Organic Process Research & Development **1998**, *2*, 305−319

Comparison of Batch Elution and Continuous Simulated Moving Bed Chromatography

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Abstract:

The production of chirality with maximum economy is one of the most challenging tasks of today's pharmaceutical industry. Apart from the use of inherent chirality (starting material from the chiral pool, e.g., amino acid derivatives, carbohydrates), the creation of chiral centers via biocatalysis or asymmetric synthesis is commonly used. Another way to obtain pure enantiomers is the separation of racemates via kinetic resolution through preferred crystallization or preparative chromatography on chiral stationary phases. This paper emphasizes this last method, explains the possibilities of this technique, especially in its application form as simulated moving bed (SMB) chromatography, and shows its benefits and limitations. Therefore, comparisons to classical batch elution chromatographic processes as well as other unit operations (such as crystallization, etc.) must take cost calculations into account. In this paper, a theoretical comparison of optimized SMB and batch elution processes by simulation studies based on rigorous process models is presented for the separation of two different binary mixtures. These examples are chosen to demonstrate the different effects which dominate the applications in large-scale isomer separations and production-scale enantiomer separation. The first example is a fructose/glucose separation with linear isotherms. The model parameters are measured by Nicoud. The second characteristic example is an enantioseparation. The corresponding isotherms are of the modified Langmuir type. The performance of each separation process is quantified by three characteristic objective functions: productivity, dilution, and solvent requirement. Last, the specific separation costs or the total costs of separation are calculated as an objective function to lay emphasis on the economy of the separation, including product recovery and solvent recycling. The comparison of these objective functions, which are determined for batch and SMB processes, leads finally to certain rules of consideration to decide what kind of process (either batch elution or SMB) is preferable as a function of the physical properties of the given binary mixture and the separation task.

1. Introduction

The basic separation principles of batch elution and the port movement of the SMB process are shown in Figure 1.

Countercurrent chromatography and especially simulated moving bed (SMB) chromatography have been known for a long time in the petrochemical industry for the separation of C_8 hydrocarbons.[1] The biggest systems produce up to 500 000 tons/year of *p*-xylene. There was never any doubt that SMB chromatography with zeolites or ion exchangers in this scale is the cheapest way to produce these pure compounds. However, there were numerous obstacles to overcome during the adoption of those big production systems to systems of a smaller dimension which would be suitable for the pharmaceutical and fine chemical industry with their typical production range of 1−50 tons/year at high purities (up to 99.9%). During the last five years, a lot of work was done to scale down the systems and optimize them for the production of pharmaceuticals.[2−5] In 1997 the first SMB unit with a production capacity of 40 tons of enantiomer/year was brought to operation.[6]

The principle of SMB chromatography is the simulation of the countercurrent movement of a stationary phase (silica, chiral modified silica, or ion-exchange resins) and a mobile phase. Due to enormous technical problems when continuously moving a solid, the setup of a true moving bed (TMB) is not feasible. Therefore, the chromatographic bed was divided into single columns, connected in series, and closed in a circle (Figure 1). Between each column, four connecting lines are present to allow the withdraw of two product lines (called extract [more retained] and raffinate [less retained]), the input of new feed solution (the educt, to be separated), and the input of fresh mobile phase to desorb the more strongly adsorbed products. All four flows are continuous with previously determined flow rates. After a given time, all four flows are shifted one position into the direction of the mobile phase movement. The feed line is now injecting into the zone of not separated products. After a series of shifts at the front and the tail of the internal concentration profile, pure products can be withdrawn from the system. It has to be pointed out that SMB systems in their normal configuration are systems to separate a feed into two product streams but not necessarily into just two products: the extract or raffinate stream can still consist of several impurities,

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(2) Nicoud, R. M. *LC-GC Int.* **1992**, 5, 43−47.
(3) Francotte, E. R. *Preparative chiral separations by chromatography: A powerful approach for the isolation of optically pure compunds*; Chiral Europe Symposium Proceedings, 1996.
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S1083-6160(98)00019-X CCC: $15.00
Published on Web 07/18/1998

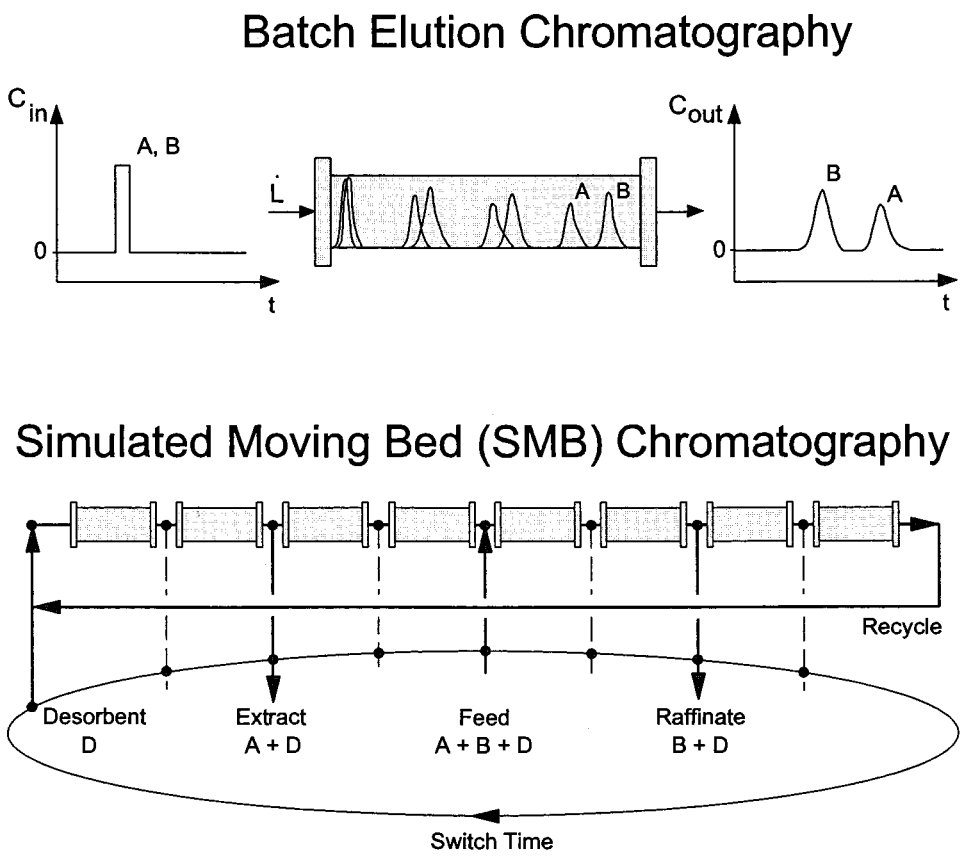

Figure 1. **Funtional scheme of batch elution and simulated moving bed (SMB) chromatography.**

separated from the value product. Through combination of different chromatographic setups, even the isolation of natural products from a big number of byproducts is possible, as it was demonstrated for the separation of cyclosporin A from a fermentation broth.[7]

Since the setup of five different flow rates (mobile phase flow rate, four input/output-line flow rates) and the line-shift timing comprises a highly complex system, it requires rigorous simulation systems which take into account the conditions of technical chromatographic separations. These are nonlinear adsorption isotherms, axial dispersion, and mass transfer resistances as well as the modeling of all parts of the plant. In addition, a high modeling accuracy requires the determination of empirical parameters by characteristic and consistent experiments for the relevant separation problem.

In this paper, a comparison by simulation studies of optimized SMB and batch elution chromatographic processes is presented for the separation of two different binary mixtures. The model parameters are summarized in Table 1. These examples are chosen to demonstrate the different effects which dominate the applications in large-scale isomer separations and production-scale enantiomer separation.

The first example is a fructose/glucose separation with linear isotherms. The model parameters are measured by Nicoud.[2] The second characteristic example is an enantioseparation (abbreviated in the following as EMD53986).[8−10] The corresponding isotherms are of the modified Langmuir type (eq 8).

Table 1. **Model parameters for the fructose/glucose and the EMD 53986 enantioseparation**

model parameters	unit	Nicoud	EN2_1
mass transfer coeff. *A*	[cm/s]	4.50E-04	3.00E-04
mass transfer coeff. *B*	[cm/s]	2.50E-04	2.50E-04
fluid density	[cm^3/s]	1	0.88
dynamic fluid viscosity	[g/cm s]	8.00E-03	4.38E-03
eluent		H_2O	ETAc/ETOH (95/5)
Henry coeff. P_a	[−]		3
Henry coeff. P_b	[−]		1.5
Henry coeff. K_{Fa}	[−]	0.45	8.33
Henry coeff. K_{Fb}	[−]	0.25	2.62
Langmuir coeff. *A*	[cm^3/g]		830
Langmuir coeff. *B*	[cm^3/g]		260
interference coeff. *A*	[cm^3/g]		260
interference coeff. *B*	[cm^3/g]		830
α ($c = c_{Feed}$)	[−]	1.80	1.90229062
$q_{s,maxA}$ ($c = c_{Feed}$)	[g/cm^3]	0.09	0.02557
$q_{s,maxB}$ ($c = c_{Feed}$)	[g/cm^3]	0.05	0.01154813
axial dispersion *A*	[cm^2/s]	4.59E-02	4.50E-04
axial dispersion *B*	[cm^2/s]	4.59E-02	4.50E-04
NLFA	[−]	1	2.214

(7) German Pat., DE 196 11 094 A1; Voigt, U.; Hempel, R.; Kinkel, J. *Chromatographisches Verfahren zur Gewinnung von hochgereinigtem Cyclosporin A und verwandten Cyclosporinen*, C 07 K 1/16, 1997.

(8) Schulte, M.; Devant, R. M.; Jonas, R.; Keil, A. *J. Prakt. Chem.* **1997**, *339*, 315−321.

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The performance of each separation process is quantified by three characteristic objective functions: productivity, dilution, and solvent requirement.

In addition, the specific separation costs or the total costs of separation are calculated as an objective function to lay emphasis on the economy of the separation, including product recovery and solvent recycling.

