Unit - I Solubility of Drugs

Solubility :- Solubility is the property of solid, liquid or gaseous chemical substances called solute to dissolve in a solid, liquid or gaseous solvent to form homogeneous sol^{n} of the solute in the solvent.

* Solubility of a compound depends on.

→ Physical, chemical properties of the solvent and solute

→ temperature, pressure and pH of solution.

⇒ An unsaturated solution is one

↓

contains dissolved solute in concentration less than → required for saturation at certain temp.

⇒ A ~~sp~~ supersaturated solution is one

↓

contains more concentration of solute in dissolved state than

↓

normally be dissolved at a defined temperature

Solubility Expression

⇒ The United States Pharmacopoeia (USP) describes

↓

the solubility of drugs as parts of solvent required for one part solute

⇒ Solubility is also quantitatively expressed as
↙ ↓ ↘
molarity | molality | mole fraction or percentage

⇒ USP ~~dd~~ describes Solubility in seven groups.

⇒ The European pharmacopoeia is Six group.

⇒ In the scientific and pharmaceutical field solubility can be expressed in following terms :-

① % W/W :- the number of grams of solute dissolved in 100 gm of solution.

(ii) % V/V :- the number of ml of solute dissolved in 100ml of solution.

(iii) % W/V :- the number of grams of solute dissolved in 100 ml of solution.

⇒ Molarity :- the number of moles of solute dissolved (or gram molecular weight) in 1 litre of solution.

⇒ Molality :- the number of moles of solute dissolve in 1000g or 1kg. of solvent.

⇒ Normality :- the number of gram equivalent weigh of solute dissolved in per litre of solution.

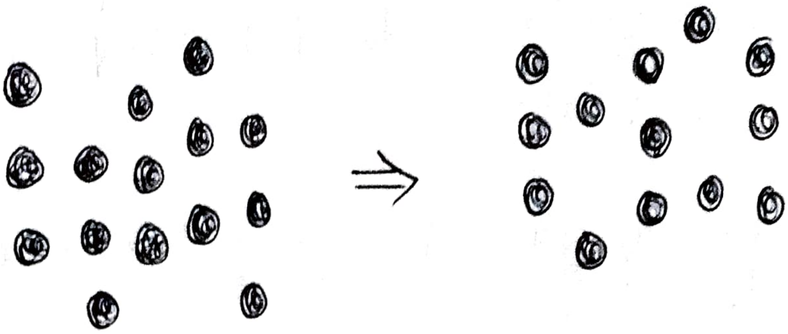
→ Mole fraction:- the ratio of the number of moles of solute to the total number of moles of solute and solvent.

Definition verses Parts of solvent required for one part of solute

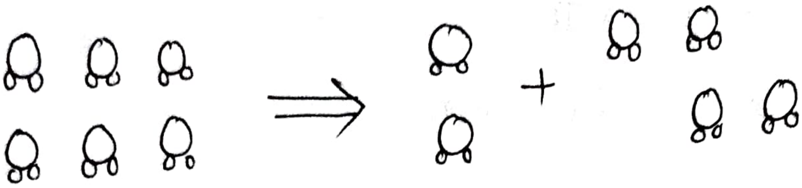
Difinition	Parts of salvent required for one part of solute
1. Very soluble →	< 1 parts
2. Freely Soluble →	1 - 10 parts
3. Soluble →	10 - 30 parts
4. Sparingly soluble →	30 - 100 parts
5. Slightly Soluble →	100 - 1,000 parts
6. Very slightly Saluble →	1000 - 10,000 parts
7. Insoluble →	> 10,000 parts

