

Brownian Movement

SEDIMENTATION



Colloidal Dispersions I

Forth Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
2022 - 2023

Dr . Anmar Ghanim Taki Alaaraj

Reference : Sinko, Patrick J. Martin's Physical Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 5th Edition 2006

2 . Colloidal Dispersions

Chapter Objectives

- 1 .Dispersed system.
- 2 . Classification of dispersed system according to particle size.
- 3 . Types of colloidal dispersions.
- 4 . Kinetic properties of colloids.
- 5 . Thermally induced (Brownian , diffusion (Fick's first law) , osmosis).
- 6 . Gravitationally induced(sedimentation (Stock's law) ,).
- 7 . Viscosity (definition , Einstein equation and viscosity coefficients and calculation of molecular weight of the colloid).
- 8 . Electrically induced motion.

Dispersed Systems

Dispersed systems consist of particulate matter, known as the *dispersed phase*, distributed throughout a *continuous or dispersion medium*. The dispersed material may range in size from particles of atomic and molecular dimensions to particles whose size is measured in millimeters. Accordingly, a convenient means of classifying dispersed systems is on the basis of the mean particle diameter of the dispersed material. Based on the size of the dispersed phase, three types of dispersed systems are generally considered:

- 1 . *molecular* dispersions
- 2 . *colloidal* dispersions
- 3 . *coarse* dispersions.

The size ranges assigned to these classes, together with some of the associated characteristics, are shown in table. There being no distinct transition between either molecular and colloidal dispersions or colloidal and coarse dispersions

For example, certain *macro* (i.e., large) molecules, such as the polysaccharides, proteins, and polymers in general, are of sufficient size that they may be classified as forming both molecular and colloidal dispersions. Some suspensions and emulsions may contain a range of particle sizes such that the smaller particles lie within the colloidal range, whereas the larger ones are classified as coarse particles.

Classification of Dispersed Systems Based on Particle

Class	Particle Size*	Characteristics of System	Examples
Molecular dispersion	Less than 1 nm	Invisible in electron microscope Pass through ultrafilter and semipermeable membrane Undergo rapid diffusion	Oxygen molecules, ordinary ions, glucose
Colloidal dispersion	From 1 nm to 0.5 μm	Invisible in electron microscope Pass through filter paper Do not pass semipermeable membrane Diffuse very slowly	Colloidal silver sols, natural and synthetic polymers, cheese, butter, jelly, paint, milk, shaving cream, etc.
Coarse dispersion	Greater than 0.5 μm	Visible under microscope Do not pass through normal filter paper Do not dialyze through semipermeable membrane Do not diffuse	Grains of sand, most pharmaceutical emulsions and suspensions, red blood cells

* 1 nm (nanometer) = 10^{-9} m; 1 μm (micrometer) = 10^{-6} m.

Colloidal Systems

All kinds of dispersed phases might form colloids in all possible kinds of media, except for a gas–gas combination. Because all gases mix uniformly at the molecular level, gases only form solutions with each other. Colloidal systems are best classified into three groups (lyophilic, lyophobic, and association) on the basis of the interaction of the particles, molecules, or ions of the dispersed phase with the molecules of the dispersion medium

Lyophilic Colloids

Systems containing colloidal particles that interact to an appreciable extent with the dispersion medium (solvent-loving) colloids (*in which the dispersed phase or the particles have a very strong affinity with the liquid*). Owing to their affinity for the dispersion medium, such materials form colloidal dispersions, or *sols*, with relative ease. (*sol, a colloid (aggregate of very fine particles dispersed in a continuous medium) in which the particles are solid and the dispersion medium is fluid. If the medium is water, the colloid may be called a hydrosol; and if air, an aerosol.*).

The various properties of colloids are due to the attraction between the dispersed phase and the dispersion medium, which leads to *solvation*, the attachment of solvent molecules to the molecules of the dispersed phase. Most lyophilic colloids are organic molecules, for example, gelatin, acacia, insulin, albumin, rubber, and polystyrene, the first four produce lyophilic colloids in aqueous dispersion media (hydrophilic sols). Rubber and polystyrene form lyophilic colloids in no aqueous, organic solvents.

A material that forms a lyophilic colloidal system in one liquid (e.g., water) may not do so in another liquid (e.g., benzene).

lyophobic colloids

The second class of colloids is composed of materials that have little attraction, if any, for the dispersion medium. These are the *lyophobic* (solvent-hating) colloids and, predictably, their properties differ from those of the lyophilic colloids. This is primarily due to the absence of a solvent cover around the particle. Lyophobic colloids are generally composed of inorganic particles dispersed in water. Examples of such materials are gold, silver, sulfur, arsenous sulfide, and silver iodide.

association colloids

The third class of colloids is the associated colloids are usually formed by surfactants (surface active agents) like soaps and synthetic detergents. The molecules of soaps and detergents are smaller than the colloidal particles

Types of Colloidal Dispersions*

Dispersion Medium	Dispersed Phase	Colloid Type	Examples
Solid	Solid	Solid sol	Pearls, opals
Solid	Liquid	Solid emulsion	Cheese, butter
Solid	Gas	Solid foam	Pumice, marshmallow
Liquid	Solid	Sol, gel	Jelly, paint
Liquid	Liquid	Emulsion	Milk, mayonnaise
Liquid	Gas	Foam	Whipped cream, shaving cream
Gas	Solid	Solid aerosols	Smoke, dust
Gas	Liquid	Liquid aerosols	Clouds, mist, fog

* A gas in a gas always produces a solution.

Kinetic Properties of Colloids

The motion may be thermally induced (Brownian movement, diffusion, osmosis), **gravitationally induced** (sedimentation), or applied externally (viscosity).

Brownian Motion

describes the **random movement of colloidal particles**. The erratic motion, **which may be observed with particles as large as about 5 μm** . The motion of the molecules **cannot be observed**, of course, because the molecules are too small to see. The velocity of the particles **increases with decreasing particle size**. **Increasing the viscosity of the medium**, which may be accomplished **by the addition of glycerin or a similar agent**, **decreases and finally stops the Brownian movement**.

Diffusion

Particles diffuse spontaneously **from a region of higher concentration to one of lower concentration** until the concentration of the system is **uniform throughout**. Diffusion is a **direct result of Brownian movement**. Brownian motion is the movement of the particle not in a fixed direction while in diffusion the particle moves in the direction of high concentration to low concentration. Brownian motion of all particles in a sample which, over time, causes diffusion.

When the molecules of a solute diffuse through a medium containing large colloidal particles, which absorb the diffusing molecules, the latter are transported in the diffusion flow not as free molecules, but as absorption compounds: solute+colloid. *Colloidal particles diffuse more rapidly than crystalloid particles in solution.*

Diffusion is an important process for living things - it is how substances move in and out of cells.

Diffusion occurs in **liquids and gases** when their particles collide randomly and spread out.

Types of diffusion

- Simple diffusion is when ions or molecules diffuse from an area of high concentration to an area of low concentration.
- In osmosis, the particles moving are water molecules.
- Facilitated diffusion is a selective process, i.e., the membrane allows only selective molecules and ions to pass through it. It, however, prevents other molecules from passing through the membrane.

According to Fick's first law, the amount, dq , of substance diffusing in time, dt , across a plane of area, S , is directly proportional to the change of concentration, dc , with distance traveled, dx . , Fick's law is written as

$$dq = -DS \frac{dc}{dx} dt \quad \dots\dots\dots (1)$$

D is the *diffusion coefficient*, the amount of material diffusing per unit time across a unit area , when dc/dx , called the *concentration gradient*, is unity. D thus has the dimensions of *area per unit time*.

If the colloidal particles can be assumed to be approximately spherical, the following equation, can be used to obtain the radius of the particle and the particle weight :

$$D = KT / 6\pi\eta r$$

or , $D = RT / 6\pi\eta rN \dots\dots\dots (2)$

where D is the diffusion coefficient obtained from Fick's law as already explained, k is the Boltzmann constant, R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, r is the radius of the spherical particle, and N is Avogadro's number

From(1) and (2) allows us to formulate three main rules of diffusion:

- (a) the velocity of the molecules increases with decreasing particle size;
- (b) the velocity of the molecules increases with increasing temperature;
- (c) the velocity of the molecules decreases with increasing viscosity of the medium.

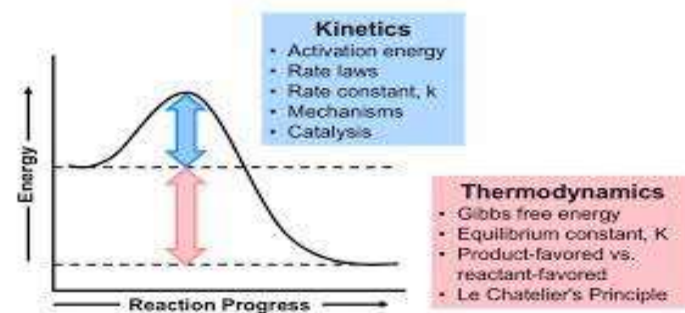
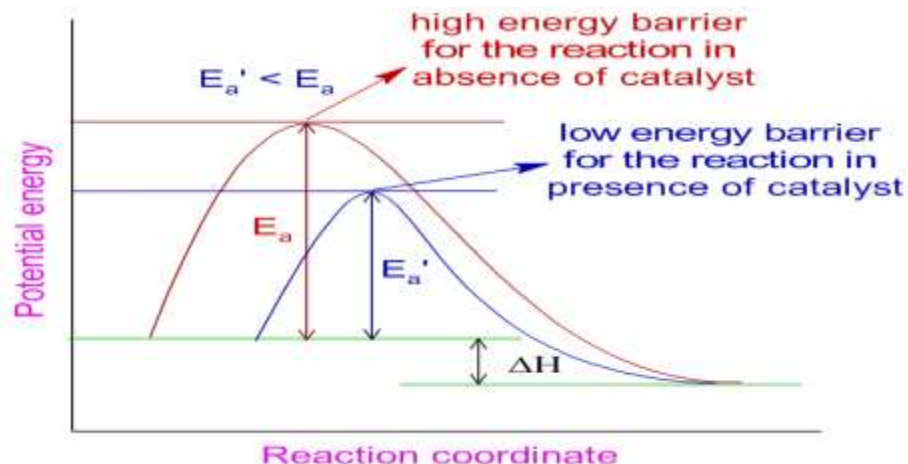
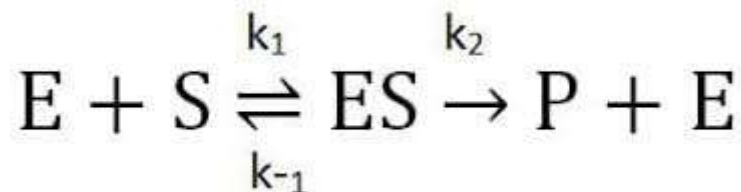


Kinetics III

Eighth Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
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Factors affect on stability

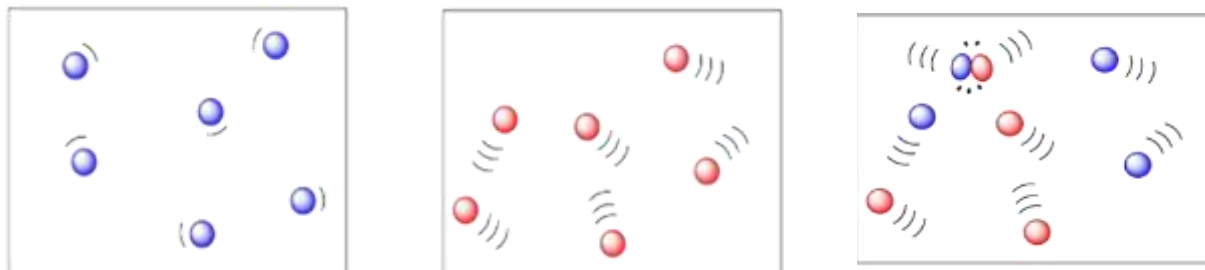
A number of factors other than concentration may affect the reaction velocity. Among these are **temperature**, **medium**, **catalysts**, and **light**.

1. Temperature effect Collision Theory

Reaction rates are expected to be proportional to the number of collisions per unit time.

Because the **number of collisions increases** as **the temperature increases**, the **reaction rate is expected to increase** with increasing temperature.

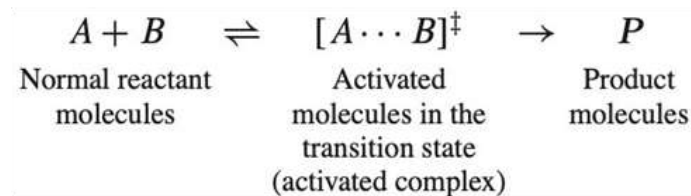
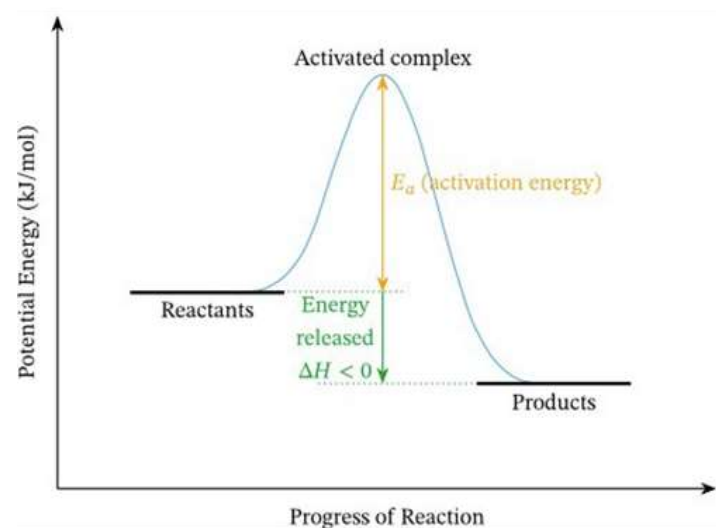
The speed of many reactions increases about **two to three** times with each **10** rise in temperature.



