in the freeze-drying and spray-drying methods. However, for water-insoluble compounds, these methods are not that useful unless organic solvents can be used. Organic solvents are also often utilized in the co-precipitation methods. One major problem with using organic solvents is that most organic solvents will compete for inclusion in the CD cavity, and thus inhibit complex formation. The neutralization method takes advantage of acidic or basic functional groups and is rather useful for insoluble compounds. It is important, however, to make sure that compounds are stable in the acidic or basic conditions. The absence of water in the grinding method makes it suitable for drugs which are unstable in aqueous solvents and/or at elevated temperatures.

Palmieri et al. (1997) studied the effect of preparation methods on the properties of solid inclusion complexes between methoxybutropate and β- and HP-β-CD. UV and HPLC analysis, DSC, XRD, and dissolution studies were carried out to characterize the complexes prepared by solid dispersion, kneading, and spray drying. Generally, it was found that for the complex with β-CD the spray drying preparation gave the best complexation effectiveness and dissolution rate, whereas for the complex with HP-β-CD, solid dispersion was the best method.

Fini et al. (1997) studied the feasibility of preparing β-CD-indomethacin (IM) complex by compacting a β-CD/IM mixture with low frequency ultrasound. Experimental results suggested that the material obtained by ultrasound had a dissolution rate comparable to that measured with the kneaded material. The use of ultrasound, however, can both reduce the production time and improve the homogeneity of the association between ID and β-CD. The proposed mechanism for this method is that in the absence of a solvent, ultrasound absorption by a solid promotes phase transition or disrupts the crystal lattice, resulting in a nearly amorphous state or, in the case of low melting compounds, can create the conditions for a low temperature fusion. In the case of the β-CD/IM complex, IM appears to be deposited on the β-CD particles as a melted film, creating an intimate contact between the two components.

Drug Release from Complexes

As mentioned earlier, complex formation is an equilibrium process and both the drug and ligand molecules are non-covalently bound. Also, it has been experimentally shown that the rates of complex formation and dissociation are very fast. It occurs at rates (> about $10^{-8}\ M^{-1} \cdot sec^{-1}$), and this is very close to diffusion controlled limits with the complexes being continually formed and broken down (Cramer et al. 1967; Thomason et al. 1990). Therefore, it is easy to picture the two major mechanisms that contribute to complex dissociation: dilution and competitive displacement (binding of drug and/or ligand molecule to other competing agents) (Stella and He 2008; Kurkov et al. 2012; Loftsson and Brewster 2013).

Consider a drug with an intrinsic solubility of 0.4 mM solubilized by 0.1M CD to 20 mM through a 1:1 complex with a binding constant of 610 M^{-1}, a dilution of 1:700 (assuming that 5 mL of the 20 mM solution was injected and the distribution volume for the complex is about 3.5 L). This will result in 92.1% dissociation of the complex (Stella and Rajewski 1997). The binding of drug and ligand molecule to other competing agents can be illustrated by the effect of *in vitro* dilution with plasma on the dissociation of HP-β-CD complexes of naproxen or flurbiprofen (Frijlink et al. 1991). Frijlink et al. found that only small fractions of the drugs remained bound to the CD in plasma. Albumin binding of the two drugs was able to compete effectively with CD binding. Displacement of the drugs from CD by a competing agent such as plasma cholesterol may have contributed to the low fraction of drug retained by the CD.

Based on an extensive review, Rajewski and Stella (1996) concluded that for parenteral delivery of complexes, except for local drug delivery where high concentrations of both drug and CDs can be maintained, drugs are qualitatively and quantitatively released from their inclusion complexes with little if any perturbation of the pharmacokinetics of the drug. For drug: CD complexes that have very strong binding constants (>10,000 M^{-1}), it will take a larger dilution to reduce the percentage of drug complexed to an insignificant level. The tendency for the drug to complex with plasma