



## Lecture 1

# Solubility and Distribution Phenomena

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## Overview

### Solubility Phenomena

- Introduction
- Solute-Solvent Interactions
- Solubility of gas in liquid
- Solubility of liquid in liquid
- Solubility of solid in liquid

### Distribution Phenomena

- Partition Coefficient (K)
- Partition Coefficient (P)
- Apparent Partition Coefficient ( $P_{app}$ )
- Extraction

# Learning Objectives

1. Define saturated solution, solubility, and unsaturated solution.
2. Describe and give examples of polar, nonpolar, and semipolar solvents.
3. Define complete and partial miscibility.
4. Understand the factors controlling the solubility of weak electrolytes.
5. Describe the influence of solvents and surfactants on solubility.
6. Describe what a distribution coefficient and partition coefficient are and their importance in pharmaceutical systems.



## Solubility Phenomena

Introduction

Solute-Solvent Interactions

Solubility of gas in liquid

Solubility of liquid in liquid

Solubility of solid in liquid

# Introduction

A *solution* is a system in which molecules of a solute are dissolved in a solvent.

*Solubility* is defined as the maximum solute concentration in a certain solvent at a certain temperature.

When a solution contains:

A solute at the limit of its solubility, it is said to be *saturated*.

A solute below the limit of its solubility, it is said to be *unsaturated* or *subsaturated*.

A solute above the limit of its solubility, it is said to be *supersaturated*, were the undissolved solute present.



## Solute-Solvent Interactions

“Like dissolves Like”

Polar substances tend to dissolve in polar solvents, while nonpolar substances tend to dissolve in nonpolar solvents.

The more similar the Intermolecular attractions are, the more likely one substance is to be soluble in another.

**Types of solvents:**

Polar solvents

Nonpolar solvents

Semipolar solvents



# Solute-Solvent Interactions

## Polar Solvents

Polar solvents dissolve ionic solutes and polar substances.

The solubility of a drug in polar solvent depends on:

- 1. The polarity of the solute and the solvent.**
- 2. The ability of the solute to form hydrogen bonds.**

Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water.

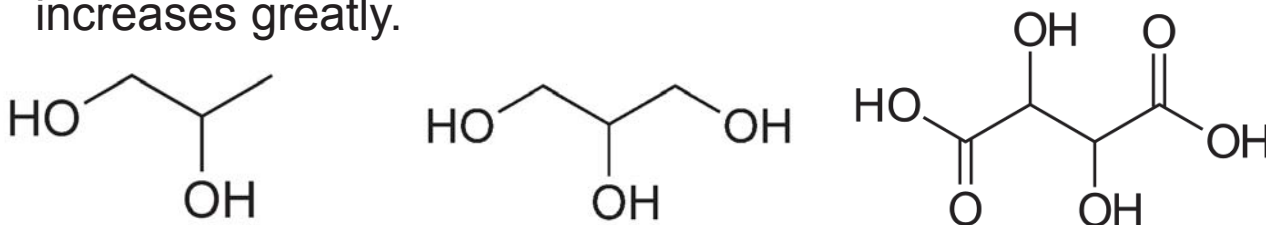


# Solute-Solvent Interactions

## Polar Solvents

### 3. The ratio of polar to nonpolar groups of the molecule

When additional polar groups are present in the molecule (e.g. propylene glycol, glycerin, and tartaric acid), water solubility increases greatly.



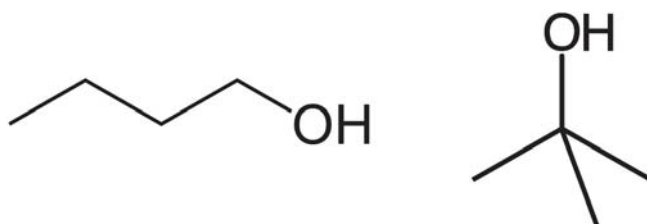
As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility in water decreases (e.g. Straight chain monohydroxy alcohols, aldehydes, and acids with more than 4 carbons cannot enter into the hydrogen-bonded structure of water and hence are slightly soluble).



