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Enantioseparation of 1-phenyl-1-propanol by simulated moving bed under linear and nonlinear conditions

Saad Khattabi^{a,b}, Djamel E. Cherrak^{b,c}, Kathleen Mihlbachler^{b,c}, Georges Guiochon^{b,c,*}

^aDepartment of Food Science and Technology, The University of Tennessee, Knoxville, TN 37901-1071, USA

^bDepartment of Chemistry, The University of Tennessee, Knoxville, TN 37996-1600, USA

^cDivision of Chemical and Analytical Sciences, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6120, USA

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Abstract

Approximately optimum operating conditions needed to separate 1-phenyl-1-propanol (PP) enantiomers by simulated moving bed (SMB) were determined using the “safety margin” approach in the linear case and the “triangle theory” in the nonlinear case. Previous results showed the adsorption isotherm data to fit well to the competitive Langmuir model. This allowed the use of the triangle theory approach that applies straightforwardly to Langmuir systems. Experimentally, the operating conditions under nonlinear isotherm behavior were determined for a feed solution with a total concentration of 5 g/l. The purity of the products exceeded 98% for the raffinate and 95% for the extract. Failing to reach complete purity while the experimental conditions were chosen inside the separation zone is explained by the nonideality of the system used, which violates one of the triangle theory assumptions. The computed overall daily production rate was 11.6 g of racemic PP processed per day per kg of stationary phase, a result that compares favorably with previous ones. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Simulated moving bed (SMB) technology [1] is now extensively used for the large-scale fractionation or purification of numerous mixtures of importance in the fine chemicals industry, particularly for the

production of valuable intermediates in the synthesis of pharmaceuticals, pesticides, and certain food additives. Although not the only one, the most important application of SMB, by far, is in large-scale enantiomeric separations. In this application, the SMB process does not suffer from its main drawback, of being either limited to the separation of binary mixtures [2] or extremely complex to design and operate [3]. Although the few initial industrial applications of SMB were under linear conditions [2], the isotherms of sugars on ion-exchange resins

*Corresponding author. Department of Chemistry, The University of Tennessee, 552 Buehler Hall, Knoxville, TN 37996-1600, USA. Tel.: +1-865-9740-733; fax: +1-865-9742-667.

E-mail address: guiochon@utk.edu (G. Guiochon).

remaining linear in a wide concentration range [4], most SMB applications of current interest and particularly those dealing with the separation of enantiomers are most often carried out under nonlinear conditions. Therefore, the nonlinear behavior of the equilibrium isotherms must be taken into account when choosing the experimental parameters for an SMB run [5].

The empirical optimization of a multiparameter nonlinear system such as an SMB unit is extremely difficult. Because of the complexity of the interactions between these parameters, modeling and computer simulation must play a pivotal role in the determination of the best operating conditions. According to Storti et al. [6], the modeling of this chromatographic process involves parameters which can be classified into three different groups: (1) the geometrical and physical characteristics of the system, i.e., the column diameter and length, the average particle size, the void fraction of the bed, the number of columns per section. An SMB unit needs several columns, most having between 4 and 16. It is of critical importance that the characteristics of these different columns be as close as possible. It was shown that, otherwise, significant production and/or purity losses take place [7]; (2) the parameters of the competitive equilibrium isotherms of the two compounds; (3) the parameters that account for the mass transfer kinetics and the axial mixing (i.e., axial dispersion). Finally, there are also a few operating parameters which are easy to adjust when these data are known, the column temperature, the flow-rates of the streams entering or leaving the SMB and the cycle time. The usefulness of modeling is, evidently, contingent on the accuracy with which these parameters are determined. Once the design parameters have been determined and the system successfully modeled, it becomes possible to optimize the operating parameters in order to operate the process as economically as possible [8,9].

This study had two objectives. The first was to determine the best experimental conditions needed to carry out the separation of the 1-phenyl-1-propanol (PP) enantiomers under overloading conditions, using a small-scale SMB system. The second objective was to implement and validate these optimum conditions.

2. Theory

2.1. SMB under linear conditions

The optimum operating conditions for an SMB operated in the linear range are easily derived using the “safety margin” approach proposed by Ruthven and Ching [10] and later developed by Zhong and Guiochon [11]. A safety margin, β , being chosen, the solid phase average flow-rate and the flow-rates in the four sections of the SMB should be given by the following equations if a complete separation of a binary mixture is to be achieved [10]. Then, the less retained component moves in the direction of the mobile phase and the more retained in the direction of the solid-phase:

$$Q_S = (1 - \epsilon)Au_s = \frac{Q_F}{K_2/\beta - K_1\beta} \quad (1a)$$

$$Q_R = \left(\frac{K_2}{\beta} - \frac{K_1}{\beta} \right) Q_S \quad (1b)$$

$$Q_E = (K_2\beta - K_1\beta)Q_S \quad (1c)$$

$$Q_D = \left(K_2\beta - \frac{K_1}{\beta} \right) Q_S \quad (1d)$$

In these equations, Q_S is the (apparent) solid phase flow-rate, Q_F , the feed flow-rate, Q_R , Q_E and Q_D are the flow-rates of the raffinate, the extract, and the desorbent, respectively, u_s is the solid phase velocity ($u_s = L/t^*$, with L column length and t^* switching time) ϵ is the column total porosity, A its cross section area, F its phase ratio, [$F = (1 - \epsilon)/\epsilon$], K_1 and K_2 are the Henry coefficients ($K_{1,2} = k_{1,2}/F$) of the two enantiomers, and k_1 and k_2 their retention factors. The largest production rate (and the lowest eluent consumption) are obtained for $\beta = 1$; however, operation with this value is unstable. Operation for β between 1 and $\sqrt{\alpha}$ is possible, the production rate decreasing with increasing value of β . Since the flow-rates must be positive, the safety margin must be smaller than $\sqrt{\alpha}$.

