

Incompatibility (Geçimsizlik)

# Incompatibility

- 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 may occur during;

- Compounding
- Formulation
- Manufacturing
- Packaging
- Dispensing
- Storage
- After administration of drugs (in-vivo incompatibilities)



In-vitro  
incompatibilities

- The incompatibilities may be detected by changes in the physical, chemical, and therapeutic qualities of the medicine.
- So you can also deffined 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.

- The incompatibilities occur when the components of a medicine interact in such a way that properties of that medicine are adversely affected.
- We can classified incompatibilities according to the occurring mechanism

# Type of incompatibilities

- Physical incompatibilities
- Chemical incompatibilities
- Physicochemical incompatibilities
- 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.

- 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)



# Physical incompatibilities (**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 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, succinyl sulphothiazole, 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.

Rx

Chalk powder –2g

Tincture catechu – 2ml

Cinnamon water – 2ml

- 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.

- 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

- Rx

Terpin hydrate ..... 2.5 g

Syrup simplex ..... 100 g

Terpin hydrate is insoluble in simple syrup, but soluble in alcohol.

- Terpin hydrate is dissolved using half the amount of syrup in alcohol (90 degrees) and completed with 100 g of simple syrup. In this way, the effectiveness of the drug does not change. But....



- Or ; Terpin hydrate is prepared as a suspension with a suspension agent such as CMC, MC, tragacanth, gum arabic...

Rx

Belladone tincture ..... 15 ml

Afyon tincture ..... 15 ml

By mixing these two tinctures, turbidity and precipitation occurs

Why, and what is the solution???



- This is because tinctures are prepared in alcohol, and when these two tinctures are mixed, the degree of alcohol in the formula decreases.
- Solution; DON'T MIX 😊

The two tinctures in the formula should be prepared and stored separately and can be mixed while using.

Rx

Phenol ..... 2%

Sodium sulfate ..... 5%

Distilled water ..... qs ..... 120 ml

When phenol and sodium sulfate come together, turbidity and decomposition (seperation) are observed.

- Phenol is soluble in glycerin. First solve it.
- Incompabilities are not observed when phenol-glycerine solution mixed with sodium sulfate.

- Dissolution status is an important condition in terms of absorption of the active substance, therefore it is preferred to give dissolved states of the active substances to the body as much as possible.
- **DONT FORGET!!**
  - Gums are insoluble in alcohol
  - Resins are insoluble in water.

# PHYSICAL INCOMPATIBILITIES:

## Immiscibility

- When two such ingredients are combined resulting in a non-homogeneous 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

- 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

# The following factors lead to immiscibility (Continue)

- Temperature
- Type of liquids.
  - Oils and water are immiscible with each other which shows physical incompatibility



# Castor oil emulsion

Rx

Castor oil – 15ml

D.water – 60ml

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

- To overcome this type of incompatibility emulsification is necessary with the help of an emulsifying agent.

Rx

Castor oil – 15ml

Acacia – 2% W/V

Water– upto 60ml

# PHYSICAL INCOMPATIBILITIES:

## Precipitation

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

- 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

# Lotion of compound tincture of benzoin

Rx

Tincture benzoin compound – 5g

Glycerin – 10ml

Rose water upto 100ml

Tincture benzoin compound contain resins.

This change in solvent system results in an unavoidable precipitate.

- Solution:

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

# PHYSICAL INCOMPATIBILITIES

## Liquefaction (eutexia)

- 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.
- 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.....

Rx

Menthol – 5g

Camphor – 5g

Water – 60ml

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

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

a) Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder.



- b) The individual medicaments is powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container

Rx

Menthol – 5g

Camphor – 5g

Light kaolin– 0.2g

# 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.

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

- pH change
- Oxidation-reduction reactions
- Acid-base hydrolysis
- Double decomposition

# These reactions may be noticed by

- Precipitation
- Effervescence
- Decomposition
- Color change
- Explosion

# Oxidation

- Air, storage temperature, light, pH value and heavy metals (iron, copper) catalysis, yeast and bacterial enzymes are effective in this event, which creates a big problem especially in solutions.

