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Laboratory-developed simulated moving bed for chiral drug separations
Design of the system and separation of Tramadol enantiomers

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Abstract

The design of a laboratory-developed simulated moving bed (SMB) is described. The main features of the system are outlined. The efficiency of the SMB to resolve chiral drugs is illustrated by the separation of Tramadol enantiomers at various feed concentrations. Advantages over preparative batch chromatography in terms of solvent and chiral phase consumption are demonstrated.

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

1. Introduction

In recent years, there has been an increasing trend towards restricting the use of chiral drugs as racemates. Amounts ranging from 1 g up to 5 kg and more of optically pure compounds as chemical intermediates or for pharmacological and toxicological testing are now needed [1–7].

A number of synthetic strategies are available for the preparation of single enantiomer drugs [8]. In addition to diastereoisomeric crystallisations and enantioselective synthesis (specific to one enantiomer), resolution by preparative chiral chromatography is getting more and more attention these days. Numerous advantages of this last technique have been described [9–12]. Among these, the possibility to obtain both enantiomers at once with a high degree of purity is beneficial to the compilation of required tests.

However, like all methods, the chromatographic approach suffers from certain drawbacks: large amounts of expensive stationary phases required, consumption of large volumes of mobile phase, high dilution of the separated products [9,13,14].

Many methods have been investigated in an attempt to improve the technique such as recycling and peak-shaving chromatography [15–17].

Recently the simulated moving bed (SMB) technology has been introduced in the field of chiral separations [18]. This technique, developed in the late 1950s by Universal Oil Products (Des Plaines, IL, USA), has been a very efficient technology for the separation of oil derivatives and sugars [19]. Here, counter-current contact maximises the driving force for mass transfer and provides more efficient utilisation of the adsorbent capacity than is possible in a simple batch system [20].

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Racemic mixtures are well suited to SMB technology because the counter-current systems generally can perform only two-component separations at a time. Today, SMB appears as a very promising tool for the resolution of chiral drugs in the pharmaceutical industry [9–14,21–24].

In view of this, our chemical research department has decided to adopt SMB technology for its own enantioseparation problems. In order to have a better understanding and control of the system, we have decided to develop our SMB system ourselves. The design of this system is described and the first results on the separation of Tramadol enantiomers are given hereafter.

2. Experimental

2.1. Description of the system

The SMB system is described in Fig. 1. It consists of twelve 100 mm×21.2 mm I.D. stainless steel columns (Alltech, Deerfield, IL, USA) each packed with 20 g of Chiralpak AD 20 μm (Daicel, Tokyo, Japan).

The columns are supplied at their top, either by the feed or by the eluent and the recycling flow, via 36 two-way valves (Whitey, Highland Heights, OH, USA) and connected at their bottom, by 24 two-way valves, to product A (more rapid or raffinate) and product B (less rapid or extract) lines. Also, 12 three-way valves allow the columns to be either bound in series or connected to the recycling line. A check valve (Nupro, Willoughby, OH, USA) is placed between each column. Pneumatic electrovalves (Burkert, Ingelfingen, Germany) are connected to the 72 valves.

The recycling pump is placed outside of the system zones; this set-up allows the pump flow-rate to be constant during the whole separation process. An UV detector (Gilson, Middleton, WI, USA) connected to the inlet of the recycling pump allows a

