Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-III

Subject Name: Physical pharmaceutics-I
Subject Code: BP302TP

CHAPTER-3-SOLUBILITY OF DRUGS

SYLLABUS:
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.

- The course deals with the various physical and physicochemical properties, and principles involved in dosage forms/formulations.
- Theory and practical components of the subject help the student to get a better insight into various areas of formulation research and development, and stability studies of pharmaceutical dosage forms.

Learning objectives

- Understand the nature of the intra and intermolecular forces that are involved in stabilizing molecular and physical structure.
- Understand the differences in these forces and their relevance to different types of molecules.
- Appreciate the differences in the strengths of the intermolecular forces that are responsible for the stability structures in the different states of matter.
- Understands properties of gaseous states.

SOLUBILITY OF DRUGS

TOPIC: Introduction of Solubility of Drugs?

Ans:

SOLUBILITY OF DRUGS

The concentration of solute in a saturated solution at the particular temperature is called solubility.

Factors Affecting Solubility Drugs

Physical properties of solute and solvent

Chemical Properties of Solute and Solvent

Ideal Solubility Parameters

Hildebrand and scott

Solvation

Enthalpy and solute and solvent interaction process

Detailing:

- In quantitative terms, solubility of a substance is defined as the concentration of solute in a saturated solution at the particular temperature.
- In qualitatively it can be defined as the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion.
- There are factor like physical, chemical properties of solute and solvent, temperature, pressure, the pH of the solution and the particle size of solute, which affects the solubility of the solute.
- Some of the phenomena which make solubility an important criterion are:
- Choice of solvent for the liquid formulation.
- Dissolution of drugs
- Bioavailability of drugs.(the drug has to dissolve before it has been absorbed)

Solubility Expression: (solubility definition as per USP)

Solubility definition	**Parts of solvent required per parts of solute.**	**Solubility range (mg/ml)**
Very soluble	<1	>1000
Freely soluble	From 1 to 10	100-1000
Soluble	From 10 to 30	33-100
Sparingly soluble	From 30 to 100	10-33
Slightly soluble	From 100 to 1000	1-10
Very slightly soluble	From1000 to 10,000	0.1-1
Pratically insoluble	>10,000	<0.1

Mechanisms of Solute-Solvent Interaction

- A good solvent is selected on the principle of the “like dissolves like”; that is a whole solute dissolves best in the solvent with silar chemical properties.
- Two rules of selecting a good solvent.
  1) Polar solutes dissolve in Polar solvents.
  2) Nonpolar solutes dissolve in Nonpolar solvents.
- The force attraction between solute and the solvent is a important parameter which plays role in order to dissolve solute in the solvent.
- (a) If X-X >> X-Y, this condition describes that the affinity of solvent molecules for its own kind of molecules is greater than its affinity for solute molecules.

- (b) If Y-Y >> X-X, this describes that solvent will not be able to break the binding forces between solute molecules.
- (c) X-Y >> Y-Y this describes that the attraction force between solvent molecules and the molecules is greater than either between own solvent molecules or between own solute molecules.
- Solvents can be broadly into three types "polar solvent", "Nonpolar solvent", and "semi polar solvent".

IDEAL SOLUBILITY PARAMETER

- Hildebrand and scott described a new parameter called solubility parameter to predict the solubility of compounds equation. It expresses the cohesion between like molecules and may be calculated by using heat of vaporization and molar volume of the solute at the desired temperature. It is square root of internal pressure,

$$\delta=(\Delta Hv\text{-}Rt/V_l)^{1/2}$$

  - ΔHv is the heat of vaporization
  - V_l is the volume of solute(liquid state at desired temperature)
  - R is the gas constant
  - T is the temperature.
  - Δ values of two component
- To, summarize a few generalization have been framed to predict the solubility of compounds.
- More similarity in the structure of solute and solvent enhance the solubility of solute in that solvent.
- Polar solute dissolves in polar solvents while nonpolar solutes dissolve in non polar solvents.
- Polar solutes dissolve in polar solvents while nonpolar solutes dissolve in non polar solvents.
- Addition of polar groups like –OH, -CHO, -CHOH, -COOH etc.

SOLVATION

- Solvation is the phenomenon in which solvent interacts strongly with the molecules or ions of solute, which leads to stabilization of the solute species in the solution. In the solvated state, an ion in a solution is surrounded or complexes by solvent molecules.

