REVIEW ARTICLE

PHARMACEUTICAL TECHNIQUES FOR THE FABRICATION OF POOR WATER SOLUBLE DRUGS – A REVIEW

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ABSTRACT
Pharmaceutical technologies for increasing the solubility of drug substances have a prime role in its faster dissolution and maximum absorption in the systemic circulation. Majority of the drugs possesses low solubility leading to poor absorption and erratic bioavailability and thus failed to achieve a desired pharmacological response. Therefore formulation scientists have adopted various techniques to overcome solubility and bioavailability issues following oral administration. The selection of technique is primarily based on the physicochemical characteristics of drug and dosage form. The present review highlights the importance of solubility with a brief description of conventional and novel approaches that could be used for solubility enhancement.

Keywords: Bioavailability, dissolution, pharmaceutical technologies, solubility.

1. INTRODUCTION
Fabrication of drugs having poor solubility is considered to be a thought-provoking research and a challenge for today’s formulation scientists. Nearly 40% of the new drug molecules and 90% in the development stages are poorly water-soluble. Many marketed drugs have poor solubility and low permeability due to which they rapidly metabolize and excreted after oral administration. It has also been reported that drugs with log p-value equivalent to 2 show erratic absorption and variable bioavailability in fasting and non-fasting patients due to their rate limiting dissolution. Examples of such drugs may include itraconazole and carbamazepine. This indicates that the desired therapeutic efficacy is possible only when the active ingredient possesses solubility in aqueous medium. Since the aqueous solubility of the drug is a prerequisite in achieving its pharmacokinetic profile for adequate absorption and reproducible bioavailability, therefore, it is deliberated as the most important challenge in oral delivery of new drug candidates. Approximately 90% or greater drugs are orally administered. Absorption of solid dosage forms follows in vivo dissolution to produce a drug solution which is transported across the gastric mucosa and finally diffuses into the bloodstream eliciting pharmacological action. Hence solubility is considered to be a key factor that brings the pharmacological response of a drug.

In Biopharmaceutical Classification System (BCS), drugs are categorized on the basis of their aqueous solubility and membrane permeability and therefore class II and IV drugs constitute poor water-soluble drugs category where bioavailability of such drugs eventually depends on the solubility (Table 1).

To achieve therapeutic excellence and market economics, it is not enough to discover and develop new drugs alone but it is more important to bring innovation or revolution in existing marketed drugs. Therefore, the improvement in existing drugs is supposed to be a more profitable business for pharmaceutical industry than the formulation of new molecules while solubility enhancement is the most important parameter for formulation development of orally administered poor water-soluble drugs.

Various methodologies are available in the literature
for increasing solubility of the drug. The technique should be selected depending on the physicochemical properties of the drug and nature of selected excipients and proposed dosage form. The present review briefly describes some of the solubility enhancement techniques for poorly soluble drugs.

### 2. Methods of Solubility Enhancement

Apart from other important parameters to be taken into account to formulate a safe and effective dosage form, increased absorption and bioavailability of the product may be controlled by enhancing its solubility in the physiological system. The following are some methods which are usually used to enhance the solubility of the drugs.

#### 2.1. Optimum pH Adjustment

The buffer capacity and pH adjustment have a great impact on the solubility of a compound. The solubility of weakly acidic drugs increases by using soluble excipients that increase pH higher than $pK_a$ of the salt while the solubility of weakly basic drugs increases when the excipients act as an alkalizer. The $pK_a$ of an ionizable compound is an important property, describing the charge state of the drug at a certain pH. However, it is not recommended to determine $pK_a$ values from the solubility-pH measurements. It has also been reported that weakly acidic drugs tend to be more soluble in an aqueous buffer solution than in the pure water as the number of polar groups and hydrogen bond donors and acceptors always have an influence on the solubility. Many drugs have different solubilities at different pH and these pH-dependent solubility differences lead to pH-dependent dissolution profiles.

