BCS CLASSIFICATION AND SOLUBILITY ENHANCEMENT TECHNIQUES FOR BCS CLASS II AND BCS CLASS IV DRUGS

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ABSTRACT

The BCS is a scientific system for classifying drug substance based upon their aqueous solubility as related to dose and permeability. The BCS is guiding for prediction of in vivo performance of the drug substance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics properties. The solubility behavior of drugs remains one of the most challenging in formulation development. Due to poor aqueous solubility of BCS Class II result in the poor oral bioavailability makes drug formulation development more difficult. Hence, various approaches have been developed with a focus on enhancement of the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs. Present article overviews the concept of Biopharmaceutical classification systems (BCS), Biopharmaceutical Drug Disposition Classification System (BDDCS) & recent classification for solubility enhancement of poorly water soluble drugs. The article also reviews various efforts taken for solubility enhancement using various techniques. Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, and solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

KEYWORDS: Poor solubility; bioavailability Formulation Development, solid dispersion, BCS Class II Drug, BCS Class IV Drug, Amorphous solid dispersion, Freeze-drying; Solid phospholipid nanoparticles; Solubility; Spray-drying.

INTRODUCTION

BCS CLASSIFICATION: The BCS is a scientific system for classifying drug substance based upon their aqueous solubility as related to dose and permeability. For BCS Class II or IV drugs, formulation designs are based on both the physicochemical and biopharmaceutical properties of the drugs which to obtained sufficient and reproducible bioavailability after oral administration. When combined with the dissolution of the drug product, the BCS depend on rate and extent of the drug absorption from immediate release solid dosage forms viz: dissolution rate, solubility and permeability.[1]

SOLUBILITY: The drug substance is considered to be highly soluble when the highest dose strength is soluble in 250 ml or less of the aqueous media over pH range of 1.0-7.5. The volume estimate of 250 ml is derived from BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water. The solubility class as per IP is described in table 1.

BCS classification is based on the 3 parameters
1. Absorption number defined as the ratio of the mean residence time to mean absorption time.
2. Dissolution number defined as the ratio of the mean residence time to mean dissolution time.

3. Dose number defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug.

Table 1: Expression for approximate solubility.

Descriptive term Solute	Parts of Solvent required for Part of
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

FDA proposed changes in class boundaries for biowaiver study on solubility and permeability based on the underlying physiology of the gastrointestinal tract are: 1.Narrowed the required solubility pH ranges from 1.0-7.5 to 1.0-6.8. 2. Reduced the high permeability requirement from 90% to 85%.

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Generally the bioavailability of BCS class II drug is rate limited by its dissolution, so that even a small increase in dissolution rate sometimes results in large increase in bioavailability. Therefore, the solubility behavior BCS Class II remains one of the most challenging aspects in formulation development for oral use. Modified Noyes-Whitney equation provides some ideas to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dc}{dt} = \frac{DA(Cs - C)}{h}$$

Where, dc/dt: the rate of dissolution
A: the surface area available for dissolution
D: the diffusion coefficient of the compound
Cs: the solubility of the compound in the dissolution medium
C: the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound

According to Noyes-Whitney equation, the dissolution rate can be improved by increasing surface area available for dissolution, decreasing the particle size of the solid compound which can be accomplished by conventional methods like grinding, ball milling, fluid energy micronization, salt formation, etc., and/or by optimizing the wetting characteristics of the compound surface, decreasing the boundary layer thickness, ensuring sink conditions for dissolution and, last but definitely not least, increasing apparent solubility of the drug under physiologically relevant conditions.[2]

BIOPHARMACEUTICAL DRUG DISPOSITION CLASSIFICATION SYSTEM:
The primary purpose of BDDCS was to predict drug disposition of new molecular entities and the importance of transporters in drug absorption and elimination. The BDDCS classifies drug substances into four classes based on aqueous solubility and extent of metabolism.

Table 2: BDDCS classification of drugs.