Once Q_F and the safety margin factor are chosen, the other flow-rates (solvent, raffinate and extract) and the switching time are easily derived from this set of equations. The values of these parameters are all what is needed to start an SMB run under linear

conditions. Although the feed flow-rate is chosen “arbitrarily”, this choice is neither unrestricted nor completely random. It must take into account the physical limitations of the system (maximum flow-rates and pressures, which depend on the pumps and valves used and on the average particle size of the packing material; influence of the flow-rates on the column efficiencies). A higher feed flow-rate gives a larger production rate but it leads also to a higher solid phase flow-rate, hence to higher raffinate, extract and desorbent flow-rates. These flow-rates cannot be set at arbitrarily large values. Finally, the feed concentration must be such that the deviation from linear isotherm behavior is small and the SMB operates in compliance with the linear model which leads to the system of Eqs. (1a–d).

2.2. SMB under nonlinear conditions

The “safety margin” procedure cannot be applied in the nonlinear range [12]. An alternative approach, the “triangle theory”, was first proposed in 1993 by Storti et al. [6]. It was successfully applied to numerous SMB separations [5,13–16]. This approach is formulated in the framework of the equilibrium theory, assuming that axial dispersion and the mass transfer resistances are negligible [9]. It further assumes that the equilibrium isotherm exhibits a Langmuirian behavior. The key parameters used in this method are the ratios (m_j , with $j=1-4$) between the net fluid flow-rate and the solid phase flow-rate in each section, j . The ratios m_j are given by the following equation [13]:

$$m_j = \frac{Q_j t^* - V\epsilon}{V(1 - \epsilon)} \quad (2)$$

where Q_j is the volumetric flow-rate inside section j , t^* is the switching time, ϵ is the total column porosity, and V is the total (geometrical) column volume.

Mazzotti and co-workers [5,14] rewrote the conditions initially proposed by Ruthven and Ching [10], and showed that, in order to achieve complete separation of the components of a binary mixture, a set of inequalities involving these flow-rates ratios (m_j), must be fulfilled. These inequalities arise from

the need for each section to perform a task that is well defined in the equilibrium theory. The first section of the SMB must assure proper regeneration of the adsorbent. Accordingly, m_1 has the following lower limit:

$$a_2 < m_1 < \infty \quad (3)$$

where a_2 is the Henry coefficient of the more retained component. Likewise, the eluent must be fully regenerated at the exit of section 4. Thus, m_4 has an upper limit. Mazzotti et al. [5] showed that this limit, m_{4cr} , is given by:

$$m_{4cr} = \frac{1}{2} \cdot \left\{ a_1 + m_3 + b_1 C_1^F (m_3 - m_2) - \sqrt{[a_1 + m_3 + b_1 C_1^F (m_3 - m_2)]^2 - 4a_1 m_3} \right\} \quad (4)$$

where a_1 and b_1 are the Henry coefficient and the second parameter of the Langmuir isotherm for component 1 (the less retained), respectively, and C_1^F is the concentration of component 1 in the feed.

The other two flow-rate ratios (m_2 and m_3) correspond to the two sections where the separation actually takes place. In the linear case, complete separation of the feed into pure raffinate and pure extract is achieved if m_2 and m_3 are larger than a_1 and smaller than a_2 , respectively. Furthermore, m_3 must be larger than m_2 since the feed flow-rate is $Q_F = Q_{III} - Q_{II}$ and must be positive. Most of these constraints (except for $m_2 < a_1$) still hold true in the nonlinear case.

To determine the best operating conditions of an SMB run, Mazzotti and co-workers [5,14] proposed to keep m_1 and m_4 constant, satisfying the constraints above, and to explore the (m_2, m_3) space to determine the region of this space within which the separation takes place. In the linear case, the region in which a separation (albeit possibly an incomplete one) takes place is constrained by $m_2 < a_2$, and $m_3 > a_1$. The combination of these two restrictions and the condition needed for a positive feed flow-rate ($m_3 > m_2$) affords a well defined separation zone. Fig. 1 illustrates this zone for a system with $a_1=3$, $a_2=4$ and a total feed concentration of 0.02 g/l. The separation zone is located above the diagonal ($m_2 = m_3$) and it can be divided into four different regions.

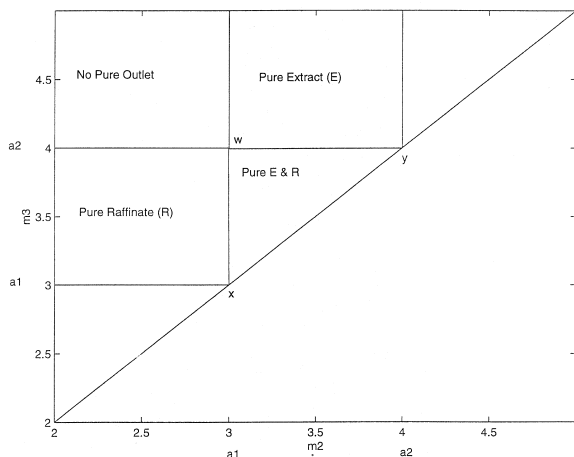


Fig. 1. The (m_2, m_3) plane with the four different regions for a system characterized by a linear isotherm: total feed concentration = 0.02 g/l, $a_1 = 3$ and $a_2 = 4$ (a_i being the Henry's coefficient for component i).

The most important one is the triangle wxy , corresponding to complete separation [14]. Provided that the constraints on m_1 and m_4 are fulfilled, any operating conditions chosen inside this triangle should generate pure products at both the raffinate and the extract ports [14]. The apex (w) of the triangle represents the optimum conditions for maximum production rate. Unfortunately, it corresponds also to the least robust operating conditions [5]. This is because it is common to all four zones of the general separation region, making the purity of the products very sensitive to small flow-rate fluctuations as well as to errors made on the adsorption isotherm coefficients or the column geometrical characteristics, and to nonideal behavior.

