

## Effect of fines dissolution on the performance of preferential crystallization for the production of pure enantiomers

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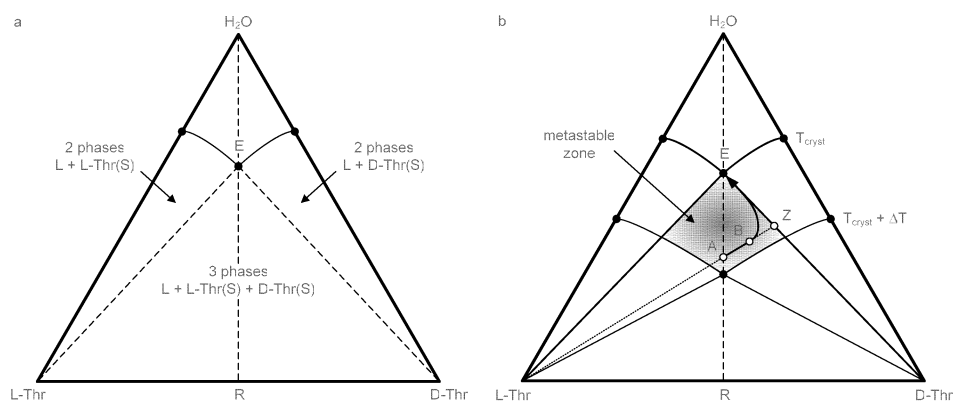
This contribution addresses the investigation of enantioseparation by means of preferential crystallization. As opposed to a simple batch oriented approach, the use of fines dissolution was included in the process to influence the overall performance. DL-threonine dissolved in water was used as a model system. During preliminary studies, fines dissolution was applied to the binary system L-threonine/water with the intention to grow large crystals by dissolving small particles originating from secondary nucleation. Subsequently, the concept was extended to the ternary system DL-threonine/water to preferentially crystallize the levo species. Comparison of the conventional batch process with the modified setup suggests a positive impact of fines destruction on product yield.

### 1. Introduction

The separation of enantiomers is an important aspect for industries providing substances that are to be administered to living organisms, since in most cases only one of the chiral molecules leads to the desired effect. Preferential crystallization is an elegant and inexpensive method which, from a process engineering point of view, is quite straight forward. It has been shown to be applicable for the conglomerate forming system DL-threonine/water (Profir, 2000) and has been studied in detail by Elsner et al. (2005) and Lorenz et al. (2006).

Figure 1a illustrates the ternary phase diagram for the case of threonine dissolved in water. A supersaturated solution with racemic composition reaches equilibrium at the eutectic point (E) while the excess precipitates as a physical 50:50-mixture of both enantiomers. A typical single batch preferential crystallization process follows a trajectory as depicted in Figure 1b. A solution of racemic composition saturated at a temperature  $T_{\text{cryst}} + \Delta T$  is cooled to a temperature  $T_{\text{cryst}}$ , upon which the solution becomes supersaturated with respect to both enantiomers (A).

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**Figure 1:** Qualitative ternary phase diagram of the conglomerate forming system DL-Thr/water

From a thermodynamical perspective the system is unstable and will tend towards equilibrium (E). It is however kinetically inhibited and temporarily remains in the metastable zone. By adding homochiral seeds of the preferred species, while the system is metastable, it is possible to obtain pure crystals of the seeded enantiomer. After seeding with L-Thr, the composition of the solution will ideally change from A to E via Z. However a decrease in purity occurs before Z is reached (B), as the counter enantiomer will ultimately undergo crystallization as well after some delay. In order to meet purity requirements, the process has to be stopped well before the occurrence of the unwanted species in the solid phase.

An extended process layout in which two crystallizers are coupled via the liquid phase has been recently scrutinized theoretically (Elsner et al., 2007) and experimentally (Elsner et al., 2009). It was shown that purity and productivity could be increased compared to the simple batch. The exchange of mother liquor results in a suitably high level of supersaturation in each vessel for a longer period of time.

