



A COMPLETE REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUE

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Abstract: Solubility is the most important Parameter to achieve the desired concentration of drug in systemic circulation for a pharmacological response. Poorly water-soluble drugs substances are required for high doses to reach therapeutic plasma concentrations after the oral administration. Water is the most important solvent for pharmaceutical liquid formulations. Low aqueous solubility is one of the major problems that occur with the formulation development of new chemical entities. The weakly acidic and weakly basic drug has poor aqueous solubility therefore various techniques are used to improve the solubility of poorly water-soluble drugs which include chemical modification, micronization, pH adjustment, co-solvency, complexation, micellar solubilization solid dispersion, hydrotropic etc. The purpose of this review article is to describe the solubilization technique for effective absorption and improved bioavailability. Any drug is to be absorbed when it is present in the form of an aqueous solution at the site of absorption.

Keywords: Solubility enhancement, Solubility, pH, co-solvent

I. INTRODUCTION

As more discussed it was not a completely solved issue, solubility or dissolution enhancement techniques remain a more Kinetic field for the researchers in the formulation of science. In recent years, the equipment of drug discovery has caused a reasonable shift in biopharmaceutical properties. Solubility & dissolution is basic fundamental concepts of physical & chemical science which include the biopharmaceutical & pharmacokinetic consideration in the therapy of any medicine. Pharmaceutical companies have been primarily employing two strategies:

- 1) Rational drug design (RDD) and,
- 2) High throughput screening (HTS) for drug discovery.

In these two strategies lead compounds are identified based on their screening in an environment concerning a biological system. Rational drug design is generally lead to compounds with a higher molecular weight eventually resulting in poor permeability & the high throughput screening are generally lead to compounds with increased lipophilicity and molecular weight which appropriately gives poor solubility characteristics. Drugs those have lipophilicity property that is a little or a bad thing. This property is expressed as Log P which gets about the drug is getting too lipophilic. The permeability and solubility characteristics had been helpful to classify the drug under four classes mention in Biopharmaceutics Classification System (BCS). The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids cause insufficient

bioavailability. Particularly class II substances, the bioavailability may increase with increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. Hence uptake of poorly soluble drug cannot be completed within the time at absorption site due to slow dissolution rate & maybe lead to possibilities of gastric decomposition of the drug due to longer GI residence time. Nowadays quantitative BCS has highlighted the importance of transit flow, in addition to solubility and permeability, on the drug absorption process. E.g. rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration & to avoid side effects of exerting a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. The BCS defines three dimensionless numbers- dissolution number (D_n), dose number (D_o) and absorption number (A_n) to characterize drug substances. These numbers are a combination of physicochemical properties of the drug and physiological application to dose by considering the volume of fluid required to dissolve the total dose. Drugs with $D_o < 1$ are classified as highly soluble, whereas those with $D_o > 1$ are termed poorly soluble.

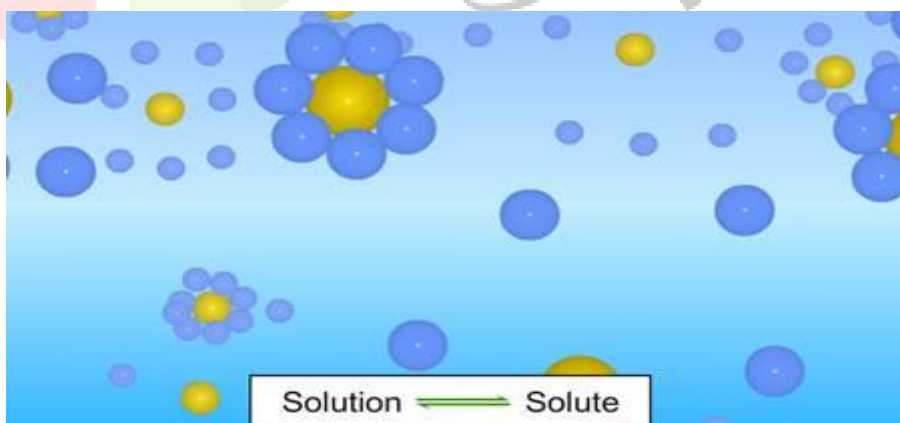
Table 1: Expression of solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

II. FACTOR AFFECTING THE SOLUBILITY

- 1) **Nature of solute and solvent:** The nature of solute and solvent is based on their concentration of solute in a specific quantity of solvent at a specific temperature.

