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Theoretical investigation of simultaneous continuous preferential crystallization in a coupled mode

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HIGHLIGHTS

- Continuous preferential crystallization is theoretically analyzed.
- Single and coupled crystallizer operation modes are studied.
- The influences of essential operating parameters are studied.
- A high resolution finite volume scheme is proposed to solve the model equations.
- In particular, the coupled mode is attractive and deserves experimental validation.

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ABSTRACT

The dynamic behavior of two coupled continuously operated crystallizers connected through exchange pipes and equipped with a fines removal system is theoretically analyzed. It is an extension of our recent work on continuous enantioselective preferential crystallization in a single vessel. A high resolution finite volume scheme is applied to solve the model in the crystal size coordinate, while an ODE-system in the time coordinate is solved by a fourth order Runge-Kutta method. The influences of different seeding and operating strategies on the process are studied systematically. To assess the quality of the process several goal functions are used, such as purity, productivity, yield and mean crystal size of the target enantiomer. Continuous and periodic seeding concepts are compared. The goal functions considered provide clear evidence about the significant potential of this new process. To prove advantages of the coupled process, corresponding results are compared with those for a single crystallizer.

1. Introduction

Separation of chiral molecules is of great interest in chemical and pharmaceutical industries as many (bio)organic molecules are chiral. In most of the cases only one enantiomer has desired properties for therapeutic activities or metabolism, while the other one may be inactive or may produce undesired effects. Several special techniques can be applied to separate enantiomeric mixtures, such as chromatography, classical non-biological resolutions via the formation of diastereomers, biological methods, non-biological asymmetric synthesis, and membrane technologies, see for example Ahuja (2010), Kemmere and Keurentjes (2001), and Subramanian (2007). An attractive alternative and energy efficient way to separate chiral substances is the enantioselective preferential crystallization. This technique is normally applied to conglomerates, a physical mixture of enantiomerically pure crystals. Several articles are available on preferential crystallization in batch mode, see for example Jacques et al. (1981), Collet (1999), Alvarez-Rodrigo et al. (2004), Elsner et al. (2005), Coquerel (2007), Czapla et al. (2009), and Elsner et al. (2011).

Recently, Qamar et al. (2012) have adopted the concept of continuous mixed-suspension-mixed-product-removal (MSMPR) crystallizers (e.g. Randolph and Larson, 1988) to obtain pure enantiomers from racemic mixtures in a single crystallizer. The drawback of decoupled mode (single crystallizer) is that only a small amount

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of pure substance can be recovered from the racemic solution. To overcome this limitation, in this work, two MSMPR crystallizers are connected through the liquid phase and operated under continuous exchange of crystal free solution. These perfectly mixed tanks are continuously fed with the racemic solutions of two enantiomers, E_1 and E_2, and solid particles and liquid phase are continuously withdrawn, see Fig. 1. Due to seeding both enantiomers, one in each vessel, the preferential crystallization of only those enantiomers could be initiated in the corresponding vessels, provided that crystallization takes place within the metastable zone where spontaneous, uncontrolled, primary nucleation is kinetically diminished. The need to stay within the metastable zone offers a relatively small operating region, which could be left due to too much cooling of the mother liquor or by giving the solution too much time to come back to the thermodynamically stable racemic composition due to counter enantiomer nucleation. To suppress that, the process is carried out at isothermal conditions, not too large residence times and permanent removal of product suspension. The substantial improvement of the process is due to the liquid phase exchange. By realizing this exchange, one mimics racemization of the liquid phase, which means that the concentration of the preferred enantiomer in each vessel increases, whereas the concentration of the counter one decreases. As a result, the supersaturation level is higher during the whole process in comparison to continuous enantioseparation performed in a single MSMPR vessel. For the theoretical case of an infinitely high exchange flow rate, racemic composition is reached in the liquid phase of both vessels which corresponds to the maximum supersaturation for both preferred enantiomers. Since the concentration of the respective counter enantiomer is decreased, the probability for its crystallization through primary nucleation is lowered. This leads to higher product purity and enhances the productivity. During a start-up period, depending on the properties of system and process parameters, the concentration of the target enantiomer is decreasing until a steady state is reached 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 maintains constant during the whole process 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 based models are frequently used for simulating crystallization processes. The theory of population balances began in 1960s when Hulburt and Katz (1964) introduced it in the field of chemical engineering. A comprehensive overview on population balance modeling, nucleation and growth kinetics terms and methods of solution can be found in the books by Mersmann (2001), Nývlt et al. (1985), and Ramkrishna (2000). During the last decades many efficient methods were developed for solving population balance models (PBMs) such as the method of characteristics introduced in various fields by Rhee et al. (1986) and adopted for PBMs by Lim et al. (2002), Qamar et al. (2009), and Ramkrishna (2000), the method of weighted residual or orthogonal collocation by Rawlings et al. (1992), the Monte Carlo simulation by Smith and Matsoukas (1998) and Tandon and Rosner (1999), the fixed and moving pivot techniques by Kumar and Ramkrishna (1996) and Kumar and Ramkrishna (1996), and the high resolution finite volume schemes by Gunawan et al. (2004), Qamar et al. (2006), and Qamar et al. (2012).

