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Journal of Chromatography A, 1006 (2003) 267–280
JOURNAL OF CHROMATOGRAPHY A
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Batch and simulated moving bed chromatographic resolution of a pharmaceutical racemate

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Abstract

The preparative chromatographic resolution of racemates has become over the past few years a standard approach for the generation of enantiomers in pharmaceutical research and development. This paper will discuss the chromatographic resolution of a racemic pharmaceutical intermediate. Initial analytical method development to determine the best preparative conditions will be presented. Batch resolution of kg quantities of racemate followed by the simulated moving bed resolution of tens and hundreds of kg of racemate will also be discussed. Finally the different approaches used for the separation will be compared.

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

1. Introduction

The necessity to generate individual enantiomers for testing has become a growing priority in pharmaceutical research and development. This necessity is directly related to the increased knowledge of the effect differing enantiomers have in biological systems. There are two approaches to obtaining enantiomerically pure chemicals. These are (1) asymmetric synthesis of the desired enantiomer and (2) resolution of a racemic mixture into individual enantiomers. While asymmetric synthesis is useful when larger quantities of enantiomers are required, the time required to develop the synthesis can make this approach impractical when small quantities (1–10 kg) are needed. Asymmetric synthesis can also be impractical in the early stages of pharmaceutical research and development when time is of the utmost priority. An additional disadvantage of asymmetric synthesis is the generation of only one of the enantiomers. Resolution of a racemic mixture has the advantage of producing both enantiomers, essential for testing. Resolution methods include recrystallization, enzymatic resolution, indirect chromatographic resolution and direct chromatographic resolution. The time required to develop a recrystallization method or an enzymatic resolution can also make this an inefficient approach for the generation of enantiomers during early pharmaceutical research

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0021-9673/03/$ – see front matter
doi:10.1016/S0021-9673(03)00782-9

and development. Indirect chromatographic resolution, involving derivatization of the enantiomers to form a pair of diastereomers, followed by separation on an achiral stationary phase is useful for the generation of individual enantiomers [1]. While the separation of diastereomers is usually easier than the separation of enantiomers (due to increased mobile phase options and increased saturation capacities of silica gel relative to chiral phases), and has the advantage of being easier to sale up, there are limitations to this approach. First, high enantiomeric purity of the derivatizing agent is essential. Also, removal of the derivative after chromatographic separation should not cause racemization of the desired enantiomer. Finally the use of indirect chromatographic separation adds two steps to the synthesis, the reaction to form the derivatives prior to chromatography and the reaction to remove the derivatives after chromatography. The Separations Group at Pharmacia has found the use of preparative chromatography using chiral stationary phases (CSPs) to be the most efficient approach for generation of small (1–10 kg) quantities of enantiomers during early pharmaceutical research and development [2–6]. In past years the preparative resolution of racemic mixtures has rapidly become a standard approach for the generation of enantiomers in pharmaceutical research and development [7–12].

Simulated moving bed (SMB) chromatography has been utilized in the food and petrochemical areas for over 30 years. SMB is often less expensive than batch chromatography. Higher productivities and decreased solvent consumption have been observed for SMB vs. batch operations. Only in the past seven years has the use of SMB for enantiomeric separations become a routine operation [12–22]. Recently the use of SMB for chromatographic resolution of enantiomers has been used at a manufacturing scale by numerous pharmaceutical companies [23].

This paper reports on the preparative chromatographic resolution of the enantiomers of a pharmaceutical intermediate from the mg to the kg scale. The batch separation of 77 kg of racemate will be presented. The use of SMB for the large-scale separation of this compound is also discussed. Finally, the productivities and solvent usage for each of the approaches used for the separation are compared.

2. Experimental

2.1. Equipment

The analytical chromatograph used was an Agilent HP1100 (San Fernando, CA, USA) system consisting of a quaternary pump, an autosampler and a diode array detector.

The batch chromatograph was a SepTech (Wakefield, RI, USA) preparative skid system consisting of two high-pressure pumps, a dedicated sample pump and a UV detector. The CSP was packed into a 15 cm I.D. Novasep (Boothwyn, PA, USA) dynamic axial compression column.

The laboratory-scale SMB system was a Licosep 12-26 (NovaSep, Nancy, France). The CSP was 20-μm Chiralpak AD and was packed into eight 5 cm I.D. stainless steel columns (Merck, Darmstadt, Germany).

All equipment used at Carbogen has recently been described in this journal [25].

The pilot-scale SMB unit is equipped with eight dynamic axial compression columns of 200 mm in diameter. The outlet extract and raffinate lines are directly connected to falling film evaporators allowing the concentration of the product before storage into 500-gallon totes (1 gallon=3.785332 l). The solvent recovered at the falling film is recycled to the eluent tank after being tested for product carry over. The feed was prepared in a 500-l tank equipped with a pneumatic mixer. Once the racemic mixture was completely dissolved a sample was taken for concentration determination. After concentration was confirmed, the feed was transferred to a 1000-l reservoir, which is connected to the SMB feed pump.

2.2. Materials

The chiral stationary phase was obtained from Chiral Technologies (Exton, PA, USA) as 20 μm bulk packing. All chemicals for purification were synthesized in the laboratories and plants of Pharmacia (Skokie, IL, USA and St. Louis, MO, USA) or Carbogen (Aarau, Switzerland). The solvents were reagent grade or better and obtained from a variety of sources.

For the work performed at Aerojet, technical-

grade methanol (97% min assay) was used as mobile phase for the SMB. All solvent for high-performance liquid chromatography (HPLC) was HPLC grade except eluent used for in-process control that was of the same quality as of the SMB eluent.

2.3. Pilot SMB column packing and testing

The columns were packed using two lots of chiral stationary phase Chiralpak AD (Daicel, Japan) prior to the first campaign. The two lots were blended to have the same ratio of each lot in each column.

