ENHANCEMENT OF SOLUBILITY BY COMPLEXATION WITH CYCLODEXTRIN AND NANOCRYSTALLISATION
Mehta Hiral, D.Akhilesh*, P.Prabhakara, Kamath J.V
Department of Quality Assurance, Shree Devi College of Pharmacy Airport Road, Mangalore - 574142 Karnataka, India

Article Received on: 02/03/12 Revised on: 20/04/12 Approved for publication: 18/05/12

*Email: akhilesh_intas@rediffmail.com

ABSTRACT
The cyclodextrins have a wide range of applications in different areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. The most common pharmaceutical application of cyclodextrin is to enhance the solubility, stability, safety and bioavailability of drug molecules. The purpose of this review is to discuss and summarize some of the findings and applications of cyclodextrin (CD) and their derivatives in different areas of drug delivery. This article highlights the molecular structure, properties like complexation, solubility etc. of cyclodextrins and focuses on its use for parenteral, oral, ophthalmic and nasal drug delivery. Other routes including dermal, rectal, sublingual and pulmonary delivery are also briefly addressed. The objective of this contribution is to focus on the potential use of chemically modified cyclodextrins as high-performance drug carriers in drug delivery systems with emphasis on the more recent developments. Thus cyclodextrins, because of their continuing ability to find several novel applications in drug delivery, are expected to solve many problems associated with the delivery of different novel drugs through different delivery routes. 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.

Key Words: Cyclodextrins, Nano Crystallization, Solubility, Milling, High pressure Homogenizer.

INTRODUCTION
To be pharmacologically active, all drugs must possess some degree of aqueous solubility, and most drugs should be lipophilic to permeate the biological membranes via passive diffusion. The water solubility of any drug is determined by its potency and its type of formulation. If a drug is hydrophilic, the dissolved drug molecule will not partition from the aqueous exterior into a lipophilic bio membrane and then permeate the membrane. High-throughput screening approaches to drug development have led to an increasing number of lipophilic water-insoluble drugs whose clinical usefulness are hampered by their insolubility in water. The effect of cyclodextrin on drug solubility, dissolution, bioavailability, safety, stability and its use as excipients in drug formulation are discussed in this article. Also some focus is given on various factors influencing inclusion complex formation of cyclodextrin. The findings and applications of cyclodextrin (CD) in different areas of drug delivery, particularly in parenteral, oral, ophthalmic, nasal, dermal, rectal, sublingual, pulmonary and other novel drug delivery systems are explained in detail.

CYCLODEXTRIN
Inclusion complexes/complexation
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. Among all the solubility enhancement techniques incursion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Cyclodextrins (CD) are a group of structurally-related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. Cyclodextrins consisting of 6, 7 and 8 D glucopyranosyl units connected to α -1, 4 glyosidic linkages are known as α, β, γ, cyclodextrins, respectively. Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl-β-cyclodextrin HP-β-CD) are most commonly used in pharmaceutical formulation. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Hydrophilic cyclodextrins are nontoxic in normal doses while lipophilic ones may be toxic; hence, methyl, hydroxypropyl, sulfalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. 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 [51]. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluiumide (DEET) and the stability and photostability of sunscreens. 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 and decrease skin penetration. Solubilization by complexation is achieved through specific interaction rather than changes in the bulk solvent properties as in other solubilizing system such as cosolvents, emulsion and pH adjustments. 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. 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. 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 solubilizing agents such as surfactant and cosolvents. 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. 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, the penetration enhancement of cyclodextrin complexation may be an overestimate. Since most complexes formed is 1:1 complexes of the AL type, the dilution of complexes will not result in solution which is supersaturated with respect to substrate. This can be important for very insoluble compounds that may precipitate upon injection when solubilized by other system such as cosolvents. 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. The solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents. The permeability through biological membrane is enhanced by the presence of cyclodextrins. 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. 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. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Solubility and oral bioavailability of Glipizide, Rofecoxib, Piroxicam and Carvedilol can be improved by using cyclodextrins inclusion complex. Solubilization by complexation is achieved through specific interaction rather than changes in the bulk solvent properties as in other solubilizing system such as cosolvents, emulsion and pH adjustments. The dissociation is very rapid, quantitative and therefore predictable. Masson 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. This can also be achieved through the double characteristics of the CDs, thus present character much lipophilic as hydrophilic. 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 solubilization 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. 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 solubilization 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. There are various technologies adapted to prepare the inclusion complexes of poorly of poorly water soluble drugs with cyclodextrins.

