Pharmaceutical Incompatibilities

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Introduction

- 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.
- Incompatibility is the result of mixing two or more antagonistic substances and is detected by changes in physical and chemical or therapeutic qualities.
- It may affect the safety,efficacy and appearance of a medicine.
- A prescription is considered to possess an incompatibility when the combination of its ingredients adversely effects the appearance, elegance, safety or therapeutic efficacy.

Incompatibilities occur during:-

- 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.

Classification of Incompatibilities

In general we can say there are two types of incompatibilities;

- Minor incompatibilities (which do not harm or which can be easily avoided)
- Major incompatibilities (which should not be dispensed)

Incompatibilities can be classified into three classes;

- Physical incompatibilities
- Chemical incompatibilities
- Therapeutic incompatibilities

1. Physical Incompatibility

Physical Incompatibilities:

- Physical incompatibilities are those incompatibilities in which the physical properties of ingredients produce a mixture unacceptable in appearance or results in inaccuracy of dosage.

- Physical incompatibilities can arise due to following reasons

- Insolubility
- Liquefaction
- Immiscibility

Physical Incompatibilities: Insolubility

- Incomplete solution
- Addition of wrong solvents e.g. gum-alcohol, silicon-water
- Amount of solvent is insufficient

For Example

In liquid preparations containing indiffusible solids such as; chalk, aromatic chalk, powder succinyl sulphathiazole and sulphadimidine (in mixture) and calamine and Zinc oxide (in lotion), a thickening agent is necessary to obtain an elegant product from which uniform dose can be removed

Physical Incompatibilities: Insolubility

- Insoluble powders e.g. sulphur, certain corticosteroids and antibiotics are difficult to wet with water, wetting agent are used.

Example:

Saponins for sulphur continuing lotions.

Polysorbates for parenteral suspensions of corticosteroids and antibiotics.

- The deflocculating action of excess surface active agent may be cause claying. This may be controlled by reducing the surfactant concentration.

Physical Incompatibilities: Insolubility

- Potent insoluble drugs are converted into salt form.

Example:

An alkaloidal salt for an alkaloids

Sodium salt of barbiturates for the corresponding free compound.

- Constituents of alcoholic vegetable extract may precipitate.

- When a resinous tincture is added to the water. The water-insoluble resin agglomerates forming indiffusible clots.

Physical Incompatibilities: Liquefaction

- When low melting point solids are powdered together with high melting point solids, a liquid or soft mass is produced due to lowering of melting point of the mixture to below room temperature

Example:

Among the medicaments exhibiting this behavior are any pair of the following;

Camphor, menthol, phenol, thymol, and chloral hydrate.

Sodium salicylate or aspirin with phenazone.

Physical Incompatibilities: Immiscibility

- Immiscibility occurs between two liquids ingredients
- Oil (fixed oil) in water emulsion (emulsification or solubilization)
- Concentrated hydrophilic solutions of volatile oils such as spirits and concentrated water used as adjuncts. (For example flavoring agents) in aqueous preparations, are either gradually diluted with the vehicle before admixture with the remaining ingredients or poured slowly into vehicle with constant stirring.
- Addition of high concentration of electrolytes to mixtures in which vehicle is a saturated aqueous solution of a volatile oil causes the oil to separate and collect as an unsightly surface layer.

Example: Potassium citrate mixture BPC, in which the large quantity of soluble solid, salts out the lemon oil and to disperse this evenly quillaia tincture is added as a suspending agent or emulsifying agents.

2. Chemical Incompatibility

Chemical Incompatibilities

Chemical incompatibilities occur as a result of chemical reaction;

- Effervescence
- Precipitation
- Color changes

It can be immediate or it can be delayed.

Chemical Incompatibilities: Types

Following are the types of reaction that occurs;

- Oxidation
- Hydrolysis
- Polymerization
- Combustion reactions
- Isomerization
- Decarboxylation
- Formation of insoluble complexes

Chemical Incompatibilities: Oxidation

Oxidation refers to the ***addition of oxygen or removal of hydrogen***.

The factors which leads to oxidation are includes;

Pressure of oxygen: Increased pressure of oxygen will lead to oxidation of the ingredients

Light: Presence of light may cause photochemical oxidation reactions

Temperature: Elevated temperature leads to oxidation of ingredients

pH: Every drug has its optimum pH for stability. Therefore, change in the pH may affect the stability of the drug and may cause its oxidation.

Pharmaceutical dosage form: Oxidation reactions occurs in solutions faster than in solid dosage forms

Chemical Incompatibilities: Oxidation

Presence of pre-oxidants: Presence of pre-oxidants leads to the oxidation of ingredients

For example; metals, peroxides.

Type of solvents/ vehicle used: Oxidation occurs faster in aqueous solvent / vehicles than others.

Presence of unsaturated bonds: Presence of unsaturation (double or triple bond) leads to easier oxidation than saturated bonds.

