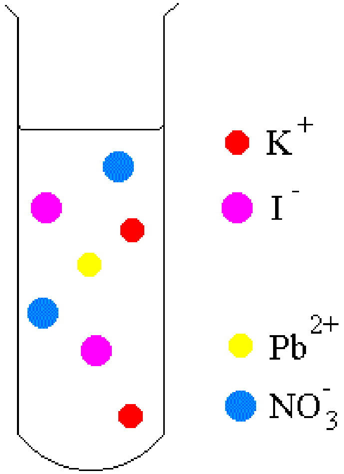
Solubility and distribution



Dr. Ghaidaa S. Hameed
Physical pharmacy II

Reference: Sinko, Patrick J. Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 6th Edition

Objectives of the Chapter

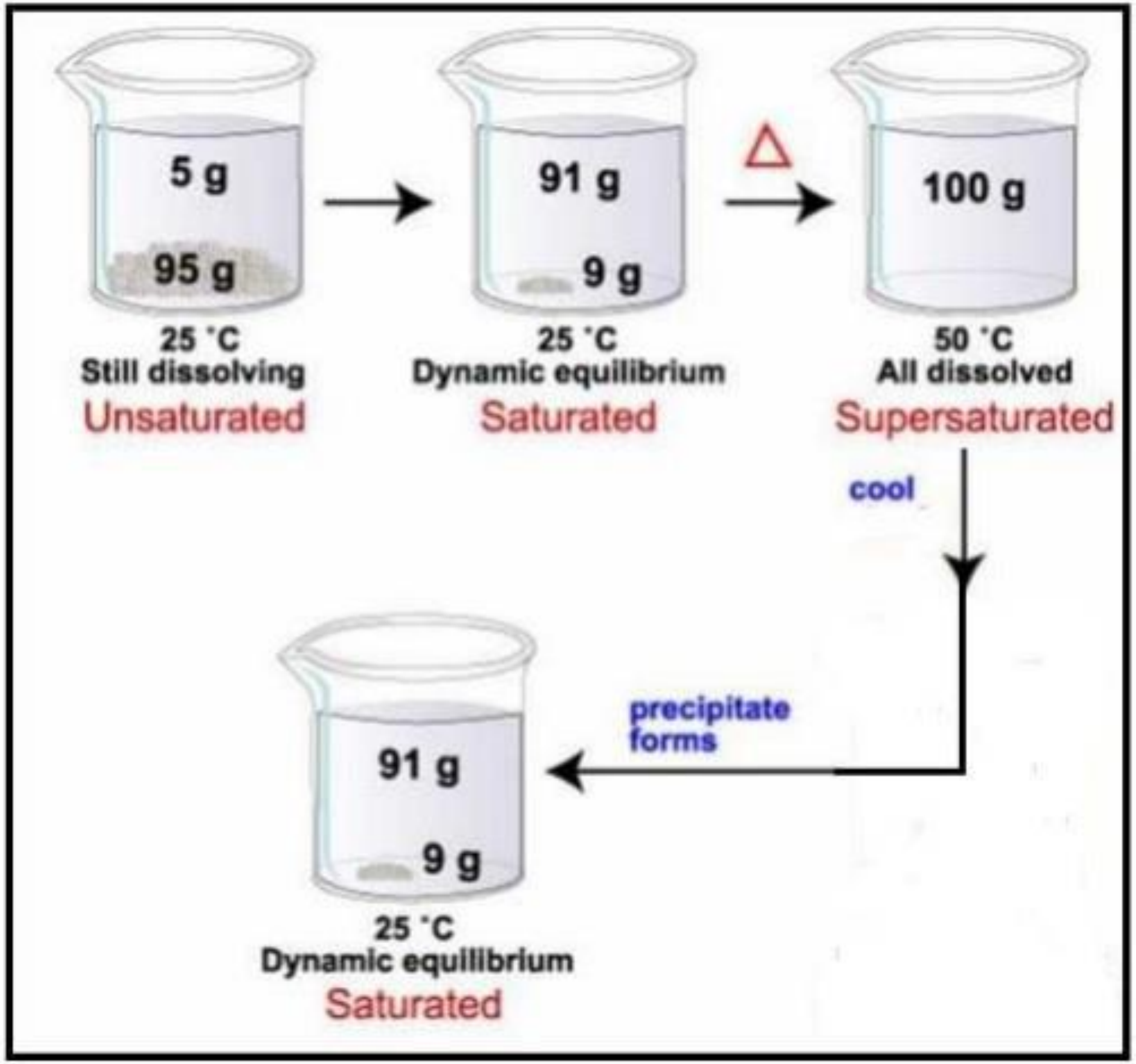
- Define solubility, saturated & unsaturated solutions and polar & non polar solvents.
- Understand the factors controlling the solubility of strong & weak electrolytes.
- Define partition coefficient & its importance in pharmaceutical systems.

