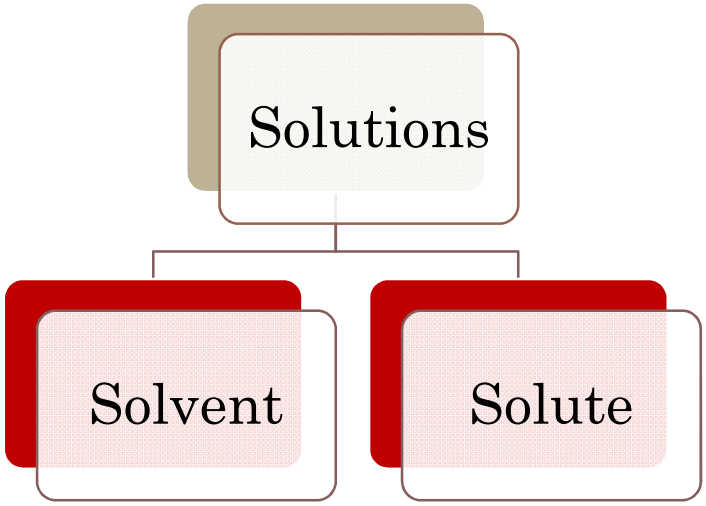
SOLUTIONS

WEEK 2

Definition (USP 29)

- Solutions are liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents.



*** True Solutions**

In true solutions, the solute is dissolved in the dissolution medium and is invisible. The solute is dispersed as small molecules or ions within the solvent.

Pharmaceutical Solutions

Aromatic water, syrup, parenteral solutions, mouthwashes, gargles, drops,…etc.

Advantages of Solutions

- Ease of administration (pedatric and geriatric patients)
- High absorption
- Dosing uniformity
- Easy and economic production

Disadvantages of Solutions

- Packaging, storage and transport difficulties
- Difficulty of masking the bad taste and odors of active agents
- Low stability (hydrolysis, oxidation, microbiological contamination)
- Short shelf life

Solute	Solvent	Sample
Liquid	Liquid	Water - acetone ★
Solid	Liquid	Salt – water ★
Gas	Liquid	Perhidrol, soda ★
Liquid	Solid	mercury-silver (Amalgam)
Solid	Solid	Copper-gold(12 Carat YellowGold)
Gas	Solid	Hydrogen in Palladium
Liquid	Gas	Water vapor in the air
Solid	Gas	I_2 vapor in the air
Gas	Gas	Air

Classification of Pharmaceutical Solutions

Depending on solvent type

- aqueous solutions
- Non-aqueous solutions
  - Polyhydric alcohols, Dimethyl sulfoxide, Ethyl, ether, chloroform, acetone, Liquid paraffin, Glycerol, Polyethylene glycol

Concentration units in solutions

Percent (%) concentration

Weight percentage (% w / w) (solid and semi-solid mixtures)

Volume percentage (% v / v) (liquid-liquid)

Weight in volüme percentage (% w / v) (solid-liquid or gas-liquid)

Molarity (M)	The number of moles of solute per liter of solution (mol / L)
Normality (N)	The number of mole equivalents per liter of solution
Molality (m)	the number of moles of solute per kilogram of solvent (mol / kg)
Mole Fraction (x or N)	The ratio of the number of moles of one of the components in the solution to the total number of moles
Mili equivalents (mEq)	Molecular weight /valence
ppm	The amount of solute in mg per kilogram of solution

