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Evaluation of Competing Process Concepts for the Production of Pure Enantiomers

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ABSTRACT: Various promising concepts exist for improving the performance of productions of pure enantiomers. An efficient approach is developed for the systematic conceptual design of such processes. The proposed three-step procedure aids a fast selection of the optimal process configuration out of many possible candidates and leads to an optimally designed process. The approach is applied in a case study for an industrially relevant compound, considering different process concepts based on simulated moving bed chromatography, enantioselective crystallization, and racemization. It is demonstrated that mixed-integer nonlinear programming is capable of predicting simultaneously the optimal process configuration and optimal design parameters.

INTRODUCTION

The production of pure enantiomers plays a critical role, in particular in the pharmaceutical industry. The two enantiomers of a chiral compound are stereoisomers structured like mirror images. Although possessing largely identical physicochemical properties they often exhibit significantly different physiological effects. This fact and the corresponding strict regulations by drug approval authorities are the reason why in 2010 enantiopure drugs accounted for approximately 40%[1] of the worldwide drug market of $856 billion (US).[2] The four top-selling drugs are pure enantiomers, accounting for sales of about $36 billion (US). Six of the ten top-selling small-molecule drugs are enantiopure, three are achiral, and only one is marketed as racemate, that is the 50/50 mixture of both enantiomers. The vast majority of drugs currently under development are enantiopure.[3]

On the other hand, drug-developing pharmaceutical companies are facing an increasing cost pressure. Despite enormous R&D expenditures, the number of new drug approvals has been decreasing[4] or, at best, has remained constant over the past decade, while the number of failures in drug development increased sharply.[5] In addition, many relevant patents for blockbusters expired recently or will expire in 2012. This trend will continue until 2015. This holds for almost 75% of the 20 top-selling drugs. Even the comparably large number of new approvals in 2011 will probably not provide for an enduring relief.

Against this background the development of advanced, economically more efficient production schemes is of high interest. This holds in particular for the generally expensive production of pure enantiomers. In addition, due to the large number of projects and the high attrition rate in drug development, there is also a strong need for faster process development.[6]

A significant potential for improving performance of enantiomer productions is offered by sophisticated process concepts that combine different separation techniques such as chromatography and crystallization, and/or (bio)chemical reactions. There exists a rather large number of corresponding options as discussed in the next section. The full potential of such concepts can be exploited only if both, the optimal process configuration and the optimal operating conditions, are chosen. Identifying the best process variant out of many alternatives and performing an optimal design is challenging; in particular, since in the drug development long-lasting design decisions have to be made at early stages when only limited substance-specific information is available.

The main goal of this work is to introduce a systematic and efficient approach for the conceptual design of advanced and more efficient process concepts for the production of pure enantiomers. A three-step approach is devised that aids the evaluation of process alternatives and the optimal design for a given production problem, while requiring only a minimum of input information.

This paper is organized as follows. The next section summarizes potential advanced process concepts for producing single pure enantiomers. Focus is on concepts based on chromatography, since they offer a high degree of flexibility together with significant potential for performance improvment. Afterwards the three-step design methodology is introduced. In the last section application of the method is demonstrated in a case study for an industrially relevant compound.

ADVANCED PROCESS CONCEPTS

Two general routes can be defined for producing a pure enantiomer. The first are (bio)chemical syntheses, either via chiral pool or stereoselective catalysis. In particular asymmetric catalysis often requires elaborate process development that can make it economicallly unattractive. As for now, the majority of industrial productions is based upon less expensive conventional

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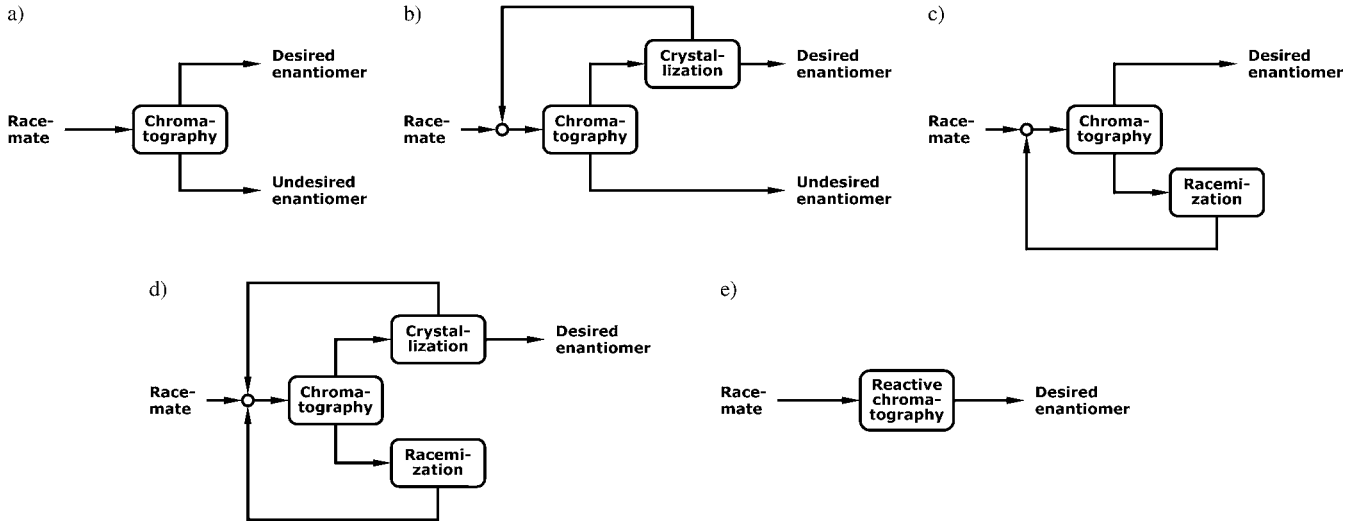

Figure 1. Selected process configurations based on chromatography for the production of pure enantiomers. (a) Stand-alone chromatographic separation. (b–e) Advanced process concepts. Chromatography combined with crystallization (b), racemization (c), both crystallization and racemization (d), and a fully integrated reactive chromatography with internal racemization (e).

chemical synthesis of the racemic 50/50 mixture and a subsequent enantioseparation. The limitations of this approach are the fact that the overall yield is restricted to 50%, since half of the synthesized material represents an undesired compound, and that the separation is challenging due to the extreme similarity of the enantiomers.

Most industrial enantioseparations are carried out in an isolated manner by stand-alone applications of different crystallization methods, chromatographic techniques or chemical resolutions. These approaches are feasible and established, but costs might be reduced significantly by improved process concepts that combine one or more of the separation methods and/or (bio)chemical reactions. Some examples will be considered below. Focus is on processes that include chromatography, since this powerful technology is usually applied to very challenging separations and entails a particular potential for performance improvement.

