



ELSEVIER

Journal of Chromatography A, 947 (2002) 59–68

JOURNAL OF
CHROMATOGRAPHY A

www.elsevier.com/locate/chroma

Application of the “VARICOL” process to the separation of the isomers of the SB-553261 racemate

O. Ludemann-Hombourger^{a,*}, G. Pigorini^a, R.M. Nicoud^a, D.S. Ross^b, G. Terfloth^c

^aNOVASEP SAS, Site Eiffel, Boulevard de la Moselle, BP50, F54340, Pompey, France

^bGlaxoSmithKline Old Powder Mills, Leigh, Tonbridge, Kent TN11 9AN, UK

^c709 Swedeland Road, King of Prussia, PA 19406, USA

Received 8 October 2001; received in revised form 28 November 2001; accepted 29 November 2001

Abstract

A new continuous chromatographic process (VARICOL) has been presented recently. The basic principle of the new VARICOL process consists of an asynchronous shift of the inlet/outlet lines in a multi-column system on a recycle loop. This process has been used to perform the separation of the optical isomers of the SB-553261 racemate. In this paper, we illustrate that for this specific separation, the VARICOL process is more efficient than the well-known SMB process. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Enantiomer separation; VARICOL process; Multi-column system; Simulated moving bed; Preparative chromatography; SB-553261

1. Introduction

VARICOL is a new multi-column continuous process that has been described in [1,2]. Both the Simulated Moving Bed (SMB) and VARICOL processes consist of columns connected in series, with inlet/outlet lines connected between the columns. In SMB, the inlet/outlet lines are shifted simultaneously. In a VARICOL process, however, these lines are never shifted at the same time. The purpose of this paper is to show how SMB compares to VARICOL for a separation of practical interest, i.e. the separation

of the enantiomers of the SB-553261 racemate.

2. Presentation of the VARICOL process

SMB is a way of implementing in practice a counter-current chromatographic process [1]. In 1961, UOP patented this process [4], allowing one to simulate the counter-current motion of the solid-phase with respect to the liquid phase via an adequate connection between columns and the periodic shift of the inlet and outlet lines. It is characterized by “periodically advancing downstream the point of introducing the feed stock and the desorbent while *simultaneously and equally* advancing downstream the point of withdrawal of raffinate and

*Corresponding author. Tel.: +33-3-8349-7071; fax: +33-3-8349-7001.

E-mail address: olivier_ludemann-hombourger@novasep.com (O. Ludemann-Hombourger).

sorbate” [5], “. . . and the feed and desorbent inlet points and the product withdrawal points being translated along the column in *equal increments* by a stream distribution means” [6], “. . . in said process streams are periodically shifted *in unison* successively from one set of transfer points to the next in a downstream direction with respect to the flow of said pumparound . . .” [7].

A simplified flowsheet of an SMB is given in Fig. 1.

In a multi-column continuous chromatographic process (SMB or VARICOL) the columns are distributed among four zones, each with a given role in the separation process. Specifically, the zone between the eluent line and the extract line is referred to as Zone I, and its role is to desorb the more strongly retained component. Zone II, between the extract line and the feed line, serves the purpose of desorbing the less retained component. The role of Zone III, between the feed line and the raffinate line, is to adsorb the more retained component, whereas the role of Zone IV, between the raffinate line and the eluent line, is to adsorb the less retained component.

In the SMB process, the lines are shifted synchronously to simulate an equivalent counter-current process called True Moving Bed (TMB) [3]. As a consequence, the number of columns in each zone stays the same at each moment, regardless of the location of the inlet/outlet lines (the length of the zones of the equivalent TMB does not change in time). It is therefore possible to characterize the configuration of an SMB process by specifying how columns are distributed among zones. For example, a

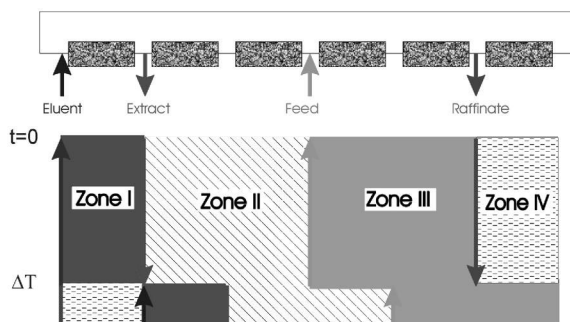


Fig. 2. Chronogram of a 6-column SMB process with column configuration 1/2/2/1.

configuration of 1/2/2/1 in a 6-column system represents a system where Zones I and IV always contain one column and Zones II and III always contain two columns. Fig. 2 shows the chronogram corresponding to that SMB configuration: the column distribution does not change during the whole period, and then, at the end of the period, all lines shift to the right by one column¹.

