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Review Article

## PHARMACEUTICAL INCOMPATIBILITIES: A REVIEW

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### ABSTRACT

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. It is of three types. It includes physical, chemical and therapeutic incompatibilities. The below described article gives the detailed information about the types, causes and how to overcome these types of incompatibilities. The occurrence of chemical incompatibilities can be overcome by two methods which include method A&B.

**Key words:** Incompatibility, pharmaceutical product, chemical incompatibilities

**Article Info:** Received: 23 Oct 2018; Review Completed: 12 Dec 2018; Accepted: 20 Dec 2018; Available online: 30 Dec 2018



#### Cite this article as:

S. Gousia Begum\*, Y.Dastagiri Reddy, B.SriDivya,S.JyothiKiranmai,P.Komali,K.Sushmitha and S.Ruksar, Pharmaceutical Incompatibilities: A Review, Asian Journal of Pharmaceutical research and Development.2018;6 (6): 56-61

**DOI:** <http://dx.doi.org/10.22270/ajprd.v6i6.448>

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### INTRODUCTION

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<sup>1</sup>.

Incompatibilities occur during<sup>2</sup>

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

The incompatibilities may be detected by changes in the physical, chemical, and therapeutic qualities of the medicine.

#### TYPES OF INCOMPATIBILITIES:-

The incompatibilities occur when the components of a medicine interact in such a way that properties of that medicine are adversely affected<sup>3,4</sup>.

1. Physical incompatibilities
2. Chemical incompatibilities
3. Therapeutic incompatibilities

#### PHYSICAL INCOMPATIBILITIES:-

When two or more than two substances are combined together, a physical change takes place and an unacceptable product is formed.

Interaction between two or more substances which may lead to change in color, odor, taste, viscosity and morphology. It is also called as pharmaceutical incompatibility<sup>5</sup>.

Manifestations of physical incompatibility:-

The following list outlines the various ways incompatibility between or among drug agents may be manifested.

- A. Insolubility:-insolubility of prescribed agents in vehicle
- B. Immiscibility:-Immiscibility of two or more liquids
- C. Precipitation:-It occurs due to solvent is insoluble when it is added to solution

D. Liquefaction:-Liquefaction of solids mixed in a dry state (called eutexia)

### INSOLUBILITY

It means the inability of material to dissolve in a particular solvent system. The majority of incompatibilities is due to insolubility of the inorganic as well as organic compounds in particular solvents<sup>6</sup>.

The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble.

- Change in PH
- Milling
- Surfactant
- Chemical reaction
- Complex formation
- Co-solvent
- Any change in previous factors may lead to precipitation of drugs and change in their properties.
- Substances like chalk, acetyl salicylic acid, succinylsulphothiazole, zinc oxide, and calamine are the common examples of in diffusible solids.
- Some tinctures containing resins or chlorophyll may provide precipitation when added to the aqueous system<sup>7</sup>.

#### E.g.-Mixture of prepared chalk

Rx

Chalk powder –2g  
Tincture catechu – 2ml  
Cinnamon water – 2ml

**Causes:** - Chalk powder is not soluble in water. It gets precipitated when added to aqueous medium. These precipitates are found in diffusible in nature which results in physical incompatibility.

**Remedy:** - Use of suspending agents is necessary to suspend the precipitated chalk particles.

Generally 2% W/V of compound tragacanth powder is recommended as suspending agent.

The corrected prescription is

Mixture of prepared chalk

Rx

Chalk powder –2g  
Tragacanth – 0.4g  
Tincture catechu – 2ml  
Cinnamon water up to 30ml

### IMMISCIBILITY

When two such ingredients are combined resulting in a non-homogenous product, such ingredients are called immiscible to each other and the phenomenon is called immiscibility. This manifestation appears clearly in emulsions, creams, lotions, some types of ointments. Separation in two phases is noticed in this pharmaceutical dosage form. Storage must be in room temperature to prevent separation<sup>9,10</sup>.