Figure 1 shows selected chromatography-based process concepts for the production of pure enantiomers. The conventional stand-alone separation Figure 1a can be performed by, for example, by simulated moving bed (SMB) chromatography, conventional single-column batch chromatography, or other concepts such as steady state recycling (SSR) chromatography,[7,8] respectively.

An advanced approach is the combination of chromatography and enantioselective[9,10] or preferential crystallization[11−13] as shown in Figure 1b. Its advantage originates from the reduced purity requirements on chromatography. While a stand-alone chromatography (Figure 1a) has to deliver pure products, already a certain enrichment is sufficient to obtain a pure enantiomer later by crystallization in Figure 1b. This "de-bottlenecks" chromatography, allows for shorter and less efficient columns, and enhances overall throughput. The concept was applied to, for example, praziquantel,[14] mandelic acid,[10] Tröger's base,[15] threonine,[16] and to the epimers of a diasteromeric compound.[17] An extension by including chemical conversions was suggested for difluoromethylornithine.[18] An application to the resolution of bicalutamide is described in the same issue.[19]

Combining the separation with the isomerization (racemization) of the undesired enantiomer as in Figure 1c has the obvious benefit of achieving a yield of 100%, thus requiring only half of the material from synthesis. Racemization can be triggered thermally, by homogeneous (e.g., nonpolar solvents) or heterogeneous catalysts (e.g., ion exchange resins, noble metals), enzymes (e.g., racemases), acids and, more commonly, bases. Ebbers et al.[20] gives an overview of racemizable classes of molecules. The concept Figure 1c was considered, for example, applying thermal racemization of Troeger's base[21] and chlorthalidone,[22] as well as enzymatic racemization of amino acids.[23−25]

It would be consequent to exploit simultaneously the benefits of both concepts above: enhancing throughput by reducing purity requirements on chromatography and increasing yield through racemization. The corresponding configuration in Figure 1d combines chromatography with a crystallization of the desired enantiomer and a racemization of the undesired form. Feasibility of this concept is demonstrated for 2′,6′-pipecoloxylidide (PPX) in the same issue.[26] PPX will also serve as example for the theoretical investigations in this work.

Figure 1e shows an integrated reactive chromatographic process with internal racemization. On the basis of the concept suggested by Hashimoto et al.,[27] where side reactors are distributed along an SMB unit, similar schemes were proposed for producing enantiomers.[28,29] Recently, a simple integrated SMB process was developed that uses an internal pH gradient instead of side reactors[30] and was successfully applied to produce enantiopure chlorthalidone at 100% yield.[31]

Finally, it should be noted that additional configurations are possible. In the processes in Figure 1, different operating modes of chromatography, crystallization, and racemization can be applied. As concerns Figure 1b, crystallizers can be used to crystallize either the desired, the undesired, or both enantiomers, respectively. Combining fractional crystallization with a racemization was proposed for producing calcium pantothenate.[32] Enzyme-catalyzed racemization and preferential crystallization was considered for asparagine and methionine.[24,33] In a similar context falls Eli Lilly's RRR (resolution–racemization–recycle) synthesis of duloxetine,[34] that combines a diasteromeric crystallization with an epimerization. Apart from that, it appears interesting to apply also other separation techniques such as membranes[35] and chemical methods such as dynamic kinetic resolution[36] within such process combinations.

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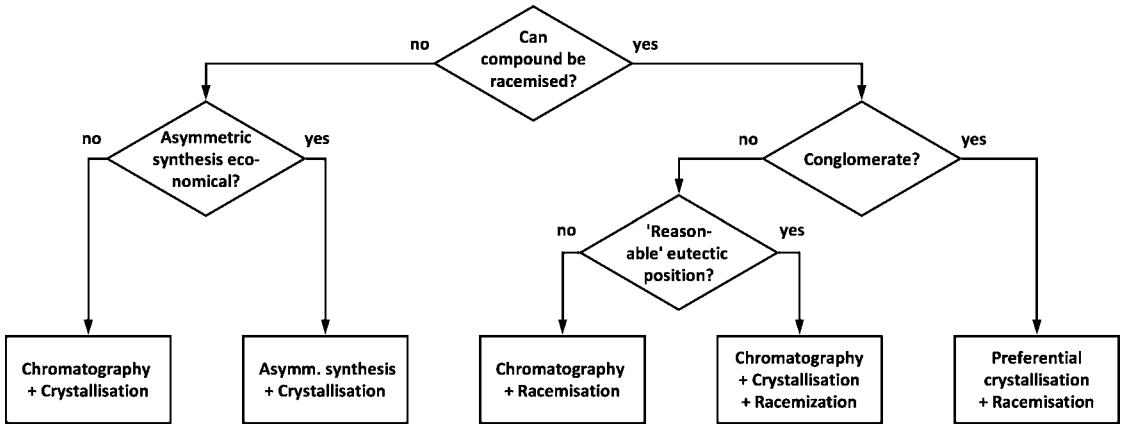

Figure 2. Decision tree based on simple qualitative criteria for the selection of a suitable combined or integrated process concept for the production of a pure enantiomer.

However, for the sake of clarity and since not all options mentioned are equally applicable to each enantiomeric system, the following investigation will be limited to the fundamental concepts sketched in Figure 1.

THREE-STEP APPROACH FOR PROCESS DEVELOPMENT

Different advanced production processes for pure enantiomers were summarized above. It remained unsettled how to select the most suitable concept out of the many alternatives and how to determine the optimal operating conditions for a given production problem. In pharmaceutical process development long-lasting design decisions have to be made at early stages when only limited time and information are available. Aggravating aspects are that chromatographic processes are particularly difficult to design and that design requirements for the units in the process combinations in Figure 1 differ from those for standalone separations.

Therefore, an efficient methodology for the optimal conceptual design of such advanced processes is of high interest. This section introduces a corresponding three-step approach that requires only few discrete pieces of input information.

Step I: Selection of Process Candidates on the Basis of Qualitative Criteria. In the first step, qualitative criteria are applied to identify feasible unit operations and one or more promising combined or integrated processes. This reduces the number of process candidates that have to be investigated further.

The criteria applied are basic physicochemical properties that determine the feasibility and affect the performance of the individual unit operations chromatography, crystallization, and racemization. Most of the input information is typically available at this stage of development.

Decision Tree for Selecting Process Candidates. An initial selection of promising process candidate(s) can be performed using the simple decision tree shown in Figure 2. This is based on experience gained with a large number of industrial compounds. The decision tree is particularly useful since it can be applied before considering specific aspects of individual unit operations.

According to Figure 2 racemization is of special interest. Asymmetric syntheses are considered only if racemization is not feasible. This aspect will be discussed later. If racemization is infeasible, the process options are either the chromatography–crystallization scheme shown in Figure 1b,[9,10,12,15−17] or—if the synthesis is economically attractive—a combination of asymmetric synthesis with crystallization.

