جامعة الجزيرة الخاصة
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Industrial Pharmacy (3)

Solutions as a dosage form

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Solutions: definition

- A solution is a homogenous one-phase system consisting of two or more components. The solvent, or mixture of solvents, is the phase in which the dispersion occurs, and the solute is the component which is dispersed as molecules or ions in the solvent
- **In physicochemical terms:** solutions may be prepared from any combination of solid, liquid, and gas, the three states of matter.
- **In pharmaceutical terms:** solutions are liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

Solutions: definition

- In general the solvent is present in the greater amount, but there are several exceptions, e.g., Simple Syrup BP contains 66.7% w/w of sucrose as the solute in 33.3% w/w of water as the solvent

Classification of Solutions

Solutions Classified by Route of Administration

- Oral solutions
- Topical solutions
- Rectal solutions
- Vaginal solution
- Otic solutions
- Nasal solutions
- Ocular solution
- Parenteral solutions
- Inhalations

Classification of Solutions

Solutions Classified by Solvent-Solute System

- Syrups
- Elixirs
- Tinctures
- Aromatic waters
- Spirits
- …….

Advantages of Solutions

A. Because solutions are molecularly dispersed systems, they offer these advantages:

١. Completely homogenous doses.

٢. Immediate availability for absorption and distribution.

B. Solutions also provide a flexible dosage form:

١. They may be used by any route of administration.

٢. They can be taken or administered to patients who cannot swallow tablets or capsules.

٣. Doses are easily adjusted.

Disadvantages of Solutions

١. Drugs and chemicals are **less stable** when in solution than when in dry form.

٢. **Some drugs are not soluble** in solvents that are acceptable for pharmaceutical use.

٣. Aqueous solutions are subject to **contamination by microorganisms**.

٤. Because solutions are more **bulky and heavy** than dry solid dosage forms, they are more difficult to handle, package, transport, and store.

٥. Oral solutions in bulk containers **require measurement by the patient or caregiver**. This is often **less accurate** than individual solid dosage forms, such as tablets and capsules.

Choice of solvent

- The **physicochemical characteristics (solubility)** of drugs that permits the selection of the proper solvent for a particular solute.
- In addition to the factors of solubility, the selection is based on such **additional characteristics** as: **clarity, low toxicity, viscosity, compatibility with other formulative ingredients, chemical inertness, palatability, odor, color, and economy**.
- water is the preferred solvent because it comes closer to meeting these criteria than other solvents.

Choice of solvent: Aqueous solvents

- When water is used as the primary solvent, commonly an auxiliary solvent (co-solvent) is also employed to enhance the solvent action of water or to contribute to a product's chemical or physical stability.
- Alcohol, glycerin, and propylene glycol, are the most widely used auxiliary solvents.
- Other solvents, such as acetone, ethyl oxide (ether), and isopropyl alcohol, are too toxic to be permitted in pharmaceutical preparations to be taken internally.

Solvents: Water

- Water is the solvent most widely used as a vehicle for pharmaceutical products, because of its physiological compatibility and lack of toxicity.
- It possesses a high dielectric constant, which is essential for ensuring the dissolution of a wide range of ionizable materials.

Types of water: 1- Tap water:

- Naturally occurring water exerts its solvent effect on most substances it contacts and thus is impure, containing varying amounts of dissolved inorganic salts, usually sodium, potassium, calcium, magnesium, and iron; chlorides; sulfates; and bicarbonates, along with dissolved and undissolved organic matter and microorganisms.
- Water found in most cities and towns where water is purified for drinking usually contains less than 0.1% of total solids.
- Acceptable drinking water should be clear, colorless, odorless, and neutral or only slightly acid or alkaline, the deviation from neutral being due to the nature of the dissolved solids and gases.

Types of water: 1- Tap water:

- Ordinary **drinking water** from the tap is **not acceptable for the manufacture** of most aqueous pharmaceutical preparations because of **possible chemical incompatibilities** between dissolved solids and the medicinal agents being added.
- Signs of such incompatibilities are: **precipitation, discoloration, and occasionally effervescence**.
- **Its use is permitted in** washing, in extraction of crude vegetable drugs, in preparation of purified water, in preparation of certain products for external use.

Types of water: 2- Purified Water :

- Purified Water, USP, is obtained by:
  ١. distillation.
  ٢. ion exchange treatment.
  ٣. reverse osmosis.

- It is prepared from drinking water, but has fewer solid impurities, not more than 0.001% of residue (1 mg of solids per 100 mL of water). Thus, purified water has only 1% as much dissolved solids as tap water.
- Purified Water, USP, is intended for use in preparation of aqueous dosage forms except those intended for parenteral administration (injections).

Types of water: 3- Water for Injection:

- Water for Injection, USP: This water is purified by distillation or by reverse osmosis. It must be sterile and pyrogen free.
- More details will be discussed under parenteral dosage forms.

