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Introduction

- It is defined as when two or more ingredients of a prescription are mixed together , the undesired changes that may takes place in the physical, chemical or therapeutic properties of the medicament is termed as "Incompatibility".

OR

- Incompatibility occurs as a result of mixing of two or more "Antagonistic Substances" & an undesirable product is formed which may affect the safety, efficacy & appearance of the pharmaceutical preparation.

OR

- Incompatibility is defined as a change resulting and an undesirable product is formed, which may affect the safety, efficacy appearance and stability of the pharmaceutical product.

Incompatibilities occurs during:

- ✓ Compounding
- ✓ Formulation
- ✓ Manufacturing
- ✓ Packaging
- ✓ Dispensing
- ✓ Storage
- ✓ Administration of drugs

General methods used to remove incompatibilities:

1. Modify the order of mixing
2. Dispense with labels like Shake well before use
3. Recommend storage condition
4. Add physical stabilizer. (Suspending or emulsifying agent)
5. Add chemical stabilizer. (Antioxidant/Buffer)
6. Add preservative
7. Select soluble, compatible or stable form of dosage form.

Types of Incompatibility

Incompatibilities are of three types as following:

Physical incompatibilities

Chemical incompatibilities

Therapeutic incompatibilities

PHYSICAL INCOMPATIBILITY

- When two or more than two substances are combined together, a physical change takes place and an unacceptable product is formed.
- These occurs during the interaction between two or more substances which may lead to change in color, odor, taste, viscosity and morphology.
- Physical changes involves such as Immiscibility, Insolubility, Precipitation formation and liquefaction of solid materials.

The physical incompatibilities may be corrected by using any one or more of the following methods:

- ✓ **Change the order of mixing of ingredients of the prescription.**
- ✓ **Emulsification**
- ✓ **Addition of suspending agent**
- ✓ **Change in the form of ingredients**
- ✓ **By addition, substitution or omission of therapeutically inactive substance to help in compounding of the prescription.**

Examples of physical incompatibilities

1. Immiscibility

Immiscibility is the result of the mixture of two or more immiscible liquids.

Example: Oils & Water are immiscible with each other. They can be made miscible with water by emulsification.

Example:

℞

Castor Oil	15 ml
Purified Water	upto 60 ml

Make an emulsion.

To overcome this incompatibility an emulsifying agent is used to make a good emulsion.

2. Insolubility:

It means the inability of material to dissolve in a particular solvent system. The liquid preparations containing Indiffusible solids such as chalk, aromatic chalk powder, acetyl salicylic acid, phenacetin, zinc oxide & calamine etc. a suspending agent may be used to increase the thickness of the preparation.

It also helps to maintain the uniform distribution of the insoluble substances which facilitating uniform measurement of each dose.

E.g. Gum Acacia, Tragacanth, SLS,

Example:

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Phenacetin	3 gm
Caffeine	1 gm
Orange syrup	12ml
Water	upto 90ml

Make a mixture.
In this prescription phenacetin is an indiffusible substance.
Compound powder of Tragacanth or mucilage of Tragacanth is used as a suspending agent to make a stable suspension.

3. Precipitation:

It occurs due to solvent is insoluble when it is added to solution.

A drug in solution may be precipitated , if the solvent in which it is insoluble is added to the solution e.g. resins are insoluble in water.

Volatile oils are soluble in alcohol. When water is added into the alcoholic solution of volatile oil, the non aromatic portion of the oil get precipitated & turbidity appears.

Liquid preparations especially those containing syrups may show crystallization of sugar in the closure , resulting in cap locking. It can be minimized by adding co-solvents like glycerine, propylene glycol or sorbitol

E.g. Alcoholic solution of resins + water =precipitated resins.

Example:

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Tincture benzoin compound	5g
Glycerin	10ml
Rose water	upto 100ml

Causes: - Tincture benzoin compound contain resins. This change in solvent system results in an unavoidable precipitate.

Remedy: - Addition of tincture with rapid stirring yields a fine colloidal dispersion. So there is no need of any suspending
agents.

