PREFORMULATION

6th week

SOLUBILITY

A basic pharmaceutical requirement is that the drug must be able to dissolve in aqueous biological media in order to exert any biological activity.

Once dissolved, the solution properties of the drug, such as the ability to cross biological membranes and interact with proteins, become critical.

SOLUBILITY

In other words, the aqueous solubility is a crucial parameter and a key physicochemical property of the drug.

** The failures during drug development are often related to the poor or insufficient solubility of drug.

** In addition, particular dosage forms such as iv injections require a solution.

Solubility is the maximum amount of the drug dissolved in a solvent at a constant temperature. This value can be called as *saturation solubility*.

Solubility is expressed as a concentration term (mg/mL or mole/L) usually as a saturated value at a constant temperature in a specified solvent.

Determination of saturated solubility is relatively easy and should be one of the first preformulation studies conducted.

Method: - Solvent and excess amount of solute are placed in contact usually in a sealed container and mixed at a constant temperature until equilibrium is achieved. A sample of solution is then extracted and supernatant is analyzed for the concentration of solute present.

- The analytical method used must be capable of accurately measuring the concentration.

- Time allowed for equilibrium will depend on the dissolution behavior.

Factors Affecting Solubility:

1- Temperature:

- The temperature of solution formation is important.

- The key temperature is 37 °C however, higher temperatures could be employed for processing especially if they aid dissolution.

- The effect of temperature on solubility can be determined calorimetrically by measuring temperature changes on dissolution and applying the "Van't Hoff Equation".

Factors Affecting Solubility:

1- Temperature:

The heat of solution (ΔH_s) represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.

Factors Affecting Solubility:

1- Temperature:

* Most commonly, the solution process is endothermic (ΔH_s is positive) and thus increasing the solution temperature increases the drug solubility.

* When the process is exothermic (ΔH_s is negative), such that higher temperatures supress the solubility.

Factors Affecting Solubility:

1- Temperature:

- Heats of solution are determined from solubility values for saturated solutions equilibrated at controlled temperatures over the range of interest.

- Typically the temperature range should include 5 °C, 25 °C, 37 °C and 50 °C.

Factors Affecting Solubility:

1- Temperature:

$$\ln S = (-\Delta H_s / RT) + C$$

S = Molar solubility at temperature T

T = Temperature (Kelvin)

R = Gas constant

Factors Affecting Solubility:

1- Temperature:

* For non-electrolytes and unionized forms of weak acids and bases dissolved in water, heats of solution are usually in the range of 4 to 8 kcal / mole.

** Salt forms of drugs are often less sensitive to temperature and may have heats of solution between -2 and 2 kcal / mole.

Factors Affecting Solubility:

2- Dielectric constant and Solubility parameter:

!!! Like will dissolve like

** So, the solvent's physicochemical properties such as dielectric constant (ε) which is a measure of polarity, and solubility parameter (δ) which is a numerical value that measures a solvent's "solvency" based on the strength of intermolecular attractive forces between the solvent molecules, are important.

** If the compound is nonionizable, these two parameters will be of overriding importance.

Any suitable biocompatible solvent may be appropriate for pharmaceutical processing, however, the major biocompatible solvent is water and hence the aqueous solubility of the compound is a key parameter to determine.

Factors Affecting Solubility:

3- Crystal properties:

- As mentioned before, the crystal properties are also important.

-In early preformulation when initial solubility experiments are conducted, polymorphic or solid state properties maybe unknown or only poorly controlled.

-In these situations, results should be treated with caution.

Factors Affecting Solubility:

4- Particle size:

The "Noyes-Whitney Equation" predicts that surface area influences dissolution and therefore the particle size employed in solubility experiments is important.

The basic relationship is that for any weight of compound the smaller the particle size, the greater the available surface area and therefore the greater the dissolution rate.

If required particle size reduction by milling, micronization or even the formation of nanocrystals can be utilized as a formulation technique to improve poor dissolution properties.

Factors Affecting Solubility:

5- pH and pK_a:

* If the drug has either weakly acidic or basic groups in its structure such as a carboxylic acid or primary amine, respectively, then these will be affected by pH in aqueous media.

** For a weak acid, alkaline pH values will promote dissociation or ionization of the acid group creating a charged molecule, which will increase solubility, through improved hydrogen bond formation, with the converse applicable to weak bases.

* An increase in acid over aqueous solubility suggests a weak base.

* An increase in alkali over aqueous solubility suggests a weak acid.