Class 1 High solubility Extensive metabolism	Class 2 Low solubility Extensive metabolism
Class 3 High solubility Poor metabolism	Class 4 Low solubility Poor metabolism

BDDCS relates to the rate of intestine and/or liver permeation. Therefore, a high degree of metabolism (≥90% of the dose) will dictate high extent of absorption (≥90%), but not vice versa. The high permeability classification in BCS reflects high extent of absorption (≥90%) as defined by the FDA Guidance. However, when the drug is extensively absorbed and classified as highly permeable under BCS, it may not have high metabolism. For BDDCS Class 2 compounds, intestinal uptake (or absorptive) transporters will be unimportant due to the rapid permeation of the molecules. Presented article represents the research work done on Gresiofulvine belonging to Class II. For class II drugs, the bioavailability is often low and variable due to insufficient dissolution in the gastrointestinal tract (GIT).

Hence, increase in solubility of selected API is first critical aspect to improve the absorption and the bioavailability of drug.

Solubility enhancement techniques for BCS class II and BCS class IV drugs: Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.

The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas.

The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds.

Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable.[3, 4,5,6,7]

Techniques for Solubility Enhancement: Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.
PhysicalModifications:
Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.
ChemicalModifications:
Change of ph, use of buffer, derivatization, complexation, and salt formation.
MiscellaneousMethods:
Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

1. Particle Size Reduction: The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility.

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level.

Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

These processes were applied to griseofulvin, progesterone, spironolactone diosmin, and fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy. Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media.[12]

2. Solid Dispersion: The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s .Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), Plasdone-S630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion.
The solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) and ritonavir with gelucire. Various techniques to prepare the solid dispersion of hydrophobic drugs with an aim to improve their aqueous solubility are listed here.[9]

2.1. Hot-Melt Method (Fusion Method): The main advantages of this direct melting method is its simplicity and economy. The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of a drug and a water-soluble carrier are heated directly until the two melts. The melted mixture is then cooled and solidified rapidly in an ice bath with rigorous stirring. The final solid mass is then crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agents. The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system.

An important requisite for the formation of solid dispersion by the hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermo stability of both the drug and the carrier.

2.2. Solvent Evaporation Method: Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier povidone. Many investigators studied solid dispersion of meloxicam, naproxen, and nimesulide using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poorly water soluble drugs. The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, the disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing the organic solvent (a regulatory perspective), the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty in reproducing crystal forms.

2.3. Hot-Melt Extrusion: Hot-melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

3. Nanosuspension: Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, high-pressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high-Pressure homogenization.[10]

3.1. Precipitation Technique: In precipitation technique the drug is dissolved in a solvent, which is then added to antisolvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments; but the challenge is the addition of the growing drug crystals to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with antisolvent. Moreover, precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media. Nanosuspension of Danazol and Naproxen has been prepared by precipitation technique to improve their dissolution rate and oral bioavailability. The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately 4-fold.

3.2. Media Milling: The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug, and stabilizer is rotated at a very high-shear rate under controlled temperatures for several days (at least 2–7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles.

3.3. High Pressure Homogenization: High-pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitations forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required. Dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole have been improved by reducing their particle size by high pressure homogenization.[11]

3.4. Combined Precipitation and Homogenization: The precipitated drug nanoparticles have a tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (homogenisation). They are in completely amorphous, partially amorphous or completely crystalline forms which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.[13]

4. Supercritical Fluid (SCF) Process: Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid that largely determine its solvent power. Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5–2,000 nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions (RESS), gas anti solvent recrystallization (GAS), and aerosol supercritical extraction system (ASES).[14]

5. Cryogenic Techniques: Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N_2, Ar, O2, and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation.

5.1. Spray Freezing onto Cryogenic Fluids: Briggs and Maxvell invented the process of spray freezing onto cryogenic fluids. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution.

5.2. Spray Freezing into Cryogenic Liquids (SFL): The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid-liquid impingement between the automatized feed solution and cryogenic liquid to provide intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders.

5.3. Spray Freezing into Vapor over Liquid (SFV/L): Freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability. During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

5.4. Ultra-Rapid Freezing (URF): Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leads to instantaneous freezing and subsequent lyophilization (for removal of solvent) forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug-carrier solid dispersions, and solid solutions.

6. Inclusion Complex Formation-Based Techniques: 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 (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs). Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin.

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules.

Various technologies adapted to prepare the inclusion complexes of poorly water soluble drugs with cyclodextrins are briefly described below.