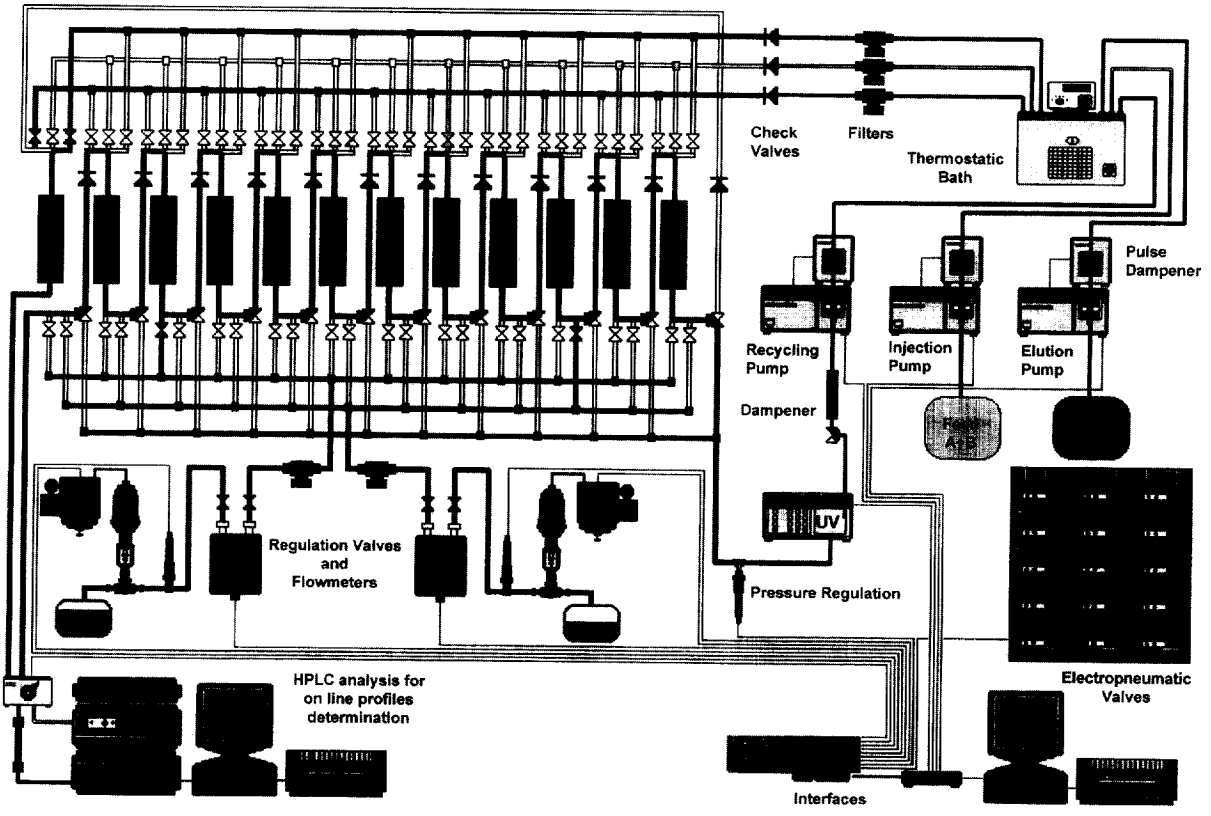

Fig. 1. Schematic diagram of the system.

rapid control of the recycling flow purity. Feed and eluent are pumped from 25 and 50 l tanks respectively. The elution and the recycling lines are independent. Each pump (Gilson) is relied to a pulse dampener (Gilson). The pump flow-rate can be up to 200 ml min^{-1} depending on the back pressure of the system.

The extract and the raffinate are withdrawn by two Research control valves (Badger Meter, Tulsa, OK, USA). The flow-rates are measured by two Coriolis mass flowmeters (Micro Motion, Rungis, France). The two valves are controlled via a PID regulation: flowmeter values are compared to the desired flow-rate values and valves aperture adjusted.

Solid impurities from eluent or feed are eliminated by 2 μm filters (Nupro) placed at the inlet of each line. To avoid any damage in the flowmeters, filters are also placed just before them. Pumps, pipes and valves are designed to accommodate larger columns (up to 5 cm I.D.). The temperature of the different flows is set at the desired value by means of a thermostatic bath (Model F18 VC, Julabo, Seelbach, Germany).

An HPLC system (HP 1100, Hewlett–Packard, Waldbronn, Germany) coupled to an automatically actuated valve (Model 7010, Rheodyne, Cotati, CA, USA) is placed just after column 1. At a given fraction of the switching time, a 10 μl injection is performed. This allows us to visualise the corresponding internal concentration profile after each cycle. Depending on the switching time period and on the elution conditions of the analytical system, it is possible to inject up to 3 times per switching period. It can indeed be interesting to observe what happens just before and after the switching of the valves to see more rapidly when we approach the steady state.

The system is entirely piloted by laboratory-developed software (VISUAL BASIC, Microsoft, Redmond, WA, USA; LABVIEW, National Instruments, Austin, TX, USA and Gilson). The main program allows to introduce the operating parameters: the initial valve positions, i.e. the number of columns per zone; the feed, eluent and recycling pump flow-rates; the desired values of the extract and raffinate flow-rates; the switching time; the limit values for temperature, pressure and UV signal in the recycling line and the parameters for the online analysis. A test program allows each device (pumps, valves, columns) of the system to be checked. After each separation, cleaning of the system can be achieved by an appropriate flushing program. In all these programs, in case of problems (a limit value reached), the system stops and a message box appears.

