For a poorly water-soluble drug, when the equilibrated drug solutions are filtered, it is important to check the filter compatibility of the drug, and to make sure a suitable filter(s) that has low or no binding capacity for the drug has been selected. Because some filters may adsorb a small amount of the drug, the adsorption may affect the measured drug solubility, considering its poor aqueous solubility.

Intrinsic Dissolution Rate Method

The dissolution rate is directly proportional to the equilibrium solubility if the appropriate experimental conditions such as the ones used for intrinsic dissolution rate (IDR) measurements are selected. The rotating-disc method is the most useful and most widely used technique for measuring IDRs. The theoretical considerations and experimental details of this method will be considered later in this chapter in the discussion dealing with dissolution.

The IDR method is very useful where the equilibrium method cannot be used. For example, when one wishes to examine the influence of crystal habit, solvates and hydrates, polymorphism, and crystal defects on apparent solubility, the IDR method will usually avoid the crystal transitions likely to occur in equilibrium methods. However, crystal transitions can still occur at the surface, as in the case of anhydrous theophylline (De Smidt 1986) where the anhydrous form converts to the hydrate and the IDR changes over time. In these cases, the application of a fiber optical probe, which permits the detection of the drug concentration every few seconds, may prove to be very advantageous.

Non-Equilibrium Method

Any methods that do not contain steps to ensure the establishment of equilibrium can be considered non-equilibrium methods. Several methods commonly used for solubility measurements in the early discovery setting have been reported (Curatolo 1996, Pan et al. 2001), and these methods typically begin with dimethyl sulfoxide (DMSO) solutions or with amorphous material. Turbidity and ultraviolet detection are commonly used because they easily can be designed into high-throughput instrumentation.

The usefulness of the solubility data from these non-equilibrium methods often is questionable. Some pharmaceutical companies use these data as a first criterion to eliminate poorly solubility compounds. However, because the contribution of crystallinity to solubility is not controlled in non-equilibrium methods, the reliability of the data cannot be guaranteed. If experimental error is minimized, it is generally safe to assume that solubility can only be less when solid material is later used to determine equilibrium solubility. Therefore, the use of these solubility data as a gatekeeper seems to be justified. However, it is questionable whether data generated by these methods are any better for this purpose than those generated by computational methods. In addition, since for highly potent drug candidates the solubility requirement is dose-dependent, compounds whose solubility is in the microgram range may still be developable. Therefore, setting the right criteria to eliminate poorly soluble compounds may be challenging.

Estimation from the Partition Coefficient

For extremely insoluble compounds, the direct measurement of solubility may be impractical and unreliable. One possible way to obtain solubility information in these cases is through estimation from the partition coefficient (Higuchi et al. 1979). Typically, these very water-insoluble compounds are sufficiently soluble in a water-immiscible organic solvent to allow direct measurement. Once the solubility in some selected organic solvents is known, the solubility in water can be calculated from the directly measured or, more usually, the estimated partition coefficients. Based on the assumptions of the group contribution approach (Davis et al. 1974), the partition coefficient for a molecule can be predicted from the partition characteristics of its constituent parts by assuming that they are additive.

Another application of this method is the solubility estimation of drugs or prodrugs that are unstable in water (Beall et al. 1993). The synthesis of prodrugs is a commonly used approach for