Ministry of Health of the Russian Federation
Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

Pharmaceutical incompatibilities

Lesson 13
IV term

Volgograd 2022

Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №13 Pharmaceutical incompatibility	Pharmaceutical incompatibility of medicines. Classification. Chemical incompatibility of drugs.

QUESTIONS FOR THE LESSON

1. What is pharmaceutical incompatibility?
2. During what times do incompatibilities occur?
3. Causes of incompatible drug combinations.
4. Types of incompatibilities.
5. Therapeutic incompatibility.
6. Physical incompatibility.
    a. Insolubility
    b. Immiscibility
    c. Liquifaction
    d. Precipitation
7. Chemical incompatibility.
    a. The main reactions:
        - ✓ Oxidation
        - ✓ Hydrolysis
        - ✓ Polymerization
        - ✓ Isomerization
        - ✓ Decarboxylation
        - ✓ CO2 – absorption
        - ✓ Combination
        - ✓ Formation of insoluble complexes
    b. Visual signs of chemical incompatibility
8. Actions to be taken by the pharmacist when an incompatible combination of medicines is detected.
9. The main ways to overcome pharmaceutical incompatibilities

INTRODUCTION

Using various combinations of medicines is very often necessary in medical practice. However, the task of selecting the right drugs when preparing prescriptions for their complex combinations is sometimes solved by medics unilaterally, taking into account only the therapeutic effect of the active substances, without analysing the possibility of physical, chemical and pharmacological compatibility of the components in the chosen dosage form. This results in irrational, difficult or incompatible prescriptions.

These terms are used in the pharmaceutical literature to describe the characteristics of drug combinations in preparations.

Pharmacists are professionally responsible for pharmaceutical and biopharmaceutical incompatibilities and legally responsible for therapeutic incompatibilities.

It should be noted that the formulation of factory-made medicinal products, as a rule, does not contain incompatibility elements.

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 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.

If the prescriptions contain incompatible combinations of medicinal substances, their the manufacture and even more so the use of them is forbidden!

CAUSES OF INCOMPATIBLE DRUG COMBINATIONS

I. Incompatible combinations in prescriptions

1. Insufficiently studied properties and nature of interaction of some medicinal substances with each other and excipients; absence of required information about properties of medicinal substances and excipients in regulatory documentation and reference literature.
2. Insufficient knowledge of the doctor about physical, physical-chemical and chemical properties of drugs and excipients and mechanisms of interaction.

3. Prescribing complex multi-component drugs in order to enhance action, obtaining complex effect or reducing side effects. Processes of interaction of complex compounds are difficult to predict and diagnose.

II. **About 50% of drugs containing incompatible combinations are dispensed to patients.**

1. Insufficiency of knowledge of the pharmacist about the physicochemical and pharmacological properties of drugs and excipients.
2. Failure to recognize "latent incompatibility" when interaction with an unfavorable outcome proceeds without visible external manifestations or the process proceeds in time manifested when the drug is stored by the patient at home, hospital (especially if the recommended storage conditions are not observed) or in the patient's body.

TYPES OF INCOMPATIBILITIES

1. Therapeutic incompatibility
2. Physical incompatibility
3. Chemical incompatibility

THERAPEUTIC INCOMPATIBILITY

Definition of Therapeutic incompatibility

It is the modification of the therapeutic effect of one drug by the prior concomitant administration of another. (It is also called drug interactions)

Mechanisms of therapeutic incompatibility

They are divided into two groups:

1. Pharmacokinetics

involve the effect of a drug on another from the point of view that includes absorption ,distribution , metabolism and excretion.

2. Pharmacodynamics

are related to the pharmacological activity of the interacting drugs (synergism, antagonism, altered cellular transport, effect on the receptor site).

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.

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 solvent
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.

The following factors affect the solubility of prescribed agent:

- ✓ 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 common examples of in diffusible solids.
- ✓ Some tinctures containing resins or chlorophyll may provide precipitation when added to the aqueous system.

Example: *Mixture of prepared chalk*

Composition: 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 tragacanth powder is recommended as suspending agent. *The corrected prescription is*

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.

The following factors lead to immiscibility:

1. Incomplete mixing
2. Addition of surfactant with:
   - Unsuitable concentration
   - False time of addition
   - Unsuitable for the type of emulsion
3. Presence of microorganisms
   - Some bacteria grow on constituents of mixture i.e. gelatin Arabic gum
   - Others produce enzymes which oxidize the surfactant
4. Temperature

Example: *Castor oil emulsion*

Composition: 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.

LIQUIFACTION

It means that when two solid substances are mixed together, conversion to a liquid state take place.

