Simulation of Separation of a Racemic Mixture of Ibuprofen by Supercritical Fluid Chromatography in Simulated Moving Bed

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Abstract

Separation of a racemic mixture of ibuprofen at a low concentration level by supercritical fluid chroma-tography in a simulated moving bed (SFC-SMB) is investigated by simulation. The feasibility of ibu-profen enantiomers separation has been experimentally examined in the literature. Our simulation results show that separation of ibuprofen enantiomers is feasible by this method, and R-ibuprofen and S-ibuprofen products with purity of over 99% can be obtained, which agrees with experimental data in the literature. For initial studies, the triangular theory is used to find the operating conditions. This simulation shows that the application of the triangular diagram is valuable in cases where none of the operating conditions is available. The operating point conditions, such as streams flow rates and switching time, are obtained with this method. Also, the effect of the location of the selected operating points in the triangular diagram on operating conditions, purity, and concentration of the products are investigated. In triangle theory, the optimal operating point should be near the vertex of the triangle diagram with a safety margin, to obtain products with high purity. The simulation also confirms that selecting the operating point away from the vertex of the triangular diagram will lead to diluted products.

Keywords

Adsorption;
Ibuprofen;
Separation;
Simulated moving bed;
Process simulation.

1. Introduction

Chromatography is a physical separation method where the mixture components are separated based on their differences in the distribution between the two phases: the mobile phase (desorbent) and the stationary phase (adsorbent). The adsorption chromatography technique principle is related to the adsorption affinity of each component in the mixture to the adsorbent, which will allow each component to be separated in a different section of the chromatography column [1].

In the case of two-phase countercurrent flow of an adsorbent and adsorbed component in a column, which is called True Moving Bed (TMB), the solid phase moves in a continuous way while inlets and outlets are fixed. Solid movement and its recovery in the column cause technical problems,

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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, 2]. To avoid this problem, Broughton and Gerald (1961) suggested a sequence of fixed bed columns, where the solid phase did not move, but by switching the inlet and outlet fluid streams (in the direction of the fluid flow using a rotary valve) to and from the columns from time to time, a relative motion between the two phases occurred [1].

In fact, the new structure is a sequencing chromatographic system with a set of equal-in-length, fixed-bed cross-section columns, which are arranged in a layered configuration inside an adsorbent chamber (Fig. 1). The locations of two inlet ports (feed and desorbent) and two outlet ports (extract and raffinate) divide the new system into four zones. The more retained compound is collected as extract, while the less retained compound is taken from the system as raffinate. These four ports are set to move periodically along the direction of liquid-phase flow. The time of switching between inlets and outlets is called switching time t_s. Although there is no solid phase movement in the new structure, there is a continuous countercurrent flow. This technology is called Simulated Moving Bed (SMB) [1, 3, 4] (Figs. 1 and 2).

