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On-line monitoring of enantiomer concentration in chiral simulated moving bed chromatography

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Abstract

Simulated moving bed chromatography is a key technology for the pilot and production scale separation of enantiomers of chiral chemical species. Product quality control is probably the most important issue in this kind of separation at both scales, and for this it is clear that on-line monitoring of absolute enantiomer concentrations plays a major role. In this work, an on-line system consisting of a UV detector and a polarimeter in series is used to monitor the composition of the extract and raffinate streams of a laboratory SMB unit. The model system adopted is the separation of the enantiomers of the Tröger's base on microcrystalline cellulose triacetate (CTA) using ethanol as mobile phase. The technique is effective and accurate, thus providing promising perspectives for SMB process control and dynamic optimization.

Keywords: Enantiomer separation; Simulated moving bed chromatography; Preparative chromatography

1. Introduction

The simulated moving bed (SMB) technology [1] embraces applications with widely different capacity scales, ranging from the tens of thousand of tons per year of hydrocarbon and sugar separations to the few kilograms or tons per year of fine chemical and pharmaceutical separations. In the former case, production scale plants have been run since the early sixties, e.g. for the separation of *p*-xylene from the alkyl-aromatic C_8 fraction using Y-zeolites as selective adsorbent [2]. In the latter case several pharmaceutical companies worldwide are using SMBs, particularly for the separations of the enantiomers of chiral chemical species with suitable chiral stationary phases. Two companies, i.e. UCB Pharma in Belgium and Daicel Chemical in Japan, have been reportedly operating SMB units since 1998 for the production of several tons per year of pure enantiomers of two different chiral drugs [3]. The promising opportunities offered by this technology for chiral separations have motivated a growing interest, which has been supported by the results obtained in several experimental studies [4–19].

The production scale application of a technology poses the problems of checking product quality and guaranteeing long-term stable and controlled operation. As far as SMBs are concerned these issues have been addressed in the open literature only in the case of *p*-xylene separation. An on-line device for com-

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position measurement using Raman spectroscopy has been recently developed [20] and then exploited within an appropriate control algorithm [21].

With the ultimate goal of developing a control system for small-scale chiral SMB separations, the on-line monitoring of the enantiomeric purity of the product streams is dealt with in this work. This is achieved by measuring the absolute enantiomer concentration in the product streams, i.e. in the extract and the raffinate streams where the more and less retained enantiomer, respectively, are collected. We report the results obtained in a liquid phase SMB unit, which is used for the separation of the enantiomers of the Tröger's base [18] and is equipped with an on-line monitoring system consisting of a UV detector and a polarimeter in series. The accuracy of the method is assessed by comparison with the results of off-line chiral HPLC analysis.

2. Experimental

2.1. Materials

The SMB separation of the Tröger's base enantiomers on microcrystalline cellulose triacetate (CTA) using ethanol as mobile phase has been considered as a model system. The chemicals and stationary phase, as well as the procedure to pack the columns of the SMB unit, are as reported in a previous paper [18]. It is worth noting that the Tröger's base racemic mixture (Aldrich, 98%) has been further purified by recrystallization from ethanol. The pure component isotherms of the two enantiomers on CTA have been measured [18]. Likewise their competitive adsorption behavior has been characterized experimentally and modeled using a Real Adsorbed Solution Theory approach [22]. Chiral analytical chromatography has been carried out on a HP 1090 liquid chromatograph using a Chiralcel OJ (Daicel) column (25 cm×0.46 cm I.D.) with a mixture ethanol–hexane 1:1 as mobile phase under isocratic conditions.

2.2. Laboratory SMB unit

The complete scheme of the laboratory SMB unit has been discussed elsewhere [18]. For the sake of clarity, we will report here only the features essential for the discussion of the on-line monitoring system.

The unit is constituted of eight HPLC columns (25 cm×0.46 cm I.D.), each section having two columns. These are located in a thermostatic chamber, to guarantee isothermal operation. An open-loop configuration has been adopted, implying that five flows (feed, eluent, extract, raffinate and recycled eluent) have to be regulated. Four HPLC pumps (JASCO PU-987) control the two inlet streams, i.e., feed and eluent, as well as two of the three outlet streams, i.e., extract and raffinate. The overall material balance in the unit determines the flow-rate of the recycled eluent. The pressure level in the unit is monitored by pressure sensors at the outlet of every column. Five (12+1)-port multi-position valves (Vici-Valco EMT-6-CSD12UW) implement the periodic port switching mechanism. A check valve (Nupro) located on the lines connecting each column to the following one determines the flow direction. The outlet ports of each column and the inlet ports of the following one are located before and after, respectively, the check valve in order to avoid cross-contamination. The volume between the multi-position valves and the main SMB loop has been minimized by using 1 mm I.D. tubing. All the other lines in the unit are 0.25 mm I.D.. It is worth noting that the extra column dead volume, i.e. the volume between each pair of successive columns in the SMB unit made of tubing, fittings and check valves, is 1.8 ml, which is non-negligible as compared to the column volume, i.e., V=4.15 ml [18,23].

The SMB operation is automated using the software package Labview® (National Instruments), which also allows proper filing of all quantities measured on-line.

