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THE GC-SMB SEPARATION OF THE ENANTIOMERS OF ISOFLURANE

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ABSTRACT

The study of separation of the enantiomers of chiral anesthetic isoflurane on a cyclodextrin based stationary phase using a gas chromatography simulated moving bed process is reported. Experiments have been performed to investigate the effect of major operating parameters such as switch time, flow rates, and temperature. The study demonstrated that it is possible to separate the enantiomers to a high level of purity for use in clinical trials. It has also been found that the separation is very sensitive to disturbances as compared to the enflurane system that was studied previously.

INTRODUCTION

In the last 150 years, several different compounds have been synthesized and tested in order to improve anesthesia by inhalation. This research has led to

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the use of fluorinated ethers; whose structure generally includes an asymmetric atom, as in the case of the most widely applied inhalation anesthetic, isoflurane (see Fig. 1). Nowadays, isoflurane is administered as a racemic mixture with the commercial name of FORENE, although no clear indication is available on the differences between the activities of the two enantiomers. In addition, the general mechanism of anesthesia is still rather controversial and it is clear that the knowledge of the role of stereochemistry in the pharmacological behavior of chiral anesthetics can give important indication on how anesthetics exert their action.

At the beginning of the 1990s, Meinwald et al. (1) published the first preparation of samples of enantiomerically pure isoflurane through gas chromatography on capillary columns coated with cyclodextrin derivatives. This opened the way to the first studies on the effects of the single enantiomers of inhalation anesthetics, both in vitro and in vivo (1–5), where some differences in the activity of the enantiomers of isoflurane have been shown. However, this is not enough to draw conclusions on possible differences in the pharmacological effect of the two enantiomers on humans, since the number of experimental studies carried out up to now is by far not enough to clearly identify such effects. Thus, the need of enantiomerically pure samples for new clinical trials.

After the study by Meinwald et al. (1), the separation of the enantiomers of isoflurane and enflurane (another important fluorinated anesthetic) has been studied on different stationary phases with larger selectivities, particularly on octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin. These efforts have led to the preparative gas chromatographic separation of these compounds in packed columns (6–12).

Recently, the separation of enflurane on the above mentioned chiral stationary phase has been scaled up to a continuous countercurrent process by applying the simulated moving bed (SMB) technology (see Fig. 2). This technique is well known in the large-scale petrochemical and agrochemical industry, where the Sorbex™ process has been applied since the 1960s in a

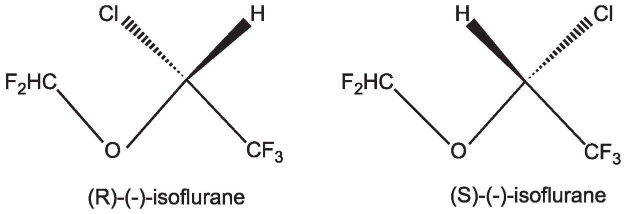

Figure 1. The chiral inhalation anesthetic isoflurane.

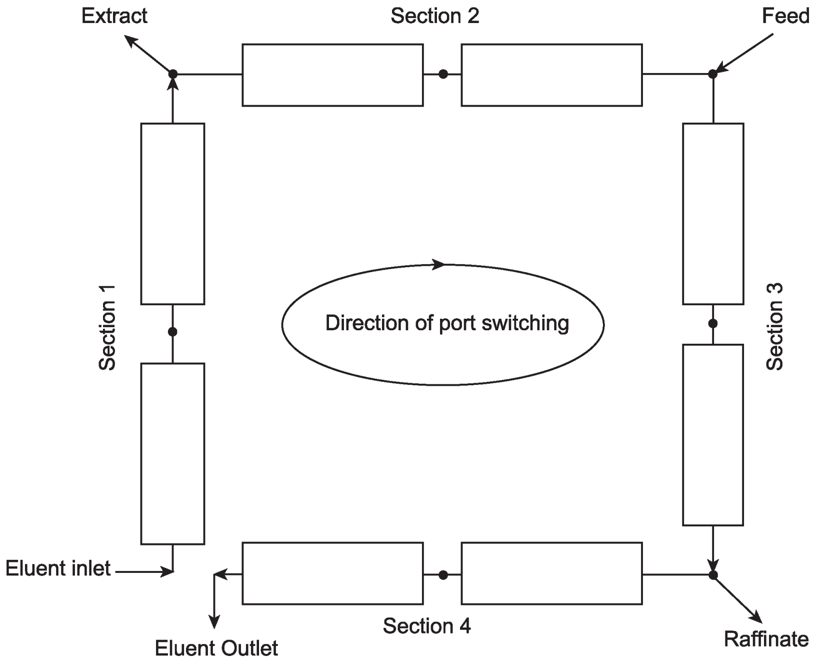

Figure 2. The open-loop simulated moving bed.