In both cases, a dissociation constant (pK_a) will be measurable and salts should form.

* An increase in both acid and alkali solubility suggests either amphoteric or zwitterionic behavior and there will be at least two pK_as, one acidic and one basic.

* No change in solubility suggests a non-ionizable, neutral molecule with no measurable pK_a.

Henderson-Hasselbach Equation;

** It provides an estimate of the ionized and unionized drug concentration at a particular pH.

For acidic compounds;

$pH = pK_a + \log [\text{ionized drug}] / [\text{unionized drug}]$

For basic compounds;

$pH = pK_a + \log [\text{unionized drug}] / [\text{ionized drug}]$

pK_a = Ionization constant of the drug

* This equation predicts that solubility will be maximum for acidic compounds at higher pH values and for basic compounds at lower pH values.

** The determination of pK_a of the drug is a key stage in preformulation.

When pH is equal to pK_a, the compound will be present in a 50:50 mixture of ionized and unionized species.

With 2 pH units on either side of the pK_a, the compound will either be 99% ionized or 1% ionized.

Over a range of 4 pH units, which easily occurs in the gastrointestinal tract, there will therefore be a vast change in solubility and also dissolution.

The methods used for pKa determination are;

- Potentiometric titration
- UV spectroscopy
- Solubility measurements
- HPLC techniques
- Capillary electrophoresis

The solubility of weak acids in strong acids or weak bases in strong bases is named as "intrinsic solubility". In other words, intrinsic solubility is the solubility of the compound which is in nonionized (unionized) form i.e the compound does not constitute a salt.

Drugs are normally processed as salts since this presents the compound in the ionized form, which has greater solubility and hence dissolution rate, thereby increasing solubility without the requirement to change pH.

Factors Affecting Solubility:

6- Partition coefficient:

If a drug is added to a system consisting of two immiscible solvents and is soluble in either of the solvents, it will naturally distribute itself or partition between the solvents and concentrate in the solvent that is most thermodynamically favorable.

The distribution ratio of the drug between the solvents can be used to determine the *partition coefficient* usually presented as a log value and defined as follows;

$$\log P_{o/w} = \log [C_o / C_w]$$

P = Partition coefficient

$[C_o]$ = The concentration of the drug in the nonaqueous phase

$[C_w]$ = The concentration of the drug in the aqueous phase

This ratio is not concentration or temperature dependent although it will be influenced by the physicochemistry of the two solvents and drug.

Generally, the nonaqueous phase employed is *n-octanol*.

n-Octanol is employed since it is immiscible with water, has properties that mimic biological membranes and through general use has a large information database available.

If the drug is capable of ionization in the aqueous phase, pH must be controlled since only the unionized form will partition into the nonaqueous phase.

In these cases [C_w] must be the total concentration of both ionized and nonionized species, log P will be pH dependent and is determined with a known aqueous phase pH.

Log P provides a measure of the drug's lipophilicity or ability to dissolve in nonaqueous phases; the higher log P values mean that the more of the compound will reside in lipid phase.

For preformulation, the utility of log P is that it provides a useful parameter which can be used to determine solubility in both aqueous and mixed solvent systems.

Log P is an important preclinical measure of the biopharmaceutical and pharmacodynamic properties of drug.

For example, compounds with high log P values tend to have higher volumes of distribution post administration which affects pharmacokinetic properties. On the other hand, lipophilicity is a major driving force for the interaction of the drug with its receptor; log P is therefore useful during the drug design phase.

"Shake-flask method" is the simplest method for measuring log P.

In this method, the drug is added to a mixture of aqueous and n-octanol phases (n-octanol needs to be equilibrated with the aqueous phase for 24 hours prior to the experiment) and permitted the drug to equilibrate at least 30 minutes and then determine the concentration of the drug in each phase.

Solubilization

For drug candidates with either poor water solubility or insufficient solubility for projected solution dosage forms, preformulation studies should include limited experiments to identify possible mechanisms for solubilization.

A general means of increasing solubility is the addition of a cosolvent to the aqueous system.

Solubilization

- The solubility of poorly soluble non-electrolytes can often be improved by orders of magnitude with suitable cosolvents such as ethanol, propylene glycol and glycerin.

- These cosolvents solubilize drug molecules by disrupting the hydrophobic interactions of water at the nonpolar solute – water interfaces.

Solubilization

- The extent of solubilization due to the addition of cosolvent depends on the chemical structure of the drug, that is, the more nonpolar the solute, the greater is the solubilization achieved by cosolvent addition.

