than 15% m/m mass gain; the deliquescent compounds simply liquefy. The dynamic model tests hygroscopic nature at various humidities; compounds showing no mass gain at 90% are called nonhygroscopic, those that do not gain at 90% are slightly hygroscopic, and those that gain 5% over a week's period are called moderately hygroscopic. Where mass increases at 40%–50% humidity, these compounds are called very hygroscopic.

Generally, a compound that is very hygroscopic would be less desirable, but if studies show that, despite moisture uptake, the compound stays stable and workable in the formulation studies, this is an important consideration.

High hygroscopicity is undesirable for many reasons, including handling problems, requirement of special storage conditions, and problems with chemical and physical stability. It is difficult to develop acceptance criteria for the amount of moisture, and large batch-to-batch variations are inevitable. Even if it were possible to define reasonable acceptance criteria, if the compound shows changes in crystal structure as a function of moisture content, this leads to problems in solubility and dissolution profiles that may not be acceptable. Stability of salts at accelerated temperature is complicated when there is significant sorption of moisture, because the properties related to the removal of moisture will be highly dependent on the choice and amount of excipients, the manufacturing process of the final dosage form, and even the impurity profile, both in the lead compound and in the excipients. As a rule, any property, such as hygroscopicity, which makes it difficult to create acceptance criterion, should be minimized. Solid-state stability, as a result of hygroscopicity, often plays a significant role in determining the dissolution rate, for example, napsylate salts often provide a more stable physical form and thus allow better dissolution.

6.8 Solubility

Solubility is a function of hygroscopicity, polymorphism, and chemical nature or pK_a of the salt. If the pK_a is at least two units lower than the pH of the medium, complete dissolution can be achieved; the opposite holds true for basic compounds. Even though in the early phase of the study, the quantity of the compound might be limited, solubility studies need to be carried out as a function of pH, leaving sufficient quantity even after the formation of salt. The solids formed (both wet and dry) should then be studied using the usual techniques, such as DSC, TGA, and XRPD. The method of determining solubility can often provide variable results. The in situ technique often proves more useful to screen out poor-solubility compounds; the traditional methods are always preferred. Solubility increase leads to improved bioavailability and liquid formulation and can be achieved by increasing the melting point or the hydrophobicity of the conjugate anion. Reduced solubility is desired for suspension and controlled-release dosage forms and can be achieved by decreasing the pK_a and increasing the solubility of the conjugate acid.

The choice of salt is greatly determined by solubility considerations; the pH of the resultant solution is important, because the salts of the stronger acids produce liquids with a lower pH to promote the dissolution of the basic compounds. However, in places where a common-ion effect can operate, such as the use of hydrochloride in gastric fluid, the useful solubility window might be limited, and this modification