The comparison of these objective functions, which are determined for batch and SMB processes, leads finally to certain rules of consideration to decide what kind of process (either batch elution or SMB) is preferable as a function of the physical properties of the given binary mixture and the separation task.

Detailed studies of binary mixtures combined with impurities have been done by the authors but are not the topic of this paper. The conclusion is that impurities influence the performance of batch elution and SMB chromatography to the same extent. The difference in process performance is still in the same magnitude.

Of course, these theoretical simulation studies have to be proven by experiments. But, there is no doubt in the literature that the rigoros process modeling approach is more exact than models with simplifying assumptions. Moreover, realistic experimental model parameters are chosen. Therefore, process simulations may function as a standardized reference for theoretical studies. The aim of this paper is to point out advantages/disadvantages and preferable ranges of application of batch elution and SMB chromatography by theoretical studies to show the benefits of both processes due to a standardized methodology. Experimental comparisons have been previously presented in the literature.

2. State of the Art: Previous Comparisons of Batch and SMB Processes

At first, chromatography was only used for analytical purposes. Elution chromatography is likewise applied for separations on the production scale. Because of the discontinuous operation batch chromatography has a demand on a high degree of automation to save personal costs and to run the equipment in a safe and reliable way. In contrast to batch chromatography, the automation of SMB chromatography is far more complex.

Feed and desorbent are injected at different inlets of the column configuration in the same manner that extract and raffinate are taken from different outlets. After a certain period of time ("switch time"), inlets and outlets are switched to the next port (all in the same direction of the fluid flow) while the columns with stationary phase remain fixed. The switching is done by a sequence of valves. The result is a simulated countercurrent flow of solid and liquid.

The driving force of the classic batch chromatographic separation is the different affinities of each adsorptive component in the fluid mixture to the stationary phase.

In the case of SMB processes, the driving force is additionally increased by the basic principle of the (simulated) countercurrent flow. Due to this principle, separations by SMB processes should lead to productivity levels which are much higher than those resulting from batch separations. In addition to this, SMB products should be achieved which are less diluted and with less solvent requirements because the solvent is recycled in the SMB process. Batch elution chromatography is an the one end of productivity range, and a countercurrent process such as SMB chromatography is on the other end. Between these methods exist modifications of batch chromatography such as recycling or peak shaving chromatography and the annular rotationg disk chromatograph, which is a cross-flow process. In this study, we compare the extremes, batch elution and SMB chromatography, to point out the different ranges of application.

Several comparisons of the chromatographic processes are documented in literature[3−5,11−13] which confirm the results discussed above by experimental comparisons. In practical applications, the SMB process is found to achieve productivity levels up to 4 times higher than those achieved by the batch process.[3,13] As a result, the factor of the resulting dilution is about 2−5 times less.

As far as Schulte's investigations[5] are concerned, the solvent requirement of the SMB process can be up to 90% less than that of the corresponding batch separation.

One problem of these current comparisons is shown by Nagamatsu.[13]

In this study the batch process is, in comparison to the SMB, a 4 times less productive separation technique which additionally has a high desorbent requirement, which leads to a solvent requirement 8 times higher. On the other hand, two completely different separations are compared and assumed as equal. However, batch and SMB separations of binary mixtures are compared in this practical study where the feed concentrations differ. This results in a different throughput at different column loadability and in a different yield. The column loadability for example is 2 times higher for the SMB than for the corresponding batch stationary phase. Furthermore, the concentration of the feed in SMB chromatography is 6 times higher than that for the analogous batch process.

Seidel-Morgenstern[12] optimizes batch elution and recycle chromatography in comparison to annular rotating disk and SMB chromatgraphy due to either productivity or product dilution. Therefore, this case study for a single separation example is limited to these boundary cases.

The study of Bauer[11] presents realistic industrial cost relations for SMB chromatography. Shortcut design rules are derived that are in agreement with these theoretical studies as shown later.

Schulte[5] describes the main problem of recent comparisons between batch and SMB technology.

Therein, Schulte reports that the application of SMB technology is connected to the use of simulative process optimization. Only during process development does the SMB process need to be optimized for the special separation problem. In this way, it is taken for granted that the plant

(11) Bauer, J. E. *A Comprehensive Look at Scaling-up SMB Chiral Separations from the Lab to Commercial Production*; ChiraTech Smposium Proceedings, Philadelphia, PA, 1997.
(12) Heuer, C.; Kniep, H.; Falk, T.; Seidel-Morgenstern, *Chem. Eng. Technol.* **1997**, *69*, 1535−1546.
(13) Nagamatsu, S. *Optical resolution of apharmazeutical intermediate by Simulated Moving Bed*; Chiral Europe Symposium Proceedings, 1996.

Table 2. **Process parameters/characteristic numbers**

	fructose/glucose		enantiomers	
	SMB	batch	SMB	batch
	Process Parameters			
concentration feed [g/cm^3]	0.2	0.2	0.00524	0.00254
u_int [cm/s]	0.78	0.78	0.25	0.25
column diameter [cm]	2.54	2.17	2.6	2.24
column length [cm]	94	1800	5.3	100
column number [−]	24	8	1	
segmentation [−]	6:6:6:6	2:2:2:2		
particle diameter [cm]	0.032	0.032	0.001	0.001
void fraction [−]	0.39	0.39	0.4	0.4
column total volume V_kol [cm^3]	11431	6657	225	394
feed [cm^3/s]	0.231		0.08307	
desorbent [cm^3/s]	0.361		0.352	
extract [cm^3/s]	0.277		0.364	
raffinate [cm^3/s]	0.315		0.703	
switch time [s]	207		232.5	
solid flow [cm^3/s]	33.69		0.58093927	
volume flow, batch [cm^3/s]		1.125		0.39
injection time [s]		330		650.00
cycle time [s]		1600		3700.00
pressure drop [bar]	9.9	7.9	31.376	74.00
	Characteristic Numbers			
productivity A [g/g/h]	0.0181	0.0301	0.007452	0.00514
productivity B [g/g/h]	0.0182	0.0302	0.007488	0.0051
dilution A [−]	1.205	2.778	4.40336134	4.45
dilution B [−]	1.361	2.273	0.84516129	0.93
solvent requirement A [g of solv/g of prod]	7.9	19.4	712.2	786.1
solvent requirement B [g of solv/g of prod]	7.8	19.4	710.2	792.4
Ca_Extr. [g/cm^3]	0.166	0.072	0.00119	0.0012
Cb_Raf. [g/cm^3]	0.147	0.088	0.0062	0.0056
yield A [%]	99.3	99.2	99.8	100
yield B [%]	100	99.3	100	99.5
purity A [%]	100	99.2	100	99.5
purity B [%]	100	99.3	100	100

is used efficiently. Batch columns are widely used as "multipurpose" columns that are not optimized to a single application at all. As a result, these batch columns are operated in production with less overload than possible if the process would be optimized as carefully as the SMB process.

The low productivity of batch columns may be just a problem due to the extent the two different technologies are applied and operated correctly. The often extremly unfavourable results of batch chromatography are due to the fact that a fully optimized SMB process is compared with a batch process that is not so carefully optimized.

3. Systematic Comparison by Simulation Studies with Rigorous Process Models

3.1. Basic Assumptions of the Methodology. *A. Comparison of Optimized Processes.* The different applications of the two chromatographic processes and the resulting afore-mentioned comparisons lead to the demand that both batch and SMB processes need to be optimized. Therefore, in this study, as a first step, this process optimization has been done. In the case of SMB processes, it is performed only with regard to maximum feed throughput, minimum solvent requirement, pressure drop, and careful consideration about the breakthrough of the axial profile in the edge sections of the columns. Apart from this, yield and purity are required up to 99%. The optimization strategies for both processes consider that the optimal experimental conditions to reach maximum productivity *and* minimal product dilution between batch elution and SMB processes may strongly differ.

B. Optimized SMB Processes Determine the Conditions for Optimized Batch Processes. On the basis of the optimum SMB process parameters determined by Strube[10,14] (see also Table 2), the batch optimization is done as follows:

First, assumptions must be made as to which process parameters have to remain constant for the sake of comparability.

1. It is obvious that feed concentrations and column loadability have to be the same for the batch and SMB processes. The first rule is to maximize the feed concentrations up to the solubility range (in practice 10% less because of the chromatographic enrichment) in order to get maximal loadibility at minimal flow rates. The next step is to maximize the throughput by increasing the flow rates to their limits.

(14) Strube, J.; Altenhöner, U.; Meurer, M.; Schmidt-Traub, H. *Chem. Eng. Technol.* **1997**, *69*, 328−331.

To minimize the simulation studies to a realistic range and to achieve significant results, the following assumptions are necessary:

2. Yield and purity have to be larger than 99%. Total separation is assumed to define plain optimal operating points of the processes which are definitely comparable. The operating optima should not be affected by the effect of the costs of product losses, because otherwise differing product values as a function of market price, etc., must be taken into account. Moreover, the advantage of chromatography against other unit operations to be operated with minimal product losses should be emphasized.

3. The interstitial velocity u_{int} in the batch column shall be as high as u_{int} in zone I with the maximum liquid flow in the SMB process. The definition of u_{int} is given in eq 1.

$$u_{int} = \frac{4\dot{V}}{\pi\epsilon_0 D^2} \tag{1}$$

The reason for this assumption is that the maximal interstitial velocity of SMB expresses the real limitation of the fluid flow due to pressure drop and mass transfer resistances. This limit is valid for batch chromatography as well. Further optimization in batch chromatography may be possible, but it is guaranteed that the order of magnitude of this extremely complex parameter (which is dominated by mass transfer and fluid dynamic effects) is correct.

4. In addition to this, the feed throughput shall be the same for the batch and SMB processes as shown in the mass balance for the demand of equal throughput (eq 2).

$$\dot{V}_{SMB}\Delta t_{cyc} c_{F_i} = \dot{V}_{Batch}\Delta t_{inj} c_{F_i} \tag{2}$$

5. For optimization of batch processes, a further assumption is necessary to give maximum productivity: The peaks of each component of the binary mixture must touch each other as shown in Figures 5 and 7. This is called the "touching band assumption".

6. The underlying model assumptions which determine that the accuracy of the simulations and

7. the degree of optimization are for both processes the same.

