



Optimized design of recycle chromatography to isolate intermediate retained solutes in ternary mixtures: Langmuir isotherm systems

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ABSTRACT

Batch chromatography with a recycle stream is a popular and simple technique to separate a single target component in a complex mixture with moderate operating conditions. Design of recycle chromatography depends on the retention behaviors of the mixture components. In this work, four nucleosides were considered as solutes. Feed concentration and recycle methods were optimized to isolate only the intermediate retained solute in ternary and pseudo-ternary mixtures. Two recycle methods introduced in our previous work for linear isotherms, the desorbent and feed recycle methods, were compared in terms of productivity and desorbent to feed ratio, D/F, with various feed concentrations for competitive Langmuir isotherm systems. The simulation results show that the target (intermediate retained solute) was separated with over 99.76% purity and 99.88% yield. Productivity of the feed recycle method was increased by up to 162% and D/F was decreased by up to 59% compared to the desorbent recycle method. For the separation of nucleosides, recycle chromatography was compared to eight column simulated moving bed (SMB) cascades with a recycle stream and D/F of the SMB cascades was 58% lower than D/F of recycle chromatography at the same productivity. However, recycle chromatography is much simpler.

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1. Introduction

Batch chromatography is a simple and popular separation technique in pharmaceutical, fine-chemical, and biological fields [1–4]. Adding a recycle stream can increase recovery of product and reduce desorbent consumption. The appropriate recycle method depends on the purpose of recycling. When a separation column cannot completely separate the target component because of low selectivity (<1.5) and a mixture is binary, the closed-loop recycle method can be used to improve recovery of product [5] or production rate [6]. The design method for steady state recycling (SSR) chromatography based on equilibrium theory was studied for Langmuir isotherms and mixed-recycle operations [7]. Recycle chromatography is also useful for the separation of pseudo-binary mixtures and out-performs a four-zone simulated moving bed (SMB) with one column per zone [8].

For separation of a single intermediate target component from a multicomponent mixture with large enough selectivities (>1.5), two recycle methods were introduced and compared in our previous work for linear isotherms [9]. First, desorbent recycle sends pure eluted desorbent to the recycle tank and reuses this desorbent. Second, feed recycle sends unseparated solutes to the recycle

tank and re-injects them in the column with the fresh feed. For linear isotherms, where no competition occurs, desorbent and feed recycle methods have the same productivity and D/F [9].

For complete separation of a ternary mixture, several SMB cascades have been studied [10,11]. In the simplest cascade, the first SMB separates one component, the most or least retained solute, and feeds the mixture of the other two components to the second SMB. However, this SMB cascade consumes a lot of desorbent to separate each component completely. For the separation of ternary mixtures, a hybrid system called JO-SMB or Pseudo-SMB, which incorporated batch chromatography and SMB concepts, was introduced [12], and the design method and performance of JO system were studied in linear and Langmuir isotherm systems [13–16]. This system uses discontinuous feed injection and disconnects a recycle line for one cycle. The cycle of the JO system was divided into two steps. Step one operates as an SMB without feed injection and with the recycle line connected. Step two is based on batch chromatography by eluting the intermediate retained solute and injecting feed solution after disconnecting the recycle line that connected neighboring columns. A different two-zone hybrid SMB/chromatography system was developed to isolate only the intermediate retained solute and was experimentally demonstrated for separation of a ternary amino acid mixture [17,18].

In this work, the operating conditions of the simplest recycle chromatography with one column and one recycle tank were optimized to separate the intermediate retained solute in ternary and pseudo-ternary mixtures. Detailed simulations were done with

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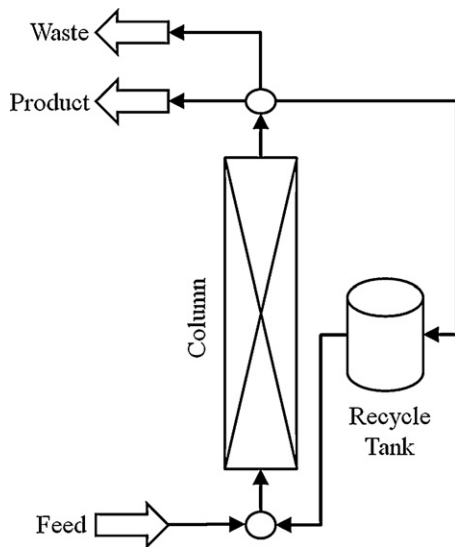


Fig. 1. Schematic flow diagram of recycle chromatography.

Aspen Chromatography® 2006 (Aspen Technology Inc., Burlington, MA, USA) to compare the recycle methods and to compare to SMB separations.

2. Recycle chromatography system

The recycle chromatography system (Fig. 1) was used to simulate center-cut separation of ternary and pseudo-ternary mixtures of nucleosides, 2'-deoxycytidine (dC), 2'-deoxyguanosine (dG), 2'-deoxythymidine (dT), and 2'-deoxyadenosine (dA) with the reversed-phase medium, Source 30RPC and water with 4 vol.% ethanol [19]. Column dimensions and operating conditions are listed in Table 1. Pure desorbent (in the desorbent recycle method) or unseparated solute mixture (in the feed recycle method) were collected at the column outlet, sent to the recycle tank, and at the appropriate time, fed into the column after mixing with fresh desorbent or feed, respectively. A fixed arbitrary threshold value (0.5% of the maximum concentration of the outlet profile) was used to

Table 1
Isotherms and kinetic parameters of nucleosides [19] and system properties.

Parameters	Values
Langmuir isotherm parameters ($a(-)/b$ (L/g))	
dA (2'-deoxyadenosine)	27.7/0.1
dT (2'-deoxythymidine)	9.60/0.1
dG (2'-deoxyguanosine)	7.40/0.1
dC (2'-deoxycytidine)	3.15/0.1
Mass-transfer coefficients ($a_p k_i$) (1/min)	
dA (2'-deoxyadenosine)	6
dT (2'-deoxythymidine)	30
dG (2'-deoxyguanosine)	30
dC (2'-deoxycytidine)	60
Axial dispersion coefficient (D_e) (cm ² /min)	0.225
Column	
Length (cm)	30
Inner diameter (cm)	0.46
Intra-particle void fraction (-)	0.667
Inter-particle void fraction (-)	0.4
Feed	
Flow-rate (ml/min)	0.5
Concentration (g/L)	
Ternary 1	Up to 75
Ternary 2	Up to 75
Ternary 3	Up to 100

Table 2
Selectivities of neighboring solutes and elution ratios for different solute systems.

Solute system	Solutes (A/B/C)	Selectivity ^b ($\alpha_{B,A}/\alpha_{C,B}$)	Elution ratio ^d
Ternary 1	dC/dT/dA	3.05/2.89	2.812
Ternary 2	dC/dG/dA	2.35/3.74	4.770
Ternary 3	dC/dG/dT/dA ^a	2.35/1.3/2.89 ^c	3.290 ^e

^a A/B1/B2/C.

^b Selectivity, $\alpha_{i,j} = a_i/a_j$ ($a_i > a_j$).

^c $\alpha_{B1,A}/\alpha_{B2,B1}/\alpha_{C,B2}$.

^d Elution ratio for ternaries = $(a_C - a_B)/(a_B - a_A)$.

^e $(a_C - a_{B2})/(a_{B1} - a_A)$.

determine where to cut elution bands from the outlet concentration profiles.

