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Guido Ströhlein[a]; Michael Schulte[b]; Jochen Strube[c]
[a] Swiss Federal Institute of Technology Zurich, Institute for Chemical- and Bioengineering, Zurich, Switzerland [b] Merck KGaA, Dept. SLP F. BS, Germany [c] Bayer AG, Bayer Technology Services, Leverkusen, Germany

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Hybrid Processes: Design Method for Optimal Coupling of Chromatography and Crystallization Units

Guido Ströhlein,[1] Michael Schulte,[2] and Jochen Strube[3,*]

[1]Swiss Federal Institute of Technology Zurich, Institute for Chemical- and Bioengineering, ETH-Hönggerberg/HCI, Zurich, Switzerland
[2]Merck KGaA, Dept. SLP F. BS, Darmstadt, Germany
[3]Bayer AG, Bayer Technology Services, Process Technology B310, Leverkusen, Germany

ABSTRACT

A general design method for the hybrid process of a chromatographic and a crystallization unit was developed. The fundamentals for the separate design of chromatographic and crystallization separation processes, as well as modeling approaches for these units, are presented. Four different test systems were chosen to show the applicability of the developed method. A focus was set on the enantioseparation of racemic compounds occurring in the pharmaceutical industry. The development of the flowsheet for the hybrid process shows that a chromatographic unit with a subsequent

*Correspondence: Jochen Strube, Bayer AG, Bayer Technology Services, Process Technology B310, D-51368 Leverkusen, Germany; Fax: + 49-214-3081554; E-mail: jochen.strube.js@bayertechnology.com.

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crystallization and recycle of the crystallizer's mother liquor to the feed of the chromatographic unit is most suitable. The possibilities of racemization and a solvent change are discussed. The influence of important operation parameters are investigated. The results for the test systems show that a hybrid process, in which both units serve as a separation process, is only suitable if the productivity of the chromatographic unit decreases sharply with increasing demands concerning the outlet purity and if the eutectic point of the racemic compound is close to 0.5.

Key Words: Chromotography; SMB; Crystallization; Hybrid processes; Design method; Enantioseparation; Optimization.

INTRODUCTION

Enantioseparations are increasingly needed in pharmaceutical industry as well as the agrochemical and food and fragrance applications.[1] A hybrid separation process is a specialized, optimized separation sequence using the synergy arising from the combination of unit operations. The hybrid process is composed of more than one classical unit operations (e.g., distillation, extraction, membrane, crystallization, and chromatography), which are alone capable of fulfilling the separation task partially or totally. Two major motivations lead to the development of hybrid processes. In the first place, if a single separation unit is not capable of reaching the required purities or only at very high cost. Secondly, if another unit for product formulation is needed in the process, which can also contribute to separation.

Therefore, typical areas of application for coupled chromatography and crystallization units are separation processes, which require a chromatographic separation, high product purity, and a crystalline product. These demands are often faced in the production of fine chemicals, food additives, and pharmaceuticals. Especially in the field of chiral drugs, there is an increasing demand for enantioselective separation processes because of new regulations of the American Food and Drug Administration (FDA). Since the optimal point of operation of a hybrid process cannot, in most cases, be derived from the optimal operation points of the single units, a method for the design of hybrid processes is needed.

It was the aim of this work to develop a general design method for coupled chromatography and crystallization processes based on simplified models of the process units involved. Without restriction of the general validity of the developed method, a special focus was set on the enantioseparation of racemic compounds. An important requirement during the development of this design method was its applicability to industrial separation problems.

To be able to find the optimal point of operation of hybrid processes, key operation parameters and an objective function have to be identified. In the case of coupled chromatography and crystallization processes, key operation parameters are, i.e., the purities of streams flowing between these two units. The specific production costs are an often-used objective function although they are more difficult to obtain with sufficient accuracy for "research" examples than for industrial relevant applications.

Furthermore, a valuation scheme based on component properties has to be established, which can be used for a preliminary estimation of the economic efficiency of the considered chromatography and crystallization process. Four different test systems consisting of a solvent or a solvent mixture and a racemate were chosen as representative examples, which cover a broad range of typical separation problems occurring in enantioseparation.

The degree of detail of the models has to be sufficient enough to allow a preliminary process design and a cost-estimation apart from thermodynamical feasibility investigations.

Currently, there is not much knowledge available from published research about the coupling of chromatography and crystallization processes. Lorenz and Seidel-Morgenstern[2,3] published the necessary component properties of mandelic acid and proposed this racemate as a suitable test system for further investigation of coupled chromatography and crystallization processes, although the maximum solubility of this system is atypically high in comparison to examples seen in daily work in pharmaceutical process development. Experimental work in this field was done by Lim et al[4] and by Painuly et al[5] to verify the general feasibility of a coupled chromatography and crystallization process.[6]

DESIGN METHOD FOR HYBRID PROCESSES

Two major approaches currently exist for the design of hybrid processes. One common approach is to write models using conventional programming languages, like FORTRAN or C++, and link these programs with a commercially available numerical solver and optimizer. A good overview concerning trends in computer-aided process modeling is given by Marquardt.[7] The drawback of this method is that the decision parameters for optimization have to be known in advance, because the model equations in the source code have to be solved manually with regard to these variables. The other major approach is based on the use of flowsheet-simulators, which include algorithms for the algebraic manipulation of equations as well as numerical solvers. This provides more flexibility and allows a higher degree of reusability of the models.[8]

The research published in this article is based on the second approach because of the mentioned advantages. Calculations for the estimation of the investment and operational costs were provided as optional modules. The detail of modeling was high enough to satisfy the requirements discussed earlier, but it still relied on parameters that are measurable, with an industrially justifiable effort.

The first step in a design method for a hybrid process is the development of a suitable model for each process unit. These models should allow an estimation of the capacity of the considered apparatus and also provide a cost assessment.

In the second step, an adequate flowsheet has to be designed. Tools and methods for process synthesis are helpful for this step. The developed flowsheet containing the previously built models is then implemented in a flowsheet-simulator.

The key operational parameters and the target variable for optimization have to be identified in the third step.

In the fourth step, an optimizer or a simple parameter variation is used to find the optimum of the target variable. There might be a need to return to step 2 to modify the existing flowsheet.

First studies to integrate chromatographic separations into process environments like solvent recycling and product recovery need to be described for enantiomers and bioreactive compounds, like proteins.[8]

Product concentration and solvent recovery by evaporation/distillation or membranes, as well as product recovery by precipitation or crystallization with following filtration and drying or lyophilization has to be considered in a generic, overall process design concept.

CHROMATOGRAPHY AND CRYSTALLIZATION IN ENANTIOSEPARATION

Crystallization Basics

Crystallization processes are commonly divided according to their physical behavior or their equipment construction. Constructions of crystallizer can be divided into crystallization processes from the suspension and layer crystallization processes. In the latter process, the crystals form a layer on a cooled surface and the enthalpy of fusion is transferred through the grown layer to the cooled wall. In suspension crystallization, the single crystals are suspended in the liquid phase and the enthalpy of fusion is removed through the liquid phase to a cooled wall. The active surface in layer crystallization is generally much lower than in the suspension crystallization because the suspended crystals are fairly small and, therefore, provide a great surface area.

To reach a reasonable time-space-yield in the layer crystallizer despite the relatively small crystallization area, a high driving force (supersaturation) has to be used. A higher driving force implies a higher growth rate of the crystal mass, which in turn, causes a higher amount of impurities in the grown crystals. Suspension crystallizers are usually operated with a comparably low driving force because undesired nucleation and incrustation of the cooling surfaces occur at high supersaturations.

