Optimal performance of single-column chromatography and simulated moving bed processes for the separation of optical isomers

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Abstract. Chromatography has been established as the method of choice for the separation and purification of optically pure drugs which has a market size of about 250 billion USD. Single column chromatography (SCC) is commonly used in the development and testing phase of drug development while multi-column Simulated Moving Bed (SMB) chromatography is more suitable for large scale production due to its continuous nature. In this study, optimal performance of SCC and SMB processes for the separation of optical isomers under linear and overloaded separation conditions has been investigated. The performance indicators, namely productivity and desorbent requirement have been compared under geometric similarity for the separation of a mixture of guaifenesin, and Tröger’s base enantiomers. SCC process has been analyzed under equilibrium assumption i.e., assuming infinite column efficiency, and zero dispersion, and its optimal performance parameters are compared with the optimal prediction of an SMB process by triangle theory. Simulation results obtained using actual experimental data indicate that SCC may compete with SMB in terms of productivity depending on the molecules to be separated. Besides, insights into the process performances in terms of degree of freedom and relationship between the optimal operating point and solubility limit of the optical isomers have been ascertained. This investigation enables appropriate selection of single or multi-column chromatographic processes based on column packing properties and isotherm parameters.

1. Introduction
Continuous chromatographic separation is the method of choice for large-scale production due to its higher productivity and robustness [1; 2]. Simulated moving bed (SMB), introduced in 1960 [3], has become the bench mark in this regard. Backed by the celebrated triangle theory [4], it is possible to identify the region of complete separation and find a relation between decision variables and performance indicators in a relatively straightforward manner. On the other hand, single-column chromatography (SCC) although does not appear to be competitive against SMB, it is still attractive due to higher flexibility, lower capital investment and quick analysis [5]. In this paper, under equilibrium theory assumptions, we present mathematical analysis of SMB and SCC under linear and nonlinear ranges of operation. For Langmuir isotherm, new analytical results are utilized for obtaining the triangular region of the SMB process [4] and elution profiles of the SCC process [6]. Thanks to equilibrium theory, it is possible to highlight optimal operating points and theoretical degrees of freedom for both processes without elaborate numerical methods and multi-objective optimization algorithms.
2. Problem statement

The schematic diagrams of the SMB and SCC processes are given in Figs. 1(a) and 1(b), respectively. It is assumed that:

- The column cross-sectional area, overall void fraction, and maximum allowable pressure drop are the same for both units.
- Complete separation and complete recovery are sought in both SCC and SMB units.
- Only physical constraints arising from maximum allowable pressure drop are considered.

Complete recovery necessitates that we collect only two fractions as products in SCC, and complete separation suggests that the purity values must be 100% in both extract and raffinate streams. The degrees of freedom are equal to the number of independent decision variables. We will derive the performance indicators and other important parameters in terms of the independent variables.

Under the assumption of complete separation and recovery, performance indicators productivity and desorbent requirement can be defined as:

\[
Pr \equiv \frac{\text{Mass of feed processed per unit time}}{\text{Mass of stationary phase}} \quad Dr \equiv \frac{\text{Overall desorbent flow rate}}{\text{Mass of feed processed per unit time}} \quad (1)
\]

The pressure drop in the column is calculated using Darcy’s law [5]:

\[
\Delta P = \frac{\phi u L \mu}{d_p^2} = \alpha u L \quad (2)
\]

![Schematic Diagrams](image)

Figure 1. 1(a). An SMB process with four sections and four identical columns (one column per section); 1(b). A single-column chromatographic process for a binary separation.