Isotherms and kinetic parameters of nucleosides are described in Table 1 [19]. Two ternary mixtures, dC/dT/dA (Ternary 1) and dC/dG/dA (Ternary 2), were studied for separation of the intermediate retained solute (dT and dG, respectively) and one pseudo-ternary mixture, dC/dG/dT/dA (Ternary 3), was studied to separate dG and dT together. Total feed concentration was varied up to 75 g/L for the ternary mixtures and to 100 g/L for the pseudo-ternary mixture. Every component in the Ternary 2 and 3 feeds had the same concentration while the compositions of the Ternary 1 system were varied as 2/1/2, 1/1/1, 1/2/1, and 1/8/1 to observe the effect of feed composition on the separations. Selectivities of neighboring solutes and the elution ratios in the different solute systems are indicated in Table 2. The elution ratio is defined as

$$\text{elution ratio} = \frac{a_C - a_B}{a_B - a_A} \quad (1)$$

where a_i is the Langmuir isotherm parameter of solute i and subscripts A, B, and C represent the least, intermediate, and most retained solutes, respectively. This elution ratio roughly indicates the ratio of retention time differences between solutes A and B divided by the difference between solutes B and C. As the elution ratio increases, more material can be recycled.

For the simulation of recycle chromatography and the SMB process, the following model equations including axial dispersion and kinetic resistance were used with Langmuir isotherm model [8,19].

$$\varepsilon_T \frac{\partial c_i}{\partial t} + (1 - \varepsilon_T) \frac{\partial q_i}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon D_e \frac{\partial^2 c_i}{\partial z^2} \quad (2)$$

$$\frac{\partial q_i}{\partial t} = a_p k_i (q_i^* - q_i) \quad (3)$$

$$q_i^* = \frac{a_i c_i}{1 + \sum_j b_j c_j} \quad (4)$$

Detailed simulations for recycle chromatography and the SMB process were performed with Aspen Chromatography® 2006. These simulations use a finite element method with biased upwind difference scheme (BUDS) and a fixed step-size implicit Euler method for the integration between the time differences to solve the partial differential equations [20]. The number of nodes for the space domain and step-size for the time domain integration were fixed as 200 and 0.01 min, respectively.

To obtain optimized operating conditions for recycle chromatography, the ends of elution bands were matched by the optimization method introduced previously [8]. The flow-rate of the mobile phase was fixed at 0.5 ml/min. The desorbent recycle method can be used when pure desorbent is eluted between the target (B) and most retained solute (C). This occurs when the difference between the target and most retained retention times is longer than the difference between the target (B) and least retained solute (A). As the elution band migrates in the column it becomes wider owing to the difference between the migration velocities of the shock wave (front end) and the simple wave (rear end). These velocities

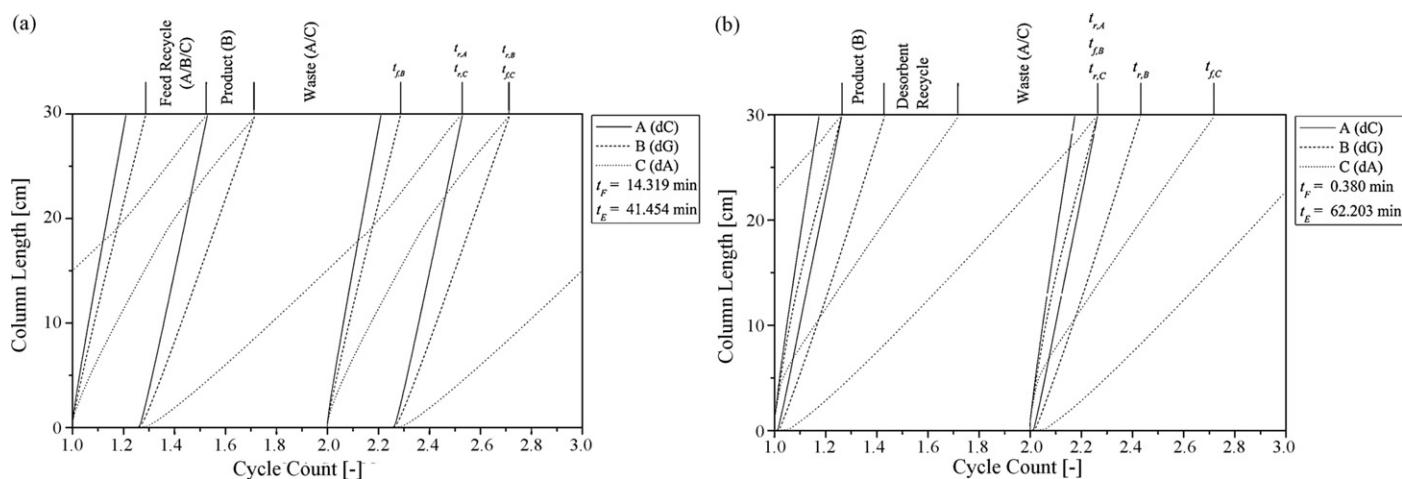


Fig. 2. Migration trace of solutes in the column for the Ternary 2 system: (a) feed recycle method, (b) desorbent recycle method. Feed concentration of each solute is 10 g/L.

are also changed as the concentration of every component changes for systems with competitive isotherms. At the optimized operating conditions, the migration trace of each bandwidth was obtained from the simulated concentration profiles in the column. Optimized migration traces of solutes are shown for the feed recycle method of the Ternary 2 system in Fig. 2a. To optimize the operating conditions for the feed recycle method, feed time (t_F) was chosen to force the rear end of solute B ($t_{r,B}$) to co-elute with the front end of solute C ($t_{f,C}$) injected during the same cycle. The cycle time (t_C), sum of feed time (t_F) and elution time (t_E), were decided by the time interval which matched the rear end of solute A ($t_{r,A}$) to the rear end of solute C ($t_{r,C}$) injected during the previous cycle. Therefore, in the optimized operating conditions for feed recycle, the rear ends of solutes A and C ($t_{r,A}$ and $t_{r,C}$), and the rear end of solute B and the front end of solute C ($t_{r,B}$ and $t_{f,C}$), respectively, elute at the same time (Fig. 2a). Fig. 2b shows the migration traces of solutes at the optimized operating conditions of the desorbent recycle method. Feed time (t_F) was chosen to force the rear end of solute A ($t_{r,A}$) to co-elute with the rear end of solute B ($t_{r,B}$) injected at the same cycle. Cycle time (t_C) was chosen to force the rear end of solute A ($t_{r,A}$) to co-elute with the rear end of solute C ($t_{r,C}$) injected during the previous cycle (Fig. 2b).

Fig. 3 shows the elution profiles of solutes at the same conditions as in Fig. 2. For the feed recycle method, separated solute B profile is collected as product and solutes A and C are collected together as waste. Owing to the broadening of solute C band, the concentration of solute C in the recycled solution is low. If solute C is also desired, one can obtain pure solute C with modest recovery by collecting waste before A exits. On the other hand, for the desorbent recycle method, solute A can be separated with relatively high purity and recovery of pure solute C can be improved compared to the feed recycle method. However, in this study, recovery of pure C or

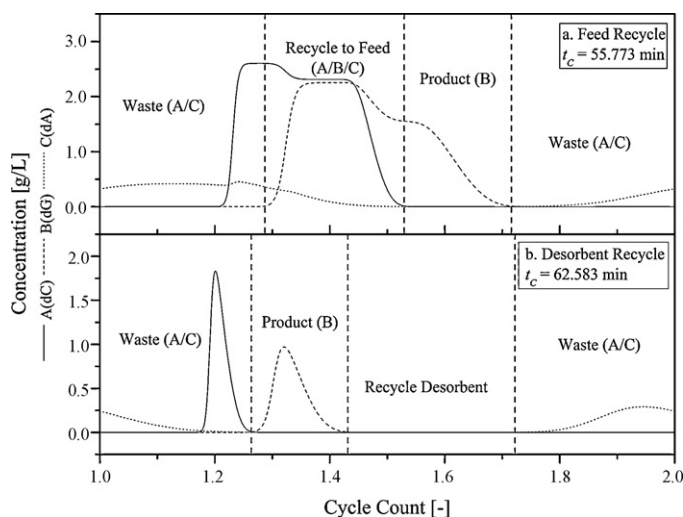


Fig. 3. Simulated elution profiles of solutes at the same conditions as Fig. 2: (a) feed recycle method, (b) desorbent recycle method.

pure A is secondary to recovery of pure target component B at high recovery with low D/F and high productivity.

