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PHYSICAL PHARMACEUTICS - I

UNIT 1

TOPIC :

- **Solubility of drugs :** Solubility expressions, mechanisms of solute solvent interactions, ideal solubility parameters, solvation & association, quantitative approach to the factors influencing solubility of drugs, diffusion principles in biological systems. Solubility of gas in liquids, solubility of liquids in liquids, (Binary solutions, ideal solutions)
  Raoult's law, real solutions. Partially miscible liquids, Critical solution temperature and applications. Distribution law, its limitations and applications

Solubility

- Solubility is defined as the maximum amount of solute that can be dissolved in a fixed volume of solvent at a constant temperature to form a homogeneous solution.
- In simple terms, solubility represents the ability of a solute to dissolve in a solvent to form a uniform mixture.

Important Definitions Related to Solubility

Term	Definition
Solute	The component that is **dissolved** in the solvent. It is usually present in a **smaller amount**.
Solvent	The component in which the solute is dissolved. It is usually present in a **larger amount**.
Solution	A **homogeneous mixture** formed by combining two or more substances (solute + solvent).

Importance of Solubility In Pharmacy

Solubility plays a crucial role in pharmaceutical sciences for the following reasons:

1. To select the appropriate solvent for preparing drug solutions or formulations.
2. To ensure bioavailability of a drug — only dissolved drugs can be absorbed by the body.
3. To overcome formulation challenges during the manufacturing of syrups, suspensions, and injections.
4. To study drug interactions and compatibility with different solvents or excipients.
5. To identify poorly water-soluble drugs which may need solubility enhancement techniques.
6. To understand the role of intermolecular forces (like hydrogen bonding, van der Waals forces) and molecular structure on solubility.

Types of Solutions (Based On Solubility Capacity)

1 Saturated Solution

- A solution that contains the maximum amount of solute that can be dissolved in the solvent at a given temperature.
- Any additional solute will remain undissolved.

2 Unsaturated Solution

- A solution that contains less than the maximum amount of solute that can be dissolved at a particular temperature.
- More solute can still be added and dissolved.

3 Supersaturated Solution

- A solution that contains more solute than what is normally soluble at a given temperature.
- It is an unstable condition and excess solute may precipitate out on slight disturbance.

SOLUBILITY EXPRESSIONS

Solubility of a substance can be expressed in two main ways:

1. Quantitative Expression

This method expresses solubility in numerical terms using various concentration units.

(a) Molarity (M)

- Definition: Number of moles of solute dissolved per litre of solution.
- Formula:

$$\text{Molarity (M)} = \frac{\text{Moles of Solute}}{\text{Volume of Solution (in L)}}$$

(b) Molality (m)

- Definition: Number of moles of solute dissolved per kilogram of solvent.
- Formula:

$$\text{Molality (m)} = \frac{\text{Moles of Solute}}{\text{Mass of Solvent (in kg)}}$$

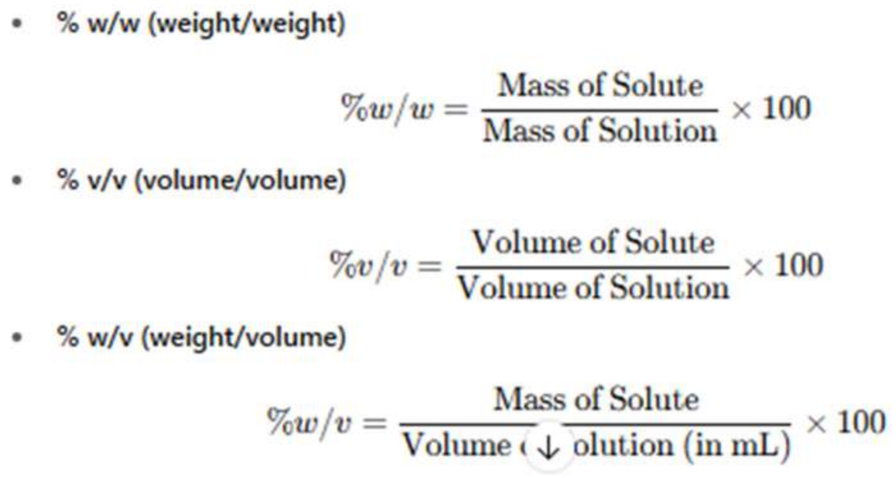
(c) Normality (N)

- Definition: Number of gram equivalents of solute dissolved per litre of solution.
- Formula:

$$\text{Normality (N)} = \frac{\text{Gram Equivalents of Solute}}{\text{Volume of Solution (in L)}}$$

(d) Percentage Concentration

This expresses solubility as a percentage.