Transition-State Theory

*An alternative to the collision theory is the *transition-state theory or absolute rate theory*, according to which an equilibrium is considered to exist between the normal reactant molecules and an activated complex of these molecules.

*As a reaction proceeds from reactants to , the system must *pass through a state* whose energy is *greater* than that of the initial reactants. This “*barrier*” is what prevents the reactants from immediately becoming products.



The Arrhenius equation is used to describe mathematically the exponential relationship between rate constant and temperature

*The activation energy, E_a , is a measure of this barrier.

*The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius, k is the specific reaction rate,

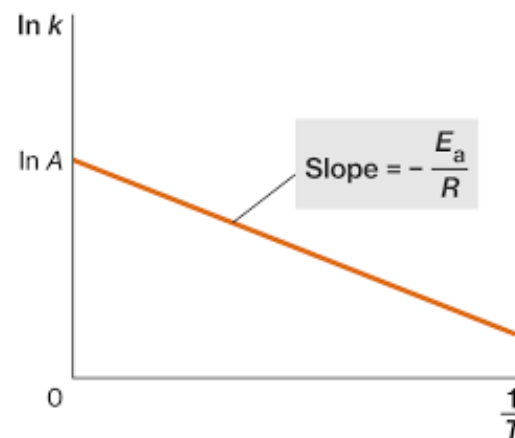
A is a constant known as the *Arrhenius factor* or the *frequency factor*,

E_a is the *energy of activation*,

R is the gas constant, 1.987 calories/deg mole,

T is the absolute temperature.

* A and E_a can be evaluated by determining k at several temperatures and plotting $1/T$ against $\log k$:



$$\log k = \log A - \frac{E_a}{2.303 R T} \quad \rightarrow \quad k = A e^{-E_a/RT}$$

*In case at 2 temperatures t_1 and t_2 , the equation becomes:

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303 R} \left(\frac{T_2 - T_1}{T_2 T_1} \right)$$

2 . Effects of medium

Effect of the Solvent

The influence of the solvent on the rate of decomposition of drugs is a *topic of great importance to the pharmacist*. Although the effects are complicated and generalizations, it appears that the reaction of nonelectrolytes is related to the *relative internal pressures or solubility parameters of the solvent and the solute*.

Influence of Dielectric Constant

The effect of the dielectric constant on the rate constant of an ionic reaction, is determined by the following equation

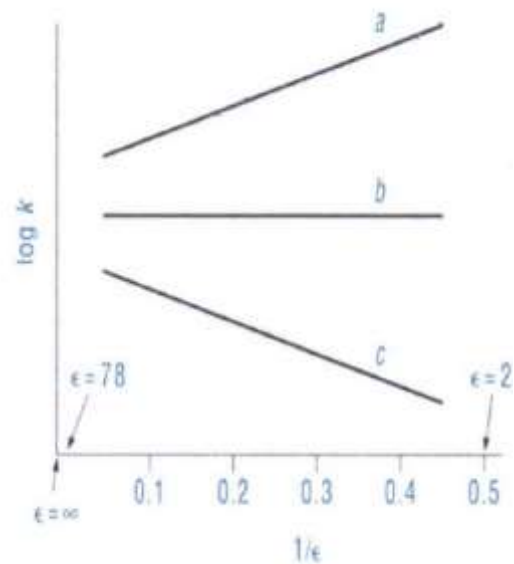
$$\log K = \log k_{\epsilon=\infty} - k Z_A Z_B / \epsilon$$

Where **k** is constant for a particular reaction at given temperature , **Z_A & Z_B** are the charge number of the two reacting ions and **$k_{\epsilon=\infty}$** is the rate constant in the theoretical solvent of infinite dielectric constant

a , ions opposite charge ,

b , ion and uncharged molecule and

c , ions of similar charge



Ionic strength

The equation which describes the influence of electrolyte on the rate constant is the Brønsted-Bjerrum equation

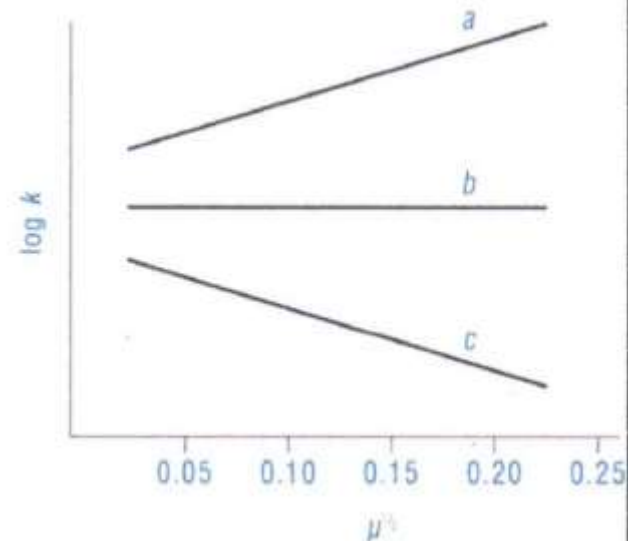
$$\text{Log } k = \log k_0 + 1.02 Z_A Z_B \sqrt{\mu}$$

Where Z_A & Z_B the charge number of the
Two interacting ions , and μ is the ionic strength

a , ions opposite charge

b , ion and uncharged molecule

c , ions of similar charge



where k_0 is the rate constant in an infinitely dilute solution in which $\mu = 0$. It follows from the equation above that a plot of $\log k$ against $\sqrt{\mu}$ should give a straight line with a slope of $1.02z_Az_B$. If one of the reactants is a neutral molecule, $z_Az_B = 0$, and the rate constant, as seen from equation, *should then be independent of the ionic strength in dilute solutions.*

3 . Catalysis

the rate of a reaction is frequently influenced by the presence of a catalyst. Although the hydrolysis of sucrose in the presence of water at room temperature proceeds with a decrease in free energy, the reaction is so slow as to be negligible. When the hydrogen ion concentration is increased by adding a small amount of acid, however, inversion proceeds at a measurable rate.

A catalyst is therefore defined as a substance that influences the speed of a reaction without itself being altered chemically. When a catalyst decreases the velocity of a reaction, it is called a *negative catalyst*.

Actually, negative catalysts often may be changed permanently during a reaction and should be called *inhibitors* rather than catalysts.

Because a catalyst remains unaltered at the end of a reaction, *it does not change the overall ΔG° of the reaction*, and, hence, according to the relationship. $\Delta G^\circ = -RT \ln K$

Catalytic action may be homogeneous or heterogeneous and may occur in either the gaseous or the liquid state. *Homogeneous catalysis occurs when the catalyst and the reactants are in the same phase.*

Presumably, the adsorption *weakens the bonds of the reactant molecules* and lowers the activation energy.

The activated molecules then can react, and *the products diffuse away from the surface*.

Catalysts may be *poisoned by extraneous substances* that are strongly adsorbed at the active centers of the catalytic surface where *the reactants would normally be held during reaction*. *Carbon monoxide* is known *to poison the catalytic action of copper in the hydrogenation of ethylene*.

Other substances, known as promoters(*substance that is usually mixed in small quantities with catalysts.*), are found to increase the activity of a catalyst. For example, *cupric ions promote the catalytic action of ferric ions in the decomposition of hydrogen peroxide*. The exact mechanism of promoter action is not understood, although the promoter is thought *to change the properties of the surface so as to enhance the adsorption of the reactants and thus increase the catalytic activity*

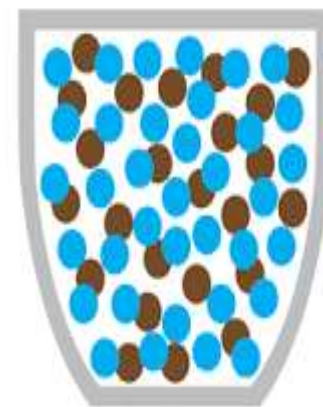
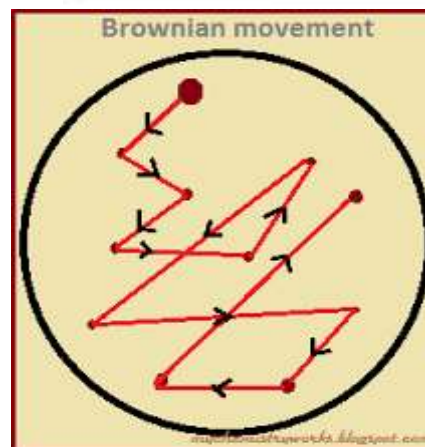
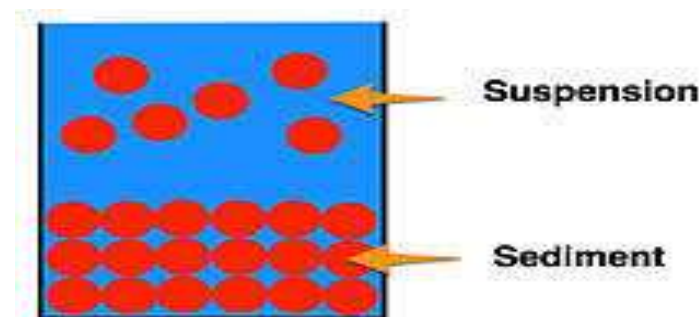
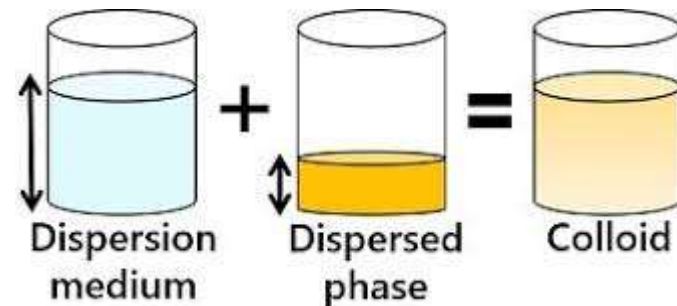
4. Effect of light

Most materials **absorb** some colors of light and **reflect** others, to varying extents, so that they are colored. Some materials will even absorb light of one color and re-emit light of another color, an effect **called fluorescence**. Exposure to light is a concern with numerous medications *due to the possibility for degradation or other chemical reactions* that affect drug stability.

The most obvious result of exposure to light is *reduced activity of the drug because of photodecomposition*. The effects due to the formation of photo degradation products during storage.

Tablets and pills made using direct compression containing light sensitive drugs should be *coated with a colored film* to *protect the product from light and prevent degradation*.

Some medicines contain components that may cause *photosensitivity*, a chemically induced change in the skin. Photosensitivity makes a person sensitive to sunlight and can cause sunburn-like symptoms, or other unwanted side effects.



Colloidal Dispersions II

Fifth Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
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Osmotic Pressure

Osmotic pressure is affected by *concentration and temperature*.

Concentration of solute and temperature each affect the amount of pressure created by the movement of water across a membrane. *Higher concentrations and higher temperatures increase osmotic pressure.*

Colloidal particles have a high molar mass so, their mole fraction is very less causing low colligative properties and hence, all colloidal dispersion give very low osmotic pressure and show very small freezing point depression or boiling point elevation

The osmotic pressure of colloidal solution represented as :

$$\text{Osmotic pressure}(\pi) = n \times C \times M \times R \times T$$

where: n is the number of particles into which the substance dissociates

C is the concentration in g/l. M is the M.wt of the molecules

The osmotic pressure, π , of a dilute colloidal solution is described by the van't Hoff equation: $\pi = CRT$ (1)

where C is molar concentration of solute. This equation can be used to calculate the molecular weight of a colloid in a dilute solution.