3. Relationship between feed concentration and operating conditions in recycle chromatography

Operating conditions, feed time (t_F) and elution time (t_E), are strongly related to the feed concentrations because of competitive adsorption and isotherm non-linearity. As shown in Table 1, the simulations of recycle chromatography were carried out up to

Table 3

Feed throughput and feed time at the highest total feed concentration for optimized operating conditions for recycle chromatography.

Solute system	Compositions	Desorbent recycle		Feed recycle	
		Feed throughput (mg/min)	Feed time (min)	Feed throughput (mg/min)	Fresh feed time ^b (min)
Ternary 1 (75 g/L) ^a	2/1/2	0.390	0.620	0.597	0.887
	1/1/1	0.435	0.699	0.618	0.951
	1/2/1	0.459	0.753	0.608	0.985
	1/8/1	0.309	0.522	0.485	0.844
Ternary 2 (75 g/L) ^a	1/1/1	0.090	0.150	0.256	0.377
Ternary 3 (100 g/L) ^a	1/1/1/1	0.139	0.111	0.329	0.384

^a The highest total feed concentration.

^b Fresh feed volume/mobile phase flow-rate.

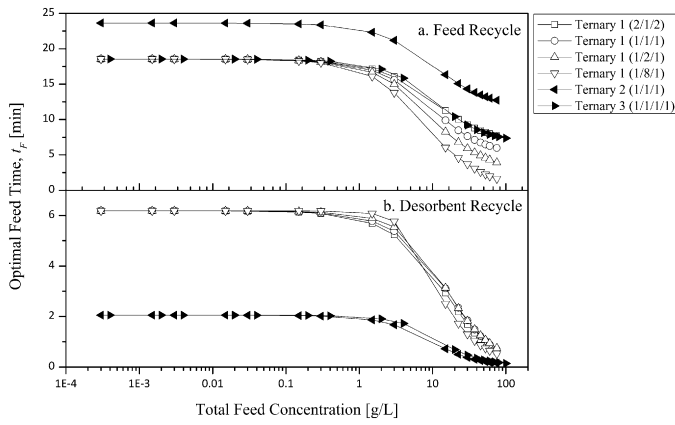


Fig. 4. Optimal feed time versus the total feed concentration: (a) feed recycle method, (b) desorbent recycle method.

a total feed concentration of 75 g/L for the ternary mixtures and up to 100 g/L for the pseudo-ternary mixture. Table 3 shows feed throughput and feed time at the highest total feed concentration of each solute system. Fresh feed time in the feed recycle method was calculated by dividing fresh feed volume by the mobile phase flow-rate to compare to feed time in the desorbent recycle method.

Fig. 4 shows the changes of optimal feed time (t_F) versus the total feed concentration for the desorbent and feed recycle methods. In the linear isotherm range (up to approximately 0.2 g/L of the total feed concentration), optimal feed times are constant because competitive adsorption and non-linearity of Langmuir isotherms are negligible in this concentration range. Optimal feed times were determined as shown in Fig. 2. For the feed recycle method, the solute systems, Ternary 1 and 3, have the same key-separation components (dT and dA) and for the desorbent recycle method, the solute systems, Ternary 2 and 3, have the same key-separation components (dC and dG). Solute systems with the same key-separation components have the same feed time in the linear isotherm range and these feed times are decreased at similar rates as the feed concentration increases in the non-linear range.

Fig. 5 shows the changes of optimal cycle time (t_C) for both recycle methods versus the total feed concentration. Cycle time was determined as shown in Fig. 2. As expected, cycle time is constant in the linear isotherm range. The linear cycle times are similar (within 5%) for all systems. For the desorbent recycle method, the cycle times in the linear isotherm range are different when the solute system has different key-separation components (dC and dT for the Ternary 1 system and dC and dG for the Ternary 2 and 3 systems). As

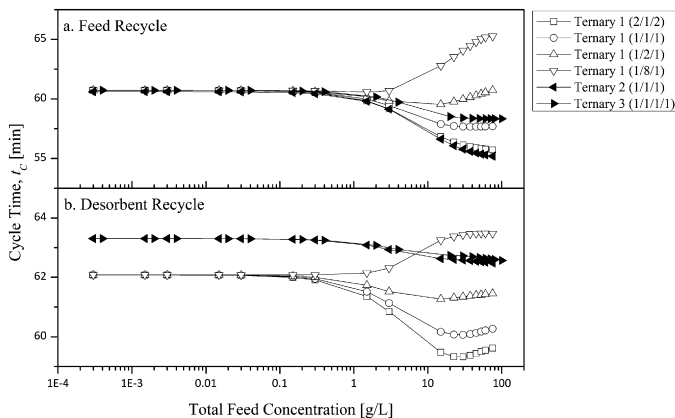


Fig. 5. Optimal cycle time versus the total feed concentration: (a) feed recycle method, (b) desorbent recycle method.

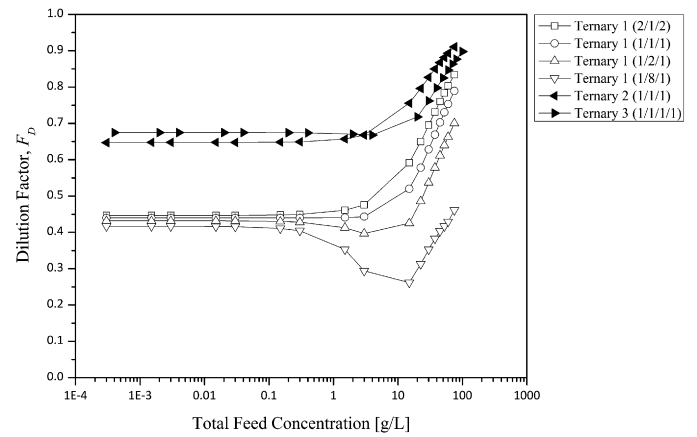


Fig. 6. Dilution factor (Eq. (5)) versus the total feed concentration for recycle chromatography.

shown in Fig. 2, the cycle times for the feed and desorbent recycle methods are decided by the retention differences between the rear end of solute A and the rear end of solute C, and between the front end of solute B and the rear end of solute C, respectively. The migration velocity of the rear end of solute C is almost constant because this velocity is mainly decided by the simple wave (the competitive region with other solutes is narrow compared to the entire migration trace). However, in the feed recycle method, because the rear end of solute A migrates with solute B, this migration velocity is strongly dependent on the concentration of solute B. In the desorbent recycle method, the migration velocity of the front end of solute B is decided by the shock wave velocity. Therefore, when the composition of solute B is large, cycle times are longer as the feed concentration is increased.

4. Comparison of the desorbent and feed recycle methods for recycle chromatography

In recycle chromatography, it is common to recycle pure desorbent that elutes between the solute bands. However, this method may require high desorbent consumption (large D/F) if the feed mixture contains more than two components. For pseudo-binary separation by recycle chromatography, recycling partially separated non-target component is better than recycling pure desorbent in linear and Langmuir isotherm systems [8,9]. For center-cut separation of a ternary mixture, there is no difference in the two recycle methods for linear isotherms [9] because the migration velocities of solutes are not changed by these concentrations and there is no competition between solutes.

