crystalline form, particularly in suspension dosage forms and even in solid dosage forms, wherein the atmospheric moisture might serve as the nucleation point.

Discovery programs frequently yield amorphous compounds as a result of time pressures, the methods used to isolate them on small scales, and the increasing complexity of newly discovered molecules. Amorphous compounds carry inherent risks because of their physicochemical nature, and as a result, very few Food and Drug Administration (FDA)-approved drugs appear in amorphous forms; examples include accupril/accuretic, intraconazole, accolate (zafirlukast), viracept (nelfinavir mesylate), and paroxetine. Other drugs that are available in amorphous forms include celecoxib, amifostine, cefuroxime axetil, cefpodoxime proxetil, and novobiocin. In addition to being a physically metastable physical form, amorphous forms are generally less stable chemically. They also tend to have very low bulk densities, making the materials difficult to isolate and handle. The irregular shape of the powder of amorphous forms creates high surface area, which attracts water molecules, making them inherently more hygroscopic.

Although all these problems can be resolved, generally, the amorphous forms are to be avoided, unless the differences in solubility make a significant impact on the bioavailability.

6.7 Hygroscopicity

Water molecules have polar ends and readily form hydrogen bonding. As a result, several compounds interact with water molecules by surface adsorption, condensation in capillaries, bulk retention, and chemical interaction and are called hygroscopic. At times, the interaction between the compounds and water is so strong that the interacting water vapors result in dissolving the compound. This process is called deliquescence, wherein a saturated layer of solution is formed around the particles. Most of these interactions are dependent on critical water vapor pressure or relative humidity (RH). Moisture also induces hydrolysis and other degradation reactions. In addition, its presence affects the physical properties, such as powder flow, dissolution, and even crystal structure. The impact of moisture on the physical or chemical properties of compounds depends on the strength of bonding between the water molecules and the surrounding space where the water molecules are contained. In a tightly bound state, the water molecules are generally not available to induce chemical reactions. Free water molecules can participate in the creation of a liquid environment around the crystal lattice, where the pH may be altered as a result of the dissolution process. Similarly, water molecules held as crystal hydrates or trapped in an amorphous form are not available to modify the milieu interior of solid powders. It is noteworthy that some hydrates on taking up moisture convert into hydrates (discussed earlier). This transition can be useful in formulation studies, and this property should be tested for hygroscopic compounds.

The classification of compounds into different hygroscopic categories is based on two types of models: (1) In the first model, the RH and temperature are kept constant, gain in the weight of compound is recorded as per the definitions of the European Pharmacopoeia, and the compound tested is stored at 25°C for 24 hours at 80% RH. A slightly hygroscopic compound would show less than 2% m/m mass gain, hygroscopic compounds show less than 15%, and very hygroscopic compounds show more