Journal of Chromatography A, 1217 (2010) 5407–5419

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

# Chiral separation by two-column, semi-continuous, open-loop simulated moving-bed chromatography

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ARTICLE INFO

*Article history:*
Received 28 November 2009
Received in revised form 24 January 2010
Accepted 16 June 2010
Available online 23 June 2010

*Keywords:*
Simulated moving bed
Open-loop configuration
Two-column process
Chiral separation

ABSTRACT

A two-column version of a multicolumn, semi-continuous, open-loop chromatograph for chiral separation is presented and validated experimentally. The heart of the process is a flexible node design and cyclic flow-rate modulation that succeed at keeping the mass-transfer zone inside the system without resorting to any recycling technique. One advantage of this streamlined design is the simplicity of its physical realization: regardless of the number of columns, it only requires two pumps to supply feed and desorbent into the system, while the flow rates of liquid withdrawn from the system are controlled by material balance using simple two-way valves. A rigorous model-based optimization approach is employed in the optimal cycle design to generate a solution that is physically realizable in the experimental apparatus. The optimized scheme for two-column operation supplies fresh feed into the system where the composition of the circulating fluid is closest to that of the feedstock fluid, and recovers the purified products, extract and raffinate, alternately at the downstream end of the unit while desorbent is supplied into the upstream end of the system. The feasibility and effectiveness of the two-column process are verified experimentally on the separation of reboxetine racemate, a norepinephrine re-uptake inhibitor, under overloaded conditions. Our set-up employs an automated on-line enantiomeric analysis system, comprising an analytical HPLC set-up with two UV detectors to monitor the composition profile at the downstream end of one of the columns; this monitoring system does not use a polarimeter.



## 1. Introduction

The production of pure enantiomers is one of the major fields of application of preparative chromatography in the pharmaceutical industry, which is subject to stringent constraints on product purity imposed by pharmaceutical and food regulatory organizations, such as the American FDA [1]. Batch chromatography is usually the preferred method when amounts from a few milligrams to about 100 g of purified substance are needed. When larger amounts are required, ranging from several hundred grams to kilograms, the simulated moving bed (SMB) is often a more efficient alternative [2]. Over the last decade, SMB chromatography has been increasingly applied to the separation of pure substances in the pharmaceutical, fine chemistry, and biotechnological industries, at all production scales [3].

The increasing use of the SMB as a multipurpose unit in the pharmaceutical industry, where SMB units can be applied to different separations at all stages of the drug-development cycle, has led to the development of novel operating schemes, some of which are substantially different from the classical process. Broadly speaking, the new operating schemes introduce modulations of selected control parameters into the operating cycle. Concepts such as asynchronous port switching [4–6], cyclic modulation of the feed concentration [7,8], time-variable manipulation of the flow rates [9–13], and modulation of solvent strength during process operation [14–16], have been thoroughly analyzed. The extra degrees of freedom available with the non-classical schemes improve the separation efficiency, thus allowing the units to have fewer columns. The advantages are obvious: less stationary phase is used, the set-up is more economic, and the overall pressure drop can be reduced. Furthermore, switching from one mixture to another is easier and faster than with more columns.

Alternative SMB schemes with less zones than the classical, four-zone SMB implementation, with one or more columns per zone, have also been studied. For example, the three-zone SMB configuration [17–19] takes the four-zone, open-loop SMB and removes zone IV. If the amount of adsorbent allocated to each zone is properly optimized by means of asynchronous port switching, then a three-zone, asynchronous SMB can perform better than a standard (i.e., synchronous) four-zone SMB [20–22]. The advantages and drawbacks of the three-zone SMB have been discussed by Chin and Wang [23].

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doi:10.1016/j.chroma.2010.06.040

**Nomenclature**

| | |
|---|---|
| $c$ | solute concentration (g/L) |
| $D_L$ | axial dispersion coefficient (cm$^2$/min) |
| $k$ | LDF coefficient (s$^{-1}$) |
| $K$ | Henry constant |
| $L$ | column length (cm) |
| $n_Q$ | number of intervals for piecewise-constant modulation |
| $N$ | number of columns |
| Pe | Péclet number |
| $q$ | adsorbed concentration (g/L) |
| $Q$ | flow rate (mL/min) |
| $t$ | time (min) |
| $v$ | linear velocity (cm/min) |
| $x$ | dimensionless axial position, $z/L$ |

*Greek letters*

| | |
|---|---|
| $\alpha$ | selectivity, $K_2/K_1$ |
| $\alpha'$ | separation factor, $(1+\beta K_2)/(1+\beta K_1)$ |
| $\beta$ | phase ratio, $(1-\epsilon)/\epsilon$ |
| $\epsilon$ | total porosity |
| $\tau$ | switching interval (min) |
| $\theta$ | dimensionless time, $t/\tau$ |