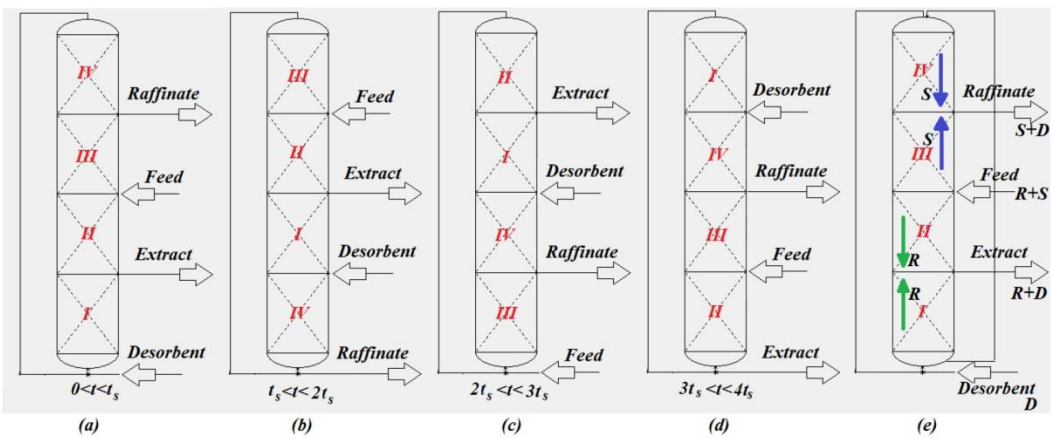

Figure 1. Schematic representation of a 4-zone SMB unit with 4 zones operating over a complete cycle, from 0 to 4ts; R: the more retained compound, S: the less retained compound, D: desorbent, Zone I: regeneration of the adsorbent (desorption of R from the solid), Zone II: desorption of S (the extract is not contaminated by the less retained compound), Zone III: adsorption of R (raffinate clean from the more adsorbed species), Zone IV: regeneration of the desorbent (adsorption of S from the fluid phase); (a) period of the first switch, (b) period of the second switch, and (c) a TMB unit

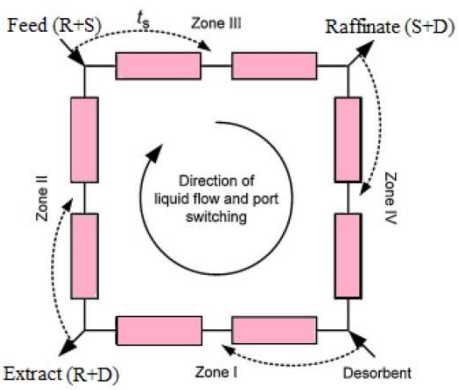

Figure 2. Schematic representation of a conventional SMB unit with 4 zones and 8 columns; R: the more retained compound (R-ibuprofen enantiomer), S: the less retained (S-ibuprofen enantiomer), D: desorbent

In fact, the UOP Company developed this technique in the early 1960s for the separation of hydrocarbons. In the last two decades, this method has been used for many other separations like sugar, racemic drugs, isomers, and enzymes. Many industrial applications of SMB technology use liquid phase chromatography [5].

However, SMB under supercritical conditions has been reported in which a supercritical fluid, usually CO_2, is used as desorbent and offers many advantages, such as reducing the consumption of desorbent, desirable physical properties, lower pressure drop, and high efficiency of the column [1, 5].

In addition to the mentioned advantages of SMB, the importance of this technology in separation of a racemic mixture of drugs is undeniable. Racemic mixture or Racemate is an equimolar mixture of left- and right-handed enantiomers of a chiral molecule. For several years prior to 1963, pregnant women consumed thalidomide drug to relieve morning nausea. The drug was made as a racemic mixture of (R)-thalidomide and (S)-thalidomide enantiomers. In 1963, it was discovered that the drug caused many congenital birth defects in newborn children of mothers who had used the drug. Later evidence showed that although the right-handed thalidomide enantiomer had a healing effect on morning sickness, the left-handed enantiomer molecule that was present in medicine could cause birth defects [6].

The lack of knowledge about differences in the chirality can be very important and sometimes disastrous. Thalidomide tragedy proves the importance of enantiomer separation of racemic mixtures of drugs. In this paper, the feasibility of separation of ibuprofen racemate (mixture of two equal enantiomers of ibuprofen) is studied to get 99% purity. To find optimal operating conditions for, e.g., stream flow rates and switching time, triangle theory is used and the SMB column is simulated in Aspen Chromatography. We will also study the effect of a shift in operating point in the triangular diagram on operating conditions and on the purity and concentration of extract and raffinate.

2. Mathematical Model

A mathematical model reported in literature for each column with sufficient advantages, both in accuracy and in computation time, is the linear driving force (LDF) model. Its ability in the prediction of the behavior of a separation process with multiple columns has been confirmed in many previous studies [7-12]. 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 the solid phase, i.e., Eqs. 1 and 2, respectively [7]:

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

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

The relationship between $\boldsymbol{q_i^*}$ and $\boldsymbol{q_i}$ is usually expressed as an equilibrium adsorption isotherm [7]:

$$q_i^* = g_i(C_R, C_S) \quad (3)$$

Initial conditions show the system state at the start of the switching period:

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

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

where k is the number of switching.

Boundary conditions should be written for both ends of a column:

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

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

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

Desorbent node:

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

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

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:

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

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

In this paper, the numerical solution is achieved with a commercial simulator (Aspen Chromatography V 7.3).