The purpose of this contribution is to investigate the influence of fines dissolution on preferential crystallization. As small particles are continuously redissolved, nucleation of the counter enantiomer is suppressed to some extent while the decrease in supersaturation of the target product is delayed compared to the case of a simple batch process. Additionally fines destruction has a direct effect on the crystal size distribution which was also shown theoretically by Qamar et al. (2008). Since secondary nucleation is reduced and the number density resulting from the seed population is increased, product quality requirements can be more readily met and additional downstream operations may be facilitated.

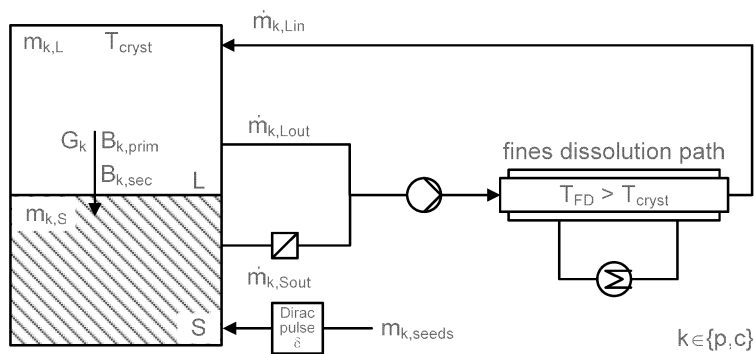
As to the authors' knowledge, investigations of preferential crystallization have so far not treated the effects of fines dissolution experimentally.

Subsequently the experimental setup is explained in more detail. In section 3, preliminary experiments with the binary system L-Thr/water are presented which served as a basis for applying fines dissolution to the ternary system DL-Thr/water. Section 4 shall briefly conclude the results of this contribution.

## 2. Experimental setup and materials

Two different sets of experiments were conducted, each one comparing a batch crystallization with and without fines dissolution. The first set was done with the binary system L-Thr/water using L-threonine (Sigma, L-threonine, purity > 98 %). For the investigation of the ternary system, DL-threonine (Sigma, DL-threonine, purity > 98 %) was used.

All results were obtained from batch experiments in a stirred jacketed glass vessel with a total working volume of 450 ml. The temperature was measured by a Pt-100 resistance thermometer and controlled by a thermostat (Julabo, FS 18). Online measurement of the optical rotation angle and solution density was done with a polarimeter (POLARmonitor, IBZ Messtechnik, Hannover, cell length: 5 cm) and a density meter (Mettler Toledo DE40). Both signals allow reconstructing the mass fraction of the dissolved enantiomer in the liquid phase. Particle free solution withdrawn from the vessel via an HPLC filter was circulated through the thermostated analytics bypass by a hose pump (Heidolph PD 5201, SP Quick.). All pipes were kept at or above solubility temperature. Fines dissolution was done using a tailored filter (pore size  $d_{\text{pore}} = 650 \mu\text{m}$ ) connected to the fines dissolution path (length: 1.2 m, inner diameter: 3.2 mm) which was thermostated above solubility temperature. The volumetric flow rate through the fines destruction path was set to  $8 \text{ ml}\cdot\text{min}^{-1}$  and  $50 \text{ ml}\cdot\text{min}^{-1}$  (Heidolph PD 5201, SP Quick), respectively. A schematic representation of the process setup and the involved mass flows is depicted in Figure 2.



**Figure 2:** Schematic representation of the crystallization process including the fines dissolution path

The solution was prepared with L- or DL-threonine dissolved in water according to solubility data determined in the group of the authors. Quantitative dissolution was guaranteed by setting the crystallizer temperature to  $50 \text{ }^\circ\text{C}$ . Subsequently the solution was cooled to the saturation temperature followed by further subcooling to the crystallization temperature  $T_{\text{cryst}}$  at a constant rate. Once the solution reached the crystallization temperature, homochiral seeds (sieve fraction  $150\text{-}200 \mu\text{m}$ ) were added to induce the process. In the case of the binary system,  $T_{\text{cryst}}$  was further lowered successively from  $37 \text{ }^\circ\text{C}$  to  $22 \text{ }^\circ\text{C}$  by steps of  $3 \text{ K}$  at the rate indicated, every time

equilibrium was reached. At the end of each experiment the solid phase was separated from the liquid by filtration and washed with 10 ml of ice-cold water and 10 ml of ice-cold ethanol.