The physical behavior of a crystallization process can be classified into crystallization from a melt or from a solution. In the latter case, a dissolved component is crystallized from a solution, but the saturation temperatures at moderate concentrations are significantly lower than the melting temperature of the dissolved component. The boiling temperature at atmospheric pressure of the solvent can be up to an order of magnitude lower than the melting temperature of the solute. Typical examples for this type of crystallization are inorganic salts dissolved in water. In crystallization processes from the melt, the melting points of the pure components are closer to each other. Typical examples for this type of crystallization are mixtures of isomers. It has to be noted, that there is obviously no sharp boundary between these two types of physical behavior of crystallization processes.

As already mentioned, a special focus in this work was set on the separation of pharmaceutical enantiomers. Since most of these enantiomers are heat sensitive and decompose with a significant rate at their atmospheric melting temperature, only crystallization from the solution is considered suitable.

Two general methods of enantioseparation are common in crystallization: separation via diastereoisomers or direct crystallization.[9] The first method is based on a reversible reaction of the enantiomers with an auxiliary enantiopure component. The resulting diastereoisomers will have different physical properties, so that a diastereoisomer containing one of the enantiomers can be crystallized selectively. This method can be applied even if the feed has racemic composition. The largest industrial process for this type of separation is reported for the anti-inflammatory drug S-(+)-naproxen, with *N*-alkyl-D-glucamine as resolving agent.[10] Since chromatographic separation processes on chiral stationary phases result in product streams enriched in one enantiomer, direct crystallization techniques can be applied. It was the goal of this study to develop general rules to be able to determine for which systems the additional crystallization step is beneficial and up to which enantiopurity the product streams have to be enriched.

For the design of a direct crystallization process, the knowledge of the solubility diagrams is crucial. Enantiomers are commonly divided into three major groups according to the shape of their solid–liquid equilibrium line in

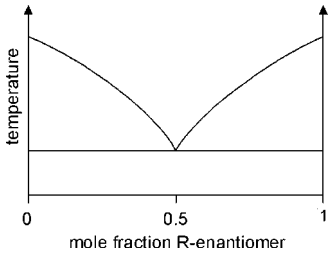

Figure 1. Melt diagram of a conglomerate.

the binary melt diagram: conglomerates, racemic compounds, and pseudoracemates.[11]

Nearly all melt diagrams of enantiomers are symmetrical with regard to the racemic concentration because the pure enantiomers exhibit exactly the same physical properties. Only 5 to 10% of the enantiomers belong to the category of conglomerates (Fig. 1). They can be recognized by the existence of only one eutectic point in the melt diagram, which is located at racemic composition. An optically pure crystal can be obtained by direct crystallization with an initial concentration, which has to be only slightly different from racemic composition. The formed crystals consist of the enantiomer, which is enriched in the feed.

Approximately 90 to 95% of the enantiomers are counted toward the racemic compounds (Figs. 2 and 3). Two eutectic points and a two-phase region between the eutectic points, in which a solid phase with racemic composition is formed, identify them. Optically pure crystals can only be obtained if the initial concentration is higher than the one at the eutectic point. The melting temperature in the melt diagram at racemic composition may be lower (see Fig. 2) or higher (see Fig. 3) than the one of the pure enantiomer.

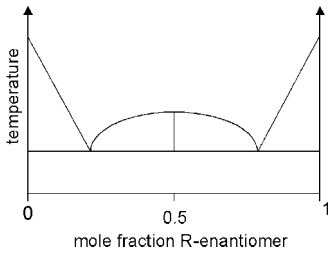

Figure 2. Melt diagram of a racemic compound (I).

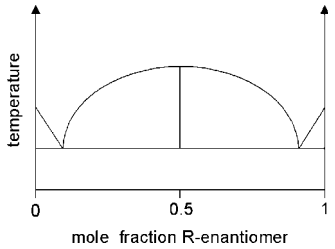

Figure 3. Melt diagram of a racemic compound (II).

Only a few enantiomers belong to the category of pseudoracemates. For further information, see Jacques et al.[11]

Since racemic compounds are the most relevant and the most common class of enantiomers, the following explanations are based on the assumption that a racemic compound with racemic composition is object of an enantioseparation.

In the case of crystallization from the solution, a mixture of two enantiomers and a solvent can be represented in a ternary phase diagram (Fig. 4). In the case of an achiral solvent, the shape of the solid–liquid equilibrium line (solid lines in Fig. 4) in the ternary phase diagram is very

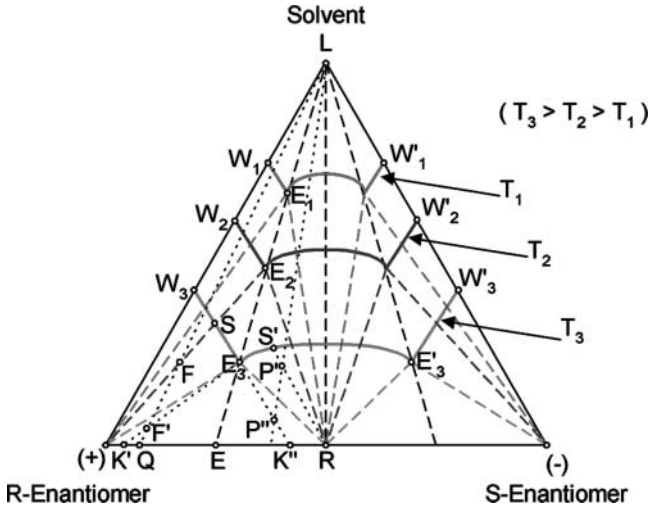

Figure 4. Ternary phase diagram.

often similar to the one in the binary melt diagram (see Fig. 2). Also, the composition in the binary system of the two enantiomers at the eutectic point in the ternary phase diagram (point E in Fig. 4) is nearly always equal to the concentration at the eutectic point in the melt diagram. In most cases, the eutectic points at different temperatures are situated on a line (i.e., point L to point E in Fig. 4).

Assuming that the ternary system has a temperature T_3, the area above the equilibrium line $W_3-E_3-E_3'-W_3'$ represents the one-phase area, the one below that line the two-phase area, in which a liquid is in equilibrium with a solid phase. Optically pure crystals can only be obtained if the overall composition of the system is situated within the triangle $W_3-E_3-(+)$. The point F, i.e., consists of pure (+)-crystal and a saturated liquid phase of composition S. If the overall composition is situated within the triangle $(+)-E_3-R$, i.e. F′ or P″, a liquid phase of composition E_3 is in equilibrium with a mixture of pure and racemic crystals. Within the triangle $E_3-E_3'-R$ (i.e., P′), a solid phase with racemic composition is in equilibrium with a liquid phase (for P′ this is S′). With decreasing temperature, the solubility usually decreases and the one-phase area is reduced. It can be seen that there is a minimum temperature for a given feed concentration, so that the crystallization process still yields pure crystals. For an overall composition of F, this minimum temperature is T_2. If the temperature is lowered to T_1, being smaller than T_2, F is situated in the triangle $(+)-E_1-R$ and the solid phase is not optically pure anymore.

Chromatography Basics

Chromatography is a thermal separation process that separates a mixture of components from a mobile phase by different affinity to a stationary phase. A separation process is called liquid chromatography if the mobile phase is made up by a liquid and the stationary phase by a porous solid. Chromatographic processes can be conducted in a batch or continuous mode. A widely applied continuous chromatographic separation process is the simulated-moving-bed (SMB) technology. Since SMB chromatography is very efficient for separations on a preparative scale, the chromatographic unit in the coupled chromatography and crystallization process is assumed to be of this type.