The model can be configured to use either the (TMB) or the (SMB) approach. When using the TMB approach, steady-state run mode can be adopted. The steady-state run is useful for rapid evaluation of the internal profiles, whereas the dynamic run mode can be used for transient stud-

ies with SMB approach, which is slower but more rigorous [1, 2].

Triangle diagram

To achieve complete separation of two components, the appropriate operating conditions should be selected for the SMB unit. Storti et al. [13] described a method in order to determine the operating conditions based on the equilibrium theory, which neglected axial dispersion and mass transfer resistance as in an ideal system [13]. With this method, called "triangle theory," both TMB and SMB processes can be described with the net flow ratios, m_j (j=1-4), which are defined for each zone as [14]:

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

The triangle theory specifies a triangle region (Fig. 3) in the m_2-m_3 coordinates for an ideal system. Triangle vertex provides the optimal operating condition for the ideal system [15]. For a system with linear adsorption isotherm, the triangle becomes rectangular [1].

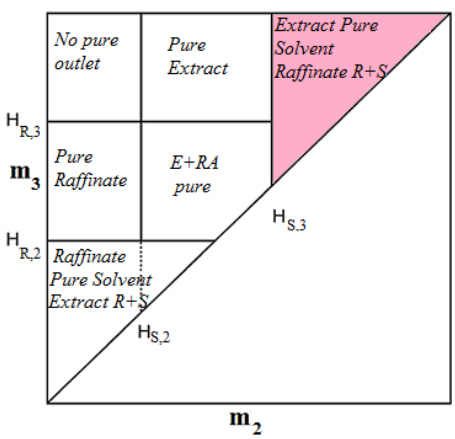

Figure 3. Regions of the (m_2, m_3) plane with different separation regimes in terms of purity of the outlet streams for a system described by the linear adsorption isotherm, where H_i represents the Henry constant for linear adsorptions isotherms (R: the more retained and S: the less retained species)

3. Separation of a Racemic Mixture of Ibuprofen by SFC-SMB

Continuous separation of a racemic mixture of ibuprofen [50% R (-) ibuprofen and 50% S (+) ibuprofen] by supercritical fluid chromatography SMB was developed by Peper et al. [5]. Their experiments were performed at low concentrations with an initial set of operating parameters obtained from the "triangle theory". They selected this material to study the feasibility of separation of a racemic mixture of ibuprofen and reached 99% purity.

When Peper et al. [5] published their paper in 2002, few empirical results [16, 17, 18] of SMB separation using supercritical carbon dioxide as the mobile phase had been reported.

The SMB chromatography using supercritical fluid (SFC) would lead to the invention of a device with special features. In addition to the aforementioned benefits for SMB, by using supercritical fluid, we can tune the elution strength of the desorbent with its density for optimizing the separation performance [5, 19].

Ibuprofen is a non-steroidal medicine with anti-inflammatory, anti-fever, and pain agents belonging to the profen pharmaceutical group [20].

Ibuprofen (2-(4-isobutylphenyl)) propionic acid, $C_{13}H_{18}O_2$ (Fig. 4), exists as S (+) and R (−) enantiomers because it has a chiral center [20, 21].

Ibuprofen is mainly used as an equimolar mixture of S (+) and R (-), even though S (+) enantiomer is about 100 times more active than the R (-) one. Therefore, much lower dose will be prescribed when active S (+) ibuprofen is used [20].

Johannsen [22] published the development of a method for SFC-SMB separation of the ibuprofen enantiomers in analytical scale. Among stationary phases tested for the separation of ibuprofen, Kromasil CHI-TBB was the best [5, 22]

Performance of the process in terms of productivity can be improved with a simulation program [5]. The process is schematically shown in Fig. 5.