If the operating point moves into the “pure extract” zone (just above the triangle, where $m_3 > a_2$ and $a_1 < m_2 < a_2$), the more retained component is not sufficiently retained and a small fraction of it is carried toward the raffinate port, polluting that stream while the extract stream remains completely pure [14]. The result is a loss of raffinate purity and a yield loss of extract. Conversely, if the operating point is in the “pure raffinate” zone (on the left of the wxy triangle), the less retained component pollutes the extract stream since the constraint $m_2 > a_1$ is no longer satisfied while the raffinate stream is still pure. Finally, if the operating point in the fourth zone

($m_3 > a_2$ and $m_2 < a_1$), the SMB unit does not generate any pure stream, since none of the constraints on m_2 and m_3 are fulfilled. Although stable, steady state operation still takes place, the purity of the two product streams decreases rapidly when the operating point goes farther out from the triangle wxy .

To generate a figure similar to Fig. 1 in the nonlinear case, an accurate knowledge of the competitive adsorption isotherms of the two components of the mixture is needed. However, under nonlinear conditions, the sides of the separation triangle are curves which depend on the feed flow-rate and composition because these parameters control the degree of nonlinear behavior of the isotherm. Furthermore, the constraints on the flow-rate ratios become interdependent [14]. Fig. 2 illustrates how an increase of the feed concentration at constant value of all the other parameters (including feed flow-rate) changes the shape, size and location of the separation triangle in the (m_2, m_3) diagram. It is clear from Fig. 2 that the separation zone shrinks markedly as the feed concentration increases. While the separation triangle changes with increasing feed concentration in Fig. 2, all the separation triangles have the same base, a segment of the diagonal on which the feed

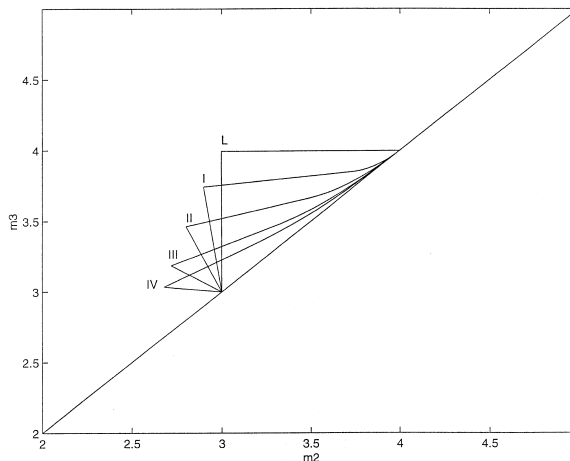


Fig. 2. Effect of increasing feed concentration on the complete separation zone in the (m_2, m_3) plane. $q_{s1} = 46.58$ g/l, $q_{s2} = 49.75$ g/l, $b_1 = 0.0644$ l/g, $b_2 = 0.0804$ l/g, $C_{F1} = C_{F2} = C_{F,T}/2$. (L) $C_{F,T} = 0.02$ g/l, (I) $C_{F,T} = 1$ g/l, (II) $C_{F,T} = 2.5$ g/l, (III) $C_{F,T} = 5$ g/l, (IV) $C_{F,T} = 7.5$ g/l. q_{si} , b_i being the saturation capacity and the capacity factor for component i , respectively.

flow-rate is equal to zero (the diagonal corresponds to $m_2 = m_3$, i.e., to $Q_F = 0$). If the operating point is close to the diagonal, Q_F may be so small that, regardless of the feed concentration, the feed becomes so dilute in the desorbent that the system operates under linear conditions [14].

In summary, the “triangle theory” approach provides a useful tool for the rapid selection of satisfactory experimental conditions for operating an SMB under either linear or nonlinear conditions. It can be used to determine the “safest”, most robust optimal conditions. Optimization using such an approach can, indeed, be quick and efficient. Generally, an optimization procedure based on the “triangle theory” would include the following steps: first, the adsorption isotherms are determined accurately in a concentration range which must include the anticipated feed concentration. Second, the feed concentration and an “arbitrary” switching time (t^*) are carefully chosen. The selection of the switching time is the result of a compromise: short switching times give a higher production rate and a shorter start-up time (the time required to reach steady-state) but they also lead to higher flow-rates. Therefore, there is a lower limit for t^* , set according to the maximum pressure and/or to the maximum flow-rate allowed. Furthermore, short switching times cause faster wear and tear of the switching valves, hence higher maintenance cost. Third, proper values are selected for m_1 and m_4 , values that must fulfill the inequalities mentioned above (see Eqs. (2) and (3)). Finally, the (m_2, m_3) diagram is plotted and m_2 and m_3 are selected so that the operating point lays inside the separation triangle. This point should be close to the triangle apex in order to achieve a high production rate, yet far enough to assure robustness and purity, which can be achieved only at the expense of separation performance [14]. The safe distance from the apex increases with decreasing column efficiency because the triangle theory assumes this efficiency to be infinite.

3. Experimental

3.1. The HPLC system

The chromatographic system used for analytical

purposes was an HP 1090 liquid chromatograph (Hewlett-Packard, Palo Alto, CA, USA), equipped with a ternary-solvent delivery system, an automatic sample injector with a 250- μ l loop, a diode-array UV detector, and a computer data acquisition system using the HP-ChemStation software (version A.05.03). This system was first used to test the eight columns and to determine the parameters characterizing them. Then, it was used to analyze the raffinate, the extract, and the recycle fractions collected at their respective ports during SMB runs. The UV detector was calibrated at 270 nm for quantitation purposes.