- % w/w (weight/weight)

$$\%w/w = \frac{\text{Mass of Solute}}{\text{Mass of Solution}} \times 100$$

- % v/v (volume/volume)

$$\%v/v = \frac{\text{Volume of Solute}}{\text{Volume of Solution}} \times 100$$

- % w/v (weight/volume)

$$\%w/v = \frac{\text{Mass of Solute}}{\text{Volume of Solution (in mL)}} \times 100$$

(e) Parts Per Million (ppm)

- Used for very dilute solutions.
- Formula:

$$\text{ppm} = \frac{\text{Mass of Solute}}{\text{Mass of Solution}} \times 10^6$$

2. Qualitative Expression

➢ In this method, solubility is expressed based on the volume of solvent required to dissolve 1 part of solute.

Descriptive Term	Parts of Solvent Required per 1 Part of Solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly Soluble	30 to 100 parts
Slightly Soluble	100 to 1,000 parts
Very Slightly Soluble	1,000 to 10,000 parts
Practically Insoluble	More than 10,000 parts

Mechanism of Solute-Solvent Interaction

Solute–solvent interaction is the process by which solute particles are stabilized by solvent molecules during the formation of a solution.

These interactions influence:

- Reactivity of solute
- Color
- Stability
- Physical properties of the solution (e.g., density, viscosity)

Types of Interactions Involved

Solute-solvent interactions can involve several types of forces:

- Attractive forces
- Repulsive forces
- Ion-dipole interactions
- Dipole-dipole interactions
- Hydrogen bonding
- Van der Waals forces

Conditions for Solubility

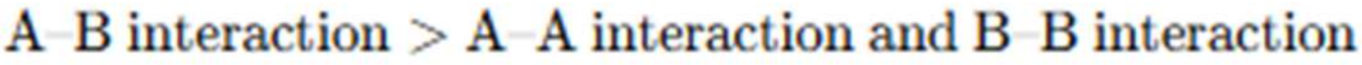
Let:

- **A** = Solvent
- **B** = Solute

There are three types of interactions:

1. **A–A interaction** (solvent–solvent)
2. **B–B interaction** (solute–solute)
3. **A–B interaction** (solute–solvent)

For a solution to form **spontaneously** under normal conditions:



$$\text{A–B interaction} > \text{A–A interaction and B–B interaction}$$

Mechanism of Solute–Solvent Interaction

The entire process of solubility occurs in 3 main steps:

1. Detachment of Solute from Bulk

- Solute molecules are held together in a crystal or aggregate form.
- A solute particle must break away from the bulk to participate in dissolution.
- Energy is required to overcome solute-solute interactions (B–B).

2. Formation of Vacant Site in Solvent

- A solvent molecule moves aside, creating a vacant space.
- This space is necessary to accommodate the incoming solute molecule.
- Energy is also needed to break solvent-solvent interactions (A–A).

3. Insertion of Solute Molecule into Solvent

- The detached solute molecule is inserted into the vacant site in the solvent.
- New solute–solvent interactions (A–B) are formed.
- If these interactions are strong enough, the process becomes energetically favorable, leading to dissolution.

Ideal Solubility Parameters

The Ideal Solubility Parameter is a numerical value used to predict the solubility behavior of a solute in a solvent.

- It helps to estimate whether two substances (a solute and a solvent) are miscible or not.
- If the solubility parameter values of the solute and solvent are similar, the solute is likely to dissolve in the solvent.
- It is denoted by the symbol δ (delta).

Types of Solubility Parameters

There are two main types:

1. **Hildebrand Solubility Parameter**
2. **Hansen Solubility Parameter**

1. Hildebrand Solubility Parameter

- Proposed by Joel H. Hildebrand in 1936.
- Based on cohesive energy density (CED) — the amount of energy required to vaporize 1 mole of a substance.
- Provides a single numerical value to represent the interaction strength.

