Modeling, Simulation and Operation Performance of a Simulated Moving Bed for Enantioseparation of Fluoxetine on New β-Cyclodextrin Columns

H.W. YU AND C.B. CHING
Department of Chemical & Environmental Engineering, National University of Singapore,
10 Kent Ridge Crescent, Singapore 119260
engp9001@nus.edu.sg

Abstract. A Simulated Moving Bed (SMB) setup, including 8 new β-cyclodextrin columns, was used to achieve the enantioseparation of fluoxetine. The effects of feed concentration and feed flowrate on the operation performance parameters: purity, enrichment, recovery and productivity were studied. A simulation approach was applied to simulate the operation and performance of the simulated counter-current system. The model predicted the performance of the transient and cyclic steady state behaviour to a reasonably good extent. The adsorption isotherm and parameters determined by pulse experiments and moment analysis seem to be adequate in simulating both the transient and steady state behaviour. Generally, this model can provide guidance for designing operation condition of the SMB system.

Keywords: modeling, simulation, simulated moving bed, enantioseparation, fluoxetine

1. Introduction

The simulated moving bed (SMB), introduced in the early 1960s, is a continuous process apparatus, whose principle of operation can be best described with reference to the equivalent true counter-current (TCC) configuration in Fig. 1 (Broughton and Gerhold, 1961). With the respect to batchwise preparative chromatography, SMB units exhibit a number of advantages. In particular, these are due to the continuous nature of the operation and to an efficient use of the stationary and mobile phases, which allows the decrease of the desorbent requirement and the improvement of the productivity per unit time and unit mass of stationary phase. Moreover, high performances can be achieved even at rather low values of selectivity and with a relatively small number of theoretical plates. These features of SMB units are due to the fact that, contrary to preparative chromatography, the concentration profiles of the components to be separated are allowed to overlap along the adsorption beds, being required that the components are pure only at the extract and raffinate outlet locations. This allows oper-

ation in concentration overload conditions (Mazzotti et al., 1997). Due to these positive features, SMB is particularly attractive in the case of enantiomer separations, since it is difficult to separate enantiomers by conventional techniques. More recent applications related to chiral technology were reported (Cavoy et al., 1997; Francotte and Richert, 1997; Schulte and Strube, 2001).

In this study, enantioseparation of fluoxetine racemic will be reported using SMB technique. Fluoxetine (FLU)($\pm$N-methyl-3-[($\alpha,\alpha,\text{-}\alpha$ trifluoro-p-tolyl)oxy]-propylamine) is an antidepressant drug. The activity is based on the selective inhibition of 5-hydroxytryptamine (5-HT) recapture in the presynaptic neurons of the central nervous system. Because of its selectivity, it has been extensively applied. (S)-Fluoxetine is highly desirable because it is a potent antidepressant and appetite suppressant and is free of many undesirable side effects found with the racemic mixture. A high yield route to enantiomerically pure (S)-fluoxetine, which could be used in the place of the racemic mixture, may have commercial value (Olsen et al., 1998; Piperaki et al., 1995).
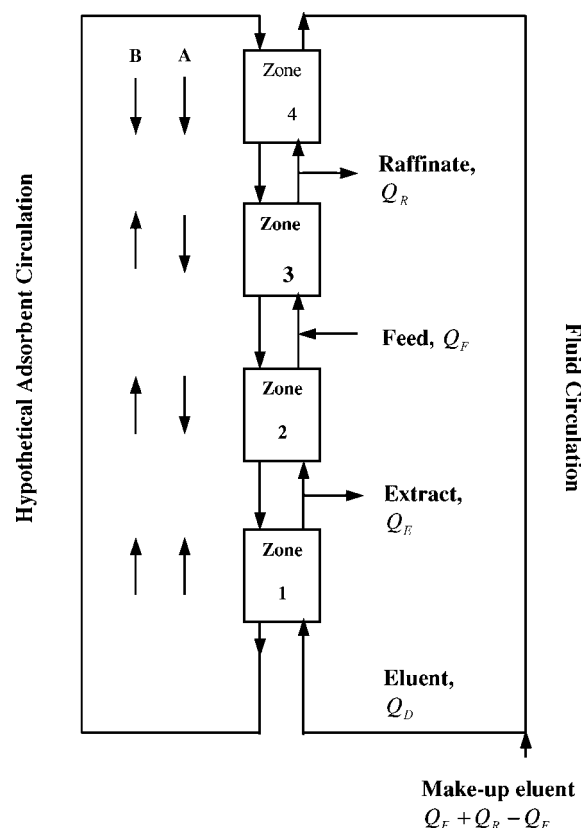
Figure 1. Scheme of a four zone true counter-current unit for continuous adsorptive separations: the binary separation of a strongly adsorbed component A and a weakly adsorbed component B is considered.

The efficiency of chiral stationary phase (CSP) is crucial in chromatographic technique. Recently, a new β-cyclodextrin phenyl isocyanate bonded chiral stationary phase (CSP) was developed. A US patent is pending. The new procedure afforded structurally well defined CSPs and easily controlled batch-batch reproducibility. This CSP is quite stable and can be used in most of HPLC solvents. Many drug enantiomers that do not have enantioseparation effect on native β-cyclodextrin column in reversed phase were separated very well on this new CSP.

In the operation of SMB, small changes in operation condition can take the system far from the optimal operation. Therefore, accurate modelling and simulation are received more and more attention recently (Altenh\ner et al., 1997; Strube et al., 1997; Heuer et al., 1998). In this work, the modelling and simulation of the SMB system will be studied and the comparisons of experimental and simulation results will be made. In addition,

because feed concentration and feed flowrate can affect the operation performance of SMB system, the effects of feed concentration and feed flowrate on performance parameters will be reported.