It happens through the following methods:

1. Formation of liquid mixture: when the solid substance is soluble in another solid substance which lead to decrease of its melting point and conversion to a liquid in certain ratios.
2. Exit of crystalline water: By mixing hydrated crystals and dry crystals, crystalline water diffuse to dry crystals.

The medicaments showing this type of behavior are camphor, menthol, phenol, thymol, chloral hydrate, aspirin, sodium salicylates, etc.

Example: *Insufflations*

Composition: Menthol – 5g

Camphor – 5g

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.

PRECIPITATION

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

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

When tinctures containing resinous matter are added in water, resin agglomerates forms in diffusible precipitates.

Example: *Lotion of compound tincture of benzoin*

Composition: 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.

Occurrence:

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

- PH change
- Oxidation-reduction reactions
- Hydrolysis
- Polymerization
- Isomerization
- Decarboxylation
- Absorption of CO_2
- Combination
- Formation of insoluble complexes

These reactions may be noticed by

- Precipitation
- Changes in the smell of medicines and the escape of gas
- Color change
- Changes without visible manifestations

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

Factors lead to oxidation:

1. Presence of oxygen
2. Light: it can cause photo-chemical reactions: chemical reaction occur in presence of light
3. Temperature: elevated temperature accelerate oxidation reaction

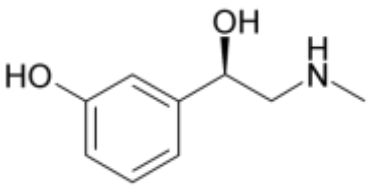
4. pH: each drug has its ideal pH for stability. Any change in pH affect drug stability and may accelerate oxidation reaction
5. Pharmaceutical dosage form: oxidation reaction occur in solutions faster than in solid dosage forms
6. Presence of pre-oxidants as metals and peroxides
7. Type of solvent used: oxidation reaction occur faster in aqueous solution than others.
8. Presence of unsaturated bonds: as double and triple bonds (oils) which undergo easier than saturated bonds (margarine) for oxidation.

Protection of drugs from oxidation:

1. Addition of Antioxidants: Vitamin E, vitamin C and inorganic sulfur compounds: thiosulfate and polysulfide
2. Addition of chemicals which form complexes with metals i.e. EDTA, Benzalkonium chloride
3. Protection from light:
    a. Using of dark container
    b. Storage in dark places
    c. Packaging with substances which absorbed light i.e. Oxybenzene
4. Choice of suitable pharmaceutical dosage forms which reduce the possibility of oxidation process (solid dosage forms are better than solutions)
5. Maintenance of pH by using buffer solution
6. choice of suitable solvent (rather than water)
7. Storage in low temperature
8. protection from air by:
    a. using good closed containers
    b. Replacement of oxygen by nitrogen

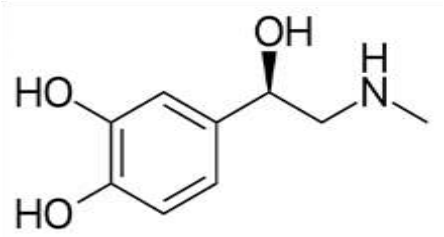
Chemical groups which undergo oxidation:

1. Phenolic compounds: Phenylephrine



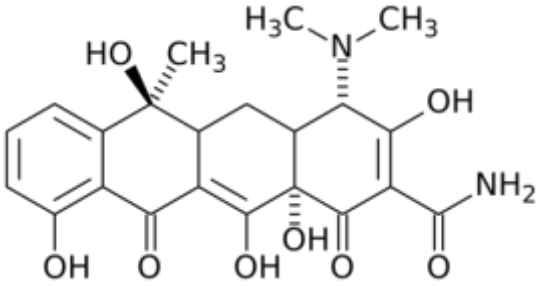
Phenylephrine

2. Catechol derivatives: Adrenaline and noradrenaline



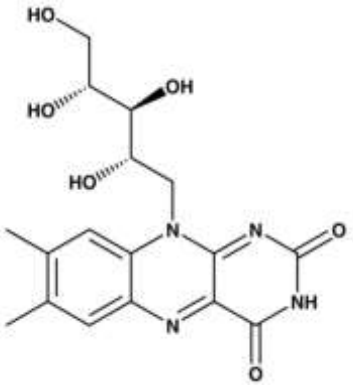
Adrenaline

3. Some antibiotics: Tetracyclines



Tetracycline

4. Oils (fixed and volatile)
5. Vitamins (lipid and water soluble)



Riboflavin

<u>How to identify oxidation in pharmaceutical dosage form?</u>

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

<u>Hydrolysis:</u>

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.