- Cosolvent effects for dissociated drug molecules are usually much less.

Solubilization

- Some poorly soluble drugs can be solubilized in micellar solutions such as 0.01 M Tween 20 or via molecular complexes for example the inclusion complexes with cyclodextrins.

DISSOLUTION RATE

- As mentioned before, for a drug to be absorbed it must first be dissolved in the fluid at the site of absorption.

- For example, an orally administered drug in tablet form is not absorbed until drug particles are dissolved or solubilized by the fluids at some point along the gastrointestinal tract, depending on the pH-solubility profile of the drug.

* Dissolution describes the process by which the drug particles dissolve.

DISSOLUTION RATE

- Dissolution rate is defined as the drug amount dissolved in a certain time period. It is a dynamic process and expressed by "Noyes-Whitney Equation".

- Dissolution of a drug is controlled by several physicochemical properties including chemical form, crystal habit, particle size, surface area, solubility and wetting properties.

DISSOLUTION RATE

- The dissolution rate of a drug is important where it is the rate-limiting step in the absorption process.
- If dissolution is fast or the drug remains in solution form, the rate of absorption is primarily dependent on its ability to traverse the absorbing membrane.
- If drug dissolution is slow due to its physicochemical properties or formulation factors, dissolution may be the rate-limiting step in absorption and influence drug bioavailability.

DISSOLUTION RATE

- When coupled with equilibrium solubility data, dissolution experiments can help to identify potential bioavailability problem areas.

DISSOLUTION RATE

- It was suggested that provided the solubility of a drug exceeded 10 mg/mL at pH<7 then no bioavailability or dissolution related problems were to be expected.

- Below 1 mg/mL, such problems were quite possible and salt formation could improve absorption and solubility by controlling the pH of the microenvironment independently of the drug and dosage form's position within the gastrointestinal tract.

DISSOLUTION RATE

The dissolution rate of a drug in which surface area is constant during dissolution is described by the Noyes-Whitney Equation;

$$dC/dt = (D.A / h.V) (C_s - C)$$

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dC / dt	=	Dissolution rate
D	=	Diffusion coefficient
h	=	Thickness of the diffusion layer at the solid-liquid interface
A	=	Surface area of drug exposed to dissolution media
V	=	Volume of media
C_s	=	Concentration of a saturated solution of the solute in the dissolution medium at the experimental temperature
C	=	Concentration of drug in solution at time t

If C is maintained at less than 10-20% of C_s ($C_s >> C$), sink conditions are said to apply, and the equation simplifies to;

$$dC/dt = (D.A / h.V).C_s$$

- There are multiple methods available to determine dissolution rate either of the drug* or its products under development.

* Only the former constitutes preformulation.

- The usual method is to compress the drug into a disc, around 1 cm in diameter, and measure dissolution from the surface into a suitable solvent over time as either the disc is rotated or the solvent stirred.

STABILITY

- Commercial pharmaceutical products require a shelf life measured in years (ideally up to 5 years) to ensure that the product's potency is identical throughout and provide a sensible time frame for manufacture, distribution, sale and administration.

- A major element of preformulation is therefore aimed at investigating and understanding the stability of drug.

STABILITY

* This information is critical since it influences handling during preformulation studies, storage (including choice of container), formulation approches (including excipient choices) and the processes that maybe employed during product manufacture, storage and distribution.

** Stability studies are applied to the solid drug and to solutions or other preparations of drug which maybe employed.

STABILITY

The effort is aimed at determining known conditions under which the drug maybe stored and handled without any degradation arising.

Physical Stability

Hygroscopicity

Chemical Stability

!! A specific separative analytical method with a key focus on the degradation products and not on the parent drug is required.

* Degradant quantification rather than the parent compound is optimal since 1% degradation will only change the parent from 100% to 99%, which is a change that analytically will be difficult to quantify, while the degradant will change from 0% to 1%, which is easily detected and quantified.

** On the other hand, chemical identification of the degradants is beneficial since it permits discovery of the degradation pathways and potential routes for avoidance.

Chemical degradation occurs by three major chemical processes;

- Hydrolysis
- Oxidation
- Photolysis

Hydrolysis:

This is the most common degradation pathway since water plays an important role in many processes especially in solutions but also in solid systems where it maybe present at low concentrations.

Hydrolysis occurs via a nucleophilic attack of the water molecule on labile bonds with susceptibility dependent on the bond type and decreasing from lactam > ester > amide > imine.