2.3. On-line monitoring system

As shown in Fig. 1 the on-line monitoring of the absolute enantiomer concentration in either the extract or the raffinate stream is made possible by the use of a UV detector (Jasco UV-970) and a Polarimeter (Jasco OR-990) in series [24–26]. The principle behind this approach is on the one hand that the signal of the achiral UV detector represents the absorbance of the mixture, which is proportional to the sum of the concentrations c_A and c_B of the more

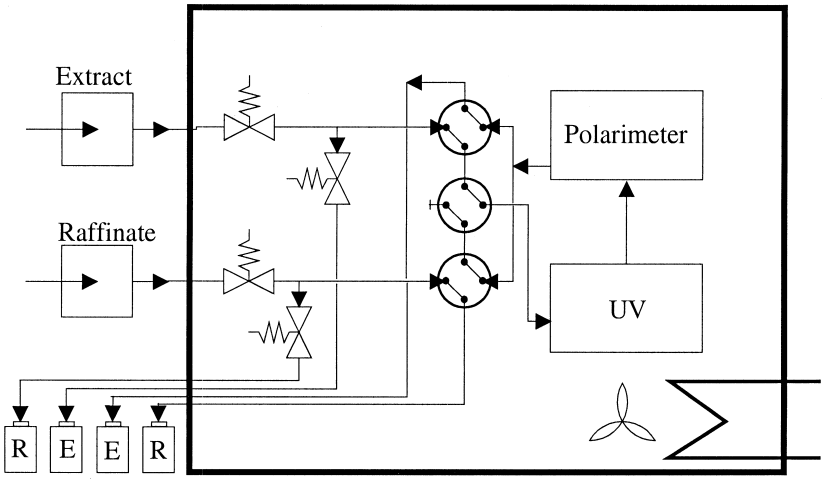

Fig. 1. Scheme of the experimental set-up of the on-line monitoring system.

retained (+)-TB enantiomer and of the less retained (−)-TB enantiomer, respectively. On the other hand the signal of the polarimeter, which emits polarized light that is rotated in opposite directions by the two enantiomers, is proportional to the difference of these two concentrations. Through proper calibration and signal processing, as discussed in the next section, the absolute concentration of the two enantiomers can be determined. It is worth noting that, since the two detectors are in series, the time needed to the monitored stream to go from one to the other has to be accounted for when elaborating the signals. In other words, the two signals have to be synchronized.

The two detectors, particularly the polarimeter, must be kept at constant temperature and pressure in order to obtain stable and reproducible signals. Therefore, the detectors and the ancillary valves are located in a thermostatic chamber, where the temperature is kept at 23±0.2°C. This has been obtained using a water heat exchanger installed in the chamber and a fan which provides air re-circulation.

Pressure in the detectors is kept within the required limits (maximum is 20 bar) by means of two back-pressure valves downstream the extract and raffinate pumps. In addition, for safety, two relief valves allow by-passing the detectors and deviating the product streams to two separated tanks if nevertheless pressure exceeds its upper bound. Though useful for pressure control, these valves have the drawback of introducing a rather significant dead volume in the withdrawal line from the internal SMB loop to the monitoring point. This implies a significant time delay, which is given by the ratio between the dead volume and the flow-rate, and a major back-mixing effect, as it will be discussed in the section on the experimental results.

2.4. Experimental procedure

The processing of the on-line signals obtained by the two detectors described above requires the solution of the following system of linear equations, where the unknowns are the enantiomer concentrations c_A and c_B, with units of g/l:

$$\begin{cases} R_{\mathrm{UV}}(t) = \alpha(c_A(t) + c_B(t)) \\ R_{\mathrm{POL}}(t + \Delta t) = \beta(c_A(t) - c_B(t)) \end{cases} \quad (1)$$

R_{uv} and R_{POL} are the measured UV and polarimeter signal, respectively and α and β are constants to be determined through calibration. The detector signals and the concentrations c_A and c_B are all functions of time. However, a given plug of fluid that reaches the UV detector at time t will reach the polarimeter only at time $t + \Delta t$, due to the volume between the two. The time delay Δt is given by this volume divided by the fluid flow-rate. The former has to be determined very precisely to guarantee accurate concentration measurements. It should also be pointed out that

contrary to the polarimeter signal, which is stable, the UV signal exhibits a linear drift during the few days of duration of a typical SMB run. In our experiments its slope was measured reproducibly to be $4.1 \cdot 10^{-8}$ V/s. Therefore, the value used in the left-hand side of the first equation above is the real signal reduced by the measured drift.

It is worth noting that the precision of the polarimeter is $\pm 10^{-3}$ V, whereas that of the UV detector is higher i.e. $\pm 10^{-6}$ V. Using Eq. (1), it can be readily shown that the corresponding error on the concentration of either enantiomer is about ± 0.0015 g/l.

Before running an SMB experiment with on-line monitoring a few actions have to be taken. First, after switching on the detector lamps, the system must be let stabilize at the desired temperature. Then the values of the coefficients α and β have to be calibrated or at least checked. This is done through a standard calibration procedure using a set (at least eight) of standard samples of pure enantiomers at different concentrations, covering the whole range of outlet concentrations expected during the forthcoming experiment. Typical values of α and β are 0.72 and 0.35 V L/g, respectively. These coefficients depend on pressure, temperature and light intensity of the two lamps, hence they have to be re-calibrated often and checked before every SMB run.