number of processes (13). Since the beginning of the 1990s, this technology has been applied in the fine chemicals and pharmaceutical industries as well, especially for chiral separations. In these industries, the use of SMB, has been recognized as a better alternative to preparative column chromatography during product development and also for the final production. Thanks to its advantages in terms of productivity and eluent consumption (14,15).

All the above-mentioned SMB applications involve liquid phase operation, but the recently reported separation of the enantiomers of enflurane is based on a chiral gas chromatographic SMB (GC-SMB), using a specifically developed stationary phase (16,17). In further studies, the effect of operating parameters such as temperature, switch time, inlet and outlet flow rates, pressure profile, and feed concentration on the product purities has been investigated. Using the GC-SMB process, 20 g of each of the two enantiomers of enflurane with high enantiomeric purity has been prepared (18).

As an extension and generalization of the results summarized above, in this work, we study the GC-SMB separation of the enantiomers of isoflurane with the same chiral stationary phase used for enflurane.

EXPERIMENTAL

Materials

Racemic isoflurane produced by Abbott Laboratories, Abbott Park, IL, under the commercial name of FORENE, was purchased from the Kantonsapotheke, Zurich, Switzerland. The stationary phase is based on octakis(3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin, dissolved in polysiloxane SE-54, and coated on Chromosorb A NAW (particle size: 20–30 mesh, corresponding to a size of about 0.6 mm). The preparation procedure has been reported by Juza et al. (16) and the composition of the column packing material is such that the Chromosorb is coated with 17% (w/w) of a Cyclodextrin/SE-54 mixture, where the Cyclodextrin fraction is 20% (w/w). This material has been used to fill a glass column (94 cm × 8 mm I.D.), which has been installed in a HP 6890 gas chromatograph (Hewlett-Packard, Wilmington, DE), and used to pack 8 SMB stainless steel columns (80 cm × 15 mm I.D.). The resulting adsorption bed volumes are around 47 mL for the glass column and 140 mL for the SMB columns.

The GC-SMB Pilot Unit

The eight stainless steel columns are installed in a chamber which is thermostatted using an automatic control system. Nitrogen is used as a carrier gas and is produced with high purity specifications by a Maxigas nitrogen generator (Domnick Hunter Ltd., Gateshead, UK). The adopted pilot plant has been described in detail by Biressi et al. (17). The eight columns are arranged in the 2–2–2–2 open-loop configuration shown in Fig. 2, where the eluent is not recycled for practical reasons. At the inlet of each column, a pressure sensor by Keller AG (Winterthur, Switzerland) is installed, while the columns are connected with each other, as well as with the inlet and outlet ports, by multiposition valves manufactured by VICI (Valco Instruments Co. Inc., Houston, TX).

Racemic isoflurane, rather diluted in a nitrogen stream, is fed to the unit. The concentration of isoflurane is controlled by saturating a nitrogen stream, which is bubbled through a stainless steel vessel filled with isoflurane and immersed in a thermostatted bath (K35/DC20, Haake GmbH, Karlsruhe, Germany). Isoflurane is collected from the extract and raffinate by condensing it in cooling traps immersed in liquid nitrogen. The present system did not have provision for an online measurement of the extract and raffinate streams, nor was the amount of product collected weighed. Hence, the collection system does not allow for a quantitative assessment of the absolute concentration of the product streams, and therefore for the check of the overall material balance. The enantiomeric purity of the collected products is determined via headspace gas chromatography using a fused silica capillary column with the same cyclodextrin derivative used in the SMB packing material as chiral selector. The column is installed in a Mega 5300 gas chromatograph (Carlo Erba Instruments, Milano, Italy). All instruments are computer assisted through a Labview program (National Instruments, Austin, TX).