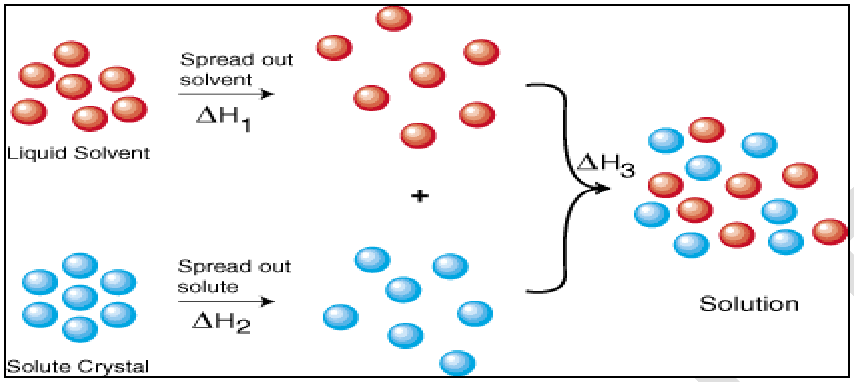
$$\underset{\text{Sodiumchloride}}{NaCL} \rightarrow \underset{\text{sodium ion}}{Na^+} + \underset{\text{chloride ion}}{CL^-}$$

- H_2O is a polar solvent which has negatively and positively charged regions. The charged regions are attracted to ions with the opposite charge. Hence the positively charged regions of water molecules are attracted to CL^- ions and negatively charged regions of water molecules are attracted to NA^+ ions.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The spontaneous interaction of two or more substance to form a homogeneous molecular dispersion is called?	Solubility
2	<1 Parts of solvent required per parts of solute indicates?	Very Soluble
3	What is Hidelbergh and Scott equation for Solubility?	$\delta=(\Delta Hv\text{-}Rt/V_l)^{1/2}$
4	Solvent interacts strongly with the molecules or ions of solute, which leads to stabilization of the solute species in the solution is called?	Solvation
5	What is the substance which dissolved in the solvent?	Solute
6	What is a solution when solute is dissolved up to its maximum limit of solubility at any given temperature and pressure?	Saturated Solution
7	What is a solution in which dissolved solute is in a concentration below the required amount necessary for the complete saturation at a definite temprature.	Unsaturated Solution
8	What is a solution which contains more of the dissolved solute than it would normally contain in a saturated sate at a definite temprature.(e.g. sodium thiosulphate)	Supersaturated solution
9	100 to 1000 Parts of solvent required per parts of solute indicates?	Sparingly Soluble

Tree types of interaction in the solution process
1) solvent – solvent interaction
2) solute – solute interaction
3) solvent solute interaction



Enthalpy

- The enthalpy change of solution refers to the overall amount of heat, which is released or absorbed during the dissolving process (at constant pressure).
- The enthalpy of solution can either be positive (endothermic reaction) or negative (exothermic reaction).
- The enthalpy of solution is commonly referred to as ΔH solution.

Solvent - Solute Interactions:

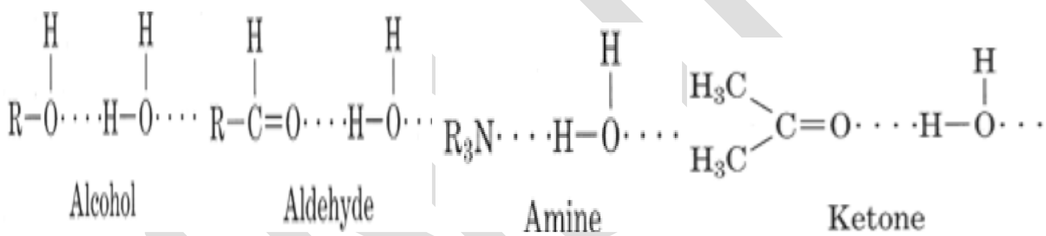
- In pre - or early formulation, selection of the most suitable solvent is based on the principle of "like dissolves like"
- That is, a solute dissolves best in a solvent with similar chemical properties. Or two substances with similar intermolecular forces are likely to be soluble in each others.
- Polar solutes dissolve in polar solvents. E.g salts & sugar dissolve in water .
- Non polar solutes dissolve in non polar solvents. Eg. naphtalene dissolves in benzene.