3. Experimental results

3.1. Column experiments

A series of column experiments have been run in order to check the operation of the on-line monitoring system before connecting it to the SMB unit. Two of these are illustrated in Figs. 2 and 3, where the concentration of the two enantiomers at the column outlet is plotted vs. time. In both cases a column with the same characteristics and same stationary phase as the SMB ones has been used. A volumetric flow-rate of 0.5 ml/min has been adopted, using pure ethanol as mobile phase. The two figures refer to a pulse and a breakthrough experiment, respectively, which have been carried out under the conditions specified in the corresponding captions. The information provided by

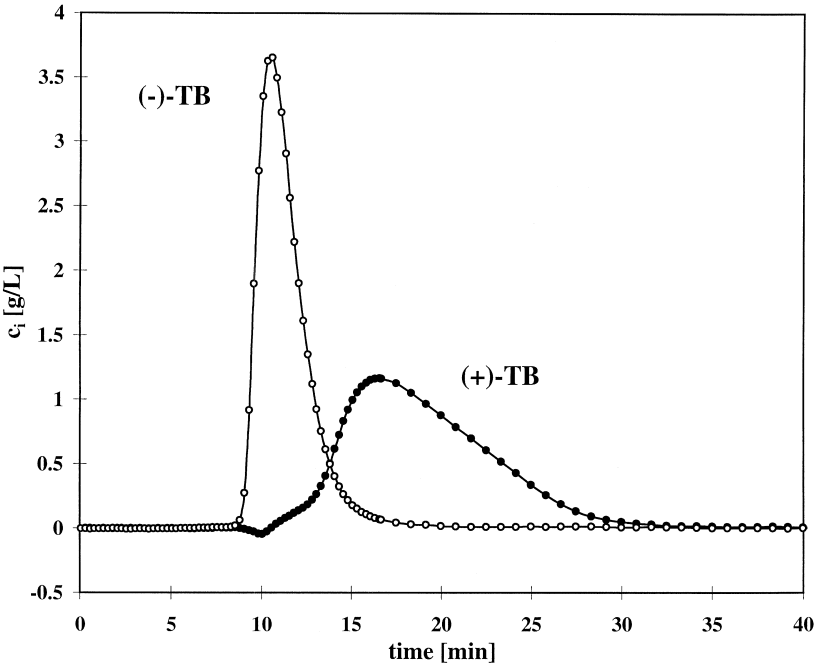

Fig. 2. Pulse experiment. Pulse duration: 210 s; concentration of the pulse feed: 3.08 g/l of each enantiomer.

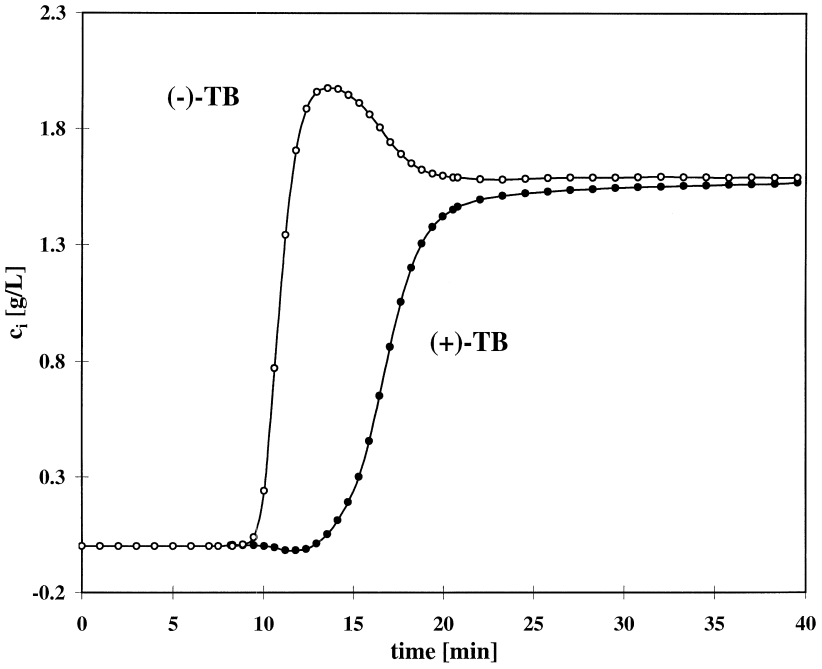

Fig. 3. Breakthrough experiment. Composition of the feed: $c_A = 1.56$ g/l; $c_B = 1.59$ g/l.

these on-line monitored experiments can be effectively used to characterize the behavior of the system under investigation, namely to determine the adsorption isotherms and the transport parameters of a column model [22]. It is worth noting that the experimental set-up for column experiments is simpler than the one illustrated in Fig. 1 and that the dead volume between column and detectors can be minimized, thus eliminating the time delay discussed at the end of Section 2.2.

3.2. SMB experiments

The experimental results discussed below refer to SMB runs where the following operating conditions have been selected: feed racemic concentration equal to 2 and 3 g/l (see Table 1); volumetric flow-rates in the four sections of the unit: $Q_1 = 0.44$ ml/min, $Q_2 = 0.19$ ml/min, $Q_3 = 0.23$ ml/min and $Q_4 = 0.11$ ml/min and switch time as reported in Table 1.