In a VARICOL process, lines are shifted

¹The dissymmetry of the SMB resulting from the dead volume of the recycling pump in the closed loop disturbs the performance of the SMB process. This dissymmetry can, however, be corrected by adding a delay for the switch of the inlet/outlet line passing the recycling pump. A detailed description of this method is provided in patent [10]. In this case the shift of all the lines is not always synchronous to compensate for the technical imperfection of the real system and to get closer to the ideal symmetrical SMB system (it is even noticeable that in one time per cycle all the inlet/outlet lines are shifted synchronously).

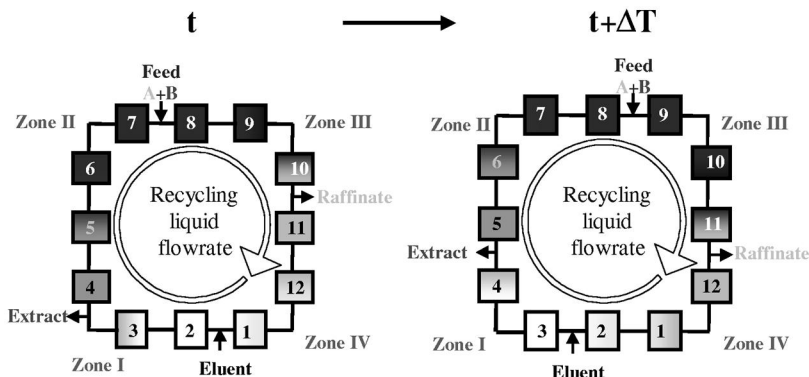


Fig. 1. Principle of SMB (12 columns). All inlet/outlet lines are shifted at every period ΔT .

asynchronously. In that case, the column distribution between zones does not stay the same during the period, because lines are shifted at different times, so that the column allocation changes accordingly. While SMB is equivalent to TMB, VARICOL is equivalent to VARIZONE presented in Fig. 3. The basic idea of the VARIZONE process is to modify the classical TMB in order to allow for the variation of the zone length in time.

Fig. 4 is the chronogram corresponding to an example of a 4-column VARICOL process.

As can be seen from the chronogram, the initial column configuration is characterized by zero columns in Zone I, two columns in Zone II, and one column each in Zones III and IV. No column separates the eluent inlet from the extract outlet. This column distribution stays the same for half a period. At $t + 0.5 \Delta T$, the extract and raffinate lines shift simultaneously, whereas the eluent and feed lines do not shift. This means that one column is now assigned to Zone I (between the eluent line and the extract line), one column only is now in Zone II (between the extract line and the feed line), two columns are in Zone III (between the feed line and the raffinate line), and zero columns are in Zone IV, since there is no column between the raffinate line

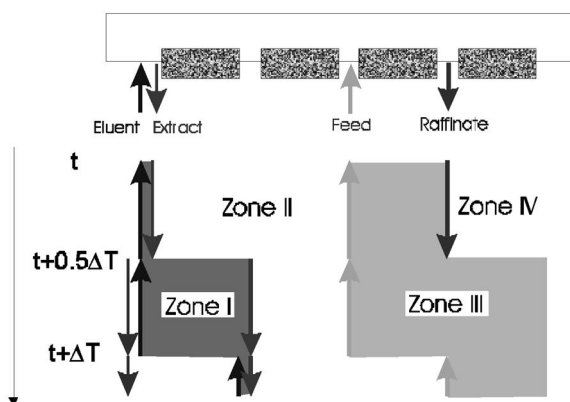


Fig. 4. Chronogram of an example of a 4-column VARICOL process.

and the eluent line. This column distribution stays constant until the end of the period, at which point the eluent and feed lines are shifted by one column and the original status is restored. This time pattern is repeated the same in the next period. In order to characterize such a distribution, it is convenient to look at the average number of columns per zone per period. Zone I contains zero column for half of the period, and one column for the rest of the period, so on average it contains 0.5 column during the period.