Mechanism of Solute - Solvent Interaction

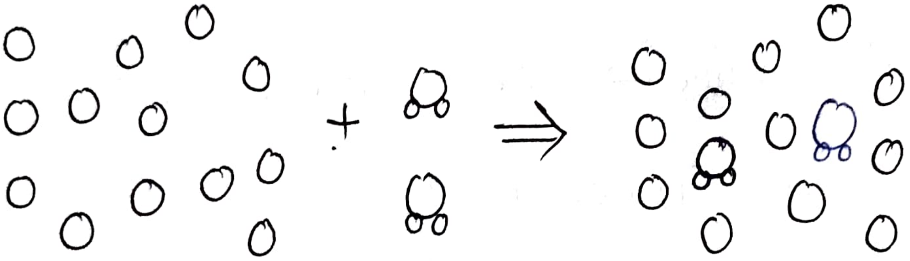
In the general process of salubilization involves the breaking of inter - ionic or ~~mo~~ inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the Solute interaction b/w the solvent and the solute molecules or ions.



Step-1 : Holes open in the salvent



Step-2 ; Molecules af Solid break away from the bulk.



Step 3: The freed solid molecule is ~~in~~ integrated into the hole in the solvent

Fig : Solubility mechanism

⇒ In generally, the solubility of solute in a salvent may be considered by the solute - solute, salvent - salvent and solvent - solute intraction.

⇒ <u>Adhesive force</u> :- attraction b/w unlike molecule.
e.g. Solute - solvent molecules

⇒ **Cohesive force** :- attraction b/w like molecules.
e.g. - solute - solute molecules
- solvent - solvent molecules.

⇒ when, Adhesive force > Cohesive force
⇓
then the solubility of solute in a solvent or miscibility of liquid in some other liquid is generally enhanced.

⇒ Polar solvents dissolve ⇒ polar solutes,
Non-polar solvents dissolve ⇒ non-polar solutes.

⇒ Semipolar solvents such as acetone and alcohol act as intermediate solvents.

⇒ The insolubility ~~e~~ nature is due to stable crystalline arrangement and low intermolecular forces b/w ~~so~~ solvent and solute.

Ideal Solubility ~~of~~ Parameters

⇒ The solubility parameter is a
↓
numerical value that indicates
↓
relative solvency behaviour of specific solvent.

⇒ It is derived from → cohesive energy density of the solvent.

Uses :

→ Solubility parameter provides numerical methods

⇓

to predict interaction between materials

⇒ It is used for estimation of wether, substances will dissolve in other material or not.

⇓

if value to solubility parameter are same the solubility will be good.

Two types of Solubility parameter :-

① Hildebrand Solubility parameter

② Hansen Solubility parameter.

① Hildebrand Solubility parameter :-

→ Joel H. Hildebrand in 1936

⇓

Definition: The solubility parameter is a numerical value that indicates relative solvency behaviour of specific solvent.

⇒ It is derived from cohesive energy density Ⓒ

⇓

it is forces of attraction per unit volume of solvent.

$$\boxed{C = \frac{\Delta H - RT}{V_m}}$$

Where,

C = Cohesive energy
ΔH = Heat of vaporisation
R = gas constant
T = temperature
V_m = molar Volume.

⇒ In 1936. Joel H. Hildebrand proposed the square root of the cohesive energy as a numerical value indicate the solvency behaviour of a specific solvent

⇒ The quantity represented by the symbol 'δ'.

$$\boxed{\delta = \sqrt{C} = \sqrt{\frac{\Delta H - RT}{V_m}}}$$

The term Hildebrand is adopted for solubility parameter units.

② Hansen Solubility Parameter :-

⇒ The most popular three component system
⇓
developed by Charles M. Hansen in 1966.

⇒ Hansen parameter divided the total Hildebrand value into three parts.

① Dispersion force component
(ii) A hydrogen bonding compound or component
(iii) A polar component

$$\boxed{\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2}$$

Where,

δ_t^2 = Tatal Ht Hansen parameter
δ_d^2 = Dispersion component
δ_p^2 = Palar Component
δ_h^2 = Hydrogen bonding component.