Adrenaline, phenylephrine, morphine, codeine, vitamin C (in aqueous medium), aspirin (in aqueous medium) are easily oxidized.

!!! Heat increases this reaction rate.

# To prevent oxidation-related incompatibility;

- Antioxidant should be added to the environment.
  - Antioxidants absorb the first energy in the environment and prevent oxidation of the substance.
- Packaging material can also prevent oxidation.
  - light and heavy metals may accelerates oxidation

# Examples of antioxidants

## Water soluble:

- Na-sulfite
- Na- bisulfite
- Cysteine
- Ascorbic acid

## Fat soluble:

- Butyl hydroxy toluene
- Butyl hydroxy anisole
- Nordihydroguaryetic acid
- Amil gallat
- Propyl gallate
- Alpha tocopherol

- Reduction

It is less common than oxidation. It is found in preparations containing Au, Ag, Hg. Thus, metallic compounds are separated from their salt and released.



- Racemization

Without any change in the chemical structure of the compounds, the optically active form may change and its inactive form may occur.

Ex: Adrenaline, ephedrine, noradrenaline ...

- Precipitation

It is the formation and collapse of an insoluble substance by effecting two or more substances on each other in solution. A flocculated precipitate is formed as a result of a slow reaction and a collapse over time.

- Gas outlet

If there is a CO<sub>2</sub> reaction with chemical reaction, the mouth of the package should be closed after the gas discharge ends after the recipe is prepared. In aqueous environment, carbonates with acids give CO<sub>2</sub>,

Eg: Magnesium citrate lemonade (MgCO<sub>2</sub> is formed)

- Color change

Incompatibility color change in most chemical reactions

Depending on pH, color change is observed in the preparations.

Fenolftalein: colorless in acidic medium, pink-purple in basic medium

- Explosive mixtures

In the presence of acid and base, there may be explosion with CO<sub>2</sub> output.

HNO<sub>3</sub> (nitric acid), alcohol, sugar, glycerin mixture explodes

Trinitroglycerin is used to treat heart conditions.

KMnO<sub>4</sub> powdered glycerine, with alcohol

Potassium chlorate explodes with coal, sugar, tannins, organic matter.

# Hydrolytic changes

- An **endothermic process (reaction)** is any process which requires or absorbs energy from its surroundings, besides an **exothermic reaction** gives off energy to the surroundings
  - Depending on whether the reaction is exothermic or endothermic, it is necessary to cool or heat the medium. (to slow down the reaction)
  - If there is heat output in the environment, it is necessary to prevent the volatile substances in the prescription from evaporating and leaving the environment.

- Hydrolysis of aspirin in aqueous medium can be given as an example. For this reason, aspirin does not exist in the form of solutions.
- The lactam bond is hydrolyzed in penicillin preparations. Only Ciliacin is available in the form of liquid preparation, this drug is in the form of a non-hydrolyzed ester.
- Penicillin suspensions are prepared in lyophilized form and diluted when used. Because it is hydrolyzed in aqueous medium and is divided into penicilloic acid and penilic acid. The penicilloic acid has no therapeutic effect.
- Atropine hydrolysis in the form of tropic acid and apoatropin in aqueous medium. Apoatropin returns to belladonin form as a result of temperature increase, and this substance is toxic

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- **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

The quantity of strychnine hydrochloride is more than its solubility in water (1:30).

The aromatic spirit of ammonia contains negligible amount alcohol

Strychnine hydrochloride gets precipitated yielding diffusible precipitate, hence

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

- E.g-2.:Quinine hydrochloride mixture

Rx

Quinine hydrochloride -0.12ml

Sodium salicylate -4g

Water -100ml

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

# 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.

# THERAPEUTIC INCOMPATIBILITY - Mechanism

**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 interacting 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

# Atropine sulphate capsules

Rx

Atropine sulphate - 0.005g

Phenobarbitone - 0.015g

Aspirin - 0.300g

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

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

The prescription is referred back to the prescriber to correct the overdose of the atropine sulphate.



