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

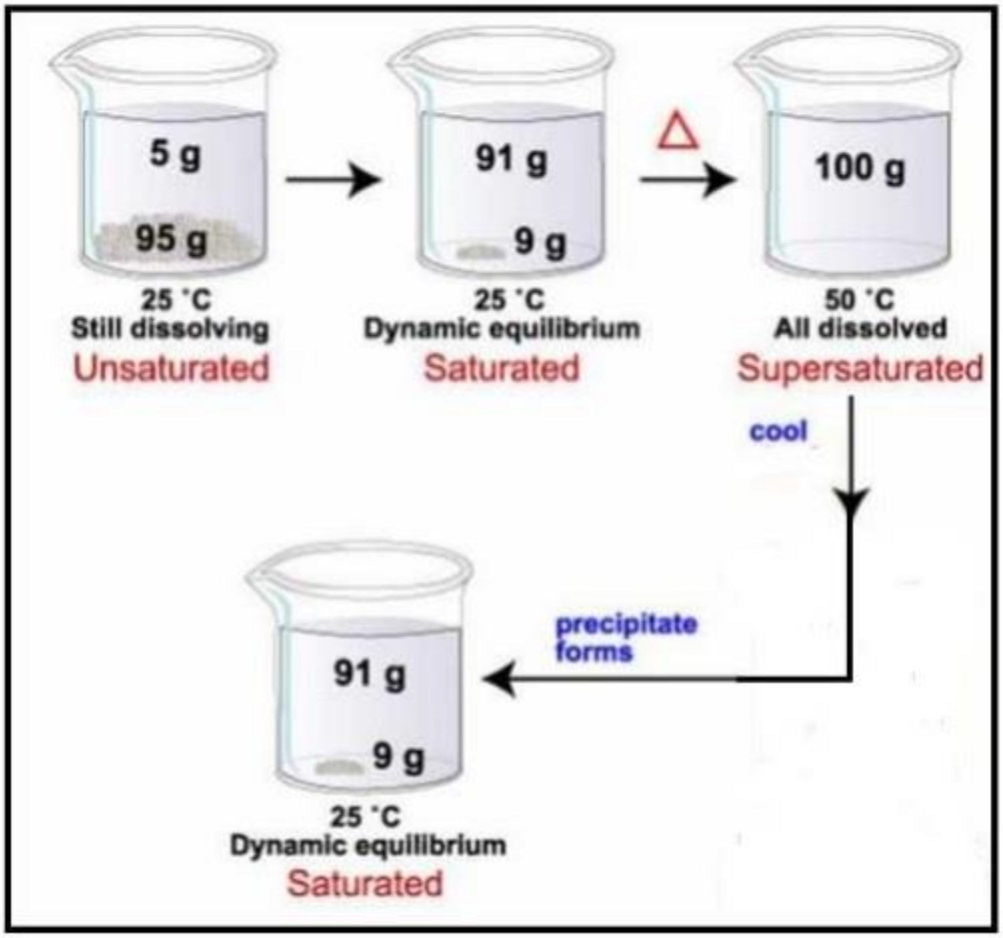
1- A **saturated solution** is one in which the solute in solution is in equilibrium with the solid phase.

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.

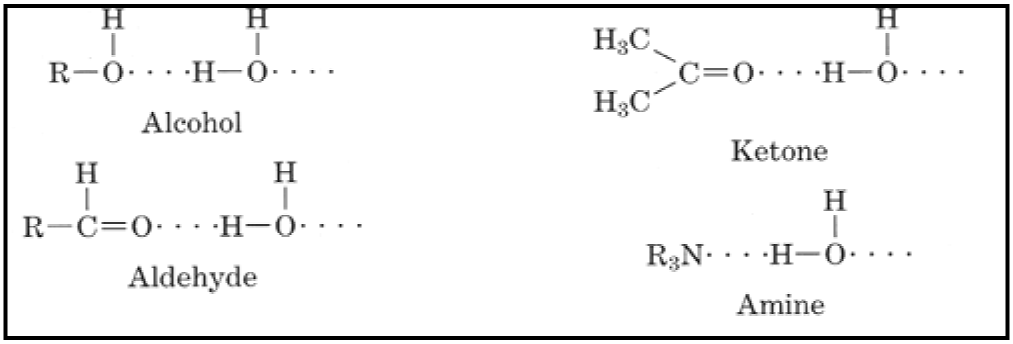
B) Solvation through dipole interaction:

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 CO2 maintained in solution under pressure.

-The solubility of a gas in a liquid ***is the concentration of dissolved gas when it is in equilibrium with some of the pure gas above the solution.***

-The solubility depends on the pressure, temperature, presence of salts & chemical reactions that sometimes the gas undergoes with the solvent

1. Effect of pressure

According to **Henry's law:**

In a very dilute solution at constant temperature, the concentration (C2) of dissolved gas is proportional to the partial pressure (*p)* of the gas above the solution at Equilibrium. (The partial pressure of the gas = total pressure above the solution minus the vapor pressure of the solvent)

$$C_2 \propto p$$

$$C_2 = \sigma p$$

where C2 is the concentration of dissolved gas in gram/l of solvent,

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

σ is proportionality constant (solubility coefficient)

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

Example

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

$$C2 = \sigma p$$

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

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

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

$C2 = \sigma p$

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

= 0.0107 g/l

=0.0027 g/250ml

2. Effect of temperature

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

Pharmaceutical application:

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

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

3. Effect of Salting out

- Adding electrolytes (NaCl) & sometimes non electrolytes (sucrose) to gaseous solutions (E.g. carbonated solutions) induces liberation of gases from the solutions.

Why?

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

II- Solubility of liquids in liquids

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

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 <u>naphthalene</u> is added to a mixture of phenol and water, it dissolves only in the phenol, the miscibility is decreased.

If <u>potassium chloride</u> 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

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

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, $a2 = X_2^i$ 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 $ɣ_2$ and find the relationship between X_2 and $ɣ_2$.

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 $ɣ_2$

$ɣ_2$= 0.99

For water

-log 1.76 x10^{-5}= $\frac{4500}{2.303x1.987}\left(\frac{353-313}{313x353}\right)$ + log $ɣ_2$

$ɣ_2$= 25003

So there is inverse relationship between X_2 and $ɣ_2$

Solubility of Strong Electrolytes

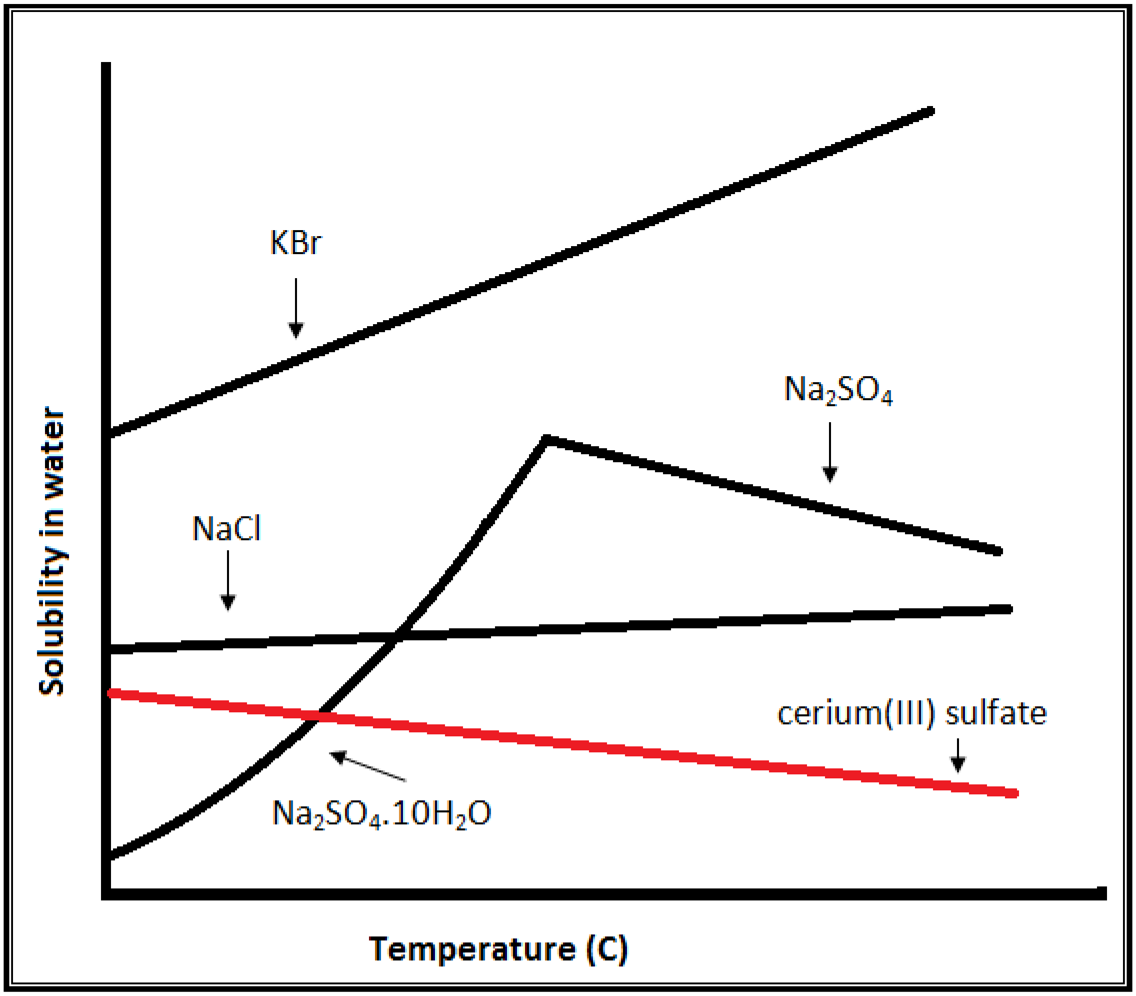
The effect of temperature on the solubility of some salts in water is shown in Figure **10-6.**

A rise in temperature increases the solubility of a solid that absorbs heat *(endothermic* process) when it dissolves. Such as KBr

Conversely, if the solution process *is exothermic*, that is, if heat is evolved, the temperature of the solution rises and the container feels warm to the touch. The solubility in this case decreases with an elevation of the temperature. such as cerium(III) sulfate

Most solids belong to the class of compounds that absorb heat when they dissolve. Sodium sulfate exists in the hydrated form. $Na_2SO_4.10H_2O$, up to a temperature of about 32°C, the solution process (dissolution) is endothermic, and solubility increase with temperature. Above this point, the compound exists as the anhydrous salt, Na_2SO_4, the dissolution is exothermic, and solubility decreases with an increase of temperature.

Sodium chloride does not absorb or evolve an appreciable amount of heat when it dissolves in water; thus, its solubility is not altered much by a change of temperature (isothermic reaction), and the heat of solution is approximately zero.


KBr
Na_2SO_4
NaCl
cerium(III) sulfate
$Na_2SO_4.10H_2O$
Solubility in water
Temperature (C)

Solubility of Weak Electrolytes

Many important drugs belong to the class of weak acids and bases.

Weak acids react with dilute alkalis to form water-soluble salts, but they can be precipitated as the free acids if stronger acidic substances are added to the solution.

For example, a 1% solution of phenobarbital sodium is soluble at pH values high in the alkaline range. The soluble ionic form is converted into molecular phenobarbital as the pH is lowered, and below 9.3, the drug begins to precipitate from solution.

Weak bases react with dilute acids (decrease the pH) to form water-soluble salts, but they can be precipitated as the free bases if stronger basic substances (increase the pH) are added to the solution.

For example, alkaloid salts such as atropine sulfate begin to precipitate as the pH is elevated.

To ensure a clear homogeneous solution and maximum therapeutic effectiveness, the preparations should be adjusted to an optimum pH.

Calculating the Solubility of Weak Electrolytes as Influenced by pH

According to the Henderson-Hasselbach equation, the relationship between pH, pKa, and relative concentrations of an acid and its salt is as follows:

$$\text{pH} = \text{pKa} + \log \frac{[A-]}{[HA]}$$

where $[A^-]$ is the molar concentration of the salt (dissociated species) and [HA] is the concentration of the undissociated acid. When the concentrations of salt and acid are equal, the pH of the system equals the pKa of the acid.

As the pH decreases, the concentration of the molecular acid increases and that of the salt decreases.

Changes in solubility brought about by alterations of solvent pH can be predicted by the pHp equation. The pHp is the pH below which an acid or above which a base will begin to precipitate.

$$\text{pH} = \text{pKa} + \log \frac{S-S0}{S0} \quad \text{(For weak acid)}$$

$$\text{pH} = \text{pKw} - \text{pKb} + \log \frac{S0}{S-S0} \quad \text{(For weak base)}$$

where,

- S_o = the molar solubility of the undissociated acid or base
- S = the molar concentration of the salt form of the drug initially added

Example 10.16

Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25°C? The molar solubility, S_o, of phenobarbital is 0.0050 and the pK_a is 7.41 at 25°C. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

(g/liter)/m.wt= 10/254= 0.039mole/liter

$\text{pHp} = 7.41 + \log \frac{(0.039-0.005)}{0.005} = 8.24$

Q38. The molar solubility of sulfathiazole (weak acid) in water is 0.002, the pka=7.12, m.wt of sodium sulfathiazole = 304, what is the lowest pH allowable for complete solubility in a 5% solution of salt?

pka =7.12 S_o=0.002

M salt = $\frac{wt}{m.wt} x \frac{1000}{vol}$

= $\frac{5}{304} x \frac{1000}{100}$ = 0.164

pHp= 7.12+log$\frac{(0.164-0.002)}{0.002}$ =9.03

The Influence of Solvents on the Solubility of Drugs

Weak electrolytes can behave like strong electrolytes or like nonelectrolytes in solution.

When the solution is of such a pH that the drug is entirely in the ionic form, it behaves as a solution of a strong electrolyte--------> no problem.

However, when the pH is adjusted to a value at which un-ionized molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs. --------> (Problem)

To solve this problem, a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency, and the solvents that, in combination, increase the solubility of the solute are called cosolvents.

For example phenobarbital solubility is increased when add alcohol or glycerin to water.

Combined Effect of pH and Solvents

The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways:

(a) The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value.

(b) Because it is less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pKa is increased).

Influence of Surfactants

Weakly acidic and basic drugs can he brought into solution by the solubilizing action of surface-active agents such as detergent.

Influence of complexation

complexation may be used to increase the solubility such as addition of potassium iodide to iodine.

Sometimes complexation cause decrease in solubility such complex between tetracycline and calcium produce insoluble complex

Influence of size and shape of particles

The size particles affect solubility. Solubility increases with decreasing particle size as consequence of increase in surface area.

The configuration of a molecule and the type of arrangement in the crystal also has some influence on solubility, and a symmetric particle can be less soluble than an unsymmetrical one.

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, Ksp , of the compound.

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

$$AgCl_{\text{solid}} \rightleftharpoons Ag^+ + Cl^-$$

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:

$$\frac{[Ag+][Cl-]}{[AgCl\ solid]} = K$$

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

$$[Ag^+][Cl^-] = Ksp$$

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, $Al(OH)_3$.

$$\boxed{Al(OH)_{3\ \text{solid}} \rightleftharpoons Al^{3+} + 3OH^-}$$

$$[A1^{3+}][OH^{-}]^{3} = Ksp$$

EXAMPLE 10-13: The measured solubility of silver chloride in water at 20°C is 1.12×10^{-5} mole/liter. This is also the concentration of the silver ion and the chloride ion because silver chloride is nearly completely dissociated. Calculate the solubility product of this salt. We have

$Ksp = (1.12 \times 10^{-5}) \times (1.12 \times 10^{-5}) = 1.25 \times 10^{-10}$

If an ion in common with AgCI, that is, Ag^{+} or Cl^{-}, is added to a solution of silver chloride, the equilibrium is altered.

The addition of sodium chloride, for example, increases the concentration of chloride ions so that momentarily $[Ag^{+}][Cl^{-}] > Ksp$
and some of the AgCl precipitates from the solution (the reaction shift to left) until the equilibrium $[Ag^{+}][Cl^{-}] = Ksp$ is reestablished. Hence, the result of adding a common ion is to reduce the solubility of a slightly soluble electrolyte

Salts having no ion in common with the slightly soluble electrolyte produce an effect opposite to that of a common ion: At moderate concentration, they increase rather than decrease the solubility because they lower the activity coefficient.

Distribution of Solutes between Immiscible Solvents

If an <u>excess</u> of substance is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated.

If the substance is added to the immiscible solvents in an amount <u>insufficient</u> to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.

If C1 and C2 are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively, the equilibrium expression becomes

$$K=\frac{C1}{C2}$$

The above equation is known as the **distribution law**

The equilibrium constant, K, is known as the distribution ratio, distribution coefficient, or partition coefficient.

The partition law states that:

- At a given temperature, the ratio of the concentrations of a solute in two immiscible solvents (solvent 1 and solvent 2) is constant when equilibrium has been reached
- This constant is known as the partition coefficient (or distribution coefficient)

Example 9-5

When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in water is found to be 0.0510 mole/liter and in amyl alcohol it is found to be 0.0155 mole/liter. What is the distribution coefficient? We have

$$K=\frac{C.H2o}{C.alc}=\frac{\mathbf{0.051}}{\mathbf{0.0155}}=3.29$$

No convention has been established with regard to whether the concentration in the water phase or that in the organic phase should be placed in the numerator. Therefore, the result can also be expressed as

$$K=\frac{C.alc}{C.H2o}=\frac{\mathbf{0.0155}}{\mathbf{0.0510}}=0.304$$

One should always specify, which of these two ways the distribution constant is being expressed.