Solvation

⇒ Solvation is the process of surrounding salute particles with solvent particles to form a solution.
⇒ Salvation in water is called = hydration.
⇒ Unit of salvation is mal/sec.
⇒ In general rule to like attracts to like applies to solvation.

i) Polar solute salvated by polar salvent not non-polar salvent.

e.g. $NaCl + H_2O \Rightarrow$ Salvated
$NaCl + C_6H_6 \Rightarrow$ not salvated.

ii) Non-polar salute salvated by non-polar salvent not by palar salvent.

e.g. $C_{20}H_{42} + C_6H_6 \Rightarrow$ Salvated
$C_{20}H_{42} + H_2O \Rightarrow$ Not salvated

[$C_{20}H_{42}$ = Icosane or eicosane
⇒ 366,319 isomers

iii) Soap molecules have
↳ polar part → palar H_2O
↳ non-polar part → non-polar such as grease

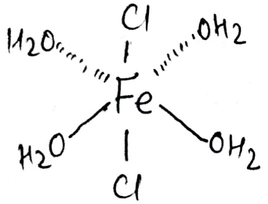
This ~~properties~~ combination of properties means soapy water is an excellent mixture in which to for example wash dirty dishesh after a meal.

Factors Affecting Salvation

- Surface Area
- Agitation & Stirring
- Temperature

Salvation number :- The number of solvent molecules bound to a solute species.

e.g. for $FeCl_2(H_2O)_4$ ~~above~~ below the Solvation number is 4.

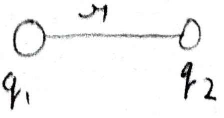


$FeCl_2(H_2O)_4$.

Association :- It is a chemical reaction whereby ions of opposite electrical charge together in solution to form a distinct chemical entity.

- It is joining or addition of ions.
- It is well explained by Coulomb's law –

$$F = k_e \frac{q_1 \times q_2}{r^2}$$



where -

F = force
K_e = Coulomb's constant
q_1 and q_2 = charged particles
r = distance

Factors Affecting Association

- Magnitude of Electric Charge
- Dielectric Constant
- Distances b/w Charges.

⇒ Quantitative Approaches to the factors influencing solubility of drugs.

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.

⇒ Solubility of most solid → significantly affected by temperature.

from Equation -

$$\boxed{\log K_s = -\frac{\Delta H}{2.3\,RT} + I}$$

Where,

$\log K_s$ = Saturation Solubility

ΔH = Heat of vaporisation
R = gas constant
J = is a constant
T = Temperature

from the above equation → Solubility of solid depends on temperature

⇒ **Effect of particle size, shape and surface Area :-**

The size of the solid particle influence the solubility because as a particle becomes smaller, the surface area to volume ratio increase

⇒ The large surface area allows a greater interactio with the solvent.

⇒ **Pressure :-** For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility.

⇒ For solid and liquid solutes, changes in pressure have practically no effect on solubility.

⇒ **Temperature :-** Temp. will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temp. increased

⇒ If the solution process release energy then the solubility will decrease with increasing temperature.

⇒ Generally, an increase in the temperature of the solution ~~wi~~ si increases the solubility of a solid solute.

⇒ A few solid solutes are less soluble in warm solutions. For all gases, solubility decreas. as the temperature of the solution increase.

⇒ **Nature of the Solute and Solvent :-**

While only 1 gm of lead(II) chloride can be dissolved in 100 gms of water at room temperature, 200 gms of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their nature.

⇒ **Molecular Size :-**

Molecular size will affect the solubility.

⇒ The larger the molecule or the higher its molecular weight, the less soluble in the substance.

⇒ Large molecules are more difficult to surround with solvent molecules in order to solvate the substance.

⇒ **Polarity :-** Polarity of the solute and solvent molecules will affect the solubility.

Polar dissolve polar & non-polar dissolve non polar.

Diffusion Principles in Biological System

Drug molecules pass through living membranes ~~show the property of mus~~ either by passive transport or active transport.

→ The ~~active~~ passive transport involves a simple diffusion process from a region of higher concentration to a region of low concentration as seen during drug transport in the gastro-intestinal tract.

