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A Review: Solubility Enhancement and its Technique

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ABSTRACT

Solubility are often defined because the amount of solute dissolved during a solvent at certain conditions to yield a single ¬phase system. Solubility of active pharmaceutical ingredients is taken into account the foremost parameter to urge the most desired drug concentration generally circulation so as to realize the specified therapeutic effect. Poor aqueous solubility considered the most problem occurs within the formulation progress of latest chemical entities; additionally to the quality improvement; solubility is that the main dispute for formulation scientists. The drug must appear as solution at the location of absorption so as to be absorbed. Many physical or chemical modification techniques are wont to improve the solubility of low aqueous soluble drugs, in addition to other techniques like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant and complexation. The selection of the solubility improvement methods depends on drug characteristics, location of absorption and therefore the features of the administered dosage form.

KEYWORDS: *Solubility, BCS Class, Bioavailability, Solvent*

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INTRODUCTION

Solubility is one of the important phenomenon having very effective and significant role in the formulation of various dosage forms. Solubility of any compound in a particular solvent can be defined as the concentration of a solute in a saturated solution at a certain temperature. It is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at specified temperature. As the solubility increases bioavailability also increases. The solubility of drug molecule is a critical factor for determining its usefulness since the solubility indicates the amount of compound that will dissolve and hence the amount available for absorption into the systemic circulation. The molecule having low aqueous solubility is subjected to dissolution rate limited absorption within the gastrointestinal residence time.

Modified Noyes-Whitney equation, gives some idea how the dissolution rate of even very poorly soluble compound might be improved to minimize the limitation to oral availability.

$$dC / dt = AD(Cs - C) / h$$

Where,

dC / dt is the rate of dissolution,

A is the surface area available for dissolution,

D is the diffusion coefficient of the compound,

Cs is the solubility of compound in the dissolution medium,

C is the concentration of drug in the medium at time t,

h is the thickness of the diffusion boundary layer adjacent to the surface of dissolving compound.

The solubility of molecules can also be expressed by variety of concentration such as quantity per quantity, percentage, parts, molarity, molality, mole fraction, milliequivalents, and parts of solvent required to solubilize for one part of solute as explained in U.S pharmacopeia which is shown in table:

Descriptive Term	Part of Solvent Required Per Part of Solute
Very Soluble	Less than 1
Freely Soluble	1 to 10
Sparingly Soluble	30 to 100
Slightly Soluble	10,000 and over
Very Slightly Soluble	1000 to 10,000
Practically Insoluble	10,000 and over

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (B.C.S.)[3]

According to the BCS, drug substances are classified in four different class:

A. Class I drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Rate of absorption is higher than rate of excretion. e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

B. Class II drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. The absorption for class II drugs is usually slower than class I and occurs over a longer period of time. In vitro-In vivo correlation (IVIVC) is usually excepted for class I and class II drugs. e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

C. Class III drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

D. Class IV drugs exhibit a lot of problems for effective oral administration. Fortunately, extreme examples of class IV compounds are the exception rather than the rule and are rarely developed and reach the market. Nevertheless a number of class IV drugs do exist. e.g. Taxol, Hydrochlorothiazide.

Class	Solubility	Permeability	Examples
I	High	High	metoprolol, diltiazem
II	Low	High	glibenclamide, phenytoin, danazol, mefenamic acid,
III	High	Low	ranitidine, acyclovir, neomycin B, atenolol, and captopril.
IV	Low	Low	hydrochlorothiazide, taxol

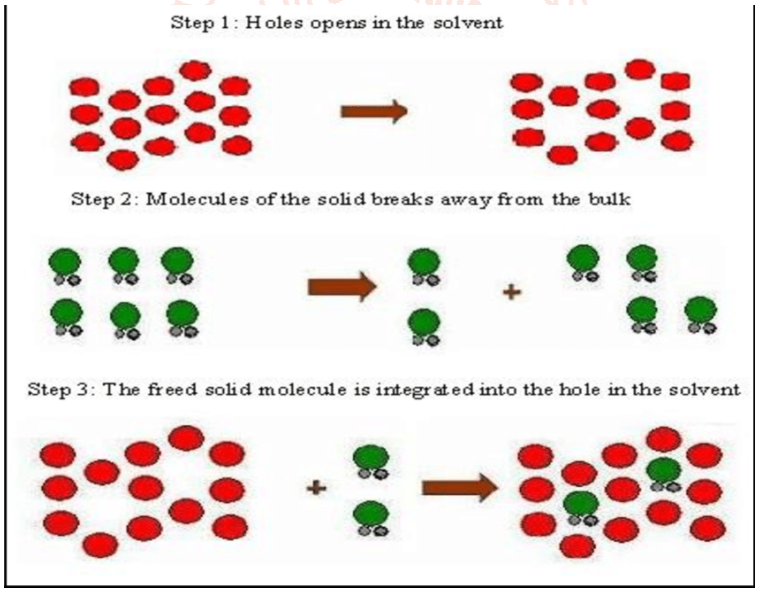
Table 1.1: Biopharmaceutical Classification System (B.C.S.)