Since with the system illustrated in Fig. 1 only one

Table 1
Average composition and corresponding purity of the product streams during the four experimental runs, as measured by the on-line monitoring system and through off-line chiral HPLC

Run	t^* [min]	c_{Feed} [mg/ml]	Stream	Off-line HPLC			On-line monitoring		
				c_A [g/l]	c_B [g/l]	*Purity [%]*	c_A [g/l]	c_B [g/l]	*Purity [%]*
1	42	3	Raffinate	0.006	0.460	*98.7*	0.005	0.448	*98.9*
			Extract	0.237	0.020	*92.2*	–	–	–
2	42	3	Raffinate	0.006	0.463	*98.7*	–	–	–
			Extract	0.239	0.021	*91.9*	0.231	0.020	*92.0*
3	48	2	Raffinate	0.005	0.324	*98.6*	0.007	0.323	98.0
			Extract	0.156	0.004	*97.7*	–	–	–
4	55	2	Raffinate	0.014	0.331	*95.6*	0.014	0.330	95.9
			Extract	0.150	0.001	*99.1*	–	–	–

product stream at a time can be analyzed, two runs under identical operating conditions have been repeated first, while monitoring the raffinate during run one and the extract during run two. As reported in Table 1, the off-line HPLC analysis of the extract and raffinate collected at the end of each run shows a good reproducibility with a 98.7% raffinate purity and a 92% extract purity. These non-complete separation conditions were chosen on purpose, based on the previous investigation of the steady state performance of the unit [18], in order to allow for the presence of both enantiomers in both outlet streams so as to better appreciate the on-line monitoring operation.

The absolute enantiomer concentration profiles during the entire SMB run are illustrated in Fig. 4 as a function of the cycle number, corresponding to eight switches of the inlet and outlet ports (hence 336 min in this case). Note that Fig. 4, as well as the following ones, comes always in pairs, since Fig. 4(a) refers to the raffinate stream, whereas Fig. 4(b) to the extract stream. The data in Fig. 4 show not only the expected cyclic stationary behavior of the unit, but also its start-up. The cyclic steady state is reached after about four complete cycles. However, it is remarkable that in the extract stream the start-up seems to be rather shorter than in the raffinate stream, which is likely due to the strong non-linearity of the SMB dynamics.

In spite of the clear cyclic steady state pattern in Fig. 4 it is however evident that the concentration profiles are not really periodic with period equal to the time interval between two successive switches of the inlet and outlet ports, i.e. of 42 min. This is due to small differences among the eight columns of the SMB unit, which cannot be completely avoided during the packing procedure as discussed in details elsewhere [18]. This is even more evident in Fig. 5, where the concentration profiles have been averaged over the switch time interval. This figure shows rather evidently that a super-period exists, with period equal to the entire cycle, i.e. 336 min. This conclusion is supported by the data shown in Fig. 6, where the concentration profiles are averaged over a time period equal to the entire cycle. Now, the average composition measured during different cycles becomes indeed constant at steady state. The sequence of Figs. 4–6 illustrates nicely how some of the peculiar dynamic features of SMBs, which look somehow complex at first sight due to the cyclic transient behavior, are in practice simple to handle when considering averages over the appropriate time interval, i.e. the cycle time.

The accuracy of the information gathered using the on-line monitoring system and reported in Figs. 4–6 has been checked by comparison with the HPLC off-line analysis as shown in Table 1 in term of the average concentrations and purities. The concentration profiles in Fig. 4 have been zoomed in and re-plotted in Fig. 7 during a period of time comprising two time periods between successive valve switches, i.e. 84 min. Since this has been taken after start-up was completed, the profiles are periodic, as expected. It is worth noting that they exhibit a marked sinusoidal character, which on the contrary is not expected when a SMB unit is operated under overload conditions, leading to nonlinear competitive adsorption behavior. Under these conditions in fact sharp shock concentration transitions develop in general, together with smoother concentration changes, thus yielding concentration peaks highly non-symmetric. The profiles illustrated in Fig. 7 can be justified based on two different arguments. First, as already observed earlier [18], the feed concentration selected in these experiments corresponds to only moderately nonlinear conditions. Secondly, the above mentioned dead volume in the line from the SMB internal loop to the UV detector, i.e. 5.1 ml, plays an important role at the rather small flow-rates used in this study in damping the concentration dynamics. The dead volume is in fact mainly concentrated in the back pressure valve and in the pump and its behavior is likely to be similar to that of a well-mixed vessel. Since this has a residence time of about 130 min, it is clear that the faster concentration dynamic of period equal to 42 min are completely damped thus leading to rather symmetric measured concentration profiles.

