

CHAPTER 1

SOLUBILITY AND DISTRIBUTION PHENOMENON

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Objectives of the chapter

After completion of this lecture, the student should be able to -

1. Understand the various types of pharmaceutical solutions.
2. Define solubility, saturated & unsaturated solutions and polar & non polar solvents.
3. Describe complete & partial miscibility.
4. Understand the factors controlling the solubility of strong & weak electrolytes.
5. Define partition coefficient & its importance in pharmaceutical systems.

Importance of studying the phenomenon of solubility

Understanding the phenomenon of solubility helps the pharmacist to:

- ✓ Select the best solvent for a drug or a mixture of drugs.
- ✓ Overcome problems arising during preparation of pharmaceutical solutions.
- ✓ Have information about the structure and intermolecular forces of the drug.

Definitions –

1. True solution -

It is a mixture of two or more components that form a homogenous molecular dispersion.

The components are referred to the solute & the solvent.

2. Solute –

It is the dissolved agent (less abundant part of the solution).

3. Solvent:

It is the component in which the solute is dissolved (more abundant part of the solution).

4. A saturated solution:

It is one in which an equilibrium is established between dissolved and undissolved solute at a definite temperature.

5. An unsaturated solution (Sub saturated solution)-

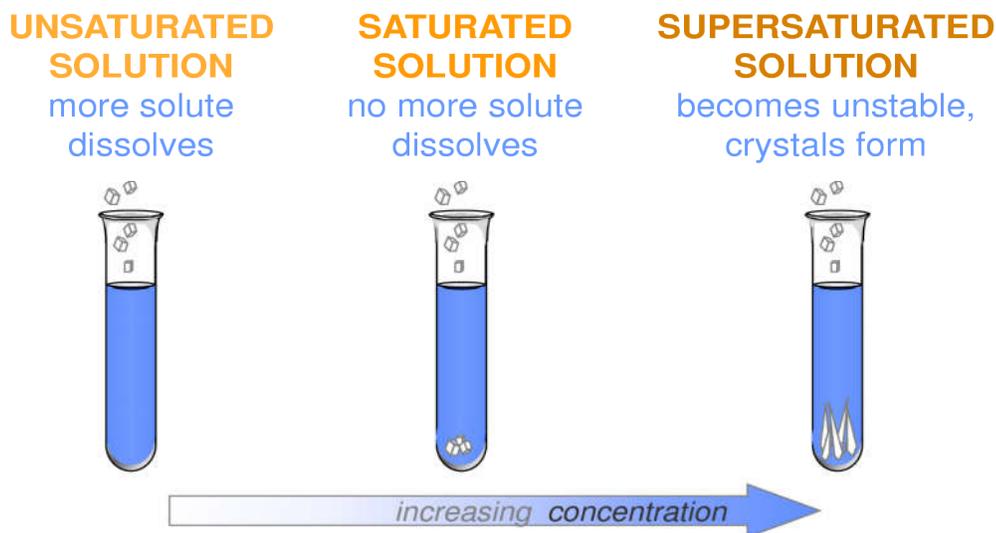
It is one containing the dissolved solute in a conc. below that necessary for complete saturation at a definite temperature.

6. A supersaturated solution-

It contains more of the dissolved solute than it would normally contain in a saturated state at a definite temperature. Some salts (eg. sod. thiosulfate) can be dissolved in large

amounts at an elevated temperature and, upon cooling fail to crystallize from the solution; these super saturated solutions can be converted to saturated ones by seeding the solution.

Solubility



7. Solubility:

In a quantitative way -

It is the concentration of solute in a saturated solution at a certain temperature.

In a qualitative way -

It is the spontaneous interaction of two - or more substances (solute & solvent) to form a homogeneous molecular dispersion.

Solubility expressions

1. The solubility of a drug / substance can be expressed in terms of
 - Molarity
 - Normality
 - Molality
 - Mole fraction
 - Percentage (% w/w, % w/v, % v/v).

2. The USP lists the solubility of drugs as the **number of ml of solvent** in which 1 g of solute will dissolve. E.g. 1g of boric acid dissolves in 18 mL of water, and in 4 mL of glycerin.
3. Substances whose solubility values are not known are described by the following terms,

Term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10 000 parts
Practically insoluble	More than 10 000 parts

Solute-Solvent interactions

- Solubility depends on chemical, electrical & structural effects that lead to mutual interactions between the solute and the solvent.
- In pre-or early formulation, selection of the most suitable solvent is based on the principle of “**like dissolves like**”. That is, a solute dissolves best in a solvent with similar chemical properties. i.e.
 - ✓ Polar solutes dissolve in polar solvents. E.g. **salts & sugar dissolve in water.**
 - ✓ Non polar solutes dissolve in non polar solvents. Eg. **naphthalene dissolves in benzene.**
- **To explain the above rule, consider the forces of attraction between solute and solvent molecules.**
 - ✓ If the solvent is **A** & the solute is **B**, and the forces of attraction are represented by **A-A**, **B-B** and **A-B**, one of the following conditions will occur,
 1. If **A-A >> A-B**: The solvent molecules will be attracted to each other & the solute will be excluded.
Example: Benzene & water, where benzene molecules are unable to penetrate the closely bound water aggregates.

2. If **B-B** \gg **A-A**: The solvent will not be able to break the binding forces between solute molecules.

Example: NaCl in benzene, where the NaCl crystal is held by strong electrovalent forces which cannot be broken by benzene.

3. If **A-B** \gg **A-A** or **B-B**: or the three forces are equal the solute will disperse & form a solution.

Example: NaCl in water.

