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Current Perspectives of Solubilization: Potential for Improved Bioavailability

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This review focuses on the recent techniques of solubilization for the attainment of effective absorption and improved bioavailability. Solubilization may be affected due to cosolvent water interaction or altered crystal structure by cosolvent addition. Micellar solubilization could be affected by both ionic strength and pH. Addition of cosolvents to the surfactant solutions offers only a small advantage because of the decrease in the solublization capacity of the micelles. Polymorphism is known to influence dissolution and bioavailability of the drugs. Molecular modeling study of cyclodextrin inclusion complexations can predict the inclusion modes, stoichiometry of the complex, and the relative complexing efficiency of cyclodextrins with various drug molecules.

Keywords cosolvent addition; micellar solubilization; polymer loading; pH adjustment; polymorphism; complexation

INTRODUCTION

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 (Bittner et al., 2002a, b). Bioavailability is defined as the rate and extent to which the active drug is absorbed from a dosage form and becomes available at the site of drug action (Pharmacos 4). Bioavailability depends on several factors, usually, drug solubility in an aqueous environment and drug permeability through lipophilic membranes (Yu et al., 2000). Actually, only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). A drug can be defined bioavailable if it belongs to the fourth class (high solubility and permeability) (Amidon et al., 1995).

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In vivo drug permeation through the intestinal mucosa mainly takes place according to a passive diffusive mechanism whose rate determining step is represented by the cellular membrane crossing, while a little effect would be exerted by the presence of aqueous stagnant layer arising at the intestinal wall (Fagerholm and Lennernas, 1995). Lipophilic drugs follow a transcellular pathway in their intestinal membrane crossing, while hydrophilic ones undertake a paracellular pathway (They would diffuse through the water filling the intercellular void). Today the transcellular way is thought to be the main transport mechanism, regardless the drug physicochemical properties (Fagerholm et al., 1996; Nilsson et al., 1994; Uhing & Kimura, 1995). Thus, solubilization of poorly soluble drugs increases dissolution rate and possibly increases absorption that can lead to a significant improvement of their bioavailability. As the oral bioavailability is strongly affected by intestinal permeability, drug permeation studies are of paramount importance for the improvement of drug absorption through the intestinal epithelium (Grassi et al., 1999; Grassi & Cadelli, 2001). P-glycoprotein (P-gp) is a transport membrane protein that exists in many tissues of the human body. Solubilizing agents often used in pharmaceutical formulations have been reported (Law et al., 2004; Nerurkar et al., 1996; Orlowski & Garrigos, 1999; Wang et al., 2004) to have inhibitory effect of P-gp. Identification of these agents and their extent of inhibition are therefore important for formulation development. It has been observed that a simplified approach represented by the in vitro intestinal permeation technique is very useful for rapid bioavailability estimation (Balimane et al., 2000; Grassi & Cadelli, 2001; Turner et al., 1970) when the rate-determining step of the drug absorption is drug solubility (Meriani et al., 2004). Absorption experiments through everted rat intestine showed that triacetin-ethanol-nimesulide solution improved nimesulide bioavailability compared to solid nimesulide in powder form (Meriani et al., 2004). Interestingly, the activated system (cogrinding PVP-nimesulide in 3:1 ratio) performance

was even better than that of nimesulude solution (Meriani et al., 2003). Indeed, the hydrodynamic conditions gave rise to the formation of a thin layer (wherein nimesulide concentration was higher than that in the bulk) surrounding the intestinal wall.

Absorption, and hence bioavailability of a drug once in solution, is also influenced by its chemical stability. The stability of drugs against oxidation and hydrolysis and the bacterial activity may be drastically changed via solubilization (Garon et al., 2002; Martin, 1994). Pharmacist should pay due attention to the factors when attempting to formulate solubilized system successfully by incorporating solubilizing agent. The solubilizing agent should give protection from the conditions typical for handling, formulation, storage, and administration of a drug candidate both in solution and solid state. If taken internally at the concentration employed, it should be non-toxic, miscible with the solvent (usually water), compatible with the drug candidate to be solubilized, free from disagreeable odour and taste and relatively non-volatile as well as should give protection from GI environment.

