Changes in the solid state can influence dissolution rate through the surface area term or the solubility term. Surface area differences can arise from simple particle-size effects between different crystal forms and also from shape factors. Different crystal habits and shapes can alter the exposed surface area without a change in median particle-size measurements, since these are often calculated by methods that assume spherical shapes. Abdou (1989) has reviewed the effect of crystalline state on the dissolution rate of pharmaceuticals, and how this contributes to bioinequivalence of various forms.

Differences in solubility between different crystal forms alter the driving force for dissolution, controlled by the difference between the solution concentration and the saturation concentration ($C_s - C_b$). Hamlin et al. (1965) have shown that dissolution rate correlates well with solubility for a large number of pharmaceutical compounds varying in solubility from 0.01 to 10 mg/mL at 37°C. Nicklasson and Brodin (1984) have shown that using cosolvent mixtures for drugs with poor aqueous solubility produces a good correlation between dissolution rate and solubility.

The dissolution rate improvement for most metastable solids is only transient; ultimately the excess solid in equilibrium with the solvent converts to the lowest energy phase. Figure 19.1 (Jozwiakowski and Connors, 1985) illustrates a typical dissolution profile for a metastable solid and a stable solid. In this case, β-cyclodextrin dissolution profiles were measured in 40°C distilled water and plotted on a molar basis (where the molecular weight difference is inconsequential). The concentration of the stable form in water at room temperature (a dodecahydrate) gradually increases to the limit of its solubility (0.0298 M). The metastable form (the anhydrate from oven drying) shows a rapid initial dissolution rate over the first 10 min, peaks at less than 30 min, and then declines to the solubility limit as the excess solid converts to the hydrated form, as verified by microscopy. The same behavior is exhibited by metastable and stable polymorphic forms, for example, forms I and II of meprobamate (Clements and Popli, 1973) and forms I and II of gepirone HCl (Behme et al., 1985). Ultimately, the same equilibrium solubility will be reached regardless of the direction of approach, although the kinetics of this transition can vary considerably for different drugs.

Dissolution rate improvement is often characterized by the IDRs or the change in the initial rate, since in many cases the advantage decreases with time. Table 19.3 shows some data from the pharmaceutical literature that indicates the typical dissolution rate increases that can be obtained by altering the solid state of drugs. Dissolution rate improvements of two to three times have been seen with some polymorphic or solvated forms, but typical increases are 20%–50% over the metastable form. Other polymorphs yield similar dissolution rates, such as tegafur (Uchida et al., 1993), disopyramide (Gunning et al., 1976), or amiloride HCl dihydrate (Jozwiakowski et al., 1993).

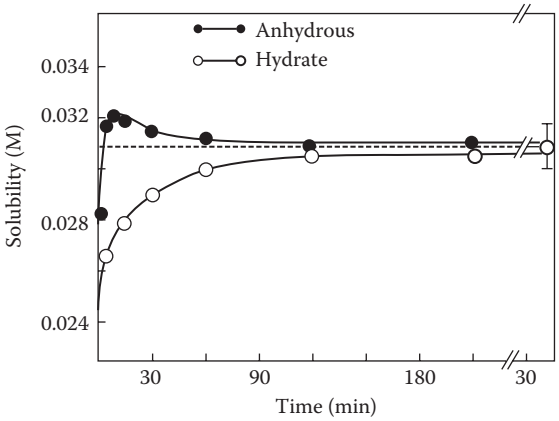

FIGURE 19.1 Dissolution rates for anhydrous and hydrated β-cyclodextrin in water at 40°C. (Reprinted from *Carbohydrate Res.*, 143, Jozwiakowski, M. J. and Connors, K. A., Aqueous solubility behavior of three cyclodextrins, 51–59, Copyright 1985, with permission from Elsevier Science.)