Optimization of a Simulated Moving Bed Based on an Approximated Langmuir Model

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Based on the "triangle method," a shortcut method was developed to establish the possible optimal operating condition of a SMB unit, because the theoretical optimal operating condition was diverted from the actual complete separation region by too many unexpected disturbances. A new CSP was used in the simulated moving bed for the enantioseparation of fluoxetine. Good separation results were obtained. The effects of the difference between m_2 and m_3 on performance parameters were studied. The results show that this method is useful for establishing the operating conditions. It can be concluded that the new CSP is efficient for the enantioseparation of chiral drugs.

Introduction

The simulated moving-bed (SMB) unit is a continuous-process apparatus, whose principle of operation can be best described with reference to the equivalent true countercurrent (TCC) [or true moving-bed (TMB)] configuration in Figure 1. In SMB technology some rotary valves or multiposition valves are used to periodically change the position of feed, eluent, extract, and raffinate lines along the bed. The concept of the technology has been known since 1961 when the first presentation by Broughton appeared (Broughton and Gerhold, 1961).

When compared to the batchwise preparative chromatography, SMB units exhibit a number of advantages. These advantages are primarily because of the continuous nature of the operation and the efficient use of the stationary and mobile phases, which allows a decrease in the desorbent requirement and an improvement of the productivity per unit time and per unit mass of stationary phase (Negawa and Shoji, 1993; Küster et al., 1995). In addition, high performances can be achieved even at rather low values of selectivity and with a relatively small number of theoretical plates (Mazzotti et al., 1997a). 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; Strube et al., 1997; Francotte and Richert, 1997; Lehoucq and Verheve, 2000; Foucault, 2001).

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In this study, the enantioseparation of fluoxetine racemic mixture is reported using the SMB technique. Fluoxetine (FLU)($\pm$ *N*-methyl-3-[($\alpha,\alpha,$ -α trifluoro-*p*-tolyl)oxy]-propylamine) is an antidepressant drug. Its 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 in the racemic mixture. A high yield route to enantiomerically pure (*S*)-fluoxetine, which could be used in place of the racemic mixture, may have commercial value (Piperaki et al., 1995; Olsen et al., 1998).

The efficiency of the chiral stationary phase (CSP) is crucial in the chromatographic technique. Recently, a new β-cyclodextrin phenyl isocyanate-bonded CSP was developed. A Singapore patent (Patent No. 9703059-7) has been filed, while a U.S. patent (Attorney Docket No. 1781-152P) 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 HPLC solvents. Many drug enantiomers that do not have enantioseparation effect on the native β-cyclodextrin column in reversed phase were very well separated on this new CSP.

The design and optimization of the operating conditions is very important in the operation of SMB. Many reports focus on how to establish robust SMB operating conditions (Storti et al., 1995; Heuer et al., 1998; Beste et al., 2000). During the past ten years, based on the equilibrium theory, a "triangle

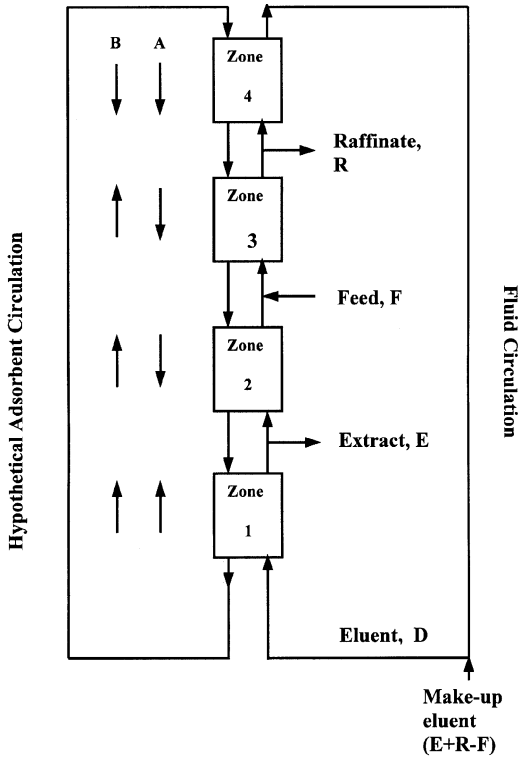

Figure 1. Four-zone true countercurrent unit for continuous adsorptive separations.

