**Selective Sequential Crystallization of Racemic and Enantiopure Mandelic Acid at The Solution Eutectic.**

Johannes Hoffmann1, Raghunath Venkatramanan 1, H. Lorenz2, A. Seidel-Morgenstern2, Joop H. ter Horst1

*1. EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), Technology and Innovation Centre, University of Strathclyde, UK*; *2Max-Plack Institute for dynamic of complex technical systems Magdeburg, Germany*

*\*Corresponding author: [johannes.hoffmann@starth.ac.uk](mailto:johannes.hoffmann@starth.ac.uk)*

**Highlights**

* Chiral Separation at the eutectic using serial crystallization works resulting in high enantiopurity
* In situ monitoring of the enantiomeric excess with Raman is possible.

**1. Introduction**

As the majority of new pharmaceutical substances are chiral, pharmaceutical industry seeks access to a broad range of chiral resolution methods to separate enantiomers of such chiral compounds. While new resolution methods such as attrition enhanced deracemization are developed, preferential crystallization (PC) has been proven to be an efficient and selective method to separate enantiomers in a conglomerate system. Interestingly, if the crystallization feed is sufficiently enriched using another separation technology, PC of the preferred enantiomer can also be applied to racemic compound forming systems [1]. Here we present a simple PC process to efficiently and robustly produce enantiopure crystals, starting with a suspension of both enantiopure and racemic compound crystals in a solution of eutectic composition.

**2. Methods**

In the feed vessel, an enriched suspension with both racemic and enantiopure mandelic acid crystals in water was equilibrated at temperature *T*1 so that the feed solution composition was equal to that of the eutectic point at the same temperature (Figure 1). A filtered solution was continuously pumped from the feed vessel into the first crystallizer (racemic compound DL crystallizer) and from that into the second crystallizer (enantiopure product D crystallizer), continuing as a recycle for the feed vessel. The crystallizer suspensions were held at a slightly lower temperature *T*2<*T*1 and were monitored by in situ Raman spectroscopy. The crystallizers initially contain solution at the eutectic composition and respectively racemic and enantiopure seed crystals.

**3. Results and discussion**

Due to the small temperature difference between feed flow and crystallizer suspension a small supersaturation is created which induces the seed crystals to grow while preventing nucleation. Therefore, DL-Mandelic acid is crystallized in the first DL crystallizer while D-Mandelic acid is crystallized in the second D crystallizer increasing suspension densities in both crystallizers. The differences in the pure D- and DL-mandelic acid solid Raman spectra allow to monitor in situ the solid composition while the intensity changes of these differences allow to estimate their suspension density changes. This thus enables detection of contamination of the undesired DL mandelic acid in the D crystallizer due to primary nucleation events.

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| **Figure 1.** Sequential Cascade Crystallizer set up for the separation of conglomerate and racemic compound forming systems at eutectic composition. | **Figure 2.** Estimated suspension densities *ρ*cr(D) and *ρ*cr(DL) (in arbitrary units) of D and DL mandelic acid in the D-Mandelic acid crystallizer during the separation process determined from in situ Raman spectroscopy. |

Typical results in figure 2 show an increase in the suspension density of D-Mandelic acid (blue line figure 2). The presence of DL-mandelic acid crystals was not detected in the D crystallizer throughout the entire experiment (red line figure 2) indicating that the supersaturation towards this compound in the D acid crystallizer was sufficiently lowered by the crystallization of DL-Mandelic acid in the DL crystallizer. Eventually, nucleation of D-Mandelic acid in the DL crystallizer occurred and the D concentration in the Feed to the D crystallizer decreased, lowering the increase of the D-Mandelic acid suspension density in the D crystallizer.

**4. Conclusions**

The sequential crystallization of DL- and D-Mandelic acid allows for a robust process that results in a fast and stable chiral separation of mandelic acid at the eutectic. In addition, we show that Raman spectroscopy can be used to monitor the purity and suspension densities of the desired and undesired products. This process will also be applied to conglomerate forming systems with and without racemizing agents.

**References**

[1] Gou, L., et al., *A hybrid process for chiral separation of compound-forming systems.* Chirality, 2011. **23**(2): p. 118-27.

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