لجنة عمداء كليات الصيدلة

لجنة توحيد منهاج مادة (Physical Pharmacy II)

Physical pharmacy II

المرحلة الثانية

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تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء . نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

Solubility is defined in **quantitative** terms as;

The concentration of solute in a saturated solution at a certain temperature,

and in a **qualitative** way, it can be defined as;

The spontaneous interaction of two or more substances to form a homogeneous molecular dispersion

Solutions and Solubility

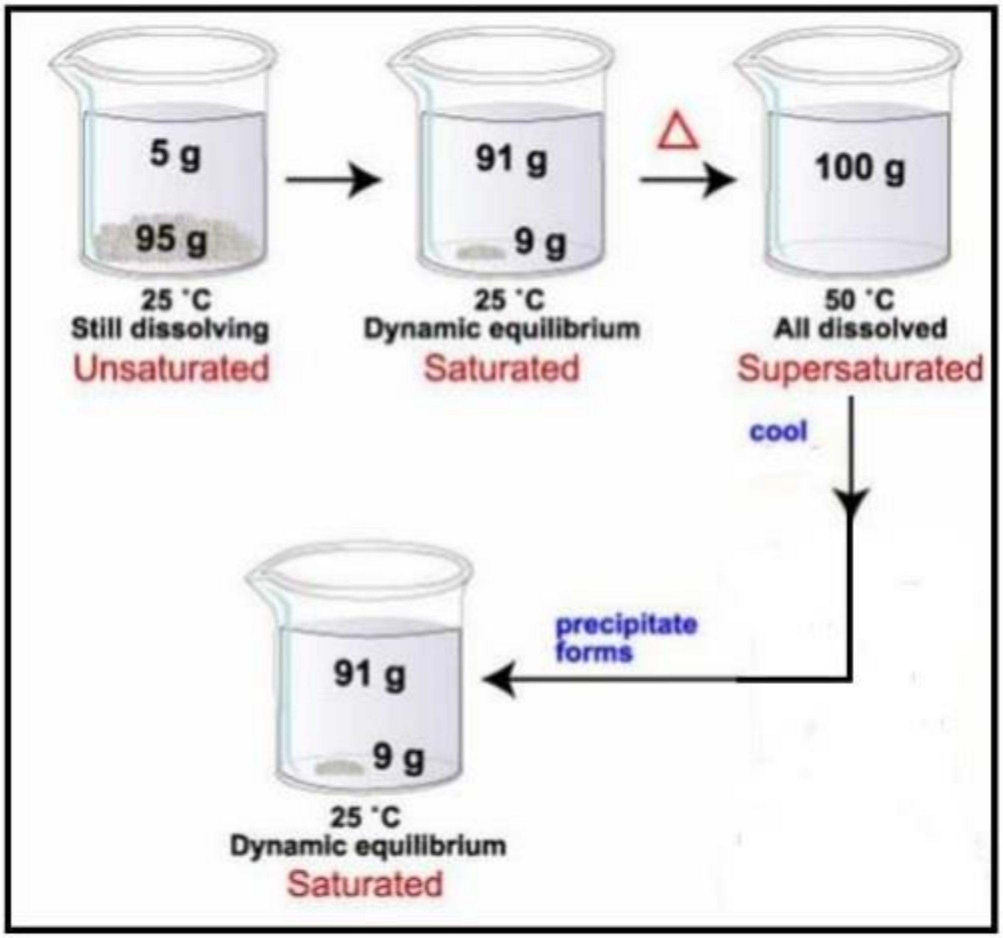
1- A **saturated solution** is one in which the solute in solution is in equilibrium with the solid phase.

2- An **unsaturated** or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

3- A **supersaturated solution** is one that contains more of the dissolved solute than it would normally contain at a definite temperature, were the undisclosed solute present.

Example: If we now slowly cool the mixture back to 25 °C, 9 g of glucose should precipitate from solution. Sometimes this happens immediately, but sometimes it takes a while for the glucose molecules to find their positions in a solid structure.

In the time between the cooling of the solution and the formation of glucose crystals, the system has a higher amount of dissolved glucose (100 grams) than is predicted by the solubility limit at 25 °C (91 grams). Because the solution contains more dissolved solute than is predicted by the solubility limit, we say the solution is ***supersaturated***.



Some salts e.g. (sod thiosulfate) can be dissolved in large amounts at an elevated temperature and, upon cooling fail to crystallize from the solution (***supersaturated***).

Factors affecting solubility

1-physical and chemical properties of the solute and the solvent

2- Temperature of the solution

3- Pressure above the solution

4- pH of the solution

5- State of subdivision of the solute

Solubility Expressions

The solubility of a drug may be expressed in a number of ways.

a) The solubility of a drug can be expressed in terms of:

- Molarity
- Normality
- Molality
- Mole fraction

-percentage (% w/w, % w/v, % v/v)

b) The United States Pharmacopeia (USP) 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.

c) The United States Pharmacopeia (USP) USP uses general description of substances solubility by the following terms:

Solubility Definition	Parts of Solvent Required for One Part of Solute
Very soluble (VS)	<1
Freely soluble (FS)	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble (SPS)	From 30 to 100
Slightly soluble (SS)	From 100 to 1000
Very slightly soluble (VSS)	From 1000 to 10,000
Practically insoluble (PI)	>10,000

Solute-Solvent interactions

Solute molecules are held together by certain intermolecular forces (dipole-dipole, induced dipole-induced dipole, ion-ion, etc.), as are molecules of solvent. In order for dissolution to occur, these cohesive forces of like molecules must be broken and adhesive forces between solute and solvent must be formed.