CHARACTERIZATION OF THE ADSORPTION EQUILIBRIUM

Headspace injections of racemic isoflurane in the glass column described in the Experimental section lead to broad, symmetric peaks, due to the low separation efficiency resulting from the large particle size. The retention times of these peaks were measured at various flow rates between 0.01 and 0.08 std./min, and at various temperatures in the range between 25 and 50°C. The Henry's constants, H_i, calculated from these data are reported in Table 1. The total porosity of the packed bed is 0.75, as measured through injections of methane, which is assumed to be inert. This same value has been used for all the columns installed in the SMB unit.

It is worth noting that the enantiomer retention depends on the partition of isoflurane between the gas and the liquid polysiloxane coating, as well as on the enantioselective interaction with the cyclodextrins. As a consequence, the Henry's constants depend linearly on the gas/liquid partition constant, and their temperature dependence has been fitted to the Antoine equation. The experimental data are compared to the calculated curves in Fig. 3. It is worth noting that the selectivity resulted to be smaller for isoflurane than for enflurane (18), hence the resolution of the enantiomers of isoflurane was expected to be more difficult.

Table 1. Measured Henry Constants for Isoflurane and Corresponding Selectivity (H_A/H_B) Values

T (°C)	H_A	H_B	Selectivity
25	116	156	1.34
30	83	107	1.30
35	61	76	1.26
40	45	56	1.22
45	35	41	1.19
50	27	31	1.15

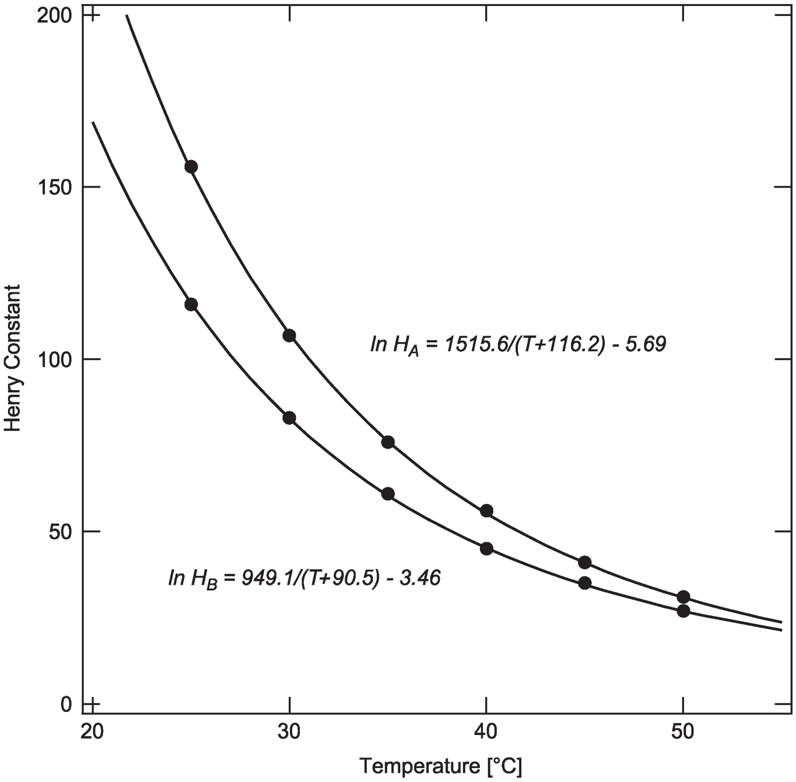

Figure 3. Henry constants of the enantiomers of isoflurane as a function of temperature compared to the fitted Antoine-like equations.

