Analysis and optimization of different configurations for preferential crystallization

Grzegorz Ziomek[*,1)], *Martin P. Elsner*[1)], *Andreas Seidel-Morgenstern*[1, 2)]

[1)] Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstr. 1, 39106 Magdeburg, Germany
[2)] Otto von Guericke University, Universitätplatz 2, 39106 Magdeburg, Germany

*Email: ziomek@*mpi-magdeburg.mpg.de*

The intention of this paper is the analysis and optimization of general concepts for preferential crystallization with the focus on aspects of quantification. In this examination, the amino acid threonine was used as a model system. The use of on-line polarimetry in combination with on-line densimetry as well as microscopic investigation enables to obtain some indispensable information about the crystallization kinetics. Taking these estimated values into consideration a simplified mathematical description as a first approach including a population balance model was established for the simulation of the time changes of liquid phase composition during the preferential crystallization process. Based on this simplified model different crystallizer configurations were optimized and investigated.

1. Introduction

The separation of chiral compounds is of large interest because most of the (bio-)organic molecules are chiral and usually only one of the enantiomers exhibits the desired properties with regard to therapeutic activities or metabolism, whereas the other enantiomer may be inactive or may even cause some undesired effects. For this reason enantiomeric separations have become increasingly important and their application ranges from the pharmaceutical and food industry to the agricultural industry. Generally, chromatographic as well as special methods (classical non-biological resolutions via the formation of diastereomers; biological methods; non-biological asymmetric synthesis; immobilization and membrane technologies [1,2]) rank among the common separation processes. An attractive alternative to these methods is the so-called (enantioselective) preferential crystallization. As generally known such systems also tend to reach equilibrium in which the liquid phase will have racemic composition and the solid phase will consist of a mixture of crystals of both enantiomers. However, before approaching this steady state it is possible to preferentially produce just one of the enantiomers after seeding with homochiral crystals under particular conditions. The process is based on the different initial surface areas of each enantiomer and the specific driving forces due to the different supersaturations. Detailed treatises can be found in the literature [3-5]. The potential of preferential crystallization as an effective and alternative technology for the production of pure enantiomers has been the subject of some considerable academic attention in the recent years with an emphasis on its chemistry [6] and on its application to separate special chiral systems [7]. Furthermore, some special aspects like the pre-treatment of the seed crystals [8-10] and the influence of the crystal size on the transients [11] have been investigated in parts.

In this work besides qualifying operation modes using several crystallizers a comparison between optimized rivaling concepts was done. Typically the productivity is taken as objective function for a quantification of the process. In our work a modified NADLER-MEAD simplex method [12] was applied. This algorithm was found to be more reliable compared to conventional deterministic methods. Using this optimizer it is possible to determine for each configuration important process variables like mass of seeds, mass of racemate, initial seed size distribution, exchange flow rate between several crystallizers, temperature etc.

2. Description of the model and possible process configurations

2.1 Description of the model

Modeling of the crystallization process was done under the following assumptions:

- isothermal operation
- ideally mixed (semi-)batch crystallizer
- constant overall volume of the liquid and solid phase
- size-independent crystal growth rate
- no interdependence of the growth rate for each of both enantiomers
- both enantiomers obey the same growth rate law
- nucleation at negligible size
- no breakage, attrition or agglomeration.

Thus, the population balance is obtained as

$$\frac{\partial F_N^{(k)}(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left(G^{(k)} \cdot F_N^{(k)}(x,t)\right),\ k = 1 \text{ or } 2, \tag{1}$$

with the boundary and initial conditions

$$F_N^{(k)}(0,t) = \frac{B^{(k)}}{G^{(k)}},\ F_N^{(k)}(x,0) = F_{N,seeds}^{(k)}(x) \tag{2}$$

where $F_N^{(k)}$ denotes the particle size distribution for each of both components k (1 = seeded, desired enantiomer; 2 = undesired counter-enantiomer).
The dependence of the growth rate on the actual degree of supersaturation $S_{(k)}$ for both, the desired as well as for the undesired enantiomer, is described by the following empirical law:

$$G^{(k)} = k_g^{(k)} \cdot (S_{(k)} - 1)^{g^{(k)}}. \tag{3}$$

If crystals are already dispersed in the crystallizing medium, secondary nucleation can occur at supersaturation levels which are significantly lower than those at which primary nucleation takes place [13]. Based on previous experiments published in [14,15] it is highly probable that for the desired (seeded) enantiomer secondary nucleation seems to be predominant. This can be described by

$$B^{(1)} = k_b^{(1)} \cdot \mu_3^{(1)} \cdot (S_{(1)} - 1)^b. \tag{4}$$

For the case that the process is not interrupted, primary (heterogeneous) nucleation is assumed to initiate the crystallization of the counter-enantiomer which would decrease the purity. To quantify this effect often the following semi-empirical expression can be used [13]

$$B^{(2)} = k_b^{(2)} \cdot e^{-\frac{a_{(2)}}{\ln^2 S_{(2)}}}. \tag{5}$$

The mass balance for each component in the continuous phase regarding a single batch crystallizer is given by Eq. (6)

$$\frac{dm_{(liq)}^{(k)}}{dt} = -3\rho_s k_V \cdot G^{(k)} \int_0^\infty x^2 \cdot F_N^{(k)}(x,t)\, dx, \tag{6}$$

whereas for crystallizers with an exchange of the liquid phase (see below) the mass flow rates for each component k of the in- and outlet for the crystallizer i must be taken into account

$$\frac{dm_{i,(liq)}^{(k)}}{dt} = \dot{m}_{i,in,(liq)}^{(k)} - \dot{m}_{i,out,(liq)}^{(k)} - 3\rho_s k_V \cdot G^{(k)} \int_0^\infty x^2 \cdot F_N^{(k)}(x,t)\, dx. \tag{7}$$

Thus, the model consists of a partial differential equation (PDE) (1) describing the temporal evolution of the number density function $F_N^{(k)}$ coupled with an integro differential equation (IDE) (6, 7) for the mass balance in the solution. This one-dimensional system of integro-partial differential equations was discretized by means of finite differences on a fixed CARTESIAN grid and then solved numerically over the temporal domain by *MATLAB*®. An upwind discretization scheme for the space coordinate was applied.

2.2 Description of two process configurations

In order to enhance the productivity, a batch mode (mode 1) is obviously the simplest one. An applicable configuration can consist of two separate crystallizers in which the separation of each enantiomer is carried out. The principle of this batch process is quite simple: In the vessel there is initially a supersaturated solution of the racemate (E_1+E_2). After addition of homochiral seeds e.g., merely E_1 is crystallizing within a limited time period. In order to gain this enantiomer as a product of high purity, the process must be stopped before the undesired counter-enantiomer occurs. For harvesting the pure solid product a filtration device is located after the crystallization vessels in each case. During batch crystallization, the concentration of the desired enantiomer in the solution is decreasing, whereas the concentration of the counter-enantiomer remains constant. Consequently, the crystal growth rate drops with progress of the batch process.

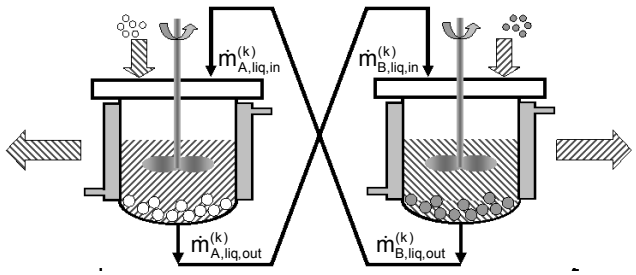

Figure 1: *Simultaneous preferential crystallization process a coupled, batch operation mode (2).*

A simultaneous crystallization (mode 2) (cf. figure2) of both enantiomers in two separated vessels with an exchange of crystal-free mother liquor, as it is depicted in Figure 1, enables to slow down this decrease of the growth rate. Since both crystallizers are coupled via the liquid phase, higher values regarding the supersaturation for each enantiomer in each vessel can be achieved (a similar connection of crystallizers can be found in [10]). This leads to an increase of the overall process and therefore, to an increase of the attainable productivity. A comparison between these different crystallizer configurations as well as an evaluation of the potential, the robustness and the control is the main subject of our common research activity.