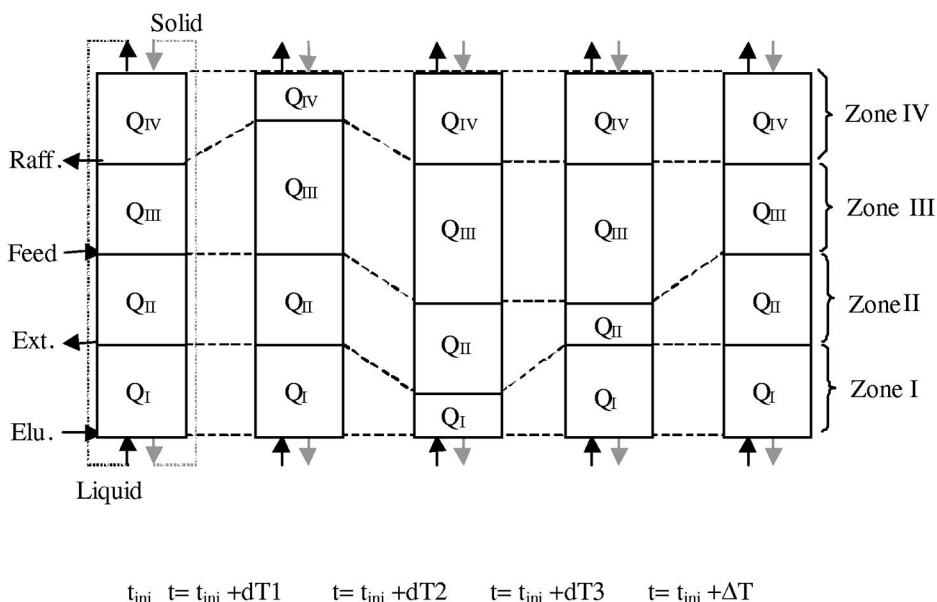


Fig. 3. The VARIZONE process.

This does not mean that it “physically” contains half a column, but that on average over the period one column is assigned to it during half of the period, and zero for the rest of the period. In much the same way, Zone II has two columns for half of the period and one column during the rest of the period, so that on average it contains 1.5 columns. The same applies to Zone III. Zone IV contains one column during the first half of the period, and zero for the rest of the period, so that on an average it has the same number of columns as Zone I. It can be shown that once the average number of columns per zone is chosen, the VARICOL configuration is fully characterized. Hence, the configuration in Fig. 4 can be defined as $\langle 0.5 \rangle / \langle 1.5 \rangle / \langle 1.5 \rangle / \langle 0.5 \rangle$.

It must be pointed out that the temporary superposition of lines (superposition of extract and eluent on the present example or other lines like raffinate and feed, ...) leads to obvious consequences for the technical design of the VARICOL machine. Between each column, the two outlets lines must be connected to the recycling line before the eluent and feed lines (following the direction of the recycling flux) as presented in Fig. 5. Using this design, the feed flux does not pollute the extract or raffinate streams when the number of column is temporary zero in Zones II and III, respectively. The eluent flux will also not unnecessarily dilute the extract or raffinate flux when the number of column is equal to zero in Zone I or IV.

Unlike in a 4-zone SMB process, where for a 4-column system only one configuration is viable (1 column in each zone is required), in a VARICOL process, there is no such limitation and the number of possible configurations is infinite. This is what

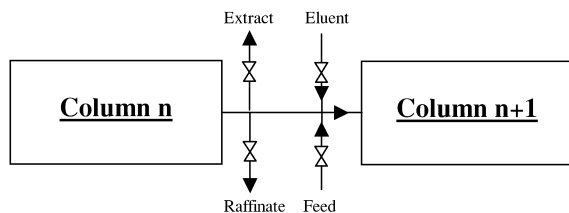


Fig. 5. Connection of the inlet/outlet lines of the VARICOL process.

makes VARICOL extremely flexible and powerful compared to SMB, especially with few columns.

3. Experimental results

3.1. Basic data

The separation of the isomers of the SB-553261 racemate provided by GSK (Fig. 6) was performed on Chiralpak AD (Chiral Technologies Europe), with an average particle size of 20 μm .

The eluent was the mixture acetonitrile/methanol 80/20 (v/v). The temperature was set to 25 °C. Fig. 7 shows the chromatogram corresponding to an analytical injection of the feed mixture into a 10 mm I.D. column (81 mm bed length). At an eluent flow-rate of 1.5 ml/min, the retention times of the two enantiomers are the following, with (*S*) enantiomer eluting first:

$$t_{\text{R}}(1) = 5.78 \text{ min} \quad \text{and} \quad t_{\text{R}}(2) = 8.89 \text{ min}$$

In order to determine the adsorption isotherms, we performed a few overloaded injections. Using the retention times corresponding to the analytical injection and the overloaded injections, we used a classical optimization procedure [8] that allows one to estimate the isotherm parameters. We obtained a good agreement between experimental results and simulation by choosing a modified competitive Langmuir adsorption isotherm to describe the equilibrium between the liquid phase and the adsorbed phase.

