Simulation of Continuous Preferential Crystallization Processes

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Abstract: This work investigates the effects of different seeding strategies and residence time characteristics on the dynamics of a Mixed Suspension Mixed Product Removal (MSMPR) crystallizer equipped with a fines dissolution unit and applied to continuous preferential enantioselective crystallization. The fines dissolution is included as recycle streams around the MSMPR crystallizer. Moreover, primary heterogeneous and secondary nucleation mechanisms along with size-dependent growth rates are taken into account. A high resolution finite volume scheme is employed for solving the given model. Several numerical case studies are carried out which support the process design and optimization.

1. INTRODUCTION

The separation techniques of chiral molecules are highly important in chemical industry as several, particularly organic, molecules are chiral. Normally, one of the enantiomers has desired properties and the other one has undesired. Several techniques are available for the separation of enantiomers namely, chromatographic process, biological methods, non-biological asymmetric synthesis, and membrane technologies, etc. An attractive alternative of these techniques is the enantioselective preferential crystallization (PC). So far, this procedure was only used in the batch crystallization process, see for example Elsner et al. (2005). For elucidating the principle of a continuous enantioselective process one might consider a suspension crystallizer revealing MSMPR characteristics, i.e. a perfectly mixed tank (concerning both phases), which is continuously fed with a solution possessing a racemic composition of two enantiomers, see Figure 1. Solid particles and liquid phase are continuously withdrawn. By a continuous supply of homochiral seed crystals of the preferred target enantiomer the preferential crystallization (PC) of only this enantiomer is initialized, i.e. growth of the seed crystals and possibly secondary nucleation of crystals of the seeded enantiomer, provided the crystallization takes place within the metastable zone where spontaneous, uncontrolled primary nucleation is kinetically inhibited. During a starting-up period, which strongly depends on the properties of the system as well as on the process parameters, the concentration of the target enantiomer is decreasing until a steady state arrives where the composition is determined by the mean residence time. Due to different kinetic mechanisms and their inherent different time constants, a different depletion of the supersaturation for each enantiomer can be realized by an appropriate choice of the process conditions. As long as a critical mean residence time, where primary nucleation may appear, is not exceeded, the concentration of the undesired counter enantiomer stays unchanged during the whole time. This fact reveals a benefit of this continuous process in comparison to the batch one. An optimal selection of the process conditions allows a constant production of the goal enantiomer at a high purity level.

The population balance models are commonly used for describing crystallization processes. The theory of population balances began in 1960s when Halburt and Katz (1964) introduced it in the field of chemical engineering. A brief overview on population balance modeling and nucleation and growth kinetics terms can be found in the books by Mersmann (2001); Nyvlt et al. (1985); Ramkrishna (2000).

Fig. 1. Illustration of the principle of continuous enantioselective crystallization.

In this work a dynamic model is developed for simulating a continuously operated ideally mixed MSMPR crystallizer applied for continuous preferential enantioselective
crystallization. The developed model includes the phenomena of primary heterogeneous nucleation, secondary nucleation, and size-dependent growth. A recycling pipe is connected to the crystallizer for the fines dissolution and it is assumed that fines are completely dissolved at the other end of the pipe. The effects of different seeding and operating strategies are investigated in simulations. The model and its parameters are based on experimental data obtained from batchwise crystallization, see Elsner et al. (2005). A high resolution finite volume scheme is implemented to approximate the given model equations in length coordinate. The ODE-system in time is solved by a Runge-Kutta method of order four, see Qamar et al. (2005). A high resolution finite volume scheme is implemented to approximate the given model equations

\[ \frac{dF}{dt} = -\frac{\partial (G_k F)}{\partial x} + F_{\text{seeds}}(x) - F_{\text{out}}(x) - F_{\text{pipe}}(x), \]

where \( k \in \{p, c\} \). Here, \( p \) stands for the preferred enantiomer and \( c \) for the counter enantiomer. Moreover, \( x \) denotes the crystal size and \( G_k \) is the size-dependent crystal growth rate. The term \( F_{\text{seeds}}(x) \) denotes the incoming particle number flux due to seeding, \( F_{\text{out}}(x) \) is the particle number flux due to product removal, and \( F_{\text{pipe}}(x) \) represents the particle number flux to the fines dissolution unit.