BACKGROUND ON GC-SMBs

The performance of a GC-SMB depends mainly on the values of the operating parameters m_j, defined as:

$$m_j = \frac{Q_{o,j} J_j t^* - V\varepsilon}{V(1-\varepsilon)} \quad j = 1, \ldots, 4 \tag{1}$$

where j indicates the section of the SMB unit, $Q_{o,j}$ is the volumetric flow rate at the outlet of the j-th section, t^* is the switch time, i.e., the period between two successive switches of inlet and outlet ports, V and ε are the volume and the total void fraction of the columns, respectively (16). The James and Martin factor, J_j, accounts for pressure changes along the j-th section and is defined as follows:

$$J_j = \frac{3}{2}\frac{\beta_j^2 - 1}{\beta_j^3 - 1} \quad j = 1, \ldots, 4 \tag{2}$$

where $\beta_j = P_{\mathrm{in},j}/P_{\mathrm{out},j}$, $P_{\mathrm{in},j}$ is the inlet pressure and $P_{\mathrm{o},j}$ the outlet pressure in section j. The value of J_j is such that the product $Q_{\mathrm{o},j}J_j$ is always between $Q_{\mathrm{o},j}$ and $Q_{\mathrm{in},j}$, i.e., the outlet and the inlet volumetric flow rate in section j, respectively.

Similar to the better known liquid phase SMB process, at a given temperature, the Henry constants of the components to be separated identify the area in the operating (m_2, m_3) plane where conditions leading to complete separation can be found (16). However, the actual shape of the complete separation region depends not only on the feed concentration, as in liquid phase SMBs, but also on the pressure profile and, thus, on the internal flow rates, due to pressure drop.

Nevertheless, if the adsorption isotherms are linear, the performance of GC-SMBs is independent of pressure and, according to the equilibrium theory, extract and raffinate streams are predicted to be pure if the following constraints on the flow rate ratios given by Eq. (1) are fulfilled (16–19):

$$\begin{aligned} &m_1 > H_A \\ &H_B < m_2 < H_A \\ &H_B < m_3 < H_A \\ &m_4 < H_B \end{aligned} \tag{3}$$

where H_i are the Henry constants and A and B indicate the more retained and the less retained components, respectively.

EXPERIMENTAL RESULTS

Four sets of experiments have been carried out, corresponding to the different combinations of two temperature levels, i.e., 25 and 35°C, and two sets of flow rates, yielding smaller and larger pressure drop, respectively; the corresponding operating conditions are reported in Table 2. In all experiments, the feed is nitrogen saturated with isoflurane at −25°C, which corresponds to a racemate concentration of 0.80%. In each group of experiments, namely, A, B, C, and D, separation performance has been varied by changing the switch time only. The 30 different experiments are reported in Tables 2 and 3: group A (runs 1–9) corresponds to low temperature and pressure drop; group B (runs 10–15) corresponds to low temperature and high pressure drop; group C (runs 16–20) corresponds to high temperature and low pressure drop; and finally group D (runs

Table 2. Classification of Experiments and Corresponding Operating Conditions. Feed Mole Fraction of the Racemate Is 0.008 (0.80%)

Group	T (°C)	P_{in} (bar)	P_{out} (bar)	Q_1 (Std./min)	Q_2 (Std./min)	Q_3 (Std./min)	Q_4 (Std./min)
A	25	4.0	3.3	3.6	1.85	1.90	0.90
B	25	4.5	3.2	5.3	2.80	2.85	1.55
C	35	4.0	3.3	3.6	1.85	1.90	0.90
D	35	4.5	3.2	5.3	2.80	2.85	1.55

21–30) corresponds to runs at high temperature and high pressure drop. Several of these runs have been repeated more than once, as apparent from Table 3. About 63 experiments were performed under 30 different operating conditions. For operating conditions where experiments were repeated, the average values of the m_j parameters (small differences were observed due to slight changes in the pressure profile for the same overall pressure drop) and the puritites are reported in Table 3. The standard deviation for each group is also reported, but for Group A where only one experiment was repeated. The overall standard deviation (considering 63 experiments in 30 groups) for the extract and raffinate was found to be 3.63 and 4.15%, respectively. It is also worth noting that the standard deviations for Group D are relatively higher, compared to the other groups. This is probably due to the fact that group D has a larger number of experiments when compared to the others.

The purity performances achieved in the four sets of experiments are shown in Fig. 4a–d according to the following criteria. The experimental average extract and raffinate purities are plotted as circles and triangles, respectively, vs. the corresponding average m_2 values. Solid lines are drawn to guide the eye and to show the trend, whereas, broken lines give the confidence limits; the overall standard deviation of 3.63% for the extract and 4.15% for the raffinate are used for plotting the confidence limits.

