www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2016; 5(1): 23-28

www.thepharmajournal.com
Received: 11-11-2015
Accepted: 14-12-2015

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Various techniques for solubility enhancement: An overview

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Abstract
Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach therapeutic range due to their poor water solubility. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. This present review details about the different approaches used for the enhancement of the solubility of poorly water-soluble drugs include particle size reduction, nanonization, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropy etc. The purpose of this article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Keywords: Solubility Enhancement, bioavailability, Dissolution, solid dispersion, inclusion complexes

1. Introduction
Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.
Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate [1]. The solubility of a drug is described in various descriptive terms which is based on the amount of drug dissolved in solvent and discussed in Table-1.

Table 1: Definitions of Solubility [1]

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
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
Insoluble	More than 10,000

Need of Solubility [2]
Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid and not the

absorption, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs [3]. BCS Classification System with examples of different drug is discussed in Table-2.

Table 2: Biopharmaceutical Classification System [4]

BCS Class I	High Solubility High Permeability	B-blockers propranolol, Metoprolol
BCS Class II	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine
BCS Class III	High Solubility Low Permeability	B blockers Atenolol,H2 antagonist Ranitidine
BCS Class IV	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, frusemide

Techniques for Solubility Enhancement

When the solubility of substances in aqueous media is limited, formulation strategies are required early on in the drug discovery and they remain of critical importance for lead substance selection and commercial drug product development [5].

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

a) Particle Size Reduction
b) Nanonization
c) Cosolvency
d) Hydrotropy
e) pH Adjustment
f) Sonocrystallization
g) Supercritical Fluid (SCF) Process
h) Solid Dispersion
i) Inclusion Complexation
j) Self-Emulsifying Or Self-Micro Emulsifying Systems
k) Liquisolid Methods

In these techniques carrier plays an important role in improving solubility and dissolution rate. Polymers, superdisintegrants, surfactants are extensively studied in recent years for dissolution enhancement in drugs. This part of this review discusses technological overview and effect of polymers, superdisintegrants and surfactants on dissolution enhancement of drugs while describes the role and applications of cyclodextrins, carbohydrates, hydrotropes, dendrimers, acids and miscellaneous carriers in enhancing dissolution of drugs [5].

(a) Particle Size Reduction [6]

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 thermo sensitive 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 [7].

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 [8, 9].

(b) Nanonization [10]

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects [11].

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.

(c) Cosolvency [12]

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

(d) Hydrotropy [3]

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

(e) pH Adjustment [13]

Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this

approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

(f) Sonocrystallisation [14]

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

(g) Supercritical Fluid (Scf) Process [5]

The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research [15]. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points [16, 17]. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nano suspensions of particles 5-2,000nm 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 [18, 19]. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Compressed Fluid Antisolvent, Impregnation or infusion of polymers with bioactive materials, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES) [20, 21].

(h) Solid Dispersion [6]

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 [22]. 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: [23].

1. Fusion Process [24]

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Several mechanisms could operate during the process of dispersion. If the drug has a high degree of solubility in the carrier, the drug could remain "dissolved" in the solid state, yielding what is known as a solid solution. Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug in the carrier matrix. These systems show very high drug dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such systems show only moderate increases in dissolution rates.

A third mechanism is the conversion of a drug to an amorphous form in the presence of the matrix, again exhibiting different dissolution rates and solubility. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties.

An important limitation of the fusion method of preparation is the exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is heat-sensitive.

2. Solvent Method [25]

In the solvent method of preparation, the carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The coprecipitate is then dried under vacuum to drive out any solvent freely adhering to the particle surface. However, there is a possibility

of the formation of a solvate within the crystal lattice. This presents a problem in terms of pharmaceutical acceptance since most of the solvents used are non-aqueous (organic) and toxic. Hence, removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), and less sensitive procedures like gravimetry and spectroscopy can be used to demonstrate complete solvent removal.

