developing stable formulations. The increase in water uptake results from the ability of amorphous solids to absorb water into their internal structure, as opposed to the surface adsorption shown by denser crystalline compounds. Ward and Schultz (1995) showed that in milled albuterol sulfate samples, even small increases in the degree of disorder caused significant changes in the water sorption of the drug. Saleki-Gerhardt et al. (1995) showed a linear correlation between the percent amorphous character in raffinose pentahydrate and the weight percent uptake of water. Burger and Ratz (1990) found that amorphous tetracycline could absorb 20% water compared to 2% for the crystalline form. The amorphous form was also more susceptible to degradation under ultraviolet light than the crystalline form, and this was exacerbated by moisture.

Although amorphous forms tend to crystallize rapidly when in contact with a solvent, the solid forms often show enhanced dissolution rates and transient solubility increases that can translate into greater bioavailability. Otsuka and Kaneniwa (1983) studied the solubility of crystalline and amorphous cephalexin. The maximum solubility in water at 10°C was about 60 mg/mL for noncrystalline drug versus 10–11 mg/mL for the crystalline drug. The difference at 35°C appeared to be less owing to a more rapid crystallization rate at this temperature. Chikaraishi et al. (1996) also reported the effects of temperature on solubility and conversion rate for a solution-mediated phase transition of an amorphous form of piretanide to a crystalline form. Apparent solubility of the amorphous solid was 1.5 times greater than the crystalline form at 45°C. Likewise, a 2-fold increase was seen at 30°C. Conversion of the amorphous solid to the crystalline form was determined to occur faster at 45°C compared to 30°C. Imaizumi et al. (1980) showed that the dissolution of amorphous indomethacin was higher than that of the crystalline form for 2 h, after which crystallization caused the two to be equivalent. Fukuoka et al. (1987) estimated that the initial dissolution rate of the amorphous form was four times that of the crystalline form (γ modification) in phosphate buffer (pH 7.2). They demonstrated that this difference caused an increased oral and rectal absorption of indomethacin in rabbits, and a higher maximum peak in the blood level versus time curve.

The magnitude of the amorphous solubility enhancement is generally much greater than that of a metastable polymorph or an anhydrate/hydrate system. Stagner and Guillory (1979) compared the IDRs of amorphous iopanoic acid to that of the commercial crystalline form in pH 6.5 aqueous buffer at 37°C. The amorphous form was about one order of magnitude faster dissolving than the crystalline state (Figure 19.2). Higuchi et al. (1963) estimated that the amorphous form of methylprednisolone was about 20 times as soluble as the crystalline form I. Doherty and York (1989) found that furosemide amorphous solids stabilized by PVP gave 31–36 times the dissolution rate relative to crystalline drug. The amorphous form of novobiocin free acid was found to be 10 times as soluble as the crystalline free acid in 0.1 N HCl at 25°C (Mullins and Macek, 1960). The amorphous form gave equivalent therapeutic blood levels when dosed to dogs (in suspension at 12.5 mg/kg) as the more water soluble calcium salt, yet the crystalline free acid was not absorbed orally at detectable levels.

Hancock and Parks (2000) have critically evaluated the theoretical and practical aspects of utilizing the amorphous state. Theoretically, the gain in solubility though the use of an amorphous was predicted to be between 10- and 1600-fold. However, these elevated solubilities also represent very favorable driving forces for crystallization, and as a result, the realized gains are appreciably less.

Physical Stability of Amorphous Solids

From the preceding section, it is apparent that the amorphous forms can have significant advantages in oral bioavailability for drugs with poor aqueous solubility. The high free energy, high solubility physical state responsible for this enhanced activity is a metastable state, and crystallization to a lower energy state is likely given the correct conditions. The commercial development of amorphous forms is limited by the ability to predict and control the physical stability of these systems so that the patient can receive the benefit of this enhanced activity.

The molecular mobility of a molecule in an amorphous solid is a function of the storage temperature in relation to the glass transition temperature (T_g). The glass transition is a second-order