium iodide solution in one bottle and Quinine sulphite and dilute HCl solution in another bottle. The patient should be advised to mix both the solutions for necessary dose before use.

(41)

Method A

For mixture that should be used within three days. Dissolve Quinine sulphate in half portion of purified water. To above solution, add dil. $H_2SO_4$ with continuous stirring. Dissolve potassium iodide in little portion of water and add to the above solution and mix uniformly. Transfer the contents to a measurer and adjust the final volume with water and mix well. Transfer the solution to a narrow mouthed amber coloured glass bottle. close tightly with metallic screw. Cap polish and label.

Method B

Dissolve potassium iodide in water and disperse in narrow mouthed amber coloured glass bottle. Dissolve Quinine sulphate and sulphuric acid and dispense seperately in a narrow mouthed amber coloured glass bottle. Mix the specific amount of solution before use.