3. Fusion-Solvent Method [25]

In the fusion methods a carrier(s) is/are melted and the drug(s) is / are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drugs that have high melting points or that are thermolabile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000.

4. Spray Drying [26]

In this type of preparation, the carrier and the active ingredient are dissolved or suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

5. Lyophilization (Spray Freeze Drying Method) [27-29]

This method is used to avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD) has been successfully developed to prepare solid dispersions at ambient temperature, which was made significant development by the research work of William III. SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area.

6. Hot-melt Extrusion [23]

It is a very common method used in the polymer industry. But Speiser [30, 31] and Huttenrach [32] were the first persons who use this technology for pharmaceutical purpose. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through heated screws, it is transformed into its “fluid like state”. This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drug that are somewhat thermolabile to be processed.

(i) Inclusion Complexation [33]

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 major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.

Various techniques are used to prepare for making inclusion complexes of poor soluble drugs with an aim to improve their aqueous solubility are listed here: [34]

a. Kneading [34]

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

b. Melting [34]

Excess quantity of guest melted, mixed with powdered cyclodextrin, after cooling excess quantity of quest is removed by washing with weak complex forming solvent. The method restricted to sublimable guest like menthol.

c. Solution-enhanced dispersion by the Supercritical fluids (SEDS) [34]

SEDS is novel, single step method, which can produce solid drug-cyclodextrin complexes. The optimization of processing conditions is essential in order to achieve the optimum complexation efficiency and to compare with drug-cyclodextrin complexation methods described earlier in the literature (e.g. kneading, freeze drying, spray drying etc). Advantages over other methods are

a) Preparation of solid-cyclodextrin complexes in single step process,
b) Achievement of high complexation efficiency (avoidance of excess cyclodextrin in powder).
c) Possibility to minimize the contact of drug with cyclodextrin during the process.
d) Achievement of enhanced dissolution rate of the drug (which is comparable to the dissolution behavior of micronized drug-cyclodextrin complex).

d. Co-evaporation/Solvent evaporation method [34]

To the alcoholic solution of guest, aqueous solution of host is added and stirred for sometimes and evaporated at room temp until dried mass obtained, pulverized and sieved and fraction is collected.

e. Microwave Irradiation [34]

This method is developed for rapid organic synthesis and reactions, which require shorter reaction time and higher aim product.

f. Freeze Drying/Lyophilisation technique [34]

The required stoichiometric quantity of host and guest were added to aqueous solution of cyclodextrin and this suspension stirred magnetically for 24 hours, and resulting mixture is freeze dried at 60 °C for 24 hours.

g. Spray drying/Atomization [34]

In this method, host solution prepared generally in ethanol: water 50% v/v. To this guest is added and resulting mixture is stirred for 24 hr. at room temperature and solution is spray dried by observing following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc. Product obtained by passing through 63-160 micrometer granulometric sieve.

(j) Self-Emulsifying or Self-Micro Emulsifying Systems [4]

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS**),** [35] in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS in relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Most self-emulsifying systems are limited to administration in lipid filled soft or hard shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell [36]. A Neoral-R is an example of self microemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine-α administered. A Neoral-R could be 174-239% of the bioavailability of cyclosporine-α from Sandimmune-R, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long term use due to the potential of causing diarrhea [37].

(k) Liquisolid Methods [38-44]

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics. Liquisolid solid system is acceptably flowing and compressible powdered forms of liquid medications. In the concept of liquisolid system, liquid drugs having low aqueous solubility dissolved in suitable non-volatile solvents, converted in to free flowing and radially compressible powder by simple admixture with selected powdered excipients referred as carrier and coating materials. Microcrystalline and amorphous cellulose and silica powders may be used as coating materials.

2. Conclusions

By this article we conclude that, Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs, therapeutic efficacy of the drug and for quantitative analysis. 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. The different techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and 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 with the help of various techniques as mentioned above.

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