3. Formulating of the optimization problem

3.1 Optimization problem

For an optimization, quantification of this preferential crystallization process and a comparison with other crystallizer configurations the so-called productivity Pr is taken into consideration [16]. This quantity describes the mass of gained product (i.e. without the mass of the enantiomer invested at the beginning for seeding as well as for generation of an initial excess) per unit time, at which the process is stopped, and per used mass of racemate:

$$\text{Productivity:} \qquad Pr_m^{(k)}(t^*) = \frac{m_S^{(k)}(t^*) - m_{seeds}^{(k)} - m_{excess,0}^{(k)}}{t^* \cdot 0.5 \cdot m_{rac}}, \quad k = 1, 2. \tag{8}$$

The following optimization problem has been considered:
The maximization of the productivity

- Max Pr

The productivity was optimized subject to constraints regarding the crystals purity demands and the minimal averaged gained crystal length. Purity of the crystals can be defined as follows:

$$Pu^{(k)} = \frac{m_{end}^{(k)}}{m_{end}^{(1)} + m_{end}^{(2)}}, \quad k = 1, 2. \tag{9}$$

and hold by following equation:

$$Pu^{(k)} \geq Pu_{min} \tag{10}$$

Minimal averaged gained crystal length can be defined as a ratio between average length of the seeded crystals at the end of the process and the average length of the seeds. This ratio can be described by the following equation:

$$Q^{(k)} = \frac{\overline{x}^{(k)}_{seed,end}}{\overline{x}^{(k)}_{seed}}, \quad k = 1, 2. \tag{11}$$

If as a $Q^{(k)}_{min}$ it will be considered minimal averaged crystal length after the batch process the following constrain can be assumed:

$$Q^{(k)} \geq Q^{(k)}_{min}, \quad k = 1, 2 \tag{12}$$

3.2 Decision variables

As it was mentioned above in the optimization routine productivity was maximized and as decision variables the process parameters were taken. Depending on the optimized configuration the following variables were optimized:

- batch mode

In this mode mass of seeds $m^{(k)}_{seed}$ added before process, total duration time t^* and the mass excess of seeded enantiomer $m^{(k)}_{excess,0}$ were taken into consideration as optimized variables.

- simultaneous preferential crystallization mode

For simultaneous preferential crystallization mode in two separated vessels which are coupled via the liquid phase the mass of seeds $m^{(k)}_{seed}$ added before process, total duration time t^*, the mass excess of seeded enantiomer $m^{(k)}_{excess,0}$, time when the liquid phase is started to be exchange between vessels and exchange flowerate were taken as a optimization variables.

3.3 Optimization algorithm

For optimization of the crystallization process the Nelder-Mead method [12] was used. The Nelder-Mead algorithm is a popular derivative free method for minimizing unconstrained real functions. However, preferential crystallization process must be considered as a nonlinear constrained problem. For this reason a few modifications have been included in the original algorithm, which increased probability of finding of a global optimum, i.e., a) initial simplex was generated randomly, b) the multi-pass optimization has been performed, where in each subsequent pass *n* number of simplex vertexes is replaced with new points randomly generated and the last of the simplex vertex obtained in a previous pass becomes the best current solution c) the algorithm can accept a point that does not meet constrains. If after the movement of the simplex an infeasible point is obtained (point for which constraints are not met) than this point is accepted at the goal function set as a large random number (in the case of minimization) Pr = $10^{12} \cdot R$, with *R* as a random number from the range <0,1>.