**Cyclodextrin**

Cyclodextrins (CD) are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in general they do not permeate lipophilic membranes. Cyclodextrins are widely used as "molecular cages" in the pharmaceutical, agrochemical, food and cosmetic industries. In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions etc. The chemical structure of β-cyclodextrin molecule Cyclodextrin consists of (α-1,4)-linked α-D-glucopyranose unit with a lipophilic central cavity and the structures are as shown in. Due to the chair formation of theglucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge. This gives cyclodextrin molecules a hydrophilic outer surface, whereas the Cyclodextrin as Drug Carrier Molecule: A Review 569 Sci Pharm. 2008; 76; 567–598. lipophilicity of their central cavity is comparable to an aqueous ethanolic solution. The naturally occurring cyclodextrins are α, β, and γ types containing 6, 7 and 8 glucopyranose units respectively. They have limited aqueous solubility due to the strong intermolecular hydrogen bonding in the crystal state. Substitution of the H-bond forming -OH group has improved their solubility. The various derivatives that have gained pharmaceutical interest include hydroxyl propyl derivatives of β, γ and methylated β-cyclodextrins, sulfo butyl ether β-cyclodextrin etc. The natural α-CD and β-CD, unlike γ-CD cannot be hydrolyzed by human salivary and pancreatic amylases; though all three are subjected to fermentation by the intestinal micro flora.Hydrophilic cyclodextrins are considered nontoxic at low to moderate oral dosages. The natural cyclodextrin and its derivatives are used in topical and oral formulations, but only α-cyclodextrin and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations. The γ-cyclodextrin forms visible aggregates in aqueous solution and is not well suited for parenteral formulations. Due to its nephrotoxicity, β-
cyclodextrin cannot be used in parenteral formulations. Lipophilic cyclodextrin derivatives, such as the methylated cyclodextrins, are to some extent absorbed from the gastrointestinal tract into the systemic circulation and have been shown to be toxic after parenteral administration. Presently, oral administration of methylated β-cyclodextrin is limited by its potential toxicity.

**Complex formation and drug solubility of cyclodextrin**

In aqueous solutions, cyclodextrins are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during complex formation, and the drug molecules in complex are in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity, hydrogen bonding, Vander Waals interaction, charge transfer interaction etc. The physicochemical properties of free cyclodextrin molecule differ from those in complex. The stoichiometry of the complexes formed and the numerical value of their stability constants can be determined by observing the changes in physicochemical properties like solubility, chemical reactivity, UV/VIS absorbance, drug retention, chemical stability, effects on drug permeability through artificial membranes etc. The formation of the inclusion complex between omeprazole (OME) and methyl-β-cyclodextrin (MβCD) has been studied and the stoichiometry of the complexes was found to be 1:1 mol:mol OME:cyclodextrin and the value of Ks was higher for OME:MβCD than for OME:βCD inclusion complexes.

**Phase-solubility diagram**

Higuchi and Connors have classified complexes based on their effect on substrate solubility and it is indicated by the phase-solubility profiles as shown in Fig. 2. A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e. drug) increases with increasing ligand (cyclodextrin) concentration. When the complex is first order with respect to ligand and first or higher order with respect to substrate then AL-type phase-solubility profile is obtained. If the complex is first order with respect to the substrate, but second or higher order with respect to the ligand then AP-type phase solubility profile is obtained. It is difficult to interpret the AN-type phase-solubility profile. The negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexion media, changes in complex solubility or self-association of cyclodextrin molecules. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexion medium.

In general, the water-soluble cyclodextrin derivatives form A-type phase solubility profiles, whereas the less soluble natural cyclodextrin forms B-type profiles. Most of the drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and the complex aggregates are capable of dissolving drugs through micelle-like structures. The phase-solubility profiles only describe how the increasing cyclodextrin concentration influences the drug solubility. The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin (D/CD) complex where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD) and is given in eq. 1.

