Controlling Crystal Polymorphism: from Stability Prediction to Crystallization Process Design

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Investigations of crystal polymorphism are usually conducted early in drug development to optimize the physical properties of a pharmaceutical solid. Although the thermodynamically most stable crystal form is generally selected for a drug product, controlling polymorph appearance must be accomplished through careful evaluation of both thermodynamic (tendency toward the formation of more stable polymorphs) and kinetic parameters (which lead to the formation of metastable polymorphs) in the crystallization process. The first step in designing a crystallization process should be to evaluate the thermodynamic stability relationship(s) (monotropy or enantiotropy), i.e., free energy differences (ΔG), between the polymorphs as a function of temperature. A number of tools (including, but not limited to, DSC analysis of pure and eutectic melting, solubility, intrinsic dissolution, solution calorimetry and slurry bridging) can be used collectively to assess ΔG over a wide range of temperatures. While qualitative approaches, which yield the sign of ΔG only, are useful for assessing the risk of unwanted phase transformations, quantitative studies allow for the thermodynamic transition temperature of enantiotropic polymorph pairs and differences in important physical properties (solubility, intrinsic dissolution rate) to be predicted. A number of factors, including structural similarities between crystal polymorphs, comparable thermodynamic stability, ease of crystal nucleation, and overlap of occurrence domains (metastable zones), have been shown to contribute to poor polymorph selectivity during crystallization. All of these factors must be considered in implementing strategies to control polymorph appearance.

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