For the feed recycle method, the concentration of recycled unseparated mixture is diluted compared to the fresh feed concentration. Therefore, when the feed recycle method is adopted, it is possible to operate recycle chromatography with lower inlet concentration than the feed concentration. Fig. 6 shows the changes of dilution factor of the total inlet concentration with various total feed concentrations. The dilution factor, F_D , was calculated as

$$F_D = 1 - \frac{\sum_i c_i^0}{\sum_i c_i^F} \quad (5)$$

where c_i^0 and c_i^F are the concentrations of solute i at the column inlet and fresh feed solution, respectively. In the linear isotherm range (up to approximately 0.2 g/L of the total feed concentration), the dilution factor is constant for each system. As shown in Fig. 3, the rear parts of solutes A and C (diluted by simple wave) and front part of solute B (concentrated part by shock wave) profiles are recycled to feed. When the concentration of the target intermediate retained

Table 4
Averages and standard deviations of the target purity and yield obtained from simulations for recycle chromatography.

Solute system	Feed composition	Recycle method	Target purity (%)		Target yield (%)	
			Average	σ^c	Average	σ^c
Ternary 1	2/1/2	DR ^a	99.760	0.062	99.945	0.021
		FR ^b	99.762	0.028	99.939	0.007
	1/1/1	DR ^a	99.884	0.027	99.952	0.015
		FR ^b	99.879	0.016	99.938	0.008
	1/2/1	DR ^a	99.945	0.011	99.967	0.005
		FR ^b	99.936	0.013	99.933	0.013
1/8/1	DR ^a	99.987	0.002	99.976	0.012	
	FR ^b	99.981	0.007	99.926	0.02	
Ternary 2	1/1/1	DR ^a	99.869	0.009	99.948	0.003
		FR ^b	99.857	0.012	99.895	0.025
Ternary 3	1/1/1	DR ^a	99.935	0.004	99.973	0.003
		FR ^b	99.928	0.008	99.883	0.311

^a The desorbent recycle method.

^b The feed recycle method.

^c Standard deviation.

solute is larger than that of other components (the Ternary 1 system with compositions 1/2/1 and 1/8/1), the dilution factor is decreased in approximately 0.2–10 g/L range.

It is difficult to obtain exactly the same (to one-tenth percent) purity and yield of intermediate product for every simulation because the threshold value to cut the elution bands is fixed. However, the simulations with fixed threshold value give almost constant (within one-tenth percent) purity and yield of product for both the desorbent and feed recycle methods at the same feed composition. Average purity and yield of the target and the standard deviations are listed in Table 4. The target (intermediate retained solute) was separated with over 99.76% purity and 99.88% yield.

Fig. 7 shows the productivity versus total feed concentration. In the linear isotherm range (easiest to see in Fig. 7b), productivity is proportional to the feed concentration and both recycle methods have almost the same productivity at the same feed concentration. On the other hand, the rate of productivity increase decreases as the feed concentration increases into the non-linear isotherm range (easiest to see in Fig. 7a). In the non-linear range of feed concentration, productivity of the feed recycle method is larger than that of the desorbent recycle method. Productivity of the desorbent

recycle method has a maximum of about 30 g/L of total feed concentration for the Ternary 1 and 2 systems and about 40 g/L for the Ternary 3 system. Productivity of the feed recycle method increases monotonically because of the dilution of the inlet concentration discussed previously.

Fig. 8 shows D/F versus total feed concentration. In the linear isotherm range (for example, Fig. 8b), D/F is constant and D/F of the feed recycle method is lower than that of the desorbent recycle method. For feed concentrations in the linear isotherm range (for example, Fig. 8a), D/F is proportional to the feed concentration, and D/F of the feed recycle method remains lower than that of the desorbent recycle method. Table 5 compares productivity and D/F of the desorbent and feed recycle methods at the maximum productivities. For all solute systems, the feed recycle method gave higher productivity at lower D/F than the desorbent recycle method. Productivity and D/F are significantly better for feed recycle when the recycled solution is strongly adsorptive (1/8/1 of the Ternary 1 system) because the volume of recycled solution is large. This explains why feed recycle is significantly better than desorbent recycle for the Ternary 3 system which has highly adsorptive recycle solution.

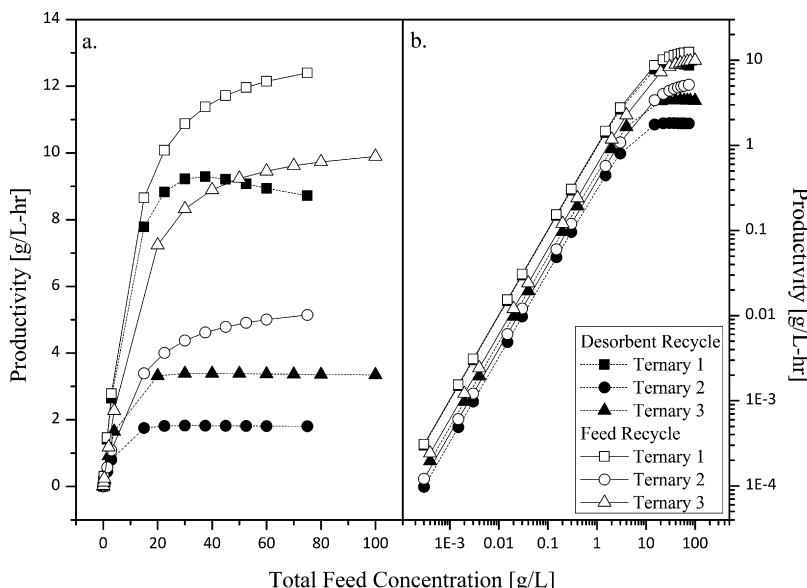


Fig. 7. Productivity versus the total feed concentration for recycle chromatography: (a) linear scale, (b) log–log scale.

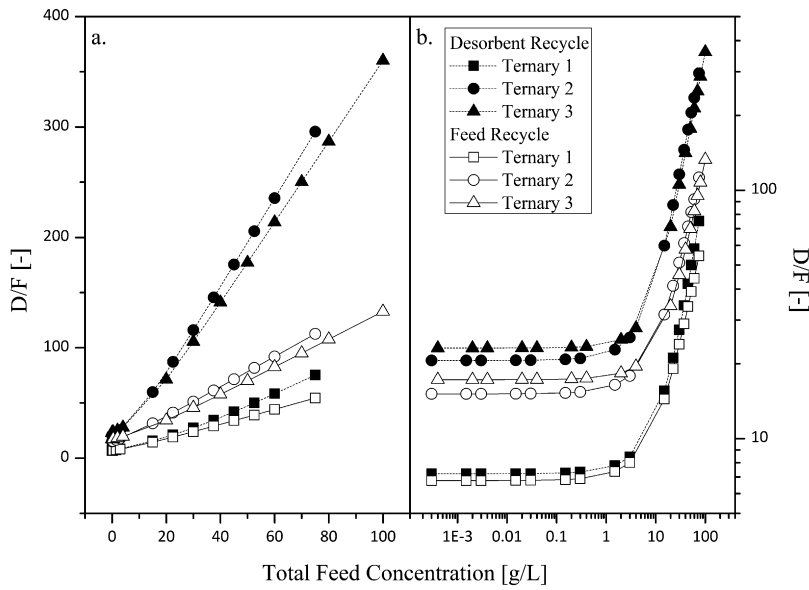


Fig. 8. D/F versus the total feed concentration for recycle chromatography: (a) linear scale, (b) log-log scale.

