Methods to Control Batch Integrity in SMB Chromatography for Linear Systems

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Abstract

For a pharmaceutical like insulin, the product should be clearly linked to its source. Therefore, it is important to track each batch throughout the production process. Tracking each batch in a simulated moving bed (SMB) process is more challenging than in conventional batch chromatography. Solutes coming from a certain feed batch in SMB can be mixed with solutes coming from adjacent feed batches as a result of periodic port movement, internal recycle, and dispersion due to mass transfer. The degree of mixing or the size of the overlap region in the product stream largely depends on solute residence time. Using partial feeding, or applying pinched wave operating conditions can effectively reduce residence time and therefore decrease the overlap region. To eliminate the overlap region completely, an eluent gap can be applied between adjacent feed batch injections. The strategies for reducing residence time can minimize the eluent gap, thereby reducing eluent consumption and increasing productivity. One can further reduce the amount of eluent by operating as a three-zone SMB during the gap period and a four-zone SMB during the feed injection period.

1. Introduction

Conventional simulated moving bed (SMB) systems have been developed for the separation of binary mixtures of low molecular weight compounds (MW< 1,000). They have been used successfully for the production of hydrocarbons since the 1970's,[1,2] high fructose corn syrup since the 1980's,[3-5] and chiral pharmaceuticals since the late 1990's.[6-9] However, SMB has been rarely attempted for protein separations at laboratory scale and has never been used for protein production.

The major barriers for the application of SMB for protein purification have been (1) that almost all protein feed stocks are complex multi-component mixtures with significant mass transfer resistances, (2) that during a long chromatography process proteins can aggregate or denature, (3) that the slow decrease of column capacity due to fouling requires periodic column regeneration, and (4) that each feed mixture comes from a specific, documented batch of fermentation broth.

The fourth barrier is particularly important in pharmaceutical purifications where all purified products should be linked to their source batches in case a certain batch is defective or contaminated. This requirement is easily attained in conventional batch chromatography, which has only one product port located at a fixed position. Moreover, there is no recycle stream and all the solutes experience the same flow rate. However, in a

four-zone SMB, the raffinate product port is located downstream from the feed port whereas the extract product port is located upstream from the feed port. The ports also move periodically along the eluent flow direction. The four zones have different flow rates and some streams are continuously recycled within the circular path. These properties plus dispersion cause some solutes from a certain feed batch in SMB to be mixed with solutes from adjacent feed batches if all the batches are fed consecutively. As a result, certain portion of the product stream may come from multiple batch sources. In addition, undesirable components in a feed batch can contaminate the product from an adjacent feed batch. Therefore, it is necessary to follow the different batches throughout the production steps. Strategies to identify and control each batch in SMB are needed in order to decrease the amount of loss if a certain feed batch is defective or contaminated.

Our previous studies have addressed the first three barriers for the use of size-exclusion SMB chromatography for insulin purification.[10-14] Insulin is a solute with intermediate migration velocity in size exclusion chromatography. The insulin crude contains two other groups of impurities, pro-insulin and high molecular weight proteins (fast-moving impurities) and zinc chloride (a slow-moving impurity). Two splitting steps involving two SMB's in series (or a tandem SMB) can be used to recover insulin (Figure 1). Pro-insulin (HPI) and other high molecular weight proteins (HMWP) are removed from the raffinate port in the first SMB (Ring I). The effluent from the extract port of Ring I is collected and loaded into the second SMB (Ring II). An efficient splitting strategy for multi-component separation based on the concept of standing concentration waves was developed and tested experiemtally.[10,11] A systematic model-based design approach was used to develop the SMB with a minimal number of experiments. Both theoretical results and experimental results showed that SMB can be used to improve recovery of insulin from a multi-component mixture.

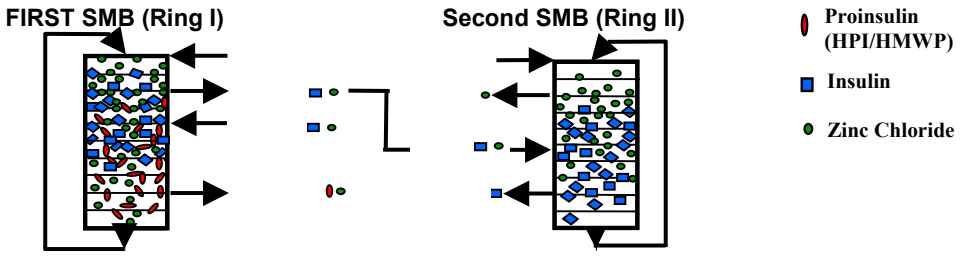

Figure 1. Schematic of a tandem SMB process for insulin purification.

