Advantages and Disadvantages of Complexation

Solubilization by complexation is achieved through specific interactions rather than changes in bulk solvent properties as in other solubilizing systems such as co-solvents, emulsions and pH-adjustment. The dissociation is very rapid (Cramer et al. 1967; Hersey et al. 1986), quantitative, and therefore, predictable. Another significant advantage of the complexation technique is that some commonly used complexing agents such as hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether of β-CD (SBE-β-CD) are less toxic compared to other solubilizing agents such as surfactants and co-solvents. Since most complexes formed are 1:1 complexes of the A linear (AL) type, dilution of the complex will not result in a solution which is supersaturated with respect to substrate. This can be rather important for very insoluble compounds that may precipitate upon injection when solubilized by other systems such as co-solvents. Furthermore, complexation can be combined together with solid dispersion approaches to improve the bioavailability of water-insoluble drugs (Zoeller et al. 2012).

Another major advantage of CD complexation is the improvement in chemical stability of the guest, for example, resistance to oxidation, photolysis, or hydrolysis (Uekama et al. 1983b). Nagase et al. (2001) reported that SBE-β-CD significantly solubilized DY-9760e, a novel cytoprotective agent, through forming a drug-CD complex. It also markedly suppressed the photo-degradation of DY-9760e in aqueous solution and inhibited the adsorption of DY-9760e from solution to polyvinyl chloride (PVC) tubes. The stability enhancement by CD complexation is important not only to the chemical and physical stability of the products but also to the *in vivo* performance of the products.

Despite all the attractive advantages of complexation, there are several disadvantages. First of all the compound has to be able to form complexes with a selected ligand. For compounds with very limited solubility to start with, the solubility enhancement can be very limited. The second limitation is that for the complexes of A_p type, dilution of a system may still result in precipitation. This is also true for solubilization *via* combined techniques such as complexation with pH adjustment. Third, the potential toxicity issue, regulatory, and quality control issues related to the presence of the ligand may add complication and cost to the development process. Lastly, the complexation efficiency is often rather low, thus relatively large amount of CDs are typically required to achieve desirable solubilization effect (Loftsson et al. 1999).

Structures and Physicochemical Properties of Cyclodextrins

CDs are cyclic oligosaccharides consisting of a variable number of D-glucose residues attached by α-(1,4) linkages (Clarke et al. 1988). The three most important of these are α-, β-, and γ-CDs, which respectively consist of six, seven, and eight D-glucose units. Their conformation and numbering are presented in Figure 8.1. As a consequence of the $^4C_1$ conformation of the α-D-glucose residues and lack of free rotation about glycosidic bonds, the compounds are not perfectly cylindrical molecules, but are somewhat cone-shaped, with all of the secondary hydroxyl groups situated at one end of the annulus and the primary hydroxyl groups at the other. The cavity is lined by a ring of hydrogen atoms (bonded to C-5), a ring of D-glucosidic oxygen atoms, and another ring of hydrogen atoms (bonded to C-3), thus making the cavity relatively apolar. The shape of the molecule is stabilized by hydrogen bonds between secondary hydroxyl groups of adjacent α-D-glucose residues. The internal cavity diameters are approximately 5.7, 7–8, and 9.5 Å for α-, β-, and γ-CDs respectively. These structural features have been determined for the crystalline state (Hursthouse et al. 1982; Koehler et al. 1987; Vicens et al. 1988; Harata 1989) and are also retained in solution (Rao and Foster 1963; Glass 1965; Casu et al. 1970). Figure 8.2 shows the physical shape of the CD molecule.

Most of the CD derivatives presently in application are synthesized from β-CD. The main drawbacks, particularly in the case of β-CD, are related to parenteral toxicity and low aqueous