3.2. The SMB system

The SMB unit used was a laboratory-scale continuous chromatography Model ICLC 16-10 from Prochrom (Champigneulle, France). The system consisted of: (1) four HP 1050 pumps (Hewlett-Packard); (2) five electro-pneumatic 16-port valves (Valco, Houston, TX, USA), (3) a network of lines delivering nitrogen under constant pressure to actuate the valves at the end of each cycle; (4) three variable-wavelength UV detectors, two of them (Spectroflow Model 757; Applied Biosystems, Ramsey, NJ, USA) were placed downstream the raffinate and the extract pumps, respectively, the third one (HP1100; Hewlett-Packard) was equipped with a high-pressure flow cell and was connected to the main stream of the SMB unit, at the end of one column; (5) a computer controlling the whole system through a software (Chrosoft) provided by Prochrom [17]; and finally (6) a front panel where up to 16 columns can be connected.

A critical step to include in the start-up of an SMB unit before beginning a new separation run is a search for potential internal leaks. In conventional preparative separations the occurrence of leaks is obvious and a periodical, cursory check of the instrument and the ground below it is all what is needed to check for leaks. In SMB, internal leaks are not obvious. Yet, small such leaks may seriously decrease the performance by affecting the purity of the collected fractions. So, the instrument must be checked periodically. The following procedure was used [18].

3.2.1. Feed and solvent valves

All columns are disconnected from the unit. A back pressure controller set at 40 bar is connected to the system in the place of a column inlet and the desorber stream is switched to the corresponding position by software (in “manual control” position). The solvent is pumped through the valve at a set flow-rate of 1 ml/min. The solvent is collected at the controller exit. Internal leaks are observed if some solvent exits from any one of the 15 other connectors on the column panel. The set pressure and the flow-rates were then raised successively to 70 bar and 3 ml/min and to 120 bar and 10 ml/min and the operation repeated. This constitute the internal leak test for one position of the 16-port valve. The back pressure controller is then removed and fastened to the next connector while the stream is switched to the next position. This procedure is repeated sixteen times to check all positions. It is then carried out with the feed stream. No leaks were observed in this series of tests.

3.2.2. Extract, raffinate, and recycle valves

The same procedure is carried out for testing these three valves, with a minor change. The back pressure controller is connected to the system in the place of a column outlet and the pump is connected to the exit stream of one of these three valves. Since the outlet of a column is internally connected to the inlet of the next one, the solvent pumped exits at the inlet of the next position and no solvent should exit in any other position. No leaks were observed except for the extract valve which, in certain positions, gave a very small leak at the highest flow-rate (10 ml/min) only (N.B. 120 bar exceeds the valve specification).

3.3. Chemicals and solvents

Racemic 1-phenyl-1-propanol (PP, $C_9H_{12}O$, molecular mass, $M_r=136.19$) was purchased from Aldrich (Milwaukee, WI, USA). The mobile phase was a solution of HPLC-grade ethyl acetate (5%) and *n*-hexane (95%), both purchased from Fisher (Fair Lawn, NJ, USA). The flow-rate in the experiments reported later was 1 ml/min.

3.4. Columns

Twelve different (20×1.0 cm I.D.) columns were

packed in the laboratory with Chiracel OB (Chiral Technologies, Exton, PA, USA), a stationary phase made of silica particles (20 μm) coated with a cellulose derivative. The eight columns with closest characteristics were used in the SMB unit. The others were kept as spares and used to replace those of the SMB columns whose characteristics drifted too much during operations (see later). For the analysis of the collected fractions, an analytical column (25×0.46 cm I.D.) packed with Chiracel OB-H (5 μm) was used, in order to improve the resolution. The same mobile phase was used as for the SMB operation.

4. Results and discussion

This study involved running several separate campaigns of SMB operation. The long-term stability of the columns was the main source of experimental difficulties encountered. We discuss first the characteristics of the columns and their stability, before presenting the results obtained under linear and nonlinear conditions.

4.1. Column characteristics and stability

Table 1 shows the characteristics of the eight columns used in the first series of SMB experiments, those carried out under linear conditions. The relative standard deviations (RSDs) of the column porosities and of the three retention times (which are all proportional to the column hold-up volume, hence to its porosity) are between 2.1 and 2.4%. Those of the phase ratio (F) and of the two retention factors (which are both proportional to F) are between 3.9 and 8.3%. Because the value of the phase ratio is critical in the derivation of the cycle time, this amplification has a detrimental influence on the production rate of an SMB or on the purity of its products. Column-to-column fluctuations of the porosity will force to adopt a larger safety margin than otherwise possible with a set of identical columns. Variations of the porosity during operations may affect the stability of an SMB [7]. The separation required ($\alpha=1.32$) being relatively easy, the set of columns prepared was suitable for our purpose (Ref. [7], Fig. 6).

After the series of analytical runs had been

Table 1

Characteristics for the eight closest columns obtained with 1-phenyl-1-propanol (PP) and used in the SMB run under linear conditions [experimental conditions: mobile phase=hexane–ethyl acetate (95:5, v/v), flow-rate=2.5 ml/min, detection at 270 nm, V_{inj} = 20 μ l]

Column	t_0 (min)	t_1 (min)	k_1^a	t_2 (min)	k_2^a	α^b	Porosity (ϵ)	F^c
1	4.61	10.64	1.31	12.56	1.72	1.32	0.734	0.363
2	4.57	10.35	1.26	12.61	1.76	1.39	0.727	0.375
3	4.68	10.34	1.21	12.19	1.60	1.33	0.745	0.343
4	4.51	10.37	1.30	12.12	1.69	1.30	0.718	0.393
7	4.50	10.8	1.40	12.63	1.81	1.29	0.716	0.396
12	4.67	10.95	1.34	12.78	1.74	1.29	0.743	0.345
14	4.77	10.91	1.29	12.89	1.70	1.32	0.759	0.317
16	4.74	10.57	1.23	12.44	1.62	1.32	0.754	0.326
Mean	4.63	10.62	1.29	12.53	1.71	1.32	0.737	0.357
SD ^d	0.10	0.25	0.06	0.27	0.07	0.03	0.016	0.030
RSD ^e (%)	2.18	2.37	4.73	2.14	3.93	2.44	2.18	8.27

$$^a k_i' = (t_i - t_0) / t_0.$$

$$^b \alpha = k_2' / k_1'.$$

$$^c \text{Phase ratio} = (1 - \epsilon) / \epsilon.$$

^d Standard deviation.