Chemical Incompatibilities: Oxidation

Preventive measures taken to prevent oxidation reactions includes

Addition of antioxidants: To avoid oxidation antioxidants are used

For example; Vitamin E, Vitamin C and inorganic sulfur compounds e.g. polysulfide and thiosulfate.

Protection form pre-oxidants: Addition of chemicals which forms complexes with metals

For example; EDTA, Benzalkonium chloride

Protection from light: The drug ingredients must be protected from light by using dark containers for packing, storage of formulation in dark places, or by packaging with substances which absorbs light

For example; oxybenzene

Chemical Incompatibilities: Oxidation

Choice dosage form: Suitable dosage form must be selected which reduces the possibility of oxidation.

For example; solids dosage forms are better over solutions.

Maintenance of pH: Buffers must be used to maintain the pH for the stability of the drug ingredients.

Choice of suitable solvent/ vehicle: Hydroalcoholic or alcoholic vehicles are used instead of aqueous vehicle to overcome oxidation.

Maintenance of temperature: Storage at low temperature prevent oxidation.

Protection from air: Oxidation can be avoided by packing the formulation in well closed container or by the replacement of oxygen by nitrogen inside the container.

Chemical Incompatibilities: Hydrolysis

Breakdown of chemical compound in presence of moisture/water is called Hydrolysis

Hydrolysis is of two types;

- **Ionic hydrolysis**: The breakdown of ionic compound into its positive and negative ions.

Example: codeine phosphate reversibly broken down to codeine and phosphate.

- **Molecular hydrolysis**: It is defined as the breakdown of whole molecule into its components.

Example: Acetyl salicylic acid irreversibly broken down into salicylic acid and acetic acid.

Chemical Incompatibilities: Hydrolysis

The factors which leads to hydrolysis are mentioned below;

Presence of water: Presence of water leads to hydrolysis of formulation ingredients.

Use of water for vehicle: Using of water as vehicle for formulation may cause hydrolysis.

pH: Every drug has its optimum pH for stability. Therefore, change in the pH may affect the stability of the drug and may cause its hydrolysis.

For example; optimum pH for Atropine is 3.1 – 4.5

Temperature: High temperature during autoclaving may leads to hydrolysis of the formulation.

Chemical Incompatibilities: Hydrolysis

Preventive measures to prevent hydrolysis during compounding includes;

Protection from moisture: it can be done by packing with such substances which are impermeable to water.

Addition of dehydration agents: hydrolysis can also be avoided by the addition of substances that absorb water.

For example; Silica gel, Calcium carbonate.

Use of vehicle: Hydrolysis can be prevented by using vehicles other than water.

For example; alcohol.

Maintenance of pH: Buffers must be used to maintain the pH for the stability of the drug ingredients.

Using of surfactants: Surfactants must be used which cause miscall formation.

Chemical Incompatibilities: Hydrolysis

Reducing the solubility: By reducing the solubility of substances drugs can be protected against hydrolysis.

For example; suspensions.

Complex formation: Formation of complexes must be done which protect the drug from effects of water.

Chemical groups undergo hydrolysis:

Esters – Benzocaine, Procaine

Amides – Chloramphenicol, Sulphonamides, Procainamide

Nitriles – drugs containing NO_2, NO_3, N_2O

Chemical Incompatibilities: Polymerization

Polymerization is a process in which small repeating units called ***monomers are bonded to form a long chain polymer***

Formaldehyde convert into para formaldehyde which appears in the form of precipitate. So, to avoid, formaldehyde must be stored at suitable temperature.

Ampicillin at high temperature form polymers which causes allergy.

The following factors induces polymerization;

Light: light may cause polymerization in the formulation or individual ingredients.

Solvent/ vehicle: certain solvents induce polymerization.

pH: Every drug has its optimum pH for stability. Therefore, change in the pH may affect the stability of the drug and may cause its polymerization of monomers.

Temperature: High temperature causes polymerization of ingredients.

Chemical Incompatibilities: Polymerization

Preventive measures to prevent Polymerization reactions during compounding;

Protection from light: The drug ingredients must be protected from light by using dark containers for packing, storage of ingredients in dark places, or by packaging with substances which absorbs light.

For example; oxybenzene.

Use of vehicle: Polymerization can be prevented by using suitable vehicles.

Maintenance of pH: Buffers must be used to maintain the pH for the stability of the drug ingredients.

Maintenance of temperature: Storage at suitable low temperature prevent polymerization.

Chemical Incompatibilities: Isomerization

- Conversion of drug to its isomer is called isomerization
- Isomers have same molecular formula and different structural formula (arrangement of atoms).

There are two types of isomerism;

Optical isomerism: these are expressed by dextro rotatory and levo rotatory.

Example: L-adrenaline is converted into d-adrenaline by change in pH and temperature.

D-tubocurarine is more active than its L form.

Geometrical isomerism: these are expressed by Cis and Trans. Most of the times the Cis form is more active than trans form.

Example: Cis form of Vitamin A is more active.