#### 2.2. Formulation of Microemulsion

Formation of the microemulsion is another technique which is used for enhancing the solubility of several drugs that are almost insoluble in water. The microemulsion is a combination of oil, hydrophilic solvent and surfactant that are used to dissolve drugs with poor solubility to appear optically clear, isotropic, thermodynamically stable and translucent. In the presence of water, drug immediately disperses and forms a transparent emulsion of extremely tiny oil droplets containing the poorly soluble drug. Additionally, solubility can also be increased when combined with proteins for oral, parenteral and percutaneous/transdermal use. Similarly, the bioavailability of a drug can be affected depending upon the emulsion droplet size. A drug having small droplet size increases the plasma level due to the direct uptake of the drug in the lymphatic system.

### Table 1. The biopharmaceutical classification system

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>These drugs dissolve promptly with enhanced absorption. There is no bioavailability problem observed in immediate release dosage forms</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
<td>Drugs have inadequate dissolution but are well absorbed. The dosage form and rate of drug release control bioavailability</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
<td>Drug possess permeability problem. When the drug is released and dissolution is not achieved within absorption window then bioavailability might not be completed</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
<td>Consistent bioavailability is difficult to achieve for such drugs. Thus preferably alternate route of administration is required</td>
</tr>
</tbody>
</table>
Self-micro emulsifying drug delivery system (SMEDDS) is defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, one or more hydrophilic solvents and co-solvents. They have a unique ability to form fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. This method is suitable for all BCS class drugs where resulting emulsification gives faster dissolution rates and absorption. Recent developments in SMEDDS includes sustained/controlled-release tablets, capsules, suppositories, pellets, solid-dispersions, microspheres, etc. along with self-nanoemulsifying drug delivery system (SNEDDS) including self-emulsifying nanoparticles, self-double-emulsifying drug delivery system (SDEDDS), supersaturated self-emulsifying drug delivery system (SSEDDS) and self-micro emulsifying floating dosage forms. An optimum bioavailability may be predicted for these microemulsions as it is not food dependent, but the only weakness of this technique is an increase in the precipitation tendency of the drug due to the dilution with the hydrophilic solvent.

2.3. Hydrotrrophy
Hydrotropic agents are organic ionic salts while hydrotropy is a solubilization technique in which solubility of the first solute is enhanced by adding an increased amount of the second solute. The concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have shown to improve the aqueous solubilities of various poorly water-soluble drugs. This technique is preferred over others such as co-solvency, micellar solubilization, salting in, etc. due to the fact that it is highly selective, pH-independent and the solvent does not need emulsification. Hydrotropes are problematic to classify on the basis of molecular structure. Some examples may include ethanol, aromatic alcohols (resorcinol, pyrogallol, and catechol), α- and β-naphthols and salicylates, alkaloids (such as caffeine and nicotine) and ionic surfactants such as diacids, sodium dodecyl sulfate and dodecylate doxidibenzene. The aromatic hydrotropes with anionic head groups are commonly studied compounds. Cationic hydrophilic group hydrotropes are infrequent, e.g. procaine hydrochloride (aromatic amine salt). They not only increase water solubilization of compounds but they also exert an effect on surfactant aggregation promoting the formation of the micelle, clouding of surfactants and polymers.

2.4. Complex Salt Formation
Salt formation is another approach that could be tried for solubility enhancement. Salts should be chemically stable, non-hygroscopic, with no processing problems and dissolve quickly from solid dosage forms. It is the easiest chemical reaction, in which a proton transfer or a neutralization reaction takes place between an acid and a base. Theoretically, every compound possessing acidic/basic properties can take part in salt formation as they have improved solubility and dissolution characteristics as compared to their parent drug. A minimum difference of three units between the pKa value of the group and its counter ion is required to form stable salts. 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. Weakly acidic or basic drugs have been selected for salt formation because they offer simple chemical alteration, which might modify the physicochemical formulation, biopharmaceutical, and therapeutic drug properties without changing the basic chemical structure. It has also been reported that organic acid salt forms of basic drugs (amines) have higher water solubility than their corresponding inorganic salts such as aspirin, theophylline, barbiturates, etc.

