Solubility and Distribution Phenomena
Solubility definitions

• *Solubility* is:
• the concentration of solute in a saturated solution at a certain temperature,
• the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

• Solubility is an *intrinsic material property* that can be altered only by chemical modification of the molecule.
the solubility of a compound depends on:
1. the physical and chemical properties of the solute and the solvent
2. temperature, pressure, the pH of the solution,

The term *miscibility* refers to the mutual solubility of the components in liquid–liquid systems.
The equilibrium involves a balance of the energy of three interactions against each other:

1. solvent with solvent,
2. solute with solute,
3. solvent and solute.

Thermodynamic equilibrium is achieved when the overall lowest energy state of the system is achieved.
Solubility Expressions

• The *United States Pharmacopeia (USP)*:
  • describes the solubility of drugs as parts of solvent required for one part solute.

• Solubility is also quantitatively expressed in terms of molality, molarity, and percentage.

• For exact solubilities of many substances: official compendia (e.g., USP) and the Merck Index.
<table>
<thead>
<tr>
<th>Description Forms (Solubility Definition)</th>
<th>Parts of Solvent Required for One Part of Solute</th>
<th>Solubility Range (mg/mL)</th>
<th>Solubility Assigned (mg/mL)</th>
</tr>
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<tbody>
<tr>
<td>Very soluble (VS)</td>
<td>&lt;1</td>
<td>&gt;1000</td>
<td>1000</td>
</tr>
<tr>
<td>Freely soluble (FS)</td>
<td>From 1 to 10</td>
<td>100–1000</td>
<td>100</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
<td>33–100</td>
<td>33</td>
</tr>
<tr>
<td>Sparingly soluble (SPS)</td>
<td>From 30 to 100</td>
<td>10–33</td>
<td>10</td>
</tr>
<tr>
<td>Slightly soluble (SS)</td>
<td>From 100 to 1000</td>
<td>1–10</td>
<td>1</td>
</tr>
<tr>
<td>Very slightly soluble (VSS)</td>
<td>From 1000 to 10,000</td>
<td>0.1–1</td>
<td>0.1</td>
</tr>
<tr>
<td>Practically insoluble (PI)</td>
<td>&gt;10,000</td>
<td>&lt;0.1</td>
<td>0.01</td>
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</tbody>
</table>
Solvent–Solute Interactions

• “like dissolves like.”

1. Polar Solvents
2. Nonpolar Solvents
3. Semipolar Solvents
Polar Solvents

- dissolve ionic solutes and other polar substances.
- reduce the attraction between the ions of strong and weak electrolytes because of the solvents' high dielectric constants.
- Water dissolves sugars, phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water:
• As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases.

• Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble.
• When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly.

• Branching of the carbon chain increase the polar effect and leads to increased water solubility. Tertiary butyl alcohol is miscible in all proportions with water, whereas \( n \)-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20°C.
Nonpolar Solvents

- such as the hydrocarbons, as carbon tetrachloride, benzene, and mineral oil

- Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants.

- they cannot form hydrogen bridges with nonelectrolytes.

- Hence, ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.
• can dissolve nonpolar solutes through induced dipole interactions.

• The solute molecules are kept in solution by the weak van der Waals–London type of forces.

• Thus, oils and fats dissolve in carbon tetrachloride, benzene, and mineral oil.

• Alkaloidal bases and fatty acids also dissolve in nonpolar solvents
Semipolar Solvents

- such as ketones and alcohols, Propylene glycol, glycerin

- can *induce* a certain degree of polarity in nonpolar solvent molecules, so that, for example, benzene, which is readily polarizable, becomes soluble in alcohol.

- act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids. (cosolvents)

- Acetone increases the solubility of ether in water.
- Propylene glycol increases the solubility of water and peppermint oil.
Solubility of Liquids in Liquids

• **Complete Miscibility:**

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

• Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible.
Partial Miscibility:

- Binary and ternary phase diagrams

The Phase Rule and Solubility

\[ F = C - P + 2 \]  

(9-12)

- Single phase and two components
- \( F = 2-1+2 = 3 \)
- Pressure is fixed so temperature and composition must be stated.
Solubility of Solids in Liquids

*The influence of Temperature*

- When heat is absorbed in the dissolution process *(endothermic)* the solubility of the compound increases with heat.
- When heat is evolved in the dissolution process *(exothermic)* the solubility of the compound decreases with heat.
- Most solids belong to the class of compounds that absorb heat when they dissolve.
**Sodium sulfate** exists in the hydrated form $\text{Na}_2\text{SO}_4\cdot10\text{H}_2\text{O}$ up to a temperature of about $32^\circ\text{C}$, the solution process is endothermic, and solubility increases with temperature. Above this point, the compound exists as the anhydrous salt, $\text{Na}_2\text{SO}_4$ the dissolution is exothermic, and solubility decreases with an increase of temperature.

**NaCl** 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.
Solubility of Solids in Liquids

The influence of PH

Weakly acidic drug or its salt
If the pH of a solution ↓
Unionized acid molecules ↑

Weakly basic drug & its salt
If the pH of a solution ↑
Unionized base molecules ↑

Precipitation may occur because the solubility of the unionized species is less than that of the ionized form (chemical incompatibility).

The relationship between pH & the solubility & pKa value of an acidic drug is given by a modified Henderson-Hasselbalch equation.