The solubility of a drug in a given solvent is largely a function of the polarity of the solvent.

The dielectric constant (Ɛ) of a compound is an index of its polarity which indicates the ability of solvent to separate two oppositely charged ions. A series of solvents of increasing polarity will show a similar increase in dielectric constant.

Solvent	**Dielectric Constant of Solvent, ε (Approximately)**	
Water	80	Decreasing Polarity
Glycols	50	↓
Methyl and ethyl alcohols	30	
Aldehydes, ketones, and higher alcohols, ethers, esters, and oxides	20	
Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	5	
Mineral oil and fixed vegetable oils	0	

- **-** Solubility depends on chemical, electrical & structural effects that lead to interactions between the solute and the solvent.

- The 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. E.g**. naphthalene dissolves in benzene.**

Classification of solvents& their mechanism of action

1-Polar, 2- nonpolar, and 3- semipolar solvents

1 - 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:**

1- The ratio of the polar to the nonpolar groups of the molecule

2-Straight chain monohydroxy alcohols, aldehydes & ketones with **>> 5 C** are slightly soluble in water.

3-Branching of the carbon chain in aliphatic alcohols increases water solubility.

Tertiary butyl alcohol >> **soluble than n-butyl alcohol**

4- Polyhydroxy compounds as glycerin, tartaric acid, PEG are water soluble (additional polar groups are present in the molecule).

1. Polar solvent acts as a solvent according to the following mechanisms**:**

A) 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 (> = 80) can dissolve NaCl, while chloroform (> = 5) & benzene (> = 2) cannot. Ionic compounds are practically insoluble in these 2 solvents.

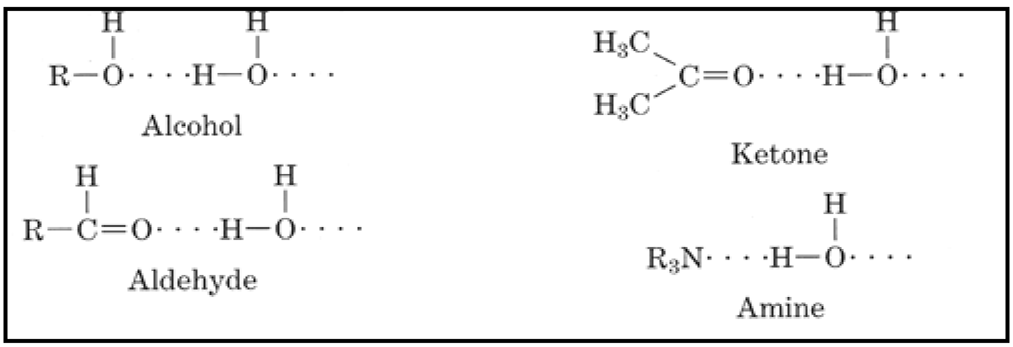
B) Solvation through dipole interaction:

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

C) Hydrogen bond formation: Water dissolves phenols, alcohols and other oxygen & nitrogen containing compounds that can form hydrogen bonds with water.



D) Acid-base reaction: Polar solvents break covalent bonds of strong electrolyte by acid-base reaction because these solvents are amphiprotic

$$HCl + H_2O \longrightarrow H_3O^+ + Cl^-$$

2. Non polar solvents

Non polar solvents such as hydrocarbon are:

1- unable to reduce the attraction between the ions due to their **low dielectric constants**.

2-They are **unable to form hydrogen bonds** with non electrolytes.

3- Cannot break the covalent bond

4- 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:

I- Gases in liquids

II- Liquids in liquids

III- Solids in liquids

I-Solubility of gases in liquids

- Examples of pharmaceutical solutions of gases include: HCl, ammonia water & effervescent preparations containing CO_2 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

1. Effect of pressure

According to **Henry's law:**

In a very dilute solution at constant temperature, the concentration (C_2) of dissolved gas is proportional to the partial pressure (*p*) of the gas above the solution at Equilibrium. (The partial pressure of the gas = total pressure above the solution minus the vapor pressure of the solvent)

$$C_2 \propto p$$

$$C_2 = \sigma p$$

where C_2 is the concentration of dissolved gas in gram/l of solvent,

p is the partial pressure of the undissolved gas above the solution,

σ is proportionality constant (solubility coefficient)

Note: 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.

Example

a- if 0.016 g O_2 dissolves in 1 liter of water at 25°C and at O_2 pressure of 300 mmHg, calculate the solubility coefficient.

$$C2= \sigma p$$

$$\sigma = \frac{C2}{p} = \frac{0.016 g/l}{300 mmHg} = 5.33 \times 10^{-5} \text{ (g/l)/mmHg}$$

b- How many grams of O_2 can be dissolved in 250ml of aqueous solution when the total pressure above the mixture is 760 mmHg? The partial pressure above the O_2 in solution is 0.263 atm and the temperature is 25° C

1 atm= 760 mmHg, so 0.263 atm x 760= 199.88 mmHg

$C2= \sigma p$

$C2= 5.33 \times 10^{-5}$ (g/l)/mmHg x (0.263 x 760) mmHg

= 0.0107 g/l

=0.0027 g/250ml

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 (E.g. 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.

II- 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 …)