The optimization strategies are described elsewhere in detail.[14−18]

3.2. Systematic Procedures. *1. Parameter Studies.* Starting from this methodology, the batch process is optimized by varying all process parameters such as column diameter, column length, cycle time, and injection time. In addition, the pressure drop must be taken into account, as well as energy costs, constructive requirements, and leakage risks.

2. Rigourous Process Modeling. The optimization of both SMB and batch processes are performed by process modeling using the dynamic process simulation package SPEEDUP (AspenTech., Cambridge, MA) as a modeling tool and numerical solver. To take into account such real effects as axial dispersion and finite mass transfer, rigorous dynamic models are used[14−18] which are characterized by eqs 3 and 4 (fluid and mass balance for a small volume of the column). The process models have been written during the last 6 years at the University of Dortmund.[19]

$$\frac{\partial c_i}{\partial t} = D_i\frac{\partial^2 c_i}{\partial x^2} - u_{int}\frac{\partial c_i}{\partial x} - k_{eff}\frac{6}{d_p}(c_i - c_{p,i})\frac{(1-\epsilon)}{\epsilon} \tag{3}$$

$$\frac{\partial q_i}{\partial t} = k_{eff,i}\frac{6}{d_p}(c_i - c_{p,i}) \tag{4}$$

combined with any multicomponent equilibrium phase isotherm equation.

The progress of the optimization is quantified by three main objective functions which take into account the requirements of solvent, of stationary phase, and of further preparation. These objective functions are productivity (Pro_i), dilution (Di_i), and solvent requirement $(SR)_i$ of a component under the use of the following definitions:

$$Pro_i = \frac{\dot{m}_i Y_i}{m_{ads}}[\text{g of Product/g of Adsorbent/hour}] \tag{5}$$

$$Di_i = \frac{c_{Feed,i}}{c_{ex,i}} \tag{6}$$

$$SR_i = \frac{m_{Solvent}}{m_i} \tag{7}$$

4. Separation Examples

In this paper, the comparison between batch and SMB processes is demonstrated on behalf of two different binary mixtures.

4.1. Example: Large-Scale Separation of Fructose/Glucose. The first separation example is an aqueous fructose/glucose system with linear adsorption behavior on resins. The isotherms are presented in Figure 2, the model parameters are in Table 1. The separation factor has the constant value of 1.8. Table 2 summarizes the optimized process parameters for batch and SMB chromatography.

It is striking that the columns for each process are extremely long. Due to the low separation factor, long columns are needed. Additionally, a relatively high interstitial velocity could be used. Because of good mass transfer in the resins, large particle diameters could be taken. This results in a low pressure drop per meter and in a relatively large HETP per meter.

4.2. Example: Production-Scale Separation of Enantiomers. The second binary mixture, EMD53986, is a racemic mixture with ethyl acetate/ethanol (95/5) as solvent. The liquid−solid equilibrium is described by eq 8.

$$q_i = P_i c_{pi} + \frac{K_{2i} c_{pi}}{1 + K_{3i} c_{pi} + K_{4j} c_{pj}} \tag{8}$$

(15) Strube, J.; Michel, S.; Paul, H.-I.; Schmidt-Traub, H. *Chem. Eng. Tech.* **1995**, *67*, 323−326.
(16) Strube, J.; Schmidt-Traub, H. *Comput. Chem. Eng. Suppl.* **1996**, *20*, S641−646.
(17) Strube, J.; Schmidt-Traub, H. *Comput. Chem. Eng.* In press.
(18) Strube, J.; Brozio, J.; Schmidt-Traub, H. Submitted for publication.
(19) Strube, J. Ph.D. Dissertation, University of Dortmund, Germany, 1994.

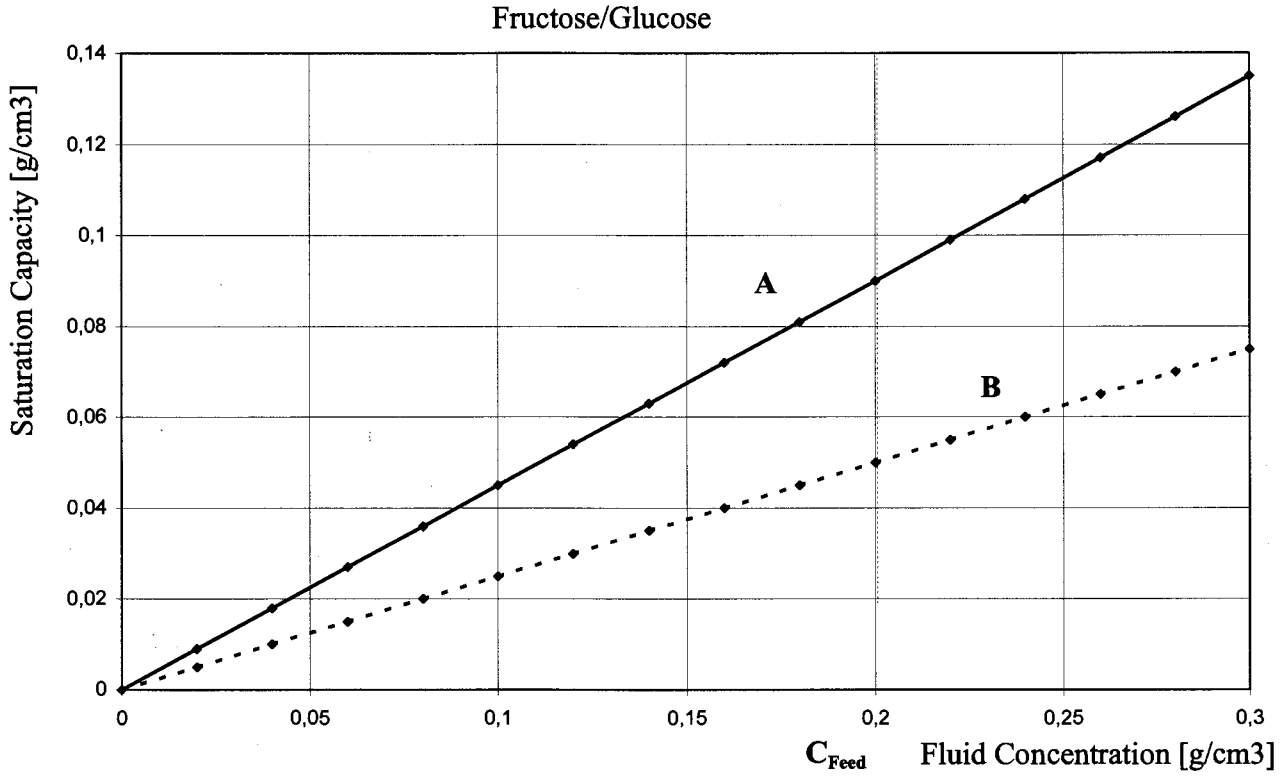

Figure 2. **Isotherms of fructose/glucose separation. Details are given in ref 1. Fructose (A); glucose (B).**

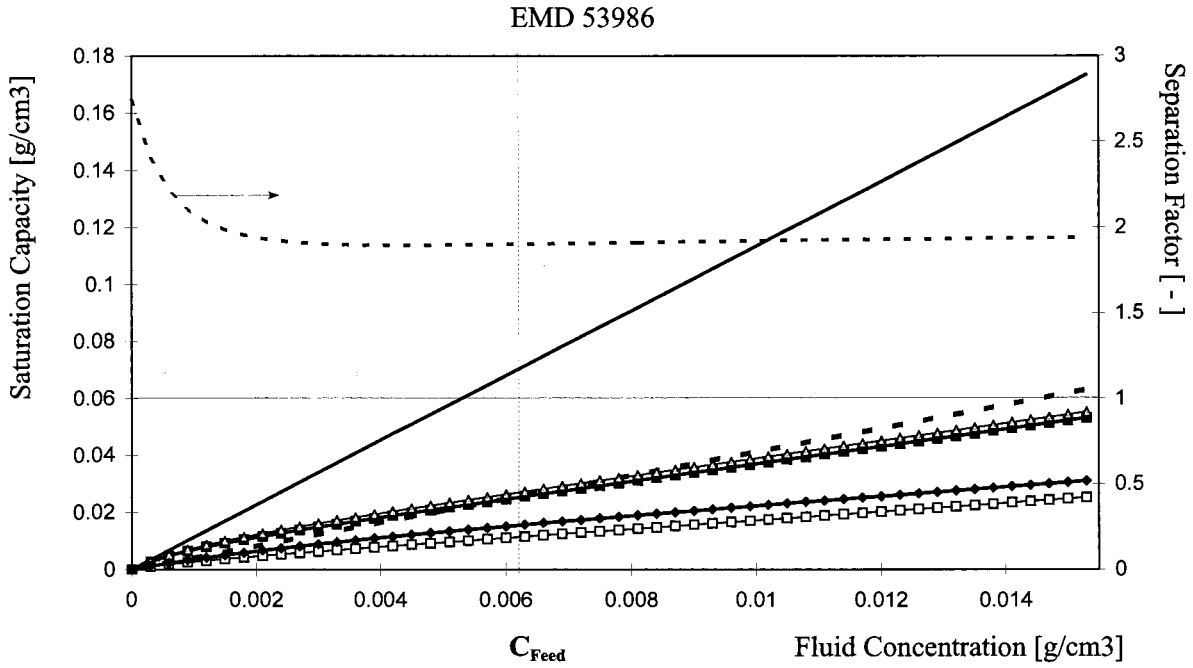

Figure 3. **Isotherms and separation factor of the enantioseparation. Details are given in refs 2 and 3. Henry isotherm (+), (−); Henry isotherm (−) pure isotherm (+) (▲); pure isotherm (−) (◆); interference isotherm (+) (■); interference isotherm (−) with $c_{(+)} = c_{(-)}$ (□); separation factor (thick dashed line).**

It is equivalent to a Langmuir isotherm with a linear prefactor due to nonselective adsorption sites of the different chiral stationary phase (CSP) compounds.

The model parameters are listed in Table 1. The separation factor and column loadability is shown in Figure 3.