4. Liquefaction:

When certain low melting point solids are mixed together, a liquid or soft mass know as **"Eutectic Mixture"** is produced.

This occurs due to the lowering of the melting point of the mixture to below room temperature and liberation of hydrates.

The medicaments showing this type of behavior are **Camphor, Menthol, Phenol, Thymol, Chloral Hydrate and aspirin.**

Causes:- This mixture is a physical incompatibility because both the ingredients in the prescription are liquefiable of mixed together.

Remedy:- These substances can be dispensed by any one of the following method.

- ✓ Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder.
- ✓ The individual medicaments is powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container.

Example:

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Menthol	5 gm
Camphor	5 gm
Ammonium chloride	30 gm
Light Magnesium carbonate	60 gm

} **To Make an insufflation**

In this prescription Camphor, menthol and Ammonium chloride get liquefied on mixing. To dispense this mix them and triturate together to form liquid. Add light magnesium carbonate and mix it thoroughly to make free flowing powder.

CHEMICAL INCOMPATIBILITY

- Chemical incompatibility is also called as immediate incompatibility.
- After compounding it shows immediate incompatibility.
- It occurs due to oxidation-reduction, acid base hydrolysis or combination reactions & those noticed by effervescence, decomposition, colour change.
- Chemical interaction occurs between the ingredients & a toxic & inactive product will be formed. **OR** Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form. As a result of this a toxic or inactive or product may be formed.

These are of two types (Based on chemical interactions):

Tolerated incompatibility: In this type of incompatibility, the chemical interactions can be minimized by changing the order of mixing or mixing the solutions in dilute forms.

Adjusted incompatibilities: In adjusted incompatibility the chemical interaction can be prevented by addition or substitution of one of the reacting ingredient with another of equal therapeutic value. E.g. caffeine citrate can be substituted with caffeine in sodium salicylate and caffeine citrate mixture.

Examples of Chemical incompatibilities

1. Precipitation:

When the precipitated product is therapeutically active it is formulated as per the procedure used to prepare mixtures containing diffusible & indiffusible solid. If the resultant precipitated is inactive or toxic the formulation should be rejected. Precipitation of the drug takes place due to:

a) pH change:-

- Most of the medicines are often salts of weak acids & weak bases. The unionized forms are insoluble in water & ionizable salts are soluble in water.
- A pH change, not only changes solubility, but it also changes rate of degradation.
- If the resultant precipitate has therapeutic value & it is chemical stable, one can tolerate the incompatibility.
- A suitable co-solvent can be used to increase solubility, otherwise a suspension is formulated.

Example 1:

Morphine hydrochloride above 2.5 % concentration , is insoluble & results in the formation of diffusible precipitate under alkaline condition.

The solubility of precipitated morphine in alcohol is 1 in 100. Thus incompatibility can be treated either by –

i) Preparing suspension of diffusible precipitate

ii) Using alcohol as co-solvent to prepare solution.

Example 2:

Caffeine citrate above 2.2 % concentration, under alkaline condition produces indiffusible precipitate but when alcohol is used, it tolerates a higher concentration of caffeine citrate without precipitation.

b) Precipitation by chemical reaction:-

i. Drug-drug interactions:

- Active ingredients react with other drugs or additives yielding diffusible or indiffusible precipitate.
- Caffeine citrate is a mixture of equal weight of caffeine & citric acid.
- The citric acid reacts with sodium salicylate to liberate salicylic acid in the form of precipitate.
- It causes gastric irritation.
- Hence only caffeine is used, it forms a soluble complexes with sodium salicylate.
- Therefore, caffeine citrate should be replaced with half the amount of caffeine to get clear solution.

ii. Flavours:- Liquorice looses its flavour due to precipitation in presence of acid. Acid reacts with glycyrrhizin, a flavouring constituent of liquorice forming glycyrrhizic acid precipitate.

2. Oxidation:

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: These are substances catalyze oxidation process i.e. metals, some impurities.

Catalyst: A catalyst is a substance that can be added to a reaction to increase the reaction rate without getting consumed in the process. The common catalyst includes metal ions, enzymes & bacteria.

