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## A Review on Solubility Enhancement Techniques



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### ABSTRACT

Solubility is the phenomenon of dissolution of solids in the liquid phase to give a homogenous system. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water-soluble drugs often require high doses to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities. Thus solubility is the most important concept presenting itself as a valuable contributor in the formulation of pharmaceuticals. If the molecule has to survive the pharmaceutical development process the formulation scientist has to come up with a new API with great demand in the market. The usable pharmaceuticals with poor solubility must be answered well by solubilization techniques such as chemical modification which involves the use of solubilizers such as soluplus, povacoat, dendrimers, and physical modification, complexation, use of surfactant. The purpose of this review article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.



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## INTRODUCTION

Solubility is a property of substance in a particular solvent. In quantitative terms, it is the concentration of dissolved solute in a saturated solution at a specific temperature. In qualitative terms it means continuous interaction of two or more compounds to form one phase, clear homogeneous molecular dispersion. It is measured as the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. A solubility chart gives a list of ions and how, when mixed with other ions, they can become precipitates or remain aqueous. [1,2]

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under the specific condition of temperature, pH, and pressure. The drug solubility in a saturated solution is a static property whereas the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. [3]

The solubility of a drug is described in various descriptive terms which are based on the amount of drug dissolved in the solvent and discussed in Table No 1.

**Table No. 1: Definitions of Solubility [3]**

Definition	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 -10
Soluble From	From 10 -30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000 -10,000
Insoluble	Greater than 10,000

**Possible Causes for Poor Oral Absorption [4]** any drug is said to be poorly soluble when:

1. Aqueous solubility <100 ug/ml
2. Poor dissolution : Intrinsic dissolution rate < 0.1 mg/cm<sup>2</sup>/min
3. High molecular weight. (>500)
4. High crystal energy.

### Process of Solubilization [5]

**Step 1** The process of solubilization involves the breaking of interionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, the interaction between the solvent and the solute molecule or ion.

**Step 2** Molecule of the solid breaks away from the bulk.

**Step 3** The feed of a solid molecule is integrated into the hole in Solvent.

**Biopharmaceutics classification system (BCS)** was introduced by the US Food and Drug Administration (FDA) and it classifies the drug into four classes according to permeability and solubility. Solubility impediment is faced in the Class II and Class IV of the system facing dissolution as the rate-limiting step for the absorption of a drug due to low solubility. The BCS classification system discussed in Table No. 2.

**Table No 2: The Biopharmaceutics Classification System for Drugs[6]**

Class	Solubility	Permeability	Absorption Pattern	Rate limiting step in the absorption	Example
I	High	High	Well absorbed	Gastric emptying	Diltiazem
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly absorbed	Case by case	Taxol

### Factors Affecting Solubility [1, 5]

**Particle size:** Particle size affects solubility. As particle size decreases, the surface area to volume ratio increases. As the surface area of the particle increases, it causes greater interaction with the solvent.

**Temperature:** Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature. [5]

**Molecular size:** The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to

surround with solvent molecules to solvate the substance. Nature of solute and solvent: The nature of solute and solvent depends on the concentration of solute in a specific quantity of solvent at a specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved. [4]

**Pressure:** For gaseous solutes, an increase in pressure increases solubility, and a decrease in a pressure decrease the solubility. For solids and liquid solutes, changes in pressure do not affect solubility.

**Polarity:** Polarity of both solute and solvent molecules affects the solubility. Generally, polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.

**Polymorphs:** The ability of a substance to crystallize in more than one crystalline form is polymorphism. Polymorph is an agent having the 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 the melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility. [4]

**Techniques for Solubility Enhancement:** When the solubility of substances in aqueous media is limited, formulation strategies are required early on in the drug discovery and they remain of critical importance for lead substance selection and commercial drug product development. [8]

Various techniques have been used in an attempt to improve solubility and dissolution rates of poorly water-soluble drugs which include as following:

- a) Particle Size Reduction
- b) Nanonization
- c) Cosolvency
- d) Hydrotrophy
- e) pH Adjustment
- f) Sonocrystallization

g) Supercritical Fluid (SCF) Process

h) Solid Dispersion

i) Inclusion Complexation

j) Self-Emulsifying or Self-Micro Emulsifying Systems

k) Liquisolid Methods

In these techniques, the carrier plays an important role in improving the solubility and dissolution rate. Polymers, super disintegrants, surfactants are extensively studied in recent years for dissolution enhancement in drugs. This part of this review discusses technological overview and effect of polymers, superdisintegrants, and surfactants on dissolution enhancement of drugs while describes the role and applications of cyclodextrins, carbohydrates, hydrotropes, dendrimers, acids and miscellaneous carriers in enhancing dissolution of drugs. [8]

**a) Particle Size Reduction:** The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction is done by milling techniques using a jet mill, rotor-stator colloid mills, etc. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. [9]

Nowadays Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different types of equipment for the reduction of the particle size. In micronization, the solubility of the drug is often intrinsically related to drug particle size. [10]

**Advantages of particle size reduction:**

1. Liquid forms can be rapidly developed for early-stage testing (pre-clinical) that can be converted into solids for later clinical development.
2. Typically, low excipient to drug ratios is required.
3. Formulations are generally well tolerated provided that strong surfactants are not required for stabilization.

