PHYSICAL PHARMACEUTICS

UNIT-1 (Solubility of drugs)

1. Express the term solubility

Solubility is defined as the maximum amount of a solute that can dissolve in a specific amount of solvent at a given temperature and pressure to form a homogeneous solution.

It is usually expressed in terms of:

- **Grams of solute per 100 mL of solvent** (g/100 mL),
- **Moles per liter** (mol/L), or
- As a **qualitative term** (e.g., soluble, sparingly soluble, insoluble).

Solubility depends on factors such as:

- Nature of the solute and solvent (like dissolves like),
- Temperature (generally increases with temperature for solids and liquids),
- Pressure (mainly affects gases).

2. Define solution, mention the mechanism of solute and solvent interaction.

A **solution** is a homogeneous mixture composed of two or more substances. In a solution, one substance (the **solute**) is uniformly dispersed at the molecular or ionic level within another substance (the **solvent**). The resulting mixture has the same composition and properties throughout.

- **Solute**: The substance that is dissolved.
- **Solvent**: The substance in which the solute is dissolved.

Examples include:

- Salt in water (solid in liquid)
- Sugar in tea (solid in liquid)
- Oxygen in air (gas in gas)

Solutions are mainly 3 types:

- Saturated solution: a solution that contain the maximum amount of solute that can be dissolved under the condition at which the solution exist.
- Unsaturated solution: condition where more solute can be added to the solvent.
- Super saturated solution: No more solute can be dissolved even after heating /changing the normal condition.

Mechanism of Solute and Solvent Interaction

The process of forming a solution involves molecular-level interactions between the solute and the solvent. This can be explained in the following steps:

1. Breaking Solute-Solute Interactions

- The solute particles (molecules or ions) are held together by intermolecular forces or ionic bonds.
- Energy is required to overcome these attractive forces and separate the solute particles.
- This step is **endothermic** (absorbs energy).

2. Breaking Solvent-Solvent Interactions

- The solvent molecules are also held together by intermolecular forces such as hydrogen bonds, Van der Waals forces, or dipole-dipole interactions.
- Energy is required to break these interactions to make space for the solute particles.
- This step is also **endothermic**.

3. Formation of cavity in solvent Phase large enough to accommodate solute molecules.

4. Transfer of solute into the cavity of solvent phase.

5. Formation of Solute-Solvent Bond

- Solute particles become surrounded by solvent molecules in a process called **solvation** (or **hydration** in case of water).
- New interactions form between the solute and solvent molecules through hydrogen bonding, dipole interactions, or ion-dipole forces.
- This step is generally **exothermic** (releases energy).

Factors Affecting Solute-Solvent Interaction

1. **Polarity**: "Like dissolves like" – polar solutes dissolve in polar solvents and nonpolar solutes in nonpolar solvents.
2. **Temperature**: Higher temperatures usually increase solubility for solids and liquids.
3. **Pressure**: Affects gas solubility in liquids.
4. **Particle size**: particle size bigger will solubility decrease.

3. Explain critical solution temperature and its application

- The solution partially mix and form a conjugate layer between them when heat is applied the conjugate layer slowly disappear. When the conjugate layer completely disappear that particular temperature is critical solution temperature.

- The **Critical Solution Temperature (CST)** is the temperature above or below which two partially miscible liquids become completely miscible in all proportions.
- It is also known as **consulate temperature**.

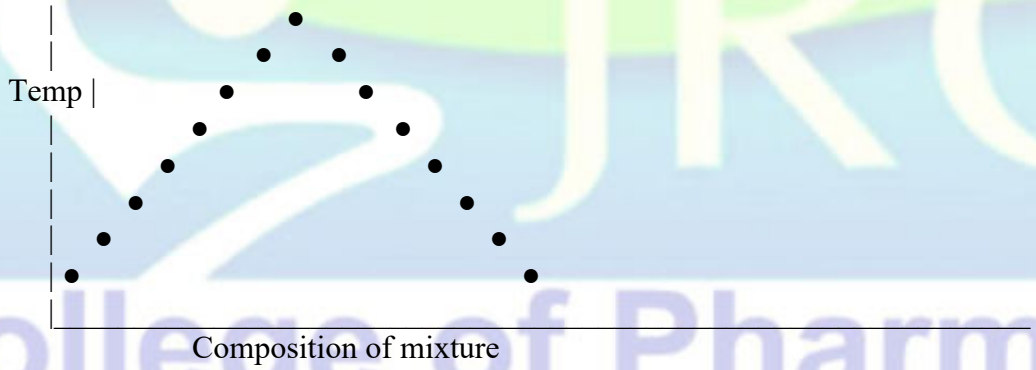
There are two types of CST:

1. **Upper Critical Solution Temperature (UCST):**
   The highest temperature at which phase separation occurs. Above this temperature, the liquids become completely miscible.
   Example: hexane & nitrobenzene (UCST ≈ 66°C)
2. **Lower Critical Solution Temperature (LCST):**
   The lowest temperature at which phase separation occurs. Below this temperature, the liquids become completely miscible.
   Example: Tri ethyl amine and Water (LCST ≈ 18°C)

Graphical Representation:

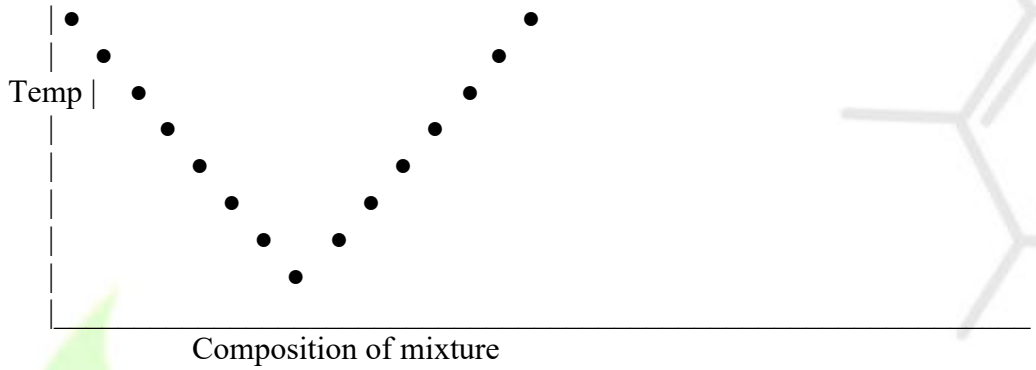
A **temperature vs. composition** graph illustrates CST clearly.

1. Upper Critical Solution Temperature (UCST):



Above the curve (above UCST): Complete miscibility
Below the curve (below UCST): Partial miscibility (two layers)

2. Lower Critical Solution Temperature (LCST):



Below the curve (Below LCST): Complete miscibility
Above the curve (Above LCST): Partial miscibility (two layers)

Applications of CST:

1. **Pharmaceutical Formulation:**
   - CST helps in selecting compatible solvents for drug solubilisation.
   - Important in emulsion and suspension systems.
2. **Extraction and Separation Processes:**
   - Used in liquid-liquid extraction to determine miscibility ranges.
3. **Polymer Chemistry:**
   - CST is used in polymer blending and solubility testing.
   - Determines temperature ranges for uniform mixing of polymers.
4. **Temperature-Sensitive Gels and Drug Delivery:**
   - CST helps design smart polymers that swell or shrink at specific temperatures.
5. **Industrial Applications:**
   - Used in detergents, cosmetics, and chemical synthesis to ensure phase stability.

4. What is Raoult's law? Describe it briefly

- Raoult's Law provides a fundamental relationship between vapor pressure and composition in liquid mixtures.
- In 1887, Francois marie Raoult develops this relationship.
- A/C to this law for a solution of volatile liquids, the partial VP of each component of a solution is proportional to the mole fraction of the component present in the solution.

$$P_{solution} = X_{solvent} \cdot P^0_{sovent}$$

Mathematical Expression:

For a **binary solution** of components A and B:

- Partial vapour pressure of component A:

$$P_A = X_A \cdot P^0_A$$

- Partial vapour pressure of component B:

$$P_B = X_B \cdot P^0_B$$

Where:

- P_B & P_A = Partial vapor pressures of A and B
- X_A & X_B = Mole fractions of A and B in the solution
- P^0_B & P^0_A = Vapor pressures of pure components A and B

Total Vapour Pressure of the Solution:

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

$$P_{total} = X_A \cdot P^0_A + X_B \cdot P^0_B$$

5. Define molarity & normality

Molarity (M):

Molarity is defined as the number of **moles of solute** present in **1 litre (1000 mL) of solution**.

$$\text{Molarity (M)} = \frac{\text{Moles of solute}}{\text{Volume of solution in litres}}$$

Unit: moles per litre (mol/L or M)

Normality (N):

Normality is defined as the number of **gram equivalents of solute** present in **1 litre of solution**.

$$\text{Normality (N)} = \frac{\text{Gram equivalents of solute}}{\text{Volume of solution in litres}}$$

Unit: equivalents per litre (eq/L or N)

6. Explain about distribution law

- When a solute distributes itself between two immiscible solvents, at constant temperature and when the solute exists in the same molecular form in both solvents, the ratio of its concentrations in the two solvents is constant.
- It is used to find out the nature of solute particle that is drug is lipophilic or hydrophilic based on how much the drug dissolve in each solvent.

$$\text{Partition coefficient} = \frac{\text{Drug dissolves in lyophilic phase}}{\text{Drug dissolve in hydrophilic phase}}$$

$$\mathbf{P = X_O/X_W}$$

Where Xo = Drug in oil phase
Xw = Drug dissolve in water phase

- If P > 1 = lyophilic
- P < 1 = hydrophilic

7. Define solvation & association

Solvation:

Solvation is the process in which **solute particles are surrounded by solvent molecules** when a solute dissolves in a solvent. This interaction stabilizes the solute in the solution.

- When the solvent is **water**, the process is specifically called **hydration**.
- It involves **intermolecular forces** such as hydrogen bonding, dipole-dipole interactions, or ion-dipole interactions.

Association:

Association refers to the process by which **individual molecules or ions of a solute combine or link together** to form larger units such as **dimers or multimers** in solution.

- It often occurs in **nonpolar solvents** where solute molecules form hydrogen bonds or van der Waals interactions with each other.
- The process leads to **a decrease in the number of free particles** in solution.