The SMB-technology is based on the simulated countercurrent flow of the liquid and the solid phase. The simulated movement of the solid phase is generated by periodic port switching of the four external streams of the unit. A simplified flowsheet is shown in Fig. 5. A more detailed description of the SMB-technology can be found in the work of Guiochon et al[12] and Strube.[13]

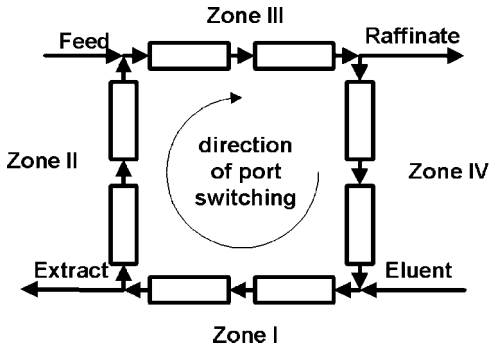

Figure 5. SMB-chromatography.

The optimal point of operation of an SMB-unit can be obtained with a method developed by Morbidelli and co-workers,[14–16] which is widely accepted for robust and rapid parameter determination.

If the demand for chromatographic separation occurs within the scope of enantioseparation in the pharmaceutical industry, SMB-technology is currently the standard choice.[1] The most advanced process is operated by UCB Pharmaceuticals, Belgium, for the production of the chiral antiepileptic drug Levetiracetam. The process, which yields the product in multiton scale per year, is performed on a chiral amylose-phase (Chiralpak AD), with a mixture of n-heptane and ethanol as solvent.

TEST SYSTEMS USED FOR CHROMATOGRAPHY AND CRYSTALLIZATION

As racemic test systems exhibiting different properties with respect to solubility and chromatographic selectivity, mandelic acid and EMD 53986 were chosen. EMD 53986 is a drug intermediate of the cardiovascular drug EMD 57033. It is a typical example of a pharmaceutical compound with low solubility and medium selectivity in the chromatographic separation system ($1.2 < \alpha < 2.0$).[17]

Mandelic acid is a flavor additive and olfactory component. It was chosen to compare the behavior of this system with an unusually high solubility and selectivity to the typical industrial application EMD 53986.

Crystallization Test Systems

Two test systems were chosen for the modeling of the crystallization from the solution:

- EMD 53986–ethanol
- Mandelic acid–water

The solubility data for EMD 53986 were determined as follows.

Fifty-mL ethanol were placed in a 100-mL Erlenmeyer-flask and thermostated at the desired temperature. One g of EMD 53986 racemate was added and stirred under temperature control for 1 h. The solution was filtered through a paper filter into an exactly weighed flask. The solvent was evaporated at 50°C by means of a rotary evaporator and the amount of dissolved EMD 53986 determined by weight measurement.

The melting points for asymmetric enantiomeric mixtures were determined by dissolving different amounts of racemate and pure enantiomer in the solvent (90 mg racemate/10 mg enantiomer, 80/20, 70/30, 60/40, 40/60, and 20/80). After complete dissolution, the solvent was evaporated. The exact enantiomeric composition was examined chromatographically. Finally the melting points of the different mixtures were evaluated. The necessary data for mandelic acid were taken from Lorenz and Seidel-Morgenstern.[2,3]

Figure 6 shows the melt diagrams of mixtures of the two enantiomers of mandelic acid and of EMD 53986. Since the melt diagrams are symmetrical to the racemic composition, only the compositional range from 0 to 0.5 is shown. It can be seen that the eutectic point of EMD 53986 at 95 wt% is by far higher than the one of mandelic acid at 70 wt%. Another important difference exists between the relationship of the melting temperature of the pure component and the one of the racemate: optically pure mandelic acid has a higher melting temperature than the mandelic acid racemate, for EMD 53986 this relation has the reverse order.

The solubilities of the enantiomers in a solvent can be represented in a triangular, ternary phase diagram. For systems in which the eutectic point in the ternary phase diagram does not change with temperature, as the one shown in Fig. 4, the solubility for certain compositions can be simplified to a binary system, because the solid phase has the same composition as the dissolved enantiomers in the liquid phase. This applies to the optically pure component, to the racemate, and to the eutectic composition.

As already discussed, the behavior of the ternary system can very often be deduced from the shape of the melt diagram. The expectation that mandelic acid with eutectic composition dissolves better in an achiral solvent than

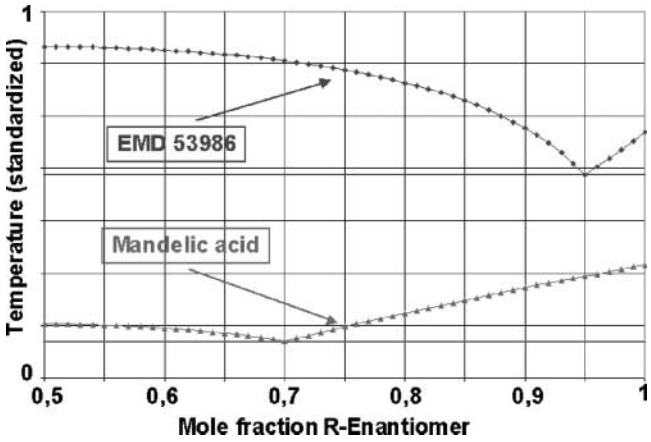

Figure 6. Melt diagrams of EMD 53986 and mandelic acid.

racemic mandelic acid, which in turn dissolves better than optically pure mandelic acid, could be verified. The same relation between the melt diagram and the solubility holds true for EMD 53986 (Fig. 7).

The solubility of mandelic acid in water is up to two orders of magnitude higher than the one of EMD 53986 in ethanol. Since the solid–liquid equilibrium line between the eutectic point in the ternary phase diagram (i.e., E_3 in Fig. 4) and the solubility of the pure enantiomer (W_3 in Fig. 4) is assumed to be a straight line, there is no immediate need to know the complete solid–liquid equilibrium line.

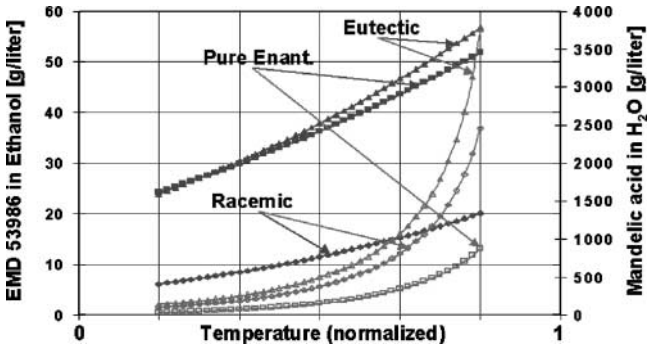

Figure 7. Solubilities of mandelic acid and EMD 53986.

Chromatographic Test Systems

The used systems for the evaluation of the chromatographic unit are:

- EMD 53986–ethanol
- EMD 53986–ethyl acetate
- Mandelic acid–methanol (54.5%)–acetonitril (45%)–buffer
- Mandelic acid–water (86.4%)–acetic acid (9.1%)–acetonitril (4.5%)

The data for EMD 53986 on two different chiral stationary phases have been published previously.[18] All necessary data for the mandelic acid systems were taken from Kaspereit et al.[19]

In Fig. 8, the adsorption isotherms and the separation factors for both enantiomers are plotted as a function of the concentration of the optically pure enantiomers up to half of the maximum feed concentration of the racemate in the chromatographic unit.

