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Der Pharmacia Lettre, 2010, 2(2): 310-318
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Enhancement of Solubility: A Pharmaceutical Overview

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Abstract

The study on solubility yields information about the structure and intermolecular forces of drugs. Use of the solubility characteristics in bioavailability, pharmacological action and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. General parameters affecting solubility are particle size, shape and surface area physicochemical properties of drugs, physical forms of drugs, solvents, pH of the medium, temperature and use of surfactants.

Keywords: Solubility, pH, temperature.

INTRODUCTION

Poorly soluble drugs present a problem in pharmaceutical formulations. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly soluble, making them poor candidates as new drugs. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. Various methods to improve the dissolution of poorly soluble drugs have been reported. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[1-5]

Solid dosage medicaments have to face several barriers and loss at sites in its sequential movement during gastrointestinal absorption takes place. Parenteral administration posses certain advantages if immediate physiological action is needed from a drug which usually can be provided by injecting an aqueous solution.

Mechanism of Solubility

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined 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 homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction.[6-8]

Spontaneous passage of poorly water soluble solute molecules into an aqueous solution of surfactant is termed as solubilisation. As difference molecules interact, both repulsive and attractive forces are operative. The intramolecular forces and valence bond are given below:

Intramolecular forces

- Dipole-dipole interaction (Keesome interactions)
- Dipole- induced dipole interaction(Debye interactions)
- Induced-dipole interaction-Induced-dipole interaction(London dispersion forces)
- Ion-dipole interaction
- Hydrogen bonds

Valence Bonds

- Electrovalent Bond
- Covalent Bond
- Homo-polar Bond
- Ionic Bond
- Heteropolar Bond

Factors influencing solubility of Drugs[9-12]

- **Solute related**: Nature of solute- Size, Shape and surface area
  Physicochemical properties- melting point, heat of fusion, molar volume and pKa
  Physical forms- Salt, crystalline state, and polymorphism
- **Solvent related**: Nature of the solvent, i.e., Polarity, pH of the medium, volume of solvent employed.
- **Environment related**: Temperature and pressure.
- **Formulation related**: Other ingredients.

Influence of particle size, shape and surface area

Solubility increases with decreasing particle size. Since surface area of solids in contact with the medium increases, rapid dissolution is obtained. This increase in solubility ceases when the particle size reaches a particular point. Hence, particle size is critical and beyond a particular value, the solubility of solid decreases. Such a change arises because of the presence of an electrical charge on the particle, which is predominant in small particles. Symmetric molecules may be less soluble than unsymmetrical ones. If crystals are compact, they possess high lattice energy and therefore, will be lowered.

Influence of physicochemical properties of drugs

The melting points of solids are indicators of molecular cohesion and hence are useful for predicting the trend in a series of similar compounds. The other parameters are molar heat of fusion, entropy of fusion and molar volume. These are discussed in the theories of solutions.

Dissociation constant of drug is useful in predicting the extent of ionisation depending on the pH of the environment. In general, the ionised species have greater aqueous solubility than the un ionised species.

Physical forms of drugs

Some of the general principles are:

- Amorphous forms of drugs have greater aqueous solubility than the crystalline forms.
- Among crystals, metastable forms of drugs have greater aqueous solubility than the stable forms.
- Anhydrous forms of drugs have greater aqueous solubility than hydrates forms.
- Organic solvates of drugs have greater aqueous solubility than unsolvated forms.
- salt forms of drugs have greater aqueous solubility than non-salt forms, provided common ion effect is not influenced.

Influence of Solvents

In the formulation, water or vegetable oils are normally used as solvents. The solubility of the drug is due to the polarity of the solvent that is dipole movement. In addition, hydrogen bonding between solute and solvent is essential. Therefore, structural features and presence of nonpolar and polar groups in the molecule are important. Syrups and liquid oral solutions are manufactured using water. The simple maxim of like-dissolve-like is the guiding principle.