8. What is ideal solution & non ideal solution?

- Ideal solution: the solution which obey Raoult's law at all compositions of solute in solvent at all temperature are called ideal solution.
- An ideal solution is a solution in which interaction between molecules are identical between all molecules in the solutions. There is no net force between components of the solution. Thus the distance between molecules of the solute does not change after mixing it with a solvent.
- The enthalpy change of an ideal solution is zero

$$\Delta H_{mix} = 0$$

- **Non ideal solution:** the solution which deviate from ideal behavior are called non ideal solution/real solution. And they do not obey Raoult's law.
- A non-ideal solution is solution that has difference in the interaction between molecules of different component in the solution. The properties of a non-ideal solution may depends on the solvent-solvent, solute-solute or solvent-solute interactions.

$$\Delta H_{mix} \neq 0$$

- It shows two types of deviation

➢ **Positive deviation:** when total vapor pressure of the solution is greater than the partial Vapor pressure of solution.

$$P_{total} > P^0_A X_A + P^0_B X_B$$

$$P_{total} > P_A + P_B$$

$$\Delta H > 0$$

➢ **Negative deviation:** when total vapor pressure of the solution is less than the partial Vapor pressure of solution.

$$P_{total} < P^0_A X_A + P^0_B X_B$$

$$P_{total} < P_A + P_B$$

$$\Delta H < 0$$

9. Describe solubility of liquid in liquids.

- The **solubility of a liquid in another liquid** refers to the ability of one liquid (the **solute**) to dissolve uniformly in another liquid (the **solvent**) to form a **homogeneous solution**.

Types of Liquid-Liquid Solubility:

1. **Completely Miscible Liquids:**
   - These liquids **mix in all proportions** to form a single-phase solution.
   - No layer separation occurs.
   - **Examples:** Ethanol and water, acetone and water.
2. **Partially Miscible Liquids:**
   - These liquids **mix only to a limited extent**.
   - Beyond a certain concentration, two layers form.
   - Their mutual solubility is often influenced by temperature.
   - **Example:** Phenol and water.
3. **Immiscible Liquids:**
   - These liquids **do not mix** appreciably and form **two separate layers**.
   - Solubility is very low (negligible).
   - **Examples:** Oil and water, carbon tetrachloride and water.

Factors Affecting Solubility of Liquids in Liquids:

1. Temperature is directly proportional to the solubility

2. Pressure is directly proportional to the solubility

3. Nature of liquid (polar/ non polar)

4. Surface area is directly proportional to the solubility

10. A solution contain 0.25 mole of solute & 0.75 mole of solvent. Calculate mole fraction of solvent in the solution?

- Moles of solute = 0.25 mol
- Moles of solvent = 0.75 mol

$$X_{solvent} = \frac{0.75}{0.25+0.75} = 0.75$$

11. What is Hildebrand solubility Parameter?

The **Hildebrand Solubility Parameter** is a numerical value that indicates the **solubility behavior** of a substance based on its **cohesive energy density**. It helps predict whether one material will dissolve in another.

It is denoted by the symbol δ\deltaδ (delta).

$$\delta = \sqrt{\frac{\Delta H - RT}{V}}$$

Where δ = solubility parameter
ΔH = enthalpy
R = gas constant
T = temperature
V = Molar volume

12. Describe law of diffusion and factors affecting diffusion.

- Movement of molecules from high concentration to low concentration.

Fick's First law (steady state diffusion)

- The rate of diffusion of a substance across a unit area is directly proportional to the concentration gradient.

$$J = -D\, dc/dt$$

J = Diffusion flux (amount of substance per unit area per unit volume)
D = Diffusion coefficient
dc /dt = concentration gradient

Fick's second law

The rate of change of concentration at a point in space is proportional to the second derivative of a concentration with respect to position.

$$\delta C/\delta t = D \quad \delta^2 C/\delta X^2$$

Where C = concentration of diffusing substance
T= time
X= distance (m)
D= diffusion co efficient
$\delta C/\delta t$ = change in concentration with time
$\delta^2 C/\delta X^2$ = change in the concentration gradient with position

Factors affecting diffusion:

- ↑temp = ↑ kinetic energy = enhance diffusion
- Particle size ↓ = diffusion faster
- Greater the concentration gradient difference = faster the diffusion
- Larger surface area faster will be diffusion

13. Define Henry's law

- Hennery was the first to give a quantitative relation between pressure and solubility of a gas in a solvent, which is known as henry's law.
- The law states that at a constant temperature the solubility of a gas in a liquid is directly proportional to the partial pressure of a gas present the surface of liquid/solution.

$$P = KHx$$

Physical Pharmaceutics-I

Unit -2

1. Define latent heat and explain its significance in pharmaceutical sciences.

Latent heat is the heat energy per mass unit required for a phase change to occur.

Latent heat (hidden heat) is defined as the total energy absorbed /released when a substance changes its physical state completely at a constant temperature.

$$Q = m \times L$$

Specific latent heat: Amount of heat energy needed to change the state of 1kg of a substance without changing its temperature.

$$L = Q/m$$

Types of latent heat.

Latent heat of fusion (Lf)	Latent heat of vaporization (Lv)
The energy needed to break the bond in a solid and change it into a liquid.	It is the energy needed to brake the bond in a liquid and change I to a gas.
It is the heat absorbed by melting solid.	It is the heat absorbed during boiling

2. Differentiate between crystalline and amorphous solids.

Property	Crystalline Solids	Amorphous Solids
Molecular Arrangement	Highly ordered, regular, repeating lattice	Disordered, random arrangement
Definite Shape	Yes, definite geometric shape	No definite shape
Definite Melting Point	Sharp melting point	No sharp melting point; softens over a range
Long-Range Order	Present	Absent
Cleavage	Cleaves along definite planes	Does not cleave along planes
Physical Properties	Uniform and anisotropic	Variable and isotropic
Examples	Sodium chloride (NaCl), sucrose, quartz	Glass, gelatin, amorphous drugs like indomethacin
Stability	Generally more stable	Less stable; may crystallize over time

3. Explain sublimation with a pharmaceutical example.

- Low pressure are required for sublimation takes place. It is an endothermic phase transition that occurs at temp and pressure below.
- In thermodynamic, the triple point of a substance is the temperature and pressure at which the three phases coexist in thermodynamic equilibrium.
- A phase transition in which a solid is converted to a gas without passing through an intermediate liquid phase.
- Eg: freeze drying process.
- Desublimation/ Deposition: it refers to the process in which gas changes directly to a solid without going through desublimation. It is an exothermic reaction.
- Eg: subfrezzing air water vapour changes directly to ice without first becoming a liquid.
- Caffeine isolation & purification by direct sublimation process: crude caffeine is extracted from coffee and contain many impurities that may have been separated with it such as tannic acids. Pure caffeine has a lower bp. By condensing the evaporated caffeine over a controlled area, we can separate & collect it from the impurities.

4. Define Eutectic Mixture.

- An eutectic mixture is defined as a mixture of two/more component which usually don't interact to form a new chemical compound but which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower mp than either of the component.

5. Describe Gas Law

The gas law deals with how gases behave with respect to pressure , volume, temperature and amount.

a. Boyle's Law (pressure volume relationship)

Robert Boyle (1662)

At constant temperature, the volume of a given mass of gas is inversely proportional to its pressure.

$$PV=C$$

Pressure will increase when volume will be decrease.

$$P1V1=P2V2$$

The product of the initial volume and pressure is equal to the product of the volume and pressure after a change in one of them under constant temperature.

Eg: compress a gas into a smaller volume.

B. Charle's Law: At constant pressure, the volume of a gas is directly proportional to its absolute temperature.

$$V/T=C$$

If volume is increase temperature also increase

$$V1/T1=V2/T2$$

C. Gay-Luussac's Law: French Chemist Joseph Louis Gay-Lussac at 1802 discovered at constant volume the pressure of gas is directly proportional to its absolute temperature.

$$P/T=C$$

Pressure will increase when temperature also increase.

$$P1/T1=P2/T2$$

D. Avogadro's Number: at 1811 amedeo avagadro Italian scientist states that at constant temperature and pressure, equal volume of all gasses contain equal no of molecules.

Gass molecules amount is directly proportional to the volume of gass.

$$V/n = C$$

Volume of gass increase if amount of gas molecule increase.

$$V1/n1=V2/n2$$

E. Combined gas law: the volume of a given amount of gas is proportional to the ratio of its kelvin temperature and its pressure.

$$PV/T=C$$

Pressure is increase then temperature also increase also volume will be decrease.

$$P1V1/T1=P2V2/T2$$

F. Ideal Gas law: it shows how pressure, volume, temperature and amount of gas are co relataed

$$PV=C,\ V/T=C,\ V/n=C$$

PV=V/T=V/n

PV=nRT

Here R= Gas Constant

n= no of moles.

G. Daltons Law: the total pressure of gas mixture is the sum of the partial pressure of individual gases.

P total= Pa+Pb+Pc+…….

Ptotal= naRT/V+nbRT/V+ncRT/V+……

= (na+nb+nc+……..) RT/V

6. A gas occupies 4.0L at 1.2atm. what will its volume be at 2.4atm temperature constant.

P1= 1.2atm V1=4L

P2=2.4atm V2= ?

P1V1=P2V2

1.2X4=2.4V2

V2= 1.2x4/2.4=2.0L

7. A gas has a volume of 2.5L at 300k. what will be its volume at 600K.

V1=2.5L V2=?

T1=300K T2=600K

V1/T1=V2/T2

2.5/300=V2/600

V2=2.5x600/300=5/0L

8. A gas is at 1.0atm, 300K and 2.0L what is its volume at 2atm and 400K.

P1=1atm P2=2atm

T1=300K T2=400K

V1=2L V2=?

P1V1/T1=P2V2/T2

1x2/300=2xV2/400

V2= 800/300 =2.67L

9. A gas has a pressure of 2atm volume 5L, and temperature 400K. How many moles of gas are present?

P=2atm V=5L T=400K

PV=nRT

n= PV/RT = 2x5/8.314x400 = 0.304mol

10. Define Aerosols. Describe its working principle with merits and demerits.

An aerosols is a colloid of fine solid particles/ liquid droplets suspended in a gas. An aerosol is a dispersed system, in which very fine solid drug particles or liquid dropltes get dispersed in the propellants which act as continuous phase.

Propellants: a propellant is agas or liquid inside an aerosol can that helps push the product out when you press the nozzle.

Principle: it works on the principle of pressure difference. ……> inside the can, the product is mixed with propellants ……..> the propellant builds pressure inside the sealed can. ……..> when you press the nozzle, a small valve opens & narrow nozzles breaks the liquid into tiny droplets. The high pressure propellant pushes the product out through a small opening, turning it intop a fine spray.