Replacing C_g/M instead of C in equation (1), in which C_g is the grams of solute per liter of solution and M is the molecular weight, we obtain

$$\pi = (C_g / M) RT \dots\dots\dots (2) \quad \text{Then} \quad \pi / C_g = RT / M \dots\dots\dots (3)$$

which applies in a very dilute solution. The quantity π/C_g for a polymer having a molecular weight of, say, 50,000 is often a linear function of the concentration, C_g , and the following equation can be written

$$\pi / C_g = RT(1/ M + BC_g) \dots\dots\dots (4)$$

where B is a constant for any particular solvent/solute system and depends on the degree of interaction between the solvent and the solute molecules. The term BC_g in equation (4) is needed because equation (3) holds only for ideal solutions, in other word, those containing low concentrations of spherocolloids. With linear lyophilic molecules, deviations occur because the solute molecules become solvated, leading to a reduction in the concentration of “free” solvent and an apparent increase in solute concentration. The role of B in estimating the asymmetry of particles and their interactions with solute

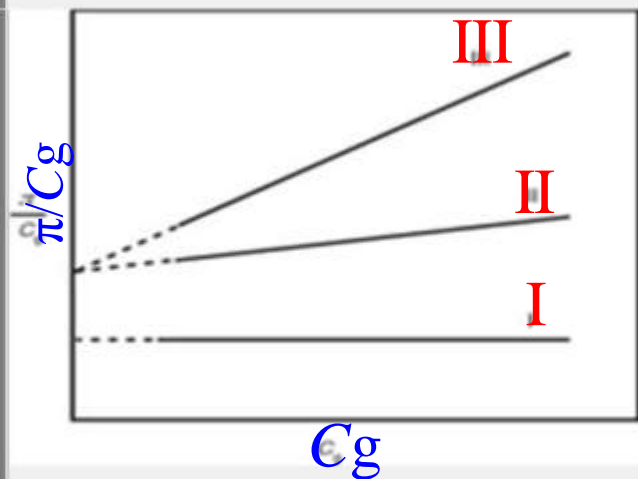


Fig. 2-2. Determination of molecular weight by means of the osmotic pressure method.

Extrapolation of the line to the vertical axis where $c_g = 0$ gives RT/M , from which M is obtained. Refer to text for significance of lines I, II, and III. Lines II and III are taken to represent two samples of a species of hemoglobin.

A plot of π/C_g against C_g generally results in one of three lines (Fig. 2-2), depending on whether the system is ideal (line I) or real (lines II and III). Equation (3) applies to line I and equation (4) describes lines II and III. The intercept is RT/M , and if the temperature at which the determination was carried out is known, the molecular weight of the solute can be calculated. In lines II and III, the slope of the line is B , the interaction constant. In line I, B equals zero and is typical of a dilute spherocolloidal system. Line III is typical of a linear colloid in a solvent having a high affinity for the dispersed particles. Such a solvent is referred to as a “good” solvent for that particular colloid.

Sedimentation

is the phenomenon that Brownian particles **reach a certain velocity** under the action of an **external field**. This translational velocity is referred to as *the sedimentation or settling velocity*. It is the process of allowing particles in suspension in water to precipitate of the suspension under the effect of **gravity**. Colloidal sediments can be classified into two distinct classes as **lypophilic** (i.e., liquid loving) and **lyophobic** (liquid-hating). Sedimentation is a separation method that is used to separate solid-liquid mixtures in which particle sizes vary from each other.

Factors that affect the sedimentation process include **the shape and size of particles, the density of particles, water temperature, particle charge, dissolved substances in the water.**

Suspensions are often used as a dosage form when the drug is **insoluble in water** and **when use of solubilizing agents is not possible**. Based on method of preparation, suspensions can be divided into two categories, **flocculated and deflocculated systems**. (*flocculation is the formation of flocs by the clumping of fine particles, whereas deflocculation is the dispersion of flocs to form a stable colloid*)

Colloids are dispersions of solid particles in a fluid. The particle size of the dispersed material is between 1 nm and 0.1 micrometer. This small size results in material which does not sediment under normal conditions. The material can be caused to sediment if put under the additional force generated in a centrifuge.

The velocity, v , of sedimentation of spherical particles having a density ρ in a medium of density ρ_0 and a viscosity η_0 is given by **Stokes's law**:

$$v = \frac{2r^2(\rho - \rho_0)g}{9\eta_0}$$

where g is the acceleration due to gravity. If the particles are subjected only to the force of gravity, then the lower size limit of particles obeying Stokes's equation *is about $0.5 \mu m$* .

This is **because** **Brownian movement becomes significant and tends to substitute sedimentation due to gravity and facilitates mixing instead.**

Therefore, a stronger force must be applied to produce the sedimentation of colloidal particles in **a quantitative and measurable method**

Viscosity

Viscosity is an expression of the resistance to flow of a system under an applied stress. The more viscous a liquid is, *the greater* is the applied force required to make it flow at *a particular rate*. The viscosity data can be used to obtain the molecular weight of material comprising the disperse phase .

Viscosity is the resistance of a fluid (liquid or gas) to a change in shape or movement of neighboring portions relative to one another. There are two types of viscosity: Dynamic viscosity and Kinematic viscosity. The viscosity of a liquid is related to the ease with which the molecules can move with respect to one another.

In general ,increase in temperature decreases viscosity. Increases in pressure increase viscosity in liquids. In water, it decreases whereas, in gases, it remains the same.

properties of viscosity

Viscosity is determined by the structural properties of the molecules.

- Raising the temperature reduces the viscosity of the solution or fluid.
- Viscosity would be a measurement of how components travel across one another.
- It is determined by the attraction between the molecules.

Liquids tend to become more viscous as the **molecules become larger**, or as the amount of intermolecular bonding increases. They become **less viscous** as the temperature **increases**.

viscosity is the bulk property which have direct dependence on **intermolecular forces in a liquid** and where as molecular weight is the measure of sum of atomic weight of atoms in a molecule. So **these two are related to each other**

solids have high viscosity because they cannot flow freely. Viscosity of liquids ranges from **low to high whereas gases have a low viscosity**.

The viscosity of the **sol is very low**, but The viscosity of the **gel is very high**, the viscosity of a liquid depends on the: strength of attractive forces between molecules, which depend on their **composition, size, and shape**.

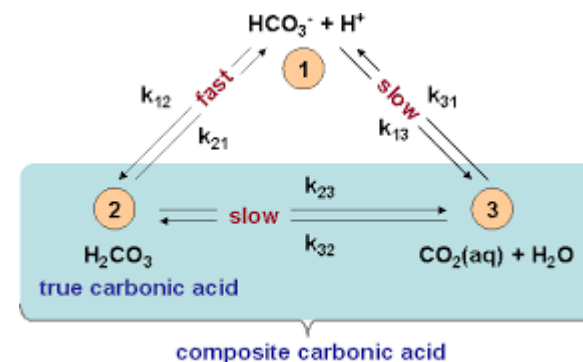
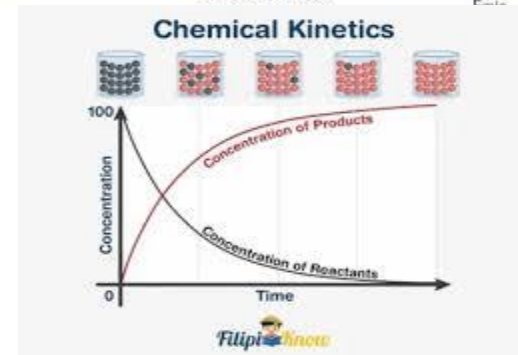
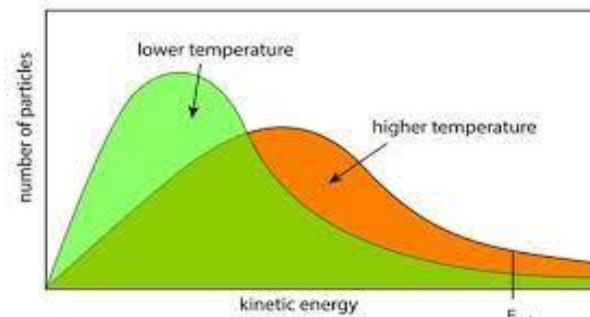


Kinetics II

Seventh Lecture

Physical Pharmacy – II
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First-Order Reactions

The **decomposition rate** of hydrogen peroxide catalyzed by 0.02 M KI was *proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time.*

The data for the reaction : $2\text{H}_2\text{O}_2 \longrightarrow 2\text{H}_2\text{O} + \text{O}_2$ (are given in Table 3-1)

Table 3-1 Decomposition of Hydrogen Peroxide at 25°C in Aqueous Solution Containing 0.02 m KI*

$t(\text{min})$	$a-x$	$K (\text{min}^{-1})$
0	57.90	-
5	50.40	0.0278
10	43.90	0.0277
25	29.10	0.0275
45	16.70	0.0276
65	9.60	0.0276
∞	0	-
*Based on H. S. Harned, J. Am. Chem. Soc. 40 , 1462, 1918.		



Although *two molecules* of hydrogen peroxide appear in the stoichiometric equation(**Theoretically**) as just written, the reaction was found to be first order. The rate equation is written as

$$-dc / dt = KC \quad \dots\dots\dots(3.7)$$

where **C** is the concentration of hydrogen peroxide remaining un decomposed at time t and k is the first- order velocity constant.

Integrating equation (3.7) between concentration C_0 at time $t = 0$ and concentration C at some later time, t , we have

$$\ln C - \ln C_0 = -K (t - 0)$$

$$\ln C = \ln C_0 - Kt \dots\dots\dots(3.8)$$

Converting to common logarithms yields :

$$\log C = \log C_0 - Kt / 2.303 \dots\dots(3.9)$$

$$\text{Or } K = (2.303 / t) \log (C_0 / C) \dots\dots(3.10)$$

In exponential form, equation (3.8) becomes :

$$C = C_0 10^{-Kt / 2.303} \dots\dots(3.11)$$

Equations (3.10) and (3.11) express the fact that, in a first-order reaction, the concentration decreases exponentially with time. As shown in Figure 3-1, the concentration begins at C_0 and decreases as the reaction becomes progressively slower. The concentration nearly approaches a final value c_∞ as time proceeds toward infinity.

Equation $K = (2.303 / t) \log (C_0 / C) \dots\dots(3.10)$ is often written as $K = (2.303 / t) \log (a / a-x) \dots\dots(3.12)$

where the symbol a is customarily used to replace C_0 , x is the decrease of concentration in time t , and $a - x = c$.

The specific reaction rates listed in Table 3-1 were calculated by using equation (3.12). Probably the best way to obtain an average k for the reaction is to plot the logarithm of the concentration against the time, as shown in Figure 3-2. The linear expression in equation(3.9)

$$\log C = \log C_0 - Kt / 2.303$$

shows that the slope of the line is $-k/2.303$, from which the rate constant is obtained. If a straight line is obtained, it *indicates that the reaction is first order*. Once *the rate constant is known*, the concentration of reactant remaining at a definite time can be computed .

First-order Reactions

- There is **no** constant **amount** decrease *per unit of time*.
- There is constant **rate** of decrease *per unite of time*.

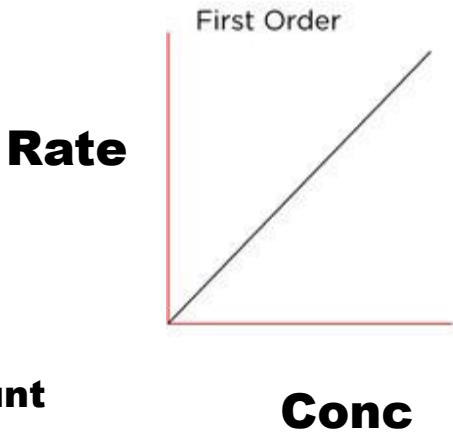
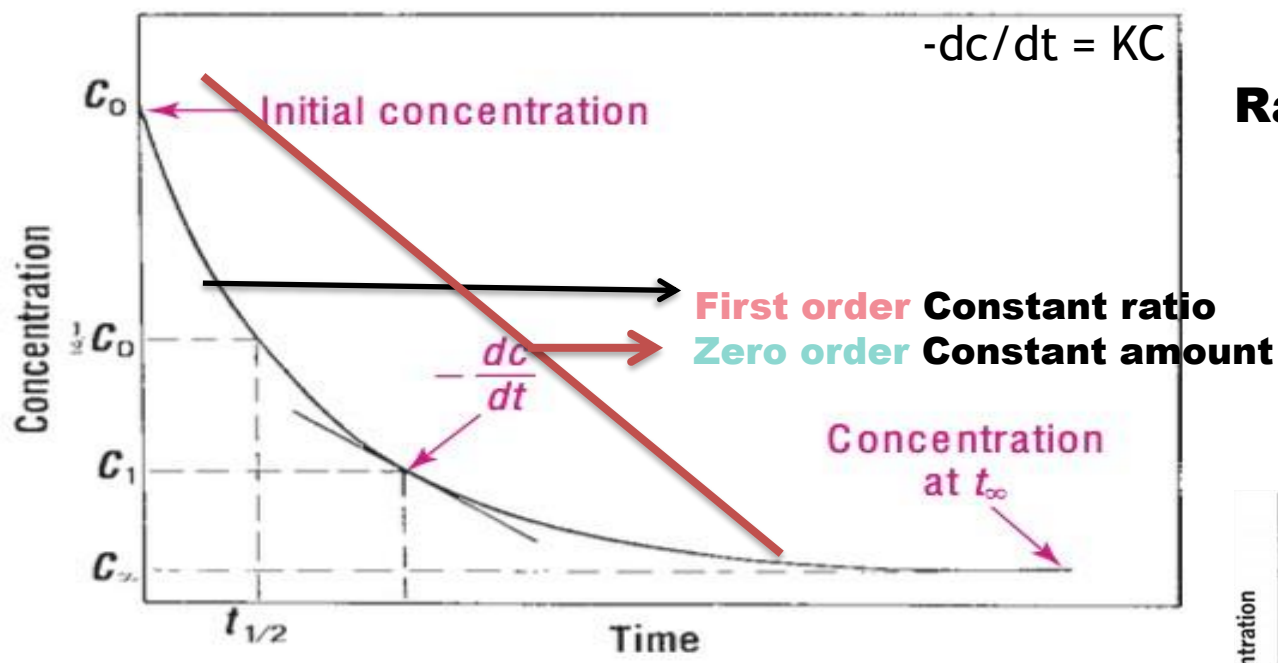


Fig. 3-1. Fall in concentration of a decomposing drug with time. In addition to C_0 and C_∞ , $\frac{1}{2}C_0$ and the corresponding time, $t_{1/2}$, are shown. The rate of decrease of concentration with time, $-dC/dt$, at an arbitrary concentration, C_1 , is also shown.

