INDUSTRIAL PHARMACY-I

UNIT I-PREFORMULATION

CLASS2

TOPIC: Physical properties-solubility profile pKa, pH

SOLUBILITY ANALYSIS

Solubility

Solubility is defined as the concentration at which solution phase is in equilibrium with solid face at a given temperature and pressure

Descriptive term	Part of the solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

- Study solubility in preformulation for bioavailability
- Solubility increase –dissolution increase –bioavailability increase
- Higuchi conners method is used to determine equilibrium solubility

The equilibrium solubility is based on the phase-solubility technique proposed by **Higuchi-Connors .** Method

- Drug dispersed in solvent in a closed container

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agitated at a constant temperature using shakers

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- samples of the slurry are withdrawn as a function of time clarified by centrifugation and assayed by HPLC, UV, GC etc

The aqueous and lipid solubility characteristics of a drug substance are important in determining whether it is capable of reaching sites of absorption, its interaction with putative therapeutic targets and its ultimate metabolism and excretion.

An assessment of solubility characteristics is, therefore, usually a starting point for preformulation studies.

Absolute (Intrinsic) Solubility

Using standard aqueous buffers the drug or excipient is vigorously stirred at a constant temperature, e.g. 37 °C, to achieve equilibrium, maximum (saturated) absolute solubility. For compounds with ionisable groups this equilibrium solubility of the unionised form is known as the intrinsic solubility.

Preformulation studies will start by measuring intrinsic solubility in a neutral, an acid and an alkaline environment; typically 0.1 M HCl, water and 0.1 M NaOH at 4 °C, 25 °C, 37 °C and an elevated temperature e.g. 50 °C.

These data can be recorded as the absolute (intrinsic) aqueous solubility at each pH and compared with data on known and related compounds.

Solubility profile helps to

- provide insight into the state of the drug substance as it is subjected to a variety of different pH environment e.g. as it passes through the gastro-intestinal tract, circulates through various cellular, organ components, arterial and venous circulation and excretory fluids such as bile and urine.

- Inform the type of the aqueous solvents that might potentially be used in formulations (e.g. parenteral injections, nasal or ophthalmic drops, oral solutions).
- Assess the possible effect that aqueous media used in dosage form manufacture, e.g. tablet wet granulation and film coating, may have on the compound.
- Pharmacokinetics studies
- Analytical methods
- Preformulation studies mainly focus on drug solvent drug delivery system

Molecular Dissociation pKa/ Ionization constant

Like partition coefficient, dissociation constant (pKa) is the property that determines the solubility in pH-dependent environment and extent of ionization.

It is the extent of ionization that determines the absorption as only unionized form can be absorbed and hence it becomes essential to determine the pKa value of molecule. pKa value determination gives idea about site of absorption.

Weakly acidic drugs having pKa value around 4 are best absorbed from stomach as they are predominantly present in unionized form.

Basic drugs having pKa value of around 8 are best absorbed from intestine as they are predominantly present in unionized form.

% ionization can be determined by the following equation:

%Ionization={10(pH-pKa)1+10(pH-pKa)}×100

%Ionization=10pH-pKa1+10pH-pKa×100E2

Most of the strong acids and strong bases are present in ionized form throughout GIT and hence poorly absorbed.

But it is also true that most of the pharmaceutical entities are derivatives of weak acids and weak bases and hence absorption is not an issue

When pH = pKa the compound is 50% ionised.

The pKa can be calculated from intrinsic solubility data, or by conductivity, potentiometry and spectroscopy.

Indications:

1. Absorption characteristics.(region of the gastrointestinal tract in which the drug will be in either the ionised or unionised state)
2. The chemical nature and concentration of the counter ion conferring solubility e.g. chloride or hydrochloride can have a significant influence on solubility and this should be examined during preformulation studies; so as to choose an optimum compound e.g. base or cation, for further development.