The columns were packed with 1.8 kg of CSP per column using methanol technical grade as slurry solvent. The average column length was 8.8 cm. The columns were tested at 40 °C using a sample of the racemic feed at ~50 g/l. A 12.5-ml volume of racemate was injected and eluted at 50 l/h. The columns were re-tested prior to the second campaign and unpacked at the end of that campaign. They were repacked for the third campaign using the same amount of CSP per column (1.8 kg). The average bed length was 8.7 cm. The average column performance is presented in Table 1. These data show the column efficiency changed between the first two campaigns but was increased after re-packing the columns. However the retention times have changed and this had an effect on the separation parameters.

Prior to campaign 1, a pulse injection was performed on three columns in series to determine the retention times and hence calculate the appropriate cycle time. The retention times were 580 s for the raffinate and 878 s for the extract after correction for the system dead volume (17 s). Efficiency was 551 and 454 plates for the three columns in series.

3. Results and discussion

3.1. Analytical method development

The racemate to be resolved was a proprietary intermediate to an API (active pharmaceutical ingredient) in early development at Pharmacia. Initial synthesis (~100 g scale) of this API was performed using an enantiomerically pure starting material. This route was sufficient for early chemical demands but had some issues (low temperature reactions, low yield steps, non-crystalline intermediates) that would make scale-up difficult. At this time alternate synthetic approaches were investigated. The most promising process involved the synthesis of a racemate followed by chromatographic resolution. This chromatographic separation needed to be evaluated to determine if this approach was viable at large-scale. The first step in this process was analytical method development. During this step, various CSPs and solvents were evaluated. The results of this work are listed in Table 2. For a high productivity chiral separation the following are required: (i) maximum selectivity ($\alpha > 2$), (ii) short retention ($k' < 3$), (iii) high solubility (>30 mg/ml) in mobile phase, (iv) ability to recycle solvents and (v) high-capacity CSP.

Based on these criteria, the best separation was achieved using Chiralpak AD with methanol. The separation is shown in Fig. 1. Although a methanol–acetonitrile combination gave better enantioseparation, the binary solvent mixture would complicate solvent recycling. In addition, racemate solubility was drastically reduced in the presence of acetonitrile. For these reasons this method was not chosen. From a chromatographic and cost viewpoint, methanol is an ideal solvent for use as a mobile phase.

Table 1
Average SMB column performance per campaign

Campaign	Raffinate retention time (s)	Raffinate efficiency (plates/column)	Extract retention time (s)	Extract efficiency (plates/column)
1	196	266	291	211
2	194	206	315	117
3	189	316	276	226

Conditions of the test: mobile phase, methanol, sample injection volume, 12.5 ml of 50 g/l racemate solution, flow-rate, 50 l/h, detection at 240 nm.

Table 2
Chromatographic results

Column	Mobile phase	k_2'*	α	Solubility (mg/ml)
Chiralpak AD	Isopropanol–heptane (20:80, v/v)	2.24	1.52	Minimal
Chiralpak AD	Methanol	1.31	3.95	>200
Chiralpak AD	Ethanol	0.57	1.79	Not determined
Chiralpak AD	Acetonitrile	6.50	2.78	10
Chiralpak AD	Acetonitrile–methanol (30:70, v/v)	1.58	4.93	Not determined
Chiralpak AS	Acetonitrile	1.05	2.82	10
Chiralpak AS	Methanol	0.03	1.00	>200
Chiralpak AS	Ethanol	0.27	1.42	Not determined

Methanol is inexpensive and has a low viscosity, allowing faster flow-rates and increased chromatographic throughput. Based on the initial analytical results, it was believed that chromatographic resolution of this racemate would be cost effective at large-scale and possibly at manufacturing scale. It was decided to use a synthetic route with chiral chromatography to produce phase 1 and 2 clinical supplies.

3.2. Batch separation

The first lot of racemate to be resolved was 77 kg produced under non-GMP (good manufacturing practice) conditions. Pharmacia's Skokie chromatography laboratories have a 15 cm batch system as well as a 5 cm SMB system. A decision on which technology to use needed to be made. The main driver for this decision was timing. To meet chemical demands the racemate needed to be resolved in 1 month. Since the batch system could resolve larger amounts of racemate per day, it was decided to use this approach for the first lot of material. An additional factor was the SMB unit was only recently installed in our laboratories and had not been utilized for a separation. To maximize probability of meeting deadlines, it was decided to hold off on using SMB until future campaigns.

A 15 cm I.D. axial compression column was packed with 3 kg of 20 μm Chiralpak AD. The bed length was 28 cm. Preparative method development involved increasing the load and flow-rate to achieve

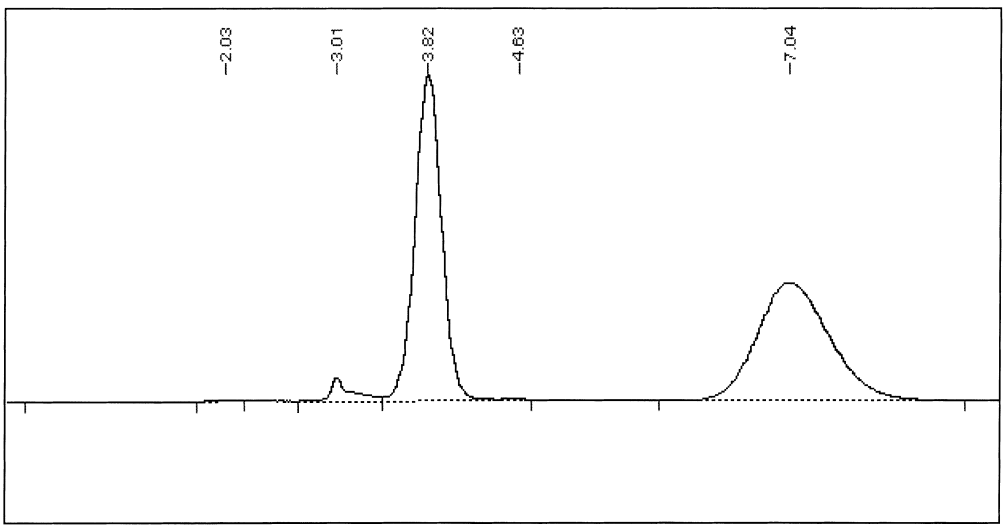

Fig. 1. Analytical HPLC separation. Analysis conducted on a Chiralpak AD column (250 mm×4.6 mm I.D.), detection at 220 nm, 0.1 AUFS. Mobile phase: methanol, flow-rate 1 ml/min.

