

Continuous Preferential Crystallization in Two Coupled Crystallizers

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This contribution investigates continuous preferential crystallization in two coupled vessels connected via liquid exchange to resolve enantiomers from a racemic mixture. A comparison is drawn between separation in single and two coupled crystallizers. Implementation of periodic and continuous seeding modes is analyzed as well as the influence of exchange flow rate. A high resolution scheme of Koren is applied to solve the models considered. Productivity, purity and mean crystal size are chosen as goal functions to evaluate the product quality and advantages of the coupled process.

1. Introduction

1.1 Motivation

Enantiomeric separation is still a challenging task despite availability of many chiral separation techniques such as enantioselective synthesis, chromatographic methods, enzymatic resolutions, membrane technologies or separation of racemates. The possibility of exhibiting different metabolic effects on a human body either by a pure enantiomer or by a racemic mixture draws attentions of manufactures to the importance of this task. Enantiomers are present in many industrial brunches e.g. pharmaceutical, agrochemical, food, cosmetic. In this contribution continuous preferential crystallization in two coupled crystallizers is investigated.

1.2 Preferential crystallization and MSMPR

Preferential crystallization is successfully applied to conglomerate forming systems where one enantiomer is separated from a racemic mixture of both (reported by Elsner et al., 2005). A representative of this group, L/D-threonine in water whose solubility and kinetics had been studied by Lorenz et al. (2006) and by Sapoundjiev et al. (2006), was chosen for further investigation.

The resolution of enantiomers occurs in the metastable zone, where spontaneous, primary nucleation is inhibited kinetically. By inserting seeds of only one enantiomer into the solution, separation driven by the seed surface takes place. In order to conduct preferential crystallization in a continuous manner, a continuous supply of seeds along with racemic feed solution and a continuous removal of the product suspension containing the seeded target enantiomer are required. This is a concept of Mixed-Suspension Mixed-Product Removal (MSMPR) (Randolph and Larson, 1988) which is applied in a single vessel. Modification of this idea could be coupling two MSMPR tanks via liquid phases and thus reducing a counter enantiomer concentration in each tank leading to higher purity. Furthermore liquid phase exchange improves productivity because supersaturation in each vessel is higher.

Operating at steady state is a goal of all continuous processes. Time required to reach the steady state may differ due to different kinetics of the model system which change with different process conditions. Finding optimum of the operating parameters may lead to a continuous separation of the target enantiomer at high purity and productivity, and in the coupled case a simultaneous production of both enantiomers in two separated vessels.

2. Mathematical model

A population balance model has been established to simulate the dynamic behaviour during continuous preferential crystallization. In each vessel each enantiomer is described by population balance equation (PBM) for the solid phase and by mass balance (MB) in a form of ordinary differential equations (ODE) for the liquid phase. In order to complete the mathematical model algebraic equations for nucleation and crystal growth kinetics together with liquid and solid mass flow rates are implemented. The population balances are given as (c.f. Qamar et al., 2012)

$$\frac{\partial F_{\alpha}^{(k)}}{\partial t} = -\frac{\partial(G_{\alpha}^{(k)} F_{\alpha}^{(k)})}{\partial x} + \dot{F}_{seeds,\alpha}^{(k)} - \dot{F}_{out,\alpha}^{(k)}, \quad k \in \{p, c\}, \alpha \in \{A, B\}, \quad (1)$$

where p stands for preferred enantiomer and c for counter one, while A and B are vessels. The term on the left hand side represents accumulation of crystals of size x . The first term on the right hand side represents convective transport in the direction of the property coordinate x due to size-dependent growth rate. The other terms on the right hand side denote particle number fluxes due to seeding and product removal, respectively. And the initial conditions, based on the assumption that at the beginning the solutions in A and B vessels are crystal free, are given as

$$F_{\alpha}^{(k)}(t=0, x) = 0, \quad k \in \{p, c\}, \alpha \in \{A, B\}, \quad (2)$$

whereas primary nucleation generates nuclei of minimum size x_{min} and at the same time the number density function vanishes for crystals of arbitrary size x_{max}

$$F_{\alpha}^{(k)}(t, x = x_{min}) = \frac{B_{0,\alpha}^{(k)}(t)}{G_{0,\alpha}^{(k)}(t, x_{min})}, \quad F_{\alpha}^{(k)}(t, x = x_{max}) = 0. \quad (3)$$

