

Morphology, Hydrates, and Solvates- Rousseau

Both the lattice structure in which constituent units are organized and the macroscopic crystal shape play critical roles in determining many of the properties of crystalline products. These properties may affect downstream processing, such as solid-liquid separations, or product properties, such as bulk density or drug efficacy. In current research we address how system thermodynamics and nucleation and growth kinetics determine the morphological crystalline form and the conditions under which hydrates or solvates are formed.

Crystal Habit. The shape of crystals can be altered by the addition of surfactants to the medium from which a product is crystallized.¹ The chemistry of many pharmaceutical products depends upon system conditions. Isoleucine and other amino acids crystallize as zwitterions or acid or base salts depending upon the pH of the solution.²

Hydrates and Solvates. It is well-known that water or other solvents may become part of a crystal structure involving the solute and solvent, usually in specific stoichiometric ratios. The solute of interest is said to be a hydrate or a solvate. The properties of these species, sometimes referred to as adducts, can vary markedly from those of the primary species, and they can be formed during the crystallization process or as a given species takes up moisture from the prevailing atmosphere.^{3, 4} An example of this behavior is found in the use of methanol as an antisolvent in the crystallization of L-serine or sodium naproxen. With L-serine, the methanol concentration in the aqueous solution from which L-serine is being crystallized and the system temperature can determine the possible formation of a hydrate.⁵ We have examined the formation of various forms of sodium naproxen, which can crystallize in either anhydrous form or as a hydrate.⁶ Further examination elucidated how hydrates were stabilized by hydrogen bonding and identified conditions and mechanisms for their transformation.⁷

Polymorphs. Sometimes crystals of a given species can form with different lattice structures, which are called polymorphs. Generally, there is a stable polymorph, while all others are considered metastable and subject to transformation into the stable form. A specific polymorph may have preferable characteristics and it is often the one sought in process development. However, transformation from one form to another can have costly consequences and generally great effort is expended in identifying all possible polymorphs of a given crystalline product. We have utilized paracetamol as a model compound in attempting to develop a rapid-cooling protocol that produces a specific polymorphic form.⁸

¹ R. C. Zumstein and R. W. Rousseau, "The Influence of Surfactants on the Crystallization of L-Isoleucine," *Industrial & Engineering Chemistry Research*, **28**, 334–340(1989).

² M. G. Brown and R. W. Rousseau, "Effect of NaOH on the Solubilities of L-Isoleucine, L-Leucine, and L-Valine," *Biotechnology Progress*, **10**, 253–257, 1994.

³ Y.-s. Kim, D. Van Derveer, R. W. Rousseau, and A. P. Wilkinson "Anhydrous Sodium Naproxen," *Acta Crystallographica Section E*, **E60**, m419–m420(2004).

⁴ Y.-s. Kim and R. W. Rousseau, "Characterization and Transformations of the Pseudopolymorphic Forms of Sodium Naproxen," *Crystal Growth and Design*, **4**, 1211–1216(2004).

⁵ Chee-wei Jennifer Luk and R. W. Rousseau, "Solubilities of and Transformations between the Anhydrous and Hydrated Forms of L-Serine in Water-Methanol Solutions," *Crystal Growth and Design*, **6**, 1808–1812(2006).

⁶ Y.-s. Kim, Jose Mendez del Rio, and R. W. Rousseau, "Solubility and Prediction of the Heat of Solution of Sodium Naproxen in Aqueous Solutions," *Journal of Pharmaceutical Sciences*, **94**, 1941–1948(2005).

⁷ Y.-s. Kim, H. Paskow, and R. W. Rousseau, "Propagation of Solid-State Transformations by Dehydration and Stabilization of Pseudopolymorphic Crystals of Sodium Naproxen," *Crystal Growth and Design*, **5**, 1623–1632(2005).

⁸ J. Mendez del Rio and R. W. Rousseau, "Batch and Tubular-Batch Crystallization of Paracetamol: Crystal Size Distribution and Polymorph Formation," *Crystal Growth and Design*, **6**, 1407–1414(2006).