Solubility:

- **In a quantitative way:** it is the **concentration** of solute in a saturated solution at a certain temperature.
- **In a qualitative way:** it is the spontaneous **interaction** of two or more substances (solute & solvent) to form a homogeneous molecular dispersion.

- **A saturated solution** is one in which the solute in solution is in equilibrium with the solid phase.
- **An unsaturated solution:** or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.
- **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).


5 g
95 g
25 °C
Still dissolving
Unsaturated
91 g
9 g
25 °C
Dynamic equilibrium
Saturated
△
100 g
50 °C
All dissolved
Supersaturated
cool
precipitate forms
91 g
9 g
25 °C
Dynamic equilibrium
Saturated

Factors affecting solubility

1-Physical and chemical properties of the solute and the solvent.

2- Temperature of the solution.

3- Pressure of the solution.

4- pH of the solution.

5- State of subdivision of the solute.

- **Solubility Expression:**

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 M, c Moles** (gram molecular weights) of solute in 1 liter (1000 ml) of solution.
- **Molality m Moles** of solute in 1000 gm of solvent.
- **Normality N** Gram equivalent weights of solute in 1 liter of solution
- **Mole Fraction x** Ration of moles of solute to total moles of solute+ solvent
- **Percentage by Weight % w/w gm** of solute in 100 gm of solution
- **Percentage by Volume %v/v ml** of solute in 100 ml of solution
- **Percentage Weight in Volume % w/v gm** of solute in 100 ml of solution Solubility expressions

- 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 as seen in the following table :

Table 9-1 Solubility Definition in the United States Pharmacopeia

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

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.

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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 reducethe 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:

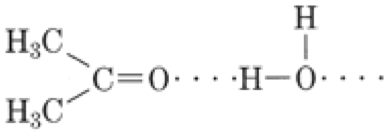
Polar solvents are capable of solvating molecules & ions through dipole interaction forces.

The solute must be polar to compete for the bonds of the already associated solvent molecules.

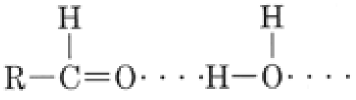
Example: Ion-dipole interaction between sodium salt of oleic acid & water

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

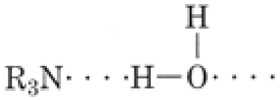
Alcohol



Ketone



Aldehyde



Amine

- **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)

$$C2 \propto p$$

$$C2 = \sigma p$$

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.

$C2 = \sigma p$

$\sigma = \frac{C2}{p} = \frac{0.016 g/l}{300 mmHg} = 5.33 \times 10^{-5}$ (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 (eg. carbonated solutions) induces liberation of gases from the solutions. ***Why?***

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

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.

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

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

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

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

Influence of Foreign Substances

If the added material is soluble in only one of the two components, the mutual solubility of the liquid pair is decreased.

Example, if naphthalene is added to a mixture of phenol and water, it dissolves only in the phenol, the miscibility is decreased.

If potassium chloride is added to a phenol-water mixture, it dissolves only in water and decreases the miscibility.

If the added material is soluble in both of the liquids, the mutual solubility of the liquid pair is increased.

Example, The addition of succinic acid or sodium oleate to a phenol-water system increases the mutual solubility.