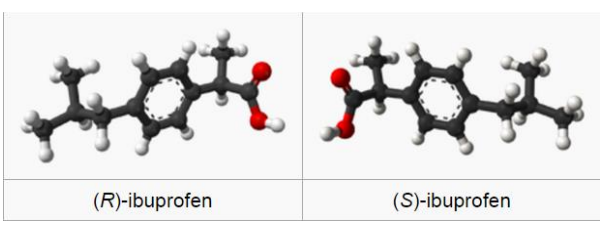

Figure 4. Ibuprofen enantiomers [21]

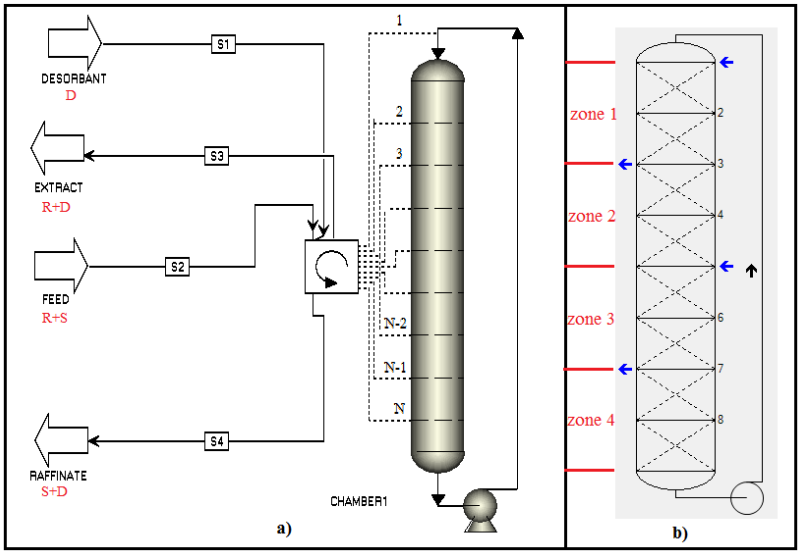

Figure 5. (a) Scheme of the SMB process; R: the more retained compound (R-ibuprofen enantiomer), S: the less retained (S-ibuprofen enantiomer), D: desorbent; (b) 4 equally zoned SMBs, each consisting of 2 fixed-bed columns of uniform cross-section and length packed with solid adsorbent material arranged inside an adsorbent chamber

SFC-SMB experiment of Peper et al. [5] was performed at low concentration feed. In this case, the adsorption equilibrium can be described by a linear adsorption isotherm (Table 1).

Pressure dependence of linear adsorption isotherm parameters of R-ibuprofen and S-ibuprofen, which is very low, is shown in Fig. 6; however, it should be noted that these values are obtained for a lower estimated concentration [5]. Therefore, in our study, we will run the simulation just at 15.6 MPa pressure, for which the experimental results of Peper et al. [5] for the SMB are reported, to validate the present simulation results.

Table 1. Linear adsorption parameters [5]

Pressure (MPa)	14.3	15.6	17.9	19.6
Density of CO2 mobile phase (kg/m3)	769	789	818	837
Linear adsorption parameter R (-) isomer	10.06	8.86	7.83	7.8
Linear adsorption parameter S (+) isomer	8.21	7.26	6.37	6.1

3.1. Specifications of SFC-SMB

In the experiment of Peper et al. [5], the SFC-SMB unit includes 8 custom columns (2 columns per zone with internal diameter of 30mm) and SMB columns packed with Kromasil CHI-TBB, 10 micro meters, which has been designed for pressures up to 40MPa and temperatures up to 200°C [5]. They determined the linear adsorption isotherms at 40°C and at the pressure of 15.6MPa (Table 1) and from the results of the mixture chromatogram, the Peclet number was estimated as 10000 at 15.6MPa**.** Column porosity measured in the analytical separation was obtained as ε= 0.703.

The first set of Peper's experiments was carried out at a low concentration level in order to prove the feasibility of high-purity separation of ibuprofen racemate in an SFC-SMB using the triangle method. Linear adsorption parameters of binary mixture at 4 different pressures are shown in Table 1. With increase in density, the linear adsorption coefficients decrease a little (Fig. 6). This agrees with the assumption that increasing the density increases the elution strength of the supercritical mobile phase.

The column specification used in the present simulation was fixed and shown in Table 2.