The focus of this study is the fourth barrier, the issues of batch integrity. In a standard procedure, all the batches are fed consecutively. If the solutes from an earlier batch stay longer in SMB, the degree of overlap with the solutes from a later batch will be greater. Therefore, solute residence time should be shortened to reduce the degree of overlap.

There has been a previous study on the residence time distribution of a solute in SMB.[13] The results showed that residence time in SMB is related to the injection time, zone flow rates, zone lengths, selectivity, and dispersion due to mass transfer. For a fast-moving solute that is recovered in the raffinate, the molecules injected earlier during the

injection period have a shorter residence time than those injected later during the injection period (first in and first out). For a slow-moving solute that is recovered in the extract, the trend is reversed (first in and last out). For this reason, a partial feeding strategy (i.e. injection of feed during only a fraction of the step time)[13,15] can effectively reduce the average solute residence time. To shorten the residence time of a fast-moving solute, one can feed during the first half of the switching period or increase zone II flow rate beyond the requirement of standing wave (or so called "pinched wave design").[13,16] To shorten the residence time of a slow-moving solute, one can feed during the second half of the switching period or decrease zone III flow rate. However, the previous study did not address the control of batch integrity in SMB.

The goal of this study is to understand how the adjacent feed batches are mixed in SMB and find strategies to control batch integrity. First, the effects of residence time of the product solute on the mixing of products from adjacent batches in the product stream are studied. Based on the analysis, strategies to control batch integrity for size-exclusion or linear isotherm) SMB are formulated. Furthermore, strategies to maintain complete batch integrity with the highest productivity and the lowest solvent consumption are proposed.

The results of this study show that solute residence time determines the degree of mixing (or overlap) of two adjacent batches in the product stream. This overlap has more serious impact on batch integrity for a smaller batch. Strategies to reduce residence time are effective in reducing the overlap between two adjacent batches. Partial feeding and pinched wave operating conditions can reduce solute residence time and thus the degree of overlap. To completely remove the overlap region, eluent can be injected into the feed port (to replace the feed) to create a gap between the two adjacent batches and maintain complete batch integrity in the product stream. The strategies to reduce residence time can minimize the amount of eluent needed during the gap period. One can further reduce the amount of eluent needed for the gap by operating as a three-zone SMB where there is no eluent flowing into the feed port during the gap period.

2. Method and Approach

This study is based on the following assumptions: (1) all the feed batches have the same volume and concentration, (2) the volume of one feed batch is sufficiently large to reach a cyclic steady state in the effluent history, and (3) the system of investigation is either a size-exclusion system or a linear isotherm system.

Several terms are introduced to facilitate the analysis. First, the amount of time needed for completing the injection of each feed batch is defined as Δ_{feed}. Unless noted otherwise, the feed batch injections are continuous.

The breakthrough time and the extinction time of the n^{th} batch are denoted as t_b^n and t_e^n, respectively. In this study, the breakthrough time is defined as the time when a product concentration in the advancing wave reaches 1% of the plateau (or steady state) concentration. Similarly, the extinction time is defined as the time when a product

concentration in the trailing wave reaches 1% of the plateau (or steady state) concentration.

2.1. Effect of Residence Time on Batch Integrity

As a series of feed batches are consecutively introduced into SMB (Figure 2a), the resulting effluent history of a product component for an ideal system is shown in Figure 2b. Although mass-transfer effects are negligible in an ideal system, the concentration band corresponding to each batch is spread, resulting in an overlap of two adjacent batches (Figure 2b). The band spread occurs in an ideal system as a result of periodic port movement and recycle in SMB.

