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Modelling geometrical and fluid-dynamic aspects of a continuous fluidized bed crystallizer for separation of enantiomers

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ABSTRACT

Continuous selective crystallization using mixed suspension mixed product removal (MSMPR) crystallizers is an attractive method for separating enantiomers. Recent experimental results confirm the feasibility of the approach, but also indicate that the operation conditions for nominal operation lie in a rather small window. A systematic analysis and an optimal design are needed to exploit the full potential of the method. In this contribution, a mathematical process model based on population balance equations is presented. In contrast to other studies in literature, the considered crystallizer is not a stirred tank, but has a conical shape that requires a spatially distributed model formulation. Parameter studies identify the key operation and design parameters for maximizing the mass of the product crystals and for shaping their size distribution. The proposed model focuses on geometrical and fluid-dynamic aspects, but at the current stage does not include purity aspects.

1. Introduction

Chiral substances or enantiomers consist of molecules which are not super-imposable on their mirror image - like right hand and left hand. Chemical synthesis commonly produces a 50:50% mixture of the enantiomers of a chiral substance. Hence, the separation of such mixtures into the sterically pure components is of vital importance, since the two enantiomers may have completely different effects on living organisms (Stinson, 2001; Myerson, 2002). However, enantiomers exhibit identical physical properties due to the mirror symmetry, and simple separation techniques like distillation are not applicable, but more advanced methods are needed. Preferential crystallization has been found to be an attractive approach to this challenging problem, if the enantiomers form conglomerates (Alvarez and Myerson, 2010; Lorenz and Seidel-Morgenstern, 2014).

A robust crystallization process for the continuous production of particles with a defined size distribution in conically shaped crystallizers was proposed already in the 1970s by Midler (1975, 1976). Recently, the process has been combined with the technique of preferential crystallization and has been studied experimentally in detail (Binev et al., 2015, 2016; Binev, 2015). The in-situ production of seed material as suggested by Midler simplifies the operation in contrary to the continuous enantio-selective crystallization utilizing the MSMPR concept (Galan et al., 2015). Furthermore, permanent removal of possibly occurring nuclei of the counter-enantiomer increases process robustness and operating time. Hence, continuous production of pure enantiomers with an adjustable crystal size distribution is attainable.

Various process configurations and substances have been considered, and the feasibility of the process could be proven. However, it also turned out that the operation is quite delicate, and that the operation window is rather small. Therefore, optimizing the process based on experimental studies alone would be rather inefficient.

The most important goal of the process is to obtain crystals of high purity. This aspect has been modeled and investigated for different process configurations of coupled stirred tank crystallizers by Qamar et al. (2013), Vetter et al. (2015). It is not considered here. Instead, the contribution focuses on the additional degrees of freedom of a conical crystallizer compared to a stirred tank crystallizer. The spatial extension of the conical crystallizer causes a spatial dependency of the crystal distribution, which has to be accounted for in a mathematical model and does not exist in a stirred tank. By choosing a suitable crystallizer geometry, i.e. a crystallizer shape and a position for product removal, the spatial dependency may be exploited to design the size distribution of the product crystals. The aim of this contribution is to provide a process model that helps to obtain an understanding of the geometrical effects in combination with other operation parameters. The model is utilized to study the effect of operation and design parameters on the

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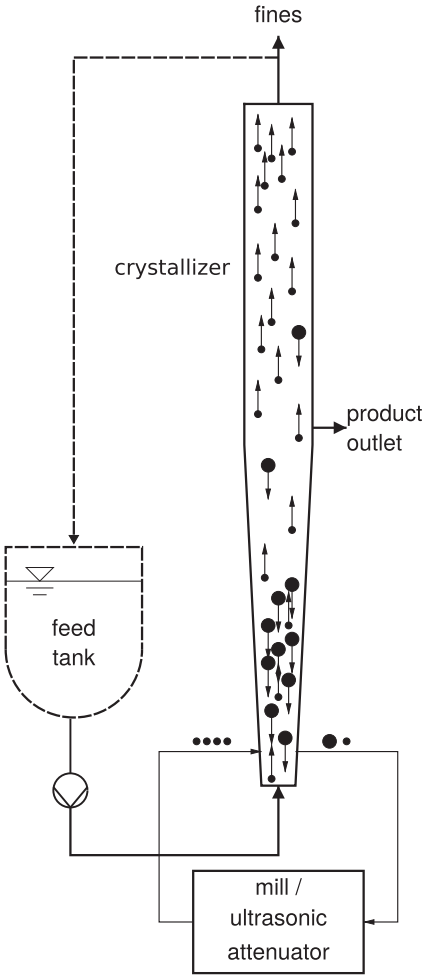

Fig. 1. Sketch of a continuous process for enantioselective crystallization consisting of a feed tank, a crystallizer, and a mill for continuous seed generation. The feed tank and the recycle loop (drawn as dashed lines) are not part of the process model.

product quality and productivity of the process.