2.5. Polymorphic Alteration
The phenomenon where drug exists in more than one crystal form possessing different physical and chemical properties such as melting point, stability, shelf-life, intrinsic solubility, dissolution rate, morphology, bioavailability, etc. is said to be polymorphism. Polymorphic alteration of the active pharmaceutical ingredient (API) and excipients also provide an opportunity for a formulation scientist to enhance the solubility of a drug. Different physical forms of drug exhibit different dissolution and
particle structural properties which are very useful in developing a new dosage form. These forms may either be stable, unstable or metastable, however, for better dissolution it is preferable to convert crystal form into metastable or amorphous form. Although the amorphous form exhibit low physical stability as compared to crystal form but it possesses high energy showing higher solubility, greater bioavailability and efficacy. Hence it is better to change the crystal form of drug into metastable or amorphous form to improve bioavailability during its shelf life at different storage conditions\textsuperscript{17,18}.

Since changing the solid state characteristics of API renders the molecule more water-soluble, the drugs with stable crystal form possessing high lattice energy produces difficulty in solubilization. Thus, disordered amorphous forms offer distinct advantage over crystal forms with regards to solubility. On the other hand, the excess of enthalpy, entropy and free energies of amorphous forms makes them susceptible to crystallization, leading to the formation of stable crystals. The arrival of new techniques for stability improvement of amorphous forms increases their use in pharmaceutical formulations. Various factors affecting the stability of amorphous drug systems and their complicated formulation process have resulted in lesser number of generic products for already approved amorphous drugs. For example cefuroxime which was practically water-insoluble and introduced as Ceftin® by GSK in amorphous form secured a couple of patents, which barred the entry of generic for a reasonable period of time\textsuperscript{2}.

2.6. Formation of Solid Dispersions
The concept of formation of solid dispersions was first presented by Sekiguchi & Obi. When one or more active pharmaceutical ingredients are dispersed in the solid state in an inert carrier, a solid dispersion is formed. More frequently two methods are known to make solid dispersions which include fusion (melt) and solvent evaporation\textsuperscript{3}. While some other methods are melt extrusion, lyophilization, melt agglomeration, use of surfactant, electrospinning, supercritical fluid (SCF) technology, etc.\textsuperscript{19}. Solid dispersion techniques can yield eutectic (non-
molecular level mixing) or solid solution (molecular level mixing) products with reduced particle size that results in a higher rate of dissolution and enhanced absorption of the drug. Dissolution of poorly aqueous soluble drug tends to increase by dispersing it into highly soluble solid hydrophilic matrix\textsuperscript{3,20}. Solid dispersions can be classified into five major types as shown in Fig. 1.

![Fig. 1. Classification of solid dispersion technique](image-url)

The hydrophilic carriers used more often for preparing solid dispersions include polyvinylpyrrolidone (povidone), polyethylene glycols (PEGs) and plasdone-S630. Surfactants such as Tween-80, docusate sodium, myrj-52, pluronic-F68, and sodium lauryl sulfate (SLS) also have a great role in solid dispersion formulations\textsuperscript{21}. Sporanox® is a classic example of itraconazole which has been formulated using solid dispersion technology. It is prepared both by hot melt extrusion and spray layering technology of solid dispersion. The resultant amorphous solid dispersed formulation showed a significant increase in the bioavailability as compared to its crystalline formulation\textsuperscript{2}. Solid dispersion technique possesses certain advantages such as it brings particle size reduction leading to a greater surface area with better dissolution rate and bioavailability. The agglomeration between the solid dispersion matrices is reduced
providing wettability resulting in improved dissolution. Solid dispersion technique replaces the crystalline structure to an amorphous form of drug molecule resulting in faster drug release. There are certain disadvantages that are associated with solid dispersion technique. During processing and storage of solid dispersions, the amorphous form can be converted into a more stable crystalline form which decreases the rate of dissolution giving rise to poor solubility, such as ritonavir which crystallizes from supersaturated solution in solid dispersion system. Generally, solid dispersions can be prepared by two methods as described below:

- Fusion (melt) method is more economical and simple than other methods of solid dispersion preparation. The drug and water-soluble carrier are mixed physically and melted under direct heat. For fusion method, the drug must be miscible in molten form with the carrier and both must be thermostable. The molten mixture then solidifies in an ice bath with vigorous stirring and the solid mass thus obtained is further subjected to sieving after pulverization that can be compacted into tablets using tableting ingredients.