The binary separation of a strongly adsorbed component A and a weakly adsorbed component B is considered.

method" was developed to design the SMB operating conditions under nonlinear conditions (Storti et al., 1989, 1993; Mazzotti et al., 1994, 1996, 1997b). Due to the uncertainty of the theoretical modeling parameters and the disturbance of operation, the theoretical optimal operating condition is not robust in actual application using this method. A shortcut method based on the triangle method is developed in this work to establish possible robust optimal operating condition.

Optimization of Nonlinear Operating Conditions to Achieve Complete Separation

The SMB performance is characterized 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 extract and the less retained component B is recovered in the raffinate, the process performance parameters are defined in Table 1.

In the table, c_E^A and c_F^A are the concentrations of A in the extract and the feed, respectively; c_R^B and c_F^B are the concentrations of B in the raffinate and the feed, respectively; Q_E, Q_R, and Q_F are the volumetric flow rates of the extract, the raffinate, and the feed, respectively; and V_S is the volume of the solid phase.

Introduction of the triangle method

Storti et al. developed an approach—the so-called triangle method—to discuss the operating conditions to improve the performance of SMB units when the adsorption equilibrium relationship is linear, the Langmuir model is stoichiometric or nonstoichiometric, where axial mixing and mass-transport resistance are neglected, and adsorption equilibrium is assumed to be established everywhere at each time in the column (Storti et al., 1993).

Table 1. Definition of Process Performance Parameters

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

In the approach, the parameters m_j, so-called flow-rate ratios, are introduced and defined as the ratio of the net fluid flow rate over the solid-phase flow rate in each section of the unit:

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

When the SMB unit is run under the optimal operating condition, the purity of the extract and the raffinate must be kept high. This requires that the optimal operating point be in the complete separation region. The complete separation region can be determined theoretically by flow constraints in every zone of the SMB unit. Let us consider a four-section countercurrent adsorption separation unit. The complete separation conditions can be easily expressed in terms of the net flow rates of the components to be separated in each section of the unit. For a given feed composition, the coordinates of the optimal point are (Mazzotti et al., 1997a)

$$m_{1,\text{opt}} = m_{1,\text{min}} = K_A \quad (2a)$$

$$m_{2,\text{opt}} = \frac{K_B \omega_G}{K_A} \quad (2b)$$

$$m_{3,\text{opt}} = \frac{\omega_G\left[\omega_F(K_A - K_B) + K_B(K_B - \omega_F)\right]}{K_B(K_A - \omega_F)} \quad (2c)$$

$$m_{4,\text{opt}} = \frac{1}{2}\left\{K_B + m_3 + b_B c_B^F (m_3 - m_2) - \sqrt{\left[K_B + m_3 + b_B c_B^F (m_3 - m_2)\right]^2 - 4K_B m_3}\right\} \quad (2d)$$

Introduction of a shortcut method to establish a robust optimal operating condition

Robustness is of great importance when choosing operation conditions for practical applications, because sensitive

operating conditions must be avoided in industrial plants. Robust conditions mean that small disturbances do not modify the qualitative behavior of the unit. With reference to complete separation conditions, this means that as a consequence of the disturbance, the actual performances change, but the unit still achieves complete separation.

But the performance of the SMB is very sensitive to various kinds of disturbance under the optimal operating condition derived from the "triangle method" because of perturbations in the operating conditions, inaccuracies in the chemicophysical parameters, and model uncertainties; in other words, the operating condition is not robust. In practice, the minimum distance of the operating point from the boundaries of the complete separation region is a measure of the maximum acceptable perturbation on the value of the flow-rate ratios m_j. The further the designed operating point is from the boundaries of the complete separation region, the more robust the operating condition is.

From these considerations it is straightforward that the theoretical optimal point is the (m_2, m_3) plane derived from the triangle method is not robust at all, since the slightest disturbance can drive the operating point in one of the three separation regions where complete separation is not achieved. In most cases, because of the inaccuracies in the model parameters, the optimal point derived from Eqs. 2b and 2c is not the actual optimal point. This point may not be in the actual complete separation region at all, even if the disturbance during operation is negligible. Therefore, the first thing to do to establish the robust optimal operating condition is to find the actual complete separation region.