maximum productivity without sacrificing purity or yield. Specifications for the separation were >90% yield and >99% [>98% enantiomeric excess (e.e.)] purity. The desired enantiomer eluted second in the Chiralpak AD/methanol system. The final conditions were 11 g of racemate per injection with a flow-rate of 1615 ml/min. The separation is shown in Fig. 2. To maximize productivity boxcar (overlapping) injections were used to produce a cycle time of 3.75 min. The separation was run 24 h/day, 5 days/week for approximately 4 weeks. A total of ~7000 injections were made. Final purity was 99.4% with an isolated yield of 94%. The productivity for the separation was 1.41 kg racemate/kg CSP per day. Solvent consumption was 0.55 l/g racemate.

3.3. Laboratory-scale SMB campaign 1

Soon after completion of the batch campaign, an additional 70 kg of racemate needed to be resolved in Pharmacia's Skokie laboratories under GMP conditions. A total of eight 5 cm columns were each packed with 110 g of Chiralpak AD. The bed length was 9.5 cm. After testing of these columns to ensure uniformity, one of the columns was used for SMB modeling studies. Isotherm measurements were made by injecting increasing quantities of racemate and measuring retention changes for both enantiomers. From this data a mathematical description of the isotherms was obtained. In addition a Van Deemter curve and pressure drop measurements were made on the same column. All measurements were performed at 25, 30 and 40 °C. These data were entered into NovaSep HELP simulation software. The HELP software predicts starting conditions for the SMB including: five flow-rates, switching period, feed concentration, purity/concentrations of streams, productivity and solvent consumption. The effect of temperature on productivity and solvent consumption, as predicted by the HELP software, is summarized in Table 3. At 40 °C maximum productivity

Table 3
SMB simulation results

Temperature (°C)	Productivity (g/kg CSP per day)	Solvent consumption (l/g racemate)
30	2153	0.202
35	2100	0.200
40	2568	0.170

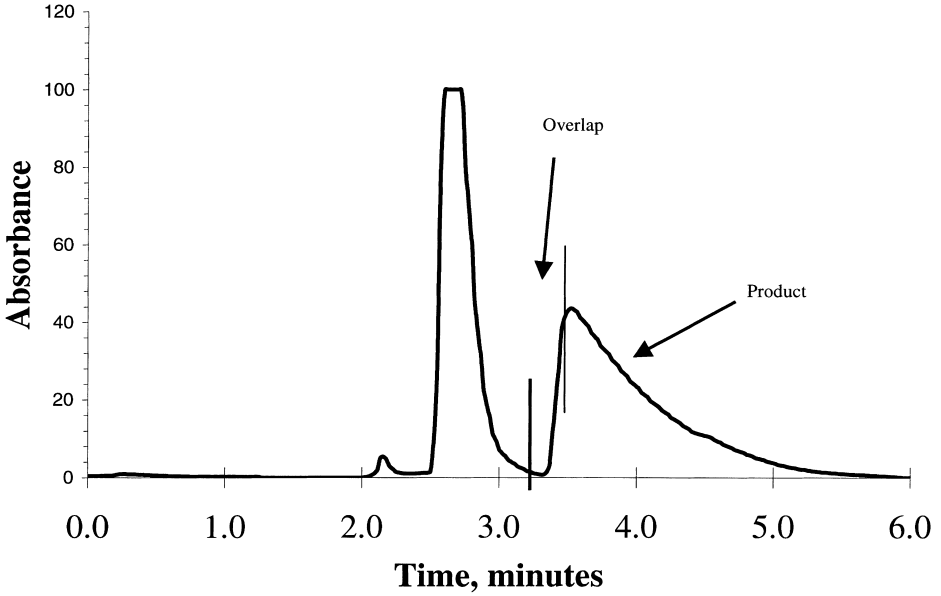

Fig. 2. Preparative HPLC separation. Purification conducted on a Chiralpak AD column (280 mm×150 mm I.D.), with a mobile phase of methanol. A flow-rate of 1615 ml/min, detection at 240 nm and a loading of 11 g were used.

and minimum solvent consumption were predicted. Based on these results the SMB system was operated at 40 °C. The operating conditions predicted by the simulation software were used as a starting point for the SMB system. These initial conditions were modified slightly to produce material at desired purity and yield. The final conditions were as follows: feed concentration=100 mg/ml, feed flow-rate=10.25 ml/min, eluent flow-rate=205 ml/min, extract flow-rate=177 ml/min, raffinate flow-rate=38.25 ml/min, recycle flow-rate=417 ml/min and column switch time=0.70 min. The internal concentration profile from these conditions is shown in Fig. 3. Utilizing these conditions both streams were greater than 99.5% pure. Productivity under these conditions was 1.68 kg racemate/kg CSP per day. Solvent consumption was 0.21 l/g racemate. The SMB was operated under these conditions for approximately 24 days straight.

After approximately two thirds of the racemate had been processed, experiments were performed to increase the feed flow-rate. The results of these experiments are summarized in Table 4. As the feed flow-rate was increased, the extract flow-rate was increased an identical amount. All other flow-rates were kept constant. As expected, as feed flow-rate increased, raffinate and extract purity decreased. The effect on extract purity is minimal, but is more pronounced for the raffinate. The internal concentration profile from a feed flow-rate of 14 ml/min is shown in Fig. 4. Although a feed flow-rate of 14 ml/min gave material of suitable purity and yield, a conservative feed flow-rate of 12.50 ml/min was selected to process the remaining racemate. The internal concentration profile from a feed flow-rate of 12.50 ml/min is shown in Fig. 5. Productivity under these conditions was 2.05 kg racemate/kg CSP per day. Solvent consumption was 0.17 l/g racemate. At the higher feed flow-rate of 14 ml/min, productivity was 2.29 kg racemate/kg CSP per day with a solvent consumption of 0.14 l/g racemate.

