solutions of polyoxyethylene (23) lauryl ether and polysorbate 80 actually decreases as temperature increases over the temperature range of 30°C–70°C (Hamid and Parrott 1971).

For solubilizing systems containing complexing agents, because the standard enthalpy change accompanying the complexing process is generally negative, increasing temperature will reduce the degree of complexation (Szejtli 1982). Depending on the binding constants of complexes formed, this decreased binding can easily surpass the intrinsic solubility increase with increasing temperature, resulting in an overall solubility decrease in the presence of complexing agent with increasing temperature.

For co-solvent systems, because the heat of solution in different solvent systems is generally different, the temperature effect on solubility in these systems is also different. Detailed solubility mapping in the solvents of interest, including the effect of pH (for ionizable compounds), temperature, and co-solvent compositions is typically required in order to develop a robust formulation, such as a soft gel formulation.

Determination of Solubility

The determination of solubility for insoluble compounds may be very challenging and time-consuming. Recognizing the advantages and limitations of various methods and choosing the proper method(s) or combination of methods for the specific preformulation requirement are essential to ensure the quality of the data. As solubility measurement is typically very labor-intensive and time-consuming, more and more high-through approaches have been developed for solubility measurement (Bard et al. 2008, Colclough et al. 2008, Heikkila et al. 2008, Alelyunas et al. 2009, Heikkilae et al. 2011, Wenlock et al. 2011).

Equilibrium Method

The equilibrium solubility of the drug candidate is obtained by equilibrating an excess of material in a vial with the solvent. The vial is shaken or stirred at constant temperature and the amount of drug determined periodically by analysis of the supernatant fluid. Generally, several samples should be assayed at different time intervals to determine if equilibrium has been achieved. When results from two successive samples are identical, equilibrium has most likely been reached. The residual solid from the solubility study should be checked to see if there are any crystal form changes.

For very insoluble compounds, using this method directly involves special difficulties, and therefore may not be practical (Higuchi et al. 1979). First of all, the analytical method may not be sensitive enough to quantitate the solubility. Secondly, the extremely low dissolution rate resulting from the low solubility may lead to difficulty in reaching equilibrium, leading to large errors in solubility results. For example, the reported solubility of cholesterol in water ranges from 0.025 to 2600 μg/mL (Madan and Cadwallader 1973).

There are several possible ways to improve the saturation rate. One reason for the delay in the attainment of equilibrium is the decrease in effective surface area during the dissolution process. This can be overcome by using a substantial excess of solid in the solubility sample (Higuchi et al. 1979). The surface area of the solid can also be increased by pre-processing the solubility samples. Both votexing after adding a small Teflon ball and sonication are very effective techniques for this purpose.

Another approach for enhancing the dissolution rate is the addition of a water-immiscible solvent in which the organic solute is more soluble, thereby increasing the effective surface area available for dissolution (Higuchi et al. 1979, Anderson et al. 1996). Since a small amount of non-aqueous solvent solubilized in water may change the solubility significantly, it is important to make sure that the water-immiscible solvent chosen is sufficiently immiscible in water so the solubility is not affected significantly. One way to check whether or not the effect of the solvent is significant is to determine solubilities in several different solvent-water systems. The solubility results should be rather independent of the solvents used. Some commonly used water-immiscible solvents include isooctane, octanol, and soy bean oil.