Solvent Systems for Crystallization and Polymorph Selection

JONATHAN M. MILLER AND NAÍR RODRÍGUEZ-HORNEDO
Department of Pharmaceutical Sciences, College of Pharmacy
University of Michigan, Ann Arbor MI, USA

ANTHONY C. BLACKBURN, DAINIUS MACIKENAS,
AND BENJAMIN M. COLLMAN
Materials Science, Research Formulations, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, MI, USA

Introduction
Crystallization plays an important role in the synthesis, scale-up, processing, formulation, and stability of active pharmaceutical ingredients (API) (Rodríguez-Hornedo and Murphy, 1999; Shekunov and York, 2000; Rodríguez-Hornedo and Sinclair, 2002). Crystallization from solvent is a particularly important process, as this is the primary means of purification during the intermediate and final stages of drug synthesis. Moreover, solution crystallization determines the final solid-state modification of the API namely polymorphs, solvates, and hydrates.

Polymorphs are crystalline solids that have the same chemical composition, yet adopt different molecular arrangements in the crystal lattice (Grant, 1999; Byrn et al., 1999; Vippagunta et al., 2001; Bernstein, 2002). Crystalline solids may also incorporate solvent into the lattice during crystallization to form a solvate, or a hydrate in the case of water, an occurrence that is commonly referred to as pseudopolymorphism (Byrn et al., 1999; Nangia and Desiraju, 1999). Adequate control over the crystallization of solid forms is of utmost importance, as each form can exhibit different pharmaceutically relevant properties including solubility, dissolution rate, bioavailability, physical and chemical stability, and mechanical properties (Grant, 1999; Bernstein, 2002).
The rate and mechanisms by which crystallization occurs are determined by numerous thermodynamic, kinetic, and molecular recognition factors. (Nývlt et al., 1985; Söhnel and Garside, 1992; Mersmann, 1995; Mullin, 2001; Myerson, 2002) These factors are summarized in Figure 1. The solvent plays a key role in crystallization as many of the factors depend directly on the solvent (Davey, 1982). Therefore, the intricate balance between thermodynamic, kinetic, and molecular recognition must be considered when designing experiments for polymorph screening, selection, and isolation.

In this chapter, the effects of these thermodynamic, kinetic, and molecular recognition phenomena on crystallization and the role of solvent in these processes will be described. The role of solvent on crystallization, polymorphic outcome, and phase transformations will also be discussed. Experimental approaches for polymorph screening will be presented with an emphasis on the important considerations and strategies for solvent selection.

**Thermodynamics**

**Free Energy Relationships and Solid-State Stability**

The relative thermodynamic stability of solids and the driving force for a transformation at constant temperature and pressure is determined by the difference