Table 4
Effect of increasing feed flow-rate on SMB separation

Feed flow-rate (ml/min)	Raffinate purity (%)	Extract purity (%)
10.25	100	100
10.75	100	99.88
11.50	99.46	99.77
12.50	97.31	99.58
13.50	97.20	99.75
14.00	96.21	99.72

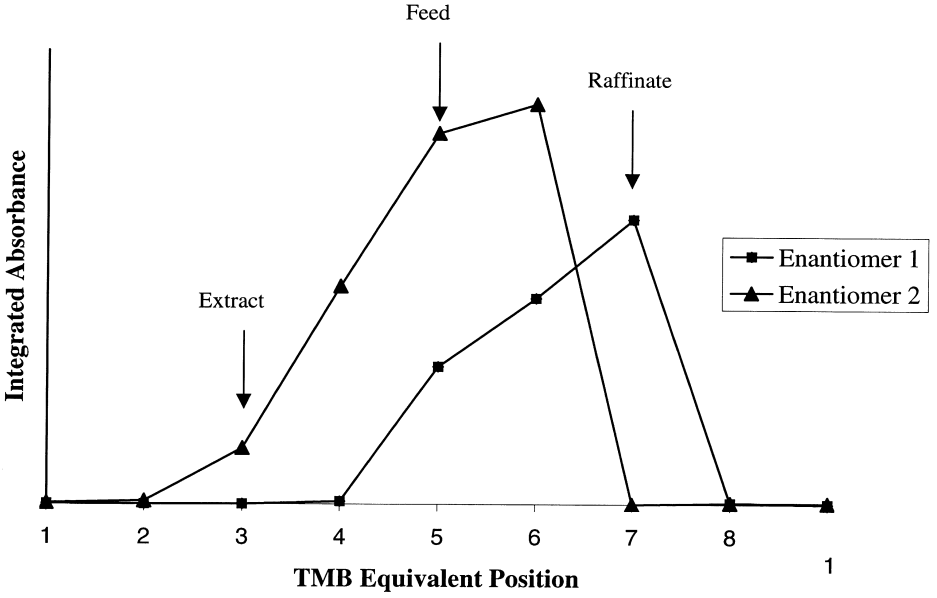

Fig. 3. Internal concentration profile. See text for conditions. TMB=True moving bed.

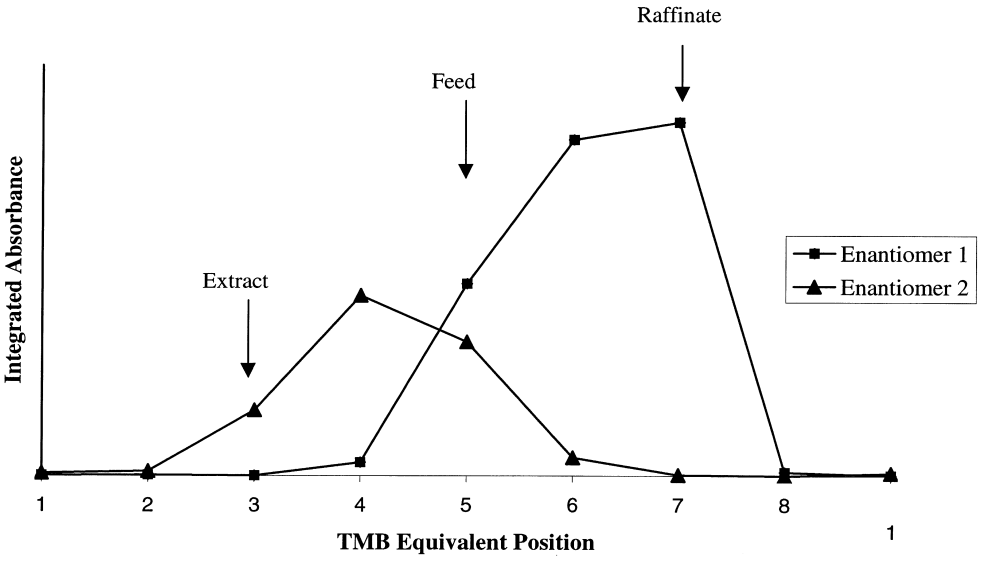

Fig. 4. Internal concentration profile. See text for conditions.

3.4. Laboratory-scale SMB campaign 2

A 37.5-kg batch of the racemate was synthesized at CarboGen under cGMP (current good manufacturing practice) guidelines in a multi-step procedure similar to the one performed at Pharmacia. Following procedures described previously [24] the competitive adsorption isotherms were determined and a starting set of operating parameters was obtained (first line in Table 5). Based on the excellent productivity predicted by the simulation calculations for Chiralpak AD and methanol, no attempts were undertaken to optimize the system of mobile and stationary phase.

In our experience it is often necessary to refine the operating point proposed by the software [25,26] in

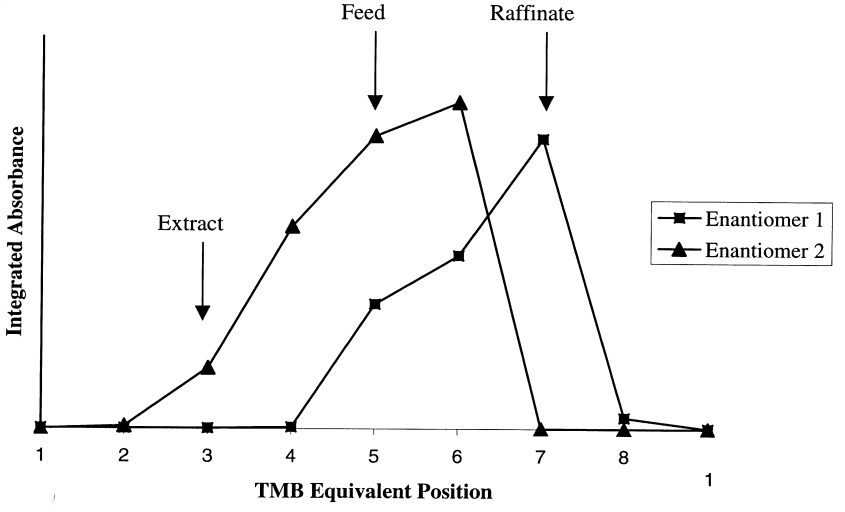

Fig. 5. Internal concentration profile. See text for conditions.