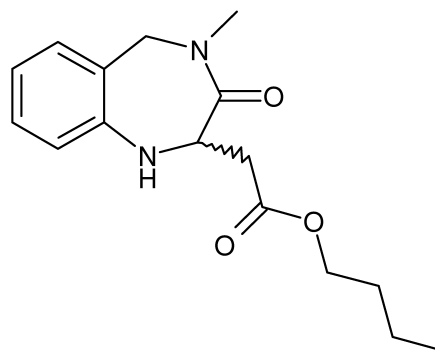


Fig. 6. Molecular structure of SB 553261.

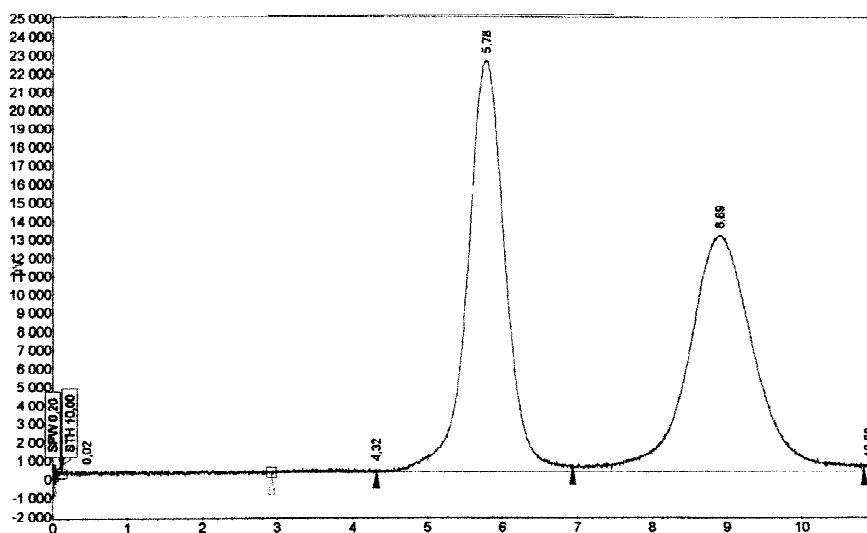


Fig. 7. Analytical injection of the feed mixture into a 10*81 mm column $Q=1.5$ ml/min, $V_{inj}=10$ μ l, $C_{inj}=1$ g/l, UV detection $\lambda=310$ nm.

The curve fitting was best with the following values for the adsorption parameters:

$$\begin{aligned} \bar{C}_1 &= 1.35 \cdot C_1 + \frac{0.294 \cdot C_1}{1 + 0.0338 \cdot C_1 + 0.1696 \cdot C_2} \\ \bar{C}_2 &= 1.17 \cdot C_2 + \frac{1.509 \cdot C_2}{1 + 0.0338 \cdot C_1 + 0.1696 \cdot C_2} \end{aligned} \quad (1)$$

In these equations, C_i and \bar{C}_i are the concentration of species i in the mobile phase and stationary phase respectively. The pressure drop was measured on the same column, so that Darcy's law coefficient could be determined:

$$\frac{\Delta P}{L} = 2.5 \cdot 10^9 \cdot u \quad (\text{SI unit}) \quad (2)$$

We characterized the column efficiency by measuring the influence of the fluid velocity on the Height Equivalent to a Theoretical Plate. We obtained the following simplified Van Deemter equations for the two enantiomers:

$$\begin{aligned} H_1 &= 6 \cdot 10^{-5} + 1.63 \cdot 10^{-3} \cdot u \\ H_2 &= 6 \cdot 10^{-5} + 2.64 \cdot 10^{-3} \cdot u \end{aligned} \quad (\text{SI unit}) \quad (3)$$

3.2. Pilot plant description

We performed the purification tests on a multi-

column system consisting of 10 mm I.D. columns. The length of the packed bed in each column was 81 mm. The system has been described in [1] and a brief overview is given below.

The multi-column experimental unit is a direct downscale of pilot and industrial scale systems, and permits to perform small-scale separations of a few grams of product per day.