3.2. Simulation based on the triangle theory

In Peper et al. [5], pressure experiment was selected so as to maintain carbon dioxide at the supercritical condition. As it was mentioned, iso-

therm parameters are presented in 4 different pressures (Table 1), but the axial dispersion coefficient and the mass transfer coefficient of ibuprofen enantiomers as well as column operating conditions, e.g., streams, flow rates of zones, and switching time, are not reported. The feed is reported equal to 20mg/min, which represents neither the feed concentration nor the feed flow rate. To simulate the SMB column in Aspen chromatography, the feed volumetric flow rate (mL/min) and feed concentration (mg/mL) are required to be known. The purpose of this study is to demonstrate the effectiveness of using the triangular theory and application of the Aspen chromatography to obtain an initial set of operating conditions for effective separation with high purity.

Table 2. Column specifications in the present simulation

Temperature (T)	40°C
Column configuration	two columns in each zone
Length (L)	96mm
Column internal diameter (ID)	30mm

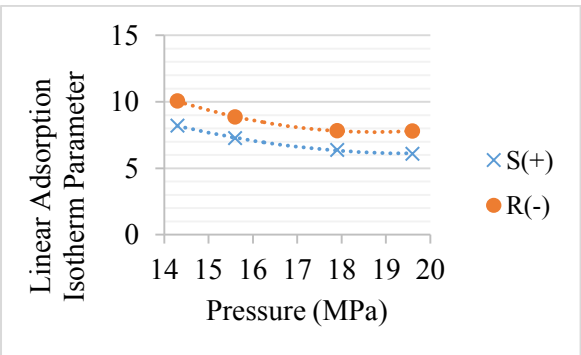

Figure 6. Pressure dependence of linear adsorption isotherm parameters of R-ibuprofen and S-ibuprofen

Assumptions

1. To simulate the SFC-SMB, pressure is selected as 15.6MPa. In addition, the supercritical condition of CO_2 at 40°C with the selected pressure is ensured using Aspen Plus (for CO_2, according to Mazzotti et al. [19]: T_c = 31°C and P_c = 7.3MPa). CO2 mobile phase density at a pressure of 15.6MPa may also be obtained from Table 1.

2. The feed volumetric flow rate is assumed to be 1mL/min with the concentration of 20mg/mL that is equal to the mass flow rate of 20mg/min, reported as a low concentration in the experiment of Peper et al. [5].

3. For the mass balance equation (Eq. 1), convection and axial dispersion are considered; but, since the axial dispersion coefficient of ibuprofen enantiomers is not available, axial dispersion coefficient is calculated based on the Peclet number (Eq. 17), reported to be 10,000 [5].

$$E_z = \frac{v_l H_b}{Pe\ \varepsilon_i} \quad (17)$$

4. As the ibuprofen enantiomers have a very low concentration in the feed, mass transfer resistances can be neglected [5].

5. To solve the model equations, an orthogonal collocation on the finite elements method (OCFEM) is employed in a Fortran subroutine and linked to Aspen Chromatography.

3.3. Results and Discussion

Based on assumptions and column specifications, as well as linear isotherm parameters, the data in Table 3 is used to draw the triangle diagram and select the operating point. As R-ibuprofen is the more retained compound, it will undergo extraction and S-ibuprofen, which is the less retained one, will undergo raffination. Therefore, the feed, which is a racemic mixture of two enantiomers, will be separated in two almost pure streams of R and S-ibuprofen.

Table 3. Inputs to calculate the separation region in the triangular diagram

Most adsorbed component	R-ibuprofen
Least adsorbed component	S-ibuprofen
R-ibuprofen concentration in feed (g/L)	10
S-ibuprofen concentration in feed (g/L)	10
Length of packed section (cm)	9.6
Internal diameter of packed section (cm)	3
External voidage (m3void/m3 bed)	0.703
Isotherm type	Linear
Henry constant for S	7.26
Henry constant for R	8.86

Although by selecting the operating point closer to the vertex of the triangular diagram, the separation performance is improved in terms of sol-

vent consumption and productivity; but as we get closer to the triangle borders, the risk of exiting complete separation region increases. Because of sensibility, some minor disturbances (like flow rate, feed composition, non-idealities due to either mass transfer resistances or axial dispersion, and uncertainties originating in the estimated isotherm parameters) could push away the operating point from the entire separation region of the triangle diagram [5].