Apparently, it is almost impossible to consider the minimum distance of the operating point from the boundaries of the complete separation region as a measurement of the robustness of the operating point, since the accuracy of the complete separation region cannot be guaranteed. But the result of the experiment can show if the operating point is robust. For instance, if the purities of the extract and raffinate products are all 100%, it means that the operating point must be in the actual complete separation region and the operating conditions must be robust. Next, let us discuss how to establish the complete separation region based on the experimental results of some operating points when the disturbance during operation is assumed to be negligible.

Since the theoretical optimal operating point does not show the actual optimal operating condition, the region on the m_2-m_3 plane it locates can be shown by the experimental result. Because the optimal operating point is derived from a theoretical isotherm, it could not be too far from the actual complete separation region, even when the model parameters are determined poorly. Based on these considerations, the theoretical optimal operating point may appear at some positions on m_2-m_3 plane represented by S_1, S_2, S_3, S_4, S_5, and S_6 in Figure 2.

Let us discuss the case where the location of the theoretical optimal operating point is at position S_1 in Figure 2. Several experimental points are established along line P, which runs diagonal to the m_2-m_3 plane, for example, E_1, E_2, E_3 . . . in Figure 3. According to the results of these experimental points, the regions on the m_2-m_3 plane in which those experimental points are located can be known. For example, E_1, E_2, and E_3 in Figure 3 are in the pure raffinate

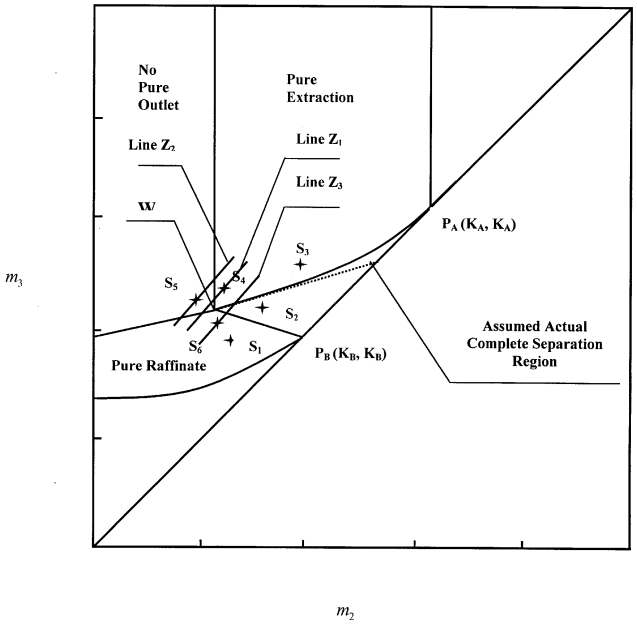

Figure 2. Possible location of the theoretical optimal operating condition on the m_2-m_3 plane.

region, the actual complete region, and the pure extract region, respectively. A triangular region is formed by extending lines $P_A E_3$ and $P_B E_1$, which intersect at point W_0. The triangle $W_0 P_B P_A$ can be used to represent the actual complete separation region, since most areas of the actual complete separation region are covered by the triangle. The possible optimal operating point is located in the triangle region.

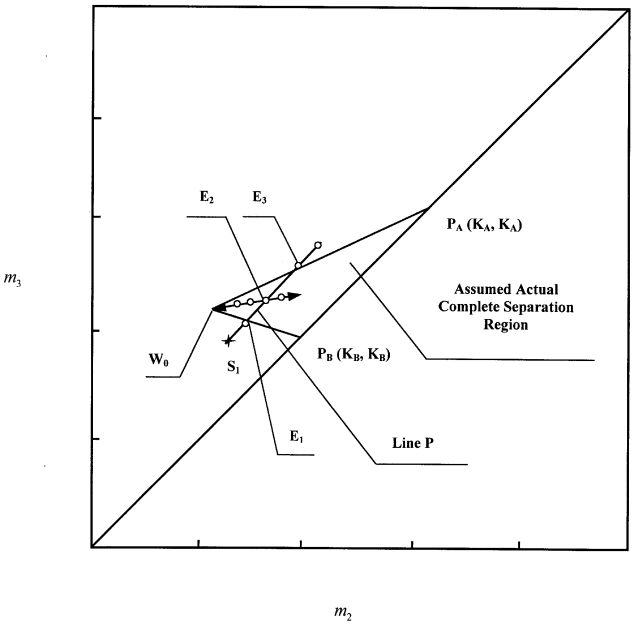

Figure 3. Establishing a complete separation region for the theoretical optimal operating point at S_1 on the m_2-m_3 plane.