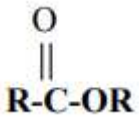
<u>Types of hydrolysis:</u>

1. Ionic hydrolysis

2. Molecular hydrolysis

Chemical groups which undergo hydrolysis:

1. Esters:



Ex: Benzocaine, Procaine

2. Amides:

Ex: Chloramphenicol, Sulfonamide, Procainamide

3. Nitriles: (NO_3, N_2O, NO_2)

Factors induce hydrolysis:

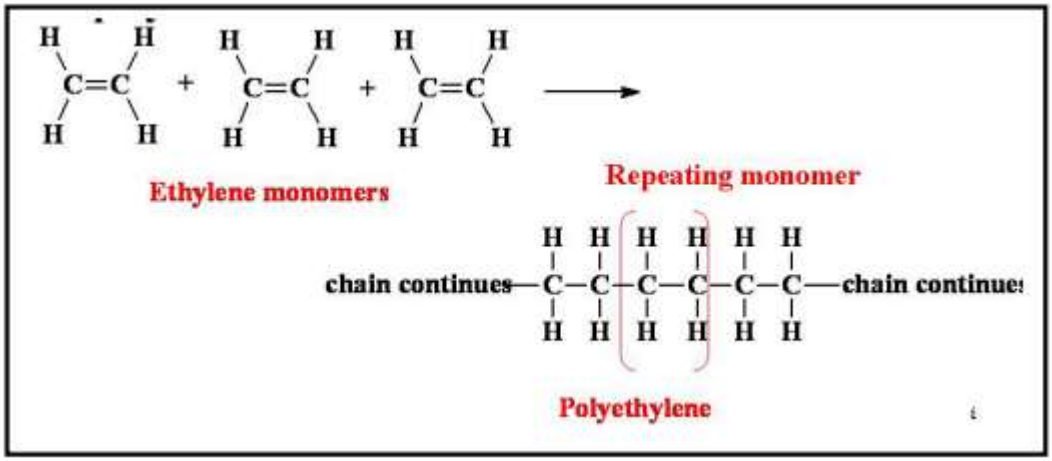
1. Presence of water
2. pH (Ex. Atropine: optimal pH=3.1-4.5)
3. High temperature (Problem by autoclave i.e. procaine)

Protection from hydrolysis:

1. Protection from moisture by :
    a. Packaging with substances impermeable for moisture
    b. Addition of substances that absorb water ($CaCO_3$)
2. Using of solvent rather than water
3. Maintenance of pH by using buffer system
4. Formation of complexes: which protect the drug from the effect of water
5. Using of surfactants (micelle formation)
6. Reducing of solubility of substance (i.e. Suspension instead of solution)

Polymerization:

In polymerization, small repeating units called monomers are bonded to form a long chain polymer.



Example:

Formaldehyde $\xrightarrow{\text{Heat}}$ Paraformaldehyde (Polymer: white precipitate)

To avoid this formaldehyde must be stored in suitable temperature and addition of methanol 15%.

- Ampicillin in high temperature forms polymers which cause allergy.

Factors induce Polymerization:

1. Temperature
2. Light
3. Solvent
4. pH
5. Impurities

Isomerization:

It means conversion of drug to its isomer.

Isomers have:

- Identical molecular formulas.
- A different arrangement of atoms.

Types of isomerization:

A. Optical isomerization:

- Conversion of optical active drug into less active
- ***Example:***
    a. l-Adrenaline is converted to d-adrenaline by change of pH or temperature

b. l-Adrenaline is more therapeutically active than d-adrenaline, a although they have the same physical properties but different arrangement of atoms.

c. This is not general for other drugs: d-tubocurarine is more active than l-type

- Factors affect optical isomerization :

1. Temperature
2. pH
3. Solvent
4. Impurities

B. Geometric isomerization:

- One type of isomers
- Expressed by cis or trans
- Cis is more therapeutically active than trans (***example:*** Vitamin A)

Decarboxylation:

Example:

$$2\ NaHCO_3 \longrightarrow Na_2CO_3 + CO_2 \uparrow + H_2O$$

All drugs contain bicarbonate are not sterilized in high temperature

CO_2 – absorption:

- When some pharmaceutical dosage forms contain CO_2, precipitate is formed:

Example:

$$CO_2 + Ca(OH)_2 = CaCO_3\downarrow + H_2O.$$

Combination:

- Take place when the pharmaceutical dosage form contain substances with different charges
- ***Example:*** Surfactants with positive and negative charges

Formation of insoluble complexes:

Example: Tetracycline + heavy metals

VISUAL SIGNS OF CHEMICAL INCOMPATIBILITY

Precipitation

The most common case of chemical incompatibility. Drug interactions result in the formation of insoluble or low-soluble compounds.

