Method used for Solubility Enhancement of Poorly water Soluble Drug: A Review

Prasad Harendra*, Verma Navneet Kumar
Rameshwaram Institute of technology and Management Lucknow, U.P. India
*E-mail: navneet_its04@rediffmail.com

Abstract
The slow dissolution rate exhibited by poorly water-soluble drugs is a major challenge in the drug development process. Following oral administration, drugs with slow dissolution rates generally show erratic and incomplete absorption which may lead to therapeutic failure. The aim of this study was to improve the dissolution rate and subsequently the oral absorption and bioavailability of a model poorly water-soluble drug. In recent years, due to application of combinational chemistry and high-throughput screening during drug discovery, a majority of new drug candidates exhibits poor aqueous solubility, compounds to be very challenging for formulation scientists in development of bioavailable dosage forms. Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts.

Keywords: Solid dispersion, Dissolution, Solubility, Bioavailability etc.

Introduction
Oral drug delivery remains the most popular route of administration however limitation in the physical-chemical properties of the drug sometimes prevents a successful therapeutic outcome. Specifically problems of poorly solubility and chemical stability in the gastrointestinal tract poor permeability and sensitivity to metabolism are often causes that result in the rejection of potential drug candidates as commercial products. The oral route of drug administration is the most important method of administrating drugs for systemic effects it is probable that best 90% of all drugs used to produce systemic effects are administered by oral route. The oral route is the preferred way of dosing, because this is the easiest and most convenient way of noninvasive administration. Most of drug substance that applied orally today is small molecule that can permeate the intestinal gut membrane by transcellular passive diffusion. This process is determined by physicochemical law and by the properties of the intestinal cells. In addition to its permeability through the gut wall, the availability of drug in the body depends on its ability to dissolve in the gastrointestinal fluid. For poorly water soluble drugs the dissolution rate is often the rate limiting step for bioavailability. The dissolution rate is a function of solubility and the surface area of the drug. Thus, dissolution rate will be increasing if the solubility of drug is increased e.g. by the use salt of a drug. It is also possible to speed up the dissolution process by incorporating into formulation a substance that forms a salt with the drug during dissolution. This has been a common means to increase the dissolution rate of aspirin by using magnesium oxide in the formulation.

The solubility behavior of drug is key determinant of its oral bioavailability. With the recent advent throughput screening of potential therapeutic agent, The number of poorly soluble drug has risen sharply and the formulation drugs for oral delivery. The dissolution rate directly propotional to saturation solubility of drug. Therefore aqueous solubility of drug can be used as first approximation of its dissolution rate. Drugs with low aqueous solubility have
low dissolution rate and suffer from oral bioavailability problems. So if solubility of drug is less than desirable steps taken to improve its solubility. Many more methods have been reported for increasing bioavailability of drug\(^5\). Biopharmaceutical classification system to provide a scientific approach for classifying drug compounds based on solubility related to dose and intestinal permeability in combination with the dissolution properties of the immediate release dosage forms\(^6\). The biopharmaceutics classification (BCS) combines physicochemical properties of compounds and physiological factor to predict the fraction dose absorbed from the gastrointestinal tract. The permeability of a given drug determines upper limit of its extent of absorption. The interaction of physiological environment (e.g. intestinal pH, transit time, etc) with physicochemical characteristics of drug (pKa, solubility in gut lumen, dissolution rate etc) can have influence on the availability of drug at the absorption site.

When permeability is the limiting factor for drug absorption (low pK\(_a\) value) structural modification of molecule is generally most the promising way to increase absorption rate. According to the BCS, drugs are classified according to their permeability and solubility to assess whether or not an in vivo correlation can be attained. The intent of the BCS was originally to determine whether a bio waiver could be made on the basis of dissolution tests for product that had undergone a scale up or post approval change classification of drugs according to the BCS can also be used as a practical starting point to select suitable dissolution test conditions for new drug products\(^7\).

### The Biopharmaceutical classification (BCS)

(a) Class -1-High solubility Good permeability  
(b) Class -2-Low solubility Good permeability  
(c) Class -3-High solubility Poor permeability  
(d) Class -4-Low solubility Poor permeability

### Methodology of dissolution enhancement of poorly soluble drugs.

#### Lipid based formulation

These formulations include lipid solution, lipid emulsion, micro-emulsion, self dispensing lipid formulations (SDLF). Bioavailability enhancements with lipid occur due to the poorly soluble drugs. Lipid solutions consists of drug dissolved in vegetable oil or medium chain triglycerides. The lipid emulsion and SDLF essentially comprise of a lipid and a surfactant mixture. The high lipophilicity facilitates absorption into the intestinal lymphatic and then systemic circulation, thus avoiding first pass metabolism. The presence of surfactant in this formulation also cause the enhanced absorption due to membrane induce permeation change.