→ The concentration gradient i.e. the differente in the conc. of the drug across the membrane is the driving force for passive transport.

⇒ In active transport, drug molecules are carried across the membrane by an enzyme ~~of~~ or biological carrier,.

→ Active transport can also occur against concentration gradient, i.e. from a region of low conc. to that of high concentration. The net movement of the drug is however towards blood.

The rate of drug transport is influenced by:

i) The physiochemical properties of the drug.

ii) The nature of the membrane.

iii) The concentration of drug across the membrane.

According to Henderson Hasselbalch equation for weak acid and bases.

$$pH = pka + \log \frac{[A^-]}{[HA]}$$

For a weak acid, $pH = pka + \log \frac{[B]}{[BH^+]}$

For weak base, [HA] = Conc. of non-ionized weak acid

[A⁻] = Conc. of the Congugate base

pka = Dissociation exponent for weak acid

[B] = Conc. of weak base

[BH⁺] = Conc. of its Congugate acid

For the weak base = $pka = pkw - pkb$

⇒ Equal amounts of ionized and unionized forms of a drug are present when $pH = pka$.

⇒ Diffusion in biological System can be studied under the following heads:

1) Gastrointestinal absorption of drugs
2) Percutaneous absorption
3) Buccal absorption, and
4) Uterine diffusion.

① Gastrointestinal absorption of drugs

Passive and carrier mediated transport are two means by which drugs cross the living membrane.

⇒ **Passive transport** of drug involves simple diffusion facilitated by drug concentration differences on both the sides of membrane.
e.g. In case of intestinal absorption, the drug moves from a high concentration ~~in gast.~~ (in GIT) region to a low concentration region via passive transport. (in systemic circulation)

⇒ **Carrier-mediated transport** of drug is classified in to active transport and facilitated diffusion.
In case of active transport, the drug moves from a low concentration region to a high concentration region by the "pumping action" of these biological transport systems.

⇒ In case of facilitated diffusion, carrier proteins cannot transport drugs or nutrients against the concentration gradient.

② Percutaneous Absorption:-

Percutaneous absorption of drug indicates its passage through the skin. This drug absorption phenomenon involves:

i) Dissolution of drug in its vehicle,
ii) Diffusion of solubilised drug (solute) from the vehicle to the skin surface, and
iii) Penetration of drug through the skin layers (mainly the stratum corneum).

③ Buccal Absorption :-

Beckett and Moffat used various organic acids and bases as drug models to study drug penetration into the lipid membrane of human mouths.

⇒ In co-ordination with the pH-partition hypothesis, absorption was related to the compound's pKa and its lipid-water partition coefficient.

④ Uterine Diffusion :-

Contraceptive drug (e.g. progesterone) and other therapeutic drugs are delivered into the uterus in microgram amounts via diffusion-controlled system.

⇒ Thus, maintaining an autonomic and continuous supply of medication to the patient, or long-term protection from pregnancy.

Solubility Of Gas In Liquid

⇛ Pharmaceutical solutions which contains gases dissolved in a liquid are
⇓
eg.

- ⇛ Effervescent preparations containing dissolved CO_2.
- ⇛ ammonia water.
- ⇛ Hydrogen chloride water.

⇛ Pharmaceutical aerosols → containing nitrogen or CO_2 as propellant.

⇛ Solubility of gas in liquid represents
⇓
the concentration of dissolved gas in liquid when it is in equilibrium with
⇓
Some of the pure gas above the solution.

Factors Affecting Solubility Of ~~g~~ gases In liquid

- Pressure (Solubility ↑ with ↑ P)
- Temperature (Solubility ↓ with ↑ temperature)
- Electrolytes (Solubility ↓ with addition of electrolytes)
- Chemical Reactio (Chemical R° b/w gas & solv generally ↑ solubility)

ⓘ Effect of Pressure :-

The effect of pressure on the solubility of the gas is given by Henry's law which states that in a dilute solution the mass of gas which dissolves in a given volume of liquid at a constant temp. is directly proportional to the partial pressure of the gas.

