311c Effect of Molecular Speciation of Impurities on Amino Acid Crystallization

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Impurities that are structurally related to the solute molecules have been known to affect the solid-state properties of the crystal products including its shape (morphology), structure (polymorphism), size and purity. These crystal properties can in turn dramatically influence the in vivo dissolution, bioavailability and stability of the active pharmaceutical ingredients, in addition to their effect on downstream processability (viz. filtration, drying, comminution, compaction and particle flow).

In this work, using glycine as a model compound, we study the effects of impurities on the crystal morphology (habit) and structure (polymorphism). Crystallization experiments were carried out using chirally resolved and racemic amino acids at different concentration levels. The impurity effects on the nucleation of glycine are studied using metastable zone measurements. The experimental results are analyzed based on intermolecular interactions between glycine crystal and the impurity molecules in order to understand the plausible mechanisms by which the impurities can affect the nucleation process. Molecular modeling and simulation is employed to evaluate the interaction of the additive molecules with the host molecules either at the crystal surface or within the crystal lattice.

The experimental observations in conjunction with the molecular modeling results demonstrate that the habit modifications agree well with the stereoselectivity mechanism for host-additive interaction in chiral systems (Weissbuch et al., 1983). Besides this, we have also observed that molecular speciation of the impurities in solution can influence the interaction of the impurities with the glycine crystal. In consequence, the impurities were found to have a greater impact on the habit modification and the nucleation kinetics. The effect of molecular speciation on the crystal growth process is explained using the ′self poisoning′ mechanism proposed by Towler et al. (2004) conjecturing the nucleation of γ glycine. From the insights obtained from this work, the effects of impurities could be diagnosed with better efficacy, enabling better control of crystallization in impure systems, and ensure more consistent batch-to-batch performance..

References: Weissbuch et al., ″Centrosymmetric Crystals for the Direct Assignment of the Absolute configuration of Chiral Molecules. Application to α-amino acids by their effect on Glycine crystals″, J. Am. Chem. Soc., 105, 6615-6621 (1983). Towler et al., ″Impact of Molecular Speciation on Crystal Nucleation in Polymorphic Systems: The Conundrum of γ Glycine and Molecular ′Self Poisoning′″, J. Am. Chem. Soc., 126, 13347-13353 (2004).