The EMD 53986–ethanol system possesses a fairly good separation factor with a nearly linear shape and a high initial slope of the isotherms. The maximum feed concentration is far lower than the one of the EMD 53986–ethyl acetate system. The latter one shows a strongly nonlinear behavior of the isotherms with a very high separation factor. The maximum loading of the stationary phase in the EMD 53986–ethyl acetate system is

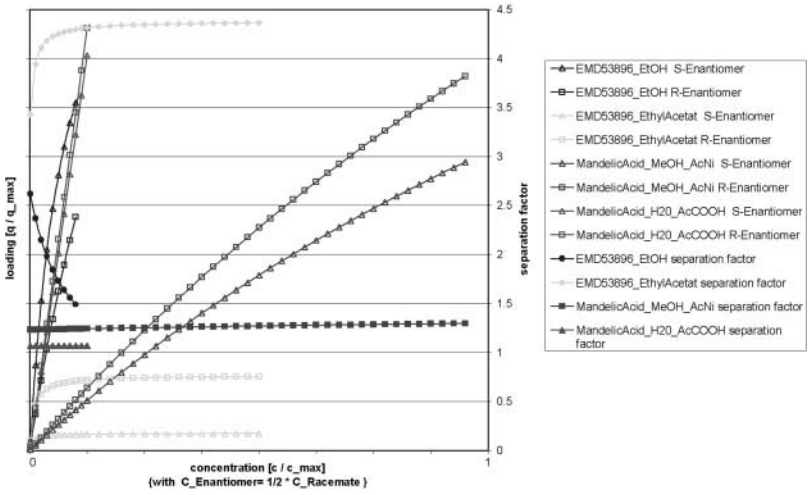

Figure 8. Qualitative comparison of adsorption isotherms and separation factors.

very small compared to the other systems. The mandelic acid–methanol–acetonitril system has a high maximum feed concentration, but only a small separation factor. The adsorption isotherms of mandelic acid–water–acetic acid show basically a linear shape with a very small separation factor, but with a high initial slope of the isotherms. This system has a maximum feed concentration, which is nearly as low as the one of the EMD 53986–ethanol system.

MODELING

Crystallization

It is supposed that the crystallization from the solution is carried out in a suspension crystallizer. As already discussed, a suspension crystallizer is mostly operated with a low supersaturation, which results in a low crystal growth rate and, therefore, in a negligible amount of impurities in the crystals. If the crystallizer is operated in the suitable triangle in the ternary phase diagram, it can be assumed that the required crystal purity is always reached.

The calculation of the crystal size distribution is only of secondary interest and will be implemented in later versions of the models. The crystal size distribution has to meet only the requirements for the solid–liquid separation (filtration, centrifugation).

It is supposed, that all crystals are spheres. Deviations from spherical shape are taken into account with a shape factor. Since the crystallizer is operated with a low supersaturation, the rate of spontaneous nucleation was set to zero as well as the rate of nucleation because of breakage of existing crystals. An initial amount of inoculation crystals provides the necessary crystallization surface. Adhesion of the mother liquor to the crystals was taken into account, the influence of the washing and the filtration step on the yield and crystal purity was neglected.

Since the crystallizer is assumed to work with a constant supersaturation over the course of the crystallization, the crystal growth rate can be approximated by a constant value.

Based on these assumptions in combination with the implementation of the ternary phase diagram, a model of a vacuum batch crystallizer was developed. This model allows the prediction of the yield of the crystallization, the operating temperatures, the residence time, and the crystallizer size. One of the key parameters of the crystallizer is the yield,

being defined as in Eq. (1).

$$\text{Yield}_{\text{Crystallizer}} = (\text{massflow crystals})/(\text{massflow of R-enantiomer at crystallizer inlet}) \quad (1)$$

A simulation was done for both test systems, EMD 53986–ethanol and mandelic acid–water, to evaluate the yield of the crystallizer as a function of the purity of the solute [Eq. (2)] at the crystallizer inlet. The inlet temperature was kept at a constant value.

$$\text{Purity}_{\text{Solute}} = (\text{mass of enriched enantiomer})/(\text{mass of both enantiomers}) \quad (2)$$

The results are shown in Fig. 9. It can be seen that the yield approaches 0 as the feed purity comes closer to the eutectic purity and 1 as the feed purity approaches 100%. Therefore, a higher eutectic point means a higher slope of the yield-versus-feed purity-curve.

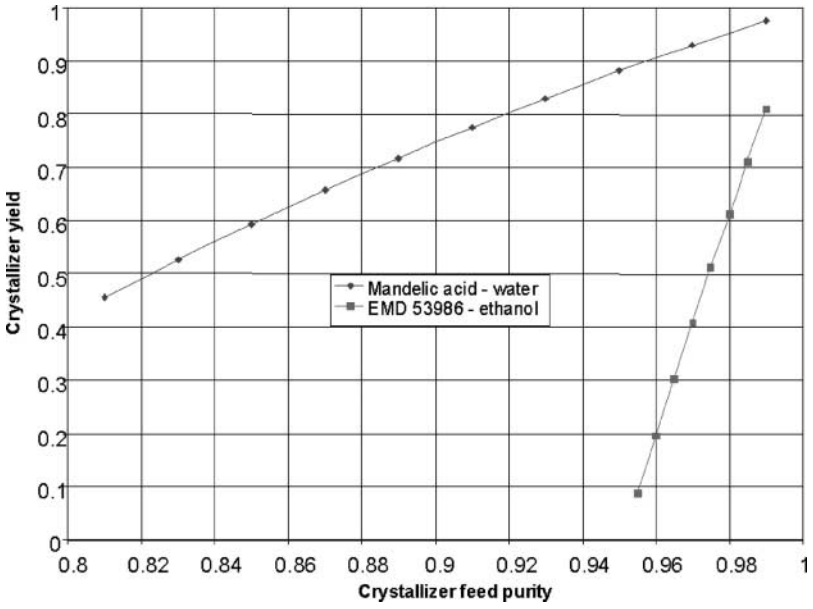

Figure 9. Crystallizer yield as a function of the feed purity of the solute.

Chromatography

As already mentioned, the chromatographic unit is represented by an SMB unit. Details about the modeling of such units can be found in the work of Guiochon et al[12] and Strube.[13] An equilibrium model based on a true-moving-bed process with a 2:2:2:2 segmentation and an overall stage number of 200 for the EMD systems and 4000 for the mandelic acid systems was used. The optimization of the segmentation is outside the scope of this work, for further details see Zhang et al.[20] The determination of the optimal point of operation was done with the aid of the triangle theory developed by Morbidelli and co-workers.[14–16]

To be able to characterize the four different chromatographic systems, the influence of the feed concentration and the raffinate purity on the eluent consumption and the productivity of the SMB-System were calculated. It has to be noted that the calculation of the productivities [defined in Eq. (3)] is very sensitive to the maximum operation pressure drop as well as to the way of pressure drop calculation.

$$\text{Productivity}_{\text{Raffinate}} = (\text{massflow of product enantiomer in raffinate})/(\text{Volume of stationary phase}) \quad (3)$$

Despite similar equations for the calculation of the pressure drop, Kaspereit et al[19] calculated productivities for the mandelic acid systems, which are up to one order of magnitude higher than the ones published in this work. This difference is based on a different assumption about the maximum operation pressure drop. The calculations of Kaspereit et al are based on a pressure drop of about 100 bar per column, which yields an overall pressure drop of approximately 320 bar for the SMB unit with a 1:1:1:1 segmentation. In the present work, a maximum overall pressure drop of 40 bars for the modeling of the SMB unit was assumed. This value lies within the range of practically applied pressure drops in preparative SMB chromatography.

