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

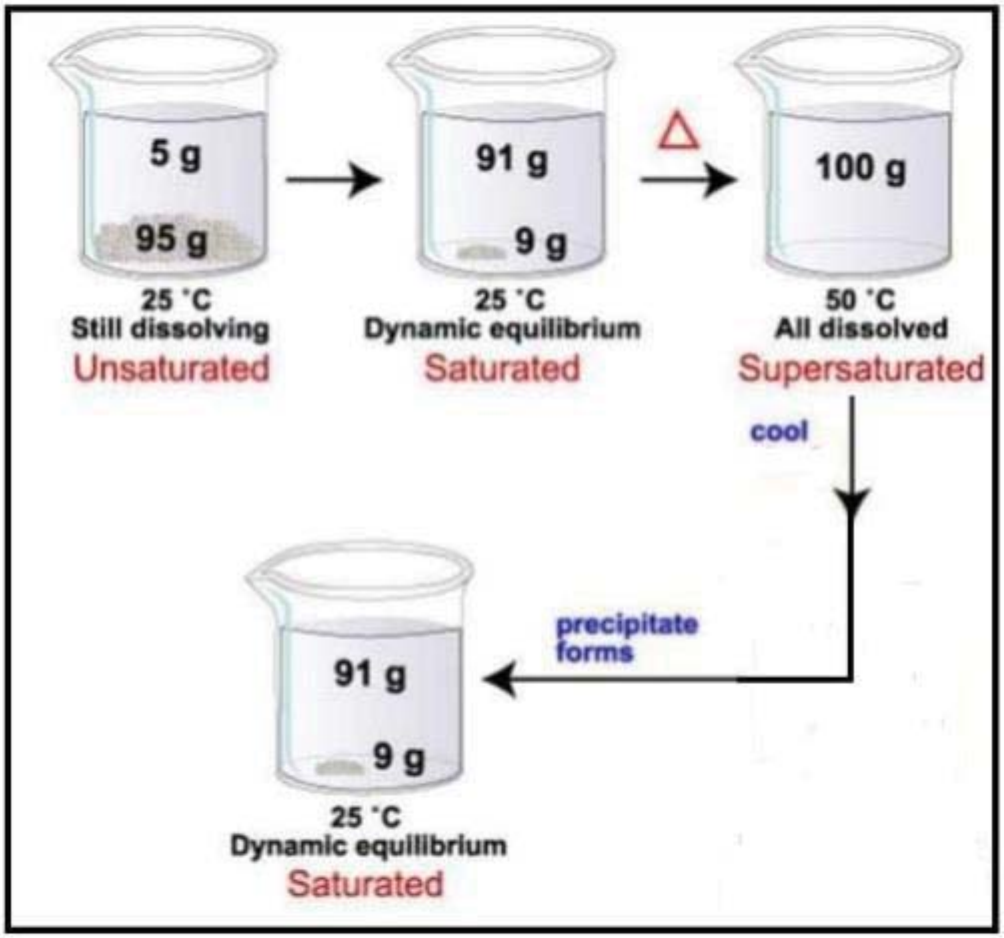
1- A **saturated solution** is one in which the solute in solution is in equilibrium with the solid phase.

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.

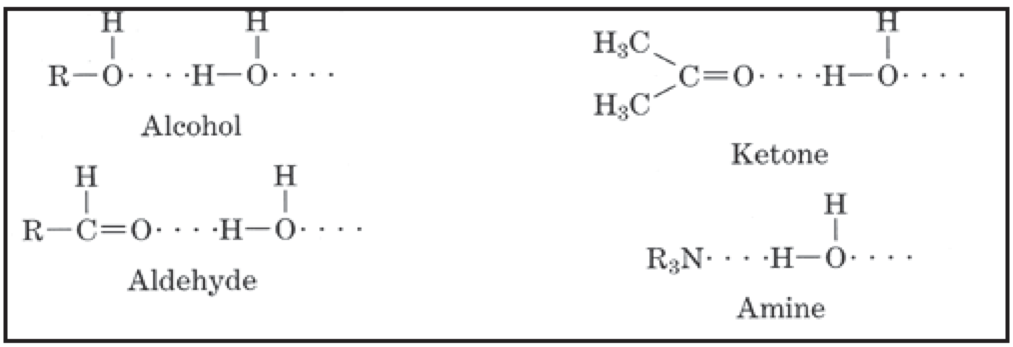
B) Solvation through dipole interaction:

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)

<u>Note</u>: 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 …)

Ideal and Real Solutions

-Ideal solution when the components of solution obey Raoult's law (adhesive forces =cohesive forces)

-Real Solutions when the components of solution not obey Raoult's law and are of two types:

a- Negative deviated (adhesive forces >>cohesive forces)

Negative deviations lead to increased solubility

b- Positive deviations (cohesive forces >>cohesive forces)

Positive deviations, leading to decreased solubility

The attractive cohesive forces, which may occur in gases, liquids, or solids, are called **internal pressures**.

- Liquid-liquid systems may be divided into 2 categories:

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

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.

Complete miscibility occurs when: The adhesive forces between different molecules (A-B) >>cohesive forces between like molecules (A-A or B-B).