Some drugs or their dosage forms undergo oxidation when exposed to air, excessive temperature & due to over dilution of liquids, incorrect pH or presence of catalyst.

Generally some chemical groups which undergo oxidation reactions are like: Phenolic compounds (Phenylephrine), Catechol derivatives (Adrenaline and noradrenaline), Some antibiotics (Tetracyclines), Oils (fixed and volatile) and Vitamins (lipid and water soluble).

How to identify oxidation in pharmaceutical dosage form?

- Change of color, odor, viscosity of dosage form
- For fixed and volatile oils: change of color, taste, odor, and viscosity

How to remove the incompatibilities during oxidation reactions?

Different situations and their methods to remove the incompatibilities in pharmaceutical dosage forms are as following:

Example 1:

The Auto oxidation of oils, fats, phenolic substances, aldehydes & vitamins. This can be prevented by addition of primary antioxidants such as alpha tocopherol, or BHT.

Example 2:

Paraaldehyde, tannins, epinephrine, sulphacetamide & related compounds undergo oxidation activated by heat. Hence for such drugs requires against trace metal ions. This can be achieved by adding antioxidants such as ascorbic acid, sodium metabisulfite or complexing agents like EDTA are used to control oxidation.

Example 3:

Preparations containing riboflavin, folic acid & ascorbic acid show incompatibility. Riboflavin is ligh sensitive, and easily degraded by heat and light. Hence should be stored at its stable pH 6 to 6.5.

Example 4:

When dry powders contains both oxidising & reducing agents, the mixture may explode. The inter-particulate friction developed during mixing increases chances of redox reaction. Therefore such reacting substances should be dispensed separately or powders should be mixed lightly by spatulation method.

3. 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.

Hydrolysis can be controlled by avoiding moisture contact or by changing pH.

- **Ionic hydrolysis:** In which the compound is broken into ions by water.
- **Molecular hydrolysis:** In which the molecule it self is broken down. E.g., Acetylsalicylic acid → Salicylic acid + Acetic acid

Other Examples:

- Aspirin is more sensitive to water & gets converted to more irritant acetyl salicylic acid. Hence it is granulared without use of water.
- Paracetamol is stable between ph 5 & 7 . While ibuprofen shows more solubility above pH 6. Therefore compound suspension of these two drugs in combination pH of solution is 5-6..

4. Effervescence (Gas formation):

Effervescence may be evolved due to chemical reaction between the ingredients of a formulation. Effervescence occurs when two or more ingredients of formulation reacts with each other to generate CO_2 gas. E.g., Carbonates or bicarbonates with an acid or acidic drug resulting in the evolution of carbon dioxide

To overcome such reactions either -

- ✓ Mix the reacting ingredients in open container & allow to complete reaction before filling in to container. The rate of reaction can be increased by using hot water.
- ✓ Change the one or more reacting ingredients.
- ✓ Dispense reacting substances separately.

Example:

Reaction of sodium bicarbonate, borax and glycerol

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Sodium bicarbonate	1.5 gm
Borax	1.5 gm
Phenol	0.75 gm
Glycerin	25 ml
Water	upto 100 ml

Prepare a spray.

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

$$Na_2B_4O_7 + 3H_2O \rightarrow Na_2B_2O_4 + 2H_3BO_3$$

Borax Water Sodium metaborate Boric acid

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

$$2C_3H_5(OH)_3 + 3H_3BO_3 \rightarrow (C_3H_3)_2(HBO_3) + 6H_2O$$

Glycerin Boric acid Glyceryl boric acid

Glyceryl boric acid reacts with bicarbonate and gas is evolved.

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

5. Incompatibility with containers:

The product filled in a container may react chemically with the container or get absorbed by the container or the closure.

- Glass containers alkali leaching.
- Rubber closures may adsorb preservatives.
- Metal containers catalyze rate of chemical reaction.

6. Colour change

The colour change is visible incompatibility. The colour of the most of the dyes used in pharmaceutical formulation is influenced by their ionization which depends on pH of the solution. The phenolphthalein dye is colorless in acid solution but red in alkaline mixture.

