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Separation of Enantiomers by SMB Chromatography: Strategies of Modeling and Process Performance

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Abstract: The paper deals with chiral separation by Simulated Moving Bed chromatography. A package for SMB simulation based on the analogy with the true moving bed is described. The package allows the prediction of regions for enantiomers separation. The influence of mass transfer resistance in the separation region is analyzed. A practical tool for choosing the better SMB operating conditions as a function of the feed flow rate is proposed.

Resumé: La séparation d'isomères optiques par chromatographie en Lit Mobile Simulé (SMB) a été étudiée. Un simulateur a été developé basé sur l'analogie avec le lit mobile vrai. Le simulateur permet la prévision des régions de séparation. L'effet de la résistance au transfert de matière sur la région de séparation a été analizé. On propose un moyen pour choisir les conditions d'opération du SMB en fonction du débit d'alimentation.

1. Introduction

The need for optically pure compounds is increasing as regulatory aspects become more stringent. The separation of enantiomers is an important issue in various areas, particularly in the health-related field. It is well known that isomers can have different and opposing pharmacological effects, so new chiral separation methods are being proposed nowadays to produce single enantiomeric forms of chiral drugs.

In the chemical engineering field the concept of the simulated moving bed (SMB) has been known since 1961 when the first patent by UOP appeared [1]. Developed for hydrocarbon separations, the SMB technology has found new applications in the areas of biotechnology, pharmaceuticals and fine chemistry. Pilot and industrial SMB for such applications are being developed by different companies, such as NOVASEP and UOP [2-3].

The SMB process basic principle is a flow scheme that takes advantages of continuous and countercurrent movement of liquid and solid without actual movement of the adsorbent. This countercurrent movement is simulated by an appropriated flow switching sequence: the adsorbent bed is divided into a number of fixed-bed columns, while the inlet and outlet lines move simultaneously one column at fixed time intervals in the direction of the liquid phase flow. Hence, the SMB process shares the same advantages of the real countercurrent scheme, bypassing the obvious problems concerning the solid movement.

SMB chiral chromatography is, in this way, a promising technique for the preparative production of single enantiomeric drugs able to compete to up to now dominating techniques such as elution batch chromatography, diastereoisomeric crystallization, or asymmetric synthesis. SMB chromatography is essentially a binary mixture separation technique, hence particularly suitable for racemic resolutions. It has the main advantage of being a continuous process able to perform high purity and recovery for low selectivity separations with reductions in eluent consumption and adsorbent requirements.

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 non-linear competitive adsorption behaviours.

Therefore, modeling and simulation tools are of crucial importance before running the system. This requires a knowledge of some basic information on equilibrium and kinetic parameters.

2. SMB Strategies of Modeling

Different models to predict the performance of a SMB separation process have been proposed in the literature [4]. Two main strategies can be carried out to model a SMB system: one. the SMB model. that considers the real shift of the injection and collection points. the other. the TMB (true moving bed) model, that considers liquid and solid flow in opposite directions. The prediction of these two models were compared in terms of steady-state performance and the influence of the degree of subdivision of the bed in the SMB model predictions was also analyzed and compared with the TMB performance. A complete study with comparison between experimental and model results, can be found elsewhere [5]. The main conclusion of this study is that the deviations between TMB and SMB predictions (averaged over a switch time interval) decrease as the degree of subdivision of the bed increases. For practical purposes, optimization and choice of SMB configuration (length of each section) can be safely carried out on the basis of analogy with TMB modeling.

Although transient evolution of the SMB and TMB approaches are different. they have similar steady-state performances. Since, for practical purposes. the primary objective is to characterize steady-state performance, one can simulate and obtain the optimum operating conditions for the SMB using the steady-state TMB model. Thereby. the problem consisting in a PDEs system can be reduced to an ODEs system, which requires lower computing times.

The package developed for the steady-state TMB model considers axial dispersion flow for the bulk fluid phase and the linear driving force (LDF) approximation is used to describe the intraparticle mass transfer rate. The model can handle any kind of adsorption isotherm. Model equations for the steady-state TMB model are summarized in *table I* with the boundary conditions, as well as with the necessary mass balances at the nodes between each section. The resulting model parameters are:

$(1-\varepsilon)/\varepsilon$, the ratio between solid and fluid volumes:

$\gamma_j = v_j / u_s$. the ratio between fluid and solid velocities;

$Pe_j = v_j L_j / D_{Lj}$. Peclet number;

$\alpha_j = k L_j / u_s$. number of mass transfer units.