^e Relative standard deviation, RSD = (SD/mean) · 100.

successfully completed, the SMB unit was stopped and kept idle for a few weeks while the adsorption isotherm data were acquired using column 1 (see Tables 1–3). Then, in order to restart the unit prior to running operations under nonlinear conditions, a run under the same linear conditions as previously implemented was attempted. It proved impossible to duplicate the previous results and to achieve the same purity. The characteristics of all eight columns

were measured again and it was found that they had drifted and that the bed of one column (16) had collapsed by a few mm. Fig. 3 compares the initial analytical chromatogram (dashed-line) and the one obtained after 6 months of use and 2 months of inoperation (solid line). Column 15 was substituted for column 16. Table 2 gives the new characteristics of the column set. Note that, unexpectedly, the RSDs of all the parameters improved.

Table 2

Characteristics for the eight closest columns obtained with 1-phenyl-1-propanol (PP) and used in the SMB run under nonlinear conditions [experimental conditions: mobile phase=hexane–ethyl acetate (95:5, v/v), flow-rate=2.5 ml/min, detection at 270 nm, V_{inj} = 20 μ l]

Column	t_0 (min)	t_1 (min)	k_1^a	t_2 (min)	k_2^a	α^b	Porosity (ϵ)	F^c
1	4.56	10.10	1.21	12.04	1.64	1.35	0.726	0.378
2	4.56	9.84	1.16	12.02	1.64	1.41	0.725	0.379
3	4.59	9.77	1.13	11.68	1.55	1.37	0.730	0.370
4	4.42	9.71	1.20	11.55	1.61	1.35	0.703	0.423
7	4.49	10.28	1.29	12.13	1.70	1.32	0.715	0.399
12	4.59	10.33	1.25	12.19	1.66	1.32	0.730	0.370
14	4.65	10.08	1.17	12.01	1.58	1.36	0.740	0.351
15	4.62	9.88	1.14	11.72	1.54	1.35	0.734	0.361
Mean	4.56	10.00	1.19	11.92	1.62	1.35	0.725	0.379
SD ^d	0.07	0.23	0.06	0.23	0.06	0.03	0.012	0.023
RSD ^e (%)	1.62	2.34	4.68	1.96	3.44	2.15	1.62	5.97

$$^a k_i' = (t_i - t_0) / t_0.$$

$$^b \alpha = k_2' / k_1'.$$

$$^c \text{Phase ratio} = (1 - \epsilon) / \epsilon.$$

^d Standard deviation.

^e Relative standard deviation, RSD = (SD/mean) · 100.

Table 3
Drift in total porosity determined with 6-month interval for eight SMB columns

Column	ϵ_1^a	ϵ_2^b	Drift ^c (%)
1	0.734	0.726	1.08
2	0.727	0.725	0.33
3	0.745	0.730	2.03
4	0.718	0.703	2.11
7	0.716	0.715	0.22
12	0.743	0.730	1.82
14	0.759	0.740	2.52
16 ^d	0.754	0.721	4.38
Mean	0.735	0.724	1.45 ^e

^a Initial porosity.

^b Porosity after 6 months of use.

^c Calculated as $[(\epsilon_1 - \epsilon_2)/\epsilon_1] \cdot 100$.

^d “Bad” column that was replaced.

^e The drift mean does NOT include column 16.

We found it important to test the SMB columns between production campaigns and even, periodically, during long ones and to replace the column whose characteristics deviate most from the average. Slow drifts of the characteristics of some columns were not infrequent during extensive periods of use [19]. Obviously, during these drifts, the experimental conditions of the SMB had to be adjusted repeatedly. It is puzzling to observe that the characteristics of eight or more columns packed the same day, by the

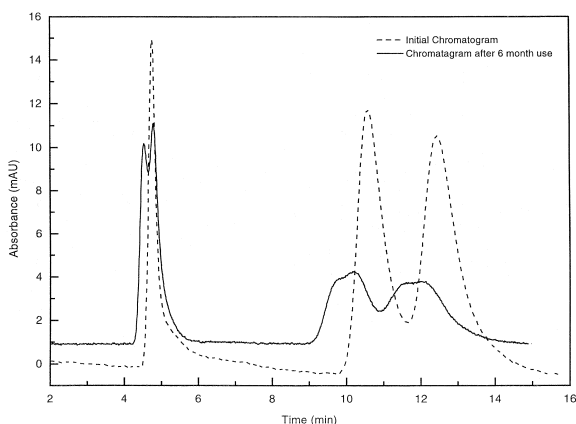


Fig. 3. Analytical chromatograms (dashed line: initial, solid line: after 6 months of use) for a column (16) which collapsed for unknown reasons. Experimental conditions: $V_{inj} = 50 \mu\text{l}$ of racemic PP with TTBB as tracer, mobile phase: hexane–ethyl acetate (95:5), flow-rate = 2.5 ml/min.

same person, with the same packing device, the same packing material, and the same packing procedure can evolve so differently. Some columns barely changed, the porosity of most drifted by 1 to 2.5%, and that of column 16 decreased by 4.4% (see Table 3). Part of the observed drifts may have been caused by the use of ethyl acetate as the mobile phase additive in the first series of experiments instead of the recommended ethanol or isopropanol. In later series of experiments during which isopropanol (5%) was used, the characteristics of the eight SMB columns (different from the ones used in this study) drifted to a much lesser extent, after a longer period (10 months). The retention times decreased by 0.9% or less and the efficiency by 5 to 10% depending on the compound (details not shown in the tables).