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

Influence of Foreign Substances

If the added material is soluble in only one of the two components, the mutual solubility of the liquid pair is decreased.
Example, if naphthalene is added to a mixture of phenol and water, it dissolves only in the phenol, the miscibility is decreased.
If potassium chloride is added to a phenol-water mixture, it dissolves only in water and decreases the miscibility.
If the added material is soluble in both of the liquids, the mutual solubility of the liquid pair is increased.

Example, The addition of succinic acid or sodium oleate to a phenol-water system increases the mutual solubility.
The increase in mutual solubility of two partially miscible solvents by another agent is ordinarily referred to as **blending.**

SOLUBILITY OF SOLIDS IN LIQUIDS

Systems of solids in liquids include the most important type of pharmaceutical solutions.

There is ideal and real (non ideal) solution of solids

Ideal solution of solids

The solubility of a solid in an ideal solution depends on

1- Temperature, (direct relationship)

2- Melting point of the solid, (inverse relationship)

3- Molar heat of fusion, ΔH_f,

(The heat absorbed when the solid melts). In an ideal solution the heat of solution is equal to the heat of fusion, which is assumed to be a constant independent of the temperature.

Note:- Ideal solubility is not affected by the nature of the solvent.

The equation derived from thermodynamic considerations for an ideal solution of a solid in a liquid is

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right)$$

where;

X_2^i is the ideal solubility of the solute expressed in mole fraction,
T_o is the melting point of the solid solute in absolute degrees, and
T is the absolute temperature of the solution.
- At temperatures above the melting point, the solute is in the liquid state, and, in an ideal solution, the liquid solute is miscible in all proportions with the solvent. Therefore, the above equation no longer applies when $T > T_o$

EXAMPLE 10-7

What is the solubility of naphthalene at 20°C in an ideal solution? The melting point of naphthalene is 80°C and the molar heat of fusion is 4500 Cal/mole. R=1.987 Cal/mole .k

$$-\log X_2^i = \frac{4500}{2.303\ x\ 1.987}\left(\frac{353-293}{293x353}\right)$$
$X_2^i = 0.27$

Homework: calculate the solubility at 10 and 75 °C? You will see that the solubility increases as the temperature increased

Q12. The m.p and molar heat of fusion of three indomethacin polymorphs I, II, VII are:

polymorph	m.p °C(K)	ΔH_f Cal/mole	X_2^i
I	158(431)	9550	0.0069
II	153(426)	9700	0.0073
VII	95(368)	2340	0.4716

Calculate the ideal mole fraction solubility at 25 °C (298) three indomethacin polymorphs and rank the solubility in decreasing order, is the m.p or ΔH_f more useful in ordering the solubility.

According to m.p VII >II> I

According to ΔH_f VII >I> II

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right)$$

For I: $-\log X_2^i = \frac{9550}{2.303\ x\ 1.987}\left(\frac{431-298}{298x431}\right)$

$X_2^i = 0.0069$

For II: $-\log X_2^i = \frac{9700}{2.303\ x\ 1.987}\left(\frac{426-298}{298x426}\right)$

$X_2^i = 0.0073$

For VII: $-\log X_2^i = \frac{2340}{2.303\ x\ 1.987}\left(\frac{368-298}{298x368}\right)$

$X_2^i = 0.4716$

According to the solubility VII>II>I, so as the m.p increases, the solubility decreased

Non ideal Solutions

In non ideal solutions, the electrostatic and intermolecular forces should be considered.

The activity of a solute in a solution is expressed as the concentration multiplied by the activity coefficient. When the concentration is given in mole fraction, the activity is expressed as

$$a_2 = X_2\gamma_2$$

where γ_2 on the mole fraction scale is known as the rational activity coefficient. Converting to logarithms, we have

$$\log a_2 = \log X_2 + \log \gamma_2$$

In an ideal solution, $a_2 = X_2^i$ because $\gamma_2 = 1$, and, accordingly, the ideal solubility equation can be expressed in terms of activity as

$$-\log a_2 = -\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right)$$

By combining the 2 equations, we find that the mole fraction solubility of a solute in a nonideal solution expressed in log form, becomes

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right) + \log \gamma_2$$

Therefore, the mole fraction solubility in various solvents can be expressed as the sum of two terms: the solubility in an ideal solution and the logarithm of the activity coefficient of the solute.

As a real solution becomes more ideal, γ_2 approaches unity, the equation returns

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right)$$

Q18. the mole fraction solubility of naphthalene (nonpolar solute) in different solvents at temperature 40 °C (313 k), m.p 80°C(353k), ΔH_f =4500 cal/mole. Calculate the γ_2 and find the relationship between X_2 and γ_2.

X_2 for chlorobenzen(nonpolar solvent)= 0.444, for water = 1.76 x10^{-5}

For chlorobenzen

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T0-T}{TT0}\right) + \log \gamma_2$$

-log 0.444= $\frac{4500}{2.303x1.987}\left(\frac{353-313}{313x353}\right)$ + log γ_2

γ_2= 0.99

For water

-log 1.76 x10^{-5}= $\frac{4500}{2.303x1.987}\left(\frac{353-313}{313x353}\right)$ + log γ_2

γ_2= 25003

So there is inverse relationship between X_2 and γ_2