The solubility of poorly water soluble drug candidates for traditional formulation system, can be improved most commonly by cosolvent addition, micellar solubilization, polymer loading, pH adjustment (only for an ionizable drug), modification of drug crystal form, complexation and combinations of techniques.

SOLUBILIZATION TECHNIQUES

Cosolvent Addition

The solubility of a poorly water soluble drug can be increased frequently (Seedher and Bhatia, 2003) by the addition of a water miscible solvent in which the drug has good solubility. Seedher and Bhatia (2003) investigated that the aqueous solubility of celecoxib, rofecoxib and nimesulide could be enhanced significantly by using ethanol as the second solvent and PEG-400-ethanol had highest solubilization potentiality among the mixed solvent systems (Seedher & Bhatia, 2003). Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely used as cosolvents (Kerns 2001; Krishna et al., 2001; Pan et al., 2001; Seethala & Fernandes, 2001) because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity.

The solubilization behaviour of poorly soluble compounds by the addition of cosolvents can be expressed by the log-linear model (Grant & Brittain, 1995; Millard et al., 2002; Rubino & Yalkowsky, 1987) as following:

$$\log S = \log S_w + \sigma f$$

where S and S_w are the solubilities in the cosolvent water mixture and water, respectively. f is the fraction of the co-solvent. σ is the solubilization capacity can be defined by following equation using the octanol-water partition coefficient, log$P$, of the solute

$$\sigma = S \log P + t$$

where S and t are constants that depend only on nature of the cosolvents. However, this log-linear model is not applicable, if the solute forms solvate or the crystal structure is altered by the addition of the cosolvent (Bustamante et al., 2002). The log-linear model could not explain also the indomethacin solubility in the cosolvent-water mixture (Kawakami et al., 2004). This might be due to interaction between cosolvent and water molecules. DMSO has been known to form 1:2 complex with water molecules when the DMSO concentration is below 10% (Shin et al., 2001, 2002) and DMA may act in a similar way. This interaction may decrease the indomethacin solubility.

Micellar Solubilization

Surfactants are widely used for improving the solubility of poorly soluble drugs. Micellar solubilization is an area of investigation for improving the pharmaceutical formulations (Alkhamis et al., 2003). A search for literature yields many journal references describing the solubilization by surfactant addition (Alkhamis et al., 2003; Attwood & Florence, 1983; Cardinal & Mukherjee, 1978a, b; Krishna & Flanagan, 1989; Yalkowsky, 1999). Literature studies (Bates et al., 1996; Levy & Jusco, 1966; Welling & Barbhaiya, 1982) have shown that naturally secreted bile salts act as surfactants enhance the dissolution rate of poorly soluble drugs and thereby increasing the bioavailability. However, when there is inadequate biliary secretion or insufficient exposure time, drug dissolution and absorption rates decrease significantly. Hence, the incorporation of another surfactant into the drug formulation may help solubilize the insoluble drug and increase its dissolution rate. The effects of counterions (Na^+) on surfactant sodium dodecyl sulphate, have been studied by Sun et al. (2003) for solubilizing danazol, an extremely low aqueous soluble drug. Solubility of danazol is highly dependent on surfactant concentration unless both ionic strength and pH are held constant. The selection of solubilizing surface-active agents is based on phase solubility study in which the solubility of a specific substance is determined as a function of surfactant concentration. The solubilization by surface active agents can be described in a simple manner as the following equation:

$$S = \xi (C_s - C_{cmc}) + pS_w$$

where ξ, C_s and C_{cmc} are the solubilizing capacity of micelles, surfactant concentration and critical micelle concentration, respectively. p is the coefficient of bulk solubility, which is affected by pH change, salting out etc., caused by the surfactant. ξ greatly depends on the solubilization site of the drugs in the micelles (Florence and Attwood, 1998), and hence, its prediction is difficult. ξ usually increases with increase of the alkyl

chain length (Florence & Attwood, 1998), if the guest drugs are localized deep in the micelles. The growth of micelles with the surfactant concentration and the structural change by the guest drug molecules are ignored in the above equation. The solubility data can also be analyzed using a pseudo-phase model with the drug partitioning into the micellar pseudo-phase. The partition coefficient (P_m) between the aqueous and the micellar pseudo-phases can be calculated using the equation as follows:

$$S_t/S_0 = 1+P_m v\,[M]$$

where S_t and S_o are total and intrinsic water solubilities, respectively, S_t/S_0 is the relative solubility, P_m is the micelle-aqueous partition coefficient, v is the partial molal volume of the micelle, and *[M]* is the micellar concentration. The slope of the relative solubility versus micellar concentration may be used to calculate the micellar-aqueous phase partition coefficient. The slope of the curve represents the partition coefficient multiplied by partial molal volume of the surfactant, which may be obtainable from the literature (Corkil et al., 1967).

