**Solubility and the Solution Process:**

 The solid dissolves rapidly at first, but as the solution approaches saturation the net rate of dissolution decreases since the process is in dynamic equilibrium.

 Once at equilibrium, the amount of solute does not change with time.

 At equilibrium- rate of dissolution = rate of solution.

**Solubility Thermodynamics:**

 The Gibbs Free Energy of Mixing- ΔG = ΔH – T.ΔS

Where ΔG= Gibbs Free Energy of Mixing, ΔH = enthalpy (energy, heat), ΔS = entropy (disorder), T = temperature.

 The entropy of mixing favours complete miscibility of all components.

 Enthalpy- balance of the:

o Drug-drug interactions (D-D) (cohesive forces).

o Solvent-solvent interactions (S-S) (cohesive forces).

o Drug-solvent interactions D-S (adhesive forces).



 ΔH is sometimes negative, and sometimes positive, as it is a sum of the following:

o S-S – energy required to break weak bonds between solvent molecules.

o D-D – energy required to break intermolecular bonds between the solute molecules.

o D-S – ΔH is negative since bonds are formed between the species.

 Intermolecular forces are important in determining the solubility of a substance as ‘like’ intermolecules forces for solute and solvent will make the solute soluble in the solvent.

 ΔG must be negative for a solution to form. (ΔG - = stable system, + = unstable system)

ΔH should be minimal.

 ΔS should be maximal (increases stability)

**Clinical Relevance of Solubility:**

 Solubility can affect bioavailability and therapeutic response.

 Need enough drug in solution to reach concentrations that are therapeutically meaningful.

 Stability of drug.

 Formulated drug product disintegrates into dispersed drug particles, which undergo dissolution into solubilised drug which passes a membrane (must be permeable to drug) and is absorbed.

Increasing no. drugs BCS Class II and IV (poorly soluble drugs). 90% and higher = high permeability. Below

90% - low permeability.

API = Active Pharmaceutical Ingredient, NCE= New Chemical Entity (still in developmental stages).



**Measurement of Solubility:**

N.B. –

 The solvent and solute must be pure.

 A saturated solution must be obtained before any solution is removed for analysis.

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 The solvent and solute must be pure.

 A saturated solution must be obtained before any solution is removed for analysis.

 The method of separating a sample of saturated solution from undissolved solute must be satisfactory (temp., volatile solvents).

 The method of analysing the solution must be reliable (UV, HPLC, Refractometry, etc.)

 Temp. must be adequately controlled.

**Static Methods-** determination of solubility is performed when an equilibrium state is reached.

o Flask Method- shake and excess of a finely powdered substance with the solvent at the required temp. until equilibrium is reached. Filter and assay (quantification of substance).

Variation- heat an excess of solid with the solvent and allow to cool to the required temp.

o Preparation of a Number of Mixtures- containing a fixed amount of the solute in variable volumes of the solvent (or varying quantities of the solute in a fixed volume of solvent) and shaking them at the required temperature until equilibrium is reached.

 Determination of approximate solubility prior to flask or other method

 Volatile solvents

Mixtures are shaken and visually checked for undissolved particles.

Approximate solubility is determined and a further method is chosen

**Dynamic Methods**- the concentration of the solute in solution is checked periodically before attaining a plateau which is considered to be an equilibrium.

 Solubility profiles of high energy solids (such as polymorphic/amorphic forms)/anhydrous forms undergoing solvation during dissolution.

o Turbidimetry- the solute is dissolved in an organic solvent. Portions of this solution added slowly to water/ an aqueous buffer. The mixture will remain clear unless the aqueous buffer solubility is reached and precipitation occurs. Volume added against turbidity (extrapolate back to the point where precipitation began).

**Physiochemical Factors Affecting Solubility:**

 Like dissolves like.

 Molecular compounds with similar chemical structures and polarities tend to be miscible.

 Homologous alcohol series have polar and non-polar ends.

 Methanol, Ethanol and 1-Propanol are miscible in water. 1-Butanol (7.9g/100g water), 1-Pentanol

(2.7g/100g water), 1-Hexanol (0.6g/100g water).



