SOLUBILITY AND DISSOLUTION FOR DRUG

INTRODUCTION

Solubility for Chemical

solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.

Dissolution for Chemical

What is dissolution, exactly? In simple terms it is the process of a solute dispersing/dissociating in a solvent, forming a molecular-level, chemically and physically homogenous dispersion, called a solution. In contrast to solubility, when we speak of dissolution, it is understood that rate is a major consideration. Solubility is an endpoint.

IMPORTANCE OF SOLUBILITY

Methods Pertaining to Drug Solubility

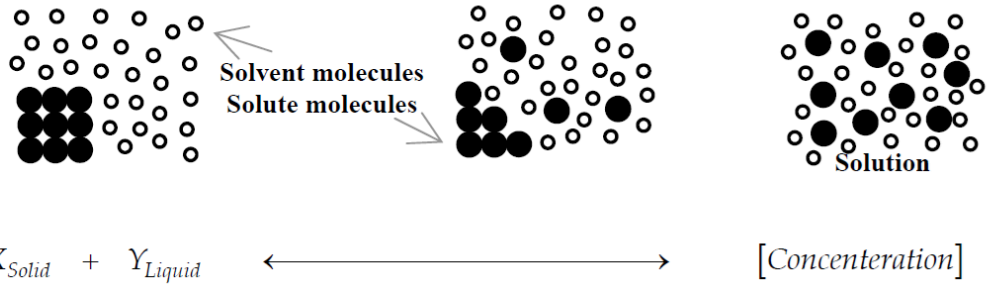
Solubility of a drug is one of its important physico-chemical properties. More attention has been paid to the aqueous solubility since water is the unique solvent of biological systems. It is obvious that a drug should be reached to its receptors in the body through the aqueous and non-aqueous media.

The solubility in non-aqueous solvents is not too important from clinical viewpoint however these solubilities play curious roles in drug discovery and development investigations. So, Most of drugs are synthesized in non-aqueous media and/or extracted from natural sources using non-aqueous extracting solvents. Different polymorphs of some drugs could be produced from their crystallization using organic solvents.

On the other hand, the solubility behaviour of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water-soluble

compounds has dramatically increased. Although solid solutions have tremendous potential for improving drug solubility, 40 years of research have resulted in only a few marketed products using this approach. With the introduction of new manufacturing technologies such as hot melt extrusion, it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance.

Therefore, when talking about solubility, there are two concepts which might be confused with each other: solubility and dissolution. The term solution (i.e. thermodynamic solution) is used to define the state which is thermodynamically stable and shows the neat result of an equilibrium between a solute (the compound which is going to be dispersed molecularly in another medium which is called solvent) and its dissolved form in the medium. The dissolving process is the migration of the molecules of the solute to the solvent medium and makes the solution which after reaching a steady state is called homogenous solution and can be represented by the following equilibrium:



How much a solute is molecularly dispersed in the solvent is called solubility and the rate of dissolving is called dissolution. Hence, the solubility value is a thermodynamic property while the dissolution rate is a kinetic one. In other words, time has no effect on solubility value and is not important in its related subjects, but it is important in dissolution related subjects.

The solubility is important in stable forms including liquid formulations and dissolution is important in transient states including the release of the drug from its formulation to biological fluids and permeability. In pharmaceutical sciences, especially in formulation, designing a stable liquid formulation requires the knowledge on the solubility value and an effective drug delivery to the body mostly depends on the dissolution rate which is affected by the solubility. However, they both affect each other based on Noyes-Whitney equation.

$$\frac{\mathrm{d}m}{\mathrm{d}t} = A\frac{D}{d}(C_s - C_b)$$

Where:-

- **dm/dt** = solute dissolution rate ($kg.s^{-1}$)
- **m** = mass of dissolved material (kg)
- **t** = time (s)
- **A** = surface area of the solute particle (m^2)
- **D** = diffusion coefficient ($m.s^{-1}$), which is related, in part, to the viscosity of the solvent.
- **d** = thickness of the concentration gradient (m)
- $\mathbf{C_s}$ = particle surface (saturation) concentration (kg or moles/L)
- $\mathbf{C_b}$ = concentration in the bulk solvent/solution (kg or moles/L).

Note, based on the discussed topics, solubility and dissolution are in relation with each other, but not the same. So, they must not be used in place of each other as the consequences can be awful! For example, a drug substance might be highly soluble, but dissolves slowly (or vice versa). So, in the formulation of such compounds, the difference between solubility and dissolution must be considered. So, solubility is an endpoint representing dissolution capacity. Dissolution rate can be expressed using the Noyes–Whitney equation.

NEED OF IMPROVING SOLUBILITY

There are variety of new drugs & their derivatives are available. But less than 40% of lipophilic drugs candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmaco-dynamic activities.

The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action.

The basic aim of the further formulation & development is to make that drug available at proper site of action within optimum dose.

Solubility of drug is largely due to,

1. Polarity of the solvents, that is, to its dipole moment. A polar solvent dissolve ionic solutes and other polar substances.
2. The ability of solute to form hydrogen bond with solvent.
3. Also depends on the ratio of the polar to non polar groups of the molecule.

- ❖ As the length of a non-polar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases.
- ❖ Straight chain monohydric alcohols, aldehyde, ketones, and acids with more than four or five carbons cannot enter into the hydrogen bonded structure of water and hence are only slightly soluble.

TECHNIQUES OF SOLUBILITY ENHANCEMENT

Process of solubilisation

1) The separation of the molecule of the solvent to provide space in the solvent for solute.

2) The breaking of intermolecular ionic bonds in the solute.