4.3. Comparison of Physical Component Properties. In the area of *Henry behaviour*, the separation factor of the enantiomers is much higher (2.75) than that of the sugar separation. Despite that, it diminishes to a value of less than 2 at high liquid concentrations. Due to this fact, combined with a relatively low interstitial velocity, major deviations

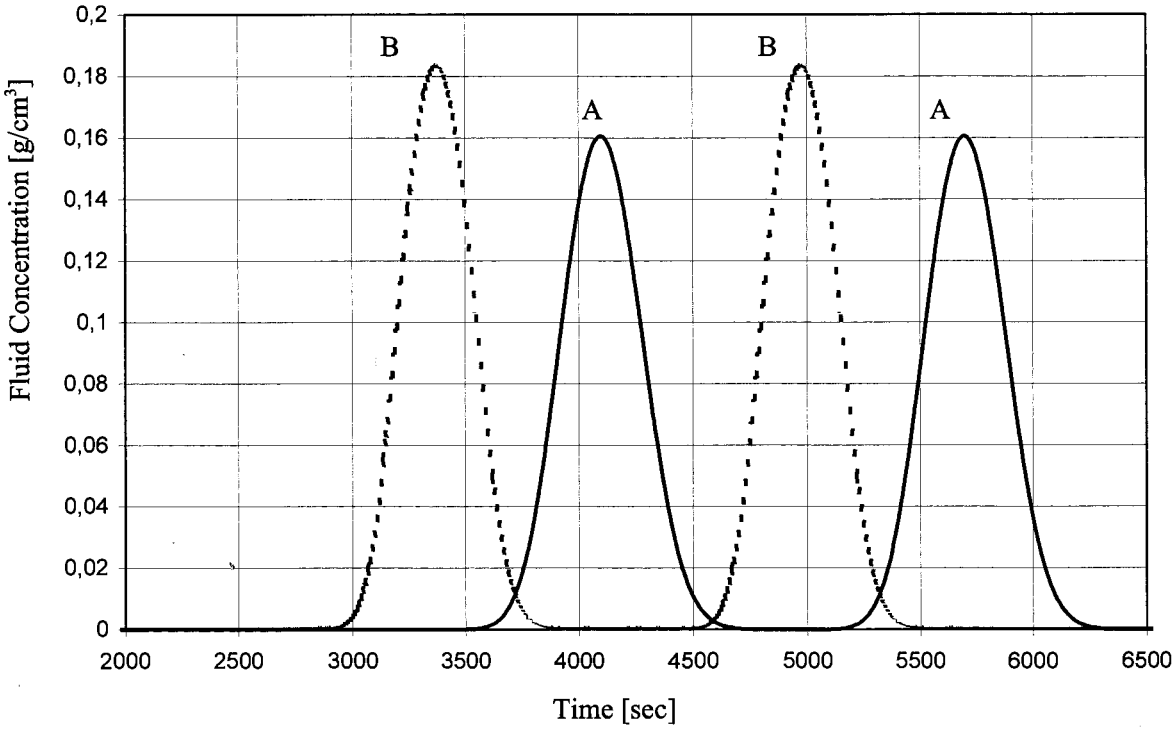

Figure 4. **Simulated chromatogram of the optimized batch elution to separate fructose/glucose. Fructose (A); glucode (B).**

of the separation tasks result. The low interstitial velocity is caused by *kinetic mass transfer resistances* which lead to low particle diameters, which in turn cause a high-pressure drop.

The *column loadabilities* of the two components are approximately 4−5 times lower than those for the sugar separation. *Mass transfer coefficients, separation factors at feed concentrations, and axial dispersion coefficients* are approximately of the same magnitude for each binary system.

The most striking difference is the *nonlinearity of the isotherm*, which is defined as the deviation from the ideal Henry isotherm at feed concentrations. In the case of EMD53986, the factor of nonlinearity is 2.2. Compared to other nonlinear systems, this is a relatively high value. The most significant difference between the two binary mixtures discussed here lies in this factor, which is a result of the wholly different equilibrium phase behaviour of these two examples.

Another striking fact concerning these binary mixtures is seen during the optimization of the separation process.

In Figures 4 and 6, the optimized concentrations which breakthrough at the column outlet are shown as a function of time, and in Figures 5 and 7, the optimized axial concentration profiles of the optimized SMB processes are plotted for the sugar separation (Figure 5) as well as for the enantioseparation (Figure 7).

Because of the *displacement* of the weaker adsorbable component B by the stronger adsorbable component A, local increase of liquid concentration of the weaker adsorbable component B over the feed concentration takes place by enantioseparation. Figures 6 and 7 demonstrate that a concentration of component B occurs which is significantly higher than the feed concentration. This displacement phenomena occurs equally in batch and SMB processes. As a result, component B can be yielded at a lower dilution than it is fed into the column.

5. Results of the Process Optimizations

The optimized parameters achieved from the simulative optimization for batch and SMB chromatography are summarized in Table 2. In addition, the optimum characteristic numbers and objective functions are listed.

For the sugar separation, one interesting fact can be noticed: the productivity of the optimum batch column is 1.7 times higher than that of the corresponding SMB column. This differs from the practical results mentioned above, where the SMB process is always much more productive than batch elution. Additional studies with other binary mixtures with linear isotherms confirm the results presented here. The reason of the differing results is the difference in the operating modes of batch chromatography: either optimized due to touching bands or not.

On the other hand, product dilution and solvent requirement of the sugar separation (and other linear systems) are much higher for the batch process: Batch chromatography has up to 2.3 times higher product dilutions and up to 2.5 times higher solvent requirements.

The latter result fits in the experimental investigations described above, although in this study this difference is not as high as described in previous literature. For example, Nicoud stated[2] that the only advantage of SMB chromatography for linear systems such as fructose/glucose separations lies in the product dilution.

For the second mixture, EMD53986, the following relations result:

(a) SMB productivity is 1.5 times higher;

(b) components are up to 1.1 times less diluted;

(c) solvent requirement is up to 1.1 times less.

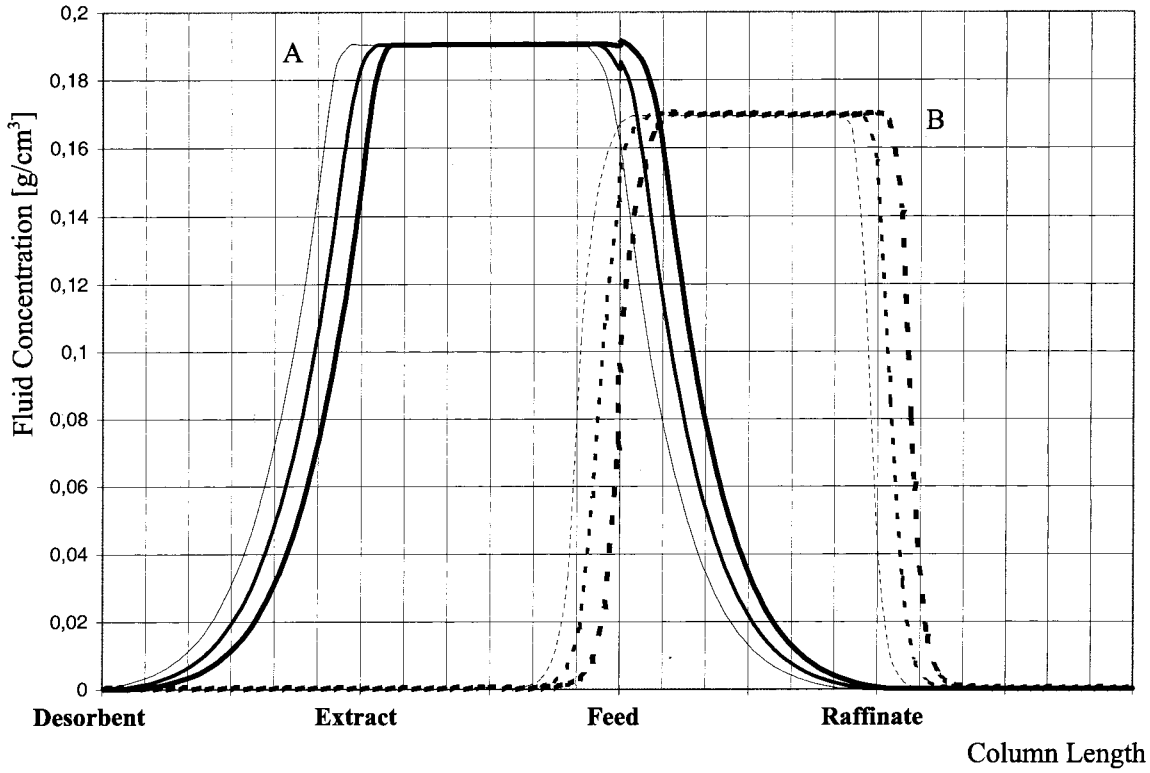

Figure 5. **Simulated axial concentration profile of the optimized SMB process to separate fructose/glucose, periodic quasi-steady-state is reached. Fructose (A); glucose (B) (with each 3 curves in fluid flow direction, beginning, middle, and end of the shown switch period).**