Importance of partition Knowledge

The principle is involved in several areas:

1- Drugs partitioning between aqueous phases and lipid biophases

2-Preservation of oil–water systems

3- Absorption and distribution of drugs throughout the body

4- Antibiotics partitioning into microorganisms

5-Solvent extraction

6-Chromatography

Partition law holds true

1-at constant temperature

2-when the solute exists in the same form in both solvents (the species are common to both phases)

Effect of Ionic Dissociation and Molecular Association on Partition

Some compounds have more than one species in oil phase and in aqueous phase which produce complicated case in calculation of partition coefficient.

Example, benzoic acid that is used as preservative present in oil phase as monomer and as dimer in equilibrium.

$$[HA]_O \overset{K_d}{\rightleftharpoons} [HA]_d$$

Benzoic acid present in aqueous phase as unionized (HA) and as ionized (A^-) in equilibrium.

$$[HA]_w \overset{K_a}{\rightleftharpoons} [A^-]_w$$

The true distribution coefficient, K is the ratio of molar concentration of the species common to both the oil and water phases

$$K = \frac{[HA]_O}{[HA]_w}$$

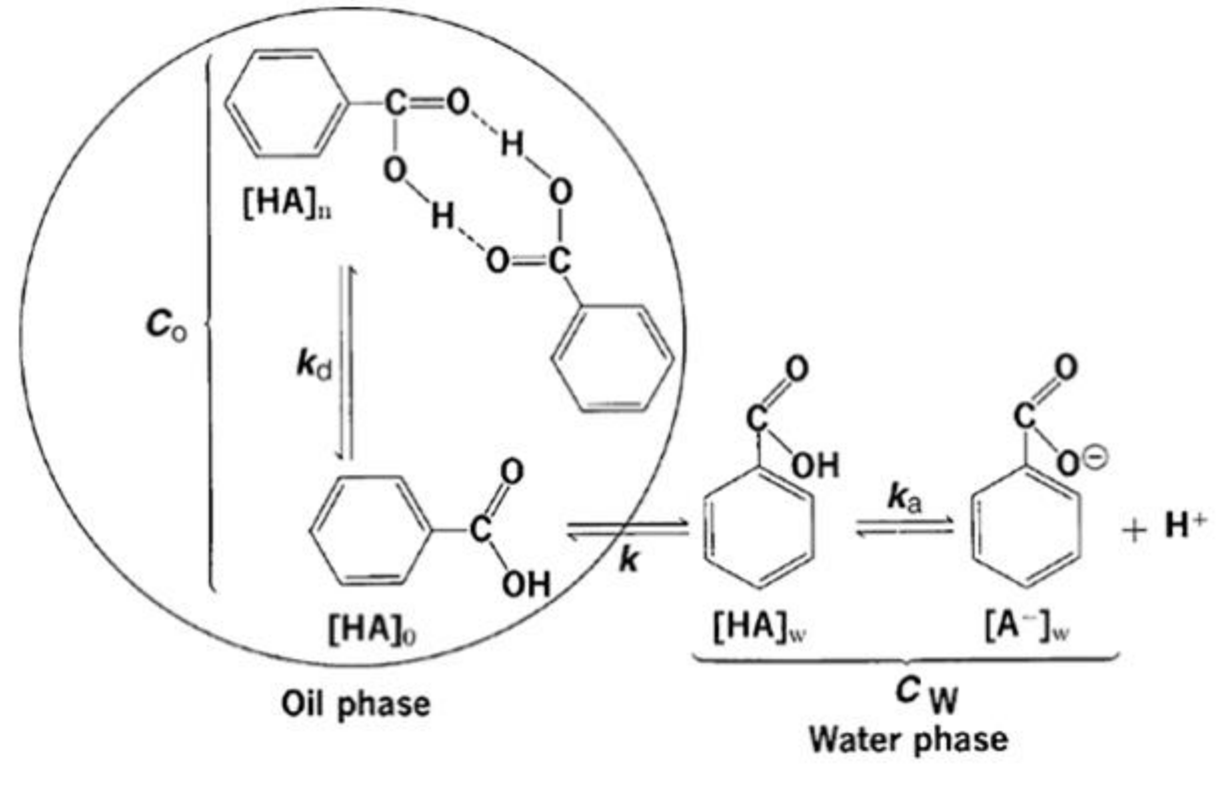
The experimentally observed or apparent distribution coefficient determined by using the total acid concentration (all species) obtained by analysis is

$$K' = \frac{[HA]_O + [HA]_d}{[HA]_w + [A^-]_w}$$

Thus the observed distribution coefficient depends on two equilibria.

In the oil phase, the concentration of monomer or dimer depends on the type of oil, for example benzoic only present as monomer in peanut oil.

In the aqueous phase, the concentration of unionized or ionized depends on the pKa of compound and pH of solvent.


C_o
$[HA]_n$
k_d
$[HA]_0$
k
$[HA]_w$
k_a
$[A^-]_w$
$+ H^+$
Oil phase
C_W
Water phase

Extraction

Liquid-liquid extraction is a useful method to separate components of a mixture. Liquid-liquid extraction is based on the transfer of a solute substance from one liquid phase into another liquid phase according to the solubility.

The success of this method depends upon the difference in solubility of a compound in various solvents. For a given compound, solubility differences between solvents is quantified as the "distribution coefficient"

Example, suppose that you have a mixture of sugar in vegetable oil (it tastes sweet!) and you want to separate the sugar from the oil. You suspect that the sugar is partially dissolved in the vegetable oil.

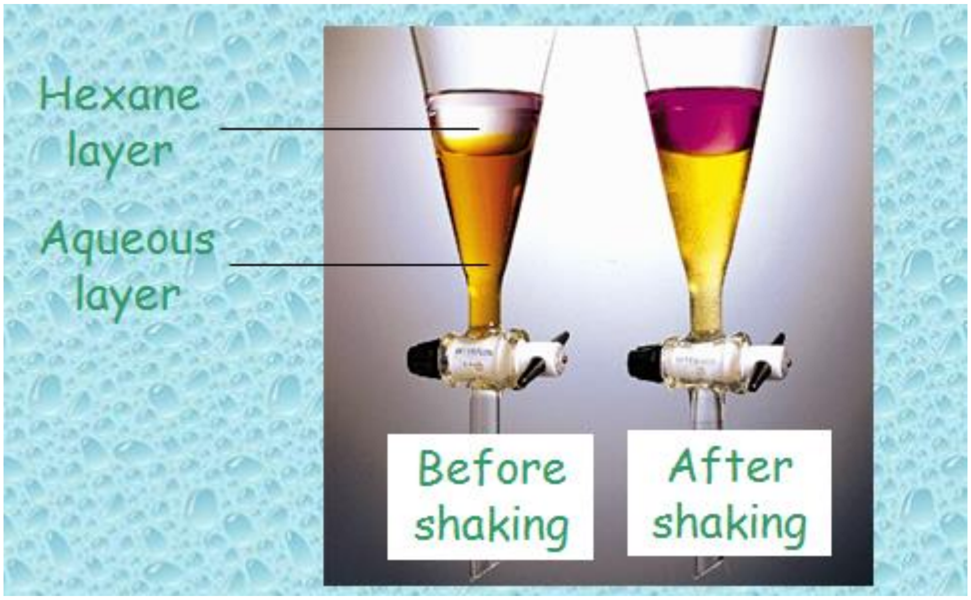
To separate the sugar from the oil we add water to the mixture with shaking.

Sugar is much more soluble in water than in vegetable oil, and water is ***immiscible*** (=not soluble) with oil.

By shaking the **sugar will move to the phase in which it is most soluble: the water layer**

At the end, the water phase tastes sweet, because the sugar is moved to the water phase upon shaking. ****You extracted sugar from the oil with water**. **

Example, Iodine can be extracted from water by adding hexane, shaking and separating the two layers in a separating funnel.



To determine the efficiency with which one solvent can extract a compound from a second solvent we use the following equations:

The distribution coefficient is

$$K = \frac{W1/V1}{(W - W1)V2}$$

By rearrangement, weight of solute extracted can be calculated using this equation:

$$\boxed{W_n = W\left(\frac{KV1}{KV1+V2}\right)^n}$$

w = weight in grams of a solute is extracted repeatedly

V_1 = volume in mL of original solvent

V_2 = volume in mL of a second solvent (extraction solvent)

w_1 = weight of the solute remaining in the original solvent after extraction

n= number of extraction repeating

Note: It can be shown from the equation that a most efficient extraction result when n is large and V_2 is small.

Example 9-7

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K=C_{H2O}/C_{CCl4} = 0.012$. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4? We have

$$W_1 = 0.10 \text{ X } \frac{0.012 \, X \, 50}{(0.012 \, X \, 50)+10}$$

= 0.0057 g remains or 0.0943 g is extracted

$$W_2 = 0.10 \text{ X } \left(\frac{0.012 \, X \, 50}{(0.012 \, X \, 50)+5} \right)^2$$

= 0.0011 g of iodine

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

Preservative Action of Weak Acids in Oil-Water Systems

Solutions of foods, drugs, and cosmetics are subject to deterioration by microorganisms. Sterilization and the addition of chemical preservatives are common methods used in pharmacy to preserve drug solutions.

Benzoic acid in the form of its soluble salt, sodium benzoate, is often used for this purpose.

The preservative action of benzoic acid and similar acids is due almost entirely to the undissociated acid and not to the ionic form and this due to the relative ease with which the un-ionized molecule penetrates living membranes, and, conversely, the difficulty with which the ion does so.

The undissociated molecule, consisting of a large nonpolar portion, is soluble in the lipoidal membrane of the microorganism and penetrates rapidly.
Bacteria in oil-water systems are generally located in the aqueous phase and at the oil-water interface. Therefore, the efficacy of a weak acid, such as benzoic acid, as a preservative for these systems is largely a result of the concentration of the undissociated acid in the aqueous phase.

The distribution of total benzoic acid among the various species in this system depends upon the distribution coefficient, K, the dissociation constant, Ka, of the acid in the aqueous phase, the phase volume ratio, and the hydrogen ion concentration of the aqueous phase.
To calculate the total concentration of benzoic acid that must be added to preserve an oil-water mixture, we can use the following equations:

$$C = (Kq+1+ Ka/[H_3O^+])[HA]_w$$

where,

C= total concentration of acid that must be added to the two-phase system to obtain a final specified concentration $[HA]_w$ of undissociated acid in the aqueous phase buffered at a definite pH or hydrogen ion concentration

K= the distribution coefficient= $[HA]_o / [HA]_w$

q = the volume ratio of the two phases, is needed when the volumes are not equal = V_o/V_w

Ka= the dissociation constant of the acid in the aqueous phase

By rearrangement the equation we can calculate the $[HA]_w$

$$[HA]_w = \frac{C}{Kq+1+ Ka/[H3O+]}$$

EXAMPLE 10-25

If benzoic acid is distributed between equal volumes of peanut oil and water, what must be the original concentration in the water phase in order that 0.25 mg/mL of undissociated acid remains in the aqueous phase buffered at a pH of 4.0? The partition coefficient,

$K = [HA]_o/[HA]_W$, is 5.33 and the dissociation constant of the acid in water is 6.4×10^{-5}. Because the two phases are present in equal amounts, $q = V_o/V_w = 1$.

$$C = (Kq + 1 + Ka/[H_3O^+])[HA]_w$$

$C = (5.33 + 1 + (6.4 \times 10^{-5}/10^{-4}))0.25$

= 1.74 mg/ml

CHEMICAL KINETICS AND STABILITY

The stability of drug product with time is important in determination of shelf life and expired date.

The stability affected by factors, such as temperature, humidity, and light.

This chapter studies the rates and mechanisms of reactions specially the decomposition and stabilization of drug products.

For example, thiamine hydrochloride is most stable at a pH of 2 to 3 and is unstable above pH 6, so in preparation, the pharmacist should select the buffered vehicle that prevents the degradation.

Applications of chemical kinetics in pharmacy result in the production of more-stable drug preparations.

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

Molecularity

Molecularity is the number of molecules, atoms, or ions reacting in an elementary process. molecularity classify the reaction into unimolecular, bimolecular, and Termolecular. molecularity cannot gives complete detail about order of reaction specially those of several steps while kinetic study gives details.

Example: $Br_2 \longrightarrow 2Br$ unimolecular

$H_2 + I_2 \longrightarrow 2HI$ bimolecular

$2NO + O_2 \longrightarrow 2NO_2$ Termolecular

While the real detail mechanism revealed by kinetic study as follows:

$$2NO \rightleftarrows N_2O_2 \text{ (Fast)}$$

$$N_2O_2 + O_2 \longrightarrow 2NO_2 \text{ (Slow)}$$

The rate of the reaction is given by the slow step.

Rate

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.

In the reaction

$$\text{Reactant} \longrightarrow \text{Products}$$

$$\text{Rate} = -\frac{d[Reactant]}{dt} = K[\text{Reactant}]^{a}$$

where k is the rate constant and exponent a represent the order of reaction.

Specific Rate Constant

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

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

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

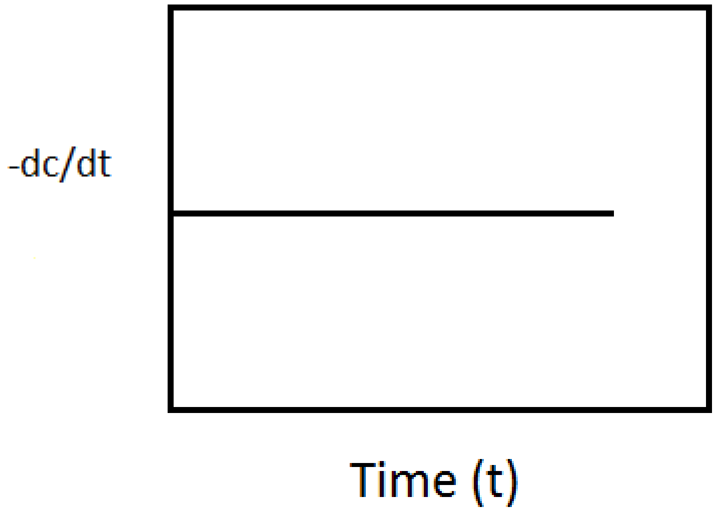
Kinetic study

Zero-Order Reactions

Garrett found that the loss in color of a multisulfa product followed a zero-order rate. The rate expression for the change of concentration, C, with time is therefore

$$-\frac{dC}{dt} = k_0$$

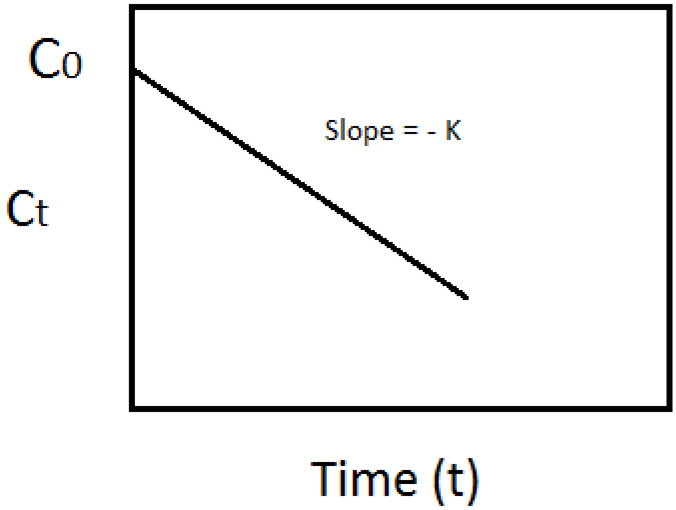
It means that the rate of reaction not depend on concentration of reactant, it is constant with time.



The rate equation can be integrated between the initial concentration, C_0, at t = 0, and C_t, the absorbance after time (t):

$$C_t = C_o - k_o t$$

$$t = \frac{Co - Ct}{ko}$$



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 $1/2C_o$.

$$t_{1/2} = \frac{Co - 1/2Co}{ko}$$

$$t_{1/2} = \frac{½Co}{ko}$$

For shelf life $$t_{90\%} = \frac{Co - 0.9Co}{ko} = \frac{0.1C0}{K0}$$

- The unit of zero order rate constant is:

k_0= - $\frac{dC}{dt}$ =$\frac{mole/liter}{second}$=$\frac{mole}{liter\ second}$ = mole liter^{-1}second^{-1}

First-Order Reactions

Harried showed that 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

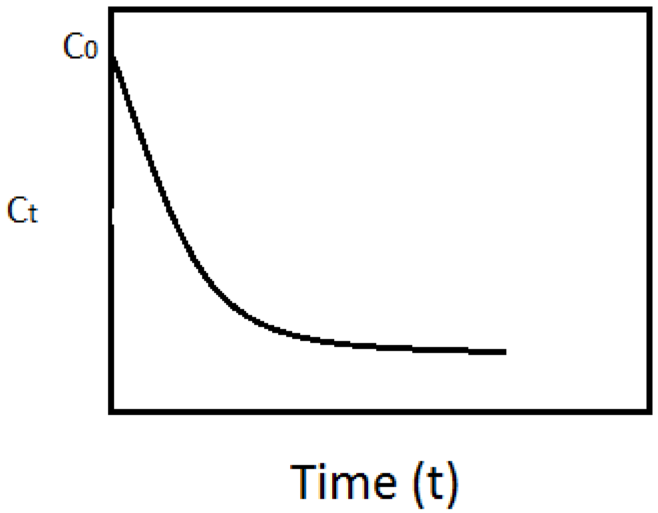
$$2H_20_2 = 2H_2O + O_2$$

Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be first order.