#### Size reduction technology

The particle size reduction techniques enhanced the dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The drug particles are reduced to micron or nano–size by nanosizing, precipitation, cryogenic and supercritical fluid technologies.

Particle size reduction results in increased surface area that generally improves drug dissolution. Attrition techniques for particle size reduction including fluid energy milling ball milling and media milling, whereby raw material is subjected to mechanical shear forces resulting in the deggregation of solid particles This approach is expensive, efficient and reproducible, and easily adaptable to most pharmaceutical manufacturing set-ups. However heat generated during the grinding process may lead to the degradation of thermo labile compounds. Also submicron size particle can become difficult to handle due to static charge that develops on the particle surface during processing, leading to contamination by fly-away powders and generation of airborne particles that may be pose serious hazards to the operator.

#### Function polymer technology

Function polymers enhance the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of surrounding medium reversibly and stoichiometrically.

The dissolution rate of poorly soluble, ionizable drug cationic, anionic and amphoteric actives can be enhanced by this technology. This can also be applicable to heat sensitive materials and oils.

#### Porous micro particle technology

In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolved drug particles. This is the core technology applied as hydrophobic drug delivery system. These drug particles provide large surface area for increased dissolution rate. The solid form has a proprietary spray drying technology that allows the size and porosity of the drug particles to be engineered as desired. The hydrophilic solubilization technology for insoluble or poorly soluble drugs uses a lecithin and gelatin based water soluble coating to improve dissolution and hydration of lecithin-gelatin coat forms micelles which improved the oral bioavailability of the insoluble drugs.

#### Controlled precipitation technology

In this process, the drug is dissolved in a water miscible organic solvent and then dispersed into aqueous medium containing stabilizers (HPMC cellulose ether, gelatin). The solvent dissolves in water and causes precipitation of the
drug in the form of micro-crystals. The stabilizers control particle growth and enhance the dissolution rate of poorly soluble drugs due to large surface area hydrophilized by the adsorbed stabilizer.

**Solid dispersions**

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. Eutectic solid dispersions are homogeneous dispersion of crystalline or amorphous drugs in crystalline or amorphous carriers. In the solid solution form, the drug could be partially or completely soluble in the dispersing matrix. Presence of the drug in microcrystalline estate, improving the wettability and formation of high free energy amorphous forms of the drug during solid dispersion formation contribute towards enhanced drug solubilisation.

**Inclusion complexes and microemulsion**

Particle size reduction, whether via traditional micronisation of novel nanosizing methods, may not be applicable to all possible soluble compounds, most notably high dose drug products and those compounds with higher melting points. In such cases, solubilisation via drug- cyclodextrin inclusion complexes may be more appropriate. In other case Traditional combination and micronising techniques may not be able to reduce particle size sufficiently to satisfactorily solubilise the drug, and self emulsifying or microemulsion techniques may be applied the synthetic CDs improve solubility significantly, they are still limited in their drug inclusion capacity and retain disadvantageous processing characteristics for oral dosage forms; the volume of CD complexes is often much greater than the volume of drug alone, which may severely limit the types of delivery technologies that may be employed. CD complexes have also been employed in conjunction with hydrophilic polymers, such as hydroxypropylmethyl cellulose, to improve the solubilising effect of the CDs.

The improvement in solubilisation ability within these water-soluble polymer/drug included CD aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available. Microemulsions and self-emulsifying systems have emerged as potential Solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant In most self-emulsifying systems is required to be in excess of 30 percent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and polyethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co-solvents increases process in complexity while improving the potential drug load of the emulsion. 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 complexity while improving the potential drug load of the emulsion. 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.

**Solubilising excipients**

The use of surfactants to improve the dissolution performance of poorly soluble products has also been successfully employed presence of surfactant the surface tension and increase the solubility of the drug it organic Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. The presence surfactants within a drug product formulation may result in and incompatibility with drug delivery technologies which rely well-regulated hydration, dissolution and erosion of a matrix or coating to achieve controlled release. The influence of the changes is pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals is well documented. The absorption of a drug largely dependent upon diffusion, which varies with the pKa of the drug and the pH of the individual regions within the gastrointestinal tract, and permeability, which is not only moderated by the surface area of the region in which it is released, but also the regional pH effect upon drug ionize.

