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Approaches In Solubility Determination of Drug

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ABSTRACT

To describe the solubility related aspects in drug discovery and development with overview on factors affecting solubility of drug along with the special focus on the practical approaches of solubility determination. The solubility is essential factor in the initial stages of drug discovery and development. The determination of solubility gives an idea about the drug response prediction. The poor solubility results in ineffective response in experimental design. The use of solubility data in appropriate setting is very important before screening of drug. The biopharmaceutical classification system is of pH dependent used to classify drugs on the basis of pH dependent solubility and permeability. This article outlines solubility aspects in drug discovery and development with factors that influences solubility and methods to determine the solubility of drug with different models developed to predict solubility. Investigators are constantly searching for different approaches to determine and predict the solubility of drug. But still there are several work is being done by the investigators to increase the efficiency and accuracy to determine the solubility.

Keywords – Solubility, factors, permeability, screening, models.

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INTRODUCTION

The solubility of drug substance is an important parameter in the process of absorption. Solubility is fundamental tool in screening assays of drug because poor solubility results in the problems with reproducibility and unpredictable outcome. If drug precipitates before reaching to targeted site it would result in exposure of site with lower concentration of drug than intended which lead to ineffective response in experimental design.

In various phases of drug discovery and development the solubility data plays essential role. In early stages of drug discovery solubility is used to characterize compounds with certain chemical series as well as determine whether these compounds are soluble enough for structure activity relationship (SAR) screens. After SAR screens the solubility data is use to estimate ADME screens, preclinical and early clinical use. The determination of solubility plays important role in all phases of drug development. In order to be successful the solubility data should be use in appropriate setting. The solubility of ionized compound is meaningless. For determination of solubility of both ionizable and non ionizable compounds specific solid state is essential.

The knowledge of solubility is essential in pharmaceutical area because it consents the investigators the choice of the best solvent for drug or combination of drugs, and helps in conquering certain difficulties arising in the preparation of pharmaceutical solution. The article outlines the basic aspects relating solubility of drug along with practical approaches in solubility determination with overview on the factors affecting solubility of drug.

Solubility

Absolute or Intrinsic solubility is defined as the maximum amount of solute dissolved in given solvent under standard condition of temperature, pressure and pH. If a drug has poor aqueous solubility then it adversely affects the dissolution date. The solubility of drug can be explained in number of ways. According to U. S. Pharmacopoeia list the solubility of drug as number of milliliters of solvent requires dissolving 1g of solute. For certain drugs whose solubility exact solubility is unknown those drugs are described in approximate solubility terms. [1]

When solubility is less than 1-2 µg/ml in pH range 1-8, it is the matter of great concern. As a matter of fact that most drugs are weakly acidic or basic and It has been proved from various studies that solubility of these drugs is strongly pH dependent.

The dissolution rate and the release rate of a drug are essential to know for drug characterization. Poor aqueous solubility is likely to give rise to increased formulation difficulties during clinical development. Dissolution is the process by which a solid substance goes into solution and may

be regarded as being composed of two consecutive stages. Initially an interfacial reaction between solid and lattice for amorphous substances occurs and solvent breaks up the solid crystal for crystalline substances and opens the amorphous This creates cavities in the solvent, a so called phase change, molecules of solid become molecules of solute

Table 1: Approximate solubility terms [1]

Solubility Terms	Parts of solvent require for 1 Part of solute
Very soluble	Less than 1
Freely soluble	1 -10
Soluble	10 - 30
Sparingly soluble	30 -100
Slightly soluble	100- 1000
Very slightly soluble	1000 -10000
Insoluble	More than 10000