Classification of solvents & their mechanism of action

Polar solvents:

- ✓ **Polar solvents** (water, glycols, methyl & ethyl alcohol), dissolve ionic solutes & other polar substances.
- ✓ Solubility of substances in polar solvents depends on **structural features**: Straight chain monohydroxy alcohols, aldehydes & ketones with \gg 5 C are slightly soluble in water.
- ✓ Branching of the carbon chain in aliphatic alcohols increases water solubility.

Tertiary butyl alcohol \gg soluble than n-butyl alcohol

- ✓ Polyhydroxy compounds as glycerin, tartaric acid, PEG are water soluble.

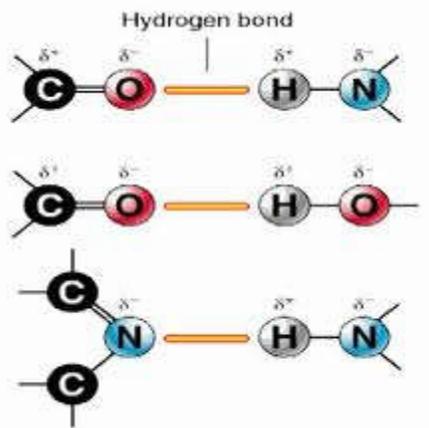
A polar solvent acts as a solvent according to the following mechanisms:

1. Dielectric constant:

Due to their high dielectric constant, polar solvents reduce the force of attraction between oppositely charged ions in crystals. Example: water possessing a high dielectric constant ($\epsilon = 80$) can dissolve NaCl, while chloroform ($\epsilon = 5$) & benzene ($\epsilon = 2$) cannot. Ionic compounds are practically insoluble in these 2 solvents.

2. Hydrogen bond formation:

Water dissolves phenols, alcohols and other oxygen & nitrogen containing compounds that can form hydrogen bonds with water.



3. Solvation through dipole interaction:

- Polar solvents are capable of solvating molecules & ions through dipole interaction forces.
- The solute must be polar to compete for the bonds of the already associated solvent molecules.

Example: Ion-dipole interaction between sodium salt of oleic acid & water

2. Non polar solvents

- ✓ **Non polar solvents** are unable to reduce the attraction between the ions due to their **low dielectric constants**.
- ✓ They are **unable to form hydrogen bonds** with non electrolytes.
- ✓ Non polar solvents can dissolve non polar solutes through **weak van der Waals forces**

Example: Solutions of oils & fats in carbon tetrachloride or benzene.

3. Semipolar solvents

- ✓ Semipolar solvents, such as ketones can induce a certain degree of polarity in non polar solvent molecules.
- ✓ They can act as **intermediate solvents** to bring about miscibility of polar & non polar liquids.

Example: **Acetone increases solubility of ether in water.**

TYPES OF SOLUTIONS

Solutions of pharmaceutical importance include:

1. Gases in liquids
2. Liquids in liquids
3. Solids in liquids

1. Solubility of gases in liquids

- ❖ Examples of pharmaceutical solutions of gases include: HCl, ammonia water & effervescent preparations containing CO₂ maintained in solution under pressure.
- ❖ The solubility of a gas in a liquid *is the concentration of dissolved gas when it is in equilibrium with some of the pure gas above the solution.*
- ❖ The solubility depends on the pressure, temperature, presence of salts & chemical reactions that sometimes the gas undergoes with the solvent

Factors affecting solubility of gases in liquids

1. Effect of pressure –

According to **Henry's law**:

$$C_2 = \sigma p$$

In a very dilute solution at constant temperature, the concentration (C₂) of dissolved gas is proportional to the partial pressure (p) of the gas above the solution at Equilibrium.

(The partial pressure = total pressure above the solution minus the vapor pressure of the solvent)

Caution: When the pressure above the solution is released (decreases), the solubility of the gas decreases, and the gas may escape from the container with violence. This phenomenon occurs in effervescent solutions when the stopper of the container is removed.

2. Effect of temperature

As the temperature increases the solubility of gases decreases, owing to the great tendency of the gas to expand.

Pharmaceutical application:

- ✓ The pharmacist should be cautious in opening containers of gaseous solutions in warm climates.

- ✓ A container filled with a gaseous solution or a liquid with high vapor pressure, such as ethyl nitrite, should be immersed in ice or cold water, before opening the container, to reduce the temperature and pressure of the gas.

3. *Effect of Salting out*

Adding electrolytes (NaCl) & sometimes non electrolytes (sucrose) to gaseous solutions (eg. carbonated solutions) induces liberation of gases from the solutions. **Why?**

Due to the attraction of the salt ions or the highly polar electrolyte for the water molecules and reduction of the aqueous environment adjacent to the gas molecules.

2. Solubility of liquids in liquids

Preparation of pharmaceutical solutions involves mixing of 2 or more liquids (alcohol & water to form hydroalcoholic solutions, volatile oils & water to form aromatic waters, volatile oils & alcohols to form spirits ...)

Liquid-liquid systems may be divided into 2 categories

1. Systems showing **Complete miscibility** such as alcohol & water, glycerin & alcohol, benzene & carbon tetrachloride

Complete miscibility occurs when - the adhesive forces between different molecules (A-B) \gg cohesive forces between like molecules (A-A or B-B).

2. Systems showing **Partial miscibility** as phenol and water; two liquid layers are formed each containing some of the other liquid in the dissolved state.

Partial miscibility results when: Cohesive forces of the constituents of a mixture are quite different, e.g. water (A) and hexane (B). A-A \gg B-B.

The non polar molecules (B) will be squeezed out by the powerful attractive forces existing between the molecules of the polar liquid.

The term miscibility refers to the mutual solubility of the components in liquid-liquid systems.

ALL THE BEST