Two more experimental runs, i.e. runs three and four, are reported in Table 1. Both have been carried out at the same flow-rates of runs one and two, but at 2 g/l of feed concentration; two different values of the switch time have been adopted. As it can be readily observed by inspection of the purity values measured through off-line HPLC analysis, raffinate purity decreases and extract purity increases as

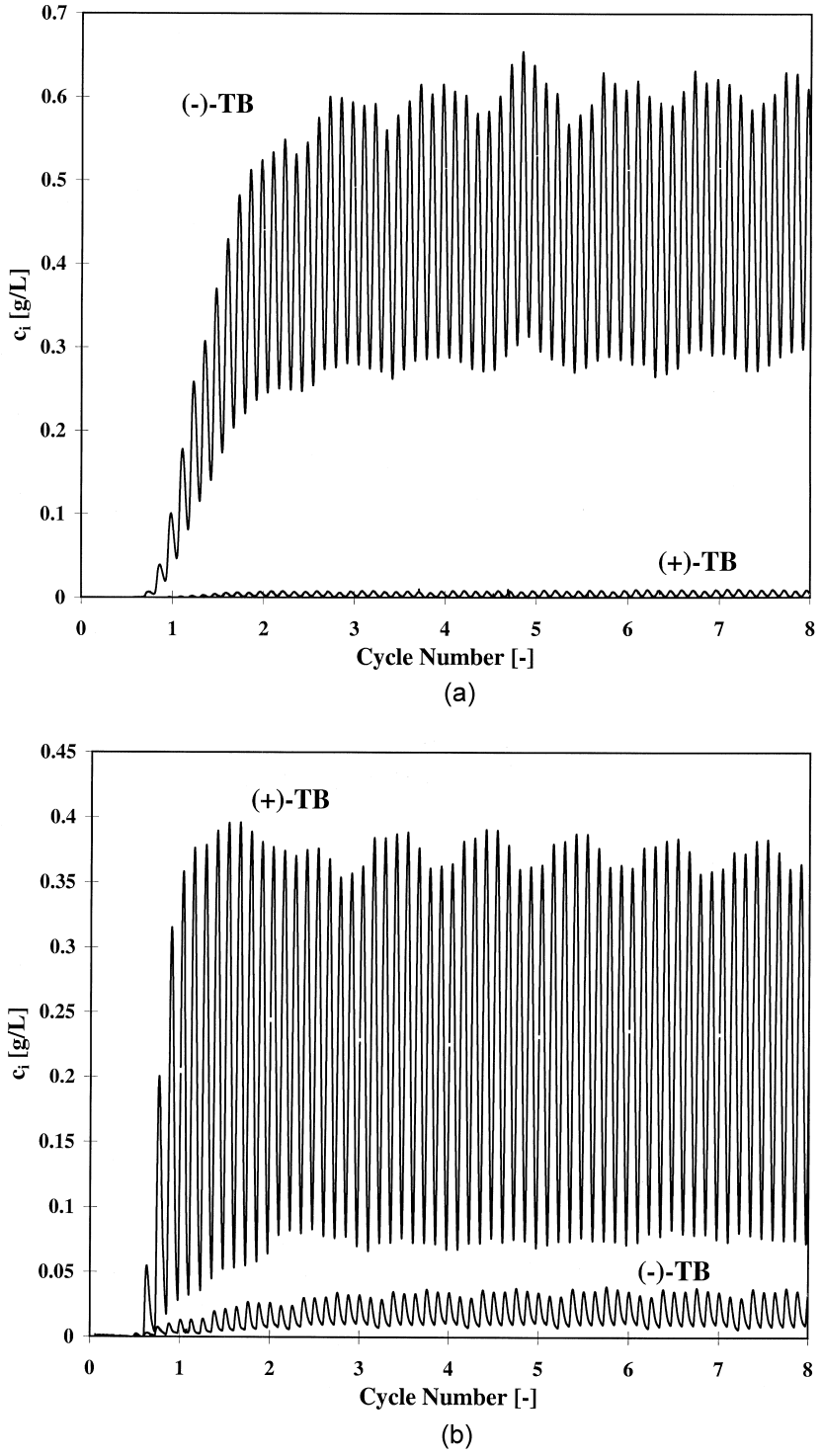

Fig. 4. On-line monitored concentration profiles of the raffinate (a) and extract (b) streams during the SMB experimental runs discussed in Section 3. The horizontal coordinate is the number of cycles, each corresponding to 336 min in this case.