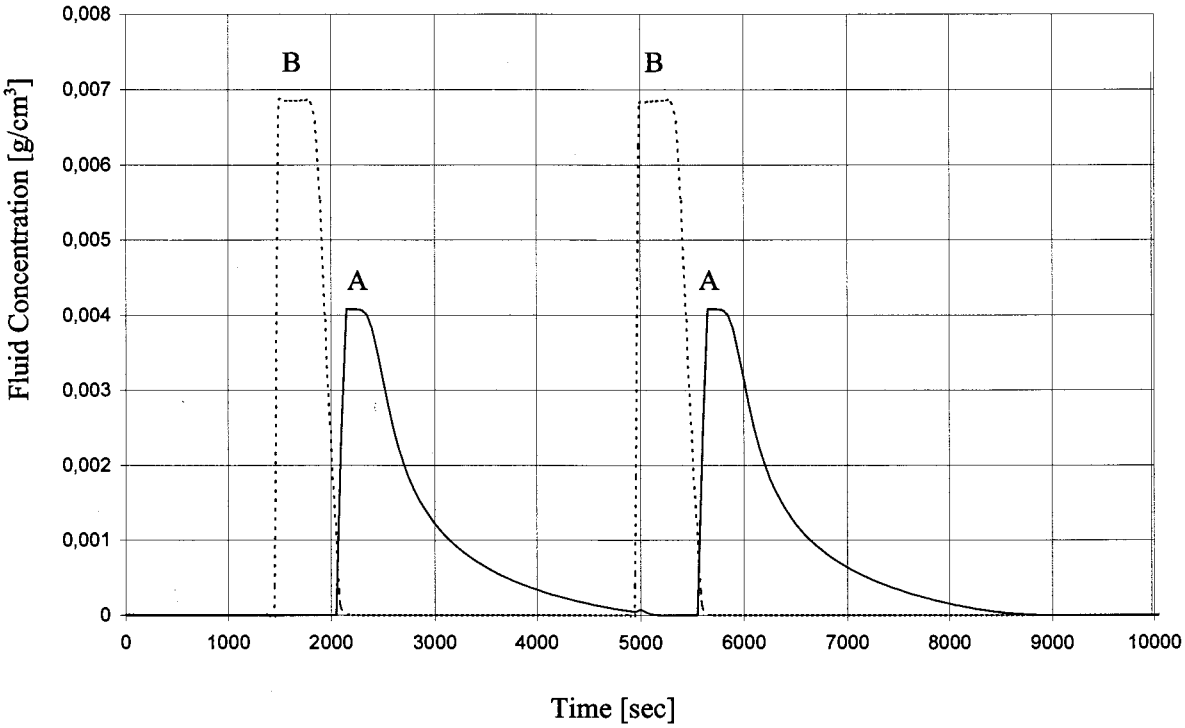

Figure 6. **Simulated chromatogram of the optimized batch elution to separate the enantiomers: (A) (+); (B) (−).**

This enantioseparation is a typical example for the class of enantioseparations in pharmaceuticals or fine chemicals, which are now scaled up into production by SMB chromatography. The separation factor is about 2, and the efficiency of CSP's is not extremely high, with relative low HETP's and extreme peak tailing due to mass transfer resistances (compare Figures 4 and 6). Therefore, small particles of about 10−40 μm diameter are chosen.

Five additional binary mixtures with nonlinear isotherms (Langmuir, modified Langmuir, and bi-Langmuir) where analyzed by process simulations in the theoretical study by the authors. The result is that there is no way to predict

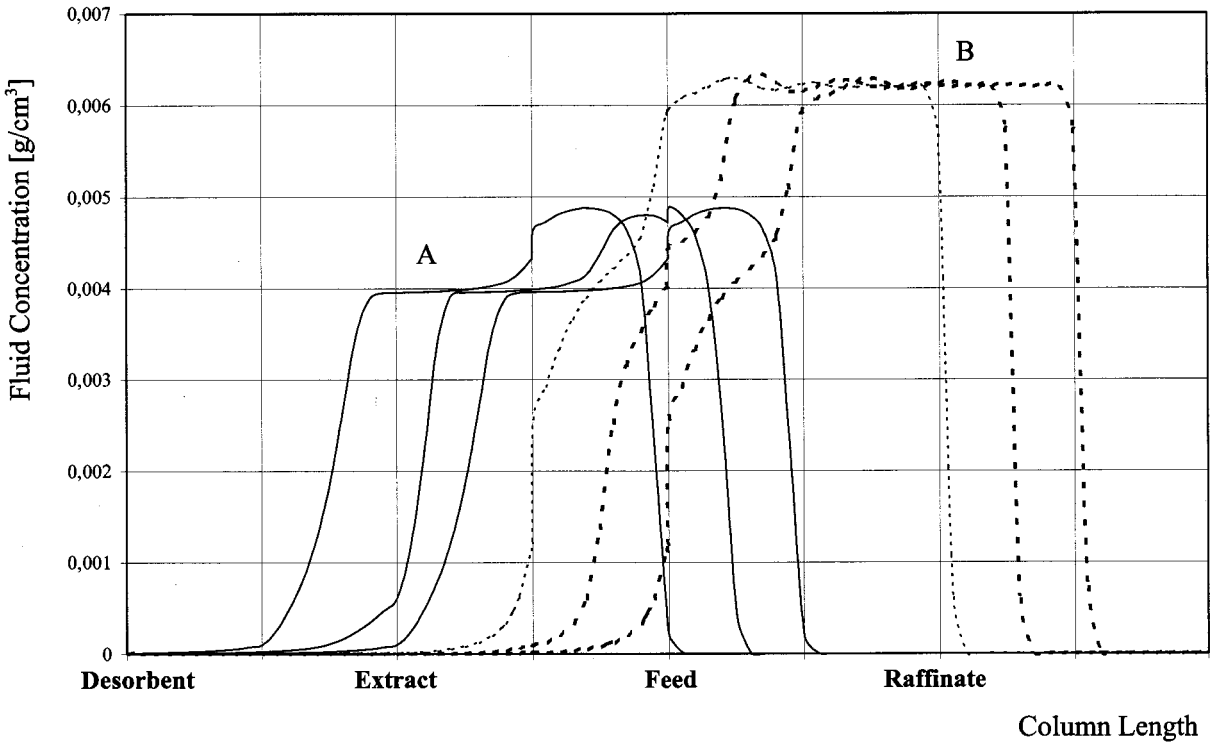

Figure 7. **Simulated axial concentration profile of the optimized SMB process to separate the enantiomers, periodic quasi-steady-state is reached. Fructose (A); glucose (B) (with each 3 curves in fluid flow direction, beginning, middle, and end of the shown switch period).**

which kind of process is the more productive one.

Dilution and solvent requirement of batch chromatography where indeed higher in each case, but the difference of both processes can be extremely small, as demonstrated for EMD53986. The reason for the generally higher solvent requirement of batch chromatography is the demand of equal throughput for batch and SMB (see eq 2). For equal concentration of the feed eq 2 simplifies:

$$\dot{V}_{SMB}\Delta t_{cyc} = \dot{V}_{Batch}\Delta t_{inj} \quad (9)$$

The cycle time must be significantly higher than the injection time otherwise the mixture cannot be separated.

Furthermore, the results demonstrate that the assumption of the touching bands for the batch process leads to yields and purities up to 99%, even 100%, if the batch process is optimized properly. On the other hand, there is a certain level of automation required for fraction collection at the optimum time cuts. The personal costs for an automated batch column is as high as for a SMB column to operate the equipment safe, reliable and 24 h per day. Due to that, the criteria of working costs is not a real advantage of the simulated moving bed technology. The same personnel are needed. This assumption is conservative in advantage of batch chromatography.[11]

6. Comparison of the Process Behavior by Cost Calculations

"It is well-known that there are no technical optima in industry, only economic optima," states Georges Guiochon.[20,21]

A comparison of batch elution and SMB chromatography just by a consideration of the three objective functions does not lead to a consistent answer of the question, "what kind of process should be preferred for a given separation task?"

In the case of *linear isotherms*, the productivities of batch chromatography are much higher than of the corresponding SMB processes, but product dilution and solvent requirements are also much higher.

The case of *nonlinear isotherms* is far more difficult because there is no homogeneous result for the process productivity at all. Even product dilution and solvent requirements of batch and SMB may not differ in a significant degree.

Due to that, at least a fourth objective function is calculated unifying productivity and solvent requirement—the separation costs. In this way, the economical relevance of each influencing parameter can be analyzed in a realistic way.

The third objective function, the product dilution, is taken into account. It includes the costs for further upgrading and, therefore, the energy necessary to separate different amounts of solvent from the product. Because batch chromatography generally provides the more diluted fractions, this objective function influences the total separation costs and also the decision about the more economic kind of process.

But in the forehand of the cost calculation, it is necessary to note that for the large scale fructose/glucose separation the separation costs of the SMB process are significantly lower than those of the corresponding batch process. As

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far as the enantioseparation is concerned, the dilution of each process differs up to 10%. The financial expense is roughly the same for batch and SMB, therefore, an additional consideration about the dilution is not necessary.

7. The Proceeding Methodology

The basis of the following calculations is a Merck KGaA inhouse cost calculation program written by Dr. M. Schulte in Microsoft Excel which was extended for the presented process comparison. The cost calulations take into account that the total separation costs (TSC) consist of (1) costs for stationary phase (SP), (2) costs for mobile phase (MP), (3) personnel costs (PC), (4) plant costs, and (5) product losses.

(1) The costs for the stationary phase are a result of the column volume and therefore related to productivity (see eq 5). For the sugar separation, the stationary phase is a resin, and for EMD53986, a chiral stationary phase is applied. As a result, the price per kilogram of stationary phase differs from about $0.5 to $20 000 in the examples. The operation time is assumed to be 2−3 years.

(2) The costs for mobile phase contain feed as well as desorbent flow, desorbent flow for the plant startup, solvent recycling, loss of desorbent, and removal. This factor is related to solvent requirement. Solvent loss is proved to be about 1−3%.

(3) Personnel costs contain the mechanical work to prepare the equipment of the plant and labor costs for one person for each batch and SMB chromatography plant in preparative-scale and nine people for large-scale production. As discussed above, it is reasonable to assume that both processes are totally automated. A fully automated production plant can run unattended but tasks such as solvent handling, product recovery, and quality control must be done manually. The different product batches have to be prepared in order to be separated. The separation cut pints and operating parameters have to be adjusted for each batch. Moreover, the process control equipment must be watched.

(4) The plant costs include investment costs, running expenses, and maintenance. The investment costs are calculated from existing prices by using a degression coefficient for either batch or SMB chromatography. Plant costs are a function of the throughput and therefore increse with column diameter (D^2).

(5) Both processes are optimized due to total separation to avoid the need to take into account different product values and keep the comparison independent of that effect. If products are extremely expensive, it is the main argument to choose chromatography in favor of other process alternatives to gain total product yield and recovery and to achieve total separation.

The separation costs are calculated for typical production quantities. For the sugar separation, these quantities range from 10 000 to 200 000 tons per year. In the case of enantioseparations, the production scale is assumed to lie between 1 and 50 tons per year. Furthermore, the cut point of equal prices as a function of production is calculated to provide additional information for the decision about the best chromatographic process.