Therefore, to decide on the operating point close to the triangle vertex, a safety margin toward the hypotenuse is considered (Fig. 7). The width of this margin has different values in the literature; for example, van Duc Long et al. [23] considered the safety margin of 15.88% toward the diagonal line. The arbitrarily selected operating point, its location in the m_2-m_3 plane, and the safety margin are shown in Fig. 7.

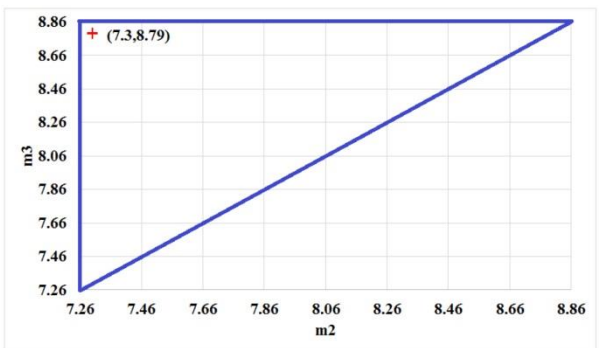

Figure 7. Triangular separation region and operating point of SFC-SMB separation of ibuprofen racemate

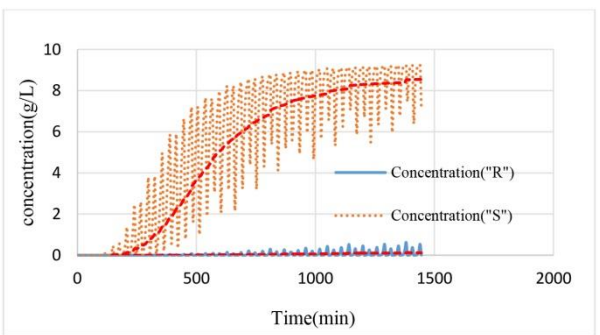

Figure 8. Raffinate concentration profile

When operating around this point, purity of over 99% for R-ibuprofen in extract and S-ibuprofen in raffinate can be achieved, which agrees with the experimental results of Peper et al. [5]. In addition, all information about the raffinate, extract, desorbent, and recycling stream flow rates and switching time can be obtained (Table 4).

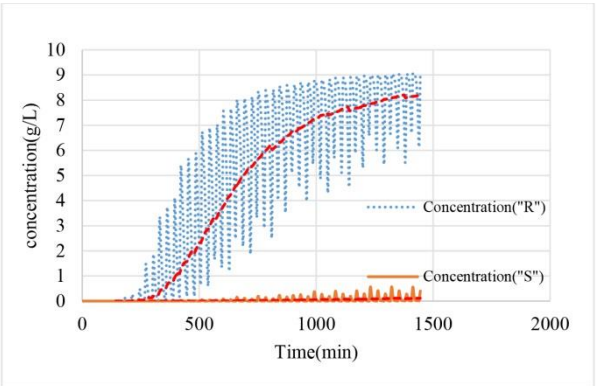

Figure 9. Extract concentration profile

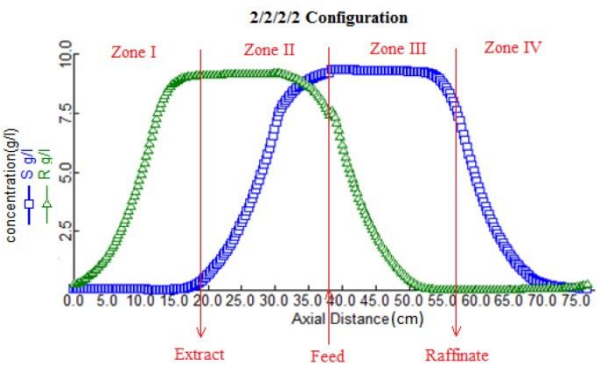

Figure 10. Steady-state concentration profile along the SMB length (with 2 identical columns per zone), (run by SMB approach); R and S represent R and S-Ibuprofen, respectively