Polar Solute - Polar Solvent E.g.Ammonia Dissolves in Water:

- Polar ammonia molecules dissolve in polar water molecules.
- These molecules mix readily because both types of molecules engage in hydrogen bonding.
- Since the intermolecular attractions are roughly equal, the molecules can break away from each other and form new solute (NH_3), solvent (H_2O) hydrogen bonds. E.g. Alcohol Dissolves in Water:
- The -OH group on alcohol is polar and mixes with the polar water through the formation of hydrogen bonds.
- A wide variety of solutions are in this category such as sugar in water, alcohol in water, acetic and hydrochloric acids.

Polarity:

- The solubility of the drug substance is attributable in large part to the polarity of the solvent, often expressed in terms of dipole moment, related to the dielectric constant.
- Solvents with high dielectric constants dissolve ionic compounds (polar drugs) readily because of ion–dipole interactions,
- Solvents with low dielectric constants dissolve hydrophobic substances (non-polar drugs)
- polar solvents, with examples such as water and glycerin;
- non-polar solvents, with example such as oils.
- Solvents with intermediate dielectric constants are classified as semipolar.
- The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances.
- The ability of the solute to form hydrogen bonds is a far more significant factor than is the polarity as reflected in a high dipole moment
- Water dissolves phenols, alcohols and other oxygen & nitrogen containing compounds that can form hydrogen bonds with water.



Polar solvents:

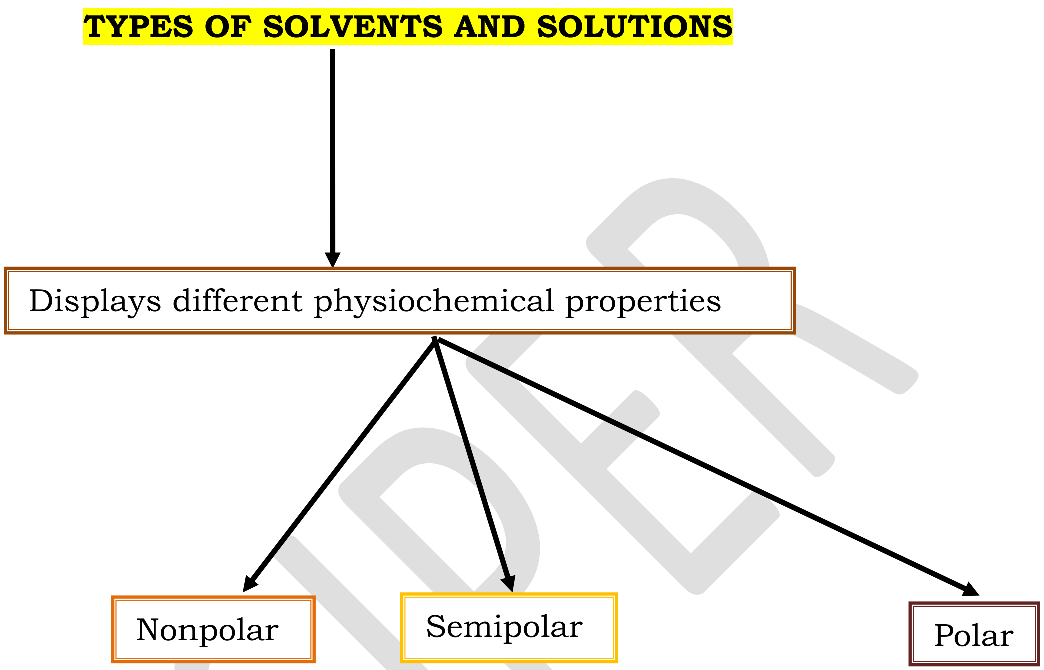
- The solubility of a substance also depends on structural features such as the ratio of the polar to the nonpolar groups of the molecule.
- As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases
- Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble.
- Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility.
- Tertiary butyl alcohol is miscible in all proportions with water, whereas n-butyl **alcohol** dissolves to the extent of about 8 g/100 mL of water at 20°C.

