**Impact of Partial Solid Miscibility on Impurity Rejection during Crystallisation**

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**Highlights**

* Workflow approach to distinguish between different mechanisms of impurity incorporation
* Impurity rejection during crystallization studied in three pharmaceutical systems
* Incorporation into the crystal lattice is experimentally observed using X-ray diffraction

**1. Introduction**

Crystallization is a purification technique used across the pharmaceutical sciences and industries. Ideally, the solid product is composed of one single target compound with all other chemical entities remaining in the liquid phase for disposal. In reality, however, this can be difficult to achieve. Due to strict control of impurities in pharmaceutical products, even a small miscibility can be a cause for serious concern.

Unwanted compounds, such as structurally similar organic impurities, have many mechanisms to end up in the isolated solid product. Particularly difficult to overcome is solid-phase miscibility of target compound and impurity, which results in impurity incorporation into the crystal lattice and very little impurity rejection. Here we present a workflow development approach to rapidly identify the mechanism of impurity incorporation, and demonstrate one case of significant solid miscibility.

**2. Methods**

Small scale cooling crystallizations were designed and carried out using the Technobis Crystal16 and Crystalline systems. The resulting solid material was analyzed using multiple physical characterization methods. Crystal purity was measured using an Agilent 1100 HPLC, and using this data the distribution and selectivity coefficients were calculated. The melting temperature of solid materials were determined using differential scanning calorimetry on a Netzsch DSC214 Polyma, enabling binary phase diagrams and Tamman plots to be constructed. Plate powder X-ray diffraction patterns of recrystallized samples were collected using a Bruker AXS D8 Advance II diffractometer, and the unit cell dimensions determined using Pawley refinement methods.

**3. Results and discussion**

A series of cooling crystallizations of paracetamol in the presence acetanilide and metacetamol revealed the two structurally similar impurities have different rejection/incorporation behavior. Especially for metacetamol the crystallization does not result in a sufficiently improved solid product purity. The experimental distribution coefficients for these crystallizations was found to vary with increasing the amounts of impurity (*Kmetacetamol* = 0.05 to 0.41, *Kacetanilide* = 0.06 to 0.12), and the same trend was observed in the experimental selectivity coefficients.

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| (a) |  | (b) |  |

**Figure 1.** (a) Purification efficiency of crystallizations as measured by HPLC. Grey dashed line indicates no purification. Metacetamol (circles) linear regression y = 0.735x - 0.386, R2 = 0.998. Acetanilide (triangles) linear regression y = 0.107x - 0.060, R2 = 0.996. (b) The amount of impurity incorporation affects the selectivity coefficient of the crystallisations.

Investigating further, it was found that metacetamol incorporates into the paracetamol crystal lattice in significant amounts. X-ray powder diffraction revealed this incorporation modifies the crystal unit cell, with an elongation of one vertex and increase in cell volume thought to accommodate the intruding impurity molecule. The construction of Tamman plots for each binary system indicated a partial solid miscibility between paracetamol and metacetamol of 6.7 ± 2.1 %, further supporting the incorporation of the latter into the API crystal lattice.

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| (a) |  | (b) |  |

**Figure 1.** Tamman triangle plots. (a) Paracetamol-acetanilide. LHS regression y = 158.2x + 0.7, R2 = 0.979, x-axis intercept = 0.002 ± 0.020. RHS regression y = -699.1x + 697.9, R2 = 0.780, x-axis intercept = 0.981 ± 0.025. (b) Paracetamol-metacetamol. LHS regression y = 261.8x – 17.1, R2 = 0.992, x-axis intercept = 0.067 ± 0.021. RHS regression y = -429.1x + 421.7, R2 = 0.923, x-axis intercept = 0.972 ± 0.037.

This methodology has been formulated into a workflow and applied to two other systems; fenofibrate and mefenamic acid. These specific pharmaceutically relevant molecules have impurities which are difficult to remove using cooling crystallization techniques.

**4. Conclusions**

By utilizing physical characterization techniques, the mechanism of impurity incorporation during a cooling crystallization is determined. The specific incorporation of metacetamol into the paracetamol crystal lattice is due to partial solid miscibility, and so this impurity very difficult to remove by cooling crystallization.