- In solvent evaporation method, a solution of both matrix material and the drug is prepared followed by the evaporation of the solvent(s) resulting in solid dispersion formation. Mixing is preferred at the molecular level for getting an optimum dissolution. This process prevents thermal deterioration of drugs or carriers as organic solvents evaporate at low temperature. However, this method lead to certain disadvantages such as higher cost of preparation and complete removal of the liquid solvent is quite troublesome, which may adversely affect chemical stability of the active ingredient.

2.7. Co-Solvency

The solubility of non-polar drugs can dramatically be enhanced by adding a co-solvent (water miscible or partial miscible organic solvent) and the technique is called co-solvency. Majority of the co-solvents have both the hydrocarbon regions and hydrogen bond donor and/or acceptor groups. Their hydrophilic hydrogen bonding groups confirm water miscibility, whereas their hydrophobic hydrocarbon regions interfere with water hydrogen bonding network thus reducing the overall intermolecular attraction of water. This results in disrupting water self-association while co-solvents reduce water ability to exclude non-polar hydrophobic compounds leading to aggregate solubility. This technique is especially used for oral liquid and parenteral formulations. Co-solvents help in reducing dielectric constant which enables increased solubility of non-polar drug candidates. In intravenous (IV) formulations in order to maximize the solubility and inhibit precipitation upon dilution, co-solvency is used in combination with surfactants and pH modifiers. This approach has also been used in the formulation of taxol, an IV injection of paclitaxel. The injection was developed using 49% of dehydrated alcohol and 527 mg of cremophore EL-35, that must be diluted before infusion. This formulation needs pretreatment of patients with antihistamines due to hypersensitivity caused by high cremophore EL content in the formulation. Later, genexol (PEG-PLA (polyactic acid) polymeric micelles with paclitaxel) and abraxane (albumin microspheres containing paclitaxel) gained FDA approval through clinical testing. These formulations were more patient compliant as they were lacking cremophore EL and opened intellectual ways for pharmaceutical companies. The co-solvency is mainly used in parenteral medicinal agents because most surfactants give irritating effect as compared to many co-solvents that show much lower toxicity. Examples of low toxic co-solvents are glycerin, PEG 300, propylene glycol, ethanol, etc.

Some of the disadvantages associated with co-solvency include intolerability on long-term chronic administration due to high levels of synthetic surfactants, dilution with aqueous media or physiological fluids form uncontrolled precipitates of drugs which might be amorphous or crystalline with varying sizes. These precipitates might cause emboli and adversely affect at the injection site.
### 2.8. Use of Surfactants

Surfactants are molecules with distinct polar (hydrophilic) and non-polar (hydrophobic) groups. They mostly comprise of a hydrocarbon part linked with a polar group. The polar group may be anionic (e.g. sodium lauryl sulfate, potassium laurate), cationic (e.g. cetrimide), zwitterionic (e.g. N-dimethyl betaine) or non-ionic (e.g. polysorbates, poloxamers)\(^3\). Surfactants can decrease the surface tension which helps in increasing the dissolution of poor water-soluble drugs. When surfactant concentration surpasses its critical micelle concentration (CMC) (0.05–0.10% for most surfactants), the formation of micelle take place resulting in capturing drug molecule within the micelle. This is called micellization that normally ensures greater solubility of poorly aqueous soluble drugs. Surfactants are also frequently employed as stabilizers in micro-emulsions and suspensions\(^3\).

