Solubility and Dissolution Enhancement: An overview

V.Rajesh Babu¹, S.H.Areefulla¹, V.Mallikarjun²
¹Department of Pharmaceutics, MESCO College of Pharmacy, Hyderabad, A.P. India-500006
²Department of Pharmaceutics, SR College of Pharmacy, Warangal, A.P. India-506009

Received on: 20-09-2009; Revised on: 16-10-2009; Accepted on:15-12-2009

ABSTRACT
Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The dissolution rate is directly proportional to solubility of drugs. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. The poor solubility and poor dissolution rate of poorly water soluble drugs in the aqueous gastro intestinal fluids often cause insufficient bioavailability. Other in-vivo consequences due to poor aqueous solubility include increased chances of food effect, more frequent incomplete drug release from the dosage form and higher inter-patient variability. Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development, nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. Aqueous solubility of any therapeutically active substance is a key property. As it governs dissolution, absorption and thus the in vivo efficacy. The present review deals in detail about the different techniques used for the improvement of the solubility and dissolution rate of poorly water soluble drugs include, Inclusion complexation with cyclodextrins, Size reduction technology, Functional polymer technology and Solid dispersions etc.

Keywords: Solubility, Dissolution, Cosolvent, Solid dispersions and Cyclodextrins.

INTRODUCTION

Solubility¹-² is defined in Quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In Qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may express as Parts, Percentage, Molarity, Molality, Volume fraction and Mole fraction. Solubility is an important determinant in drug liberation and absorption and hence plays a key role in its bioavailability. For a drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic components. The mechanism of solubilization involves the property of surface active agents to form colloidal aggregates known as “micelles”. When surfactants are added to a liquid at low concentrations, they tend to orient at the air-liquid interface. As additional surfactant is added, the interface becomes fully occupied, and the excess molecules are forced into the bulk of the liquid. At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form oriented aggregates or micelles; this change in orientation occurs rather abruptly, and the concentration of surfactant at which it occurs is known as the “critical micelle concentration”. The solubility of a substance is the amount of it that passes into solution when equilibrium is established between the solute in solution and the excess (un dissolved) substance. The solution that is obtained under these conditions is said to be saturated. A solution with a concentration less than that at equilibrium is said to be sub-saturated. Solution with a concentration greater than equilibrium can be obtained. These are known as super-saturated solutions.

The transfer of molecules or ions from a solid state into solution is known as dissolution. In essence, when a drug dissolves, solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase. If particles remain in the solid phase once they are introduced into a solution, a pharmaceutical suspension results. In the vast majority of circumstances, only drugs in solution can be absorbed, distributed, metabolized, excreted, or even exert pharmacologic action. Thus, dissolution is an important process in

*Corresponding author.
V. Rajesh Babu
MESCO College of Pharmacy
Mustaidpura, Karwan Road,
Hyderabad-500006
A.P. India.
Tel.: + 91-9989818594
Telefax: +91-
E-mail:rajeshbabavemula@gmail.com

141-145
the pharmaceutical sciences. Fundamentally the process is controlled by the relative affinity between the molecules of the solid substance and those of the solvent. The extent to which the dissolution proceeds under a given set of experimental condition is referred to as the solubility of the solute in the solvent. The extent to which the dissolution proceeds under a given set of experimental condition is referred to as the solubility of the solute in the solvent. The use of poorly soluble drugs has a number of drawbacks such as increasing the dosage, administration frequency and the resultant occurrence of side effects. Furthermore, the rate-limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall; it is however, important to improve the oral bioavailability of poorly water-soluble drugs by improving their dissolution rate and solubility.

Factors affecting Solubility:

The solubility of a compound depends upon the physical and chemical properties of the solute and the solvent as well as various other factors like:

1. Temperature: Solubility of material can be increased by raising temperature of the solvent.

2. Dielectric constant: the solubility is a function of dielectric constant of polar and non-polar medium. Most, often with hydrophobic drugs, the solubility decreases with increasing dielectric constant.

3. pH: pH of a substance is related to its pKa and concentration of the ionized forms of the substance by the equation: pH = pKa + log [A^-]/[HA] Where, pKa = dissociation constant

4. Solvent: Solubility is greatest between materials with similar polarities and this is defined by hydrogen bonding.

• Weak hydrogen bond liquid: For example, Hydrocarbons, Chlorinated hydrocarbons and Nitro-hydrocarbons.

• Moderate hydrogen bond liquid: For example, Ketones, Esters, Ethers and Glycol mono-ethers.

• Strong hydrogen bond liquid: For example, Alcohols, Amines, Acids, Amides and Aldehydes.

5. Particle size: The size of the solid particle influences the solubility because as particle becomes smaller, the surface area to volume ratio increases the surface area, which allows a greater interaction with the solvent.

6. Polymorphism: the capacity for a substance to crystallize in more than one crystalline form is polymorphism. Polymorphs can vary in melting point. Since the melting point of the solid is related to its solubility, then polymorphs will most likely have different solubilities.

