protein and to be replaced from the CD complex by endogenous lipids (e.g., cholesterol) will also be reduced (Mesens and Putteman 1991). As a result of these combined effects, the earlier time point pharmacokinetics may be perturbed (Frijlink et al. 1991). Similar statements should be applicable to other complexes based on the mechanism of the dissociation of all complexes. The reader is directed to the recent reviews for a summary of work that address the issue of CDs and drug pharmacokinetics (Palem et al. 2012; Kumar et al. 2013; Kurkov and Loftsson 2013).

Although most of the complexes dissociate upon dilution in the blood, Guo and his colleagues discovered that amphotericin B, a potential fungicidal agent, forms a very tight complex with sodium cholesteryl sulfate that does not readily dissociate after intravenous injection (Guo et al. 1991). The unique structure and tight association of the drug with this stable discoidal complex seem to prevent the incorporation of amphotericin B into the host tissues and cells. Both the toxic effects and the therapeutic index of the drug are significantly improved by using the complex.

For oral delivery, complexes will also dissociate rapidly upon dilution in the stomach and intestinal contents and it is generally believed that only the drug, and not the complex, is absorbed (Thompson 1997). Therefore, the primary function of complexes is to increase the dissolution rate and extent of drug dissolution. Other reported effects of CDs on oral absorption of drugs include enhancement of mucosal membrane permeation by CD as mentioned earlier in this chapter.

Ophthalmic, transmucosal, nasal, and transdermal products will be the most sensitive to the strength of binding (Abdul Rasool and Salmo 2012; Kumar et al. 2013; Juluri and Narasimha Murthy 2014; Kim et al. 2014). These routes of administration experience minimal dilution. However, this may not be a significant concern because the drug typically can also be displaced from the CD cavity at the delivery site by competing lipophiles at the delivery site, such as triglycerides, cholesterol, bile salts, and other hydrophobic compounds, which are often in much higher concentrations (Thompson 1997).

Safety Considerations

When a complex is used in a formulation, the toxicity of both the drug and the complexing agent must be evaluated. The presence of the complexing agent may alter the toxicity profile of the drug and *vice versa*. These factors need to be considered in designing toxicity studies.

Stella and He have reviewed the safety profiles of various CDs, and pointed out that human experience with CD derivatives, specifically SBE-β-CD and HP-β-CD, showed that these two CDs are well tolerated in humans and have no adverse effects on the kidneys or other organs following either oral or intravenous administration (Stella and He 2008). In summary, CDs are not absorbed upon oral administration and consequently exhibit a good oral safety profile (Thompson 1997). The main adverse effect observed with oral use occurs at very high doses and results from a secondary effect caused by removal of bile salts from enteroheptic recirculation. This effect is typically not observed at doses utilized in pharmaceutical formulations. It is expected to be less favorable to complex bile salts by anionic SBE-β-CD than by neutral CDs because the anionic charge on the bile salt may repel anionic CD.

Parent CDs α- and β-CD are not suitable for parenteral formulations because of renal toxicity, but nephrotic damage is not observed with γ-CD, HP-β-CD, or SBE-β-CD (Stella and He 2008). HP-β-CD is suitable for parenteral application because of its considerable solubility in water and low hemolytic activity (Dilova et al. 2004). Doses up to 2 g/kg body weight/day have been tested in animal safety studies for SBE-β-CD and human studies have been conducted for intravenous administration of 3 gm of HP-β-CD at an infusion rate of 100 mg/min. Because of the membrane-damaging effects of dimethyl-β-CD, it is probably suitable only as a penetration enhancer.

Regulatory Considerations

When a complex is formulated, the complexing agent is not considered a standard inactive ingredient. Currently there is no approval process in place for evaluating new excipients. Regulatory authorities are charged with evaluating and approving final commercial drug formulations, but they