Primarily hydrophilic surfactants were used to solubilize drugs intended for the oral and IV route. However, the potential adverse effects following IV administration, higher critical micelle concentration and inadequate solubilization lead to their limited application. The polymeric micelles possess more benefits in terms of solubilization capacity, lower CMC, and greater tolerability. Polymeric micelles are formed using di-block such as PEG-PLA or tri-block polymers such as PLA-PEG-PLA. The hydrophilic component is usually PEG in the polymer for micelles and hydrophobic chain can be of PLA, polyaspartic acid, polycaprolactic acid, etc. The polymeric micelles at low CMC are stable at low polymer concentration after dilution with body fluids. The nano-particle sized polymeric micelles have enhanced permeation and retention effect (EPR) making them capable for tumor targeting. The hydrophilic PEG surface makes micelles less prone to reticuloendothelial scavenging, providing drugs more circulation time. The first FDA approved polymeric micelle is genexol-PM comprising of PEG-(D,L-lactide) polymer with paclitaxel encapsulated in the micelles. It has been found superior in terms of safety and tolerability with enhanced antitumor activity as compared to its marketed formulation (ethanol / cremophore EL)\(^24\). Thus polymeric micelles are one of the most promising techniques for reducing systemic toxicity of chemotherapeutics by target drug delivery\(^25\).

### 2.9. Complex Formation

The process of forming a complex between two or more molecules to make a non-bonded entity with a definite stoichiometry is called complex formation. It consists of two types that are stacking and inclusion\(^2\). Water possesses strong hydrogen bonding interactions which cause non-polar moieties to get squeezed out due to which hydrocarbon moieties and water molecules get closer. This leads to augment the solubility of poor water-soluble drugs. Stacked complexes can be homogenous or mixed\(^2\). When a guest molecule (non-polar molecule or the non-polar region of one molecule) is inserted into the cavity of host molecule (another molecule or group of molecules) inclusion complex is formed\(^21\). The enzymatic degradation of starch produces a group of cyclic oligosaccharides called cyclodextrins (CDs). There are three types of CD (\(\alpha\), \(\beta\), and \(\gamma\)) having six, seven, and eight D-\((+)-\)glucopyranose units, respectively. The CDs are hydrophilic from exterior and hydrophobic from their interior. CDs and their derivatives are used as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery\(^22\). This technique has been used to increase solubility and oral bioavailability of glipizide, rofecoxib, piroxicam, and carvedilol. There are various other technologies such as kneading, lyophilization and microwave irradiation method which can also be taken into account to prepare inclusion complexes\(^6\).

### 2.10. Pharmaceutical Co-Crystal Technology

Pharmaceutical co-crystal technique is another way through which problem of poor water solubility can be solved. Co-crystals are the new crystals, formed by the arrangement of two or more separate molecules, and possess more superior properties than each of the separate molecule\(^26\). The pharmaceutical co-crystals are crystalline solids containing an API and a co-crystal former. The co-crystal former is supposed to be an excipient or
2.11. Particle Size Reduction

Particle size reduction is the phenomenon of reducing particle size allowing greater interaction of drug particles with the solvent thereby increasing the solubility of poorly soluble drugs. The methods of particle size reduction include comminution, spray drying, and micronization. Milling and grinding are the two processes of comminution that significantly impart pressure upon the drug product physically resulting in size reduction thus providing a reproducible and cost-effective way for solubility improvement. The thermal stress generated during comminution and spray drying may sometime result in instability of thermosensitive compounds.

Micronization proliferates the surface area thereby increases dissolution. Different milling techniques are used for micronization such as jet mill and rotator colloid mill, etc. These processes result in improved digestive and clinical efficacy in griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. However, micronization is not sufficient for solubility enhancement of many new chemical entities because the micronized product is capable to agglomerate owing poor dissolution, therefore, the next process to consider is nanonization.

Nanonization is a process in which the active drug is converted to nanosize (1–100 nm) particles to improve dissolution characteristics of the drug. Nanonization not only results in increased drug solubility and pharmacokinetics, but it has a key role in decreasing systemic side effects. Nanoparticle technology serves as a screening aid during preclinical efficacy and safety studies of new chemical entities (NCEs). Nanoparticle-based drug delivery system is used in the manufacturing of existing drugs with maximal drug exposure, lesser toxicity and lesser competition during drug’s lifetime. It has also opened the doors for existing marketed drugs with poor solubility problem leading suboptimal drug delivery thus facilitating clinical and commercial benefits. Various methods have been utilized for the preparation of nanosuspensions such as precipitation, media milling, high-pressure homogenization in water, high-pressure homogenization in non-aqueous media and combination of precipitation and high-pressure homogenization.

