The objective of this PhD project is to experimentally and theoretically investigate the separation performance and to improve the process understanding of a newly developed continuous preferential crystallization (PC) process for the separation of enantiomers forming conglomerates. This PC process is regarded as a first step towards a fully continuous PC process. The current knowledge of the importance of crystallization processes in the pharmaceutical industry and the complex thermodynamic and kinetic phenomena accompanied with the separation of chiral compounds are addressed. The experimental work covers laboratory studies and the theoretical work is based on the experimental data and observations.

A large fraction of active pharmaceutical ingredients (APIs) are enantiomers and the desired biological activity is provided only by one of the enantiomers. Strict regulatory requirements, increasing public demand, and fierce competition have forced the pharmaceutical industry to redevelop existing methods or develop completely new methods to produce pharmaceuticals consisting of APIs of the desired enantiomer. PC is one of several methods used industrially to obtain pure enantiomers by separation of a racemic mixture. The potential application of PC is strongly dependent on requirements to the thermodynamics and crystallization kinetics of the considered solute-solvent(s) system, and the desired operating conditions. Meeting these requirements are essential to achieve predefined physical attributes of the final product and process economical targets. In this respect, an increasing interest in converting from the conventional batch to continuous PC has initiated the search for new process development opportunities of PC processes. The reason is the many advantages of continuous operation, especially in the case of separation of enantiomers.

A newly developed lab-scale continuous PC process, so-called continuous coupled preferential crystallization (CC-PC) process, consisting of two mixed flow crystallizers coupled via crystal-free mother liquor exchange streams and with only the liquid phases operated continuously, was built as the main part of this PhD project. Experiments in triplicate were conducted for the experimental investigation to assess the robustness of the CC-PC process and to investigate the achievement of simultaneous separation of the enantiomers of the conglomerate forming system of the amino acid asparagine monohydrate by crystal growth of seed crystals. The achievement of a racemic liquid phase composition consisting of nearly equal distribution of enantiomers in solution was also investigated. Finally, the performance of the CC-PC process and its potential for further development to a fully continuous PC process was discussed. A nearly racemic composition of the liquid phase in the crystallizers was obtained. Successfull enantioseparation by crystal growth was verified, with the repeatability being within 10% deviation. Productivities, yields, and purities of solid products were influenced by the morphological differences in the seed crystals. Due to irregularly shaped seed crystals of L-asparagine monohydrate (L-AsnH$_2$O), increase in the productivities and yields were achieved in the L-Tank, i.e. the crystallizer in which L-AsnH$_2$O crystals grow. Lower purities of solid products from the L-Tank compared to solid products from the d-Tank, in which seeds of d-asparagine monohydrate (D-AsnH$_2$O) were used, were obtained. This could be due to surface nucleation of D-AsnH$_2$O, ascribed to the surface structure of the seeds of L-AsnH$_2$O supplied. An additional experiment was also carried out using seed crystals of a smaller average particle size having a smoother surface structure than used in the reference experiments. Productivity, yield, and purity were slightly improved in the L-Tank, for the same process duration. It should be emphasized, however, that it was found that the growth rate of the desired enantiomer was very low at the given experimental conditions and therefore practically no consumption of the enantiomer in the feed occurred in the crystallizer. This was ascribed to the nature of the controlling mechanism for crystal growth comprising slow surface integration of the asparagine monohydrate molecules onto the surfaces of the supplied seed crystals. The main advantages of the CC-PC process compared to other separation processes are low capital cost, high crystal purity and yield, ease of upscaling, increased safety, and reduced environmental impact due to reduction in amount of solvent used.

Currently, the application is, however, limited to conglomerate forming systems. Nevertheless, the separation concept may open new possibilities for process improvements for enantioseparation of racemic compound forming systems as well. The theoretical investigation of the CC-PC process consisted of the establishment of a dynamic one-dimensional model describing the continuous separation of enantiomers by simultaneous preferential crystallization. The evolution in the moments of the crystal population balances in combination with the liquid phase mass balances for the enantiomers were presented. The model was validated against experimental data for the conglomerate forming system of asparagine monohydrate in aqueous solution. The kinetic parameters required were taken from available literature sources and simulations compared to experimental data. The simulations were found to be in good agreement with the experimental data. The sensitivity analysis conducted suggests that the separation process can be improved by increasing the mean residence time of the liquid phase in the crystallizers, the crystallization temperature, and the mass of seeds supplied. Reducing the size of seed crystals will also lead to an improved separation. The model can be used to simulate the performance of the continuous crystallization process for a racemic compound forming system. The racemic compound and the pure enantiomer can be separated simultaneously in each crystallizer having sufficient enrichment of the pure enantiomer in the feed solution. The model can also be extended to represent a fully continuous separation process taking into account the continuous supply of enantiopure seed crystals and liquid feed solution and the continuous removal of solid product and mother liquor.

**General information**

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