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AN OVERVIEW ON INCOMPATIBILITY STUDIES

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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. Pharmaceutical incompatibility is a combination of ingredients in which, because of the interaction of medicinal substances between themselves or with excipients, their physical and chemical properties change and thus the stability and effect of the medicine. 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 given information of the problem of pharmaceutical incompatibilities, in our opinion, will increase the professional knowledge of pharmacists about the physical phenomena and chemical interactions that may occur in dosage forms, types of pharmacological incompatibilities and will guide them in practical activities in preparation of extemporaneous medicines in different dosage forms.

Keywords: Incompatibility, overcome, medicines

INDRODUCTION:

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 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 incompability.[1]

Pharmaceutical incompatibility is a combination of ingredients in which, because of the interaction of medicinal substances between themselves or with excipients, their physical and chemical properties change and thus the stability and effect of the medicine.Incompatibilities occur during:

- Compounding
- Formulation
- Manufacturing
- Packaging
- Dispensing
- Storage
- Administration of the drug.

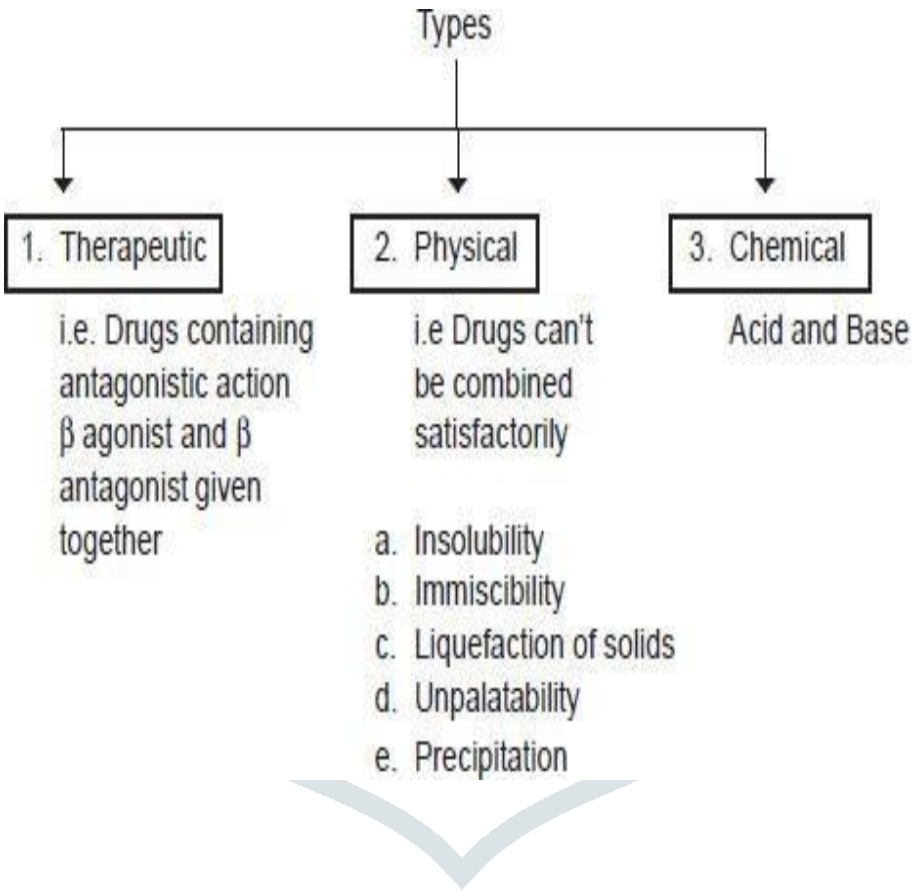
The incompatibilities may be detected by changes in the physical, chemical, and therapeutically qualities of the medicines.

Objective

- The pharmaceutical incompability, drug excipient studies are carried out with an intent to identify, quantify and predict potential interactions [physical , chemical , therapeutic]along with impact of these interactions on the manufacturability , quality and performance of the final drug product .

- Pharmaceutical incompatibility is a combination of ingredients in which, because of the interaction of medicinal substances between themselves or with excipients, their physical and chemical properties change and thus the stability and effect of the medicine

Types



The incompatibilities occur when the components of a medicine interact in such a way that properties of that medicine are adversely affected.