The increase in mutual solubility of two partially miscible solvents by another agent is ordinarily referred to as **blending.**

SOLUBILITY OF SOLIDS IN LIQUIDS

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

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

Ideal solution of solids

The solubility of a solid in an ideal solution depends on

1- Temperature, (direct relationship)

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

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

4- 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.

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

where;

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T_0 - T}{TT_0}\right)$$

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:
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 I>II>VII
According to ΔH_f II>I>VII

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

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T_0 - T}{TT_0}\right)$$

For I: $-\log X_2^i = 9550/2.303 \times 1.987\,(431-298/298\text{x}431)$
$X_2^i = 0.0069$
For II: $-\log X_2^i = 9700/2.303 \times 1.987\,(426-298/298\text{x}426)$
$X_2^i = 0.0073$
For VII: $-\log X_2^i = 2340/2.303 \times 1.987\,(368-298/298\text{x}368)$
$X_2^i = 0.4716$
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

$$a2 = X_2\gamma_2$$

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

$$\log a2 = \log X2 + \log \gamma_2$$

In an ideal solution, $a2 = X_2^{i}$ because $ɣ_2 = 1$, and, accordingly, the ideal solubility equation can be expressed in terms of activity as

$$-\log \alpha 2 = -\log X_2^{i} = \frac{\Delta H f}{2.303R}\left(\frac{T_0 - T}{T T_0}\right)$$

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

$$\boxed{-\log X_2^{i} = \frac{\Delta H f}{2.303R}\left(\frac{T_0 - T}{T T_0}\right)}$$

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

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

$$-\log X_2^i = \frac{\Delta Hf}{2.303R}\left(\frac{T_0 - T}{TT_0}\right)$$

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

X_2 for chlorobenzene (nonpolar solvent)= 0.444, for water = $1.76 \text{ x} 10^{-5}$

$$-\log X_2 = \frac{\Delta Hf}{2.303R}\left(\frac{T_0 - T}{TT_0}\right) + \log \gamma_2$$

$-\log 0.444 = 4500/2.303\text{x}1.987(353\text{-}313/313\text{x}353) + \log \gamma_2$

$\gamma_2 = 0.99$

For water

$-\log 1.76 \text{ x}10^{-5} = 4500/2.303\text{x}1.987(353\text{-}313/313\text{x}353) + \log \gamma_2$