Figure 1: Nature of solute and solvent



- 2) **Particle size:** Particle size affects their solubility. If the particle size decreases, the volume of surface area will be increase & the surface area of particle increases causing the greater interaction with the solvent. The effect of particle size on solubility is described by the given formula.

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

(Equation 1)

Where,

S	=	solubility of fine particles
V	=	molar volume
g	=	surface tension of the solid
r	=	radius of the fine particle

- 3) **Molecular size:** Solubility is affected by the molecular size of particles. When molecules have higher molecular weight and higher molecular size the solubility of the substance decreased because larger molecules are difficult to surround with solvent molecules to solvate the substance.
- 4) **Temperature:** Solubility is also affected by temperature. Solubility increases with increasing temperature if the solution process absorbs energy & solubility decreases with increasing temperature if the solution process releases energy.
- 5) **Pressure:** Solids and liquid solutes, solubility is not affected by a change in pressure & gaseous solutes, solubility is increased if pressure is increased & solubility is decreased if pressure is decreased.
- 6) **Polarity:** The polarity of solute & solvent molecules has affected the solubility. The polar solute molecules are dissolved in the polar solvent system and nonpolar solute molecules are dissolved in the nonpolar solvent system. If the solute molecule is polar it has positive and negative ends & if the solvent is polar it consists of positive & negative ends, the positive ends of the solute molecule get to interact with the negative ends of the solvent molecules. This type of interaction is known as dipole-dipole interactions & is a type of intermolecular force.
- 7) **Polymorphs:** Solids have a rigid form & which has a definite shape. The shape or crystal habit of solid is different but angles between the faces are remains constant. This repeating arrangement is known as a unit cell. The substance can form more than one crystalline form is known as polymorphism. The polymorphs are different in their melting points. The melting point of a solid is associated with its solubility.
- 8) **Rate of solution:** The rate of solution is known as the measure of how fast the substance dissolves in a solvent. The various factors that can affect the rate of solution are as follows:
- Size of particles
 - Temperature
 - Amount of solute dissolved
 - Stirring

III. METHODS OF SOLUBILITY ENHANCEMENT

Classical and highly employed approaches to increase the aqueous solubility and the bioavailability of poorly soluble drugs particularly BCS Class II drugs involve the solubilization of principles like pH adjustment, solvency, micro emulsification, self-emulsification, micelles, liposomes and emulsions. Every method has some merits and demerits so the decision of the method is an essential step in the formulation process.

1) **Surfactants:** The standard approach to solubilize the poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and preservation interaction. Amphiphilic surfactants are used to improvement of drug solubility because it has a lowering surface tension between drug and solvent & to improve the wetting characteristics & micellar solubilization. A wide variety of surfactants like Polyglycolized glyceride, Spans, Tweens, Polyoxyethylene stearates & synthetic block copolymers like Poly (ethylene oxide)-poly (propylene oxide) like Poloxamersbasemicelles, Poly(beta-benzyl-L-aspartate)-b-poly (ethylene oxide), etc are very useful as excipient & carrier for dissolution enhancement.

2) **pH adjustments:** Adjustment of micro-environmental pH to modify the ionization behavior is the simple & commonly used method to increase the water solubility of ionizable compounds. As per the pH-partition hypothesis & Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of the drug. The change in the ionic milieu can result in a situ salt formation. Hence the formation of salt is infeasible for unionized compounds. The formation of salts may converse to respective acid or base forms in the gastrointestinal tract.