Water Purification Methods

١. **Distillation Method**

٢. **Ion Exchange Method**

٣. **Reverse Osmosis**

Distillation Method

- Many stills in various sizes and styles with capacities ranging from about 0.5 to 100 gallons (a gallon is 3.78 liters) of distillate per hour are available to prepare purified water.
- Generally 10-20% of the first portion of aqueous distillate must be discarded, since it contains many foreign volatile substances usually found in urban drinking water. Also, the last portion of water (about 10% of the original volume of water) remaining in the distillation apparatus must be discarded because distillation to dryness would undoubtedly result in decomposition of the remaining solid impurities to volatile substances that would distill and contaminate the previously collected portion of distillate.

Ion Exchange Method

- On a large or small scale, ion exchange for the preparation of purified water offers a number of advantages over distillation. For one thing, the requirement of heat is eliminated and with it costly and troublesome maintenance frequently encountered in the operation of the more complex distillation apparatus.
- Because of the simpler equipment and the nature of the method, ion exchange permits ease of operation, minimal maintenance, and a more mobile facility.
- The ion exchange equipment passes water through a column of cation and anion exchangers consisting of water-insoluble synthetic polymerized phenolic, carboxylic, amino, or sulfonated resins of high molecular weight.

Ion Exchange Method

- These resins are mainly of two types:

(a) **the cation, or acid exchangers (phenolic, carboxylic, sulfonated):** which permit the exchange of the cations in solution with hydrogen ion from the resin:

$$H\text{-resin} + M^+ + X^- + H_20 \rightarrow M\text{-resin} + H^+ + X^- + H_20(pure)$$

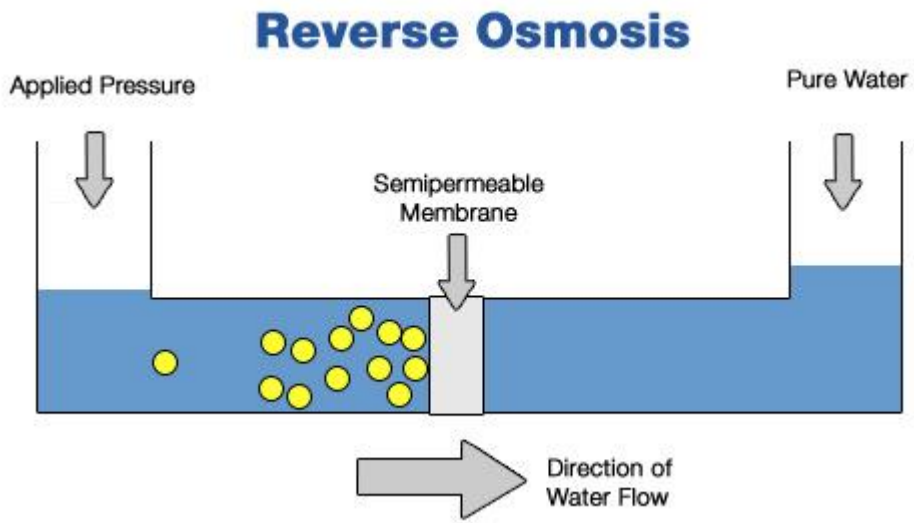
(b) the anion, or base exchange resins (amino): which permit the removal of anions:

$$Resin\text{-}NH2 + H^+ + X^- + H_20 \rightarrow Resin\text{-}NH2 \bullet HX + H_20\ (pure)$$

- These two processes are successively or simultaneously employed to remove both cations and anions from water.
- Water purified in this manner, referred to as **demineralized or deionized water**, may be used in any pharmaceutical preparation or prescription calling for distilled water.

Reverse Osmosis

- Reverse osmosis: referred to in the industry as cross-flow (or tangential flow) membrane filtration.
- Reverse osmosis is a separation process that uses pressure to force a solution through a membrane that retains the solute on one side and allows the pure solvent to pass to the other side.
- In this process a solvent is forced from a region of high solute concentration through a semipermeable membrane to a region of low solute concentration by applying a pressure in excess of the osmotic pressure. This is the reverse of the normal osmosis process.



Reverse Osmosis

- Depending on their pore size, cross-flow filter membranes can remove particles defined in the range of microfiltration (0.1-2 µg, e.g., bacteria); ultrafiltration (0.01-0.1 µg, e.g., virus); nanofiltration (0.001-0.01 µg, e.g., organic compounds in the molecular weight range of 300-1000); and reverse osmosis (particles smaller than 0.001 µg).
- Reverse osmosis removes virtually all viruses, bacteria, pyrogens, and organic molecules and 90 to 99% of ions.

Non-aqueous solvents

Alcohol (ethanol)

- Next to water, alcohol is the most useful solvent in pharmacy. Usually used as a cosolvent with water. In addition, it is used as a primary solvent for many organic compounds.
- Certain drugs are insoluble in water and must be dissolved in an alternative vehicle. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives.
- Together with water it forms a hydroalcoholic mixture that dissolves both alcohol-soluble and water-soluble substances.
- Alcohol is frequently used with other solvents, such as glycols and glycerin, to reduce the amount of alcohol required.
- It also is used in liquid products as an antimicrobial preservative (15-20%).

