International Journal of Pharmaceutical Sciences and Nanotechnology
Volume 10 • Issue 3 • May – June 2017
MS ID: IJPSN-2-15-17-DESHMUKH

Review Article

Solubility Enhancement Techniques for Poorly Water-Soluble Drugs

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Received March 24, 2017; accepted April 22, 2017

ABSTRACT

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 optimum pharmacological response. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Poor aqueous solubility is a major problem encountered with formulation development of new chemical entities. There are over 40% of new chemical entities that exhibit poor solubility and low bioavailability. As per BCS classification system, these drugs comes under BCS class II that show poor solubility and high permeability. The bioavailability of these drugs can be dramatically improved by increasing the solubility of these drugs. This review article highlights a number of techniques for enhancing the solubility of poorly water-soluble drugs.

KEYWORDS: Solubility, BCS class II drugs, solubility enhancement, bioavailability.

Introduction

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poor aqueous solubility of lipophilic drugs creates problems in formulation as well as in oral administration. Various approaches have been developed to resolve poor aqueous solubility of lipophilic drugs (Deshmukh et al., 2015; Deshmukh et al., 2014; Deshmukh et al., 2015). Most of the BCS class II drugs has poor aqueous solubility and high permeability (Deshmukh et al., 2015; Mahale et al., 2014). A number of methodologies are adopted to improve solubility of poor water-soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development (Vemula et al., 2010).

Factors Affecting Solubility of Solute in Liquids

1. **Temperature:** The solubility of solid in a liquid depends on the temperature. In the process of solution, if heat is absorbed, the solubility of the solute increases with increase in temperature. Such is the case for most of the salts. If a solute gives off heat during the process of solution, the solubility of the solute will decrease with increase in temperature.
2. **Molecular structure of solute:** A small change in the molecular structure of a compound can have a marked effect on its solubility in a given liquid. For example, the introduction of a hydrophilic hydroxyl group can produce a large improvement in water solubility. In addition, the conversion of a weak acid to its sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The overall interaction between solute and solvent is markedly increased and the solubility consequently rises. In addition, the esterification of drug will decrease the solubility.
3. **Nature of solvent:** The importance of the nature of the solvent has been discussed in terms of the statement 'like dissolves like', and in relation to solubility parameters. In addition, the point has been made that mixtures of solvents may be employed. Such mixtures are often used in pharmaceutical practice to obtain aqueous-based systems that contain solutes in excess of their solubility in pure water. This is achieved by using cosolvents such as ethanol or propylene glycol, which are miscible with water and which act as better solvents for the solute.
4. **Crystal characteristics:** Different crystalline forms of the same substance, which are known as ***polymorphs,*** consequently possess different lattice

energies, and this difference is reflected by changes in other properties. The effect of polymorphism on solubility is particularly important from a pharmaceutical point of view, because it provides a means of increasing the solubility of a crystalline material and hence its rate of dissolution by using a metastable polymorph. The absence of crystalline structure that is usually associated with a so-called ***amorphous*** powder may also lead to an increase in the solubility of a drug compared to that of its crystalline form.

5. **Particle size of the solid:** The changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size. The increase in solubility with decrease in particle size ceases when the particles have a very small radius, and any further decrease in size causes a decrease in solubility.
6. **pH:** If the pH of a solution of either a weakly acidic drug or a salt of such a drug is reduced then the proportion of unionized acid molecules in the solution increases. Precipitation may therefore occur because the solubility of the unionized species is less than that of the ionized form. Conversely, in the case of solutions of weakly basic drugs or their salts precipitation is favoured by an increase in pH. Such precipitation is an example of one type of chemical incompatibility that may be encountered in the formulation of liquid medicines.
7. **Complex formation:** The apparent solubility of a solute in a particular liquid may be increased or decreased by the addition of a third substance, which forms an intermolecular complex with the solute. The solubility of the complex will determine the apparent change in the solubility of the original solute.
8. **Solubilizing agent:** These agents are capable of forming large aggregates or micelles in solution when their concentrations exceed certain values. In aqueous solution, the center of these aggregates resembles a separate organic phase and organic solutes may be taken up by the aggregates, thus producing an apparent increase in their solubility in water. This phenomenon is known as ***solubilization.*** A similar phenomenon occurs in organic solvents containing dissolved solubilizing agents, because the center of the aggregates in these systems constitutes a more polar region than the bulk of the organic solvent. If polar solutes are taken up into these regions their apparent solubility in the organic solvents are increased (Aulton 2002; Gennaro 2000).
9. **Polarity:** Polarity of the solute and solvent molecules will affect the solubility. Generally 'like dissolves like' means non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force is known as dipole-dipole interaction. The other forces called London dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolar solvent a chance to solvate the solute molecules (Chaudhary et al., 2012).