The crystallizer is initially filled with pure liquid only, i.e.

\[ F(x, t = 0, x) = 0, \quad k \in \{p, c\}. \]

It is further assumed that primary nucleation produces nuclei of minimum size \( x_{\text{min}} \) and that crystal size distribution (CSD), \( F(x, t) \), vanishes for a arbitrary large size \( x_{\text{max}} \), holds

\[ F(x, t, x_{\text{min}}) = \frac{B_0(t)}{G(t, x_{\text{min}})} F(x, t, x_{\text{max}}) = 0, \]

where \( B_0(t) \) denotes the nucleation rate. The crystallizer is only seeded with preferred enantiomer, thus

\[ F_{\text{seeds}}(x) = \begin{cases} F_{\text{seeds}}(x) & \text{for } k = p, \\ 0 & \text{for } k = c. \end{cases} \]

For the operation of the configuration shown in Figure 1, three types of residence times are relevant (e.g. Qamar et al. (2011)):

1. The liquid mean residence time in the perfectly mixed crystallizer, \( \tau_L = V_L/V_{\text{in}} \), where \( V_L \) denotes the liquid volume in the crystallizer and \( V_{\text{in}} \) is the liquid volumetric flow rate.
2. A characteristic solid mean residence time in a perfectly mixed crystallizer, \( \tau_S = V_S/\rho_S \), where \( V_S \) represents the overall volume of the solid phase, \( \rho_S \) is the density of the solid phase and \( \nu^{(p)}_{\text{seeds}} \) is the mass flow rate of the seeds of preferred enantiomer.
3. The residence time in the pipe (plug flow), \( \tau_{\text{pipe}} = V_{\text{pipe}}/V_{\text{pipe}} \). Here, \( V_{\text{pipe}} \) denotes volume of the pipe and \( V_{\text{pipe}} \) is the volumetric flow rate to the pipe.

The right hand sided second and third terms of Eq. (1) are given as

\[ \frac{\dot{F}_{\text{seeds}}(t,x)}{\dot{V}_{\text{pipe}}} + \frac{\dot{F}_{\text{out}}(t,x)}{\dot{V}_{\text{pipe}}} = \frac{\dot{F}(t,x)}{\dot{V}_{\text{pipe}}}, \]

where \( k \in \{p, c\} \). The term corresponding to the dissolution unit in Eq. (1) is expressed by?

\[ \frac{\dot{F}(t,x)}{\dot{V}_{\text{pipe}}} = \frac{h(x)F(t,x)}{\tau_{\text{pipe}}}, \]

where \( h(x) \) represents the classification (death) function.

The \( i \)-th moment of the CSD is defined as

\[ \mu_i^{(k)}(t) = \int_0^\infty x^i F(x,t) \, dx, \quad i = 0, 1, 2, \ldots. \]

According to Figure 1, the corresponding mass balances of the liquid phase are given as (e.g. Mersmann (2001)):

\[ \frac{dm_L^{(k)}(t)}{dt} = m_L^{(k)}(t) - m_{L,\text{out}}^{(k)} - 3\rho_S k_v \int_0^\infty x^2 G_x(t,x) F(t,x) \, dx, \]

with the initial conditions

\[ m_L^{(k)}(t = 0) = m_{I,L}^{(k)}, \quad m_{L,\text{out}}^{(k)} = m_{L,\text{out},c}^{(k)} + m_{L,\text{out},p}^{(k)}. \]

