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Simulation of separation of a racemic mixture of Bupivacaine by simulated moving bed

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Abstract

Separation of a racemic mixture of Bupivacaine by simulated moving bed chromatography was simulated using Aspen Chromatography based on literature experimental data. The simulation results showed that separation of Bupivacaine enantiomers is feasible by this method and products with a purity of about 99% could be obtained. In this study, the discretization method and mathematical solution is different from that of previous literature and results are more consistent with experimental data.Higher order orthogonal collocation in the solution scheme provides more accurate simulationresults. With the actual mathematical tools are corporate within Aspen chromatography there would be no need to external mathematical tools like gPROMS to get better results. For this study, the triangular theory was used to find the operating conditions. The operating point conditions such as streams flow rates and beds switching time were obtained. In addition, the effect of feed concentration on the triangular region and operating conditions such as switching time, recycle and desorbent flow rate were also investigated. The simulation confirms that the higher feed concentration leads tosmaller triangular region, the switching time decrease and desorbent and recycle flow rates increase.

Keywords:
Adsorption, Bupivacaine, Simulated moving bed, Simulation

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1. Introduction

Adsorption chromatography is based on separation of two-phase Countercurrent flow of an adsorbent and adsorbed component. In true countercurrent moving bed adsorption systems (TMB), solid phase bed moves in a continuous way while inlets and outlets connections are fixed. Solid movement and its recovery in the column cause technical problems, such as equipment and adsorbent erosion, and difficulties in maintaining the plug flow behavior for solid (especially along the beds of large diameter). Technically, there are limitations to the implementation of such technology [1].

To avoid this problem, Broughton and Gerald (1961) suggested a sequence of fixed bed columns, where the solid phase does not move, but by switching the inlet and outlet fluid streams to and from the columns from time to time, a relative motion between the two phases occurs. The time between switching inlets and outputs is called switching time t_s. Although in the new structure there is no solid phase movement, however there is a continuous countercurrent flow. This technology is called simulated moving bed (SMB) [1] (Fig.1).

UOP Company developed this technique in the early 1960s for the separation of hydrocarbons. In last two decades, this method was applied for a number of other separations like sugar, racemic drugs, isomers and enzymes [2].

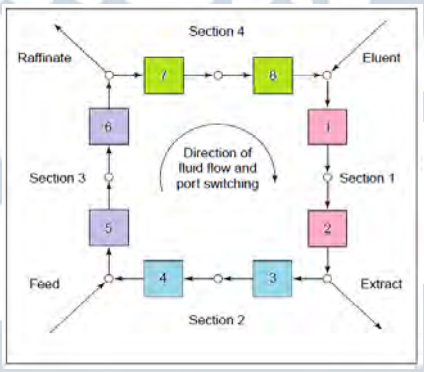
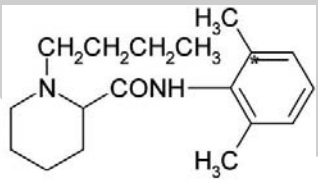


Figure 1A four-section simulated moving-bed (SMB) unit [3]

Bupivacaine (Fig.2) is a racemic anesthetic that was investigated before by Choi et al. Because of its mirror molecular structure the S-Bupivacaine has therapeutic benefits, while the R- Bupivacaine has toxic sideeffects [4].



***Chiral center**

Figure 2Chemical structure of Bupivacaine hydrochloride with chiral center shown with* [4]

Choi et al simulated the separation of this drug by SMB using Aspen chromatography and gPROMS software. They validated their simulation with experimental results[4].In this study, separation of a racemic mixture of Bupivacaine is simulated based on experimental data of Choi et al but with a different discretization method and mathematical solution in order to obtain more consistent with experimental results.