The performance parameters would be better under the optimal operating condition, compared to other operating conditions. It has been demonstrated by Storti et al. (1993) that it is very helpful to improve the performance of the operation by increasing the difference between m_2 and m_3, but it will sacrifice the robustness of the operation. Hence, the difference between m_2 and m_3 should be increased to look for the optimal operating condition. The best direction to optimize the operation points is along the line, which bisects the vertex angle of the actual complete separation region to keep it as robust as possible. Due to the uncertainty of the vertex of the actual complete separation region, it is impossible to find this line. For simplicity, this line can be replaced by E_2W_0. Several experimental points are made along E_2W_0, and the possible optimal operating condition to achieve complete separation can be found. If the experiments are made in the opposite direction of E_2W_0, the robustness of the operation will be increased, but the performance of the operation will be damaged.

The same procedure can be used when the theoretical optimal operating point is at position S_2 or S_3 in Figure 2. For the case when the theoretical optimal point is around the actual optimal point, W, for example, S_4, S_5, and S_6 in Figure 2, it is almost impossible to find complete separation points when the experiments are carried out along the line (line Z_1, Z_2, Z_3) that parallels the diagonal and passes through these points. This is because these lines do not pass through the complete separation region at all, or they pass through only a very small region, which is not enough to hinder the disturbance of the actual operation. Actually, it is