In Fig. 10, the eluent consumption, defined in Eq. (4), and the productivity of the described SMB unit are calculated as a function of the feed concentration for a racemic feed.

$$\text{Eluent consumption}_{\text{Raffinate}} = (\text{volume flow eluent})/(\text{mass flow product}) \quad (4)$$

It has to be noted that the eluent consumption for the EMD 53986–ethyl acetate system is scaled down by a factor of 30 to allow an adequate representation in one diagram.

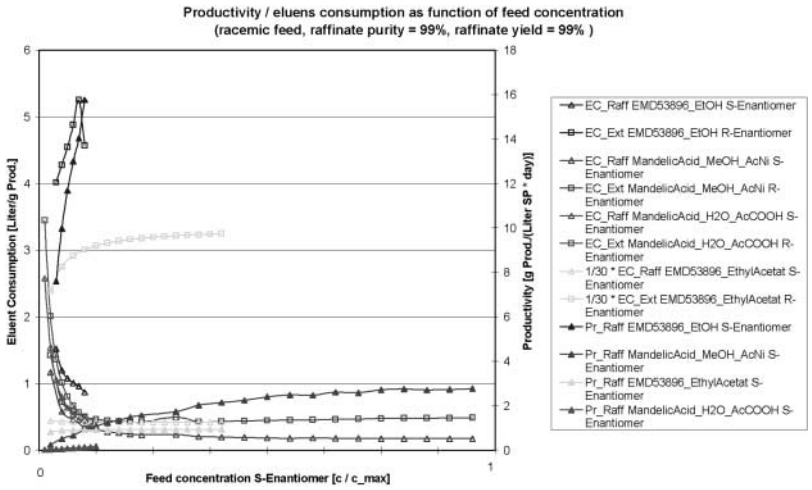

Figure 10. Qualitative comparison of eluent consumption and productivity as a function of feed concentration.

The productivity increases for all four systems with an increasing feed concentration. Therefore, the optimal feed concentration for the SMB unit is equal to the maximum feed concentration. The slope of the productivity curve for EMD 53986–ethyl acetate is nearly zero because of the highly nonlinear adsorption isotherm, while the curve of the EMD 53986–ethanol system shows a relatively high slope.

In Fig. 11, the influence of the raffinate purity on the productivity and eluent consumption is shown. The raffinate productivity for all test systems decreases with increasing raffinate purity because, obviously, more effort is needed if higher purities are to be obtained.

Cost Calculation

The specific production costs are calculated from the sum of the operational and investment costs divided by the amount of product. The operational costs include the cost for electricity, steam, solvent, cooling liquids, adsorbent, and the racemate fed. The investment costs are based on a linear depreciation of the apparatus cost. The apparatus cost estimation is based on the scaling of the price vs the equipment capacity with a logarithmic

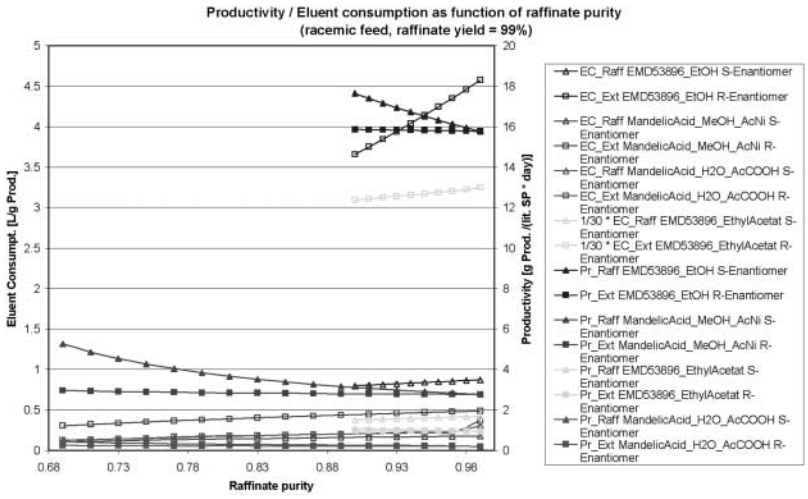

Figure 11. Eluent consumption and productivity as a function of raffinate purity.

relationship.[21] A cost index was included to update price data where appropriate.

COUPLED CHROMATOGRAPHY AND CRYSTALLIZATION PROCESS DESIGN

Since SMB chromatography is a continuous process and the suspension crystallization is assumed to be operated as a batch process, the storage of intermediate products, like the raffinate flow, is necessary. To ease modeling and to avoid the scheduling problem, which is outside of the scope of this work, the process is modeled as a quasicontinuous process.

BASIC PROCESS SYNTHESIS

To evaluate all possible combinations of crystallization and chromatographic units, a triangle, as shown in Fig. 12, can be drawn.

As explained, the focus in this work was set on the enantioseparation of racemic compounds. Since no purification can be achieved by crystallization from a feed with racemic composition, all combinations with crystallization as the first separation step are useless. Combinations with a multiple

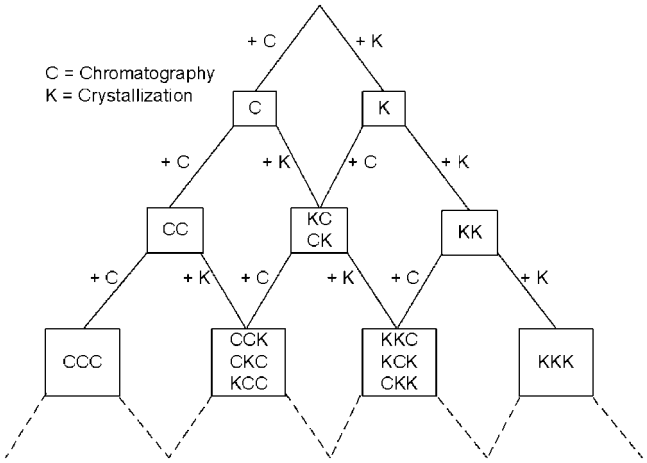

Figure 12. Combinatorial tree of chromatography and crystallization units.

chromatographic unit are obviously uneconomical. The last step of the hybrid process has to be a crystallization step to reach the required product formulation as a powder. Therefore, only a chromatography with a subsequent multistage crystallization is suitable for the described separation problem. As discussed earlier, the crystallization unit is represented by a suspension crystallization from the solution. The usefulness of a multistage crystallization from the solution with respect to the model described is examined in the next section.

MULTISTAGE SUSPENSION CRYSTALLIZATION FROM THE SOLUTION

It can be derived from the description of the crystallizer model that the crystallization unit is equal to one theoretical stage. Thus, the separation reaches the maximum purification possible according to the ternary phase diagram. The impurities in the crystals leaving the crystallizer can be neglected. The mother liquor has eutectic composition and cannot be purified further by crystallization.

With regard to the assumptions made in the modeling of the crystallizer, there exists no justification for a multistage suspension crystallization from the solution.