Advantages: a fine mist of the drug is produced which is suitable for inhalation.

No contamination of remaning material after withdrawl .

Easy to administered and medicament is directly applied to the affected area.

The onset action is faster compared to other dosage form.

Photosensitive material can be protected.

Disadvantages: cost high

Disposal are difficult

11. Define Relative Humidity.

It is meseaured how much water vapour is in the air compared to how much air could hold at a given temperature. Relative Humidity is the ratio of the actual amount of water vapor present in the air at a given temperature to the maximum amount of water vapor that the air can hold at the same temperature (saturation vapor content). It is expressed as a percentage.

$$\text{Relative Humidity (RH)} = \text{Actual vapor pressure} / \text{Saturation vapor pressure} \times 100$$

12. What are liquid crystals? Mention their applications.

Liquid crystals are **states of matter** that have properties between those of **conventional liquids** and **solid crystals**.

- Like liquids, they can **flow**.
- Like crystals, they have a certain degree of **molecular order or orientation**.

Molecules in liquid crystals are typically elongated (rod-like) and can align in a particular direction while still moving like a fluid.

Types of Liquid Crystals

1. **Nematic** – molecules are parallel but not arranged in layers.
2. **Smectic** – molecules are parallel and arranged in distinct layers.
3. **Cholesteric (or chiral nematic)** – molecules are arranged in a helical structure.

Applications of Liquid Crystals

1. **Display technology (LCDs):**
   - Used in calculators, watches, mobile phones, TVs, laptops.
2. **Thermography (Temperature sensors):**
   - Show color changes with temperature (e.g., fever strips, aquarium thermometers).
3. **Optical devices:**
   - Polarizers, tunable lenses, and light modulators.
4. **Biological studies:**
   - Used to study cell membranes (as they also exhibit liquid crystal behavior).
5. **Drug delivery systems (Pharmacy):**
   - Some liquid crystal phases are used as carriers for controlled release of drugs.

13. Define Glassy state.

The **glassy state** is a **solid state of matter** in which a substance appears rigid like a crystal but lacks the **long-range orderly arrangement of atoms or molecules** that is characteristic of crystalline solids.

- It is an **amorphous solid** formed when a liquid is cooled rapidly without crystallization.
- Molecules are arranged in a disordered (random) manner, similar to liquids, but the material behaves mechanically like a solid.

14. Define Interfacial Angle.

The **interfacial angle** is the angle formed at the intersection of two adjacent faces of a crystal.

It is a **characteristic property of crystals** and remains **constant** for a given substance, regardless of crystal size or method of preparation.

15. Explain physicochemical properties of drug molecules with examples.

The physical and chemical charecteristics of a drug that influence its pharmacokintectics and pharmacodynamics . these properties help in understanding the behavior of drugs in biological system.

1. molecular weight: drug with mw > 500Da generally show poor oral absorption in GIT.

2. Solubility: ability of the drug to dissolve in solvent. Aq. Solubility is essential for dissolution and absortption. Lipid solubility affect membrane permeability and distribution.

3. Partition Coeffiecient (K): Ratio of drug concentration is lipid and water phase.

Higher K = More lipophilic = better membrane permeability but poor solubility.

4. distribution coefficient (D): Considered ionized and unionized form at a specific PH.

5. Melting point: purity and solid state stability

Increase MP = decrease solubility

6. polar surface area (PSA): PSA os the surface area occupied by polar atoms.

Low PSA (<140A°) is favourable for oral bioavailability.

7. Refractive Index (RI): Ratio of the velocity of the light in a vaccum to its velocity in a given medium.

n=Velocity of light in medium (v)/Velocity of light in vacuum (c)

Pharmaceutical Importance:

1. **Identification & purity testing** – each substance has a specific refractive index.
   - *Example:* Used to check purity of oils, solvents.
2. **Concentration determination** – refractive index changes with solution concentration.
   - *Example:* Used in sugar solutions (Brix scale).
3. **Characterization of drugs** – helps in detecting adulteration.

Factors affecting : temperature is inversely proportional to refractive index.

Wavelength of light is inversely proportional to the refractive index.

Pressure is directly proportional to the refractive index.

8. Optical Rotation/ Optical Activity: Optical rotation is the ability of a substance to rotate the plane of polarized light. Some drug molecules are optically active.

$$[\alpha] = (\text{observed rotation}/ \text{path length} \times \text{concentration}) \times 100$$

where:

- α = observed angle of rotation
- l = length of solution cell in **dm**
- c= concentration of solution in **g/mL**

it is two types: Dextrorotatory (+ or d): Rotates plane of light to the **right/clockwise**.

Levorotatory (– or l): Rotates plane of light to the **left/anticlockwise**.

Application: Differentiating enantiomers.

Confirming Chiral Purity of Drug.

9. Dielectric Constant (ε):

The **dielectric constant** is the measure of a substance's ability to **store electrical energy** in an electric field, compared to a vacuum.

ε= Capacitance of capacitor in vacuum/ Capacitance of capacitor with dielectric

Pharmaceutical Importance:

1. **Solubility of drugs**
   - Solvents with high dielectric constants (e.g., water) dissolve **polar/ionic drugs**.
   - Solvents with low dielectric constants (e.g., hexane) dissolve **nonpolar drugs**.
2. **Formulation of dosage forms**
   - Used in selecting suitable solvents for syrups, injections, emulsions, etc.
3. **Ionization and stability**
   - Affects the **degree of ionization** of electrolytes and hence drug stability.
   - Example: Weak electrolytes ionize better in high dielectric constant solvents.
4. **Drug–membrane interaction**
   - Biological membranes have lower dielectric constant than water → affects drug partitioning and absorption.

10. Dipole moment (μ):

The **dipole moment** is a measure of the separation of positive and negative charges in a molecule.
It indicates the **polarity** of a molecule.

$$\mu = q \times d$$

where:

- qqq = magnitude of charge (in coulombs)
- ddd = distance between charges (in meters)

Unit: **Debye (D)** (1 D = 3.33564×10^{-30} C·m)

11. Dissociation Constant (Ka, PKa):

the **dissociation constant** is a measure of the **extent to which a chemical compound (usually an acid or a base) ionizes in solution**. It shows the equilibrium between the **unionized form** and the **ionized form**.

$$Ka = [HA]/[H^+][A^-]$$

Where:

- [H+] = concentration of hydrogen ions
- [A−] = concentration of conjugate base
- [HA] = concentration of undissociated acid

Higher Ka_aa → stronger acid (more ionized in solution).

Lower Ka_aa → weaker acid (less ionized).

Pharmaceutical Importance:

1. **Drug absorption:** Only **unionized forms** cross lipid membranes.
2. **Solubility:** Ionized forms are more water-soluble.
3. **Formulation:** Helps in preparing **buffered solutions**.
4. **Drug distribution:** Affects partitioning into tissues.

16. Short Answer.

Heat required to change state without temperature change – *Latent Heat*

Direct solid → gas transition – *Sublimation*

Temperature at which gas and liquid are indistinguishable – *Critical Point*

Mixture with lower melting point than individual components – *Eutectic Mixture*

Solids with definite arrangement of atoms – *Crystalline*

Solids without long-range order – *Amorphous*

Ability of a substance to exist in more than one crystalline form – *Polymorphism*

Drugs delivered by aerosol systems – *Inhalers*

Ratio of actual vapor pressure to saturated vapor pressure × 100 – *Relative Humidity*

State with properties between solid and liquid – *Liquid Crystal*

Non-crystalline, rigid solid without sharp melting point – *Glassy State*

Property describing bending of light – *Refractive Index*

Ability of chiral substances to rotate polarized light – *Optical Rotation*

Measure of solvent polarity – *Dielectric Constant*

Vector measure of molecular polarity – *Dipole Moment*

pH at which 50% ionization occurs – *pKa*

Process used in lyophilization – *Sublimation*

Example of polymorphic drug – *Ritonavir*

Supercooled liquid with disordered structure – *Amorphous Solid*

Unit of dipole moment – *Debye*

PHYSICAL PHARMACEUTICS-I

UNIT – III &IV

UNIT -III (Surface tension and interfacial tension)

10 marks question:

Q1. Define surface tension. Describe in detail the various methods used for the determination of surface tension with relevant principles and formulas.

Answer:

Definition:

Surface tension is defined as the force acting along the surface of a liquid at right angles to any line drawn in the surface, tending to minimize the surface area. It is expressed in **N/m** or **dyne/cm**.

This phenomenon occurs because molecules at the surface experience unbalanced cohesive forces (only inward attraction), which results in a tension that causes the surface to behave like a stretched elastic membrane.

Methods for Surface Tension Measurement:

1. Drop Count Method (Stalagmometric Method):

- **Principle:** The number of drops formed by a fixed volume of liquid is inversely proportional to the surface tension.
- **Apparatus:** Stalagmometer
- **Formula: $\gamma 1 n1 = \gamma 2 n2$**

$$\gamma 2 = \gamma 1 n1 / n2$$

where $\gamma 1$ = surface tension of ref. sample, n1 = number of drops of ref sample, $\gamma 2$= surface tension of test sample, n2 = number of drops of test sample

- **Application:** Useful for comparing relative surface tensions of different liquids.

2. Drop Weight Method:

- **Principle:** Surface tension is proportional to the weight of the drop that detaches from the capillary.
- **Formula: $\gamma 1 w1 = \gamma 2 w2$**

$$\gamma 2 = \gamma 1 w1 / w2$$

where $\gamma 1$ = surface tension of ref. sample, w1 = wt. of ref sample, $\gamma 2$= surface tension of test sample, w2 = **wt. of test sample,**

-

where m = mass of one drop, g = gravity, r = radius of the tube

- **Application:** More accurate than the drop count method; suitable for analytical applications.

3. Capillary Rise Method:

- **Principle:** A liquid rises in a capillary tube due to surface tension, forming a concave meniscus.
- **Formula: $\gamma = hr\rho g/2$**

  Where:

  γ = Surface tension (in N/m)

  h = Height of the liquid column in the capillary (in meters)

  r = Radius of the capillary tube (in meters)

  ρ = Density of the liquid (in kg/m^3)

  g = Acceleration due to gravity (9.8 m/s^2)

  Note: This formula assumes the contact angle is approximately 0° (perfect wetting).
- **Application:** Common method for water and aqueous liquids.