The second branch of the tree in Figure 2 applies to racemizable compounds. A racemization should be applied in combination with a resolution that is chosen depending on the crystallization properties of the system. For conglomerate-forming systems that have a eutectic composition at racemic composition (0% enantiomeric excess, ee), preferential crystallization[37−40] is suggested. For the more common compound-forming systems with two eutectics at symmetrical compositions, the position of the eutectic determines which route should be considered. The closer eutectic and racemic compositions are, the higher the achievable per-pass yield of the crystallization in a combined process.[9,10,15−17] On the basis of experience with a number of enantiomeric systems, as a rough approximation for a "reasonable" value, a eutectic ee of 80% and less is proposed. For such favorable systems, the fully integrated process in Figure 1d is suggested that combines chromatography, crystallization and racemization. For systems with a high eutectic ee, it is proposed to combine chromatography and racemization according to the setups in c and e of Figure 1.

If a certain process scheme is for some reason not feasible, the decision has to be revised by taking a different branch in Figure 2.

The proposed decision tree gives clear guidelines that are valid for cost structures typical for the pharmaceutical industry. However, it cannot apply equally well to all enantiomeric systems. It implies in particular that combining a resolution with a racemization is more attractive than asymmetric synthesis. While this is often true,[6,41,42] exceptions can be envisaged. Furthermore, the tree focusses on advanced process concepts only. It could could be extended to include, for example, diastereomeric salt crystallization, dynamic kinetic resolution[43,44] or chiral pool syntheses.

Qualitative Aspects of Integrated Processes. Integrating chromatography and/or crystallization and/or racemization into a single process entails additional aspects that are not relevant in standalone applications. Below the main aspects will be discussed. More specific information on the individual unit operations are found in the literature, including further articles in this issue.[19,25,26,39,40,45−47]

It is important to realize that fully exploiting the potential of the integrated processes in Figure 1b–d requires adjusting

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limited purities, i.e. purity values below 100%, *in the recycle streams*. Consider, for example, chromatography–crystallization in Figure 1b. On one hand, separation efforts in chromatography reduce exponentially when reducing the purity of the stream delivered to crystallization.[10,16,17] On the other hand, lowering this purity also reduces the amount of crystals obtainable by crystallization, since the exploitable distance to the eutectic composition decreases. Due to this interplay there exist optimal values of the "transition purities" between the unit operations in such processes.

As a consequence, the separation units in a combined scheme should not be designed in isolated manner.

Optimal operating policies and design for single units within an integrated process can differ significantly from a standalone application. Considering *chromatography*, within the coupled processes in Figure 1 a cheaper chiral stationary phase (CSP) and solvent can be sufficient than required for a complete separation by standalone chromatography, and higher throughput is achieved by using fewer and shorter columns with less stationary phase and possibly larger particles. Operating enantioselective *crystallization* close to the eutectic composition might require special control of supersaturation and washing policies to guarantee purity. Continuous crystallization appears attractive since it simplifies a direct coupling to the other steps. Efforts in *racemization* can be limited, since complete conversion into the racemate is not required. This allows for faster processing and/or using a cheaper catalyst. Since the synthesized feed is usually expensive, minimizing side reactions or decomposition in racemization is more important than high conversion.

Besides the enantiomers to be processed, the *solvent* is the most important "physical link" between the unit operations and its choice greatly affects process performance.

Finding a globally optimal solvent is basically impossible due to the indefinite number of possible mixtures. Furthermore, a solvent that gives a good performance in one unit might turn out unfavorable or even useless for the next process step. Therefore, one or more "compatible" solvent systems should be identified, which can require additional experiments. The final solvent choice is to be made after evaluating process performance.

In *chromatography*, a "good" solvent provides for an intermediate to high solubility of the enantiomers, high resolution, high loading factor, low pressure drop and sufficient phase stability. In *crystallization*, again sufficient solubility is required. It should be checked if the eutectic composition is depends on the solvent. Supersaturation can be created by changing temperature (preferred method), removing solvent, or by using an antisolvent. A significant solubility change should be achieved by manipulating the corresponding parameter. In *racemization*, a "fast" reaction rate is preferred and stability and recovery of the catalyst must be considered. An interesting option could be not to separate a homogeneous catalyst from the enantiomers, but to allow for its circulation through the separation units. This could be viable if the reaction rate is moderate and, thus, does not prohibit the separation.

Ideally, the same single-component solvent is applicable in all units of a process combination. Also having similar concentration levels in all process steps is attractive. However, usually a compromise must be made and at least a partial solvent removal is necessary between two units. When removing solvent by distillation, using an azeotropic mixture can be attractive. Using nanofiltration instead of distillation could simplify readjusting the solvent's composition after enrichment.

Step II: Process Evaluation Based on Shortcut Methods. The second design stage is to apply shortcut design methods for estimating the performance of the process candidate(s) selected in the first step. Less attractive candidates are then eliminated.

In contrast to rigorous process simulation, shortcut methods do not require all properties of the involved substances and processing steps. In general, they are easy-to-implement, fast and robust and, thus, particularly suited for conceptual design if many process alternatives exist.[48] Based on simplifying assumptions, they provide simple procedures for estimating optimal values for the main design parameters, as well as the amounts and concentrations of the enantiomers in the different streams of a process. Below useful shortcut methods for the different unit operations are summarized.

Shortcut Design of Chromatographic Processes. The design of the chromatographic units in the process schemes in Figure 1 is difficult due to their nonlinear dynamics and periodic operation as well as the limited outlet purities required here.

Simulated moving bed (SMB) chromatography plays an important role in enantioseparations due to its superior performance in comparison to conventional batch chromatography. A detailed design of an SMB process is complex, but the main parameters can be estimated by the "triangle theory" of Mazzotti and co-workers.[49] This predicts optimal values for the internal flow rates and the switching time of an SMB unit. Explicit solutions exist for completely separating a racemate into the pure enantiomers, if they adsorb according to linear or Langmuir isotherms,[49] and a simple numerical procedure for the bi-Langmuir isotherms frequently applied in enantioseparations.[50] A further simplified explicit version of the latter was proposed recently.[51]

Since they hold for complete separation, the methods above are suited for designing standalone SMB separations as in Figure 1(a). The processes in Figure 1(b-d) require limited outlet purities. For such cases, explicit procedures exist for linear isotherms,[52,53] and a numerical procedure was given for Langmuir systems.[54]

Another chromatographic concept that can achieve a better performance than batch chromatography is steady state recycling (SSR).[7,8,55] This process performs a clever internal recycling. Simple shortcut methods exist for Langmuir isotherms,[55,56] and for favorable isotherms in general, also under arbitrary purity requirements.[51] The latter method was applied to the separation of the 2′,6′-Pipecoloxylidide enantiomers (PPX) described in the same issue.[26]

Chromatograms for conventional batch chromatography can be predicted explicitly for some isotherm types. Options and models for this can be found in the standard literature.[57]

An extension of the triangle theory exists for designing reactive SMB-based processes as in Figure 1e.[58]

Except for the SSR design method,[51] the mentioned methods require knowing the adsorption isotherms. These can be determined by simple standard experiments.[59]

Finally, it should be noted that not for all cases a shortcut design method exists, in particular not for limited purity requirements. In such case it is recommended to revert to simplified process models, like the True moving bed (TMB) model applied in the last section of this manuscript, or to one of the various available simulation tools.