The rate equation is written

$$-\frac{dC}{dt} = k\,C$$

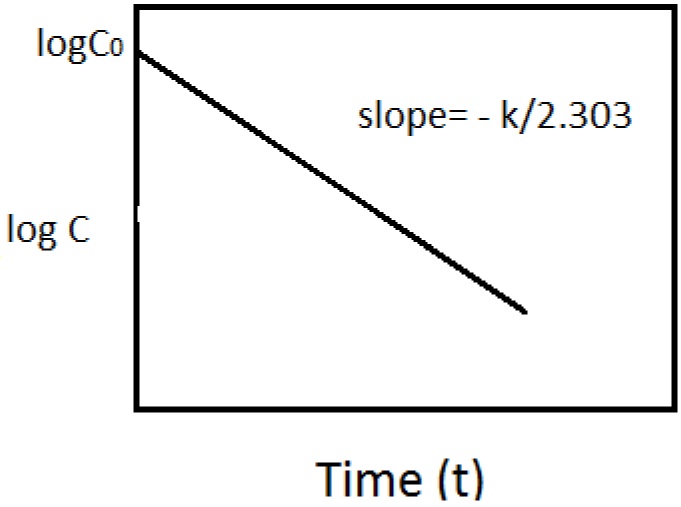
where c is the concentration of hydrogen peroxide remaining undecomposed at time t and k is the first-order rate constant.



Integrating above equation, we have

$$\ln C = \ln C_0 - Kt$$

(Common logarithm) $\log C = \log C_0 - \frac{k}{2.303}\ t$



For calculation of half life of reaction follows first order;

$\log \frac{C0}{Ct} = \frac{K\,t}{2.303}$

at half life; t= t1/2, Ct= ½ C_0

$\log \frac{C0}{½\ C0} = \frac{K\,t1/2}{2.303}$

$$t\ ½ = 0.693/k$$

For shelf life $t_{90;}$

$\log \frac{C0}{0.9\ C0} = \frac{K\ t10\%}{2.303}$, $t_{90} = 0.105/k$

- The unit of first order rate constant is:

$k = -\frac{dC}{dt}\frac{1}{C} = \frac{mole/liter}{second.mole/liter} = \frac{1}{second} = \text{second}^{-1}$

Determination of Order

The order of a reaction can be determined by several methods.

1. **Substitution Method**. The data from kinetic study can be substituted in the equations for each order. When the calculated k values remain constant for different Ct, the reaction is considered to be of that order.

2. **Graphic Method**. A plot of the data in the form of a graph can also be used to ascertain the order.
If a straight line results when concentration is plotted against t, the reaction is zero order.
The reaction is first order if log (concentration) versus t yields a straight line, and it is second-order if 1/(concentration) versus t gives a straight line.

3. **Half-Life Method**. In a zero-order reaction, the half-life is proportional to the initial concentration, a, as observed in Table 15-2. The half-life of a first-order reaction is independent of initial concentration a;
t1/2 for a second-order reaction, in which a = b, is proportional to 1 /a.

Suspensions, Apparent Zero-Order Kinetics

Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant. The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

$-d[C]/dt = k_f[C]$ where c= concentration of drug in solution

= solubility

K_f= first order rate constant of solution

When the concentration [C] is rendered constant, as in the case of a suspension, we can write

$K_f [C] = K_0$ where K_0= zero order rate constant of suspension

Thus, $K_0 = K_f$ x Solubility

$-d[C]/dt = K_0$

Second-Order Reactions

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

$$A + B \longrightarrow \text{Products}$$

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 according to 3 possibilities:

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

$$\frac{x}{a(a-x)} = Kt$$

The rate constant, k, in a second-order reaction therefore has the dimensions liter/ (mole sec) or liter mole^{-1} sec^{-1}.

The half-life of a second-order reaction is

$$t1/2= 1/ak$$

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:

$$\frac{2.303}{a-b} \log \frac{b(a-x)}{a(b-x)} = Kt$$

3. When A and B are not present in equal concentrations and the difference in concentration is very big

(*Pseudo-first-order reaction):*

Suppose that in this reaction, A was in great excess and B was in a relatively low concentration.

As the reaction proceeded, B would change appreciably from its original concentration, whereas the concentrations of A would remain essentially unchanged because they are present in great excess. In this case the contribution of A to the rate expression is considered constant and the reaction rate can be written as

$$A + B \longrightarrow \text{Products}$$

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

K is constant and [A] is constant

$$-\frac{d[B]}{dt} = K'\,[B]$$

where K'= K [A], K'= Pseudo-first-order constant

Factors effects on stability

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

1. Temperature effect

Collision Theory

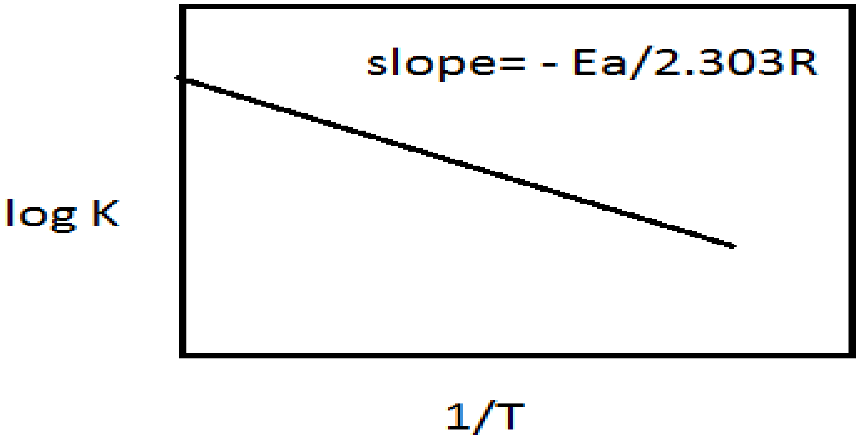
Reaction rates are expected to be proportional to the number of collisions per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.

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

$$k = Ae^{-Ea/RT}$$

$$\text{or} \qquad \log K = \log A - \frac{Ea}{2.303R}\frac{1}{T}$$

where k is the specific reaction rate, A is a constant known as the Arrhenius factor or the frequency factor, *Ea* is the energy of activation. R is the gas constant, 1.987 calories/deg mole, and T is the absolute temperature.

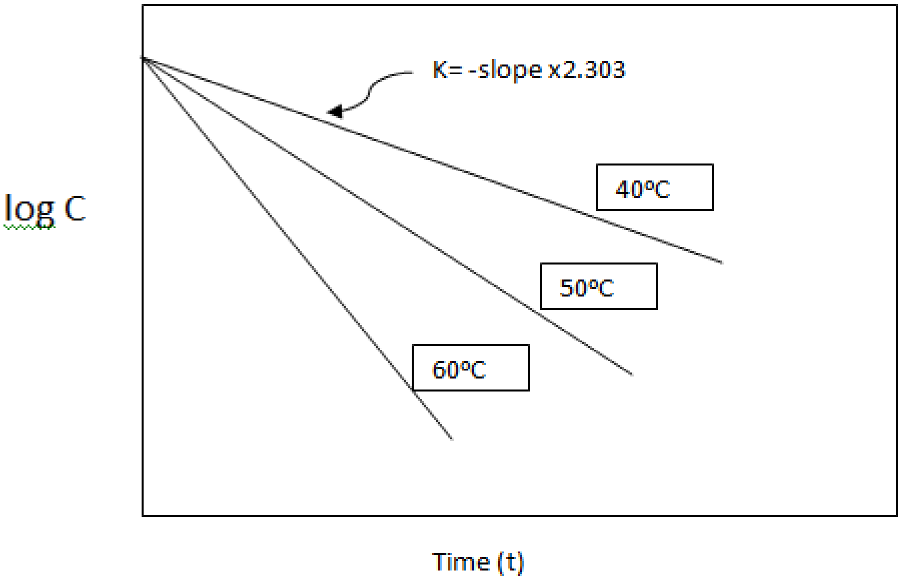


In case at 2 temperatures t1 and t2, the equation becomes:

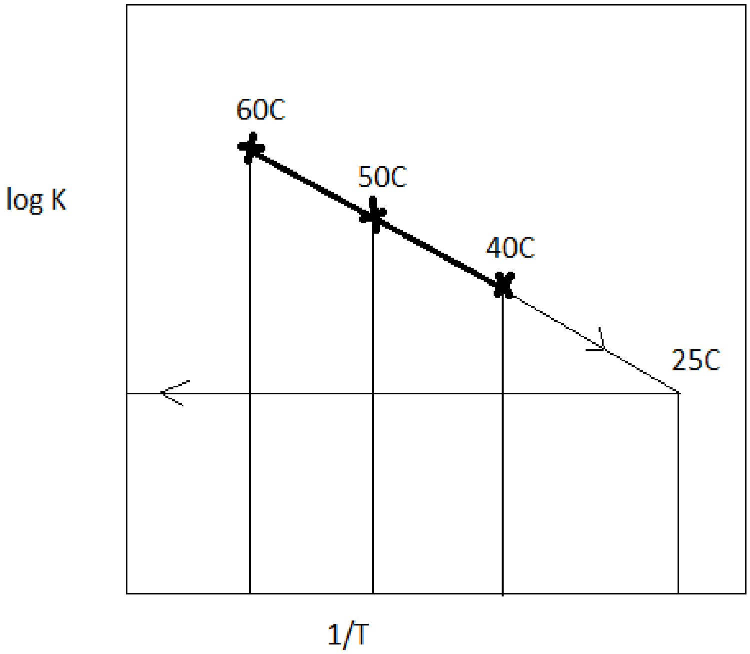
$$\log \frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

Accelerated stability testing

The k values for the decomposition of drug at various elevated temperatures are obtained by plotting log of concentration against time as shown in this figure:



Then the logarithm of rate constants (k) at various temperatures are plotted against reciprocal of absolute temperature and the resulting line extrapolated to the room temperature to get K_{25}°C as shown in this figure:



The shelf life $t_{90\%}$ can be calculated from equation

$$t_{90\%} = 0.105/ K_{25}°C$$

2. **Medium Effects: Solvent, Ionic Strength, Dielectric Constant**

a. Effect of the Solvent

In summary, it can be said that the polarity of solvents affect the rate of reactions depending on the polarity of reactant.

b. Effect of the ionic strength

For ionic compound, the ionic strength affects the rate of reaction while for neutral molecule, the rate of reaction independent on ionic strength.

c. Effect of the Dielectric Constant

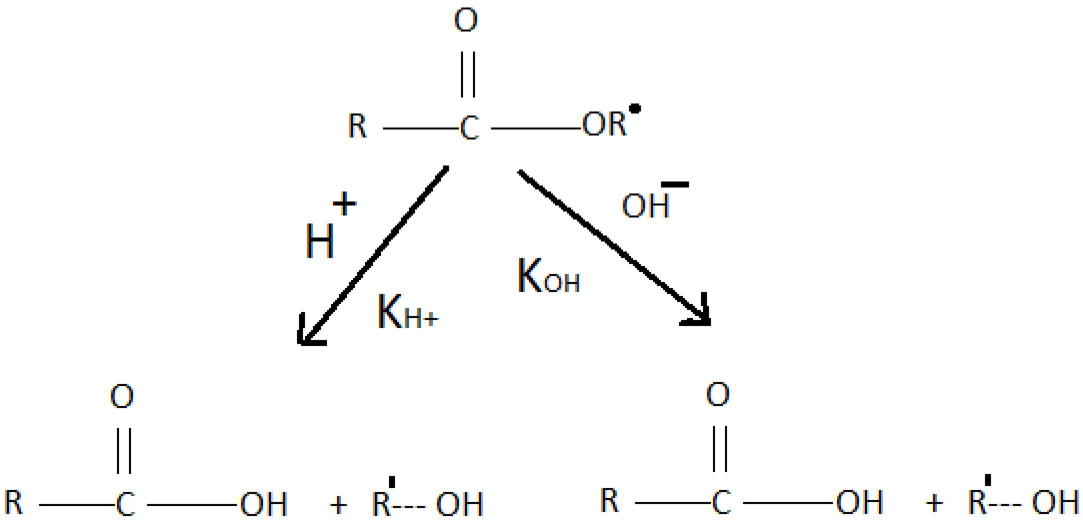
The dielectric constant affects the rate constant of an ionic reaction. For a reaction between ions of opposite sign, an increase in dielectric constant of the solvent results in a decrease in the rate constant. For ions of like charge, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.

3. **Catalysis effect: Specific Acid-Base Catalysis Effects**

The rate of a reaction is frequently influenced by the presence of a catalyst. A catalyst is defined as a substance that influences the speed of a reaction without itself being altered chemically.

Solutions of a number of drugs undergo accelerated decomposition on the addition of acids or bases.

If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base, so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions. Best example of specific acid-base catalysis, is the hydrolysis of esters.



The general formula for hydrolysis of ester which affected by both H^+ and OH^- is $-\frac{dc}{dt} = K_{observed}$ [ester]

$$K_{observed} = K_{H^+} [H^+] + K_{OH^-}[OH^-]$$

$K_{observed}$ = total rate constant of the system

K_{H^+} = rate constant for acid catalysis reaction

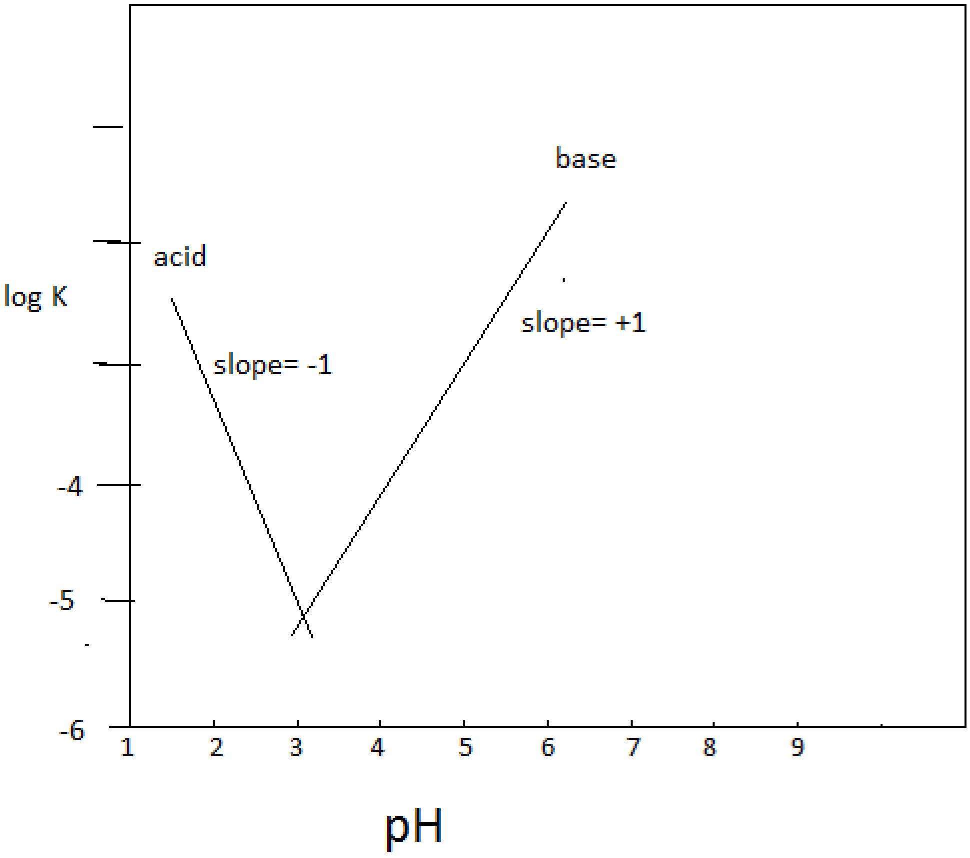
K_{OH^-} = rate constant for base catalysis reaction

$[H^+]$ = hydrogen ion concentration

$[OH^-]$ = hydroxide ion concentration

Note: K_{H^+} and K_{OH^-} are second order rate constants.

The pH- Rate profile for the specific acid-base-catalyzed hydrolysis of ester as shown in this figure:



Explanation of pH- Rate profile

1. at low PH

$$K_{\text{observed}} = K_{H^+} [H^+] + K_{OH^-}[OH^-]$$

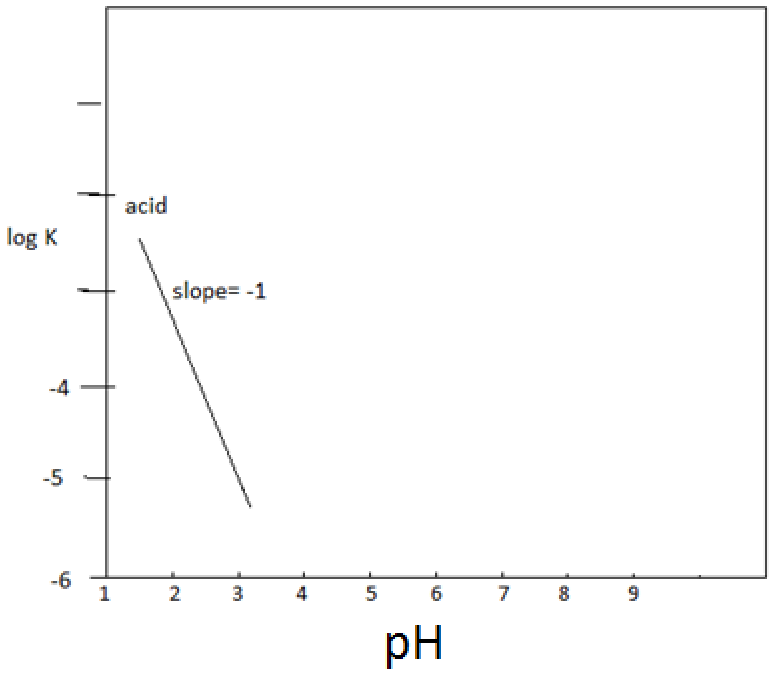
Since $[OH^-]$ concentration value is very low, thus the part ($K_{OH^-}[OH^-]$) is neglected from equation at low pH.

