Review Article

SOLUBILITY ENHANCEMENT TECHNIQUES

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Received on: 07-09-2010**; Finalized on:** 05-11-2010.

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 pharmacological response to be shown. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Hence various techniques are used for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability.

Keywords: Solubility, solubility enhancement, co-solvent, pH, emulsions.

INTRODUCTION

A number of methodologies can be adapted to improve solubilization 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.[1, 2] Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[3-6] As Solubility & permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like.[7] The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction.[8-10]

This review thus begins with discussion regarding the traditional approaches to drug solubilisation include pH adjustment, cosolvency and particle size reduction. While microemulsion and self-emulsifying systems are novel approaches. The different approaches of solubility enhancement are discussed below.

pH ADJUSTMENT

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.[11-14] Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.[15, 16]

The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the

precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

Advantages:

- Simple to formulate and analyse.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Commercial products using pH adjustment : Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na^+ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents.

CO-SOLVENCY

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents.[17] Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Parenteral formulations may require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co-Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilization approaches. However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. In this case, dissolution of this precipitate is required for oral absorption. Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds. The use of co-solvents is a highly effective technique to enhance the solubility of poorly-soluble drugs.[18–20] The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol.[21-24] Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely used as cosolvents because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity.[25-27]

Advantages:

- Simple and rapid to formulate and produce.

Disadvantages:

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size. Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.
- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

Co-solvent products: Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

PARTICLE SIZE REDUCTION

The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction, it is done by milling techniques using jet mill,

rotor stator colloid mills etc. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. [28]

Nowadays Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size. In micronization the solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Nanosuspensions are produced by homogenization and wet milling process.[29]

Advantages:

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Typically, low excipient to drug ratios is required.
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation.
- Generally, crystal forms are chemically and physically more stable than amorphous particles.
- A method to consider for stubborn compounds that defeat previous attempts to increase solubility.

Disadvantages:

- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
- Developing a solid dosage form with a high pay load without encouraging agglomeration may be technically challenging.
- Technically, development of sterile intravenous formulations is even more challenging.

Ball milled products: This process is widely used in non-pharmaceutical applications particularly in cosmetics to obtain ultra fine particles for sun block. Examples of pharmaceutical products include rapamycin (Rapamune®, 1 mg and 2 mg tablets, Wyeth).

MICROEMULSIONS

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use.[30-31] 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 co-surfactant 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.[32-34] The surfactant can be non-ionic like polyoxyethylene surfactants e.g. Brij or sugar esters like sorbitan monooleate (Span 80), cationic, or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate, or zwitterionic such as phospholipids like lecithin (phosphatidylcholine) commercially available from soybean and eggs. Lecithin is very popular because it exhibits excellent biocompatibility. Combinations of ionic and non-ionic surfactants are also found to be effective. The major disadvantage of microemulsions is their high concentration of surfactant/cosurfactant, making them unsuitable for IV administration. Dilution of microemulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug; however, the fine particle size of the resulting precipitate would still enhance absorption.[35-40] Compared to macroemulsion pre-concentrates, microemulsion pre-concentrates remain optically clear after dilution and usually contain a higher amount of water soluble surfactant and a higher content of a hydrophilic solvent. These formulations are only administered orally due to the nature of the excipients. Solubilization using microemulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactants mixtures. 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.[41, 42] 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.[43]

Advantages:

- The pre-concentrates are relatively easy to manufacture.
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state).

Disadvantages:

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
- Formulations containing several components become more challenging to validate.

Microemulsion products: Examples of poorly soluble compounds that use micro-emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus® capsules, Boehringer Ingelheim GmBH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral® capsules, Novartis AG).[44]

MICELLAR SOLUBLIZATION

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.[45-47] They can also be 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, entrapping the drugs within the micelles.[48] 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 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.[49-51] Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs.[52-54]

Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone.[55]

COMPLEXATION

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability.[56] Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl-β-cyclodextrin HP-β-CD) are most commonly used in pharmaceutical formulation. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide (DEET) [57] and the stability and photostability of sunscreens.[58, 59] Cyclodextrins are large molecules, with molecular weights greater than 1000Da, therefore it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase[60, 61] and decrease skin penetration.[62-64] In a recent review of the available data, Loftsson and Masson concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased flux.[65] As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug which is in excess of its solubility, an increase in flux might be expected. However, at higher cyclodextrin concentrations, the excess cyclodextrin would be expected to complex free drug and hence reduce flux. Skin penetration enhancement has also been attributed to extraction of stratum corneum lipids by cyclodextrins.[66] Given that most experiments that have reported cyclodextrin mediated flux enhancement have used rodent model membranes in which lipid extraction is considerably easier than human skin [67], the penetration enhancement of cyclodextrin complexation may be an overestimate. Shaker and colleagues recently concluded that complexation with HP- β-CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms.[68]