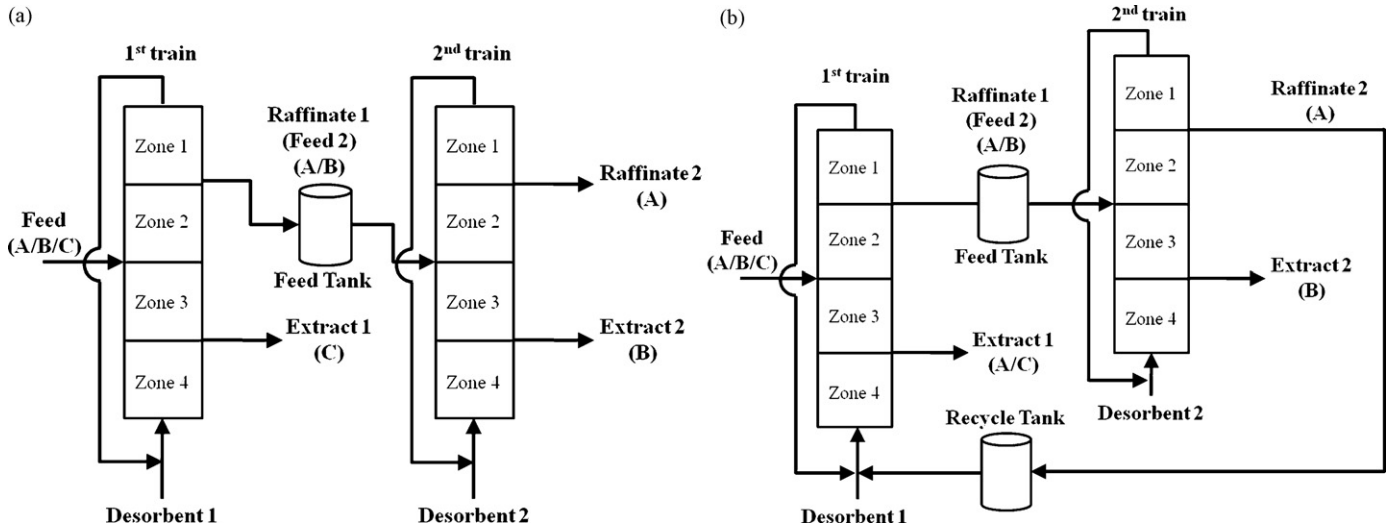


Fig. 9. Schematic flow diagram of the SMB cascade processes. (a) Complete separation of ternary mixture. (b) Center-cut separation of ternary mixture.

5. Optimized operating condition for the SMB cascade processes

For the separation of ternary mixtures, two types of SMB cascade processes were simulated. The first one is complete separation of

ternary mixture (Fig. 9a). Because the most retained solute (C) is easier to separate than the least retained solute (A), pseudo-binary components A/B and C are separated in the 1st train, and components A and B are separated in the 2nd train. All three components (C at the extract port of 1st train, B at the extract port of 2nd train,

Table 5

Comparison of productivity and D/F of the desorbent and feed recycle methods at the maximum productivity concentration of the desorbent recycle method.

Solutes	Compositions	Desorbent recycle		Feed recycle		Improvement	
		Productivity (g/L-h)	D/F (-)	Productivity (g/L-h)	D/F (-)	Productivity (%) ^a	D/F (%) ^b
Ternary 1 (30 g/L) ^c	2/1/2	5.134	28.97	6.220	24.22	21.15	16.38
	1/1/1	9.224	27.42	10.879	23.98	17.94	12.53
	1/2/1	13.408	29.09	16.136	25.20	20.35	13.35
	1/8/1	14.784	42.43	22.734	29.94	53.77	29.44
Ternary 2 (30 g/L) ^c	1/1/1	1.825	115.95	4.372	51.15	139.59	55.89
Ternary 3 (40 g/L) ^c	1/1/1/1	3.387	141.18	8.894	57.73	162.59	59.11

^a $(P_{\text{feed recycle}} - P_{\text{desorbent recycle}}) / P_{\text{desorbent recycle}} \times 100$.

^b $(D/F_{\text{desorbent recycle}} - D/F_{\text{feed recycle}}) / D/F_{\text{desorbent recycle}} \times 100$.

^c Total feed concentration.

and A at the raffinate port of 2nd train) can be separated by the SMB cascade. The second system is a center-cut separation of the ternary mixture (Fig. 9b). Component A (with desorbent) separated in the 2nd train is recycled to the desorbent port of the 1st train and is used as desorbent containing a gradient modifier (component A) in the 1st train to separate components B and C. Therefore, components A and C are collected at the extract port of the 1st train and component B, the target component, is isolated at the extract port in the 2nd train.

For the complete separation (Fig. 9a), pseudo-binary separation in the 1st train and binary separation in the 2nd train can be optimized independently. An approximate optimization method for binary and pseudo-binary SMB process based on the Triangle method was introduced previously [8]. For the full optimization of operating conditions, one more step is added in the optimization method. The objective functions, f_m , for the optimization method is defined by differences between the observed purity P obtained from the simulation and the target purity T .

$$f_{m_2} = (P_{\text{Extr}} - T_{\text{Extr}}) - (P_{\text{Raff}} - T_{\text{Raff}}) \quad (6a)$$

$$f_{m_3-m_2} = \frac{(P_{\text{Extr}} - T_{\text{Extr}}) + (P_{\text{Raff}} - T_{\text{Raff}})}{2} \quad (6b)$$

$$f_{m_1} = (P_{\text{Raff}} - T_{\text{Raff}}) \quad (6c)$$

$$f_{m_4} = (P_{\text{Extr}} - T_{\text{Extr}}) \quad (6d)$$

Terms are defined in the nomenclature. Target purities T_{Extr} and T_{Raff} were fixed at 99.9%. To modify the operating conditions of the SMB process, the ratio of the liquid phase flow-rate to the solid phase flow-rate of the equivalent true moving bed (TMB) process was used. The flow-rate ratio in zone j , m_j , is defined as [21],

$$m_j = \frac{Q_j^{\text{TMB}} - \varepsilon_P Q_S}{(1 - \varepsilon_P) Q_S} = \frac{Q_j^{\text{SMB}} - \varepsilon_T V / t_S}{(1 - \varepsilon_T) V / t_S} \quad (7)$$

Each zone has its main role. Zones 1 and 4, respectively, hold the most retained and least retained solutes to prevent recycling these solutes between zones 1 and 4. Zones 2 and 3 separate the more and less retained key-separation solutes with different zone flow-rate ratios [22,23]. The flow-rate ratios are changed according to the main role of the corresponding zones to make the objective functions (Eq. (6)) zero. In the first step of the optimization method, the equal difference point from target purities of extract and raffinate ports are found with the given $m_3 - m_2$, m_1 , and m_4 (where the objective function, Eq. (6a), is zero). In the second step of the optimization method, the $m_3 - m_2$ level to obtain the target purities is found (where the objective function, Eq. (6b), is zero). At every $m_3 - m_2$ level, the first step is performed to find the equal difference points. In the last step, m_1 and m_4 are simultaneously optimized to obtain optimum D/F with fixed m_2 and m_3 values (where the objective functions, Eqs. (6c) and (6d), are zero). For fast and accurate convergence, quadratic interpolation is used to find the next point in each step of the optimization method [8].