4.2. SMB separation under linear conditions

A feed concentration of 0.5 g/l was chosen, corresponding to values of the product bC of 0.016 and 0.020 for the two compounds (see below, isotherm parameters). Under such conditions, the deviation from linear behavior is small. The Henry coefficients (K_i) were derived from the retention factors k'_i ($K_i = k'_i/F$). The corresponding optimum operating parameters were derived using Eqs. (1a–d), for a value of the safety margin, $\beta = 1.047$ and a feed flow-rate of 0.3 ml/min. Eq. (1a) gives the solid-phase flow-rate (Q_S) for a given set of (Q_F, β). Q_S was then used to derive the other flow-rates (Eqs. (1b–d)), and the switching time (t^*) through Eq. (1e). The values of the parameters are shown in Table 4. Care should be taken not to choose a value of β too close to one. Otherwise, the system may become unstable and the risk of it crashing upon a slight drift of any parameter far outweighs any potential increase in the production rate.

After the steady state was reached, the raffinate, extract and recycle streams were collected during a super-period (eight times the switching time for an eight-column SMB unit). These fractions and the feed were analyzed (see Experimental section). Fig. 4 shows the analytical chromatograms obtained for the analysis of the different fractions. The raffinate was nearly 100% pure and the extract more than 97% pure. These purities are sufficient for the accurate measurement of the isotherm data. The recycle

Table 4
SMB experimental conditions for PP enantiomer separation under linear conditions

β^a	Q_F	Q_D	Q_R	Q_E	Q_I	Q_{II}	Q_{III}	Q_{IV}	Switch time (s)
1.047	0.3	0.59	0.43	0.47	2.96	2.49	2.79	2.36	654

^a β : safety factor, Q_F : feed flow-rate (ml/min), Q_D : desorbent flow-rate (ml/min), Q_R : raffinate flow-rate (ml/min), Q_E : extract flow-rate (ml/min), Q_j ($j=I, II, III, IV$): flow-rate (ml/min) in section j , switch time: switching time in seconds.

desorbent was free from enantiomers, which allowed its recycling and is the necessary condition to take advantage of the reduction in mobile phase consumption possible with the SMB process.

4.3. Adsorption isotherms

The measurement and the modeling of the competitive adsorption isotherms of the two enantiomers studied here were previously reported [19,20]. The competitive Langmuir model accounted well for the adsorption behavior of the two PP enantiomers on the CSP used here (Chiracel OB). An advantage of this model is that it allows the straightforward use of the “triangle theory” approach [5] described earlier. This method, initially developed for systems ex-

hibiting Langmuirian type adsorption behavior, can be extended to more complex competitive isotherm models. Only with the Langmuir model, however, can the coordinates of the separation triangle be derived as simple algebraic expressions, easily calculated for any practical application. In the following, we used the set of parameters derived from the fit of the combined single-component and competitive data to the isotherm model (see Ref. [20], Table 3): $a_1=2.97$, $b_1=0.0644$ l/g, $a_2=3.96$, and $b_2=0.0804$ l/g (a_i , Henry coefficient, b_i capacity factor of component I).

4.4. Determination of the operating conditions of SMB under nonlinear conditions

Preliminary experiments showed that a concentration of 5 g/l was appropriate for the total feed concentration (i.e., with $C_{F,1}=C_{F,2}=2.5$ g/l). This concentration is well within the concentration range of the measurements of the adsorption isotherm [19,20]. We note that the products $bC_{F,1}$ and $bC_{F,2}$ are 0.16 and 0.20 for the first and second components, respectively. This value corresponds to a significant degree of isotherm overload, the velocity associated with the feed concentration being 14% and 17% higher than those associated with the zero concentration, respectively [9]. The switching time was first assigned the arbitrary value of 558 s. It was later adjusted to 580 s to take the dead volume of the system into account.

The feed concentration and the switching time being set, we selected values of m_1 and m_4 fulfilling their respective requirements: a lower limit equal to a_2 (here, 3.96) for m_1 and an upper limit for m_4 given by Eq. (4). A value of 4 was assigned to m_1 . For m_4 , the upper limit was calculated from Eq. (4) which gave $m_{4cr}=2.69$. A value of 2.5 was assigned to m_4 . These two values were kept constant during the entire work. With these two values, we obtained

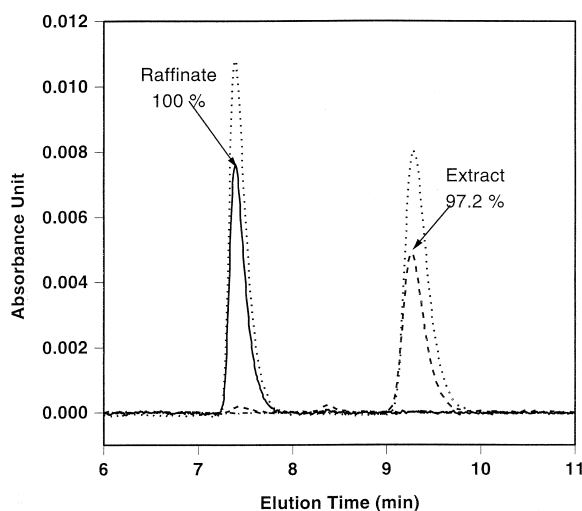


Fig. 4. Analytical chromatograms for samples collected during PP enantiomer separation by SMB under linear conditions (see experimental conditions in Table 2, total feed concentration=0.5 g/l). Solid line: raffinate, dashed line: extract, dashed-dotted line: recycle, dotted line: feed. Analytical conditions: column: 25×0.46 cm I.D. Chiracel OB-H, $V_{inj}=50$ μ l, mobile phase: hexane–ethyl acetate (95:5), flow-rate=1 ml/min, detection at 270 nm.