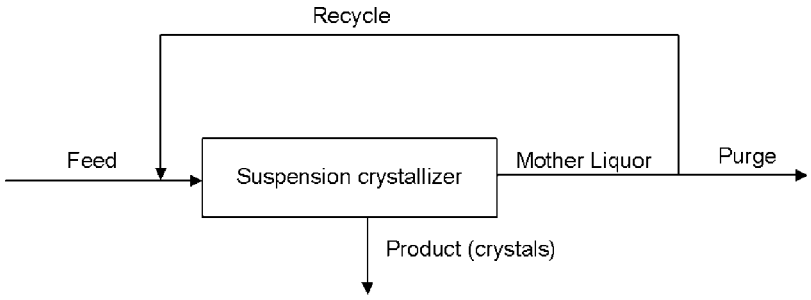

Figure 13. Recycle of mother liquor in suspension crystallizer.

The possibility of recycling the mother liquor to the feed of the crystallizer (Fig. 13) was evaluated by increasing the fraction of the recycled mother liquor and observing the resulting yield and flows. The results for mandelic acid with a feed purity of 90% and a constant crystallizer inlet temperature are shown in Fig. 14. While the throughput in the crystallizer increases exponentially, there is no significant rise in the overall yield. One important aim in process design is to keep the throughput always as small as possible to minimize the size of the equipment used. Therefore, a recycle of the mother liquor is not a suitable option for the considered process. This conclusion leads to the core of the hybrid process flowsheet. It is assumed that the desired enantiomer is enriched in the raffinate stream (Fig. 15).

Figure 14. Influence of mother liquor recycle on crystallizer yield.

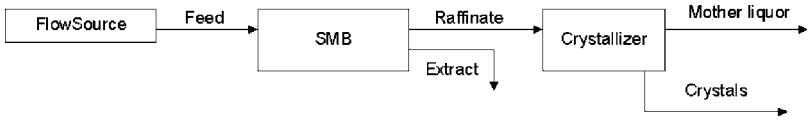

Figure 15. Core of hybrid process flowsheet.

EXCHANGE OF SOLVENT

Unfortunately, there are contradictory requirements for the optimal solvent in a chromatographic unit and the solvent for crystallization.

A good solvent for chromatographic separation requires:

- Constant separation factor at varying concentrations
- High solubility
- High level of the separation factor

Needless to count are requirements like chemical stability of the solute in the solvent, toxicity, price, etc. If a suitable single solvent cannot be found, a mixture of solvents has to be considered as eluent. Adding another solvent usually increases the solubility, but the separation factor reduces in most cases.

Requirements for a good solvent in crystallization are:

- Low respectively high solubility at minimum respectively maximum crystallization temperature
- Favorable influence on the crystal size distribution and on the crystal shape

The closer the crystallization step is situated to the final formulation, the more important are the requirements mentioned secondly. If the produced crystals are just used as an intermediate product, the solubility requirement has a higher weight on the decision about the solvent.

In a coupled chromatography and crystallization process, the question of a solvent exchange between the chromatographic unit and the crystallizer always arises. The solvent can be changed by completely evaporating the eluent from the raffinate or extract stream and then redissolve the obtained solid in another solvent.

The advantage of a solvent exchange is that the optimal solvent can be chosen for each separation unit and the obligation to find compromises can be avoided. Disadvantages are the high energy consumption of the evaporators

and the cost for the use of a second solvent. As a general rule of thumb, a solvent exchange is more likely to be used if the crystallization step is close to the final formulation.

Racemization

Since the production of racemates is rather expensive, there is an immediate interest to reuse the undesired enantiomer, which is enriched in one of the streams leaving the SMB unit. Racemization describes a reaction, in which a mixture of two enantiomers with nonracemic composition is converted into a racemic mixture by means of thermal treatment, free radicals, or acid- or base-catalyzed processes.[22] With the aid of these mechanisms, the enriched enantiomer in the feed to the racemization unit can be transformed into its mirror-inverted counterpart.

Without restriction of the general validity of the proposed design method, it is assumed that the desired enantiomer is enriched in the raffinate and the undesired one in the extract. The flowsheet of the hybrid process including a racemization unit is shown in Fig. 16. With the proper use of an evaporator and a heat exchanger, the stream leaving the racemization unit can be adjusted to the conditions of the feed to the SMB unit.

The use of a racemization unit is recommended if the specific costs for the racemate leaving the racemization unit are lower than the ones of the racemate produced in the preceding process. The cost for the disposal of the extract have to be taken into account if the extract stream is not recycled. The decision about the racemization unit has no influence on the optimal purity of the raffinate stream but on the optimal yield of the raffinate.

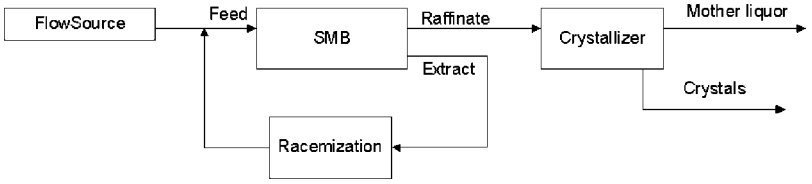

Figure 16. Flowsheet of coupled chromatography and crystallization process with racemization.

Recycle of Mother Liquor from Crystallizer

The mother liquor leaving the crystallization unit contains the desired enantiomer at enriched concentration and has usually eutectic composition. For the EMD 53986 systems, this means that the solute in the mother liquor still has purity of 95%. To reduce the expenditures for separation, a recycle of the mother liquor seems to be useful. It can be seen from Fig. 16 that there are, in principle, three possibilities for the recycle of the mother liquor: to the raffinate or extract stream or to the feed stream of the SMB unit.

A recycle to the raffinate stream is equivalent to the case discussed earlier and is, therefore, not a suitable option. A recycle to the extract stream would annihilate the separation effort achieved in the SMB unit. Thus, this possibility is also not suitable. A recycle to the feed stream of the chromatographic unit seems to ease the separation because the desired enantiomer would then already be enriched in the feed to the SMB unit.

To investigate this proposal, the influence of a recycle to the feed is evaluated by discussing the relationship between major parameters of the coupled process. A sketch of the hybrid process, including racemization and recycle of the mother liquor, is shown in Fig. 17. It can be shown generally, for all systems, that a mother liquor recycle reduces the specific separation costs.

The scale-up of the SMB unit is done by increasing the column diameter at a constant column length. The column diameter is calculated from a pressure drop equation with the given flow rates. Since a constant overall pressure drop for the SMB unit is assumed, an increase in column diameter is caused by an increase in the solvent flow rate. An increase in the solvent flow rate, in turn, leads to a higher throughput in the whole process and, therefore, to bigger apparatuses, higher energy requirements for evaporation and cooling, and so forth. It can be derived that a smaller column diameter in the SMB unit always means lower specific separations costs if all other

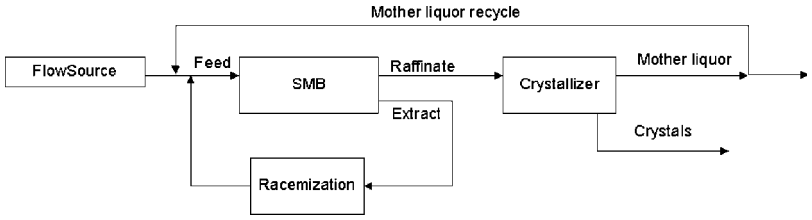

Figure 17. Flowsheet of coupled process with racemization and mother liquor recycle.

operational parameters are kept constant. In the following discussions, the column diameter is used as a qualitative indicator for the specific separation costs including invest as well as operation costs.

The relations between major operational parameters with an increasing fraction of mother liquid recycled are shown in Fig. 18. Without restriction of the general validity of the developed method, it is assumed that the desired enantiomer is called the R-enantiomer and that it is enriched in the raffinate.