Table 5
Operating conditions and purities of the outlet streams in the experimental runs

Run No.	Switch time (min)	Flow-rate (ml/min)				Flow-rate ratios*				Experimental purity (%)	
		Q_1	Q_2	Q_3	Q_4	m_1	m_2	m_3	m_4	Extract	Raffinate
N	0.7	427	238	272	215	2.171	0.915	1.141	0.762	99.4	99.9
A	0.7	427	238	272	215	2.171	0.915	1.141	0.762	99.7	80.9
B	0.7	427	234	268	215	2.171	0.889	1.115	0.762	99.7	87.1
C	0.7	427	231	265	215	2.171	0.869	1.095	0.762	99.4	91.2
D	0.7	427	228	262	215	2.171	0.849	1.075	0.762	99.2	94.6
E	0.7	427	226	260	215	2.171	0.835	1.061	0.762	99.3	99.7

* Porosity of $\varepsilon^* = 0.4$.

order to achieve a complete separation of the racemate to be resolved. For this purpose the so-called ''triangle-theory'' can be a very powerful tool. This theory allows an easy graphical description of the internal flow-rates and the switch time which determines the flow-rate ratios, m_j, defined in Eq. (1):

$$m_j = \frac{Q_j t^* - V\varepsilon^*}{V(1-\varepsilon^*)} \quad (j = 1, ..., 4) \tag{1}$$

Here, Q_j, $j = 1, ..., 4$, are the volumetric flow-rates in Sections 1–4 of the SMB, ε^* is the overall void fraction of the columns, t^* the switch time, and V the single column volume. Based on these flow-rate ratios m_j, the experimental performances of SMB units can be properly designed, interpreted and optimized. The projection of the regions of separation on the m_2, m_3 plane spanned by the flow-rate ratios of the two key Sections (2 and 3) is drawn in Fig. 6.

Several areas in this plane can be distinguished. A triangular region describes an area where the flow-rates in Sections 2 and 3 of the SMB lead to a complete separation. This triangle is determined through the adsorption isotherm and the two Henry constants H_i of the two enantiomers [27–29]. Above this triangle a region is found where only the extract stream is pure, and on the left side of this triangle a region can be found where only the raffinate stream is pure. Over the vertex of the triangle another region is located, where neither stream is pure. The area under the diagonal of the m_2, m_3 plane has no physical meaning. The interested reader is referred to the literature where the ''triangle theory'' is explained and applied in great detail [27–29].

Eight columns (4.8 cm I.D.) were packed with 110 g Chiralpak AD each, resulting in an average bed length of 9.7 cm. A Licosep 50×10 SMB unit was started at an operating temperature of 40 °C with the parameters obtained by the simulation calculations using the Novasep software ''soft-SMB'' [25,26] (first line in Table 5, ''run N''): feed concentration = 50.2 mg/ml, feed flow-rate = 34.0 ml/min, eluent flow-rate = 212.0 ml/min, extract flow-rate = 189.0 ml/min, raffinate flow-rate = 57.0 ml/min, recycle flow-rate (Section 1) =

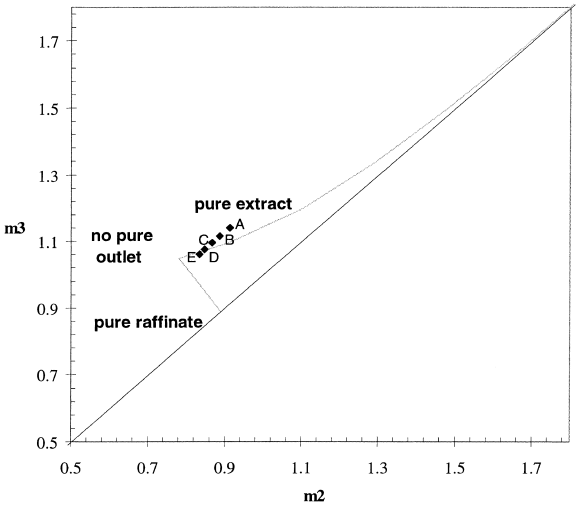

Fig. 6. Regions in the m_2, m_3 plane with different separation regimes in terms of purity of the outlet streams. Predicted region of complete separation: (——) isotherm parameters: $\lambda = 0.7$, $H_1 = 0.89$, $H_2 = 1.86$, $K_1 = 0.01352$ l/g, $K_2 = 0.0829$ l/g, $c_1 = c_2 = 25.1$ g/l; (♦) operating points corresponding to the runs A–E in Table 5.

427.0 ml/min and column switch time = 0.70 min. After 10 complete cycles (55 min), the collection of extract and raffinate streams was started. The system was allowed to run for 2 h and the streams produced were then analyzed. In the extract stream only a minor amount of less retained compound could be detected, the raffinate stream had a purity of 80.9%.