Shortcut Design of Crystallization, Racemization, and Solvent Removal. In the context of this work chromatography is assumed as the performance-limiting process step. Thus, the process steps racemization, crystallization and solvent removal are described by simple steady state mass balances.

For enantioselective crystallization it is sufficient to calculate the amounts and purities of the crystals and the mother liquor as a function of the feed purity and the adjusted composition of the mother liquor. The optimal value for the latter is the eutectic composition. Corresponding simple explicit expressions are given in.[16]

For racemization it is sufficient to specify the desired conversion and possible losses due to side reactions. Solvent removal steps can be assumed as "ideal switches" from one solvent to another. Specifying the required concentration in the new solvent allows for calculating the amounts of liquids to be processed.

The mass balances can be extended by kinetic expressions for crystal growth and reaction rates. This facilitates estimating residence times, catalyst amounts and equipment size. Chromatographic columns can be scaled up by simple relations in combination with expressions for pressure drop and column efficiency.[10]

Shortcut Design of Combined Processes. Process combinations can be designed by combining the shortcut methods for the individual steps above. Goal is to determine all relevant mass streams within the complete flow sheet and to obtain an initial performance evaluation against simple performance criteria or a cost function.

A possible approach is to perform parametric studies by varying systematically requirements and operating parameters. Most relevant for combined processes are the purities of the chromatographic outlets and that of the mother liquor in crystallization, the conversion and yield in racemization and, for example, the injection volume in batch or SSR chromatography. On such basis a shortcut design method was proposed for SMB-crystallization processes.[10,16,17] This can be extended to include also a racemization.[26]

An alternative to parametric studies the individual shortcut methods can be implemented into a single mathematical formulation. This can then be subjected to an optimization. Also simplified models of the complete process can be implemented, for example on the basis of simple stage and CSTR balances as discussed in the next section.

Step III: Process Development Based on Optimization Methods. In the third design step mathematical optimization is applied to determine the optimal operating conditions for the remaining process candidate(s). As will be explained below, this approach can be extended to simultaneously determine also the optimal process configurations.

Generally different options exist for developing a production process. The process setup can be chosen based on intuition and experience, possibly using additionally heuristic rules and qualitative quidelines like given earlier. Required operating parameters might be found by trial and error, either experimentally or using a model. This can be extremely time-consuming and inherits the risk of determining suboptimal conditions.

It is therefore more expedient to perform as a final step of process design a rigorous optimization on the basis of suitable mathematical process models. While this is common practice in the chemical industries, it is less commonly applied in pharmaceutical process development.

A general mathematical formulation of such problem can be written as

$$\begin{aligned} &\min f(\bar{x}, \bar{y}) \\ &\text{s.t. } h(\bar{x}, \bar{y}) = 0 \\ &\quad g(\bar{x}, \bar{y}) \leq 0 \end{aligned} \tag{1}$$

Equation 1 formulates the task of minimizing an objective or cost function, f, that depends on two types of variables x and y (see below). Equality constraints guarantee the fulfillment of the process model equations, h. The (in)equality constraints g specify process requirements such as minimum purities or yields. h and g are given here in implicit form.

The formulation in eq 1 allows tackling two different design problems. The first is to determine *optimal operating conditions* for a *known process setup* by minimizing the objective function $f(\bar{x})$. The vector $\bar{x}$ contains all adjustable operating conditions as real-value variables, for example, flow rates and temperatures. Since model equations for chemical processes are typically nonlinear, this is denoted as nonlinear programming (NLP) problem.

The second type of problem is to determine *simultaneously* optimal operating parameters *and* the optimal process setup. In addition to the operating conditions in $\bar{x}$, a vector $\bar{y}$ is introduced that contains an integer or, in this work, binary decision variables. These take a value of either 0 or 1, $y = 0,1$. A value of $y_k = 1$ denotes that a certain stream or process steps k exists, while $y_k = 0$ marks its absence. On this basis a so-called superstructure can be implemented that inherits all interesting process setups. Out of these the optimization determines the optimal one. This type of problem is known as mixed-integer nonlinear programming (MINLP).

Solving NLP and MINLP problems requires a suitable programming environment with corresponding solvers. Here we apply the program package GAMS.[60,61] However, there exists a number of environments and solvers for such problems, in particular for NLP tasks.

The application of both NLP and MINLP to the development and design of improved production processes for a pure enantiomer is demonstrated in the next section.

CASE STUDY FOR THE INDUSTRIAL COMPOUND 2′,6′-PIPECOLOXYLIDIDE

2′,6′-Pipecoloxylidide (PPX) is an intermediate in the manufacture of several anaestethics. It has a number of properties that make its production by an integrated process interesting. A process combination for the production of the pure *S*-enantiomer by SSR chromatography, metal-catalyzed racemization, and enantioselective crystallization is described in this special section.[26]

Here we demonstrate the application of the proposed three-step approach to the development of improved production processes for PPX. In contrast to the mentioned work, focus is on the methodology for evaluation of competing process concepts. Furthermore, considered process concepts employ the powerful SMB technology.

Step I: Selection of a Process Concept Based on Qualitative Criteria. In the first design step, qualitative criteria are applied to identify promising process candidates for producing enantiopure PPX. Since PPX can be racemized by metal catalysis or stoichiometric base, the concepts in the right branch of the decision tree in Figure 2 are of interest. PPX is a

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compound-forming substance, i.e. it has two eutectics at symmetrical compositions. The value of the eutectic purity of about 67% can be seen as favorable for applying a process combination. On the basis of this property, the decision tree suggests a process combination consisting of chromatography, crystallization, and racemization as illustrated in Figure 1d. Since the statement of a "reasonable" eutectic composition is not quantitative, the chromatography–racemization process in Figure 1c is also an interesting candidate.

The chromatographic separation can be performed using a mixture of dibutylether (DBE) and ethanol as eluent. The solubility of the racemate in this solvent is about 75 g/L at 25 °C. Crystallization and racemization catalyzed by Shvo's catalyst are performed in pure DBE. The solubilities in DBE at 25 °C are 0.729 wt % for the pure enantiomer, 0.84 wt % for the racemate, and 0.987 wt % for the eutectic composition, respectively. Two partial solvent adjustments are required to completely remove ethanol before crystallization and racemization. Ethanol is added again to the recycle streams towards chromatography.[26]

Step II: Process Evaluation Based on Shortcut Methods. After identifying a chromatography–crystallization–racemization process as the most promising option, in a second step the possible performance should be evaluated using a corresponding shortcut method.