In the 1st train for the center-cut separation (Fig. 9b), component A in zone 1 is allowed to recycle to zone 4 in the 1st train and is in the recycle stream from the 2nd train. Therefore, component A acts as a gradient modifier in the 1st train. If component A does not adsorb, the concentrations of component A are identical in zones 1 and 2 and in zones 3 and 4 [24,25]. However, if the gradient modifier (component A) is adsorbed and has competitive interaction with the other solutes, the concentration of gradient modifier is changed in each zone. For ternary mixtures, when the least retained solute becomes a gradient modifier, the concentrations on each plateau can be obtained by the hodograph transformation of the equilibrium model [23] as shown in Fig. 10. If the components B and C are completely separated in the equivalent TMB, the concentrations of components B and C on plateaus 1 and 6 must be zero

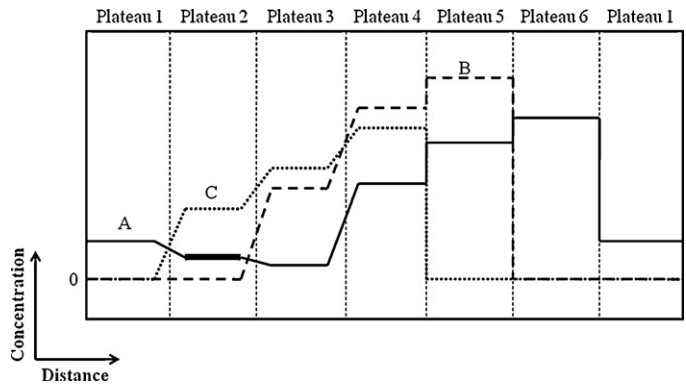


Fig. 10. Schematic concentration profiles in a column in the 1st train of the SMB in Fig. 9b for ternary mixture with competitive Langmuir isotherms. A (solid), B (dash), and C (dot) represent the least, intermediate, and most retained solutes, respectively.

and the desorbent, extract, and raffinate ports are located between plateaus 1 and 6, between plateaus 1 and 2, and between plateaus 5 and 6, respectively. The feed port is located between plateaus 2 and 5, so that plateaus 3 and 4 are collapsed into the feed port. To calculate the concentration of each component on the plateaus, one fixed concentration is required. We fixed the concentration of component A on plateau 2 because this concentration is the lowest concentration level observed in the TMB and SMB units. From the conditions for the complete separation of component B and C with competitive Langmuir isotherms, the overall mass balance for the component C between plateaus 2 and 5 is

$$m_2 c_{C,2} + (m_3 - m_2) c_C^F = \frac{a_C c_{C,2}}{1 + b_{A,C,A,2} + b_{C,C,2}} \quad (8a)$$

$$\{a_C - (1 + b_{A,C,A,2})m_2 - b_C(m_3 - m_2)c_C^F\}^2 - 4b_C m_2 (1 + b_{A,C,A,2})(m_3 - m_2)c_C^F > 0 \quad (8b)$$

where $c_{A,2}$ is the known concentration of component A on plateau 2. Eq. (8b) is the necessary condition for the complete separation of component C. When the flow-rate ratios of zones 2 and 3 (m_2 and m_3) and feed conditions are fixed, the concentration of component C in the plateau 2 can be obtained from Eq. (8). In the same manner, the concentrations of component A and B can be obtained from the following mass balances.

$$c_{A,3} = \frac{a_B c_{B,3} \{ (m_3 - m_2) c_A^F + m_2 c_{A,2} - a_{A,C,A,2} / (1 + b_{A,C,A,2} + b_{C,C,2}) \}}{a_B (m_3 - m_2) c_B^F + (a_B - a_A) m_3 c_{B,3}} \quad (9a)$$

$$m_3 c_{B,3} - (m_3 - m_2) c_B^F = \frac{a_B c_{B,3}}{1 + b_{A,C,A,3} + b_{B,C,B,3}} \quad (9b)$$

with the concentrations of components on plateaus 2 and 5, all concentrations can be obtained by the ω -transformation introduced by Rhee et al. [26], and then the conditions of zone flow-rate ratios for the separation of components B and C can be obtained from the following inequalities.

$$\frac{a_B}{1 + b_{A,C,A,2} + b_{C,C,2}} < m_2 < m_3 < \frac{a_C}{1 + b_{A,C,A,4} + b_{B,C,B,4} + b_{C,C,4}} \quad (10a)$$

$$\frac{a_C}{1 + b_{A,C,A,1}} < m_1 \quad (10b)$$

$$m_4 < \frac{a_B}{1 + b_{A,C,A,5} + b_{B,C,B,5}} \quad (10c)$$

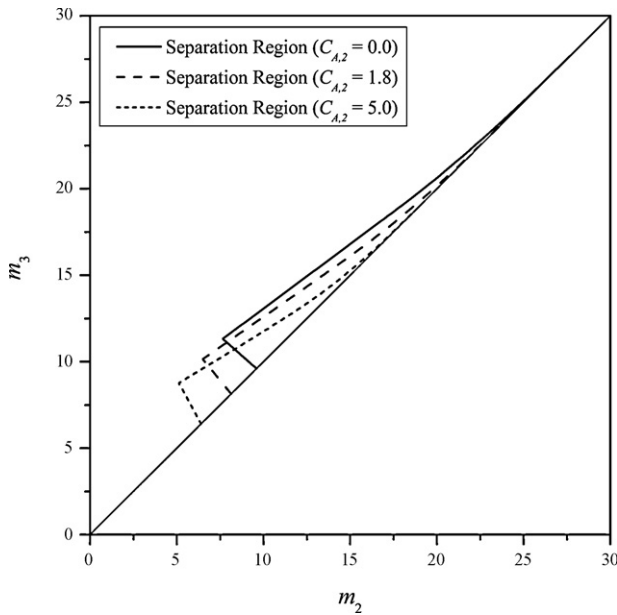


Fig. 11. Separation regions on $m_2 - m_3$ plane with different concentrations of solute A on plateau 2 ($c_{A,2}$) of Fig. 10 for the 1st train in Fig. 9b.

If $c_{A,2}$ is zero, the inequality conditions for the pseudo-binary separation (C and A/B, 1st train of Fig. 9a) is

$$\frac{a_B}{1 + b_{CC,2}} < m_2 < m_3 < \frac{a_C}{1 + b_{AC,4} + b_{BC,4} + b_{CC,4}} \quad (11a)$$

$$a_C < m_1 \quad (11b)$$

$$m_4 < \frac{a_A}{1 + b_{AC,6}} \quad (11c)$$

The minimum m_1 for the pseudo-binary separation, Eq. (11b), is larger than that for the separation of component B and C with recycling component A, Eq. (10b), and the maximum m_4 for the pseudo-binary separation, Eq. (11c) is also smaller than that for separation of component B and C with recycling component A, Eq. (10c). Therefore, desorbent use in the 1st train can be reduced by recycling component A if the difference between m_2 and m_3 is the same. Fig. 11 shows the separation regions on $m_2 - m_3$ plane with three different concentrations of component A on plateau 2 ($c_{A,2}$). As $c_{A,2}$ is larger, the separation region moves to the origin and the width on the diagonal line is narrower. However, the height of the vertex point from the diagonal line is not changed. It is possible to operate the 1st train of Fig. 9b with the same difference of m_2 and m_3 compared to the 1st train of Fig. 9a.

To satisfy the recycling of the entire raffinate stream from the 2nd train to the desorbent port in the 1st train (Fig. 9b), the mass fluxes of the feed and extract ports have to be same for components A and C. The required m_1 value can be obtained from the following equations.

$$c_{C,E} = \frac{c_{C,2}c_{A,1}}{c_{C,2} - (c_{A,2} - c_{A,1})} = \frac{m_3 - m_2}{m_1 - m_2} c_{C,F} \quad (12a)$$

$$m_{1,Req.} = \frac{c_{C,2} - (c_{A,2} - c_{A,1})}{c_{C,2}c_{A,1}} (m_3 - m_2)c_{C,F} + m_2 \quad (12b)$$

when $m_{1,Req.}$ is smaller than the optimized m_1 , more amount of component A is required. It means that an additional desorbent stream which includes component A is required in the 1st train. On the other hand, excess amount of desorbent is used in the 1st train when $m_{1,Req.}$ is larger than the optimized m_1 , and it is not advisable to recycle the entire raffinate stream of the 2nd train into the desorbent port of the 1st train.