The unit is composed of a maximum number of eight columns (10 mm I.D., 100 mm length) connected in series. HPLC pumps (μ -pompe, ARMEN instrument, France) provide the appropriate re-circulation flow-rate through the recycling line and the appropriate flow-rate through the inlet/outlet lines.

A 6-port valve is installed on the recycling line at the inlet to the first column. This 6-port valve allows one to collect a liquid sample and to measure how the internal concentration changes with time at the inlet to the first column. As the concentration profile shifts in the system due to recycling, the measurement of the internal concentration at set times allows one to identify the internal concentration profile. This profile is of major importance for optimizing the process. An oven is used to control and regulate the temperature of the columns and valves on the unit.

We conducted all tests with a feed concentration

of 32 g of racemate per liter of eluent. The goal was to achieve a raffinate purity greater than 99% and an extract purity greater than 95%. The operating conditions were selected to reach the maximum productivity with the lowest eluent consumption. A numerical method for SMB process optimization was developed and described in [9]. The VARICOL process is optimized based on a similar approach.

As a technology constraint, we decided to set the working pressure at around 30 bars. This means that, from Darcy's Law, we keep $\bar{u} \times L = \text{const}$ in all the configurations that we consider, where \bar{u} is the average fluid velocity in the columns (proportional to the average liquid flow-rate \bar{Q}), and L is the total column length (i.e., length of packed bed in one column times the number of columns).

3.3. Six-column SMB

Initially, we performed the separation on a 6-column SMB characterized by the column distribution 1/2/2/1 (one column in Zones I and IV). We obtained an initial guess for the set of flow-rates through a classical numerical optimization [3,9], and then slightly readjusted the flow-rates to achieve the required purities. The following setting was found to give satisfactory results when implemented experimentally:

$$\begin{aligned} Q_{\text{rec}} &= 15.3 \text{ ml/min} \\ Q_{\text{ext}} &= 7.06 \text{ ml/min} \\ Q_{\text{feed}} &= 0.30 \text{ ml/min} \\ Q_{\text{raf}} &= 1.79 \text{ ml/min} \\ Q_{\text{elu}} &= 8.55 \text{ ml/min} \\ \Delta T &= 1.11 \text{ min} \end{aligned} \quad (4)$$

With the optimized set of flow-rates, we obtained a 99.6% pure raffinate and a 95.6% pure extract. The recovery of the more retained component was very high (99.9%), while that of the less retained component was 85%. This is mainly due to the fact that the extract flow-rate is significantly higher than that of the raffinate, so that even though the percentage of raffinate in the extract stream is low, the absolute amount of the less retained component lost in the extract stream is not negligible. This also explains why the concentration of the less retained component in the raffinate line (2.64 g/l) was much higher than

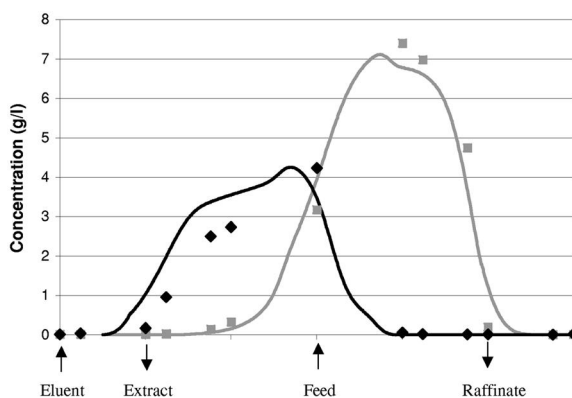


Fig. 8. Comparison of experimental and simulated periodic concentration profile on 6-column SMB.

that of the more retained component in the extract line (0.51 g/l).

Fig. 8 shows the internal concentration profile at the periodic steady state (attained after around 20 cycles). This profile shows at a selected time the concentrations of the two enantiomers as a function of inlet/outlet lines. As time progresses, the profile shifts in the direction of the recycling flow-rate, but its shape does not change. We can notice that both enantiomers have a very long tail to the left (in Zones I and II), and that is mainly what prevents us from injecting more feed.

3.4. Six-column VARICOL

We then proceeded to consider a 6-column VARICOL process. The goal was to show that VARICOL is a more efficient process than SMB, and that it can lead to a better performance than the optimized SMB while using the same amount of stationary phase.