# Solute-Solvent Interactions

## Polar Solvents

Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility (e.g. Tertiary butyl alcohol is miscible in all proportions with water, whereas n-butyl alcohol dissolves only to a small extent).



# Solute-Solvent Interactions

## Non-polar Solvents

Ionic and polar solutes are not soluble or are only slightly in nonpolar solvents (e.g. hydrocarbons) because:

- Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants.
- Nonpolar solvents cannot break covalent bonds and ionize weak electrolytes, because they are aprotic.
- Nonpolar solvents cannot form hydrogen bridges with nonelectrolytes.

Non polar solvents dissolve non polar solutes with similar attractive forces through induced dipole interactions (London forces) (e.g.  $\text{CCl}_4$  can dissolve oils and fats).



# Solute-Solvent Interactions

## Semi-polar Solvents

Semipolar solvents act as intermediate solvents that generate miscibility between polar and non-polar liquids (e.g. Acetone increases the solubility of ether in water).



## Solubility of Gas in Liquid

The solubility of gases in liquids depends on:

1. The mass of gas molecules
2. Pressure
3. Temperature
4. Presence of salt
5. Chemical reactions with solvent

### The Mass of Gas Molecules

The solubility of gas molecules typically increases with increasing mass of the gas molecules.

The larger the mass of gas molecules, the stronger London and Debye forces are between gas and solvent molecules.



# Solubility of Gas in Liquid

## Pressure

Gases increase in solubility with an increase in pressure.

Increasing the pressure results in more collisions of the gas molecules with the surface of the solvent (more solvation); and hence greater solubility.

## Temperature

Gases decrease in solubility with an increase in temperature.

Increasing temperature causes an increase in kinetic energy of gas molecules which leads to breakdown of intermolecular bonds and gas escaping from solution.

E.g. Carbon dioxide gases escape faster from a carbonated drink as the temperature increases.



# Solubility of Gas in Liquid

## Presence of Salts

Dissolved gases are often liberated from solutions by the introduction of an electrolyte (e.g. NaCl) and sometimes by a non electrolyte (e.g. sucrose) (How?). This phenomenon is known as SALTING OUT.

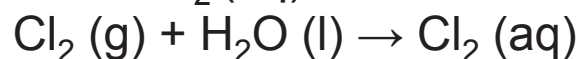
## Effect of Chemical Reaction

Some gases are a lot more soluble than what their mass would predict (e.g. Cl<sub>2</sub> is 50 times more soluble than Kr).

Cl<sub>2</sub> dissolved in H<sub>2</sub>O can undergo a chemical reaction to produce HClO:



This chemical reaction removes Cl<sub>2</sub> (aq) from solution allowing more Cl<sub>2</sub> (g) to dissolve:



# Solubility of Liquid in Liquid

Frequently two or more liquids are mixed together in the preparation of pharmaceutical products (e.g. aromatic waters, spirits, elixirs, lotions, sprays, and medicated oils).

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

1. Complete miscibility
2. Partial miscibility.



## Solubility of Liquid in Liquid Complete Miscibility

Polar and semipolar solvents, such as water and alcohol, alcohol and acetone, are said to be completely miscible because they mix in all proportions.

Nonpolar solvents such as benzene and  $\text{CCl}_4$  are also completely miscible.

These liquids are miscible because the broken attractive forces in both pure liquids are re-established in the mixture.





# Solubility of Liquid in Liquid

## Partial Miscibility

When water and phenol are mixed, two liquid layers are formed each containing some of the other liquid in the dissolved state.

It is possible to calculate the composition of each component in the two conjugate phases and the relative amount of each phase from the **tie lines** that cut the **binodal curve**.

