

# A Review On The Solubility Enhancement Technique For Pharmaceutical Formulations

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#### Abstract

Several properties of potential drug molecules such as the solubility of the drug molecule must be determined prior to developing dosage forms as the solubility of a drug molecule is one of the key criteria in achieving an effective drug concentration. Solubility is expressed as the number of parts by volume of solvent necessary to dissolve one part by weight of a solid or one part by volume of a liquid according to pharmacopoeias. Poor water solubility is a critical issue in the formulation development with more than 40% of the novel chemical entities being insoluble in water. Different strategies have been used to enhance the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant and so. The properties of a drug, site of absorption, and required dosage form characteristics helps in the selection of solubility enhancing techniques.

# 1.0 Solubility

Solubility is defined in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid or one part by volume of a liquid according to pharmacopoeias. Solubility occurs under dynamic equilibrium and results from the simultaneous and opposing processes of dissolution and phase joining. Solubility equilibrium occurs when dissolution and phase joining processes proceed at a constant rate. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. (Martin, 2011)

To understand the quality control and drug delivery issues for pharmaceutical formulations, accurate determination of the aqueous solubility of a drug and its components is important. The ability to measure a compound's aqueous solubility accurately is influenced by the properties of the solvent, the compound's physicochemical properties and also the control of the solubility measurement parameters. The key to acquiring accurate and reliable values is to control the factors mentioned during the measurement of solubility. (Aulton, 2002)

The solubility of a substance can be described in a plethora of different ways including units of mole fraction, molality, mole ratio, concentration and so. The USP and BP characterize the solubility with regard to quantification regardless of which solvent was used and the criteria have been listed as given in Table 1.1.

Solubility	Part of solvent required per part of solute	
Very soluble	Less than 1	
Freely soluble	From 1 to 10	
Soluble	From 10 to 30	
Sparingly soluble	From 30 to 100	
Slightly soluble	From 100 to 1000	
Very slightly soluble	From 1000 to 10,000	
Practically insoluble	10,000 and over	

Table 1.1 : USP and BP Solubility Classification

A framework to characterize a drug according to its intestinal permeability and the drug's aqueous solubility has been established and it is known as the Biopharmaceutics Classification System (BCS). This system presents an in vitro-in vivo correlation (IVIVC) which happens to be the primary step in validating a product based on the product's in vitro dissolution tests instead of bioequivalence studies done in human subjects. The solubility of a pharmaceutical product is based on the strongest dose and if the pharmaceutical product solubilize in 250 mL or fewer of aqueous solutions between a pH of 1.0 to a pH of 7.5, the product is termed as extremely soluble, otherwise, it will be considered as weakly soluble. The estimation of a volume of 250 mL comes from a standard

bioequivalence study protocols which prescribes a drug product to be administered to volunteers that are fasting, with a glass of water. Drugs are classified into four different classes by the BCS which are class I (high permeability and high solubility), class II (high permeability but low solubility), class III (low permeability but high solubility) and lastly class IV (low permeability and low solubility). Figure 1.1 shows the four classes of BCS and their example of drugs. (Mohd, Mohd et al., 2010)

#### **1.2 Importance of Solubility**

Poor drug solubility will result in a low dissolution rate resulting in a low bioavailability of orally administered drugs. The degree and rate at which a drug's active component enters the systemic circulation and allowing the drug to get to the action site, is known as bioavailability. When the bioavailability of a drug is low, it will result in a therapeutic potential that is minimal leading to unsatisfactory clinical results. In certain circumstances, dose escalation is required to achieve therapeutic drug concentrations in the blood, which might result in topical toxicity in the gastrointestinal tract (GIT) and reduce patient adherence to the therapy. As a result of having poor water solubility, most of the new drugs pose a difficulty in formulating into drug delivery systems. This is the reason why achieving an enhanced solubility of weakly water soluble drugs is an important preformulation step in the pharmaceutical product development research. (Jambhekar and Breen, 2013)

#### **1.3 Factors Affecting Drug Solubility**

A drug candidate molecule's solubility is determined by the solid's particle form, the composition that makes up the solvent medium, the nature of the solvent medium and also the system's temperature and pressure.