4. Du Noüy Ring Method (Tensiometer Method):

- **Principle:** Measures the force needed to detach a platinum ring from the liquid surface.
- **Application:** Precise and widely used in industry and research.
- **Formula:** $ST/IT = \frac{\text{Reading Dial (Dynes)}}{2 \times \text{Ring Circumference}} \times \text{Correction factor}$

5. Maximum Bubble Pressure Method:

- Measures the pressure required to form a bubble at the tip of a submerged capillary tube.

6. Sessile drop method:

The Sessile Drop Method is an experimental technique used to measure the contact angle between a liquid droplet and a solid surface. The contact angle provides critical information about the surface properties, particularly wettability, adhesion, and surface free energy.

Principle:

When a liquid drop is placed on a solid surface, it may either **spread out** (wet the surface) or form a **spherical shape** (non-wetting). The **contact angle (θ)** is the angle formed at the three-phase boundary where the **solid, liquid, and vapor** meet.

- A **low contact angle (< 90°)** indicates **good wetting** and **high surface energy** of the solid.
- A **high contact angle (> 90°)** indicates **poor wetting** and **low surface energy**.

7. Wilhelmy method:

The Wilhelmy Plate Method, also known as the Wilhelmy Method, is a widely used and highly accurate technique for measuring surface tension (liquid–air interface) and interfacial tension (liquid–liquid interface).

It is based on measuring the force exerted by the liquid on a thin vertically suspended plate as it interacts with the surface or interface of the liquid.

Conclusion: The choice of method depends on the type of liquid, required accuracy, and available instruments. Surface tension measurement is essential in pharmaceutical formulations like emulsions, suspensions, and surfactant efficiency testing.

☑ Q2. Discuss the factors affecting surface tension and interfacial tension. Explain with examples and their pharmaceutical significance.

Answer:

Factors Affecting Surface and Interfacial Tension:

1. Temperature:

- **Effect:** As temperature increases, kinetic energy increases, weakening cohesive forces.
- **Result:** Surface tension decreases with increasing temperature.
- **Example:** Warm water has a lower surface tension than cold water.
- **Pharma Application:** Drug solubility and spreadability increase at higher temperatures.

2. Nature of Liquid:

- Polar liquids (like water) exhibit high surface tension due to strong hydrogen bonding.
- Nonpolar liquids (like benzene) have lower surface tension.
- **Example:** Surface tension of water = ~72.8 dyne/cm; benzene = ~28.9 dyne/cm

3. Presence of Impurities:

- Soluble substances like salt or acids can increase ST.
- Surface-active agents like surfactants reduce ST by concentrating at the interface.
- **Example:** Sodium lauryl sulfate reduces ST in mouthwash formulations.

4. Intermolecular Forces:

- Stronger cohesive forces result in higher surface tension.
- Van der Waals forces, hydrogen bonds, and dipole interactions influence ST/IT.

5. Addition of Surfactants (Surface-Active Agents):

- Reduce both ST and IT by orienting at the interface with hydrophilic and hydrophobic ends.
- **Example:** Tween 80 in emulsions lowers interfacial tension between oil and water phases.

Pharmaceutical Significance:

- **Emulsion Stability:** Lower interfacial tension aids in stable emulsion formation.
- **Wetting Agents:** Aid in spreading aqueous solutions on solid surfaces (e.g., tablet disintegration).
- **Foaming Agents:** In syrups or cleaning agents, surfactants help foam formation by reducing ST.
- **Drug Absorption:** Reduced surface tension promotes better solubilization and absorption.

☑ **Q3. Write in detail the pharmaceutical applications of surface and interfacial tension. Support your answer with examples.**

Answer:

Surface and interfacial tensions play crucial roles in various pharmaceutical processes and product formulations.

1. Formulation of Emulsions:

- Emulsions consist of two immiscible liquids (e.g., oil and water).
- Interfacial tension must be reduced to form stable droplets.
- **Use of surfactants:** e.g., Span and Tween are used to stabilize oil-in-water emulsions.

2. Suspension Stability:

- Suspensions require wetting of solid particles by the dispersion medium.
- Lowering surface tension ensures better wetting and uniform dispersion.
- **Example:** Magnesium hydroxide suspension uses wetting agents like sodium lauryl sulfate.

3. Tablet Manufacturing:

- Wet granulation involves wetting powders before compression.
- Surface tension affects granule formation and binding.
- **Application:** Ensures proper adhesion and compressibility of granules.

4. Aerosol Formulations:

- Fine mist or spray requires uniform droplet formation.
- Low surface tension ensures the drug forms small, evenly distributed droplets.
- **Example:** Inhalers for asthma (e.g., salbutamol aerosols) need controlled ST.

5. Drug Solubilization:

- Hydrophobic drugs are difficult to dissolve in aqueous media.
- Surfactants reduce ST and increase solubility.
- **Example:** Micellar solubilization of poorly soluble drugs like itraconazole.

6. Coating of Tablets:

- Film coating requires spreading of liquid over solid tablets.
- Proper ST ensures uniform coating without cracks or peeling.
- **Example:** Coated tablets for delayed release formulations.

7. Cleaning and Sterilization:

- In pharmaceutical manufacturing, effective cleaning of glassware or stainless steel equipment depends on the surface activity of cleaning agents.

Conclusion:

Control and understanding of surface and interfacial tension are essential for drug formulation, manufacturing processes, and ensuring drug stability and bioavailability.

5 marks qn:

1. **What Do You Mean by Spreading Coefficient?**

What Do You Mean by Spreading Coefficient?

Definition:

The **spreading coefficient (S)** is a **thermodynamic parameter** that determines the **ability of one liquid to spread over another liquid** or over a **solid surface**. It is used to predict whether a liquid will **wet** the surface and form a continuous film or **bead up** and form droplets.

Concept:

The spreading of a liquid depends on the balance between **adhesive forces** (between the liquid and the surface) and **cohesive forces** (within the liquid molecules themselves).

- If **adhesive forces > cohesive forces** → the liquid **spreads**.
- If **cohesive forces > adhesive forces** → the liquid **does not spread** and forms droplets.

Formula:

There are **two equivalent ways** to express the spreading coefficient:

1. Using Work of Adhesion and Cohesion:

$$S = W_a - W_c$$

Where:

- W_a = Work of adhesion (energy required to separate two different substances)
- W_c = Work of cohesion (energy required to separate molecules of the same substance)

2. Using Surface and Interfacial Tensions (common in pharmacy):

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

Where:

- γ_S = Surface tension of the underlying surface (e.g., water or solid)
- γ_L = Surface tension of the spreading liquid
- γ_{SL}= Interfacial tension between the liquid and the surface

Interpretation:

Value of S	Meaning	Resulting Action
S>0	Favorable spreading	Liquid spreads completely
S<0	Unfavorable spreading	Liquid forms droplets
S=0	Neutral condition	May form a partial film

Key Terms:

- **Work of Adhesion (Wa):**
  Energy needed to **separate** two **dissimilar surfaces** (e.g., water and glass).
- **Work of Cohesion (Wc):**
  Energy needed to **separate** two **identical surfaces** (e.g., two water molecules).

Relationship to Surface Tension:

The **spreading coefficient is directly related** to surface and interfacial tensions.

- **Surface tension** arises from cohesive forces between molecules in a liquid.
- **Interfacial tension** exists between **two immiscible liquids** (e.g., oil and water).

The spreading coefficient combines these values to predict spreading behavior.

Significance in Pharmaceutical Context:

📌 **1. Topical Drug Delivery:**

- In creams and ointments, a **positive S** ensures the drug spreads uniformly over the skin.
- Enhances **bioavailability** and **patient compliance**.

📌 **2. Emulsions:**

- Affects **emulsion stability** by indicating whether one liquid will spread over another.
- Crucial in designing **oil-in-water or water-in-oil** emulsions.

📌 **3. Tablet Coating:**

- Determines how well a **coating solution** wets and adheres to a tablet surface.
- Impacts appearance, uniformity, and protection of the dosage form.

📌 **4. Bioadhesives and Mucosal Delivery:**

- Helps evaluate the **adhesion and spreading** of gels or films over biological membranes.

Conclusion:

The **spreading coefficient** is a key physical parameter in pharmaceutical sciences. It explains **wetting behavior**, guides **formulation development**, and influences **drug delivery** effectiveness. A **positive S** signifies good spreading and adhesion — vital for efficient topical and surface-based formulations.

Example:

Suppose a liquid (e.g., oil) is placed on a water surface.

If:

- Surface tension of water (γS) = 72.8 mN/m
- Surface tension of oil (γL) = 30.0 mN/m
- Interfacial tension between oil and water (γSL) = 35.0 mN/m

Then:

$S=72.8-(30.0+35.0)=7.8$ mN/m

→ **S > 0**, so **oil will spread** over water.

2. **Write a short note on Langmuir adsorption isotherm.**

Definition:

The **Langmuir adsorption isotherm** is a theoretical model that describes the **adsorption of a gas or solute onto a solid surface**, forming a **monolayer**. It assumes that the adsorption occurs on a **homogeneous surface** with a **fixed number of identical sites** and no interaction between adsorbed molecules.

Key Assumptions:

1. **Monolayer Adsorption:**
   Adsorption is limited to **one molecule per site** — once a site is occupied, no further adsorption can occur at that site.
2. **Homogeneous Surface:**
   All adsorption sites are **energetically identical** (same affinity for the adsorbate).
3. **No Lateral Interactions:**
   Adsorbed molecules do **not interact** with each other on the surface.
4. **Dynamic Equilibrium:**
   The rate of **adsorption equals** the rate of **desorption** at equilibrium.

Langmuir Equation:

The isotherm is mathematically expressed as:

$$\theta=KP/1+KP$$

Where:

- θ = fraction of surface sites occupied
- K = Langmuir adsorption constant (related to affinity)
- P = partial pressure (for gases) or concentration (for solutions)

Alternate form (for amount adsorbed):

$$x/m = abC/1+bC$$

Where:

- x/m = amount of adsorbate per unit mass of adsorbent
- C = concentration of adsorbate
- a, b = Langmuir constants

Graphical Representation:

- A plot of **C/ x/m** vs C yields a **straight line**, validating the model.

Applications in Pharmacy and Industry:

1. **Catalysis:**
   Used to design **heterogeneous catalysts** where gases adsorb onto metal surfaces.
2. **Gas Mask Design:**
   Models how **activated charcoal** adsorbs toxic gases — crucial in **protective respirators**.
3. **Moisture Adsorption:**
   Helps study how **excipients** or packaging materials absorb water vapor.
4. **Chromatography:**
   Explains how **adsorption onto stationary phase** impacts **separation efficiency**.