A constant raffinate purity, which is equal to the feed purity of the crystallizer, leads to constant concentrations in the outlet of the crystallizer (see Fig. 4). The yield of the crystallizer is only a function of the feed purity and is, therefore, constant too. Since the amount of crystals leaving the crystallizer per unit of time is set as a constraint, the mass flow of R-enantiomer is also constant. Thus, the conditions at the outlet of the crystallizer do not change with a varying fraction of mother liquor recycled. The concentration of the R-enantiomers in the feed of the SMB unit always increases with a rising recycle as well as the ratio of the feed concentrations of the enantiomers. In turn, this leads to a higher productivity of the SMB unit and to a lower column diameter. The decreasing solvent flow also contributes to smaller columns. It can be concluded that a recycle, as shown in Fig. 17, improves the efficiency of the hybrid process and lowers the specific separation costs.

It has to be mentioned that a recycle with an eluent composed of different solvents faces severe problems in practice. A change of the solvents between the SMB unit and the crystallization might become necessary.

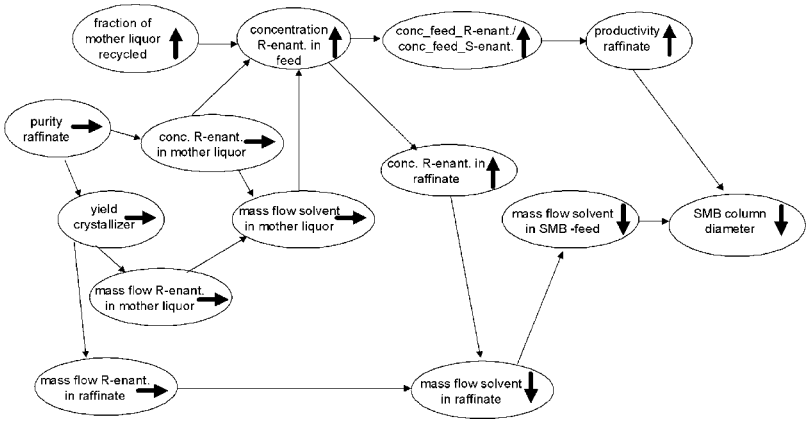

Figure 18. Influence of mother liquor recycle.

RESULTS

Prior to presenting the results of the modeling, some boundary condition and further assumption for the hybrid process will be discussed.

The maximum diameter of the chromatographic columns was set to 1.5 m. This is the currently the maximum diameter for units with an operating pressure of about 40 bars and 8 to 50 cm length.

The production rate of crystals was set to a constant value. The maximum production rate of crystals can be derived from the boundary condition of the maximum column diameter.

The maximum operation temperature for the suspension crystallizer is set to a constant value, which was derived from thermal stability considerations.

It is assumed that the solubility data of the EMD 53986–ethyl acetate system does not differ significantly from the data of the EMD 53986–ethanol system; the same applies to the mandelic acid–water and the mandelic acid–methanol–acetonitril system.

As already discussed, the main free parameters for optimization of the hybrid process are the raffinate purity and yield. The specific production costs as a function of these two variables are shown in Figs. 19 through 22.

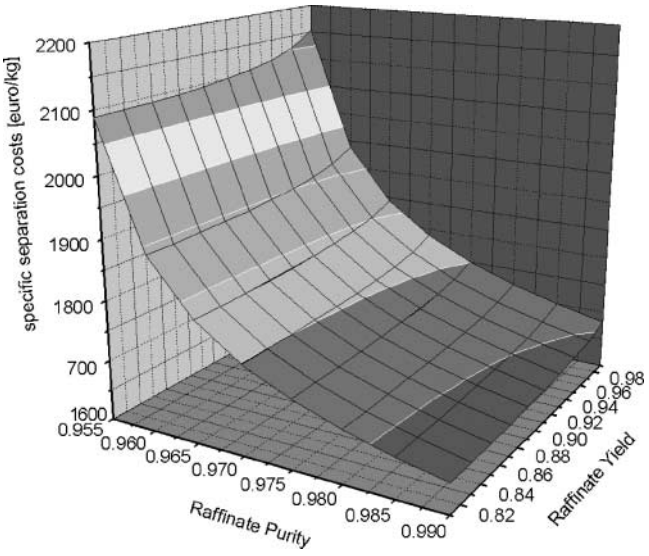

Figure 19. Specific separation costs for EMD 53986–ethanol (0.5 tons per year).

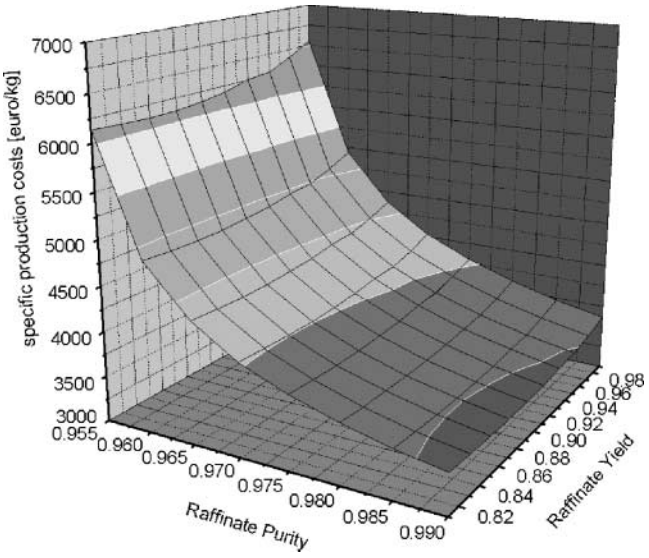

Figure 20. Specific production costs for EMD 53986–ethyl acetate (0.1 tons per year).

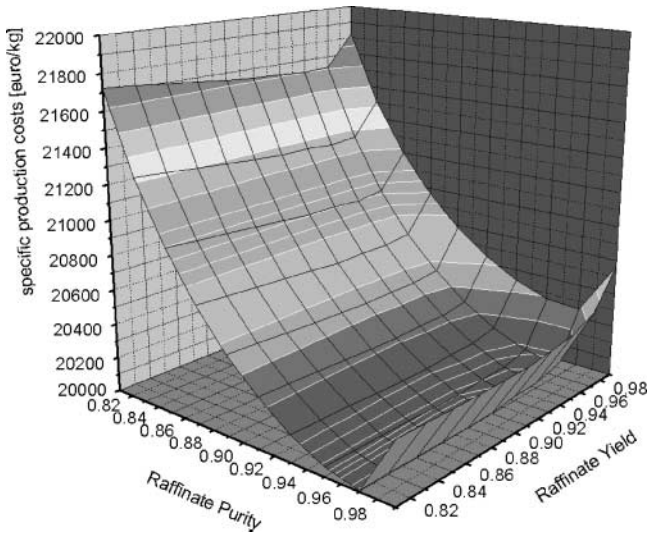

Figure 21. Specific production costs for mandelic acid–water–acetic acid (0.03 tons per year).

