to be limited by the solubility of the base and did not adequately represent the solubility of the salt. One way to avoid this problem is to determine solubility in a diluted acidic solution using the same acid that formed the salt with the base. The solubility can then be estimated by correcting for the common ion effect from the acid. Keep in mind that it is only from a solubility experiment at a pH below pH_{max} that the solubility of the salt can be estimated.

Solubilization

Various techniques for solubilization are discussed in other chapters in this book, and will not be considered individually here. When one particular technique does not give a satisfactory outcome, a combination of techniques should be considered. However, it is important to keep in mind that a combination of techniques may not always give a synergistic effect because of competitive mechanisms.

The commonly used solubilizing excipients for oral and injectable dosage forms include pH adjusters, water-soluble solvents, surfactants, water-insoluble organic solvents, medium-chain triglycerides, long-chain triglycerides, cyclodextrins, and phospholipids (Strickley 2004). Drug solubility in commonly used pharmaceutical solvents is often very useful in selecting suitable solubilization methods. Those solvents include, but are not limited to, ethanol, benzyl alcohol, Tween 80, PEG 400, propylene glycol, and glycerin.

Combining a cyclodextrin (CD) and a surfactant typically results in reduced solubilizing ability compared to each of these solubilizers used alone. This is due to the formation of an inclusion compound between the CD and the surfactant. On studying the effect of the presence of β-CD on the micellization process of sodium dodecyl sulfate or sodium perfluorooctanoate in water, Junquera et al. (1993) concluded that all the parameters directly related to the complexation process depend mainly on the hydrophobicity of the surfactant chain and its length, revealing that this is the part of the surfactant which is included into the CD cavity. Several other cases have also been reported. Methyltestosterone can be solubilized by HP-β-CD. However, when the micelle-forming excipient sodium deoxycholate is added, the drug is completely displaced from the cavity (Albers and Muller 1995). Both the nonionic surfactant Solutol HS 15 and β-CD increase the solubility of diazepam in water. However, a mixed solution of the two solubilizers does not increase diazepam solubility. Because of the high stability constant of the surfactant/β-CD, diazepam is displaced from its complex with β-CD (Kraus et al. 1991). Muller and Albers (1991) also reported that the combination of 1,2 propylene glycol and 2-HP-β-CD induced a decrease in the solubilizing capacity of the system as compared with 2-HP-β-CD alone.

Dissolution

Dissolution of a drug substance is controlled by several physicochemical properties, including solubility, surface area, and wetting properties. For insoluble compounds, dissolution is often the rate-limiting step in the absorption process. Knowledge of the dissolution rate of a drug substance is therefore very useful for formulation development. The appropriate dissolution experiments can help to identify factors that contribute to bioavailability problems, and also assist in the selection of the appropriate crystal form and/or salt form. Dissolution tests are also used for other purposes such as quality control and assisting with the determination of bioequivalence (Dressman et al. 1998).

Experimentally for IDR measurement, a constant surface area is obtained by compressing powder into a disc of known area with a die and punch apparatus. Both rotating and static disks have been used extensively. Potential problems with this method are crystal form conversions during compression of powder into a pellet or during the dissolution experiment. Since many drug candidates are weak acids or bases, pH and common ion gradients at the solid-liquid interface can lead to erroneous conclusions, as discussed by Mooney and co-workers (Mooney et al. 1981a, 1981b).