The main difference between the SMB and the corresponding batch column, resulting from the previous optimization, is the difference in column length and diameter. The optimized laboratory-scale columns are scaled up in relation to throughput, which increases in proportion to D^2. Due to this, the differences between batch and SMB column dimensions still remain. The column length has to be kept constant for different feed throughputs because a variation influences the separation behavior.

It is important to point out that cost distributions never can be represented in a gerneral form, because the cost structure of companies can be strongly different. Therefore, a case study is presented here with the same assumptions for both processes.

8. The Results

8.1. Large-Scale Sugar Separation. Figures 8 and 9 visualize the cost distribution for the fructose/glucose separation.

As discussed above, the optimum batch *productivity* is 1.7 times higher than the optimized SMB productivity.

The optimized *solvent requirement* is twice as high. This difference can also be noticed in the separation costs as a function of the annual production.

Stationary and mobile phase feed throughput increases linearly. The *operating costs* are assumed to remain constant and are negligible in relation to the other factors.

The *plant costs* rise with a degression exponent; near 1 for batch and about 0.5 for SMB. The reason for this sharp difference can be explained as follows: The investment costs for SMB chromatography are—compared to batch—extremely high because of the large number of equipment and high degree of automation. By scaling up the processes, the automation level remains almost the same. In the case of batch chromatography, the automation level rises faster with rising plant capacity because the demand to the single units (e.g., pumps) is much higher. The reason is that a single volume flow is set through, instead of the 4 fluid flows in the case of SMB columns. The differences in total equipment cost between batch elution chromatography and SMB are due to the fact that to operate batch chromatography units 24 h a day basis, larger storage tanks for solvent and recovered fractions as well as larger equipment for product recovery and solved recycling are required.

As a result, one interesting influence becomes visible by these cost calculations: While SMB columns of laboratory scale are significantly more expensive, this relation is reversed in production scale due to of the different degression coefficients.

The difference between batch and SMB plant costs can easily be seen in the Figures 8 and 9.

The most important factor is the cost of the mobile phase, and therefore, the different solvent requirements for batch and SMB chromatography turn the scale between the two processes. The effects on cost of alternative techniques (for example, membrane technology, crystallization, precipitation, evaporation, centrifugation, freeze-drying) to recover the isolated products and the solvent are considered in a different

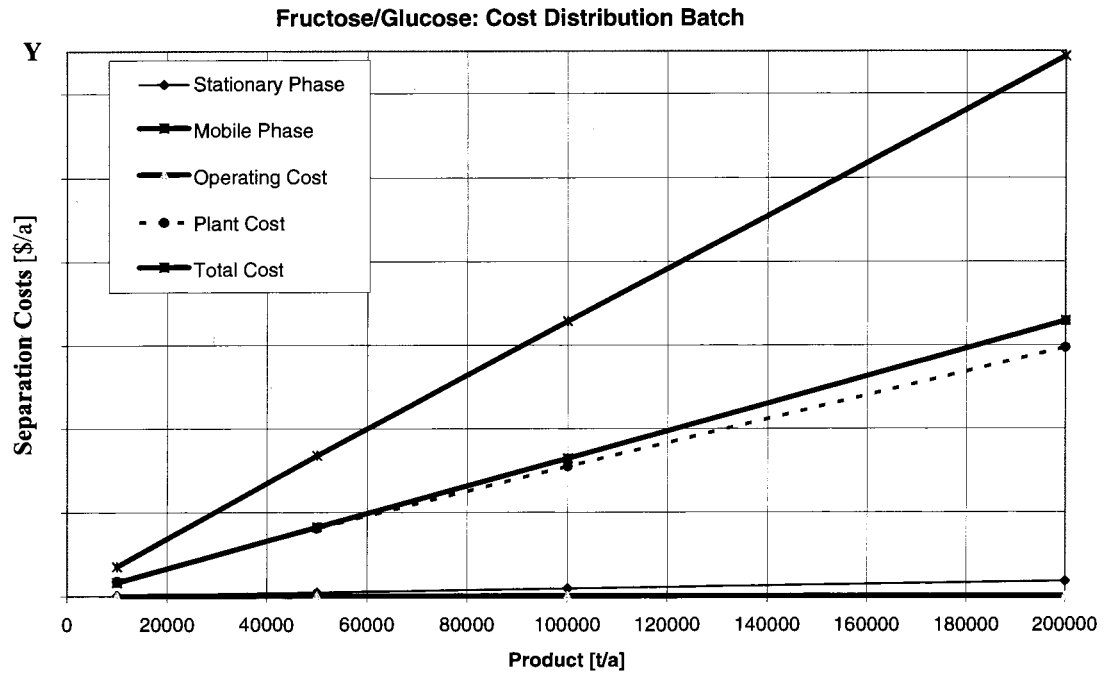

Figure 8. **Cost distribution of the optimized batch elution chromatography, fructose/glucose separation, separation costs [dollar/a] vs production in tons per year.**

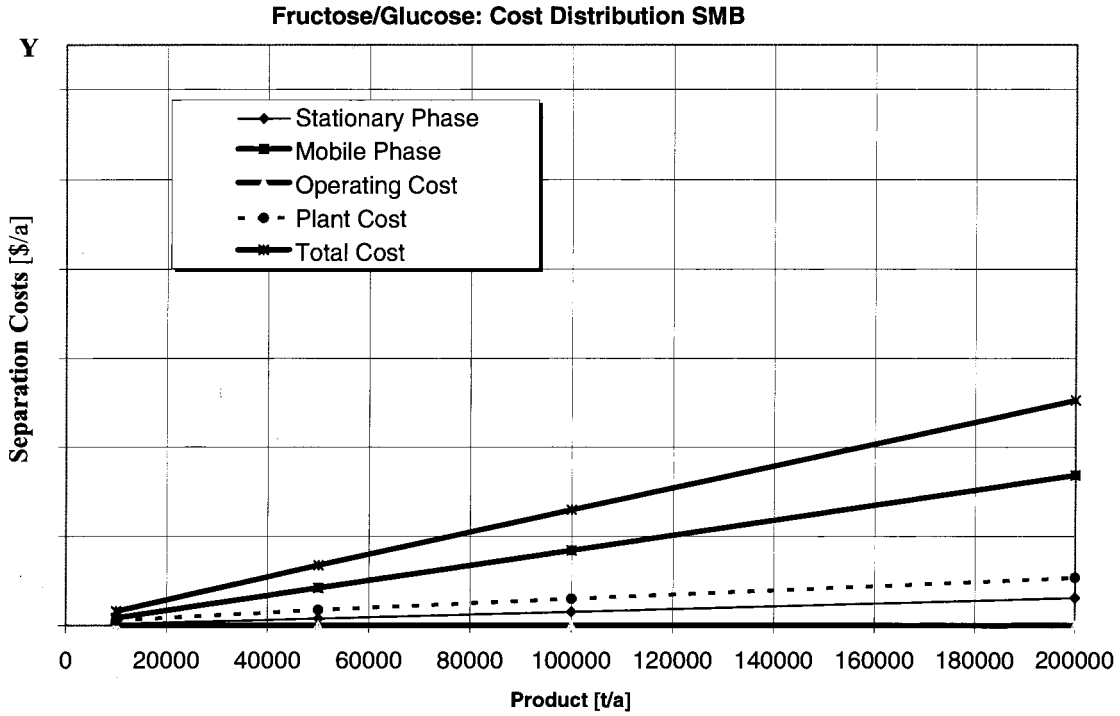

Figure 9. **Cost distribution of the optimized SMB chromatography, fructose/glucose separation, separation costs [dollar/a] vs production in tons per year.**

study at the moment. The higher productivity of the batch columns, economically characterized by the costs of the stationary phase, is not of any consequence. The reason is the relatively low price of the resins.

Finally, the specific separation costs for fructose/glucose, shown in Figure 10, are much lower for the SMB process than by applying the batchwise process.

Additionally, the annual production that provides equal separation costs by the two processes was calculated. Without taking into account different product dilutions, which determines the costs of further upgrading, this cut point is reached at 350 tons of product per year and is far below any economic production scale.

8.2. Production-Scale Enantioseparation. Figures 11 and 12 demonstrate the cost distribution for the enantioseparation of EMD53986.

An important difference to the previous sugar separation example is the much lower range of annual production (from

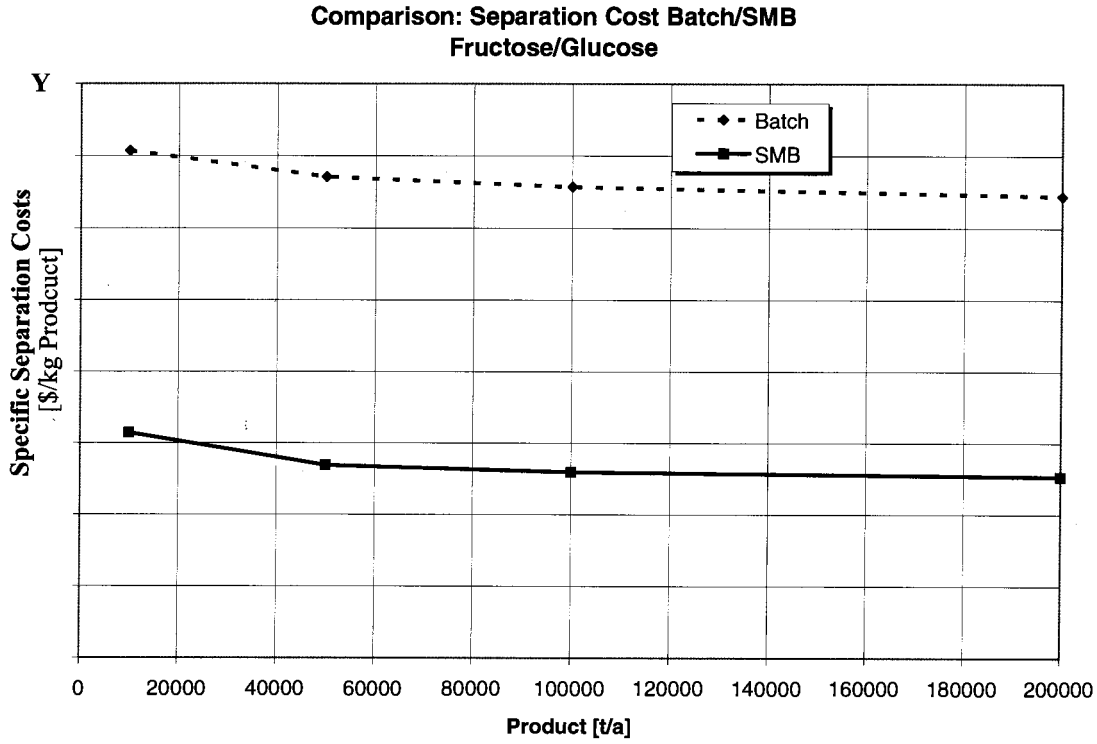

Figure 10. **Comparison of the total separation costs for the optimized batch elution and SMB chromatography, fructose/glucose separation, specific total separation costs [dollar/kg of product] vs production in tons per year.**

