Pais, L.S., and Rodrigues, A.E.

Chiral Separation by Simulated Moving Bed Chromatography: Comparison Between Configurations Using a Low Number of Columns

in *Proceedings of CHEMPOR'2001 8th International Chemical Engineering Conference*, Aveiro, Portugal, p. 1201-1206 (2001).

8th INTERNATIONAL CHEMICAL ENGINEERING CONFERENCE

CHEMPOR' 2001

2

Editors
F. Ramôa Ribeiro
J.J.C. Cruz Pinto

Organized by

UNIVERSIDADE de AVEIRO

Centro Cultural e de Congressos de Aveiro

Aveiro, Portugal
12-14 September 2001

CHEMPOR' 2001

8TH INTERNATIONAL CHEMICAL ENGINEERING CONFERENCE

Aveiro, Portugal, 12-14 September 2001

Organized by

ORDEM DOS ENGENHEIROS

UNIVERSIDADE DE AVEIRO

VOLUME II

Edited by

F. Ramôa Ribeiro and J. J. C. Cruz Pinto

ISBN 972-789-041-5

Chiral Separation by Simulated Moving Bed Chromatography: Comparison Between Configurations Using a Low Number of Columns.

Luís S. Pais[1,2] and Alírio E. Rodrigues[2,*]

1. Escola Superior de Tecnologia e de Gestão, Instituto Politécnico de Bragança, Campus de Santa Apolónia, Apartado 1134, 5301-857 Bragança, Portugal.
2. Laboratory of Separation and Reaction Engineering, Faculdade de Engenharia, Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal.

ABSTRACT

Simulated Moving Bed (SMB) chromatography has received significant attention in the last decade, particularly in the production of high valuable products, such as enantiomerically pure pharmaceutical compounds. Recent applications in the pharmaceutical industry uses SMB systems containing a low total number of columns, usually four to eight. The objective of this work is to evaluate and compare the performance of SMB systems with a low number of columns. Simulation results will be shown for SMB units with 4, 5, and 6 columns. Also the two strategies of modeling, TMB and SMB, will be compared for these configurations.

INTRODUCTION

Chiral chromatographic resolution of enantiomeric species is becoming of increasing importance in the development and the production of pharmaceutical drugs. Large-scale chromatographic separations were in the past limited mainly due to the high cost of the adsorbent, the high dilution of products, and the large amounts of mobile phase needed. In view of these demands, SMB technology (Broughton and Gerhold, 1961) has been recently applied to the pharmaceutical industry and its use at production-scale has been considered as an alternative to up to now leading techniques such as enantioselective synthesis or diastereoisomeric crystallization. One reason SMB chromatography is preferred is that the process results in both high yields and purities of both enantiomers, and low solvent consumption (Nicoud, 1992; Gattuso *et al.*, 1996). Several pharmaceutical companies and custom chemical manufactures are installing commercial-scale SMB units for producing enantiomeric compounds. The list is rapidly increasing and includes Aerojet Fine Chemicals (USA), Bayer (Germany), CarboGen Laboratories (Switzerland), Chiral Technologies (USA), Daicel (Japan), Honeywell Specialty Chemicals (Ireland), H. Lundbeck (Denmark), Merck (Germany), UCB Pharma (Belgium), and Universal Pharma Technologies (USA) (Nicoud, 1999a,b; McCoy, 2000; Cox, 2001; Stinson, 2001).

Modeling and simulation of a chemical engineering process always attracted a special attention since it could lead to significant savings in time and materials. The selection of the SMB operating conditions is not straightforward. The main problem of the SMB operation consists in choosing the right solid (switch time interval) and liquid flow-rates. Designed for high productivity separations, SMB units usually operate at high feed concentrations leading to nonlinear competitive adsorption behaviors. Therefore, modeling and simulation tools are of crucial importance before running the system. In a recent paper (Pais *et al.*, 1998a), we concluded that the prediction of the SMB operation can be carried out through the equivalent TMB approach when the SMB unit is constituted by two columns per section (a total of eight

columns). However, recent applications in the pharmaceutical industry use SMB systems containing a low total number of columns. According to Nicoud and Majors (2000), for pharmaceutical applications, the number of columns tends to be a maximum of 12 for pilot-plant uses and 8 for industrial applications. The largest unit in operation for a chiral separation has only 6 columns (Blehault *et al.*, 2001). The objective of this work is to evaluate the performance of SMB systems with a low number of columns and to compare the two strategies of modeling, TMB and SMB, for these cases.