3. Methods

The ability of our SMB system to resolve chiral separation problems was demonstrated by the separation of Tramadol (Fig. 2) enantiomers chosen as a reference compound. Tramadol is an analgesic drug [25].

An analytical screening was performed to select the best stationary and mobile phase combination, as well as a suitable temperature for the separation. The HPLC (HP 1100) experiments were performed by injections of 10 μl solution, in the mobile phase, of 1 g l^{-1} Tramadol. A 250 mm×4.6 mm I.D. Chiralpack AD 10 μm column and HPLC-grade solvents (Rathburn, Walkerburn, UK) were utilised. Diethylamine (Acros, Geel, Belgium) was added to the mobile phase to avoid peak tailing.

The SMB results were obtained using preparative solvents (Roland, Brussels, Belgium). The eluent composition was 2-propanol–benzine (light petroleum, b.p. 60–95°C)–diethylamine (5:95:0.1, v/v/v). The feed was a solution of Tramadol, at the desired concentration, in the eluent. The system was used as a four-zone SMB process. The function of each zone, and the desired movement of the components in each one are described in Fig. 3 [14,19,20,22,26–28]. The following distribution of the columns was adopted: 3 columns in zone 1; 4 columns in zone 2; 3 columns in zone 3; 2 columns in zone 4, with the following initial inlet and outlet flow positions (see Fig. 1): elution and recycling flows in column number 1; extract flow out of

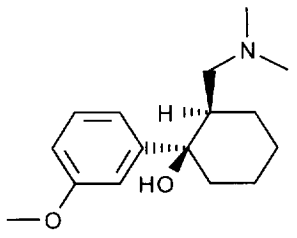

Fig. 2. Structure of Tramadol.

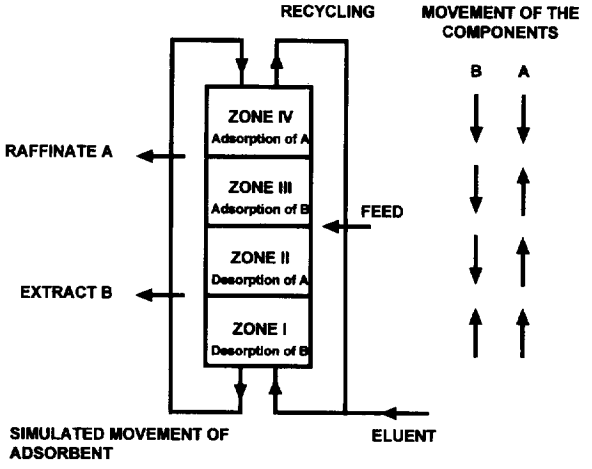

Fig. 3. Schematic diagram of a four-zone SMB. Desired movement of components A (raffinate) and B (extract) in each zone.

column number 3; feed flow in column number 8; raffinate flow out of column number 10. Flow-rates and switching time of the SMB system, for dilute feed solutions, were determined via the procedure reported earlier by Nicoud [21,22,26]. A pulse injection was achieved using the SMB as a batch system. The columns were bound in series and an injection was performed in column number 1. The outlet of column number 12 was connected to the UV detector. Recording of the chromatogram was started after the end of the injection. Three pulse injections were done under the same conditions. The mean retention times of the two enantiomers were used to calculate the operating parameters. These parameters were further slightly modified, by an empirical approach, to maintain a high purity of the products with a higher concentration feed solution.

On-line analysis profiles were obtained on a slurry packed 100 mm×4.6 mm I.D. Chiralpack AD 10 μm column with 2-propanol–hexane–diethylamine (10:90:0.1, v/v/v) as mobile phase.

4. Results

The chosen solution of the analytical screening is shown in Fig. 4. A result of a pulse injection on the SMB, under equivalent preparative conditions, is given in Fig. 5. For feed concentrations ranging from 1–10 g l^{-1}, the calculated operating parameters were