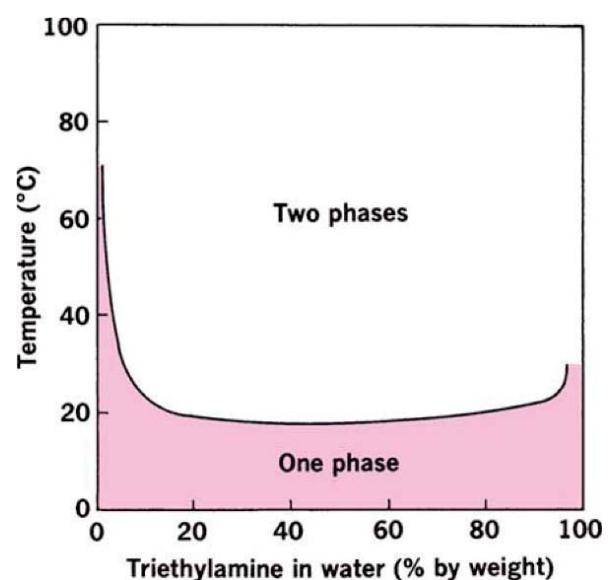


# Solubility of Liquid in Liquid

## Partial Miscibility

Partially miscible liquids are influenced by temperature. The two conjugate phases changed to a homogenous single phase at the **critical solution temperature (or upper consolute temperature)**.

Some liquid pairs (e.g. trimethylamine and water) exhibit a **lower consolute temperature**, below which the two members are soluble in all proportions and above which two separate layers form.

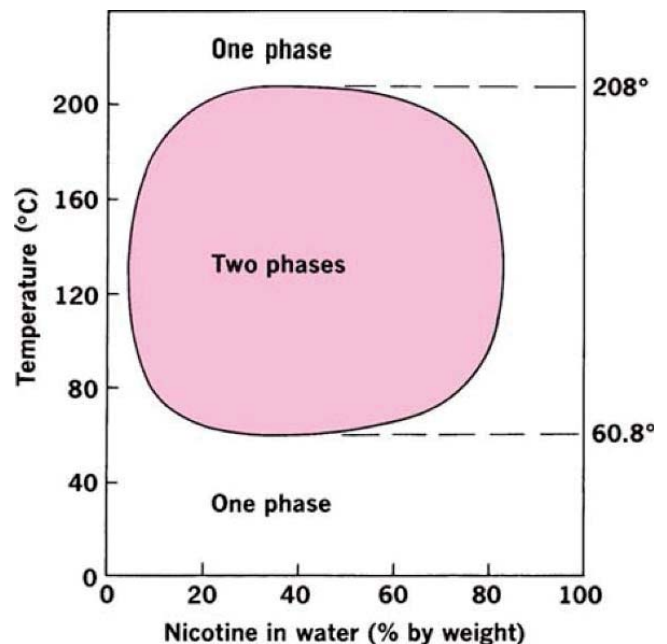


# Solubility of Liquid in Liquid

## Partial Miscibility

Few mixtures (e.g. nicotine and water) show both an upper and a lower consolute temp. with an intermediate temp. region in which the two liquids are only partially miscible.

A final type exhibits no critical solution temperature (e.g. ethyl ether and water shows partial miscibility over the entire temperature range at which the mixture exists).



# Solubility of Solid in Liquid

## pH

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

Most drugs belong to the class of weak acids and bases. They react with strong acids or bases to form water soluble salts.

Acidic drugs (e.g. NSAIDs), are more soluble in alkaline solutions where the ionized form is the predominant.

$$pH - pK_a = \log \frac{[Ionized]}{[Unionized]}$$

Basic drugs (e.g. ranitidine), are more soluble in acidic solutions where the ionized form of the drug is predominant.