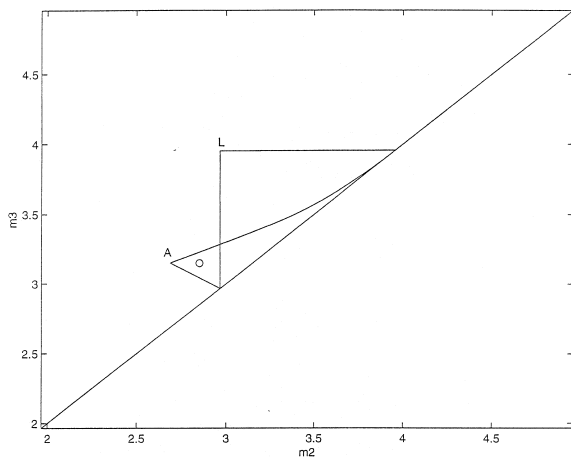


Fig. 5. Separation zone for PP enantiomers in the (m_2, m_3) plane. $q_{s1} = 46.05$ g/l, $q_{s2} = 49.23$ g/l, $b_1 = 0.0644$ l/g, $b_2 = 0.0804$ l/g, $C_{F,T} = 5$ g/l. The point-circle corresponds to: $m_1 = 4$, $m_2 = 2.85$, $m_3 = 3.15$, $m_4 = 2.5$. Triangle A: separation zone for our experiment. Triangle L: separation zone for the linear case.

the triangle with its apex in A (Fig. 5) in the m_2 – m_3 plane. It corresponds to separations carried out with a racemic feed at a total concentration of 5 g/l. The large rectangular triangle with its apex in L corresponds to separations carried out under linear conditions. Various operating conditions corresponding to different points in the A triangle were tried. Excellent results were obtained under the conditions corresponding to $m_2 = 2.85$ and $m_3 = 3.15$ and represented by the \circ symbol in triangle A (Fig. 5). This operating point was a satisfactory compromise between the separation performance (i.e., the purity and the production rate of the two fractions) and its robustness. The corresponding experimental conditions are summarized in Table 5. The feed flow-rate was 0.14 ml/min.

After steady state was reached, the outgoing streams (raffinate, extract, and recycle) were collected during an entire super-period. These fractions were analyzed as indicated earlier (Experimental

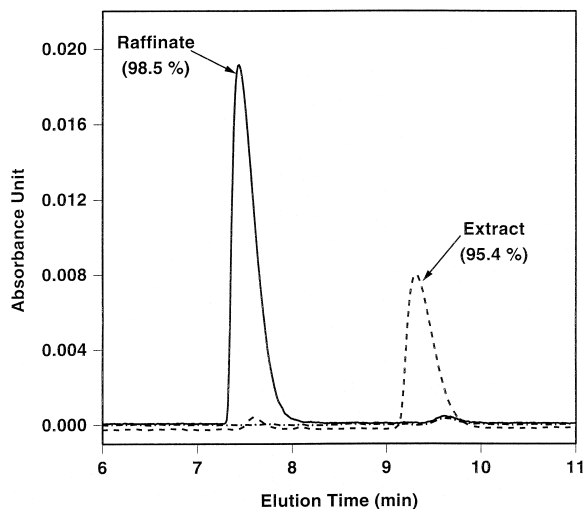


Fig. 6. Analytical chromatograms for samples collected during PP enantiomer separation by SMB under nonlinear conditions (see experimental conditions in Table 5, total feed concentration = 5 g/l). Solid line: raffinate, dashed line: extract, dashed-dotted line: recycle. Analytical conditions: as in Fig. 4.

section). The results of the analyses are shown in Fig. 6. The raffinate stream was more than 98% and the extract more than 95% pure. These purity values are usually considered as satisfactory for industrial production. They could be improved but at the cost of a drastic loss of production rate. If the purity is deemed insufficient, crystallization of these fractions offers a less expensive approach [21].

These results may seem inconsistent with the expectation of a total separation that is suggested by the position of the operating point corresponding to the experimental conditions selected, well within the separation triangle (Fig. 5, triangle A and symbol). Although some inaccuracy in the adsorption isotherm determination may contribute to explain it, this apparent contradiction is most probably due to the nonideal behavior of the chromatographic system. The “triangle theory” [6] assumes an infinite column

Table 5
SMB experimental conditions for PP enantiomer separation under nonlinear conditions (total feed concentration = 5 g/l)^a

Q_F	Q_D	Q_R	Q_E	Q_I	Q_{II}	Q_{III}	Q_{IV}	Switch time
0.14	0.71	0.31	0.54	3.11	2.56	2.7	2.4	558 then 580 s

^a Q_F : Feed flow-rate (ml/min), Q_D : desorbent flow-rate (ml/min), Q_R : raffinate flow-rate (ml/min), Q_E : extract flow-rate (ml/min), Q_j ($j = I, II, III, IV$): flow-rate (ml/min) in section j , switch time: switching time in seconds.