Based on our expertise as well as on a few numerical optimisations, we came to the conclusion that a good column distribution for this system was $\langle 1 \rangle / \langle 2.25 \rangle / \langle 2 \rangle / \langle 0.75 \rangle$ (average number of columns per zone): with respect to the configuration of the 6-column SMB system, we decided to assign a higher average number of columns to Zone II and to reduce the number of columns in Zone IV. This decision is easily justified considering that Zone II is a desorption zone characterized by diffusive fronts that are more difficult to retain than compressive

fronts (hence the need for more stationary phase in that zone vs. Zone III). On the other hand, based on how well the raffinate was adsorbed in Zone IV, less than a full column on average was deemed necessary in that zone.

This column distribution was implemented in practice by switching asynchronously the inlet/outlet lines according to the chronogram shown in Fig. 9.

Based on a numerical optimization of the operating flow-rates, we arrived at the following setting:

$$\begin{aligned} Q_{\text{rec}} &= 15.3 \text{ ml/min} \\ Q_{\text{ext}} &= 7.49 \text{ ml/min} \\ Q_{\text{feed}} &= 0.33 \text{ ml/min} \\ Q_{\text{raf}} &= 1.89 \text{ ml/min} \\ Q_{\text{elu}} &= 9.05 \text{ ml/min} \\ \Delta T &= 1.11 \text{ min} \end{aligned} \quad (5)$$

This configuration results in a raffinate purity of 99.7% and an extract purity of 95.6%, virtually the same as in the 6-column SMB. The recovery of the less retained component was 85.1% (with a concentration of 3.40 g/l) and that of the more retained component was 99.9% (with a concentration of 0.65 g/l). *What is noticeable is that with VARICOL the feed flow-rate is higher than with SMB, while eluent consumption (measured in liters per gram of feed) is lower, as will be illustrated more in detail in the discussion section.*

This example shows clearly that by adequately selecting the average length of each zone (by choosing an optimal average column configuration) it is possible to assign more stationary phase to the zones

that are more critical to the separation, and in so doing to make sure that the phase is used more efficiently. That is indeed the main achievement of VARICOL.

3.5. Five-column VARICOL

In an effort to increase the specific productivity of the system (expressed in terms of kg purified product/kg CSP/day), we decided to remove one column and to consider a 5-column VARICOL process. Keeping the same constraint regarding the pressure drop (30 bars for the complete system), we performed a few trials and finally settled on a column distribution among zones given by $\langle 0.95 \rangle / \langle 1.85 \rangle / \langle 1.5 \rangle / \langle 0.7 \rangle$. In order to get such a configuration, the inlet/outlet lines are shifted according to the chronogram presented in Fig. 10.

This column distribution confirms that, in general, priority is often given to Zones II and III, which are directly and primarily responsible for the separation of the feed. Moreover, Zone II, being a desorption zone, requires in general a higher average number of columns than Zone III. We therefore decided to consider less than one column on average in Zones I and IV. Also, due to the absorptive nature of Zone IV and the desorptive nature of Zone I, a lower average number of columns is required in the former.

Using this column distribution, we selected the following setting:

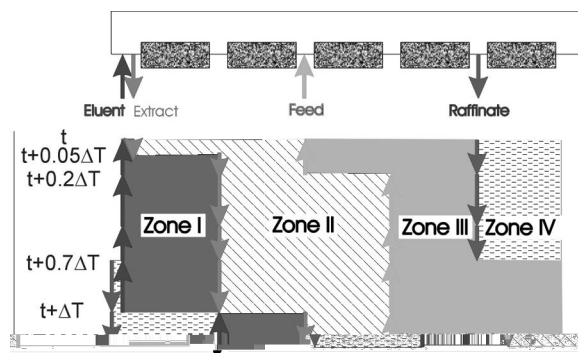


Fig. 9. Chronogram of a 6-column VARICOL process with column configuration $\langle 1 \rangle / \langle 2.25 \rangle / \langle 2 \rangle / \langle 0.75 \rangle$.

Fig. 10. Chronogram of a 5-column VARICOL process with column configuration $\langle 0.95 \rangle / \langle 1.85 \rangle / \langle 1.5 \rangle / \langle 0.7 \rangle$.

$$\begin{aligned}
 Q_{\text{rec}} &= 17.49 \text{ ml/min} \\
 Q_{\text{ext}} &= 7.59 \text{ ml/min} \\
 Q_{\text{feed}} &= 0.30 \text{ ml/min} \\
 Q_{\text{raf}} &= 2.49 \text{ ml/min} \\
 Q_{\text{elu}} &= 9.78 \text{ ml/min} \\
 \Delta T &= 0.925 \text{ min}
 \end{aligned} \quad (6)$$

This configuration is characterized by a raffinate purity of 99.7% and an extract purity of 96.8%. The latter is higher than that obtained in the 6-column SMB. The recovery of the more retained component is 99.9% (with a concentration in the extract stream of 0.55 g/l) and that of the less retained component is 96.8% (with a concentration in the raffinate stream of 2.04 g/l). A remarkable result is that while injecting the same feed as in the 6-column SMB, we obtain roughly the same purities *with one less column!* That of course is at the expense of a higher eluent consumption as will be illustrated more in detail in the discussion section.