2. Mathematical Model

A mathematical model, reported in literature for each column and with sufficient advantages both in accuracy and in computation time, is the linear driving force (LDF) model. Its ability on the prediction of the behavior of a multiple columns separation process is confirmed in many previous studies. The model includes equations of accumulation, convection and axial dispersion. This model is based on the mass balance equations in the bulk liquid phase and solid phase, equations 1 and 2 respectively [5-10].

$$\frac{\partial C_i}{\partial t} + \upsilon\frac{\partial C_i}{\partial x} + \frac{(1-\varepsilon_b)}{\varepsilon_b}k_{e,i}(q_i^* - q_i) - D_{a,i}\frac{\partial^2 C_i}{\partial^2 x} = 0 \quad (1)$$

$$\frac{\partial q_i}{\partial t} = k_{e,i}(q_i^* - q_i) \quad (2)$$

The relationship between $\mathbf{q_i^*}$and$\mathbf{q_i}$is usually expressed as an equilibrium adsorption isotherm, and for example in the case of a linear isotherm it is written as:

$$q_i = H_i q_i^* \quad (3)$$

Where H_i is the Henry's constant.

Initial and boundary conditions are needed to complete the modeling of the system. Initial conditions,represents the system state at the start of switching period:

$$c_i^{(k)}(0,x) = c_i^{(k-1)}(ts,x) \quad (4)$$

$$q_i^{(k)}(0,x) = q_i^{(k-1)}(ts,x) \quad (5)$$

Where k is the number of switching.

Boundary conditionsshould be written for both ends of a column:

$$\left.\frac{\partial C_i}{\partial x}\right|_{x=0} = \frac{\upsilon}{D_{a,i}}(C_i - C_i^{in}) \quad (6)$$

$$\left.\frac{\partial C_i}{\partial x}\right|_{x=L} = 0 \quad (7)$$

$C_i^{in}$is related to mass balance in nodes that are defined as:

Desorbent node:

$$C_{i,I}^{in}Q_I = C_{i,IV}^{out}Q_{IV} + C_{i,D}Q_D \quad (8)$$

$$Q_I = Q_{IV} + Q_D \quad (8)$$

$$Q_I = Q_{IV} + Q_D \quad (9)$$

Extract node:

$$C_{i,II}^{in} = C_{i,I}^{out} = C_{i,E} \quad (10)$$

$$Q_{II} = Q_I - Q_E \quad (11)$$

Feed node:

$$C_{i,III}^{in} Q_{III} = C_{i,II}^{out} Q_{II} + C_{i,F} Q_F \quad (12)$$

$$Q_{III} = Q_{II} + Q_F \quad (13)$$

Raffinate node:

$$C_{i,IV}^{in} = C_{i,III}^{out} = C_{i,RA} \quad (14)$$

$$Q_{IV} = Q_{III} - Q_{RA} \quad (15)$$

Choi et al used Aspen Chromatography ver. 12.1-2006 and the upwinddifferential scheme (UDS) discretization method. Also as a proof of consistency, they used gPROMS with third order orthogonal collocation on finite element method with 200 grid points. They concluded that the results of simulation with gPROMS software are more consistent with experimental data than Aspen chromatography's results [4].

In this study, the numerical solution is achieved with version.7.3(2011) of the same simulator (Aspen chromatography). The discretization method is the fourth order orthogonal collocation on finite element method (OCFEM4) with 200 elements. This study is performed to obtain more accurate results with Aspen chromatography software and to show that in order to compare between simulator's results, the same discretization method should be applied in both simulators.

2.1 Triangle Diagram

To achieve complete separation of two components, the appropriate operating conditions should be selected for SMB unit. Storti et al. have described a method for determining operating conditions based on the equilibrium theory, neglecting axial dispersion and mass transfer resistance like an ideal system [11]. With this method, called

"triangle theory," both TMB and SMB process can be described with the net flow ratios, m_j (j=1-4), which is defined [12] for each zone as:

$$m_j = \frac{\dot{V}_j^{SMB} t_s - V\varepsilon}{V(1-\varepsilon)} \quad (16)$$

The triangle theory specifies a triangle region (Fig.2) in the m2-m3 coordinates for an ideal system and triangle vertex provides the optimal operating condition for ideal system [4]. The triangle becomes rectangular for systems with linear adsorption isotherm**.**