SMB STRATEGIES OF MODELING

The problem of modeling a SMB separation process can be analyzed by two different strategies: one, by simulating the system directly, taking into account its intermittent behavior, other by representing its operation in terms of a true countercurrent system. The first model represents the real SMB and considers the periodic switch of the injection and collection points. The second is developed by assuming the equivalence with the true moving bed (TMB), where solid and fluid phases flow in opposite directions.

The model equations result from the mass balance over a volume element of the bed and at a particle level. Axial dispersion flow for the bulk fluid phase is included and the linear driving force approximation is used to describe the intraparticle mass-transfer rate; the model can handle any kind of adsorption isotherm. The model equations for the transient SMB model are summarized below:

$$\frac{\partial C_{ik}}{\partial \theta} = \gamma_k^* \left\{ \frac{1}{Pe_k} \frac{\partial^2 C_{ik}}{\partial x^2} - \frac{\partial C_{ik}}{\partial x} \right\} - \frac{(1-\varepsilon)}{\varepsilon} \alpha_k (q_{ik}^* - q_{ik}) \tag{1a}$$

$$\frac{\partial q_{ik}}{\partial \theta} = \alpha_k (q_{ik}^* - q_{ik}) \tag{1b}$$

where the subscript i refers to the component, and k refers to the chromatographic column. To complete the modeling of the SMB system, initial and boundary conditions, as well as mass balances at the nodes between each column, must be added. Due to the switch of inlet and outlet lines, each column plays different functions during a whole cycle, depending on its location. In this way, for the SMB model, the boundary conditions for each column change after the end of each switch time interval. This time-dependence of the boundary conditions leads to a cyclic steady state for this system, instead of a real steady state achieved for the true countercurrent model. In the TMB model, the solid phase is assumed to move in plug flow in the opposite direction of the fluid phase, while the inlet and outlet lines remain fixed. As a consequence, each column plays the same function, depending on its location. Model equations for the TMB model are equivalent to the ones presented before, but include the term that represents the countercurrent movement of the solid phase:

$$\frac{\partial C_{ij}}{\partial \theta} = \gamma_j \left\{ \frac{1}{Pe_j} \frac{\partial^2 C_{ij}}{\partial x^2} - \frac{\partial C_{ij}}{\partial x} \right\} - \frac{(1-\varepsilon)}{\varepsilon} \alpha_j (q_{ij}^* - q_{ij}) \tag{2a}$$

$$\frac{\partial q_{ij}}{\partial \theta} = \frac{\partial q_{ij}}{\partial x} + \alpha_j (q_{ij}^* - q_{ij}) \tag{2b}$$

where the subscript i refers to the component, and j refers to the section. A more precise description of both models can be found elsewhere (Pais *et al.*, 1998a). The model parameters

are: the ratio between solid and fluid volumes, $(1-\varepsilon)/\varepsilon$; the ratio between fluid and solid interstitial velocities, $\gamma_j = v_j / u_s$; the Peclet number, $Pe = v_j L_j / D_{Lj}$; the number of mass transfer units, $\alpha_j = kL_j / u_s$; and the adsorption equilibrium parameters. The equivalence between the TMB and the SMB models is made by keeping constant the liquid velocity relative to the solid velocity, that is, the liquid velocity in the SMB system is equal to the sum of liquid and solid velocities in the TMB model. Also, the solid velocity in the TMB model must be evaluated from the value of the switch time interval t^* of the SMB model, as $u_s = L_c / t^*$, where L_c is the length of one SMB column. This implies that the internal liquid flow-rates in both systems are not the same, but related by $Q_j^* = Q_j + \varepsilon V_c / t^*$, where Q_j^* and Q_j are the internal liquid flow-rates in the SMB and TMB models, respectively, and V_c is the volume of one SMB column.