The ''triangle theory'' suggests that by moving the operating point in a straight line parallel to the diagonal (i.e., without changing Q_{Feed} and Q_{Eluent}) one enters from the region of pure extract (run A) either into the triangle of complete separation or the region of pure raffinate. This was done in runs B–E (Table 5). As can be seen in Table 5 the purity in the raffinate stream is increasing steadily the nearer the operating point is to the triangle. The extract purity remains essentially unaffected during this decrease parallel to the diagonal. The operating point E resulted in complete separation (purity for both streams >99%), which is a confirmation of this approach. Therefore it can be assumed that the region of complete separation has a similar shape as the predicted triangle under non-linear conditions (Fig. 6). The productivity was 2.8 kg racemate (extract: >99.3%, raffinate: >99.7%) per day/kg CSP with a solvent consumption of 0.127 L/g racemate. The pressure in the system was 37 bar. The internal concentration profile under the final conditions (i.e., run E in Table 5) is shown in Fig. 7.

As can be seen in Fig. 7 the fronts of the extract and raffinate are very close to the outlets (between columns 2 and 3, and 6 and 7, respectively). This implies that a further increase in the feed flow-rate may not be possible without loss of purity in one of the streams. This is also reflected by the position of operating point E in Fig. 6, which is close to the vertex of the triangle of complete separation. It should be noted that a further improvement of the productivity might to be possible by increasing the flow-rates and shortening the switch time according to Eq. (1), keeping the same m values for the four zones. However, increasing the flow-rates will increase the operating pressure of the system and must be carefully balanced against the wear of the system.

Even though the vertex of the triangle of complete separations represents the operating point resulting in the highest productivity, it cannot be considered a stable operating point for pilot scale production. Already minor changes in the feed composition, the operating temperature or small deviations in the flow-rates of one of the five pumps, or an accumulation of a minor impurity in the feed on the CSP will result in a decrease in purity in one, or even both streams.

3.5. Pilot-scale SMB separation campaigns 1–3

The target for the separation was 98% e.e. and

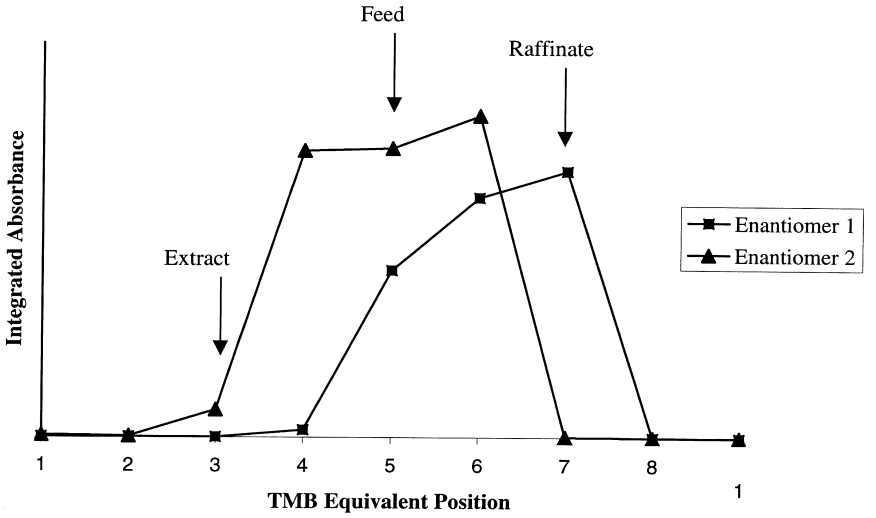

Fig. 7. Internal concentration profile for run E in Table 5.

Table 6
SMB parameters at beginning and end of each campaign

Campaign	Feed (l/hr)	Eluent (l/hr)	Extract (l/hr)	Raffinate (l/hr)	Zone I (l/hr)	DT (min)	Pressure (bar)
1 start	28.3	217.5	190.8	55.0	380.0	0.90	22–24
1 end	20.0	217.5	190.8	46.7	381.0	0.87	22–24
2 start	20.0	217.5	190.8	46.7	381.0	0.87	22–24
2 end	20.0	239.2	209.8	49.4	419.1	0.77	32
3 start	20	239.2	209.8	49.4	419.1	0.77	32
3 end	18	239.2	209.8	47.4	424.0	0.81	32

>95% recovery for the extract, which means that the purity of the raffinate had to be maintained above 95% to reach the recovery target. Table 6 gives the sets of parameters at the beginning and the end of each campaign. The set of parameters used to start the first campaign were obtained from the run on the Licosep laboratory unit performed at Carbogen. Adjustments of the cycle time were necessary to take into account the difference in column length. The expected feed flow-rate was 28.3 l/h at 50 g/l corresponding to a production rate of 34.0 kg feed/day. Unfortunately this feed flow-rate lead to a unstable situation where the front of extract (most retained compound) was moving slowly in the direction of the raffinate port. This usually means that the selected switch time is too long for the given separation condition.. Adjustment of the switch time was not successful in producing the desired purity for both outlet streams and a reduction of the feed flow-rate was required. An example of the internal profile is given in Fig. 8. This profile shows that the front of extract is moving toward the raffinate port. The feed was reduced to 20 l/h at 49.6 g/l corresponding to a production rate of 23.8 kg/day. The resulting profile can be seen in Fig. 9. The internal profile looks much less overloaded but the raffinate is starting to tail into the extract. The operating pressure in the system was 23–24 bar indicating that the overall flow-rates could be increased to improve the production rate.