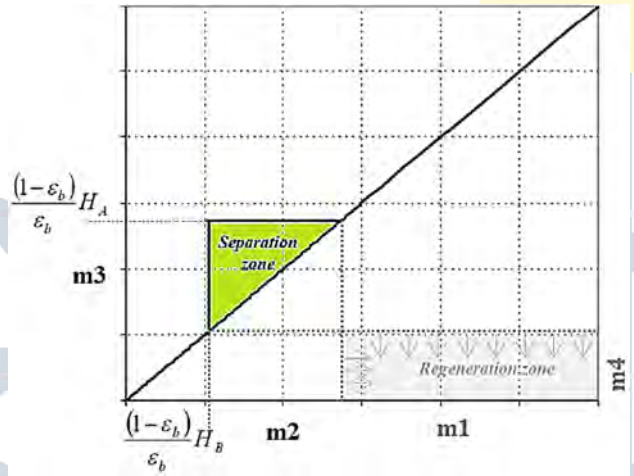


Figure 3"Triangle Theory", separation and regeneration regions for linear isotherms, where H_i represents the Henry constant for linear adsorptions isotherms (A: the more retained and B: the less retained species) [1]

3. Process specifications

As it was mentioned, Choi et al simulated the separation of a racemic mixture of Bupivacaine and validated their results with experiment.

In their experiment they used a mixture of n-hexane with calculated viscosity of about μ = 0.3034 cP as mobile phase. D_m molecular diffusion coefficient in mobile phase was calculated from Wilke-Chang equation as $1.93*10^{-5}(cm^2/s)$[4]. The mass transfer coefficient was calculated based on D_m and it was 0.308 cm/s.

The column parameters are summarized in table 1.

Table 1 SMB column parameters [4]

Parameters	Value
Number of column	8
Column length (m)	0.1
Column diameter (m)	0.01
Column volume (m^3)	7.854×10^{-6}
Bed porosity (−)	0.7

Particle diameter (m)	1×10^{-5}
Column configuration	(2-2-2-2)
Packing	Kromasil

In prediction of adsorption mechanism in a SMB, adsorption isotherm is very important.It describes the equilibrium concentration in the mobile and stationary phase [4].

Choi et al assumes the competitive Langmuir isotherm (eq. (17)). The predicted kinetic and the competitive adsorption isotherm parameters are shown in table 2:

$$q^*(i,j,z) = \frac{a(i)C(i,j,z)}{1+\sum_{k=1}^{2} b(k)C(k,j,z)} \qquad \forall z \in [0,L] \qquad (17)$$

Table 2 Estimated equilibrium and kinetic parameters in the mathematical model [4]

Parameter (1: R-form, 2: S-form)	Estimated value
a(1) (−)	6.375
a(2) (−)	8.746
b(1) (mL/mg)	0.516
b(2) (mL/mg)	0.899
k(1) (1/min)	3.033×10^{-3}
k (2) (1/min)	1.167×10^{-3}

Optimum operating condition based on triangle theory (Fig.4) and Choi et al experiment is calculated and is shown in table 3. The operating point is shown in Fig.4 with '+' near the left vertex.

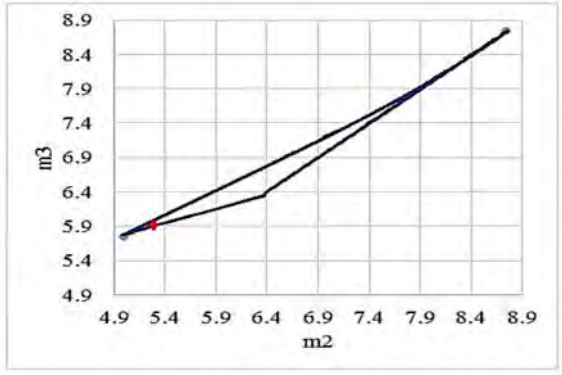


Figure 4 Triangle diagram and operating point for Feed concentration=1.5 mg/ml in this study