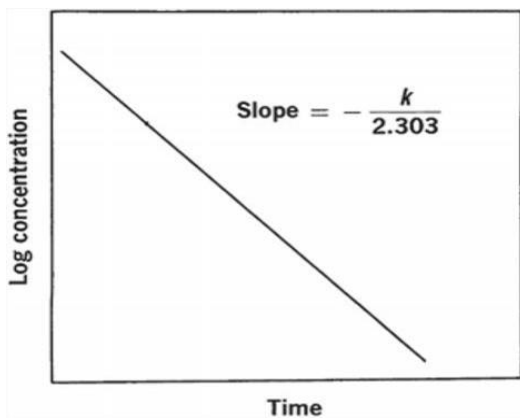
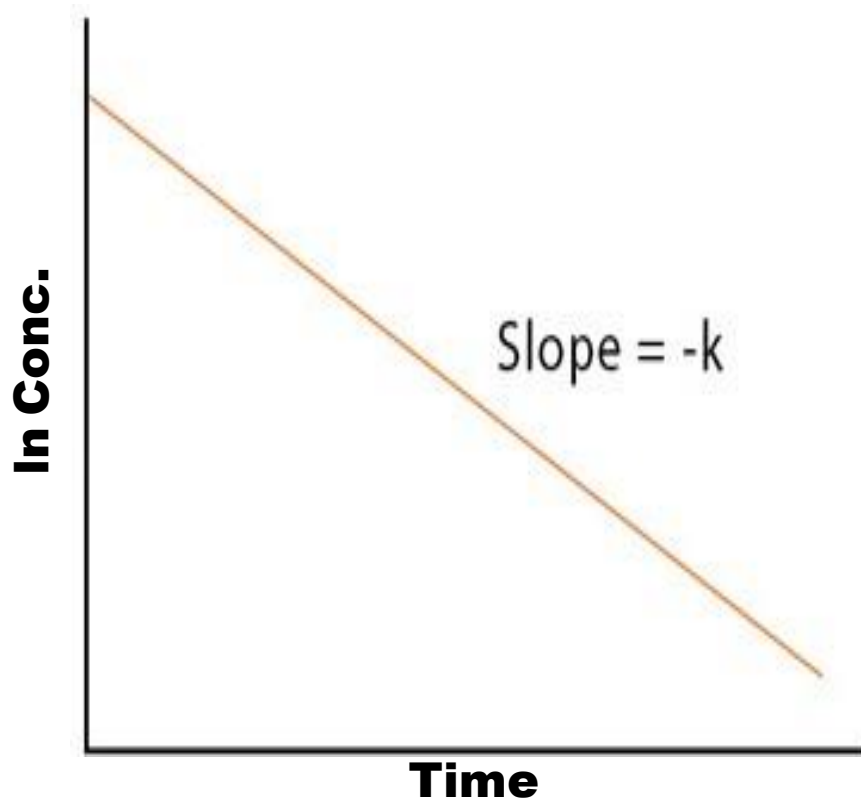
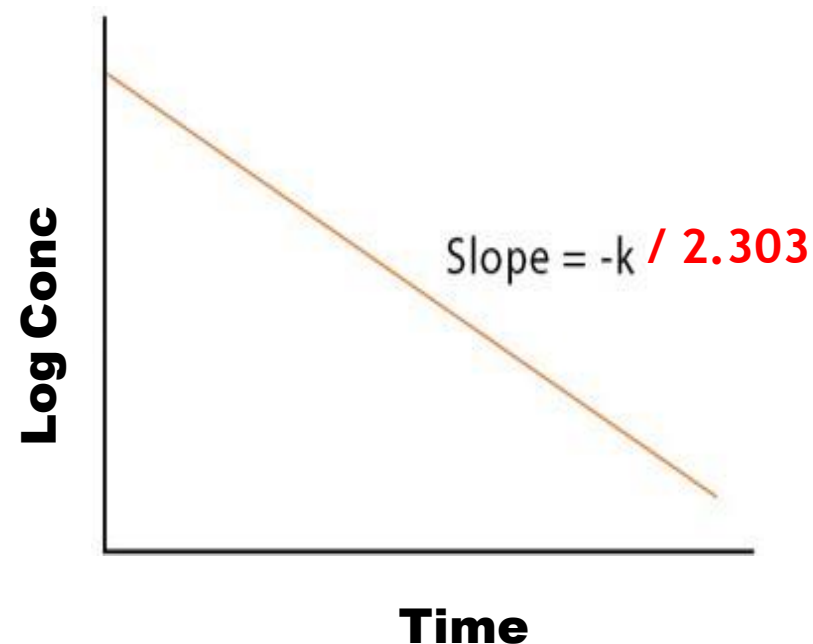


Fig. 3-2. A linear plot of $\log C$ versus time for a first-order reaction.

First-order Reactions



$$\ln c = \ln c_0 - kt$$



Converting to common logarithms yields

$$\log c = \log c_0 - kt/2.303$$

$$k = \frac{2.303}{t} \log \frac{c_0}{c}$$

For calculation of **half life** of reaction follows first order;
 from equation 3 - 10

$$K = 2.303/t \log C_0/C \longrightarrow t = 2.303 /k \log C_0 / C$$

At half life: $t = t_{1/2}$, $C_t = 1/2 C_0$

$$t_{1/2} = 2.303/k \log 2 /1 \longrightarrow t_{1/2} = 0.693/k \text{ minutes}$$

The unit of first order rate constant is:

$$K = (dC/dt)(1/C) \\ = (\text{mol/liter})/\text{second} \times 1 /(\text{mol/liter}) = 1/\text{second} = \text{second}^{-1}$$

For calculation **Shelf life** of reaction follows first order

$$K = 2.303/t \log C_0 / C \longrightarrow t = 2.303 /k \log C_0 / C$$

At shelf life: $t = t_{0.9}$, $C_t = 0.9C_0$

$$t_{0.9} = 2.303/k \log 10 /9 \longrightarrow t_{0.9} = 2.303 \times 0.045/k = 0.105 /k \text{ minutes}$$

Example 1: Decomposition of Hydrogen Peroxide , catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide **remaining after 65 min**, expressed as the volume in milliliters of gas evolved, was **9.60** from an initial concentration of 57.90.

(a) Calculate k.

(b) How much hydrogen peroxide remained undecomposed after 25 min

$$(a) \quad k = \frac{2.303}{65} \log \frac{57.90}{9.60} = 0.0277 \text{ min}^{-1}$$

$$(b) \quad 0.0277 = \frac{2.303}{25} \log \frac{57.90}{c}; c = 29.01$$

Example 2: Half life A solution of a drug contained **500** units/ml when prepared. It was analyzed after **40** days and was found to contain **300** units/ml. Assuming the decomposition is **first order**, at what time will the drug have decomposed to one-half of its original concentration

$$k = \frac{2.303}{40} \log \frac{500}{300} = 0.0128 \text{ day}^{-1}$$

$$t = \frac{2.303}{0.0128} \log \frac{500}{250} = 54.3 \text{ days}$$

Or

$$t_{1/2} = \frac{0.693}{k}$$

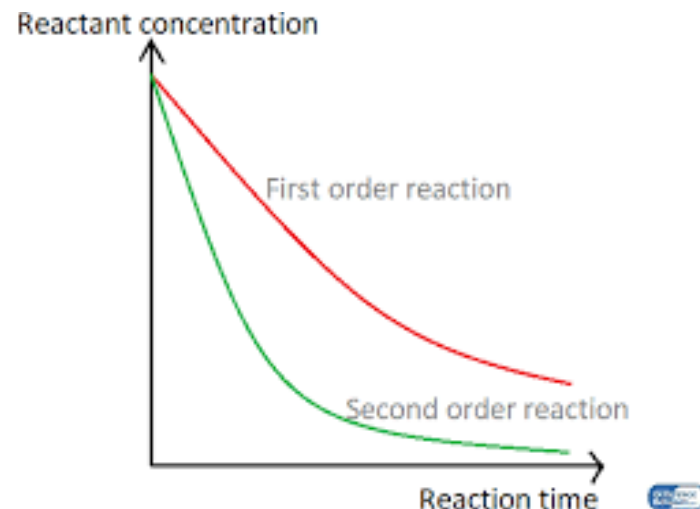
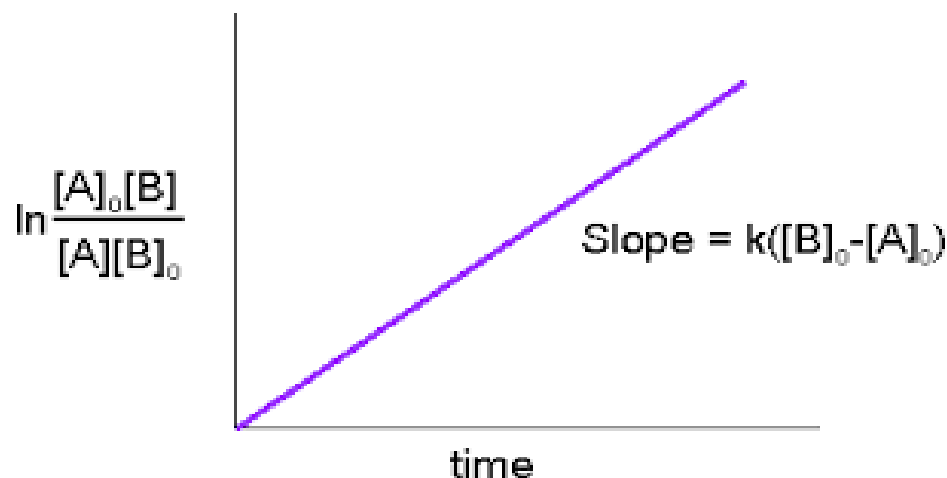
Second-Order Reactions

The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the second-order equation.



When the speed of the reaction *depends on the concentrations of A and B with each term raised to the first power*, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

$$-\frac{d[A]}{dt} = \frac{d[B]}{dt} = k[A][B]$$



If **a** and **b** are the initial concentrations of A and B respectively, and **x** *is the concentration of each species reacting in time t*, the rate law can be integrated and written as:

1. When, in the simplest case, both A and B are present in the same concentration so that a = b

$$\frac{x}{a(a - x)} = kt \quad \text{..... (3.16)}$$

$$k = \frac{1}{at} \left(\frac{x}{a - x} \right) \quad \text{..... (3.17)}$$

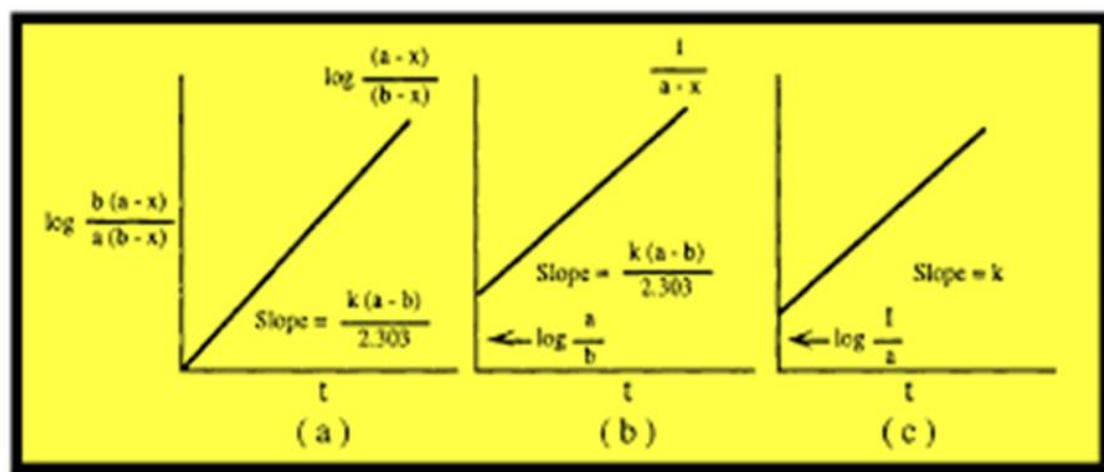
2. When, in the general case, A and B are not present in equal concentrations but the difference in concentration is not big, integration of equation yields:

$$\frac{2.303}{a - b} \log \frac{b(a - x)}{a(b - x)} = kt \quad \text{Or} \quad k = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)} \quad \text{.... (3.19)}$$

- The half-life of a second-order reaction is: $t_{1/2} = \frac{1}{ak}$
- For second-order $k = \frac{dA}{dt} \frac{1}{A^2} = \frac{\text{moles/liter}}{\text{second (moles/liter)}^2} = \frac{\text{liter}}{\text{moles-second}} = \text{liter second}^{-1} \text{ mole}^{-1}$

It can be seen by reference to equation (3.16) that when $x/a(a - x)$ is plotted against t , a straight line results if the reaction is second order. *The slope of the line is k .*

When the initial concentrations a and b are not equal, a plot of $\log [b(a - x)/a(b - x)]$ against t should yield a straight line with a slope of $(a - b)k/2.303$. The value of k can thus be obtained. It is readily seen from equation (3.17) or (3.19) that the units in which k must be expressed for a second-order reaction are $1/(\text{mole/liter}) \times 1/\text{sec}$ where the concentrations are given in mole/liter and the time in seconds. The rate constant, k , in a second-order reaction therefore has the dimensions liter/(mole sec) or **liter mole⁻¹ sec⁻¹**.