Limitations:

- Not applicable to **multilayer adsorption**.
- Assumes **ideal behavior** — real surfaces may be **heterogeneous**.
- Ignores **adsorbate-adsorbate interactions**.

Conclusion:

The **Langmuir isotherm** is a foundational concept in surface science and pharmaceutics. It provides insight into **monolayer adsorption** behavior and is widely used to optimize **adsorption-based drug delivery systems, purification processes, and analytical techniques** like chromatography.

3. Write a short note on Freundlich adsorption isotherm.

Definition:

The **Freundlich adsorption isotherm** is an **empirical relationship** that describes how a gas or solute is **adsorbed onto a solid surface** at a constant temperature. It explains that **adsorption increases with pressure** or concentration but **not linearly**.

Freundlich Equation:

$$\mathbf{x/m = kP^{1/n}}$$

Where:

- x/m = amount of adsorbate adsorbed per unit mass of adsorbent
- P = pressure (or concentration)
- k, n = empirical constants depending on temperature and nature of adsorbent/adsorbate

Logarithmic form:

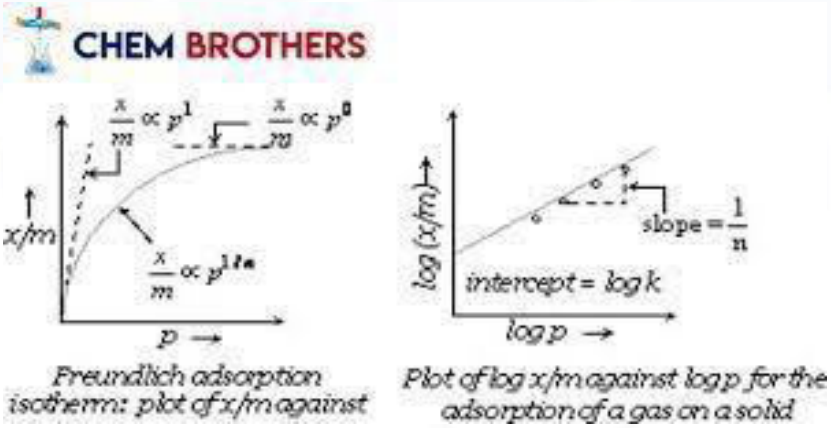
$$\log(x/m) = \log k + 1/n \log P$$

→ Gives a **straight line** when plotted as log (x/m) Vs log P.

Graph Explanation:

The graph you provided is a plot of:

- x/m (adsorption per unit mass of adsorbent) **vs.** Pressure P.
- As pressure increases, **adsorption increases**, but the curve **flattens**, showing **no fixed saturation point**, unlike Langmuir's isotherm.
- Indicates that **adsorption is more favorable at lower pressures**, and becomes less efficient at higher pressures.



Freundlich adsorption isotherm: plot of x/m against p

Plot of log x/m against log p for the adsorption of a gas on a solid

Key Features:

- Applicable to **heterogeneous surfaces**.
- **1/n < 1** indicates favorable adsorption.
- Adsorption increases with pressure but is **not proportional**.
- Does **not predict monolayer formation**.

Limitations:

- Not valid at **very high pressures** where adsorption sites may become saturated.
- Being **empirical**, it lacks a strong theoretical foundation.

Applications in Pharmacy:

- Used in **adsorption of drugs** onto carriers or excipients.
- Helps in designing **activated charcoal formulations** for toxin removal.
- Useful in **purification**, **chromatography**, and **controlled release systems**.

4. **Write a short note on adsorption at liquid surface.**

Definition:

Adsorption at the liquid surface refers to the **accumulation or orientation of molecules** (solutes, gases, or surfactants) at the **interface between a liquid and another phase**, such as **air** or **another immiscible liquid**. This occurs due to **unequal molecular forces** acting at the interface.

Key Concepts:

- Molecules at the liquid surface experience **different intermolecular forces** than those in the bulk, causing **surface tension**.
- Certain molecules (e.g., surfactants) tend to **adsorb at the surface**, reducing surface tension.
- Adsorption may occur at:
    - **Liquid–air interface** (e.g., water surface exposed to air)
    - **Liquid–liquid interface** (e.g., oil–water emulsions)

Types of Adsorbed Molecules:

1. **Surface-Active Agents (Surfactants):**
    - Have both **hydrophilic** and **hydrophobic** groups.
    - Adsorb at liquid surfaces, orienting themselves to lower surface tension.
2. **Polymers or Proteins:**

- May also adsorb at liquid interfaces, affecting the viscosity and stability of solutions or emulsions.

Factors Affecting Adsorption:

- **Concentration of solute**
- **Temperature**
- **Nature of the solute and solvent**
- **Presence of electrolytes**

Applications in Pharmacy:

- **Emulsion and suspension stability:** Surfactants adsorb at the oil–water interface to stabilize emulsions.
- **Wetting agents in formulations:** Adsorption improves **spreadability** on surfaces.
- **Aerosol and foam formation:** Depends on surface activity at the liquid–gas interface.
- **Controlled drug delivery:** Interfaces play a key role in nanoparticle-based systems.

Conclusion:

Adsorption at the liquid surface is a vital concept in pharmaceutics, impacting the **behavior, stability, and efficacy** of many pharmaceutical formulations like emulsions, foams, suspensions, and transdermal systems.

5. **Write a short note on adsorption at solid surface.**

Definition:

Adsorption at a solid surface refers to the **accumulation of gas or liquid molecules (adsorbate)** on the **surface of a solid (adsorbent)** due to the presence of **unbalanced surface forces**. This is a surface phenomenon where molecules from a fluid phase adhere to a solid surface.

Types of Adsorption:

1. **Physical Adsorption (Physisorption):**
   - Weak van der Waals forces
   - Low heat of adsorption
   - Reversible and multilayer adsorption
2. **Chemical Adsorption (Chemisorption):**
   - Involves chemical bond formation
   - Strong, irreversible

- Usually monolayer

Factors Influencing Adsorption:

- **Surface area** of the solid (larger area → higher adsorption)
- **Temperature** (physisorption decreases with temperature; chemisorption may increase)
- **Pressure/concentration** of the adsorbate
- **Nature of adsorbate and adsorbent**

Adsorption Isotherms:

- **Freundlich Isotherm:** Empirical model describing heterogeneous surface adsorption.
- **Langmuir Isotherm:** Theoretical model assuming monolayer adsorption on homogeneous surfaces.

Applications in Pharmacy:

- **Activated charcoal** for **poison and toxin removal**
- **Adsorbent excipients** for drug stabilization
- **Chromatography techniques** (TLC, HPLC) rely on differential adsorption
- **Sustained-release formulations** using adsorptive matrices

6. Define surfactant. Classify it with examples.

A **surfactant** (short for *surface-active agent*) is a compound that **reduces the surface tension** or **interfacial tension** between two phases such as:

- Liquid–air
- Liquid–liquid
- Solid–liquid

Surfactants have a **bipolar molecular structure**:

- A **hydrophilic (water-loving)** "head"
- A **hydrophobic (water-repelling)** "tail"

This dual nature allows them to accumulate at interfaces and **improve wetting, spreading, emulsification, solubilization**, and **foaming**.

☑ **Classification of Surfactants:**

Surfactants are classified based on the **nature of the charge** on the hydrophilic head:

1. Anionic Surfactants

- The hydrophilic group carries a **negative charge**.

- Commonly used in soaps, detergents, and emulsifiers.

Examples:

- **Sodium lauryl sulfate (SLS)**
- **Sodium stearate**

2. Cationic Surfactants

- The hydrophilic part carries a **positive charge**.
- Often used as **antimicrobial agents** and **preservatives**.

Examples:

- **Cetyltrimethylammonium bromide (CTAB)**
- **Benzalkonium chloride**

3. Non-Ionic Surfactants

- Do **not carry any charge**.
- Rely on **hydrogen bonding or polar groups** for solubility.
- Less irritating, often used in **ophthalmic and parenteral preparations**.

Examples:

- **Polysorbates (e.g., Tween 80)**
- **Sorbitan esters (e.g., Span 20)**

4. Ampholytic (Zwitterionic) Surfactants

- Contain **both positive and negative charges** depending on the pH.
- Used in **mild shampoos and skin products**.

Examples:

- **Lecithin**
- **Cocamidopropyl betaine**

☑ **Conclusion:**

Surfactants are vital components in pharmaceutical formulations due to their ability to **modify interfacial properties**. Their classification helps in selecting the right surfactant for **emulsions, suspensions, creams, gels, and drug delivery systems**.

7. Give an account of following:

a) Hydrophlic – lipophilic balance

1. Hydrophilic-Lipophilic Balance (HLB):

Definition:

The **Hydrophilic-Lipophilic Balance (HLB)** is a numerical scale that expresses the **relative degree of hydrophilicity (water-loving)** and **lipophilicity (oil-loving)** of a surfactant.

- **HLB values range from 0 to 20.**

Interpretation:

HLB Value	Function
1–3	Antifoaming agents
3–6	Water-in-oil (W/O) emulsifiers
7–9	Wetting and spreading agents
8–16	Oil-in-water (O/W) emulsifiers
13–18	Solubilizing agents

Examples:

- **Span 80 (HLB ≈ 4.3):** W/O emulsifier
- **Tween 80 (HLB ≈ 15):** O/W emulsifier and solubilizer

Pharmaceutical Application:

HLB guides the **selection of surfactants** for stable emulsions and other formulations by matching the required HLB of the oil phase with the surfactant or surfactant blend.

☑ **2. Solubilization:**

Definition:

Solubilization is the process of increasing the solubility of a poorly water-soluble substance by incorporating it into **micelles** formed by surfactants.

Mechanism:

- When the surfactant concentration exceeds its **critical micelle concentration (CMC)**, it forms micelles.

- The **hydrophobic core** of the micelle can incorporate **lipophilic drugs**, thereby **solubilizing them in aqueous media**.

Types of Solubilization:

- **Aqueous solubilization:** Using hydrophilic surfactants in water
- **Non-aqueous solubilization:** Using surfactants in non-polar media

Pharmaceutical Applications:

- **Improving bioavailability** of poorly soluble drugs
- Used in **oral, parenteral, and ophthalmic** formulations
- Example: **Tween 80** for solubilizing essential oils or vitamins

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☑ **3. Detergency:**

Definition:

Detergency is the ability of a surfactant to **remove dirt, grease, or impurities** from a surface (solid or skin) by **wetting, emulsifying, and suspending** unwanted materials in the cleaning solution.