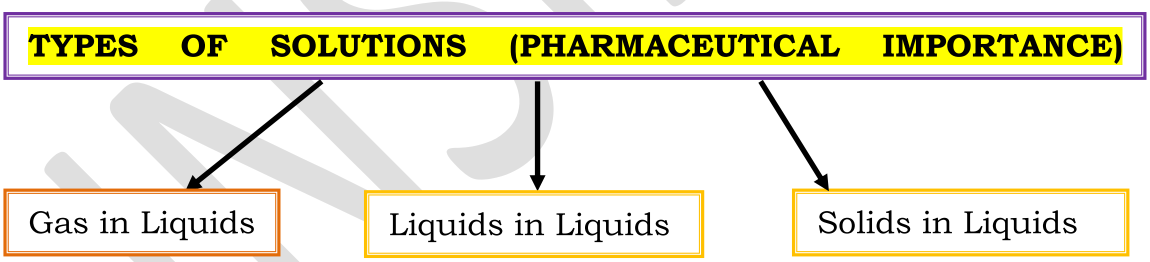
One Word Question Answer

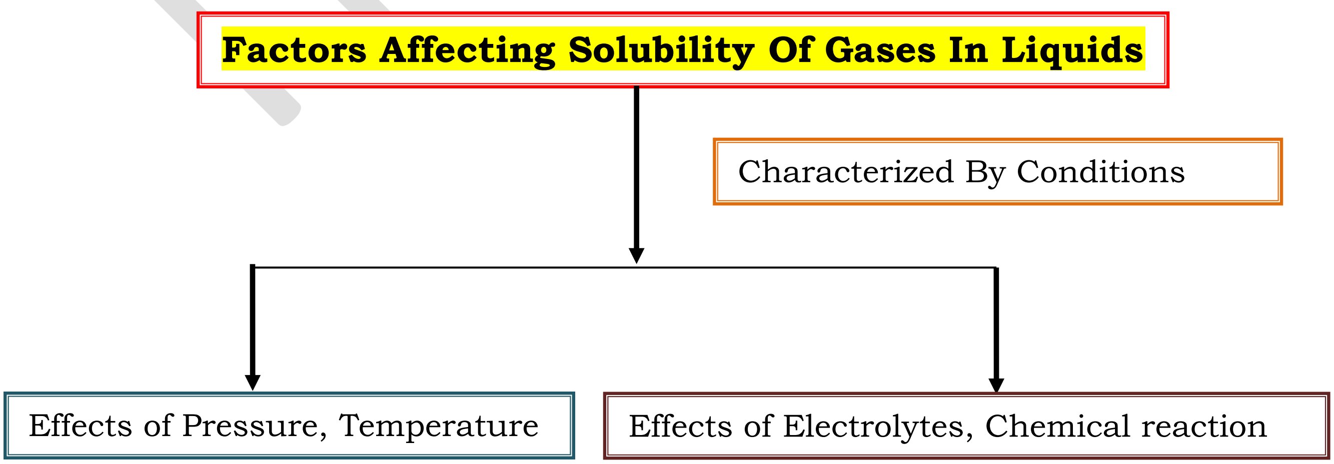
SR NO.	QUESTION	ANSWER
1	Moles (gram molecular weights) of solute in 1 liter (1000 ml) of solution.	Molarity
2	Moles of solute in 1000 gm of solvent.	Molality
3	Gram equivalent weights of solute in 1 liter of solution	Normality
4	Ration of moles of solute to total moles of solute+ solvent	Mole Fraction
5	gm of solute in 100 gm of solution	% w/w
6	ml of solute in 100 ml of solution	%v/v
7	gm of solute in 100 ml of solution	% w/v
8	Which is change of solution refers to the overall amount of heat, which is released or absorbed during the dissolving process (at constant pressure).	Enthalpy
9	non-polar solvents example	Oils

TOPIC: Types of Solvents and solutions?

Ans







Detailing:

Non Polar Solvents

- Non-polar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants.
- They are unable to form hydrogen bonds with non-electrolytes.
- Non polar solvents can dissolve non polar solutes through weak van der Waals forces
- Example: Solutions of oils & fats in carbon tetrachloride or benzene.
- **Polyethylene glycol 400, Caster oil.**