**Others Methods for enhancing the solubility of drugs:**

The ability to increase the aqueous solubility can be valuable aid to increasing efficacy or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility of a solid drug solute:

**Use of co-solvent:**

The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol propylene glycol, glycerin, sorbitol and polyethylene glycol, can be used. Ternary diagrams are used to visualize where maximum solubility occurs when more than one solvent is used.

**Hydrotropy method:**

Hydrotropy is a solubilization process whereby addition of large amount of second solute results in an increased in the aqueous solubility of another solute. Solute consist of alkali metals salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increased solubility in given solvents are said to “salt in” the solute an those salts that decreased solubility “salt out” the solute.

**Change in dielectric content of solvent:**

The addition of a co-solvent can increase solubility of hydrophobic molecules by reducing the electric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has high dielectric
constant. The dielectric constant is measure of the effects a substance has on the energy needed to separate to oppositely charges bodies. A vacuum is arbitrary given a dielectric constant of one. The energy required to separate to oppositely charge bodies is inversely proportional to the dielectric constant of the medium.

Chemical modification of the drug.

By the addition of polar groups like carboxylic acids, ketons and amines can increase solubility by increasing hydrogen bonding and the interaction with water.

Complexation method (inclusion complex or cathrates)

Considering increasing in solubility and dissolution of the drugs has been achieved by the use of cyclodextrin. β-cyclodextrin can solubilized water insoluble drugs. In the same way, the solubility of β-cyclodextrin can be significantly enhanced by the addition of some water soluble drugs such as sodium salicylate, or water soluble polymers such as hydroxypropylemethylecellulose to the aqueous solution. Other complex like inorganic coordination, chelates, metal-olefins, and molecular complexes can also be increased as complexes relies on relatively weak forces such as london forces, hydrogen bonding and hydrophobic interactions.

Alteration of pH of solvent

pH of solvent when reduced causes solubility enhancement. A combined effect of pH and complexation on solubilization is also synergistic in nature.

Uses of surfactants

Surfactants are amphilic in nature, meaning it has polar end (circular head) and a non polar end (the tail). When a surfactant (e.g. tween 80, sodium lauryal sulphate, polyethylene glycol) is place in water, it will from micelles. A non polar drug will partition into the micelle and the polar tails will solubilize the complex.

Uses of hydrates or solvates

A crystalline compounds may be contains either a stoichiometric or non stoichiometric adducts; involve entrapped solvents molecules within the crystals lattice. A stoichiometric adducts, commonly referred to as solvate , is a molecular complex that has incorporated the crystallizing solvent molecules into the specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as hydrate. A compound not containing any water within its crystals structure is termed anhydrous. Aqueous solubility of anhydrous forms are higher than the hydrate forms

Use of soluble prodrug

The physico-chemical properties of the drug are improved by bio reversible chemical alteration. The most common prod rug strategy involves the incorporation of polar or ioniziable moiety into the parent compound to improve aqueous solubility. The’ post hoc prod rug approach ‘has been successfully used to improve water solubility of corticosteroids vitamins and benzodiazepine.

Amorphous forms

Amorphous forms have atoms or molecules randomly placed as in a liquid and higher thermodynamic energy than corresponding crystalline forms. Solubility as well as dissolution rates are generally greater.

Application of ultrasonic waves

Solubility increase by use of ultrasonic vibrators is also possible. An oscillator of high frequency (100- 500) is used and device known as Pohlaman whistle. Solubility increase by use of ultrasonic vibrators is also possible. An oscillator of high frequency (100- 500) is used and device known as Pohlaman whistle.

Solid dispersions method

Solid dispersions method reduces the drug particle size and changes the microenvirment of the drug particle, increase the rate of dissolution and absorption and thus changes the biopharmaceutical properties of poorly water soluble drugs. Solid dispersions are prepared by fusion, solvent evaporation and fusion solvent method.

Solid dispersion

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitation with bioavailability enhancement of poorly water soluble drugs just mentioned can be overcome. This method, which has later termed solid dispersion, involved the formation of eutectic mixture in microcrystalline state. Chiu and riegelman defined the solid dispersion as A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting or solvent, or melting-solvent method.

Classification of solid dispersions

The term solid dispersion refers to group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can dispersed molecularly, in amorphous particles (clusters) or crystalline particles. Therefore, based on their molecular arrangement six different type’s solid dispersions can be distinguished. Some molecules present in clusters while some are molecularly dispersed.

The solid dispersion is classified as.

1. Simple eutectic mixture.
2. solid solutions.
3. Glasssolution and glass suspensions.
4. Amorphous precipitation in a crystalline carrier.

Simple eutectic mixture
These are prepared by rapid solidification of fused the melt of two components that show complete liquid miscibility but negligible solid --solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two components. Thus, the x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components.

