Effect of Solvents, Surfactants, and Complexing Agents on Stability

For insoluble drugs, to achieve desirable bioavailability, many approaches have been used, such as pH control, cosolvents, surfactants, and complexing agents. Sometimes, several approaches can be used together to achieve the best solubilization effects. Ran et al. (2005) studied three combined techniques in solubilizing a poorly water-soluble anti-HIV drug, and achieved good stability as well. However, it is crucial to ensure that the solubilizing agents do not adversely affect the drug stability.

Effect of Solvents on Stability

Kearney and his colleagues (1994) studied the kinetics of degradation of PD144872, a dual-action hypoxic cell radiosensitizer in co-solvent systems containing 10% ethanol, varying amounts of propylene glycol (PG) (ranging from 0% to 30% v/v), and water. They found that increasing the percentage of PG from 0% to 10% had little to no effect on the stability of PD144872, whereas increasing the percentage of PG from 10% to 30% resulted in about a 1.3-fold increase in the degradation rate. They attributed this increased rate to changes in the apparent pH of the media and/or to a PG-induced increase in the apparent pK_a of PD144872. Similar changes of pK_a have been reported for other weak bases such as triethanolamine (Rubino 1987).

Ni et al. (2002) studied the stability of SarCNU (NSC364432) in water, ethanol, PG, Capmul PG, and DMSO, as well as their combinations over the temperature range of 25°C–60°C. The two cosolvents are an 80% PG: 20% ethanol mixture (PE), and a semi-aqueous vehicle (WPE) containing 50% water: 40% PG: 10% ethanol. The degradation mechanism in all the studied solvents is the same, and the stabilization by these vehicles follows the order of Capmul PG > Ethanol > PE > PE > PG > WPE > water, which is in agreement with their decreasing polarities.

Oxidative degradation is as important as hydrolysis in the stability evaluation of new drug substances. The oxygen concentration in solution is a factor in many cases and often depends upon the solvent employed. It was reported that ascorbic acid is more stable in 90% propylene glycol or in Syrup USP than in water, presumably because of the lower oxygen concentration in these vehicles (Ravin and Radebaugh 1990).

Effect of Surfactants on Stability

Many organic reactions have been found to be accelerated or inhibited in the presence of micellar media. The apparent reaction rates are altered in micellar solutions because of the distribution of substrate between the micellar and aqueous bulk phases in which different reaction rates occur (Fendler and Fendler 1975).

The effect of micelles on organic reactions can be attributed to both electrostatic and hydrophobic interactions (Rosen 1979). Electrostatic interaction is important because it may affect the transition state of a reaction or the concentration of reactant in the vicinity of the reaction site. The hydrophobic interactions are important because they determine the extent and the locus of solubilization in the micelle.

These principles have been demonstrated by a large number of reactions. The reader is directed to the excellent reviews by Fendler (1975) and Rosen (1979) for detailed discussions.

Effect of Complexing Agents on Stability

The stability of insoluble compounds will often change as a result of inclusion complex formation. This stability change may be the result of a microsolvent effect, hydrogen bonding, and/or a conformational effect (Szejtli 1982). The effect of CDs on the stability of a drug depends decisively on the geometry of the complex, as well as on the distance and relative orientation of the labile partial structure of the guest molecule with respect to the nucleophilic, catalytic center of CD (Albers and Muller 1995). In the case of ester hydrolysis, a nucleophilic attack at high pHs by one of the hydroxyl groups of the CD can accelerate the hydrolysis. Therefore, the closer the spatial approximation of ester groups to ionizable hydroxyl groups of the CDs is, the more drastic the increase