2. Theory

2.1. Modeling for Counter-Current Process

There are essentially two approaches to modeling chromatographic processes

- Simulated Moving Bed (SMB).
- True Moving Bed (TMB).

In the SMB sketched in Fig. 2, the counter-current movement of the solid is simulated by periodic switching of the points of inlet and outlet in the direction of the fluid flow. This can be done either by rotary valves (as in Sorbex and our operation) or through a set of individual valves programmed to switch at preset times. In the True Moving Bed, the solid actually flows and provides for the counter-current action. The liquid flowing out of Zone 4 is recycled to Zone 1 and the solid from Zone 1 to Zone 4. In both approaches, Zone 1 is between the Eluent and Extract nodes, Zone 2 between Extract and Feed, Zone 3 between Feed and Raffinate and Zone 4 between Raffinate and Eluent. In both cases the less retained component B is collected in the Raffinate stream and the more retained component A is collected in the Extract stream.

The parameters m_j, so-called flow-rate ratios, are defined as the ratio of the net fluid flow-rate over the solid phase flow-rate in each zone of the unit (Mazzotti et al., 1997):

$$m_j = \frac{\text{net fluid flow} - \text{rate}}{\text{adsorbed phase flow} - \text{rate}} \\ = \frac{Q_j^{\text{SMB}} t^* - V \varepsilon^*}{V(1 - \varepsilon^*)} \tag{1}$$

Where Q_j^{SMB} is the internal flowrate in each zone of SMB, ε^* is overall void fraction and V is volume of the column.

To keep a high purity of extract and raffinate, the operation points are required to be in the complete separation region. The complete separation region can be determined theoretically by flow constraints in every zone of SMB unit. Let us consider a four-section
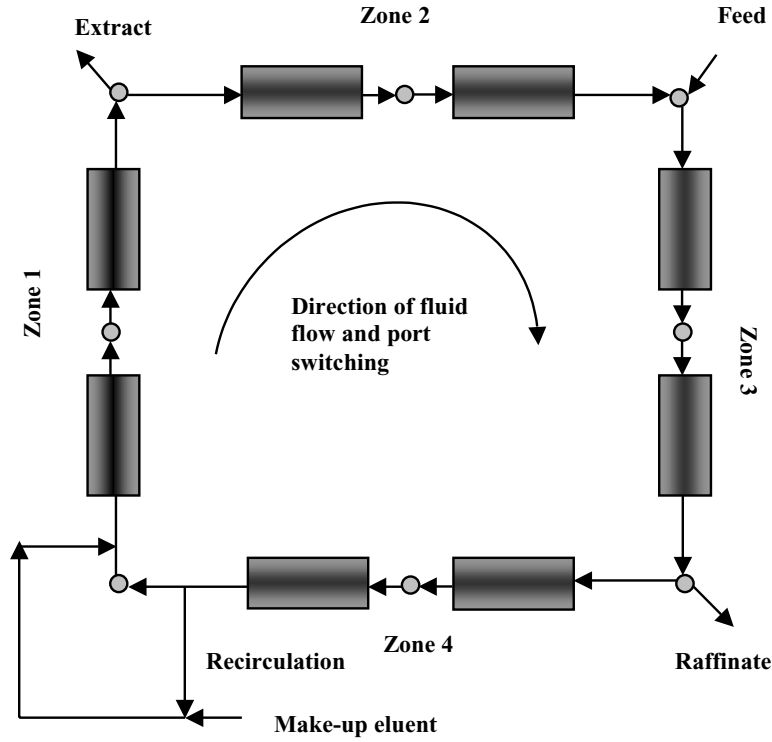
Figure 2. Schematic diagram of flow regimes of a four zone counter current system.

countercurrent adsorption separation unit. The complete separation conditions can be easily expressed in the term of the net flow rates of the components to be separated in each section of the unit. To achieve complete separation of a two component system, the net flow rates of component A, the most adsorbable one, must be conveyed to the extract outlet, whereas, component B, the least adsorbable one, must be conveyed to the raffinate outlet. From these considerations, the following conditions in terms of net flow rate ratios must be fulfilled to achieve complete separation (Storti et al., 1993):

Zone 1: $m_1 > \dfrac{q_A^{*1}}{c_A^1}, m_1 > \dfrac{q_B^{*1}}{c_B^1}$ where $Q_1 = Q_D$

$$\text{(2a)}$$

Zone 2: $\dfrac{q_B^{*2}}{c_B^2} < m_2 < \dfrac{q_A^{*2}}{c_A^2}$ where $Q_2 = Q_D - Q_E$

$$\text{(2b)}$$

Zone 3: $\dfrac{q_B^{*3}}{c_B^3} < m_3 < \dfrac{q_A^{*3}}{c_A^3}$

where $Q_3 = Q_D - Q_E + Q_F$ (2c)

Zone 4: $m_4 < \dfrac{q_A^{*4}}{c_A^4}, m_4 < \dfrac{q_B^{*4}}{c_B^4}$

where $Q_4 = Q_D - Q_E - Q_R + Q_F$ (2d)

The SMB and TMB have similar cyclic steady state performances and one can obtain optimal operating values for the SMB using the TMB model, as it requires lower computational time.

2.2. Modeling of Transient and Steady State Behavior

The model is developed assuming axially dispersed plug flow for the fluid and a linear mass transfer rate expression. The following assumptions are considered in the development of the model (Ruthven and Ching, 1989; Beste et al., 2000).

- Negligible thermal effects.
- Complete radial mixing.
- Mass transfer coefficients and physiochemical parameters independent of mixture composition.