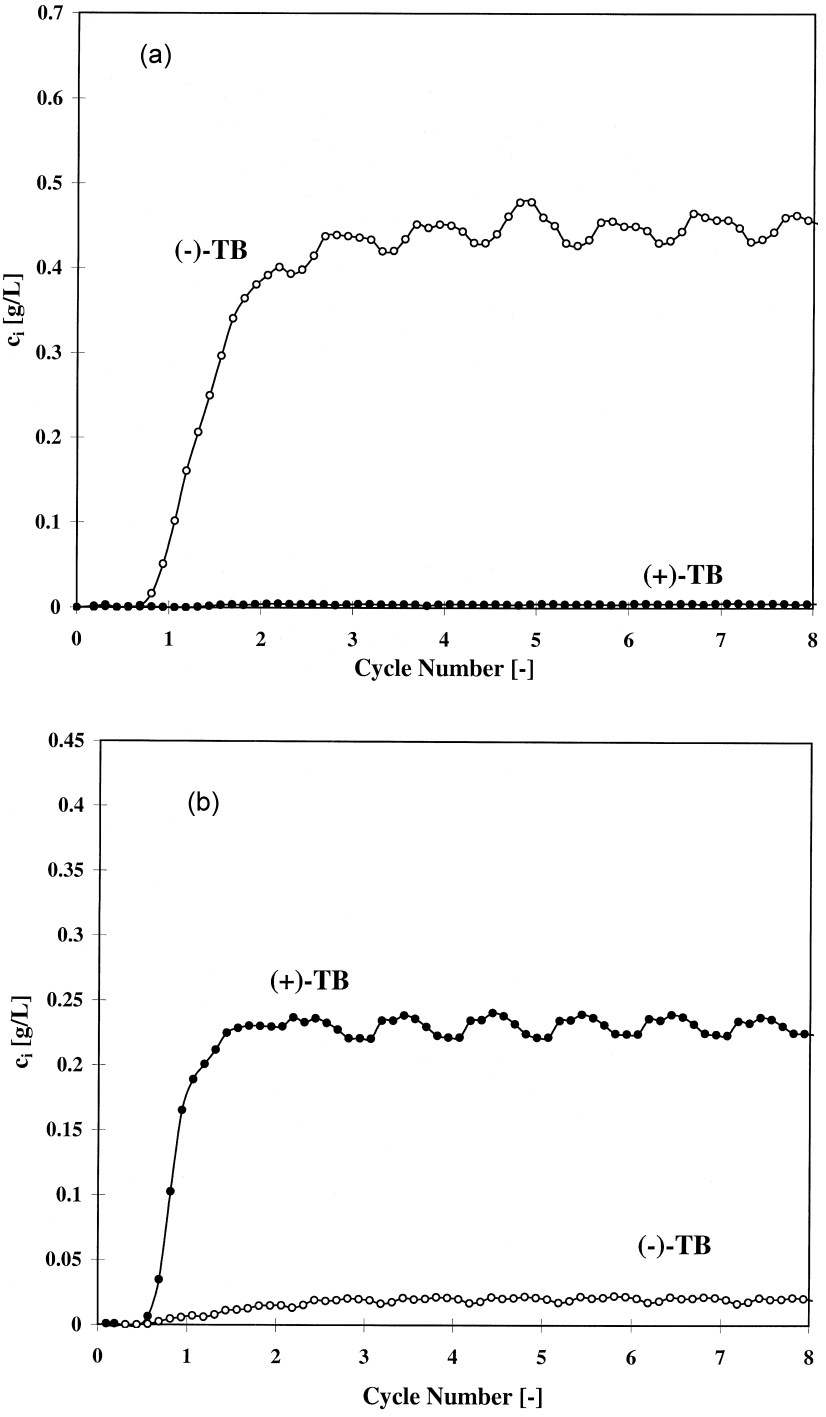

Fig. 5. Concentration profiles in Fig. 4 after averaging over a time period equal to the switch time, i.e. the time between two successive switches of the inlet and outlet ports; (a) raffinate; (b) extract.