*Subscripts and superscripts*

| | |
|---|---|
| E | eluent |
| F | feed |
| $i$ | solute index |
| I–IV | zone index |
| in | inlet effluent |
| $j$ | column index |
| out | outlet effluent |
| R | raffinate |
| X | extract |
| 1 | ($R$, $R$)-reboxetine |
| 2 | ($S$, $S$)-reboxetine |

A two-zone SMB with continuous feeding and partial withdrawal was developed by Lee [24] for glucose-fructose separation; this process appears to be more suitable for enriching products than for high-purity separations [23]. Another two-zone SMB scheme uses intermittent feeding and withdrawal to achieve ternary separations [25]. More recently, Wankat et al. [26,27] developed two-zone SMBs for binary separation, which incorporate a storage tank to temporarily hold desorbent for later use. The results show that good separation can be achieved with their two-zone SMB systems, but with more desorbent than required by a four-zone SMB. However, partial feed was shown to improve the product purities and recoveries considerably. One-column processes that reproduce the cyclic behavior of multicolumn SMB chromatography, by means of a recycle lag, have also been proposed [28–30].

We have recently developed a semi-continuous, two-column chromatograph with a flexible node design, robust pump configuration, and cyclic flow-rate modulation to exploit the benefits of both batch and simulated counter-current modes [31]. The cycle itself is optimized and adapted to the difficulty of separation and process specifications. The feasibility of the proposed two-column system was demonstrated on a linear problem with a separation factor, $\alpha'$, of only 1.1, where $\alpha'$ represents the ratio of factors by which the solute velocities are reduced with respect to the fluid velocity:

$$\alpha' = \frac{1+\beta K_2}{1+\beta K_1}, \tag{1}$$

Here, $\beta = (1-\epsilon)/\epsilon$ is the phase ratio, $\epsilon$ is the bed porosity, and $K_i$ is the Henry constant for component $i$. We favor the use of $\alpha'$ over the standard definition of selectivity, $\alpha = K_2/K_1$, because the latter does not properly represent the difficulty of separation for small $K_i$. The separation is somewhat arbitrarily classified as *hard* for $\alpha' \approx 1.1$, *moderate* for $\alpha' \approx 1.5$ and *easy* for $\alpha' > 4$ [32].

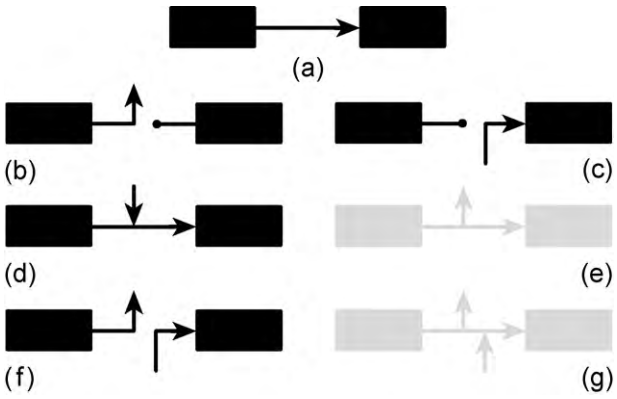


**Fig. 1.** Flow diagram for the different types of port configuration: (a) complete direction of flow to the next column; (b) downstream frozen bed; (c) upstream frozen bed; (d) flow addition to circulating stream; (e) partial withdrawal; (f) complete withdrawal and flow injection at the same node, and (g) partial withdrawal and flow addition at the same node. Configurations (e) and (g) are not considered in the present work, as they imply partial withdrawal of the exit stream from a column.

Fig. 1 shows the different port configurations that can be achieved with our original node design; they are the building blocks for establishing the cyclic operating schemes reported in [31]. Streams can be partially, or totally, added or removed, or flown to the next column; an inlet port and an outlet port can be simultaneously open at the same node, and the flow through a column can be temporarily frozen.

In the present study we are particularly interested in streamlined versions of our original design. A first step towards this goal is to suppress partial withdrawal, i.e., to discard port configurations *e* and *g* from the design. It is worth noting that partial withdrawal is a direct consequence of the analogy between the steady state of the true moving bed (TMB) process and the cyclic steady state of the analogous SMB. However, when very few columns are considered, as is the case here, the analogy between TMB and SMB is only weak, to say the least.[2] For example, batch chromatography and steady-state recycling [33–35] do not employ partial withdrawal; instead, product or waste fractions are always obtained by completely withdrawing the outlet stream of a column over a certain period of the cycle.

Another, less obvious, consequence of discarding port configurations *e* and *g* is that internal recycling can only be carried out by circulating the fluid without supplying any external fluid into the beds or withdrawing any fluid from the system. Interestingly, this recirculation step is similar to the step implemented in the improved SMB (I-SMB) process [36], where the inlet and outlet ports are closed and the internal flow through the four sections is set to move the concentration profiles along the columns and adjust their relative position with respect to the outlet ports.

[2] This, however, may not be as clear-cut as it seems because of a few counter-examples; e.g., single-column processes can match exactly the cyclic behavior of multicolumn SMB chromatography, by means of a recycle lag [29].