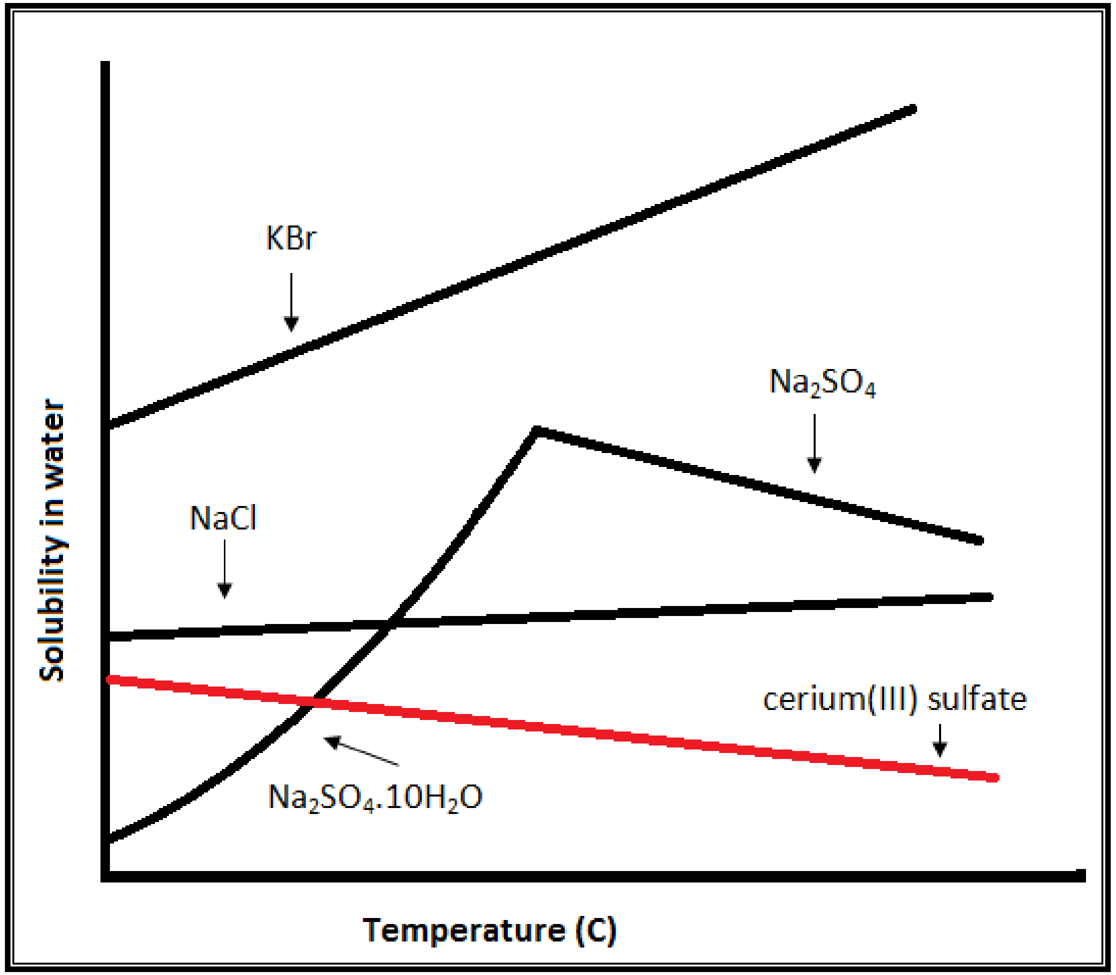
$\gamma_2 = 25003$

So there is inverse relationship between X_2 and γ_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, and the heat of solution is approximately zero.


KBr
Na$_2$SO$_4$
NaCl
cerium(III) sulfate
Na$_2$SO$_4$.10H$_2$O
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 alkalies 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, alkaloidal 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:

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

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.

$$pHp = pKa + \log \frac{S - S_o}{S_o} \qquad \text{(for a weak acid)}$$

$$pHp = pKw - pKb + \log \frac{S_o}{S - S_o} \qquad \text{(for a weak base)}$$

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

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

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

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

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

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

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 unsymmetric 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

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

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 $[Ag^+][Cl^-] > K_{sp}$

and some of the AgCl precipitates from the solution (the reaction shift to left) until the equilibrium $[Ag^+][Cl^-] = K_{sp}$ 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 excess 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 insufficient 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

