the saturation level (C_s), because of the large volume of fluid and the rapid dilution into the bloodstream. This sink effect allows bioavailability increases despite the tendency of these solids to revert to the less soluble form in suspension. Shibata et al. (1983) have shown that faster-dissolving forms of cimetidine are more effective at curing ulcers in the rat than the thermodynamically stable form. Haleblian and McCrone (1969) reported on the adrenal cortex atrophy in rats for a variety of solid forms of fluprednisolone. Doubling the *in vitro* dissolution rate (changing from the α-monohydrate to form I) produced a 50% greater effect of the drug. Amorphous indomethacin provided faster dissolution rates than the crystalline form (Fukuoka et al., 1987) and showed enhanced activity dosed orally in rabbits. Clearly, metastable solids can improve the dissolution rates of poorly soluble drugs and this effect can have therapeutic significance.

Solubility Increases

The solubility of a metastable solid form can be estimated from the maximum in the dissolution rate curve (Shefter and Higuchi, 1963). The accuracy of this determination depends on the rate of transformation versus the rate of dissolution. For systems such as anhydrous/hydrated theophylline in water (Shefter and Higuchi, 1963) that have the general shape given in Figure 19.1, the actual solubility is probably underestimated. The peak of the curve in this case has been described as a steady state involving equal rates of dissolution of the metastable form and conversion to the stable form. Behme et al. (1985) estimated the solubilities of gepirone HCl polymorphs by this method. Chauvet et al. (1992) estimated the solubilities of polymorphs of an anxiolytic agent after 1 h, and obtained linear van't Hoff plots from 30°C to 58°C. Suleiman and Najib (1989) measured the solubility of glibenclamide polymorphs and solvates after 8 h. Kaneniwa et al. (1985) found that the α and γ forms of indomethacin reached plateaus on their respective dissolution–time curves after 8 h, providing accurate estimates of their solubilities. Ghodbane and McCauley (1990) did not see any conversion after 24–72 h in their studies on MK571, which enabled accurate determination of the solubility of both forms in isopropanol and methyl ethyl ketone. Gerber et al. (1991) found that cyclopenthiazide did not convert to its more stable form after 7 days in water or ethanol/water. Hoelgaard and Moller (1983) reported that the aqueous solubility of the anhydrate of metronidazole benzoate could be determined after 48 h without any conversion to the stable monohydrate in the temperature range of 16°C–30°C.

Solubility values based on a plateau in the dissolution rate curve, when dissolution of the metastable form is essentially complete and the system reaches a pseudoequilibrium state before conversion to the stable solid state, are reasonably accurate. Those based on peaks in these curves or obtained by fitting exponential functions to estimate the plateau that might be reached in the absence of conversion should be considered only estimates of the metastable form solubility. The quantitative gain in these systems may be estimated more accurately by comparing initial dissolution rates for the two forms. In most cases, amorphous form solubilities must be estimated by these techniques due to their rapid crystallization when in contact with solvents.

The vitamin riboflavin exists in two polymorphic forms; form II is highly water-soluble and the higher melting form I has poor aqueous solubility (Goyan and Day, 1970). A patent was issued for the more soluble form of riboflavin based on its increased solubility (Biles, 1962). Since then, many examples of solubility differences among crystal forms of the same drug have been cited in the literature. Shefter (1981) compiled a brief list of metastable polymorphs exhibiting a greater solubility than their corresponding stable forms in his review of solubilization by solid-state manipulation. In most cases, the solubility gain was 50%–100%, but chloramphenicol palmitate (3.6 times) and Su-1777DB (4.2 times) showed substantial gains in solubility. Wells (1988) has reported the effect of hydration on the solubilities of ampicillin and glutethimide. The trihydrate form of ampicillin was only 0.75 times as soluble as the anhydrate, and the hydrate of glutethimide was only 0.62 times as soluble as its anhydrate in water. Using the anhydrate forms in dry dosage forms in these cases may impart a transiently higher dissolution rate that can alter the amount absorbed. There are also numerous cases of isoenergetic polymorphs that do not show differences in solubility