by an abrupt decrease in the amount of light transmitted through the solution. The concentration at this point is equivalent to a kinetic solubility. Chasing equilibrium then begins—HCl and KOH are added sequentially to force the solution to become supersaturated or subsaturated, and the state of saturation is determined from subsequent small changes in the pH reading. The concentration of unionized species at the crossing points, when the pH change is zero and the sample is neither super- nor subsaturated, is equal to the intrinsic solubility. For "chasers," such as diclofenac, that supersaturate and chase equilibrium, CheqSol often finds an equilibrium solubility result within 20 minutes and confirms it several times during a 60-minute experiment. For "nonchasers," such as chlorpromazine, that do not chase equilibrium, the pH after precipitation follows the precipitation Bjerrum curve, and the software calculates the result from the shape of the curve.

Predicting aqueous solubility with in silico tools is a key drug property. It is, however, difficult to measure accurately, especially for poorly soluble compounds, and thus, numerous in silico models have been developed for their prediction. Some in silico models can predict aqueous solubility of simple, uncharged organic chemicals reasonably well; however, solubility prediction for charged species and drug-like chemicals is not very accurate. However, extrapolating solubility data to intestinal absorption from pharmacokinetic and physicochemical data, elucidating crucial parameters for absorption, and assessing the potential for improvement of bioavailability are important at the preformulation stages.

Solubilizers (e.g., organic solvents, detergents, and Pluronics) are often used to solubilize drugs in the aqueous solution, without considering their effects on biological systems, such as (i) lipid membranes and (ii) multidrug resistance (MDR) efflux transporters (e.g., Pgp and MDR1).

The modulatory role of solubilizers on drug efflux by Pgp and in silico prediction of the effect of solubilizers on Pgp are some of the newer goals of preformulation studies.

Liposomal solubilization is an effective approach for the delivery of potent, insoluble drug candidates. However, careful consideration of the various lipid and drug properties, along with an emphasis on manufacturing conditions, is needed for the successful development of a marketable formulation.

Increasing dissolution rates by using nanocrystal technologies is becoming common. The NanoCrystal Technology was developed by Elan Corporation (Dublin 2, Ireland). For poorly water-soluble compounds, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. The NanoCrystal technology can be incorporated into all dosage forms, including solid, liquid, fast-melt, pulsed release, and controlled-release dosage forms, both parenterally and orally. Poor water solubility correlates with slow dissolution rate, and decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently by using NanoCrystal technology (4). NanoCrystal particles are small particles of the drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance, using a proprietary wet milling technique (Figure 3.1). The NanoCrystal particles of the drug are stabilized against agglomeration by surface adsorption of selected GRAS (generally regarded as safe) stabilizers. The result is an aqueous dispersion of the drug substance that behaves like a solution—a NanoCrystal colloidal dispersion, which can be processed into finished dosage forms for all routes of administration.