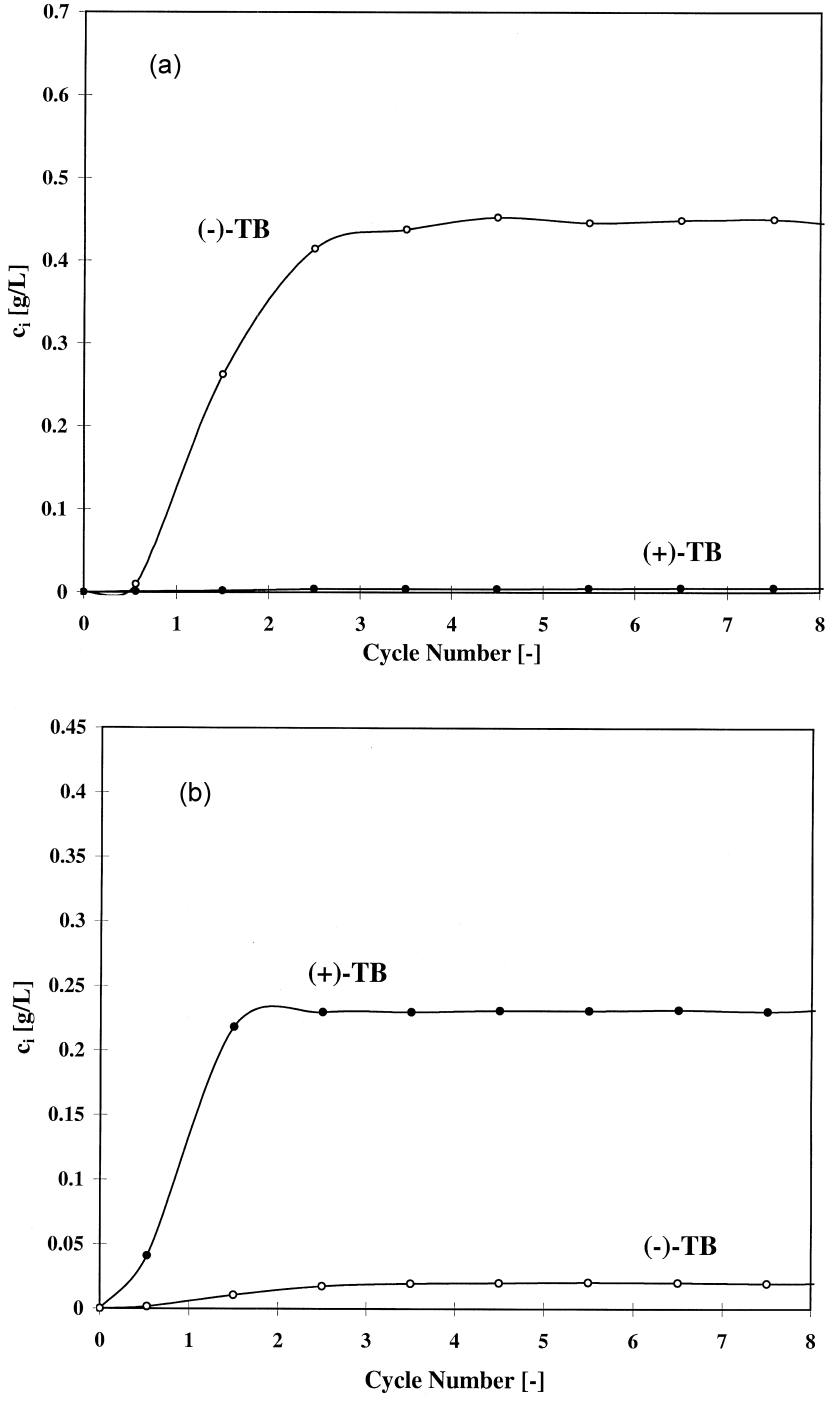

Fig. 6. Concentration profiles in Fig. 4 after averaging over a time period equal to the time to go through an entire cycle, i.e. 336 min; (a) raffinate; (b) extract.

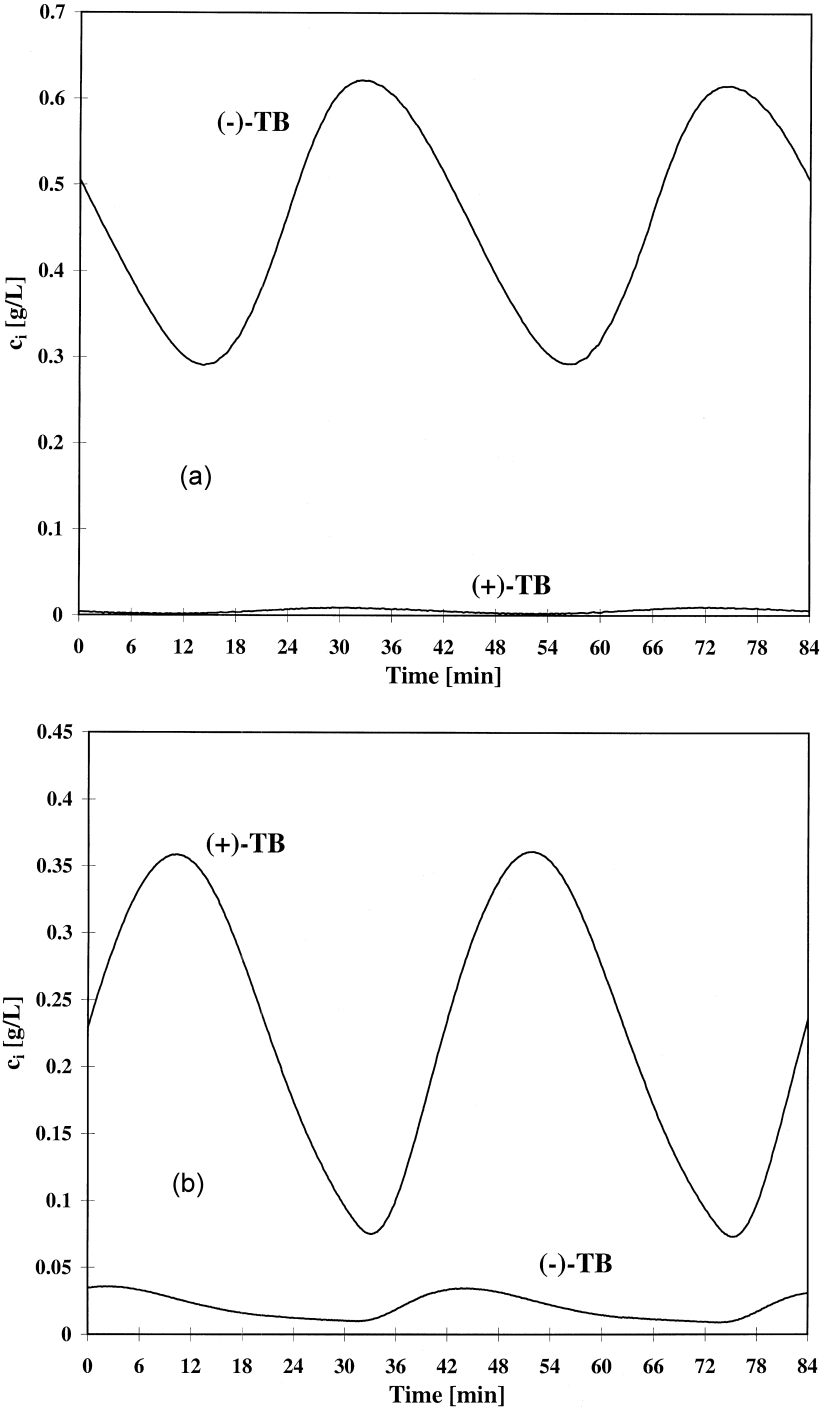

Fig. 7. Zoom in of the concentration profiles in Fig. 4 when the unit has already achieved cyclic steady state; (a) raffinate; (b) extract.

expected when the switch time is increased [18]. The fact that on-line monitoring (of the raffinate stream in both cases) provides exactly the same concentration and purity values as the off-line analysis constitutes a further confirmation of the accuracy of the proposed approach.