The following section introduces the details of the continuous crystallization process. Section 3 presents model assumptions and model equations. A simulation study based on the process model follows in Section 4. The contribution ends with some conclusions and an outlook in Section 5.

2. Process description

The aims of the continuous enantioselective crystallization process are to grow crystals of one enantiomer while keeping the counter enantiomer in the liquid solution, to selectively extract crystals of a certain desired size, and to provide the process continuously with fresh seed crystals. A setup consisting of a feed tank, a crystallizer, and a device for seed generation, as sketched in Fig. 1, is utilized. For further details on process conditions, the reader is referred to Binev et al. (2015), Binev (2015).

Selective crystallization is achieved by providing seed crystals of the desired enantiomer only. Hence, exclusively the desired dissolved stereoisomer is attached to the crystal surface due to the unique properties of the crystal lattice. Temperature and solute concentration in the crystallizer have to be chosen such that the crystallizer operates in the metastable zone. Then the supplied seed crystals are able to grow, but the nucleation of the counter-enantiomer is avoided to a certain extent.

The experimental set-up (Fig. 1) is operated as follows: A solid racemic (50:50 mixture of both enantiomers) feed is provided in excess in a solution saturated at a certain temperature in the feed tank. The feed tank contains a clear racemic solution without crystals. The fresh solution is fed from the feed tank to the bottom of the crystallizer. By keeping the feed tank at a slightly higher temperature level than the crystallizer, the liquid in the column is super-saturated. An additional sieve between feed tank and crystallizer guarantees that the crystallizer feed is virtually free of particles. Subsequently, the process is seeded once *ex situ*. The feed flow rate is adjusted properly, so that a fluidized bed forms inside the crystallizer. Because the column has a conical shape, the fluid flow velocity is highest at the bottom of the crystallizer and decreases towards the top of the conical section. Therefore, the average size of the crystals in the fluidized bed decreases from bottom to top, as well. By choosing the position of the product outlet, a classifying product removal is attempted. Product crystals may either be withdrawn continuously or, as in the experiments by Binev et al. (2015), product samples are taken in a pulse-wise manner. The large crystals accumulating at the crystallizer bottom are withdrawn and sent to a mill or ultrasonic attenuator, where they are broken into smaller fragments and sent back to the crystallizer. In this way, the process generates the required seed crystals. Very small crystals move with the fluid flow and escape through the top of the crystallizer. This has a purifying effect, because it washes out undesired nuclei of the counter-enantiomer. The fines leaving the crystallizer are not lost, but dissolved on their way back to the feed tank. The valuable material is in this way recycled for the crystallization process.

3. Model equations

Mathematical models of the considered process were published by Palis et al. (2013), Mangold et al. (2015), Binev et al. (2016). The process model presented in the following is based on those previous publications. The model consists of a population balance for the particles in the crystallizer, a mass balance for the solute in the liquid phase, and a population balance for the particles in the disperser/mill.

Fig. 2 gives a schematic representation of the process showing the flow rates and the main geometrical parameters.

The main model assumptions are:

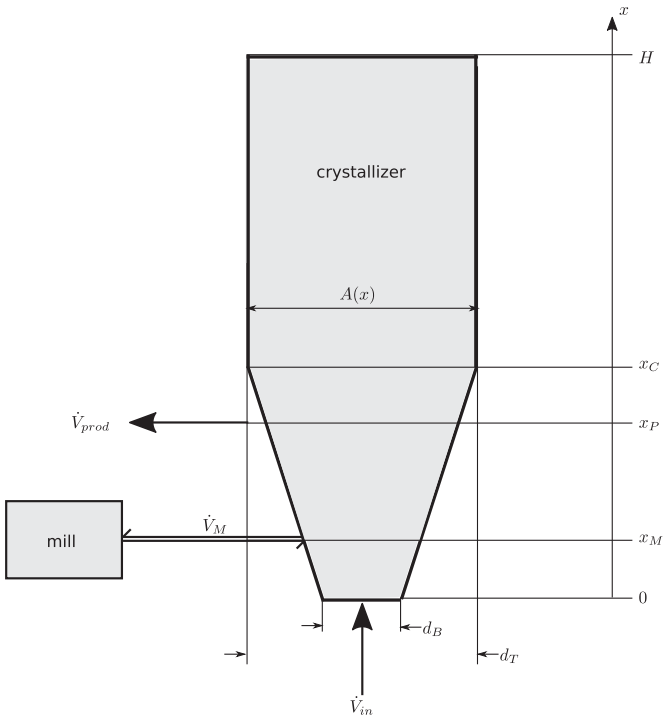

Fig. 2. Schematic representation of the selective crystallization process.