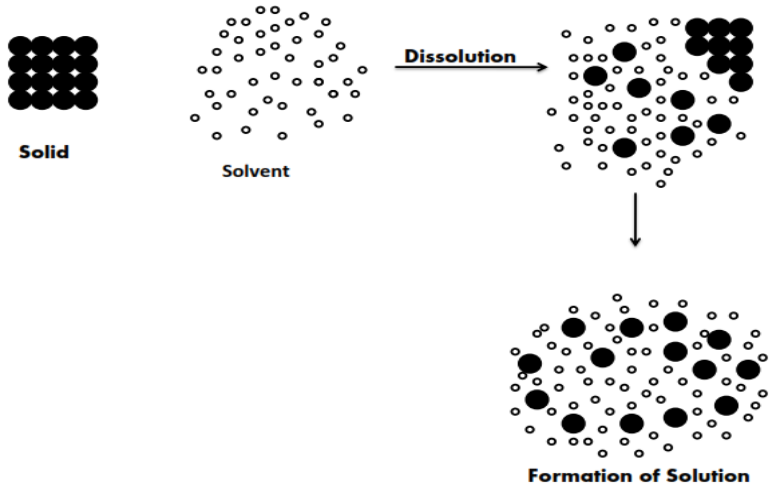

Figure.1: Dissolution of solid particles in liquid

Biopharmaceutical classification system

The BCS concept was developed by Gordon Amidon in 1995. The Biopharmaceutics Classification System is guidance for assessment of the drug absorption. It is classification system involving scientific framework of drug classification based on their aqueous solubility and intestinal permeability. There are three major pedestals of BCS that governs the rate and extent of drug absorption from dosage form.[2]

The Biopharmaceutical classification system was developed based on solubility and permeability. The pH dependent solubility is considered while classifying. The solubility class boundary is differing with regulatory authority guidelines. The class boundaries depend on the highest dose strength of drug. According to World Health Organization guidance an API is

considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media over the pH range of 1.2-6.8.

Table 2: Biopharmaceutical Classification System with examples

BCS Class	Description	Examples
I	High Solubility	Metoprolol Succinate
	High Permeability	Chloroquine Phosphate
II	Low Solubility	Ibuprofen
	High Permeability	Pioglitazone
III	High Solubility	Metformin HCl
	Low Permeability	Valsartan
IV	Low Solubility	Furosemide
	Low Permeability	Acetazolamide

According to U.S. Food and Drug Administration BCS guidance a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. A minimum of three replicate determinations of solubility at each pH condition is recommended according to European Medicines Academy BCS guidance a drug substance is considered highly soluble if the highest single dose administered as formulation is completely dissolved in 250 ml of buffers within the range of pH 1-6.8. The volume of medium estimates 250ml is obtained from protocol of bioequivalence study. [3]

Factors affecting solubility of drug

Surface area of drug particles

The changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size, as indicated

$$log\ \frac{S}{So} = \frac{2\gamma M}{2.303RTpr}$$

Where S is the solubility of small particles of radius *r*,

S0 is the normal solubility of a solid consisting of fairly large particles,

y is the interfacial energy,

M is the molecular weight of the solid,

p is the density of the bulk solid,

R is the gas constant and

T is the thermodynamic temperature.

The increase in solubility with decrease in particle size stops when the particles have a very small radius, and any more decrease in size causes a decrease in solubility. It has been suggested that this change arises from the presence of an electrical charge on the particles and that the effect of this charge becomes more important as the size of the particles decreases [4].

pH and pKa

This connection between pH and the solubility of ionized solutes is extremely significant with respect to the ionization of weakly acidic and basic drugs as they pass through the GIT and experience pH vary between about 1-8. This will influence the degree of ionization of the drug molecules, which in turn influences their solubility and their ability to be absorbed.[5]

]According to the Henderson-Hasselbach equation, the relationship between pH, pKa, and relative concentrations of an acid and its salt is as follows

$$pH = pKa + \frac{[\text{Ionized Drug}]}{[\text{Unionized Drug}]} \quad \text{For Acidic Drugs}$$

$$pH = pKa + \frac{[\text{Unionized Drug}]}{[\text{Ionized Drug}]} \quad \text{For Basic Drugs}$$

When the concentrations of salt and acid are equal, the pH of the system equals the pKa of the acid. This has some interesting propositions regarding the aqueous solubility of the acid, since the un dissociated form is much less soluble than its salt. Thus, in formulating the product, some balance must be struck between the more soluble salt form and the biologically active acid and factors other than pKa and pH must be considered. [6]

Temperature

The solubility of substances is a function of temperature. Most substances are endothermic, absorbing heat in the process of dissolution. For these substances, an increase in temperature results in an increase in solubility. The application of this aspect of solubility is of limited use to us, since pharmaceutical solutions must be administered at or near room or body temperature. It is more a factor to be considered for product storage than for formulation. [6]

Physical Characteristics

The interactions between neighboring molecules of crystal will depend on the packing arrangement of molecules of in the crystal. When the conditions under which crystallization is allowed to occur are diverse, some substances produce crystals in which the constituent molecules are aligned in different behavior with respect to one another in the lattice structure. [7] These Different crystalline forms of the same substance, which are known as polymorphs, consequently possess different lattice energies, and this difference is reflected by changes in other properties.

