each $(SBE)_{7\ m}$-β-CD molecule has an average of seven negative charges and seven sodium ions, it can act as a osmotic pump agent in addition to solubilize insoluble drug through complexation. Furthermore, a sustained drug delivery system for a very lipophilic, water-insoluble antibacterial agent triclosan, was designed based on the ionic interactions between anionic SBE-β-CD and an anionic polymer, that is, hexadimethrine bromide (Loftsson et al. 2001).

Factors Affecting Complexation Effectiveness

To enhance the solubilization powder of complexation, many researchers have tried adding various agents in the complexation systems. Readers are directed to the recent review for six different types of ternary cyclodextrin complexes (Kurkov and Loftsson 2013). Water-soluble polymers, such as HPMC, PVP, and high-molecular PEGs, have been shown to enhance the drug dissolution rate of poorly water-soluble drugs in drug-CD complexes (Taneri et al. 2003; Duan et al. 2005; Ammar et al. 2006; Zoeller et al. 2012; Dahiya and Tayde 2013; Zaki et al. 2013). For example, addition of hydrophilic polymers (Soluplus® and two types of hydroxypropyl methylcellulose-Metolose® 90SH-100 and Metolose 65SH-1500) significantly increased solubilization capacity of HP-β-CD for carbamazepine (Djordje et al. 2015). The dissolution rate of the drug from these ternary systems was found to be highly dependent on polymer type and concentration. The optimum increase in dissolution rate of glimepiride was observed at a polymer concentration of 5% for PEG4000 or PEG6000 and at 20% for HPMC or PVP.

Some small molecules can also enhance the complexation of CDs with insoluble drugs. Basavaraj et al. (2006) studied the influence of a polyhydroxyl base, *N*-acetyl glucamine (also known as meglumine) on the complexation of DRF-4367, a poorly water-soluble molecule, with HP-β-CD. Phase solubility studies suggested that meglumine further enhanced the dissolution rate of drug through multiple factors, including specific hydrogen bonding and/or spatial alignment with the host. Other excipients like lysine, ascorbic acid and magnesium chloride have also been showed to enhance the solubilizing effects of HP-β-CD and randomly methylated-β-cyclodextrin (RM-β-CD) for several insoluble drugs (Duan et al. 2005). Using complexation with HP-β-CD as well as salt formation with arginine, the solubility and dissolution profiles for naproxen were significantly improved (Mura et al. 2005).

It is worthwhile to mention that the combined use of two solubilizing agents sometimes may result in a decreased solubilization capability. For example, the combined use of sodium lauryl sulfate (SLS) and $(SBE)_{7\ m}$-β-CD resulted in a much lower solubility for a insoluble drug, NSC-639829, than when either was used alone (Yang et al. 2004). In this case, the surfactant molecule acts as a competitive inhibitor in the solubilization of the drug by the complexing agent, and in turn the complexing agent makes surfactant unavailable for solubilizing the drug.

The effects of temperature on complexation are somehow complicated. In general, temperature has limited impact of complexation effectiveness. Although increase temperature can increase intrinsic solubility, higher temperature typically results in lower complexation binding constant due to a negative standard enthalpy change ($\Delta H°$) accompanying the complexation process. For example, this effect was seen with the complex formed between alfaxalone, a poorly water-soluble compound, and HP-β-CD (Peeters et al. 2002)

OTHER COMPLEXATIONS

In addition to the inclusion complexes formed by CDs, other types of molecular complexes also have been reported extensively (Murugan et al. 2014; Zhang and Isaacs 2014). For example, quaternized poly(propylene imine) dendrimer has been successfully used as a drug carrier for a poorly soluble drug nimesulide to enhance its solubility (Murugan et al. 2014). Devarakonda et al. (2005)