is actually more soluble than the white monoclinic needle form. The anhydrous needles also show a negative enthalpy of solution (solubility decreases as temperature increases), which is unusual compared to most organic compounds.

Lamivudine is an example of the effect of hydrates in nonaqueous solvents (Jozwiakowski et al., 1996). In distilled water at 25°C, the anhydrate free base (form II) is 1.2 times as soluble as the 0.2 hydrate (form I). In ethanol at 25°C, the hydrate is 1.6 times as soluble as the anhydrate. The maximum solubility in ethanol–water mixtures was found to be at 40%–60% water in ethanol, when form I is the most stable solid phase. The transition composition was with 18%–20% water in ethanol; in binary mixtures with more than 20% water, only the hydrate was found at equilibrium, and with less than 18% water, only the anhydrate was found at equilibrium.

UTILITY OF AMORPHOUS (NONCRYSTALLINE) FORMS

Methods of Producing Amorphous Drugs

Amorphous drugs are formed either by prevention of the crystal lattice formation (rapid solidification or phase separation) or by disruption of an existing crystal structure (processing energy or desolvation). Examples of formation of amorphous sites during processing have already been cited for digoxin, spironolactone, lactose, and other solids.

The production of partially disordered solids by these techniques will generally result in properties intermediate between the pure crystalline and amorphous phases. Florence and Salole (1976) found that the generation of partial amorphous character in digoxin samples by milling resulted in 7%–118% increases in the apparent solubility, depending on the type and comminution.

Small-scale lots of NCEs are often produced in amorphous forms early in the development process, when the bulk drug synthesis is still being refined. Rapid precipitation from solution to gain high yields is often more important at this stage than optimum crystallization. Huang et al. (1991) have noted that the physical properties, including degree of crystallinity, can vary considerably by batch at this early research stage of development. The antipsychotic CI-936 was found to be more than 90% orally available in the dog as an amorphous form, and poorly and unpredictably absorbed as a crystalline form. The IDR of the amorphous form was 1.4–4.4 times as large as either crystalline lot. The effect was greater in phosphate buffer at pH 7.5, where the bulk powder dissolution of the amorphous form was approximately 10 times that of the slowest dissolving crystalline lot.

Purposeful synthesis of amorphous pharmaceuticals often involves lyophilization from solution or spray drying from a volatile solvent. Cooling of the melt can also produce a noncrystalline form if the drug does not decompose during melting. Similar to freeze drying, Overhoff et al. (2007) have described an ultra-rapid freezing (URF) process. In this process a solution of API and polymer are frozen onto a cold solid surface and then lyophilized. Utilizing danazol, this process was shown to produce amorphous material with high surface area and enhanced dissolution rate. The use of metastable amorphous forms may be required to achieve optimum performance of the solid oral dosage form for poorly soluble drugs. Cefuroxime axetil USP used in the marketed tablet formulation is amorphous, and the USP test specifies the lack of birefrigence under the polarized microscope. Numerous lyophilized formulations of antibiotics and peptides are marketed for injectable use; the dry state limits stability and preservative concerns, and the amorphous solids rapidly dissolve on reconstitution.

Examples of Solubility Increases of Amorphous Drugs

Amorphous solids have a lower density than their crystalline counterparts. This greater free volume results in a higher molecular mobility and a higher free energy, which is the basis for the enhanced dissolution rates, solubility, and bioavailability exhibited by some amorphous drugs. The crystallization of amorphous solids, their greater hygroscopicity, and their reactivity can cause difficulties in