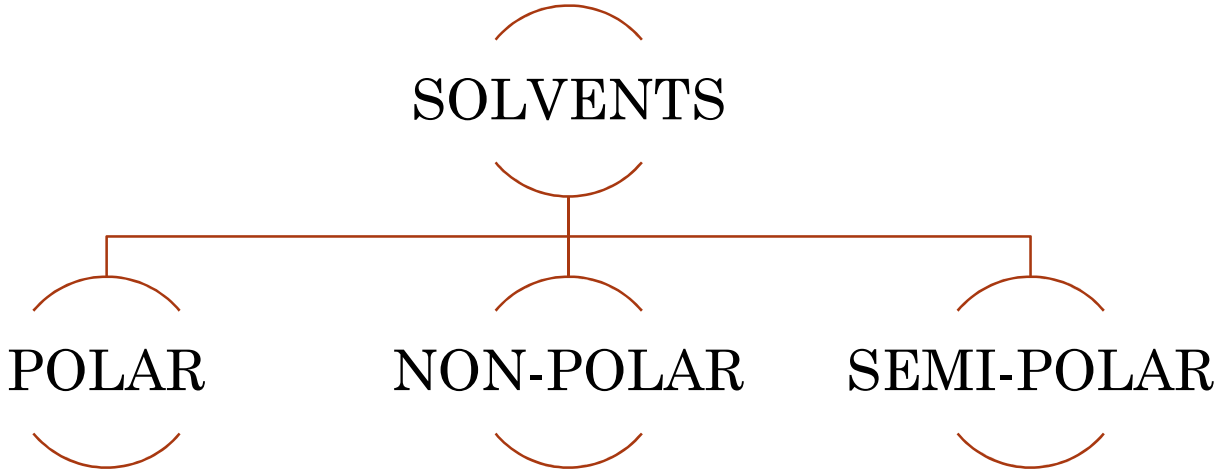
Solubility

- Amount of the solute that dissolves in a unit volume of a solvent to form a saturated solution under specified conditions of temperature and pressure.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

1 Part Boric acid
16 Parts Ethanol

Solvent-solute Interactions

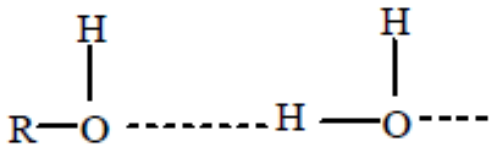


- The polarity of the solvent is also effective on solubility and is divided into 3 classes according to their polarity.

POLAR SOLVENTS

- They dissolve ionic and other polar compounds.
- Eg: Water, Dimethyl sulfoxide (DMSO), Formamide

- Water (dissolves: aldehyde, ketones, alcohol, phenols)



Alcohol with water

NON-POLAR SOLVENTS

- Have low dielectric constant
- Do not reduce attraction between weak or strong electrolytes
- Can not disrupt covalent bonds
- Can not dissolve ionic or polar compounds

- Eg: Chloroform, diethyl ether, benzene, toluene

SEMI-POLAR SOLVENTS

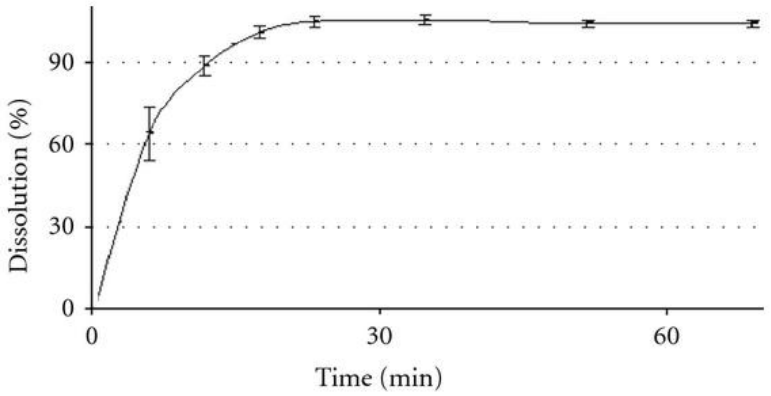
- Also called intermediate solvents
- Miscible with polar and non-polar solvents

- Eg:
- Acetone: (Ether solubility in water ↑)
- Popilen glycol: (Water solubility of peppermint oil↑)

