



## Review Article

# Solubility Enhancement Techniques: A Review

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Solubility is one of the important parameter to achieve desired concentration of drugs in systemic circulation for pharmacological response to be shown. A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. But most of the time it becomes challenging to formulate poorly water soluble drugs. Therefore it is necessary to improve solubility of drug by various techniques.

**Keywords:** Solubility, Solubility Enhancement, Micronization, Co-solvent, Complexation, Hydrotrophy, Salt Formation.

## INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown<sup>1</sup>. The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water<sup>2</sup>. Solubility is central to *in vitro* screening assays,

because poor solubility leads to problems with reproducibility and unreliable results. If a drug precipitates in either the source plate or the screening well before reaching its cellular target, the target will be exposed to a lower concentration of free drug than was intended in the experimental design and could yield a response that is diminished, undetectable or independent of the input concentration. Thus, this problem of physical chemistry can appear as a biological problem. *In vivo*, inadequate solubility of the desired dose results in incomplete absorption of orally administered drugs. In addition, low solubility of compounds also contributes to extended timelines, owing to the heroic measures required to produce dosage

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forms that consistently deliver the desired quantities of drug at the site of absorption<sup>3</sup>.

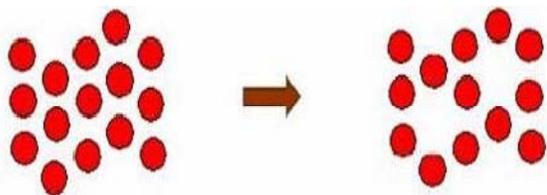
**Solubility Definitions<sup>4</sup>**

Definition	Parts of solvent required for one part of solute
Very Soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

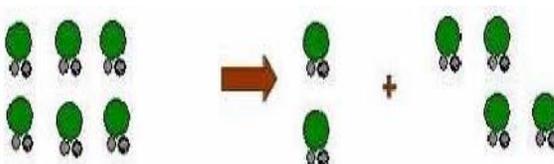
**PROCESS OF SOLUBLISATION**

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute<sup>5</sup>, 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<sup>6</sup>.

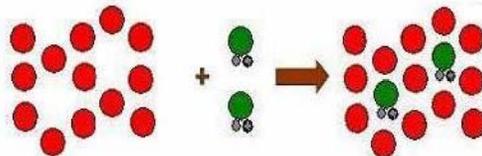
**Step 1: Holes opens in the solvent**



**Step2: Molecules of the solid breaks away from the bulk**



**Step 3: The freed solid molecule is integrated into the hole in the solvent**



**FACTORS AFFECTING SOLUBILITY**

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system<sup>7</sup>.

**1. Particle Size:**

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by<sup>8</sup>

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

Where,

- S is the solubility of infinitely large particles
- S<sub>0</sub> 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 temp in degree Kelvin
- R universal gas constant



## 2. Temperature:

Temperature will affect solubility. If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature<sup>9</sup>. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases<sup>10</sup>.

## 3. Pressure:

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 practically no effect on solubility<sup>11</sup>.

## 4. Nature of the solute and solvent:

While only 1 gram of lead (II) 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's of these two substances is the result of differences in their natures<sup>12</sup>.

## 5. Molecular size:

The larger the molecule or the higher its molecular weight the less soluble the substance. In the case of organic compounds the amount of carbon

branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

## 6. Polarity:

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<sup>13</sup>.

## 7. Polymorphs:

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities<sup>14</sup>. Generally the range of solubility differences between different polymorphs is only 2-3 folds due



relatively small differences in free energy<sup>15</sup>.

### NEED OF SOLUBILITY

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

**Bioavailability** is rate and extent of therapeutically active drug that reaches systemic circulation and is available at the site of action. It is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosage for non intravenous routes of administration.

### Poor aqueous solubility is caused by two main factors

- 1) Strong intermolecular interactions which make the solubilization of the solid energetically costly
- 2) High lipophilicity.

Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, the main pathway for drug absorption, is the product of solubility and permeability. Compounds with insufficient solubility carry a higher risk of failure

during discovery and development. Currently only 8% of new drug candidates have both high solubility and permeability. As solubility and permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques<sup>16</sup>.

### TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are

**1. Micronization:** The solubility of drug is often intrinsically related to drug particle size<sup>17</sup>. Particle size reduction, leading to increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water-soluble compounds<sup>18-20</sup>. According to the Noyes- Whitney equation, the rate of dissolution ( $dC/dt$ ) depends on the effective surface area ( $A$ ) of the drug particles. The rate of mass lost from the particle is given by

$$-dM/dt = DS/h (CS - CB)$$

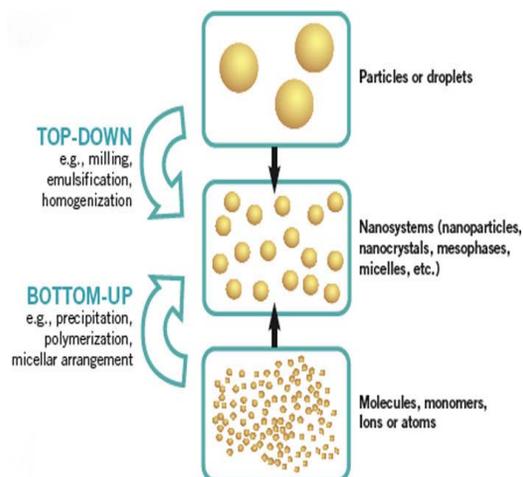
Where,  $M$  is the mass of compound dissolved in time  $t$ ,  $D$  is the diffusion coefficient of the compound in medium,  $S$  is surface area,  $h$  is thickness of the stagnant film layer,  $CS$  is the saturated solubility of the compound at the particle-media interface, and  $CB$  is the

concentration of compound in the bulk medium<sup>21</sup>.

Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug<sup>22</sup>.

**2. Nanonization:** 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. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc<sup>23</sup>.

**Nanocrystals:** The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals can be produced by bottom up technologies (precipitation methods) or alternatively by top down technologies (size reduction methods). At present most



**Fig. 1: Approaches to Fabricating nano-based System**

industrially feasible methods are the top down technologies, all products on the market are made by size reduction<sup>24-25</sup>.

**Nanosuspension:** Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed. Techniques for the production of nanosuspensions include Homogenization and wet milling Active drug in the presence of surfactant is defragmented by milling<sup>26</sup>.

**1. Nanoemulsion:** Nanoemulsions are nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20–200 nm) are often referred to as submicron emulsions. Nanoemulsions are composed



of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. The methods used for the production of nanoemulsions include HPH, microfluidization, ultrasonication and spontaneous emulsification<sup>27</sup>.

**2. Supercritical fluid process:** A supercritical fluid (SCF) is one of which the temperature and pressure exceed its critical temperature  $T_c$  and pressure  $P_c$ . In the supercritical region, the density of a SCF is a continuous function of its pressure (or temperature) at a given temperature (or pressure)<sup>28</sup>. SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas. Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points<sup>29</sup>.

**3. Use of Metastable Polymorphs:** The presence of metastable, polymorphic crystalline forms can exert a great influence on the solubility, dissolution rate, and biological activity of medicaments. The separation and selective use of a specific polymorphic form that possesses the highest solubility is a technique that can be applied, in certain cases, for the

increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms<sup>30-31</sup>.

### **1. Drug dispersion in carriers:**

**A. Solid Solutions:** A solid solution is a binary system comprising a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one-phase system, solid solutions are also called molecular dispersions or mixed crystals. They are generally prepared by a fusion method, whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. The solid solution of griseofulvin–succinic acid dissolves 6–7 times faster than pure griseofulvin<sup>32</sup>.

**B. Eutectic Mixtures:** These systems are prepared by a fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute and solvent show complete miscibility but negligible solid–solid solubility (i.e., such systems are basically an intimately blended physical mixture of two crystalline components). When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of



microcrystalline dispersion of very fine particles. Examples of eutectic mixtures include paracetamol–urea, griseofulvin–urea, and griseofulvin–succinic acid<sup>33</sup>.