Cardinal and Mukherjee (1978a, b) have described the total uptake of solubilizate by micelles to be divided into an adsorbed and a dissolved state. These investigators also used spectroscopy to establish the state of solubilization. Krishna and Flanagan (1989) studied the solubilization of b-arteether in several anionic, cationic, and nonionic surfactant solutions. They found that anionic and cationic surfactants increased the solubility dramatically by micellar solubilization. Alkhamis et al. (2003) suggested that significant solubilization of gliclazide can be achieved by using both cationic and anionic surfactants. They indicated that glyclazide was solubilized mainly in the inner core of the cationic surfactant micelles and in the outer regions of the anionic surfactant micelles. Non-ionic surfactants are often added to prevent and/or minimize protein aggregation during fermentation, purification, freeze-drying, shipping, and/or storage (Randolph & Jones, 2002). Tween 20 and Tween 80 protected Albutropin against agitation-induced aggregation, even at concentrations below the cmc (Chou et al., 2005).

Cosolvent addition into micellar solution significantly changes the solution conditions, which affect the interaction between surfactant molecules (Aguiar et al., 2003; Almgren et al., 1985; Aveyard et al., 1990; Israelachvili 1991; Kawakami, et al., 2006). Solubility of phenytoin was observed to increase upon addition of ethanol with tween-80 solution, while a dramatic decrease was found with sodium dodecyl sulphate solution (Kawakami et al., 2006).The addition of glycerol or PEG to the surfactant solutions has only a minor impact on solubility of phenytoin. Possible behaviours of the cosolvent molecules are (i) increase of surfactant solubility and inhibition of micelle formation, (Almgren et al., 1985; Aveyard et al., 1990), (ii) action as a cosurfactant and alteration of micelle characteristics (Aveyard et al., 1990), (iii) formation of pools inside micelles, (iv) decrease of surfactant solubility and enhancement of micelle formation (Almgren et al., 1985), (v) existence in the continuum phase with no effect on micelle formation.

Polymer Loading

The solubility and dissolution related bioavailability of poorly soluble pharmaceuticals could also be improved by loading a drug into a polymeric carrier in a nanocrystalline or amorphous state (Debetti et al., 2001; Grassi et al., 2000). Both nanocrystals and amorphous drug are not physically stable and they tend to recrystallize into the more thermodynamically stable macrocrystal size (Buckton & Beezer, 1992). Various stabilizing methods have been reported, including the usage of polymer excipients having high glass transition temperature (T_g). The recent report has been described that the water soluble polymers such as gelatin, polyvinyl pyrrolidone (PVP), polyethylene glycol significantly inhibit the crystal growth of poorly water soluble drugs in the liquid state (Law et al., 2001; Mallick et al., 2003, 2004c, d; Mallick 2004a, b) and have shown an increase in dissolution rate. Similarly addition of alginate inhibited the crystallization of amorphous lactose prepared by spray drying (Takeuchi et al., 2000). Stabilization of amorphous drugs have been reported for the systems of excipients with a pyrrolidone ring (PVP and polyvinyl pyrrolidone-co-vinyl acetate) and drugs with hydrogen donor groups such as indomethacin, lacidipine, nifedipine, and tolbutamide (Forster et al., 2001). Miyazaki et al. (2004) suggested that the stronger stabilizing effect of polyacrylic acid is due to the stronger interaction with acetaminophen in solid dispersions. The addition of hydroxypropylmethylcellulose resulted in a significant decreased rate of hydrolysis of cefixime in aqueous environment performed in our laboratory (Mondal & Mallick, 2005a). In organs involved in absorption (intestines) and elimination (Kidney, liver), P-gp can have a key role in limiting drug bioavailability (Hunter and Hirst, 1997; Fromm 2000). Ritonavir has moderate permeability across the commonly used cell culture models (Caco-2 cells) of intestinal mucosa and is a substrate for P-gp efflux. Law et al. (2004) improved the oral bioavailability of ritonavir significantly by incorporating the drug in PEG-8000. Whether the absorption of ritonavir is dissolution limited or limited by poor permeation due to P-gp efflux, the improved bioavailability can be explained by the higher luminal concentrations of the drug when dosed as drug-polymer dispersion. The in vitro in vivo correlation can be used to guide formulation development. The compounds that can inhibit P-gp efflux of drugs can potentially increase oral bioavailability or reduce multidrug resistance if they are successfully incorporated into a drug formulation (Asperen et al., 1998; Hugger, 2003; Malingre et al., 2001; Terwort et al., 1999). Evaluation of the existing literature suggested that excipients with a polyethylene glycol (PEG) polymeric segment afford P-gp inhibiting characteristics to the molecule (Asperen et al., 1998; Dintaman, 2003; Fromm 2000; Hugger et al., 2003; Hunter & Hirst, 1997; Malingre et al., 2001; Nerurkar et al., 1996; Orlowski & Garrigos, 1999; Seebulluck et al., 2003; Terwogt et al., 1999). Wang et al. (2004) described that the binary excipient combinations showed some sort of synergistic inhibition. The automated high-throughput P-gp screening process now allows more