Mechanism:

1. **Wetting:** Surfactant lowers surface tension, allowing water to spread and penetrate.
2. **Emulsification:** Oils and greases are emulsified by micelle formation.
3. **Suspension:** Dirt and oils are kept suspended and removed by rinsing.

Key Requirements of a Good Detergent:

- Strong **wetting** and **emulsifying** power
- High **CMC** to ensure good cleaning
- Non-toxic and non-irritant

Applications in Pharmacy:

- Cleaning of **lab glassware**, instruments, and manufacturing equipment

- Used in **medicated shampoos**, **oral cleansers**, **denture cleaners**
- Example: **Sodium lauryl sulfate (SLS)** as a detergent and wetting agent

☑ **Conclusion:**

- **HLB** helps in the selection of appropriate surfactants for formulation.
- **Solubilization** enhances drug solubility and bioavailability.
- **Detergency** ensures cleanliness and hygiene in pharmaceutical and personal care products.

8. Write down the different formulas to determine HLB.

Formulas to Determine HLB (Hydrophilic–Lipophilic Balance)

HLB is a numerical value (0–20) that indicates the balance between the hydrophilic and lipophilic parts of a surfactant. Different formulas are used depending on the type of surfactant and available data.

⬭ **1. Griffin's Formula (For Non-Ionic Surfactants)**

$$HLB = E/5$$

Where:

- E = Percentage by weight of the hydrophilic portion
- HLB value typically ranges from 0 (very lipophilic) to 20 (very hydrophilic)

☑ Example:
If hydrophilic portion is 75%

$$HLB = 75/5 = 15$$

⬭ **2. Davies' Formula (For Ionic and Complex Surfactants)**

$$HLB = 7 + \sum(\text{hydrophilic group numbers}) - \sum(\text{lipophilic group numbers})$$

Where:

- Each functional group (–OH, –COOH, $–CH_3$, etc.) is assigned a specific value
- More hydrophilic groups raise the HLB; lipophilic groups reduce it

☑ Example:

$$HLB = 7 + 9.6(\text{hydrophilic}) - 0.475(\text{lipophilic}) = 16.125$$

3. HLB from Saponification and Acid Numbers

$$HLB = 20(1 - S/A)$$

Where:

- S = Saponification number of the fatty (lipophilic) portion
- A = Acid number of the hydrophilic (acidic) portion

☑ This method is mainly used for fatty acid esters.

⬭ **4. Modified Griffin-Like Formula (Rarely Used)**

$$HLB = E - P/5$$

Where:

- E = % of hydrophilic portion
- P = % of lipophilic portion

📌 Not standard, but can be used to compare contributions of both parts in a molecule.

⬭ **5. HLB of a Surfactant Blend**

$$HLB\ mixture = (f1 \times HLB1) + (f2 \times HLB2)$$

Where:

- f1, f2 = Weight fractions of surfactants
- HLB1, HLB2 = HLB values of each surfactant

☑ Used to prepare emulsions when combining surfactants to match the required HLB (rHLB) of the oil phase.

20 One-Mark Questions with Answers (ST & IT)

1. Q: What is the SI unit of surface tension?
   A: Newton per meter (N/m)
2. Q: Which method uses a stalagmometer?
   A: Drop count method
3. Q: What is the principle of the capillary rise method?
   A: Liquid rises in a capillary due to surface tension pulling it up against gravity.
4. Q: Name one method used to determine interfacial tension.
   A: Wilhelmy Plate Method
5. Q: What is the force responsible for surface tension?
   A: Cohesive force between liquid molecules

6. Q: What is the unit of interfacial tension?
   A: N/m (same as surface tension)
7. Q: What happens to surface tension with an increase in temperature?
   A: It decreases.
8. Q: What kind of force is involved in adhesion?
   A: Force between dissimilar molecules
9. Q: What does a tensiometer measure?
   A: Surface or interfacial tension
10. Q: Which type of molecule reduces surface tension when added to water?
    A: Surfactant
11. Q: What is meant by a "wetting agent"?
    A: A substance that lowers surface tension and increases wetting of a surface
12. Q: Name a method that directly measures the force of detachment.
    A: Wilhelmy Plate Method
13. Q: Which method measures the weight of drops to determine surface tension?
    A: Drop weight method
14. Q: What kind of interface does interfacial tension occur at?
    A: Between two immiscible liquids
15. Q: Which method is used to determine surface tension by observing a rising liquid column?
    A: Capillary rise method
16. Q: What effect do electrolytes generally have on surface tension?
    A: They may increase surface tension.
17. Q: Surface tension is highest in which of the following: water, ethanol, benzene?
    A: Water
18. Q: What type of molecule orientation occurs at a liquid–air interface?
    A: Surfactant molecules align with hydrophilic head in water and hydrophobic tail in air.
19. Q: Name one application of interfacial tension in pharmacy.
    A: Emulsion formulation
20. Q: What is the relationship between surface tension and droplet formation?
    A: Higher surface tension leads to larger, fewer drops.

20 Multiple Choice Questions (MCQs) with Answers

1. **Surface tension is caused by:**

a) Gravitational force
b) Adhesive force
c) Cohesive force
d) Magnetic force

☑ **Answer: c) Cohesive force**

2. **Which instrument is used in the drop count method?**

a) Tensiometer
b) Viscometer
c) Stalagmometer
d) Hydrometer

☑ **Answer: c) Stalagmometer**

3. **The SI unit of surface tension is:**

a) Dyne/cm
b) Pascal
c) N/m
d) m/s^2

☑ **Answer: c) N/m**

4. **What happens to surface tension as temperature increases?**

a) Increases
b) Remains unchanged
c) Decreases
d) Becomes zero

☑ **Answer: c) Decreases**

5. **Which of the following methods uses a platinum plate or ring?**

a) Capillary rise method
b) Drop weight method
c) Wilhelmy plate method
d) Bubble pressure method

☑ **Answer: c) Wilhelmy plate method**

6. **Interfacial tension exists between:**

a) Gas and gas
b) Solid and solid
c) Two immiscible liquids
d) Miscible liquids

☑ **Answer: c) Two immiscible liquids**

7. **Which property is utilized in the capillary rise method?**

a) Drop size
b) Surface area
c) Height of liquid column
d) Volume of container

☑ **Answer: c) Height of liquid column**

8. **Which of the following is a surfactant?**

a) Sodium chloride
b) Glucose
c) Tween 80
d) Acetone

☑ **Answer: c) Tween 80**

9. **Surfactants decrease:**

a) Viscosity
b) Boiling point
c) Surface tension
d) Density

☑ **Answer: c) Surface tension**

10. **Which force is responsible for wetting?**

a) Electrostatic force
b) Adhesive force
c) Gravitational force
d) Nuclear force

☑ **Answer: b) Adhesive force**

11. **Surface tension is measured in terms of:**

a) Energy per area
b) Force per unit length
c) Pressure per unit time
d) Mass per second

☑ **Answer: b) Force per unit length**

12. **Wilhelmy method measures:**

a) Viscosity
b) Surface tension
c) Density
d) Optical rotation

☑ **Answer: b) Surface tension**

13. **Which of the following increases surface tension?**

a) Adding ethanol
b) Increasing temperature
c) Adding salt
d) Adding soap

☑ **Answer: c) Adding salt**

14. **In which method is the weight of a drop used to calculate surface tension?**

a) Drop count method
b) Drop weight method
c) Capillary rise method
d) Tensiometer method

☑ **Answer: b) Drop weight method**

15. **What is the role of surfactants in emulsions?**

a) Increase interfacial tension
b) Prevent mixing of liquids
c) Reduce interfacial tension
d) Increase solubility of solids

☑ **Answer: c) Reduce interfacial tension**

16. **Which of the following is used to measure interfacial tension between oil and water?**

a) Viscometer
b) Tensiometer
c) Thermometer
d) Pycnometer

☑ **Answer: b) Tensiometer**

17. **Surface tension tends to:**

a) Increase surface area
b) Minimize surface area
c) Increase volume
d) Decrease temperature

☑ **Answer: b) Minimize surface area**

18. **What happens to interfacial tension in the presence of surfactants?**

a) Increases
b) Decreases

c) Remains constant
d) Doubles

☑ **Answer: b) Decreases**

19. **Which of the following methods is not used to determine surface tension?**

a) Capillary rise method
b) Drop weight method
c) Titration method
d) Wilhelmy plate method

☑ **Answer: c) Titration method**

20. **The unit of interfacial tension is the same as that of:**

a) Density
b) Viscosity
c) Surface tension
d) Pressure

☑ **Answer: c) Surface tension**

UNIT – IV

COMPLEXATION AND PROTEIN BINDING

Q1. Discuss the classification of complexation and describe major pharmaceutical applications of different types of complexes.

Answer

Introduction (definition & general idea):

Complexation is the reversible association of two or more chemical species—typically a central atom or ion (often a metal ion) and one or more ligands—through coordinate bonds (dative covalent) or non-covalent interactions. The product is called a complex (or coordination compound). Complexation alters physicochemical properties (solubility, stability, reactivity) and is widely exploited in pharmacy.

Classification (with brief examples and characteristics):

1. Coordination (Metal–Ligand) Complexes
    - Involve a central metal ion and ligands that donate electron pairs (e.g., $[Fe(CN)_6]^{3-}$).
    - Characterized by coordination number and geometry (octahedral, tetrahedral, square planar).
    - Example pharmaceutical: cisplatin (a platinum coordination complex) used as an anticancer drug.
2. Chelates
    - Special class where a multidentate ligand binds a metal ion through two or more donor atoms (e.g., EDTA, penicillamine).
    - Chelation increases stability (chelate effect).
    - Therapeutic use: EDTA for lead poisoning; deferoxamine for iron overload.
3. Inclusion (Host–Guest) Complexes
    - Non-covalent encapsulation of a "guest" molecule inside a host cavity (e.g., cyclodextrins hosting hydrophobic drug molecules).
    - Do not form coordinate bonds; stabilization via van der Waals, hydrophobic interactions, H-bonding.
    - Uses: increase aqueous solubility of poorly soluble drugs (e.g., itraconazole–cyclodextrin), reduce volatility, mask odor/taste.
4. Molecular Complexes (Charge-Transfer, Hydrogen-Bonded, π-Complexes)
    - Formed via charge transfer (donor–acceptor), hydrogen bonding, or π–π interactions (e.g., drug co-crystals).
    - Used to modify drug dissolution or stability.
5. Inorganic Complexes & Mixed Ligand Complexes
    - Combinations of inorganic ions with organic/inorganic ligands used in assays and diagnostics.

