When the molecule is too lipophilic to have adequate aqueous solubility, cosolvents, prodrugs, or emulsions are effective in increasing the solubility. Altering the solid state in this case may have little effect on its solubility, since poor aqueous solubility is due to the molecular lipophilicity. In contrast, cosolvents and emulsions do not have much impact if the reason for low solubility is the stability of the crystal lattice. When a drug has low log *P* and a high melting point (>250°C), it is likely that disruption of the lattice is needed to increase the effective solubility. This can be done by altering the crystal form (polymorphs or solvates/hydrates), or by producing the amorphous form and stabilizing it to spontaneous crystallization. The effect of altering the salt form of the drug is discussed in Chapter 15, and has also been reviewed by Berge et al. (1977).

Historical Perspective and Definitions

The effect of the solid state on drug solubility has been known for decades, and pioneer articles by Haleblian and McCrone (1969), Shefter and Higuchi (1963), and Higuchi et al. (1963) have formed the basis for further studies in this area. More recent reviews by Shefter (1981), Abdou (1989), Byrn (1982), Wall (1986), Fiese and Hagen (1986), Brittain (1995), Huang and Tong (2004), Pudipeddi and Serajuddin (2005), and Mao et al. (2005) have summarized the effects of polymorphism or solvate formation on drug solubility. The existence of different internal crystalline arrangements for the same chemical structure has been termed *polymorphism*. Verma and Krishna (1966) observed that the great majority of substances seem to be capable of multiple solid states. The work of Kuhnert-Brandstatter on steroids and barbiturates (as reviewed by Haleblian and McCrone, 1969) seems to indicate that simple organic drug molecules with multiple functional groups can arrange into numerous crystal-packing structures. McCrone et al. (1987), Carstensen (1993), and Byrn (1982) have reviewed the seven different crystal systems, which are uniquely identified by the length of the axes and the angles between them in the unit cell. Chen et al. (2005) have illustrated through the persistent evaluation of a given compound that polymorphic forms can be elusive. Indeed, many drugs crystallize into multiple polymorphic forms, especially monoclinic, triclinic, or orthorhombic types (Wall, 1986; Borka and Haleblian, 1990; Giron, 1995). This relatively common diversity in solid forms gives the formulation scientist variations in physical properties to exploit.

In general, the crystalline form with the closest packing (greatest density) and the highest melting point is the stable form. The stable form will have the lowest solubility and lowest free energy of the different solid phases of the drug. All other phases with the same composition are termed *metastable* forms at this temperature and pressure. In practical terms, the energy barrier for conversion to the stable form can be high enough that the metastable forms can be examined and formulated. This is especially true if the free-energy difference is small (leading to a small driving force) or if significant bond breaking, molecular motion, and bond formation are required for transformation.

If the crystals contain solvent molecules within the lattice structure in defined locations and stoichiometry, these are referred to as *solvates* (*hydrates* if the solvent is water). The term *pseudopolymorph* has been used historically, but is not as specific and should be avoided if the composition is known. In most cases, the solvated form of the drug is the least soluble form in that solvent (e.g., hydrates are the low-energy forms in water). Owing to additional mixing terms, solvates are often more soluble in a solvent of different composition than the nonsolvated crystal (Shefter and Higuchi, 1963). The types of solvates that appear in pharmaceutical systems and their properties of interest are covered in the "Solvates and Hydrates of Drugs" section of this chapter.

Amorphous forms can be made for most pharmaceuticals by producing the solid form faster than the molecules can arrange into a crystalline lattice. Noncrystalline solids may have some short-range order but lack the long-range periodicity and regular intermolecular bonding of crystalline solids. Their synthesis and properties differ markedly from their crystalline forms, as will be described in detail in the section on amorphous drugs. In general,