3. Simulated moving bed

3.1. Linear isotherm

For SMB, the productivity and the dimensionless flow rates are defined as [2]:

\[
Pr = \frac{c_0^F Q^F}{(1-\varepsilon) \rho_s V_T} \quad m_j = \frac{Q^i t^s - \varepsilon V}{(1-\varepsilon) V} \quad (3)
\]
$Q^F$ is proportional to $(m_2 - m_3)$. For a linear isotherm maximum productivity and minimum desorbent consumption occur when $m_1 = H_2$, $m_2 = H_1$, $m_3 = H_2$, $m_4 = H_1$. Therefore,

$$Pr = \frac{c_T^F (m_3 - m_2)}{4 \rho_s t^*} = \frac{c_T^F (H_2 - H_1)}{4 \rho_s t^*} \tag{4}$$

Sum of all the flow rates in all sections of the SMB unit at the optimal operating point is obtained as:

$$\Sigma Q^j = \frac{4 \varepsilon V}{t^*} \left( 1 + \frac{1 - \varepsilon}{\varepsilon} \frac{(H_2 + H_1)}{2} \right) \tag{5}$$

From Eq. 5, we can derive $t^*$. Maximum value of $Q^j$ is limited by the maximum allowable pressure drop that the stationary phase can withstand.

$$\Delta P_{max} = \Sigma \Delta P_j = \alpha \frac{\Sigma Q^j L}{A} \tag{6}$$

Cycle time can be obtained in terms of $t^*$ as:

$$t_{cy} = 4t^* \frac{\alpha L^2}{\Delta P_{max}} \left( \varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right) \tag{7}$$

Substitution of $t^*$ to Eq 3 gives $Pr$ as:

$$Pr = \frac{c_T^F \Delta P_{max}}{\rho_s \alpha L^2} \left( \frac{(H_2 - H_1)}{\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2}} \right) \tag{8}$$

Desorbent requirement at the optimal operating point for a linear isotherm is found as:

$$Dr = \frac{Q^F + Q^D}{c_T^F Q^F} = \frac{1}{c_T^F} \left( 1 + \frac{m_1 - m_4}{m_3 - m_2} \right) = \frac{1}{c_T^F} \left( 1 + \frac{H_2 - H_1}{H_2 - H_1} \right) = \frac{2}{c_T^F} \tag{9}$$

3.2. Langmuir isotherm

The values of dimensionless flow rates at the optimal operating point for Langmuir isotherm are given as [6]:

$$m_1 = H_2; \quad m_2 = \frac{\omega^F H_1}{H_2}; \quad m_3 = \frac{\omega^F (H_1 - \omega^F) + \omega^F (H_2 - H_1)}{H_1 (H_2 - \omega^F)} \tag{10}$$

$$m_4 = \frac{1}{2} \left\{ m_3 + H_1 + K_1 c_T^F (m_3 - m_2) - \sqrt{[m_3 + H_1 + K_1 c_T^F (m_3 - m_2)]^2 - 4 m_3 H_1} \right\} \tag{11}$$

Substitution of these values and taking same steps as in the case of linear isotherm provides expressions for $Q^F$, $t_{cy}$, $Pr$ and $Dr$ as:

$$Q^F = A \frac{\Delta P_{max}}{\alpha L} \left( \frac{1 - \varepsilon}{\varepsilon + (1 - \varepsilon) \frac{\sum m_j}{4}} \right) \tag{12}$$

$$t_{cy} = \frac{\alpha L^2}{\Delta P_{max}} \left( \varepsilon + (1 - \varepsilon) \frac{\Sigma m_j}{4} \right)$$

$$Pr = \frac{c_T^F \Delta P_{max}}{\rho_s \alpha L^2} \left( \frac{\omega^F \omega^F (H_2 - H_1)^2}{H_1 H_2 H_2 - \omega^F} \right) \tag{13}$$

$$Dr = \frac{1 + \frac{H_1 H_2 (H_2 - m_4)}{\omega^F \omega^F (H_2 - m_4)^2}}{c_T^F}$$
4. Single-column chromatography

4.1. Linear isotherm

We adopt similar methodology as SMB to obtain equivalent expressions for SCC. As shown in Fig. 2(a), maximum productivity at complete separation and recovery is achieved at touching-band condition, where there is no overlapping or gap between eluted peaks. In such conditions, we have 

\[ t_{cy} = 2t_p = \frac{2V_{inj}}{Q^D} \]