Methods for Solubility Enhancement

Solubility is one of the important parameter to achieve desired concentration of drugs in systemic circulation for optimal pharmacological response. A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules, especially in oral formulation. However, most of the time it becomes challenging to formulate poorly water soluble drugs. Therefore, it is necessary to improve solubility of drug by various techniques (Ghule et al., 2014; Deshmukh et al., 2014; Sharma et al., 2011; Ojha and Prabhakar 2013).

1. **Co-solvency:** 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 (Prasad et al., 2012; Nayak et al., 2012; Babu et al., 2008).
2. **Complexation- stacking and inclusion complex:** Complexation is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. In complexation, relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions are involved.

   There are two types of complexes they are:

   (a) **Stacking complexes:** It is driven by association of non-polar area of drug and complexes agent. This results in exclusion of the non-polar area from contact with water, thereby reducing

total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.

(b) **Inclusion complexes:** It is formed by inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bonds. Hence, these are also called as no-bond complexes. Cyclodextrins (CD) are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß and γ-CD are composed of six, seven, and eight D-(+) - glucopyranose units. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrins and their derivatives are commonly used in complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug. Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation (Saravana et al., 2013; Mehta et al., 2012; Jiao et al., 2015; Shekh et al., 2011; Desale et al., 2015).

3. **Cryogenic method:** 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, O_2, 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 lyophilization (Patil et al., 2013; Savjani et al., 2012).
4. **High-pressure homogenization:** In high-pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenization can be performed in water or alternatively in nonaqueous media or water-reduced media. The particles are disintegrated by cavitations and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves, which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high-pressure homogenization causes increase in the sample temperature. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles (Chaudhary et al., 2012; Thorat et al., 2011; Anjana et al., 2013).
5. **Hydrotrophy:** Hydrotrophy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility in given solvent are said to "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". Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. 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 (Dhapte et al., 2015; Kapadia et al., 2011; Kumar et al., 2014; Pentewar et al., 2015).
6. **Liquisolid compacts:** The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface, which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained (Manogar et al., 2011; Nalinishastri et al., 2012; Chandel et al., 2013).
7. **Manipulation of solid state/polymeric alteration:** Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. From the stability and bioavailability aspects, the crystalline form of a

drug is of pharmaceutical importance. Polymorphism (existence of a drug substance in multiple crystalline forms) can cause variations in melting point, density, stability and drug solubility as these properties depend on the escaping tendency of the molecules from a particular crystalline structure. As a rule, for a drug that have the highest order of crystallinity is the most stable form, exists in multiple polymorphic forms, i.e. with the least amount of free energy and consequently, possesses the highest melting point and the least solubility. By controlling the crystallization process, amorphous or metastable forms of drugs possessing high free energy can be forcibly created. They offer the advantage of higher solubility but suffer from stability issues unless stabilizers intended to inhibit crystal growth are incorporated in the formulation. A high profile case involving polymorphism was withdrawal of ritonavir (Norvir®) capsules from the market in 1998 because a less soluble (and consequently less bioavailable) polymorph was identified two years after the product was approved and marketed, causing a decrease in bioavailability of the drug. This incident sensitized the pharmaceutical industry to the critical importance of polymorphism and encouraged the inclusion of polymorph screening as a routine component of preformulation studies (Chaudhary et al., 2012; Ojha et al., 2013; Patel et al., 2012).