Table 6

Production rate of raffinate and extract produced during PP enantiomer separation by SMB under nonlinear conditions (total $C_F = 5$ g/l)

Product	Flow-rate		Concentration, C^a (g/l)	Production rate ^b	
	ml/min	ml/day		g/day	g/day/kg of CSP ^c
Raffinate	0.31	446.4	1.24	0.55	6.27
Extract	0.54	777.6	0.61	0.48	5.42
Total	–	–	–	1.03	11.69
Feed	0.14	20.16	5.04	1.02	–

^a Determined from calibration curve at 270 nm.^b PR calculated without including impurities.^c Chiral stationary phase.

efficiency, which is not realistic. Deviations from ideal behavior cause band spreading and reduces fraction purity, especially close to the boundaries of the separation triangle [14].

Finally, the daily production rates of both the raffinate and the extract were calculated. The concentration of each stream was determined from the calibration curve of the detector. These concentrations and the corresponding flow-rates were converted into amounts produced per day and kilogram of stationary phase in the SMB unit. The results are reported in Table 6. Overall, the total production rate of purified enantiomers from the racemic mixture was more than 11.6 g/day per kg of CSP. This result is satisfactory and compares well to other found in the literature for similar separations. A slight difference was observed between the production rates of the raffinate and the extract (6.27 versus 5.42 g/day per kg of CSP). This difference is explained in part by errors of measurements on the flow-rates, in part by the difference between the purity of the extract and the raffinate. The amount of feedstock injected was 1.02 g/day, in agreement within the experimental errors on flow-rate measurements with the amount recovered (1.03 g/day). All these results are consistent with a near total recovery yield and errors of a few percent on the measurements of effluent composition and/or on the concentration of the feed stock.

5. Conclusion

In our laboratory, we face two type of problems.

First, we need to generate rapidly sufficient amounts of pure enantiomers in order to be able to measure their competitive equilibrium isotherms on a CSP. Second, we want to check the validity of theoretical predictions based on the fundamentals of chromatography.

Pure enantiomers are costly. A small SMB unit such as the one used in this study, operated under quasi-linear conditions, is easily capable of producing in 1 day one to a few grams of the two enantiomers nearly pure. The procedure consists in first optimizing the SMB for linear conditions, starting its operation with a low feed concentration (ca. 0.2 g/l), and increasing progressively this concentration while checking regularly the product purity. The extract and raffinate streams are collected and concentrated. Purity degrades when the concentration is sufficient for the isotherm curvature to raise the velocity of the extract front above the threshold provided by the safety margin. The feed concentration is then kept constant at the value giving an acceptable product purity. Soon the amounts collected are sufficient to allow the determination of approximate single component isotherms by ECP. This affords an estimate of the parameters of the competitive isotherms (assuming a simple reasonable model). Approximate separation triangles based on these isotherms are drawn for feed concentrations of 1, 2 and 5 g/l. The base of the separation triangle is divided into three equal segments. The apex is connected to the closer of the two points so defined on the diagonal of the plot and an operating point is selected at one third of this new segment from the apex (Fig. 2). Although not

optimum, this operating point gives conditions that allow the rapid production of the few grams needed for the determination of accurate isotherms by frontal analysis and pulse methods [9,20].

The validation of the results of calculations of band profiles, production rates, purities and composition histories of the raffinate and extract ports can be done by selecting favorable operating conditions based on the shape and location of the separation triangle calculated from the accurate isotherms. This validation is made easier by the inclusion of a high-pressure detector cell in the SMB fluid loop [22]. With simple calibration, this cell gives the sum of the two enantiomer concentrations. The determination of the exact optimum conditions is more complex, especially when low efficiency columns are used. The extent of axial mixing (from intra- and extra-column sources) and its influence on product purity must be calculated. The dependence of axial mixing on the mobile phase velocity (different in each section and for extra-column sources) must be taken into account. The influence of the selection of the values of m_1 and m_4 must be assessed. A sophisticated program based on a sound model of nonlinear, nonideal chromatography [9] and able of doing nonlinear optimization [23] is needed. On the other hand, the triangle theory offers a useful method of rapid determination of reasonable values of the operating parameters of an SMB under nonlinear conditions when the isotherm is Langmuirian and its parameters are known. The extension of this method to other isotherms is in progress.

6. Nomenclature

A	Column cross section
a_i	Henry's coefficient for compound I
b_i	Capacity factor for compound I (l/g)
C	Concentration in mobile phase (g/l)
$C_{F,T}$	Total feed concentration (g/l)
F	Phase ratio
K_i	Henry's coefficient of compound I (equivalent to a_i)
k'_i	Retention factor of component I
L	Column length
m_j	Ratio of liquid flow-rate over adsorbed phase flow-rate in section j

Q_j	Flow-rate in section j ($j=I, II, III$ or IV) (ml/min)
Q_D	Desorbent flow-rate (ml/min)
Q_E	Extract flow-rate (ml/min)
Q_F	Feed flow-rate (ml/min)
Q_R	Raffinate flow-rate (ml/min)
Q_S	Solid phase flow-rate (ml/min)
q_s	Saturation capacity (l/g)
t^*	Switching time
t_0	Hold-up time (nonretained compound residence time)
t_i	Retention time of compound I
u_s	Solid phase velocity
V, V_t	Total column volume
V_{inj}	Sample injection volume
<i>Greek symbols</i>	
α	Separation factor
β	Safety margin
ϵ	Total column porosity
λ	Wavelength (nm)
<i>Subscripts and superscripts</i>	
1	Compound 1, the less retained compound
2	Compound 2, the more retained compound
E	Extract
F	Feed
j	SMB section number ($j=I, II, III$ and IV)
R	Raffinate
<i>Abbreviations</i>	
CSP	Chiral stationary phase
ECP	Elution by characteristic point
HPLC	High-performance liquid chromatography
I.D.	Internal diameter
PP	1-Phenyl-1-propanol
PR	Production rate
RSD	Relative standard deviation
SMB	Simulated moving bed
SD	Standard deviation
TTBB	Tri- <i>tert.</i> -butylbenzene

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