So, $K_{\text{observed}} = K_{H^+} [H^+]$

$\log K_{\text{observed}} = \log K_{H^+} + \log [H^+]$

$\log K_{\text{observed}} = \log K_{H^+} - \text{pH}$

$\log K_{\text{observed}} = \log K_{H^+} \mathbf{-1} \text{x pH}$



2. at high PH

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

Since $[H^+]$ concentration value is very low, thus the part $(K_{H^+}[H^+])$ is neglected from equation at high pH.

So, $K_{observed} = K_{OH^-}[OH^-]$

$Kw = [H^+][OH^-] \longrightarrow [OH^-] = Kw/[H^+]$

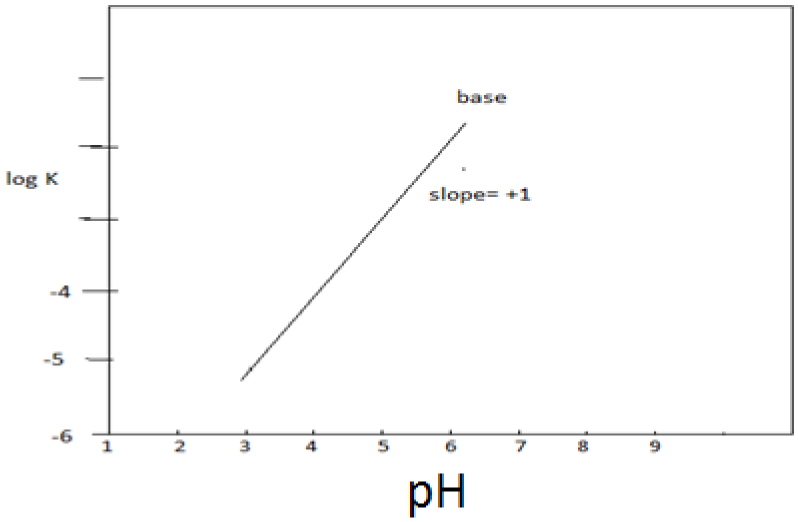
$K_{observed} = K_{OH^-}[OH^-]$

$K_{observed} = K_{OH^-}\frac{kw}{[H+]}$

$\log K_{observed} = \log K_{OH^-} + \log kw - \log [H^+]$

$\log K_{observed} = \log K_{OH^-} + \log kw + pH$

$\log K_{observed} = (\log K_{OH^-} + \log kw) + \mathbf{1} x\ pH$



STABILITY OF PHARMACEUTICALS

Decomposition and Stabilization of Medicinal Agents

Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis, and these processes may affect the stability of drugs in liquid, solid, and semisolid products.

Examples of Martin physical pharmacy text book

Example 1 In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$

The rate of reaction is

$$\text{Rate} = -\frac{d[(CH3CO)2O]}{dt}$$

$= k\,[(CH_3CO)_2O]\,[C_2H_5OH]^2$

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 serves 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

$-d\,[(CH_3C0)_2O]/dt = k'[(CH_3CO)_2O]$

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

Example .2

Shelf Life of an Aspirin Suspension-

A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is 4.5×10^{-6} sec^{-1}. Calculate the zero-order rate constant. Determine the shelf life, t_{90}, for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

Answer: $k_o = k \times$ [Aspirin in solution], from equation ($k\,[A] = k_0$). Thus,

$k_o = (4.5 \times 10^{-6}\ sec^{-1}) \times (0.33\ g/100\ mL)$

$k_o = 1.5 \times 10^{-6}\ g/100\ mL\ sec^{-1}$

$t_{90} = 0.10[A]_o / k_0 =$

$[(0.10 X 6.5\ g/100\ mL)] / [(1.5 \times 10^{-6}\ g/100\ mLsec^{-1})]$

$= 4.3 \times 10^{5}$ sec = 5.0 days

EXAMPLE .3

Decomposition of Hydrogen Peroxide

The 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 using equation ($k=\frac{2.303}{t}\log\frac{C0}{C}$).

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

(a)

$$k=\frac{2.303}{t}\log\frac{C0}{C}$$

$$k=\frac{2.303}{t}\log\frac{57.90}{9.60} = 0.0277\ \text{min}^{-1}$$

(b)

$$0.0277 = \frac{2.303}{25}\log\frac{57.90}{C}$$

c = 29.01

EXAMPLE .4

First-Order 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?

We have

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

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

Example .5

Saponification of Ethyl Acetate

Walker investigated the saponification of ethyl acetate at 25°C:

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 *M*. The change in concentration, *x*, of alkali during 20 min was 0.000566 mole/liter, therefore, (a - x) = 0.01000 - 0.00566 = 0.00434.

Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation

$$\frac{x}{a(a-x)} = Kt$$

or

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

, we obtain

a=0.01

x=0.000566

a-x=0.009434

$$K = \frac{1}{0.01\times 20}\frac{0.000566}{0.009434} = 0.299 \text{ liter mole}^{-1}\text{min}^{-1}$$

(b) The half-life of a second-order reaction is

$$t1/2 = 1/ak$$

It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t_{1/2}=\frac{1}{0.01\times 0.299}=334.44\text{min}$$

Example .6

The rate constant k_1 for the decomposition of 5-HMF (5-hydroxymethylfurfural) at 120°C (393 K) is 1.173 hr^{-1} or 3.258 x 10^{-4} sec^{-1}, and k_2 at 140°C (413 K) is 4.860 hr^{-1}. What is the activation energy, Ea, in kcal/mole and the frequency factor, A, in sec^{-1} for the breakdown of 5-HMF within this temperature range?

We have

$$\log \frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

$$\log \frac{4.860}{1.173} = \frac{Ea}{2.303x1.987}\left(\frac{413-393}{413 \text{ x } 393}\right)$$

Ea = 23000 cal/mole

Ea = 23 kcal/mole

At 120°C, using equation

$\log K = \log A - \frac{Ea}{2.303R}\frac{1}{T}$

, we obtain

$\log (3.258 \text{ x } 10^{-4} \text{ sec}^{-1}) = \log A - \frac{23{,}000 \text{ cal}}{2.303x1.987}\frac{1}{393}$

A = 2 x 10^9 sec^{-1}

Example .7

Increased Shelf Life of Aspirin

Aspirin is most stable at pH 2.5. At this pH the apparent fist-order rate constant is 5 x 10^{-7} sec^{-1} at 25°C. The shelf life of aspirin in solution under these conditions can be calculated as follows:

t_{90} = 0.105/(5 x 10^{-7})= 2.1 x 10^{5} sec

= 2 days

As one can see, aspirin is very unstable in aqueous solution.

Would making a suspension increase the shelf life of aspirin?

The solubility of aspirin is 0.33g/100mL. At pH 2.5, the apparent zero- order rate constant for an aspirin suspension is

ko = 5 x 10^{-7} sec $^{-1}$ x 0.33 g/100 mL = 1.65 x 10^{-7} g/mL • sec

If one dose of aspirin at 650 mg per teaspoonful is administered, then one has 650 mg/5 mL = 13 g/100 mL. For this aspirin suspension,

t_{90} = [(0.1) (13)]/ [1.65 x 10^{-7}] = 7.9 x 10^{6} sec = 91 days

The increase in the shelf-life of suspensions as compared to solutions is a result of the interplay between the solubility and the stability of the drug. In the case of aspirin, the solid form of the drug is stable, whereas when aspirin is in solution it is unstable. As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.

Interfacial Phenomena

When phases exist together, the boundary between two of them is known as an interface. The properties of the molecules forming the interface are often sufficiently different from those in the bulk of each phase that they are referred to as forming an interfacial phase.

Several types of interface can exist, depending on whether the two adjacent phases are in the solid, liquid, or gaseous state as shown in the table. For convenience, these various combinations are divided into two groups, namely, liquid interfaces and solid interfaces.

liquid interfaces involve the association of a liquid phase with a gaseous or another liquid phase , while the solid interfaces will deal with systems containing solid–gas and solid–liquid interfaces. Although solid–solid interfaces have practical significance in pharmacy (e.g., the adhesion between granules, the preparation of layered tablets, and the flow of particles)

The term **surface** is customarily used when referring to either a gas–solid or a gas–liquid interface. Thus, a table top surface forms a gas–solid interface with the atmosphere above it, and the surface of a rain drop constitutes a gas–liquid interface.

Classification of Interfaces

Phase	**Interfacial Tension**	**Types and Examples of Interfaces**
Gas–Gas	—	No interface possible
Gas–liquid	γ_{LV}	Liquid surface, body of water exposed to atmosphere
Gas–solid	γ_{SV}	Solid surface, table top
Liquid–liquid	γ_{LL}	Liquid–liquid interface, emulsion
Liquid–solid	γ_{LS}	Liquid–solid interface, suspension
Solid–solid	γ_{SS}	Solid–solid interface, powder particles in contact

where the subscript L stands for liquid, V for vapor or gas, and S for solid

Liquid Interfaces

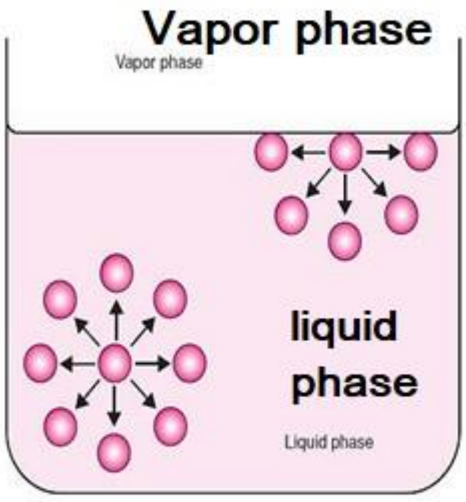
Surface and Interfacial Tensions

Surface tension :-

It is a property of the surface of the liquid that causes it to behave as an elastic sheet. It is caused by the attraction between molecules of the liquid by various intermolecular forces.

In the liquid state, the cohesive forces between adjacent molecules are well developed. Molecules in the bulk liquid are surrounded in all directions by other molecules for which they have an equal attraction. On the other hand, molecules at the surface (i.e., at the liquid–air interface) can only develop attractive cohesive forces with other liquid molecules that are situated below and adjacent to them.

They can develop adhesive forces of attraction with the molecules constituting the other phase involved in the interface, although, in the case of the liquid–gas interface, this adhesive force of attraction is small. The net effect is that the molecules at the surface of the liquid experience an inward force toward the bulk, as shown in the Figure. Such a force pulls the molecules of the interface together and, as a result, contracts the surface, resulting in a surface tension.



Unequal attractive forces acting on molecules at the surface of a liquid as compared with molecular forces in the bulk of the liquid

Interfacial tension

Is the force per unit length existing at the interface between two immiscible liquid phases and, like surface tension, has the units of dynes/cm.

Ordinarily, interfacial tensions are less than surface tensions because the adhesive forces between two liquid phases forming an interface are greater than when a liquid and a gas phase exist together. That’s mean:-

Adhesive forces between two liquids **More than** cohesive forces with the liquids

If two liquids are completely miscible, no interfacial tension exists between them.

Some representative surface and interfacial tensions are listed in the following table

Surface Tension and Interfacial Tension (Against Water) at 20°C

Substance	Surface Tension (dynes/cm)	Substance	Interfacial Tension (dynes/cm)
Mercury	476	Mercury	375
Water	72.8	Water	-------
Glycerin	63.4	Glycerin	Zero (miscible liquids)
Oleic acid (Carboxylic acid)	32.5	Oleic acid	15.6
Benzene	28.9	Benzene	35.0
Chloroform	27.1	Chloroform	32.8
Olive oil (Oleic acid is the chief constituent)	35.8	Olive oil	22.9
Octanol (alcohol)	26.5	Octanol	8.5

The values for surface tension reflect the nature of intermolecular forces present.
Large values for mercury (metallic bonds) and water (H-bond) and the lower values for benzene and chloroform (London forces)

Values of interfacial tensions reflects the differences in chemical structure of the two phases involved, the greater the tendency to interact, the less interfacial tension.
In each case the presence of chemical groups capable of hydrogen bonding with water markedly decrease interfacial tension.

Interfacial tension causes immiscible liquids to resist mixing. Oil and water do not mix because of interfacial tension. To dispense one in the other, it is necessary to introduce another kind of molecule that has affinity for both oil and water like an amphiphile molecule. This type of molecule is called surface active agent (S.A.A). These molecules when place them at the interface of oil and water will decrease the interfacial tension, allowing oil and water to mix

Both Surface and interfacial tensions decrease by increasing the temperature, due to increase in the kinetic energy of the molecules. They are also decrease by addition of S.A.A

Adsorption at Liquid Interfaces

Adsorption is a spontaneous phenomenon, adsorption can occur at the surface or interfaces of liquid with other liquids (**positive adsorption**).

It is the amphiphilic nature of surface-active agents that causes them to be adsorbed at interfaces, whether these are liquid–gas or liquid–liquid interfaces

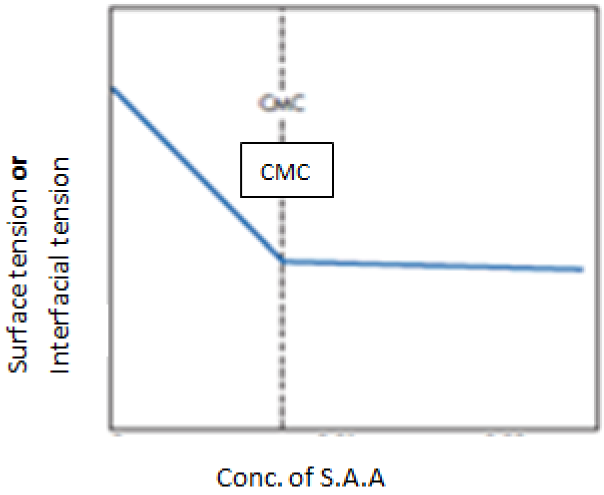
For the amphiphile to be concentrated at the interface, it must be balanced with the proper amount of polar and nonpolar groups. If the molecule is too hydrophilic, it remains within the body of the aqueous phase and exerts no effect at the interface. Likewise, if it is too lipophilic, it dissolves completely in the oil phase and little appears at the interface

On the other hand, **negative adsorption** is related to materials that are found in the bulk of liquid.

Effect of Surface active agents on surface and interfacial tension of water

The surface active agents reduce surface tension because when surfactant molecules adsorb at the water surface, the surfactant molecules replace some of the water molecules in the surface and the forces of attraction between surfactant and water molecules are less than those between two water molecules (interfere with hydrogen of water), hence the contraction force is reduced.

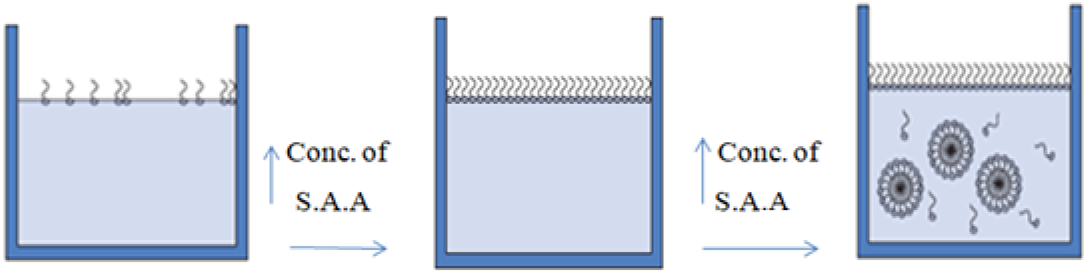
The surface tension decreases with increasing concentrations of the surface active agent; however, after a certain concentration of the surface active agent, the surface tension stops decreasing and reaches a plateau. This concentration is called critical micelle concentration (CMC).



(Note:- materials that concentrated in the bulk of liquid increase the surface tension of a liquid and they are called surface inactive agents like (e.g., inorganic electrolytes such as NaCl and sugar**)**

Why surface tension stops decreasing and reaches a plateau?

This is because at this concentration the surface is saturated with surface active molecules and any increase in their concentration will cause them to form micelles in the bulk



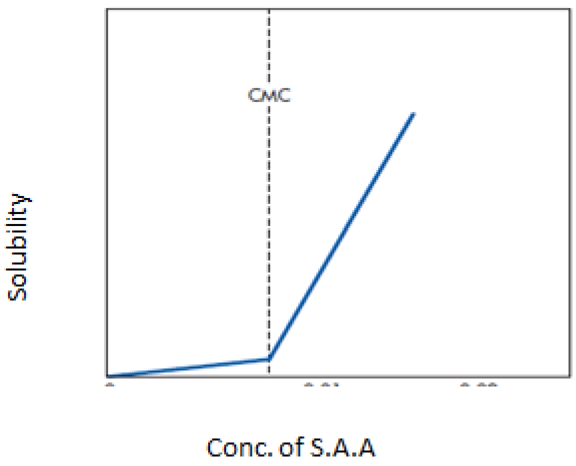
As more surface active agent is added to water, the surface of the water is covered by molecules of the surface active agent, and then micelles start forming

Why micells are formed?