4. Generally, crystal forms are chemically and physically more stable than amorphous particles.

**Disadvantages of particle size reduction:**

1. Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
2. Technically, the development of sterile intravenous formulations is even more challenging.

**b) Nanonization [11]:** 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. [12]

There are different techniques used for the nanonization of drugs including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying, etc. There are many examples of the nanonization of drugs.

**Advantages of nanonization [13] :**

It results in the production of the nano or micro-sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

**Disadvantage of nanonization:**

The agglomeration problem is inherent and difficult to overcome.

**c) Co-solvency:** It is also known as “Solvent blending”. It enhances the solubility of a poorly water-soluble drug by the addition of water-miscible solvent in which drug has good solubility by reducing the interfacial tension between the aqueous solution and hydrophobic solute. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. It has found its main use in parenteral dosage forms because of the low toxicity of many co-solvents, and the relatively greater ability of co-solvents to solubilize nonpolar drugs. Commonly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl

Sulfoxide, Dimethyl Acetamide, Ethanol, n-octanol are the commonly used cosolvents. [14,15]

**Advantages of co-solvency:**

1. Has large solubilization capacity for poorly soluble drugs, simple and rapid to formulate, produce and evaluate.
2. It can be combined with other solubilization techniques and pH adjustments to further increase the solubility of poorly soluble compounds.

**Disadvantages of co-solvency:**

1. Toxicity and tolerability related with the level of solvent administered has to be considered.
2. Sometimes even uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size.
3. As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

**d) Hydrotrophy:** Hydrotrophy is a solubilization process whereby the addition of a large amount of the second solute increases the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. [16]

The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and poorly soluble drugs. Hydrotropic agents are ionic organic salts. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. [17]

**Classification of hydrotropes [15]**

**Table No. 3: Classification of hydrotropes**

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate
Aromatic cationic	p-aminobenzoic acid hydrochloride, caffeine
Aliphatics & linear anionics	Sodium alkanoate

### Advantages of hydrotrophy:

1. Hydrotrophy is suggested to be superior to other solubilization methods, such as miscibility, micellar solubilization, co solvency, and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
2. Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.
3. It only requires mixing the drug with the hydrotrope in water and does not require chemical modification of hydrophobic drugs, the use of organic solvents, or preparation of the emulsion system.

**Mixed Hydrotrophy [18]:** It is a new, simple, cost-effective, safe, accurate, precise method that involves the blends of hydrotropes which gives a synergistic effect on the solubility of the poorly water- soluble drug.

### Advantages of mixed hydrotrophy:

1. It may reduce the large total concentration of hydrotropic agents necessary to produce a modest increase in solubility by employing a combination of agents in a lower concentration.
2. The use of hydrotropic solubilizers as permeation enhancers.
3. Application of hydrotropic solubilization in nanotechnology.

**e) pH Adjustment:** Poorly water-soluble drugs with parts of the molecule that can be base or 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 to 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.[19,20]



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.[21, 22]

**Advantages of pH Adjustment:**

1. Simple to formulate and analyze.
2. Simple to produce and fast track.
3. Uses small quantities of the compound, amenable to high throughput evaluations.

**Disadvantages of pH Adjustment:**

1. The risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
2. Tolerability and toxicity (local and systemic) related to the use of a non-physiological pH and extreme pHs.



**f) Sonocrystallization [23]:**

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction based on crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It does not only enhance the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range of 20 kHz-5 MHz.

**g) Supercritical Fluid (SCF) Process:** The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. [24]

A SCF exists as a single-phase above its critical temperature ( $T_c$ ) and pressure ( $P_c$ ). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity, and higher diffusivity than liquids). 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. [25, 26]

Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Compressed Fluid Antisolvent, Impregnation or infusion of polymers with bioactive materials, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES). [27, 28]

**h) Solid Dispersion [29]:** Solid solution is a blend of two crystalline solids that exist as a new crystalline solid. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, it is expected to yield much higher rates of dissolution than simple eutectic systems.

**Amorphous precipitation:** Amorphous precipitation occurs when drug precipitates as an amorphous form in an inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

**Applications of solid dispersions:** Such a technique may be used[30]:

1. To obtain a homogeneous distribution of a minute amount of drug in solid-state.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released dosage form.
5. To reduce pre systemic inactivation of drugs like morphine and progesterone.

6. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
7. To convert polymorphs in a given system into isomorphous, solid.

#### **Advantages of solid dispersion [31]**

1. It has rapid dissolution rates.
2. Increase the absorption rate of drugs.
3. Improve dissolvability in the water of a poorly water-soluble drug in a pharmaceutical.
4. Decrease the crystalline structure of drugs into an amorphous form.
5. Prepare rapid disintegration oral tablets.
6. Mask the taste of the drug substance.
7. Avoid degradation or decomposition of drugs.