#### 1.3.1 Molecular structure of solute

The individual ions, molecules or atoms of a solute interact with the solvent when it is dissolved. The solute then becomes solvated allowing the solute to independently disperse throughout the mixture. However, the process is not as unidirectional as it seems. The ion or molecule may cling to the particle in a process called crystallization if the ion or molecule collides with the surface of an undissolved solute particle. As long as there is extra solid present, crystallisation and dissolution will occur, resulting in a dynamic equilibrium similar to the one that keeps a liquid's vapour pressure constant. (Harwood, William et al., 2007)

#### 1.3.2 Nature of solvent/ co-solvents

In terms of their natures, the solubility of two or more distinct compounds varies greatly. For example, at ambient temperature, only one gram of lead can dissolve in 100 ml of water while 200

grammes of zinc chloride may dissolve in the same quantity of water. The discrepancies in solubilities observed between these two compounds are related to their different natures. (Martin, 2011)

#### 1.3.3. Polymorphism

A crystal consists of atoms, ions or molecules arranged in a lattice or a standard geometric arrangement which repeats in three dimensions continuously. A solid chemical compound can be found in several crystalline forms which is also referred as polymorphism. Since the melting point of polymorph varies, they have varied solubility as their melting points are related to their solubility. Generally the differences in solubility between different polymorphs is usually between two to three folds due to the minor alterations in free energy. (Martin, 2011)

#### 1.3.4 Particle size of the solid

The solubility of solid particles are usually influenced by their size because as the particle size of a solid decreases, the ratio of surface area to volume of the solid particle increases. The bigger surface area of the solid particle results in the particle to interact better with the solvent. (Myrdal and Yarkowsky, 2007)

#### 1.3.5 Polarity

As a general rule, molecules of nonpolar solute dissolve in nonpolar solvent systems while molecules of polar solute dissolve in polar solvent systems. Consequently, if the nature of the solvent is polar it should possess both the negative and positive ends. So, if the solute is also polar in nature then it should also consists of the positive and negative ends causing the solute molecule's positive end to get attracted to the solvent molecule's negative end. Dipole-dipole interactions are the sort of intermolecular force that causes these types of interactions.. (Chaudary, Nagaitch et al.,2012)

#### 1.3.6 Temperature

With the rise in temperature, the energy is absorbed by the solution process and thus the solubility will be increased. However, in cases where the solution process releases the energy when there is a temperature rise, the solubility will be reduced. Generally, when there is a rise in the temperature of a solution, the solid solute's solubility also increases. (Myrdal and Yarkowsky, 2007

#### 1.3.7 Common ion effect

When a compound that is soluble possesses the same ion as the precipitate that is mixed into a solution and causes the solubility of the ionic precipitate to decrease, it is known as the common ion

effect. This manner is a result of Le Chatelier's principle which states when an equilibrium is no longer balanced, the reaction will try to restore balance by shifting (Harwood, William et al., 2007)

#### **1.4 Solubility Enhancement Techniques**

Poor aqueous solubility is one of the most common issues faced during the formulation of new chemical entities (NCEs) and also in the formulation of generics. Some pharmaceutical industry-developed NCEs are practically insoluble in water. To accomplish an enhanced solubility of weakly soluble drugs, a myriad of different techniques have been utilized including chemical and physical modification of the drug and other methods for instance crystal engineering, formation of salt and so. Choosing the right method to be used to for solubility enhancement of a drug is influenced by the drug's absorption site, the drug's properties and the necessary characteristics of dosage form.

# 1.4.1 Particle size reduction

Reducing a drug's particle size is one of the methods frequently used to achieve an enhanced solubility. When the size of a particle decreases, it cause the particle's ratio of surface area to volume to increase resulting in the particle to have a better interaction with the solvent hence increasing its solubility. One example of reducing the particle size using conventional methods is spray drying in which it depends on mechanical stress to separate the active compound. An alternative conventional method that can be employed to reduce particle size include micronization in which it is accomplished by techniques of milling such as by utilizing a jet mill. The absorption of drugs like griseofulvin and fenofibrate have been improved by applying the micronization technique. Consequently, their improved digestive absorption also improves their bioavailability and clinical efficacy. (Vemula, Lagishetty et al., 2010)

#### 1.4.2 Solid Dispersion

When a drug that is hydrophobic and a hydrophilic matrix form a group of solid products, these solid products are known as solid dispersions which can be prepared by employing a few methods for instance the method of hot-melt extrusion and also the method of solvent evaporation. (Sinha, Ali et al., 2010)

### 1.4.3 Nanosuspension

One technology that is employed to drugs that have poor solubility and are insoluble in oils and water, is the nanosuspension technology. This technology produces a biphasic system consisting of surfactants that helps to stabilize drug particles that are of nano size for either topical or oral use and even administration parenterally. In nanosuspensions, the mean particle size is anywhere between 200 nm to 600 nm and the distribution of the particle size is typically smaller than one

micron. The formulation of nanosuspensions uses a myriad of different methods that includes media milling, technique of precipitation, homogenization under high pressure in water or in media which are nonaqueous and also combining the method of high-pressure homogenization and precipitation. (Muller et al, 2012)