The inflow rate \( m_{I,L}^{(k)} \) is the sum of two incoming streams to the crystallizer, the first one \( m_{L,\text{in},c}^{(k)} \) stands for the incoming flux of fresh solution to the crystallizer and the second one \( m_{L,\text{in},p}^{(k)} \) denotes the incoming flux of particle-free solution from the dissolution pipe. Similarly, the mass outflow rate \( m_{L,\text{out}}^{(k)} \) is the sum of two outgoing streams, i.e. mass flow rate of the utilized solution from the crystallizer and the mass flow rate of the solution containing the fraction of fines flowing to the dissolution pipe. The mass flow rate of the incoming fresh supersaturated solution is defined as

\[ m_{L,\text{in},c}^{(k)} = w^{(k)}(t = 0) m_{L,\text{in}} V_{L}, \quad k \in \{p, c\}, \]

where \( w^{(k)} \) represents the mass fraction of \( k \)-th enantiomer which is defined for \( k \in \{p, c\} \) as

\[ w^{(k)}(t) = \frac{m_L^{(k)}(t)}{m_L^{(p)}(t) + m_L^{(c)}(t) + m_{\text{solvent}}}. \]

The terms \( m_L^{(k)} \), \( m_L^{(p)} \) and \( m_L^{(c)} \) represent the masses of \( k \)-th, preferred, and counter enantiomers, respectively.
Moreover, $m_{\text{solvent}}$ is mass of the solvent (water). The composition dependence solution density is defined as
\[ \rho_n(t) = 1000(\rho_0 + K_3 w_{\text{tot}}(t)), \quad \rho_0 = \frac{1}{K_1 + K_2 T^2}. \] (14)

The parameters $K_1$, $K_2$, $K_3$ are given in Table 1 and $T$ denotes the temperature which is kept constant at 33°C. The total mass fraction $w_{\text{tot}}$ is given as
\[ w_{\text{tot}}(t) = w^{(p)}(t) + w^{(c)}(t). \] (15)
The outgoing mass flux of the solution from the crystallizer are defined as
\[ n^{(k)}_{\text{L,out,c}}(t) = n^{(k)}_{\text{L,cat}}(t) \rho_n(t) V_L, \quad k \in \{p,c\}. \] (16)
The outgoing mass flux from the crystallizer to the dissolution unit is given as
\[ n^{(k)}_{\text{L,in,pipe}}(t) = n^{(k)}_{\text{L,cat}}(t) (t - \tau_{\text{pipe}}) \] (18)

Due to racemic solution, the initial masses of both enantiomers are the same and the mass fluxes of both enantiomers are equal in the feed stream, holds
\[ m^{(p)}_{\text{L,0}} = m^{(c)}_{\text{L,0}}, \quad m^{(p)}_{\text{L,in}} = m^{(c)}_{\text{L,in}}. \] (19)

A size-dependent growth rate approach is applied (e.g. Mersmann (2001))
\[ G^{(k)}(t,x) = k_{g,\text{eff}}(T) S^{(k)}(t) - 1)^g (1 + a_{\text{ASL}} x)^d_{\text{ASL}}. \] (20)
The exponent $g$ denotes the growth order and the constants $a_{\text{ASL}}$ and $d_{\text{ASL}}$ represent the size dependency. The temperature dependence of the growth rate constant $k_{g,\text{eff}}$ is given by an Arrhenius approach
\[ k_{g,\text{eff}} = k_{g,\text{eff,0}} \exp \left( - \frac{E_{A,b}}{RT} \right). \] (21)