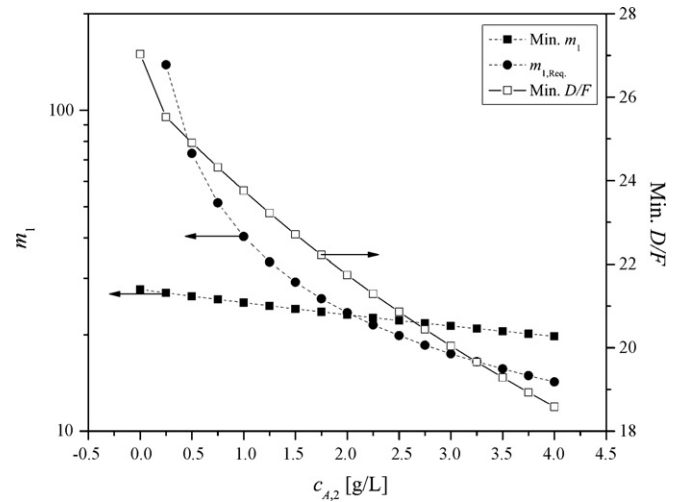


Fig. 12. Minimum and required m_1 , and minimum D/F versus the concentration of component A on the plateau 2 ($c_{A,2}$) for the 1st train of Fig. 9b. Minimum m_1 and D/F are obtained from the equilibrium theory.

6. Comparison of recycle chromatography and SMB cascade processes

Recycle chromatography and SMB cascade processes were compared for the Ternary 1 system with a feed concentration of 30 g/L (10 g/L of each solute). Previous work showed that one column recycle chromatography was better than a four column SMB process, but an eight column SMB process was better than one column recycle chromatography for pseudo-binary separations of nucleosides [8]. Thus, an SMB cascade with two 4.0 cm long columns per zone (16 columns total) was studied. To compare D/F of each process, the feed flow-rates of SMB cascade processes were fixed at 0.0385 ml/min which gives the same productivity as recycle chromatography. To decide the condition for the recycle of all the raffinate from the 2nd train (Fig. 9b), the minimum m_1 and D/F obtained from the equilibrium theory, and required m_1 for entire recycling, $m_{1,Req.}$, were calculated with various $c_{A,2}$ (Fig. 12). When $c_{A,2}$ is larger than 2 g/L, $m_{1,Req.}$ is smaller than minimum m_1 , and an additional source of component A is required. On the contrary, when $c_{A,2}$ is smaller than 2 g/L, $m_{1,Req.}$ is smaller than minimum m_1 . This means that excessive amounts of component A plus desorbent could be recycled to the desorbent port of the 1st train. To obtain the optimized operating conditions of Fig. 9b (no additional desorbent use in the 1st train), $m_{1,Req.}$ is equal to or greater than minimum m_1 . With a certain safety margin of m_1 , $c_{A,2}$ was fixed at 1.8 g/L. Table 6

Table 6
Operating conditions of SMB cascade processes.

1st train		2nd train	
Flow-rates (ml/min)		Flow-rates (ml/min)	
No recycling component A (Fig. 9a)			
Feed	0.0385	Feed	0.1170
Desorbent	0.3371	Desorbent	0.2810
Extract	0.1170	Extract	0.1367
Raffinate	0.2586	Raffinate	0.2613
Recycle	0.0634	Recycle	0.2284
Switching time (min)	11.589	Switching time (min)	3.653
Recycling component A (Fig. 9b)			
Feed	0.0385	Feed	0.0758
Desorbent	0.2491	Desorbent	0.2344
Extract	0.2119	Extract	0.2159
Raffinate	0.0758	Raffinate	0.0942
Recycle	0.0876	Recycle	0.1835
Switching time (min)	11.583	Switching time (min)	4.439

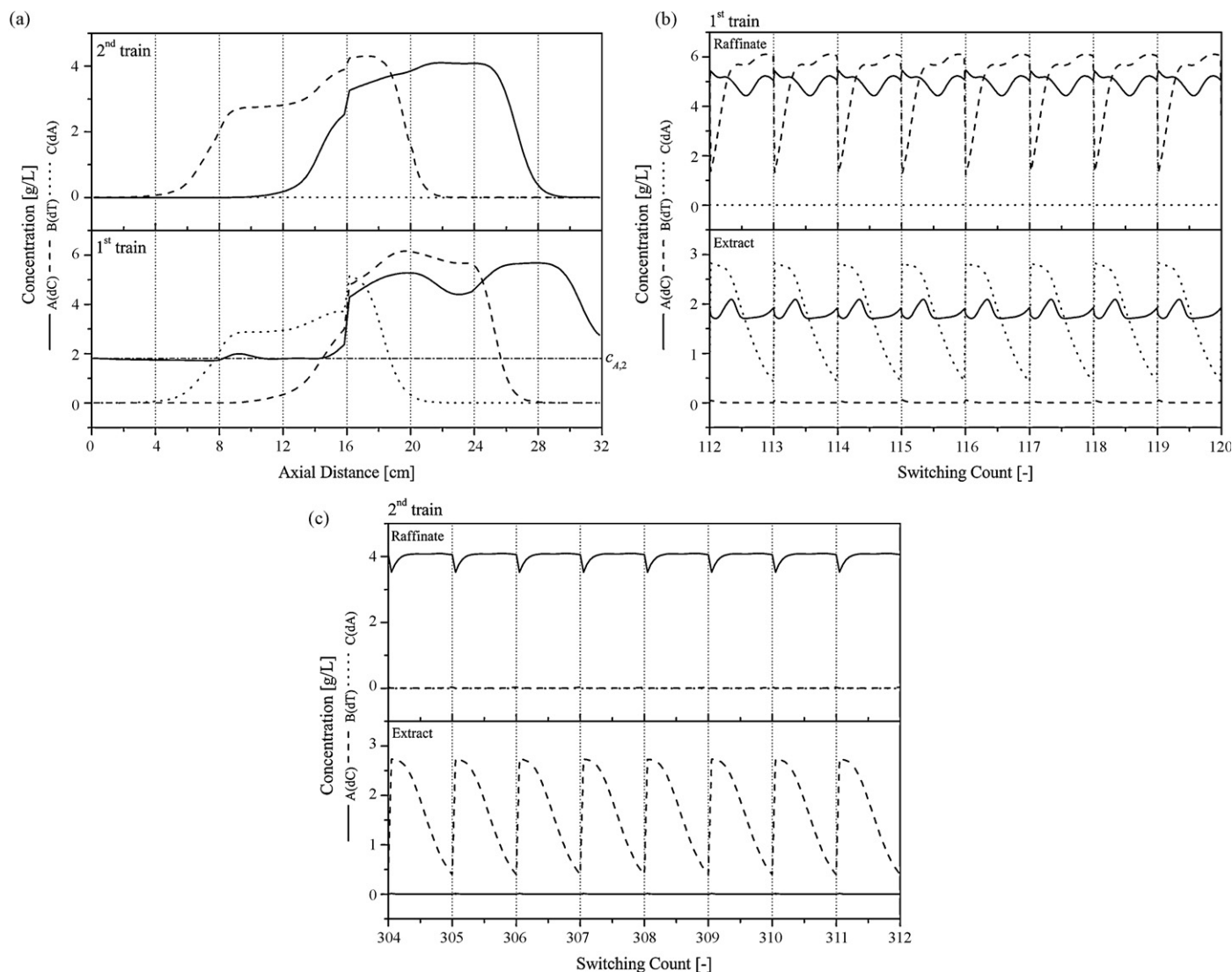


Fig. 13. Internal and outlet concentration profiles of SMB cascade with recycle of component A (Fig. 9b) after cyclic steady state is reached. Operating conditions are described in Table 6. Solid, dash, and dotted lines represent the least (dC), intermediate (dT), most (dA) retained solutes. (a) Internal concentration profiles of the 1st and 2nd trains at the middle of switching time. (b) Extract and raffinate concentration profiles of the 1st train. (c) Extract and raffinate concentration profiles of the 2nd train.

shows the operating conditions and Fig. 13 shows the concentration profiles for the SMB cascade processes. As described above, the lowest observable concentration of component A in the 1st train is the concentration in plateau 2, $c_{A,2}$. The internal profile of component A in the 1st train is above the lowest concentration level obtained from the equilibrium theory (Fig. 13a). Fig. 13b and c shows the concentration profiles of the extract and raffinate ports for 1st and 2nd trains, respectively, after these trains reach the cyclic steady state. Purity and yield of the target component are given in Table 7. Note that both SMB cascades (Fig. 9a and b) produce essentially the same purity of dT as recycle chromatography, but with considerably less desorbent.