Order of Reaction	Unit of k
Zero	$\text{mol L}^{-1} \text{s}^{-1}$
First	s^{-1}
Second	$\text{L mol}^{-1} \text{s}^{-1}$
Third	$\text{L}^2 \text{mol}^{-2} \text{s}^{-1}$

Apparent or Pseudo-Order

“Apparent” or “pseudo”-order describes a situation where one of the reactants is present *in large excess or does not effect the overall reaction and can be held constant*. For example, many hydrolysis decomposition reactions of drug molecules *are second order*. Usually the *amount of water present is in excess of what is needed for the reaction to proceed*. In other words, the concentration of water is essentially *constant* throughout the reaction. In this case, *the second-order reaction behaves like a first-order reaction* and is called an apparent or pseudo–first-order reaction.

and for a second-order reaction,

$$k = \frac{dA}{dt} \frac{1}{A^2} = \frac{\text{moles/liter}}{\text{second (moles/liter)}^2}$$
$$= \frac{\text{liter}}{\text{moles-second}} = \text{liter second}^{-1} \text{ mole}^{-1}$$

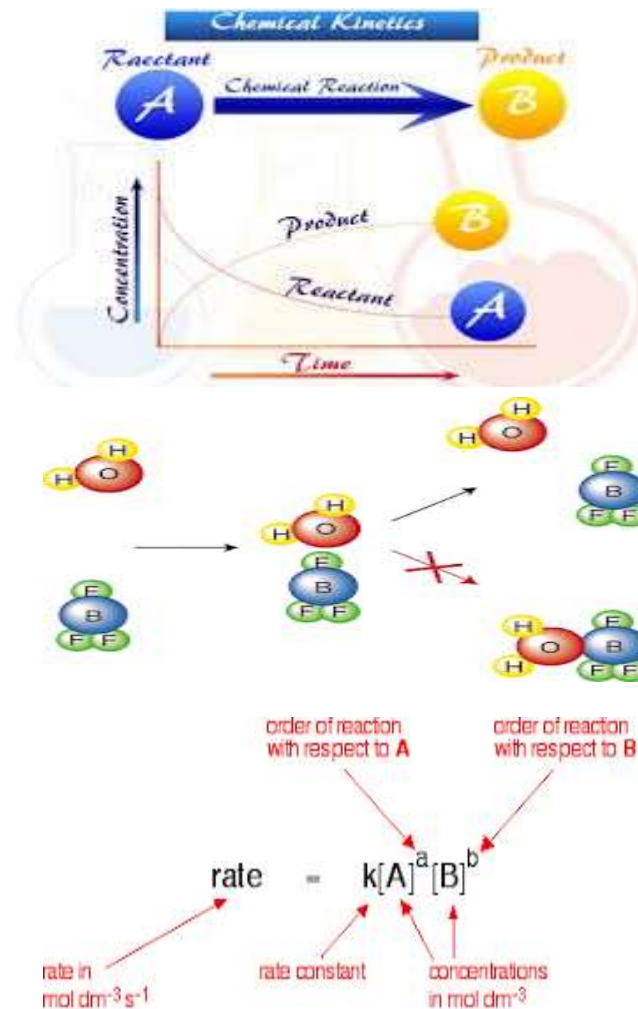


Kinetics I

Sixth Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
2022 - 2023

Dr . Anmar Ghanim Taki Alaaraji



Reference : Sinko, Patrick J. Martin's Physical Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 5th Edition 2006

Rates of Reactions

The rate, velocity, or speed of a reaction is given by the expression dc/dt , where dc is the *increase or decrease* of concentration over an infinitesimal time interval dt . According to the law of mass action, **a** and **b**, of the substances A and B, respectively, undergoing reaction. In the reaction.



the rate of the reaction is

$$\begin{aligned} \text{Rate} &= \frac{1}{a} \frac{d[A]}{dt} \\ &= \frac{1}{b} \frac{d[B]}{dt} = \dots k[A]^a[B]^b \dots \end{aligned} \quad (3.2)$$

where **k** is the *rate constant*.

The overall *order* of a reaction is the sum of the exponents [$a + b$, e.g., in equation (3.2)] of the concentration terms, A and B. The order with respect to one of the reactants, A or B, is the *a* or *b* of that particular concentration term.

Order

1. The order of reaction is the **method** by which the **concentration** affects the **rate** of the reaction.



Rate of the reaction = $k [\text{A}]^1 [\text{B}]^2$

k is the rate constant

Order of reaction with respect to **A** = *first order*

Order of reaction with respect to **B** = *second order*

overall order of reaction (*sum of exponent= third order*)

2. If, order of reaction is known we can *predict rate of reaction* if concentration of reactant is changed. Also if order is known one can *predict the mechanism of the reaction*.

In general , the order may be Zero , First , Second , Third . Also may be Fractions .

The term [] means the molar concentration

In the reaction of ethyl acetate with sodium hydroxide in aqueous solution, for example



the rate expression is

$$\text{Rate} = - d [\text{CH}_3\text{COOC}_2\text{H}_5] / dt \quad (\text{consumption})$$

$$= - d [\text{NaOH}] / dt = K [\text{CH}_3\text{COOC}_2\text{H}_5]^1 [\text{NaOH}]^1 \dots\dots (3.3)$$

The reaction is first order ($a = 1$) with respect to ethyl acetate and first order ($b = 1$) with respect to sodium hydroxide solution; overall the reaction is second order ($a + b = 2$). Suppose that in this reaction, *sodium hydroxide as well as water (solvent)* was in *great excess* and *ethyl acetate* was in a relatively *low concentration*. Ethyl acetate would *change* appreciably from its original concentration, whereas the concentrations of NaOH and water would *remain essentially unchanged* because they are present in great excess.

In this case, the contribution of sodium hydroxide to the rate expression is considered constant and the reaction rate can be written as

$$d [\text{CH}_3\text{COOC}_2\text{H}_5] / dt = k' [\text{CH}_3\text{COOC}_2\text{H}_5] \dots\dots (3.4)$$

where $k' = k[\text{NaOH}]$. The reaction is then said to be a *pseudo-first-order* reaction because it depends only on the first power ($a = 1$) of the concentration of ethyl acetate. In general, when one of the reactants is present in such great excess that its concentration may be considered constant or nearly so, the reaction is said to be of *pseudo-order*

Example Order Reaction

In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,



the rate of reaction is

$$\begin{aligned} R &= - d [(\text{CH}_3\text{CO})_2\text{O}] / dt \\ &= K [(\text{CH}_3\text{CO})_2\text{O}] [\text{C}_2\text{H}_5\text{OH}]^2 \end{aligned}$$

What is the order of the reaction *with respect to acetic anhydride*? *With respect to ethyl alcohol*? What is the overall order of the reaction?

If the alcohol, which acts here as the solvent for acetic anhydride, is in *large excess* such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

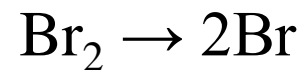
Answer: The reaction appears to be *first order with respect to acetic anhydride*, *second order with respect to ethyl alcohol*, and overall third order. However, **because** alcohol is the solvent, its concentration *remains essentially constant*, and the rate expression can be written as

$$- \frac{d[(\text{CH}_3\text{CO})_2\text{O}]}{dt} = k[(\text{CH}_3\text{CO})_2\text{O}]$$

Kinetically the reaction is therefore a pseudo-first-order reaction,

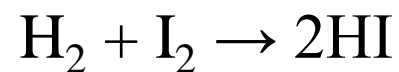
*Molecularity

Is the number of molecules, atoms, or ions reacting in an elementary process.



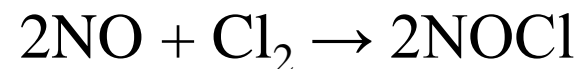
The process is *unimolecular* because the single molecule, Br_2 , decomposes to form two bromine atoms.

In the single-step reaction



The process is *bimolecular* because two molecules, one of H_2 and one of I_2 , must come together to form the product HI.

Termolecular reaction, that are processes in which three molecules must come together simultaneously, are **rare**.



$$\therefore \text{Rate} = k [\text{NO}]^2[\text{Cl}_2]$$

For an elementary reaction, the overall reaction order is always equal to molecularity.

Chemical reactions that proceed through more than one step are known as *complex reactions*.

The overall order determined kinetically may *not be identical* with the molecularity because the reaction consists of several steps, each with its own molecularity.



The order has been found *experimentally to be 2*.

The mechanism is postulated to consist of two elementary steps, each being bimolecular:



Rate Constants, Half-Life, Shelf Life, and Apparent or Pseudo-order

*The constant, k , appearing in the rate law associated with a single-step (elementary) reaction is called the *specific rate constant* for that reaction.

Any change in the conditions of the reaction, for example, in *temperature* or *solvent*, or a *slight change in one of the reacting species*, will lead to a rate law having a different value for the specific rate constant.

* The *half-life* is the time required for one-half of the material to disappear; it is the time at which A has decreased to $1/2 A$.

*The *shelf life* is the time required for 10% of the material to disappear; it is the time at which A has decreased to 90% of its original concentration (i.e., $0.9 A$).

Variations in the specific rate constant are of great physical significance because a change in this constant necessarily represents a change at the molecular level as a result of a variation in the reaction conditions.

Zero-Order Reactions

The loss in color of a multi sulfa product (as measured by the decrease of spectrophotometric absorbance at a wavelength of 500 nm) followed a zero-order rate. The rate expression for the change of absorbance, A, with time is therefore

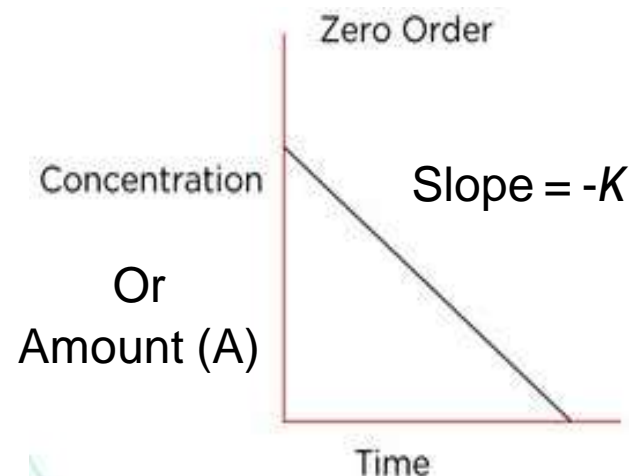
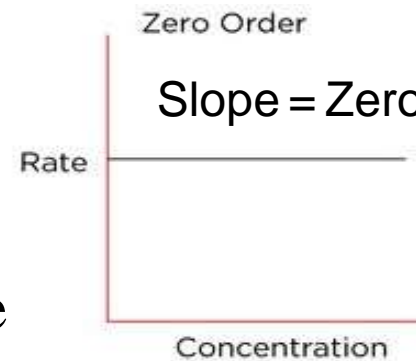
$$- dA / dt = K_o \dots\dots\dots(3.5)$$

where the minus sign signifies that the absorbance is decreasing (i.e., the color is fading). The velocity of fading is seen to be constant and *independent of the concentration of the colorant used*. The rate equation can be integrated between the initial absorbance, A_0 , corresponding to the original color of the preparation at $t = 0$, and at, the absorbance A after t hours

$$A_t = A_o - K_o t \dots\dots\dots(3.6)$$

Zero-Order Reactions

- It means that the **rate** of reaction **not depend** on **concentration** of reactant, it is **constant with time**.
- $-dA/dt = \text{or } -dC/dt = k_0$
- The rate equation can be integrated between the initial concentration, C_0 , at $t = 0$, and C_t , the absorbance after time (t):/ k
- $t = C_0 - C_t / k$



The unit of zero order rate constant is

$$dC/dt = (\text{mol/liter}) / \text{second} = \text{mol/liter} \cdot \text{second} = \text{mol liter}^{-1} \text{second}^{-1}$$

Zero-Order Reactions

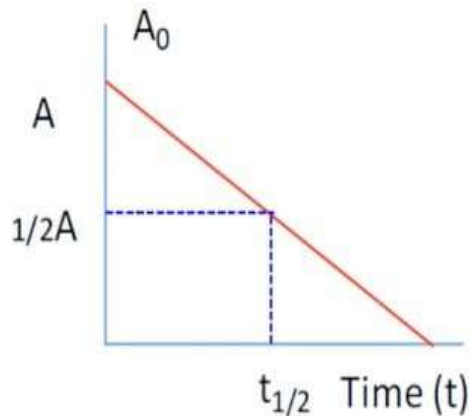
Because the half-life is the time required for one-half of the material to disappear, in the present case, after one half, the concentration becomes $1/2C_0$.