Percentage of ethyl alcohol	Density(g/ml)
Alcohol:	
95.1-96.9 % v/v	0.8051-0.8124
92.6-95.2 % w/w	
Absolut (or anhydrous) alcohol:	
99.5 % v/v	0.7907-0.7932
99.2 % w/w	
Diluted alcohol	
69.1-71.0 % v/v	0.8860-0.8883
61.5-63.5 % w/w	

Dissolution Rate

- Amount of solute dissolved in unit time in a given dissolution medium under certain pressure and temperature



Solubility

- Maximum amount of solute that can be dissolved under a certain pressure and temperature in a given dissolution medium
- **Ex:** Solubility of acetyl salicylic acid in water at 37 ° C is 10mg/mL.

Factors affecting the dissolution rate

- Particle size
- Mixing
- Temperature

Noyes-Whitney equation

$$\frac{dC}{dt} = \frac{D \cdot A(C_S - C)}{h}$$

dc/dt = Dissolution rate.
k= Dissolution rate constant (1st order).
D = Diffusion coefficient/diffusivity
Cs = Saturation/ maximum drug solubility.
C =Con. Of drug in bulk solution.
Cs-C=concentration gradient.
h =Thickness of diffusion layer.

- Generally, the rate of dissolution of substances in solvents is slow. Therefore, in order to achieve complete dissolution and increase the rate of dissolution:
- the temperature application may be carried
- Size can be reduced
- solubilizing agents can be used
- mixing can be applied

Generally, because of the endothermic properties of the substances, their solubility is higher at temperatures above room temperature. Therefore, if the dissolution is accelerated by increasing the heat, make sure that the material is stable and not volatile.

Factors affecting solubility

- Molecular size
- Solvent type
- Temperature

★ Stability and volatile property should be checked

  - Endothermic reaction (sugar-water)
  - Exothermic reaction (methyl cellulose-water)

- Solvent pH
- Cosolvents
- Surface Active Agents

Molecular size

- It is reported that large and organic molecules have less solubility in water than small molecules and that the solubility decreases with increasing molecular weight.

pH and pKa effect

- SOLVENT: Water
- SOLUTE: Weak acid or weak base

Water is generally used as solvent in formulation studies. The active substances are generally weak acid or weak base. Water sometimes ionizes these substances without sometimes decomposing them into ions

pH ve pKa effect

- SOLVENT: Water
- SOLUTE: Weak acid or weak base

→ Dissolved by ionization ★ pH

→ Dissolution without ionization

If there is better solubility in acidic medium compared to water: Weak base

If there is better solubility in basic medium compared to water: Weak acid

If there is better solubility is obtained both in asidic and basic medium compared to water: amphoteric structure or zwitterion behavior

The **intrinsic solubility** is the equilibrium **solubility** of the free acid or base form of an ionizable compound at a pH where it is fully non-ionized.

Compounds do not constitute salt since they are non-ionized and therefore only themselves can be mentioned.

Cosolvent effect

- Generally, the solubility of solids in solvent mixtures is greater than the solubility in a single solvent. This is called cosolvent effect and the other solvents which increase the solubility are called cosolvent.

Surface active agents (Surfactants)

Crystal structure

AMORPHOUS> CRYSTAL

Dissolution Rate & Solubility

	Dissolution Rate	Solibility of Solids	Solubility of Gases
Heating	Increase ↑	Increase ↑	Decrease ↓
Mixing	Increase ↑	X	Decrease ↓
Increasing surface area	Increase ↑	X	X
Increasing the surface pressure of solution	X	X	Increase ↑

Excipients Used in Solution Formulations

Active Agents

- The purity and physicochemical properties of the active agent(s) should be well known.