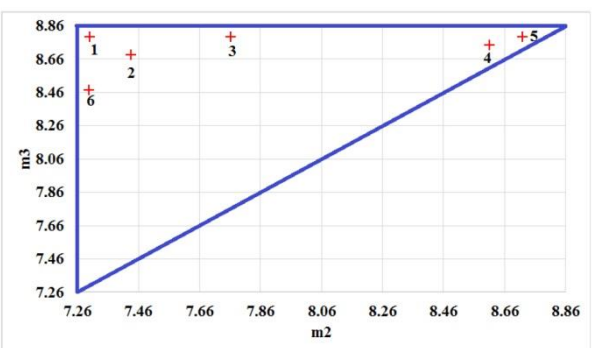

Figure 11. Six different operating points in the triangular diagram

Raffinate and extract concentration profiles versus time are shown in Fig. 8 and Fig. 9, respectively. As it can be seen, the concentration profiles reach steady state after about 1500 minutes. The raffinate stream in Fig. 8 is enriched with S-ibuprofen (less retained compound), while the concentration of R ibuprofen (more retained compound) is very low in it. Also, according to Fig. 9, the purity of R-ibuprofen in the extract stream is high with a little S-ibuprofen; thus, the purity of products is over 99%.

Table 4. Operating conditions calculated by the triangular diagram

Feed flow rate (mL/min)	1
Desorbent flow rate (mL/min)	1.07
Extract flow rate (mL/min)	1.04
Raffinate flow rate (mL/min)	1.03
Recycle flow rate (mL/min)	6.45
Switching time (min)	30.0

The steady-state concentration profile along the SMB length is shown in Fig. 10. According to the position of streams, two separate peaks can be found. In fact, in the left side of the extract stream and the right side of the raffinate stream, there is not any merging between green and blue curves and we can get almost pure R-ibuprofen and S-ibuprofen from extract and raffinate, respectively; however, in the feed stream position, two curves overlap, because the feed is an equimolar mixture of two enantiomers (racemate).

The packing pressure drop in each of the 8 packed columns is calculated according to Karman-Kozeny equation for steady state (Table 5). The operating pressure is 15.6 MPa. As mentioned, the effect of pressure on the adsorption isotherm parameters is negligible and the pressure drops, compared with the operating pressure, are insignificant. Thus, adsorption isotherm parameters are almost constant along the column.

Table 5. Pressure drop in each of the 8 columns

Column number	Pressure drop, bar
1	0.019702
2	0.019702
3	0.016969
4	0.016969
5	0.019584
6	0.019584
7	0.016893
8	0.016893

In order to evaluate the effect of the operating point location on purity and operating condition, 6 different arbitrary operating points are selected in the diagram. Steady predictions of the program for TMB and SMB are very close to each other [24].

Therefore, in this study, TMB approach is used for quickly solving the model equations and investigating the effect of the operating point location in the triangular diagram [1, 24].

Table 6. Simulation results for the operating conditions and purities of points 1-5

Point	EXTRACT X("R")%	RAFFINATE X("S")%	ts (min)	Raffinate flow (mL/min)	Extract flow (mL/min)	Recycle flow (mL/min)	Desorbent flow (mL/min)
1	99.9561	99.9918	30.04	1.029	1.045	6.459	1.073
2	99.9676	99.9721	25.23	1.134	1.138	7.690	1.278
3	99.9774	99.9597	20.78	1.487	1.064	9.335	1.551
4	99.9949	99.8228	2.68	11.126	1.872	72.193	11.99
5	99.9971	99.6859	1.518	20.348	1.885	127.76	21.23

The 6 different operating points chosen for this purpose are shown in the triangular diagram in Fig. 11.

The obtained results for the operating conditions and purities for points 1-5 are shown in Table 6. From the results in this table, it can be deduced that as the operating point moves to the top right of the triangle, the purity of the extract and desorbent consumption increases. The results are in accordance with the triangle theory and, as well, with the region within the triangular diagram of Fig. 3, where pure extract, raffinate, and desorbent exist simultaneously. In fact, additional desorbent will be consumed by the raffinate and a substantial decrease in the raffinate concentra-

tion occurs. Concentration profile along the SMB length for the fifth point is shown in Fig. 12, which shows the raffinate dilution. The switching time decreases by shifting the operating point to the right of the triangle; however, the recycling flow rate increases substantially.