* Nature of the solute:

o Molecular weight (if high, has a low solubility).

o The D-D Interactions arising from the crystallinity of the drug (the lattice energy)- Melting Point.

 Crystal structure and solvation (polymorphism).

o Particle sixe (low size, greater solubility) (applies only to very small particle sizes (100nm and below)

* Nature of the solvent:

Dipole moment (used to quantify polarity of solvents).

o pH (ionisation is determined by the pKa value of the compound and pH of the medium).

 Henderson-Hasselbalch Equation: pH = pKa + log [Base ]/[ Acid ]

 At pH = pKa, 50% species ionised and 50% unionised. (Ionised form more soluble).

*  Temperature: Most compounds demonstrate increased solubility at higher temps.

o All gases are less soluble at higher temps. Temp. related to sign of ΔH

soln. (negative meaning less soluble at high temps, positive means more soluble (Le Chatelier’s Principle).

*  Pressure: little effect on solubility of a liquid/solid, has a dramatic effect on gas solubility in a liquid.
* Solution Additives:

o Salting out- when an electrolyte is added to an aqueous solution.

o Salting in- hydrotropism.

o Common ion effect.

*  Energy of attraction (due to ion-dipole forces) (hydration energy).

o Energy of hydration increases for smaller ions than bigger ones.

o Lattice energy (energy holding the ions together in the lattice).

o Related to the charge on the ions (larger charge, higher lattices energy). Inversely proportional to size of the ion (large ions, smaller lattice energy). Solubility increases with increasing ion size (due to decreasing lattice energy).

**Solubility- Effect of Drug Ionisation:**

 Degree of ionisation is determined by the pKa value(s) of the compound and the pH of the medium.

 Henderson-Hasselbalch Equations: pH = pKa + log [Base ]/[ Acid ]

 At pH = pKa, 50% species ionised and 50% unionised. (Ionised form more soluble).

 Unionised (Neutral) species = poorly soluble. (Then solubility varies by a factor of 10 per pH unit).

 Improve solubility of an unionisable drug by choosing a solution with optimum pH.

 **Solubility trends are as follows:**

o Acidic drugs (e.g. indomethacin) are more soluble in alkaline solutions (high pH).

o Basic drugs (e.g. chlorpromazine) are more soluble in acidic solutions (low pH).

o Amphoteric drugs (e.g. oxytetracycline) have complicated pH/solubility profiles.

o Logarithim of solubility of indomethacin, chlorpromazine and oxytetracycline:

**Intrinsic and Apparent Solubility:**

• They are two types of solubility: intrinsic solubility and apparent solubility.

• The intrinsic solubility (S0) is solubility of the free acid or free base form of an ionisable compound at a pH where it is fully unionised. It is a single numeric value (0.5 mg/ml) that is independent of the environmental factors (e.g. pH).

• The apparent solubility is dependent on the environmental factors such as pH and ionic strength.

• The apparent solubility is higher because it comprises both the ionised and neutral forms.

**Salts:** A salt is the product generated upon neutralisation of an acid/base. Salification (process of salt formation) is traditionally used to improve drug stability.

• The term pharmaceutical salt is used to refer to an ionisable drug that has been combined with a counterion to form a neutral complex.

• Salt selection is a common standard operation performed with small ionisable molecules during drug development (in many cases the drug salts display preferential properties as compared with the parent molecule).

• Today around half of the clinically used drugs are salts.

• Many drugs are now produced in more than one salt form.

• All acidic and basic compounds can participate in salt formation, but the success and stability of salt formation depends upon the relative strength of the acid/base.

**Role of pKa**:

• For stable salt formation to be complete, ionisation must be effectively complete such that a single ionisation state is formed.

• At least 2 pH units difference between the pKas of the base and the acid typically necessary.

**Impact of Salts:**

• Impact on pharmaceutical properties required for a successful dosage form (bioavailability and stability (both chemically and physically)).