- Voidage and radius of the column constant along its length.
- Constant flow rates in each section.
- Pressure and velocity variations have no effect on equilibrium relation.

The mass balance equation is written as

$$\frac{\partial c}{\partial t} = D_L \frac{\partial^2 c}{\partial z^2} - v \frac{\partial c}{\partial z} - \frac{1-\varepsilon}{\varepsilon} \frac{\partial q}{\partial t} \qquad (3)$$

For steady state:

$$\frac{\partial c}{\partial t} = 0 \qquad (4)$$

The Linear Driving force approximation gives us

$$\frac{\partial q}{\partial t} = k(q^* - q) \qquad (5)$$

With Danckwert boundary conditions:

$$D_L \frac{\partial c}{\partial z}(z=0,t) = -v[c(z=0^-,t) - c(z=0^+,t)]$$
$$\frac{\partial c}{\partial z}(z=L,t) = 0 \qquad (6)$$

Where, q^* is the solid phase concentration which is in equilibrium with the fluid phase concentration.

The equilibrium relationships for the two components are expressed following:

$$\frac{q^*}{c} = f(c_1, c_2) \qquad (7)$$

The set of Eqs. (3) to (6) defines a boundary value problem with a pair of coupled partial differential equations. By applying orthogonal collocation with respect to the axial coordinate, this set of equations can be reduced to a set of ordinary differential equations (Fubkatsib, 1980; Villadsen and Michaelson, 1978).

In the study there are eight columns with two components. Sixteen (16) internal collocation points are used for each column. Therefore, there are $8*2*2*16 = 512$ ordinary differential equations which are solved by Gear's method. The column switching is achieved by moving the concentrations appropriately at the end of each switch time. Using the IMSL integration routine IVPAG, the differential equations are solved and the transient and steady state concentration profiles can be calculated.

2.3. Model Parameters

To calculate the concentration profiles of the two enantiomers in the eight columns of the SMB system using the dispersed plug flow model, knowledge of the bed voidage, adsorption isotherms and the dispersion characteristic of the SMB system is required. These equilibrium and kinetic parameters were obtained from single batch chromatography (Ruthven, 1984; Duan et al., 1998).

The bed voidage was found to be 0.51. This was calculated from total porosity of column which was determined from retention time measurement of 1,3,5-tri-tert-butyl-benzene by pulse chromatographic experiments. Similar experiments were also carried out to measure the dead volumes which consist of the hold-up in the valves and the inter-column transfer tubing. The axial mixing in the columns as well as in the dead volumes were also determined by pulse chromatographic experiments using 1,3,5-tri-tert-butyl-benzene as the tracer. This mixing was assumed to be accounted for by an effective axial dispersion coefficient D_L and dependent on liquid velocity. From moment analysis of the chromatogram, the dispersion coefficient was approximated to be 0.0066v. Generally, the mass transfer coefficient may be influenced by the concentration, fluid velocity and the presence of the other component. But in this system, these influences were not considered to be severe because the gross features of the dynamic behavior of the system were determined by the equilibrium relationship. The coefficients for the (R)-Fluoxetine and (S)-Fluoxetine were found to be 72.6 and 58.0 min^{-1}, respectively. These values were determined from the moment analysis of the response peaks obtained from pulse chromatographic experiments over a range of liquid velocities.

In this study, the adsorption isotherm of fluoxetine on the new CSP is expressed in the following:

$$q_A^* = \frac{5.94c_A}{1 + 0.715c_A + 0.214c_B}$$
$$q_B^* = \frac{5.18c_B}{1 + 0.715c_A + 0.214c_B} \qquad (8)$$

3. Experimental

3.1. Introduction of a New CSP

This CSP was prepared with a pre-derived procedure. Perfunctionalised cyclodextrins were first synthesized,

purified and characterized and then chemically anchored on the surface of aminized silica gel via the hydrolytically stable urethane linkage. All chemicals were purchased from Fluka, Fisher and TCI and directly used without any further purification. Silica gel was supplied by Hypersil (UK) with a particle size of 15 μm. All solvents were purchased from Fluka of analytical grade and were distilled before use. Empty columns (250 mm × 10 mm) assembly were purchased from Phenomenex (USA). The column was packed using an Alltech pneumatic HPLC pump (Alltech, USA).

3.2. Chemicals

The eluent used was methanol and buffer (40:60). The concentration of triethylamine acetate in buffer was 2%, pH of buffer was 5.0 adjusted by addition of glacial acetic acid. The feed was prepared by dissolving racemic fluoxetine in the mobile phase. Fluoxetine was extracted from Prazce capsule, provided by Elly Lilly Company.

3.3. Instrumentation

The SMB system consists of 8 columns (250 mm · 10 mm) packed by the new CSP (Fig. 3). The columns are fed with either the feed or the eluent (inlet and outlet) via 5, 8 port rotary valves (VICI). The configuration tested is 2222 (two columns per zone). The valve switching is attained by software provided by the manufacturer. The T joints at the top and bottom of each column allow them to be connected in series or to a recycling line. A check valve (Nupro, Willoughby, OH, USA) is placed between each column to avoid backmixing. The extract and raffinate are withdrawn from the column via two other rotary valves with similar configuration. Two volume meters are used to control the exit flow rates. To avoid solid impurities in the feed and the eluent, a 2 μm filter is placed at the inlet of each line. An online vacuum degasser (SUPELCO) degasses all the liquid being pumped into the system.

Solvent metering pumps controlled the flow rates of the feed and eluent. The feed was pumped in using a Waters 610 Fluid Unit with a 600E System Controller and the eluent was pumped using a Shimadzu LC-10AT (Tokyo, Japan) Solvent Delivery System.