8. **Micellar solubilization:** The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They can also be used to stabilize 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, entrapping the drugs within the micelles. This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl macro-glycerides 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. Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs (Desale et al., 2015; Singh et al., 2013; Kumar et al., 2013).
9. **Microemulsion and self-emulsifying system:** A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent, which dissolves a poorly water-soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. A self-microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions. It has also been referred to as microemulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility. 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 cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self micro-emulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water. The poorly soluble drug can be dissolved in a mixture of surfactant and oil, which is widely known as preconcentrate. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions. Compared with ready-to-use microemulsions, the SEDDS and SMEDDS have been shown to improve physical stability profile in long-term storage (Deshmukh et al., 2015; Sriamoransak et al., 2015; Sapra et al., 2012; Mandawgade et al., 2008).
10. **Micronization:** Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area by decreasing particle size; it does not increase equilibrium solubility. 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 (Vandana et al., 2014; Yohei et al., 2011; Pant et al., 2011).
11. **Nanocrystallization:** The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nanometers. There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and

Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components (Naofumi et al., 2016; Dandagi et al., 2011; Guo et al., 2015; Hecqa et al., 2005; Lua et al., 2016).

12. **Nanosuspension:** This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems 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 nanosuspension are usually less than one micron with an average particle size ranging between 200 and 600 nm (Attari et al., 2016).
13. **Neutralization:** Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β-Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried (Thorat et al., 2011).
14. **Particle size reduction:** The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area increases. The larger surface area allows a greater interaction with the solvent, which cause increase in solubility. By reducing particle size, increased surface area improves the dissolution properties (Dhillon et al., 2014).
15. **pH adjustment:** 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 (Patil et al., 2013).
16. **Precipitation:** In the precipitation method, a dilute solution is first produced by dissolving the substance in a solvent. The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air (Wadher et al., 2014).
17. **Salt formation:** Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. 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. 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 (Kumar et al., 2013).
18. **Solid dispersion:** For increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms, a useful pharmaceutical technique is Solid dispersion. "The term Solid dispersion is defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid state prepared by the melting (fusion), solvent, or melting-solvent method". Solid dispersion refers to a group of solid products consisting of atleast two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The most commonly used solvents for solid dispersions include water, methanol, ethanol, chloroform, DMSO, acetic acid (Rahman et al., 2014).
19. **Solubilization:** Surfactants are molecules with distinct polar and non-polar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very significant in industrial and natural processes. The addition of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent. The use of surfactants to improve the dissolution performance of poorly soluble drug products is possibly the fundamental, chief, and the oldest method. Surfactants are the agents, which reduces surface tension, and enhance the dissolution of lipophilic drugs in aqueous medium. The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants is more than 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.

    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 (Vemula et al., 2010; Kumar et al., 2013).

20. **Solvent deposition:** 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. Successfully solubility of aceclofenac has increased by solvent deposition technique using lactose (Thorat et al., 2011).
21. **Sonocrystallization:** Melt sonocrystallization is newer particle engineering technique. In this method by applying ultrasound energy in range of 20 to 100 kHz crystallization process is achieved. In pharmaceutical industry, ultra sound energy was introduced traditionally to increase the solubility of sparingly soluble drug. Ultrasound system use to influence the initial nucleation stage of crystallisation. The ultrasonication causes disaggretion or deagglomeration of particle. Cavitation is an important phenomenon of ultrasonication. In sonocrysatllization the energy of ultrasound cause repeated compression and expansion. After several cycles the bubble forms, grows and collapses. Due to bubble collapses, the energy is produced. This energy is responsible for breaking of particles. This results in high repeatable and predictable crystallization. Applying ultrasound to crystallization results in:
    (a) Nucleation at the lowest level of super saturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution.
    (b) Narrowing of the metastable zone width.
    (c) Narrow particle size distribution.
    (d) Decrease in the level of cooling necessary to achieve crystallization.
    (e) Highly repeatable and predictable crystallization.
    (f) Polymorph control (Zaheer et al., 2011; Shinde et al., 2014).
22. **Spherical Agglomeration:** It is a particle engineering technique. It is combined process of crystallization, agglomeration and Spheronization, which convert fine crystal in spherical shape particle. This method is important for improving the flow property wettability and dissolution rate of poorly soluble drug. Amount and mode of addition of spherical liquid, temperature and agitation speed this parameter must be optimize in this technique for production of spherical crystal (Saini et al., 2013; Saritha et al., 2012)
23. **Spray drying:** Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin, Aerosol 200 is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried. It gives the dried powder which is more soluble as well as more stable (Thorat et al., 2011).
24. **Supercritical fluid Process:** Once the drug particles are solubilized within SCF, they may be re-crystallized 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. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. 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 (Furqan et al., 2009).