Half life

$$A_t = A_0 - k_0 t$$

$$0.5A_0 = A_0 - k_0 t_{0.5}$$

$$t_{0.5} = \frac{A_0 - 0.5A_0}{k_0} = \frac{0.5A_0}{k_0}$$



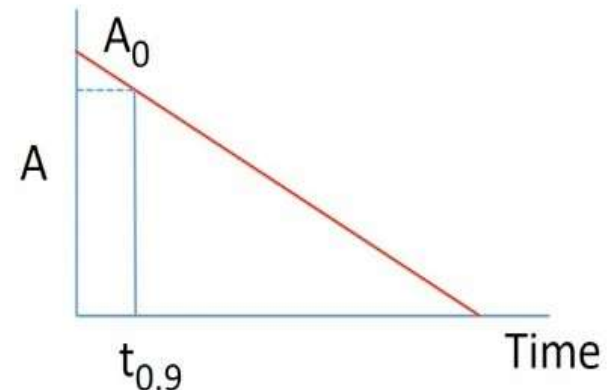
A_0 : Intercept
 A : Y axis
Time: X axis

Shelf life

$$A_t = A_0 - k_0 t$$

$$0.9 A_0 = A_0 - k_0 t_{0.9}$$

$$t_{0.9} = \frac{A_0 - 0.9 A_0}{k_0} = \frac{0.1 A_0}{k_0}$$



Zero-order reaction

Time (m)	Concentration (M)
0	100
10	95
20	90
30	85
40	80
50	75
60	70



$$A_t = A_0 - k_0 t$$

$$\text{Rate} = -\frac{dA}{dt} = k_0$$

$$= -\frac{95 - 100}{10 - 0} = \frac{5}{10} = 0.5 \text{ Mole Liter}^{-1} \text{ Minute}^{-1}$$

$$\text{Half-life} = t_{0.5} = \frac{0.5 A_0}{k} = \frac{50}{0.5} = 100 \text{ minutes}$$

$$\text{Shelf-life} = t_{0.9} = \frac{0.1 A_0}{k} = \frac{10}{0.5} = 20 \text{ minutes}$$

In Zero-Order reaction

- Rate is constant = k_0
- $t_{0.5}$ and $t_{0.9}$ are not constants, differ from one point to another



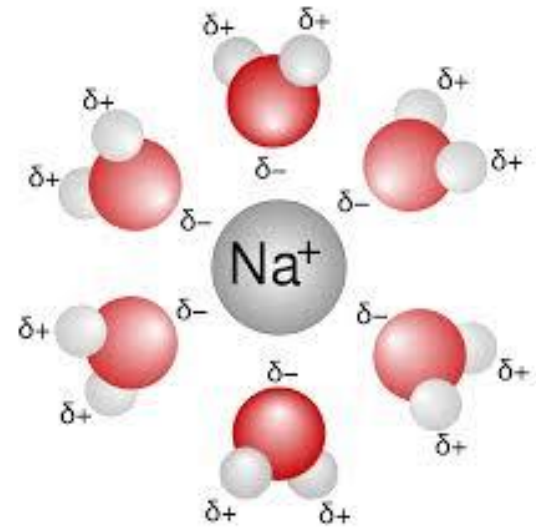
Solubility and distribution phenomena I

Chapter One First Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
2022 - 2023

Dr . Anmar Ghanim Taki Alaaraji

Reference : Sinko, Patrick J. Martin's Physical Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 5th Edition 2006



a measure of how much solute will dissolve in a solvent



Chapter One :Solubility and Distribution Phenomena

Chapter Objectives

- 1 .Definition and importance.
- 2 . Types of solution (saturated , sub saturated , super saturated .
- 3 . Solubility expressions.
- 4 . Types of solvents and their properties.
- 5 . Structural features of compounds and their solubility.
- 6 . Solubility of gas in liquid (Henry's law , factors affecting solubility) .
- 7 . Solubility of liquid in liquid.
- 8 . Solubility of solid in liquid.
- 9 . Ideal solution.
- 10 . Nonideal (real solutions) .
- 11 . Solubility of salt in water .
- 12 . Solubility of weak electrolytes (effect of pH , effect of solvents , combined effect of pH and solvent) .
- 13 . Solubility of slightly soluble salts (K_{sp} and common ion) .
- 14 . Distribution of solutes between immiscible solvents (Extraction) .
- 15 . Preservation action of weak acids in oil-water systems .

Solubility definition and importance

Solubility in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and *in a qualitative way*, it is the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Solubility is an *intrinsic* material property that can be changed only by chemical modification of the molecule. The solubility of a compound depends on the physical and chemical properties of the solute and the solvent as well as on such factors as temperature, pressure, the pH of the solution, and, to a lesser extent, the state of subdivision of the solute.

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (expected) pharmacological response.

Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water.

Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like **particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation**. Selection of solubility improving method **depends on** drug property, site of absorption, and required dosage form characteristics.

Types of solutions

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

An unsaturated or sub saturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

A supersaturated solution A solution that contains more amount of solute than that of saturated which is able to dissolve in solvent at a particular given temperature.

Concept of Solubility

The simple principle that *like dissolves like* can be rephrased by stating that the solubility of a substance can be predicted only in a qualitative way in most cases and only after considerations of polarity, dielectric constant, association, solvation, internal pressures, acid–base reactions, and other factors. In short, solubility depends on chemical, electrical, and structural effects that lead to mutual interactions between the solute and the solvent.

Solubility Expressions

The solubility of a drug may be expressed in a number of ways. The *United States Pharmacopeia (USP)* describes the solubility of drugs as parts of solvent required for one part solute. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage. The USP describes solubility using the seven groups listed in table 1. The European Pharmacopoeia lists six categories (it does not use the *practically insoluble* grouping). For exact solubilities of many substances.

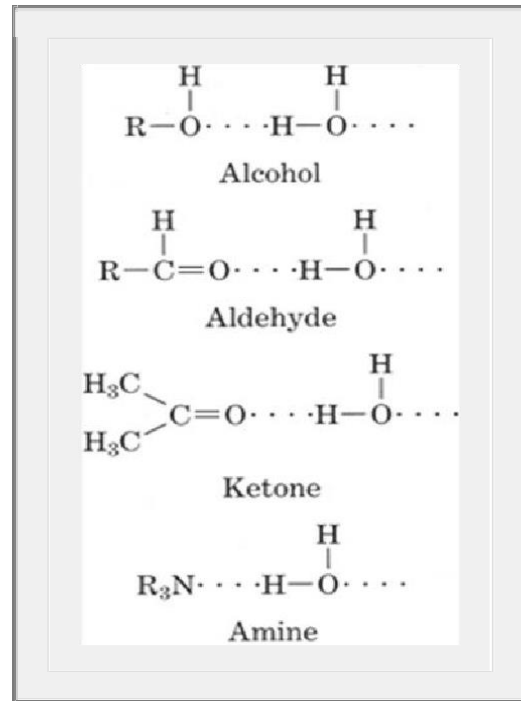
Table 1 Solubility Definition in the United States Pharmacopeia

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (mg/mL)	Solubility Assigned (mg/mL)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100–1000	100
Soluble	From 10 to 30	33–100	33
Sparingly soluble (SPS)	From 30 to 100	10–33	10
Slightly soluble (SS)	From 100 to 1000	1–10	1
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1	0.1
Practically insoluble (PI)	>10,000	<0.1	0.01

Types of solvent

Polar Solvents

The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its **dipole moment**(is a measurement of the separation of two opposite electrical charges). Polar solvents dissolve ionic solutes and other polar substances. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other polyhydroxy compounds.



However, that a consideration of **dipole moments alone is not adequate to explain the solubility of polar substances in water**. The ability of the solute to **form hydrogen bonds is a far more significant factor** than is the polarity as reflected in a high dipole moment. Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water:

A difference in **acidic and basic character of the constituents** in the Lewis electron donor–acceptor sense also contributes to specific interactions in solutions.

In addition to the factors already enumerated, the solubility of a substance also **depends on structural features** such as **the ratio of the polar to the nonpolar groups of the molecule**. As the length of a nonpolar chain of an aliphatic alcohol **increases**, the solubility of the compound in water **decreases**. *Straight-chain monohydroxy alcohols*, aldehydes, ketones, and acids **with more than four or five carbons** cannot enter into the hydrogen-bonded structure of water and *hence are only slightly soluble*. When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, **water solubility increases greatly**. Branching of the carbon chain **reduces the nonpolar effect and leads to increased water solubility**. Tertiary butyl alcohol is miscible in all proportions with water, whereas *n*-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20°C.

Nonpolar Solvents

The solvent action of nonpolar liquids, such as the hydrocarbons, differs from that of polar substances. Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes *because of the solvent's low dielectric constants*. Nor can the solvents *break covalent bonds* and ionize weak electrolytes, **because** they belong to the group known as aprotic solvents, and they **cannot** form hydrogen bridges with nonelectrolytes. Hence, ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.

Nonpolar compounds, however, can dissolve nonpolar solutes with similar internal pressures *through induced dipole interactions*. The solute molecules are kept in solution by the weak van der Waals—London type of forces. **Thus**, oils and fats dissolve in carbon tetrachloride, benzene, and mineral oil. Alkaloidal bases and fatty acids also dissolve in nonpolar solvents.

Protic solvents are polar liquid compounds that have *dissociable hydrogen atoms*.

Aprotic solvents are polar liquid compounds that have *no dissociable hydrogen atoms*. Protic solvents are capable of hydrogen bond formation. Aprotic solvents are unable to form hydrogen bonds.

Polar Solvents	Non-Polar Solvents
DMF	Alkanes
DMSO	Benzene
Water	Toluene
Acetone	Acetic acid
Methanol	Chloroform
Isopropanol	Diethyl ether
Acetonitrile	Ethyl acetate

Polar solvents	
Protic	Aprotic
Water	Acetone
Formic acid	Ethyl acetate
Acetic acid	DMSO
Ammonia	DMF
Methanol	THF/Oxolane
Ethanol	HMF
HF	Crown ethers
HCl	Acetonitrile



Semipolar Solvents

typically are strong dipolar molecules that do not form hydrogen bonds but can induce polarity in nonpolar molecules.

Semipolar solvents, such as ketones and alcohols, can *induce* a certain degree of polarity in nonpolar solvent molecules, so that, for example, benzene, which is readily polarizable, *becomes soluble in alcohol*. In fact, semipolar compounds can act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids. Accordingly, acetone increases the solubility of ether in water. Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate.

A number of common solvent types are listed in the order of decreasing “polarity” in Table 2, together with corresponding solute classes. The term *polarity* is loosely used here to represent not only the dielectric constants of the solvents and solutes **but** also the other factors enumerated previously.

Table 2 Solubility of solvents

	Dielectric constant Of solvent, ϵ	solvent	solute	
 decreasing Polarity	80	Water	Inorganic salts, org. salts.	 decreasing Water Solubility
	50	Glycols	Sugar ,tannins,	
	30	MeOH , EtOH	caster Oil, Waxes. Soluble	
	20	Aldehydes, ketones And higher alcohols, ether ,esters and oxide.	Resins, volatile oils, Weak electrolyte, Alcohols ,phenols	
	5	Hexane ,benzene,CCl ₄ ,Et ₂ O	Fixed oils ,fats ,petroleum ether, paraffin	
	0	Mineral Oil and vegetables Oils.		

Tyndall effect

also called Tyndall phenomenon, *scattering of a beam of light by a medium containing small suspended particles*—e.g., smoke or dust in a room, which makes visible a light beam entering a window.

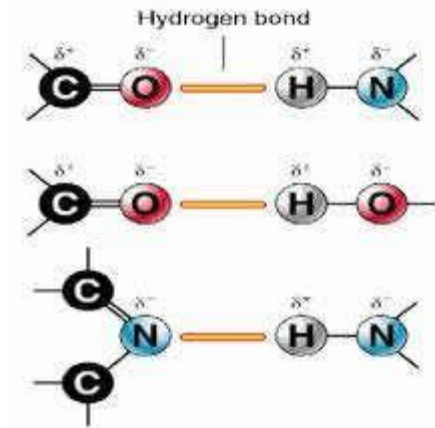
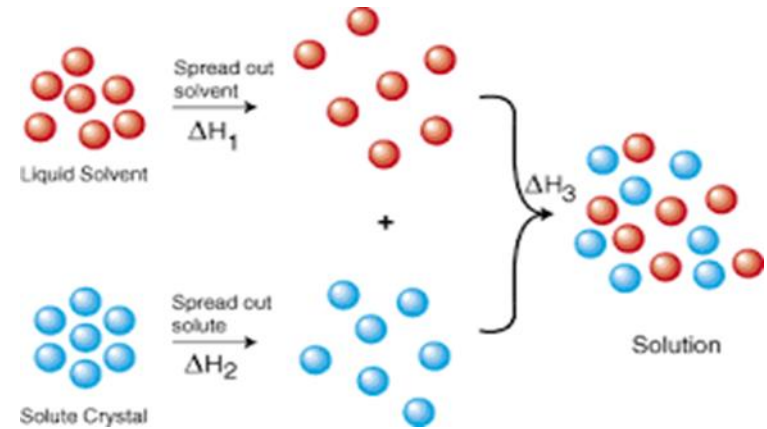
The phenomenon in which light is scattered by particles of matter in its path. It enables a beam of light to become visible by illuminating dust particles, etc.”