Solvents

- ***a- Polar solvents:*** *The solvents in this group are mainly water-miscible solvents. (water, glycols, propylene glycol)*
- ***b-Semi-polar solvents*** *(ethanol, isopropyl alcohol and acetone)*
- ***c- Nonpolar solvents:*** *This group contains water-immiscible solvents. (oils, benzene, carbon tetrachloride, chloroform and liquid paraffin)*

Sweeteners

- Sucrose (often used in combination with sorbitol, glycerin and other polyols to prevent crystallization)
- Saccharin, Aspartame (phenylalanine and methyl ester of aspartic acid)

- Saccharin is 250-500 times sweeter than sucrose.
- However, if not properly used in the formulation, it leaves a bitter taste in the mouth.
- As an alternative aspartame is used as an artificial sweetener.
- Aspartame is methyl ester of aspartic acid and phenylalanine. It is 200 times sweeter than sucrose. It doesn't leave bitter taste like saccharin.

Viscosity Enhancers

- Adjustment of viscosity in solutions is important for the flowability of the preparation.
- This can be achieved by adjusting the sucrose concentration or with viscosity enhancing agents. Examples include polyvinyl pyrrolidone, various cellulose derivatives (eg, methyl cellulose, sodium carboxymethyl cellulose).

Flavors and fragrances

- They are added to oral or oramucosal solutions. They are used to mask unwanted taste and odors. The aromas that can be preferred in the selection of appropriate flavors and fragrances are given in the Table.

Felt taste	
Salty	Apricot, peach, mint, etc.
Spicy	Cherry, walnut, chocolate, anise, etc.
Sweet	Fruit, vanilla, etc.
Sour	Lemon etc.

Coloring agents

- The color and clarity of the preparation should be considered in solutions.
- Appropriate color is selected by considering the taste and odor of the solution.
- For example, for a solution with mint taste, blue or green color agents can be used. While red color is more appropriate for cherry flavor.
- Coloring agents to be used in dossage forms should be FDC (Food, Drug and Cosmetics) coded.
- Their concentration in the solutions should be less than 0.001%.

Preservatives

a) Antioxidants

b) Antibacterial agents

Antioxidants

Antioxidants are currently used as efficient **excipients** that delay or inhibit the oxidation process of molecules. Usually **antioxidants themselves** become oxidized and prevent the pharmaceutical solution.

Oil based solutions

- Butyl hydroxy anisole (BHA)
  Butyl hydroxy toluene (BHT)
  Propyl gallate → (0.005-0.02%)
- Tocopherol → (0.05-0.075%)

Aqueous solutions

- Sodium sulphite
  Sodium bisulfite
  Sodium metabisulphite → (0.1-0.2%)
- Ascorbic acid → (0.01-0.05 %)

Antibacterials:

They show bactericide effects.

Benzalkonium chloride - 0.01%,
Chlorbutanol 0.3-0.5%
Chlorocresol 0.03-0.05%
Nipa esters (methyl, ethyl and propyl esters of p-hydroxy benzoic acid) 0.1-0.3%,
Sorbic acid 0.2%
Phenol 0.5%
Mercury compounds (phenyl mercury nitrate, phenyl mercury borate, phenyl mercury acetate) 0.002-0.005%
Thiomersal% 0.001

Benzalkonium chloride: is a type of cationic surfactant. It is an organic salt classified as a quaternary ammonium compound . They are active against bacteria and some viruses, fungi, and protozoa.

Used for germicide and antiseptic purposes in the disinfection of heat sensitive instruments. Diluted aqueous solution (DF:750) and alcoholic solutions are used for disinfection of wounds and skin surfaces.
For nasal and ocular preparations, it should be diluted (DF:5000).

Chlorbutanol: Used as antiseptic and local anesthetic. It is used orally with the same therapeutic effects. In addition, there are sedative and hypnotic effects. It is used as an antiseptic and local anesthetic in the veterinary and orally as a sedative and hypnotic.

Benzoic Acid: Sodium benzoate is one of the most widely used derivatives. It is widely used in foods, syrups, solutions and similar preparations.