The following factors lead to immiscibility<sup>11</sup>

- Incomplete mixing
- Addition of surfactant with
  - ❖ Unsuitable concentration

- ❖ False time of addition
- ❖ Unsuitable for the type of emulsion
- Presence of micro-organisms
  - ❖ Some bacteria grow on constituents of mixture.

E.g.- Gelatin Arabic gum

- ❖ Others produce enzymes which oxidize the surfactant.
- Temperature
- ❖ Oils and water are immiscible with each other which shows physical incompatibility

#### E.g.- Castor oil emulsion

Rx

Castor oil – 15ml  
Water – 60ml

**Causes:** -In this prescription castor oil is immiscible with water due to high interfacial tensions, which is a sign of incompatibility.

**Remedy:** -To overcome this type of incompatibility emulsification is necessary with the help of an emulsifying agent. The corrected prescription is

Castor oil emulsion

Rx

Castor oil – 15ml  
Acacia – 2% W/V  
Water – upto 60ml

### LIQUIFACTION

When certain low melting point solids are mixed together, a liquid or soft mass known 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<sup>12</sup>.

If such conditions take place, compounding such powders becomes difficult since the ultimate mixture turns to liquid. The medicaments showing this type of behavior are camphor, menthol, phenol, thymol, chloral hydrate, aspirin, sodium salicylates, etc.....

#### E.g.-Insufflations

Rx

Menthol – 5g  
Camphor – 5g  
Water – 60ml

**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 methods. Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder. The individual medicaments are powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container<sup>12</sup>.

Hence the corrected prescription is

Rx

Menthol – 5g  
Camphor – 5g  
Light kaolin – 0.2g

## PRECIPITATION

Solubilized substances may precipitate from its solution if a non-solvent for the substances is added to the solution.

E.g.: - Resins are insoluble in water

Alcoholic solution of resins + water = precipitated resins.

Aqueous dispersions of hydrophilic colloids (polysaccharide mucilage + high concentration of alcohol or salts) = precipitated colloids.

a) High concentration of electrolytes causes cracking of soap emulsion by salting out the emulsifying agents.

Vehicles (one or more organic liquids) use to dissolve medicaments of low solubility; water soluble adjuvant practically inorganic salts may be precipitated in such vehicles. When tinctures containing resinous matter are added in water, resin agglomerates forms in diffusible precipitates. This can be prevented by slowly adding the undiluted tincture with vigorous shake. Suspension or by adding some suitable thickening agent<sup>13,14</sup>.

**E.g.:- Lotion of compound tincture of benzoin**

Rx

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.

## CHEMICAL INCOMPATIBILITIES

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<sup>15</sup>.

**Occurrence:-**

Chemical incompatibilities occur, due to the chemical properties of drugs and additive like<sup>16</sup>,

- PH change
- Oxidation-reduction reactions
- Acid-base hydrolysis
- Double decomposition
- Complex formation

These reactions may be noticed by

- Precipitation
- Effervescence
- Decomposition
- Color change
- Explosion

## TYPES OF CHEMICAL INCOMPATIBILITIES

**Based on chemical interactions**

Tolerated incompatibility: - In this type incompatibility, the chemical interactions can be changing the order of mixing the solutions in dilute forms, without or by changing the order of mixing.

Adjusted incompatibilities: - In adjusted incompatibility change in the formulation is needed with a compound having equal therapeutic value<sup>17</sup>.

E.g.: substitution of caffeine citrate with caffeine in sodium salicylate and caffeine citrate mixture.

**Based on nature of chemical reaction**

Immediate incompatibilities: - If the chemical reaction takes place, immediately after combining the prescription ingredients, they are called immediate incompatibilities. Hence, they should be dispensed only after correction.

Delayed incompatibility: - When the chemical reaction proceeds at a very slow rate and no appreciable visible change occurs which may develop on keeping the product for a long time are called delayed incompatibility<sup>18</sup>.