For this purpose the competitive adsorption isotherms of the PPX enantiomers were determined.[26] These might be characterized as "approximately favorable", with the exception of an inflection point for the stronger adsorbing *R*-enantiomer at low concentration. Proper description requires using the quadratic isotherm model in eq 8 and Table 3 in Appendix A.[26]

For this type of isotherm, a shortcut method exists to design SSR chromatography.[51] This could be applied even without knowing the isotherm parameters. The method was applied successfully by von Langermann et al.[26] to design the SSR process within the mentioned process combination.

However, there exists no simple explicit shortcut method for an SMB process with limited outlet purity and quadratic isotherms. A possible work-around is to perform parametric studies using available simulation software for SMB processes or developing a corresponding SMB or TMB model. The latter can be extended by mass balances for the other unit operations. This approach was applied here. However, instead of performing expensive parametric studies, we apply this model directly in optimization studies as described in the next section.

Step III: Process Design Based on Optimization Methods. *Design Studies Based on NLP Optimization.* In a third step mathematical optimization is applied to determine optimal process configurations *and* optimal operating conditions. First, focus is on NLP optimization to determine optimal operating conditions for given process configurations. Although in the first step of the design methodology only the two configurations chromatography–crystallization–racemization and chromatography–racemization were identified as promising candidates, the study below covers also further alternative setups. Process configurations to be considered comprise the following:

(i) stand-alone SMB process according to Figure 1a
(ii) three different types of SMB processes with crystallization, Figure 1b, namely:
  (a) SMB with a crystallizer at the raffinate (product stream)
  (b) SMB with a crystallizer at the extract (waste stream)
  (c) SMB with a crystallizer at the raffinate as well as the extract
(iii) SMB with racemization, Figure 1c
(iv) SMB with racemization and crystallization at the raffinate outlet, Figure 1d

For comparing and evaluating the different process candidates on a common basis, a suitable cost function and suitable process models are required. The process models used in this study are described in Appendix A. Since focus is on a conceptual study, the SMB unit is approximated by a true moving bed (TMB) model. Conversion of the TMB parameters obtained from the conceptual study to SMB plant parameters is discussed afterwards.

In the following, focus is on the cost function f provided in the optimization problem, eq 1. A detailed economic evaluation of different process candidates will depend on company-specific cost structures and is therefore clearly beyond the scope of this paper. Instead a simplified cost function is applied to elucidate and discuss the main effects of process integration. It is worth mentioning, however, that an implementation of much more detailed cost functions into the optimization framework described below is straightforward and has been accomplished for undisclosed case studies within the INTENANT project.

Costs are measured in money units per kg of product, i.e. [MU/kg product]. The cost function used here comprises cost contributions due to feed cost C_f, personal costs C_{op}, and investment costs C_{inv} according to

$$f = C_f + C_{op} + C_{inv} \tag{2}$$

Feed and investment costs depend on the amount of racemate to be processed M_{rac} in kg racemate/h, personal costs are fixed in a given time frame leading to

$$f = \frac{(w_f + w_{inv})M_{rac} + w_{op}}{YM_{rac}} = \frac{(w_f + w_{inv})M_{prod}/Y + w_{op}}{M_{prod}} \tag{3}$$

with cost or weighting factors w_f in [MU/kg racemate], w_{inv} in [MU/kg racemate] and w_{op} in [MU/h]. $M_{prod} = YM_{rac}$ in [kg product/h] is the amount of desired enantiomer produced, with Y being the yield.

Inspecting the expression in eq 3, one observes that at low production rates M_{prod} the personal costs are dominating and tending to infinity as the production rate goes to zero. At high production rates the other costs are dominating and tending towards the asymptotic value $(w_f + w_{inv})/Y$.

In the remainder some basic principles of process combinations will be discussed. First, focus is on the effect of racemization. For that purpose, a stand-alone SMB chromatographic unit as in Figure 1a is compared with a coupled process, where the undesired enantiomer is racemized and subsequently fed back to the SMB unit according to Figure 1c. In the PPX example the undesired enantiomer is obtained at the extract outlet of the SMB.

The main effect of the racemization is an increase of the overall yield from 50% in the stand-alone SMB to a maximum of 100% in the coupled process. It is worth noting that this effect on the simple cost function can be readily predicted without knowing the optimal process conditions, i.e. without optimization. The effect is illustrated in Figure 3 as a function

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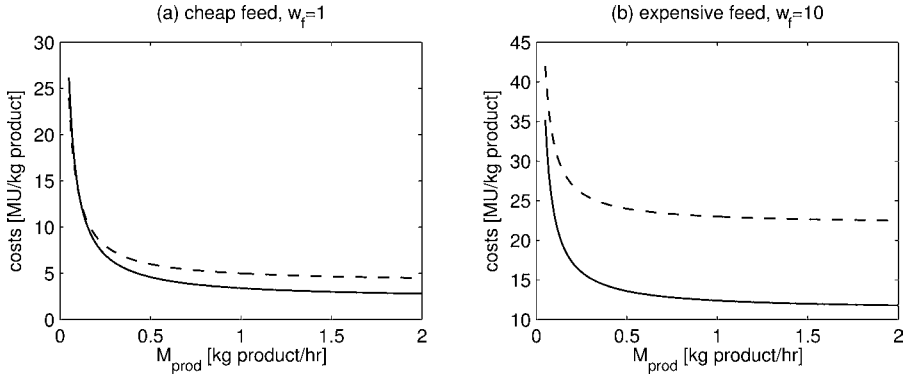

Figure 3. Costs as a function of production rate of a stand-alone SMB as in Figure 1a (dashed line), compared to an SMB process coupled with a racemizer as in Figure 1c (solid line) for two different feed cost scenarios.

of the production rate. For illustration purposes equal cost factors w_p, w_{inv}, w_{op} of 1.0 are assumed for the stand-alone process, whereas a 20% increase in investment and operational costs are assumed for the racemization (i.e., w_{inv},w_{op} = 1.2 for the coupled process) in Figure 3a). At low production rates personal costs are dominating, overcompensating the gain through an improved overall yield. At high production rates the other costs are dominating, leading to a significant cost reduction for the coupled process. In between, there is a break-even point at a production rate of 0.1 in Figure 3a. The difference between stand-alone and coupled process increases with increasing feed costs as illustrated in Figure 3b for w_f = 10, shifting the break even point to even lower production rates not shown anymore in Figure 3b.

Cost reduction for the coupled process will tend to a maximum of 100% for increasing production rates and increasing feed costs due to a 100% increase of yield compared to the standalone process.

Additional potential for improvement of the coupled process follows from the fact that purity requirements for the feed to the racemizer can be relaxed, leading to an increase of productivity of the SMB unit. However, to quantify this effect, rigorous optimization of the coupled process is required. Details will be discussed later.