Semi Polar solvents

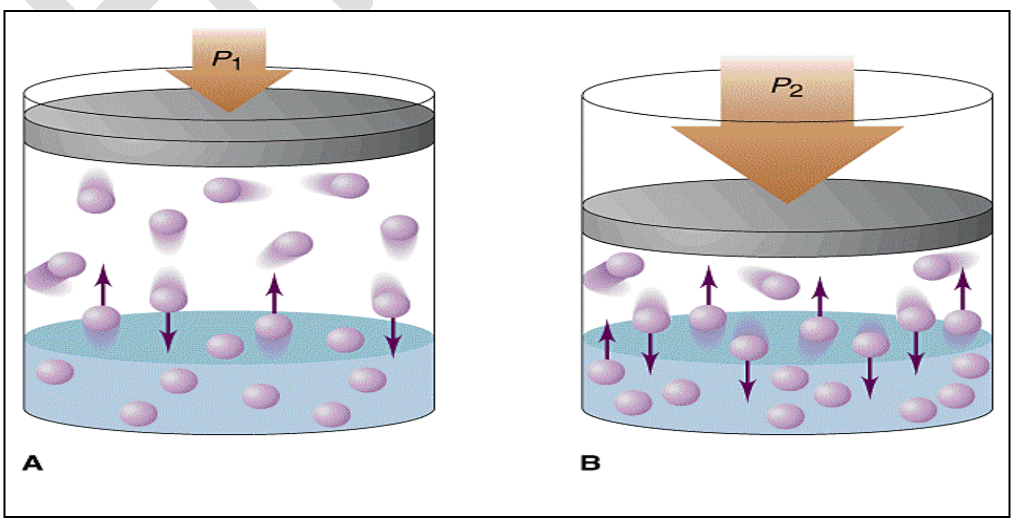
- Semi polar solvents, such as ketones can induce a certain degree of polarity in non polar solvent molecules. For example, benzene, which is readily polarizable, becomes soluble in alcohol.
- They can act as intermediate solvents to bring about miscibility of polar & non polar liquids.
- Example: acetone increases solubility of ether in water.
- Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate.
- **Polarity as Dielectric Constant of Solvent, ε decrease, the solubility also decrease.**

Types of solutions

Solutions of pharmaceutical importance include:

- Gases in liquids
- Liquids in liquids
- Solids in liquids

Solubility of gases in liquids



When the pressure above the solution is released (decreases) the solubility of the gas decreases. As the temperature increases the solubility of gases decreases

Factors affecting solubility of gases in liquids

- Effects of pressure
- Effects of temperature
- Effects of electrolytes and non electrolytes
- Effects of chemical reaction

Solubility of liquids in liquids:

- Preparation of pharmaceutical solutions involves mixing of 2 or more liquids. e.g. volatile oils & alcohols to form spirits , elixirs

Liquid-liquid systems may be divided into 2 categories:

1. Systems showing *complete miscibility* such as alcohol & water, glycerin & alcohol, benzene & carbon tetrachloride.
2. Systems showing *Partial miscibility* as phenol and water; two liquid layers are formed each containing some of the other liquid in the dissolved state.

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

- **Complete miscibility** occurs when: The adhesive forces between different molecules (A-B) **>>** cohesive forces between like molecules (A-A or B-B).
- Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they mix in all proportions.
- Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible.
- **Partial miscibility** results when: Cohesive forces of the constituents of a mixture are quite different, e.g. water (A) and hexane (B). A-A » B-B.
- When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state.
- The effect of temperature on the miscibility of two-component liquids is expressed by phase diagrams.
- In the phase diagrams of two-component liquids, the mixture will have an upper critical solution temperature, a lower critical solution temperature, or both.