RESULTS AND DISCUSSION

The chromatographic resolution of a racemic mixture of chiral epoxide enantiomers (*Sandoz Pharma, Basel, Switzerland*) was considered for simulation purposes. The chiral stationary phase used in this system is microcrystalline cellulose triacetate (*Merck, Darmstadt, Germany*) with an average particle diameter of 45 μm and pure methanol is used as eluent. The adsorption equilibrium isotherms were measured at 25 °C and represented by a linear + Langmuir competitive model (Pais *et al.*, 1998b):

$$q_A^* = 1.35C_A + \frac{7.32 \times 0.087 C_A}{1 + 0.087C_A + 0.163C_B} \quad ; \quad q_B^* = 1.35C_B + \frac{7.32 \times 0.163 C_B}{1 + 0.087C_A + 0.163C_B} \qquad (3)$$

The first part of this work consists in the evaluation of the separation regions for different configurations and using the equivalent TMB model. A separation region is the area in a $\gamma_3 \times \gamma_2$ plot where both extract and raffinate are pure. This plot, first proposed by Morbidelli and co-workers (Mazzotti *et al.*, 1997), is an important tool in the choice of the best operating conditions, providing that the constraints in sections 1 and 4 are fulfilled, i.e., the flow-rate ratios in sections 1 and 4, γ_1 and γ_4, are chosen away from its critical values. *Table 1* presents the system characteristics and TMB model parameters. We considered a system constituted by a total bed volume of $V_T = 420.5$ mL. Different SMB configurations were tacking into consideration: a SMB system constituted by only one column per section (configuration 1111); two SMB systems constituted by 5 columns (configuration 1211, with two columns in section 2; and configuration 1121, with two columns in section 3); and a SMB unit with 6 columns and a configuration of 1221. *Table 2* presents the SMB configuration for each case and the correspondent TMB equivalence and model parameters.

Table 1. SMB unit characteristics and TMB model parameters.

Total bed volume:	$V_T = 420.5$ mL	Solid/fluid volumes:	$(1-\varepsilon)/\varepsilon = 1.5$
Column diameter:	$D_c = 2.6$ cm	Flow-rate ratios:	$\gamma_1 = 5.722$
Total bed length:	$L_T = 79.2$ cm		$\gamma_4 = 1.793$
Feed concentration:	$C_A^F = C_B^F = 5$ g/L	Mass transfer coefficient:	$k = 0.4$ s^{-1}

Table 2. SMB configurations, TMB equivalence and model parameters.

SMB configuration				TMB equivalence and model parameters			
Number of columns, N_c	Configuration	Column length, L_c (cm)	t^* (min)	$u_s = L_c / t^*$ (cm/min)	$\alpha_c = kL_c / u_s$	$\alpha_T = N_c \alpha_c$	Pe_c
4	1111	19.80	6.60	3.00	158.40	633.6	2000
5	1211	15.84	5.28		126.72		1600
5	1121	15.84	5.28		126.72		1600
6	1221	13.20	4.40		105.60		1333

It should be pointed out that the length of each column depends on the number of columns used and is defined in such a way that the total bed volume and bed length are the same for all the SMB configurations. The switch time interval also depends on the length of each SMB column and is evaluated in order to keep constant the solid velocity for all the SMB configurations.

The results obtained are presented in *Figure 1*. A purity criteria of 99.9 % was used for all the configurations considered, which means that inside each separation region both extract and raffinate are, at least, 99.9% pure. Also shown is the separation region obtained considering

