Effects of impurities on crystallisation

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Pharmaceutical active ingredients, drug excipients and fine chemical compounds are complex organic molecules which are frequently purified by crystallisation from solution. Often in the industrial systems, the impurities present in the crystallisation solution are found to have serious and unpredictable impact on the morphology, structure, size and purity of the product crystal, thus leading to inconsistent batch-to-batch performance. Using "tailor-made" (structurally related) additives as a probe for investigating the impurity effects on nucleation and crystal growth of organic molecular crystals has provided for a methodological analysis of this subject.

In this work, the effects of impurities on the crystal habit and polymorphism of glycine as a model system are studied in the presence of other chirally resolved and racemic amino acids. The experimental observations are rationalised using molecular modelling and simulation in which the interaction of the impurity molecules with the host crystal is evaluated using atomistic potential energy calculations. The simulation environment is also used to derive theoretical crystal morphologies in the presence of impurities, and further explain the mechanisms by which impurities affect the crystal nucleation and growth process.

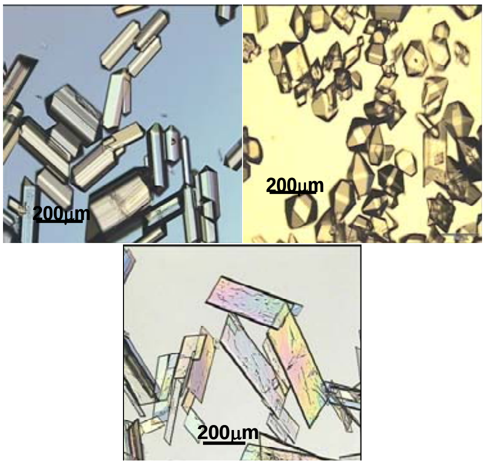

Fig. 1. Habit modification in α-glycine crystals

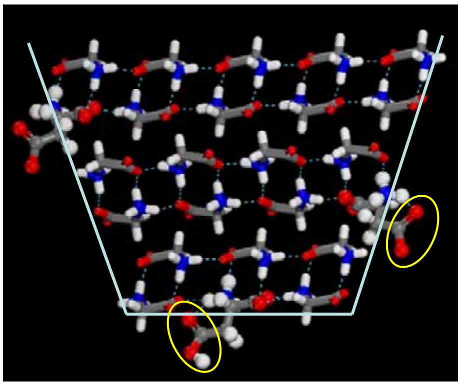

Fig. 2. Molecular modelling of impurity interactions with α-glycine crystals

With a motivation to glean insights into the impurity effects on crystal growth process at a molecular level, we use Atomic Force Microscopy (AFM), the state-of-the-art technology, for imaging crystal surfaces in a solution environment. In-situ observations provide information on the impurity incorporation mechanisms as well as their impact on the growth kinetics.

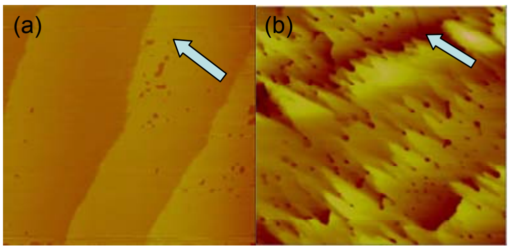

Fig. 3. AFM snapshots during in-situ imaging of α-glycine crystal surface in (a) pure and (b) impure aqueous glycine solution

Our objective is to have a better understanding of crystallisation in impure systems so as to enable a robust process and product design.

Publications:

Poornachary, S. K.; Kwek, J. W.; Chow, P. S.; Tan, R. B. H., Recovering α-glycine crystal growth from impurity poisoning: In situ monitoring using Atomic Force Microscopy. *Langmuir* **2007**, Submitted.

Poornachary, S. K.; Chow, P. S.; Tan, R. B. H., Influence of solution speciation of impurities on polymorphic nucleation in glycine. *Crystal Growth & Design* **2006**, Submitted.

Poornachary, S. K.; Chow, P. S.; Tan, R. B. H.; Davey, R. J., Molecular Speciation Controlling Stereoselectivity of Additives: Impact on the Habit Modification in α-Glycine Crystals. *Crystal Growth & Design* **2007,** 7, (2), 254-261.