Table 1: Influencing of solvent on solubility: Intra venous

Solvent	Nature of Solute	Examples of Drug	Dosage forms
Water(Polar)	Polar Substances	Vitamin B1&B2	Elixer
	Strong Electrolytes	Sodium chloride	i.v. infusion
	Weak Electrolytes	Sodium Phenobarbitone	Injection
	Nonelectrolytes	Dextrose	i.v. injection
Oil(nonpolar)	Nonpolar substances	Progeteron	Oil injection

Poorly water soluble drugs are normally dissolved in non-aqueous vehicles such as liquid paraffin, arachis oil and ethyl oleate. In most cases, a mixture of solvents is used for maximum solubility of drugs.

Influence of pH of the medium:

Most of the drugs are weak electrolytes. Weak acids and weak bases undergo ionisation in solution. Drugs are more soluble in water when they are in ionised form. Unionised drugs are poorly water soluble. The extent of ionisation of drug in a solution depends on the dissociation constant and the pH of the medium. For example, alkaloidal salts are more soluble in acidic pH and begin to precipitate as the pH increases. On the other hand, phenobarbitone is more soluble in alkaline Ph and begins to precipitate as the pH decreases.

The relationship between pHp(of the preparation), solubility and pKa value of the drug is expressed as :

$$\text{Acidic drugs: } pHp = pKa + \log s\text{-}s_{0/}\, s_0$$

$$\text{Basic drugs: } pHp = pKa + \log s_{0/}S\text{-}\, s_0$$

Where pKa = dissociation constant of drug, s_0 = solubility of unionised form, moles/litre, S= overall solubility of drug,moles/litre

If pH of the solution is known, solubility of drugs can be calculated using equations(1) and (2). Similarly minimum pH can be determined in order to maintain a solution of known concentration without precipitation.

Influence of Cosolvents

Frequently a solute is more soluble in a mixture of solvents rather than in a single solvent. The solvents, which are used to increase the solubility of a drug in water, are called as cosolvents. The phenomenon is known as cosolvency. Ethanol, propylene glycol, glycerine, PEG 300, and PEG 400(polyethylene glycols) are the commonly used cosolvents, since these are water miscible. The concept of cosolvency is applied in the manufacture of liquid dosage forms such as syrups, elixirs, injections, creams and lotions. In addition, solvents such as benzyl alcohol, dimethyl sulphoxide(DMSO), Dimethyl acetamide(DMA) and Dimethyl formamide(DMF) are used as supplementary solvents.

Influence of Temperature

Increase in temperature involves the absorption of heat and it influences the solubility of the drugs.

- If the dissolution involves positive hit of solution, a rise in temperature leads to an increase in solubility of solid. Example is potassium nitrate in water.
- Conversely if the dissolution of a solid involves the liberation of heat then an increase in temperature leads to decrease in solubility. Example is calcium acetate in water.

Influence of Surfactants

Surface active agents enhance the solubility of poorly water-soluble drugs due to the formation of micelles. This phenomenon is known as micellar solubilisation. For Example, Solubility of procaine is enhancing by 25% in aqueous buffer, owing to the formation of surfactant micells.

Influence of other ingredients

Several ingredients of diverse nature are added in the formulation of dosage forms. The solubility of a sparingly soluble electrolyte is decreased by the addition of a second electrolyte that posses a similar ion to the first. The phenomenon is known as common ion effect. The behaviour is predicted from the concept of solubility product.

Effect of other electrolytes

The solubility of a sparingly soluble electrolytes may be increased by the addition of a second electrolyte that does not possess same ions. The ions produced by dissociation of electrolytes are strongly associated with oppositely charged ions.

Factors affecting Solubility[13-26]

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:

- Temperature
- Concentration of the solute
- pH of the solvent
- Molecular structure of the solute
- Complex formation
- Types of Solute and Solvent
- Salting out(electrolytes and non-electrolytes)
- Combined effect of solvent and pH
- Pressure

- Surfactants(Wetting agents)
- Particle size of solute
- Common ion effect
- Dielectric Constant

Temperature
Increasing the temperature of material solubility enhancement is often possible.