Types of Pharmaceutical Solutions

- Aromatic waters
- Syrups
- Elixirs
- Linctus
- Mouthwashes and gargles
- Nasal solutions
- Ear drops
- Enemas
- Other externally used preparations

Classification of Solutions by Administration Route

- Oral Solutions
- Topical Solutions
- Oromucosal Solutions
- Rectal Solutions
- Ophtalmic, otic and nasal solutions
- Irrigation Solutions
- Inhalation Solutions
- Lens Solutions

Syrups

- Syrups are concentrated solutions of sugar in water or other aqueous liquids.
- Flavoring and active agents (±)
- Their density is always greater than one.
- Polyols such as glycerin and sorbitol are also added to the syrups to prevent crystallization, correct the taste and alter the solubility.

Sirupus Simplex (BP 2002)

Sugar		667 g
Purified water	q.s.	1000 g

Syrup (USP 27)

Sugar		850 g
Purified water	q.s.	1000 ml

Oramucosal solutions

- Oromucosal solutions are solutions that contain antiseptic, local anesthetic or astringent active agents and aromatic excipients which are applied in the oral cavity. They are simple or mixed, aqueous or concentrated solutions with good fragrance and flavor.

- Externally used for local effect. Their labels should indicate their preparation and administration (dilution, spreading, rinsing, mouthwash) information.

Mouthwashes

- Mouthwashes are aqueous solutions, often in concentrated form,, containing one or more active ingredients and excipients. In these preparations, alcohol, glycerin and water are generally used as solvents. The ideal pH should be between 6.5-7.0.

- Mouthwashes can be used for two purposes:
  - therapeutic
  - cosmetic.

- Therapeutic rinses or washes can be formulated to reduce plaque, gingivitis, dental caries, and stomatitis. Cosmetic mouthwashes may be formulated to reduce bad breath through the use of antimicrobial and/or flavoring agents.

- Antimicrobials
- Colorants
- Synthetic sweeteners
- Surfactants

Gargles

Gargles are aqueous solutions frequently containing antiseptics, antibiotics, and/or anesthetics used for treating the pharynx and nasopharynx by forcing air from the lungs through the gargle held in the throat; subsequently, the gargle is expectorated. Many gargles must be diluted with water prior to use.

- Antiseptic, antibiotic, anesthetic
- Colorants
- Synthetic sweeteners

Collutoire

- These preparations are locally applied on the lesions of oral or throat mucosa. Antiseptic and local anesthetic active agents are used.

- Solvent (glycerin, alcohol or water)
- Colorants
- Synthetic sweeteners

Rectal Solutions
Enemas

- Enamas are rectally administered preparations in aqueous or oily solution, emulsion or suspension form.
- Evacuation enemas: Enema preparations which are employed to evacuate the bowel
- Retention enemas: Enema preparations which are employed to influence the general system by absorption, or to affect a local disease. They may possess anthelmintic, nutritive, sedative, or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel.

Irrigation Solutions-Lavages

- Irrigation solutions are sterile, non-pyrogenic solutions used to wash or bathe surgical incisions, wounds, or body tissues. Because they come in contact with exposed tissue, they must meet stringent USP requirements for sterility, total solids, and bacterial endotoxins. These products may be prepared by dissolving the active ingredient in Water for Injection.

Inhalation solutions

- These are solutions used in the bronchial and nasal symptoms to provide comfort to the patient. Their effect can be local or systemic. They are administered via aerosols or nebulizers for inhalation. They are prepared in sterile water or sodium chloride solution and contain an inert, propellant gas.

Lens solutions

- Wetting solutions
- Cleaning solutions
- Disinfection solutions
- Storage solutions
- Artificial tear solutions
- Multi Purpose Solutions

Importance of Solubility in Pharmaceutical Technology

- **Formulation step**
- **In vivo performance:** Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response.
  - Eg: Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption
  - Since solutions are already dissolved, they do not need to undergo dissolution before being absorbed.