Formula:

$$\delta = \sqrt{C}$$

Where:

- **δ** = Hildebrand solubility parameter
- **C** = Cohesive energy density

2. Hansen Solubility Parameter

- Proposed by Charles M. Hansen in 1966.
- Improves upon Hildebrand's theory by dividing total solubility into three components:

Components:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

Where:

- δd = Dispersion forces (van der Waals)
- δp = Polar interactions
- δh = Hydrogen bonding interactions
- δ = Total Hansen Solubility Parameter

Solvation

- Solvation is the process of interaction between solute molecules or ions and solvent molecules, resulting in the stabilization of solute particles in the solution.

Process of Solvation

- During solvation, solute particles (atoms, ions, or molecules) become surrounded by solvent molecules.
- This leads to the formation of a solvation complex.
- Solvation helps the solute disperse uniformly throughout the solvent.

Steps in Solvation

1. **Separation of solute particles**
2. **Separation of solvent molecules**
3. **Formation of solute–solvent (A–B) interactions**

Importance of Solvation

- Helps in dissolution of solutes
- Enhances stability of ionic species
- Affects properties like:
    - Conductivity
    - Viscosity
    - Boiling and melting points

Factors Affecting Solvation

Factor	Description
1. Surface Area of Solute	Greater surface area → Faster and more effective solvation. Finely powdered solutes dissolve faster than bulk solids.
2. Agitation (Stirring/Shaking)	Increases contact between solute and solvent molecules, enhancing the solvation rate.
3. Temperature	Higher temperature increases kinetic energy, reduces solute–solute attractions, and increases solute–solvent interactions. Hence, solvation becomes faster.

Association

Association is a chemical process where oppositely charged ions in a solution come together to form a distinct chemical species (ion pair or complex).

- It involves joining or clustering of ions due to electrostatic attraction.
- The process helps reduce the free ion concentration in solution.

Coulomb's Law (Basic Principle)

The force of attraction between two opposite charges is given by:

$$F = \frac{1}{4\pi\varepsilon_0\varepsilon_r} \cdot \frac{q_1 q_2}{r^2}$$

Where:

- **F** = Force of attraction
- **q_1, q_2** = Magnitude of the two charges
- **r** = Distance between the charges
- **ε_0** = Vacuum permittivity
- **ε_r** = Relative permittivity (dielectric constant) of the medium

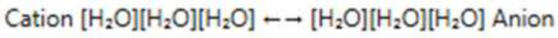
Types of Association

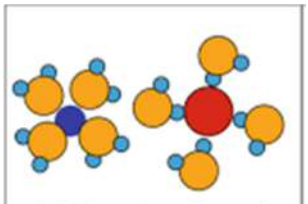
Association can be classified into three main types based on how solute ions interact with the solvent:

1. Fully Solvated Ion Pair

- The cation and anion are completely surrounded by solvent molecules (fully separated).
- No direct interaction between the oppositely charged ions.
- Typical of highly polar solvents like water.

Diagram:

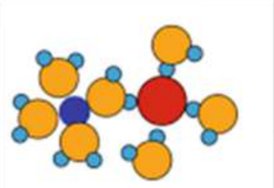

Cation $[H_2O][H_2O][H_2O]$ ←→ $[H_2O][H_2O][H_2O]$ Anion


A. Fully solvated ion pair

2. Solvent Shared Ion Pair

- A single layer of solvent molecules is shared between the cation and anion.
- Partial interaction exists between ions.
- Acts as a bridge between fully solvated and contact ion pair.

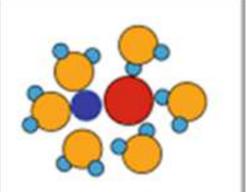
Diagram:
Cation — $[H_2O]$ — Anion
(shared solvent layer)


B. Solvent-shared ion pair

3. Contact Ion Pair

- The cation and anion are in direct contact with each other (no solvent layer between).
- The solvent molecules surround the ion pair externally.
- Common in low polarity solvents or with strong electrolytes.

Diagram:
[Cation^+ Anion^-] surrounded by solvent


C. Contact ion pair

Factors Affecting Solubility of Drugs

Solubility is defined as the maximum amount of a solute that can dissolve in a solvent at a given temperature and pressure. Several **physicochemical factors** influence the solubility of drugs:

1. Temperature

Solubility depends on whether the process is:

- Endothermic (Absorbs Heat) → Solubility increases with temperature.
- Exothermic (Releases Heat) → Solubility decreases with temperature.