Assuming complete separation and complete recovery, for single-column chromatography and using Darcy’s law for \( Q^D \), the productivity is:

\[ P_R = \frac{c_T^F V_{inj}}{(1-\varepsilon)\rho_s V_T t_{cy}} = \frac{c_T^F Q^D}{2(1-\varepsilon)\rho_s V_T} = \frac{c_T^F \Delta P_{max}}{\alpha L^2} \frac{1}{2(1-\varepsilon)} \]  \hspace{1cm} (14)

Under the linear condition, the retention time of component \( i \) is defined as

\[ t_{R,i} = \frac{\varepsilon V_T}{Q^D} \left( 1 + \frac{(1-\varepsilon)}{\varepsilon} H_i \right) \]  \hspace{1cm} (15)

Under the condition of complete separation and complete recovery, the value of cycle time must be equal to twice the difference between retention time values of components 2 and 1. Substituting \( Q^D \) as a function of maximum allowable pressure drop:

\[ t_{cy} = 2(t_{R,2} - t_{R,1}) = \frac{2(1-\varepsilon)V_T}{Q^D}(H_2 - H_1) = \frac{\alpha L^2}{\Delta P_{max}} [2(1-\varepsilon)(H_2 - H_1)] \]  \hspace{1cm} (16)

Given that \( t_p = \frac{V_{inj}}{Q^D} \), injection volume can also be represented by:

\[ \frac{V_{inj}}{V_T} = (1-\varepsilon)(H_2 - H_1) \]

To compare with SMB, an average feed flow rate can be defined for single-column chromatography as \( Q^F = \frac{V_{inj}}{t_{cy}} \). Substituting \( t_{cy} \) and \( V_{inj} \), we obtain:

\[ Q^F = \frac{A}{\alpha L} \frac{\Delta P_{max}}{2} \frac{1}{2} \]  \hspace{1cm} (17)

Similarly, like the case of SMB, desorbent requirement is obtained as:

\[ D_r = \frac{Q^D t_{cy} + V_{inj}}{V_{inj} c_T^F} = \frac{Q^D V_{inj}}{V_{inj} c_T^F} + \frac{V_{inj}}{c_T^F} = \frac{3}{c_T^F} \]  \hspace{1cm} (18)
4.2. Langmuir isotherm

Similar approach can be taken to obtain explicit values for productivity and desorbed requirement of SCC under Langmuir isotherm. Maximum productivity at complete separation and recovery must be sought at touching-band condition. In such a condition, we have incipient baseline separation between peaks, which imposes an additional constraint on the problem. Here we need explicit relations for the retention time values of two components and a criterion on incipient baseline separation. A typical chromatogram is shown in Fig. 2(b). The relations for productivity, desorbed requirement, feed flow rate, and cycle time for SCC and SMB under linear and Langmuir isotherms are summarized in Tables 1 and 2, respectively. Note that a detail derivation of $P_r, Dr, Q^F$ and $t_{cy}$ for SCC with Langmuir isotherm is beyond the scope of this paper.

### Table 1. Summary of important equations obtained for SCC and SMB subject to linear isotherm.

| Parameter | SCC | SMB |
|-----------|-----|-----|
| $P_r$     | $\frac{c_F^p}{\rho_s} \frac{\Delta P_{\text{max}}}{\alpha L^2 \frac{1}{2(1-\varepsilon)}}$ | $\frac{c_F^p}{\rho_s} \frac{\Delta P_{\text{max}}}{\alpha L^2 \left(\frac{(H_2-H_1)}{(\varepsilon+(1-\varepsilon))(H_2+H_1)}\right)}$ |
| $Dr$      | $\frac{3}{c_F^p}$ | $\frac{2}{c_F^p}$ |
| $Q^F$     | $A \frac{\Delta P_{\text{max}}}{\alpha L} \frac{1}{2}$ | $A \frac{\Delta P_{\text{max}}}{\alpha L} \left(\frac{(1-\varepsilon)(H_2-H_1)}{(\varepsilon+(1-\varepsilon))(H_2+H_1)}\right)$ |
| $t_{cy}$  | $\alpha L^2 \frac{1}{\Delta P_{\text{max}}} \left[2(1-\varepsilon)(H_2-H_1)\right]$ | $\alpha L^2 \frac{1}{\Delta P_{\text{max}}} \left(\varepsilon + (1-\varepsilon)\frac{(H_2+H_1)}{2}\right)$ |