Conclusions

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. Hence, solubility enhancement becomes necessary. It is now possible to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

References

Anjana MN, Joseph J and Nair SC (2013). Solubility Enhancement Methods- A Promising Technology for Poorly Water Soluble Drugs. *International Journal of Pharmaceutical Sciences Review and Research* **20(2):** 127-134.

Attari Z, Bhandari A, Jagadish PC and Lewis S (2016). Enhanced ex-vivo intestinal absorption of Olmesartan medoxomil nanosuspension: Preparation by combinative technology. *Saudi Pharmaceutical Journal* **24:** 57-63.

Aulton ME (2002). Pharmaceutics: The science of dosage form design. Churchill Livingstone Publication. 2nd ed.: 15-32.

Babu PRS, Subrahmanyam CVS, Thimmasetty J, Manavalan R, Valliappan K and Kedarnath SA (2008). Solubility Enhancement of Cox-Ii Inhibitors by Co-solvency Approach. *Dhaka University Journal of Pharmaceutical Sciences* **7(2):** 119-126.

Chandel P, Raj K and Kapoor A (2013). Liquisolid Technique: An Approach for Enhancement of Solubility. *Journal of Drug Delivery & Therapeutics* **3(4):** 131-137.

Chaudhary A, Nagaich U, Gulati N, Sharma VK and Khosa RL (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. *Journal of Advanced Pharmacy Education & Research* **2(1):** 32-67.

Dandagi PM, Kaushik S and Telsang S (2011). Enhancement of Solubility and Dissolution Property of Griseofulvin by Nanocrystallization. *International Journal of Drug Development & Research* **3(2):** 180-191.

Desale SL, Deshmukh AS and Mahajan VR (2015). Solubility enhancement of poorly water-soluble drug Fenofibrate by

inclusion complex. *World Journal of Pharmacological Research and Technology* **4(3):** 242-255.

Deshmukh AS (2015). Recent advances in self-emulsifying drug delivery system. *International Journal of Pharmaceutical Sciences and Nanotechnology* **8(1):** 1-5.

Deshmukh AS (2014). Solid Lipid Nanoparticles. *Research Journal of Pharmaceutical Dosage Forms and Technology* **6(4):** 282-285.

Deshmukh AS and Mahajan VR (2015). Advanced delivery of poorly water-soluble drug Atorvastatin by lipid based formulation as SMEDDS. *Asian Journal of Pharmaceutical Research and Development* **3(2):** 21-38.

Deshmukh AS and Mahajan VR (2015). Advanced delivery of poorly water-soluble drugs by lipid based formulation as SMEDDS. *Asian Journal of Research in Biological and Pharmaceutical Sciences.* **3(1):** 14-24.

Deshmukh AS, Mahale VG and Mahajan VR (2014). Liquisolid compact techniques: A Review. *Research Journal of Pharmaceutical Dosage Forms and Technology* **6(3):** 161-166.

Dhapte V and Mehta P (2015). Advances in Hydrotropic Solutions: An Updated Review. *St. Petersburg Polytechnical University Journal: Physics and Mathematics* **1:** 424-435.

Dhillon B, Goyal NK, Malviya R and Sharma PK (2014). Poorly Water Soluble Drugs: Change in Solubility for Improved Dissolution Characteristics a Review. *Global Journal of Pharmacology* **8(1):** 26-35.

Furqan M, Thakkar VT, Soni TG, Gohel MC and Gandhi TR (2009). Supercritical fluid technology: A promising approach to enhance the drug solubility. *Journal of pharmaceutical sciences and research* **1(4):** 1-14.

Gennaro AR (2000). Remington; The science and practice of Pharmacy. Lippincott Williams and Wilkins, 20th ed. Vol. 1.: 208-214.

Ghule PN, Deshmukh AS and Mahajan VR (2014). Floating Drug Delivery System (FDDS): An Overview. *Research Journal of Pharmaceutical Dosage Forms and Technology.* **6(3):** 174-182.

Guo Y, Wang Y and Xu L (2015). Enhanced bioavailability of Rebamipide nanocrystal tablets: Formulation and *in vitro*/ *in vivo* evaluation. *Asian journal of pharmaceutical sciences* **10:** 223-229.

