Miller et al. (2007) demonstrated thatanitraconazole-hydroxypropyl methylcellulose (HPMC) amorphous solid dispersion (1/1) increased the bioavailability 2.48 times compared to the crystalline form in rats. Zerrouk et al. (2001) found that a carbamazepine-PEG6000 amorphous solid dispersion (1/1) increased the bioavailability 1.26 times in rabbits. The use of amorphous solid dispersion technology dates back several decades, including Sugimoto et al. (1980), who showed a nifedipine-PVP amorphous solid dispersion (1/3) led to a 2.92 increase in the bioavailability in dogs.

COMPLICATIONS OF DEVELOPING METASTABLE DRUGS

Solution-Phase Transformations

In contrast to the solubility enhancing effect of metastable solids, there are some potential disadvantages that must be taken into account. In most cases, suspensions of metastable solids are not feasible owing to rapid transformation of the excess solid to the stable (low solubility) form. Shefter and Higuchi (1963) showed that many nonsolvated forms transform to the hydrated form in aqueous suspension within a few hours near ambient temperatures. Haleblian and McCrone (1969) gave some general rules for solution-mediated transformation. The greater the solubility difference, the faster the transition, because of the greater driving force. In addition, higher diffusion rates and dissolution rates lead to faster transitions, as do higher solubilities in the media.

Hoelgaard and Moller (1983) noted that the relative free-energy differences between the two forms will determine the rate of transformation. In the metronidazole benzoate system they studied, with an anhydrate and a monohydrate, the transition temperature (where the free energies of the two forms are equal) was 38°C. In this case, lower temperatures resulted in faster conversion to the monohydrate, because the solubility difference became greater the farther away from the transition temperature. Borka (1971) studied solution-mediated transformations of chloramphenicol palmitate polymorphs. Amorphous drugs converted to the stable α-form in 2 min after it was formed from the melt. Aqueous suspensions of the β-form did not convert to the α-form even after temperature cycling up to 45°C. The transformation occurred readily in isopropanol, which is a better solvent for the drug. This illustrates the role of solubility in determining the rate of conversion.

Clements and Popli (1973) summarized transformation times during dissolution of pharmaceutical compounds from the literature. Their study with meprobamate found that it took 168 h to convert to form I. Other than the example of chloramphenicol palmitate, this was much longer than most systems, which converted to the stable modification in 300 s (theophylline) to 24 h (ampicillin). This is generally slow enough to allow therapeutic advantages to dosing the metastable solid orally, but too rapid to market suspensions of these forms with adequate physical stability.

When a metastable solid dissolves, the solution becomes supersaturated with respect to the stable form. The degree of supersaturation is an important determinant of the tendency to nucleate the stable form. Phase transitions by crystallization of the stable form occur by rearrangement of the molecules in the excess solid or by crystallization of the stable solid from its supersaturated solution. The crystallization process involves nucleation, crystal growth, and Ostwald ripening (dissolution of small crystals and growth of the larger crystals). The nucleation may be either spontaneous (homogeneous) or induced by foreign particles (heterogeneous). Rodriguez-Hornedo et al. (1992) studied the theophylline anhydrate–monohydrate system and concluded that the transformation was solvent-mediated, with the growth rate of the monohydrate crystals dependent on the degree of supersaturation. The anhydrate crystals were acting as heterogeneous nucleation sites for the monohydrate, and kinetic equations were derived showing the relative dissolution rates of the two forms.

Kaneniwa et al. (1988) studied the transformation of phenylbutazone β-form to the α-form in ethanol at 4°C by DSC and XRD. The reaction was essentially complete in 4 days. Kaneniwa et al. (1985) also studied the transformation kinetics of indomethacin polymorphs in ethanol and fit the data to nine different kinetic models. The data fit the Avrami equation best, which assumes two-dimensional nuclear growth. The transformation of the α-form to the γ-form was a function of temperature with an activation energy of 14.2 kcal/mol.