To protect their hydrophobic groups from the aqueous environment

Effect of surfactant on solubility of slightly soluble substance

The ability of the solution to solubilize a drug, increase sharply when the concentration of the surface active agent increases beyond the CMC concentration since the nonpolar molecules in aqueous systems would be located in the hydrocarbon core of the micelle



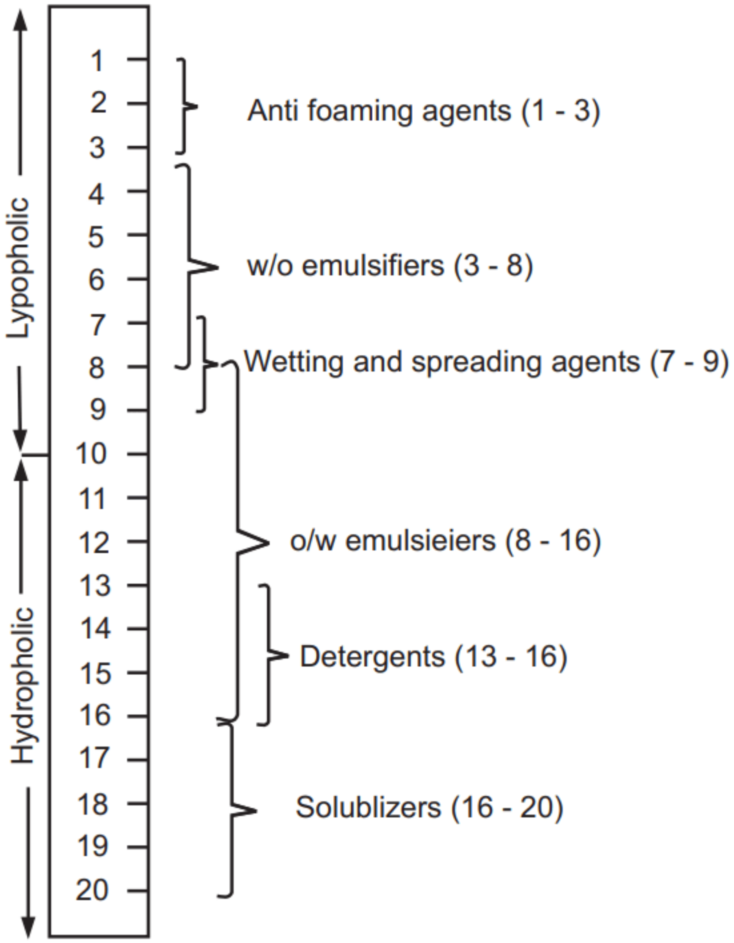
Hydrophile-Lipophile Balance

The hydrophile–lipophile balance (HLB) number is a measure of the balance between hydrophobic and hydrophilic portions of a surfactant.

The HLB of a surfactant is expressed using an arbitrary scale which ranges from 0 to 20

At the higher end of the scale, the surfactants are hydrophilic and act as solubilizing agents, detergents and oil-in-water emulsifiers.

Oil-soluble surfactants have low HLB and act as water-in-oil emulsifiers.



A scale showing surfactant function on the basis of hydrophilic–lipophilic balance (HLB) values. Key: O/W = oil in water, w/o= water in oil

Wetting phenomena and wetting agents

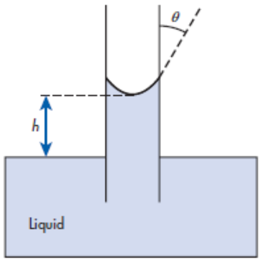
Wettability: - is the property that indicate the affinity between solid and fluid phase Talc or charcoal sprinkled on the surface of water, they will float despite the fact that their densities are higher than that of water.

In order for wetting of solid to occur, the liquid must displace air and spread over the surface of the solid, otherwise, we say that the solid is NOT wetted

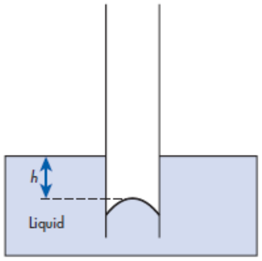
When a liquid comes into contact with the solid, the behavior of the liquid will depend on the balance between the forces of attraction of molecules in the liquid (cohesion) and the forces of attraction between the liquid and the solid phases (adhesion) .

In the case of mercury and glass, attractive forces between molecules of mercury and glass are much smaller than the forces of attraction between molecules of mercury themselves. As a result, mercury will come together as a single spherical drop.

In contrast, for water and glass, attractive forces between the solid and liquid molecules are greater than the forces between molecules of liquid themselves, and so the liquid is able to wet the surface of the glass.



A



B

A. Water can wet the glass

Because Adhesive forces more than cohesive

So water rise in side the capillary tube with concave surface

B .Mercury cannot wet the glass

Because cohesive forces more than adhesive

So mercury rise in side the capillary tube with convex surface

Many pharmaceutical preparations require dispersion of solid in liquids

Example: The preparation of **suspension** requires that the fine solid particles **immersed** and then **dispersed** in a liquid vehicle, that is mean the solid particles have to be wetted in order to be dispersed in a liquid.

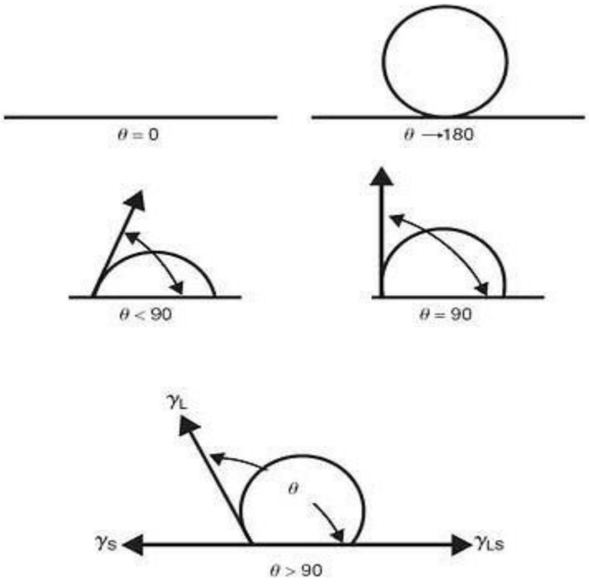
The parameter that reflects the degree of wetting is known as contact angle

Contact angle (Ɵ): - which is the angle between a liquid droplet and surface over which it spread it range from 0- 180° **(Figure below)**

Ɵ = zero means complete wetting (glass and water)

Ɵ= 180° weans no wetting (water and greasy surface)

The contact angle may also have any value between these limits (partial wetting)



Contact angles between 0°-180°

Hydrophilic materials have small contact angle with water while hydrophobic material have large contact angle

To increase wetting, the contact angle should be decreased this is done by adding surfactant which is called wetting agent

A wetting agent is a surfactant that, when dissolved in water, lowers the contact angle, aids in displacing an air phase at the surface, and replaces it with a liquid phase.

Examples of the application of wetting to pharmacy and medicine:-

The displacement of air from the surface of sulfur, charcoal, and other powders for the purpose of dispersing these drugs in liquid vehicles

The displacement of dirt by the use of detergents in the washing of wounds; and the application of medicinal lotions and sprays to the surface of the skin and mucous membranes

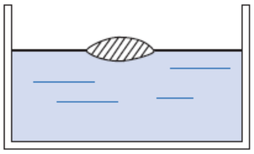
Spreading Coefficient

Lotions, creams, sunscreens, and many cosmetics have to be spread on the skin to exert their effect.

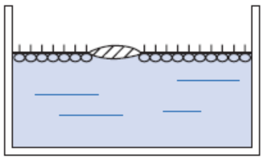
When a liquid spreads over the surface of a substrate, it covers all or a part of the surface. The substrate can be a solid or another liquid that is immiscible with the spreading liquid.

When a drop of oil is added on the surface of water, three things may happen:

1. The drop may spread as a thin film on the surface of water.
2. It may form a liquid lens if the oil cannot spread on the surface of water.
3. The drop may spread as a monolayer film with areas that are identified as lenses



A



B

A. Formation of a lens when a drop of oil is added to water.

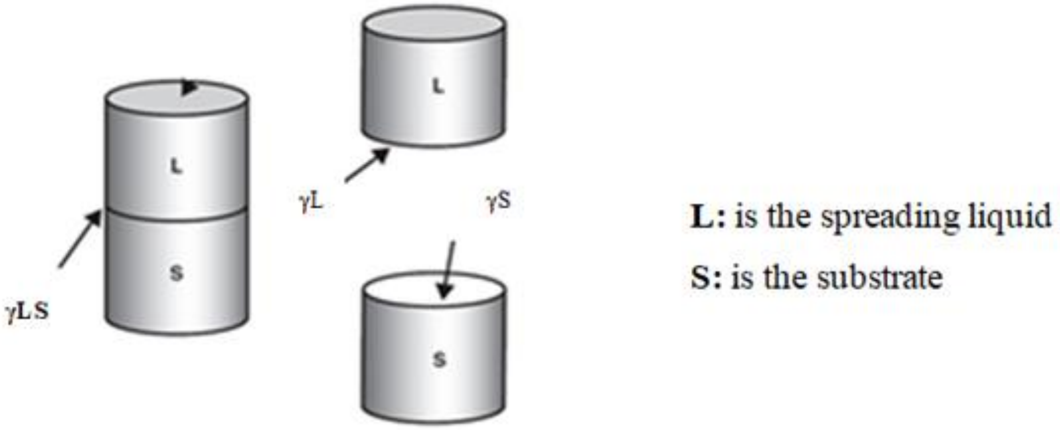
B. Monolayer of oil with a lens.

Spreading depends on the surface tension of the liquids involved and on the interfacial tension between them, that is mean spreading depends on the force of cohesion and adhesion.

For example : oleic acid is placed on the surface of water, it will spread as a film if the force of adhesion between the oleic acid molecules and the water molecules is greater than the cohesive forces between the oleic acid molecules themselves

Since spreading is dependent on the forces of adhesion and cohesion
That is mean it depend on work of adhesion and work of cohesion

Work of adhesion: is the energy required to break the attraction between the unlike molecules. OR to separate two immiscible liquids that form an interface



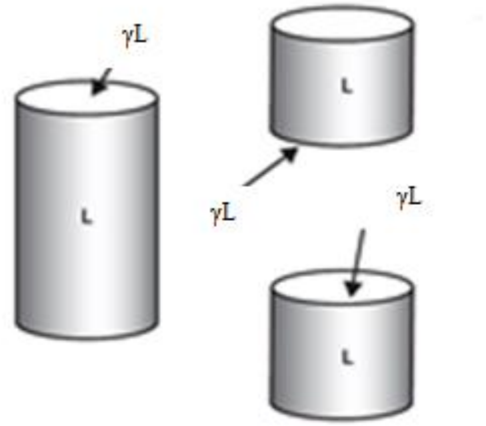
L: is the spreading liquid

S: is the substrate

The work of adhesion : is equal to the newly created surface tensions, γL and γS, minus the interfacial tension, γLS, that has been destroyed in the process. The work of adhesion is thus

Wa= γL + γS – γLS

The work of cohesion: is the work required to separate the molecules of the spreading liquid so that it can flow over the substrate



Wc= 2 γL

For spreading to occur the work of adhesion should be greater than the work of cohesion

Wa- Wc= S (S is known as spreading coefficient)

OR

$$S = W_a - W_c$$

$$= (\gamma_L + \gamma_S - \gamma_{LS}) - 2\gamma_L$$

$$= \gamma_L + \gamma_S - \gamma_{LS} - 2\gamma_L$$

$$= \gamma_S - \gamma_{LS} - \gamma_L$$

$$\mathbf{S = \gamma_S - (\gamma_L + \gamma_{LS})}$$

S = +ve value ; the liquid spread as a film

S = -ve value ; the liquid form globules or floating lens and fail to spread over the liquid

Example : Which liquid is spread over the other?

γHexane = 18 dyne/cm γwater = 72.8dyne/cm γHexane/water= 50.8

If we want to spread hexane over water

$S = \gamma S- (\gamma L +\gamma LS)$

S= 72.8 – (18+50.8)

S= 4.0 dyne/cm

If we want to spread water over hexane

$S = \gamma S- (\gamma L +\gamma LS)$

S= 18 – (72.8+50.8)

S= - 105.6 dyne/cm

Therefore the fact that both liquids are the same, the high surface tension of water prevent its spreading over hexane, while hexane with low surface tension and low cohesive forces can spread over water

Home Work

If you know that

γ_{water} = 72.8 dyne /cm $\gamma_{\text{oleic acid}}$ = 32.5 dyne/cm $\gamma_{\text{water/ oleic acid}}$=15.6dyne/cm

Which liquid can spread over the other ? Explain

Sometimes spreading will occur only initially, and later the spreading liquid will be converted and a lens will form.

The conversion of the liquid to a lens occurs because the two substances in contact with each other become mutually saturated and their respective surface tensions become different from the initial surface tensions (when the liquids were pure).

If we use a prime (′) to denote the values following equilibration (saturation) (i.e., final rather than initial values) , then the new surface tensions are $\gamma S'$ and $\gamma L'$. When mutual saturation has taken place, the **spreading coefficient may be reduced or may even become negative**

Example 16-7 :-If the surface tension of water γS is 72.8 dynes/cm at 20°C, the surface tension of benzene, γL, is 28.9 dynes/cm, and the interfacial tension between benzene and water, γLS, is 35.0 dynes/cm, what is the initial spreading coefficient? Following equilibration, $\gamma S'$ is 62.2 dynes/cm and $\gamma L'$ is 28.8 dynes/cm. What is the final spreading coefficient?

$S = \gamma S - (\gamma L + \gamma LS)$

$S = 72.8 - (28.9 + 35)$

$S = 8.9$ dyne/cm

After equilibrium

$S^{\backslash} = \gamma S^{\backslash} - (\gamma L^{\backslash} + \gamma LS)$

$S^{\backslash} = 62.2 - (28.8 + 35)$

$= -1.6$ dyne/cm

Therefore when benzene is added to water, one will observe an initial rapid spreading of benzene on the surface of the water, but later when benzene and water become mutually saturated with each other, the benzene retracts and forms a lens

Q11,12,13 مطلوب

In the case of organic liquids spread on water, it is found that although the initial spreading coefficient may be positive or negative, the final spreading coefficient always has a negative value

It is important to consider the types of molecular structures that lead to high spreading coefficient.

Initial Spreading Coefficient, S, at 20°C

Ethyl alcohol	50.4
Propionic acid	45.8
Ethyl ether	45.5
Acetic acid	45.2
Acetone	42.4
Undecylenic acid	32 (25°C)
Oleic acid	24.6
Chloroform	13
Benzene	8.9
Hexane	3.4
Octane	0.22
Ethylene dibromide	-3.19
Liquid petrolatum	-13.4

A material spreads over water because it contains polar groups such as COOH or OH.

But the carbon chain, increases, the ratio of polar–nonpolar character decreases and the spreading coefficient on water decreases

Many nonpolar substances, such as liquid petrolatum (S = -13.4), fail to spread on water. Benzene spreads on water not because it is polar but because the cohesive forces between its molecules are much weaker than the adhesion for water

Surface active agents (SAA) increase S because they interfere because the interfere with cohesive forces

Application of S.A.A

1- As emulsifying agents by decrease Interfacial tension

2- Wetting agents by decreasing the contact angle; wetting is the first step for dispersing a solid in a liquid vehicle

3-Detergents; which are surfactants that are used for removal of dirt

4- Solubilizing agents by formation of micells

5- A surfactant may affect the activity of a drug.

The presence of a low concentration of surfactant will potentiate the activity of anthelmintic drug. This potentiation of activity is due to a reduction in interfacial tension between the liquid phase and the cell wall of the organism. As a result, the adsorption and spreading of the drug over the surface of the organism is facilitated. When the concentration of surface-active agent present exceeds that required amount it will form micelles and the rate of penetration of the anthelmintic decreases nearly to zero. This is because the drug is now partitioned between the micelles and the aqueous phase, resulting in a reduction in the effective concentration. or may itself exert drug action

6- A surfactant may exert a drug action

Quaternary ammonium compounds are examples of surface-active agents that in themselves possess antibacterial activity. This may depend in part on interfacial phenomena, but other factors are also important. The agents are adsorbed on the cell surface and supposedly bring about destruction by increasing the permeability or “leakiness” of the lipid cell membrane. Death then occurs through a loss of essential materials from the cell. Both gram-negative and gram-positive organisms are susceptible to the action of the cationic quaternary compounds

Electrical Properties of interfaces

Electric Properties - charge on the surface of a particle

Particles dispersed in liquid media may become charged mainly in one of two ways.

The first involves the selective adsorption of a particular ionic species present in solution. This may be an **ion added to the solution** or, in the **case of pure water, it may be the hydronium or hydroxyl ion**. The majority of particles dispersed in water acquire a negative charge due to preferential adsorption of the hydroxyl ion because the hydronium ion is more hydrated than hydroxyl ion , so they have greater tendency to be in the bulk of aqueous medium , whereas the less hydrated hydroxyl ion have greater tendency to be adsorbed at the surface of particle

Second, charges on particles arise from ionization of groups that may be situated at the surface of the particle. In these cases, the charge is a function of pH and pKa .