According to Henry's law, $\boxed{C = \sigma P}$

where,

C = Conc. of the dissolved gas in gram per litre of solvent
P = Partial pressure in mm of Hg.
σ = Proportionality constant and is referred to as the solubility coefficient.

⇒ The solubility of gases generally increases with increase in pressure and on the release of pressure, the solubility decreases and gases escape.

ⓘⓘ Effect of Temperature :-

Solubility of most gases decreases with the rise in temperature because of the greater tendency of the gases to expand in comparison to the solvent.

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Solubility of most gases decreases with the rise in temperature because of the greater tendency of the gases to expand in comparison to the solvent.

(iii) Effect of Electrolytes and Non-electrolytes :-

Solubility of a gas in a solvent is generally reduced by the addition of electrolytes such as sodium chloride or non-electrolytes such as sugar. This is referred as salting out.

(iv) Effect of Chemical Reaction :-

Henry's law generally applies to gases that are only slightly soluble in solvent and that do not react in any way with the solvent.

⇒ Chemical reaction, if any, between a gas and a solvent greatly increases the solubility of the gas in the solvent.

Solubility of Liquid in Liquid

When both solute and solvent is in liquid form.

Factors :

1. Nature → "Like dissolve like" method.
2. Temperature → T $\propto$ Solubility
3. Pressure → P $\propto$ Solubility
4. Surface Area → S.A $\propto$ Solubility

⇒ **Binary Solution** :- When we mixed solute in to two solvent mixture, then the solution formed is called binary solution.

Types → Completely miscibility (Alcohal + Water)
→ Partial Miscibility (Phenal + water)
→ Immisible (oil + water)

① Complete Miscibility :-

When the solute and solvent are very similar then they dissolves completelly.

⇒ Alcohal dissolves in water because of hydrogen bonding.

② Partial miscibility :-

When two liquid are mixed, there is formation of two different layer of liquid.

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

Ex. phenal + water.

⇒ Ideal & Real Solution :-

Ideal Solⁿ :- The solution which obey Raoult's law over the whole range of composition at all temperature.

Real or non-ideal Solⁿ :- which does not fallow Raoult's law. or which solution that are showing deviation are called real solutions.

⇒ The deviation may be negative leading to increased solubility because of hydrogen bonding b/w the polar components.

⇒ If the deviation is positive, it leads to a decreased solubility because of the association of the molecules of one th of the components to form dimers or polymers of high order.

Raoult's ~~R~~ Law :-

According to the Raoult's law:-

" at a definite temprsetuure, the partial pressure (P_A) of a component(A) in a liquid mixture is equal to vapour pressure in the pure state (P_A^0) multiplied by the mole fraction of the component (X_A) in the solution."

It is expressed as

$$\boxed{P_A = P_A^0 X_A}$$

Critical Solution Temperature :-

When two partially miscible liquid are mixed and shaken together, we get two solutions of different composition. For example, phenal and water, we get two layers, upper layer is a solution of water in phenol and the lower layer is a solution of phenal in water. At a fixed temperature, the composition of each solution is fixed and both solutions are in equilibrium.

→ Above a particular temperature, such solutions are completely miscible in all proportions. Such temperature is known as cristical solution temp. or consalute temp.

→ As in this case, the mutual solubility increase with temp. hence it is also known as upper consalute temperature.

Applications of CST :-

- ⇒ This method is useful to separate the liquid by the addition of third substances. This technique is used for the extraction of drugs in the analysis.
- ⇒ Useful in determination of percent composition of added substances.
- ⇒ The purity of substance can be determined by CST. e.g. Phenol.

Distribution law

⇒ **What is Distribution law:-** (Nernst's Distribution Law)

* When a solute is added to two immiscible liquids (in both of which solute is soluble)

↓

the solute distribute itself b/w the two liquid in such a way

↓

that ratio of its concentration in two liquid phases is constant at a given temp.