7. Salts: salts selection is often a sought after approach to improve dissolution rate and oral absorption of poorly soluble drugs. Water solubility increases in order of selected counter ions as follows: Iodide < Tosylate < Glycolate < Mesylate < Acetate < Chloride

8. Pressure: the solubility of liquids and solids in water are not appreciably affected by increased pressure. The solubility of gases significantly increases with pressure. According to Henry’s law, the increase in solubility is directly proportional to the increase in pressure.

9. Stearic factors: solubility is also affected by dimension of the structure and its configuration.

METHODOLOGY:

The ability to increase the aqueous solubility and dissolution can be a valuable aid to increasing efficacy or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility and dissolution of a solid drug solute:

- **Use of co-solvent**: weak electrolytes and nonpolar molecules frequently have poor water solubility. Their solubility usually can be increased by the addition of water miscible solvent in which the drug has good solubility. This process is known as cosolvency, and the solvents used in combination to increase the solubility of the drugs are known as cosolvents. The cosolvent system works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. Cosolvents are employed not only to enhance solubility of the drug, but also improve the solubility of volatile constituents used to impart a desirable flavor and odor to the product. The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxylethylene glycols can be used. Ternary diagrams are used to visualize where maximum solubility occurs when more than one solvent is used.

- **Hydrotropy method**: Hydrotropy is a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several slats with large anions or cat ions that are themselves very soluble in water result in “salting in” of non-electrolytes called “hydrotropic salts” a phenomenon known as “Hydrotropism”. Hydroscopic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agents and solute. The term “Hydrotropy” has been used to designate the increase in aqueous solubility of various poorly water soluble compounds due to the presence of a large amount of additives, concentrated solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been employed to enhance the aqueous solubility and dissolution of a large number of drugs.

- **Micronization**: The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill). The process is also called as “Micro-milling”. Examples of drugs whose bioavailability have been increased by micronization include griseofulvin and several steroidal and sulpha drugs.

- **Nanisolation**: It is a process whereby the drug powder is converted to nanocrystals of sizes 200-600 nm, e.g. Amphoteric B. The nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid, typically called “Nanosuspension”. There are three basic technologies currently in use to prepare nanoparticles:

  1. Pearl milling
2. Homogenization in water (wet milling as in a colloid mill)
3. Homogenization in non-aqueous media or n water with water-miscible liquids.

- **Change in dielectric constant of solvent:** The addition of a cosolvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect a substance has on the energy needed to separate two oppositely charged bodies. A vacuum is arbitrarily given a dielectric constant of one. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium.

- **Amorphous forms:** have atoms or molecules randomly placed as in a liquid and have higher thermodynamic energy than corresponding crystalline forms. Solubilities as well as dissolution rates are generally greater.

- **Chemical modification of the drug:** by the addition of polar groups like carboxylic acids, ketones and amines can increase solubility by increasing hydrogen bonding and the interaction with water.

- **Lipid based formulations:** The formulations include lipid solutions, lipid emulsions, micro-emulsions and self dispensing lipid formulations (SDLF). Bioavailability enhancement with lipids occurs due to the solubilization of the poorly soluble drugs. Lipid solutions consist of drug dissolved in vegetable oil or medium chain triglycerides. The lipid emulsions and SDLF essentially comprise of a lipid and a surfactant mixture. These formulations are mainly employed for oral use. Co-administration of lungs with lipids influences their path of absorption. The high lipophilicity facilitates absorption into the intestinal lymphatics and then to the systemic circulation, thus avoiding first pass metabolism. The presence of surfactant in this formulation also causes the enhanced absorption due to membrane induced permeation changes.

- **Use of surfactant:** Surfactants are amphipathic in nature, meaning it has polar end (the circular head) and non-polar end (the tail). When a surfactant (e.g. Tween-80, sodium lauryl sulphate, propylene glycol, polynvinyl pyrrolidone K30) is placed in water, it will form micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubilize the complex.

- **Inclusion complexes or Clathrates:** Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. β-Cyclodextrins can solubilize water insoluble drugs. In the same way, the solubility β-cyclodextrin can be significantly enhanced by the addition of some water soluble drugs, such as sodium salicylate or water soluble polymers such as hydroxypropyl methyl cellulose (HPMC) to the aqueous solution. Other complexes like inorganic coordination chelates, metal-olefin, and molecular complexes can also be increased as complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. These complexes can be prepared with β-cyclodextrin (β-CD) and HP-β-CD: the required quantity of β-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60°C for 2 hours. The dried mass is sieved through mesh no.120.

- **Alteration of pH of solvent:** pH of solvent when reduced causes solubility enhancement. A combined effect of pH and complexation on solubilization is also synergistic in nature.

- **Use of Hydrates or Solvates:** A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts, commonly referred to as “Solvate”, is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as “Hydrate”. A compound not containing any water within its crystal structure is termed “Anhydrous”. Aqueous solubilities of anhydrous forms are higher than the hydrate forms.

