improve rate and extent of absorption, and mask the taste. Complexation and simultaneous salt formation allow higher solubility in comparison with simple binary complexes (Redenti et al., 2000, 2001).

The combination of CD complexation and cosolvent has been reported extensively in the literature. In early 1990s, it was believed that cosolvents reduced the solubilization capacity of CDs. The solubility of testosterone with HP-β-CD was reported to be lower in the presence of 80% ethanol (Pitha and Hoshino, 1992). In aqueous CD solutions, the addition of propylene glycol or ethanol has been reported to reduce the solubility of testosterone and ibuprofen (Loftsson et al., 1993). However, in recent years, polymers have been reported to improve the solubilization capacity of CDs. A synergism between CDs and water-soluble polymers in solubilizing naproxen was observed (Faucci and Mura, 2001). The water-soluble polymers increased the complexation efficacy of CDs toward naproxen. Hydroxypropyl methylcellulose (HPMC) was observed to increase the solubilization effect of CDs. The amount of CD needed in the solid dosage form was significantly lower in the presence of HPMC (Savolainen et al., 1998). A mathematical model was developed to describe the combined effect of cosolvency and complexation on fluasterone solubilization (Li et al., 1999). Nandi et al. (2003) have observed that in solutions containing Trappsol HPB (HP-β-CD), at lower PEG-400 concentrations (<50%), the observed solubility was significantly greater than the expected solubility. In systems containing PEG-400 concentrations greater than 60%, the synergistic effect decreased, yielding observed solubilities close to the theoretical values. Overall, PEG-400 and Trappsol HPB showed a synergistic effect in improving progesterone solubility in water. In the case of systems containing Captisol, no synergism was observed in improving the solubility of progesterone. The observed solubility was less than the theoretical solubility. The author speculated that the synergistic effect of CD and PEG-400 could be attributed to additional breaking of hydrogen bonds in water's structure and a decrease in the dipole moment. At PEG-400 concentrations of 50% and higher, the synergistic effect diminished.

The application of CDs in formulation is by no means limited to solution formulations for parenteral and solution administrations. Solid dispersion of CD and drug has been studied extensively in the literature (Nagarsenker et al., 2000; Govindarajan and Nagarsenker, 2005). However, owing to the large molecular weight of CDs, this approach usually applies to drugs of high potency.

The pharmacokinetics of β-CD and HP-β-CD after intravenous administration have been assessed (Frijlink et al., 1990). As determined at doses of 25, 100, and 200 mg/kg in permanently cannulated rats, plasma levels of both CDs decreased rapidly upon injection. Within 24 h after administration, most of the doses were excreted unchanged via urine. There was no evidence for significant metabolism of the intravenously administered CDs. The pharmacokinetics and the tissue concentrations of methyl-β-cyclodextrin (MEBCD) and doxorubicin (DOX) in rabbits following administration of MEBCD and DOX, alone or in combination, were studied (Grosse et al., 1999). Results indicated that DOX did not modify MEBCD pharmacokinetic profile, but MEBCD reduced significantly the distribution half-life of DOX. Tissue determination showed that MEBCD did not enhance the cardiac accumulation of DOX.

The disadvantages of CD include (1) strict correlation between the structure of the guest molecule and the cavity size of the CD molecule; (2) limited solubility of CD in water, and thus limited the maximum concentrations this approach can achieve; and (3) CDs can significantly modify absorption-distribution-metabolism-excretion/elimination (ADME) parameters if the binding constant K is too high, and thus limited the amount of free drug for absorption (Miller et al., 2006).

Surfactants and Micelles

There are mainly three reasons that surfactants are used in formulation: (1) to increase wetting of drugs, which in turn increase the dissolution; (2) to prevent drug precipitation from formulation; and (3) to increase solubilization through micellization.