comprehensive exploration of excipient combinations. That could be utilized to perform screens with multiple variables; such as the concentration dependence of surfactants both above and below the critical micelle concentration (Lo 2003; Rege et al., 2002) and structure based dependence of P-gp inhibitions for a particular drug having poor bioavailability.

pH Adjustment

The solubility of weak electrolytes (most of the drugs) is strongly influenced by the pH of the solution. Ketoprofen, being a weak acid (pKa 4.6), can be solubilized by adjusting the pH to a higher value. Solubility at pH > 5 (pH in duodenum) may be more appropriate because most compounds are mainly absorbed in intestinal region. To ensure a clear solution and maximum therapeutic effectiveness, the preparation of PG300975 (an anti-HIV agent) has been adjusted to an optimum pH (Jain et al., 2004). Solubility of nimesulide and meloxicam increases significantly with the increase in pH value in the mixed solvent systems (Seethala & Fernandes, 2001). A new system has been developed by Kobayashi and coworkers (Kobayashi et al., 2001) for the prediction of drug absorption that takes into account drug dissolution and pH adjustment in the gastrointestinal tract. Phenanthrene solubilization and biodegradation with a biosurfactant (rhamnolipid) solution were investigated as a function of pH (Shin et al., 2004). Without the biosurfactant, the specific growth rate of *Pseudomonas putida* CRE 7 at pH 6 was higher than at other pH values. In presence of the rhamnolipid, the maximum growth rate shifted to around pH 5, which showed maximum enhancement of solubility.

Solubilization of drugs exhibiting low water solubility is possible by using a combination of pH adjustment and cyclodextrin complexation (Tinwalla et al., 1993; Tommasini et al., 2004). Recent investigations (Li et al., 1998) into the combined use of pH and complexation for solubilization of lipophilic drugs have resulted in greater solubilization of the drugs in their ionized state. Ionic form of NSAIDS have been shown to have better flux via improved solubility (Hadgraft & Valenta, 2000; Sridevi & Diwan, 2002) contrary to the exceptions of the well-documented pH partition theory. The combined effect of pH and complexation with beta-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, and methyl-beta-cyclodextrin increases the solubility of both the ionized and unionized species of naringenin (Tommasini et al., 2004). The study determined by the single components in solution, as ionized and unionized naringenin both in free and complexed forms. In the other study the experimental drug, used for the treatment of AIDS is difficult to administer in an injectable solution dosage form because of its very low solubility (Tinwalla et al., 1993). Using a combined approach of pH adjustment and complexation of neutral or protonated form of the drug with hydroxy-propyl beta-cyclodextrin, solubility enhancement is possible.