**C. Solid Dispersions:** Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert excipient or matrix (carrier), where the active ingredients could exist in finely crystalline, solubilised or amorphous state. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs are expected to be high. Various pharmaceutical approaches for the preparation of SDs, include coprecipitation, lyophilization, spray drying, melting solvent method, melt extrusion method, solvent evaporation, fusion and powder mixing methods<sup>34-35</sup>.

**1. Spray freezing into liquid and lyophilization:** 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. carbon dioxide, 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 acetonitrile as the solvent increases drug loading and decreases the drying time for lyophilization. The dissolution rate is enhanced from the SFL powder containing amorphous nanostructured aggregates with surface area and excellent wettability<sup>36-37</sup>.

**2. Evaporative precipitation into aqueous solution:** 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. The solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization<sup>38</sup>.

**3. Solubilization by surfactants:** Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small apolar molecules are added they can accumulate in the hydrophobic core of the



micelles. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-L-aspartate) etc used as carrier for solubility and dissolution enhancement<sup>39-40</sup>.

**4. Use of co-solvent:** Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility is known as cosolvent. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used<sup>41-42</sup>.

**5. Salt Formation:** Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Salts of acidic and basic drugs have, in general, higher

solubilities than their corresponding acid or base forms. For solid dosage forms, dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water soluble than the parent drug<sup>43</sup>.

**6. Hydrotropy:** Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. Hydrotropic agents are ionic organic salts. Hydrotropy is used for solubility enhancement of different class of drugs such as anti-tumor, anti-viral, anti-inflammatory, antipyretic and analgesic drugs, xanthine derivatives etc. e.g. Sublimation of Theophylline with Sodium acetate & Sodium alginate<sup>44-45</sup>.

**7. Solvent deposition:** In this technique drug is dissolved in a solvent like methylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is



removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier. Successfully solubility of aceclofenac has increase by solvent deposition technique using lactose<sup>46</sup>.

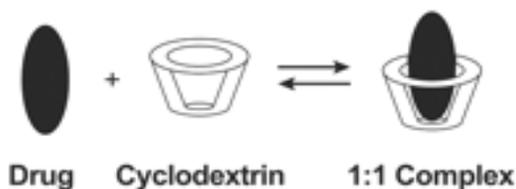
**8. Solubilizing agents:** Solubilizing materials like superdisintegrants such as crospovidone, crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations which increase the solubility and dissolution rate of poorly water soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water soluble drug. PEG 400 used to improve the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug nimodipine<sup>47</sup>.

**9. Co-crystallisation:** new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A Co-crystals may be defined as crystalline material that consist of two or more molecular (& electrical neutral)

species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt & slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds<sup>48</sup>.

**10. Complexation:** Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, and inclusion complexes cyclodextrins<sup>59</sup>.

**Inclusion complexes** are formed due to the ability of a compound to enclose in another complex. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of



**Fig. 2: Complex Formation by Cyclodextrin**

host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. Three naturally occurring CDs are  $\alpha$ -Cyclodextrin,  $\beta$ -Cyclodextrin, and  $\gamma$ -Cyclodextrin. The complexation with cyclodextrin is used for enhancement of solubility<sup>50-51</sup>.

**1. Use of precipitation inhibitors:** A significant increase in free drug concentration above equilibrium solubility results in super saturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc.

**2. Alteration of pH of the drug microenvironment:** This can be achieved in two ways- in situ salt formation, and addition of buffers to the formulation e.g. buffered aspirin tablets<sup>52</sup>.

**3. 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 ionizable moiety 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<sup>53</sup>.

**4. 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<sup>54-55</sup>.

## CONCLUSION

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8%



of new drug candidates have both high solubility and permeability.

The basic approaches followed by all the currently available technologies engaged in the solubility enhancement are to maximize the bioavailability and therapeutic efficacy. 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. Solubility 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.

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