Cyclodextrins as Drug Carrier Molecule.

Eq. 1: \( D + CD \rightarrow K \ 1:1 \rightarrow D/CD \)

**Drug stability**

The feasibility of a pharmaceutical formulation can be limited by stability issues, especially for aqueous formulation of drugs that are prone to hydrolysis or oxidation. The reaction rates can be affected by inclusion of the chemically liable moiety of the drug into the cyclodextrin cavity. In cyclodextrin solutions the observed degradation rate for a chemically unstable compound forming 1:1 complex, will be the weighted average of the degradation rates of the free drug and drug in cyclodextrin complex. In first-order and pseudo-first order reactions, such as hydrolysis or oxidation, the stabilizing effect will depends on three parameters like the cyclodextrin concentration, the stability constant of the complex and the degradation rate constant for the drug degradation within the cyclodextrin cavity. Many studies have shown that stability of chemically liable drugs like steroid esters, alkylating anti-cancer agents, prostaglandins, prodrugs and various other compounds can be significantly improved through formulation with cyclodextrin. The studies also revealed that cyclodextrin can increase the physical stability of various drugs. For example, evaporation of volatile compounds can be significantly reduced through complex formation. The cyclodextrin will also reduce denaturation in peptide and protein formulations. Cyclodextrin can sometimes have a destabilizing effect on drugs through direct catalysis, for example, by enhancing drug solubility in aqueous drug suspensions. The catalytic effect is associated with deprotonisation of the hydroxyl groups located at the rim of the cyclodextrin cavity. This catalytic effect is mainly observed under basic conditions and increases with increasing pH.

**Drug Delivery through biological membrane**

The cyclodextrin do not readily permeate the biological membranes due to its chemical structure, molecular weight and very low octanol/water partition coefficient. Only the free form of drug, which is in equilibrium with the D/CD complexes are capable of penetrating lipophilic membranes. Cyclodextrins, in general, do not enhance permeability of hydrophilic water-soluble drugs through lipophilic biological membranes. The physicochemical properties of the drug (e.g., its solubility in water), the composition of the drug formulation (e.g., aqueous or non-aqueous) and physiological composition of the membrane barrier (e.g., presence of an aqueous diffusion layer), will determine whether the cyclodextrins will enhance or will hamper drug delivery through a biological membrane. The cyclodextrins will enhance drug delivery through aqueous diffusion-controlled barriers, but can hamper drug delivery through lipophilic membrane-controlled barriers. Cyclodextrins can also
enhance the drug bioavailability by stabilization of drug molecules at the bio-membrane surface. For example, the cyclodextrin-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect. In general, drug stabilization associated with cyclodextrin complexation plays only a very minor role when it comes to drug delivery through biological membranes. It is their solubilising effect that is usually related to improved drug delivery. However, as cyclodextrins can both enhance and hamper drug delivery through biological membranes, it is of utmost importance to optimize cyclodextrin-containing drug formulations with regard to drug delivery from the formulations. Too much or too little cyclodextrin can result in less than optimum drug bioavailability.

Cyclodextrin based drug delivery
On the basis of the multifunctional characteristics of cyclodextrins, this section is mainly concerned with the latest applications of cyclodextrins in oral, rectal, sublingual, ocular, nasal, pulmonary, dermal and other novel drug delivery systems like liposomal, microspheres, osmotic pump, peptide and protein delivery, site-specific drug targeting and nanoparticles.

Rectal drug delivery
The release of drugs from suppository bases is one of the important factors in the rectal absorption of the drugs, since the rectal fluid is small in volume and viscous compared to gastrointestinal fluid. In general, hydrophilic cyclodextrins enhance the release of poorly water-soluble drugs from oleaginous suppository bases because of the lesser interaction of the resultant complexes with the vehicles. The complexation of lipophilic drugs with hydrophilic cyclodextrins makes them insoluble in hydrophobic vehicles, the complex existing as well-dispersed fine particles in the vehicles. This manipulation not only enhances drug dissolution at an interface between the molten bases and the surrounding fluid but also inhibits the reverse diffusion of the drugs into the vehicles. In comparison with the parent cyclodextrins, the methylated cyclodextrins significantly enhance the rectal absorption of hydrophobic drugs, which are anti inflammatory agents, such as flurbiprofen, carmofur and biphenyl acetic acid from the oleaginous suppository. The superior effect of the methylated cyclodextrins can be explained by the faster release of the drugs together with the lowering affinity of the complexed drugs to the oleaginous suppository base.