Table 3 Optimum operating condition [4]

Operating condition	
Feed concentration (mg/mL)	1.5
Feed flow rate (mL/min)	0.1
Eluent flow rate (mL/min)	0.86
Extract flow rate (mL/min)	0.66
Raffinate flow rate (mL/min)	0.3
Recycle flow rate (mL/min)	1
Switching time (min)	15

4. Results and Discussion

The steady state concentration profile in SMB column of this study in comparison with that of Choi et al is shown in Fig.5. As it can be seen both simulation results shows the same trend but with little difference in concentration values. In fact, the obtained concentration profile is between two concentration profiles of Choi et al simulations with gPROMS and Aspen chromatography. This little difference is because of different discretization method and mathematical solution. There is a concentration jump at column length of 40 cm, because it is the feed entrance port.

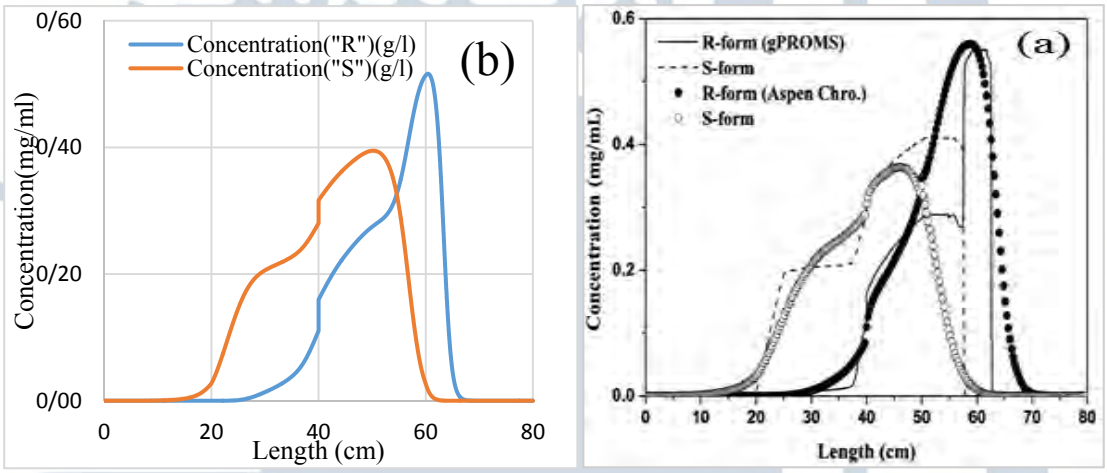


Figure 5 Comparison of steady state concentration profile. (a) Choi et al simulation [4] (b) this study simulation

The concentration profile of raffinate and extract streams versus time of this study are shown in Fig.s 6 and 7. The solid lines in these figures are average concentration of R and S-Bupivacaine in raffinate and extract streams.

The experimental concentration of the extract and raffinate were 0.0946 and 0.280 mg/ml in Choi et al experiment [4]. As it can be seen in Figs.6 and 7, the average concentration of extract and raffinate that were calculated in this study are almost in agreement with experimental data.

The R-Bupivacaine goes to raffinate stream and it is concentrated in raffinate stream. The S-Bupivacaine has more adsorption tendency and goes to extract stream and it's concentration increases in extract stream versus time.