Hydrolysis:

Hydrolysis can be influenced by pH if the molecule is ionizable with maximum instability in the ionized form since it has the greatest solubility and therefore exposure.

If the solvent is not water, *solvolysis* is also possible if the solvent and compound react.

Oxidation:

* Oxidation is an environmental phenomenon requiring oxygen (or an oxidizing agent), light and trace metals capable of catalyzing the reaction.

** If molecular oxygen is involved the reaction is generally rapid and termed as *auto-oxidation*.

*** Oxidation reactions generally involve free radical chain reactions and the initial free radical may arise through thermal or photolytic bond cleavage or a redox process involving a trace metal ion.

Oxidation:

* Once formed the radical can then be propagated, catalyzed by the metal ions present, until a suitable chemical inhibitor (antioxidant) or termination reaction intervenes.

** Oxidation reactions usually produce highly colored degradation products, which can be detected by eye before chemical detection is possible.

Photolysis:

* If the compound absorbs light, it is absorbing energy with the potential to break or rearrange bonds, produce light emission such as fluorescence or phosphorescence, or increase temperature.

** Light energy is inversely proportional to wavelenght therefore UV light (220 – 370 nm) with the shortest wavelenght has the highest energy.

Photolysis:

* Photodegradation is therefore dependent on the wavelenght of the light and also its intensity.

** Most degradation occurs through UV light which is present in sunlight and also artificial lighting such as fluorescent tubes (320-380 nm).

*** Prevention of photodegradation is achieved by suitable light opaque packaging such as foil wraps or amber glass.

!!! Since degradation is a chemical reaction, it is significantly influenced by the TEMPERATURE.

An increase in temperature produces an increase in reaction rate. Generally a 10 °C rise producing a twofold to fivefold increase in reaction rate.

"Arrhenius Equation" describes the link between the temperature and the reaction rate.

Arrhenius Equation

$\ln k = \ln A - (E_a / RT)$

$$\ln k = \ln A - \frac{E_a}{R}\frac{1}{T}$$

T = Temperature (°K)

R = Gas constant

E_a = Activation energy of reaction

A = The frequency factor

k = Reaction rate constant

Determination of this relationship allows the reaction rate constant to be determined at any temperature and from this it is possible to calculate the time taken to reach a predetermined level of degradation.

STABILITY TESTING

* Several factors affect drug stability.

** It is important within preformulation to test these factors and define storage and handling parameters that permit development studies.

*** A key factor in stability is time and it is important to initiate these studies as timely as possible.

Accelerated studies are normally conducted in an attempt to speed up time by deliberately stressing the compound through elevated temperatures and utilizing the relationships above to calculate stability at the proposed storage temperature.

One other feature is the container and closure system employed.

If the effect of humidity is under examination, then a sealed glass container, which prevents water vapor ingress, may provide a very different result to a polymeric container where water vapor and oxygen transmission rates maybe appreciable, especially over prolonged time periods.

Initial Studies:

Initial studies are directed at quickly determining suitable handling and storage parameters and a range of conditions usually accelerated will be tested possibly in combination with analytical development studies.

This dual approach determines stability and ensures that degradation products will be detected by the analytical method.

Initial Studies:

For solutions a quick accelerated approach is to autoclave at terminal sterilization conditions of 121 °C for 15 minutes.

Initial Studies:

Since a large number of parameters can influence stability, these can be examined either using a structured approach or statistically using a factorial approach.

Factorial approach can provide useful information related to the interaction of the various stability parameters.

Regulatory Stability:

If the compound looks as though it may progress beyond development, regulatory-compliant stability studies will be required for the active pharmaceutical ingredient (API).

The conditions are detailed in published guidelines and permit accelerated and real-time data to be presented.

Regulatory Stability:

There are requirements that the material is in its final container during the test and that three batches, which have been manufactured at close to final production levels, are tested to ensure consistency.

In addition, long-term testing at the proposed storage conditions should be for a minimum of one year or the proposed shelf life of the API.

COMPATIBILITY OF EXCIPIENTS

* Preformulation excipient compatibility studies can be performed to screen potential formulation mixtures.

** The current accepted technique is to mix the compound and excipient together in a 50:50 ratio and examine the mix using DSC over a temperature range that encompasses thermal changes due to both the drug and excipient.

*** If the resulting trace contains new thermal events or gross changes to existing events, this is indicative of an interaction.