# 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.

E.g., Prednisone and Prednisolone // Digoxin and Digoxin

- 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 contraindicated in a particular disease or a particular patient who is allergic to it.

Corticosteroids are contra-indicated in the patients having peptic ulcers

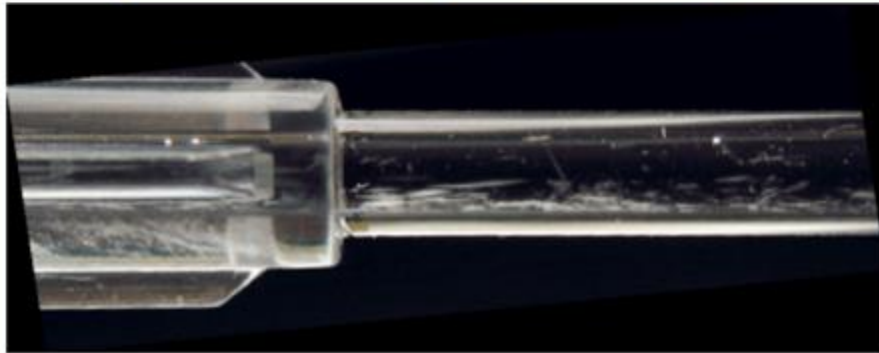
The penicillin and sulphur drugs are contraindicated in the patients who are allergic.

Vasoconstrictors are contra-indicated in hypertensive patients.

Barbiturates and morphine should not be given to the asthmatic patients.

- 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

- 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.



Midazolam and Ketamine particle formation-Chemical precipitation – It returns to basic form on a weak basis and formation of water-insoluble form.

Precipitation of Midazolam according to pH change





## Incompatible drugs in combination with any other drug

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Aminoglycosides

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Chlordiazepoxide

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Diazepam

---

Digitalis glycosides

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Pentobarbital

---

Phenytoin

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Secobarbital

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Sodium bicarbonate

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Theophylline derivatives

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## Drugs with limited compatibility