Solubilizing agent

These agents are capable of forming large aggregates or micelles in solution when their concentrations exceed certain values. In aqueous solution the centre of these aggregates

resembles a separate organic phase and organic solutes may be taken up by the aggregates, thus producing an apparent increase in their solubilities in water. This phenomenon is known as Solubilization. A similar phenomenon occurs in organic solvents containing dissolved Solublizing agents, because the centre of the aggregates in these systems constitutes a more polar region than the bulk of the organic solvent. If polar solutes are taken up into these regions their apparent solubilities in the organic solvents are increased. [8]

Practical approaches of solubility determination

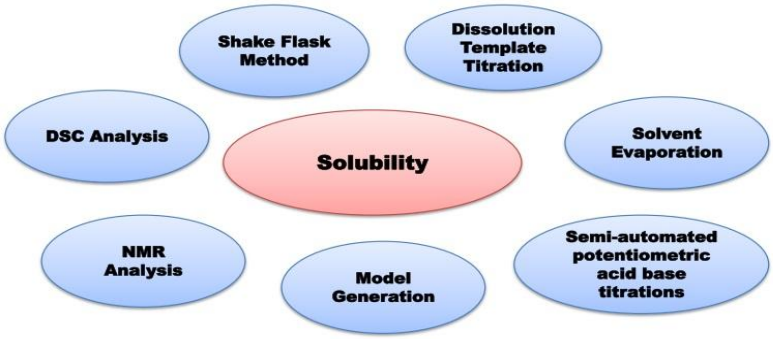

Figure.2: Methods for solubility Analysis

Shake flask Method

In the classic saturated shake flask method the concentration is determined by using UV spectroscopy. The first step is to determine specific absorptivity of drug at specific pH after that the plotting of calibration curve by making series of dilution according to beers lamberts' law limit. The slope will give the equation from which concentration can be calculated.

The drug which is to be examined is dissolved in 1-10ml of buffer. Three to six samples were prepared for compound.

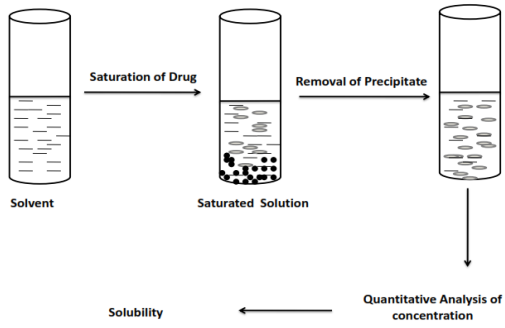

Figure.3: Saturated shake flask method

The solid is added in excessive amount for 48 hrs. The time for stirring depends on nature of compound if compound is unstable in such condition then time is less.[10] Due to excessive addition of solid the solvent becomes saturated and it precipitates. The resultant sample solution

is filtrated and diluted to limited concentration.[9] The absorption is measured with UV spectrophotometer. The concentration determined by equation obtained from calibration curve.

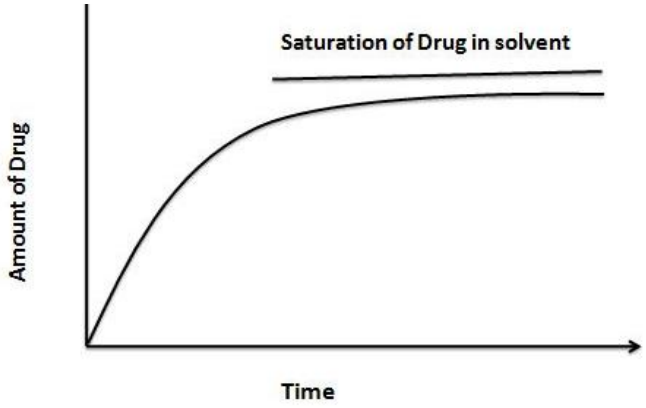

Figure.4: Saturation of drug in solvent after equilibrium attained

Dissolution Template Titration

A recent theory of dissolution kinetics was applied to acid base titration. The component model based thermodynamic method was developed. The aim was to determine diffusion layer, Interfacial layer concentration on saturated solution of compound agitated by acid base titration.