Pharmaceutical Applications (detailed):

- Solubility enhancement & formulation: Cyclodextrin complexes improve solubility, dissolution rate, bioavailability, and stability of lipophilic drugs.
- Stabilization & protection: Complexation can protect drugs from oxidation, hydrolysis, or photodegradation (e.g., complexation with metal chelators to prevent catalyzed oxidation).
- Controlled/targeted delivery: Metal complexes or inclusion complexes can alter tissue distribution or allow sustained release. Example: platinum complexes for tumor targeting; lipophilic drugs complexed with carriers for better cellular uptake.
- Analytical/assay uses: Metal-ligand complexes used in colorimetric assays (e.g., Fe-thiocyanate), EDTA titrations for metal quantification.
- Detoxification: Chelating agents bind toxic metals (lead, mercury, iron) facilitating excretion.
- Pharmacodynamic modulation: Some drugs require complexation for activity (e.g., metalloenzymes inhibitors) or form complexes in vivo that modify potency/toxicity (tetracyclines chelate Ca^{2+} reducing absorption).
- Drug-excipient interactions: Awareness of complexation with packaging materials or excipients is crucial to avoid loss of drug potency.

Conclusion:
Classification helps predict physical behavior and therapeutic use. Understanding ligand types, bond nature, and stability is essential for rational design of formulations, analytic methods, and clinical interventions.

Q2. Explain methods of analysis of complexes and provide a thermodynamic treatment for stability constants including calculation relations and interpretation.

Answer
Introduction:
Quantifying complexes and determining their stability constants are central to understanding complex formation, predicting behavior in formulations and biological systems.

Analytical methods (principles and pharma relevance):

1. Spectrophotometry (UV–Vis):
    - Many complexes have characteristic absorbance; Beer–Lambert law used to quantify complex concentration.
    - Job's method (continuous variation) determines stoichiometry; Benesi–Hildebrand analysis estimates formation constants.
    - Widely used due to sensitivity and simplicity.
2. Potentiometry / pH-metric titration:
    - Measures pH changes during ligand addition to calculate stepwise formation constants; useful for metal–ligand equilibria and protonation states.
3. Conductometry:
    - Changes in ionic conductivity reflect complexation; used for charged complexes.
4. Polarography / Voltammetry:

- Electrochemical techniques detect redox-active complexes and can give information about formation kinetics and stoichiometry.

5. NMR Spectroscopy:
    - Chemical shift changes indicate binding; useful for organic/inclusion complexes to map binding sites.
6. Isothermal Titration Calorimetry (ITC):
    - Direct measurement of enthalpy changes and binding constants; yields ΔH, K, and ΔS (thermodynamic profile).
7. X-ray Crystallography:
    - Determines crystalline structure, coordination geometry, bond lengths—definitive structural evidence.
8. Mass Spectrometry:
    - Confirms stoichiometry and identities of complexes.

Thermodynamic treatment of stability constants:

- Consider reaction: $M + L \rightleftharpoons ML$
  Stepwise formation constant: $Kf=[ML]/[M][L]$
- For sequential addition to form ML_2, ML_3 etc., stepwise constants K1,K2,...K_1, K_2, ...K1 ,K2,... and overall constants $\beta_n = [MLn]/[M][L]^n$
- Relation to free energy:
- Gibbs free energy change: $\Delta G^\circ = -RT \ln K$.
    - If K large, ln K positive, ΔG° negative → spontaneous complex formation.
- Van 't Hoff equation links temperature dependence:
  $d \ln K/dT=\Delta H^\circ/RT^2$
  Integrating gives: $\ln K= -\Delta H^\circ/RT+\Delta S^\circ/R$
    - Plot ln K vs 1/T (Van 't Hoff plot) → slope = $-\Delta H^\circ/R$, intercept = $\Delta S^\circ/R$.

Interpretation:

- ΔH° negative → exothermic binding; ΔS° positive → increased disorder (often from release of bound solvent).
- Combination of ΔH and ΔS explains driving force (enthalpy vs entropy) for complexation.
- High K indicates stable complex; compare stepwise K values to detect cooperativity or negative cooperativity.

Conclusion:
Combining analytical data and thermodynamic parameters yields quantitative and mechanistic insight necessary for formulation design and predicting in vivo behavior.

5 MARKS

Q1. Define complexation and explain briefly how it affects drug action.

Answer: Complexation is the reversible association between a ligand and a central atom/ion or a host molecule resulting in a complex. In drug action, complexation can alter absorption (e.g., tetracycline–Ca^{2+} complexes reduce GI absorption), distribution (binding to plasma proteins or formation of metal complexes that distribute differently), metabolism (complexation may protect drugs from metabolic enzymes), and excretion (chelates are often more readily excreted). It may also change pharmacodynamics by forming an active or inactive complex. Thus complexation can increase bioavailability, reduce toxicity, or decrease therapeutic effect depending on context.

Q2. Describe inclusion complexes with cyclodextrin and list two pharmaceutical examples.

Answer: Inclusion complexes involve encapsulation of a guest molecule within the hydrophobic cavity of a host without forming covalent bonds. Cyclodextrins (α, β, γ) are cyclic oligosaccharides with hydrophobic interiors that host lipophilic drugs, improving aqueous solubility and stability. Examples: (1) Itraconazole–hydroxypropyl-β-cyclodextrin (oral solution) — solubility and bioavailability enhancement; (2) Ketoconazole and certain NSAIDs formulated with cyclodextrins to mask taste and improve dissolution.

Q3. What is a stability (formation) constant? How is it experimentally determined?

Answer: The stability constant (K_f) quantifies the equilibrium between complexed and free species: Kf=[ML]/([M][L])K_f = [ML]/([M][L])Kf=[ML]/([M][L]). Experimentally determined by spectrophotometry (monitoring absorbance vs concentration and applying Job's method or Benesi–Hildebrand), potentiometric titration (tracking pH changes), ITC (heat of binding gives K), or electrochemical methods. Data fitting to equilibrium models yields K and stoichiometry.

Q4. Explain protein binding of drugs and its clinical significance.

Answer: Protein binding refers to reversible association of drugs with plasma proteins (primarily albumin for acidic drugs and α1-acid glycoprotein for basic drugs). Only unbound (free) drug is pharmacologically active and is available for distribution and elimination. High protein binding increases half-life and can lead to drug–drug interactions if one drug displaces another from binding sites, potentially causing toxicity. Changes in protein levels (e.g., hypoalbuminemia) alter free drug fraction and dosing considerations.

Q5. Outline two analytical methods used for determining metal–drug complexes and mention an advantage of each.

Answer: (1) UV–Vis Spectrophotometry — advantage: simple, sensitive, allows rapid quantification and stoichiometry via Job's plot. (2) Isothermal Titration Calorimetry (ITC) — advantage: direct measurement of thermodynamics (ΔH, K, ΔS) without labeling or immobilization.

Q6. Briefly describe the chelate effect and its relevance in drug therapy.

Answer: The chelate effect is the increased stability of complexes formed by multidentate ligands compared to equivalent monodentate ligands, due largely to entropy gains upon binding. Clinically, chelating drugs (e.g., EDTA, deferoxamine) tightly bind toxic metals facilitating removal; chelation can also modulate drug activity and distribution (e.g.,

tetracycline binding to Ca^{2+}).

1 MARK

1. **The ligand type that binds through several donor atoms: Chelating**
2. **Complex formed by cyclodextrin is an _____ complex: Inclusion**
3. **Unit used for stability constant when written as log value: Log K**
4. **Protein that binds most acidic drugs in plasma: Albumin**
5. **Method that gives ΔH and K directly for binding: ITC**
6. **Van ’t Hoff plot axes: ln K vs 1/T**
7. **Geometry with coordination number 6: Octahedral**
8. **Common chelating agent used in lead poisoning: EDTA**
9. **Spectrophotometric continuous variation method is called: Job’s (method)**
10. **Type of interaction in charge-transfer complexes: Donor–acceptor**
11. **Effect that increases stability for multidentate ligands: Chelate effect**
12. **Drug example that forms insoluble complexes with calcium: Tetracycline**
13. **Property primarily altered by inclusion in cyclodextrin: Solubility**
14. **The thermodynamic relation linking ΔG° and K: $\Delta G^\circ = -RT \ln K$**
15. **Protein that mainly binds basic drugs: α1-acid glycoprotein**

Physical Pharmaceutics

Unit 5

1. Define the following term:

PH:
pH stands for "potential of Hydrogen." It is a measure of how acidic or basic a solution is. It depends on the concentration of hydrogen ions (H^+) in the solution. The pH scale ranges from 0 to 14. A pH less than 7 means the solution is acidic, pH equal to 7 means neutral, and pH greater than 7 means the solution is basic or alkaline. For example, lemon juice is acidic (pH ~2), pure water is neutral (pH 7), and milk of magnesia is basic (pH ~10). Maintaining proper pH is important in biological systems because many enzymes work at specific pH levels.

Buffer and Buffer Solution:
A **buffer** is a solution that resists sudden changes in pH when small amounts of acid or base are added. A **buffer solution** is usually made from a weak acid and its salt (e.g., acetic acid and sodium acetate) or a weak base and its salt (e.g., ammonium hydroxide and ammonium chloride). Buffers are essential in living systems. For example, the blood contains a bicarbonate buffer system which keeps its pH around 7.4, preventing harmful changes.

Buffer Action:
Buffer action refers to the ability of the buffer solution to maintain a constant pH. When an acid (H^+ ions) is added to a buffer, the weak base component of the buffer neutralizes the acid. When a base (OH^- ions) is added, the weak acid component neutralizes the base. This dual action helps prevent large changes in pH.

Buffer Equation (Henderson-Hasselbalch Equation):
The pH of a buffer solution can be calculated using the Henderson-Hasselbalch equation:

$$pH=pKa+\log[Acid]/[Salt]$$

This equation helps in preparing buffers of required pH by adjusting the ratio of acid and its salt.

Buffer Capacity:
Buffer capacity is the ability of a buffer solution to resist pH change. It depends on the concentration of the buffer components. Higher concentration buffers have greater buffer capacity, meaning they can neutralize more acid or base before the pH changes significantly.