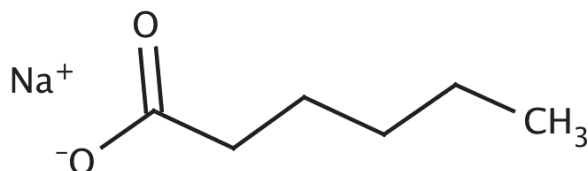
$$pH - pK_a = \log \frac{[Unionized]}{[Ionized]}$$



# Solubility of Solid in Liquid

## pH

Carboxylic acids containing more than 5 carbons are relatively insoluble in water; however, they react with dilute NaOH, carbonates, and bicarbonates to form soluble salts.



The fatty acids (> 10 carbon) form soluble soaps with the alkali metals and insoluble soaps with other metal ions.

Phenol is weakly acidic and only slightly soluble in water but is quite soluble in dilute sodium hydroxide.



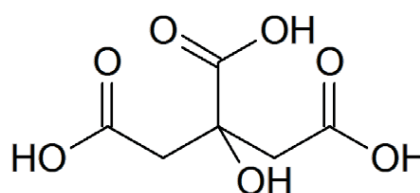
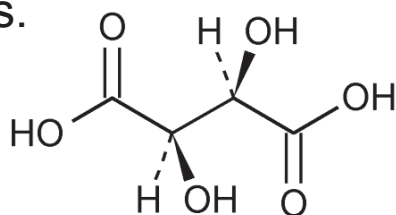
# Solubility of Solid in Liquid

## Substituents

Substituents can influence solubility by affecting the solute molecular cohesion and its interaction with water molecules.

Polar groups such as -OH are capable of hydrogen bonding (high solubility).

E.g. Hydroxy acids, such as tartaric and citric acids, are quite soluble in water because they are solvated through their hydroxyl groups.



Non-polar groups such as -CH<sub>3</sub> and -Cl are hydrophobic (low solubility).

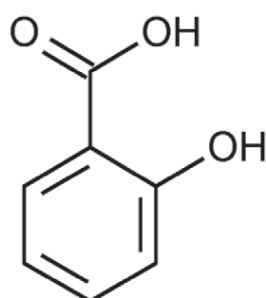


# Solubility of Solid in Liquid

## Substituents

The position of the substituent on the molecule can affect the solute molecular cohesion and its interaction with water molecules, and hence its solubility.

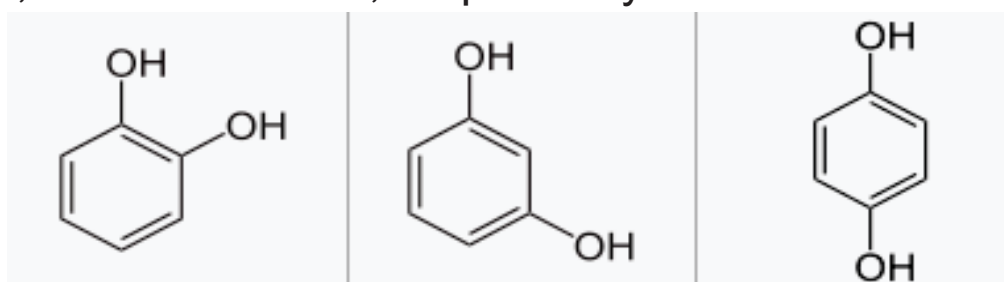
E.g. the OH group of salicylic acid cannot contribute to the solubility because it is involved in an intramolecular hydrogen bond.



# Solubility of Solid in Liquid

## Substituents

E.g. the aqueous solubility of o-, m- and p-dihydroxybenzenes are 4, 9 and 0.6 mol/L, respectively.



Symmetric particles (p-dihydroxybenzenes) can be less soluble than asymmetric ones (m-dihydroxybenzenes) because they form compact crystals (which require more work to separate the particles), while the asymmetric particles pack less efficiently in crystals.



# Solubility of Solid in Liquid

## Crystal Characteristics

Different crystalline forms of the same substance (known as **polymorphs**) possess different lattice energies.

The polymorphic form with the lowest free energy will be the most stable.

