

a further 40 μL of the solvent is added, and its effect is noted. Successive amounts of the solvent are then added until the compound is observed to dissolve. This procedure should give an approximate value of the solubility. This method does not take into account the kinetic aspects of the dissolution processes involved in solubility measurements. To determine more accurately the concentration of a saturated solution of a compound, the following procedure can be used. A known volume of the solvent, water, or buffer is taken into a scintillation vial, and the compound is added until saturation is observed. The solution is then stirred or shaken, and the experiment is restarted. It is recommended that the experiment be conducted at least overnight or longer, for low-solubility compounds. Depending on the amount of the compound available, replicate experiments should be carried out. After stirring or shaking, the solvent should be separated from the suspension by centrifugation or by filtration, using polytetrafluoroethylene (PTFE) filters. The filtrate is then assayed preferably by HPLC; however, ultraviolet (UV)–visible spectroscopy can also be used to determine the solubility, if compound stability or impurities are not an issue. This is termed the thermodynamic solubility. It is also useful to measure the pH of the filtrate and to characterize any undissolved material by DSC to detect any phase changes that might have occurred.

For high-throughput screening (HTS) of solubility, where the amount of the compound might be severely restricted, reporting kinetic solubility might be adequate. This can be accomplished by using techniques such as a 96-well microtiter technique with an integral nephelometer, where aliquots of the aqueous solution are placed in the microtiter wells, to which 1 μL of the compounds in dimethylsulfoxide (DMSO) is added, and the plate is shaken. The turbidity of the solutions is then measured using the nephelometer. The process is repeated up to 10 times. If turbidity is detected in a cell, the experiment is terminated; that is, solution additions are stopped, and the solutions are ranked in terms of the number of additions that caused turbidity. This method is suitable to rank the compounds in terms of their solubility and not to measure solubility accurately. A transformation of the amorphous form to a crystalline form would decrease the dissolution rate in most instances. Once the presence of polymorphs is established, the solubility of the polymorphs and the thermodynamic quantities involved in the transition from a metastable to stable polymorph can be calculated. Experimentally, the solubility of the polymorphs is determined at various temperatures, and subsequently, the log of the solubility is plotted against the reciprocal of the temperature (the van't Hoff method), from which the enthalpy of solution can be calculated from the slope. If the lines intersect, it is known as the transition temperature, and one consequence of this is that there may be a transition from one polymorph to another, depending on the storage conditions.

6.9.10 Dynamic Vapor Sorption

Measurement of the hygroscopic properties of a compound can be conveniently carried out on small quantities of compound by using a DVS system (10) from Surface Measurement Systems (U.K.) that allows highly accurate measurements under different conditions and materials. The IGA_{sorp} is designed to measure accurately the magnitude and kinetics of moisture sorption onto materials. It is fully automated and combines an ultrasensitive microbalance with precise measurement and control of both humidity and temperature. The IGA[®] (11) series of instruments uniquely utilizes the IGA method to intelligently determine the equilibrium uptakes and kinetics, and