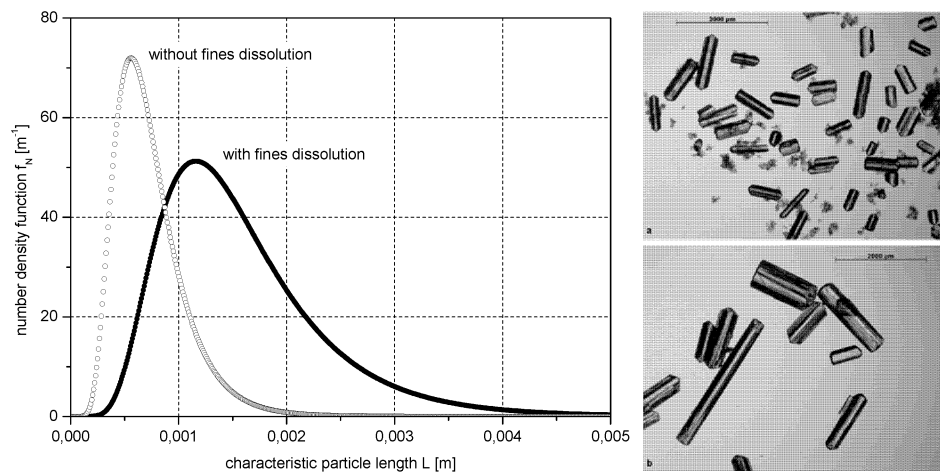
**Table 1:** Experimental conditions for fines dissolution experiments with threonine

	L-Thr/H <sub>2</sub> O	DL-Thr/H <sub>2</sub> O	Unit
Mass of water	401.58	359.19	[g]
Mass of L-Thr	48.42	-	[g]
Mass of DL-Thr	-	90.81	[g]
Mass of seeds (L-Thr)	0.5	1	[g]
Saturation temperature	40	34	[°C]
Cooling rate	-5	-14	[K/h]
Crystallization temperature	37-22	30	[°C]

### 3. Results and discussion

#### 3.1 Binary system L-threonine/water

The concept of fines dissolution was initially applied to the system L-Thr/H<sub>2</sub>O to produce homochiral seed crystals of large size. Figure 3 shows the final crystal size distributions after 7 days process time for the case of no fines dissolution and fines dissolution at a volumetric flow rate  $F_{FD}$  of 8 ml·min<sup>-1</sup>. In the latter case no small particles emerging from secondary nucleation can be seen in photograph b. In both experiments the stepwise subcooling and thus the supersaturation was marginal to additionally prevent excessive nucleation caused by an otherwise higher driving force.



**Figure 3:** Crystal size distributions without (a) and with (b) fines dissolution at the end of each experiment

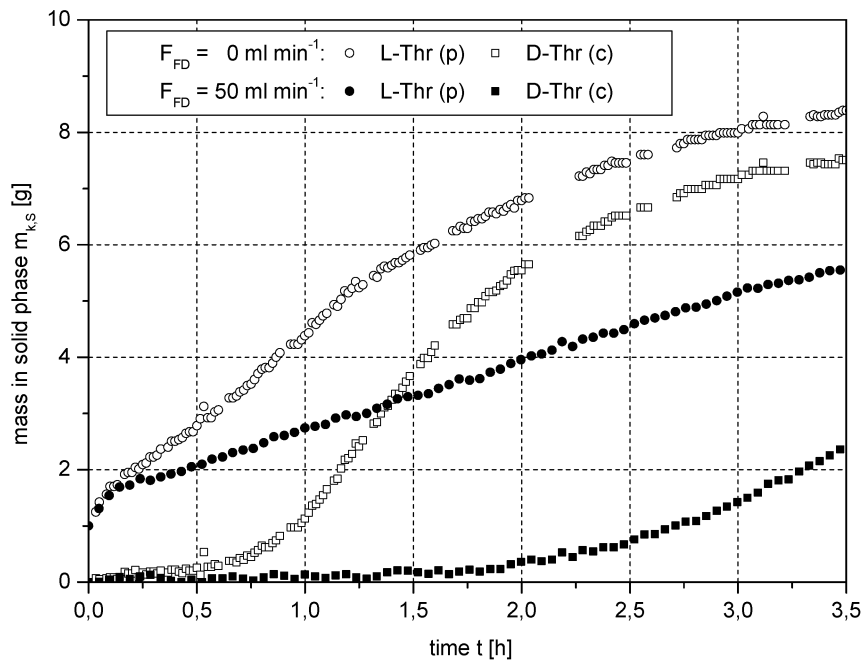
### 3.2 Ternary system DL-threonine/water