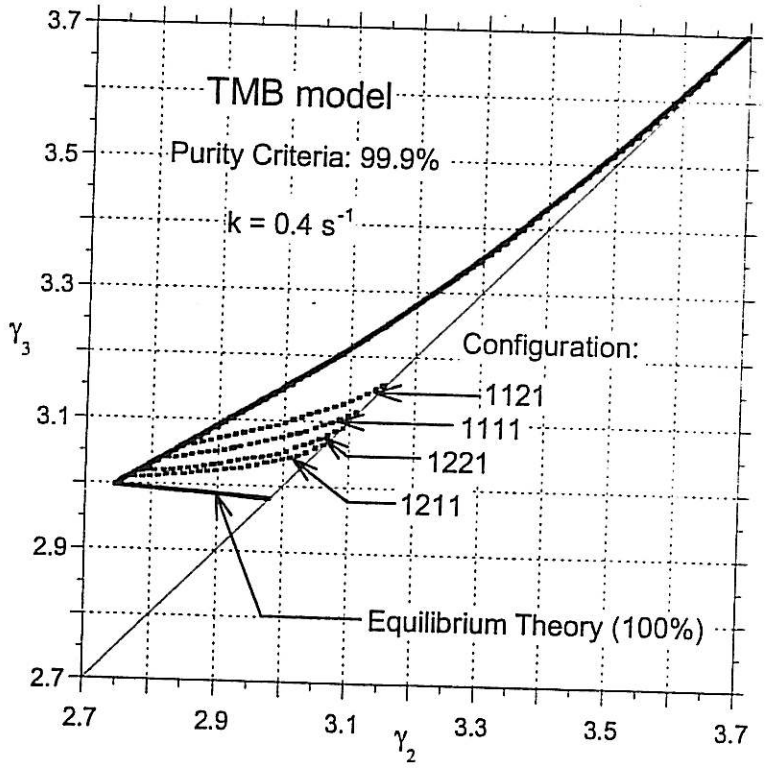

Figure 1. $\gamma_3 \times \gamma_2$ separation region for a 99.9% purity criteria using the TMB model. Operating conditions and model parameters as in *Tables 1* and *2*. Also shown is the separation region considering Equilibrium Theory (100%).

the Equilibrium Theory, where axial dispersion and mass transfer resistances are neglected. The mass transfer coefficient used in this study was $k = 0.4\ s^{-1}$, which represents a situation where mass transfer resistance is not very important. Even in this situation, differences appear between the separation region obtained in this case and the one predicted by the Equilibrium Theory. More pronounced differences would appear for lower values of mass transfer coefficient (Pais *et al.*, 1998b).

From *Figure 1* we conclude that, considering the TMB equivalence, the best results (larger separation regions) occur for the configurations that present a longer section 2 (between the extract and the feed nodes): in configuration 1211, section 2 is 40% of the total bed length; in configuration 1221, 33.3%; in configuration 1111, 25%; and in configuration 1121, 20%. The dimension of the separation regions obtained for the different configurations and shown in *Figure 1* are in agreement with this rule.

However, we may question if this is valid when considering the SMB model. Moreover, we shall notice that SMB units with low number of columns may have a steady state performance far away from the one predicted by the TMB model. For instance, there is no 99.9% separation region using the SMB model for the 1211 configuration. *Figure 2* compares the 99.0% separation regions for the 1211 configuration obtained considering the TMB and SMB models. This figure clearly shows the differences obtained with the two strategies in terms of steady state purities, and justifies the need of using the more precise SMB model when the unit has a low number of chromatographic columns.

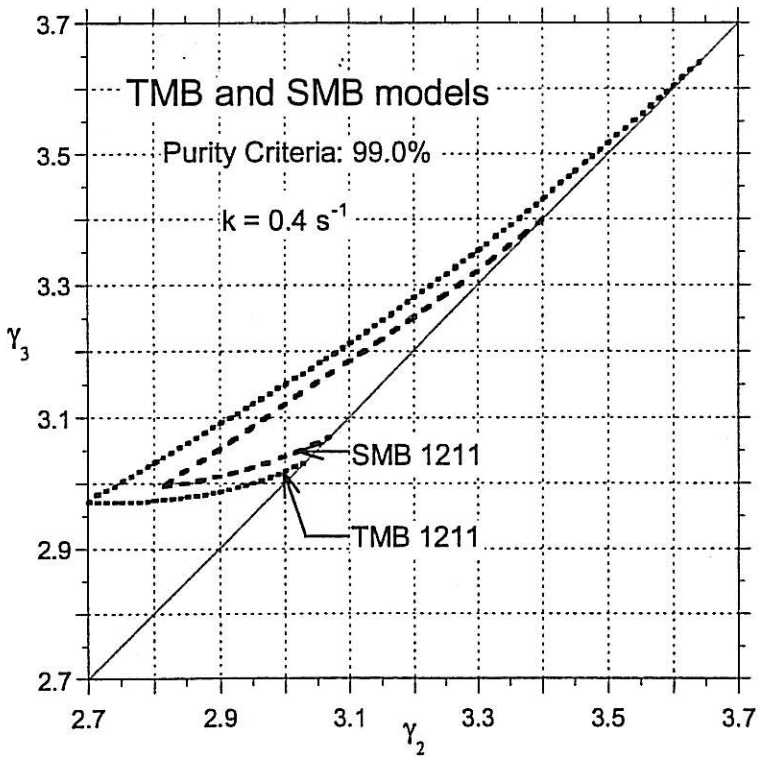

Figure 2. $\gamma_3 \times \gamma_2$ separation region for a 99.0% purity criteria: comparison between TMB and SMB model results for the 1211 configuration. Operating conditions and model parameters as in *Tables 1* and *2*.