- However, concern has been expressed over the undesired pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products, particularly by children.
- FDA has proposed recommended limits in over-the-counter (OTC) oral products:
  - Under 6 years: 0.5%
  - 6-12 years: 5%
  - Above 12 years and adults: 10%

Non-aqueous solvents

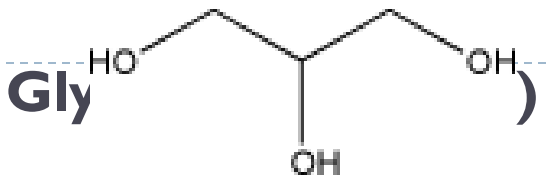
- **Polyhydric alcohols (polyols)**
  - They are used as cosolvents; miscible with each other and with water and alcohol

1- Propylene glycol

2- Glycerol

3- Polyehtylene glycol (PEG) or macrogols

Non-aqueous solvents



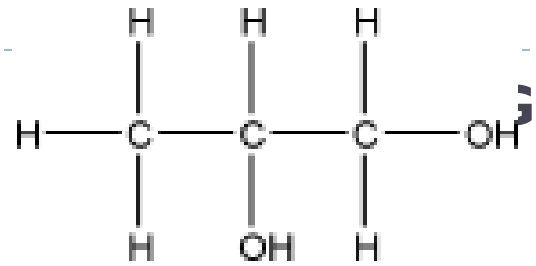
- Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.
- It is miscible with both water and alcohol.
- As a solvent, it is comparable with alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating.
- Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations.
- In topical pharmaceutical formulations (such as creams and emulsions) and cosmetics, glycerin is used primarily for its humectant and emollient properties.
- In parenteral formulations, glycerin is used mainly as a solvent.

- In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent.
- It is also used as a plasticizer in film coatings.
- Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories.

Uses of glycerin

Use	Concentration (%)
Antimicrobial preservative	<20
Emollient	⩽30
Humectant	⩽30
Ophthalmic formulations	0.5–3.0
Plasticizer in tablet film coating	Variable
Solvent for parenteral formulations	⩽50
Sweetening agent in alcoholic elixirs	⩽20

Non-aqueous solvents



- Glycol
- Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin. It is miscible with water and alcohol.
- It is a useful solvent with a wide range of applications and is frequently substituted for glycerin in modern pharmaceutical formulations. It is a better general solvent than glycerin.
- It is used as an antimicrobial preservative; humectant; plasticizer in aqueous film-coating formulations.
- As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.
- Propylene glycol is estimated to be one-third as intoxicating as ethanol.

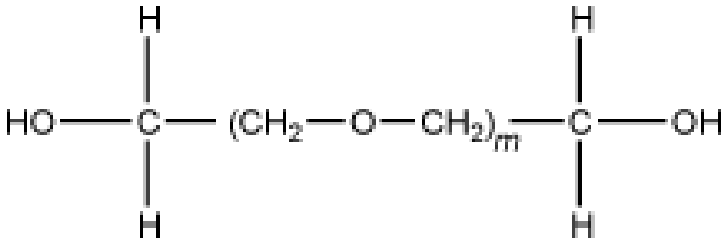
Uses of propylene glycol

Use	Dosage form	Concentration (%)
Humectant	Topicals	≈15
Preservative	Solutions, semisolids	15–30
Solvent or cosolvent	Aerosol solutions	10–30
	Oral solutions	10–25
	Parenterals	10–60
	Topicals	5–80

Non-aqueous solvents

Polyehtylene glycol (PEG or macrogols)

Grade	*m*	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613



- Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin.
- Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.
- Low molecular weight PEG (200 – 600) are fluid and used as water-miscible solvents.
- In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

Choice of solvent: Non-aqueous solvents

- **Fixed oils of vegetable origin**
  - A number of fixed oils, such as corn oil, cottonseed oil, peanut oil (arachis oil), and sesame oil, are useful solvents, consisted mainly of fatty acid esters of glycerol (glycerides)
  - They are used as solvents for topical solutions and sustained-release intramuscular injections. The oily solution remains within the muscle tissue, releasing the drug slowly into the surrounding tissue by partitioning

Preparation of solutions

- **Most pharmaceutical solutions are unsaturated with solute.** Thus the amounts of solute to be dissolved are usually well below the capacity of the volume of solvent employed.
- Some chemical agents in a given solvent require an extended time for dissolving. To hasten dissolution, a pharmacist may employ one of several techniques, such as **applying heat, reducing the particle size of the solute, using a solubilizing agent, or subjecting the ingredients to vigorous agitation**.

Preparation of solutions

- The only equipment necessary is suitable mixing vessels, a means of agitation and a filtration system.
- The solute is simply added to the solvent in a mixing vessel and stirring is continued until dissolution is complete.
- If the solute is more soluble at elevated temperatures, heat may be applied. Care must be taken if any volatile or thermolabile materials be present.
- Volatile materials, such as flavours, are added at the end of a process and after any cooling, to reduce loss by evaporation.
- Finally, filtration is done to ensure clarity of the final solution.