Based on the outcome of the previous experiment it was reasonable to employ fines dissolution in a preferential crystallization process. In order to investigate the effect, identical experiments with respect to the conditions (see Table 1) were carried out. Two cases were considered. Enantioseparation without fines dissolution ( $F_{FD} = 0 \text{ ml}\cdot\text{min}^{-1}$ ) and in the other case with the volumetric flow rate set to  $50 \text{ ml}\cdot\text{min}^{-1}$ .

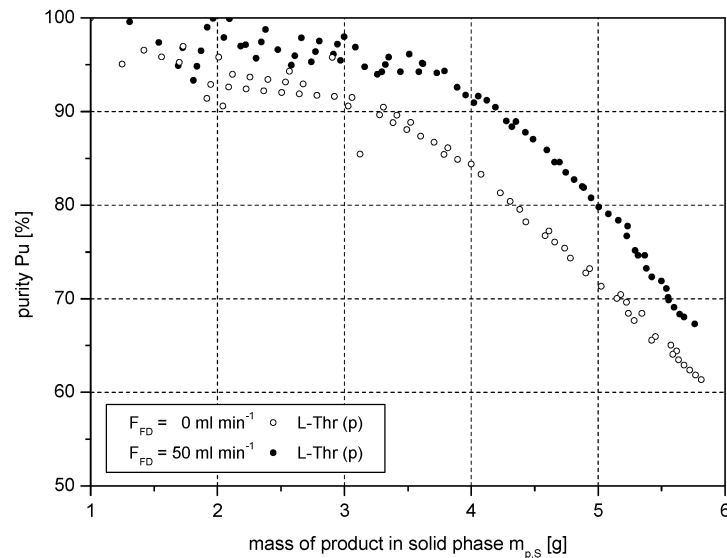
Figure 4 compares the temporal change of the masses of each enantiomer in the solid phase. It can be clearly seen, that the process without fines dissolution runs faster as expected. The occurrence of D-Thr in the solid phase is delayed by approximately 1.2 h when the suspension is circulated through the thermostated ( $T_{FD} = 50 \text{ }^\circ\text{C}$ ) bypass. Another interesting aspect is the fact that in the case of fines dissolution, the product mass  $m_{p,S}$  is increased by approximately 0.75 g compared to the simple batch process just before the counter enantiomer starts to crystallize. Since nuclei of D-Thr formed by primary nucleation are continuously dissolved, L-Thr crystals can grow for a longer period of time resulting in a higher product mass at equal purity. This circumstance is reflected in Figure 5. Crystal purity was calculated from solid masses reconstructed from the online measurement using the following definition:

$$Pu_{p,S}(t) = \frac{m_{p,S}(t)}{m_{p,S}(t) + m_{c,S}(t)}. \quad (1)$$

However, at some stage the nucleation rate of the counter enantiomer exceeds the removal rate which leads to a decrease in purity.



**Figure 4:** Changes of D- and L-Thr masses in the solid phase



**Figure 5:** Comparison of purity versus product mass

#### 4. Conclusions

It was shown that fines dissolution has strong effects on the crystal size when applied to crystallization of only one species. First results derived from preferential crystallization processes show that it leads to a prolonged growth of the seeded enantiomer resulting in a higher product mass at equal purity. By introducing two additional process variables (filter pore size and fines dissolution rate  $F_{FD}$ ) it is possible to influence the performance of the separation with respect to crystal size and product yield.

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