A similar effect is observed when selective crystallization is coupled to an SMB unit to "share the separation workload" between the two processes as illustrated in Figure 1b. The overall yield is not affected by the hybrid separation process, but coupling purities can be relaxed, leading to an increased productivity of the SMB sub unit in this coupled process. Further, investment costs for the chromatographic columns may be reduced due to reduced purity requirements, and finally also the solvent consumption can be reduced. To elucidate the main effects, solvent issues are neglected in the remainder but could be included easily in a more detailed cost evaluation.

To quantify the above mentioned effects for PPX a parametric optimization study is presented in Figures 4−6 using the models and parameters described in Appendix A. For the optimization the models were implemented in the modeling language GAMS.[60,61] CONOPT was used for NLP optimization. In all three cases a fresh feed concentration of 25 g/L of racemate is used, which was found optimal for the present system due to the rather specific adsorption behavior described in Appendix A.

Figure 4 shows the maximum production rate of a stand-alone SMB chromatographic unit, Figure 1a, compared to a

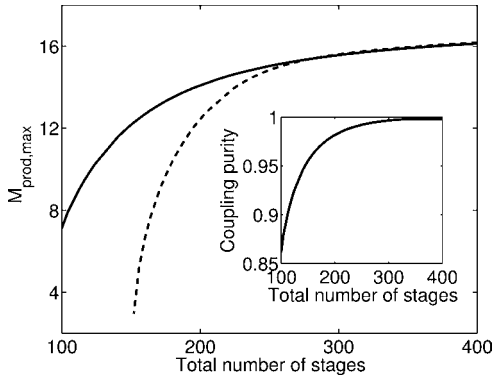

Figure 4. Maximum production rates and coupling purity as a function of the total number of theoretical stages of a standalone SMB (dashed line) compared to an SMB process with a crystallizer at the raffinate.

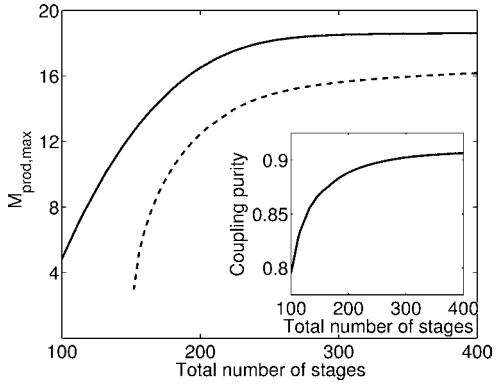

Figure 5. Maximum production rates and coupling purity as a function of the total number of theoretical stages of a stand-alone SMB (dashed line) compared to an SMB process with a crystallizer at the extract.

coupled SMB-crystallization process according to Figure 1b, where the crystallizer is located at the product, i.e. the raffinate, port. The maximum production rate was obtained by rigorous optimization for different numbers of theoretical stages of the SMB unit. Further, the corresponding coupling purities between the SMB unit and the crystallizer are shown. For the optimization outlet purities of the SMB were fixed to 99.8%. Coupling purities were restricted to a range between the eutectic composition at 67.5% and 99.8%.

From Figure 4 a large difference between the stand-alone SMB and the coupled process is observed for moderate numbers

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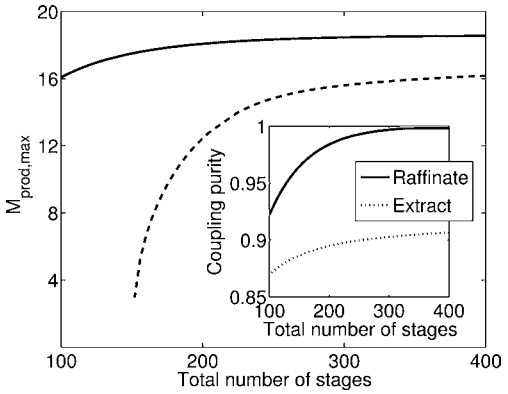

Figure 6. Maximum production rates and coupling purity as a function of the total number of theoretical stages of a stand-alone SMB (dashed line) compared to an SMB process with two crystallizers connected to the raffinate and the extract, respectively.

of theoretical stages below 300. For a fixed number of 160 theoretical stages, for example, the maximum production rate of the coupled process is almost 2 times higher compared to that of the stand-alone SMB. Alternatively, if the production rate is fixed in Figure 4, the number of theoretical stages can be reduced significantly for the coupled process compared to the stand-alone SMB. In the remainder, the total number of theoretical column stages will be fixed to 160.

Similar effects can be observed in Figure 5, where the SMB is coupled to a crystallizer at the extract outlet, i.e. the port delivering the undesired enantiomer, and in Figure 6 where each of the two outlets is coupled to a crystallizer.

Now, after illustrating the basic effects, the effect of various process combinations mentioned above on the simplified cost functions will be evaluated in detail by means of rigorous NLP optimization. Results are given in Table 1. Cost factors w_p, w_{inv}, w_{op} for the SMB unit are assumed to be equal to 1. Again, for the racemization a 20% increase in investment and operational costs are assumed. Since crystallization is required anyhow in most cases to obtain crystalline products, no extra costs for the crystallization were taken into account.

Table 1. NLP calculations for PPX for a total number of 160 theoretical stages

process	objective function	optimal production rate	raffinate, extract purity
SMB	4.301	3.315	99.8, 99.8
SMB - cryst. (raff.)	4.158	6.330	96.3, 99.8
SMB - cryst. (extr.)	4.148	6.735	99.8, 87.3
SMB - cryst. (raff. & extr.)	4.113	8.831	97.0, 88.8
SMB - rac.	2.364	7.289	99.8, 79.0
SMB - rac. - cryst.	2.318	10.211	96.2, 74.4

Rigorous optimization results presented in Table 1 are fully consistent with our earlier discussion. Namely, productivity of the overall process can be increased significantly if a crystallizer is coupled to the SMB process. Although the effect on costs is moderate for the present somewhat arbitrary cost model. It can be much more pronounced if operational (personal) costs have a stronger weight. The strongest improvement is observed for the racemization, which almost gives 100% cost reduction. Besides increased overall yield by factor 2, an additional increase in the optimal production rate is observed due to reduced coupling purity as discussed above.

MINLP Optimization. To determine optimal operating conditions and optimal process structures simultaneously, mixed integer nonlinear (MINLP) optimization can be applied. While MINLP was used successfully to synthesize classical heat exchanger networks and distillation sequences,[62] it has hardly been applied to the class of processes considered in the special section of this issue. Exceptions are reported in Kawajiri and Biegler[63,64] for the design of advanced operating modes for SMB processes and in García et al.,[30] where optimal integration of racemization and SMB chromatography is studied. There, a new process is identified, which delivers a pure enantiomer from a racemate with almost 100% yield in a single step. Note, that such an advanced process concept, however, is beyond the scope of this work and is therefore not included in the present discussion.