3) The interaction between the solvent and the solute molecule or ion.

Measuring solubility

In pharmaceutical practice, one important task is to measure the solubility of solids in liquids. The following precautions serve as guidelines when running solubility tests:

• The solvent and the solute must be pure.

• The sample is removed for analysis after confirmation of saturation.

• Sample separation from saturated solution with un-dissolved solute must be reliable and satisfactory.

• The method used to analyses the solution must be reliable and reproducible.

• Temperature must be adequately controlled

Traditionally, the equilibrium solubility at a given pH and temperature is determined by the shake flask method.

According to this method the compound is added in surplus to a certain medium and shaken at a predetermined time, usually 24h or longer.

The saturation is confirmed by observation of the presence of un-dissolved material.

Saturation can also be reached if the solvent and excess solute is heated and then allowed to cool to the given temperature.

Some solutions can hold a certain amount of excess solute in the solvent, commonly called a supersaturated solution.

This often occurs when the saturated solution is cooled slowly.

Super saturation for salts can be avoided by slow cooling and continuous shaking of the sample during cool down.

After filtration of the slurry a sample for analysis can be taken.

Both filtration and analysis should be performed under the same temperature as the solubility determination and under conditions to minimize loss of volatile components.

Often the sample is diluted to prevent crystallization.

The amount of solute contained in the sample is determined by an appropriate method affected by the nature of the solute/solvent and by the concentration.

Due to the growing need to determine solubility faster new devices and automated methods have been developed.

The shake-flask method is the most accurate method to determine solubility but it is time consuming.

1) Miniaturized shake-flask method can be used for almost all compounds. Its precision and throughput was proven greater the potentiometric method. Up to 20 compounds per week can be studied with one set-up. The miniaturized shake-flask method needs more drug though to ensure an equilibrium between solid and dissolved drug.
2) Semiautomated potentiometric acid/base titrations method is a very economical method and is able to create a pH/solubility profile with one single determination. Only 100μg of poorly soluble compound is needed. The time required for a potentiometric titration vary depending on the compound, whereas the time consumption with a shake-flask method is fixed but overall it requires more time. However, this method is limited to ionizable compounds.
3) A computational screening model is used for the prediction of intrisic solubility, which is based on lipophilicity and molecular surface areas.
4) Another devise, simply called miniature device, was developed for measuring aqueous and non-aqueous equilibrium solubility during drug discovery. With only ≈ 1mg of compound, it was possible to determine the entire pH-solubility profile. This devise even got similar solubility values compared to other conventional shake-flask methods.

The drug can be prepared in another way;

1- added in alkaline solution like sodium hydroxide, ammonium hydroxide.
2- A solution of β- Cyclodextrin is then added to dissolve the joined drug.
3- The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point.
4- At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound.
5- The precipitate is then filtered and dried.

Biopharmaceutics classification system

- The Biopharmaceutics classification system (BCS) is a framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. BCS introduces an in vitro-in vivo correlation and is the first step for approving a product based on in vitro dissolution tests rather than bioequivalence studies in human subjects. As a result unnecessary human experiments can be avoided thus lowering development costs of new drugs.
- Solubility is based on the highest dose strength and is considered highly soluble if soluble in 250 mL or less of aqueous media over the pH range of 1.0-7.5, otherwise considered to be poorly soluble.
- Permeability is based indirectly on the measurement of the rate of mass transfer across the human intestinal membrane. Models capable of predicting the extent of intestinal absorption in humans may be used as alternatives. A drug substance is considered highly permeable when the intestinal absorption is determined to be 90% or higher, otherwise considered to be poorly permeable.

APPLICATION OF SOLUBILITY

1) Solubility is represents a fundamental concept in fields of research such as chemistry, physics, food science, pharmaceutical, and biological sciences.
2) The solubility of a substance becomes specially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance.
3) Solubility is commonly used to describe the substance, to indicate a substance's polarity, to help to distinguish it from other substances, and as a guide to applications of the substance.
4) Solubility of a substance is useful when separating mixtures.
5) Moreover, solubility and solubility-related properties can also provide important information regarding the structure of drug substances, and in their range of possible intermolecular interactions.

Conclusion

The aqueous solubility of drug is often a limiting factor in developing most desirable dosage form. A highly solubilized formulation is highly desired to minimize dissolution limited absorption. Often, these early stage formulations become the backbone for the later stage commercial formulations. But still there has been a lot of research going on in this topic and many newer and advanced methods are used to enhance the solubility of the drug.

Why is solubility test important?

The size and polarity of an unknown compound and the presence of fundamental or acidic functional groups can be inferred by solubility measures. The solubility of a compound in aqueous acid or base requires the compound's ionisation and, thus, a chemical reaction.

What causes solubility?

Usually, the solubility of a given solute in a given solvent depends on temperature. Solubility tends to equate with rising temperature for several solids dissolved in liquid water. They vibrate faster as water molecules heat up, and are better able to communicate with and split the solution apart.

Does pH affect solubility?

The solubility of the solute can affect the pH of an aqueous solution. If the solution's pH is such that no net electrical charge is borne by a specific molecule, the solution also has minimal solubility and precipitates out of the solution.

Does temperature affect solubility?

The solubility increases with temperature for certain solids that are dissolved in liquid water. The rise in higher temperature kinetic energy helps the solvent molecules to break apart the solute molecules that are kept together by intermolecular attractions more effectively.

How does temperature and pressure affect solubility?

In this reaction, an increase in pressure and a rise in temperature contributes to greater solubility. To decrease the partial pressure, an increase in pressure results in more gas particles entering the liquid. The solubility will, therefore, increase.