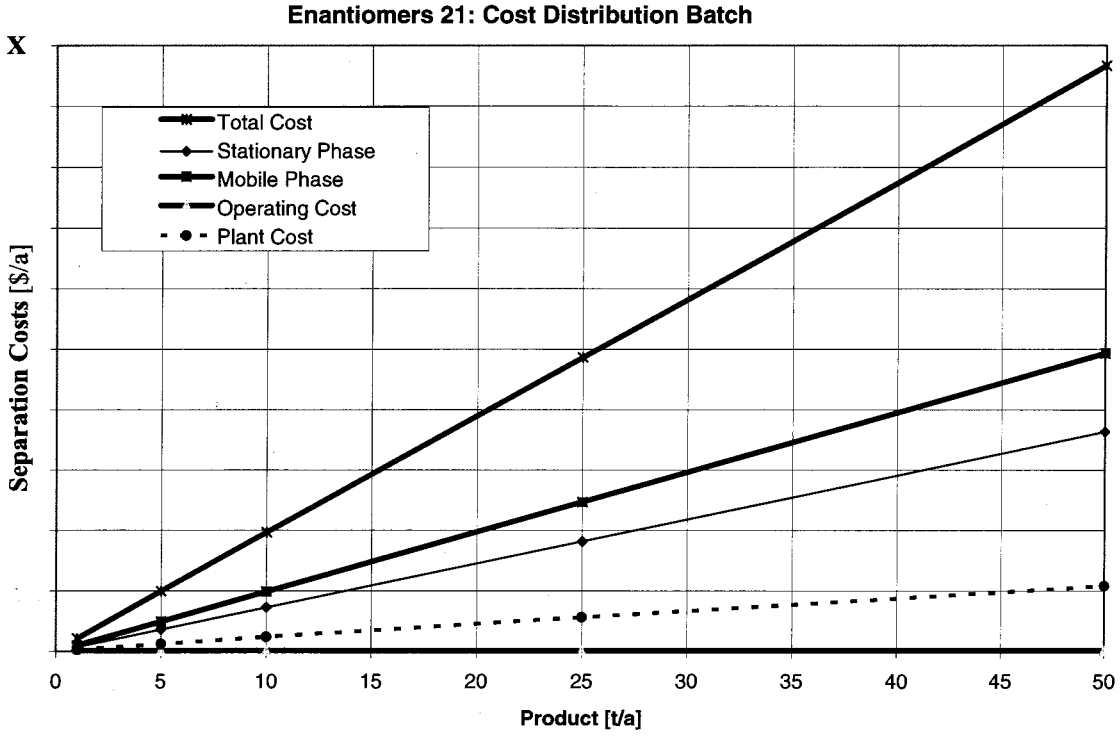

Figure 11. **Cost distribution of the optimized batch elution chromatography, enantioseparation, separation costs [dollar/a] vs production in tons per year.**

1 to 50 tons). As summarized in Table 2, the batch productivity is 1.5 times lower than for SMB, while the dilution and solvent requirement for each component differ only up to 10%—in favor of the SMB process.

In this range of annual production, the influence of plant costs is much smaller. Still, the mobile phase takes the greatest part of the total costs of the separation. But the second largest influence is the stationary phase, due to the high expenses for chiral phases. Figure 13 compares the specific separation costs of the batch and SMB process. The cut point where the costs are equal for both processes is at an annual production of 1.35 tons (see Figure 14).

As a result, the separation costs of enantiomers mostly depend on the costs of stationary phase and mobile phase.

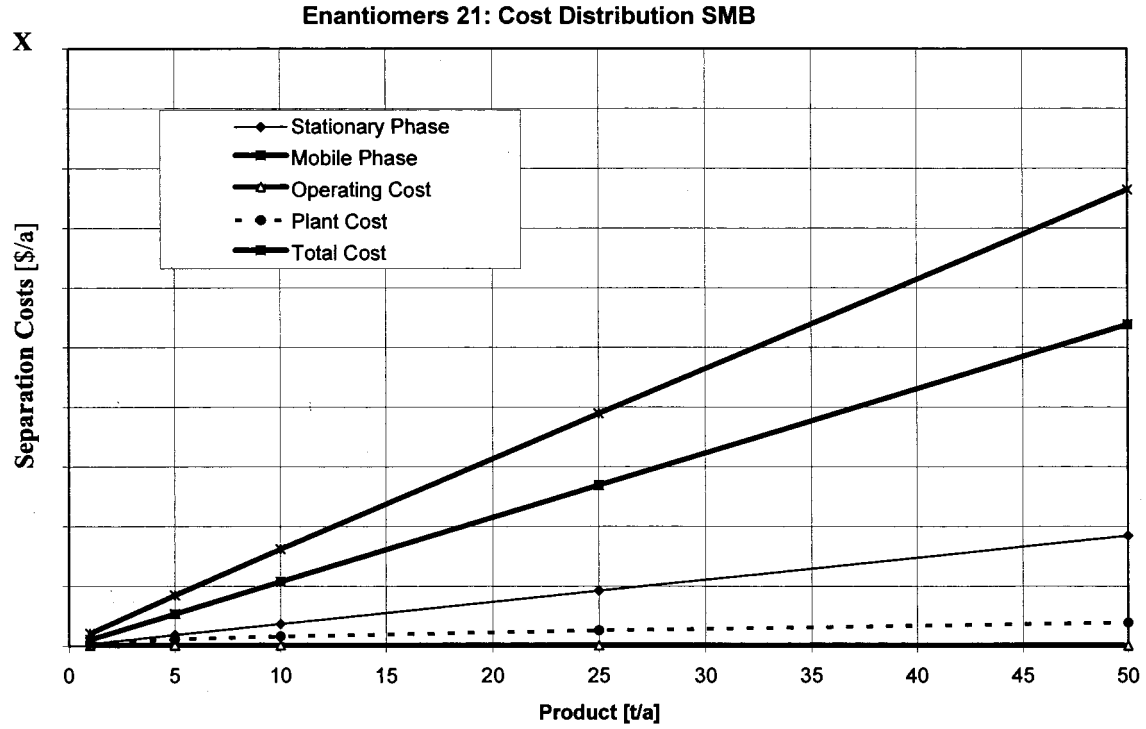

Figure 12. **Cost distribution of the optimized SMB chromatography, enantioseparation, separation costs [dollar/a] vs production in tons per year.**

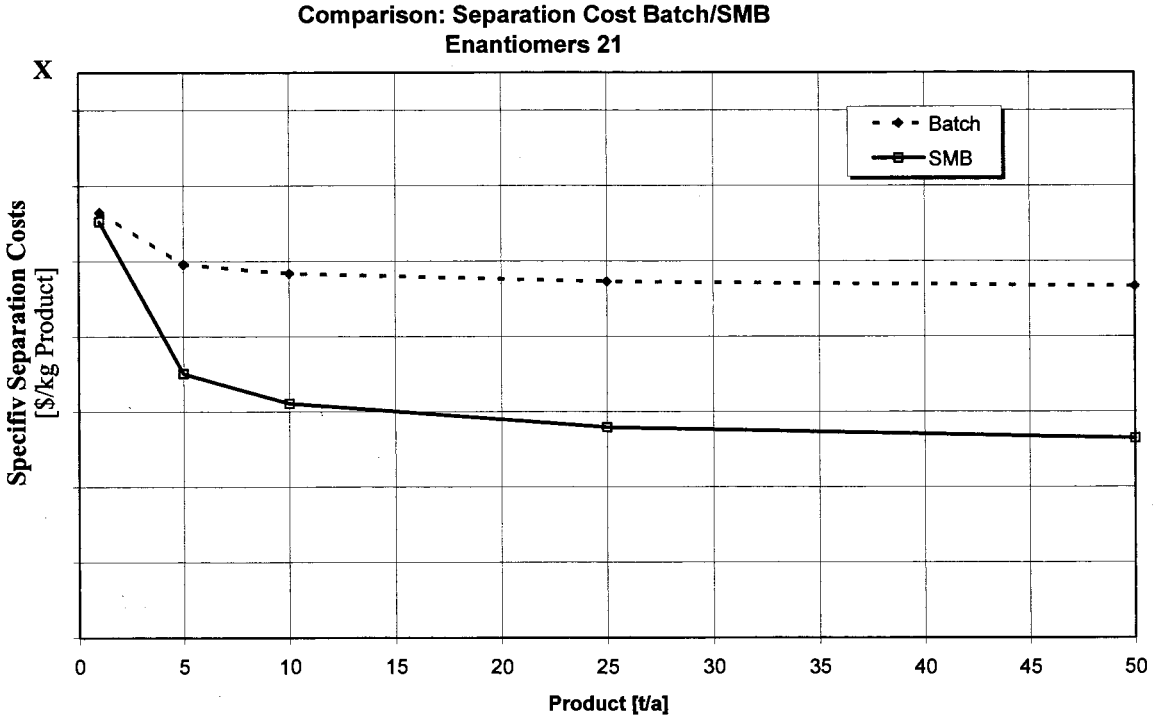

Figure 13. **Comparison of the total separation costs for the optimized batch elution and SMB chromatography, enantioseparation, specific total separation costs [dollar/kg of product] vs production in tons per year.**

But as mentioned above, these factors can be influenced strongly by optimization.