⇒ Explanation:-

- If a solute x distributed itself b/w two immiscible solvents A and B at constant temp. and x is in same molecular condition in both solvent,

then

$$\frac{\text{Concentration of X in A}}{\text{Concentration of X in B}} = K_D$$

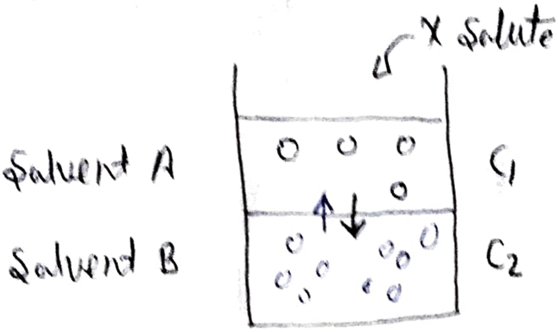
⇒ If C_1 is concentration of solute in solvent A and C_2 is concentration of solute in solvent B

⇒ It can be expressed as

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

Where K_D or simply K is called → Distribution Coefficient "or" → Partition Coefficient "or" → Distribution ratio

⇒ This is an equilibrium law -



when the distribution of solute X reached dynamic equilibrium -

⇒ the rate (R_1) at which molecules of X pass from solvent A to B is proportional to its conc. C_1 in A.

$$R_1 \propto C_1$$
$$R_1 = K_1 C_1 \quad — ①$$

where, K_1 is a constant

⇒ The rate (R_2) at which molecules of X pass from solvent B to A is proportional to its concentration C_2 in B.

$$R_2 \propto C_2$$
$$R_2 = K_2 C_2 \quad — (ii)$$

where, K_2 is a constant

⇒ Since at Equilibrium.

$$R_1 = R_2$$

$$K_1C_1 = K_2C_2$$

$$\frac{C_1}{C_2} = \frac{K_2}{K_1} = K_D$$

$$\boxed{\frac{C_1}{C_2} = K_D}$$ ↳ Nernst's Distribution law equation.

Limitations of Distribution Law :-

1. <u>Temperature</u> ;- Temp. is kept constant throughout the experiment.

2. <u>Same Molecular State</u> ;- Solute must be in same molecular state in both solvent.

3. Equilibrium Concentration ;- The concentration of the Solute are noted after the equilibrium has been established.

4. Dilute Solution ;- The conc. of Solute must be low in two Solvents.

5. Non-miscibility of Solvents ;- Solvents should be non-miscible so that can be separated or they should only slightly soluble in each other.

⇒ Applications of Distribution Law:-

① Salvent Extraction;-

⇒ Distribution law is used for separation of organic substances from aqueous solutions.

⇒ A aqueous solution ⇒ shaken with an immiscible organic solvent such as ether or benzene. (in separating funnel)

⇓

ethereal layer separated by distillation ⇐ Organic substance passes into ethereal layer

⇓

organic substance is left behind.

② Partition Chromatography:-

⇒ A paste of mixture is applied at top of the column of silica soaked in water

⇓

immiscible solvent (hexane) is allowed to flow down the column

⇓

Each component of mixture partitioned b/w stationary liquid phase water and mobile liquid phase hexane.

③ Release of Drug from Dosage forms;-

The study the release of drug from gels, ointments, creams, partition coefficient important phenomenon and it is obtained ~~by~~ from distribution law.

~~④ Determination of~~

④ Passage of drug through membrane :-

A biological membrane are lipoidal in nature, the rate of drug tranfer far passive absorbed drug is directly related to liphophilicity of molecule.

⑤ Determination of Solubility :-

⇒ Suppose the solubility of iodine in benzene is to be determined

⇓

iodine is shaken with water and benzene.

⇓

at equilibrium iodine in benzene (C_b) and water (C_w)

So,

$$\frac{C_b}{C_w} = K_d$$

$$\frac{S_b}{S_w} = k_d$$

Where,

S_b = Solubisity in benzene

S_w = Solubility in water