**Based on the prescriber**

Intentional:- When the prescriber knowingly prescribes the incompatible drugs.

Unidirectional:- When the prescriber prescribes the drugs without knowing that there is incompatibility between the prescribed drugs<sup>19</sup>.

Generally reaction between strong solution proceed at a faster rate and the precipitates are 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<sup>20</sup>.

**Precipitate yielding interactions**

The precipitates so formed may be diffusible or indiffusible. The method A or B is followed in dispensing the prescription yielding diffusible and indiffusible precipitates respectively. The preparation should contain a thickening agent if the precipitate is non-diffusible<sup>21</sup>.

**Method A:**

This method is suitable for diffusible precipitates following steps are carried out<sup>22</sup>.

Divide the vehicle into two portions.

Dissolve the reactants in separate portions and mix the two portions by slowly by adding one into other with constant stirring.

**Method B:**

This method is suitable for in diffusible precipitates following steps are carried out<sup>23</sup>.

Divide the vehicle into two portions.

Dissolve the one of the reacting substance in one portion.

Place second portion of vehicle in mortar and incorporate suitable amount of compound. Tragacanth powder (2g/100ml of preparation) with constant trituration until a smooth mucilage is produced.

Add and dissolve the other reacting substance to the mucilage.

Add the solution of first reactant to the mucilage slowly with constant stirring.

A secondary label “**SHAKE THE BOTTLE BEFORE USE**” should be fixed on the container whenever method A or method B is followed in dispensing the prescription.

Examples of chemical incompatibilities and their correction<sup>24</sup>

## ❖ Alkaloid incompatibility:-

1. Alkaloidal salts with alkaloid substances
2. Alkaloidal salts with soluble iodides
3. Alkaloidal salts with tannins
4. Alkaloid salts with salicylates
5. Alkaloid with soluble iodides and bromides.

## ❖ Soluble salicylates incompatibility:-

1. Soluble salicylates with ferric salts
2. Soluble salicylates with alkali bicarbonates
3. Soluble salicylates and benzoates with acids.

## ❖ Soluble iodides incompatibility:-

1. Oxidation of iodides with potassium chlorate
2. Oxidation of iodides with quinine sulphate.

## ❖ Chemical incompatibility causing evolution of carbon dioxide gas:-

1. Sodium bicarbonate with soluble calcium or magnesium salts
2. Bismuthsubnitrate and sodium bicarbonate
3. Borax with sodium bicarbonate and glycerin.

## ❖ Miscellaneous incompatibilities:-

1. Soluble barbiturates with ammonium bromide
2. Potassium chlorate with oxidisable substances
3. Incompatibility of emulsifying agent
4. Color stability of dyes
5. Incompatibilities of liquorices liquid extract

**eg-1: strychnine hydrochloride mixture**

Rx

Strychnine hydrochloride solution	-6ml
Aromatic spirit of ammonia	-4ml
Water up to	- 120ml

**Causes:-**

- ❖ The quantity of strychnine hydrochloride is more than its solubility in water (1:30).
- ❖ The aromatic spirit of ammonia contains negligible amount alcohol.

**Remedy:** - Strychnine hydrochloride gets precipitated yielding diffusible precipitate, hence follow method A.

**E.g-2.:Quinine hydrochloride mixture**

Rx

Quinine hydrochloride	-0.12ml
Sodium salicylate	-4g
Water	-100ml

**Causes:** - When quinine hydrochloride combined with the sodium salicylates it forms quinine salicylates which is an in diffusible precipitate.

**Remedy:** - Hence follow method B for precipitate yielding interactions.

**THERAPEUTIC INCOMPATIBILITY**

It is the modification of the therapeutic effect of one drug by the prior concomitant administration of another. It may be as a result of prescribing certain drugs to a patient with the intention to produce a specific degree of pharmacological action, but have restore or intensity of

the action produced is different room that intended by the prescriber<sup>25</sup>.