Here, the symbol $k_{g,\text{eff,0}}$ is the pre-exponential factor of the growth rate constant, $E_{A,b}$ is the activation energy, and $R$ is the universal gas constant. Their values are given in Table 1. The symbol $S^{(k)}(t)$ denotes the supersaturation of the $k$-th enantiomer which is defined as
\[ S^{(k)}(t) = \frac{w^{(k)}(t)}{w_{\text{eq}}^{(k)}}. \] (22)

where $w_{\text{eq}}^{(k)}$ is the saturated mass fraction of the $k$-th enantiomer defined as
\[ w_{\text{eq}}^{(k)}(t) = a_{\text{eq}} + b_{\text{eq}} w^{(k)}(t). \] (23)
The terms $a_{\text{eq}}$ and $b_{\text{eq}}$ are solubility constants given in Table 1. The nucleation rate is defined as the sum of primary (heterogeneous) nucleation rate and secondary nucleation rate (e.g. Mersmann (2001))
\[ B_0^{(k)}(t) = B_{0,\text{prim}}^{(k)}(t) + B_{0,\text{sec}}^{(k)}(t), \quad k \in \{p,c\}. \] (24)
The primary nucleation rate is given by a semi-empirical equation derived from Mersmann model (see Mersmann (2001))
\[ B_{0,\text{prim}}^{(k)}(t) = \eta^{(k)}(t) \exp \left( - a_{\text{prim}} \ln \left( \frac{\rho_T}{C_{\text{eq}}^{(k)}} \right)^3 \right), \] (25)

where
\[ \eta^{(k)}(t) = \alpha(t) \sqrt{\ln \left( \frac{\rho_T}{C_{\text{eq}}^{(k)}} \right) (S^{(k)}(t) C_{\text{eq}}^{(k)}(t))^{\frac{1}{2}}}, \] (26)
\[ \alpha(t) = \kappa_{h,\text{prim}} T e^{-\frac{K_T}{T}} \exp \left( - \kappa_w^{(k)}(t) \right). \] (27)

Here, $C_{\text{eq}}^{(k)}$ denotes the concentrations of the $k$-th enantiomer at equilibrium as defined below
\[ C_{\text{eq}}^{(k)}(t) = \rho_L(t) w_{\text{eq}}^{(k)}(t). \] (28)
The secondary nucleation rate is given as
\[ B_{0,\text{sec}}^{(k)}(t) = k_{h,\text{sec}} \left( S^{(k)}(t) - 1 \right)^{b_{\text{sec}}} \left( \mu_3^{(k)}(t) \right)^{n_{\text{sec}}}, \] (29)

where $b_{\text{sec}}$ is the secondary nucleation rate exponent and $n_{\text{sec}}$ is the third moment exponent. The secondary nucleation rate constant is given as
\[ k_{h,\text{sec}} = k_{h,\text{sec,0}} \exp \left( - \frac{E_{A,b}}{RT} \right). \] (30)

The symbol $k_{h,\text{sec,0}}$ is the pre-exponential factor of the secondary nucleation rate constant and $E_{A,b}$ is the corresponding activation energy.

Although the steady state results are crucial for an assessment of the process, a better experimental realization can be achieved by investigating the process dynamically.

3. NUMERICAL SCHEME

For the numerical approximation of PBE in Eq. (1), a high resolution finite volume scheme (HR-FVS) is implemented. In this approach, the HR-FVS is adopted in length coordinate only. The Runge-Kutta method of fourth order is used for the discretization of the time derivatives. For detailed derivation of the scheme the reader is referred to Qamar et al. (2006) and references therein.

4. CASE STUDIES

In this section the simulation results are presented. Firstly, the crystallizer is operated without fines dissolution unit and is either seeded continuously or periodically with seeds of the preferred enantiomer. In this case the last terms on the right hand side of Eq. (1) are neglected. Secondly, the crystallizer is connected with an external fines dissolution unit and is continuously seeded with seeds of the preferred enantiomer.

To judge the quality of the process some goal functions can be used such as product purity, productivity, yield and mean crystal size of the preferred enantiomer, see Qamar et al. (2011) for more details. These goal functions give detailed information about the success and potential of continuous preferential crystallization.