Model equations were numerically solved by using the COLNEW software [6] which implements a finite-element collocation technique for mixed-order systems of linear or nonlinear boundary-value ordinary differential equations.

3. Prediction of the Separation Regions and Process Performance

The SMB performance is characterized by four process parameters: purity. recovery. solvent consumption and adsorbent productivity. For the case of a binary separation in which the less retained species A is recovered in the raffinate and the more retained component B is recovered in the extract, process performance parameters are defined in *table II.*

The effect of the operating and model parameters on the SMB performance is analyzed for the case of the separation of bi-naphthol enantiomers. The purified bi-naphthol enantiomers are used as chiral building blocks in asymmetric synthesis. The enantioseparation can be carried out using 3,5-dinitrobenzoyl phenylglycine bonded to silica gel as stationary phase and heptane isopropanol (72:28) as eluent [7,8]. A bi-Langmuir model is proposed for adsorption equilibrium isotherms and were measured by the NOVASEP group (personal communication

$$q_A^* = \frac{2.69 c_A}{1 + 0.0336 c_A + 0.0466 c_B} + \frac{0.10 c_A}{1 + c_A + 3 c_B}$$

$$q_B^* = \frac{3.73 c_B}{1 + 0.0336 c_A + 0.0466 c_B} + \frac{0.30 c_B}{1 + c_A + 3 c_B}$$

Table I. Model equations for the steady-state TMB model.

Mass balance in a volume element of the bed j:

$$D_{L_j}\frac{d^2c_{ij}}{dz^2}-v_j\frac{dc_{ij}}{dz}-\frac{(1-\varepsilon)}{\varepsilon}k(q_{ij}^*-q_{ij})=0 \tag{2}$$

Mass balance in the particle:

$$u_s\frac{dq_{ij}}{dz}+k(q_{ij}^*-q_{ij})=0 \tag{3}$$

Boundary conditions for section j:

$$z=0: \qquad c_{ij}-\frac{D_{L_j}}{v_j}\frac{dc_{ij}}{dz}=c_{ij,0} \tag{4}$$

where $c_{ij,0}$ is the inlet concentration of species i in section j.

$$z=L_j: \qquad c_{ij}=c_{ij+1,0} \quad \text{for extract and raffinate nodes} \tag{5a}$$

$$c_{ij}=\frac{v_I}{v_{IV}}c_{ij+1,0} \quad \text{for the eluent node} \tag{5b}$$

$$c_{ij}=\frac{v_{III}}{v_{II}}c_{ij+1,0}-\frac{v_F}{v_{II}}c_i^F \quad \text{for the feed node} \tag{5c}$$

and

$$q_{ij}=q_{ij+1,0} \tag{6}$$

Global balances:

$$v_I=v_{IV}+v_E \quad \text{eluent node} \tag{7a}$$

$$v_{II}=v_I-v_X \quad \text{extract node} \tag{7b}$$

$$v_{III}=v_{II}+v_F \quad \text{feed node} \tag{7c}$$

$$v_{IV}=v_{III}-v_R \quad \text{raffinate node} \tag{7d}$$

Multicomponent adsorption equilibrium isotherm:

$$q_{Aj}^*=f_A(c_{Aj},c_{Bj}) \quad \text{and} \quad q_{Bj}^*=f_B(c_{Aj},c_{Bj}) \tag{8}$$

where $i = A, B$ refers to the species in the mixture, and $j = I, II, III, IV$ is the section number.

Table II. SMB performance criteria.

Performance Parameter	Extract	Raffinate
Purity (%)	$PUX=100C_B^X/(C_A^X+C_B^X)$	$PUR=100C_A^R/(C_A^R+C_B^R)$
Recovery (%)	$RCX=100Q_XC_B^X/Q_FC_B^F$	$RCR=100Q_RC_A^R/Q_FC_A^F$
Solvent Consumption (l/g)	$SC=(Q_E+Q_F)/[Q_F(C_A^F+C_B^F)]$	
Productivity (g/hr l of solid)	$PR=Q_F(C_A^F+C_B^F)/V_S$	

The conditions for enantiomers separation can be defined in terms of the γ_j model parameters, which are directly related with the TMB operating variables (fluid and solid velocities in the four sections of the TMB unit). From the four γ_j values, those related to sections *II* and *III* are the ones that play the key role in the separation performance. Taking into account this consideration, a region of complete separation in a γ_{III}-γ_{II} plane can be defined. The conditions for complete enantiomer separation were analyzed in the frame of the equilibrium theory, where mass transfer resistances and axial dispersion are neglected, by Morbidelli and co-workers [9,10].