From equation we can calculate:
Minimum pH that must be maintained in order to prevent precipitation from a solution of known concentration.
the equation for the solubility of a weak acid as a function of the pH of a solution:

\[ \text{pH}_p = pK_a + \log \frac{S - S_o}{S_o} \]  \hspace{1cm} (9-9)

- \( \text{pH}_p \) is the pH below which the drug separates from solution as the undissociated acid.
- \( S_o \) is the solubility of the acid in water
- \( S \) is the molar concentration of salt initially added.
• the equation for the solubility of a weak base as a function of the pH of a solution.

\[ \text{pH}_p = \text{pK}_w - \text{pK}_b + \log \frac{S_o}{S - S_o} \]  

(9–10)

• \( \text{pH}_p \) is the pH \textit{above} which the drug begins to precipitate from solution as the free base.
• \( S_o \) is the molar solubility of the free base in water.
• \( S \) is the molar concentration of salt initially added.
Example

Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of $1 \text{ g of sodium phenobarbital}$ 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

$$\frac{\text{g/liter}}{\text{mol.wt.}} = \frac{10}{254} = 0.039 \text{ mole/liter}$$

$$pH_p = 7.41 + \log \left( \frac{0.039 - 0.005}{0.005} \right) = 8.24$$
Nature of solvent: cosolvents

- 'like dissolves like'

- using cosolvents such as ethanol or propylene glycol, which are miscible with water and which" act as better solvents for the solute in question.

  e.g.
  The aqueous solubility of metronidazole is about 100 mg in 10 ml; the solubility of this drug can be increased exponentially by the incorporation of one or more water-miscible cosolvents so that the solubility is increased up to 500mg in 10 ml
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, and solubility does not constitute a serious problem.

• 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.
• 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*.
The solubility of phenobarbital in a mixture of water, alcohol, and glycerin.
Combined Effect of pH and Solvents

• the pKa of phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing 30% by volume of alcohol.

• the solubility, $S_o$, of un-ionized phenobarbital is increased from 0.005 M in water to 0.0276 M in a 30% alcoholic solution (five times more)
Example
What is the minimum pH required for the complete solubility of the drug in a stock solution containing \(6\) g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution?

So, the solubility of phenobarbital is 0.028 in 100 mL of a 30% by volume alcoholic solution and the pKa is 7.41 at 25°C. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

\[
\frac{\text{g/liter}}{\text{mol.wt.}} = \frac{60}{254} = 0.236 \text{ mole/liter}
\]

\[
\text{pH}_p = \text{pK}_a + \log \frac{S - S_0}{S_0} \tag{9-9}
\]

\[
\text{pH}_p = 7.92 + \log \frac{0.236 - 0.028}{0.028}
\]

\[
\text{pH}_p = 7.92 + 0.87 = 8.79
\]
For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is:

$$\text{pH}_p = 7.41 + \log \frac{0.236 - 0.005}{0.005} = 9.07$$
pH–solubility profile

• Shows the relationship between pH and solubility.

• Example:
Distribution of Solutes between Immiscible Solvents

• If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two layers in a definite concentration ratio.

• If $C_1$ and $C_2$ are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively, the equilibrium expression becomes:
The equilibrium constant, $K$, is known as the distribution ratio, distribution coefficient, or partition coefficient.

It is strictly applicable only in dilute solutions where activity coefficients can be neglected.
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? We have

\[
K = \frac{C_{\text{H}_2\text{O}}}{C_{\text{alc}}} = \frac{0.0510}{0.0155} = 3.29
\]

\[
K = \frac{C_{\text{alc}}}{C_{\text{H}_2\text{O}}} = \frac{0.0155}{0.0510} = 0.304
\]

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

- Extraction
- preservation of oil–water systems,
- the absorption and distribution of drugs throughout the body.
**Effect of Ionic Dissociation and Molecular Association on Partition**

- The solute can exist partly or wholly as associated molecules in one of the phases or it may dissociate into ions in either of the liquid phases.

- The distribution law applies only to the concentration of the species common to both phases, namely, the *monomer* or simple molecules of the solute. unassociated and undissociated
• distribution of benzoic acid between an oil phase and a water phase.

• benzoic acid associates in the oil phase and dissociates in the aqueous phase

• The species common to both the oil and water phases are the unassociated and undissociated benzoic acid molecules.
Extraction

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

• most efficient extraction results when a large number of extractions are carried out with small portions of extracting liquid.
Importance of distribution coefficient in pharmaceutical areas

1. Extraction in order to determine the efficiency with which one solvent can extract a compound from a second solvent.

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

- Original solvent $V_1$ contains $w_1$ of solute.
- Extracting solvent $V_2$ contains $w - w_1$ of solute.

Concentration of solute in original solvent

Concentration of solute in extracting solvent
The distribution coefficient

**K** The distribution coefficient

**w** grams of a solute is extracted repeatedly from **V1 mL** of one solvent with successive portions of **V2 mL** of a second solvent, which is immiscible with the first.

Let **w1** 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 **(w1/V1) g/mL**
- the concentration of the solute in the extracting solvent is **(w - w1)/V2 g/mL**. The distribution coefficient is thus:

\[
K = \frac{w_1/V_1}{(w - w_1)V_2}
\]
The process can be repeated. It is more efficient to divide the extracting solvent into a number of smaller volumes that are used in successive extractions rather than to use the total amount of solvent in one single process.

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

(9–24)

\[
w_1 = w \frac{KV_1}{KV_1 + V_2}
\]  

(9–25)

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

(9–26)
Example

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is \( K = \frac{C_{\text{H}_2\text{O}}}{C_{\text{CCl}_4}} = 0.012 \).

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 CCl4?

How many grams are extracted by two 5-mL portions of CCl4?
Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl4 have extracted 0.0989 g.