PRACTICAL CONSIDERATIONS

Identification of Useful Systems

As shown in Equation 8.1, complexation is an equilibrium process. Most drugs (substrates) form 1:1 complexes with various ligands (e.g., CDs). These 1:1 complexes are defined by a binding constant, K_{11}. In solubility considerations, if S represents the solubility of a drug in the absence of any ligand, then the increase in solubility of a drug is largely driven by the product of K_{11} and [L], with [L] equal to [L_{total}] minus [SL]. Since most values of K_{11} are less than 20,000M^{-1} and [L_{total}] usually is less than 0.1–0.2 M, the maximum increases in solubility that can be expected from a 1:1 complexation are in the range of 1,000–2,000 times the intrinsic solubility (Stella and Rajewski 1997). This means that in order to solubilize a drug to the mg/mL range, the solubility of the drug in the absence of any ligand will have to be in the μg/mL range. For example, if the intrinsic solubility of the drug is 10 ng/mL, it is almost impossible to find a ligand which is capable of raising the solubility of this drug into the mg/mL range through just a 1:1 interaction. The only way to overcome this limitation is to increase the intrinsic solubility through other means such as pH adjustment. Although ionization of drug molecules may reduce the binding constants of complexes, an improvement in intrinsic solubility can often offset the binding constant decrease and the desired solubility can be achieved (Johnson et al. 1994).

While in some cases binding ability could be correlated with certain structure features (Tong et al. 1991a,b), no general rule is available to predict binding constants without carrying out an actual experiment. Fortunately it is relatively easy to determine whether or not certain ligands are capable of forming complexes with the compound of interest. A quick solubility screen of potentially useful ligands can provide a means of identifying the most useful system. For example, if 20% HP-β-CD and 40% SBE-β-CD do not improve solubility to the desirable levels, it is clear that solubility enhancement by these CDs will not be very successful.

In additional to the binding constant and safety considerations, economics and quality control issues also play a role in considering which ligands to use. Because of the difficulty in selectively derivatizing a specific hydroxyl or family of hydroxyls, most modified CDs of pharmaceutical interest are likely to be complex mixtures (Stella and Rajewski 1997). Methods to characterize these mixtures, therefore, need to be in place to assure lot to lot reproducibility. The costs of acute and chronic safety studies required to evaluate any new CD derivatives are very high, and this prohibits them from being widely evaluated for pharmaceutical applications.

Preparation of Complexes

Various methods have been reported for the preparations of complexes. The complexation effectiveness is dependent on the properties of the complexes formed and the preparation methods. The ability to consistently make the complexes with reproducible properties should be evaluated when developing methods for complex preparation.

In solution, the complexes can be formed at a diffusion-controlled rate by mixing solutions containing the host and the guest. The amount of the complex formed is dependent on the binding constant. Solid complexes can be prepared by co-precipitation (Celebi and Nagai 1988; Ficarra et al. 2002), neutralization (Celebi and Nagai 1988), kneading (Lengyel and Szejtli 1985), freeze-drying (Kurozumi et al. 1975; Fugioka et al. 1983; Pralhad and Rajendrakumar 2004), spray-drying (Tokumura et al. 1984; Fukuda et al. 1986; Miro et al. 2004) and coevaporation (Zugasti et al. 2009), grinding methods (Nakai et al. 1977, 1980; Lin et al. 1988; Mukne and Nagarsenker 2004; Mura et al. 2005). The melting method has been shown to be very effective in preparing solid complexes for some ternary systems of drug-CD and polymers like PEG6000 and PEG4000 (Lahiani-Skiba et al. 2006). The reader is directed to a recent review (Chordiya and Senthilkumaran 2012).

In the kneading method, the solid complex is formed by adding the substrate to a slurry of the ligand (e.g., CDs) and kneading until a paste is obtained. This material is dried and washed with a small amount of solvent to remove any free substrate. Aqueous solutions are typically employed