As previously noted, it is not possible to generally predict which kind of process will provide the greater productivity. If the productivity of the batch process is higher than that for the continuous one, batch chromatography may be the more economic route. On the other hand, the costs of mobile phase and their influence on the total separation costs depend, last but not least, on the specific desorbent price. The price for water is relatively low in comparison with hexane, for example, but the necessary energy for evaporation is high in product upgrading and solvent recovery.

9. Conclusions

9.1. Rules of Decision: Which Chromatographic Process Should Be Applied? Finally, the decision about

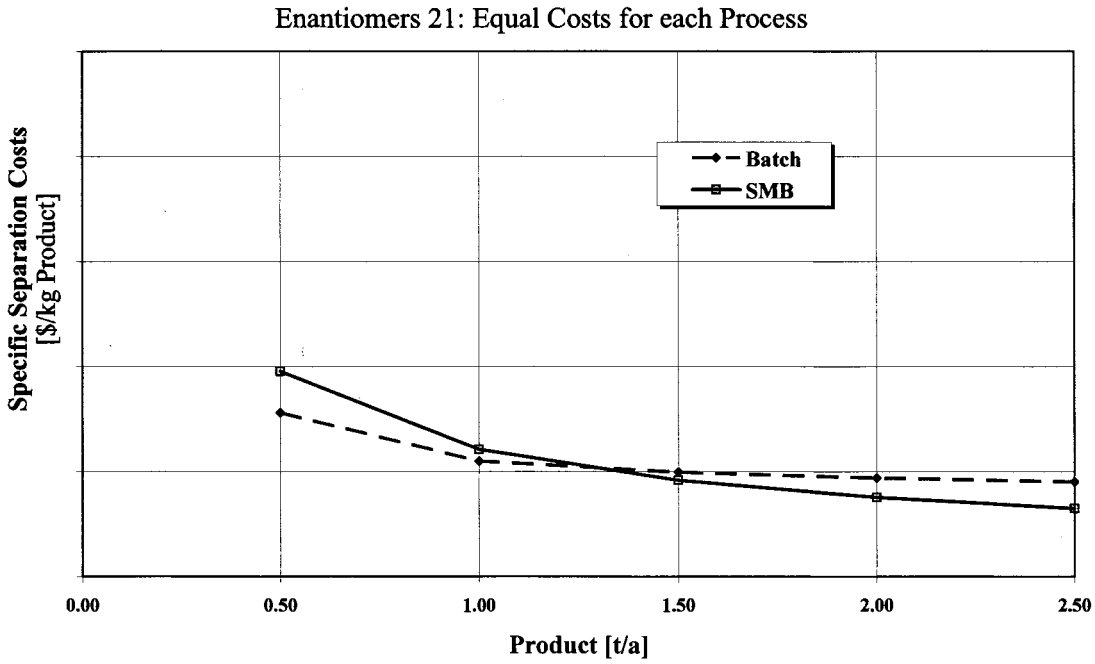

Figure 14. **Equal costs for the optimized batch elution and SMB chromatography, enantioseparation, specific total separation costs [dollar/kg of product] vs production in tons per year.**

the more economic chromatographic process is at first a question of the adsorbent used for separation:

For resins, zeolithes, and similar low-priced adsorbents, the influence of the stationary phase on the total separation costs can be neglected. Furthermore, the influence of the productivity is not remarkable as demonstrated in the fructose/glucose separation. In this case, the SMB process should be preferred—as it is done in the sugar industry since 1960s.

For expensive adsorbents, the specific separation costs depend on many details which must be considered carefully: optimum solvent requirement, optimum productivity of each process, and, of course, the relation of these objective functions.

Additionally, the prices of stationary and mobile phase should be taken into account because these prices concisely determine the degree of influence on each objective function of the different processes.

For enantioseparations in pharmaceutical or fine chemical product development or production, SMB chromatography has major advantages over batch elution such as higher productivity, lower product dilution, and lower separation costs. Both technologies have their advantages and limitations. This strongly depends on the type of problem to be handled. Often forgotten is the factor solubility. In batch chromatography, it is for example possible to inject the sample in a completely different solvent as the eluent composition, which is not so easy to perform in an SMB process.

If impurities in the binary separation cut are taken into account, as they occur in reality, the relations between the two chromatographic processes remain at the same magnitudes.

In detail, the more economic process can only be found by detailed process optimization, done by process simulations. Rigorous models are necessary because real effects for peak tailing have to be considered to optimize chromatographic processes.

The feasibility of SMB technology is demonstrated, and the process is established in product research and development and accepted by the involved scientists. Now, chemical engineers are called to develop and prove the profits of SMB chromatography in production and to identify separation task of interest. Therefore, the authors intend to give arguments for the process decision with the presented comparisons of batch elution and SMB chromatography by cost calculations. The design and optimization methodologies are described in detail in refs 14−18 and 22.

Looking at a complex production scheme, more questions must be answered. First of all, the whole process has to be taken into account. This would lead us to a very broad approach of general optimization of the chromatographic step within a production route. Some of the necessary considerations are the following:

(a) The best step for a separation has to be chosen. This depends on the selectivity and the solubility of the educts.

(b) Saving of reagents in following synthetic steps have to be achieved.

(c) An increase in yield in the following steps due to higher purity of educts should be gained.

(d) Should the mobile phase be removed or is the concentration/enrichment of the product sufficient?

(e) The costs for connecting the separation unit with the previous or next steps have to be considered: whether it is possible to take the same solvent or whether the product has to be crystallized and resoluted before the next step.

(f) The chosen separation has to be optimization as described before because process optima have to be compared.

Chemical engineers should accept chromatography as an efficient and economic unit operation which has many advantages:

1. Most pharmaceutical and fine chemical products are analyzed by chromatography in the early stage of product development. Therefore, stationary and mobile phases are chosen and experiments are done. Optimized analytical parameters are not (always) the best conditions for an optimal preparative process. Few experiments must be done on an analytical HPLC column to optimize stationary and mobile phases for the production scale and to determine the equilibrium phase isotherms. It should be kept in mind that analytical method development has the goal to achieve a total baseline separation of all components of the mixture. As a result, complex eluent mixtures may be needed in most cases. But in production, only one main or at least two main products are needed out of the feedstock. Therefore, first, the separation task is quite different and, second, taking the costs of product recovery and eluent recycling into account, pure eluents or simple mixtures have to be chosen.

2. It is not possible to derive general rules in detail. But, for single applications, the design and optimization methodology is developed and can easily be applied to industrial separation tasks as described above.

3. In product development, this methodology is a reliable method to evaluate the separation task by chromatography, to benchmark different products. Detailed optimization and consideration of unit operation alternatives could be done if the production decision is made.

4. SMB technology is accepted in laboratory scale for the production of value product. The feasibility is proven.[3,4,8,23]

5. The authors have proven[10,14,18,19] that detailed optimization of SMB chromatography by rigorous simulation studies, in contrast to an empirical trial and error approach, optimizes the operation conditions to about double feed throughput and half desorbent requirements. In production, these efforts for process optimization are of great benefit.[11]

These theoretical simulation studies need to be proven by experimentation. However, process simulations based on rigorous models function as a standardized reference for theoretical studies. Due to a standardized methodology, the advantages and limitations as well as the preferable ranges of application of batch elution and SMB chromatography are demonstrated by theoretical studies to show the benefits of both processes.

Acknowledgment

The authors are very grateful to the other lecturers of the DECHEMA e.V. course in Dortmund "Design and Operation of Preparative and Production Scale Chromatographic Processes", Prof. K. K. Unger of Mainz, Prof. J. N. Kinkel of Nürnberg, and Dr. S. Michel of Bayer AG for their comments, ideas, encouragement, and enthusiasm. The authors thank Tom Mihlbachler and Prof. G. Guiochon, University of Tennessee, very much for their great help to get this paper finished.

Appendix 1. Symbols and Abbreviations Used

c	[g/cm^3]	fluid concentration
c_P	[g/cm^3]	fluid concentration in the adsorbent pores
D	[cm]	column diameter
D_L	[cm^2/s]	axial dispersion coefficient
d_P	[cm]	particle diameter
Δt_{cyc}	[s]	cycle time
Δt_{inj}	[s]	injection time
E	[cm^3/s]	extract volume flow
F	[cm^3/s]	feed volume flow
H_i	[−]	Henry coefficient of component i
P	[−]	coefficient of the modified Langmuir isotherm
k_{eff}	[cm/s]	effective, overal mass transfer coefficient
k_{1-4}	[cm^3/g]	Langmuir coefficient of component i
L	[cm^3/s]	liquid fluid flow
m_{ads}	[g]	mass of adsorbent
m_j	[−]	relative mass flow in section j
m_i	[g/s]	mass flow component i
P_i	[−]	adsorbility of component i (Bi−Langmuir)
Pr	[1/s]	productivity [g of produkt/g of adsorbent/h]
q_i	[g/cm^3]	solid load of componet i
R	[cm^3/s]	raffinate fluid flow
r	[−]	point in the operating diagram
Rec	[cm^3/s]	recycle fluid flow
t	[s]	time domain
t^*	[s]	switch time
u_{int}	[cm/s]	interstitial fluid velocity
$\dot{V}$	[cm^3/s]	recycle fluid flow
V	[cm^3]	column volume
w	[−]	point in the operating diagram
w_c	[cm/s]	velocity of the movement of a concentration front
x	[cm]	space domain
Y	[%]	yield [g of product/g of feed]
ϵ_0	[−]	voidage
π	[−]	circle constant
A		stronger adsorbable component
B		weeker adsorbable component
Batch		batch elution chromatography
D		desorbent
E		extract
F		feed
i		component number
j		section number
R		raffinate
Rec		recycle
SMB		simulated moving bed chromatography
CSP		chiral stationary phases
D		dilution
HETP		height equivalent to theoretical plate
Pr		productivity
Pu		purity
SR		solvent requirement
Y		yield

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Received for review February 23, 1998.

OP980019A