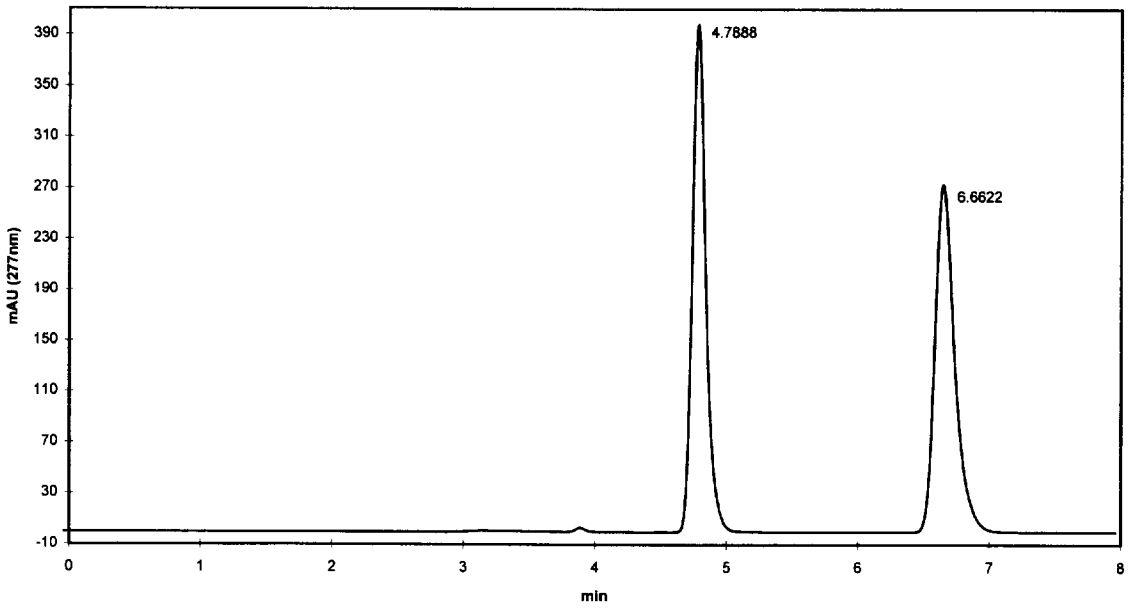

Fig. 4. Chromatogram obtained under the best analytical conditions. Column: 250 mm×4.6 mm I.D. Chiralpack AD 10 μm. Mobile phase: 2-propanol–hexane–diethylamine (5:95:0.1, v/v/v). Injection: 10 μl of 1 g l^{-1} Tramadol solution in the mobile phase. Flow-rate 1 ml min^{-1}. Temperature: 24 °C. UV detection at 277 nm.