Sublingual drug delivery
Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism. In this method the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations the complexation of poorly water soluble drugs with cyclodextrin has been shown to increase the bioavailability of various lipophilic drugs. For example, 2-hydroxy propyl-β-CD has been shown to increase the bioavailability of 17β-oestradiol, androstenediol, clomipramine and danazol. In case of lipophilic compounds, the aqueous solubility and dissolution rate of a drug is usually the rate-limiting step for drug absorption. The increased bioavailability achieved by cyclodextrins are due to the increased aqueous solubility and drug resolution rate. In addition to this, they also act as conventional penetration enhancers. There are some basic differences between sublingual and oral administration of cyclodextrin containing formulation. The drug must be released from the inclusion complex before it can be absorbed. This can be a problem for sublingual application due to the small volume of aqueous saliva and the relatively short residence time. The dissolved drug is removed from the buccal area within few minutes after administration, therefore not allowing enough time for the drug to be released from cyclodextrin complex. One limitation in the use of cyclodextrin in sublingual administration is the effect of cyclodextrins on formulation bulk. For example, the development of sublingual formulation of Δ9-tetrahydrocannabinol (THC), the complexation of THC with 2-hydroxypropyl-β-CD and methylated α-CD was studied. Results from studies showed that the estimated therapeutic dose (1mg) of THC could form a water soluble complex with 400 mg of 2-hydroxy propyl-β-CD, but formulation bulk of 400 mg is considered too large for sublingual administration. The same amount of THC (1 mg) could form a soluble complex with 25 mg of randomly methylated β-cyclodextrin. Thus sublingual administration of randomly methylated β-CD containing THC formulation increases bioavailability of THC compared with oral administration.

Ocular drug delivery
The possible advantages in ocular use of cyclodextrins are the increase in solubility and stability and avoidance of incompatibilities of drugs such as irritation and discomfort. One of the pre requisites for a new vehicle to be used in ophthalmic preparations is that it is not irritating to the ocular surface, because irritation causes reflex tearing and blinking, which results in a fast washout of the instilled drug. Hydrophilic cyclodextrins, especially 2-hydroxy propyl-β-cyclodextrin and sulfo butyl-β-cyclodextrin, have been shown to be nontoxic to the eye and are well tolerated in aqueous eye drop formulations. Another major problem with eye drops is its inability to sustain high local concentration of drugs. The administration of ophthalmic drugs in gels and in polymer matrix has been shown to increase the contact time of the drugs with the cornea, a situation which increases their ocular bioavailability. However, patient acceptance of such delivery systems is unsatisfactory. Conversely, eye drops with low viscosity appears to be the most acceptable delivery form of ophthalmic drugs. Hydrophilic cyclodextrins do not penetrate tight biological barriers such as the eye cornea but enhance the ocular bioavailability of lipophilic drugs by keeping the drugs in solution and increasing their availability at the surface of the corneal barrier. The cyclodextrin increases the dose to solubility ratio of water soluble drugs. For example, acetazolamide is a carbonic anhydrase inhibitor used to treat glaucoma. Its aqueous solubility in pure water is 0.7 mg/ml, but in 20% (w/v) aqueous 2-hydroxy propyl-β-CD solution, it is 7 mg/ml. Addition of water-soluble polymers to the aqueous cyclodextrin solution increases the solubility further. Cyclodextrin solubilization of the drug will increase the amount of dissolved drug at lipophilic membrane surface but excess will decrease the drug delivery through cornea. Thus, cyclodextrins are used to decrease ophthalmic drug irritation and to increase the chemical stability of drugs in aqueous ophthalmic formulations.