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

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

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

- 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

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

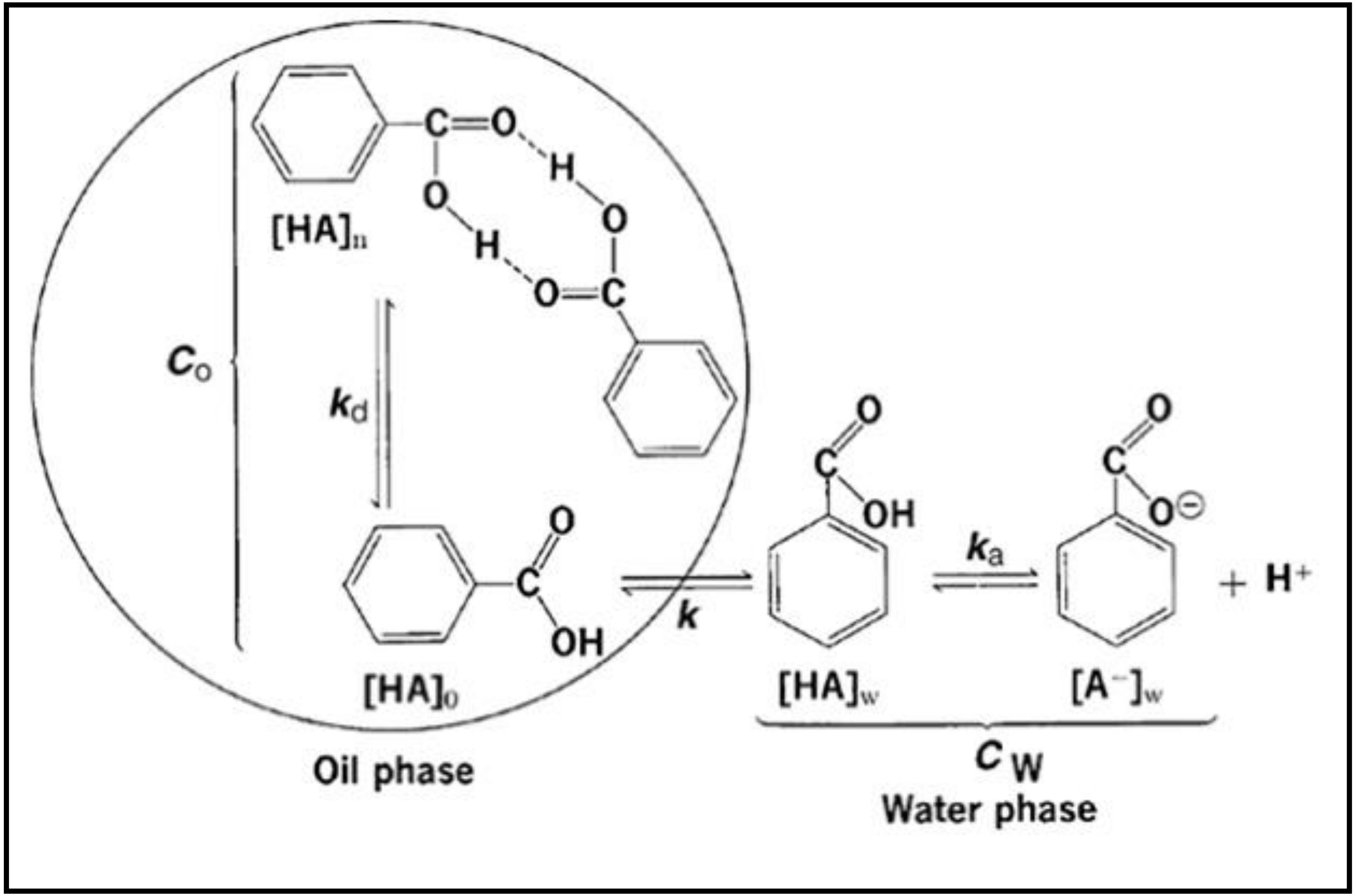
The experimentally observed or apparent distribution coefficient determined by using the total acid concentration (all species) obtained by analysis is

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

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
$[A^-]_w$
$+ H^+$
C_W
Oil phase
Water phase

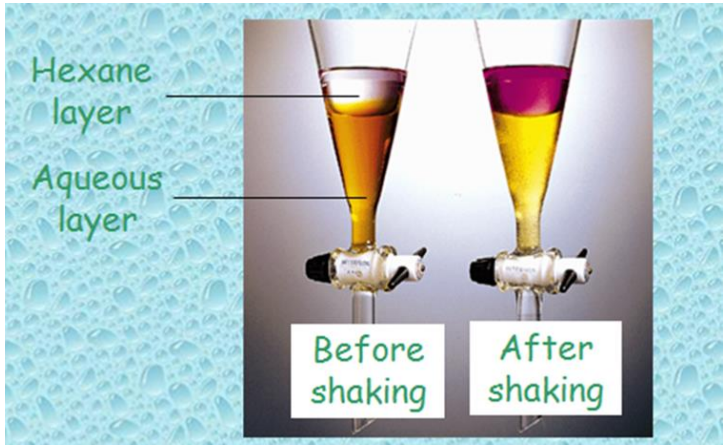
Extraction

- 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, $q = V_o/V_w = 1$.

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

$C= (5.33+1+ (6.4x10^{-5}/10^{-4}))0.25$

= 1.74 mg/ml