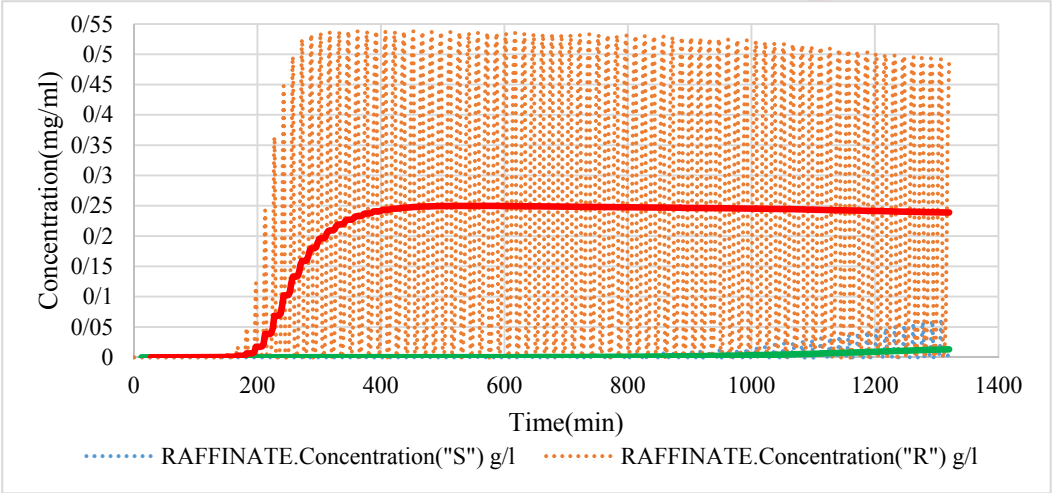


Figure 6 Concentration profile of raffinate stream in this study (S=S Bupivacaine, R= R Bupivacaine)

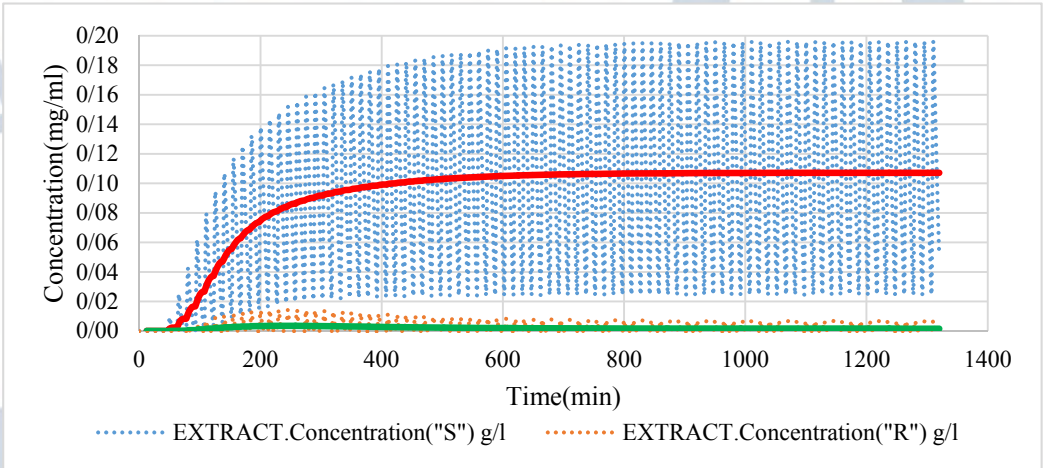


Figure 7 Concentration profile of extract stream in this study (S=S Bupivacaine, R= R Bupivacaine)

Concentration of raffinate and extract streams in the quasi steady state are shown in Figs.8 and 9. As it can be seen in these figures, concentration reaches steady state after about 1200 minutes.