The optimization of process structures with MINLP optimization is based on a superstructure which includes all process configurations of interest. Specific process configurations are generated from this superstructure by means of binary decision variables $y_i \in \{0,1\}$, cf. eq 1. The superstructure to be discussed below is shown in Figure 7. In this figure, SR stands for solvent removal, SM for solvent make up, rac for racemization, and crys for enantioselective crystallization. The binary decision variables y_i with i = RR,RO,RC,EC,ER,EO also shown in Figure 7 specify, whether the corresponding flow rate is zero ($y_i = 0$) or finite ($y_i = 1$). In this notation, the first index refers to the raffinate (R) or extract (E) outlet of the SMB, whereas the second index refers to the type of process connected to this outlet, i.e. R for racemizer, C for crystallizer, and O for an outlet, i.e. if no further processing step is connected to the stream.

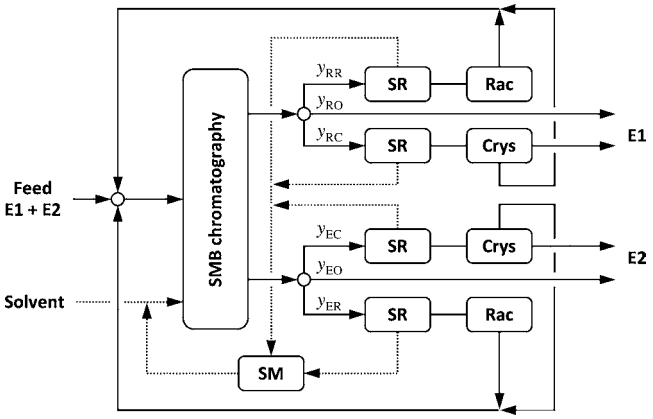

Figure 7. Superstructure inheriting the different process configurations as considered in the MINLP calculations. E1, E2 denote the two enantiomers; the y values mark the decision variables that define the process setup.

In the present case additional constraints have to be taken into account according to

$$y_{RR} = 0, \sum_i y_{R,i} = 1, \sum_i y_{E,i} = 1 \quad (4)$$

meaning that exactly one flow is active at the raffinate and extract side and that no racemizer is used at the raffinate side, where the desired enantiomer is obtained with high purity. It is worth noting that the number of stages for the SMB unit can be

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optimized in a similar way with additional binary decision variables, which specify whether a tray in a given SMB superstructure is active or not. For simplicity, however, focus in the following is on a fixed total number of 160 stages as in the previous section.

For the MINLP optimization the simplified cost function from the previous section is extended to account for the various process combinations in an explicit way. The extended cost function reads

$$f = \frac{(w_f + w_{inv})M_{rac} + w_{op}}{((1 - y_{ER})0.5 + y_{ER}Y)M_{rac}} \quad (5)$$

with

$$w_{inv} = w_{inv,SMB} + y_{RC}w_{inv,RC} + y_{EC}w_{inv,EC} + y_{ER}w_{inv,ER}$$

and

$$w_{op} = w_{op,SMB} + y_{RC}w_{op,RC} + y_{EC}w_{op,EC} + y_{ER}w_{op,ER}$$

besides feed costs w_f it comprises investment costs of the SMB process $w_{inv,SMB}$, a possible raffinate $y_{RC}w_{inv,RC}$ and/or extract crystallizer $y_{EC}w_{inv,EC}$, and a possible extract racemizer $y_{ER}w_{inv,ER}$. Additional operational costs are covered in an analogous way. Again, feed and investment costs are proportional to the amount of racemate M_{rac} to be processed. Further, it should be noted that the formula for the production rate in the denominator also admits racemization with overall yields smaller than 100%.

At this point it is important to note that the optimal process configuration crucially depends on the specific cost factors of the different contributions in eq 5. The decision tree presented above is based on practical experience and is valid for some characteristic cost structures often observed in pharmaceutical industry. In individual cases or different fields of application, however, cost structures may deviate from this average, giving rise to other optimal process configurations. For a given cost function these can be determined directly by MINLP optimization. Examples are given in Table 2.

Table 2. MINLP calculations for PPX for a total number of 160 theoretical stages[a]

optimal process	$w_{inv,ER}$	$w_{inv,EC}$	$w_{inv,RC}$	$w_{op,EC}$	$w_{op,RC}$	Y_{rac}
SMB - rac. - cryst.	0.2	0.0	0.0	0.0	0.0	1.0
SMB - rac.	0.2	0.2	0.2	0.2	0.2	1.0
SMB - cryst. (raff. & extr.)	0.5	0.0	0.0	0.0	0.0	0.7
SMB	0.5	0.2	0.2	0.2	0.2	0.7
SMB - cryst. (extr.)	0.5	0.0	0.2	0.0	0.2	0.7
SMB - cryst. (raff.)	0.5	0.2	0.0	0.2	0.0	0.7

[a]All MINLP calculations were performed in GAMS using the DICOPT MINLP solver with CPLEX for the MILP sub-problems and CONOPT for the NLP sub-problems. The following constant values were used for the cost factors not listed in the table: $w_f = 1.0$, $w_{inv,SMB} = 1.0$, $w_{op,SMB} = 1.0$, $w_{op,ER} = 0.2$.

The process configuration given in the first line of Table 2 is obtained when using the same weighting factors as in the cost function as in the previous section. According to the expectation, SMB plus racemization at the extract and crystallization at the raffinate is the best configuration, if—following our earlier arguments—no additional costs for the crystallization are taken into account. In the second line, additional investment and operating costs for crystallization are considered ($w_{inv,RC} = w_{inv,EC} = 0.2$, $w_{op,RC} = w_{op,EC} = 0.2$). This overcompensates the benefit of potential crystallizers leading to an elimination of the crystallizers in the optimal process structure denoted in the first row. In a similar way, the racemizer will be eliminated for an expensive racemization ($w_{inv,ER} = 0.5$, $w_{op,ER} = 0.2$) with reduced yields ($Y_{rac} = 0.7$) in line 3. High investment costs may be due to expensive catalyst, for example. Both racemizers and crystallizers will be eliminated if the previously used "penalties" for the crystallizers are added, leading to the stand-alone SMB process as optimum in line four. In a similar way, the combinations of the SMB unit with a crystallizer at the extract or the raffinate are obtained in lines 5 and 6 of Table 2 for an expensive racemization with low yield, if the respective other crystallizer is penalized with high costs. The two latter examples are a bit artifical, but are useful to demonstrate the full capacity of the MINLP optimization employed here.

To summarize, the MINLP approach was demonstrated to yield each of the possible process configurations inherited by the superstructure in Figure 7. The optimal process configuration depends on the specific cost structure represented here by corresponding values for the various weighting factors.To the best of our knowledge this is the first time that MINLP has been applied to this kind of process synthesis problem. An extension to synthesis problems from other fields of application appears straightforward.

