IJMPR 2021, 5(3), 42-48

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

ENHANCEMENT OF SOLUBILITY AND RATE OF ABSORPTION OF POORLY WATER-SOLUBLE DRUGS: A REVIEW

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Received on: 07/04/2021
Revised on: 28/04/2021
Accepted on: 18/05/2021

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ABSTRACT

Solubility of a drug is an important parameter in the formulation development. Hence various techniques are used for the improvement of the solubility of poorly water-soluble and water insoluble drugs include Particle Size Reduction, Solid Dispersion, Nanosuspension, Supercritical Fluid Technology, Cryogenic Technology, Inclusion Complex Formation Techniques, and Floating Granules etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Dendrimers are the novel class of polymer and it is used to enhance the solubility for the delivery of many water insoluble drugs, eg; anticancer, anti-inflammatory etc. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include micronization, nanonization, sonocrystallization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilising agents, modification of the crystal habit, co-crystallisation, complexation and drug dispersion in carriers. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

KEYWORDS: Solubility, solubility enhancement, bioavailability, water insoluble drugs.

INTRODUCTION

The role of aqueous-solubility of any new chemical entity (NCE) or a drug is crucial and decisive in the development of its formulation. When an active agent given orally, it must first dissolves in gastric and/or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving the oral bioavailability of active agents include.

1. Enhancing solubility and dissolution rate of poorly water-soluble drugs.
2. Enhancing permeability of poorly permeable drugs.[1]

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature,.[2] Almost More than 90% drugs are orally administered. Drug absorption, bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble.[3] Solvent is defined as the component which forms major constituent of a solution and is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level. Solute is defined as a substance that present in small quantity and dissolves in solvent.[2]

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Oral drug delivery is the simplest and easiest way of administering drugs due to its convenience, good patient compliance, greater stability, accurate dosage and easy production. Drug solubility is the maximum concentration of the drug dissolved in the solvent under specific condition of temperature, pH and pressure. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[4]

Table 1: Solubility description table[5]

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	100 – 1000
Very slightly soluble	1000 – 10,000
Insoluble	> 10,000

BCS CLASSIFICATION[4,6]

Class I: High permeability and solubility.

Formulation independent: The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

Examples: Loxoprofen, Benzapril, Sumatriptan etc.

Class II: High permeability but low solubility

Formulation dependent

The bioavailability of class II compounds is limited by drug solubility/dissolution. **Examples:** Aceclofenac, Valsartan, Nimesulide, Loratadine etc.

Class III: Low permeability but high solubility

Dependent on barrier properties: The bioavailability of class III compounds is limited by intestinal permeability. **Examples:** Atropine, Gabapentine, Topiramate etc.

Class IV: Low permeability and low solubility

Formulation and barrier properties dependent: The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

Examples: Hydrochlorthiazide, Meloxicam, Furosemide etc.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

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

Micronization[4,8]

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronization technique is used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Particle size reduction methods include recrystallization of the solute particles from solutions using liquid antisolvents, along with labour intensive techniques like crushing, milling, grinding, freeze drying and spray-drying. The rapid expansion of supercritical solutions (RESS) is an alternative technique for the micronization of particles using supercritical carbon dioxide to quickly and naturally reduce the particle sizes of various drugs. Micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate of dissolution.

Nanonization[2,4,8]

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. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc. There are many examples of nanonization of drugs.

A. 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). The at present most industrially feasible methods are the top down technologies, all products on the market are made by size reduction.

B. Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology. Nanosuspensions are prepared by using wet mill, highpressure homogenizer, emulsion?solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes.

C. Nanoemulsion

Nanoemulsion are a 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. Nano emulsions 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. Commercial products that are nanoemulsions include Estrasorb and Flexogan.

Sonocrystallization[4,9]

Sonocrystallization is a novel particle engineering technique to enhance solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size by using ultrasound. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz. Melt sonocrystallization (MSC) is promising technique of sonocrystallization to obtain porous, amorphous material with high stability.

Supercritical fluid method[4,10,11,12]

A supercritical fluid (SCF) can be defined as a dense noncondensable fluid is a novel nanosizing and solubilisation technology. A SCF process allows the micronization of drug particles within submicron levels. Supercritical fluids are fluids whose temperature and pressure are greater than critical temperature (Tc) and critical pressure (Tp). At near-critical temperature, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle size. Carbon dioxide and water are the most commonly used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5–2000 nm in diameter.

Spray freezing into liquid and lyophilisation[4]

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 hydrofluroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. The dissolution rate is enhanced from the SFL (Spray freezing into liquid) powder containing amorphous nanostructured aggregates with surface area and excellent wettability.

Evaporative precipitation into aqueous solution[4]

This process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. 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.

Use of surfactant[4]

Surface active agents (surfactants) are substances which at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension. Surface active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. Thus, surfactants are said to be amphipathic in nature. Depending on their charge characteristics the surface-active molecules may be anionic, cationic, zwitterionic (ampholytic) or non-ionic. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-Aspartate), b-poly (ethylene oxide) etc used as carrier for solubility and dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get any substantial solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of

the media. The amount of surfactant needed depends on the CMC and the degree to which the compound partitions into the surfactant micelles.