3.6. Four-column VARICOL

Finally, we decided to look at a 4-column VARICOL process, to check whether the trends observed in the examples shown were confirmed there. We selected the configuration $\langle 0.85 \rangle / \langle 1.5 \rangle / \langle 1.15 \rangle / \langle 0.5 \rangle$. In terms of column distribution among zones, the same considerations as formulated in the previous cases apply. The chronogram corresponding to such a process is illustrated in Fig. 11:

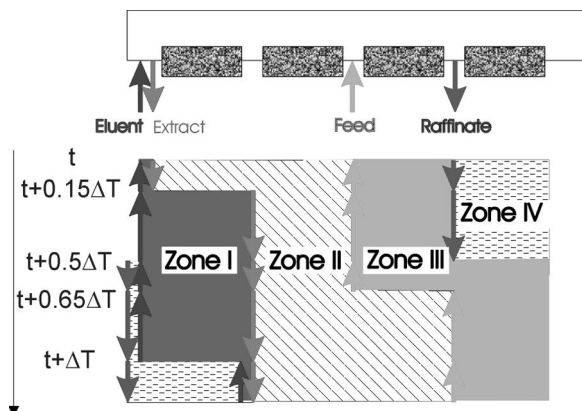


Fig. 11. Chronogram of a 4-column VARICOL process with column configuration $\langle 0.85 \rangle / \langle 1.5 \rangle / \langle 1.15 \rangle / \langle 0.5 \rangle$.

By optimizing the system we arrived at the following setting:

$$\begin{aligned}
 Q_{\text{rec}} &= 21.29 \text{ ml/min} \\
 Q_{\text{ext}} &= 8.78 \text{ ml/min} \\
 Q_{\text{feed}} &= 0.30 \text{ ml/min} \\
 Q_{\text{raf}} &= 4.58 \text{ ml/min} \\
 Q_{\text{elu}} &= 13.06 \text{ ml/min} \\
 \Delta T &= 0.8 \text{ min}
 \end{aligned} \quad (7)$$

This system is characterized by a raffinate purity of 99.6% and an extract purity of 96.6% (higher than in 6-column SMB). The recovery of the more retained component is 99.9% (with a concentration in the extract stream of 0.46 g/l) and that of the less retained component is 87.8% (with a concentration in the raffinate system of 1.12 g/l).

4. Discussion

It is interesting as well as necessary to find a common ground to compare the different processes and configurations considered in the experimental section. This can shed light on significant trends. All along, our goal was to increase the specific productivity of the system (expressed in terms of $\text{kg}_{\text{purified product}} / \text{kg}_{\text{stat.phase}} / \text{day}$), while keeping the constraint regarding the pressure drop (around 30 bars). The pressure drop is proportional to the average internal flow-rate \bar{Q} , so that it seems logical to consider the feed flow-rate normalized with respect to such a flow, i.e. $Q_{\text{Feed}} / \bar{Q}$, as a measure of the performance of the process.

Two options can be contemplated:

1. Keep the same number of columns and the same internal flow-rates and try to increase the $Q_{\text{Feed}} / \bar{Q}$ ratio.
2. Decrease the number of columns, increase the internal flow-rates to keep the same pressure drop and determine an adequate $Q_{\text{Feed}} / \bar{Q}$ ratio.

We addressed the first option by switching from a 6-column SMB to a 6-column VARICOL process. We showed that if the number of columns was held constant, it was possible to increase the feed-to-recycle ratio as well as reduce the eluent consumption while respecting the constraints on the product purities.

Table 1
Trends in key parameters

	Productivity (Kg _{prod} /Kg _{CSP} /day)	Eluent Cons. (m ³ _{eluent} /Kg _{prod})	Q_{Feed}/\bar{Q}
6-column SMB 1/2/2/1	0.604	0.922	0.0369
6-column VARICOL (1)/(2.25)/(2)/(0.75)	0.664	0.888	0.0409
5-column VARICOL (0.95)/(1.85)/(1.5)/(0.7)	0.725	1.050	0.0297
4-column VARICOL (0.85)/(1.5)/(1.15)/(0.5)	0.906	1.392	0.0233

We then decided to consider the second option: we removed one column at a time and considered VARICOL processes with fewer columns. Table 1 illustrates the evolution of specific productivity, eluent consumption and the feed-to-recycle ratio in the various systems examined.