The expressions for nucleation and growth are taken from Mersmann (2001). Each crystallizer is only seeded with preferred enantiomer, thus

$$\dot{F}_{seeds,\alpha}^{(k)}(x) = \begin{cases} \dot{F}_{seeds,\alpha}^{(p)}(x) & \text{for } k = p, \\ 0 & \text{for } k = c. \end{cases} \quad (4)$$

The overall mass of the liquid phase in the system is described by Qamar et al., (2012)

$$\frac{dm_{L,\alpha}^{(k)}(t)}{dt} = \dot{m}_{L,in,\alpha}^{(k)}(t) - \dot{m}_{L,out,\alpha}^{(k)}(t) - 3k_v \rho_s \int_0^{\infty} x^2 G_{\alpha}^{(k)}(t, x) F_{\alpha}^{(k)}(t, x) dx \quad (5)$$

with initial conditions

$$m_{L,\alpha}^{(k)}(t=0) = m_{L,0,\alpha}^{(k)} = w_{L,0,\alpha}^{(k)} \rho_{L,0,\alpha} V_{L,\alpha}, \quad k \in \{p, c\}, \alpha \in \{A, B\}, \quad (6)$$

where an initial concentration of a racemic solution is included.

A high resolution finite volume scheme of Koren is used to solve the model in a length coordinate, while a fourth order Runge-Kutta method is applied for an ODE system in a time coordinate, see Koren (1993) and Qamar et al., (2012). To be able to compare different process variations, goal functions are introduced and defined as:

Productivity

$$P_{\alpha}^{(p)} = \frac{\dot{m}_{S,out,\alpha}^{(p)} - \dot{m}_{seeds,\alpha}^{(p)}}{V_{L,\alpha}}, \quad (7)$$

Purity

$$Pu_{\alpha}^{(p)} = \frac{\dot{m}_{S,out,\alpha}^{(p)}}{\dot{m}_{S,out,\alpha}^{(p)} + \dot{m}_{S,out,\alpha}^{(c)}}, \quad \dot{m}_{S,out,\alpha}^{(k)} = k_v \rho_s \int_0^{\infty} x^3 \dot{F}_{\alpha}^{(k)}(t, x) dx, \quad (8)$$

Mean crystal size

$$\bar{x}_{\alpha}^{(p)} = \frac{\mu_{1,\alpha}^{(p)}}{\mu_{0,\alpha}^{(p)}}. \quad (9)$$

An explanation of all equations and all kinetic parameters is covered by Qamar et al. (2012).