Example amino acid and protein (have COOH and NH2) groups on their structure

At low pH , the protein will have +ve charge due to ionization of -NH2 groups to $-NH_3^+$

At high pH the protein will have –ve charge due to ionization of –COOH groups to $-COO^-$

At certain pH (specific for each protein), the total no. of +ve charge equal to the total no. of –ve charge and the net charge will be zero

This pH is termed as isoelectric point of protein and the protein exists as Zwitterion

The Electric Double Layer

Consider a solid surface in contact with a polar solution containing ions, for example, an aqueous solution of an electrolyte. Furthermore, let us suppose that some of the cations are adsorbed onto the surface, giving it a positive charge. Remaining in solution are the rest of the cations plus the total number of anions added. These anions are attracted to the positively charged surface by electric forces that also serve to repel the approach of any further cations once the initial adsorption is complete.

In addition to these electric forces, thermal motion tends to produce an equal distribution of all the ions in solution.

As a result, an equilibrium situation is set up in which some of the excess anions approach the surface, whereas the remainders are distributed in decreasing amounts as one proceeds away from the charged surface. At a particular distance from the surface, the concentrations of anions and cations are equal, that is, conditions of electric neutrality prevail. It is important to remember that the system as a whole is electrically neutral, even though there are regions of unequal distribution of anions and cations. Such a situation is shown in the Figure 1, where aa′ is the surface of the solid.

The adsorbed ions that give the surface its positive charge are referred to as the **potential-determining ions**. Immediately adjacent to this surface layer is a region of tightly bound solvent molecules, together with some negative ions, also tightly bound to the surface. The limit of this region is given by the line bb′ in the Figure 1. These ions, having a charge opposite to that of the potential-determining ions, are known as **counterions or gegenions**. The degree of attraction of the solvent molecules and counterions is such that if the surface is moved relative to the liquid, the shear plane is bb′ rather than aa′, the true surface.

In the region bounded by the lines bb′ and cc′, there is an excess of negative ions. The potential at bb′ is still positive because, as previously mentioned, there are fewer anions in the tightly bound layer than cations adsorbed onto the surface of the solid. Beyond cc′, the distribution of ions is uniform and electric neutrality is obtained.

Thus, the electric distribution at the interface is equivalent to a double layer of charge, the **first layer** (extending from aa′ to bb′) **tightly bound** and a **second layer** (from bb′ to cc′) that is **more diffuse**. **The so-called diffuse double layer therefore extends from aa′ to cc′.**

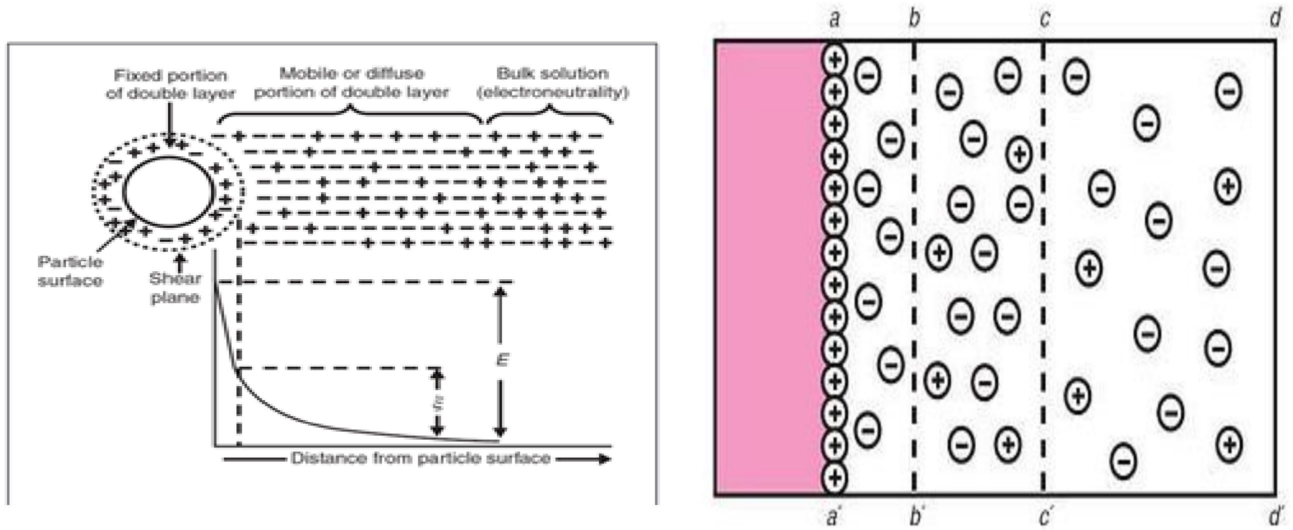


Fig. 1. The electric double layer at the surface of separation between two phases, showing distribution of ions. The system as a whole is electrically neutral.

Two situations other than that represented by the figure are possible:

(a) If the counterions in the tightly bound, solvated layer equal the positive charge on the solid surface, then electric neutrality occurs at the plane bb′ rather than cc′.

(b) Should the total charge of the counterions in the region aa′–bb′ exceed the charge due to the potential-determining ions, then the net charge at bb′ will be negative rather than less positive, as shown in the figure 2. This means that, in this instance, for electric neutrality to be obtained at cc′, an excess of positive ions must be present in the region bb′–cc′.

The student should appreciate that if the potential-determining ion is negative, the arguments just given still apply, although now positive ions will be present in the tightly bound layer.

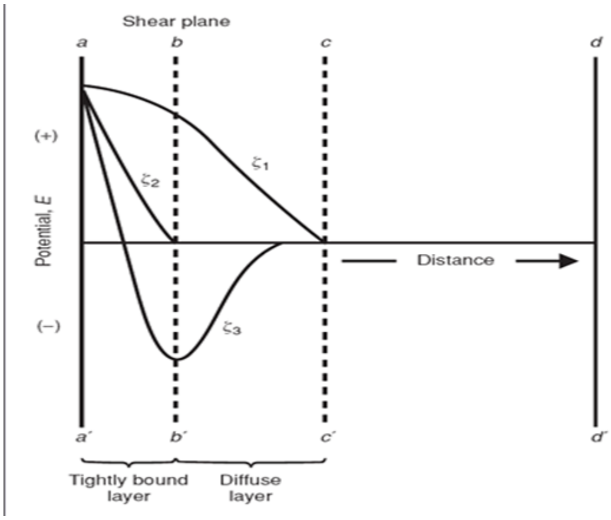


Fig. 2. Electrokinetic potential, E, at solid–liquid boundaries. Curves are shown for three cases characteristic of the ions or molecules in the liquid phase. Note that although E is the same in all three cases, the zeta potentials are positive (ζ1), zero (ζ2), and negative (ζ3).

Nernst and Zeta Potentials

The changes in potential with distance from the surface for the various situations discussed in the previous section can be represented as shown in Figure 2.

The potential at the solid surface aa′ due to the potential-determining ion is the electrothermodynamic **(Nernst) potential, E**, and is defined as the difference in potential +between the actual surface and the electroneutral region of the solution.

The potential located at the shear plane bb′ is known as the electrokinetic, or zeta, potential, **The zeta potential**, ζ is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electroneutral region of the solution.

As shown in Figure 2, the potential initially drops off rapidly, followed by a more gradual decrease as the distance from the surface increases. This is because the counterions close to the surface act as a screen that reduces the electrostatic attraction between the charged surface and those counterions further away from the surface.

The zeta potential has practical application in the stability of systems containing dispersed particles because this potential, rather than the Nernst potential, it governs the degree of repulsion between adjacent, similarly charged, dispersed particles.

If the zeta potential is reduced below a certain value (which depends on the particular system being used), the attractive forces exceed the repulsive forces, and the particles come together. This phenomenon is known as flocculation.

Effect of Electrolytes

As the concentration of electrolyte present in the system is increased, , the potential falls off more rapidly with distance and the thickness of the double layer decreased. A similar situation occurs when the valency of the counterion is increased while the total concentration of electrolyte is held constant. The overall effect frequently causes a reduction in zeta potential.

Application of Zeta potential

1- Interfacial Properties of Suspended Particles

The particles in a liquid suspension tend to **flocculate**, that is, to form light, fluffy conglomerates that are held together by weak van der Waals forces, but under certain conditions, the particles may adhere by stronger forces to form what are termed **aggregates** or **cake**

When the repulsion energy (zeta potential) is high, the collision of the particles is opposed. The system remains **deflocculated** (dispersed or suspended), and, when sedimentation is complete, the particles form a close-packed arrangement with the smaller particles filling the voids between the larger ones. Those particles lowest in the sediment are gradually pressed together by the weight of the ones above and they will adhere together by strong forces to form **aggregares or cake .**To resuspend and redisperse these particles, it is again necessary to overcome these forces .Because this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard **cake**.

Flocculated particles are weakly bonded, settle rapidly, do not form a cake, and are easily resuspended.

Therefore, a very high +ve or –ve zeta potential is not preferred in preparation of suspension, but its value should be controlled within certain limit as shown in the figure below, and this is done by adding a flocculating agents

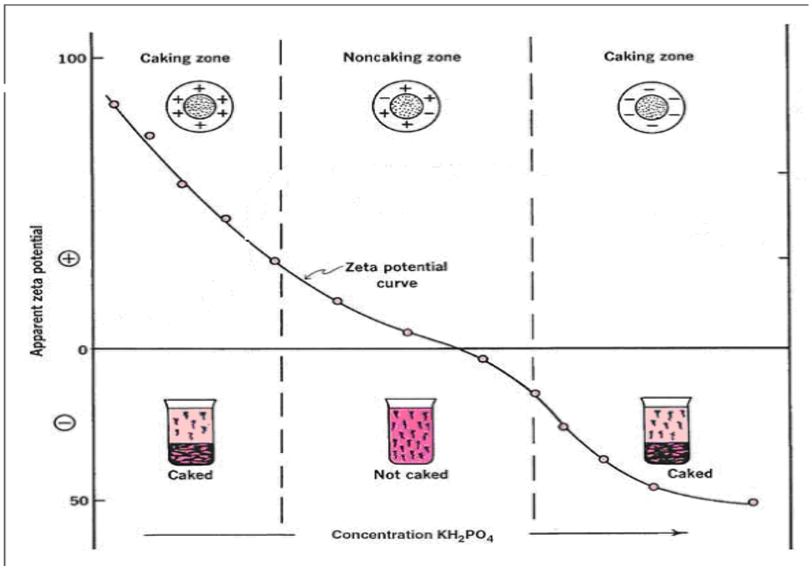


Fig. 3. Caking diagram, showing the flocculation of suspension by means of the flocculating agent monobasic potassium phosphate

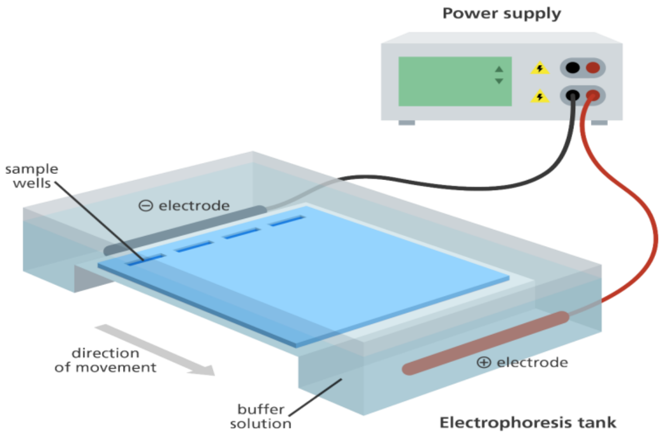
2- Electrokinetic Phenomena

The movement of a charged surface with respect to an adjacent liquid phase . The most important application of this phenomena is electrophoresis

3- Electrophoresis:

Involves the movement of a charged particle through a liquid under the influence of an applied potential difference. An electrophoresis cell fitted with two electrodes contains the dispersion. When a potential is applied across the electrodes, the particles migrate to the oppositely charged electrode. From knowledge of the direction and rate of migration , the sign and magnitude of zeta potential can be determined

It is mainly used for separation of plasma protein



Electrophoresis tank

Electrophoresis sheet

Colloidal Dispersions

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.

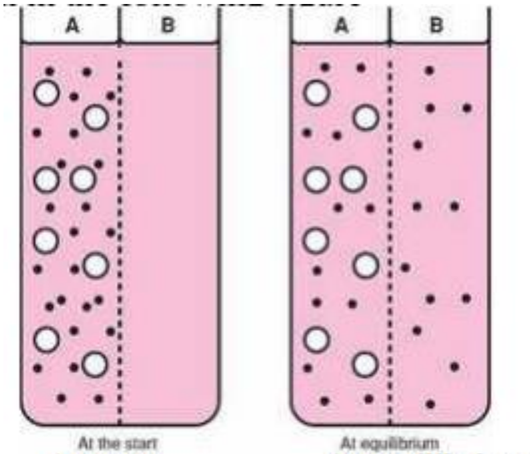
Based on the size of the dispersed phase, three types of dispersed systems are generally considered: (a) molecular dispersions, (b) colloidal dispersions, and (c) coarse dispersions. The size ranges assigned to these classes, together with some of the associated characteristics, are shown in the accompanying table

Classification of Dispersed Systems Based on Particle Size

Class	Particle Size*	Characteristics of System	Examples
Molecular dispersion	Less than 1 nm	1- Invisible in electron microscope 2- Pass through ultrafilter and semipermeable membrane 3- Undergo rapid diffusion	Oxygen molecules, ordinary ions, glucose
Colloidal dispersion	From 1 nm to 0.5 µm	1- Not resolved by ordinary microscope (although may be detected under ultramicroscope) Visible in electron microscope 2- Pass through filter paper 3- Do not pass semipermeable membrane 4- 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	1-Visible under microscope 2- Do not pass through normal filter paper 3-Do not pass through semipermeable membrane 4- 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.			

Diffusion through a semipermeable membrane

Because the size of colloidal particles, they can be separated from molecular particles by the use of semipermeable membrane. This technique is known as **Dialysis.** As shown in the following figure



At start At equilibrium

Conditions on the two sides, A and B, of the membrane are shown at the start and at equilibrium. The open circles are the colloidal particles that are too large to pass through the membrane. The solid dots are the electrolyte particles that pass through the pores of the membrane.

Dialysis occurs in vivo. Thus, ions and small molecules pass readily from the blood, through a natural semipermeable membrane, to the tissue fluids; the colloidal components of the blood remain within the capillary system. The principle of dialysis is utilized in the artificial kidney, which removes low–molecular-weight impurities from the body by passage through a semipermeable membrane

Types of Colloidal Dispersions*

(According to the type of dispersed phase and dispersion medium)

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

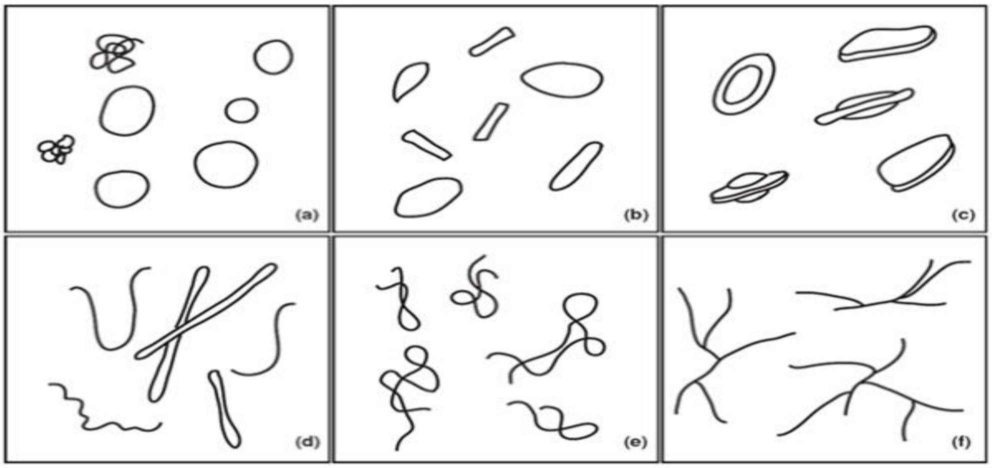
Note :- a gas in gas always produce a solution

Types of Colloidal Dispersion

(According to the shape of dispersed particles)

The shape adopted by particles in dispersion is important because the more extended the particle, the greater is its specific surface and the greater is the opportunity for attractive forces to develop between the particles of the dispersed phase and the dispersion medium.

Some representative shapes of spherocolloids and fibrous colloids are shown in Figure below



Some shapes that can be assumed by colloidal particles: (a) spheres and globules, (b) short rods and prolate ellipsoids, (c) oblate ellipsoids and flakes, (d) long rods and threads, (e) loosely coiled threads, and (f) branched threads**.**

Types of Colloidal Systems

(According to the interaction between the dispersed phase and dispersion medium)

Lyophilic Colloids

Systems containing colloidal particles that interact to an appreciable extent with the dispersion medium are referred to as lyophilic (solvent-loving) colloids. Owing to their affinity for the dispersion medium, such materials form colloidal dispersions, or sols, with relative ease. Thus, lyophilic colloidal sols are usually obtained simply by dissolving the material in the solvent being used.

For example, the dissolution of acacia or gelatin in water leads to the formation of a sol.

The various properties of this class 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). In the case of hydrophilic colloids, in which water is the dispersion medium, this is term is known as hydration.

((One of the most important property of lyophilic colloid is the presence of solvent sheath))

Most lyophilic colloids are organic molecules, for example, gelatin, acacia, insulin, albumin, rubber, and polystyrene. Of these, the first four produce lyophilic colloids in aqueous dispersion media (hydrophilic sols). Rubber and polystyrene form lyophilic colloids in nonaqueous, organic solvents. These materials accordingly are referred to as lipophilic colloids.