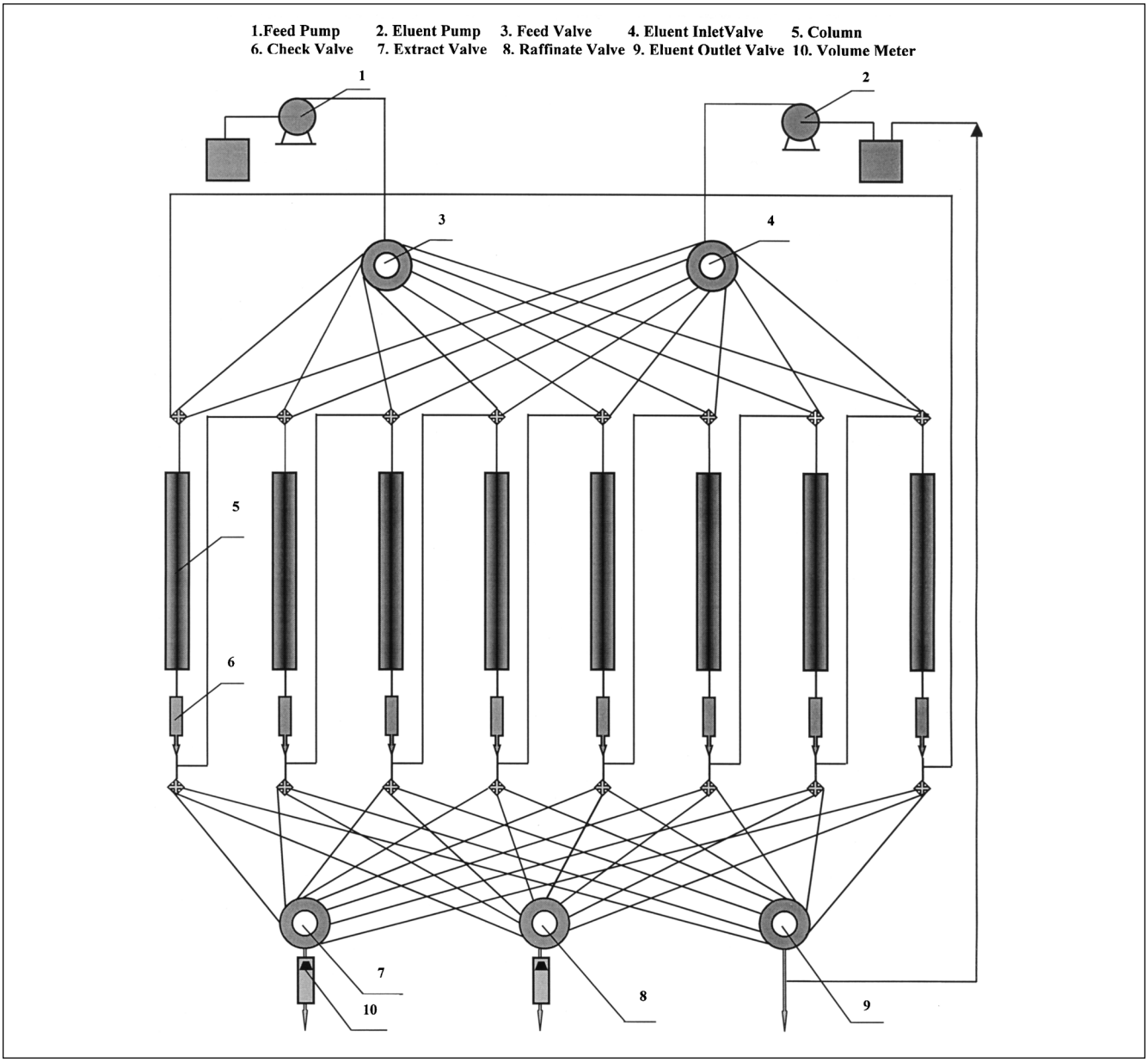

Figure 4. Experimental setup.

easy to know if the theoretical optimal point is near the actual optimal point, since a slight change of m_2 and m_3 along line Z_1, Z_2, Z_3 can drive the experimental point into a different region on the m_2-m_3 plane. Based on this knowledge, the actual complete separation region can be established only if the difference between m_2 and m_3 is decreased to a suitable value, for example, point S_1. Then the possible optimal operation point can be found by following the procedure just described.

It must be mentioned that because these experimental results are achieved under all the disturbances during actual operation, those operational conditions under which complete separation can be achieved must be robust. In other words, some operating points under which the complete separation cannot be achieved because of the disturbance of operation are not covered in the triangle $P_A W_0 P_B$, even if they are in the actual complete separation region. This means that the triangle region can cover only some robust operating points if the operational disturbances are considered. The modified method can be summarized by the following steps:

1. A starting experiment is carried out using the theoretical optimal operating condition determined from Eqs. 2a–2d. According to the experimental result, the region in which the operating point lies will be determined. It must be mentioned that it is not safe for the operation to select $m_{1,\min}$ and $m_{4,\max}$ to be m_1 and m_4, respectively. In actual application, m_1 and m_4 should be adjusted slightly around the theoretical optimal value to achieve good operation performance of the SMB unit.

2. A line is made that passes through the starting operating point and parallels the diagonal of m_2-m_3 plane. Several runs are carried out following operating points along this line.

3. The two operating points that are closest to the actual complete separation region (in other words, the operating results following these two operating points show that they are almost in the complete separation region) and in the pure raffinate region and the pure extract region, respectively, are selected, for example, E_1 and E_3 in Figure 3. One operating point in the complete separation region—point E_2—is determined, too. The operating point should make the extract (Q_E) and raffinate (Q_R) be as close as possible. If the point in the complete separation region cannot be found, the difference between m_2 and m_3 should be decreased. Go back to the step 2.

4. Line $P_A E_3$ and $P_B E_1$ are extended to intersect at W_0. Several operating points are made along line $E_2 W_0$. Based on these operating points, several runs are carried out. According to the experimental results, the possible optimal operating condition can be determined.

Experimental Studies

Introduction of a new CSP

This CSP was prepared with a prederived procedure. Perfunctionalized 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, were of analytical grade, and were distilled before use. Empty-column (250 mm $\times$ 4.6 mm) assembly was purchased from Phenomenex (USA). The column was packed using an Alltech pneumatic HPLC pump (Alltech, USA).

Chemicals

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

Instrument

The SMB system consists of eight columns (250 mm $\times$ 10 mm) packed by the new CSP (Figure 4). The columns are fed with either the feed or the eluent (inlet and outlet) via 5- or 8-port rotary valves (VICI). The configuration tested is 2222 (two columns per zone). The valve switching is attained by sofware 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) is placed between each column to avoid back mixing. The extract and raffinate are withdrawn from the column via two other rotary valves with a 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 on-line vacuum degasser (SUPELCO) degasses all the liquid being pumped into the system.