The concentrations of the extract and raffinate streams were analyzed for each stage using a standard analytical chromatographic system. The samples collected at the middle of the switch times were analyzed. An analytical column (250 mm · 4.6 mm) packed by 5 μm CSP was used to analyze the concentration of samples. The Perkin-Elmer (USA) chromatographic system consisted of a series 200 vacuum degasser, series 200 IC pump, 785 UV/VIS detector and a series 200 autosampler for multiple runs was used to analyze. The adsorbance wavelength was set at 225 nm. The system was controlled by the Turbochrom software.

4. Operation Performance

4.1. Operation Performance Parameters

The SMB performance is characterised by four process parameters: purity, recovery, enrichment and productivity. For the case of a two component separation in the SMB in which the more retained species A is recovered in the raffinate and the less retained component B is recovered in the extract, process performance parameters are defined in Table 1 (Pais et al., 1997).

Where c_E^A and c_F^A are the concentration of A in extract and feed, respectively; c_R^B and c_F^B are the concentration of B in raffinate and feed, respectively; Q_E, Q_R and Q_F are the volumetic flowrates of extract, raffinate and feed, respectively; V_S is volume of solid phase.

4.2. Effect of Feed Concentration

Several runs are carried out when feed flow rate, Q_F, is 0.2 ml/min, $c_A^F = c_B^F$ are adjusted from 0.6 to 0.2. The positions of operation points on the $m_2 - m_3$ are the same. The operation conditions: Q_D, Q_E, Q_R, and switch time t^* are shown in Table 2.

With the increasing of feed concentration, m_4 is decreased. It causes the raffinate flow rate decreased. The eluent and extract flow rates are not changed since m_1, m_2 and m_3 are the same at these operation points. Based on the "triangle method", the theoretical

Table 1. Definition of process performance parameters.

Performance parameter	Extract	Raffinate
Purity (%)	$\frac{100c_E^A}{c_E^A + c_E^B}$	$\frac{100c_R^B}{c_R^A + c_R^B}$
Recovery (%)	$\frac{100c_E^A Q_E}{c_F^A Q_F}$	$\frac{100c_R^B Q_R}{c_F^B Q_F}$
Enrichment (%)	$\frac{100c_E^A}{c_F^A}$	$\frac{100c_R^B}{c_F^B}$
Productivity (g/h/l of solid)	$\frac{c_E^A Q_E}{V_S}$	$\frac{c_R^B Q_R}{V_S}$

1.Feed Pump   2. Eluent Pump   3. Feed Valve   4. Eluent Inlet Valve   5. Column
6. Check Valve   7. Extract Valve   8. Raffinate Valve   9. Eluent Outlet Valve   10. Volume Meter
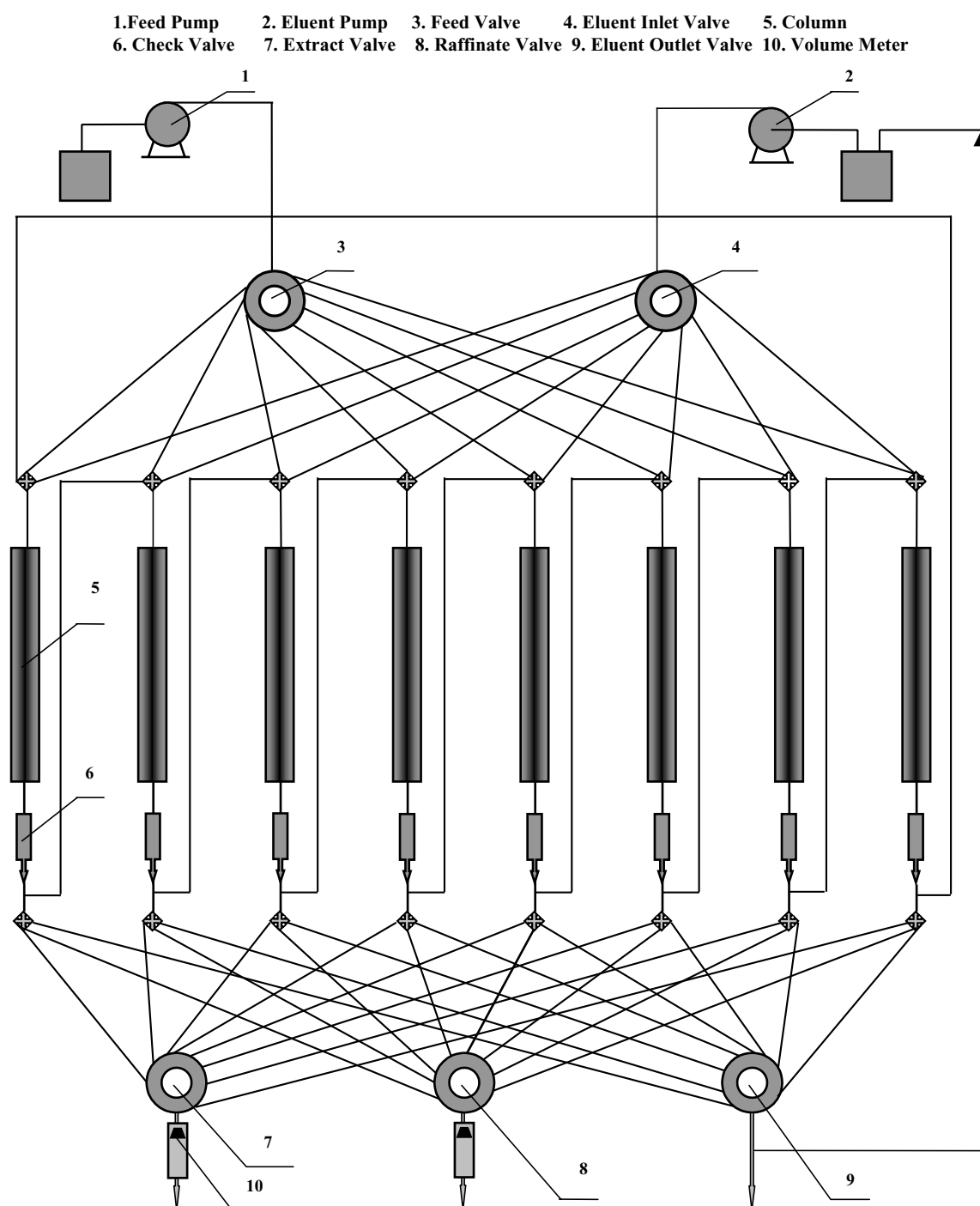