### 1.4.4 Supercritical Fluid (SCF) Process

Reducing the particle size by using supercritical fluid (SCF) processes happens to be a different nanosizing technique and solubilization. Fluids possessing a higher temperature and a higher pressure than its critical temperature and pressure are referred to as supercritical fluids. This greater pressure and temperature allows the supercritical fluid to demonstrate the characteristics of both a liquid and a gas. Since SCF are extremely compressible, small changes in pressure can dramatically modify the characteristics of mass transport and density of the fluid which are key factor in determining its solvent power at near critical temperature. The drug particles tend to recrystallized at much smaller particle sizes once they are solubilized in the SCF. The precision and versatility displayed by the SCF processes allows the drug particles to be micronized within narrow particle size rages and usually to submicron levels. The formulation of nanoparticulate suspensions with particles of five to 2000 nm in diameter has been demonstrated using CSF processes. (Sunkara and Kompella, 2012)

#### 1.4.5 Cryogenic Techniques

The goal of the development of cryogenic techniques was to achieve an enhanced rate of drug dissolution by formulating drug particles that are nanostructured and amorphous drug with a greater porosity degree in conditions with extremely low temperature. The sort of injection device, the placement of the nozzle and the cryogenic liquid composition can all be used to describe cryogenic inventions. After cryogenic processing, a plethora of different drying methods such as atmospheric freeze drying, lyophilization and spray freeze drying can be employed to obtain the dry powder. (Surasarang and Williams, 2016)

# 1.4.6 Micellar Solubilization

Utilizing surfactants is an example of the primary methods used to improve the performance of dissolution of weakly soluble drugs. The incorporation of surfactants is to stabilise suspensions of drug and to achieve an enhanced dissolution of lipophilic drugs by lowering the surface tension. Micelle forms when the surfactant's concentration passes their critical micelle concentration (CMC), causing drugs to be entrapped within the micelles. The formation of micelles is referred to as micellization and which enhances the solubility of weakly soluble drugs. (Ranger-Yagui at al., 2005)

#### 1.4.7 Hydrotrophy

Hydrotrophy is a method of enhancing the aqueous solubility of a solute by adding a significant quantity of another solute which is the hydrotropic agent. Hydrotropic agents are generally organic salts that are ionic and made up of salts of alkali metals of different organic acids. The term hydrotrophy refers to the increase in water solubility caused by the presence of a substantial number of chemicals. Complexation that requires the hydrotrophic agents like sodium acetate to moderately interact with the poorly soluble drugs relates the mechanism of solubility enhancement of hydrotrophy methods. (Roy and Moulik, 2002)

#### 1.4.8 Crystal Engineering

The ability of a drug to be wetted by luminal fluids and the drug's particle size is the key in determining the amount of surface area accessible for dissolution of the drug. This particle size is determined by crystallisation conditions as well as comminution processes such as fluid energy milling and impact milling. The production of hydrates and solvates to increase the dissolution rate is also part of the crystal engineering method. There is a possibility to trap solvent molecules within the lattice during the crystallisation process. The crystal formed is referred to as hydrate if the solvent employed is water, and solvate if any other solvent is used. (Blangden, Matas et al. 2007)

#### **Solvent Evaporation**

Solvent evaporation method is an example of the solid dispersion method. Solvent evaporation method dissolves both the drug and the carrier in a common solvent and the solvent is then evaporated to produce a solid solution. The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, the disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing the organic solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent and the difficulty in reproducing crystal forms. (Sinha, Ali et al., 2010)

### Microemulsion

On the other hand, microemulsions are mixtures of oil, surfactant and water that form spontaneously in contrast to ordinary emulsions which require the high shear conditions. One of the advantages of microemulsions is that they are thermodynamically stable and their formation is facilitated by the ultralow interfacial tension of these systems, which leads to the formation of extremely small droplets of the dispersed phase. These microemulsions can take different forms which include, among others, oil, water, and oil/water bicontinuous microemulsions. Microemulsion

domains are usually characterized by the construction of a ternary-phase diagram. Three components are the basic requirement to form a microemulsion which are two immiscible liquids and a surfactant. The majority of microemulsions use oil and water as immiscible liquid pairs. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. (Gibaud and Attivi, 2012)

# Literature review on solubility enhancement techniques

The Table 2 below summarized the solubility enhancement techniques studies found in the literature.