If mass transfer resistance is important, we may not obtain a region for complete separation (100% pure enantiomers). In these cases, a purity criteria can be proposed and the region for separation (where both enantiomers purities are at least equal to the proposed purity criteria) can be evaluated using the steady-state TMB model described before.

A study of the influence of the mass transfer resistance in the separation region is carry out. The γ_{III}-γ_{II} plots were built keeping constant the recycling (flow rate in section *IV*) and solid flow rates, and so γ_{IV} . The total inlet or outlet flow rates were kept constant in all simulations and equal to 25.09 ml/min. Other operating conditions and model parameters are summarized in *table III*. A recycling flow rate of 27.95 ml/min in the TMB corresponds to a recycling flow rate of 35.38 ml/min in the SMB; a TMB solid flow rate of 11.15 ml/min corresponds to a switch time interval of 3 min in the SMB unit [5].

Figures 1 and 2 show the γ_{III}-γ_{II} plots obtained for a mass transfer coefficient of k=0.5 s^{-1} (α=180) (open squares) and k=0.1 s^{-1} (α=36) (closed squares) using a 95% and 99% purity criteria, respectively. Inside the region delimited by the square points obtained numerically, both the raffinate and the extract are at least 95% (*figure 1*) or 99% (*figure 2*) pure. It can be concluded that mass transfer resistance reduces the region of separation of both enantiomers and that the region obtained for a lower mass transfer coefficient (k=0.1 s^{-1}) lies inside the region obtained when mass transfer resistance is not so important (k=0.5 s^{-1}). Hence, the choice of the best operating conditions must take into account the mass transfer resistance phenomenon.

Table III. Operating conditions and model parameters for the γ_{III} - γ_{II} plot.

TMB operation conditions		Model parameters
Feed concentration:	2.9 g/l each	Solid/fluid volumes: $(1-\varepsilon)/\varepsilon = 1.5$
Solid flow rate:	11.15 ml/min	Peclet number: $Pe = 2000$
Recycling flow rate:	27.95 ml/min	Ratio between fluid and solid velocities
Column diameter:	2.6 cm	in zone *IV*: $\gamma_{IV} = 3.76$
Zone length:	21.0 cm	

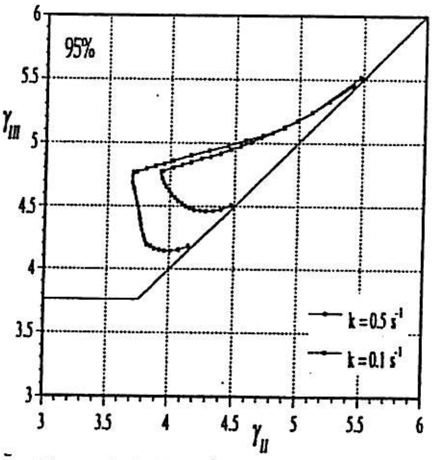

Figure 1. Influence of the mass transfer resistance on the separation region: γ_{III}-γ_{II} plot for a 95% purity criteria.

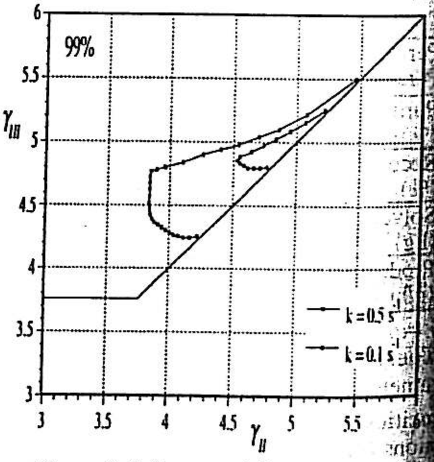

Figure 2. Influence of the mass transfer resistance on the separation region: γ_{III}-γ_{II} plot for a 99% purity criteria.