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Alprostadile

---

Clonidine

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Dobutamine

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Dopamine

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Doxaprame

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Epinephrine

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Glycerol trinitrate

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Milrinon

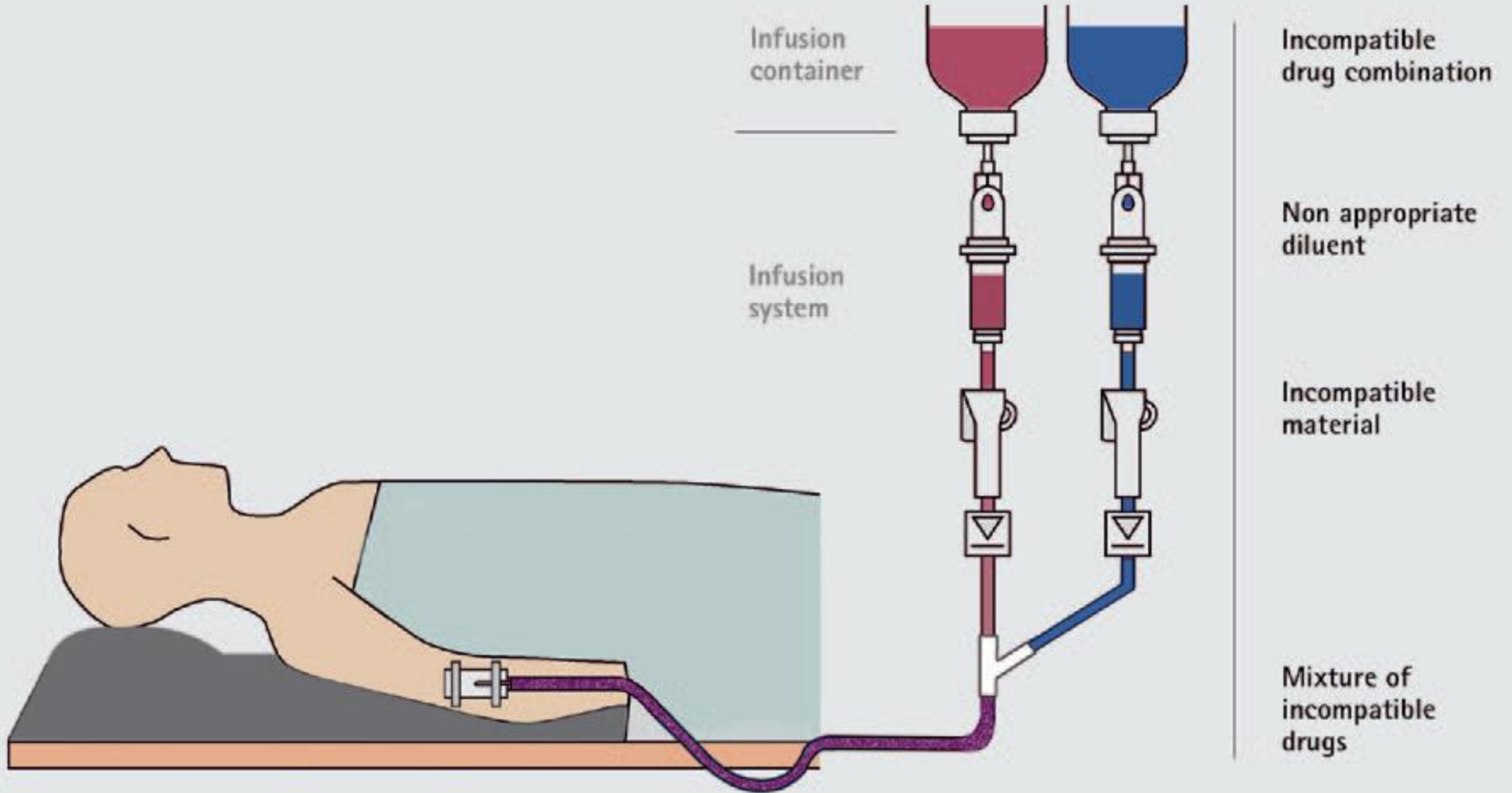
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Norepinephrine

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Sodium nitroprusside

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Infusion container

Infusion system

Incompatible drug combination

Non appropriate diluent

Incompatible material

Mixture of incompatible drugs



# Önleme Yolları



Ayrı uygulanması gereken ilaçların birlikte verilmemesi.



Uygun referanslardan geçimsizliği kontrol etmek



Renklerle kodlandırma ve geçimsiz olacak ilacın diğerleri ile karışmasını önlemek

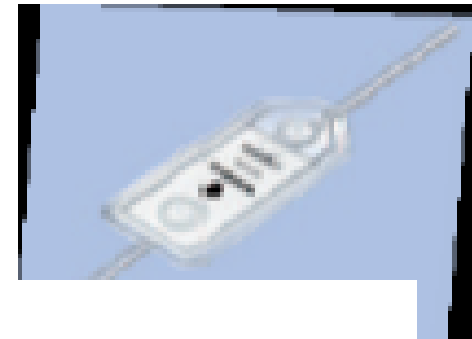
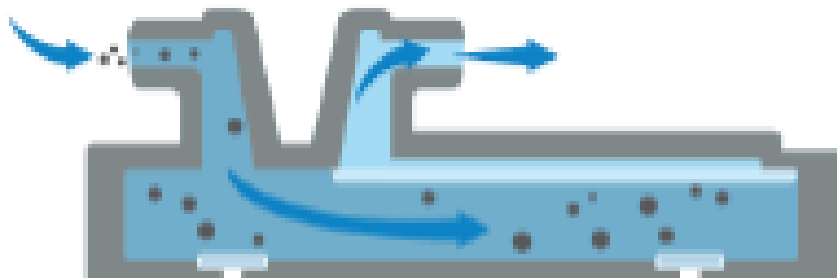
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- like an indicator when filter blocks as a result of chemical or physical reactions.



cross-section