Figure 3.   Schematic diagram of the experimental setup.

complete separation region can be determined. The different complete separation regions under the different concentrations are shown in Fig. 4. With the reference of Fig. 4, it is found that the complete separation region is reduced with the increasing of feed concentration. The bounds for complete separation region can be extended by a lowering of feed concentration. The effects of feed concentration on performance parameters are

Table 2. Operation conditions of SMB on effect of feed concentrations.

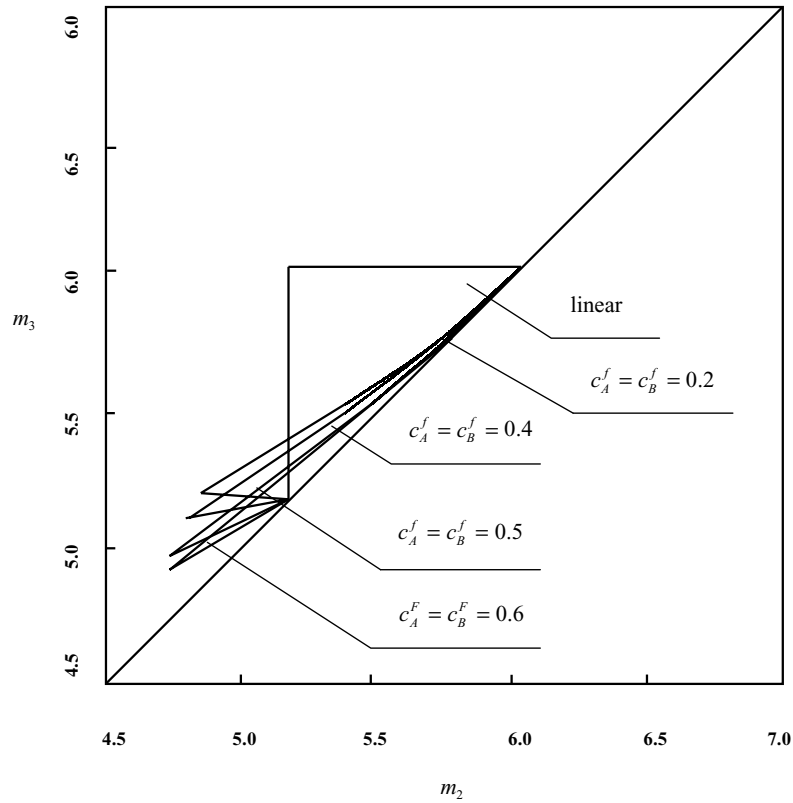| Run	Concentration (mg/ml)	Flowrates (ml/min)			t^* (min)	Flow-rate ratios			
		Q_D	Q_E	Q_R		m_1	m_2	m_3	m_4
C1	0.6	6.40	0.95	0.32	7.4	6.24	4.92	5.20	4.76
C2	0.5	6.40	0.95	0.30	7.4	6.24	4.92	5.20	4.78
C3	0.4	6.40	0.95	0.28	7.4	6.24	4.92	5.20	4.82
C4	0.2	6.40	0.95	0.21	7.4	6.24	4.92	5.20	4.90

Figure 4. Effect of feed concentration on theoretical complete separation region.

shown in Fig. 5. The results show that purities, recovery and enrichment of extract and raffinate improve with decreasing feed concentration with a compromise in productivity.

4.3. Effect of Feed Flow Rate

Several runs are carried out when $c_A^F = c_B^F = 0.5$ mg/ml, feed flow rate, Q_F, is adjusted from 0.32 to 0.1 ml/min. The flow rate ratios of all operation points are the same, respectively. The operation conditions: Q_D, Q_E, Q_R and switch time, t^*, are shown in Table 3:

If the switch time is kept constant, increasing the feed flowrate will result in an increase of both m_3 and m_4. This will lead to contamination of the raffinate stream by the heavier species in Zone 3. Also the increase in m_4 will warrant the movement of the lighter species in the upward direction hence contaminating the extract stream (Pais et al., 1997). In this study, every operation point was kept in the same position in $m_2 - m_3$ plan. In other words, m_2 and m_3 must be the same for all operation points when the feed flowrate was increased. Hence the switch time must be shortened according to the definition of m_j (Eq. (1)), Increasing feed flow rate

Table 3. Operation conditions of SMB on effect of feed flowrate.