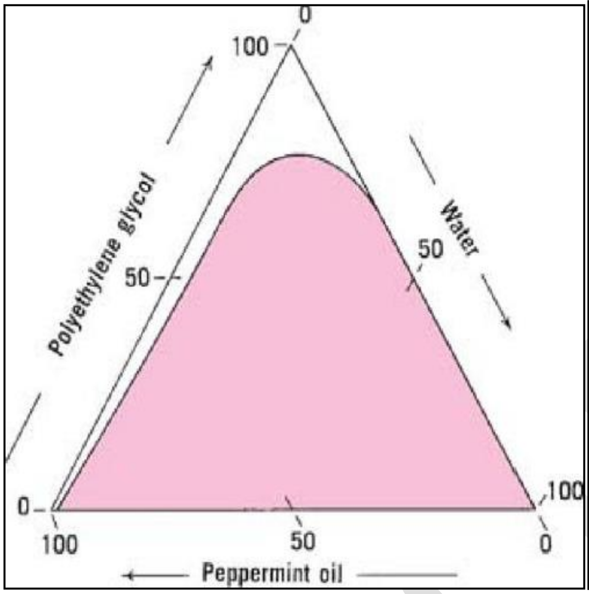
One Word Question Answer

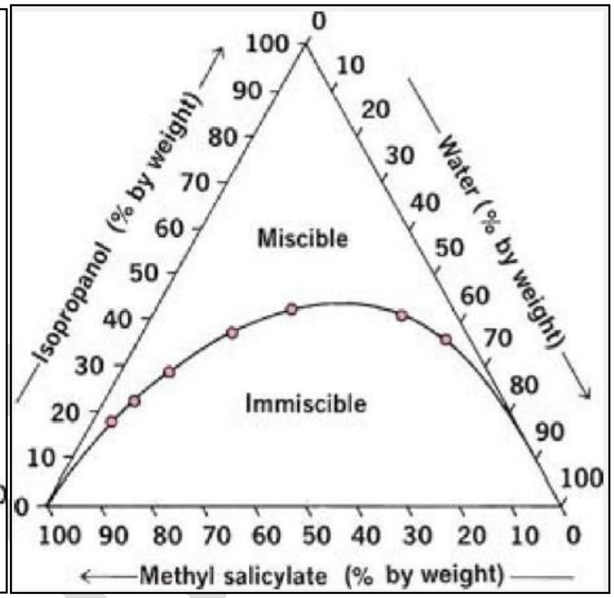
SR NO.	QUESTION	ANSWER
1	Solvents' low dielectric constants.	Non-Polar Solvent
2	Non polar solvents can dissolve non polar solutes by which bond?	van der Waals force
3	Which solvents act as intermediate solvents to bring about miscibility of polar & non polar liquids?	Semi polar solvent
4	The adhesive forces between different molecules (A-B) >> cohesive forces between like molecules produce?	Complete miscibility
5	Cohesive forces of the constituents of a mixture are quite different and produce solution?	Partiality Miscibility
6	The effect of temperature on the miscibility of two-component liquids is expressed by which technique?	Phase Diagrame

Detailing:

- Ideal and real solutions
- Roult's law: $P_a = P_{a0} * X_a$
- +ve deviation
- -ve deviation

Three-Component Systems





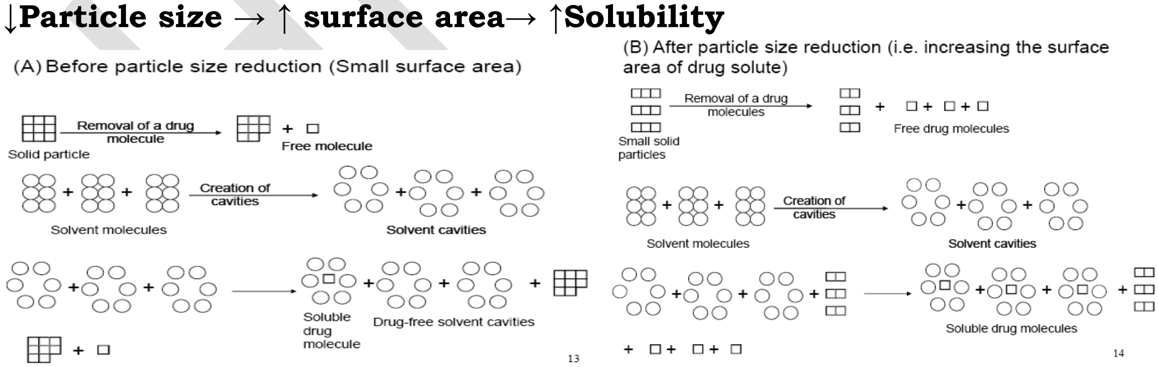
F= number of degrees of freedom
C= number of components
P=number of phases of the system

Solubility of solids in liquids

Solubility of solids in liquids Factors influencing solubility

1) Particle size (surface area) of drug particles

↓Particle size → ↑ surface area→ ↑Solubility



$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

- S_o is the solubility of large particles
- S is the solubility of fine particles

- γ is the surface tension of the particles
- V is molar volume
- T is the absolute temperature
- r is the radius of the fine particle
- R is the gas constant

2) Molecular size

- Molecular size will affect the solubility.
- The larger the molecule or the higher its molecular weight the less soluble the substance.
- Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.
- In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent

3) The Boiling point of Liquids and the Melting Point of Solids:

- Both reflect the strengths of interactions between the molecules in the pure liquid or the solid state.
- In general, aqueous solubility decreases with increasing boiling point and melting point.