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. [2]

Manifestations of physical incompatibility:-

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 eutexit)[3]

E.

2.1.1.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 solvent.[4] The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble.[5]

- 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, succinylsulphothiazzole, zinc oxide, and calamine are the commonexamples of in diffusible solids Some tinctures containing resins or chlorophyll may provide precipitation when added to the aqueous system[6].

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. [7]
The corrected prescription is Mixture of prepared chalk Rx

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

2.1.1. IMMISCIBILITY

When two suchingredients 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.[8]

The following factors lead to immiscibility.

- 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.:- 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.[9] The corrected prescription is
Castor oil emulsion Rx
Castor oil – 15ml Acacia – 2% W/V Water– upto 60ml

2.1.3.LIQUIFACTION

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.[10]

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.[11] **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.

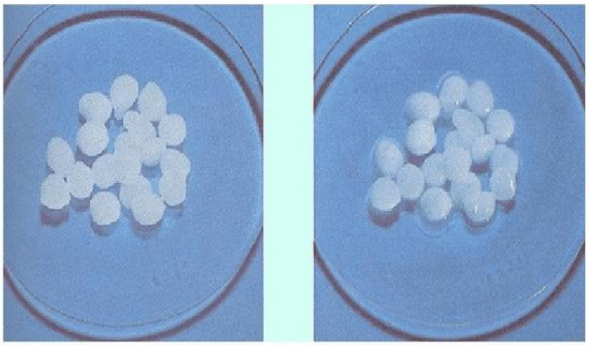
Remedy:-These substances can be dispensed by any one of the following method.Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder.The

individual medicaments is powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container[12].

Hence the corrected prescription is Rx

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

EXAMPLES OF PHYSICAL INCOMPATIBILITY

Physical Incompatibility	Illustration
Hygroscopic	
Deliquescent	
Effervescent	

2.1.4 PRECIPITATION

Solubilized substances may precipitate from it solution if a non solvent for the substances is added to the solution. [13]

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

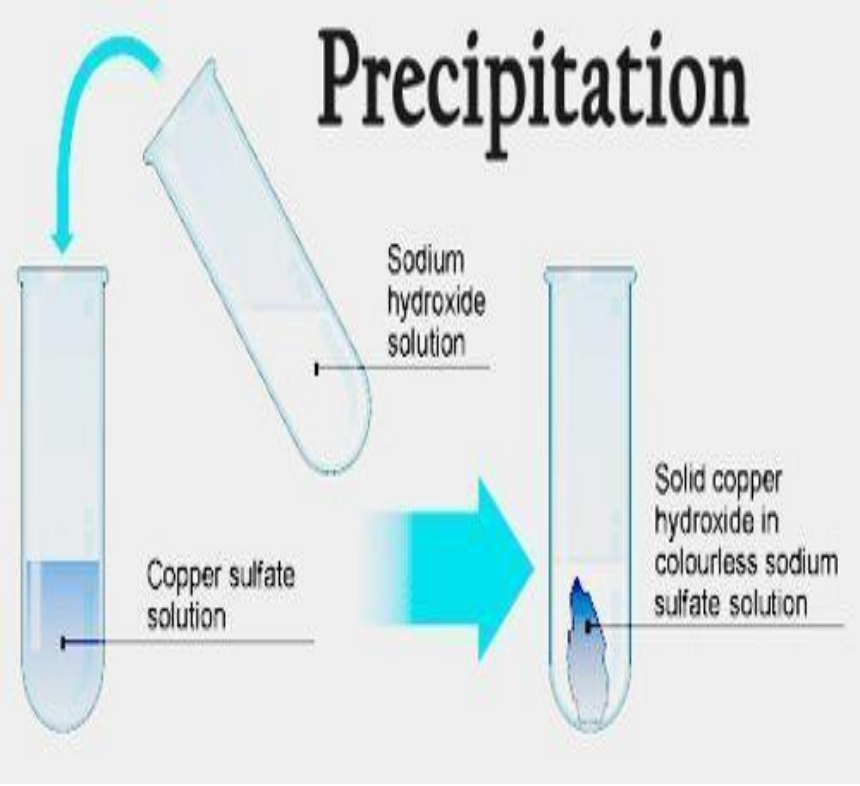
Rx

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[14].



