Drug manufacturers need to confirm that each batch of API has the same crystalline structure and that this crystal form remains constant throughout the formulation and life of the drug product (particularly for solid oral dosage forms, powders, creams, ointments, and suspensions). The crystalline structure can also place physical constraints on the ability to manufacture a particular dosage form. For example, needle-shaped crystals tend to entangle and often do not flow well in manufacturing equipment. This can cause formulation of "hot spots," with high concentrations of the API in some areas and deficits in others. If the compound comes in different crystal shapes, then formulators will prefer the shape that is most conducive to the physical manufacture of the desired dosage form—other things being equal. For example, if drug manufacturers prefer a tablet or capsule, we may recommend that they synthesize more spherically shaped crystals rather than flat plates or needles. The crystalline structure also affects a compound's stability and solubility, which again have important implications for formulating, manufacturing, packaging, and storing pharmaceutical products and API. A trade-off may often present itself when selecting a crystal form. For example, crystalline structures that are more desirable from the standpoint of synthesis or formulation manufacture may be less advantageous when considering stability or solubility.

3.4.2 pK_a, Partitioning, and Solubility

Critical variables that should be considered when making formulation decisions are pK_a, lipophilicity, and solubility. The pK_a and lipophilicity can be measured using Sirius GLpK_a, and a pION pSOL instrument is used to measure the intrinsic solubility of the compound. The pK_a value is the pH at which acidic or basic groups attached to molecules exist as 50% ionized and 50% nonionized in aqueous solution. The pK_a value provides valuable data on the interaction of an ionizable drug with charged biological membranes and receptor sites and information on where the drug may be absorbed in the digestive tract. Knowing the pK_a also enables the scientist to know how much to alter the pH to drive a compound to its fully ionized or nonionized form for analytical and other purposes, such as formulation, solubility, and stability. Formulators need to know where a drug will dissolve in the digestive tract and whether that corresponds to the optimal region for absorption, especially if they are planning to create a dosage form that will be taken orally. If the drug dissolves too early, it may reprecipitate in a form that is absorbed poorly. But if a drug does not dissolve until after it travels through the stomach or small intestine, it is not likely to get absorbed. In the first case, scientists may want to create a formulation that slows the dissolution, and in the second case, they may want to create a formulation that speeds it up. Another option would be to formulate a dosage that could be administered by injection. Often, it is preferred to use a traditional, manual test process to evaluate solubility. For example, one may place samples into three buffer solutions at different pH, shake them mechanically overnight, and then measure how much of the compound has dissolved into the solutions. The measure of the intrinsic solubility of a compound (i.e., the fundamental solubility at which the compound is completely unionized) is useful for formulators in many ways. Working over a pH range from 2 to 11, the pSOL instrument can typically determine the intrinsic solubility across a range of 5–50 mg/mL. The use of the Sirius GLpK_a to create lipophilicity profiles is very useful. Drugs that can be taken orally must fall into a fairly narrow window