The second campaign was started with the last set of parameters from the first campaign. Raffinate purity was not satisfactory and adjustment on the cycle time was made to improve the situation. The

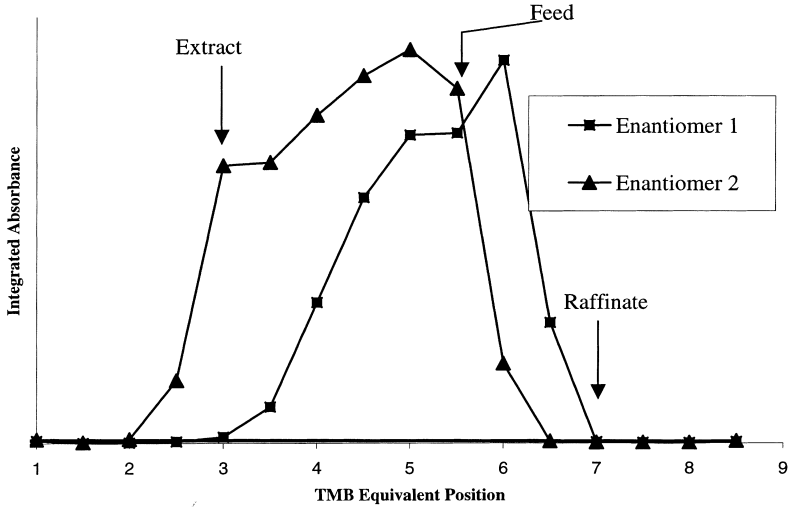

Fig. 8. Internal concentration profile first campaign cycle 197B. ♦=First enantiomer, ■=second enantiomer. Flow-rates: feed: 27 l/h, eluent: 217.5 l/h, extract: 190.8 l/h, raffinate: 53.7 l/h, recycle: 380 l/h. Switch time: 0.84 min, extract purity: 99.12%, raffinate purity: 94.07%.

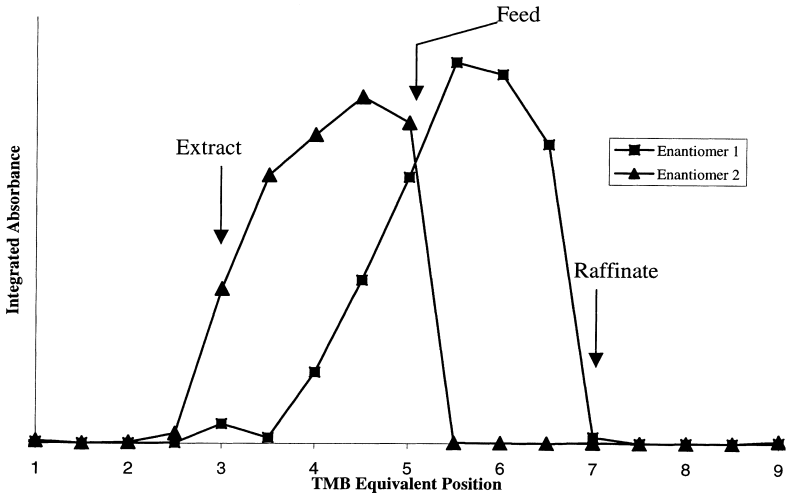

Fig. 9. Internal concentration profile first campaign cycle 284C. ♦ = First enantiomer, ■ = second enantiomer. Flow-rates: feed: 20 l/h, eluent: 217.5 l/h, extract: 190.8 l/h, raffinate: 46.7 l/h, recycle: 380 l/h. Switch time: 0.87 min, extract purity: 99.08%, raffinate purity: 99.79%.

separation seemed to be stable for a long period of time and then the raffinate purity started to reduce gradually. This time the extract was starting to tail and was recycled into zone IV. To avoid that effect it was necessary to increase the flow-rate in zone I and hence the solvent consumption and operating pressure to 32 bar. A typical profile of the last set of parameters for this campaign can be seen in Fig. 10. The columns were unpacked at the end of that campaign and the CSP was dried and stored.

The third campaign was started with re-packing and testing of the columns. The final operating

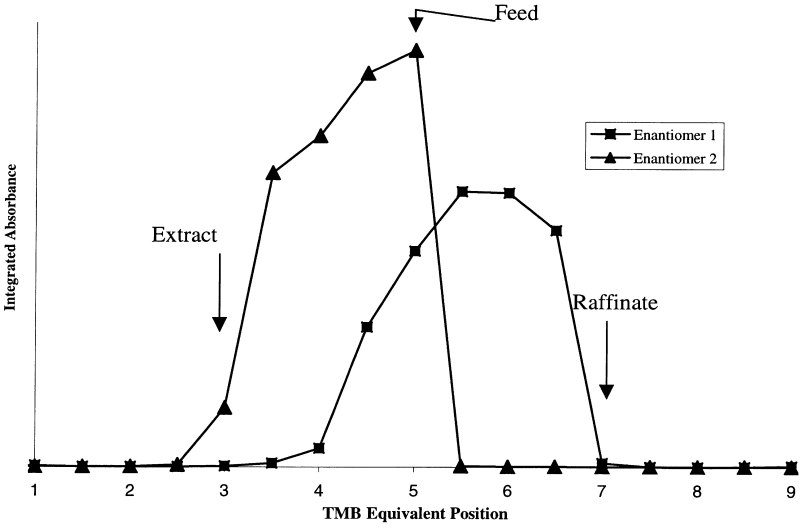

Fig. 10. Internal concentration profile second campaign cycle 1031D. ♦ = First enantiomer, ■ = second enantiomer. Flow-rates: feed: 20 l/h, eluent: 239.2 l/h, extract: 209.8 l/h, raffinate: 49.4 l/h, recycle: 419.1 l/h. Switch time: 0.77 min, extract purity: 99.31%, raffinate purity: 99.92%.

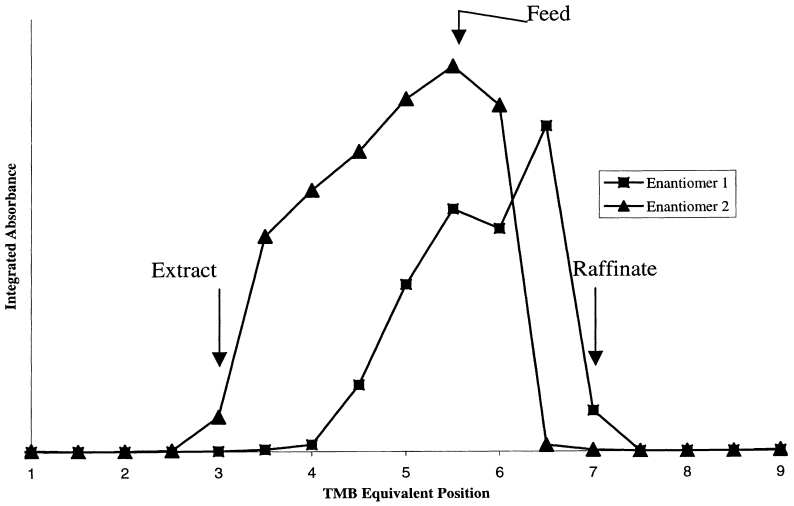

Fig. 11. Internal concentration profile third campaign cycle 668C. ♦ = First enantiomer, ■ = second enantiomer. Flow-rates: feed: 20 l/h, eluent: 239.2 l/h, extract: 209.8 l/h, raffinate: 49.4 l/h, recycle: 420 l/h. Switch time: 0.79 min, extract purity: 99.04%, raffinate purity: 97.74%.