First of all, we notice an improvement in terms of specific productivity, eluent consumption as well as feed-to-recycle ratio as we go from a 6-column SMB to a 6-column VARICOL.

Specifically, we observe a 10% increase in specific productivity and a 3.7% drop in eluent consumption. This result shows clearly that when the number of columns does not change (the total amount of chiral stationary phase is constant) VARICOL is better performing than SMB because it optimizes the distribution of the stationary phase among columns.

As we start removing columns, the picture changes. We do manage to increase specific productivity steadily (which is what we intended to do), but in order to achieve that goal we need to consume more eluent. This is because overall we have a lower amount of CSP and as a consequence we need a higher eluent flow-rate in Zone I to desorb the more strongly retained component. Because of the lower amount of CSP, the feed-to-recycle ratio decreases. Specifically, when going from a 6-column SMB to a 4-column VARICOL process, we see a 50% increase in specific productivity, a 50% increase in eluent consumption and a 28% drop in feed-to-recycle ratio. This, however, requires two fewer columns than before, which in turn means a simpler system, as well as 33% less stationary phase. Considering the price of the chiral stationary phase (and of the hardware), and considering the increase in prod-

uctivity, it is often the case that the increase in eluent consumption is not a limiting factor.

At this point, it is important to stress that we could have performed the comparison between SMB and VARICOL from a different perspective. Namely, all along in our experiments our goal was to optimize productivity. However, we might be interested in minimizing the separation cost instead. This cost is a function of both the productivity and the eluent consumption. Based on the relative contribution of these two parameters on the objective function, the VARICOL configuration can be adjusted accordingly.

The type of objective function selected strongly affects the optimization of the column distribution.

5. Conclusions

Both the well-known SMB process and the new VARICOL process permit continuous separation of a mixture into two pure streams via an appropriate shift of inlet/outlet lines between columns. However, while SMB consists of well-defined zones containing a fixed number of columns, VARICOL consists of zones of variable length, containing a number of columns that changes during the period (so that the period-averaged number of columns in a zone is not an integer). Therefore, a VARICOL process is not constrained by constant zone lengths and constant solid flow-rates (equivalent moving bed).

On a practical example (the separation of the isomers of the SB-553261 racemate), we have shown that for a 6-column system (same amount of CSP), VARICOL performs better than SMB, in terms of

both increased specific productivity and reduced eluent consumption. We also showed that by accurately distributing columns among zones, *VARICOL* makes it possible to reduce the number of columns in the system, while improving the specific productivity, which is what we intended to do: even with a 4-column *VARICOL* process, the same feed flow-rate as in a 6-column SMB can be used. With this example we have shown that this comes at the expense of higher eluent consumption.

References

- [1] O. Ludemann-Homburger, R.M. Nicoud, M. Bailly, The *VARICOL* process: a new multicolumn continuous chromatographic process, *Sep. Sci. Technol.* 35 (12) (2000) 1829.
- [2] P. Adam, R.M. Nicoud, M. Bailly, O. Ludemann-Homburger, Process and device for separation with variable length, US Patent 6,136,198 (2000).
- [3] F. Charton, R.M. Nicoud, Complete design of a simulated moving bed, *J. Chromatogr. A* 702 (1995) 97.
- [4] D.B. Broughton, Continuous sorption process employing fixed beds of sorbent and moving inlets and outlets, US Patent 2 985 589 (1961).
- [5] D.B. Broughton, US Patent 3 291 726.
- [6] D.M. Boyd, US Patent 3 268 605 (1966).
- [7] D.M. Boyd, US Patent 3 266 604 (1966).
- [8] R.M. Nicoud, A. Seidel-Morgenstern, Adsorption isotherms: Experimental determination and application to preparative chromatography, *Isolation and Purification* 2 (1996) 165.
- [9] G. Biressi, O. Ludemann-Homburger, M. Mazzotti, R.M. Nicoud, M. Morbidelli, Design and optimisation of a simulated moving bed unit: role of deviations from equilibrium theory, *J. Chromatogr. A* 976 (2000) 3.
- [10] G. Hotier, R.M. Nicoud, US Patent 5 578 215 (1996).