3. Results

3.1 Single tank and coupled crystallization

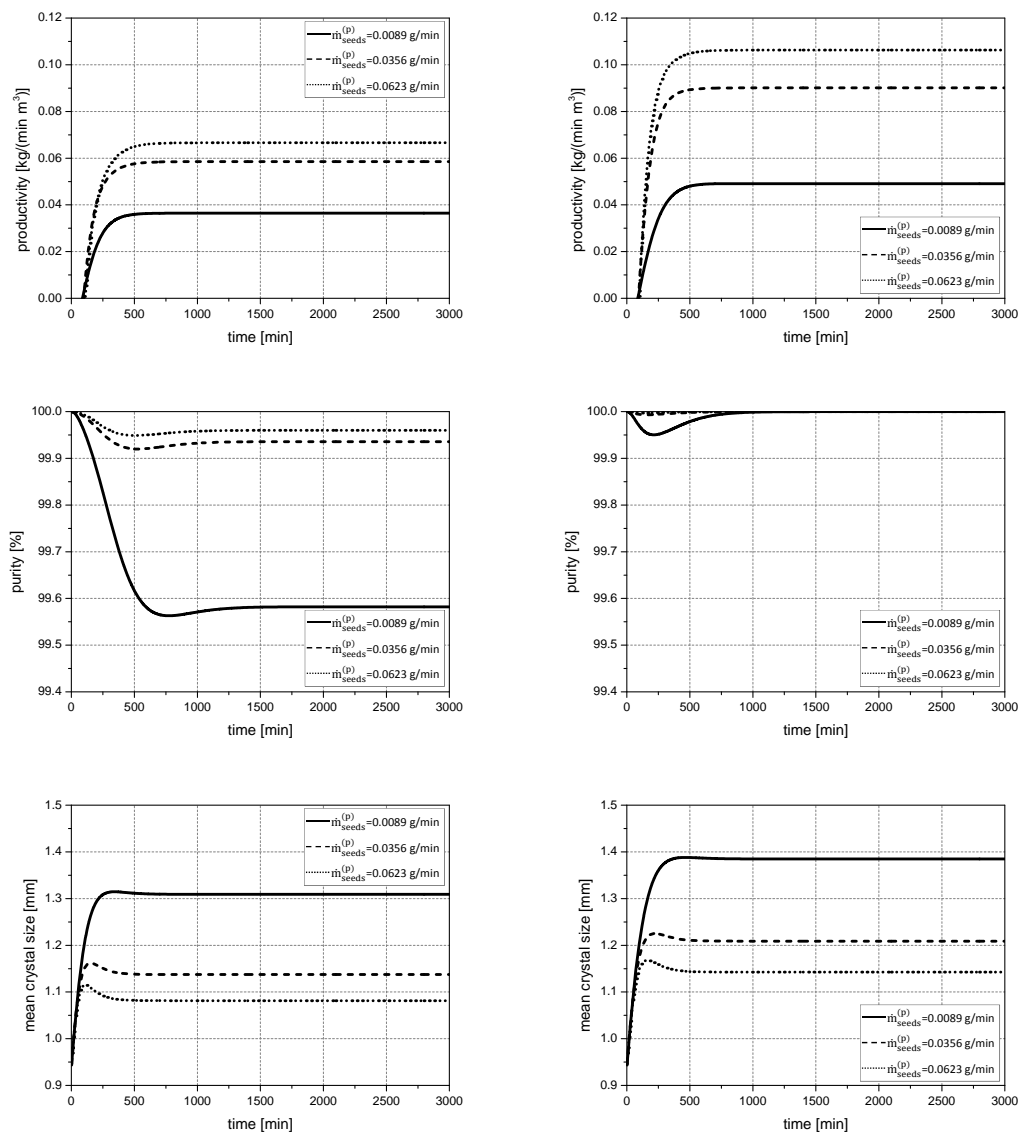


Figure 1: Simulation results for continuous preferential crystallization with a continuous seeding mode in a single crystallizer (left side) and two coupled ones (right side).

This study focuses on continuous enantioseparation in a single vessel and in two coupled ones where seeds are added continuously. Coupling of two tanks via their mother liquor leads to a concentration increase of the target enantiomer in the liquid phase and lowers the probability of primary nucleation of the counter enantiomer. Thus, productivity, purity and mean crystal size are improved. Moreover, the coupled case yields both enantiomers in an enantiopure form simultaneously (see Figure 1). Results of the coupled case depict values for only one tank because conditions in both tanks should be the same. Due to a higher mass flow rate of seeds, better productivity and purity can be reached, although the mean crystal size gets smaller (because a larger number of seed crystals utilizes supersaturation).

3.2 Different seed crystal distributions

Continuous seeding with different seed size distributions during continuous preferential crystallization in two coupled vessels is analyzed in this case. The properties of seeds are very crucial for the process trajectory. Their size, especially their surface, induces separation by crystal growth and secondary nucleation. For this reason the smaller available seeds, the higher productivity and purity. On the other hand bigger seeds will lead to a bigger product size which can be observed on Figure 2. Increasing mass flow rate of seeds enhances productivity and purity.