6.1. Kneading Method: This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a

specified time. The kneaded mixture is then dried and passed through a sieve if required. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

6.2. Lyophilization/Freeze-Drying Technique: In order to get a porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitation of this technique is the use of specialized equipment, time consuming process, and yield poor flowing powdered product. Lyophilization/freeze drying technique is considered as an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent.[15]

6.3. Microwave Irradiation Method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round-bottom flask. The mixture is reacted for short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40°C. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction times and higher yield of the product.

7. Micellar Solubilization: The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and the oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are also used to stabilise drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs. Surfactant also improves wetting of solids and increases the rate of disintegration of solid into finer particles. Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved.

Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.[16]

8. Hydrotrophy; Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designate the increase in solubility in water due to the presence of 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 like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs.

The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive pi (π) orbital.

Hydrotropes with cationic hydrophilic group are rare, for example salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, and so forth.[17]

9. Crystal Engineering: The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can

produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy. By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs.

As a result, polymorphs for the same drug may differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions. A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. It was shown that the stable polymorph of chloramphenicol palmitate produced low serum levels, whereas the metastable polymorph yielded much higher serum levels when the same dose was administered. In another study, it was found that tablets prepared from the form A polymorph of oxytetracycline dissolved significantly more slowly than the tablets with form B polymorph. The tablets with form A polymorph exhibited about 55% dissolution at 30 min, while the tablets with form B polymorph exhibited almost complete (95%) dissolution at the same time.

Crystal engineering approach also involves the preparation of hydrates and solvates for enhancing the dissolution rate. During the crystallization process, it is possible to trap molecules of the solvent within the lattice. If the solvent used is water, the resultant crystal is a hydrate; if any other solvent is used, it is referred to as solvate. The dissolution rate and solubility of a drug can differ significantly for different solvates. For example, glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibited higher solubility and dissolution rate than two nonsolvated polymorphs. It is possible for the hydrates to have either a faster or slower dissolution rate than the anhydrous form. The most usual situation is for the anhydrous form to have a faster dissolution rate than the hydrate. For example, the dissolution rate of theophylline anhydrate was faster than its hydrate form. In certain cases, hydrate form of the drug may show rapid dissolution rate than its anhydrous form. Erythromycin dihydrate was found to exhibit significant differences in the dissolution rate when compared to monohydrate and anhydrate forms. In general, it is undesirable to use solvates for drugs and pharmaceuticals as the presence of organic solvent residues may be toxic. Also all the organic solvents have

specific limits for daily exposure to human as residual solvent in the formulated preparation.

Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through indepth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. The process involves dissolving the drug in a solvent and precipitating it in a controlled manner to produce nanoparticles through addition of an antisolvent (usually, water).

Pharmaceutical cocrystals open a new avenue to address the problems of poorly soluble drugs. They contain two or more distinct molecules arranged to create a new crystal form whose properties are often superior to those of each of the separate entities. The pharmaceutical cocrystals are formed between a molecular or ionic drug and a cocrystal former that is a solid under ambient conditions. These are prepared by slow evaporation from a drug solution containing stoichiometric amounts of the components (cocrystal formers); however, sublimation, growth from the melt, or grinding of two or more solid cocrystal formers in a ball mill are also suitable methodologies.

Carbamazepine: saccharin cocrystal was shown to be superior to crystal forms of carbamazepine alone in terms of stability, dissolution, suspension stability, and oral absorption profile in dogs. In another study by Childs et al., fluoxetine HCl succinic acid cocrystal was found to exhibit an approximately twofold increase in aqueous solubility after only 5min.It was observed that the itraconazole L-malic acid cocrystal exhibited a similar dissolution profile to that of the marketed formulation.

Traditional crystallization methods include sublimation, crystallization from solutions, evaporation, thermal treatment, desolvation, or grinding/milling. These are being replaced with novel methods of crystal engineering such as SCF technologies to produce pharmaceutical solids with desired dissolution rate and stability. Melt sonocrystallization is yet another emerging technology that uses ultrasonic energy to produce porous fast dissolving particles for hydrophobic drug molecules. Based on these exciting reports, it appears that crystal engineering techniques need to be exploited more for enhancing the dissolution rate of poorly soluble drugs.

Other techniques that enhance the solubility of poorly water soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble prodrug, application of ultrasonic waves, and spherical crystallization.[18,19,20]

CONCLUSION
Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and

solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

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