**Solid Solution**
In a solid solution, the two components crystalline together in in a homogenous one- phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solution can be classified two methods. According to the extent of miscibility of the two components. In continuous solid solution, the two components are miscible in the solid state in all proportional. Discontinuous solid solution exists at extremes of composition. In general, some solid state solubility can be expected for all two components systems.

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional or interstitial. In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice. The molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. For this occur, the solute molecular diameter should less than 0.59 times that of solvent molecule. Therefore, the volume of the solute molecule should be less than 20% of solvent molecule. Owing to their large molecular size, polymers favor the formation of interstitial solid solutions.

**Glass solution and suspension**
A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy carrier. A glass suspension refers to a mixture in which precipitated particles are suspended in glassy solvent. The glassy state is characterized by transparency and brittleness below the glass glass transition temperature. Glass do not have sharp melting points. Instead, they soften progressively on heating .The lattice energy, which represented a barrier to rapid dissolution, is much lowers in glass solutions that in solid solutions.

**Amorphous Precipitation in crystalline carrier**
This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous forms. In a simple eutectic mixture, the drug is the precipitated in crystalline forms. An example of this is the precipitation of sulfathiazole in amorphous forms in a crystalline urea.

It is postulated that a drug with propensity to super cooling has more tendency to solidify as an amorphous form in the presence of carrier.

**Mechanism of increased dissolution rate of solid dispersions**
The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high 400-fold to less than two fold. Corrigan reviews the current understanding of the mechanism of release from solid dispersions. The increase in dissolution rate for solid dispersions can attribute to a number of factors. it is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulate for the observed improvement dissolution of these systems is as follows.

1. **Reduction of particle size**
   In the case of glass, solid solutions, and amorphous dispersions, particle size reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area of solubilization.

2. **Solubilization effect**
   The carrier material, as it dissolves, may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and Chlorpromide in urea, as well as for numerous other drugs.

3. **Wettability and dispersibility**
   The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.

4. **Metastable forms.**
   Formulation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. it was found that the activation energies of dissolution furosemide was 17 kcal per mole, whereas that for 1:2 furosemide:PVP co precipitate was only 7.3 kcal per mole. Depending on classification of drug, different strategies can be applied to increase or accelerate the absorption of drug either increasing the permeability of absorbing membrane .The strategy for class --II drugs, having dissolution limitation but no permeation limitations, is to increase the amount of dissolved drug molecules at the absorption site

**Method for preparing solid dispersion**
(i) Melting or fusion method.
(ii) Hot melt extrusion method.
(iii) Solvent method.

**The newer methods include**
(i) Spray- Drying method.
(ii) Supercritical fluid process.

**Melting or fusion method**
The fusion method is sometimes referred to as the melt method, which starting materials are crystalline this method was first reported by Sekiguchi and obi. A physical mixture of an active agent and water soluble carrier is heated until it is melted. The melted is solidified rapidly in an ice bath under vigorous stirring, pulverizing and then sieving. Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well that heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture. Which results in an inhomogeneous solid dispersion? This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it observed that when the mixture, which results in an inhomogeneous solid dispersion. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug.

**Hot melt extrusion**

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

**Solvent method**

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution. Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water. But this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical.

Solubilisers like cyclodextrins or surfactants like Tween80 increase the aqueous solubility of the drug substantially. However, the amount of solubilisers or surfactants in the final product is often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol, dichloromethane and ethanol have been used for this purpose. However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio. The second challenge in the solvent method is to prevent phase separation, crystallization of either drug or matrix, during removal of the solvent. Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favouring phase separation (ex crystallization). To dry the solutions, vacuum drying is often the solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccators to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly.

**Supercritical fluid method**

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent when supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as ‘solvent free’. The technique is known as Rapid Expansion of Supercritical Solution.11

**Conclusion**

Solid dispersion prepared by using different methods and various polymeric carriers. The result of DSC and XRD studies showed that solid dispersion crystalline into the amorphous state. The growing percentage of solubility issues demands that technologies for enhancing drug solubility be developed to reduce the percentage of poorly soluble drug candidates eliminated from development as a result. Drug cyclodextrin inclusion complexes, surfactant addition and particle size reduction via combination, spray drying and solvent recrystallisation, possess significant limitations on the extent to which they may solubilise insoluble and nearly insoluble compounds. Novel technologies, such as supercritical fluid processing, nanosizing and pH modification, present novel methods of solubilisation that may allow for greater opportunities to deliver poorly soluble drugs.
References