Solvent metering pumps controlled the flow rates of the feed and the 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 the raffinate streams were analyzed for each stage using a standard analytical chromatographic system. The samples collected during the middle of the switch times were analyzed. An analytical column (250 mm $\times$ 4.6 mm) packed by 5 μm CSP was used to analyze the concentration of these samples. The Perkin-Elmer (USA) chromatographic system, consisting 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.

Adsorption isotherm

In the study, the Langmuir model was assumed to fit the adsorption equilibrium relationship of fluoxetine on the column packed by the new CSP, and the following approximated extended Langmuir model was used to describe the adsorption behavior

$$q_A^* = \frac{5.94 c_A}{1 + 0.715 c_A + 0.214 c_B}$$

$$q_B^* = \frac{5.18 c_B}{1 + 0.715 c_A + 0.214 c_B} \tag{3}$$

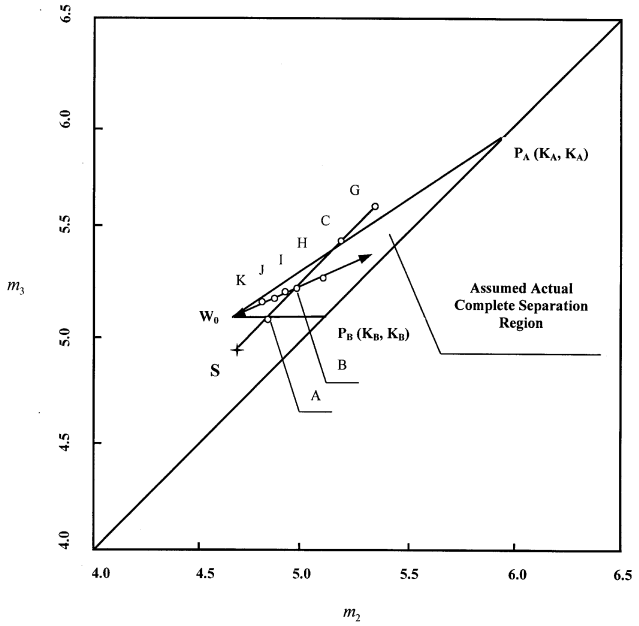

Figure 5. Establishing an optimal robust operating condition.

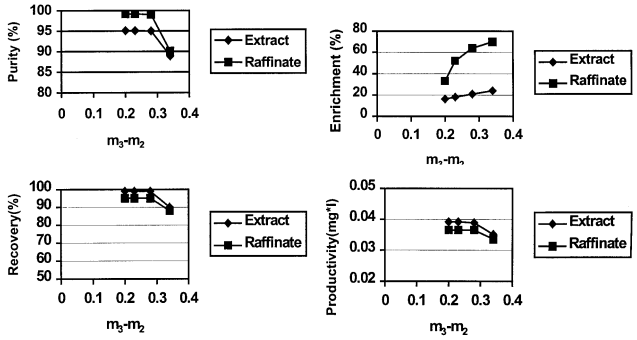

Figure 6. Effect of difference of m_2 and m_3 on performance parameters.

Results and Discussions

Now let us design the operating conditions following the process just discussed. When $c_A^F = c_B^F = 0.5$ mg/mL, the feed flow rate, Q_F, is 0.2 mL/min, and the operating conditions Q_E, Q_R, Q_D, and switch time t^* are shown in Table 2:

Several runs were carried out following the conditions shown in Table 2. The position of every operating point on the m_2-m_3 plane was shown in Figure 5. Every sample was collected after the system was stable.

Operating point S is the theoretical optimal operating condition derived from Eqs. 2a–2d. The purity of the extract and the raffinate at this experimental point is 83.4% and 99.8%, respectively. Experimental results show that the theoretical optimal operation condition is not robust or diverges from the actual complete separation region; points A and C are close to the actual complete separation region and point B is in the actual complete separation region. When P_AC and P_BA are extended to intersect at W_0, a triangle $W_0P_AP_B$ is formed. This is assumed to be the actual complete separation region. After considering the operational disturbance, it must be mentioned that A and C could be in the theoretical complete separation region.