Modification of Drug Crystal Form

Drug crystal form may be altered to other distinct crystalline species with different internal lattices (polymorphism, solvatomorphism). Polymorphism is known to influence not only the technological feature but also physicochemical stability and the intrinsic dissolution rate that directly affects absorption and bioavailability of drugs (Foppoli et al., 2004; Grant 1998; Kachrimanis & Malamataris 1999; Mallick 2004a; Mallick et al., 2004d). Further, reproducible behaviour of drug formulations may depend critically on the precise solid form of the drug employed and the particular forms of a given drug are recognized as essential practice in the pharmaceutical industry (Bernstein, 2002).

Aguiar and Zelmer (1969) observed that a high free energy difference between the polymorphic forms could result in different absorption profiles after oral administration, which is related to the bioavailability. It is important to identify the polymorph during preformulation study, that is stable at room temperature and to determine whether the polymorphic transition are possible within the temperature range used during processing of solid dosages forms. Polymorphs have the same free energy, identical solubilities and identical vapour pressure at their transition temperatures.

Two unsolvated forms of fluconazole designated polymorphic forms I and II were first reported by Gu and Jiang (1995). Other studies on polymorphism of fluconazole reported the physicochemical characterization of polymorphs, monohydrate, solvates of acetone and benzene, and an amorphous form. Anhydrate form II was identified as a new, metastable phase that transforms to the more stable anhydrate form I on compression and during storage at ambient temperature and pressure. The dissolution rates of these species were in the order: Amorphous form > acetone solvate > anhydrate form I > benzene solvate > monohydrate. The most recent study showed that recrystallization of fluconazole from propane-2-ol yielded a polymorphic form III. Whereas the solvents water and ethyl acetate yielded the solvated products fluconazole monohydrate and fluconazole.$(\text{ethyl acetate})_{0.25}$, respectively (Caira et al., 2004; Dash and Elmquist, 2001; Lo and Mackay, 1994; MacSweeney, 1999). The thermodynamic stability of the two crystal phases can be assessed according to the v'ant Hoff equation:

$$\ln IDR = -\frac{\Delta H_{diss}}{R} * \frac{1}{T} + C$$

where IDR is the intrinsic dissolution rate, ΔH_{diss} is the heat of dissolution, R is gas constant, T is temperature in K, and C is constant. The transition temperature can be extrapolated by the interaction of the curves of the two forms, where they present the same IDR and hence the same free energy. The values of heat of dissolution (ΔH_{diss}) for each form, calculated from the slopes of the curves. The other thermodynamic parameters

such as the enthalpy change for the transition of one form to another form (ΔH), the free energy difference (ΔG) and entropy difference (ΔS) between the two forms at a particular temperature, say lab temperature *(T)* calculated from the following equation respectively:

$$\frac{\text{In } IDR}{IDR'} = -\frac{\Delta H}{R} * \frac{1}{T}$$

$$\Delta G = -RT * \frac{\text{In } IDR}{IDR'}$$

$$\Delta G = \Delta H - T\Delta S$$

Complexation

The traditional formulation system for poorly soluble drug involving combination of organic solvents, surfactants and extreme pH conditions are often irritating and may cause adverse reactions. At times, these methods are inadequate for solubilizing enough drugs particularly for parenteral delivery system. Another recent method for solubilizing poorly soluble drugs involves by cyclodextrin complexation.

Cyclodextrins are cyclic oligosaccharides containing a varing number of glycopyranose ring. Cyclodextrins possess a lipophilic cavity and a hydrophilic exterion, thus making them ideal for forming inclusion complexes with non polar molecule or the non polar part of the molecule in relatively polar solvents. Complexation occurs, with some exceptions, through a non-covalent interaction between the molecule and the cyclodextrin cavity. Phase-solubility studies have traditionally been used to study cyclodextrin complexation and provide important information regarding the stability constant and stoichiometory of the inclusion complex formed. The total solubility of a drug that forms a 1:1 complex (A_L-type) is:

$$S_{Tot} = S_w + Slope \ * \ C_L$$

where C_L is the concentration of the ligand added and the slope of the phase diagram (<1) is its solubilization power for the unionized drug (Yalkowsky, 1999). S_W is the intrinsic solubility of the drug. The apparent stability constant *(K)* can be calculated using Connors method (Connors and Mollica, 1966):