Hecqa J, Deleers M, Fanara D, Vranckx H and Amighi K (2005). Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of Nifedipine. *International Journal of Pharmaceutics* **299:** 167-177.

Jiao D, Jinfeng L and Shirui M (2015). Development and Evaluation of Vinpocetine Inclusion Complex for Brain Targeting. *Asian journal of pharmaceutical sciences* **10:** 114-120.

Kapadiya N, Singhvi I, Mehta K, Karwani G and Dhrubo J (2011). Hydrotropy: A Promising Tool for Solubility Enhancement: A Review. *International Journal of Drug Development & Research* **3(2):** 26-33.

Kumar K and Bhandari A (2013). Solubility and dissolution enhancement: Technologies and research emerged. *Journal of Biological and Scientific Opinion* **1(2):** 105-116.

Kumar TA, Nirmala and Harikumar SL (2013). Various Techniques Enhancing Bioavailabilty of Poorly Water Soluble Drugs. *Journal of Drug Delivery & Therapeutics* **3(2):** 215-221.

Kumar VS, Raja C and Jayakumar C (2014). A Review on Solubility Enhancement Using Hydrotropic Phenomena. *International Journal of Pharmacy and Pharmaceutical Sciences.* **6(6):** 1-7.

Lua Y, Lib Y and Wu W (2016). Injected nanocrystals for targeted drug delivery. *Acta Pharmaceutica Sinica B.* **6(2):** 106-113.

Mahale VG, Deshmukh AS and Mahajan VR (2014). Formulation and Characterization of Inclusion Complexes: A Review. *Pharmtechmedica* **3(3):** 476-480.

Mandawgade SD, Sharma S, Pathak S and Patravale VB (2008). Development of SMEDDS using natural lipophile: Application to- Artemether delivery. *International Journal of Pharmaceutics* **362:** 179-83.

Manogar PG, Hari BV and Devi DR (2011). Emerging Liquisolid Compact Technology for Solubility Enhancement of BCS Class-II Drug. *Journal of Pharmaceutical Sciences and Research* **3(12):** 1604-1611.

Mehta H, Akhilesh D, Prabhakara P and Kamath JV (2012). Enhancement of Solubility by Complexation with Clyclodextrin and Nanocrystallisation. *International Research Journal of Pharmacy*. **3(5):** 100-105.

Nalinishastri CN and Tadikonda RR (2012). Use of the Liquisolid Compact Technique for Improvement of the Dissolution Rate of Valsartan. *Acta Pharmaceutica Sinica* B **2(5):** 502-508.

Naofumi H, Kayo Y, Haruka T and Chiaki O (2016). Development of nanocrystal formulation of mebendazole with improved dissolution and pharmacokinetic behaviors. *Asian Journal of Pharmaceutical Sciences* **11:** 122-123.

Nayak AK and Panigrahi PP (2012). Solubility Enhancement of Etoricoxib by Cosolvency Approach. *International Scholarly Research Network ISRN Physical Chemistry*. Article Id 820653: 1-5.

Ojha N and Prabhakar B (2013). Advances in Solubility Enhancement Techniques. *International Journal of Pharmaceutical Sciences Review and Research* **21(2):** 351-358.

Pant P, Bansal K, Rama P, Therdana R, Padhee K, Sathapathy A and Singh KP (2011). Micronization: An Efficient Tool for Dissolution Enhancement of Dienogest. *International Journal of Drug Development & Research* **3(2):** 329-333.

Patel JN, Rathod DM, Patel NA and Modasiya MK (2012). Techniques to Improve the Solubility of Poorly Soluble Drugs. *International Journal of Pharmacy & Life Sciences* **3(2):** 1459-1469.

Patil MS, Godse SZ and Saudagar RB (2013). Solubility enhancement by various techniques: An overview. *World journal of Pharmacy and Pharmaceutical Sciences* **2(6):** 4558-4572.

Pentewar RS, Utikar M, Gaikwad SS, Thonte SS, Bhange M and Sugave RV (2015). A Review on Extraction of Herbal Drugs and the Enhancement of Solubility by Hydrotropy Technique. *World Journal of Pharmaceutical Research* **4(9):** 614-623.