**MECHANISM:**

It is divided into two groups. They are

**Pharmacokinetic:** It involves the effect of a drug on another from the point of view that includes absorption, distribution, metabolism and excretion.

**Pharmacodynamics:** These are related to the pharmacological activity of the inter-acting drugs.

E.g., Synergism, antagonism, altered cellular transport, effect on the receptor site.

Therapeutic incompatibilities occurs due to following reasons

- a. Error in dosage
- b. Wrong dose or dosage form
- c. Contra-indicated drugs
- d. Synergistic and antagonistic drugs
- e. Drug interactions

**ERROR IN DOSAGE**

Many therapeutic incompatibilities result from errors in writing or interpreting the prescription order. The most serious type of the dosage error in the dispensing is overdose of a medication<sup>26</sup>.

**E.g., Atropine sulphate capsules**

Rx

Atropine sulphate	- 0.005g
Phenobarbitone	- 0.015g
Aspirin	- 0.300g

**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. The recommended dose of atropine for a single capsule is 0.25 to 2mg.

**WRONG DOSE OR DOSAGE FORM**

There are certain drugs which have quite similar names and there is always a danger of dispensing the wrong drug<sup>27</sup>.

E.g., Prednisone and Prednisolone

Digoxin and Dig toxin

Some times many drugs are available in the different dosage forms and hence, if the dosage form is not clearly mentioned on the prescription, it becomes necessary to seek clarification from the prescriber.

The responsibility of the pharmacist becomes to check the prescription intensively and if he finds these types of errors he should immediately consult the prescriber for the clarification.

**PRESCRIBING CONTRA-INDICATED DRUGS**

There are certain drugs which may be contra-indicated in a particular disease or a particular patient who is allergic to it<sup>28</sup>.

- Corticosteroids are contra-indicated in the patients having peptic ulcers.

- The penicillin and sulphur drugs are contra-indicated in the patients who are allergic.
- Vasoconstrictors are contra-indicated in hypertensive patients.
- Barbiturates and morphine should not be given to the asthmatic patients.

#### E.g., Sulphadiazine capsules

**Causes:-**Ammonium chloride is a urinary acidifier. It causes the deposition of the Sulphonamide crystals in the kidney.

**Remedy: -** Before prescribing such substances a doctor must be careful. If he does not, a Pharmacist shows his caliber to point out such type of the doctor's error. Such must Immediately be referred back to the concerned doctor and get corrected.

#### PRESCRIBING SYNERGISTIC OR ANTAGONISTIC DRUGS

When two drugs are prescribed together, they tend to increase the activity of each other which is known as SYNERGISM. When two drugs are prescribed together, they tend to decrease the activity of each other which is known as ANTAGONISM<sup>29</sup>.

#### E.g.,

- A combination of aspirin and paracetamol increases the analgesic activity.
- A combination of penicillin and streptomycin increases the antibacterial activity.
- Amphetamines show its antagonists effect with the barbiturates.

#### E.g., Amphetamine sulphate syrup

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**Causes:-**In this prescription, there is a combination of two sympathomimetic drugs

There by causing additive effect.

**Remedy:-** The prescription is referred back to the prescriber for necessary corrections.

#### DRUG INTERACTIONS

The effect of one drug is altered by the prior or simultaneous administration of another drug. The drug interaction can usually be corrected by the proper adjustment of dosage if the suspected interaction is detected<sup>30</sup>.

#### E.g., Tetracycline capsule - 250mg capsules

Direction: Take one capsule every 6 hours with milk.

**Causes:-**Tetracycline is inactivated by calcium present in milk. So, it should not be taken with milk.

**Remedy:** In this prescription, the therapeutic incompatibility is unintentional. So, the prescription is referred back to the prescriber to change the direction.

#### CONCLUSION:

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. It is of three types. It includes physical, chemical and therapeutic incompatibilities. The below described article gives the detailed information about the types, causes and how to overcome these types of incompatibilities. The occurrence of chemical incompatibilities can be overcome by two methods which include method A&B.

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