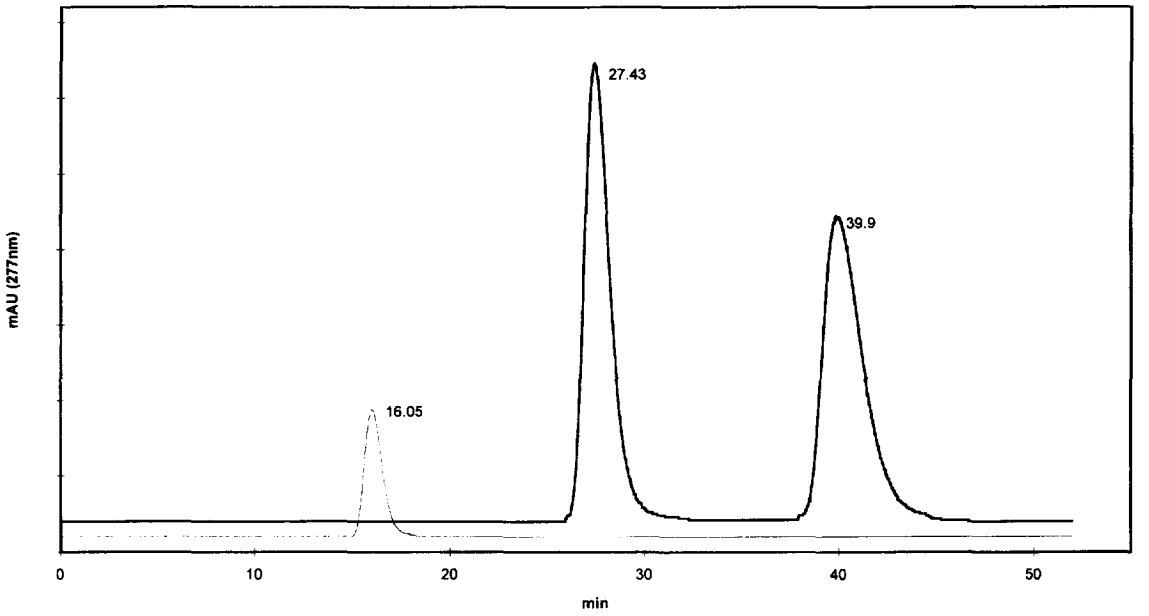

Fig. 5. Chromatogram obtained with a pulse injection on the SMB system. Column: 12 columns 100 mm×21.2 mm I.D., each packed with 20 g of Chiralpack AD 20 μm phase. Mobile phase: 2-propanol–benzine–diethylamine (5:95:0.1, v/v/v). Injection: 10 g l^{-1} Tramadol solution for 12 s at 20 ml min^{-1}. Flow-rate 20 ml min^{-1}. Temperature: 24 °C. UV detection at 277 nm. k_1=0.7, k_2=1.49, α=2.1, R_s=6.7, N=1837. t_0 of the SMB (grey line) was obtained by a pulse injection of a 1,3,5-tri-*tert.*-butylbenzene solution. UV detection at 220 nm. Data collected with a LAB PC card interface and the DAQWARE software (National Instruments).

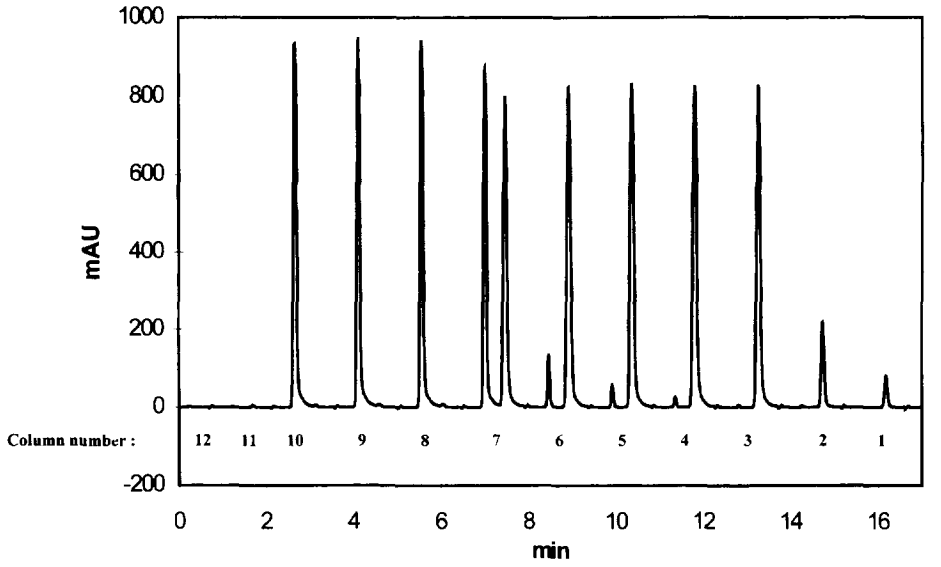

Fig. 6. On-line analysis profile at 50% of the switching time for a 10 g l^{-1} SMB feed concentration. SMB conditions: feed flow-rate=10 ml min^{-1}, eluent flow-rate=17.8 ml min^{-1}, recycling flow-rate=30.1 ml min^{-1}, raffinate flow-rate=13 ml min^{-1}, extract flow-rate=14.8 ml min^{-1} and switching time=87 s. Steady state reached. Analysis performed on a stainless steel 100 mm×4.6 mm I.D. column slurry packed with Chiralpack AD 10 μm phase. Mobile phase: 2-propanol–hexane–diethylamine (10:90:0.1, v/v/v). Flow-rate 1 ml min^{-1}. Room temperature. UV detection at 277 nm.

the following: feed flow-rate, 10 ml min^{-1}; eluent flow-rate, 17.8 ml min^{-1}; recycling flow-rate, 30.1 ml min^{-1}; raffinate flow-rate, 13 ml min^{-1}; extract flow-rate, 14.8 ml m^{-1}; and switching time, 87 s. The pressures generated in the system by the different flow-rates are around 23 bar at the elution and the recycling pumps, 8 bar at the feed pump, 4 bar at the raffinate valve and 18 bar at the extract valve. Fig. 6 shows an online analysis profile acquired under these conditions, for a 10 g l^{-1} feed concentration, at 50% of the switching time, the steady state being reached. Internal concentration profiles