These examples illustrate the important point that the term lyophilic has meaning only when applied to the material dispersed in a specific dispersion medium. **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, so, their properties differ from those of the lyophilic colloids. This is primarily due to the absence of a solvent sheath 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.

In contrast to lyophilic colloids, it is necessary to use special methods to prepare lyophobic colloids.

Association Colloid

Association or amphiphilic colloids form the third group in this classification. They are certain organic molecules or ions, termed amphiphiles or surface-active agents, are characterized by having two distinct regions of opposing solution affinities within the same molecule or ion. When present in a liquid medium at low concentrations, the amphiphiles exist separately and are of such a size as to be subcolloidal. As the concentration is increased, aggregation occurs over a narrow concentration range. These aggregates, which may contain 50 or more monomers, are called micelles. **Because the diameter of each micelle is of the order of 50 Å, micelles lie within the size range of colloidal particles , such compounds are called association colloidal**.

Lyophilic	**Lyophobic**	**Association (Amphiphilic)**
Dispersed phase consists generally of large organic *molecules* lying within colloidal size range	Dispersed phase ordinarily consists of inorganic particles, such as gold or silver	Dispersed phase consists of aggregates (*micelles*) of small organic molecules or ions whose size *individually* is below the colloidal range
Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium	Little if any interaction occurs between particles and dispersion medium (no solvation)	Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or nonaqueous
Molecules disperse spontaneously to form colloidal solution	Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration
Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually highly asymmetric	Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be unsolvated and symmetric	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and become asymmetric
Dispersions are stable generally in the presence of electrolytes; they may be salted out by high concentrations of very soluble electrolytes; effect is due primarily to desolvation of lyophilic molecules	Lyophobic dispersions are unstable in the presence of even small concentrations of electrolytes; effect is due to neutralization of the charge on the particles; lyophilic colloids exert a protective effect	In aqueous solutions, the critical micelle concentration is reduced by the addition of electrolytes; salting out may occur at higher salt concentrations

Kinetic Properties of Colloids

There are several properties of colloidal systems that relate to the motion of particles with respect to the dispersion medium. The motion may be:-

1-Thermally induced
2- Gravitationally induced
3- Applied externally
4- Electrically induced motion

1-Thermally induced (increased by increasing temp)

Brownian motion

Brownian motion describes the random movement of colloidal particles. The erratic motion, resulting from the bombardment of the particles by the molecules of the dispersion medium. 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, while increasing the viscosity of the medium decreases and finally stops the Brownian movement.

Diffusion

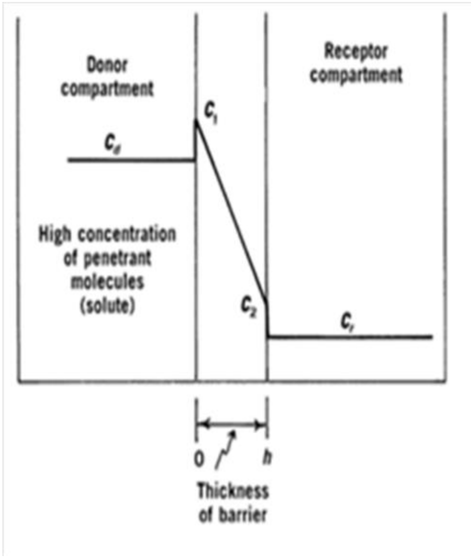
Particles diffuse spontaneously from a region of higher concentration to one of lower concentration until the concentration of the system is uniform throughout. Diffusion is a direct result of Brownian movement, therefore (all factors affect Brownian movement will affect diffusion)

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

$$dq = -\,DS\,\frac{dc}{dx}\,dt$$

$$g = -\,D\,cm^2\,\frac{g/cm\,3}{cm}\,sec \quad \rightarrow\rightarrow \quad D = cm^2\,/\,sec.$$ **(Units)**



It is normal for the concentration curve to increase or decrease sharply at the boundaries of the barrier because, in general, C1 is different from Cd, and C2 is different from Cr

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.

Negative sign in the equation, signifies that the diffusion occurs in decreasing concentration of diffusion

The passage of a substance may be through porous membrane or through tortuous pores or channels (example. Skin)

Smaller particles diffuse faster in a given media

Molecular > colloid > coarse

Passive diffusion caused by a concentration gradient and carried out through Brownian motion

It is important for the release of drug from topical preparation and in the GIT absorption of drugs

Osmosis

It is the action in which only the solvent is transferred, while the diffusion involve the passage of solute.

The osmotic pressure, π, of a dilute colloidal solution is described by the van't Hoff equation:

$\pi = cRT$

where c is molar concentration of solute , R, gas constant = 0.082 atm.mole/ L.deg

This equation can be used to calculate the molecular weight of a colloid in a dilute solution.

2- Gravitationally induced

Sedimentation

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

$$V = \frac{2r^2(\rho - \rho_0)\,g}{9\,\eta 0}$$

r = radius of particle, ρ = density of particle, ρ_0 = density of the dispersion medium

η_0 = viscosity of the dispersion medium, g = is the acceleration due to gravity

Factors affecting sedimentation

- Particle size (↓ particle size → ↓ sedimentation)
- Viscosity (↑ viscosity → ↓ sedimentation)
- Difference between the densities of the dispersed particles and the dispersion medium (↑ difference → ↑ sedimentation)

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 µm. This is because Brownian movement becomes significant and tends to offset sedimentation due to gravity and promotes mixing instead.

Consequently, a stronger force must be applied to bring about the sedimentation of colloidal particles in a quantitative and measurable manner. This is accomplished by use of the ultracentrifuge, which can produce a force one million times that of gravity.

3- Applied externally

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.

Viscosity study can give us information about

- The shape of particles in dispersion
- The molecular weight of the dispersed phase

The shape of particles in dispersion

The shapes of particles of the disperse phase affect the viscosity of colloidal dispersions. Spherocolloids form dispersions of relatively low viscosity, whereas systems containing linear particles are more viscous. The relationship of shape and viscosity reflects the degree of solvation of the particles. If a linear colloid is placed in a solvent for which it has a low affinity, it tends to “ball up,” that is, to assume a spherical shape, and the viscosity falls. This provides a means of detecting changes in the shape of flexible colloidal particles and macromolecules.

The molecular weight of the dispersed phase

The molecular weight of the is measured by using viscometer and the molecular weight obtained by this technique is called viscosity average molecular weight . The molecular weight of the polymer solution is very high so the viscosity of polymer solution is very high compared to that of pure solvent.

From the Mark-Houwink equation the relationship between the molecular weight and viscosity is given below

$$[\eta] = KM^{\alpha}$$

Where $[\eta]$ is the intrinsic viscosity, M is the molecular weight, K and α are constants for a particular polymer solvent system.

If we know the k and α values for a given polymer solution, the intrinsic viscosity and molecular weight can be calculated using the above equation.

4- Electrically induced motion

It is the movement of charged surface with respect to an adjacent liquid phase. One of the most important application for such movement is the electrophoresis.

RHEOLOGY

The term rheology, comes from the Greek rheo ("to flow") and logos ("science"). Rheology is used to describe the flow of liquids and the deformation of solids.

Viscosity is an expression of the resistance of a fluid to flow; the higher the viscosity, the greater is the resistance.

The simple liquids can be described in terms of absolute viscosity (single value).

The heterogeneous dispersions rheologic properties are more complex, however, and cannot be expressed by a single value.
Manufacturers of medicinal and cosmetic creams, pastes, and lotions must be capable of producing products with acceptable consistency and smoothness.

Valuable information can be obtained by use of analytic methods of rheology, for formulating better pharmaceutical products.
The rheology of product can affect patient acceptability, physical stability, and even biologic availability.
Rheologic properties of a pharmaceutical system can influence the selection of processing equipment.

Classes of materials according to types of flow:

1. Newtonian systems or
2. Non-Newtonian systems.

NEWTONIAN SYSTEMS

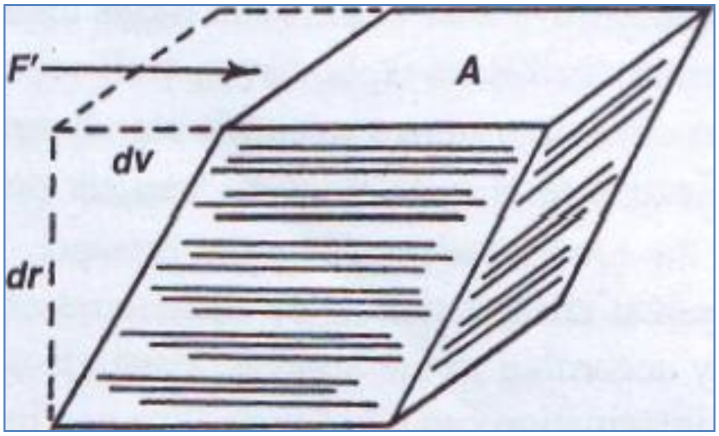
Newton's Law of Flow

<u>Rate of shear</u> or the velocity gradient: $(\frac{dv}{dr})=G$

Is the difference of velocity, dv, between two planes of liquid separated by an infinitesimal distance dr.

<u>Shearing stress</u> :$(\frac{F'}{A})=F$

Is the force per unit area required to bring about flow.



<u>Newton</u> was recognized that the higher the viscosity of a liquid, the greater is the force per unit area (shearing stress) required to produce a certain rate of shear. Hence, rate of shear should be directly proportional to shearing stress, or

$$\frac{F'}{A}=\eta\frac{dv}{dr}$$

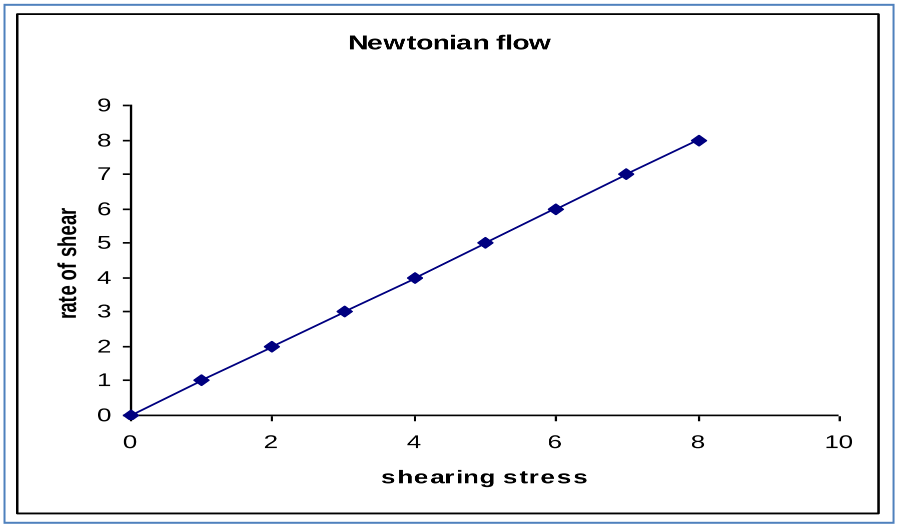
Where, η is the coefficient of viscosity, usually referred to simply as viscosity.

Above equation is frequently written as

$$\eta = \frac{F}{G}$$

where, F = F'/A and G = dv/dr.

A representative flow curve, or rheogram, obtained by plotting F versus G for a Newtonian system is shown in this figure.



The unit of viscosity is the poise, defined as the shearing force required to produce a velocity of 1 cm/sec between two parallel planes of liquid each 1 cm^2 in area and separated by a distance of 1 cm. The units for poise are dyne sec cm^{-2} (i.e., dyne sec/cm^2) or g cm^{-1} sec^{-1} (i.e., g/cm sec).

A more convenient unit for most work is the centipoise (cp), 1 cp being equal to 0.01 poise.

Fluidity, φ, a term sometimes used, is defined as the reciprocal of viscosity:

$$\varphi = \frac{1}{\eta}$$

Kinematic Viscosity

Kinematic viscosity is the absolute viscosity divided by the density of the liquid at a specific temperature:

$$\text{Kinematic viscosity} = \frac{\eta}{\rho}$$

The units of kinematic viscosity are the stoke (s) and the centistoke (cs).

Absolute viscosities of some Newtonian liquids at 20 C° commonly used in pharmacy are given in this table

Liquid	Viscosity (cp)
Castor oil	1000
Olive oil	100
Water	1.0019

Note. Water is ordinarily used as a standard for viscosity of liquids. Its viscosity at 25°C is 0.8904 cp.

Temperature Dependence and the Theory of Viscosity

The viscosity of liquid decreases as temperature is raised, and the fluidity of a liquid (the reciprocal of viscosity) increases with temperature. The dependence of the viscosity of a liquid on temperature is expressed approximately for many substances by an equation analogous to the Arrhenius equation of chemical kinetics:

$$\eta = Ae^{EvRT}$$

where A is a constant depending on the molecular weight and molar volume of the liquid and E_V, is an "activation energy" required to initiate flow between molecules.

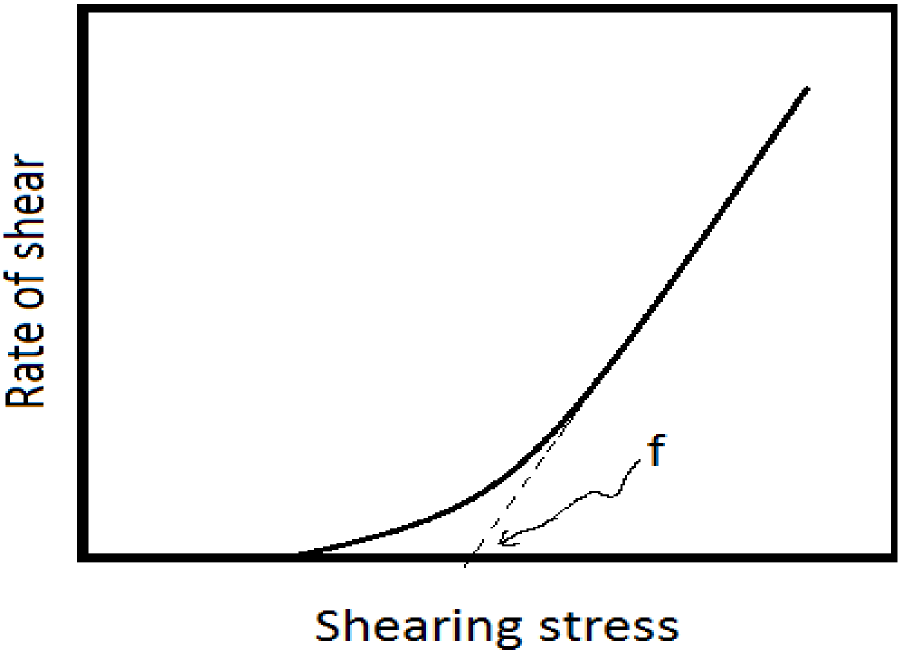
NON-NEWTONIAN SYSTEMS

The majority of fluid pharmaceutical products are not simple liquids and do not follow Newton's law of flow. These systems are referred to as non-Newtonian. Non-Newtonian behavior is generally exhibited by liquid and solid heterogeneous dispersions such as colloidal solutions, emulsions, liquid suspensions, and ointments. When non-Newtonian materials are analyzed in a rotational viscometer and results are plotted, various consistency curves, representing three classes of flow, are recognized:

Plastic, pseudoplastic, and dilatant.

Plastic Flow

In Figure below, the curve represents a body that exhibits plastic flow; such materials are known as Bingham bodies.



Plastic flow curves do not pass through the origin, but rather intersect the shearing stress axis (or will if the straight part of the curve is extrapolated to the axis) at a particular point referred to as the yield value.

A Bingham body does not begin to flow until a shearing stress corresponding to the yield value is exceeded. At stresses below the yield value, the substance acts as an elastic material.

Yield value is an important property of certain dispersions.

The slope of the rheogram in the Figure is termed the mobility, analogous to fluidity in Newtonian systems, and its reciprocal is known as the plastic viscosity, U. The equation describing plastic flow is

$$U = \frac{F - f}{G}$$

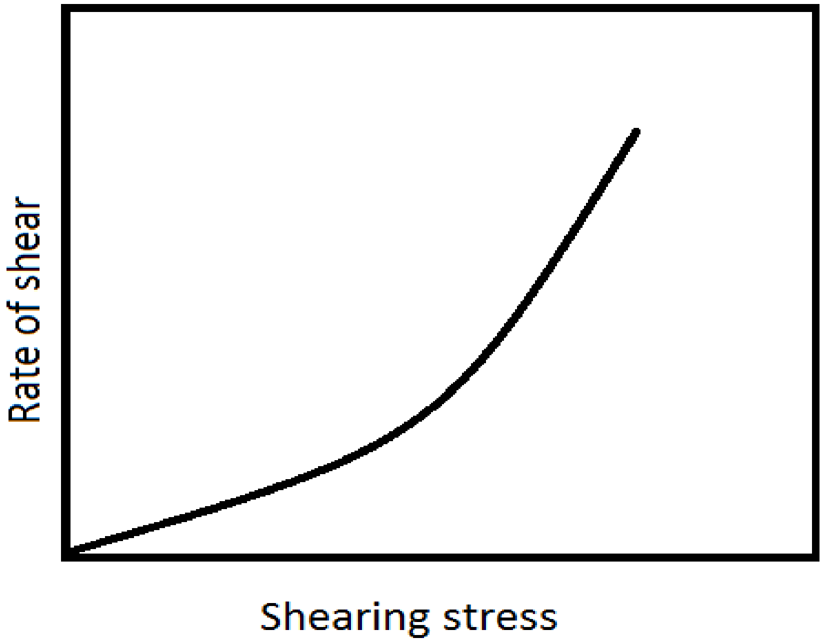
Where, f is the yield value, or intercept, on the shear stress axis in dynes/cm^2.