Use of co-solvent[4,13]

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. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerine, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used.

Hydrotropy method[4,14,15]

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. The term "Hydrotropy" has been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents and the solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Specific examples include ethanol, aromatic alcohols like resorcinol, urea, sodium ascorbate, pyrogallol, catechol, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene. Hydrotropy is used for solubility enhancement of different class of drugs such as antitumor, antiviral, anti-inflammatory, antipyretic and analgesic drugs, xanthine derivatives etc. Hydrotropy issuccessfully applied for solubility enhancement of nimesulide, riboflavin, nifedipine, xanthine derivatives like theophylline and caffeine.

Use of salt forms[4]

A major improvement in solubility and dissolution rate can be achieved by forming a salt. 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. This may be attributed the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. 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.

Solvent deposition[4]

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. Succesfully solubility of aceclofenac has increase by solvent deposition technique using lactose.

Solubilizing agents[4]

Solubilizing materials like superdisintegrants such as crospovidone, crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations which increase the solubilty 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. The aqueous solubility of the antimalarial agent halofantrine was increased by the addition of caffeine and nicotinamide.

Modification of the crystal habit[4]

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotrope and monotropes on the basis of thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotrope. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly, the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area. Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates. Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered

as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is amorphous > metastable polymorph > stable polymorph**.** Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

Co-crystallisation[4]

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, also referred as molecular complexes. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognized as safe (GRAS) which includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionisable groups.

Complexation[4]

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide. Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring cyclodextrins are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic; this is due to the arrangement of hydroxyl group within the molecule. Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.

Drug dispersion in carriers[4,16-19]

A. Solid solution

A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two compartments crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method whereby physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems prepared by fusion are called as melts e.g. griseofulvin- succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin. Mechanism of solid solution for solubility enhancement is when the binary mixture exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles, and when the solid solution, which is said to be in a state of randomly arranged solute and solvent molecules in the crystal lattice, is exposed to the dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.

B. Eutectic mixtures

When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in microcrystalline state which solubilizes rapidly. Eutectic mixture differs from solid solution in that the fused melt of solute-solvent show complete miscibility but negligible solid-solid solubility i.e. such system are basically intimately blended physical mixture of two crystalline components. A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

C. Solid dispersion

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. Once the solid dispersion is exposed to aqueous media and the carrier dissolve, the drug is released as very fine to colloidal particles. 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. The enhanced solubility and

dissolution rate of drugs from solid dispersions is based on following mechanisms.

a. Reduction in particle size provides large surface area.

b. Particles with improved wettability and dispersibility of drug.

c. Particles with higher porosity.

d. Drugs in amorphous state.

e. Solubilizing effect on the drug by water soluble carrier.

f. Formation of metastable dispersion.

Various pharmaceutical approaches for the preparation of solid dispersion include co-precipitation, lyophilization, spray drying, melting solvent method, melt extrusion method, solvent evaporation, fusion and powder mixing methods.

CARRIERS FOR SOLUBILITY ENHANCEMENT[2,4,16-20]

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance solubility and dissolution of drugs. Various carriers are used for solubility enhancement listed mentioned in the table 2.

Table 2: List of carriers used for solubility enhancement.

Sr. no.	Category	Examples of carrier
1	Surfactants	Deoxycholic acid, tweens, spans, polyoxyethylene stearate, renex, poloxamer 188.
2	Hydrotrops	Urea, sodium acetate, nicotinamide, sodium benzoate, sodium salicylate, sodium-o-hydroxy benzoate.
3	Insoluble or enteric polymer	Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS, Hydroxy propyl methyl cellulose phthalate.
4	Acids	Citric acid, succinic acid.
5	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, mannitol, lactose.
6	Polymeric materials	Povidone (PVP), polyethylene glycol (PEG), cyclodextrin, hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, hydroxy propyl cellulose.
7	Miscellaneous	Microcrystalline cellulose, dicalcium phosphate, silica gel, sodium chloride.

Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilizing behavior. **Examples:** Poly (amidoamine) dendrimers (PAMAM), Poly (Propylene Imine) dendrimers (PPI), Chiral dendrimers, Liquid crystalline dendrimers, Hybrid dendrimers, Tecto dendrimer, Multilingual Dendrimers, Micellar Dendrimers, Amphiphilic Dendrimers, Peptide dendrimers etc.

CONCLUSION

Solubility is the most critical factor in the formulation development that controls the formulation of the drug as well as therapeutic efficacy of the drug. Dissolution of drug 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 form of different drugs. The various techniques designated above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs. Defferent types of dendrimers are also useful in the solubility enhancement for the delivery of many class of drugs. The solubility of the drug is the factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. There are various available techniques, alone or in combination can be used to enhance the solubility of the drug. A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a solid dosage form such as tablet or capsule. 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 8-10% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above. Numerous technological advancements have been introduced for solubility and dissolution enhancement of poorly water-soluble drugs.

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