CONCLUSIONS AND FUTURE WORK

SMB chromatography is now a well-established technique and the announcement of industrial applications is increasing, particularly for chiral chromatographic resolution of enantiomeric species. These units generally use a low number of chromatographic columns. In this situation, the evaluation of the SMB operating conditions shall avoid the use of the countercurrent TMB model, and a more realistic SMB model, which takes into account the periodic switch of the injection and collection points, is needed. For an effective comparison between the predictions given by the two strategies of modeling, the $\gamma_3 \times \gamma_2$ separation regions can be evaluated using the TMB and SMB models. The differences obtained by the two models depend particularly on the number of columns used and its configuration.

Recently, Novasep (Vandoeuvre Les Nancy, France) proposed a new continuous chromatographic process, called Varicol (Ludemann-Hombourger, 2000). The principle of the Varicol process is based on a non-synchronous shift of the inlet and outlet valves in a multicolumn system, in contrast to the SMB operation where this shift is synchronous. This new process makes possible the operation with a number of columns per section that is not constant in time, and can show advantages over the classical SMB operation, particularly when using a low number of columns. Model equations to simulate the Varicol process are similar to the ones used in the SMB model, but must take into account the non-synchronous shift of the inlet and outlet lines. The $\gamma_3 \times \gamma_2$ separation regions can be evaluated also for the Varicol process in order to compare its performance with the classical SMB operation and to study the influence of the number of columns and its configuration on the system performances.

LITERATURE CITED

Blehaut, J., W. Hauck, and R.-M. Nicoud, "Simulated Moving Bed (S.M.B.): Principle and Application to Chiral Separations," *Seminar on Batch and SMB Design and Applications, AIChE Meeting*, Chicago, March (2001).

Broughton, D.B., and C.G. Gerhold, "Continuous Sorption Process Employing Fixed Bed of Sorbent and Moving Inlets and Outlets", *U.S. Patent No. 2,985,589* (1961).

Cox, G.B., "Preparative Enantioselective Chromatography. Current Status and Future Trends," *PREPTECH – Preparative and Process Scale Technology in the Manufacturing of Chemicals and Pharmaceuticals*, Mainz, Germany, April 18-20 (2001).

Gattuso, M.J., B. McCulloch, D.W. House, W.M. Baumann, and K. Gottschall, "Simulated Moving Bed Technology – The Preparation of Single Enantiomer Drugs," *Pharm. Tech. Europe*, **8**, 20 (1996).

Ludemann-Hombourger, O.; R.-M. Nicoud, and M. Bailly, "The Varicol Process: A New Multicolumn Continuous Chromatographic Process," *Sep. Sci. Tech.*, **35**, 1829 (2000).

Mazzotti, M., G. Storti, and M. Morbidelli, "Optimal Operation of Simulated Moving Bed Units for Nonlinear Chromatographic Separations," *J. Chromatogr. A*, **769**, 3 (1997).

McCoy, M., "SMB Emerges as Chiral Technique," *C&EN*, June 19, 17 (2000).

Nicoud, R.-M., "The Simulated Moving Bed: A Powerful Chromatographic Process," *LC-GC Int.*, **5**, 43 (1992).

Nicoud, R.-M., "The Separation of Optical Isomers by Simulated Moving Bed Chromatography," *Pharm. Tech. Europe*, **11** (3), 36 (1999a).

Nicoud, R.-M., "The Separation of Optical Isomers by Simulated Moving Bed Chromatography," *Pharm. Tech. Europe*, **11** (4), 28 (1999b).

Nicoud, R.-M., and R.E. Majors, "Simulated Moving Bed Chromatography for Preparative Separations," *LC-GC Europe*, **13**, 887 (2000).

Pais, L.S., J.M. Loureiro, and A.E. Rodrigues, "Modeling, Strategies for Enantiomers Separation by SMB Chromatography," *AIChE J.*, **44**, 561 (1998a).

Pais, L.S., J.M. Loureiro, and A.E. Rodrigues, "Separation of Enantiomers of a Chiral Epoxide by Simulated Moving Bed Chromatography," *J. Chromatogr. A*, **827**, 215 (1998b).

Stinson, S.C., "Chiral Chemistry," *C&EN*, May 14, 45 (2001).