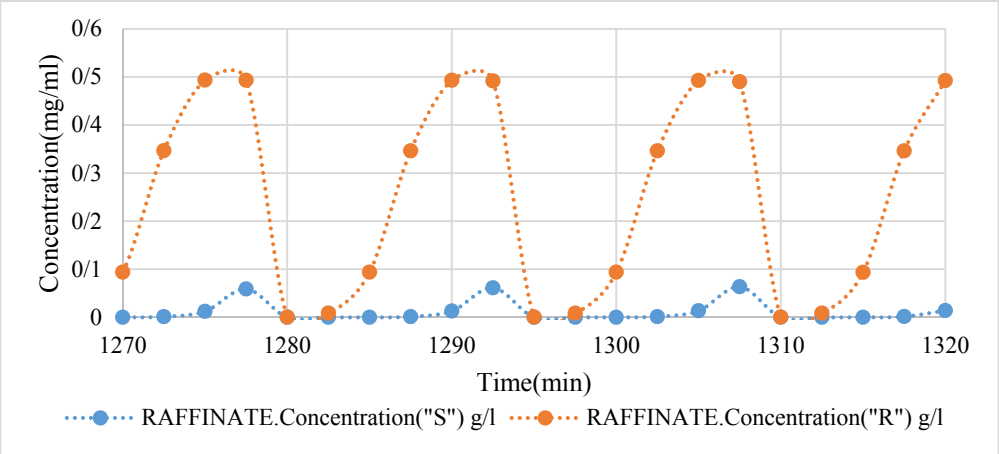


Figure 8 Concentration of raffinate stream in the quasi steady state in this study

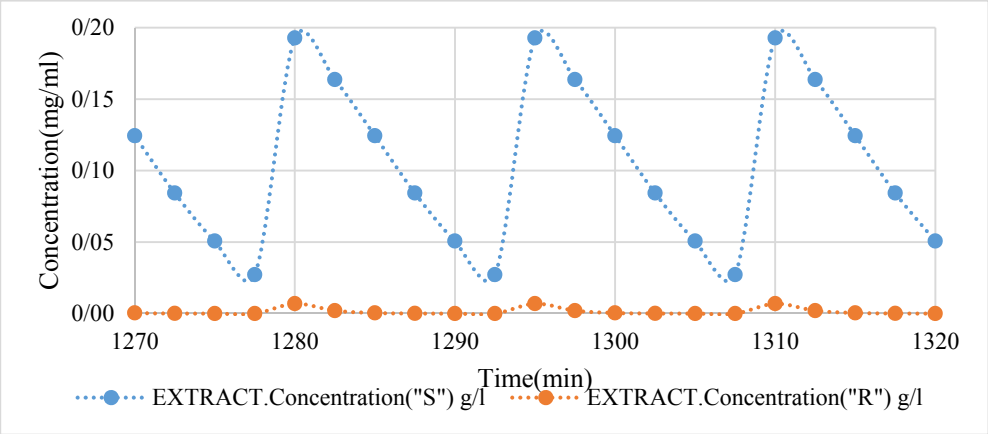


Figure 9Concentration of extract stream in the quasi steady state in this study

The purity of S-Bupivacaine in the extract and the R-Bupivacaine in raffinate in Choi et al experiment based on peak area of concentration profiles are given in table 4.Choi et al simulation results and this study results are compared with experimental data in table 4. For better visualization, the deviation from experimental data is defined as:

$$dev\% = \left|\frac{simulation\ result - experimental\ data}{experimental\ data}\right| * 100$$

Comparison of deviation from experimental data and simulation results of this study and Choi et al work is visualized in Fig.10.

Table 4 Comparison of simulation results for purity of extract and raffinate phases of this study and Choi et al article with experimental data

	Extract phase		Raffinate phase	
	R-form (%)	S-form (%)	R-form (%)	S-form (%)

Experimental data of Choi et al	1.1	98.9	98.3	1.7
Simulation of This study	**1.11**	**98.89**	**98.88**	**1.12**
Simulation of Choi et al	1.34	98.66	99.29	0.71