Nature of the drug	Ionized	unionized	Absorption	Examples	pKa
Very weak acid and very weak base		Through out GIT	Rapid	Phenytoin Ethosuximide Diazepam Theophylline	>8 <5
Weakly acidic drug	Neutral media of the intestine	Acidic contents of the stomach	Stomach	Asprin Ibuprofen	3-7
Weakly	Acidic	Neutral	Intestine	Morphine	5-8

basic	contents of the stomach	media of the intestine		Chloroquine	
Strongly acidic Srongly basic	Both in stomach and intestine		Poor	Cromolyn sodium Guanethidine	<2 >11

pKa determination

Potentiometric titration

UV spectroscopy

Solubility measurement

HPLC techniques

Capillary zone electrophoresis

Foaming activity

Importance of pKa

- ✓ The pKa value provides valuable data
  - on the interaction of an ionizable drug with charged biological membranes and receptor sites;
  - information on where the drug may be absorbed in the GIT; The pH varies in GIT regions so the ionization and hence the absorption of drugs varies throughout the GIT
  - to know how much to alter the pH to drive a compound to its fully ionized or nonionized form for analytical and other purposes, such as formulation, solubility, and stability.

Solubility in Various Solvents

Prelliminary data on solubility of the drug/excipient in non-aqueous solvents is essential, e.g. topical ointments/liniments or oily injections,

Selection of solvents for manufacture of the active ingredient, e.g. extraction or crystallisation, and for the final formulation, e.g. tablet granulation.

organic solvents such as Ethyl alcohol Glycerin Propylene glycol ,Arachis oil ,Ethyl oleate, Liquid paraffin

For Manufacture Industrial methylated ,Isopropyl alcohol, Benzyl alcohol ,Polyethylene glycol used

Diffusion

Once in solution in an organ or cell in a biological fluid, e.g. synovial fluid, vitreous humour, mucous etc., a drug will need to diffuse to the site of transfer or action.

The rate at which the drug can diffuse is dependent on a variety of physiochemical properties such as the viscosity of the fluid through which it is diffusing, the temperature of the fluid, the concentration gradient across the fluid—and hence the amount of drug in solution and the surface area with which it is in contact.

In a fluid with pure Newtonian rheological properties the rate of diffusion of a chemical entity can be calculated using the Noyes–Whitney Equation.

$dM/dt = DS(Cs - Cb)/H$ where

dM/dt is the rate of dissolution (i.e. the amount M diffusing in time t)

D is the diffusion coefficient from the saturated liquid layer adjacent to the crystal surface.

S is the surface area exposed.

Cs is the concentration in a saturated liquid layer directly adjacent to the crystalline solid surface.

Cb is the concentration in the bulk solution further out from the crystal, (Cs − Cb) is the concentration gradient.

H is the thickness of the liquid saturated layer.

Preformulation diffusion studies can be conducted using a Franz cell.

In addition to determining the rate and quantity of drug that has permeated, the diffusion coefficient provides another means of comparing related compounds and those with known in vivo characteristics.

Permeability

Once in solution in physiological fluids e.g. gastric juices or plasma, a drug must permeate cells and tissues to reach its target site of action. This will involve passive and/or active transport mechanisms. For passive diffusion the drug will need to partition with the lipid components of cells and/or diffuse through aqueous pores in tissues.

An index of its permeability can be obtained in vitro by measuring the permeability across a model membrane at a constant temperature, Typically the drug in solution is placed in one side of a two-compartment cell separated from the second compartment by a polymeric membrane, the second compartment containing a physiological representation fluid, e.g. normal saline.

The amount of drug permeating through the membrane can be measured at various time intervals. A variety of membranes may be chosen each differing in their lipid composition.

The data obtained permits the calculation of the diffusion rates and a comparison of permeability with that of drugs whose properties are known or comparison with related drug candidates.

Permeability is not therefore a single characteristics but depends primarily on solubility, partition (aqueous : lipids), diffusion coefficient and the nature of the membrane (chemical and biological composition and thickness).

The rate of permeability will also depend upon other physicochemical properties of solutions (e.g. fluid temperature, viscosity, density).

Ph-Solubility Profile

pH pH = − Log [H+]

pH scales from 1 to 14

acid pH < 7

neutral = 7

alkali/basic= >7

Importance of pH in preformulation

1. Injections should be in range of pH 3-9 to prevent tissue damage and pain at injection site.

2. Oral syrups can not be formulated too acidic for palatability reasons.

3. More alkali may attack the glass container.

4. If drug is susceptible to degradation in acidic pH, then its delayed release formulation is to be prepared.

5. The pH of formulation must not sensitize the site of application. e.g. pH for buccal application should in the range of 6.6 to 6.8.

6. GIT shows a variety of pH [pH 6.6 (buccal), pH 1.2 (stomach), pH 6.8 duodenum, pH 7-8 (small intestine)] throughout its length from oral cavity to

colon. The dosage form should be stable at the pH of the intended or target site of absorption.