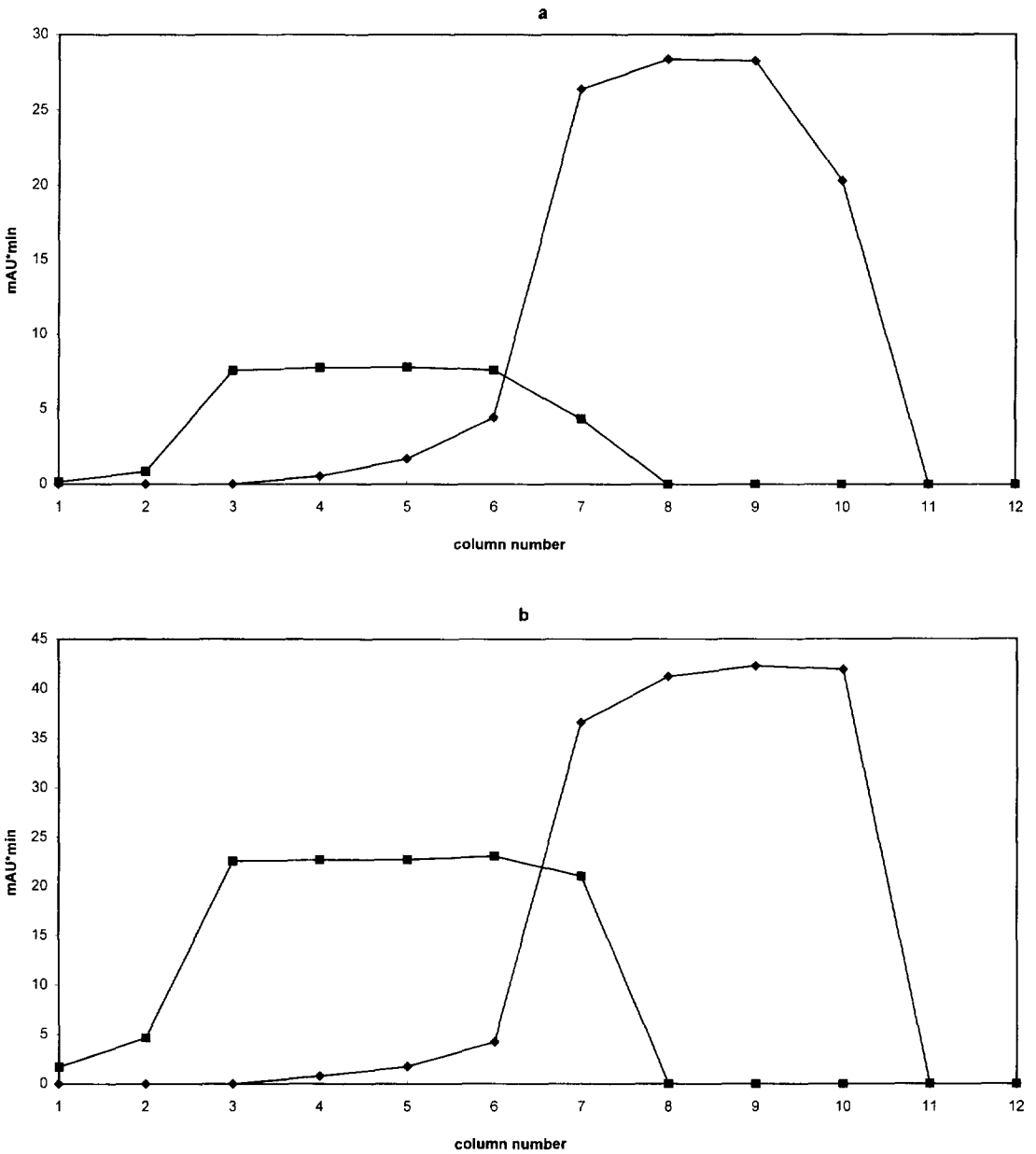

Fig. 7. Internal concentration profiles at 50% of the switching time. ■ extract profile, ♦ raffinate profile. Concentration expressed in terms of peak areas (mAU min). Same conditions as Fig. 6. (a) SMB feed concentration: 3 g l^{-1}. (b) SMB feed concentration: 10 g l^{-1}.