Nasal Drug Delivery
The nasal route is another effective way to bypass first-pass metabolism. In order to enter the systemic circulation the drug has to dissolve in the aqueous nasal fluids. In nasal formulations, cyclodextrins are normally used to increase the aqueous solubility of lipophilic drugs. The lipophilic cyclodextrins acts as penetration enhancers, especially in nasal delivery of peptides. The methylated cyclodextrin derivatives increase the bioavailability. For example, the nasal bio availability of insulin in rats was increased from
Pulmonary administration of drugs is usually intended for pulmonary drug delivery. For dermal drug delivery, the skin is a rate determining factor, then cyclodextrins can acts as penetration enhancers like alcohols, fatty acids etc. A suitable vehicle is used to decrease barrier properties. The cyclodextrins enhance drug absorption through a narrow homogenization gap with a very high pressure. This degradation is achieved by using both attrition forces. The most common models are a tumbling ball mill and a stirred media mill. The degradation of mill surfaces and subsequent suspension contamination are problems of this method.

**Dermal drug delivery**

Cyclodextrins have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drugs intended either for local or systemic use. They also improves the solubility and stability of drugs in the topical preparations, enhances the transdermal absorption of drugs, sustains the drug release from the vehicle and avoids undesirable side effects associated with dermally applied drugs. The main barrier for dermal drug absorption through the skin is the outer most layer stratum corneum. Penetration enhancers like alcohols, fatty acids etc. are used to decrease its barrier properties. The cyclodextrins enhance drug delivery through aqueous diffusion barriers, but not through lipophilic barriers like stratum corneum. A suitable vehicle must be selected so that cyclodextrins fully exert their functions. If the drug release is from an aqueous based vehicle or if an aqueous diffusion layer at outer surface of skin is a rate determining factor, then cyclodextrins can acts as penetration enhancers. But if drug penetration through the lipophilic stratum corneum is the main rate determining factor then cyclodextrins are unable to enhance the drug delivery. For instance, the in vitro release rate of corticosteroids from water-containing ointments is markedly increased by hydrophilic cyclodextrins, whereas in other ointments the cyclodextrins retard the drug release. The enhancement of drug release can be ascribed to an increase in solubility, diffusibility and concentration of the drug in the aqueous phase of the ointment through water-soluble complex formation. In ointments, as with suppositories, the drug in its cyclodextrin complex may be displaced by some components of the ointment, depending on the magnitude of the stability constant of the complex. Thus, an optimized release of the drug from the preparation containing its cyclodextrin complex may be obtained by using a vehicle in which the complex is barely dissociated and maintains a high thermodynamic activity. Generally, cyclodextrins do not enhance drug delivery from non aqueous vehicles. Cyclodextrins have also been used to reduce permeability of compounds into skin. It has been indicated that complexation of sunscreen enhances its photo protective effects by preventing permeation of the sunlight into the skin.

**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.

**Milling**

Nanoscale particles can be produced by wet milling process. In ball mills, particle size reduction is achieved by using both impact and attrition forces. The most common models are a tumbling ball mill and a stirred media mill. The degradation of mill surfaces and subsequent suspension contamination are problems of this method.

**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 non-aqueous 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.

**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.

**Cryo-vacuum-method**

In the cryo-vacuum method, the active ingredient is first
dissolved in water to attain a quasi-saturated solution. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C) which causes a very fast rise in the degree of saturation based on the decrease of solubility and development of ice crystals when the temperature drops below 0 °C. This leads to a fast nucleation of the dissolved substance at the edges of the ice crystals. The solvent must be completely frozen before the vessel is removed from the liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant -22 °C and the pressure is lowered to 10-2 mbar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of the particles produced, so they will remain crystalline. The method yields very pure nanocrystals since there is no need to use surfactants or harmful reagents. Nanomorph

The Nanomorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Water re-dispersible dry powders can be obtained from the nanosized dispersion by conventional methods, e.g. spray-drying. Using this technology the coarse crystalline drug substances are transformed into a nano-dispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles.

CONCLUSION

By this article we concluded 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. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability 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, such as complexation by cyclodextrins and nanocrystallisation which increases the solubility of poorly soluble drugs.

REFERENCES