Causes:

- Changes in the pH of the solution;
- complexation;
- racemization;
- polycondensation and polymerisation;
- Neutralisation, exchange, oxidation-reduction reactions

In liquid dosage forms, it is very common for silver, mercury, lead, zinc, aluminium and other compounds to precipitate. This can be caused by the interaction of Metal compounds with alkaloids, nitrogenous bases, tannins, ichthyol, dyes and enzymes, cardiac glycosides, sodium salts of barbituric acid derivatives, sulphonamides, halogen compounds, salts alkali and alkaline earth metals.

Color change

The colour change of a medicinal product usually occurs as a result of chemical interactions between its components. In most cases, this process is accompanied by a decrease in the therapeutic activity or even loss in most cases.

Examples: When potassium iodide ointment is mixed with lead (II) acetate solution according to the prescription

Rp.: Unguenti Ikalii iodidi 30,0

Solutionis Plumbi subacetatis 2,0

M. f. ung.

D. S. Exterior use

It acquires a bright yellow color due to the formation of lead iodide. Therapeutic activity may change.

Changes in the smell of medicines and the escape of gas

The release of gases and a change in the smell of the medicinal product usually go together. A characteristic feature of the resulting products is not only a absence of specific pharmacological activity, but also the appearance of toxicity.

In the manufacture of a medicinal product, gas emission is often observed if sodium nitrite, ammonium salts, carbonates and bicarbonates, hydrogen peroxide

are included in the composition, and a change in smell occurs when hexamethylenetetramine, chloral hydrate, etc. are destroyed.

Changes without visible manifestations

The most dangerous form of incompatibility because it is very difficult to recognise and eliminate.

Such incompatibilities may occur in medicines containing antibiotics, enzymes, vitamins, alkaloid salts, nitrogenous bases and cardiac glycosides.

In the case of cardiac glycosides, for example:

Changes without external manifestation occur under the influence of acids and alkalis: in an alkaline environment five- and six-membered rings open with complete loss of activity, in an acidic environment the gradual hydrolysis of glycosides with the formation of aglycones, which are 10-15 times less active than the native glycosides.

Tetracyclines form insoluble complexes with polyvalent metal cations, boric acid, borax, phosphoric acid and its salts, salts of oxycarboxylic acids, etc.

In pharmaceuticals containing enzymes, incompatible combinations are formed mainly by pepsin and pancreatin.

The therapeutic effect of drugs as a result of such interactions is significantly reduced.

ACTIONS TO BE TAKEN BY THE PHARMACIST WHEN AN INCOMPATIBLE COMBINATION OF MEDICINES IS DETECTED

The pharmacist must be able to identify incompatibilities, know how to overcome them and advise the doctor on how to overcome incompatibilities.

When a pharmacy receives a prescription containing incompatible combinations of drugs, the pharmacist must contact the doctor, explain to him the reason for the incompatibility and suggest ways to overcome it.

If it is impossible to do this, he should ask the patient to go back to the doctor about finding out the prescription. During this time, you should contact doctor about incompatibility.

THE MAIN WAYS TO OVERCOME PHARMACEUTICAL INCOMPATIBILITIES

There are the following ways to overcome incompatibilities:

1. Change in technology and the use of special technological methods without changing the composition of the prescription. These technologies include:
    - separate dissolution of substances,
    - changing the dissolution sequence,

- separate mixing of components in ointments in order to isolate them with layers of a viscous base, etc.

2. Removal of one of the components of the medicinal product from the composition of the prescription, and dispensing it in a similar or different dosage form. However, it should be borne in mind that poisonous, narcotic, potent, psychotropic substances are prohibited to be dispensed not as part of the manufactured medicinal product.
3. Changing of some drugs with a pharmacological analogue.
4. Introduction of excipients into the composition of the medicinal product. It can be surfactants, thickeners, solubilizers, antioxidants, co-solvents, buffer solvents.
5. Changing the dosage form, for example, a solution for powders, a solution for tablets, drops for a medicine.

In cases where a single change in the technology is sufficient to overcome incompatibility, the pharmacist may not agree with the physician and **proceed independently**.

In cases where overcoming incompatibility involves

- changing the composition or quantity of active ingredients,
- introducing excipients,
- dividing one dosage form into two
- to changing the composition or quantity of the active ingredients,
- introducing excipients,
- splitting one dosage form into two or more
- changing one form into another, **the issue must be agreed with the physician.**