Tonicity:
Tonicity refers to the effect of a solution on the movement of water across a cell membrane. It depends on the concentration of solutes (particles) that cannot cross the membrane. Tonicity determines whether cells will swell, shrink, or remain the same size when placed in a solution.

Isotonic Solution:
An isotonic solution has the *same* solute concentration as body fluids. When cells are placed in an isotonic solution, there is no net movement of water and the cell size remains unchanged.
Example: Normal saline (0.9% NaCl).

Hypertonic Solution:
A hypertonic solution has a *higher* solute concentration than body fluids. Water moves out of the cells, causing them to shrink (crenation).

Hypotonic Solution:
A hypotonic solution has a *lower* solute concentration than body fluids. Water enters the cells, causing them to swell and burst (hemolysis).

2. Draw the Sorensen's PH Scale. Give its limitations and applications.

Sorensen's pH Scale (Diagram)

The pH scale was introduced by **Søren Sørensen** to indicate the acidity or alkalinity of a solution.

```
Acidic                    Neutral                Basic (Alkaline)
0   1   2   3   4   5   6   7   8   9   10  11  12  13  14
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
Strong acids      Weak acids      Water     Weak bases      Strong bases
(HCl)                             (Blood ~7.4)      (NaOH)
```

- **pH < 7** → Acidic
- **pH = 7** → Neutral
- **pH > 7** → Basic/Alkaline

Limitations of Sorensen's pH Scale

1. **Valid only for dilute solutions:**
   The pH scale works accurately for dilute aqueous (water-based) solutions. It does not work well for strong concentrated acids or non-aqueous solutions.
2. **Temperature dependent:**
   The pH value changes with temperature, so pH measured at different temperatures may differ.
3. **Not suitable for highly colored or turbid solutions:**
   In colored solutions, the indicator-based pH measurement may give incorrect results.
4. **Does not tell strength fully:**
   pH shows acidity or alkalinity but does *not* indicate how strong the acid or base is in terms of total amount present.

5. **Assumes pure water activity:**
   The scale assumes ideal behavior of ions, which is not true for all solutions (especially high salt or electrolyte content).

Applications of Sorensen's pH Scale

1. **Biological and Medical Use:**
   pH control is essential in blood, urine, and body fluids. For example, blood pH must remain around **7.35–7.45**.
2. **Pharmaceuticals:**
   pH is used in **formulation of injections, eye drops, oral syrups, and buffers** to ensure stability and safety.
3. **Agriculture:**
   Soil pH is measured to determine nutrient availability and suitability for plant growth.
4. **Food Industry:**
   pH is monitored in foods to control fermentation and prevent microbial growth.
5. **Water Treatment:**
   pH testing is important in drinking water purification and waste-water treatment.
6. **Chemical and Industrial Processes:**
   Many chemical reactions depend on controlled pH for optimal efficiency.

3. Explain different methods used for measurement of PH.

Methods Used for Measurement of pH

The pH of a solution can be measured using several methods. The most common methods include **indicator methods**, **pH paper**, **pH meter**, and **electrometric methods**. Each method works on a different principle and is chosen depending on the accuracy required.

1. Indicator Method

This method uses **acid-base indicators**, which are chemicals that change color at a specific pH range.

Indicators exhibit different colors in acidic and basic solutions due to changes in their molecular structure.

Indicator	Color in Acid	Color in Base	pH Range
Litmus	Red	Blue	5 – 8
Phenolphthalein	Colorless	Pink	8.3 – 10
Methyl Orange	Red	Yellow	3.1 – 4.4

This method is **not very accurate** and cannot be used for colored or turbid solutions.

2. pH Paper (Indicator Strips)

These are strips impregnated with a mixture of indicators to give a broad range measurement of pH.

Dip the strip into the solution → Compare the resulting color with a standard pH color chart.

Advantages:

- Simple and quick
- Suitable for field testing

Limitation:

Not highly accurate (approximate value only).

3. Universal Indicator

It is a mixture of several indicators that changes color gradually over a range of pH values (pH 1 to 14).

Useful for determining approximate pH of unknown solutions.

Limitation:

Cannot provide precise pH readings.

4. pH Meter (Electrometric Method)

This is the **most accurate and widely used** method.

A **glass electrode** and a **reference electrode** generate a voltage proportional to the hydrogen ion concentration. The pH meter converts this voltage into a pH value.

1. Standardize the pH meter using buffer solutions (pH 4, 7, 9.2).
2. Dip the electrode in the sample solution.
3. Read the pH value displayed on the meter.

Advantages:

- Highly accurate
- Can be used for clear, colored, and viscous solutions
- Suitable for laboratory and industrial use

Limitation:

Requires calibration and careful handling of electrodes.

5. Glass Electrode Method

The **glass electrode** is specifically sensitive to hydrogen ions. The potential difference between inner and outer surfaces of a special glass membrane varies with pH.

It is commonly used in pH meters.

6. Quinhydrone Electrode Method (Old Method)

Used historically for pH measurement. Potential is produced by the presence of **hydrogen ions** interacting with quinhydrone.

Limitation:

Cannot be used in strong alkaline solutions (pH > 8).

4. State buffer equation.

Buffer Equation (Henderson–Hasselbalch Equation)

The buffer equation is used to calculate the **pH of a buffer solution**. It relates the pH of a buffer to the **pKa (dissociation constant) of the weak acid** and the **ratio of salt to acid concentration**.

For Acidic Buffer (Weak Acid + Salt of Weak Acid)

$$pH = pKa + \log([Acid][Salt])$$

- **pH** = hydrogen ion concentration of the buffer solution
- **pKa** = negative logarithm of the dissociation constant (Ka) of the weak acid
- **[Salt]** = concentration of the salt of the weak acid (e.g., sodium acetate)
- **[Acid]** = concentration of the weak acid (e.g., acetic acid)

5. Explain various application of buffer in Pharmacy.

Applications of Buffers in Pharmacy

Buffers play role in pharmaceutical preparations and biological systems by maintaining a **constant pH**. Many drugs, enzymes, and body fluids are stable and effective only within a particular pH range. Therefore, buffers are used to control and maintain the required pH in different pharmaceutical processes.

1. In Pharmaceutical Formulations

Many dosage forms such as **injections, eye drops, nasal drops, syrups and tablets** require a specific pH for safety, stability and effectiveness.
Buffers are added to maintain this pH so that the drug:

- Does not degrade
- Remains soluble
- Does not irritate body tissues

For example: **Ophthalmic solutions** use buffers to match the pH of natural tears.

2. In Blood and Body Fluids

Human blood has a natural buffer system that maintains its pH around **7.35–7.45**.
If blood pH changes even slightly, it can lead to serious health issues.
Thus, understanding buffers helps in designing **intravenous fluids** and **plasma expanders** that do not disturb blood pH.

3. In Controlling Drug Absorption

The rate of drug absorption in the body depends on whether the drug is **ionized or unionized**, and this depends on pH.
Buffers are used to **adjust pH** to ensure maximum absorption of the drug through the gastrointestinal tract.

Example: Weak acidic drugs are better absorbed in **stomach (acidic pH)**, while weak basic drugs are absorbed in **intestine (slightly alkaline pH)**.

4. In Stability of Drugs

Some drugs are stable only in acidic conditions, while others are stable in alkaline conditions.
Buffers maintain the **required pH**, preventing:

- Chemical decomposition
- Hydrolysis
- Oxidation

Example: **Penicillin** is stable only at slightly acidic pH.

5. In Analytical Chemistry

During **titrations and assays**, buffers are used to maintain constant pH to ensure accurate and reproducible results.
They are important in **spectrophotometric and chromatographic** analysis of drugs.

6. In Manufacturing of Biological Products

Biological products like **enzymes, vaccines, hormones and antibodies** require strict pH control for stability and activity.
Buffers maintain the correct environment during production and storage.

7. In Cosmetic and Personal Care Products

Shampoos, skin creams and lotions use buffers to maintain skin-friendly pH (around 5.5) to avoid irritation and maintain product stability.

6. Describe in detail methods of adjustment of tonicity.

Methods of Adjustment of Tonicity

Tonicity refers to the osmotic pressure a solution exerts on cells or body fluids. **Pharmaceutical solutions** such as **eye drops, injections, and nasal solutions** must be **isotonic** to avoid pain, irritation, tissue damage, or red blood cell destruction.

To make a solution isotonic, the tonicity must be adjusted. The commonly used methods are:

1. Cryoscopic Method (Freezing Point Depression Method)

Principle:

- The **freezing point of body fluids (blood, tears)** is **−0.52°C**.
- A solution is **isotonic** if it **depresses** the freezing point by **0.52°C**.
- If a solution depresses less, additional solute (like NaCl) is added to reach −0.52°C.

Procedure:

1. Determine the freezing point lowering of the drug solution.
2. Calculate how much additional NaCl is needed to make the total depression −0.52°C.

Usefulness:

- **Accurate** and widely used for ophthalmic and injectable solutions.

2. Sodium Chloride Equivalent (E-Value) Method

Principle:

Each drug contributes to tonicity like **a certain amount of NaCl**.
This relative effect is known as **E-value** (Sodium chloride equivalent).

Amount of NaCl required=(0.9%×volume)−(Drug amount×E-value)

Steps:

1. Calculate how much NaCl is needed to make the final solution isotonic.
2. Subtract the NaCl equivalent contributed by the drug.
3. Add the remaining NaCl to the solution.

Example:

If a drug has **E = 0.18**, then **1 g of the drug** produces the same tonicity as **0.18 g NaCl**.

Advantages:

- Simple and widely used in formulations.

3. Class I Method (Add Water First)

Principle:

Used when the drug and other components **do not significantly affect tonicity**.

Procedure:

1. Add NaCl to make the solution isotonic.
2. Then add water to make up the final volume.

Example: Preparing isotonic **saline solutions**.

4. Class II Method (Add Water Last)

Principle:

Used when **drug volume is large** or affects tonicity.

Procedure:

1. Dissolve drug and NaCl in **part of the water**.
2. Then add water **only after adjusting tonicity** to final volume.

Common for **syringes and injectable preparations**.

5. White-Vincent Method

Used to determine how much **water** should be added to the drug to make an **isotonic solution**.

V=weight of drug (g)×white-vincent factor

Then NaCl is added to make final isotonic volume.

6. Method Using Molecular Concentration (Molarity / Osmolarity)

Tonicity can also be adjusted by calculating **osmolarity** using:

Osmolarity (mOsm/L)=Molarity×Number of particles produced

This method is used mainly in **intravenous infusion preparations**.