The minimum and maximum crystal sizes of interest are taken as $x_{\text{min}} = 1.0 \times 10^{-10}$ m and $x_{\text{max}} = 1.0 \times 10^{-2}$ m, respectively. The computational domain is subdivided into 200 grid points. The remaining parameters are given in Table 1. The physicochemical parameters correspond to the enantiomers of the amino acid threonine and the solvent water, see Elsner et al. (2005). The temperature of the crystallizer was assumed to be constant at 33°C.
The mean residence time of the liquid phase is fixed at 112.41 min, while the solid phase residence time was considered as either \( \tau_S = \tau_L \) or \( \tau_S = 2\tau_L \). In actual operation, it may be difficult to decouple the residence times of the liquid and solid phases. Thus, it is most likely to set \( \tau_S = \tau_L \). However, larger residence times of the solid compared to the liquid could eventually be realized by installing a filter for the solid particles at the outlet, thus, allowing a longer residence of the solid phase.

**Problem 1:** Continuous seeding without fines dissolution

In this problem, the crystallizer is continuously seeded with the preferred enantiomer. The corresponding seeds size distribution is given as:

\[
F_{\text{seeds}}^{(p)} = \frac{a_1}{x A_a} \exp\left(-0.5 \left( \frac{1}{a_3} \ln \left( \frac{x}{a_2} \right) \right)^2 \right),
\]

where the values of constants \( a_1, a_2 \) and \( a_3 \) are given in the Table 1. Moreover, the normalization factor is given as:

\[
A_a = \frac{k_c p_S}{\mu_{3}^{(p)} \cdot T_S}.
\]

The initial masses of the preferred and counter enantiomers are taken as \( m_0^{(p)} = m_0^{(c)} = 0.0478 \text{ kg} \).

The simulation results corresponding to steady state conditions are displayed in Table 2 for different mass flow of seeds. It can be observed that an increase in the ratio of solid to the liquid residence times, \( \tau_S / \tau_L \), diminishes the purity of the preferred enantiomer due to the production of increasing amount of counter enantiomer as an impurity, while the productivity, yield, and mean crystal size of the preferred enantiomer are improved. As \( \tau_S \) increases, the crystals of the preferred enantiomer have more time to grow and, hence, the overall productivity, yield and the mean crystal size are enhanced. The productivity and yield along with the investment of seeds are increased by increasing the mass flow of seeds. It is clear that with large amount of seeding more crystals are produced, providing the potential for high productivity. However, the mean crystal size reduces on increasing the mass of seeds. The reason is obvious, by increasing the mass flow (amount) of seeds the existing supersaturation is consumed by large number of crystals and, therefore, the mean crystal size becomes smaller. However, by investing less seeds, the existing supersaturation is utilized by only a few crystals, leading to larger mean size of the crystals. Finally, the steady-state is reached after a longer time when the ratio \( \tau_S / \tau_L \) is larger. However, the time needed for steady state reduces by increasing the mass flow of seeds. Figure 2 also justify and support the above discussion.

In summary, the purity diminishes by increasing the ratio between residence times of the solid to the liquid phases, while the productivity, yield, and mean crystal size are enhanced. An increase in this ratio reduces the mass flow of seeds and increases the time needed to achieve steady state. Moreover, the supersaturation and mean crystal size are reduced with increasing the mass flow of seeds, while productivity, yield and purity are improved.

**Problem 2:** Continuous seeding with fines dissolution

![Fig. 2. Problem 1: Comparison of the results for different masses of seeds: Left \( \tau_S / \tau_L = 1.0 \), right: \( \tau_S / \tau_L = 2.0 \).](image-url)
In this problem, a continuous seeding with fines dissolution is investigated. Fine particles below the critical size $x_{\text{crit}} = 6.0 \times 10^{-4} m$ are removed from the crystallizer along with the solution into the dissolution unit (the pipe). After a certain time delay the particle-free solution re-enters to the crystallizer. The fines dissolution unit is usually equipped with a heat exchanger for dissolving fines followed by a heat sink which brings back the solution temperature to that of the crystallizer. A complete model Eq. (1) is employed in this problem. The selection (death) function is taken as

$$h(x) = \begin{cases} 
0.6, & \text{if } z \leq x_{\text{crit}}, \\
0, & \text{otherwise}
\end{cases}$$