As reported in Table 3, with all four sets of operating conditions, it was possible to achieve high purity values in both extract and raffinate. In particular, raffinate purity, P_{R}, above 99% has been obtained in all four groups of experiments at small switch time values, as expected (16,17,19). Accordingly, for large switch time values, the extract purity, P_{E}, was high, namely above 99% in groups A and D, and above 98% in groups B and C. Despite the lower selectivity, this performance is only slightly worse than the best performance obtained in the case of separation of the enantiomers of enflurane (17). It is worth noting that as far as operating temperature and pressure drop are concerned, no systematic optimization has been carried out. This implies that at this stage, it is not possible to draw conclusions either about which set of operating conditions (temperature

Table 3. Operating Conditions of the Experimental Runs, Switch Times, Calculated Average m_j Values, Corresponding Average Purity of Extract and Raffinate, and Calculated Standard Deviations (see Table 2)

Group	Run Number (Number of Repeated Runs)	t^* (min)	Average m_1	Average m_2	Average m_3	Average m_4	Average P_E (%)	Average P_R (%)	Standard Deviation of P_E (%)	Standard Deviation of P_R (%)
A	1 (0)	6.00	170.0	91.6	198.3	46.9	80.8	99.5	—	—
	2 (0)	6.17	174.0	94.2	101.1	48.3	86.5	99.6		
	3 (0)	6.40	181.0	97.9	105.0	50.2	84.8	99.8		
	4 (0)	6.43	182.0	98.4	105.6	50.5	91.9	93.9		
	5 (0)	6.47	183.0	98.9	106.2	50.8	92.7	99.6		
	6 (2)	6.50	184.0	99.4	106.7	51.0	92.6	85.0		
	7 (0)	6.67	189.0	102.1	109.5	52.4	94.0	65.4		
	8 (0)	7.00	198.0	107.3	115.2	55.2	96.0	94.5		
	9 (0)	8.00	227.0	123.1	132.0	63.5	99.3	61.1		
B	10 (0)	4.57	182.0	104.7	114.8	65.8	90.5	99.7	0.66	2.32
	11 (3)	4.67	186.0	107.1	117.4	67.3	95.0	98.9		
	12 (3)	4.73	189.0	108.6	119.1	68.3	96.0	96.9		
	13 (2)	4.77	190.0	109.4	119.9	68.8	96.6	93.8		
	14 (2)	4.83	193.0	111.0	121.7	69.8	97.1	88.0		
	15 (0)	5.00	199.0	114.9	126.0	72.3	98.5	77.4		
C	16 (0)	3.77	109.0	58.4	62.7	29.4	92.5	99.7	0.18	1.67
	17 (2)	3.83	111.0	59.4	63.9	29.9	95.9	95.7		
	18 (3)	3.93	114.3	61.0	65.5	30.9	97.1	88.6		
	19 (3)	4.00	115.7	62.0	66.7	31.4	97.6	83.3		
	20 (3)	4.07	117.3	62.9	67.5	31.8	98.1	79.8		
D	21 (0)	2.50	98.0	56.0	61.5	31.0	69.8	99.7	4.77	4.97
	22 (0)	2.67	105.0	59.9	65.8	37.2	89.0	99.5		
	23 (2)	2.73	108.5	61.5	67.5	38.2	95.3	99.5		
	24 (2)	2.77	109.0	62.4	68.5	38.7	94.9	99.8		
	25 (3)	2.80	110.7	63.0	69.2	35.1	92.1	95.6		
	26 (9)	2.83	111.7	63.9	70.2	39.7	97.1	94.9		
	27 (3)	2.87	112.7	64.5	70.9	40.2	96.1	92.1		
	28 (5)	2.90	113.4	65.2	71.8	40.7	93.3	96.0		
	29 (0)	2.97	116.0	67.3	73.6	41.7	98.7	76.5		
	30 (2)	3.07	121.0	69.3	76.1	38.7	99.1	68.4		