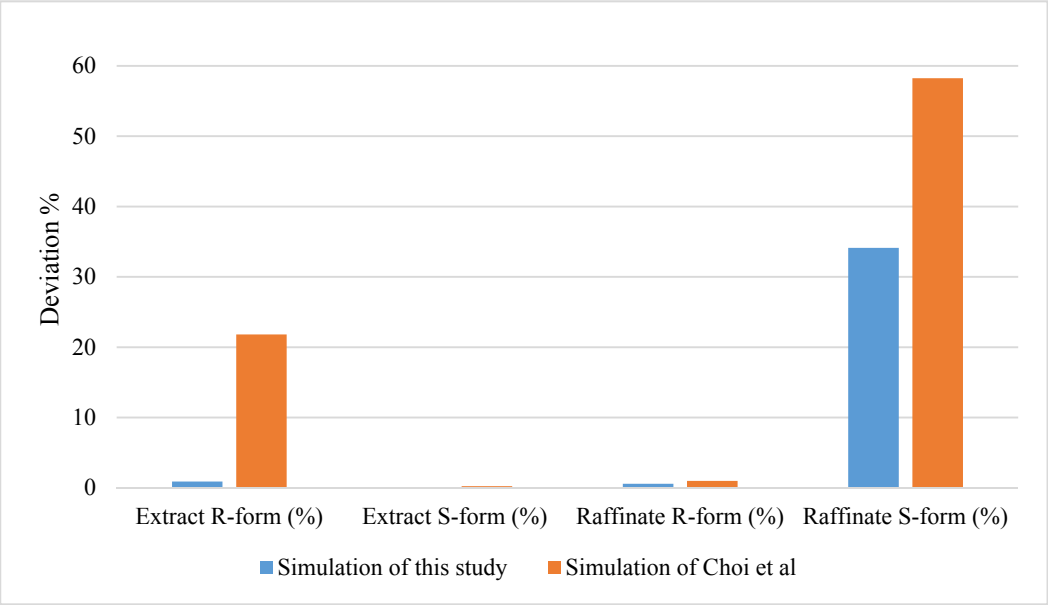


Figure 10 comparison of deviation from experimental data and simulation of this study and simulation of Choi et al

As it can be seen in table 4 and Fig.10 our simulation results for extract and raffinate purity are more consistent with experimental data than the simulation results of Choi et al.

As it was mentioned,Choi et al concluded that gPROMS results are more accurate than Aspen chromatography results but the discretization method were different in each of the simulators. In this study OCFEM4 discretization method was applied to solve the differential equations and the results are closer to experimental data.As it can be seen, with latest version of Aspen chromatography with the actual mathematical tool corporate within and higher order orthogonal collocation method, there would be no need to use external mathematical tool like gPROMS to get better performance.

Now in order to investigate the effect of feed concentration at constant feed flow rate of 0.1 ml/min on separation region and operating condition such as switching time, recycle and desorbent flow rates, the triangle diagrams are drawn in Fig.11 and the results are shown in table 5.As it can be seen in Fig.11 the higher the feed concentration, smaller the separation region.

Also according to table 5, with increasing the feed concentration the switching time decreases and desorbent and recycle flow rates increases. This means that port switching should be faster and desorbent cost increases.

Table 5 effect of feed concentration at constant feed flow rate on operating condition based on triangle vertex

Feed concentration(mg/ml)	ts(min)	Recycle Flow(ml/min)	Desorbent Flow(ml/min)
1	23.26	0.75	0.36
2	14.69	1.11	0.65
3	10.73	1.47	0.95
4	8.45	1.83	1.25
10	3.72	3.98	3.02