CHEMICAL INCOMPATIBILITIES:

Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form. As aresult of this a toxic or inactive or product may be formed.[14]

Occurrence:-

Chemical incompatibilities occur, due to the chemical properties of drugs and additive like,

- 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

A] Based on chemical interactions

1.**Tolerated incompatibility**: - In this type incompatibility, the chemical interactions can be changing the order of mixing the solutions indilute forms, without or by changing the order of mixing. [15]

2.**Adjusted incompatibilities**: - In adjusted incompatibility change in the formulation is needed with a compound having equal therapeutic value. [16]

B] 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.
[17].

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[18].

- 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.

Precipitate yielding interactions:

Method A:

This method is suitable for diffusible precipitates following steps are carried out
--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.[19]

Method B:

This method is suitable for in diffusible precipitates following steps are carried out.[20]
--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.[21]

❖ **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.[23]

❖ **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.

❖ **Miscellaneous incompatibilities:-**

1 Soluble barbiturates with ammonium bromide

2 Potassium chlorate with oxdisible substances

3 Incompatibility of emulsifying agent

4 Color stability of dyes

5 Incompatibilities of liquorices liquid extract[24]

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[25].

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[26.]

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.

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.[31

Pharmacodynamics:

These are related to the pharmacological activity of the inter- acing drugs.[32]

E.g., Synergism, antagonism, altered cellular transport, effect on the receptor site. Therapeutic incompatibilities occurs due to following reasons

a. Error in dosage

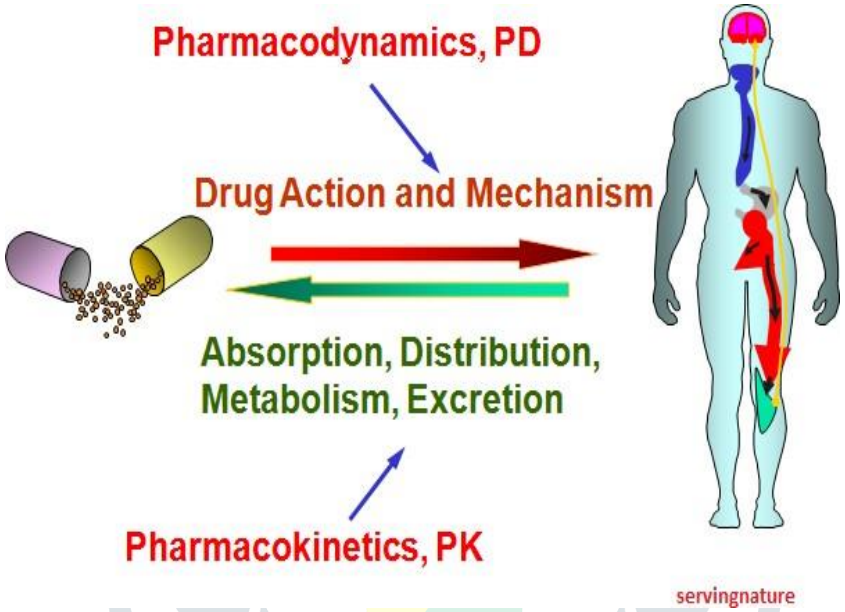
b. Wrong dose or dosage form

c. Contra-indicated drugs

d. Synergistic and antagonistic drugs

e. Drug interactions

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[33].