conditions from the second campaign were used as initial operating conditions for campaign 3. Adjustment was necessary to compensate for the difference in retention times. During the course of the campaign minor adjustments were done to maintain the extract purity above 99.0% and the raffinate purity above 95%. The cycle time was increased to try to remove the raffinate tail from the extract port and increase the extract purity, but as a consequence the extract front moved towards the raffinate port. This can be seen by comparing the internal profile at cycle 668C for the third campaign (Fig. 11) with the profile at cycle 1031D of the second campaign (Fig. 10). The feed flow-rate had to be reduced by 10% to avoid the extract front to reach the raffinate port. A few more adjustments were made to the zone I flow-rate to fine tune the system.

Despite some minor adjustment the separation was fairly stable over the three campaigns (Tables 6 and 7). However a slow degradation of the performance was observed. This degradation was apparently not observed during the laboratory-scale experiment at Carbogen or Pharmacia. The degradation may be due to an unknown impurity being generated during the preparation of the feed or present in the technical-grade methanol. That impurity may be strongly adsorbed on the CSP reducing the availability of the chiral sites for the separation. This degradation was also observed on the analytical column used for in-process control. After several days of operation the peaks started to tail. The analytical column was equilibrated with isopropanol (HPLC grade) for more than 2 h at 0.3 ml/min and then in heptane–isopropanol (90:10) (HPLC grade) at 1 ml/min. The column was tested with the standard *trans*-stilbene oxide, tri-*tert*.-butylbenzene efficiency test. The re-

Table 7
Average SMB performance per campaign

Campaign	Production rate (kg/day) (kg/day)	Solvent consumption (l/kg feed)	Recovery (%)	Enantiomeric purity (%)	Assay (%, w/w)	Operating pressure (bar)
1 (two batches)	23.8	0.24	98.2	99.03, 99.20	9.9, 11.1	23–24
2	24.0	0.26	97.4	99.06	13.8	32
3	21.6	0.29	98.2	99.07	16.4	32

sults of the test were satisfactory in term of peak shape and efficiency. The column was reconditioned in methanol for the in-process control. A significant improvement of the peak shape was observed and then gradually the peak tail reappeared. The impurity causing the tailing must be identified and removed from its source if the process is to be used at a larger production scale.

3.6. Comparison of batch and SMB results

A total of ~1070 kg of racemate was resolved in six campaigns. These campaigns used both batch and SMB chromatography and occurred at three sites (Pharmacia, Carbogen and Aerojet). Both SMB and batch processes were fully optimized. Further optimization could be achieved by utilizing alternate purification techniques such as steady state recycle or Varicol. The results from these campaigns are summarized in Table 8. As expected, SMB was more productive and used less solvent than batch chromatography. One other advantage not evident from the data is the manpower required to operate this equipment. Since both the batch separation and the first SMB campaign were both performed in the same laboratory, it is possible to directly compare manpower requirements. Operation of the batch system required two people per shift. The SMB required approximately 6 h of attendance per 24-h day. If one normalizes manhours utilized to kg racemate resolved, one obtains a value of 11.35 manhours/kg racemate for the batch separation and 3.33 manhours/kg racemate for the SMB separation. While these figures are not all inclusive, time for column packing and process development are higher for the SMB separation, it is clearly evident that SMB requires fewer personnel to operate relative to batch chromatography. This difference is mainly due to the batch chromatography system utilizing larger volumes of solvent per day, the separation required near constant attendance. At a flow-rate of 1615 ml/min, a 55-gallon drum was used approximately every 2 h. The SMB unit operated for approximately 14 h using the same volume of solvent. This allowed the unit to operate unattended overnight. This was not possible with the batch chromatography operation. An additional advantage of the SMB is the products eluting from the system at higher concentrations relative to batch. The product concentrations of the batch and SMB process are summarized in Table 9. The higher product concentrations translate to decreased distillation times, resulting in additional savings for SMB over batch chromatography.

Table 9
Product concentrations for batch and SMB separation

Technique	Peak 1 concentration (mg/ml)	Peak 2 concentration (mg/ml)
Batch	4.48	1.8
SMB	19.0	4.2

4. Conclusions

Batch and SMB chromatography were utilized for the chromatographic resolution of more than 1 metric ton of racemate. Sufficiently high productivities were obtained for both batch and SMB separation to make this separation cost effective at manufacturing scale. Higher productivities and lower solvent usage were observed with SMB relative to batch chromatography. At the pilot scale decreased productivity was observed with time. This decrease may be due to

Table 8
Comparison of campaign results

Technique	Amount processed (kg)	Productivity (kg racemate/kg CSP per day)	Solvent consumption (l/g racemate)
Batch	77	1.41	0.55
SMB (campaign 1)	70	2.05	0.174
SMB (campaign 2)	37	2.8	0.127
SMB (campaign 3)	297	1.65	0.24
SMB (campaign 4)	289	1.67	0.26
SMB (campaign 5)	304	1.50	0.286

low-level impurities in the feed or solvent that are accumulating on the stationary phase over time.

Acknowledgements

The authors thank Vera Leshchinskaya, Trisha Hoover, Ignacio Cua and Carlos Orihuela of Pharmacia for their support.

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