The scattering of a beam of light by the particles of a colloid is called the Tyndall effect. When we apply torch light on a glass of milk then the path of the light becomes visible but it is not so in case of water because in milk light is scattered by its very fine particles. The *scattering of light by colloidal particles* is the cause of the Tyndall effect.



Solubility of Liquids in Liquids

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions. For example, alcohol is added to water to form *hydro alcoholic solutions* of various concentrations; volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield *spirits and elixirs*; ether and alcohol are combined in collodions; and various fixed oils are blended into lotions, sprays, and medicated oils. Liquid–liquid systems can be divided into two categories according to the solubility of the substances in one another: (a) complete miscibility (b) partial miscibility. The term *miscibility* refers *to the mutual solubilities of the components in liquid–liquid systems*.



Solubility and distribution phenomena II

Chapter One Second Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
2022 - 2023

Dr . Anmar Ghanim Taki Alaaraji

Reference : Sinko, Patrick J. Martin's *Physical Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences*, 5th Edition 2006

Solubility of gas in liquids

Pharmaceutical solutions of gases include hydrochloric acid, ammonia water, and effervescent preparations containing carbon dioxide that are dissolved and maintained in solution under positive pressure. Aerosol products in which the propellant is either carbon dioxide or nitrogen, some of which is dissolved under pressure, *can also* be considered to fall under this classification.

The solubility of *a gas* in a liquid is the concentration of the dissolved gas when it is in equilibrium with some of the pure gas above the solution. The solubility *depends* primarily on the pressure, temperature, presence of salts, and chemical reactions that the *gas* sometimes undergoes with the solvent

Effect of Pressure

The pressure of a gas above the solution is an important consideration in gaseous solutions *because* it changes the solubility of the dissolved gas in equilibrium with it. The effect of the pressure on the solubility of a gas is expressed by **Henry's law**, which states that in **a very dilute solution at constant temperature**, the *concentration of dissolved gas* is **proportional to the partial pressure** of the gas above the solution *at equilibrium*. The partial pressure of the gas is obtained by lowering the vapor pressure of the solvent from the total pressure above the solution. If C_2 is the *concentration of the dissolved gas* in **grams per liter** of solvent and p is *the partial pressure in millimeters* of the dissolved gas above the solution *Henry's relationship can be written as*

$$C_2 = \sigma p$$

in which σ is the inverse of the Henry's law constant.

It is sometimes referred to as the *solubility Coefficient*. Mole fraction is more properly used here, but in dilute solutions, molarity can be used.

$$(P_{solute} = K_{solute} X_{solute}).$$

*The significance or Henry's law for the pharmacist rests upon the fact that the solubility of a gas **increases directly with the pressure on the gas**, **and conversely**, that the solubility of the gas is **decreases**. so that sometimes the gas escapes with violence when the pressure above the solution is released. This phenomenon is commonly recognized in effervescent solutions ; when the stopper of the container is removed.*

Effect of Temperature

Temperature also has a marked influence on the solubility of a gas in a liquid. **As the temperature increases, the solubility of most gases decreases**, owing to the greater tendency of the gas to expand. The property of expansion, coupled with the pressure phenomenon, requires that the pharmacist exercise caution in opening containers of gaseous solutions in warm climates and under other condition of elevated temperatures. A vessel containing a gaseous solution or a liquid with a high vapor pressure, such as ethyl nitrite , **should be immersed in ice or cold water for sometimes** to reduce the temperature and pressure of the gas before opening the container.

Salting Out

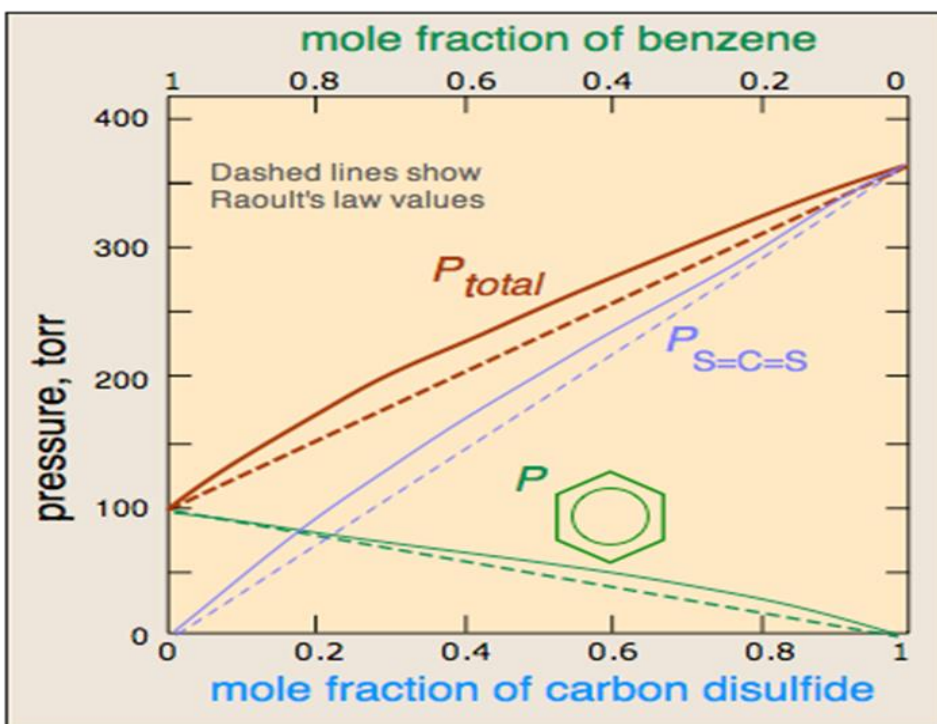
Gases are often liberated from solutions in which they are dissolved by the introduction of an electrolyte such as sodium chloride and sometimes by a nonelectrolyte such as sucrose. This phenomenon is known as **salting out**. The salting out effect can be demonstrated by adding a small amount of salt to a 'carbonated' solution. The escape of gas is due to the attraction of the salt ions or the highly polar for the water molecules, which reduce the density of the aqueous environment adjacent to the gas molecules. Salting out can also occur in solutions of liquids in liquids and solids in liquids.

Effect of Chemical Reaction

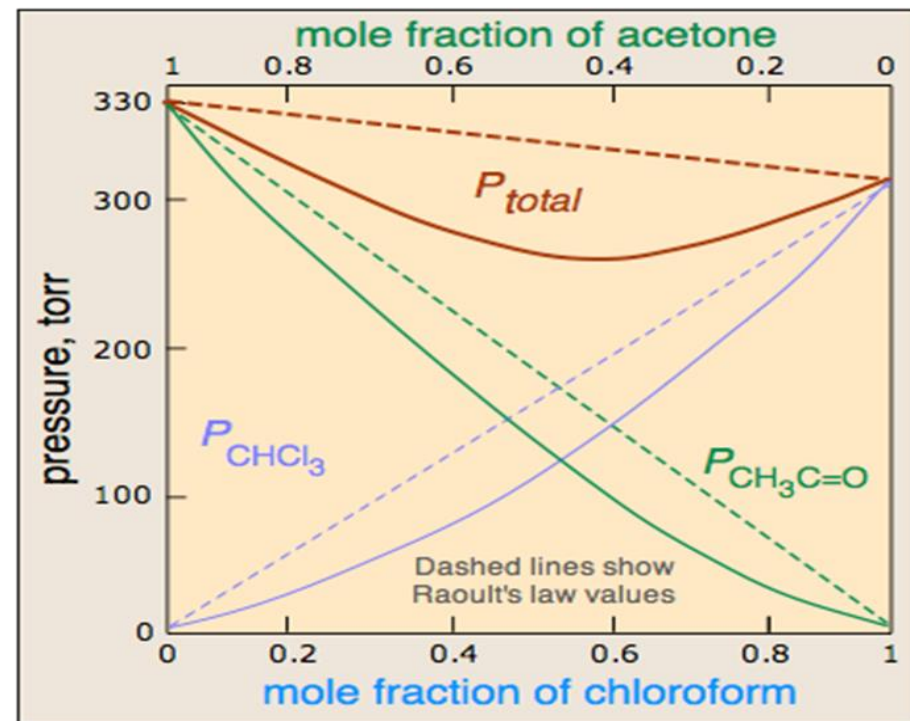
The relation between the solute and solvent is very important in determining solubility. *Strong solute-solvent attractions equate to greater solubility* while weak solute-solvent attractions equate to lesser solubility. In turn, polar solutes tend to dissolve best in polar solvents while non-polar solutes tend to dissolve best in non-polar solvents. In the case of a polar solute and non-polar solvent (or vice versa), it tends to be insoluble or only soluble to a miniscule degree. the rule "Like dissolves like."

Ideal and Real Solutions

According to Raoult's law($P_i = P_i^0 X_i$)the partial pressure p , of a component in a liquid mixture at a definite temperature is equal to the vapor pressure in the **pure** state multiplied by the mole fraction of the component in the solution. The mixture is said to be ideal **when both components of a binary solution obey Raoult's law over the whole range of composition**. If one of the components shows a negative deviation, it can be demonstrated *by the use of thermodynamics* that the other component must also show negative deviation. The corresponding statement can also be made for positive deviations from Raoult's law. The reason for the negative deviation from Raoult's law is that *the intermolecular attractive forces between A-A & B-B are weaker than those between A-B and leads to decrease in vapour pressure* *The vapour pressure of such a solution is either higher or lower than that predicted by Raoult's law. If it is higher*, the solution exhibits **positive deviation** and if it is lower, it exhibits **negative deviation** from Raoult



positive deviation from Raoult's



negative deviation from Raoult's

Negative deviation lead to increased solubility and are frequently associated with hydrogen bonding between polar compounds. The interaction of the solvent with the solute is known as solvation. **Positive deviations** leading to decreased solubility, are interpreted as resulting from association of the molecules of one of the constituents to form double molecules (dimer) or polymer of higher order. The positive deviation is better accounted for in most cases by the difference in the cohesive forces of the molecules of each constituent. These **attractive forces**, which may occur in gases, liquids, or solids, are called internal pressure.

When the vapor is assumed to be nearly ideal. the internal pressure in cal/cm³ is obtained by using the equation

$$P_i = \Delta H_v - RT / V$$

where ΔH , is the **heat of vaporization** and **V** is **the molar volume of the liquid** at temperature T.

When the **internal pressures or cohesive forces** of the constituents of mixture such as hexane and water are quite different, the molecules of one constituents **cannot mix** with those of the other, and **partial solubility results**. Polar liquid have **high cohesive forces** that is, large internal pressures, and they are solvents only for compounds of **similar nature**. Nonpolar substances with low internal pressures are 'reduced' by the powerful attractive forces existing between **the molecules of the polar liquid**. This results in positive deviation from rault law .

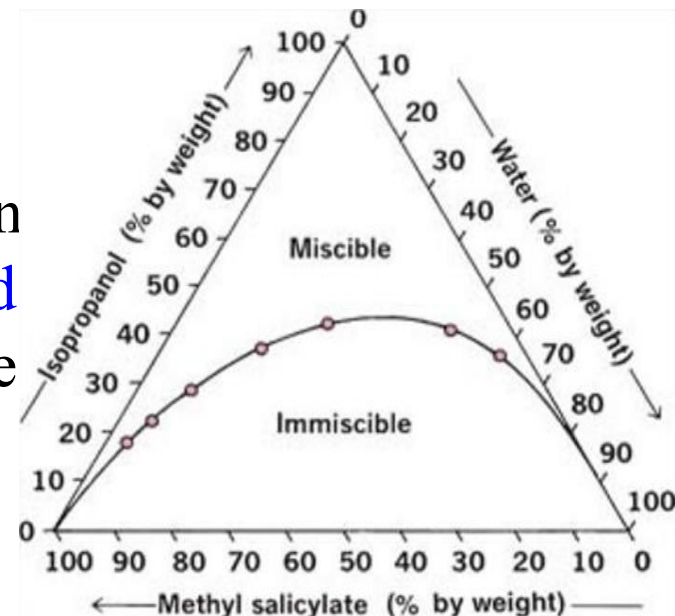
It must be noticed that **limited solubility of nonpolar solutes in highly polar solvents, and particularly in those solvents that associate through hydrogen bonds**, cannot be attributed entirely to a difference of internal pressures.

Liquid-liquid systems can be divided into two categories according to the solubility of the substances in one another.

(a) complete miscibility and (b) partial miscibility. The term miscibility refers **to the mutual solubilities of the components in liquid-liquid systems**.