Example:

- KNO_3 (endothermic) → solubility increases with temperature.
- $Ca(OH)_2$ (exothermic) → solubility decreases with temperature.

2. Nature of Solvent

Based on the rule: “Like dissolves like”

- Polar solutes dissolve in polar solvents (e.g., salt in water).
- Non-polar solutes dissolve in non-polar solvents (e.g., oil in hexane).

Solubility is higher when the solute and solvent have similar polarity or dielectric constants.

3. Pressure

- Has no significant effect on solubility of solids or liquids.
- Gases: Solubility increases with increased pressure (Henry’s Law).
- Example: Carbon dioxide in soft drinks is more soluble under pressure.

4. pH of the Medium

Drugs with ionizable functional groups are highly influenced by pH.

- Weak acids: Solubility increases in basic pH.
- Weak bases: Solubility increases in acidic pH.

Note: Strong acids/bases are ionized over a wide pH range, so pH has little effect.

5. Crystalline Structure

- Drugs can exist in:
    - Crystalline form – organized, low solubility.
    - Amorphous form – disordered, higher solubility.

Amorphous drugs dissolve faster due to lack of lattice energy.

6. Particle Size

- Smaller particle size → larger surface area → greater solubility.
- This is because more surface is available for interaction with the solvent.

Micronization of poorly soluble drugs enhances dissolution.

7. Molecular Structure

- Large molecules or higher molecular weight → lower solubility.
- Reason: It's harder for large molecules to be surrounded (solvated) by solvent molecules.

Highly branched or bulky drugs often have reduced solubility.

Diffusion in Biological System

- Diffusion is a physical process in which molecules move from a region of higher concentration to a region of lower concentration under the influence of a concentration gradient.
- Alternatively, it can be defined as:
- The mass transfer of individual molecules caused by random molecular motion, driven by a concentration gradient.

Applications of Diffusion in Pharmaceutical Studies

- Release of drug from dosage forms (e.g., tablets, capsules).
- Ultrafiltration, Microfiltration, Dialysis, and Hemodialysis.
- Permeation and distribution of drugs in living tissues.
- Estimation of molecular weight of polymers.
- Prediction of drug absorption and elimination from the body.

Types of Diffusion

1. Passive Diffusion:

- Most common mechanism for drug transport across membranes.
- No energy required.
- Drug moves along the concentration gradient (high to low concentration).
- Occurs without carrier proteins.

2. Facilitated Diffusion:

- Also known as Carrier-Mediated Diffusion.
- Occurs along concentration gradient, but with the help of carrier proteins in the cell membrane.
- No ATP or energy used, but it is selective and faster than passive diffusion.

Laws of Diffusion

Fick's Laws of Diffusion (given by Adolf Fick in 1856):

1. Fick's First Law (Steady-State Diffusion):

➢ It describes diffusion under steady-state conditions, where concentration does not change with time.

$$J = -D\frac{dc}{dx}$$

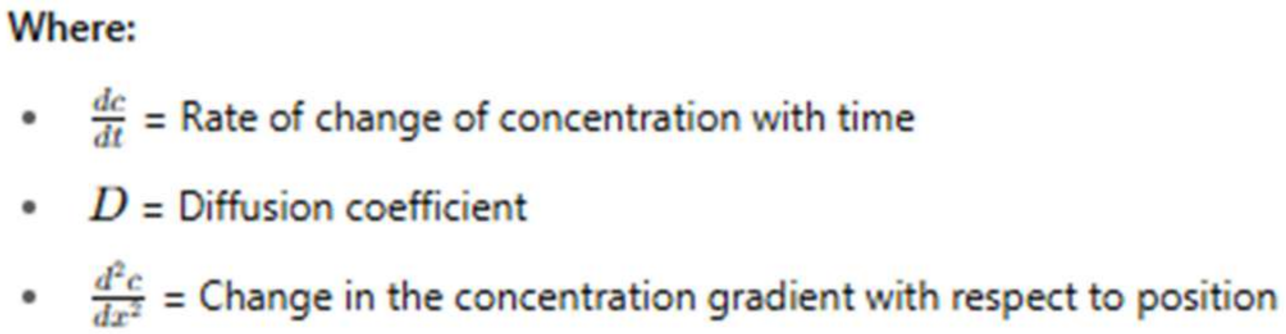
Where:

- J = Diffusion flux (amount of substance diffused per unit area per unit time)
- D = Diffusion coefficient (depends on temperature, solvent, and solute)
- dc/dx = Concentration gradient (change in concentration over distance)

2. Fick's Second Law (Non-Steady-State Diffusion):

➢ Applies when the concentration changes with time (non-steady state).

$$\frac{dc}{dt} = D\frac{d^2c}{dx^2}$$



Where:

- $\frac{dc}{dt}$ = Rate of change of concentration with time
- D = Diffusion coefficient
- $\frac{d^2c}{dx^2}$ = Change in the concentration gradient with respect to position

Factors Affecting Rate of Diffusion

Factor	Effect
Concentration Gradient	Greater gradient → Faster diffusion
Temperature	Higher temperature → Faster molecular motion → Faster diffusion
Surface Area	Larger area → More diffusion
Diffusion Coefficient (D)	Higher D → Faster diffusion
Permeability of Membrane	More permeable → Faster diffusion
Molecular Size	Smaller molecules diffuse faster
Thickness of Membrane	Thinner membrane → Faster diffusion

Solubility of Gas in Liquids

Solubility of a gas in a liquid is defined as the concentration of the dissolved gas in the liquid when it is in equilibrium with the pure gas above the solution.

Examples

- Ammonia water (NH_3 dissolved in water)
- Hydrogen chloride gas dissolved in water
- Effervescent preparations (e.g., carbonated drinks containing dissolved CO_2)
- Aerosols (contain gases dissolved in liquid propellants)

Factors Affecting Solubility of Gas In Liquids

There are **four major factors**:

1. Pressure

- Most important factor
- Solubility of gas in a liquid is directly proportional to the pressure of the gas above the liquid.

Henry's Law:

$$P = K_H \cdot X$$

Where:

- P = Partial pressure of gas
- X = Mole fraction of gas in solution
- K_H = Henry's Law constant

As pressure increases, more gas dissolves into the liquid; when pressure decreases, gas escapes.

2. Temperature

- Solubility of gases decreases with increase in temperature.

Why?

- Higher temperature → Higher kinetic energy → Gas molecules move faster
- Intermolecular interactions between gas and liquid are broken
- Gas molecules escape from solution → Decreased solubility

Exothermic process : Gas dissolution in liquids releases heat, so heating shifts equilibrium towards gas release.

3. Salting Out

- Addition of salts (e.g., NaCl) to a gas-liquid solution often reduces gas solubility.

Reason

- Salts are highly polar and strongly attract water molecules.
- Water molecules get more attracted to salt than gas.
- Gas gets surrounded less by water → Escapes out of solution.

This is known as the "salting-out effect".

4. Chemical Reactions

- If a chemical reaction occurs between the gas and the solvent, solubility generally increases.

Examples:

- HCl reacts with water to form hydrochloric acid:

$$HCl(g) + H_2O(l) \rightarrow H_3O^+ + Cl^-$$

- This ch solubility.

That's why HCl is 10,000 times more soluble in water than gases like oxygen which don't react.

Solubility of Liquid in Liquid

Solubility of liquid in liquid refers to the mixing of two or more liquids to form a homogeneous solution, commonly used in pharmaceutical preparations.

Examples:

- Alcohol + Water → Forms Hydro-alcoholic solution
- Volatile oils + Alcohol → Forms Spirits

Types of Liquid–Liquid Systems

Based on the degree of miscibility, liquid–liquid systems are classified into three types:

1. Completely Miscible Liquids

- These liquids are miscible in all proportions, i.e., they dissolve completely in each other.
- Form a single-phase solution.

Examples:

- Alcohol + Water, Glycerin + Alcohol

2. Partially Miscible Liquids

- These liquids mix with each other up to a certain limit only.
- Beyond that limit, phase separation occurs.

Examples:

- Phenol + Water, Ether + Water

These systems often form two layers, but can form a homogeneous phase within a certain temperature or composition range.