Lipophilic drug- cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipient together, resulting in enhanced drug solubilization. Cyclodextrins (CD) are a group of structurally-related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. Cyclodextrins consisting of 6, 7 and 8 D- glucopyranosyl units connected to α -1, 4 glycosidic linkages are known as α, β, γ, cyclodextrins, respectively.[69] Hydrophilic

cyclodextrins are nontoxic in normal doses while lipophilic ones may be toxic; hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use. The solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents.[70] The permeability through biological membrane is enhanced by the presence of cyclodextrins. Masson[71] reported about the permeation enhancement property of poorly water soluble drugs in presence of the CDs. These acts as permeation enhancers by carrying the drug through the aqueous barrier which exists before the lipophilic surface of biological membranes.[72] This can also be achieved through the double characteristics of the CDs, thus present character much lipophilic as hydrophilic. CDs can also be used as nasal permeation enhancers acting by interaction with nasal epithelium by modifying tight junction & lipid and protein content of the membrane, which enhances the permeation of the membrane.[73] CDs can also be utilized as permeation enhancer in pulmonary drug delivery systems. Rifampicin is a so- called concentration-dependent antibiotic, the rate and extent of bacterial kill is related to the attainment of high maximum concentration relative to the minimal inhibitory concentration. The rifampicin-CD inclusion compound can improve the lung transport of drug when nebulized with compatible pulmonary deposition and achieve required concentration of drug in broncho-alveolar epithelium lining-fluid when administered as aerosolized solution.[74-77] The forces driving complexation were attributed to (i) the exclusion of high energy water from the cavity, (ii) the release of ring strain particularly in the case of α -CD, (iii) Vander walls interactions, and (iv) hydrogen and hydrophobic bindings.[78] Solublization by complexation is achieved through specific interaction rather than changes in the bulk solvent properties as in other solublizing system such as cosolvents, emulsion and pH adjustments. The dissociation is very rapid, quantitative and therefore predictable. Another significant advantage of complexation technique is that some commonly used complexing agents such as hydroxy propyl beta cyclodextrin and sulfobutyl beta cyclodextrin are less toxic compared to other solublizing agents such as surfactant and cosolvents. Since most complexes formed is 1:1 complexes of the AL type, the dilution of complexes will not result in solution which is super saturated with respect to substrate. This can be important for very insoluble compounds that may precipitate upon injection when solublized by other system such as cosolvents. Despite all the attractive advantage of complexation, there are disadvantages. First of all the compound has to be able to form complexes with selected ligand. For compounds with very limited solubility to start with, solubility enhancement can be very limited. The second limitation is the complexes of Ap type, dilution of system may still result in precipitation. This is also true for solublization via combined technique such as complexation with pH adjustment. Lastly the potential toxicity issue, regulatory and quality control issue related to presence of ligand may add complication and cost to the development process.[79-80]

SUPERCRITICAL FLUID (SCF) PROCESS

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 (Markku Rantakyla et al., 2004). 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.[81,82] 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 solubilised within SCF, 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 sub-micron levels. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specialising in particle engineering via SCF technologies for particle size reduction and solubility enhancement.[83, 84] 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 Recrystallisation, 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).[85, 86]

SOLID DISPERSIONS

SCF techniques can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the

solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products.[87-89] A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation vessel was loaded with solution of carbamazepine and PEG4000 in acetone, which was expanded with supercritical CO_2 from the bottom of the vessel to obtain solvent-free particles. Solid dispersions are prepared by using several methods, such as the fusion (melt) method and the solvent method. A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available. Despite the promising aspects of dissolution enhancement and simplicity of concept, the solid dispersion technique has failed to gain popularity due to manufacturing, stability and scale-up issues. [90-93]

HYDROTROPHY

Hydrotrophy is a solubilisation 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 "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.[94-97]

Advantages of Hydrotropic Solubilization Technique:

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

The hydrotropes are known to self-assemble in solution[98].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, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.[99] 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-orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. 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, etc. 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, spherical crystallization.[100]

CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques 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.

Acknowledgment: The authors are thankful to the Directors V.Prasad Rao, V.Vinay Kumar, K.Rajashekar Reddy, and principals of Vikas College of Pharmacy and Prasad Institute of Pharmaceutical Sciences, Warangal, for providing necessary support to carry out the work.

Table 1: Limitation of some of the methods to increase the solubility of poorly soluble drugs.

Method	Limitations
1. Micronization	Difficult to control important character of the final particle such as size, shape, morphology, surface properties and electrostatic charges. High-energy process, which causes disruptions in the drug crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions (Takano et al., 2004).
2. Salt formation	High reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity. Even though use of co solvent to improve dissolution rate pose problems such as patient compliance and commercilation (Gibaldi et al., 2005).
3. Spray drying	Mechanical forces during comminution may degrade some pharmaceuticals, and spray drying may cause thermal stress and degradation of some products. Use of the organic solvent (Chen et al., 2004).
4. Hot-melt Extrusion`	Hot-melt extrusion technologies have been limited due to the temperature-sensitive nature of the drugs (Zajc et al., 2005).
5. Solvent Evaporation	High preparation costs and difficulties in completely removing the liquid solvent. Toxicity potential of organic solvents (Kim Eun et al., 2000).
6. Conventional methods for manufacturing of solid dispersions.	Laborious and expensive methods of preparation, Reproducibility of physicochemical characteristics, Difficulty in incorporating into formulation of dosage forms, Scale-up of manufacturing process, and Stability of the drug and vehicle (Hamsaraj Karanth et al., 2006)

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