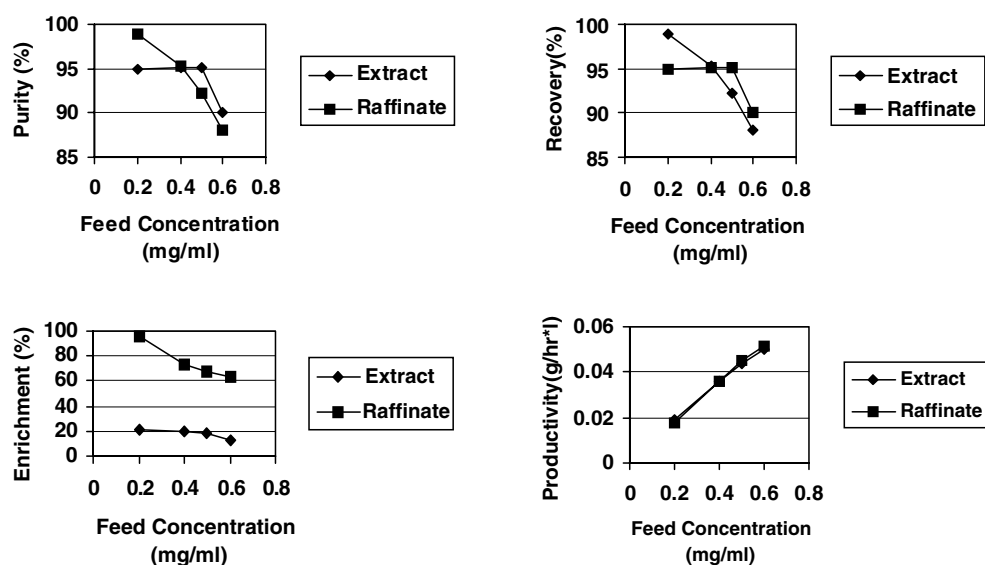|	Flowrates (ml/min)					Flow-rate ratios			
Run	Q_F	Q_D	Q_E	Q_R	t^* (min)	m_1	m_2	m_3	m_4
F1	0.32	10.0	1.52	0.48	4.6	6.24	4.92	5.20	4.78
F2	0.30	9.61	1.43	0.45	4.9	6.24	4.92	5.20	4.78
F3	0.25	8.00	1.20	0.38	5.9	6.24	4.92	5.20	4.78
F4	0.2	6.40	0.95	0.30	7.4	6.24	4.92	5.20	4.78
F5	0.1	3.21	0.48	0.15	14.8	6.24	4.92	5.20	4.78

Figure 5. Effect of feed concentration on performance parameters.

must cause the eluent flow rate, extract flow rate and raffinate flow rate to be increased. The system pressure must be considered because there is an upper limit of pressure for every column. The higher pressure can make the SMB operation unstable. Hence, the performance parameters could be damaged due to the instability of system. The effects of feed flow rate on performance parameters are shown in Fig. 6. The results

show that the increasing of feed flowrate will increase the productivity but purity, recovery and enrichment of extract and raffinate will be decreased when the flow rate reaches a high level which can causes the operation of system unstable.

5. Simulation Results and Discussions

5.1. Transient Behavior

Experimental transient concentration profiles for (R)- and (S)-Fluoxetine in the eight columns for Run 1 are shown in Fig. 7 and the operating conditions are shown in Table 4. The samples were collected from each column at the mid-time of various switches during the run. The theoretical profiles also correspond to the mid-time of the various switches. Comparisons between the

Table 4. Operation condition used in simulation.

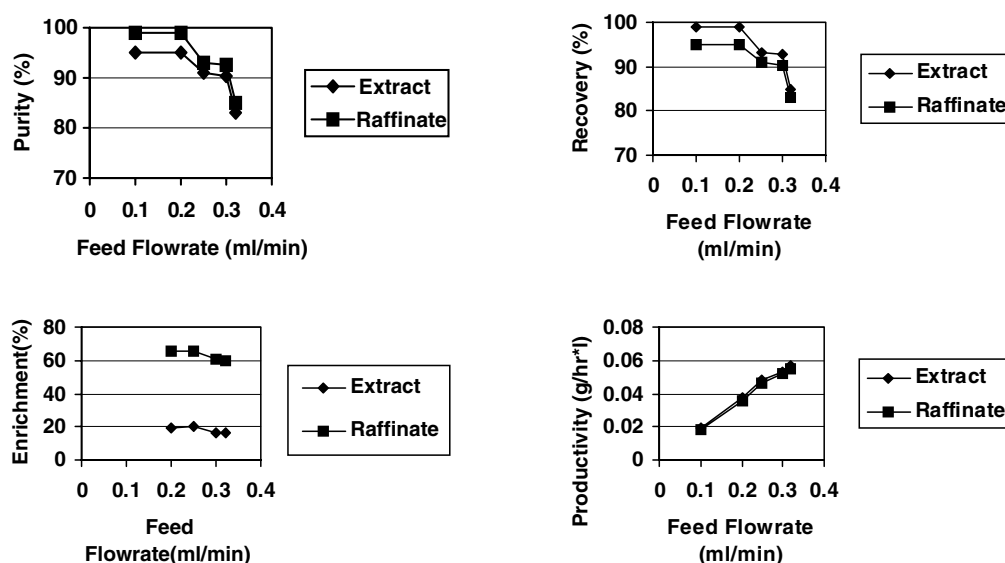| Feed flowrate (ml/min)	Q_F	0.2
Feed concentration (mg/ml)	$c_A = c_B$	0.5
Eluent flowrate (ml/min)	Q_D	6.4
Extraction flowrate (ml/min)	Q_E	0.95
Raffinate flowrate (ml/min)	Q_R	0.3
Switch time (min)	t^*	7.4