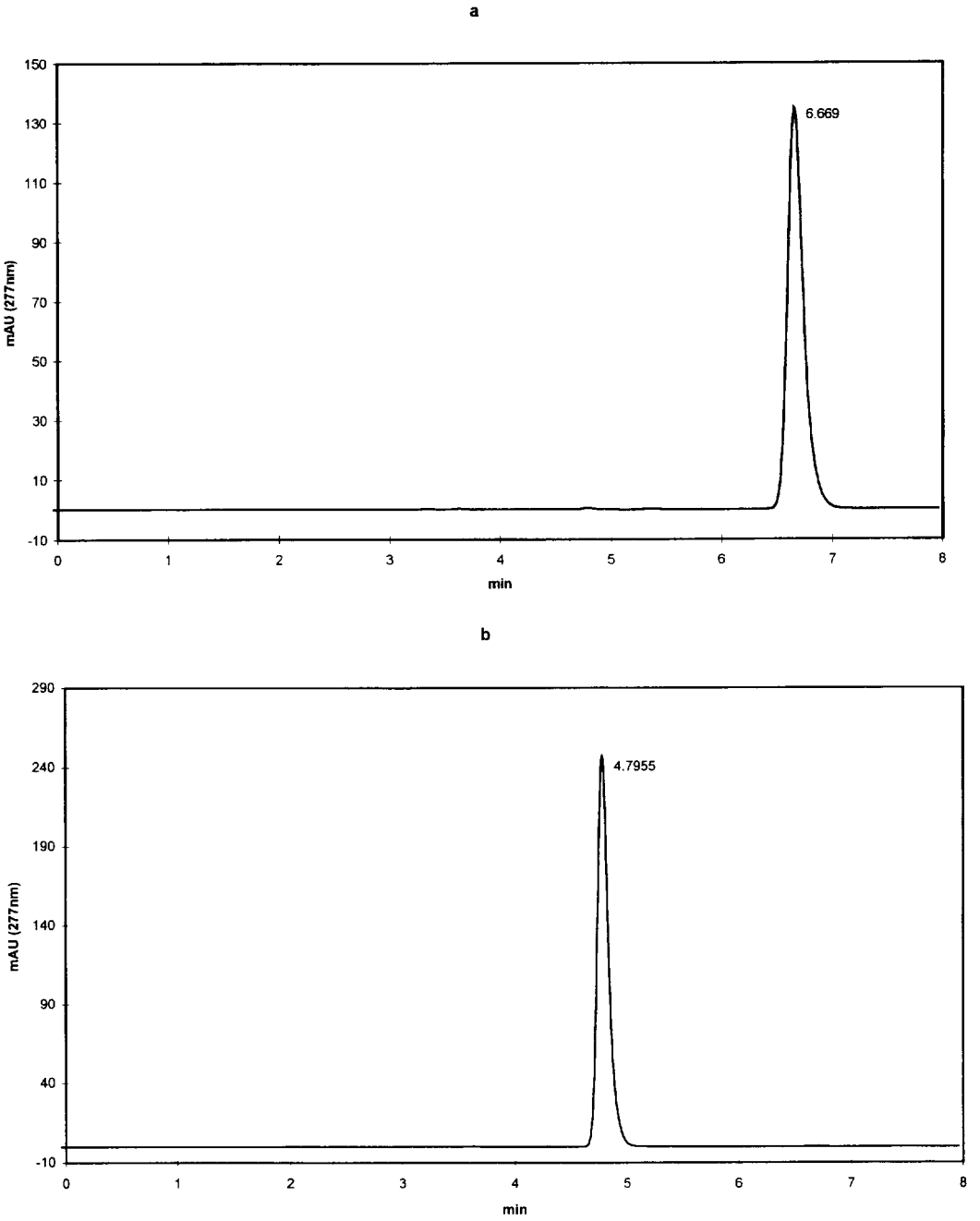

Fig. 8. Chiral chromatographic purity of the products for a 10 g l^{-1} SMB feed concentration. Column: 250 mm×4.6 mm I.D. Chiralpack AD 10 μm. Mobile phase: 2-propanol–hexane–diethylamine (5:95:0.1, v/v/v). Injection volume: 10 μl. Flow-rate: 1 ml min^{-1}. Temperature: 24 °C. UV detection at 277 nm. (a) Extract chiral chromatographic purity >99.9%. (b) Raffinate chiral chromatographic purity >99.9%.

for different feed concentrations are drawn in Fig. 7a and b. The actual working of the system was confirmed by the absence of pollution in the recycling flow and a high purity of the separated enantiomers (Fig. 8a and b).

For the separation of a 20 g l^{-1} feed concentration, the operating parameters were slightly modified: feed flow-rate, 10 ml min^{-1}; eluent flow-rate, 18.8 ml min^{-1}; recycling flow-rate, 28.6 ml min^{-1}; raffinate flow-rate, 13 ml min^{-1}; extract flow-rate, 15.8 ml min^{-1}; and switching time, 87 s. Fig. 9 gives the internal concentration profile at 50% of the switching time; the chiral chromatographic purities [29] are here: extract purity=99.5% and raffinate purity >99.9%.