3. Selected results and discussions

A typical experimental run, which was carried out for preferentially crystallizing L-threonine (E_1) at first, is shown in Figure 2. It shows the profile of the optical rotation

angle without an initial enantiomeric excess in comparison with a simulated profile based on the estimated parameters for the crystallization kinetics. The profile is satisfactorily described by the model selected and for the established parameters for the time period (< 300 min) in which the desired enantiomer E_1 is exclusively crystallized. With increasing time (> 300 min) the simulation shows a disagreement compared to the measured data, because the nucleation of the (undesired) counter-enantiomer E_2 is rather difficult to determine.
However, based on this simplified model a prediction of the productivity for the preferential crystallization process in a coupled operation mode (mode 2) (cf. Figure 1) for an enantiomer with a demanded purity of 90% has been examined theoretically. The results for the special case with an initial enantiomeric excess of 2% and under the assumption of trouble-free and exactly simultaneous operation, i.e. exact symmetric progress of the considered process in both vessels, are shown in Figure 3. It could be demonstrated that there is exist an optimal exchange flowrate and time when exchange should be started. With increasing exchange flowrate between both vessels the productivity to achieve becomes higher. In case of infinitely high exchange rate the productivity reaches a limit. It is quite interesting that the productivity reveals an optimum in dependence on the time in which the exchange of the liquid phases of both crystallizers is switched on. The reason for the occurrence of an optimum is that the initial enantiomeric excess must be first decomposed before both liquid phases are mixed in order to achieve overall growth rates as high as possible and to exploit effectively the "enhancement effect" of this crystallizer configuration.

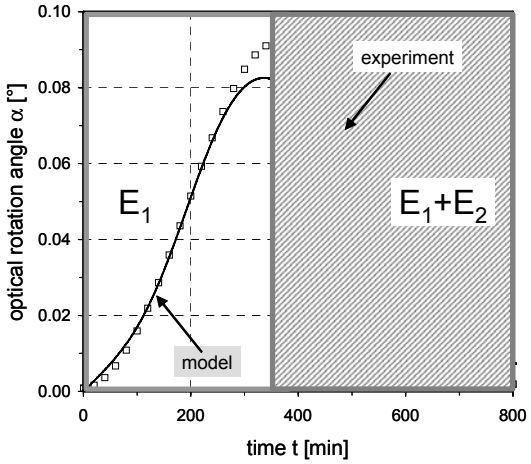

Figure 2: *Comparison of the experimental optical rotation angle obtained by seeding with L-threonine (E_1) crystals with the simulations.*

The model described above supplies a satisfying description of the process as a first approach. Currently, further experiments are performed in which the influence of the crystallization temperature, size of the seed crystals as well as the presence of the counter-enantiomer on the crystal growth of the desired enantiomer is studied in detail. These results shall be used for a refinement of the existing model. Moreover, the knowledge of the temperature-dependency enables studies on the fines dissolution and thus on the shape of the crystal size distribution.

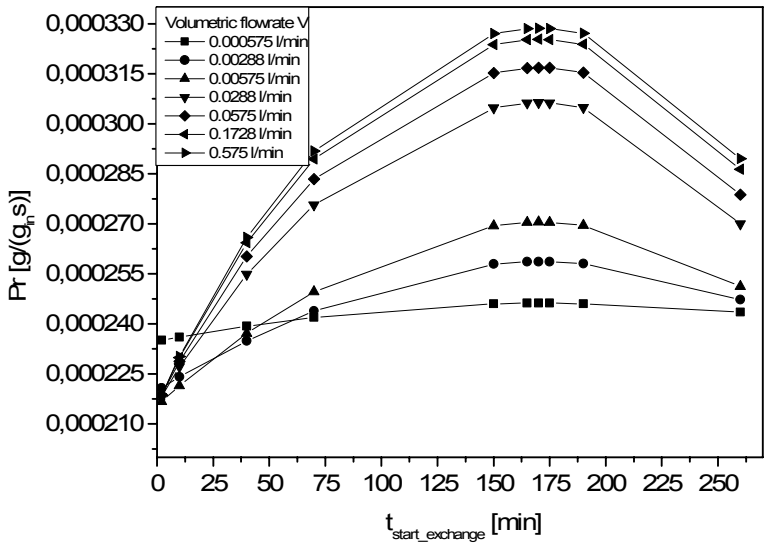

Figure 3: *Productivity for the preferential crystallization in a coupled crystallizer configuration (cf. Figure 1) in dependence on the switching time.*

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