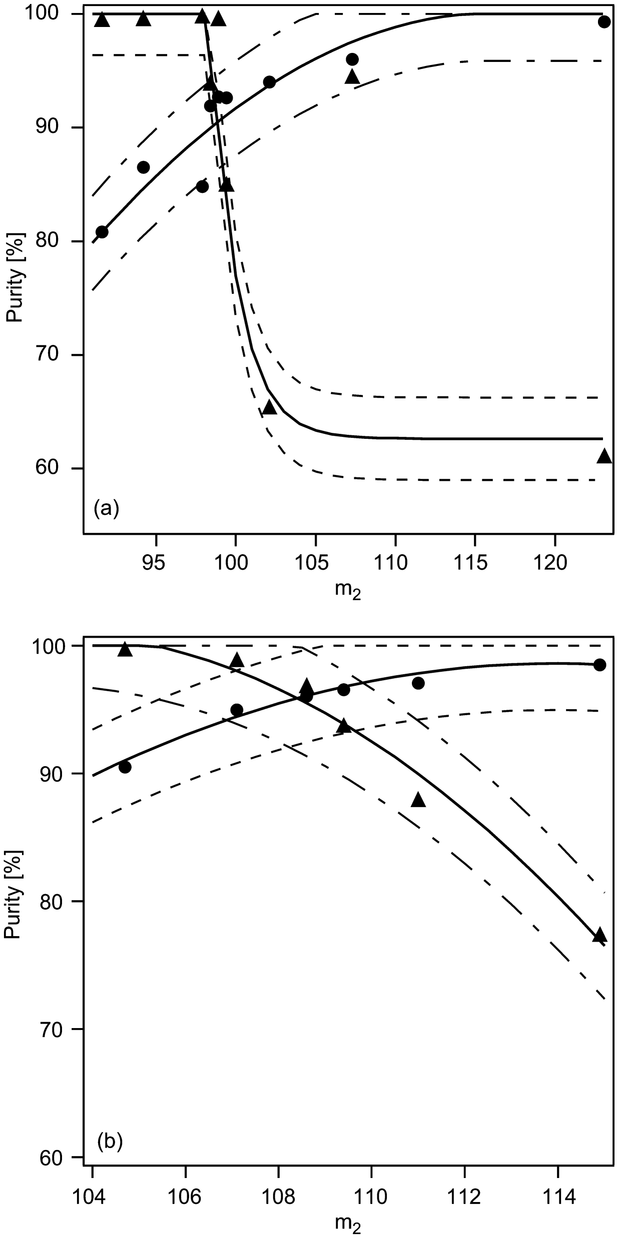

Figure 4. Purity of the extract and raffinate streams as a function of the operating parameter m_2 for experiments in (a) Group A, (b) Group B, (c) Group C, (d) Group D. Circles indicate extract purity; triangles indicate raffinate purity. Lines are drawn as a guide for the eye. Broken lines show the confidence limits based on 3.63% for the extract and 4.15% for the raffinate. (For operating conditions refer to Tables 2 and 3).