For practical purposes, it is desirable to work with variables directly related with the SMB unit. Instead of presenting the separation region in a γ_{III}-γ_{II} plot, we can report the same information in a Q_X versus Q_F plot. *Equations 9* and *10* present the conversion rules between the TMB operating conditions and feed and extract flow rates. The eluent flow rate will be 25.09-Q_F and the raffinate flow rate 25.09-Q_X. *Figure 3* presents the separation region for k=0.1 s^{-1} following a 95% purity criteria. In the region limited by the closed squares both raffinate and extract purities are at least 95%. Open squares in *figure 3* show the path of equal purities for extract and raffinate. Since the objective of the SMB operation is to obtain the two enantiomers, the path of equal purities is the optimum trajectory that must be followed.

$$Q_F = \frac{\varepsilon}{1-\varepsilon}(\gamma_{III} - \gamma_{II})Q_s \tag{9}$$

$$Q_X = \frac{\varepsilon}{1-\varepsilon}(\gamma_{I} - \gamma_{II})Q_s \tag{10}$$

Figure 4 presents the optimum purities (and recoveries) that can be expected for a given feed flow rate. It should be pointed out that, when racemic mixtures are fed into a SMB unit, if extract and raffinate purities are equal, recoveries of both extract and raffinate are also equal and with the same value of the purity obtained. *Figure 5* presents the solvent consumption and adsorbent productivity obtained as a function of the feed flow rate. Of course, this figure should not be used without looking for *figure 4*: the increase of the feed flow rate lead to better solvent consumption and productivity performances, but it is followed by a decrease in both purities and recoveries of extract and raffinate. Furthermore, the higher the feed flow rate, the smaller the range of extract flow rates that lead to both enantiomer separation. This means that the process robustness also decrease with the increase of the feed flow rate.

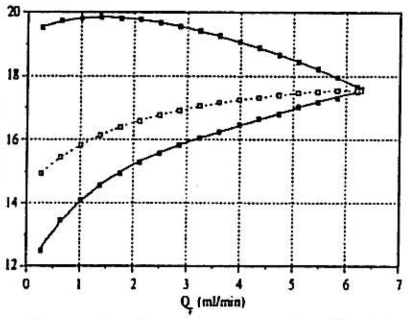

Figure 3. Separation region in a Q_X versus Q_F plot (closed squares). Open squares present the path of equal raffinate and extract purities. (mass transfer coefficient, k=0.1 s^{-1} ; purity criteria: 95%)

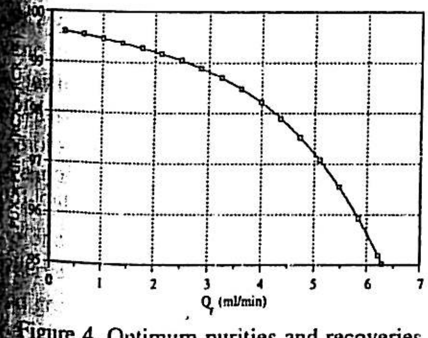

Figure 4. Optimum purities and recoveries as a function of the feed flow rate (same conditions as in *figure 3*).

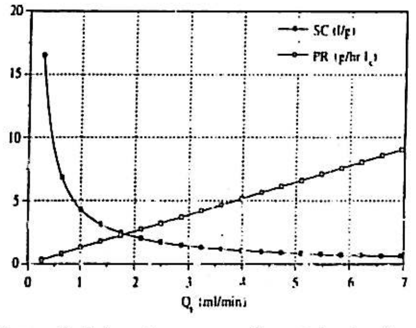

Figure 5. Solvent consumption and adsorbent productivity as a function of the feed flow rate (same conditions as in *figure 3*).

4. Conclusions

The main problem of the SMB operation consists in choosing the better solid (switch time interval) and liquid flow rates. using a simulation procedure that takes into account non-linear competitive adsorption behaviours. The mass transfer resistance phenomenon affects the separation region of both enantiomers.

The set of *figures 3. 4* and *5* provide a practical tool for choosing the better SMB operating conditions as a function of the feed flow rate. The optimum will result from a compromise between solvent consumption/adsorbent productivity and purity and recovery requirements.

5. Nomenclature

c	fluid phase concentration
D_L	axial dispersion coefficient
k	mass transfer coefficient
L_j	length of section j
Pe	Peclet number
Q	volumetric liquid flow rate
Q_s	solid flow rate
q	average adsorbed phase concentration
q^*	adsorbed concentration in equilibrium with c
u_s	solid velocity
V_S	volume of the solid phase
v_j	interstitial fluid velocity
z	axial coordinate

Greek symbols:

α_j	number of mass transfer units
ε	bed porosity
γ_j	ratio between fluid and solid velocities

Subscripts and superscripts:

A	less retained component
B	more retained component
E	eluent
F	feed
R	raffinate
X	extract

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