### Table 2. Summary of important equations obtained for SCC and SMB subject to Langmuir isotherm.

| Parameter | SCC | SMB |
|-----------|-----|-----|
| $P_r$     | $\frac{c_F^p}{\rho_s} \frac{\Delta P_{\text{max}}}{\alpha L^2 \frac{1}{(1-\varepsilon)} \left[1+\frac{H_1 H_2}{\omega_F^2}(\frac{H_2-\omega_F^2}{H_2-H_1})^2\right]}$ | $\frac{c_F^p}{\rho_s} \frac{\Delta P_{\text{max}}}{\alpha L^2 \left(\frac{(H_2-H_1)^2}{(\varepsilon+(1-\varepsilon))\frac{\sum m_j}{4}}\right)}$ |
| $Dr$      | $\frac{2+\frac{H_1 H_2}{\omega_F^2}(\frac{H_2-\omega_F^2}{H_2-H_1})^2}{c_F^p}$ | $1+\frac{H_1 H_2}{\omega_F^2}(\frac{H_2-\omega_F^2}{H_2-H_1})^2$ |
| $Q^F$     | $A \frac{\Delta P_{\text{max}}}{\alpha L} \frac{1}{2}$ | $A \frac{\Delta P_{\text{max}}}{\alpha L} \left(\frac{(1-\varepsilon)\omega_F^2(H_2-H_1)^2}{(H_2-H_1)^4}\right)$ |
| $t_{cy}$  | $\alpha L^2 \frac{1}{\Delta P_{\text{max}}} \left(1-\varepsilon\right) \left(\frac{(H_2-\omega_F^2)}{H_2-H_1} + \frac{\omega_F^2}{H_1 H_2} \frac{(H_2-H_1)^2}{H_2-\omega_F^2}\right)$ | $\frac{\alpha}{\Delta F_{\text{max}}} \left(\varepsilon + (1-\varepsilon)\frac{\sum m_j}{4}\right)$ |

5. Results and discussion

Equations summarized in Tables 1 and 2, show that at optimal points, there are one-to-one similarities between SCC and SMB process in terms of corresponding parameters, namely productivity, desorbent requirement, feed flow rate, and cycle time. The similarities are not limited to linear isotherm and are clearly extended to the case of Langmuir isotherm. Furthermore, it is worthy of attention that the equations obtained for Langmuir isotherm can be simplified to the case of linear isotherm either at very low feed concentrations or where Langmuir equilibrium constants are set to zero ($K_i = 0$). Equivalently, we can set $\omega_F^1 = H_1$ and $\omega_F^2 = H_2$.

It is also important to note that meaningful groups of parameters are identified in the results and have their counterparts for SCC and SMB as given in Tables 1 and 2. Looking at the productivity for example, the first group carries the effect of feed concentration. The second group carries the effect of pressure drop and geometry, and the third one carries the effect of isotherm parameters.
We have investigated the effects of change in feed concentration and Henry constants on the process performance by simulation case studies. We have considered two case studies: case study A: separation of a mixture of guaifenesin enantiomers and case study B: separation of Tröger’s base enantiomers. Isotherm parameters and physical parameters are given in Table 3.

### Table 3. Isotherm parameters and physical properties used in the case studies. Note that for the linear isotherms, $K_i$ values are simply set to zero.

| Parameter | Case A (guaifenesin) | Case B (Tröger’s base) | Unit |
|-----------|----------------------|-------------------------|------|
| $H_1$     | 1.41                 | 2.18                    | -    |
| $H_2$     | 3.49                 | 6.45                    | -    |
| $K_1$     | 0.0135               | 0.065                   | L/g  |
| $K_2$     | 0.0550               | 0.39                    | L/g  |
| $D$       | 1                    | 1                       | cm   |
| $L$       | 10                   | 10                      | cm   |
| $\varepsilon$ | 0.704               | 0.704                   | -    |
| $\alpha$  | $7.59 \times 10^8$  | $7.59 \times 10^8$     | Pa.s/m² |
| $\rho_s$  | 2027.03              | 2027.03                 | g/L  |