This work is an extension of our recent work on continuous preferential crystallization in a single vessel, see Qamar et al. (2012). A dynamic mathematical model is derived for simulating two coupled continuously operated ideally mixed MSMPR crystallizers applied for continuous preferential enantioselective crystallization. Both crystallizer are connected through exchange pipes and are equipped with fines dissolution loops for dissolving small crystals below a certain critical size. It is assumed that fines are completely dissolved at the other end of the dissolution pipes. The developed model includes the phenomena of primary heterogeneous nucleations, secondary nucleations and size-dependent growth rates in each crystallizer. The effects of different seeding and operating strategies are investigated in simulations. For the theoretical investigations, D/L-threonine in water was considered. This compound belongs to the group of conglomerate forming systems, which can be successfully resolved via preferential crystallization. The parameters, which are used in the model, were chosen from batch experiments performed in the metastable zone, see Elsner et al. (2005), Czapla et al. (2009), Elsner et al. (2011), and Perlberg (2006). On the basis of systematic measurements the width of the metastable zone was quantified experimentally. It was found to be in the range of 16 K for the given saturation temperature of 40 °C. The width of this metastable region is not explicitly included in the mathematical approach but is a result of the primary nucleation kinetics based on Mersmann (2001). The semi-discrete flux-limiting finite volume scheme of Koren (1993) is implemented to solve the model equations. To judge the quality of process some goal functions are used, such as purity, productivity, yield and mean crystal size of the preferred enantiomer. These goal functions provide useful information about the success and potential of the process. To realize the advantages of the coupled process, its results are compared with those of single

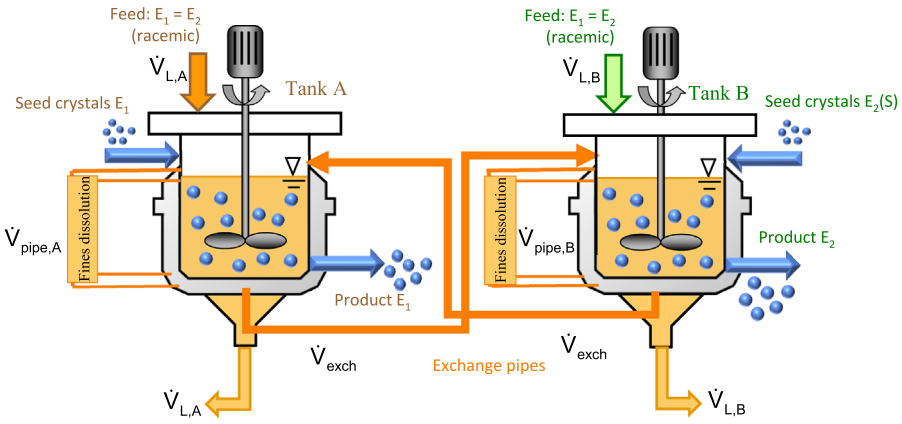

Fig. 1. Illustration of the principle of coupled continuous enantioselective crystallization.