In contrast, as the operating point moves to the lower left in the triangular region, raffinate concentration (S-ibuprofen) increases and extract concentration (R-ibuprofen) decreases. For example, for the sixth point, the concentration profile shows an increase in raffinate concentration (Fig. 13).

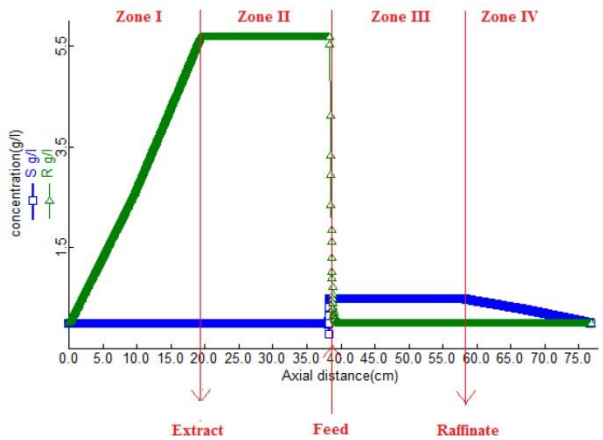

Figure 12. Steady-state concentration profile along the SMB length (run by TMB approach) for the 5th-point raffinate dilution, where concentration of S—ibuprofen decreases in the raffinate

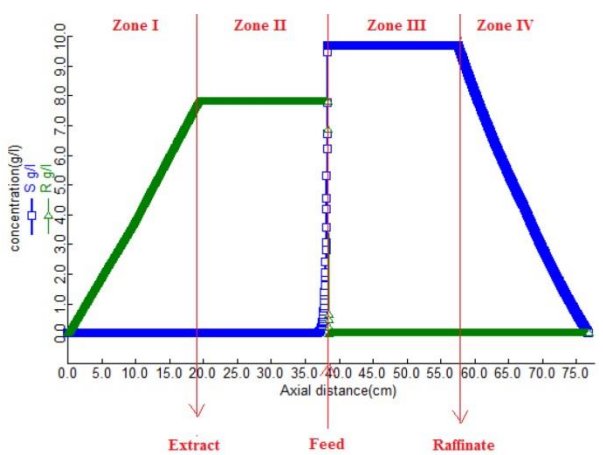

Figure 13. Impact of selected operating point shift toward the lower left side of the triangular diagram (the 6th point) on the steady-state concentration profile along the SMB length (run by TMB approach), the concentration of S—ibuprofen increases in the raffinate

4. Conclusion

Separation of ibuprofen enantiomers by SFC-SMB method with linear isotherm and low concentration feed was simulated. The results showed that the separation of ibuprofen enantiomers to achieve high product purity of above 99% was feasible. The results were consistent with the experimental data in the literature. Initial studies were carried out based on the triangular theory to find out the operating conditions. The simulation showed that a triangular diagram was helpful to determine the unknown operating condition of an SFC-SMB. The effect of the operating point shift in the triangular diagram separation region on operating conditions, purity, and concentration of products was investigated and the profiles were presented. This study showed that, by selecting an appropriate operating point away from the vertex of the triangular diagram, diluted products would be obtained and more desorbent would be consumed.

Nomenclature

C_i	Mobile phase concentration (g/L)
$D_{a,i}$	Apparent axial dispersion 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)
Q	Volumetric flow rate (mL/min)
t_s	Switching time (min)
υ	Liquid interstitial velocity (cm/min)
υ_l	Liquid velocity (cm/min)
V	Column volume (m3)
$\dot{V}_j^{SMB}$	Volumetric flow rate (m^3/sec)
x	Axial distance (cm)
X	Purity%
ε_b	Bed porosity

Superscripts

(k)	the kth switching period

Subscripts

D	Desorbent
E	Extract
F	Feed
I	Component index, i = R or S ibuprofen
J	Zone index j=1-4
I,II,III,IV	Zone index in SMB
R	R-Ibuprofen
RA	Raffinate
S	S-Ibuprofen

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