2.12. Liquisolid Technique

In this technique, liquid medications (i.e. suspensions or emulsions of water-insoluble solid drugs in non-volatile liquid, oily liquid, and solutions) are transformed into apparently dry, non-adherent, free-flowing and compressible powder mixtures suitable for tableting or encapsulation. This may be done by blending the liquid medications with suitable excipients, which are generally known as carriers and coating materials. The liquid medication is first absorbed into the interior of the carrier. Once it gets saturated, a layer of liquid is formed on the exterior of carrier particles, which is instantly adsorbed by the fine coating materials giving apparently dry and free-flowing compressible powder mixture. These liquisolid formulations have greater wetting properties and high surface area promoting greater dissolution characteristics with increased drug release and improved oral bioavailability. This technique favors the formulation of a large number of BCS class II drugs due to its cost effectiveness in comparison to soft gelatin capsules. Immediate or sustained release dosage forms may also be formulated through this technique, however, one of the restrictions is to formulate high dose insoluble...
drugs. Another disadvantage is the use of high concentration of carrier and coating materials for acceptable flowability and compressibility resulting in a high weight of tablet above one gram making them difficult to swallow. Apart from dissolution enhancement, the liquisolid technique has recently been investigated as a tool to retard drug release, to minimize the influence of pH variation on dissolution profile and to improve drug photostability. Due to this, it is worth mentioning that liquisolid systems are not associated with stability issues.

2.13. Solid-Lipid Nanoparticles
Solid lipid nanoparticles (SLNs) are submicron sized lipid emulsions termed as colloidal carriers in which solid lipid is used instead of liquid lipid (oil). They are considered as an alternative system to traditional carriers (emulsions, liposomes, and polymeric nanoparticles). They possess exclusive properties such as smaller size, large surface area and interaction of phases at the interfaces. SLNs are considered as promising drug carriers with remarkable applications in poorly soluble drug delivery. Most of the lipid excipients used in SLNs are physiological components and are generally regarded as safe (GRAS) due to their biocompatibility and biodegradability. The site-specific drug delivery, particularly for poorly soluble proteins and peptide drugs is possible by applying SLN technology. The bioavailability of ofloxacin has been reported to increase using SLN technology because of the high surface area and enhanced ofloxacin concentration in gastrointestinal fluids. The residence time of drug in a lipid nanoparticle is high due to their adherence to intestinal wall resulting in enhanced bioavailability.

Some of the major advantages of this technique are target and/or control drug release, improved stability of pharmaceuticals, high and enhanced drug content, carrying both lipophilic and hydrophilic drugs and water-based technology avoiding organic solvents. Possible disadvantages include particle growth, unpredictable gelation tendency and drug expulsion after polymeric transition. There are various methods used for the preparation of SLNs such as high pressure homogenization, ultrasonication, high speed homogenization, solvent evaporation, solvent emulsification-diffusion, supercritical fluid, microemulsion, spray drying, double emulsion, precipitation and film-ultrasound dispersion.

3. CONCLUSIONS
The possibility of increasing solubility of poor soluble drugs can be foreseen from utilizing various techniques having their own importance, advantages and limitations. The conventional methods possess more limitation in terms of low efficiency, stability and dosage form characteristic which can be overcome by utilizing various novel approaches. The selection of technique is based on physical and chemical nature of drug, its solubility, melting point, pharmacokinetic parameters and specific dosage form properties. In the light of above mentioned facts it appears that still newer techniques are needed with minimum limitations for future endeavors.

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CONFLICT OF INTEREST
The author declares no conflict of interest.

REFERENCES


42. Garces A, Amaral MH, Sousa Lobo JM, Silva AC. Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. Eur J Pharm Sci. 2018;112:159-167.