To improve the robustness of the operation, the difference between m_3 and m_2 for point B is decreased to point H. Due to the increase in eluent flow rate, the pressure of the system is increased to an extent that the system cannot tolerate. Thus, the stability of the operation is damaged, and good separation results are not achieved. This means that, although decreasing the difference between m_3 and m_2 could improve the robustness of the operation, the operation performance parameters will be sacrificed, sometimes even the SMB system cannot be run smoothly. Unstable operation should be avoided in real applications.

Runs I, J, and K are carried out to find the possible optimal operating condition by increasing the difference between m_3 and m_2. The experimental results show that the opera-

Table 2. Operation Conditions on SMB

	Flow Rates (mL/min)				Flow-Rate Ratios				Purity (%)	
Run	Q_D	Q_E	Q_R	t^* (min)	m_1 ($m_{1,opt}$)	m_2 ($m_{2,opt}$)	m_3 ($m_{3,opt}$)	m_4 ($m_{4,opt}$)	P_E	P_R
S	9.0	1.52	0.45	5.3	6.24 (5.94)	4.72 (4.72)	4.92 (4.92)	4.47 (4.71)	83.4	99.8
A	9.0	1.36	0.36	5.3	6.24 (5.94)	4.88	5.08	4.57 (4.81)	92.5	99.0
B	9.0	1.21	0.45	5.3	6.24 (5.94)	5.04	5.24	4.65 (4.89)	95.1	99.2
C	9.0	1.04	0.62	5.3	6.24 (5.94)	5.20	5.40	4.69 (4.94)	95.2	92.2
G	9.0	0.87	0.76	5.3	6.24 (5.94)	5.37	5.57	4.74 (4.99)	95.1	87.1
H	10.0	1.40	0.53	4.5	6.24 (5.94)	5.10	5.25	4.89 (4.93)	—	—
I	7.63	1.10	0.35	6.1	6.24 (5.94)	4.98	5.21	4.80 (4.85)	95.1	99.2
J	6.22	0.95	0.3	7.4	6.24 (5.94)	4.92	5.20	4.78 (4.81)	95.0	99.0
K	5.12	0.82	0.27	9.0	6.24 (5.94)	4.85	5.19	4.73 (4.77)	83.1	90.2

tion parameters can be improved by increasing the difference between m_3 and m_2, but the robustness of the operation will be lost. At point K, the robustness of the operation cannot hinder the disturbance of the operation, so the purity of the extract and the raffinate are all decreased. The effects of the difference between m_3 and m_2 on the operation parameters are shown in Figure 6. Enrichment of the extract and the raffinate is increased when the difference between m_3 and m_2 is increased. In other words, the raffinate show the same trend. Because of the decreasing of the robustness, these three operation parameters all decreased slightly. With reference to the operation parameters of B, I, J, K, operating point J can be considered to be the possible optimal operation point.

Conclusions

In this work, a new CSP was developed to separate a chiral drug using the chromatographic technique, and a pragmatic method was developed to establish the operating conditions of the SMB system based on the theoretical triangle method. A triangle region determined from the experimental results was assumed to be an actual complete separation region. In this region, possible an optimal operation condition of the SMB was found. Good separation results can be obtained. Compared to the conventional method, in which many experiments must be run to establish operating conditions along some operating lines paralleling the diagonal of the m_2-m_3 plane, this approach requires fewer experiments to establish the possible optimal operating condition. It is shown that this method can be used to establish operating conditions and reduces the experimental efforts effectively. It can be concluded that, according to the separation results of fluoxetine on the SMB, the new CSP is efficient for enantioseparation of chiral drugs.

Notation

c = fluid-phase mass concentration
f^{eq} = adsorbent equilibrium relationship
K = adsorbent equilibrium constant
m_j = mass flow-rate ratio in section j
P_E = desorbent extract purity
P_R = desorbent raffinate purity
q^* = equilibrium solidphase concentration
t^* = switch time

Greek letters

ϵ^* = overall void fraction
τ = dimensionless time
ω = equilibrium theory parameter

Subscripts and superscripts

a = incoming fluid state
b = incoming solid state
0 = initial conditions
A = strong component of the feed
B = weak component of the feed
D = desorbent
E = extract
F = feed
j = section index
R = raffinate

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