• Impact of the physiochemical properties of the drug substance (solubility, dissolution rate,

hygroscopicity, chemical stability, crystal form, mechanical properties).

• Changing the salt changes the drug.

**Stoichiometry of Salts and Implications: ???**

E.g.

• Diclofenac sodium -> Diclofenac + Sodium.

Stoichiometry- drug:counterion = 1:1, therefore, 1 mole of drug gives 1 mole of salt. 1 mole of salt gives mole of drug upon dissociation in solution. 318g of salt gives 295g of drug upon dissociation in solution.

• Salbutamol sulphate -> Salbutamol + Sulphate.

Stiochiometry- drug:counterion = 2:1, therefore 2 moles of drug gives 1 mole of salt. 1 mole of salt gives 2 moles of drug upon dissociation in solution. 577g of salt gives 472g of drug upon dissociation in solution.

**Co-Solvation:** (used to improve solubilities- only in liquid formulations).

 Weak electrolytes and non-polar molecules frequently have poor aqueous solubilities.

 Solubility in water can be increased by co-solvency (the addition of water miscible solvents in which the drug has good solubility) (the added solvents = co-solvents).

 The solubilising effect by co-solvency is primarily dependent upon the polarity of drug with respect to solvent and co-solvents.

**Mechanism of Action of Co-Solvents:**

 Drug-Water Interactions (adhesive forces)- hydrophilic hydrogen bonding groups ensure water miscibility while their hydrophobic hydrocarbon regions interfere with water’s hydrogen bonding network, reducing the overall intermolecular attraction of water

 Water-Water Interactions (cohesive forces)- co-solvents make the polar water environment more polar like the solute.

**Co-Solvents:**

 Can increase solubility of the non-polar drug up to several orders of magnitude compared to its aqueous solubility.

 Co-solvent must meet certain requirements (such as non-toxicity, compatibility with blood, be non-sensitising, non-irritating, physically and chemically stable and inert).

**Polarity:**

 Measure of polarity- dielectric constant (ε), solubility parameter (δ), surface tension (γ), octanol-water partition coefficient (Kow).

 The best solvent for a particular solute is the one which most closely matches its polarity.

 Non-polar – less polar than either solvent component.

 Polar – more polar than either solvent component.

 Semi-polar – polarities between the polarities of the solvent and co-solvent.

 Disadvantages of using a co-solvent- toxicity, poor taste of a formulation (corn syrup, citric acid and fructose are often added when co-solvents are used)

**Non-Polar Solutes:**

Yalkowsky’s Log-Linear Model – Assumptions:

 The mixed solvent’s solubilisation power changes as a log-linear composition-weighted mixture of its pure components (the molar solubility of a solute in a mixed solvent system is a linear combination of its molar solubilities in the pure component solvents).

 The solute is not altered in any way by changes in the solvent.

 The volume contribution from dissolved solute is negligible and can be ignored.

 The log-linear model describes an exponential increase in a non-polar drug’s solubility with a linear increase in co-solvent concentration:

logSmix = logSw + σ . fc

Where Smix = the total solubilities in the co-solvent-water mixture, S

w = solubility in water, σ = the co-solvent solubilisation power for the particular co-solvent-solute system, fc = the volume fraction of the

co-solvent in the aqueous mixture.



Co-solvent power:

σ = log Sc/Sw

Values of σ can be positive, near zero or negative, depending on the relative polarity of water, co-solvent and solute.

 Order of solvating power:

Ethanol > Propylene Glycol > PEG 400 > Glycerol

1. B. 2011 JF Exam Question: “List 3 co-solvents that can be used in liquid formulations for the oral use”).

Semi-polar drugs-

o Have poor aqueous solubility due to strong crystalline interactions.

o Rarely have large activity coefficients in water (they tend not to be solubilised greatly by co-solvents).

o There is an appreciable amount of structuring of the solvent molecules in the vicinity of the solute.

Polar solutes:

 Most can dissociate in aqueous solutions.

 Tend to be soluble in water.

 Addition of a less polar solvent decreases solubility, thus polar solutes tend to have gradually decreasing solubilisation curves