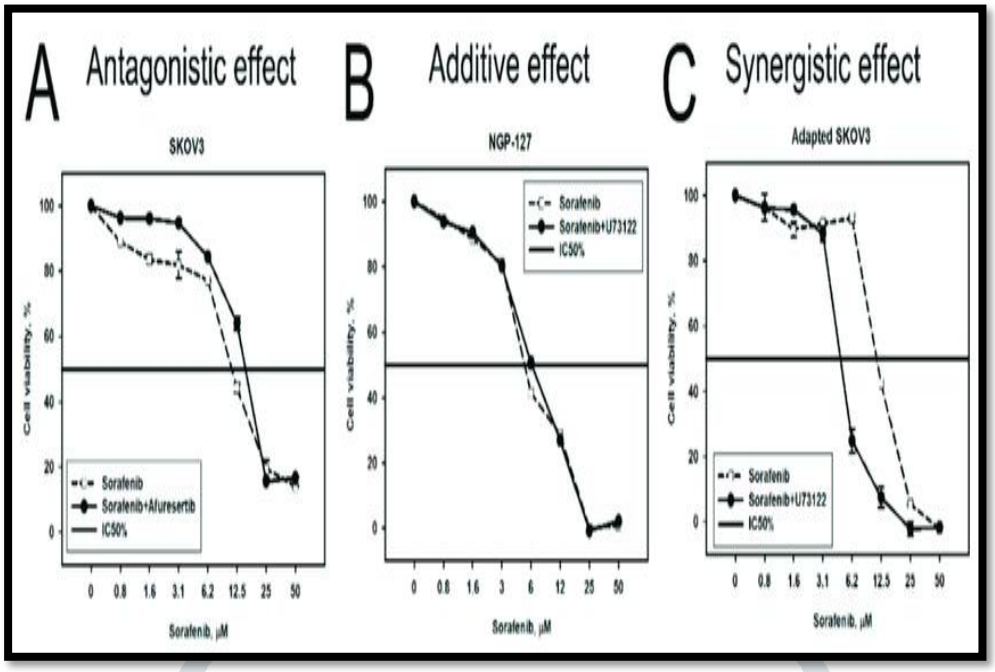
Corticosteroids are contra-indicated in the patients having peptic ulcers.

PRESCRIBING SYNERGISTICS OR ANTAGONISTIC DRUGS

When two drugs prescribed together, they tend to increase the activity of each other which is known **as synergism**. [27]

When two drugs are prescribed together, they tend to decrease the activity of each other which is known as **antagonism**.[28]

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



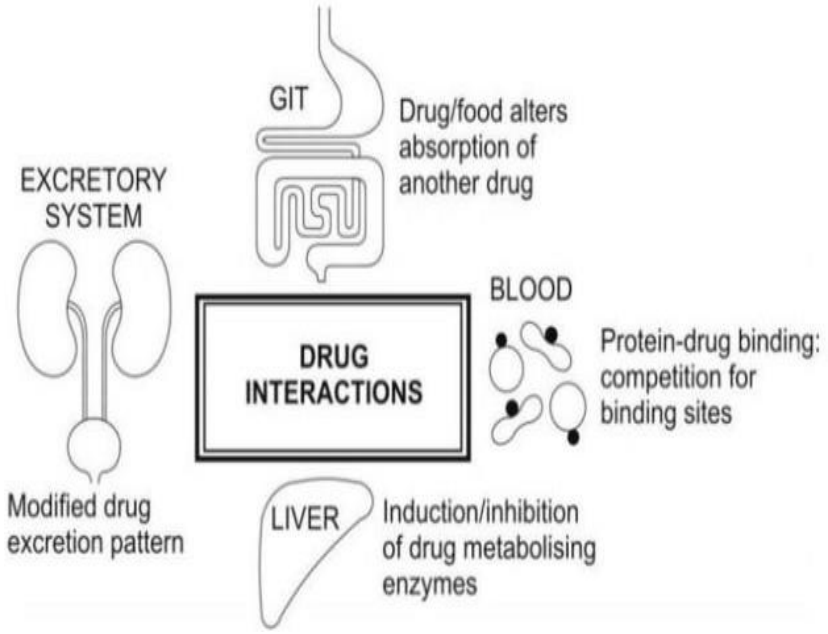
DRUG INTERACTIONS

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[29]

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.[30].



2 Herbs and their interaction with allopathic drugs

Herb-allopathic drug interaction is an important factor to be measured because there is always a chance to get undesirable therapeutic effect of the prescribed allopathic drug, as like allopathic (prescription) drugs. Herbal medicines also have different pharmacokinetic and pharmacodynamic properties which ultimately lead to produce therapeutic responses, but sometimes cause adverse actions and/or drug-herbal interactions. Drug interaction refers to the situation where two or more separate drugs have been absorbed into the body and their effects are affected by each other, i.e. the effects are increased or they produce a new effect that neither produces on its own.

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. This described article gives the detailed information about the types, causes and how to overcome these types of incompatibilities. The drug incompatibilities reduce the effectiveness of the treatment, it is a complex and difficult to manage problem, but it can be prevented by various ways like: The use of chart of compatibility, to use an online filter in case of risk of precipitation, use multi-lumen catheters, utilize all available pathways, limit essential drugs, IV and PO and sequencing, jurisdiction**.**

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