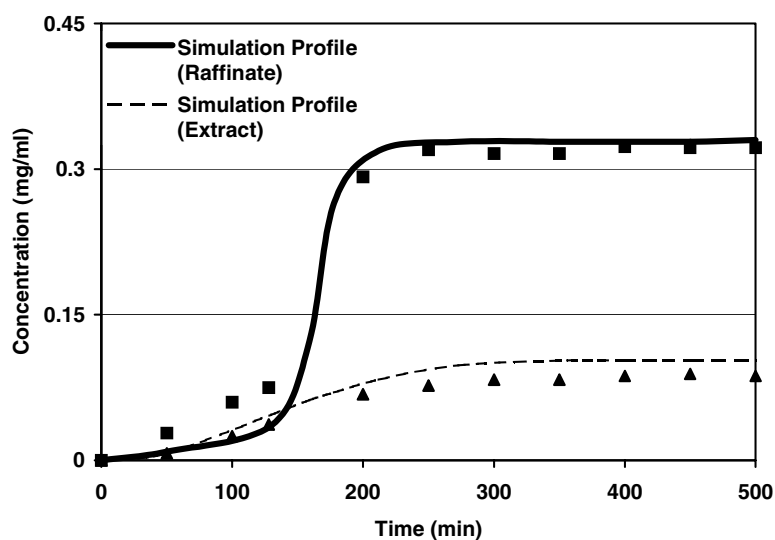*Figure 6.*   Effect of feed flowrate on performance parameters.

Figure 7.   Experimental (points) and theoretical (curves) transient changes in concentration of (S)-Fluoxetine in extrat and (R)-Fluoxetine in raffinate.

estimated and experimental concentration profiles show reasonably good agreement although slight discrepancies were observed. During the experiments, it has been observed that a slight deviation of the flowrate in Zones 2 and 3 could lead to a significant difference in the concentration profile. The high sensitivity of the flowrate to the concentration profile could have contributed to the discrepancies of the theoretical and experimental concentration profiles. The discrepancies

could also be attributed to the variation of the column parameters among the eight columns. This was due to the different batches of adsorbent used in packing the columns.

Ching et al. (1990) have pointed out that the rate of approach to cyclic steady-state for the less adsorbed component is higher than that for the more adsorbed component which followed the breakthrough in a fixed bed adsorber. This was also observed in the present
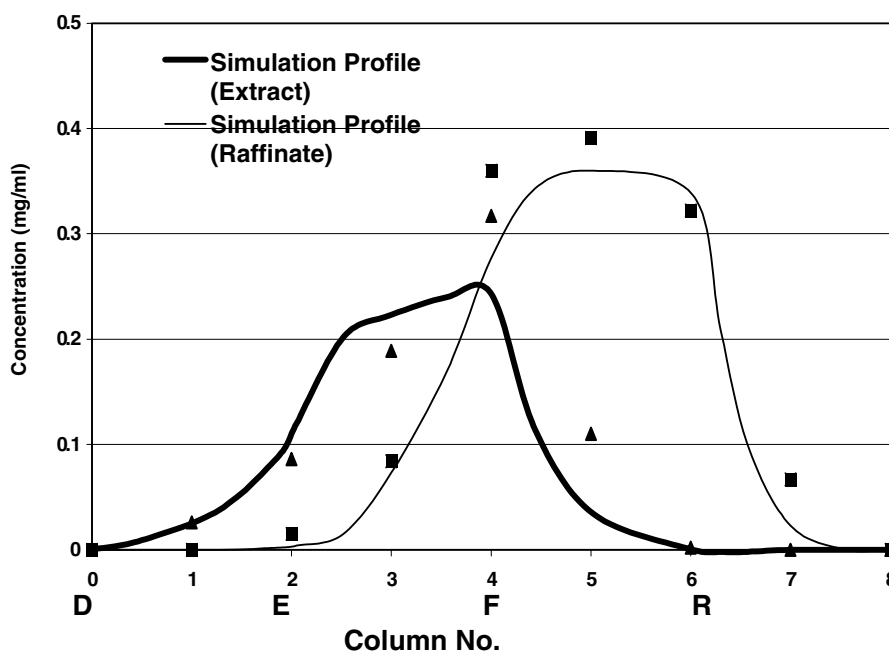
Figure 8. Experimental (points) and simulation (curves) steady state concentration at the exit of every colunm.

study although the elution velocities in Zones 2 and 3 were also believed to play a role in the rate of approach to cyclic steady-state. (R)-Fluoxetine, being less adsorbed by this new CSP, had a higher rate of approach to cyclic steady-state compared to the more adsorbed component, (S)-Fluoxetine.

5.2.   *Cyclic Steady-State Behavior*

The cyclic steady-state concentration profile is shown in Fig. 8. This profile was obtained by sampling the outlet solution at column 8 for eight consecutive switches. The samples collected during the first switch represent the column outlet concentration of column 8 and the second switch, column 7 and so on. The first collection for each switch was performed at 2.5 min after the switch. The progression of the concentration profiles within a switch interval for the 8 columns was compared with the values calculated from the mathematical model. Generally, good agreement between the theoretical and experimental profiles was observed. Some experimental points were distorted from theoretical profile a little. This error could be due to the difference in the performance of the various columns used which was caused by the use of different batches of adsorbent. This problem could also be due to the use

of the linear rate model. Furthermore, the assumption of constant mass transfer resistance might not be valid in the present study as the system was not close to linear. However, it was observed that the theoretical profiles were much more sensitive to the equilibrium relationship than to the precise value assumed for the mass transfer resistances. In general, the cyclic steady-state profiles calculated from the model used in this study are in good agreement with the experimental values and the model is adequate in simulating the performance of the SMB in this study.