$$K = \frac{slope}{(1 - slope) * S_W}$$

The anti-malarial drugs artemisinin and its analogs have poor aqueous solubility. Their poor solubility limits their ability to be formulated in solution for intravenous use. Cyclodextrins have been shown to increase the solubility of the sparingly soluble drugs by forming inclusion complexes (Ni et al., 2001; Stella & Rajewski, 1997), which are utilized for preformulation studies (Jumaa et al., 2001; Loftsson et al., 2001a; Nguyen et al., 2001). Besides oral and parenteral delivery systems, literature studies find numerous applications of cyclodextrin complexation in other delivery systems with improved bioavailability such as ophthalmic (Jarho et al., 1997; Lyons et al., 2001; Saarinen-Savolainen et al., 1998), subcutaneous/transdermal (Sridevi & Diwan, 2002; Tokihiro et al., 2000), pulmonary/nasal (Gudmundsdottir et al., 2000; Loftsson et al., 2001b; Worth et al., 1997) and so on. Carotenoid incorporation in cyclodextrins has been reported for other commercially important carotenoids, including ß-carotene, lutein, and canthaxanthin (Lancrajan et al., 2001). Lancrajan et al. (2001) confirmed that as a delivery mechanism, carotenoid incorporation into a ß-cyclodextrin carrier is more efficient than liposomal delivery, or the traditional method of dissolving the carotenoid in an organic solvent, such as tetrahydrofuran or ethanol. The potential breakdown of the cyclodextrin to individual sugar moieties is likely less toxic to the cells in culture than organic solvents. Especially methylated ß-cyclodextrins (pure dimethyl-ß-cyclodextrin, randomly methylated ß-cyclodextrin (RMCD), trimethyl-ß-cyclodextrin) offer several advantages for mucosal drug delivery system which includes improved drug solubilization, protection against physicochemical and enzymatic degradation, as well as most effective penetration enhancers at low concentrations (2–5%) safely (Hermens et al., 1990; Irie et al., 1992; Merkus et al., 1999; Vollmer et al., 1994). Recently, physicochemical studies based on lipid vesicle interactions with RMCD have demonstrated a detergent like mechanism, responsible for lipid membrane solubilization (Boulmedarat et al., 2004). Furthermore, RMCD is able to penetrate deeply skin until epidermis and dermis (Weisse et al., 2004). In a recent toxicity study on buccal mucosa RMCD resulted in cytotoxic and inflammatory effects at 10% concentration depending on time exposure, whereas 2% and 5% did not induce tissue damages even after 5 days of repeated exposures (Boulmedarat et al., 2005). Among the various cyclodextrins, sulfobutyl ethers ß-cyclodextrin has shown low toxicity in cell culture (Saarinen-Savolainen et al., 1998), and in drug formulation (Rajewski et al., 1995; Totterman et al., 1997). The increased aqueous solubility described by Lockwood et al. (2003), for crystalline astaxanthin may find utility in the introduction of crystalline astaxanthin into mammalian cell culture systems that has previously been dependent upon lyposomes, or toxic organic solvents. Various cyclodextrin in combination with polymers have been shown to increase the solubility of antemisinin significantly (Usuda et al., 2000). The solubility potential of cyclodextrins allows a greater amount of the drug to be loaded in the donor phase and increase the drug transport through a kinetic barrier that exists at the skin-vehicle interface (Loftsson & Masson, 2001b). Drug cyclodextrin complexation can reduce decomposition of drug by protecting the labile region from the potential reactants in the aqueous environment. Usuda et al. (2000) have