In this case, the simulation results with continuous seeding and fines dissolution are analyzed. Table 3 shows a comparison of fines dissolution (yes) and without fines dissolution (no) by considering different ratios of residence times and fixed mass flow of seeds. It can be seen that the purity is higher in the case of fines dissolution compared to that without fines dissolution, as the fines dissolution diminishes the number of counter enantiomer crystals in the crystallizer. From the Table 3, it can be realized that the productivity and yield are slightly lower in the case of fines dissolution for both ratios of residence times. The fines dissolution enhances the supersaturation of the solution which in turn increases the growth rate, thus, improves the mean crystal size.

### Problem 3: Periodic seeding without fines dissolution

In this test problem, continuous crystallization along with periodic seeding of preferred enantiomer is analyzed. The model equations are exactly the same as for the continuous seeding case in test problem 1. In the Table 4, $t_{\text{on}}$ represents the time at which seeding is switched on and $t_{\text{off}}$ denotes the period of time at which seeding is switched off. The seed flow rate can be varied in contrast to the continuous seeding. In this table, a comparison of simulation results for continuous and periodic seeding strategies are presented.

In Table 4, the simulation results are presented for different ratios of the residence times. The increase in $\tau$ reduces the purity of the preferred enantiomer in the periodic case. As residence time increases, more nuclei of the counter enantiomer are produced as an impurity of the product and, thus, the purity is lower. It can also be observed that the purity has decreasing behavior for increasing $t_{\text{off}}$. On the other hand, as $\tau$ increases the crystals of the preferred enantiomer get more time to grow and, thus, the overall productivity and yield enhances. Additionally, the productivity and yield are decreased by increasing $t_{\text{off}}$. It is obvious that when seeding is switched off for a longer time, the mean crystal size will increase by increasing the residence time $\tau$ due to longer stay of seeds in the crystallizer and because of utilizing the existing supersaturation by fewer crystals. The mean crystal size also increases by increasing $t_{\text{off}}$ for all considered residence times due to the utilization of existing supersaturation by fewer crystals. Table 4 also shows that the feed flow rate of seeds decreases by increasing the residence time. A comparison of the continuous seeding case in Table 2 with the current periodic case in Table 4 shows that continuous seeding gives better purity, productivity and yield, while the mean crystal size is smaller and investment (mass flow of seeds) remains the same in all considered residence times. On the other hand, the periodic seeding gives larger crystals at low investment (feed flow rate) of seeds per residence time. Finally, the time needed to achieve steady-state becomes longer on increasing $\tau$, while keeping the liquid residence time $\tau$ fixed. This behavior is exactly similar to the continuous seeding case.
In summary, the periodic seeding reduces the productivity and yield, while improves the mean crystal size. The purity is slightly reduced with periodic seeding (approx. 0.1%). Moreover, the investment of seed crystals is reduced.

5. CONCLUSION

A dynamic mathematical model was derived for simulating continuously operated ideally mixed MSMPR crystallizer applied for continuous preferential enantioselective crystallization. The model incorporate the removal and subsequent dissolution of fines in the outer fines dissolution loop connected to the crystallizer. The effects of different seeding strategies and residence time characteristics were analyzed. The effect due to varying residence times ratios of solid and liquid phases was also analyzed. A high resolution finite volume scheme was used to solve the model. Several case studies were carried out. The results could be used to find the optimum operating conditions for enhancing the quality of product and for reducing the operational cost of continuous preferential crystallization. Altogether, the process appears to possess large potential and deserves practical realization which is in progress.

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REFERENCES


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