4. Discussion and conclusions

The on-line system that has been developed in this work has proved effective for monitoring the absolute enantiomer concentrations in the product streams of a chiral SMB unit. This has allowed characterizing both the low frequency dynamics, i.e. on the scale of the start up time, and the high frequency dynamics, i.e. on the scale of the switch time, of the laboratory SMB unit.

An important effect observed in our experimental set-up is the significant back mixing in the line between the internal SMB loop and the detectors, producing significant extra column band broadening. This is a drawback since it causes time delay in the measurement. However, this is well characterized and known and therefore the drawback can be overcome using an appropriate control algorithm that compensates for such delay, e.g. a dead-time compensator or Smith predictor [27]. The relevance of the results obtained with the monitoring system presented in this work is related to its potential uses. The most evident one is process control.

However, the optimization of start-up and shut-down periods may also be relevant particularly for small scale SMB applications where the same SMB unit is used repeatedly to separate small batches of different racemic mixtures in operations lasting for short periods of time.

References

[1] D.M. Ruthven, C.B. Ching, Chem. Eng. Sci. 44 (1989) 1011.
[2] M.J. Gattuso, B. McCulloch, J.W. Priegnitz, Chem. Tech. Europe 3 (1996) 27.
[3] R.-M. Nicoud, Pharm. Technol. Eur. 11 (1999) 28.
[4] G. Fuchs, R.-M. Nicoud, M. Bailly, in: Proc. of the 9th Int. Symp. on Preparative and Industrial Chromatography and Related Techniques, Basel, 1992.
[5] M. Negawa, F. Shoji, J. Chromatogr. 590 (1992) 113.
[6] C.B. Ching, B.G. Lim, E.J.D. Lee, S.C. Ng, J. Chromatogr. 634 (1993) 215.
[7] R.-M. Nicoud, G. Fuchs, P. Adam, M. Bailly, E. Küsters, F.D. Antia, R. Reuille, E. Schmid, Chirality 5 (1993) 267.
[8] F. Charton, R.-M. Nicoud, J. Chromatogr. A 702 (1995) 97.
[9] E. Küsters, G. Gerber, F.D. Antia, Chromatographia 40 (1995) 387.
[10] E. Cavoy, M.-F. Deltent, S. Lehoucq, D. Miggiano, J. Chromatogr. A 769 (1997) 49.
[11] R.M. Devant, R. Jonas, M. Schulte, A. Keil, F. Charton, J. Prakt. Chem. 339 (1997) 315.
[12] E. Francotte, P. Richert, J. Chromatogr. A 769 (1997) 101.
[13] D.W. Guest, J. Chromatogr. A 760 (1997) 159.
[14] L.S. Pais, J.M. Loureiro, A.E. Rodrigues, Chem. Eng. Sci. 52 (1997) 245.
[15] M. Schulte, R. Ditz, R.M. Devant, J. Kinkel, F. Charton, J. Chromatogr. A 769 (1997) 93.
[16] M. Juza, O. Di Giovanni, G. Biressi, V. Schurig, M. Mazzotti, M. Morbidelli, J. Chromatogr. A 813 (1998) 333.
[17] D. Seebach, M. Hoffmann, A.R. Sting, J.N. Kinkel, M. Schulte, E. Küsters, J. Chromatogr. A 769 (1998) 299.
[18] M. Pedeferri, G. Zenoni, M. Mazzotti, M. Morbidelli, Chem. Eng. Sci. 54 (1999) 3735.
[19] S. Nagamatsu, K. Murazumi, S. Makino, J. Chromatogr. A 832 (1999) 55.
[20] P. Marteau, G. Hotier, N. Zanier-Szydlowski, A. Aoufi, F. Cansell, Process Control and Quality 6 (1994) 133.
[21] E. Kloppenburg, E.D. Gilles, J. Process Control 9 (1999) 41.
[22] C. Migliorini, M. Mazzotti, G. Zenoni, M. Pedeferri, M. Morbidelli, AlChE J. (2000), submitted for publication.
[23] C. Migliorini, M. Mazzotti, M. Morbidelli, AlChE J. 45 (1999) 1411.
[24] K.-H. Rimböck, F. Kastner, A. Mannschreck, J. Chromatogr. 351 (1986) 346.
[25] M. Pedeferri, S. Petrozzi, M. Mazzotti, M. Morbidelli, Chimica Oggi, Chemistry Today 16 (3/4) (1998) 38.
[26] G.B. Cox, O. Dapremont, H. Colin, J. de Tournemire, Poster presented at the SPICA 98 Symposium, Strasbourg, France, September 1998.
[27] G. Stephanopoulos, Chemical Process Control, Prentice-Hall, Inc, Englewood Cliffs, NJ, 1984.