In this titration the addition of titrant agitates the saturated solution of ionized compound which results in dissolution of suspended particles. This procedure is slow and affected by different factors. It is essential to attain equilibrium before addition of titrant. The pSOL titrator is used for collection of data. The template used for this procedure is pre calculation titration curves. There are few parameters i.e. k, log P, pKa calculated by any commercial software. These parameters are provided for determination of intrinsic solubility. [11]

Semi-automated potentiometric acid base titrations

This method is generalized titration method to determine pH solubility profile. It requires few amount of sample. The process takes less time than shake flask method. But major drawback of this method that it is limited to ionizable compounds. [10]

Miniature device for solubility determination

A miniature device was created to measure solubility during drug development process. The device is having tygon tubes and multichannel cartridge pump which rest on pump which is connected to syringe filter. The drug solution added in the tubing with constant circulation and collected at syringe filter. The solubility values obtained are tested against shake flask method found to be effective. The collected filtrate analyzed by HPLC. [12]

Solvent Evaporation method

Solvent evaporation method is one of advanced methods for solubility determination the method involves robotic liquid handling, automated centrifugal separation and HPLC analysis. The drug dissolved in organic solvent and pour in 96 well plate. After evaporation of solvent the aqueous media is added. When saturated solution attains equilibrium it is filtered through plate analyzed with HPLC. The method uses little amount of sample and provide assay in three media in concentration range up to 250µg/ml.[13]

Nephlometric analysis

The analysis is mainly based on turbidometry. The sample is prepared by dissolution of small amount of solute in DMSO. All the dilutions are done in 96 well plate. The sample is prepared contain 5% DMSO with final volume up to 200ml. The sample prepared should be optimum for light scattering to be constant. The sample is placed in plate in a nephlometer apparatus for measuring the light scattering. The apparatus consist of laser beam as light source and detector. The result is plotted based on the turbidity and concentration is plotted along with the melting point.[14, 15]

DSC analysis

Differential scanning calorimetry techniques are commonly used to quantify the compatibility of drugs within polymeric delivery systems. Method of the DSC experiment, and in particular the relatively slow heating rates employed, bound its use to the measurement of drug solubility at the drug's melting temperature. The description has been made to apply hyper-DSC which involves extremely rapid heating rates, to calculate of the solubility of a model drug. [16]

NMR solubility analysis

The NMR method is fast, and sample preparation is simple if the formulation materials processed before time in larger batches. In addition, the process can be easily automated. Therefore, solubility determination by NMR provides an easy and practical approach to screening Discovery formulations.[17]

Solubility can be carried out using internal standard using isolated aromatic resonances, without a calibration curve, which makes using NMR for quantitation convenient and provides a time saving over the UV method. NMR method requires less amount of sample than UV. NMR solubility analysis is the relatively lower sensitivity compared with UV detection and mass spectrometry techniques, which limits analysis of samples having low solute concentrations.

Prediction of solubility from using different models

Based on fragments of substructures

This model predicts solubility as a sum of structural input such as contributions of atoms, bonds or larger substructures. This approach is based on principle that molecule properties are determined completely by molecule structure and estimated by input of fragments in the molecule. Fragment-based methods work finely for purely additional molecule properties where substructures have constant input to the property. [18] However this is not the case for solubility, where effects like electron donating or accepting contributions of substituent and intramolecular hydrogen bonding can play an essential role. Such complex effects cannot be properly described solely by fragment contributions. In other approach the fragment contributions approach presents the option of describing, at least to some extent, the effect of crystal packing.[19] That would otherwise be accessible only with expensive computations.[20] When application of fragment contribution methods for prediction of solubility, one needs to use quite a large number of fragments to get rational performance and this put high requirements on the number of data points essential for development of the model. This excludes the development of general fragment based models for smaller data sets.

Models based on molecular descriptors

Solubility prediction through Quantitative Structure–Property Relationships (QSPR) modeling is a growing area of modern pharmaceutical research, being compatible with both High Throughput Screening technologies and limited compound availability characteristic of early stages of drug development. The molecular descriptors in QSPR can be grouped into three categories:

1D (molecular weight, C logP, rotatable bonds),

2D (atom type counts, topological indices) and

3D (solvent accessible surface areas).

Most of them are obtained through analyzing 2D or 3D structures, or by conducting quantum mechanical and molecular mechanical calculations, The molecular descriptors that describe the energetic terms, namely, the lattice energy for crystal packing, the energy of forming cavity in solvent, and the solvation energy, are suitable to model.[21]

CONCLUSION

Solubility of a substance is one of the most essential factors for drug development. So that, accurate measurement and prediction of solubility in any media is become a critical task there were many methods developed by investigators to determine the solubility of drug using different approaches and analytical instruments to accurately determine amount of drug concentration in particular solvent. Among the methods discussed in above section some gives

good and accurate results. But still progress has to be made in this area to make solubility determination less time consuming.

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