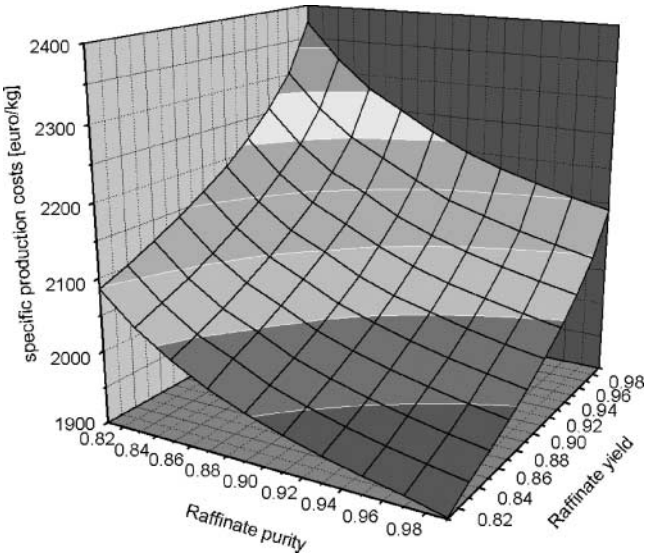

Figure 22. Specific production costs for mandelic acid–methanol–acetonitril (0.3 tons per year).

The optimal raffinate purity is equal to the specified product purity (= 99%) for both EMD 53986 systems as well as for the mandelic acid–methanol–acetonitril system. Only for the mandelic acid–water–acetic acid system, an optimal raffinate purity at around 97% occurs. The raffinate yield does not have much influence on the value of the optimal raffinate purity. The optimal raffinate yield varies between about 80% for the EMD 53986–ethanol and the mandelic acid–methanol–acetonitril system, 88% for the EMD 53986–ethyl acetate system, and 96% for the mandelic acid–water–acetic acid system.

Short Cut for the Prediction of the Optimal Raffinate Purity

To be able to predict the optimal raffinate purity, a short cut was developed on the basis of the flowsheet shown in Fig. 17. The development of the short cut is based on the fact that the productivity and the yield of the crystallizer are the major parameter influencing the column diameter of the SMB unit and, therefore, the specific operation costs.

With the definition of the raffinate productivity and the definition of the crystallizer yield [Eq. (5)], the volume of the stationary phase can be calculated, as in Eq. (6).

$$\text{Yield}_{\text{Crystallizer}} = (\text{massflow crystals})/(\text{massflow of R-enantiomer at crystallizer inlet}) \quad (5)$$

$$\text{Volume}_{\text{Stationary Phase}} = (\text{massflow crystals})/(\text{Productivity}_{\text{Raffinate}} * \text{Yield}_{\text{Crystallizer}}) \quad (6)$$

Since the scale-up of the SMB columns is done up increasing the diameter and keeping the length constant, the volume of the stationary phase is proportional to the square of the diameter. A minimum of the specific separation costs is equivalent to the minimum of the column diameter and equivalent to the minimum of the volume of the stationary phase. From Fig. 11, it can be seen that the productivity as a function of the raffinate purity can be approximated as a linear function [Eq. (7)]

$$\text{Productivity}_{\text{Raffinate}} = a_1 * \text{Purity}_{\text{Raffinate}} + a_0 \quad (7)$$

The same holds true for the yield of the crystallizer, but the boundary conditions that the yield is zero if the feed has eutectic composition and that the yield is unity if the feed is optically pure have to be kept in mind. This leads to Eq. (8).

$$\text{Yield}_{\text{Crystallizer}} = (\text{Purity}_{\text{Raffinate}} - \text{Purity}_{\text{Eutectic}})/(1 - \text{Purity}_{\text{Eutectic}}) \quad (8)$$

From boundary conditions for the productivity curve and the optimal raffinate purity, it can be derived that an optimal raffinate purity between eutectic purity and 100% purity only exists if the productivity of the raffinate at 100% raffinate purity is less than half of the raffinate productivity at eutectic purity [Eq. (9)].

$$\text{Productivity}_{\text{Raffinate}}[\text{Purity}_{\text{Raffinate}} = 100\%]/\text{Productivity}_{\text{Raffinate}}[\text{Purity}_{\text{Raffinate}} = \text{Purity}_{\text{Eutectic}}] < 1/2 \quad (9)$$

If this ratio of productivities is bigger than one-half, the optimal raffinate purity is 100%. This means that the crystallization serves only for formulation. If the inequality is fulfilled, a curve tracing for the search of the minimum of the volume of the stationary phase yields the optimal raffinate purity, according to Eq. (10).

$$\text{Purity}_{\text{Raffinate}} = \text{Purity}_{\text{Eutectic}}/2 - a_0/(2*a_1) \quad (10)$$

The procedure for applying the short cut can be divided into 4 steps.

Table 1. Comparison of flowsheet simulator and shortcut results for optimal raffinate purity.

	$Pu_{Eutectic}$	a_0/a_1	$Pr_{100\%}/Pr_{Eutectic}$	Optimal Pu_{Raff} (shortcut)	Optimal Pu_{Raff} (cost minimum determined with flowsheet simulator)
EMD 53986–Ethanol	0.95	− 1.13	0.72	1	1
EMD 53986–Ethyl acetate	0.95	− 1.79	0.94	1	1
Mandelic acid–MeOH–AcN	0.7	− 1.38	0.56	1	1
Mandelic acid–H_2O–AcCOOH	0.7	− 1.21	0.42	0.957	0.965

Step 1: The feed concentrations for the SMB unit can be calculated from overall mass balances if the yield of the crystallizer is known as a function of the crystallizer feed purity.

Step 2: With the known feed concentrations, the productivities of the SMB unit can be determined.

Step 3: A linear least-squares fit to the raffinate productivity curve as a function of the raffinate purity yields the parameter a_0 and a_1.

Step 4: If the raffinate productivity more than halves between the raffinate purity being equal to eutectic purity and 100% purity, the optimal raffinate purity can be predicted by Eq. (10). Otherwise, the optimal raffinate purity is equal to 100%.

The presented short cut was applied to the four test systems. The results can be found in Table 1. The short cut predicts the optimal raffinate purity for all four systems with high accuracy.

CONCLUSION

The objective of this work to develop a unified, generally valid design method for coupled chromatography and crystallization processes was achieved. The applicability of the method for industrial systems was shown. In addition to the developed tools, a short-cut model is presented, which

predicts from an economical point of view the optimal transfer purity between the chromatography and the crystallization unit with high accuracy.

It was shown with the aid of a model of a suspension crystallizer, that neither a multistage suspension crystallization nor a recycle of the mother liquor to the inlet of the crystallizer makes sense.

With regard to the boundary conditions, it could be shown that the core element of the coupled process has to be a chromatography with a subsequent crystallization. The possibility of a racemization of the undesired enantiomer was discussed and decision criteria were provided. The general advantage of a recycle of the mother liquor of the crystallization unit to the feed of the chromatographic unit was shown.

The modeling of the complete hybrid process on the basis of the developed flowsheet was done for four representative test systems, which cover a broad range of problems typically occurring in enantioseparation. The key variables for the optimal design of the hybrid process are the raffinate purity and the raffinate yield, assuming that the desired enantiomer is enriched in the raffinate. The influence of these two variables on the specific separation costs was investigated. The optimal point of operation for each test system was determined by parameter variation.

The results show that a transfer purity between the chromatography and the crystallization unit, which is below the specified product purity, is only economically useful for the mandelic acid–water–acetic acid system. In this case, the crystallization unit is used a separation process as well as a formulation unit. For all other systems, the calculations showed that the optimal transfer purity is equal to the specified product purity. In this case, the crystallization only serves as a formulation unit. As a rule of thumb, coupled chromatography and crystallization processes in which both units contribute to the purification are useful, if:

1. The considered chromatographic system decreases sharply with increasing outlet purity. This occurs especially if the separation factor is fairly small (< 1.3).
2. The considered crystallization system possesses a low eutectic point (near to 0.5).

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