shown that the presence of cyclodextrin slowed the rate of alkaline hydrolysis of antimisinin. Cyclodextrin complexation does not always show synergistic effects resulting in greater solubility enhancement when used in combination with a surfactant than if they used alone at the same concentration (Yang et al., 2004). The surfactant molecules act as a competitive inhibitor in the solubilization of the drug by the complexant. The combined use of sodium lauryl sulphate and (SBE) ß-cyclodextrin on the solubilization of NSC-639829, a poorly soluble anti-tumor compound (Okada et al., 1999) results in a much lower solubility than when either is used alone. Traditional organic co-solvents, pH-adjustment or cyclodextrin complexation approaches are unlikely to yield sufficient solubility for formulation of ricobendazole (RBZ) solutions for parenteral product (Wu et al., 2005). Greatest solubility of RBZ was observed in DMSO, glycerol formal (mixture of 5-hydroxy-1,3-dioxane and 4-hydroxymethyl-1,3-dioxol, 60:40), and benzyl alcohol. Addition of surfactants, Tween-80 or Cremophor EL to water or co-solvents resulted in increased solubility but without lowering the pH was not sufficient to yield an acceptable injectable product. The study suggests only weak binding between RBZ and HP-ß-cyclodextrin and solubility is too low to be practically useful (Wu et al., 2005). As per our recent conference proceedings cyclodextrin complexation does not show any significantly better stabilizing effect on cefixime hydrolysis when used in combination with HPMC, PVP and PEG (1%w/v) than if cyclodextrin used alone (Mondal and Mallick, 2005b).

Molecular modeling studies can serve as a supplementary tool in understanding inclusion complexation. It can predict the inclusion modes, the stoichiometry of the complex, and the relative complexing efficiency of cyclodextrins with various drug molecules. Commercially available software allows for various approaches for the study of cyclodextrin inclusion complexes. The use of molecular mechanics (Madrid and Villafruela 1998) and dynamic simulations (Melani et al., 1998) has been reported in the study of cyclodextrin complexes. Docking program has also been used to study inclusion complexes for qualitative purposes (Oteri,-Espinar et al., 1992). In the work reported by Illapakurthy et al. (2003), three docking methods for modeling cyclodextrin complexation were evaluated.

The solubility of a non-polar drug D_A in presence of other non-polar drugs D_1,D_2,…D_n in a complexing ligand cyclodextrin, C_d, system may be predicted as (Zhao et al., 2002)

$$KA = \frac{[D_A C_d]}{[D_A][C_d]}$$

where,

K_A = drug cyclodextrin complexation constant

D_A = intrinsic solubility of the drug,

$[D_A C_d]$ = drug in-complex,

$[C_d]$ = free cyclodextrin concentration after rearrangement.

$[D_A C_d] = K_A[D_A][C_d]$

For a given type of cyclodextrin, $[C_{dtot}]$ is the total concentration of cyclodextrin in solution is expressed as:

$$\begin{aligned}[C_{dtot}] &= [C_d] + {}^{n}\sum_{A=1}[D_A C_d] \\ &= [C_d] + {}^{n}\sum_{A=1}(K_A[D_A][C_d]) \\ &= [C_d](1 + {}^{n}\sum_{A=1}(K_A[C_d]))\end{aligned}$$

Rearranging:

$$[Cd] = \frac{[C_{dtot}]}{1 + {}^{n}\sum_{A=1}(K_A[C_d])}$$

for D_A, the total solubility.

CONCLUSION

Solubilization of poorly soluble drugs is very much useful for possible increase in absorption that can lead to a significant improvement of their bioavailability. Solubilization behaviour could not be described by log-linear model if the poorly soluble drug forms a solvate or the crystal structure is altered by the addition of cosolvent. Solubilization by the addition of cosolvents may also be affected due to interaction between cosolvent and water molecules. Sometimes solubility of the drug is highly dependent on surfactant concentration unless both counterionic strength and pH are held constant. The stability of the drug against hydrolysis, oxidation and bacterial activity may be improved significantly via solubilization. Stabilization of drugs in amorphous form and its bioavailability can significantly be improved when the drug is incorporated in solid polymer dispersion. Certain combinations of solubilization techniques show synergistic effects; resulting in greater solubility enhancement than if they were used alone. Molecular modeling studies in inclusion complexation can serve as a supplementary tool. Because, it can predict the inclusion modes, the stoichiometry of the complex, and the relative complexing efficiency of cyclodextrins with various drug molecules. The solubility of any particular drug decreases in the presence of other drugs. This decrease in solubility is related to the sum of the products of the intrinsic solubilities of the other drugs and drug-legand complexation constants. Combined use of a surfactant and a complexant, results in a much lower solubility if the surfactant molecule acts as a competitive inhibitor in the solubilization of the drug by the complexant. The automated high-throughput P-gp screening process could be established which will allow more comprehensive exploration of combination of solubilizing agents.

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