Solubility of Solids in Liquids

Systems of solids in liquids include the most important type of pharmaceutical solutions. Many important drugs belong to the class of **weak acid and bases**. They react with strong acids and bases and, within definite ranges of **pH**, exist as ions that are ordinarily soluble in water.



Although carboxylic acids containing more than **five carbons** are **relatively insoluble in water**, they react with dilute sodium hydroxide, carbonates, and bicarbonates to **form soluble salts**. The fatty acids containing **more than 10 carbon atoms** form **soluble soaps** with the **alkali metals** and **insoluble soaps** with other metal ions. They are soluble in solvents **having low dielectric constants**; for example, oleic acid ($C_{17}H_{33}COOH$) is insoluble in water but is soluble in alcohol and in **ether, hydroxy acids**, such as **tartaric and citric acids**, are quite soluble in **water** **because** they are solvated through their hydroxyl groups.

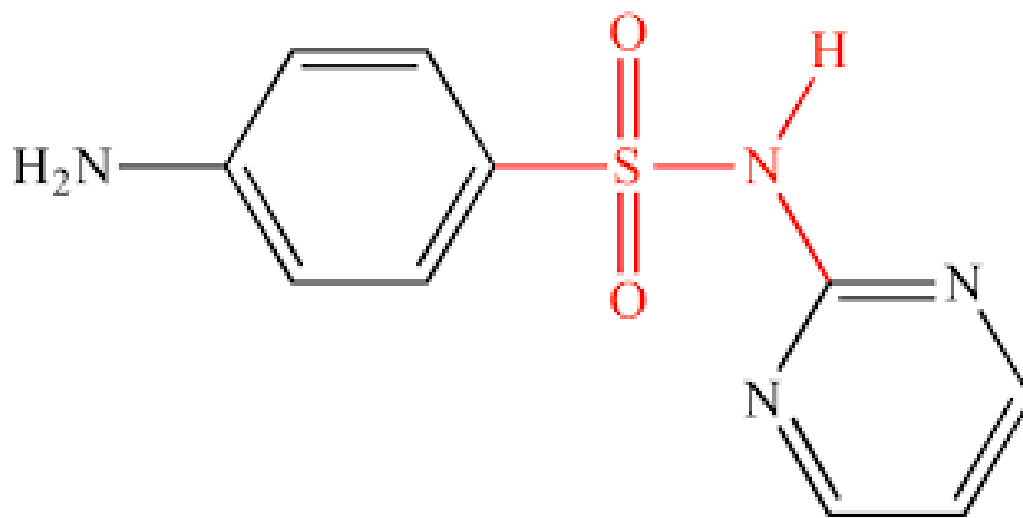
Sodium citrate is used sometimes to dissolve water-insoluble acetylsalicylic acid **because the soluble acetylsalicylate ion is formed in the reaction.**

Aromatic acids **react** with dilute alkalies **to form water-soluble salts, but** they can be precipitated as the free acids if **stronger acidic substances are added to the solution.** **Salicylic acid is soluble in alkalies and in alcohol.** The **OH** group of salicylic acid **cannot contribute to the solubility because it is involved in an intramolecular hydrogen bond.**

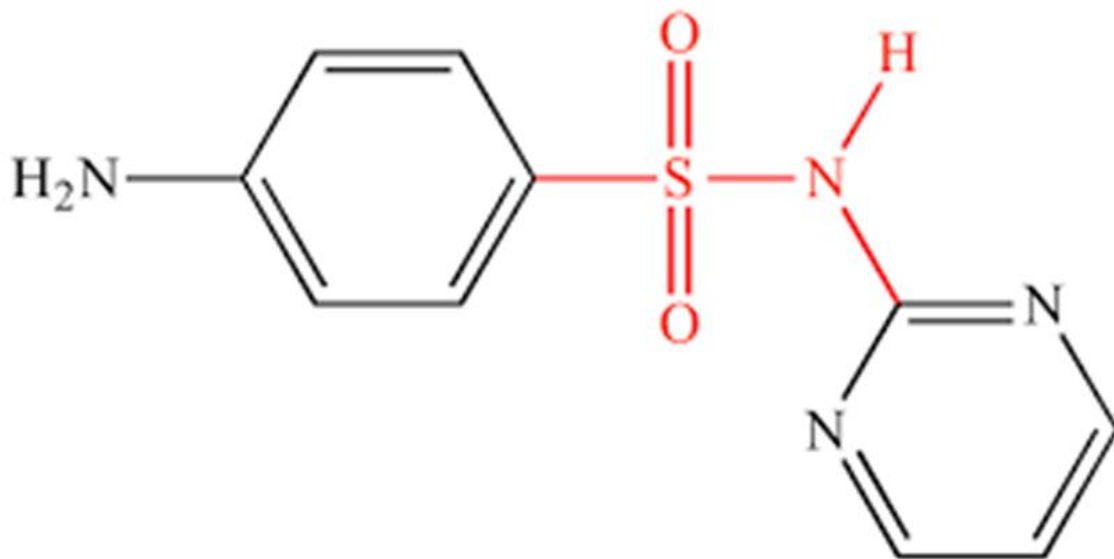
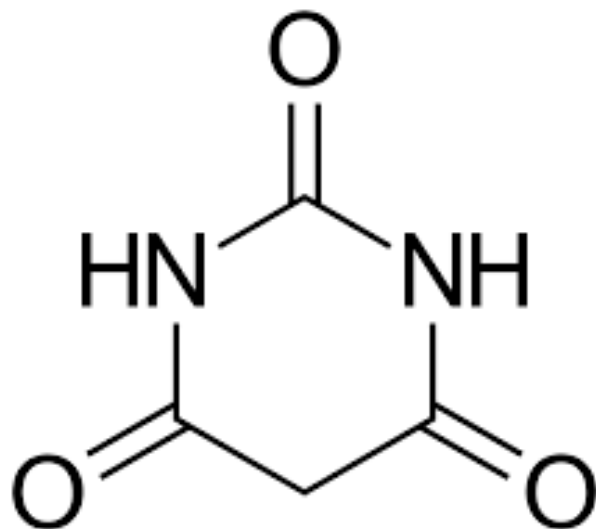


Phenol is **weakly acidic** and only slightly soluble in water **but** is quite soluble in dilute sodium hydroxide solution, The aliphatic nitrogen of the sulfonamides is sufficiently negative so that these drugs **act as slightly soluble weak acids rather than as bases.**

They form water-soluble salts in alkaline solution by the following mechanism. The oxygen's of the sulfonyl ($\text{—SO}_2\text{—}$) group withdraw electrons, and the resulting electron deficiency of the sulfur atom results in the electrons of the N:H bond being held more closely to the nitrogen atom. The hydrogen therefore is bound less firmly, and, in alkaline solution, the soluble sulfonamide anion is readily formed. The sodium salts of the sulfonamides are precipitated from solution by the addition of a strong acid or by a salt of a strong acid and a weak base such as ephedrine hydrochloride.



The barbiturates, like the sulfonamides, are weak acids because the electronegative oxygen of each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly. Thus, in sodium hydroxide solution, the hydrogen is readily lost, and the molecule exists as a soluble anion of the weak acid in highly alkaline solutions, the second hydrogen ionizes.



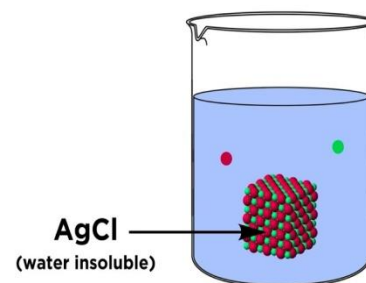
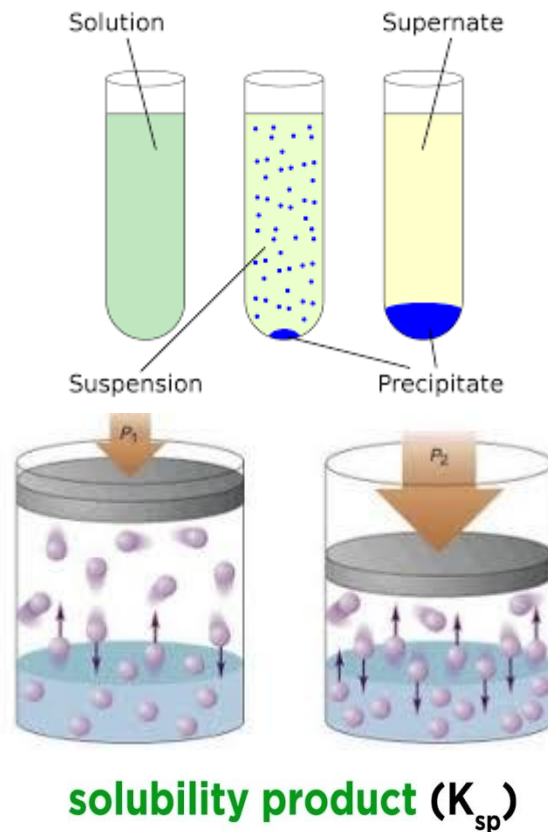


Solubility and distribution phenomena III

Chapter One Third Lecture

Physical Pharmacy – II
2nd Class 2nd Semester
2022 - 2023

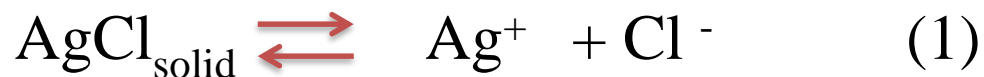
Dr . Anmar Ghanim Taki Alaaraji



Reference : Sinko, Patrick J. Martin's *Physical Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences*, 5th Edition 2006

Solubility of Slightly Soluble Electrolytes

When slightly soluble electrolytes are dissolved to form saturated solutions, the solubility is described by a special constant, known as the *solubility product*, K_{sp} of the compound. The solubility product, K_s , *of an ionic compound* is defined as the product of the concentration of the ions that exist in equilibrium with the solid compound in a saturated solution. Silver chloride is an example of *such a slightly soluble salt*. The excess solid in equilibrium with the ions in saturated solution at a specific temperature is represented by the equation



and because the salt dissolves only with difficulty and the *ionic strength is low*, the equilibrium expression can *be written* in terms of *concentrations instead of activities*:

$$K = [\text{Ag}^+] [\text{Cl}^-] / [\text{AgCl}_{\text{solid}}] \dots\dots\dots (2)$$

Moreover, because the concentration of the solid phase is *essentially constant*,

$$K_{sp} = [\text{Ag}^+] [\text{Cl}^-] \dots\dots\dots (3)$$

The equation is **only approximate** for sparingly soluble salts, or **in the presence of other salts**, when **activities rather than concentrations** should be used. **It does not hold** for salts that are freely soluble water such as **sodium chloride**.

As in the case of *other equilibrium* expressions, the *concentration* of each ion is raised to a power equal to the number of ions appearing in the formula. Thus, for aluminum hydroxide, $\text{Al}(\text{OH})_3$,



$$[\text{Al}^{3+}] [\text{OH}^{-}]^3 = K_{sp} \dots\dots\dots(4)$$

If an ion in common with AgCl , that is, Ag^{+} or Cl^{-} is added to a solution of silver chloride, the equilibrium is changed. The addition of sodium chloride, for example, **increases the concentration of chloride ions** so that momentarily.

Solubility product is the product of *the molar concentrations of the ions in a saturated solutions* **but ionic product is for any solution**.

For a given chemical species and solvent system, the main factor which affects the value of K_{sp} is *the temperature*. Most often, an increase in the temperature causes an increase in the solubility and value.

Extraction

the process of selectively removing a compound of interest from a mixture using a solvent. For an extraction to be successful the compound must be more soluble in the *solvent* than in the *mixture*. Additionally, the solvent and mixture must be immiscible (not soluble in one another).

types of extraction

The three most common types of extractions are: *liquid/liquid*, *liquid/solid*, and *acid/base* (also known as a chemically active extraction)

methods of extraction

Extraction methods include **solvent extraction**, distillation method, pressing and sublimation according to the extraction principle. Solvent extraction is the most widely used method

properties of a good extraction solvent

- *Immiscibility.
- *Dissolves the compound to be extracted.
- *Does not dissolve impurities

solvent extraction method

Solvent extraction is the process in which a compound transfers from one solvent to another owing to the difference in solubility or distribution coefficient between these two immiscible (or slightly soluble) solvents

Distribution and Partitioning Qualitative Description

When two immiscible liquids are added to each other they form two separate and distinct phases.

- Systems of water and ether or amyl alcohol, octanol or peanut oil are examples of such liquid systems.
- If an excess solid or liquid is added to such a system, it will distribute itself between the two phases so that each become saturated, if the substance is added in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.
- The movement of a solute from one phase to another is partitioning.

- If C_1 and C_2 are the equilibrium concentration of the substance in solvent 1 and solvent 2, the equilibrium expression is:
 $K = C_1 / C_2$
- The above equation is known as the distribution law.
- The equilibrium constant K is known as the distribution or partitioning coefficient.
- When calculating the partitioning coefficient., It should be notified which concentration (oil or aqueous phase) in the numerator.
 $K = o/w$ or $K = w/o$