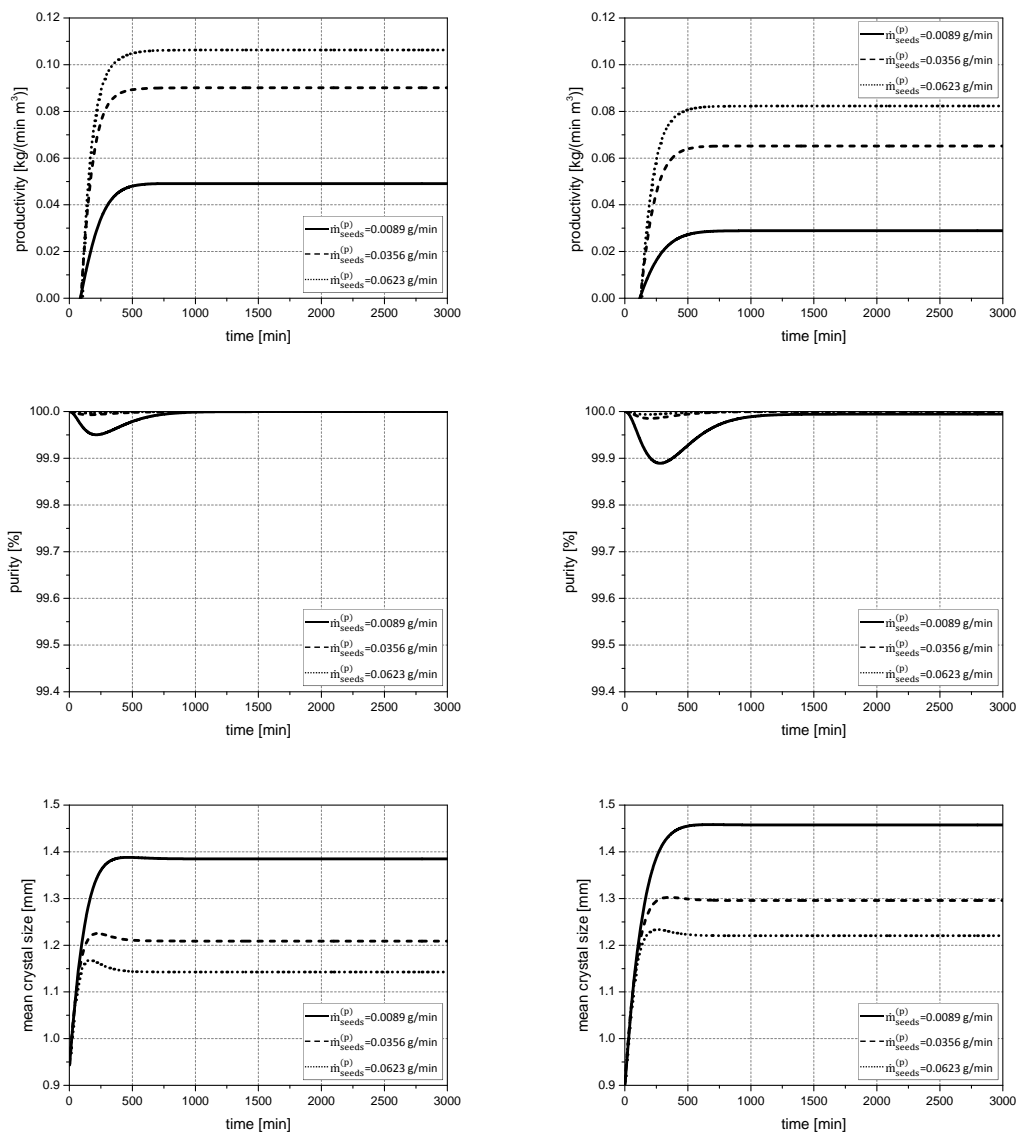


Figure 2: Simulation results for smaller ($x_{mean}=288$ nm, left side) and bigger ($x_{mean}=730$ nm right side) seeds for continuous seeding during continuous preferential crystallization in two coupled crystallizers.