4-The Influence of Substituent

- On the solubility of molecules in water can be due to their effect on the properties of the solid or liquid (for example, on its molecular cohesion, or to the effect of the substituent on its interaction with water molecules.
- Substituent's can be classified as either hydrophobic or hydrophilic, depending on their polarity.
- Polar groups such as –OH capable of hydrogen bonding with water molecules impart high solubility
- Non-polar groups such as $–CH_3$ and –Cl are hydrophobic and impart low solubility.
- Ionization of the substituent increases solubility, e.g. –COOH and $–NH_2$ are slightly hydrophilic whereas –COO– and $–NH_3$ are very hydrophilic.
- The position of the substituent on the molecule can influence its effect on solubility, for example the aqueous solubilities of *o*-, *m*- and *p*-dihydroxybenzenes.

5-Temperature

- Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased.
- If the solution process releases energy then the solubility will decrease with increasing temperature.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The larger the molecule or the higher its molecular weight shows solubility?	Less solubility
2	Organic compounds the amount of carbon branching will shows?	Increase solubility
3	Solubility with increasing boiling point and melting point?	Decrease solubility
4	Ionization of the substituent affects solubility?	Increase solubility
5	Non-polar groups such as $-CH_3$ and $-Cl$ are hydrophobic and impart which type of solubility?	Low Solubility
6	Increasing boiling point and melting point affects solubility?	Low Solubility

- Generally, an increase in the temperature of the solution increases the solubility of a solid solute.
- A few solid solutes are less soluble in warm solutions.
- For all gases, solubility decreases as the temperature of the solution increases.

6-Crystal Properties

- Polymorphic Crystals, Solvates, Amorphous forms
- Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics.
- A drug that exists as an amorphous form (non-crystalline form) generally dissolves more rapidly than the same drug in crystalline form.

7- pH

- It is one of the primary influences on the solubility of most drugs that contain ionizable groups.
- Large numbers of drugs are weak acids or weak base.
- Solubility depends on the degree of ionization.
- Degree of ionization depends on the pH.

8-Ionization and pH

<u>Strong vs. weak acids and bases</u>

1. **Strong – ionized at all pHs**
2. **Weak – only ionized at certain pHs (most drugs are weak acids or weak bases**
3. **Ionized drugs are not very lipid soluble- only nonionized form of drug crosses membrane readily**
4. **Percent ionization is pH dependent**
5. **pKa is the negative log of the ionization constant and is equal to the pH at which a drug is 50% ionized**
6. **Weak acids become highly ionized as pH increases**
7. **Weak bases become highly ionized as pH decreases**

Henderson-Hasselbalch equation

- **<u>Determines extent of ionization</u>**
  pKa = pH at which 50% of drug is ionized.
- **<u>WEAK ACIDS:</u>**
  Log (ionized form/nonionized form)= pH – pKa

$$pH - pK_a = \log(\frac{[P^-]}{[HP]})$$

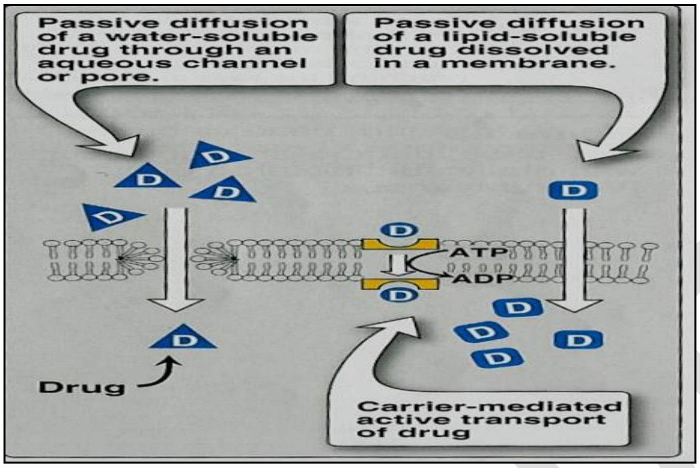
- **<u>WEAK BASES:</u>**

Log (Nonionized form/Ionized form)= pH – pKa

$$pH - pK_a = \log(\frac{[B]}{[BH^+]})$$

PASSIVE DIFFUSION:

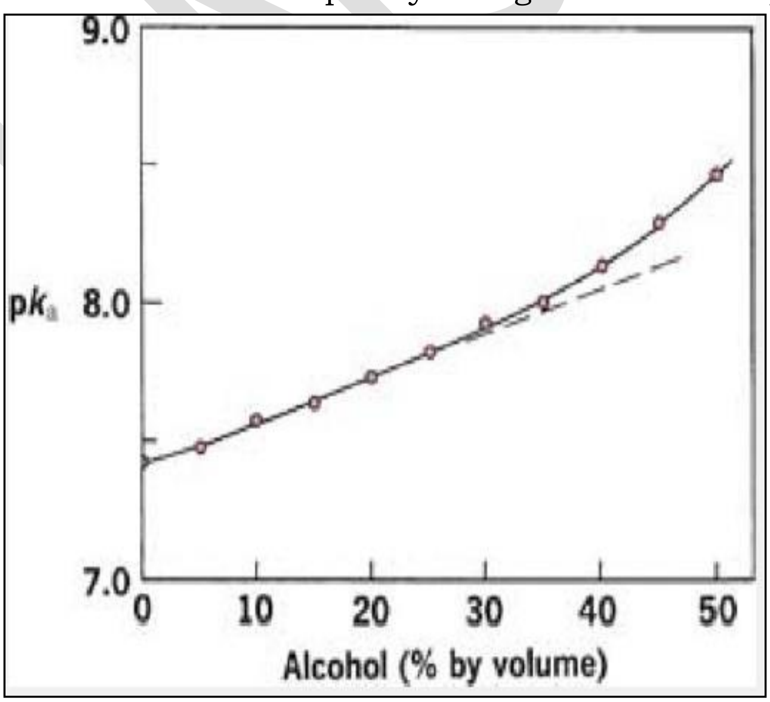
- Water soluble drug (ionized or polar) is readily absorbed via aqueous channels or pores in cell membrane.
- Lipid soluble drug (nonionized or non polar) is readily absorbed via cell membrane itself.



(2) Co-solvent effect on solubility

The nonelectrolytes and the undissociated molecules of weak electrolytes more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as *cosolvency*, and the solvents that, in combination, increase the solubility of the solute are called *cosolvents.*

- The presence of a co-solvent can increase the solubility of hydrophobic organic chemicals
- Co-solvents can completely change the solvation properties of "water".



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	For all gases, solubility in which way affects the temperature of the solution increases?	Decrease Solubility
2	Substance has same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics	Polymorph
3	Which form generally dissolves more rapidly than the same drug in crystalline form.	Amorphous
4	Which equation determines extent of ionization?	Henderson-Hasselbalch
5	What is equation relating to Degree of ionization for weak acid?	$pH - pK_a = \log(\frac{[P^-]}{[HP]})$
6	Water soluble drug (ionized or polar) is readily absorbed via?	Pores in a cell membrane
7	Which solvent can increase the solubility of hydrophobic organic chemicals	Cosolvent

Partition coefficients

$$X_{aqueous} \rightleftharpoons X_{octano}$$

Partition coefficient P (usually expressed as $\log_{10}P$ or logP) is defined as:

$$P = \frac{[X]_{octanol}}{[X]_{aqueous}}$$

P is a measure of the relative affinity of a molecule for the lipid and aqueous phases in the absence of ionisation

1-Octanol is the most frequently used lipid phase in pharmaceutical research. This is because:

- It has a polar and non polar region (like a membrane phospholipid)
- Po/w is fairly easy to measure
- Po/w often correlates well with many biological properties

Application:

- Extraction
- Preservative action of weak acids in o/w systems
- Drug absorption/distribution/action

Extraction

- it is used to determine the efficiency with which one solvent can extract a compound from a second solvent
- extract natural drugs from a solvent with several portions of an immiscible solvent

Preservative action

- the concentration of preservative to be used in an emulsion can be calculated from the distribution law to give the effective antimicrobial concentration in the water phase

Drug Absorption/Distribution/Action

- Hydrophobic drugs (high partition coefficients) are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells
- Hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum.
- extent of solubility enhancement depends on type of cosolvent and solute
- Solubility increases exponentially as cosolvent fraction increases.
- need 5-10 volume % of cosolvent to see an effort