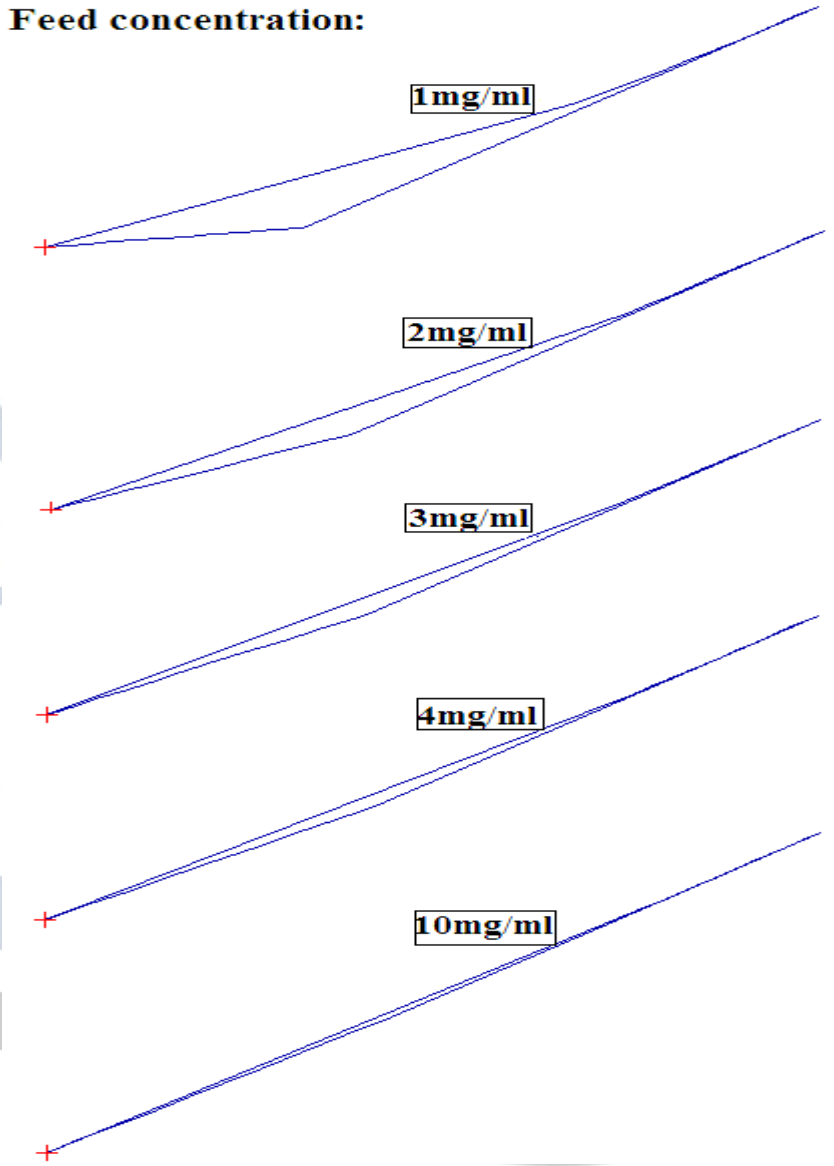


Figure 11 effect of feed concentration of separation region

5. Conclusion

In this study, separation of a racemic mixture of Bupivacaine by simulated moving bed chromatography was simulated using Aspen Chromatography software. According to simulation results, products with a purity of about 99% were obtained and this was almost consistent with experimental results of the literatures.The effect of discretization method and mathematical solution on the simulation results was investigated and the results showed that OCFEM4 discretization method leads to more accurate results compare to UDS method. In addition, the effect of feed concentration on the separation region and operating conditions such as switching time and recycle and desorbent flow rate were investigated. The simulation confirms that the higher feed concentration the smaller separation region. Also the switching time decreases and desorbent and recycle flow rates increases.

Nomenclature

a	parameter of competitive Langmuir isotherm (−)
b	parameter of competitive Langmuir isotherm (ml/ml)
C_i	Mobile phase concentration(g/L)
$D_{a,i}$	Apparent axial dispersion coefficient (cm^2/min)
D_m	Molecular diffusion coefficient (cm^2/min)
E_z	Axial dispersion coefficient (cm^2/min)
H_b	Column height (cm)
H_i	Linear adsorption coefficient(Henry constant)
$k_{e,i}$	Effective Mass transfer coefficient (min−1)
m_j	Net flow ratio
Pe	Peclet number
q_i^*	equilibrium concentration in interface between two phases (g/L)
q_i	concentration in stationary phase (g/L)
t_s	Switching time(min)
v	Liquid interstitial velocity (cm/min)
V	Column volume(m^3)
$\dot{V}_j^{SMB}$	Volumetric flow rate(m^3/sec)
ε_b	Bed porosity
i	component index, i = R or S ibuprofen
j	Zone index j=1-4
I, II, III, IV	Zone index in SMB

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