Chemical Incompatibilities: Isomerization

The following factors induces isomerization;

Solvent/ vehicle: certain solvents induce isomerization of ingredients.

pH: Every drug has its optimum pH for stability. Therefore, change in the pH may affect the stability of the drug and may cause its isomerization.

Temperature: Variation in temperature causes isomerization of ingredients.

Impurities: certain impurities leads to isomerization of ingredients.

Chemical Incompatibilities: Isomerization

Preventive measures to prevent isomerization of ingredients during compounding includes;

Use of vehicle: isomerization can be prevented by using suitable vehicles.

Maintenance of pH: Buffers must be used to maintain the pH for the stability of the drug ingredients.

Maintenance of temperature: Storage at suitable temperature prevent isomerization of drug ingredients.

Protection from Impurities: Drugs can be protected against impurities by filtering them out.

Chemical Incompatibilities: Decarboxylation Reaction

In general it can be understand by; evolution of Carbon dioxide during the formulation.

- Carbon dioxide is evolved if a carbonate or bicarbonate is dispensed in a liquid medicine containing an acid of an acidic drug. To prevent leakage or explosion the reaction must be completed before the preparation is bottled.
- In some instances the reaction is slow and should be hastened by using a hot vehicle.
- All drugs containing bicarbonate are not sterilized at high temperature.

Chemical Incompatibilities: Decarboxylation Reaction

Preventive measures to prevent decarboxylation of ingredients during compounding includes;

Use of vehicle: isomerization can be prevented by using suitable vehicles.

Maintenance of pH: Buffers must be used to maintain the pH for the stability of the drug ingredients.

Maintenance of temperature: Storage at suitable temperature prevent isomerization of drug ingredients.

Protection from Impurities: Drugs can be protected against impurities by filtering them out.

Chemical Incompatibilities: Formation of Insoluble Complexes

Complexes are formed either due to drug or due to adjuncts used in formulation.

Drugs: tetracycline form complex with heavy metals removed with EDTA molecules.

Adjuncts: Many molecular adjuncts used which medicaments and preservations are bound to the macromolecules or trapped within miscall. The behavior is most common in non-ionic macromolecules.

Therapeutic activity or adjunct efficacy may be seriously impaired by complex formation particularly emulgents (macrobol esters and ethers) and solublizers (polysorbates) exhibit this phenomenon

3. Therapeutic Incompatibility

Therapeutic Incompatibilities

Undesirable pharmacological interactions between two or more ingredients that leads to

- Potentiation of each other's therapeutic effect
- Destruction of effectiveness of any ingredient
- Occurrence of toxic manifestations within the patient

Therapeutic incompatibility arises when a drug error, dosage error or a dosage form error is made either by the physician in prescribing or by pharmacist in counselling, prescription handling or compounding.

Therapeutic Incompatibilities: Drug Error

Drug error can be made either by the physician or by the pharmacist. It can be due to;

- Writing or speaking error by the physician in the verbal or non-verbal prescription
- Reading or hearing error by the pharmacist in prescription handling

Example:

Such problems tends to arise with, incorrect drug due to trademark or nomenclature error.

Alphaden – Mineral supplement

Alphalin – Vitamin A product

Alphyllin – A diuretic

Therapeutic Incompatibilities: Contraindicated Drugs

Pharmacist should take history before dispensing the drug to the patient. So that;

- He must be aware of any sort of drug interaction
- He avoid dispensing a drug which undergo renal clearance, to a patient with renal insufficiency
- He avoid dispensing a drug which mainly undergo hepatic metabolism, to a patient with liver dysfunctioning
- He avoid dispensing morphine to an asthmatic patient
- He avoid dispensing vasoconstrictor to a hypersensitive patient

Therapeutic Incompatibilities: Dosage Form Error

These are the errors which occurs due to

- If the physician has asked to compound topical product and pharmacist compounded an oral product
- If topical products is swallowed by the patient
- If skin dosages are instilled into eyes, nose or ears
- If auxiliary label is not mentioned on the final compounded product

Therapeutic Incompatibilities: Dosage Error

- If there is an error in dosage requirement, i.e. how to take? When to take? How much to take? How long to take?
- **Over dosage**; Excessive single dosage because of decimal errors. It occurs if the doctor wrote it wrong or pharmacist read it in a wrong way.
- **Excessive daily dose**; suppose doctor has to write 'after every 4 hours' but mistakenly he wrote 'after every 1 hour' then by this error the patient will receive over dosage of the medicament.
- **Addictive or synergistic combination**; Two drugs may have such relation that when they are administered together, leads to more intense effect.

Example: Morphine with Barbiturates produce intense CNS depressant action.

Therapeutic Incompatibilities: Dosage Error

- **Antagonistic combination**; Two drugs may have such relation leads to under dosage to the patients.

Example: The reduction of the anticoagulant effect of warfarin when an agent that accelerates its hepatic metabolism, such as phenobarbital.

- In case of emulsion or suspension if patient forget to shaken the preparation before usage, leads to unequal dosage to user.


Thank you