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. As a result, a continuous structure is set up throughout the system. A yield value exists because of the contacts between adjacent particles (brought about by van der Waals forces), which must be broken down before flow can occur. Consequently, the yield value is an indication of force of flocculation: The more flocculated the suspension, the higher will be the yield value.

Pseudoplastic Flow

Many pharmaceutical products, including liquid dispersions of natural and synthetic gums (e.g., sodium alginate, and methylcellulose) exhibit pseudoplastic flow.

Pseudoplastic flow is typically exhibited by polymers in solution, in contrast to plastic systems, which are composed of flocculated particles in suspension. As seen in this Figure, the consistency curve for a pseudoplastic material begins at the origin. Therefore, there is no yield value as there is in a plastic system.



Furthermore, because no part of the curve is linear, the viscosity of a pseudoplastic material cannot be expressed by any single value.

The viscosity of a pseudoplastic substance decreases with increasing rate of shear.

An apparent viscosity can be obtained at any rate of shear from the slope of the tangent to the curve at the specified point.

The most satisfactory representation for a pseudoplastic material, however, is probably a graphic plot of the entire consistency curve.

Objective comparisons between different pseudoplastic systems are more difficult than with either Newtonian or plastic systems. For example, Newtonian systems are completely described by viscosity, η, and plastic systems are adequately described by yield value, f, and plastic viscosity, U.

However, the exponential formula can be used to compare rheology of pseudoplastic materials to be compared.

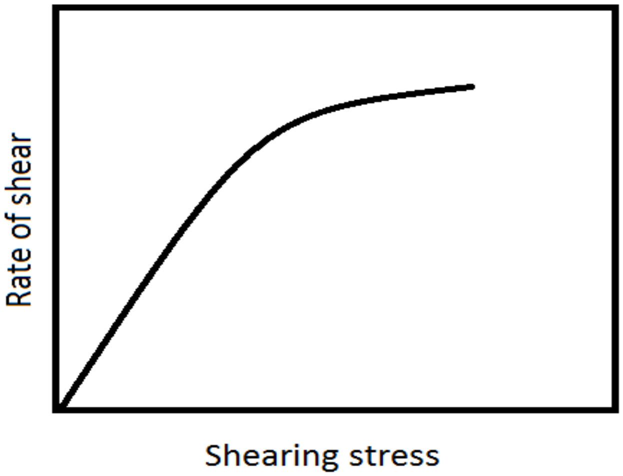
$$F^N = \eta\,'G$$

The exponent N rises as flow becomes increasingly non-Newtonian.

When N = 1, the equation reduces to equation ($\eta = \frac{F}{G}$) and flow is Newtonian. The term η ' is a viscosity coefficient.

Dilatant Flow

Certain suspensions with a high percentage of dispersed solids exhibit an increase in resistance to flow with increasing rates of shear. Such systems actually increase in volume when sheared and are hence termed dilatant; Figure illustrates their flow properties.



This type of flow is the inverse of that possessed by pseudoplastic systems.

Whereas pseudoplastic materials are frequently referred to as "shear-thinning systems," dilatant materials are often termed "shear-thickening systems." When stress is removed, a dilatant system returns to its original state of fluidity. Equation ($F^N = \eta$ 'G) can be used to describe dilatancy in quantitative terms. In this case, N is always less than 1 and decreases as degree of dilatancy increases. As N approaches 1, the system becomes increasingly Newtonian in behavior. Substances possessing dilatant flow properties are invariably suspensions containing a high concentration (about 50 % or greater) of small, deflocculated particles.

THIXOTROPY

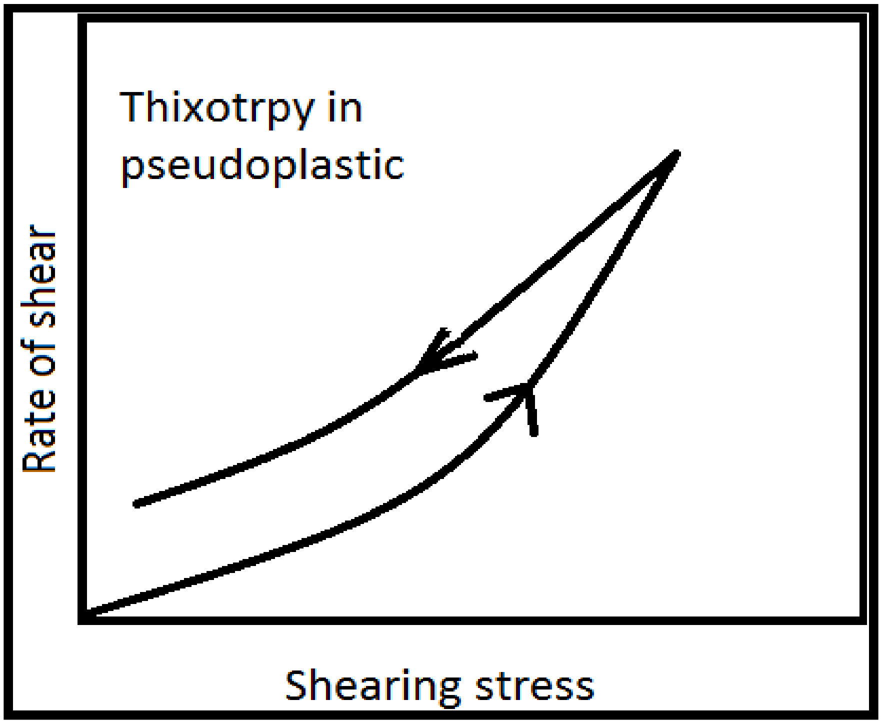
Several types of behavior are observed when rate of shear is progressively increased and plotted against resulting shear stress.

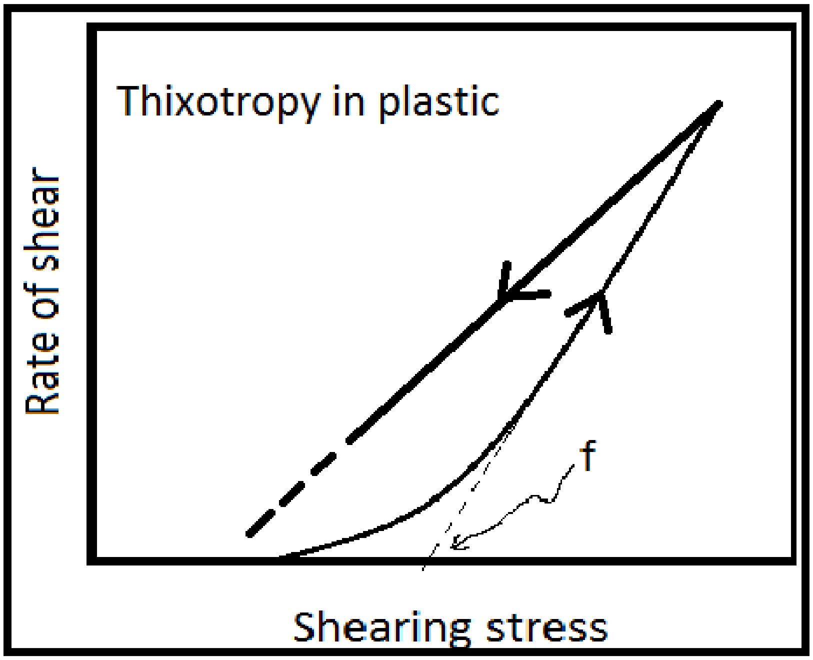
If the rate of shear were reduced when the maximum had been reached, and the resulted downcurve is identical with the upcurve, this system is Newtonian systems.

With shear-thinning systems (i.e., pseudoplastic), the downcurve is frequently displaced to the left of the upcurve (Figure), showing that the material has a lower consistency at the downcurve than at upcurve.

This phenomenon, known as thixotropy, can be defined as "an isothermal and comparatively slow recovery, on standing of a material, of a consistency lost through shearing."

Typical rheograms for plastic and pseudoplastic systems exhibiting this behavior are shown in the following Figure.





Rheograms obtained with thixotropic materials are highly dependent on the rate at which shear is increased or decreased and the length of time a sample is subjected to any one rate of shear.

<u>Hysteresis loop</u>: Is the area between the upcurve and downcurve of rheogram.

So the rheogram for same product is different depending on time of shear, rate of shear, and degree of structure in the sample.

This is an important point to bear in mind when attempting to obtain a quantitative measure of thixotropy.

Measurement of Thixotropy

The area of hysteresis has been proposed as a measure of thixotropic breakdown; it can be obtained readily by means of a planimeter or other suitable technique.

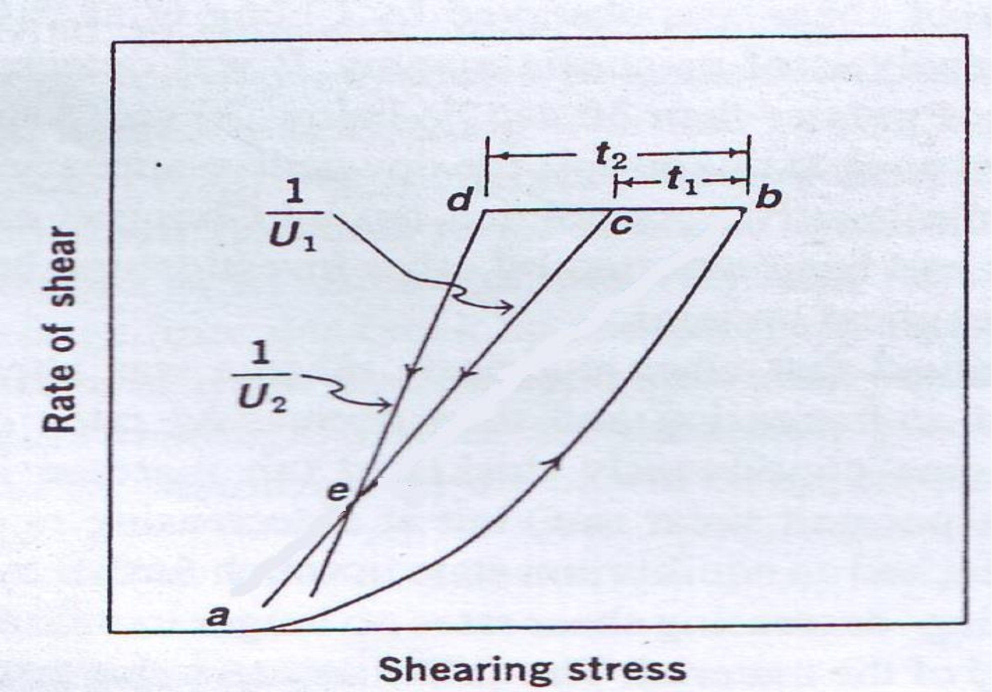
With plastic (Bingham) bodies, two approaches are frequently used to estimate degree of thixotropy. The first is to determine structural breakdown with time of a plastic system possessing thixotropy when subjected to a constant rate of shear for t. (the maximum shear rate is constant, the time of holding before reducing shearing stress is different)

Based on such a rheogram,

a thixotropic coefficient, B, the rate of breakdown with time at constant shear rate, is calculated as follows:

$$B = \frac{U1 - U2}{\ln \frac{t2}{t1}}$$

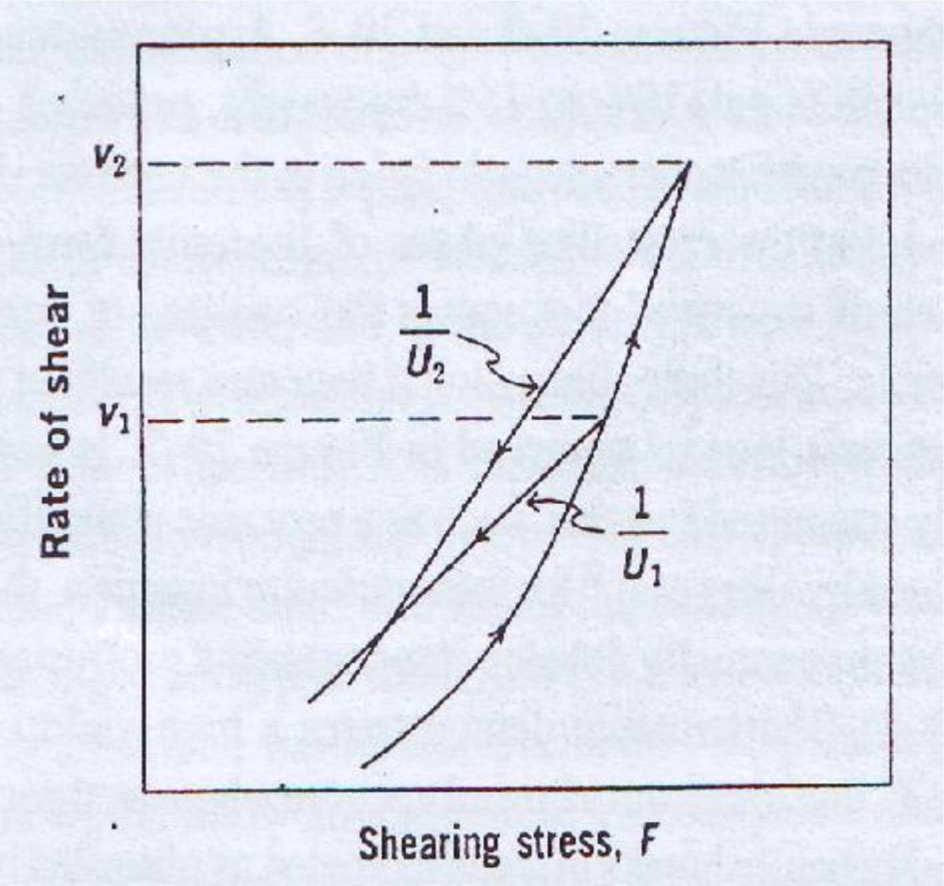
where U1, and U2 are the plastic viscosities of the two downcurves, calculated from equation ($U = \frac{F - f}{G}$), after shearing at a constant rate for t1 and t2 seconds, respectively.



The second approach is to determine the Structural breakdown of a plastic system possessing thixotropy when subjected to increasing shear rates. (The maximum shear rate is different; the time of holding before reducing shearing stress is constant). The principle involved in this approach is two hysteresis loops are obtained having different maximum rates of shear, v1, and v2. In this case, a thixotropic coefficient, M, the loss in shearing stress per unit increase in shear rate, is obtained from

$$M = \frac{U1 - U2}{\ln(\frac{v2}{v1})}$$

where M is in dynes sec/cm^2 and U1, and U2 are the plastic viscosities for two separate downcurves having maximum shearing rates of v1 and v2, respectively.


V_2
V_1
$\frac{1}{U_2}$
$\frac{1}{U_1}$
Rate of shear
Shearing stress, F

Negative Thixotropy

Negative thixotropy or antithixotropy, it is phenomenon represents an increase rather than a decrease in consistency on the downcurve. This increase in thickness with increased time of shear was observed in the rheologic analysis of magnesia magma. It was detected at shear rates of greater than 30 sec^{-1}; below 30 sec^{-1} the magma showed normal thixotropy, the downcurve appearing to the left of the upcurve

Negative thixotropy or antithixotropy should not be confused with dilatancy or rheopexy.

Dilatant systems are deflocculated and ordinarily contain greater than 50% by volume of solid dispersed phase, whereas antithixotropic systems have low solids content (1%-10%) and are flocculated.

Rheopexy is a phenomenon in which solid forms a gel more readily when gently shaken than when allowed to form the gel while the material is kept at rest. In a rheopectic system, the gel is the equilibrium form, whereas in antithixotropy, the equilibrium state is the sol.

DETERMINATION OF RHEOLOGIC PROPERTIES

Choice of Viscometer

Because shear rate in a Newtonian system is directly proportional to shearing stress, instruments that operate at a single shear rate can be used. These "single-point" instruments provide a single point on the rheogram; extrapolation of a line through this point to the origin will result in a complete rheogram.

For Non-Newtonian, a single-point determination is virtually useless in characterizing its flow properties. It is therefore essential that, with non-Newtonian systems, the instrument can operate at a variety of shear rates. Such multipoint instruments are capable of producing a complete rheogram for non-Newtonian systems.

The main instruments used for determination of rheological properties : Capillary, falling-sphere, cup-and-bob, and cone-and-plate viscometers. The first two are single-shear-rate instruments suitable for use only with Newtonian materials, whereas the latter two (multipoint, rotational instruments) can be used with both Newtonian and non-Newtonian systems.

VISCOELASTICITY

Viscoelastic measurements are based on the mechanical properties of materials that exhibit both viscous properties of liquids and elastic properties of solids. Many of the systems studied in pharmacy belong to this class, examples being creams, lotions, ointments, suppositories, suspensions, and the colloidal dispersing, emulsifying, and suspending agents.

Pharmaceutical areas in which rheology is significant

1. Fluids

a. Mixing

b. Particle-size reduction of disperse systems with shear

c. Passage through orifices, including pouring, packaging in bottles, and passage through hypodermic needles

d. Fluid transfer, including pumping and flow through pipes e. Physical stability of disperse systems

2. Quasisolids

a. Spreading and adherence on the skin

b. Removal from jars or extrusion from tubes

c. Capacity of solids to mix with miscible liquids d. Release of the drug from the base

3. Solids

a. Flow of powders from hoppers and into die cavities in tabletting or into capsules during encapsulation

b. Packagability of powdered or granular solids

4. Processing

a. Production capacity of the equipment

b. Processing efficiency