The comparison of D/F values for recycle chromatography and the SMB cascades is not the entire picture since the SMB systems are more complex than recycle chromatography. As a first step on quantifying complexity, we have defined two complexity indexes. The structural (I_{SC}) and operational (I_{OC}) complexity indexes are defined as,

$$I_{SC} = w_C(\# \text{ of columns}) + w_V(\# \text{ of valves}) + w_P(\# \text{ of pumps}) + w_T(\# \text{ of tanks}) \quad (13a)$$

$$I_{OC} = w_S(\# \text{ of operation steps}) + w_R(\# \text{ of recycles}) \quad (13b)$$

All weighting factors w were arbitrarily fixed as 1. In recycle chromatography, two pumps (one for constant mobile phase delivery and the other for recycling desorbent or feed solution), one column, one tank, and six valves (three valves at the column inlet and three valves at the column outlet) were used. All the valves were assumed to be on-off solenoid valves. In batch chromatography, one pump for constant mobile phase delivery, one column, and four valves (two valves at the column inlet and two valves at the column outlet) were used. In the SMB cascade process (Fig. 9a), four pumps per train, eight columns per train, four valves per column, and one tank were used. When component A was recycled to the 1st train (Fig. 9b), one pump and one tank were added to the additional recycle stream. Recycle chromatography is operated with independent steps at the column inlet and outlet. The three steps at the column inlet are feed, recycle, and desorbent, and the three steps at the column outlet are product, waste, and recycle. Batch chromatography is operated with the same method as recycle chromatography except there is no recycling, so that two operation steps at the column inlet and two operation steps at the column outlet are required. In normal SMB operation, each column is located

Table 7

Comparison of recycle chromatography, batch chromatography, and SMB cascade at the same productivity for the same feed compositions of the Ternary 1 system at cyclic steady state.

Process	Purity of dT (%)	Yield of dT (%)	Productivity (g/L-h)	D/F (-)	Ratio D/F values ^a	I_{SC}^b	I_{OC}^c
Recycle chromatography	99.88	99.94	10.879	23.98	1.00	10	7
Batch chromatography	99.86	99.94	9.224	31.62	1.32	6	4
SMB cascade 1 (Fig. 9a)	99.84	99.82	10.879	16.04	0.67	89	10
SMB cascade 2 (Fig. 9b)	99.83	99.60	10.879	10.10	0.42	91	11

^a Ratio D/F values = (D/F of process)/(D/F of recycle chromatography).

^b Structural complexity index (Eq. (13a)) with all weighting factors = 1.

^c Operational complexity index (Eq. (13b)) with $w_S = w_R = 1$.

in zones 1–4 during one cycle, so that one SMB has four operation steps and one internal recycle stream. For the Varicol or partial feed operating modes I_{OC} will be higher. Table 7 compares recycle chromatography, batch chromatography and the two SMB cascade processes at the same productivity. Structural and operational complexities of batch chromatography are smaller than other processes. However, it cannot obtain the same productivity as recycle chromatography at the same purity and yield of the target product, and moreover D/F of batch chromatography is 32% larger than that of recycle chromatography. D/F of the SMB cascade processes in Fig. 9a and b are 67% and 42% of D/F of recycle chromatography, respectively. Operational complexities of recycle chromatography and cascade SMB processes were similar although recycle chromatography is a bit simpler. However, the structural complexity of the SMB cascade processes are approximately nine times that of recycle chromatography when the weighting factors in Eq. (13) are identical. The structural complexity index, I_{SC} , is expected to be related to capital cost and the operational complexity index, I_{OC} , is expected to be related to the complexity and cost of the control system. It would be useful if industrial operating experiences were used to determine appropriate weighting factors for the complexity indexes.

7. Summary

A single recycle chromatography system composed of one column and one recycle stream with a tank was simulated to purify only the intermediate retained solutes in ternary and pseudo-ternary mixtures. Two recycle methods, desorbent and feed recycle, were optimized and compared in terms of productivity and D/F. For competitive Langmuir isotherms, feed recycle had higher productivity and lower D/F than desorbent recycle. The feed recycle method worked best for systems of competitively adsorbed solutes with a strongly and most retained solute. At the same productivity, D/F of the SMB cascade processes with two columns per zone is lower than D/F of recycle chromatography. However, the SMB cascade process had a structural complexity index approximately 9 times greater than recycle chromatography.

Nomenclature

a_i	Langmuir isotherm parameter of solute i (-)
$a_p k_i$	mass-transfer coefficient of solute i (1/min)
b_i	Langmuir isotherm parameter of solute i (L/g)
c_i	concentration of solute i in the mobile phase (g/L)
$c_{i,j}$	concentration of solute i on plateau j (g/L)
c_i^0	feed concentration of solute i at the column inlet (g/L)
c_i^F	fresh feed concentration of solute i (g/L)
D_e	axial dispersion coefficient (cm ² /min)
f_{m1}	objective function for zone 1 flow-rate ratio optimization, Eq. (6c) (-)

f_{m2}	objective function to find equal difference point, Eq. (6a) (-)
f_{m3-m2}	objective function for the $m_3 - m_2$ level optimization, Eq. (6b) (-)
f_{m4}	objective function for zone 4 flow-rate ratio optimization, Eq. (6d) (-)
F_D	dilution factor, Eq. (5) (-)
I_{OC}	operational complexity index, Eq. (13b) (-)
I_{SC}	structural complexity index, Eq. (13a) (-)
m_j	flow-rate ratio of liquid phase to solid phase in zone j (-)
P_{Extr}	purity of the extract port (-)
P_{Raff}	purity of the raffinate port (-)
q_i	concentration of solute i in the stationary phase (g/L)
q_i^*	concentration of solute i in the stationary phase at equilibrium with the mobile phase concentration (g/L)
Q_j^{SMB}	volumetric flow-rate of the liquid phase in zone j of SMB process (ml/min)
Q_j^{TMB}	volumetric flow-rate of the liquid phase in zone j of TMB process (ml/min)
Q_S	volumetric flow-rate of the solid phase in TMB process (ml/min)
t_C	cycle time (min)
t_E	elution time (min)
t_F	feed time (min)
t_S	time interval of port switching in SMB process (min)
t_f	retention time of the front end elution band (min)
t_r	retention time of the rear end elution band (min)
T_{Extr}	target purity of the extract port (-)
T_{Raff}	target purity of the raffinate port (-)
u	superficial velocity of the mobile phase (cm/min)
V	volume of the column (ml)
w	weighting factor for complexity indexes (-)

Greek letters

ε	inter-particle void fraction of the column (-)
ε_p	intra-particle void fraction of the column (-)
ε_T	total void fraction of the column (-)
σ	standard deviation in Table 4 (-)

Subscripts

A	the least retained solute
B	the intermediate retained solute
C	the most retained solute

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