#### **Disadvantages of solid dispersion [31]**

1. Instability of solid dispersion.
2. Moisture and temperature have a deteriorating effect on solid dispersion.
3. It shows crystallinity and a decrease in the dissolution rate with aging.

#### **Methods of preparing solid dispersions**

**a) Fusion Process:** The carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. Disadvantages Exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is thermolabile.[32]

**b) Solvent Method:** The carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The co-precipitate is then dried under vacuum to drain out any solvent freely adhering to the particle. The removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and less sensitive procedures like spectroscopy, gravimetry and can be used to demonstrate complete solvent removal. [33]

**c) Fusion-Solvent Method:** Carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. The method is useful for drugs with high melting points or that are thermolabile.

**d) Spray Drying:** The carrier and the active ingredient are dissolved, suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

**e) Lyophilization (Spray Freeze Drying Method)** this method has been successfully developed to prepare solid dispersions at ambient temperature and avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD). SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including the amorphous structure and high surface area. [34,35]

**f) Dropping Method:** A solid dispersion of a melted drug carrier mixture is pipetted then dropped onto a plate, where it solidifies into round particles. The size, shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped on the plate it solidifies to a spherical shape. [36]

**i) Inclusion Complexation [37]:** Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs.

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of the host molecule. Various techniques are used to prepare for making inclusion complexes of poorly soluble drugs to improve their aqueous solubility are listed here: [38]

**a) Kneading:** The method involves the formation of a paste of cyclodextrin with guest molecules by using a small quantity of either water or ethanol to form a kneaded mass. Kneaded mass can be dried at 45 °C and pulverized. [38]

**b) Melting:** Excess quantity of guest melted, mixed with powdered cyclodextrin, after cooling excess quantity of guest is removed by washing with weak complex-forming solvent. The method restricted to sublimable guests like menthol. [38]

**c) Solution-enhanced dispersion by the Supercritical fluids (SEDS):** SEDS is a novel, single-step method, which can produce solid drug-cyclodextrin complexes. The optimization of processing conditions is essential to achieve optimum complexation efficiency and to compare with drug cyclodextrin complexation methods described earlier in the literature (e.g. kneading, freeze-drying, spray drying, etc). [38]

**Advantages over other methods are:**

a) Preparation of solid-cyclodextrin complexes in a single-step process,

b) Achievement of high complexation efficiency (avoidance of excess cyclodextrin in powder.

**d) Co-evaporation/Solvent evaporation method:** To the alcoholic solution of a guest, aqueous solution of the host is added and stirred for sometimes and evaporated at room temp until dried mass obtained, pulverized and sieved and the fraction is collected. [38]

**e) Microwave Irradiation:** This method is developed for rapid organic synthesis and reactions, which require shorter reaction time and higher aim products. [38]

**f) Freeze Drying/Lyophilisation technique:** The required stoichiometric quantity of host and guests were added to an aqueous solution of cyclodextrin and this suspension stirred magnetically for 24 hours, and the resulting mixture is freeze-dried at 60 °C for 24 hours. [38]

**g) Spray drying/Atomization:** In this method, host solution prepared generally in ethanol: water 50% v/v. To this guest is added and the resulting mixture is stirred for 24 hr. at room temperature and solution is spray-dried by observing the following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, the flow rate of solution, etc. [38]

**j) Self-Emulsifying or Self-Micro Emulsifying Systems [39]:** Self-emulsifying or self-micro emulsifying systems use the concept of in situ formations of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents, and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). [40]

The absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS about scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. [41]

**k) Liquisolid Methods:** When the drug dissolved in the liquid vehicle is introduced into a carrier material which has a porous surface and fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles

occur. Then, the coating material having high adsorptive properties and a large specific surface area gives the liquisolid system with desirable flow characteristics. Microcrystalline and amorphous cellulose and silica powders may be used as coating materials. [42]

#### **Advantages of Liquisolid Methods:**

1. Provides acceptably flowing and compressible powdered forms of liquid medications.
2. The method improves the solubility, bioavailability of orally administered water-insoluble, and is applicable in industry.
3. Useful for the formulation of oily drugs/liquid drugs.
4. Drug release can be modified by using different carriers and additives like PVP, PEG 60000, HPMC, and Eudragit, etc.
5. Several poorly soluble drugs can be formulated into the system.
6. This system is specifically for powdered liquid medications.
7. Production cost is low compared to that of the preparation of soft gelatin capsules.

#### **Disadvantages of liquisolid Methods:**

1. It requires recipients of high adsorption properties and a high specific surface area.
2. It does not apply to high dose insoluble drugs (>10).

#### **CONCLUSIONS:**

Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage forms of different drugs, the therapeutic efficacy of the drug, and for quantitative analysis. Dissolution of drugs is the rate-determining step for oral absorption of the poorly water-soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage forms of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and the number of folds increase in solubility. Because of the solubility problem of many drugs, the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It





is now possible to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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