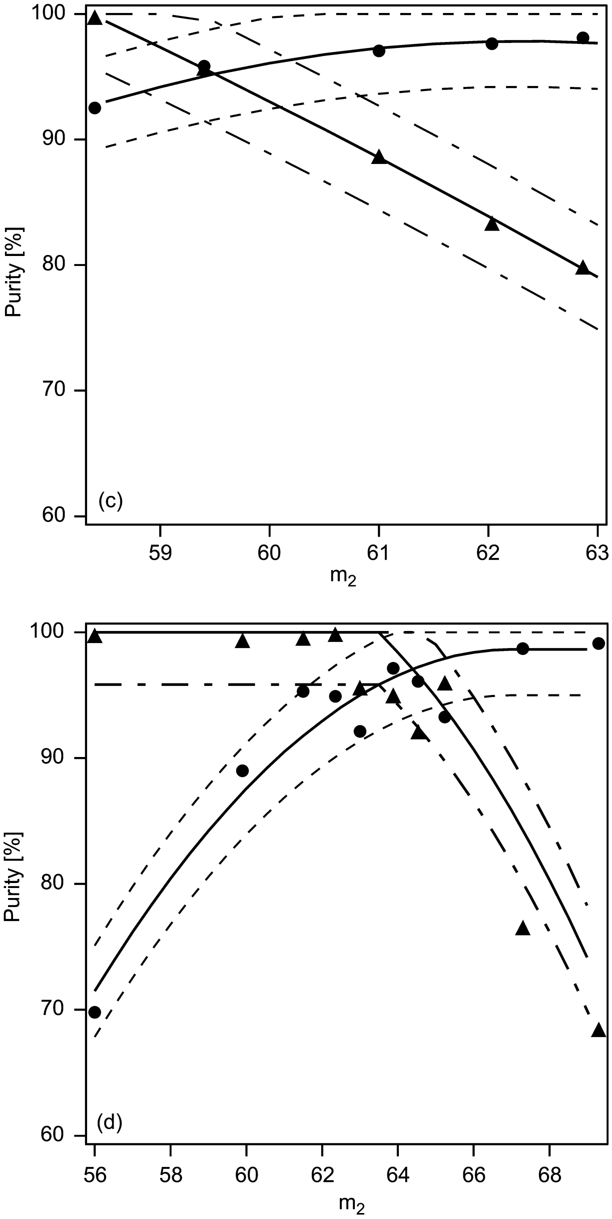

Figure 4. Continued.

and pressure drop) is best, or about what is the best performance that can be achieved for this separation in this experimental set-up.

By observing Fig. 4a–d, it is apparent that in general, the effect of increasing the switch time at constant flow rates (which corresponds to increasing the m_2 value that is used as abscissa in all these figures) is as expected (16,17,19). In fact, the average extract purity values increase, and the average raffinate purity values decrease on going from left to right in these diagrams, but for a few exceptions. It is also worth noting that the range of m_2 and m_3 values, where high purity in both extract and raffinate is obtained at the same time, is close to Henry's constants of the two enantiomers at the corresponding operating temperature. Thus, m_2 values of interest at $T = 25°\mathrm{C}$ are between 100 and 110, whereas at $T = 35°\mathrm{C}$, these are close to 60.

It was generally observed that reproducibility was not satisfactory in this separation. As an example, let us consider experiment 26, which was repeated several times under the same nominal operating conditions. Despite the average value of the extract purity, i.e., 97.1% and that of the raffinate purity, i.e., 94.9% being consistent with the other runs in group D, the measured purity values ranged between 93.2 and 98.3% for the raffinate, and between 86.4 and 99.6% for the extract. It was not possible to clarify thoroughly the reason for a behavior that was not observed in other SMB operations before, particularly not in the case of enflurane (17). It is only possible to make some conjectures about possible causes. The selectivity is smaller than in the case of enflurane, and the adopted feed concentration is larger. Both differences contribute in making the separation more difficult; this might explain why the system is more sensitive to small temperature gradients in the SMB chamber, and to pressure profiles along the unit that periodically change to adapt to the small differences in the packing of the eight SMB columns. In this context, it is worth noting that the same columns as in the case of the enflurane separation have been used. Therefore, it might be that the stationary material has undergone aging or degradation, which manifests itself in the form of poor reproducibility. The development of a technique to check the mass balance might clarify some of these issues.

Despite these difficulties, it was possible to complete the preparative part of the project, i.e., the production of the pure isoflurane enantiomers in the multi-gram scale, in particular, 13 g of (*S*)-(+)-isoflurane at 98.1% purity and 12 g of (*R*)-(−)-isoflurane at 96.7% purity.

CONCLUSIONS

In this work, the separation of the enantiomers of the inhalation anesthetic isoflurane with a gas phase simulated moving bed has been studied, based on the experience gained in the separation of the enantiomers of enflurane (16–18). It has been found that the enantioseparation of isoflurane exhibits the same qualitative behavior as the one of enflurane, but the sensitivity to disturbances is larger. Temperature or pressure variations in the columns and a relatively low selectivity are suspected to be the cause for the observed difficulty in reproducing the results. With our laboratory SMB unit, it was possible to prepare gram-amounts of isoflurane with enantiomeric purity high enough for medical trials.

NOMENCLATURE

H_i	Henry's constant
J_j	James Martin factor for section j
m_j	Operating parameter defined by Eq. (1)
$P_{\mathrm{in},j}$	Pressure at the inlet of section j
$P_{\mathrm{o},j}$	Pressure at the exit of section j
P_{E}	Purity of the extract stream
P_{R}	Purity of the extract stream
$Q_{\mathrm{in},j}$	Gas flow rate at the inlet of section j
$Q_{\mathrm{o},j}$	Gas flow rate at the exit of section j
t^*	Switch time
V	Column volume

Greek Letters

ε	Bed porosity
β_j	Gas expansion ratio

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