311d Estimation of Critical Supersaturation Using a Microdroplet Evaporation Technique

Guangwen He, Venkateswarlu Bhamidi, Reginald B. H. Tan, Paul J. A. Kenis, and Charles F. Zukoski

Crystallization of pharmaceutical compounds from solution is usually limited by inadequate knowledge of nucleation and crystal growth kinetics. In this work, we present an evaporation-based method that facilitates rapid generation of experimental data useful in understanding crystallization processes. Solution droplets at various initial conditions are introduced into a microdevice, in which crystallization is driven by different rates of evaporation of the solvent. The droplets are observed periodically using an optical microscope and the nucleation time for any crystals formed is recorded.

For a wide range of initial conditions ($0.12 <$ Initial supersaturation < 4.60, where initial supersaturation is the ratio of initial concentration to solubility), plots of nucleation time versus initial concentration of the solution show that the data vary linearly for a given rate of evaporation. Extrapolating the line to zero nucleation time gives the initial concentration of solute where spontaneous nucleation is expected without any solvent evaporation. We call the supersaturation at this concentration the critical supersaturation. This metastable limit is independent of the rate of solvent evaporation, i.e. the rate of change of supersaturation. Several model systems, ranging from amino acids to bio-macromolecules, exhibit the same behavior. Furthermore, we observe that this critical supersaturation is strongly correlated to the solubility for different chemical compounds. We will discuss this phenomenon in light of the theoretical relationships among critical supersaturation, interfacial tension and solubility.