Scale-Up and Transformation to SMB Processes. The optimization results above were obtained using TMB models. The most relevant design parameters of TMB processes obtained from the optimization are the dimensionless ratios of liquid and solid flow rates in each of the four zones of such unit.[49] These data have to be "translated" into the main design variables for a corresponding SMB process, which are the four internal flow rates, the switching time, the column length, and column diameter.

These data can be obtained using a simple scale-up procedure once a value for the desired throughput has been specified.[10] In addition to specifying the throughput, i.e. the feed flow rate, correlations for pressure drop and column efficiency have to be determined from simple experiments. These are typically linear functions of the interstitial fluid velocity. Demanding the same stage number as in the TMB calculations and operation at maximum tolerable pressure drop allows calculating the remaining SMB design variables. These can then be validated by simulation with detailed dynamic SMB models.

These scale-up relations can also be implemented directly into the optimization problem which facilitates using more detailed cost functions that also consider, for example, investment costs as function of column size and geometry.

More rigorous results can be obtained by an optimization using a full-blown dynamic SMB model as performed as NLP for an SMB-crystallization process[15] and as MINLP for reactive SMB processes.[30] Such a time-consuming procedure is suitable, however, for a detailed design and is beyond the scope of this work.

CONCLUSIONS

A number of promising process concepts exists for developing economically more efficient productions of pure enantiomers. An efficient three-step methodology was proposed that aids a fast selection of the optimal process concept and its optimal design for a given production problem in a pharmaceutical development environment.

In a first step, simple qualitative criteria and information are applied to identify the most promising process candidate(s).

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Subsequently, shortcut methods are, if available, applied to obtain a fast performance evaluation and to narrow down further the number of process options. In the final step, rigorous model-based optimization is used to obtain an optimally designed process.

The approach was applied to design a process combination for the production of pure 2′,6′-pipecoloxylidide. A detailed optimization study using TMB-based process models confirmed the suggested procedure. A general evaluation of the different process options is already possible on the basis of simple cost functions. However, the results also indicate the dependency of the optimal process configuration on the specific cost structure.

For the first time mixed-integer nonlinear programming (MINLP) was applied to this type of problem. It was found to be capable of identifying simultaneously the optimal process configuration and optimal operating conditions as functions of the cost structure. This approach appears particularly useful for applications where it is difficult to establish the optimal process setup on the basis of experience or intuition.

APPENDIX A: MODEL EQUATIONS

For the PPX optimization studies in this paper, the following model equations were used.

SMB chromatography was modeled with a steady state true moving bed (TMB) equilibrium model, according to

$$\dot{Q}_{\text{solid}}[q_{i,k+1} - q_{i,k}] + \dot{Q}_{k-1}c_{i,k-1} - \dot{Q}_k c_{i,k} + \dot{Q}_{\text{ext}}c_{i,\text{ext}} = 0 \quad (6)$$

$$\dot{Q}_{k-1} - \dot{Q}_k + \dot{Q}_{\text{ext}} = 0 \quad (7)$$

where $\dot{Q}_{\text{ext}}$ refers to possible external streams due to feed, desorbent, extract, or raffinate. k is the stage index, i = S-PPX,R-PPX is the component index. Without loss of generality $\dot{Q}_{\text{solid}}$ is set to 1 for the TMB calculations.

Adsorption equilibrium for PPX is described by the following quadratic isotherm[26]

$$q_i = q^I_{\text{sat}} \frac{b^I_i c_i + 2b^q_i c_i^2 + c_S c_R(b^m_S + b^m_R)}{1 + \sum_j b^I_j c_j + \sum_k b^q_k c_k^2 + c_S c_R(b^m_S + b^m_R)} + q^{II}_{\text{sat}} \frac{b^{II}_i c_i}{1 + \sum_l c_l} + \lambda c_i \quad (8)$$

with i = S-PPX,R-PPX. Parameters for PPX enantiomers are listed in Table 3.

Table 3. Parameter values for the adsorption isotherms of PPX enantiomers

parameter	unit	S-PPX	R-PPX
q^I_{sat}	[g/L]	46.78	
b^I_i	[L/g]	0.10351	0.20556
b^q_i	[L/g]	0.00555	0.02581
b^m_i	[L/g]	0.00334	0.01555
q^{II}_{sat}	[g/L]	64.66	
b^{II}_i	[l/g]	0.03162	1.63×10^{-8}
λ		0.6331	

For the other units, simple mass balances have been applied. The governing equations for the enrichment step before the crystallizers and racemizers can be written as

$$\dot{Q}_{\text{ext}} = \dot{Q}_{\text{evap}} + \text{SR} \quad (9)$$

$$\dot{Q}_{\text{ext}}c_{i,\text{ext}} = \dot{Q}_{\text{evap}}c_{i,\text{evap}} \quad (10)$$

where $\dot{Q}_{\text{ext}}$ refers to the corresponding product stream from the SMB unit and SR is a solvent removal, which is adjusted for the crystallizers in such a way that the resulting composition lies on the boundary of the corresponding two-phase region. For the racemizer it is adjusted in such a way that the concentration of the recycle from the racemizer is equal to the concentration of the fresh feed.

The racemizer is modeled as a continuous stirred tank reactor with an isomerization reaction according to.

$$\dot{Q}_{\text{evap}} = \dot{Q}_{\text{reac}} \quad (11)$$

$$\dot{Q}_{\text{evap}}c_{i,\text{evap}} = \dot{Q}_{\text{reac}}c_{i,\text{reac}} - \nu_i V_{\text{reac}} k_{\text{forward}} [c_{R\text{-PPX,reac}} - c_{S\text{-PPX,reac}}] \quad (12)$$

For the calculation a high value of $V_{\text{reac}}k_{\text{forward}}$ of 10^7 was assumed, which is close to thermodynamic equilibrium. ν_i is the stoichiometric coefficient, which is equal to +1 for the desired S-enantiomer and −1 for the undesired R-enantiomer.

The crystallizer is assumed to be a mixed-suspension/mixed-product removal (MSMPR) crystallizer operating at steady state. It is assumed that the crystallizer delivers pure crystalline product. The change in flow rate due to crystallization is neglected. The mass balances are

$$\dot{Q}_{\text{evap}}c_{1,\text{evap}} = \dot{Q}_{\text{ML}}c_{1,\text{ML}} + \text{crystal} \quad (13)$$

$$\dot{Q}_{\text{evap}}c_{2,\text{evap}} = \dot{Q}_{\text{ML}}c_{2,\text{ML}} \quad (14)$$

In this notation component 1 is the component which is selectively crystallized. ML stands for the mother liquor. The composition of the mother liquor is assumed to be the eutectic composition, which is 67.5% in the present study.

After crystallization diluent is added again to the recycle stream in such a way that the recycle concentration of the more concentrated component should be equal to external feed concentration.

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