Dielectric Constant
The solubility is a function of dielectric constant of polar and nonpolar medium. Most often, with hydrophobic drugs, the solubility decreases with increasing dielectric constant.

pH
pH of a substance is related to its pKa and concentration of ionised and un-ionised forms of the substance by the equation:

$$pH = pKa + \log [A^-/HA]$$

where pKa = Dissociation constant.

If the substance is brought outside its pKa (pH value where half of the substance is ionised and half un-ionised), then solubility will be changed because of introduction of new intermolecular forces, mainly ionic attraction forces.

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

Weak hydrogen bond liquid
Hydrocarbons, chlorinated hydrocarbons, and nitro-hydrocarbons.

Moderate Hydrogen bond liquid
Ketones, esters, ethers, and glycol mono-ethers.

Strong Hydrogen bond liquid
Alcohols, amines, acids, amides and aldehydes.

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.

Polymorphism
The capacity for 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.

Salts
Salt selection is often a sought after approach to improve dissolution rate and oral absorption of poor soluble drugs. Water solubility increases in order of selected counter ions as follows:

Iodide<tosylate<glycolate<mesylate<acetate<chloride

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 Henery's law, the increase in solubility is directly proportional to the increase in pressure.

Stearic factors
Solubility is also affected by dimension of structure and its configurations.

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

Use of co-solvent
The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, polyethylene glycol, glycerine, sorbitol and polyoxyethylene glycols can be used.

Hydrotrophy method
Hydrotrophy is a solubilisation process whereby addition of a large amount of 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 salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism".

Hydrotropics solutions donot show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.

Change in dielectric constant of solvent
The addition of a co-solvent 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 of 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.

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

Complexation Methods (inclusion complex or clathrates)
Considerable increase in solubility and dissolution of the drugs has been achieved by the use of Betacyclodextrins. Betacyclodextrin can solubilise water insoluble drugs. In the same way, the solubility of beta cyclodextrin can be significantly enhanced by the addition of some water soluble drugs, Such as sodium salicylate, or water-soluble polymers such as hydroxyl propyl 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 force such as London forces, hydrogen bonding and hydrophobic interactions.

Alteration of pH of solvent

pH of solvent when reduced causes solubility enhancement combined effect of pH and complexation on solubilisation is also synergistic in nature.

Use of surfactactants

surfactants are amphipathic in nature, meaning it has polar end (the circular head) and a non –polar end (the tail). When a surfactant is placed in water, it will form micelles. A non –polar drug will partition into the hydrophobic core of the micelle and the polar tails will solubilise the complex.

Use of hydrates or solvates

A crystalline compound may contain either a stoichimetric or nonstochiometric amount of solvent. Non stochometric adducts, such as inclusions, involves entrapped solvent molecules.with in the crystal lattice. A stoichiometric adduct, commonly referred to a solvate, is a molecular complex that has incorporated the crystallising solvent molecules nto 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 and higher than the hydrate forms.

Use of Soluble prodrug

Where in the physic chemical properties of the drug are improved by bioreverssible chemical alteration. The most common prodrug strategy involves the incorporation o polar or ionosable moiety into the parent compound to improve aqueous solubility. The post hoc pro drug approach has been successfully used to imrove water solubility of corticosteroids, vitamins and benzodiazepines.

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.

Application of ultrasonic waves

Solubility increases by use o ultrasonic vibrators. A n oscillator of high frequency(100-500KHz) is use and device is known as Pohlman whistle.

Solid dispersion method: It reduces the drug particle size and changes the micro-environment of the drug particle, increase the rate of dissolution and absorption and thus changes the Biopharmaceutical properties of poorly alter soluble drugs. Solid dispersions are prepared by fusion, solvent evaporation an fusion solvent method.

Spherical crystallization [27]

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement solubility of poorly water soluble drugs. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time.

Methods for solubility Determination

No universally acceptable method for determining solubility is known. Solubility of solids in liquids may be determined by phase solubility analysis, conductance, solute method and turbidity method. For determination of solubility of sparingly soluble salts several methods available are: Electrical method such as determination of solubility product by electromotive force method, and determination of conductivity of the solution; colorimetric method and radioactive method[28-32].

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