3.3 Continuous and periodic seeding

Provision of seeds can be realized in a continuous or periodic mode. During periodic addition of seeds t_{on} represents the time when seeds are inserted into the crystallizer and t_{off} is the time when no seeds are provided. By seeding periodically, the mass of invested seeds can be reduced (see Table 1). Increasing t_{off} leads to a lower productivity because the seed investment is lowered. On the other hand the mean crystal size is bigger due to a smaller number of crystals in the solution consuming supersaturation.

Table 1: Simulation results for continuous and periodic seeding during continuous preferential crystallization in two coupled vessels.

Seeding	t_{on} [min]	t_{off} [min]	$\dot{m}_{Seeds,\alpha}^{(p)} \left[\frac{g}{min} \right]$	$Pu_{\alpha}^{(p)} [\%]$	$Pr_{\alpha}^{(p)} \left[\frac{kg}{min m^3} \right]$	$\bar{z}_{\alpha}^{(p)} [mm]$
C	-	-	0.0356	99.99	0.090	1.20
P	10	5	0.0244	99.99	0.076	1.26
P	10	10	0.0189	99.99	0.065	1.30
P	10	20	0.0126	99.99	0.054	1.36

3.4 Different exchange flow rates

Exchange of the liquid phase between two vessels should keep the concentration at a racemic level throughout the process time. The exchange flow rate should be adjusted to improve the performance of the process. This study case investigates different exchange flow rates during continuous preferential crystallization in two coupled tanks with continuous seeding. Increasing exchange flow rate improves productivity and mean crystal size which can be seen from Figure 3. The mean crystal size can only slightly be enhanced because crystal size depends on a residence time inside the crystallizer which in this study is the same.

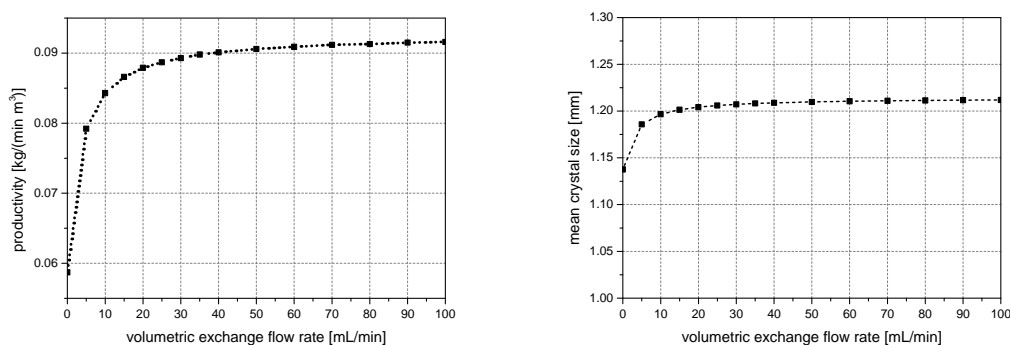


Figure 3: Simulation results for different exchange flow rates during continuous preferential crystallization in two coupled crystallizers.

4. Conclusions

Continuous preferential crystallization in two crystallizers connected through exchange pipes was studied. A concept of MSMPR crystallizer was implemented for enantiomeric resolution. Different process strategies were simulated by means of mathematical models. The effect of connecting two crystallizers via the mother liquor exchange was presented. Seeds with different mean crystal size were compared. Both continuous and periodic modes of seeding were analyzed. The influence of exchange flow rate was shown. It was found that coupled process has improved the values of all goal functions. Seeds with small mean crystal sizes have produced a product of better quality. Periodic seeding could reduce the overall investment of seeds and the mean crystal size of the product could be larger. By increasing the exchange flow rate between the coupled crystallizers, productivity is enhanced. These results could be used to find optimal operating conditions to improve the product quality and reduce operational costs. The experimental validation of this work is currently in progress.

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