#### 5.1. Effects of feed concentration

Analytical expressions reported in Tables 1 and 2 suggest that for fixed geometry and constant physical properties, the only degree of freedom is the feed concentration for both SCC and SMB units at optimal points. Feed concentration has a positive effect on productivity for both SCC and SMB under linear or Langmuir isotherm. For linear isotherm, the effect is just linear. For Langmuir isotherm however, productivity is a complex, but still increasing function of feed concentration as can be seen in Figs. 3(a) and 4(a), respectively. Nevertheless, the rate of change in productivity for Langmuir isotherm is less than that of the linear isotherm.

It is worthy of attention that for case A, the productivity of SCC is higher than that of SMB for the entire range of concentration, but for case B, this order is reversed. This finding suggests that theoretically, SCC can be better than SMB in terms of productivity for the separation of certain enantiomers.

Eqs. 9 and 18, clearly show that single-column chromatography demands more desorbent than SMB under linear range of operation. For Langmuir isotherm, the same argument holds for the case studies considered here as can be seen in Figs. 3(b) and 4(b), although drawing a general conclusion for Langmuir isotherm is not straightforward. Moreover, desorbent requirement appears as a sole function of feed concentration for linear isotherm, but it is affected by isotherm parameters for Langmuir isotherm. In contrast with the common practice of considering cycle time as an independent decision variable, for a fixed set of physical properties and geometry, it is a constant for linear isotherm and a sole function of feed concentration for Langmuir isotherm.

#### 5.2. Effects of pressure drop and overall length

The effect of maximum allowable pressure drop is the same for all cases; productivity linearly increases with increasing allowable pressure drop. On the other hand, productivity is always inversely related to the square of the overall length of the unit. Therefore, ideally, shorter columns are favored to increase productivity. Besides, the fact that productivity appears as a function of the length of unit necessitates that a fair comparison between SCC and SMB must be made at a fixed overall length. Conversely, column cross-sectional area has no effect on productivity and may be used as a scaling parameter. On the other hand, desorbent requirement is not affected by any of these parameters.

Feed flow rate has similar functionality when it is compared to productivity. The major difference is that the cross-sectional area of unit directly affects the feed flow rate. Therefore, feed flow rate not
only is related to the geometry of process through length, but also a function of cross-sectional area, which means feed flow rate for the two processes must be compared at a fixed $A/L$ ratio. Besides, these results affirm that shorter columns are ideally favored for more feed throughput.

It must be emphasized that optimal cycle time varies with the square of the length of the unit. This means, in practical applications, minimum possible switching time might become the active constraint when the length of the unit is used as a decision variable to increase productivity. The lower limit may be dictated by the response time of switching valves and communication devices.

5.3. Effects of Henry constants

Tables 1 and 2 indicates that, Henry constants have a complex effect on the productivity of SMB, but relatively simpler effect on the productivity of SCC. In fact, they have no effect on the productivity of SCC in linear range of operation. This may result in a higher productivity for SCC compared to SMB if for example, highly retentive or low-selectivity materials are processed.

Figs. 5 and 6 show that, productivity increases as the difference between two Henry constants
increases. It is worthy of attention that for a small region, where the difference between Henry constants is small, it is possible that theoretically the productivity of SCC will be greater than that of SMB.

In linear range of operation, desorbent requirement is solely a function of feed concentration. For Langmuir isotherm, it is also a function of isotherm parameters, but not any other parameter. This contrasts the common belief that desorbent requirement must be a function of desorbent flow rate. Moreover, the results reveal that in contrast to productivity, desorbent requirement is completely independent of the process scale.

For desorbent requirement, the difference between SCC and SMB is small for small Henry constants, but it approaches a certain limit when $H_2$ increases as can be seen in Fig. 7. Moreover, SMB always has a smaller desorbent requirement compared to SCC.