PROCESS OF SOLUBILISATION[4,5]

The process of solubilisation involves the breaking down of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

During the process, breaking of solute bond occurs leading to the formation of holes. When solubilisation process occur solid molecules break down because of breaking of inter molecular bonding and integrating of freed solute molecule in the solvent.

The different steps involved in the process of solubilisation can be illustrated in the figures as given below:



FACTORS AFFECTING ON SOLUBILITY

Particle Size[5]

area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where,

S is the solubility of infinitely large particles

S0 is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle

T absolute temperature in degree Kelvin.

R universal gas constant.

Temperature[6]

As the temperature is increased than the solution process absorbs energy and the solubility will be increased but if the solution process releases energy then the solubility will decrease with increasing temperature. A few solid solutes are less soluble in warm solutions. For examples all gases, solubility decreases as the temperature of the solution increases.

Pressure[7]

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have no effect on solubility.

pH [8]

pH of a substance is related to its pKa and concentration of ionised and un-ionised forms of the substance bythe 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.

Nature of the Solute and Solvent[9]

While only 1 gram of lead chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility of these two substances is due to the result of differences in their nature.

Molecular Size[10]

The molecular size will affect the solubility of the drug as larger the molecule or higher the molecular weight of the drug, less is the solubility of that substance. In organic compounds, the amount of carbon branching increases the solubility because more branching will reduce the size of molecule and also make it easier for the solvent to solvate the molecules.

Polarity[11]

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces which give the non-polar solvent a chance to solvate the solute molecules

Polymorphs[12]

The ability of a substance to crystallize in more than one crystalline form is polymorphism. Polymorph is an agent having ability to crystallize in more than one crystalline form. It is possible that solid can crystallize in different forms or polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility.

METHOD OF SILUBILITY ENHANCEMENT

1. Particle size reduction[13]

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level.

2. pH Adjustment[14]

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.11-14 Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.

3. Use of Surfactant[15]

A conventional approach to solubilize a poorly soluble substance is to reduce the inerfacial tension between the surface of solute and solvent for better wetting salvation interaction. A wide variety of surfactants like Tweens, Spans, Polyoxyetylene glycerides, Polyoxyetylene stearates and Synthetic block copolymer etc. are very successful as excipient and carrier for dissolution enhancement.

Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristic and micellar solubilization of the drugs. Micelles are supramolecular self assemblies of macromolecular where unimers are held by non-covalent interactions. The core of the micelles solubilizes drugs whereas the corona/shell allows for their suspension in aqueous media.

4. Hydrotropy[16]

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

5. Nanonization[17,18]

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc. There are many examples of nanonization of drugs.

7. Cosolvent[19]

Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. For example, Procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d-α- tocopherol (vitamin E) and oleic acid. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil.

8. High Pressure Homogenization[20]

Disso Cubes manufacture involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently nanosuspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from microparticles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. The possible interesting features of nanosuspensions are:

1. Increase in saturation solubility and dissolution rate of drug
2. Increase in adhesive nature, thus resulting in enhanced bioavailability
3. Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility
4. Possibility of surface modification of nanosuspensions for site-specific delivery
5. Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market.

9. Supercritical Fluid Recrystallization (S.C.F.)[21]

Those fluidsare referred to as supercritical fluids which are having temperature andpressuregreater than its critical temperature and critical pressure so as they are acquireproperties of both gas and liquid.The best example of this is carbon dioxide.SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure.As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug

10. Co-Grinding or Co- Micronization[22,23]

Cogrinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small amount of water is extremely effective to improve its apparent solubility with maintenance of drug crystallinity to some extent 20. Small particles produced by milling or micronization have increased surface area and expected to have enhanced dissolution rate. However, energy added to reduce particle size results in increased Van der Waal's interactions and electrostatic attraction between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate.

Co-micronization of drugs by using excipients like microcrystalline cellulose can be used as an alternative to reduce or eliminate cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a reduction in particle-particle agglomeration or by reducing Van der Waal's interactions. Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of microcrystalline cellulose-Drug mixture

11. Self-Emulsifying Drug Delivery System[24]

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). This isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water which improves dissolution and absorption of lipophilic drugs. Rate of emulsification, the emulsion size distribution and the charge of resulting droplets are the parameters for self-emulsifying performance. One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT.

12. Liquisolid Technique[25]

Liquisolid formulation is a technique that utilizes hydrophobic drugs dissolved in non-volatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerine, propyleneglycol, or polysorbate-80 (well known as Liquid Medications) mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone- K30 using coating materials like silica. The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained.

13. Spray Drying Technique[26,27]

Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination. This method represents one of the most employed methods to produce the inclusion complex strating from a solution. The mixture pass to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form.

14. Solid Dispersion[28]

The term solid dispersion refers to a group of solid product consisting of at least two different compound, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Pharmaceutical polymer are used to create this

matrix and their selection is based on many factor, including Physicochemical Pharmacokinetics constraints.

Conclusion

The solubility of the drug in the GIT is the rate limiting step in the absorption of poorly soluble drugs and hence its bioavailability at its site of action. For this reason, various technologies could be implemented to achieve this goal. The selection of the proper method to increase the solubility of a specific product depends On the propertios of given product, the dosage form requirement and the special requirement for both drug and excipient in addition to the cost and the yield of given process.

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