3. Immiscible Liquids

- These liquids do not mix with each other and form two separate layers.
- No solubility or very negligible solubility occurs between them.

Examples:

- Benzene + Water, Benzene + Alcohol, Oil + Water

These systems require emulsifying agents to be used together in pharmaceutical emulsions.

RAOULT'S LAW

The partial vapour pressure of a component in a solution is directly proportional to its mole fraction in the solution.

$$P = P^0 \times X$$

Where:

- P = Partial vapour pressure of the component in solution
- P^o = Vapour pressure of the pure component
- X = Mole fraction of the component in the solution

For a Binary Solution of Two Volatile Liquids A and B:

Let's consider a solution with two volatile and completely miscible liquids A and B.

According to Raoult's Law:

- Partial vapour pressure of A:

$$P_A = P_A^0 \times X_A$$

- Partial vapour pressure of B:

$$P_B = P_B^0 \times X_B$$

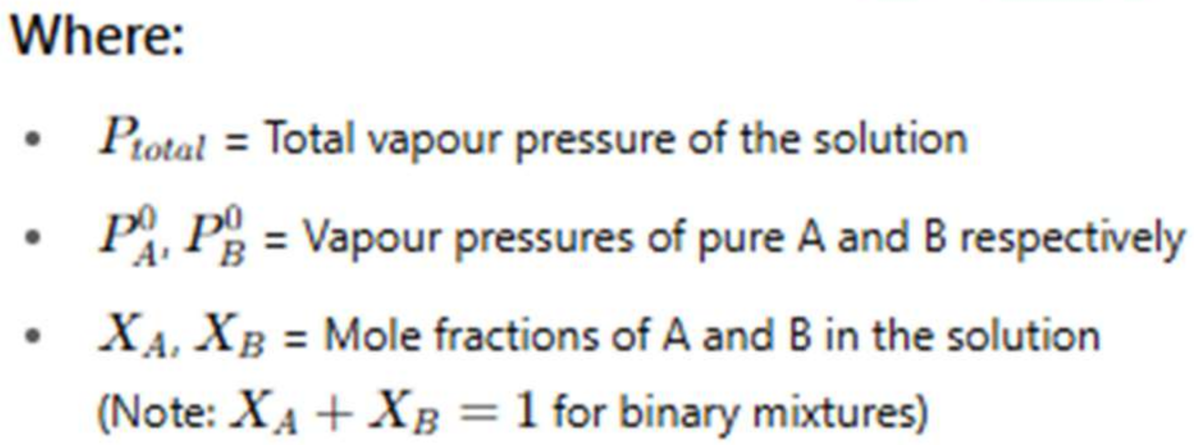
According to Dalton’s Law

The total vapour pressure of the solution is the sum of the partial vapour pressures of all components.

So, $P_{total} = P_A + P_B$

By substituting values from Raoult’s Law:

$$P_{total} = P_A^0 X_A + P_B^0 X_B$$



Where:

- P_{total} = Total vapour pressure of the solution
- P_A^0, P_B^0 = Vapour pressures of pure A and B respectively
- X_A, X_B = Mole fractions of A and B in the solution

  (Note: $X_A + X_B = 1$ for binary mixtures)

Limitations Of Raoult’s Law

Raoult’s Law holds true only under certain conditions:

1. Dilute Solutions :
   Accurate mainly for very dilute solutions.
2. No Association or Dissociation :
   Not applicable if the solute associates (e.g., acetic acid in benzene) or dissociates (e.g., NaCl in water).
3. Ideal Solutions Only :
   Only valid for ideal solutions, where:
   - No enthalpy change on mixing (ΔH = 0)
   - No volume change on mixing (ΔV = 0)
   - Intermolecular forces between A-B are equal to A-A and B-B

Real Solutions

→ Real solutions are those liquid-liquid mixtures where attractive forces between molecules are not uniform, i.e., adhesive ≠ cohesive forces.

→ Unlike ideal solutions (which follow Raoult's Law strictly), real solutions show deviations from it.

→ This occurs due to differences in molecular interactions (intermolecular forces) between unlike molecules.

Types of Deviations From Raoult's Law

1 Negative Deviation

If the observed vapour pressure of a solution is lower than the predicted value from Raoult's Law, the solution shows negative deviation.