Prasad BSG, Gupta VRM, Devanna N, Rama DM, Rao GVV and Harish N (2012). Mixed Co-Solvency Concept: A Promising Tool To Enhance Solubility of Poor Soluble Drug Aceclofenac. *International Journal of Pharmaceutical, Chemical and Biological Sciences* **2(3):** 338-342.

Rahman MM, Khalipha ABR, Azad MAK, Hossain S and Haque S (2014). Methods of Solubility and Dissolution Enhancement for Poorly Water Soluble Drugs: A Review. *World Journal of Pharmacy and Pharmaceutical Sciences* **3(5):** 107-130.

Saini P, Kumar A and Visht S (2013). Spherical Agglomeration: A Novel Technique of Particulate Modification & Developing Niche Drug Delivery System. *International Science Press* **6(2):** 86-101.

Sapra K, Sapra A, Singh SK and Kakkar S (2012). Self-Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs. *Indo Global Journal of Pharmaceutical Sciences* **2(3):** 313-332.

Saravana KK, Sushma M and Prasanna RY (2013). Dissolution Enhancement of Poorly Soluble Drugs by Using Complexation Technique– A Review. *Journal of Pharmaceutical Sciences and Research* **5(5):** 120-124.

Saritha A, Shastri N, Sadanandam and Anantha L (2012). Enhancement of Dissolution and Anti- inflammatory Activity of Meloxicam by Spherical Agglomeration Technique. *Journal of pharmaceutical Sciences and Research* **4(1):** 1657-1661.

Savjani KT, Gajjar AK and Savjani JK (2012). Drug Solubility: Importance and Enhancement Techniques. *International Scholarly Research Network ISRN Pharmaceutics.* Article ID 195727: 1-10.

Sharma N and Bharkatia M (2011). Solubility enhancement techniques: A review. *International Journal of Pharmaceutical Erudition* **1(3):** 40-53.

Shekh I, Gupta V, Jain A and Gupta N (2011). Preparation and Characterisation of β- Cyclodextrin Aspirin Inclusion Complex. *International Journal of Pharmacy & Life Sciences* **2(4):** 704-710.

Shinde PR, Parve BS, Rawat S and Rathod SS (2014). Different Approaches towards the Solubility Enhancement of Drug: A Review. *World Journal of Pharmacy and Pharmaceutical Sciences* **3(4):** 625-646.

Singh N, Allawadi D, Singh S and Arora S (2013). Techniques for Bioavailability Enhancement of BCS Class II Drugs: A Review. *International Journal of Pharmaceutical and Chemical Sciences* **2(2):** 1092-1101.

Sriamornsak P, Limmatvapirat S, Piriyaprasarth S, Mansukmanee P and Huang Z (2015). A New Self-Emulsifying Formulation of Mefenamic Acid with Enhanced Drug Dissolution. *Asian Journal of Pharmaceutical Sciences* **10:** 121-127.

Thorat YS, Gonjari ID and Hosmani AH (2011). Solubility Enhancement Techniques: A Review on Conventional and Novel Approaches. *International Journal of Pharmaceutical Sciences and Research* **2(10):** 2501-2513.

Vandana KR, Raju YP, Chowdary VH, Sushma M and Kumar NV (2014). An overview on in situ micronization technique– An emerging novel concept in advanced drug delivery. *Saudi Pharmaceutical Journal* **22:** 283-289.

Vemula VR, Lagishetty V and Lingala S (2010). Solubility Enhancement Techniques. *International Journal of Pharmaceutical Sciences Review and Research.* **5(1):** 41-51.

Wadher SJ, Gattani SG, Jadhav YA and Kalyankar TM (2014). Recent Approaches in Solubility Enhancement of Poorly Water Soluble Drug Simvastatin: A Review. *World Journal of Pharmacy and Pharmaceutical Sciences* **3(4):** 366-384.

Yohei K, Koichi W, Manabu N, Shizuo Y and Satomi O (2011). Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *International Journal of Pharmaceutics* **420:** 1-10

Zaheer A, Maurya N, Mishra KS and Khan I (2011). Solubility Enhancement of Poorly Water Soluble Drugs: A Review. *International Journal of Pharmacy & Technology* **3(1):** 807-823.

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