The delayed color change in formulation, also creates confusion in the mind of patient.

THERAPEUTIC INCOMPATIBILITY

Therapeutic incompatibility is that form of disagreement whereby drug or excipients of antagonistic medicinal activity to one another are prescribed together.

OR

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

Therapeutic incompatibility occurs due to following reasons:

1. Error in dosage
2. Wrong dose or dosage forms
3. Contra-indicated drugs
4. Synergistic and antagonistic drugs
5. Drug interactions

1. Error in dosage:

Many therapeutic incompatibilities may occurs resulting from errors in writing like spelling mistakes and poor handwriting by the registered medical practitioner; or interpreting the prescription order by the Pharmacist. So to overcome this type of incompatibility, the prescription should be neatly & correctly written by the medical practitioner, otherwise it is major hassle for the pharmacists.

The most serious type of the dosage error in the dispensing is overdose of a medication. Pharmacists are required to carefully check the prescriptions before dispensing it.

Example:

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Atropine sulphate	0.005 gm
Phenobarbitone	0.015 gm
Aspirin	0.75 gm

Causes:- In this prescription, the quantity of the atropine sulphate in each capsule is more than its recommended dose.

Remedy:- The prescription is referred back to the prescriber to correct the overdose of the atropine sulphate. Because the recommended dose of atropine for a single capsule is 0.25 to 2mg.

2. Wrong dose or dosage forms:

There are certain drugs like SALA Medicines (Sound Alike Look Alike) present in the market which have quite similar names and there is always a danger of dispensing the wrong drug.

Example:

1. **Tab. Dulcolax (a laxative) & Tab . Duoclox (an antibacterial agent)**
2. **Prednisone and Prednisolone**
3. **Digoxin and Digitoxin**

Some times a number of same drugs are available in the different dosage forms such as tablet, capsule, suspensions and injections for different patients (like adults and paediatric). Selection of dosage form is based on ability of patients to take that medicines. Hence, if the dosage form is not clearly mentioned on the prescription, it becomes the responsibility of the pharmacist to check the prescription intensively and if he finds these types of errors he should immediately consult the prescriber for the clarification.

3. Contra-indicated drugs

There are certain drugs which may be contraindicated in a particular disease or a particular patient who is allergic to it.

Example:

- ✓ **Corticosteroids are contra-indicated in the patients having peptic ulcers.**
- ✓ **Vasoconstrictors are contra-indicated in hypertensive patients.**
- ✓ **Barbiturates and morphine should not be given to the asthmatic patients.**
- ✓ **The penicillin and sulphur drugs are contraindicated in the patients who are allergic.**
- ✓ **Drugs like Phenytoin, Phenobarbitone, Chloramphenicol should not be prescribed to lactating mother because it will excrete into milk.**

4. Synergistic & antagonistic drugs

Many drugs exhibit Synergism & Antagonism when administered in combination.

When the two drugs are prescribed together, they tend to increase the activity of each other, called as **"Synergism"**. **E.g.,** A combination of aspirin & Paracetamol increase the analgesic activity. **OR**
A combination of penicillin and streptomycin increases the antibacterial activity.

When two drugs are prescribed together, they tend to decrease the activity of each other or having the opposing pharmacological effects, known as **"Antagonism"**. **E.g.,** Amphetamines show its antagonists effect with the barbiturates.

5. Drug interactions

a) Unintentional drug interaction: The effect of one drug is altered by the prior or simultaneous administration of another drug.

Example: Tetracycline hydrochloride 250mg

Direction:- Take one capsule with milk.

Tetracycline is inactivated by calcium which is present in milk.

b) Intentional drug interaction:

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Acetophenetidin	150 mg
Acetyl salicylic acid	200 mg
Caffeine	30 mg

Dispense 10 capsules.

- **Acetophenetidin & Acetyl salicylic acid are Analgesics.**
- **Acetophenetidin depresses the CNS & this side effect is undesirable.**
- **Caffeine is CNS stimulant to neutralize the side effect of acetophenetidin.**

THANKS

Book reference: Pharmaceutics-II by R.M. Mehta, Vallabh Prakashan