Less stable (**metastable**) forms with the highest energy will be the most soluble one. They tend to transform into the most stable form over time.

The solubility of a crystalline material and its rate of dissolution can be increased by using a metastable polymorph.

Many drugs exhibit polymorphism, e.g. steroids, barbiturates and sulphonamides.



# Solubility of Solid in Liquid

## Crystal Characteristics

Incorporation of solvent molecules into the lattice structure of crystalline material during crystallization will result in solids that are called **solvates**. If water is the solvating molecule, the solids are called **hydrate**.

The interaction between the substance and water that occurs in the crystal phase reduces the amount of energy liberated when the solid interact with the solvent (water). Therefore unsolvated crystals will dissolve faster.



# Solubility of Solid in Liquid

## Complexation

Complexation can increase or decrease the solubility of drugs depending whether the formed complex is water soluble or insoluble.

e.g. Cyclodextrin can form water soluble complexes with most drugs, thus increasing their water solubility.

e.g. Tetracycline can form water insoluble complexes with various metal cations. Therefore tetracycline solubility is decreased in the presence of those metals.



# Solubility of Solid in Liquid

## Boiling and Melting Point

In general, aqueous solubility decreases with increasing boiling and melting point.

This is because the higher the boiling point of liquids and melting point of solids, the stronger the interactions between the molecules in the pure liquid or the solid state.

## Particle Size

Solubility increases with decreasing particle size, due to the increased particle surface area; meaning more of the solid is in contact with the solvent.





# Distribution Phenomena

Partition Coefficient (K)

Partition Coefficient (P)

Apparent Partition Coefficient ( $P_{app}$ )

Extraction

## Partition Coefficient (K) Definition

If a **liquid** or solid substance is added to a mixture of two immiscible liquids, it will become distributed between the two layers in a definite concentration ratio.

If  $C_1$  and  $C_2$  are the equilibrium concentrations of the substance in Solvent<sub>1</sub> and Solvent<sub>2</sub>, respectively, the equilibrium expression becomes:

$$C_1 / C_2 = K$$

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





# Partition Coefficient (K)

## Example

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?

$$K_{(w/o)} = C_{H_2O} / C_{al} = 0.0510 / 0.0155 = 3.29$$

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:

$$K_{(o/w)} = C_{al} / C_{H_2O} = 0.0155 / 0.0510 = 0.304$$

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



# Partition Coefficient (P)

## Definition

Partition coefficient (**P**) is a parameter that characterizes the relative affinity of a compound in its unionized form for water and an immiscible model lipid solvent (octanol).

Octanol was chosen as the model lipid phase because it most closely simulates the properties of biological membranes.

Determination of P (or log P) values involves the placing of a drug compound along with the two immiscible solvents in a separation funnel. Molecules of the solute will distribute in each phase until equilibrium is established.

The ratio of the two concentrations is the **partition coefficient** or **distribution coefficient P**, i.e.  $P = C_o / C_w$ .





# Partition Coefficient (P)

## Interpretation

$P > 1$  or  $\text{Log } P > 0$  implies that the drug has affinity for lipid membranes.

$P = 1$  or  $\text{Log } P = 0$  there is equal distribution between the water and oil layer.

$P < 1$  or  $\text{Log } P < 0$  the drug has affinity for water or hydrophilic layer.

Structure affect the value of partition coefficient  $P$  e.g. substituent that increase  $P$  value are -alkyl, -aryl, -halogens and substituent that decrease  $P$  decrease are -OH, -COOH, -NH<sub>2</sub>, -O, -CO.



# Partition Coefficient (P)

## Pharmaceutical Applications

Knowledge of partition is important to the pharmacist because the principle is involved in several areas of current pharmaceutical interest. These include:

1. Preservation of oil–water systems.
2. The absorption and distribution of drugs throughout the body.
3. Extraction of active ingredients from crude drugs.



