

Paracetamol Habit Modification by Impurities

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The presence of impurities during crystallisation can affect final crystal attributes other than chemical purity. For example, metacetamol, a regioisomer of paracetamol, has been reported to modify the morphology of the API, leading to the isolation of columnar crystals in place of crystals with an equant habit. Small scale recrystallisation of pure paracetamol from 2-propanol was found here to produce small, relatively equant crystals. In the presence of increasing amounts of metacetamol or acetanilide (des-hydroxyl analogue) paracetamol nucleated at the same initial supersaturation contains increasing concentrations of the impurities. Microscopic inspection of the crystals shows the crystals elongate along one face to produce lath-shaped crystals, seemingly as a function of the impurity concentration. Quantification of this using Malvern Morphologi G3 methods confirms this observation for the bulk material. By means of the impurity concentration increases, the aspect ratio D50 decreases. X-ray powder diffraction of crystals contaminated with metacetamol revealed that this impurity is capable of slightly modifying the paracetamol unit cell. An elongation of one vertex and increase in cell volume accommodates the intruding impurity molecule into the crystal lattice. This observation is supported by examination of the Tamman relationship for this binary system, which indicates a partial solid miscibility of $6.7 \pm 2.1\%$ metacetamol in paracetamol. It is proposed that this solid-state interaction makes metacetamol more difficult to purge than acetanilide, and leads to the higher impurity concentrations after crystallisation.

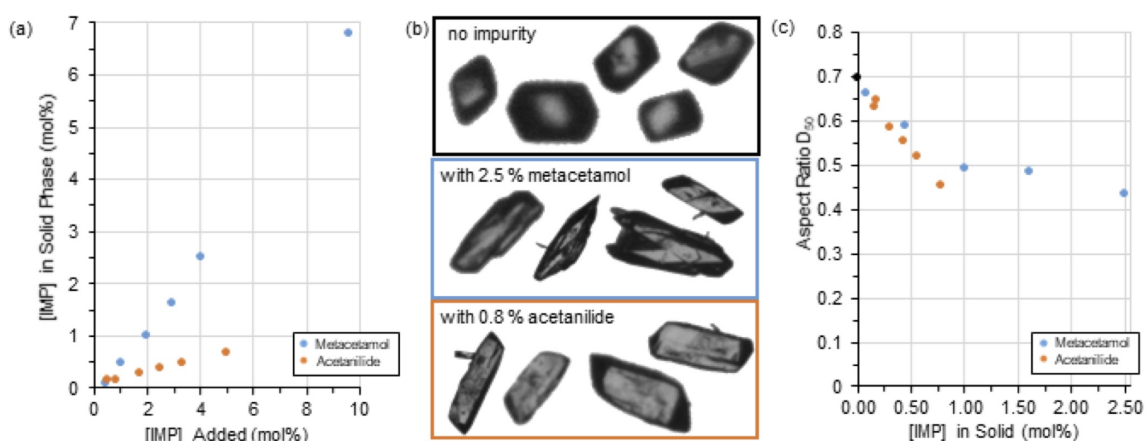


Figure 1: (a) Increasing the starting concentration of impurity linearly increases the concentration of impurity in the isolated solid phase. Metacetamol is more readily incorporated into the paracetamol crystals. (b) Representative Morphologi images of particles bearing the D50 aspect ratio of the sample indicated, not to scale (c) Aspect ratio D50 as a function of bulk crystal impurity concentration.