- **Use of soluble Prodrug:** wherein the physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionicizable moieties into the parent compound to improve aqueous solubility. The ‘post hoc pro-drug approach’ (prodrug of established drugs) has been successfully used to improve water solubility of corticosteroids, vitamins and benzodiazepines.

- **Application of ultrasonic waves:** solubility increase by use of ultrasonic vibrators is also possible. An oscillator of high frequency (100-500 KHz) is used and device is known as “Pohlman whistle”.

- **Functional polymer technology:** Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, “Resinate”, can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from the resinate on exposure to the physiological fluids. In other word, the dissolution rate of poorly soluble, ionizable drug like cationic, anionic and amphoteric actives can be enhanced by this technology. This can also be heat applicable to heat sensitive materials and oils. The functional polymers are DUOLITE™ AP 143 which is a cation exchange resin and AMBERLITE™ IPR69 which is an ion exchange resin.

- **Porous microparticle technology:** In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology applied as HDDSM (Hydrophobic Drug Delivery System). These drug particles provide large surface area for increased dissolution rate. The solid form has a proprietary spray drying technology that allows the size and porosity of the drug particles to be engineered as desired. Alliance Inc of USA and Mektar Therapeutics are also in the process of incorporating this technology.

The Hydrophobic Solubiization Technology (HST) for insoluble or poorly soluble drugs uses a lecithin and gelatin based water soluble coating to improve dissolution rate and hydration of lecithin-gelatin coat forms micelles which improve the oral
bioavailability of the insoluble drugs. Macro-particles produce Hysol, a co-polymer which acts as a simple non-ionic surfactant and solubilizes poorly soluble compounds 200-500 fold their water solubility. Labopharm’s polymeric nano delivery system comprises micelles low cost nano carriers. Each micelle comprises a novel construction of polymers that associate to form nanomeric vehicles and solubilize the drug.

Controlled precipitation technology: In this process, the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. The stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer.

Supercritical fluid recrystallisation: Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids (e.g.: carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperature, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle size.

Spray freezing into liquid (SFL): This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO2, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or Hydrofluoroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders use of acetone or the solvent increases drug loading and decreases the drying time for lyophilization. The dissolution rate is remarkably enhanced from the SFL powder containing amorphous nanostructure aggregates with high surface area and excellent wettability.

Evaporative precipitation into aqueous solution (EPAS): The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent and then dissolved into an aqueous medium containing precipitators (such as nifedipine is dissolved in alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose.)

Precipitation: In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called “Hydrosol”.

Selective Adsorption on insoluble Carriers: A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are – the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media.

Solid dispersion (SD) method: solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by Fusion method Solvent evaporation method and Fusion-Solvent method. SD reduces the particle size and changes the micro-environment of the drug particle, increases the rate of dissolution and absorption and thus changes the biopharmaceutical properties of poorly water soluble drugs. The solid dispersion method, by which a drug is dispersed in a carrier to make it amorphous, is one of the pharmaceutical approaches most commonly employed to enhance bioavailability of poorly water soluble drugs. Various pharmaceutical approaches for the preparation of SDs, including co-precipitation, lyophilization, spray drying, solvent evaporation, fusion and powder mixing methods, have been reported. The enhanced dissolution rate of drugs from solid dispersions is mainly based on four different mechanisms:

Wetting of the drug is improved by direct contact of the drug with the hydrophilic matrix.

The saturation concentration around small particles is higher than around large particles.

The surface area is increased.

The drug has higher energy in the amorphous state than in the crystalline state, through which the saturation concentration is increased.

An important mechanism is the reduction of the drugs particle size to the micro-crystalline or molecular level for rapid dissolution and absorption.

Classification of solid dispersions:
1. Simple eutectic mixtures
2. Solid solutions
3. Glass solutions of suspensions
4. Compound or complex formation between the drug and the carriers
5. Amorphous precipitation of drug in crystalline carrier.
CONCLUSION:
A lot of research has been carried out in this area and for better clinical efficiency, some improvements in solubility and dissolution rate has to be made generally. The basic approaches followed by all the currently available technologies engaged in the solubility and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy. Solubility and Dissolution are an important phenomenon in pharmaceutical sciences as it plays an important role in formulation of different dosage forms. Solubility, in simple words, is the continuous interaction of two or more compounds to form homogeneous molecular dispersion and Dissolution, in simple words, is the process by which a solid phase goes into a solution phase. A study of solubility also yields information about the structure and inter-molecular forces of drugs. Use of solubility characteristics in bioavailability, pharmaceutical actions and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Dissolution enhancement of poorly water soluble drugs constitute an innovative approach, which overcome the problems of solubility and dissolution rate limiting step and provide a quick onset of action.

ACKNOWLEDGEMENTS:
The authors wish to thank Dr. Mohib Khan (Principal), Ms. P. Nivethithai (Asst. Professor) and Ms. Syeda Rana Nikhat (Asst. Professor), MESCO College of Pharmacy, Hyderabad, for their constant encouragement, support and inspiration to carryout this study.

REFERENCES:
12. V. S. N. Murty, “Dissolution enhancement of itraconazole by lyophilization technique”, The Indian pharmacist may-2008