No	Model Drug	Solubility Enhancement Technique	Comments	Reference
1	Fenofibrate	Micronization	Micronized fenofibrate shows that the increase in dissolution was greater than ten fold.	M. Vogt, K. Kunath, and J. B. Dressman, "Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations."
2	Celecoxib	Solid dispersion	A solid dispersion containing 20% PVP with celecoxib demonstrated an enhanced solubility of celecoxib.	Gupta, Kakumanu, and Bansal, "Stability and solubility of celecoxib-PVP amorphous dispersions: a molecular perspective."
3	Naproxen	Nanosuspension	The enhancement in the absorption rate by nearly 4-fold	G. G. Liversidge and P. Conzentino, "Drug particle size reduction for

# Table 2: Summary of solubility enhancement techniques studies found in the literature

			was associated with the	decreasing gastric irritancy and
			reduction in naproxen particle	enhancing absorption of naproxen
			size.	in rats."
4	Spironolactone	High Pressure	The results of the study showed	P Langguth A Hanafy D Frenzel
		Homogenization	improved dissolution rate and	et al "Nanosusnension
			hispusilability of spiropolastone	formulations for low soluble drugs
			bioavailability of spironolactorie.	tormulations for low-soluble drugs.
				pharmacokinetic evaluation using
				spironolactone as model
				compound."
5	Ketoprofen	SCF Process		
			The results showed that the	L. Manna, M. Banchero, D. Sola, A.
			composition of the tablets	Ferri, S. Ronchetti, and S. Sicardi,
			determines the mechanism of	"Impregnation of PVP
			drug release and that working	microparticles with ketoprofen in
			with low drug content was	the presence of supercritical CO2."
			deemed important to	
			significantly enhance the	
			dissolution kinetics.	
				C. H. Hsu, Z. Cui, R. J. Mumper, and
6	Glyburide	Micellar	Antidiabetic drugs that are	M. Jay,
		solubilisation	very poorly soluble like	"Micellar solubilization of some
7	Glimepiride	Glimepiride	glyburide, glimepiride, and	poorly soluble antidiabetic drugs."
			pioglitazone could be	
8	Pioglitazone		dissolved up to 5.24. 4.27.	
-			and 7.06 mg/ml	
	<b>-</b>		A very high solubility of up	
9	Rosiglitazone			

			to about 15 mg/mL could be	
10	Gliclazide		obtained for gliclazide	
11	Carbamazepine	Spray freezing	The corey freezing into liquid	Hu L Johnston KD Williams PO 2rd
			newdors domonstrated an	"Spray freezing into liquid (SEL)
			powders demonstrated an	spray neezing into iiquid (SFL)
			increased rate of dissolution in	particle engineering technology to
			comparison to the bulk	enhance dissolution of poorly
			carbamazepine.	water soluble drugs: organic
				solvent versus organic/aqueous co-
				solvent systems."
12	Raloxifene	Solid dispersion	The solubility and rate of	Tran TH, Poudel BK, Marasini N,
			dissolution of raloxifene was	Woo JS, Choi HG, Yong CS, Kim JO.
			enhanced significantly with the	"Development of raloxifene-solid
			preparation of solid dispersion	dispersion with improved oral
			of the drug using the	bioavailability via sprav-drving
			microwave-induced fusion	technique "
			method	
			methou.	
13	Atorvastatin	Microemulsion	Microemulsion method had	Rana H. Jesadiva B and Mandal S:
			significantly improved the	Development of "Microemulsion
			solubility of atomastatin	for solubility enhancement of
				Atomicstatin colours "
			Calcium.	ALOIVASLALIN CAICIUM.
14	Clopidogrel	Microemulsion	By employing microemulsion	Patel, V., Kukadiya, H., Mashru, R.,
			method, the enhancement in	Surti, N., & Mandal, S.

			solubility by 80.66 times of clopidogrel was achieved.	"Development of microemulsion for solubility enhancement of clopidogrel."
15	Etoricoxib	Solid dispersion	The solid dispersions prepared with lactose showed better dissolution profile in comparison to the solid dispersions with mannitol and sucrose.	Abhisekh Das, Amit Kumar Nayak, Biswaranjan Mohanty, Satyabrata Panda. "Solubility and Dissolution Enhancement of Etoricoxib by Solid Dispersion Technique using Sugar Carriers."

# Conclusion

Poor drug solubility will result in a low dissolution rate resulting in a low bioavailability of orally administered drugs. A number of drugs that are available in the pharmaceutical industry are poorly soluble and requires solubility enhancement as a limited solubility profile would result in poor bioavailability. The various strategies and methods described above can be used either by itself or in combination with other methods to enhance the solubility of poorly soluble drugs. The key in ensuring that the aims of a good formulation are accomplished is to choose a proper solubility enhancement method.

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