For SCC, cycle time is related to difference between Henry constants, but for SMB, it is a function of the sum of Henry constants. For a Langmuir isotherm, a similar but more complex functionality is observed. This finding shows that two different phenomena decide on the optimal cycle time values for SCC and SMB.

![Figure 5. Productivity vs. Henry constants for linear isotherm. Numbers next to the lines are $H_1$ values. $c_F^E$ is 24 g/L. (Results are the same for the two case studies).](image)

On the other hand, for SCC, similar to cycle time, injection volume is no longer an independent decision variable. For linear isotherm, it is just a function of the length of unit, physical properties, and Henry constants. For Langmuir isotherm, however, the effect of feed concentration is added and therefore, injection volume also becomes a function of feed concentration.

6. Concluding remarks
In this paper, analytical investigation of the separation behavior in single-column chromatography and simulated moving bed at their optimal operating points for the case of complete separation and recovery has been presented. It is shown that performance indicators namely, productivity and desorbent requirement can be expressed in similar terms for these processes under equilibrium theory assumptions.

Feed concentration has been identified as the only degree of freedom when geometry and physical properties are kept constant. Hence, all other parameters, such as cycle time, feed flow rate, and injection volume can be expressed as a function of feed concentration for a fixed problem. In addition, feed concentration has positive effect on both performance indicators (i.e., it increases productivity and decreases desorbent requirement) in the case studies investigated in this work and therefore, the optimal operating point must occur at the maximum feed concentration determined by solubility.
Figure 6. Productivity vs. Henry constants for Langmuir isotherm: (a) guaifenesin (case A); (b) Tröger’s base (case B). Numbers next to the lines are $H_1$ values. $c_F^c$ is 24 g/L.

Figure 7. Desorbent requirement vs. Henry constants for Langmuir isotherm: (a) guaifenesin (case A); (b) Tröger’s base (case B). Numbers next to the lines are $H_1$ values. $c_F^c$ is 24 g/L.

It is also noted that in some ranges of Henry constants, single-column chromatography can outperform simulated moving bed in terms of productivity, but it is always inferior in terms of desorbent requirement.

Results showed that productivity is proportional to the inverse of the square of column length. Therefore, shorter columns are favored for increasing the productivity. Use of shorter columns implies smaller switching time which is constrained by switching valves’ hardware limitation.

Nomenclature

$A$ column cross sectional area $[m^2]$
$c_F$ total feed concentration $[g/L]$
$Dr$ desorbent requirement $[L/g]$
$d_P$ particles diameter $[\mu m]$
$H_i$ Henry constant of component i $[-]$
$K_i$ equilibrium constant of component $i$ in Langmuir isotherm [L/g]
$L$ overall length [cm]
$m_j$ dimensionless flow-rate ratio [-]
$Pr$ productivity [g/(min g)]
$\Delta P$ pressure drop [bar]
$Q$ volumetric flow rate [mL/min]
$t^*$ switching time [s]
$t_{cy}$ cycle time [s]
$t_p$ pulse width = $V_{inj}/Q_D$ [s]
$t_{R,20}$ time where the tail of more retained compound ends [s]
$t_{R,i}$ retention time of component $i$ [s]
$u$ superficial velocity [cm/s]
$V$ volume of one column (SMB) [m$^3$]
$V_{inj}$ injection volume [µL]
$V_T$ overall volume [m$^3$]
$v$ interstitial velocity [cm/s]
$z$ axial coordinate [m]

Greek letters
$\alpha$ lumped physical parameter defined as $\alpha = \phi\mu/d_p^2$ [Pa.s/m$^2$]
$\varepsilon$ overall void fraction of column [-]
$\phi$ resistance parameter [-]
$\omega$ characteristic parameter [-]
$\mu$ viscosity [Pa.s]
$\rho$ density [g/L]

Subscripts and superscripts
1 less retained compound
2 more retained compound
ax axial
$D$ desorbent
$F$ feed
$i$ component index
$in$ inlet
$j$ section
$p$ pulse width
$s$ solid/stationary phase

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