# Apparent Partition Coefficient ( $P_{app}$ )

When association and dissociation of drugs occur, the situation becomes more complicated, e.g. benzoic acid associates in the oil phase and dissociates in the aqueous phase.

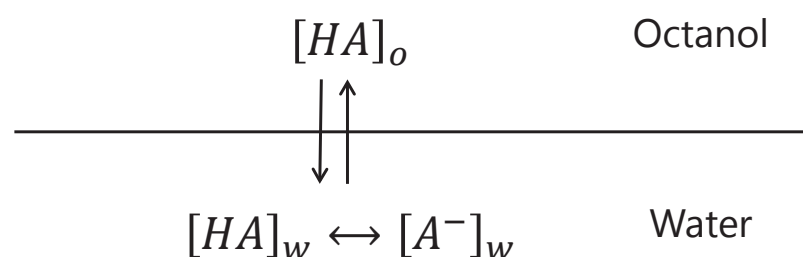
Drugs that are weak acids or weak bases ionize in water, depending on their  $pK_a$ s and on the pH of the aqueous phase.

In general, **ionized structures cannot partition in octanol** or other hydrophobic solvents.

$P$  value cannot be used to assess the true distribution of the ionizable drug in the two immiscible phases, simply because its value is dependent on the ionic state of the drug (which in turn depends on pH).



# Apparent Partition Coefficient ( $P_{app}$ )



$$P = \frac{C_o}{C_w}$$

$$C_o = [HA]_o$$

$$C_w = [HA]_w + [A^-]_w$$

$$P_{app} = \frac{[HA]_o}{[HA]_w + [A^-]_w}$$



# Extraction

Partition coefficient is used to determine the efficiency with which one solvent can extract a compound from a second solvent.

Suppose that  $w$  grams of a solute is extracted repeatedly from  $V_1$  mL of one solvent with successive portions of  $V_2$  mL of a second solvent, which is immiscible with the first.

Let  $w_1$  be the weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent.

The concentration of solute remaining in the first solvent is  $(w_1/V_1)$  g/mL and the concentration of the solute in the extracting solvent is  $(w - w_1)/V_2$  g/mL.



# Extraction

The distribution coefficient is thus:

$$K = \frac{w_1/V_1}{(w - w_1)/V_2}$$

$$w_1 = w \frac{KV_1}{KV_1 + V_2}$$

The process can be repeated, and after  $n$  extractions:

$$w_n = w \left( \frac{KV_1}{KV_1 + V_2} \right)^n$$

By use of this equation, it can be shown that most efficient extraction results when  $n$  is large and  $V_2$  is small (when a large number of extractions are carried out with small portions of extracting liquid).



# Extraction

The equation assumes complete immiscibility of the two liquids.

When ether is used to extract organic compounds from water, the equation is not accurate (why?).

However, the equations provide approximate values that are satisfactory for practical purposes.

The presence of other solutes, such as salts, can affect the results by complexing with the solute or by salting out one of the phases.



## Extraction Example

**The distribution coefficient for iodine in (water/ $\text{CCl}_4$ ) is 0.012. How many (g) of iodine are extracted from a solution of water containing 0.1 g in 50 mL by one extraction with 10 mL of  $\text{CCl}_4$ ? How many (g) are extracted by two 5-mL portions of  $\text{CCl}_4$ ?**

$$w_n = w \left( \frac{KV_1}{KV_1 + V_2} \right)^n$$
$$w_1 = 0.1 \times \frac{0.012 \times 50}{(0.012 \times 50) + 10}$$
$$= 0.0057 \text{ g remains or } 0.0943 \text{ is extracted}$$
$$w_1 = 0.1 \left( \frac{0.012 \times 50}{(0.012 \times 50) + 5} \right)^2$$
$$= 0.0011 \text{ g of iodine or } 0.0989 \text{ g is extracted}$$



# References

Sinko, P. J. M. A. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences*, Philadelphia, Lippincott Williams & Wilkins.