In view of these first results, we can assume that equilibrium isotherms are linear up to a Tramadol concentration somewhere between 10 and 20 g l^{-1}. This has to be confirmed.

The SMB productivity, with a feed concentration of 20 g l^{-1}, at a feed flow-rate of 10 ml min^{-1}, is thus 680 g of racemate per litre stationary phase per day (1200 g of racemate per kg stationary phase per day), and the solvent consumption 144 l kg^{-1} of racemate. The concentration of the extract is then 6.33 g l^{-1} and the raffinate 7.69 g l^{-1}.

5. Comparison between SMB and preparative batch chromatography

The same purity (>99.5%) and the same yield (100%) were obtained on a 50 cm×10 cm I.D. preparative Chiralpack AD 20 μm column. Injections of 9 g of a 10 g l^{-1} Tramadol solution were performed every 15 min, the eluent being the same as the one used for the SMB. The flow-rate was 300 ml min^{-1} (maximum recommended by Daicel: 240 ml min^{-1}, typically 190 ml min^{-1}). This load gave a touching bands separation.

The productivity is 220 g of racemate per litre stationary phase per day (388 grams of racemate per kg stationary phase per day, assuming that the packing density is the same in the SMB and batch columns) and the solvent consumption is 500 l kg^{-1} of racemate.

6. Conclusion

The preliminary study on the preparative resolution by chiral chromatography of racemic Tramadol, a reference compound, showed a very good efficiency of our SMB system.

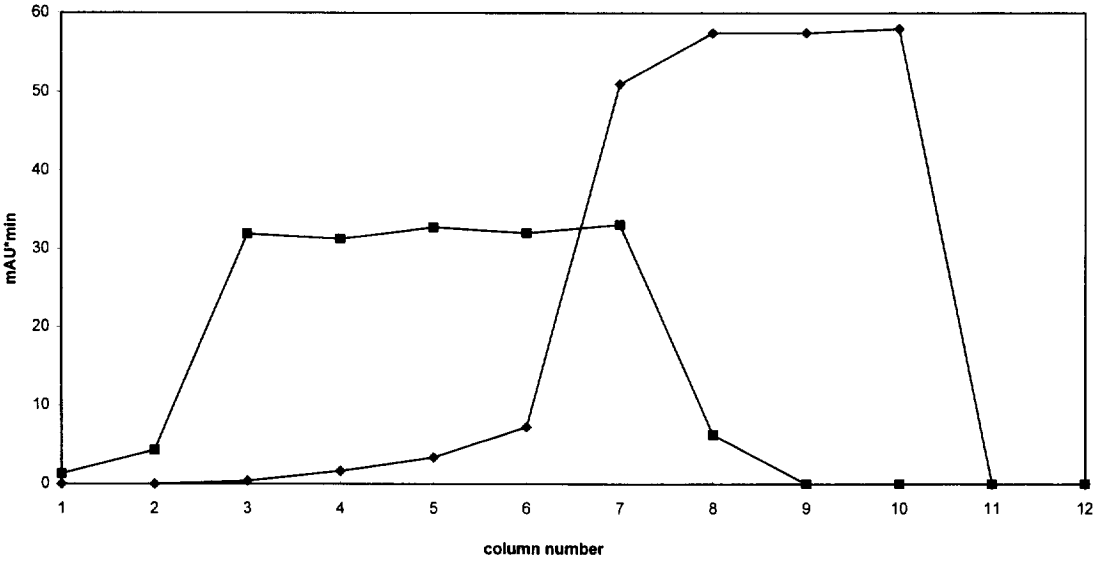

Fig. 9. Internal concentration profile at 50% of the switching time for a 20 g l^{-1} SMB feed concentration. ■ extract profile, ♦ raffinate profile. SMB conditions: feed flow-rate=10 ml min^{-1}, eluent flow-rate=18.8 ml min^{-1}, recycling flow-rate=28.6 ml min^{-1}, raffinate flow-rate=13 ml min^{-1}, extract flow-rate=15.8 ml min^{-1} and switching time=87 s. Steady state reached. Analysis performed as in Fig. 6.

Even without any real optimisation of the operating conditions, the SMB technique was more economical than the batch technique, be it for the stationary phase (factor 3.1) or the mobile phase consumption (factor 3.5).

Because Tramadol appeared to have an especially good batch chromatographic behaviour, as well as a high solubility in the solvents used, we should expect even greater advantages of the SMB with other less soluble chiral compounds.

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