3) Salt formation: The formation of salt is poorly soluble drug candidates i.e. weak acid & weak bases has been a strategy for several decades to enhance solubility. This method is effective for parenteral as well as other liquid formulations & in solid dosage forms. For marketing, approximately 300 new chemical entities were approved by the FDA during the 12 years from 1995 to 2006 in that 120 are in salt forms. The aqueous solubility of the acidic or basic drug is a function of pH whether the compound will give suitable salts. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how can salt easily dissociate into their free acid or base forms, what their dissolution behavior is under different GI pH conditions & solubility and dissolution rate of salts will be influenced by common ion. Most of the reviews have outlined general strategies and considerations for salt selection. In the salt formation process, drugs should have ionizable groups that will assist salt formation. The criterion for the selection of counter ion is as follows:

- 1) There should be a minimum difference of 2-3 pKa units between the drug and the counter ion.
- 2) Sufficient toxicological data is required to obtain FDA approval or to support the selection of a counter ion.

4) Co solvents: The Co solvent system is a mixture of miscible solvents which is used to solubilize lipophilic drugs. Nowadays, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. The water-insoluble solvents include the long-chain triglycerides (i.e. peanut oil, soybean oil, peppermint oil, olive oil, corn oil hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d- α -tocopherol (vitamin E) and oleic acid. A commercially available example is Progesterone; a water-insoluble steroid that is solubilized in peanut oil.

5) Polymeric Alteration: Different crystalline forms of a drug have different properties are known as Polymorphs. Polymorphs are differing in different physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution rate, morphology, density, biological activities & bioavailability. To ensure reproducible bioavailability of the product, it is best to develop the most thermodynamically stable drug polymorph. Of the stable, unstable, and metastable crystalline polymorphs, the metastable form has higher energy associated with increased surface area, followed by solubility & bioavailability. Hence the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage.

6) Particle Size Reduction: Micronization or nanonization is one of the important approaches for the improvement of bioavailability of lipophilic drugs by increasing the surface area and saturation solubility for reduction of the particle size to the sub-micron level. At the time of preformulation studies of any formulations, particle size is a critical parameter so it should be strictly controlled. Particle size reduction is a successful way to enhance the solubility, if the particle size uncontrolled and un-optimized, it can be lead to re-crystallization and re-aggregation of the drug on storage. So the study of particle size and physical stability should be done. In conventional milling techniques, size reduction to the submicron range is not possible.

7) Co-evaporate System / Co-precipitation: Weak basic drugs such as prochlorperazine maleate have good solubility at acidic pH, but their solubility decreases at alkaline pH, while conventional preparations containing weak bases precipitate as slightly soluble free bases in intestinal fluids when administered orally. The precipitated drug is no longer capable of release from formulation leading to a decrease in bioavailability of the drug. This problem can be solved by the use of a co-evaporate system which incorporates a carrier with solubilizing effect in an alkaline intestinal fluid that may operate in the microenvironment, immediately surrounding the drug particle and polymers for controlling the dissolution rate to formulate dosage forms ensuring maximum bioavailability with controlled release of a weak base.

8) Solvent Deposition/Evaporation: In this technique, the drug is dissolved in a solvent like methylene chloride to produce a clear solution. The resultant mass is then dried, pulverized, and passed through a sieve. The improved dissolution rate is due to the reduced particle size of the drug deposited on the carrier and the improved particle wettability caused by the carrier. The support is then dispersed in the solution by stirring and the solvent is removed by evaporation at temperature and pressure.

9) Inclusion Complexes: Cyclodextrins is a group of cyclic oligosaccharides which is obtained from the enzymatic degradation of starch. In cyclodextrin complexation lower the aqueous solubility of pure drug greater the aqueous relative solubility enhancement obtained. There are three major cyclodextrins α , β , and γ -CD are composed of six, seven, and eight D-(+) -glucopyranose units. Pharmaceutical applications of cyclodextrins in drug solubilization and stabilization in vivo drug delivery toxicological issues and safety evaluation and mechanisms of Cyclodextrins modifying drug release from polymeric drug delivery systems have been previously reviewed.

IV. CONCLUSION

Dissolution of the drug is an important rate-determining step for oral absorption of poorly water-soluble drugs and solubility, which is the basic requirement for the absorption of the drug from GIT. The various techniques described in combination can be used to increase the solubility of the drugs. Selection of a method for solubility enhancement based upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and dosage form requirements like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like a maximum daily dose of any excipients or drug, approved excipients, analytical accuracy.

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