Cause:

- Stronger adhesive forces (between dissimilar molecules) than cohesive forces (between like molecules).
- Molecules are held more tightly in the solution → less tendency to escape into vapour phase → lower vapour pressure.

Result:

- Exothermic mixing (heat is released)
- Possibility of minimum boiling azeotropes (e.g., Chloroform + Acetone)

Example Mixtures:

- Chloroform + Acetone
- Acetic acid + Pyridine
- HCl + Water

2 Positive Deviation

If the observed vapour pressure of a solution is higher than predicted from Raoult's Law, the solution shows positive deviation.

Cause:

- Weaker adhesive forces than cohesive forces.
- Molecules escape more easily into vapour phase → higher vapour pressure.

Result:

- Endothermic mixing (heat absorbed)
- Possibility of maximum boiling azeotropes (e.g., Ethanol + Water)

Example Mixtures:

- Ethanol + Water
- Acetone + Carbon disulfide
- Benzene + Methanol
- Chloroform + Ethanol

Partially Miscible Liquids

A pair of liquids is said to be partially miscible if they do not dissolve completely in each other but form two liquid layers, each containing some amount of both liquids.

- The liquids are miscible only to a certain extent.
- Beyond that limit, they separate into two immiscible layers, each enriched in one component.

Characteristics :

- Forms a two-phase system: one phase rich in liquid A, the other in liquid B.
- Both phases contain some fraction of each component.
- Typically occurs when one liquid is polar and the other is non-polar.
- Temperature can affect miscibility — increasing temperature often increases mutual solubility.

Examples of Partially Miscible Pairs :

Liquid A	Liquid B
Water	Phenol
Ether	Water
Nicotine	Water
Triethylamine	Water
Water	Butanol

Critical Solution Temperature (CST)

- The Critical Solution Temperature is the temperature at which two partially miscible liquids become completely miscible in all proportions.
- It is also called the Consolute Temperature.
- At this temperature, the liquids form a single homogeneous phase.
- Beyond or below this temperature (depending on the type), the liquids become fully miscible.

Types of CST

1. ***Upper Critical Solution Temperature (UCST):***

- It is the minimum temperature above which the two liquids become completely miscible.
- Below this temperature, phase separation occurs.
- Example: Phenol + Water
    - UCST = ~66°C
    - Below 66°C → Two layers
    - Above 66°C → One uniform layer

2. ***Lower Critical Solution Temperature (LCST):***

- It is the maximum temperature below which the two liquids become completely miscible.
- Above this temperature, the liquids separate into two layers.
- Example: Triethylamine + Water
    - LCST ≈ 19°C

3. ***Systems Showing Both UCST and LCST:***

- Some systems have both upper and lower CST.
- Example: Nicotine + Water
    - Below LCST: miscible
    - Between LCST and UCST: partially miscible
    - Above UCST: miscible

Distribution Law (Nernst's Distribution Law)

- The Distribution Law was given by Walther Hermann Nernst, a German chemist.
- It describes the behavior of a solute that is distributed between two immiscible solvents at equilibrium.

Statement of the Law

- *If a solute distributes itself between two immiscible solvents at constant temperature and remains in the same molecular state, then the ratio of its concentrations in the two solvents is constant.*

$$\frac{C_1}{C_2} = K_d$$

Where:

- C_1 = Concentration of solute in **Solvent A**
- C_2 = Concentration of solute in **Solvent B**
- K_d = Distribution coefficient or Partition coefficient

Limitations of Distribution Law

- Not valid for concentrated solutions.
- Not applicable if solute dissociates or associates in any of the solvents.
- Temperature must be strictly maintained.
- Solvents must be completely immiscible.
- Law assumes no chemical interaction between solute and solvents.

Applications of Distribution Law:

1. ***Solvent Extraction***:

- Used to extract a drug from an aqueous phase using an organic solvent.
- Efficiency increases with multiple extractions using smaller volumes.

2. ***Determination of Degree of Dissociation***:

- If solute dissociates in one solvent, deviations from the expected K_d value help determine the degree of dissociation.

3. ***Determination of Degree of Association***:

- When the solute associates (like dimerization), changes in K_d indicate the extent of association.

4. ***Determination of Solubility***:

- Can be used to find solubility of a compound in one solvent by knowing the solubility in the other and the K_d