6.   Conclusions

The operation performances of different feed concentration and flowrate on a simulated moving bed were studied. It is important to select a suitable feed concentration and feed flowrate for achieving complete separation. A direct simulation approach was used to simulate the operation and performance of a simulated countercurrent system. The model predicted the performance of the transient and cyclic steady state behaviour to a reasonably good extent. The model did not account for the variation in mass transfer coefficient and dead volume introduced due to the tubing between the columns. The parameters determined by pulse experiments and

moment analysis and adsorption isotherm seem to be adequate in simulating both the transient and steady state behaviour. The simulation showed that the performance was quite sensitive to the accurate determination of the adsorption isotherms of the two isomers. Also the concentration profile and purities were sensitive to the flow rates in the different zones. These could have led to the discrepancies between the experimental and calculated profiles. Generally, this model provided guidance for designing operation condition of SMB.

Nomenclature

c Concentration (μg/ml)

c_F Feed concentration (μg/ml)

c_0 Concentration of outlet (μg/ml)

D_L Axial dispersion coefficient (min^{-1})

q Solid phase concentration (μg/ml)

q^* Solid phase equilibrium concentration (μg/ml)

k Overall mass transfer coefficient (min^{-1})

L Length of the chromatographic column (cm)

t Time (min)

u Superficial velocity (cm/min)

v Interstitial fluid velocity (cm/min)

z Axial coordinate (cm)

Greek Symbols

ε External porosity or bed voidage

ε^* Overall void fraction

References

Altenh\ner, U., M. Meurer, J. Strube, and H. Schmidt-Traub, "Parameter Estimation for the Simulation of Liquid Chromatography," *J. Chromatogr. A*, **769**, 59–69 (1997).

Beste, Y.A., M. Lisso, G. Wozny, and W. Arlt, "Optimization of Simulated Moving Bed Plants with Low Efficient Stationary Phases: Separation of Frucose and Glucose," *J. Chromatogr. A*, **868**, 169–188 (2000).

Broughton, D.B. and C.G. Gerhold, "Continuous Sorption Process Employing Fixed Beds of Sorbent and Moving Inlets and Outlets," U.S. Patent 2,985,589 (May 23, 1961).

Cavoy, E., M.-F. Deltent, S. Lehoucq, and D. Miggiano, "Laboratory-Developed Simulated Moving Bed for Chiral Drug Separations and Design of the System and Separation of Tramadol Enantiomers," *J. Chromatogr. A*, **769**, 49–57 (1997).

Ching, C.B., K.H. Chu, and D.M. Ruthven, "A study of Multicomponent Adsorption Equilibria by Liquid Chromatography," *AICHE J.*, **36**, 275 (1990).

Duan, G., S. Swarup, and C.B. Ching, "Kinetic and Equilibrium Study of the Separation of Propranolol Enantiomers by High Performance Liquid Chromatography on A Chiral Adsorbent," *Chem. Eng. J.*, **69**, 111–117 (1998).

Francotte, E.R. and P. Richert, "Applications of Simulated Moving-Bed Chromatography to the Separation of the Enantiomers of Chiral Drugs," *J. Chromatogr. A*, **769**, 101–107 (1997).

Fubkatsib, B.A., *Nonlinear Analysis in Chemical Engineering*, McGraw Hill, New York, 1980.

Heuer, C., E. K\lsters, T. Plattner, and A. Seidel-Morgenstern, "Design of the Simulated Moving Bed Process Based on Adsorption Isotherm Measurement Using a Perturbation Method," *J. Chromatogr. A*, **827**, 175–191 (1998).

Mazzotti, M., G. Storti, and M. Morbidelli, "Optimal Operation of Simulated Moving Bed Units for Nonlinear Chromatographic Separations," *J. Chromatogr. A*, **769**, 3–24 (1997).

Olsen, B.A., D.D. Wirth, and J.S. Larew, "Determination of Fluoxetine Hydrochloride Enantiomeric Excess Using High-Performance Liquid Chromatography with Chiral Stationary Phases," *J. Pharm. Biomed. Anal.*, **17**, 623–630 (1998).

Pais, L.S., J.M. Loureiro, and A.E. Rodrigues, "Modeling, Simulation and Operation of a Simulated Moving Bed for Continuous Chromatographic Separation of 1,1′-bi-2-naphthol Enantiomers," *J. Chromatogr. A*, **769**, 25–35 (1997).

Piperaki, S., S.G. Penn, and D.M. Goodall, "Systematic Approach to Treatment of Enantiomeric Separations in Capillary Electrophoresis and Liquid Chromatography II. A Study of the Enantiomeric Separation of Fluoxetine and Norfluoxetine," *J. Chromatogr. A*, **700**, 59–67 (1995).

Ruthven, D.M., *Principle of Adsorption and Adsorption Processes*, John Wiley and Sons, New York, 1984.

Ruthven, D.M. and C.B. Ching, "Counter-Current and Simulated Counter-Current Adsorption Separation Processes," *Chem. Eng. Sci.*, **44**, 1011–1038 (1989).

Schulte, M. and J. Strube, "Preparative Enantioseparaiton by Simulated Moving Bed Chromatography," *J. Chromatogr. A*, **906**, 399–416 (2001).

Storti, G., M. Mazzotti, and M. Morbidelli, "Robust Design of Binary Countercurrent Adsorption Separation Processes," *AICHE J.*, **39**, 471–492 (1993).

Strube, J., U. Altenh\ner, M. Meurer, H. Schmidt-Traub, and M. Schulte, "Dynamic Simulation of Simulated Moving Bed Chromatographic Processes for the Optimization of Chiral Separation," *J. Chromatogr. A*, **769**, 81–92 (1997).

Villadsen, J. and M. Michaelson, *Solution of Differential Equation by Polynomial Approximation*, Prentice Hall, Englewood Cliffs, 1978.