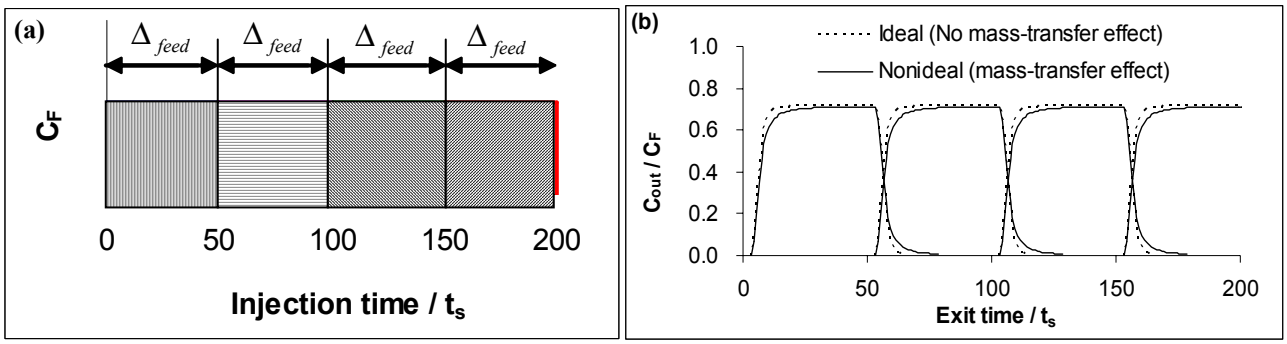

Figure 2. Batch integrity in the first ring of a tandem SMB for insulin purification. (a) Injections of a series of feed batches with a size of 50 t_s; (b) Effluent history of insulin at the extract port. Concentrations in the effluent history are averaged over one switching period.

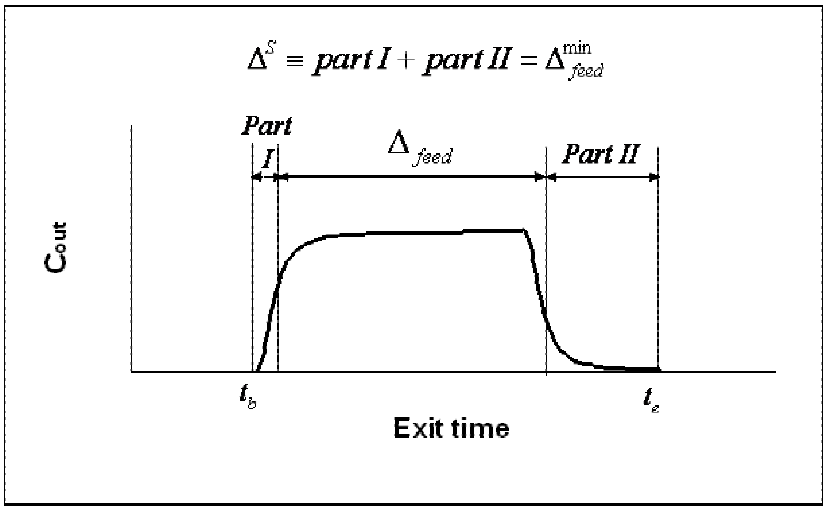

Figure 3. Representation of Δ_{feed}^{min} in the effluent history. Concentrations in the effluent history are averaged over one switching period.

In a non-ideal system, the concentration band is more broadened because of mass-transfer effects. The broadening effects are further enhanced by the combined effects of mass-transfer plus port movement and recycle (Figure 2b). As a result, the amount of time needed for collecting all the solutes from the batch becomes much larger than Δ_{feed} as shown in Figure 3. This leads to an increase in an overlapping region in the effluent history and has undesirable effects on batch integrity. The additional time required for complete collection of the batch, which is defined here as Δ^S, is compared with the batch size (Δ_{feed}) in Figure 4b.

$$\Delta^S \equiv (t_e - t_b) - \Delta_{feed} \tag{1}$$

where Δ_{feed} is also the length of time between the mass centers of the advancing wave and the trailing wave in the effluent history.

In order to explain further the meaning of Δ^S, we compare Figure 2a with Figure 2b. The comparison reveals that a decrease in Δ_{feed} may cause an overlap between solutes coming from the 1st batch and solutes coming from the 3rd batch (or solutes coming from the nth batch and solutes coming from the (n+2)th batch). This indicates the existence of a minimum Δ_{feed} to prevent the overlap of the nth batch and the (n+2)th batch. The minimum Δ_{feed} is denoted here as $\Delta_{feed}^{\min}$ and will play an important role in controlling batch integrity. On the basis of the mass balance in the product stream, one can prove that $\Delta_{feed}^{\min}$ is equal to Δ^S as follows:

$$\Delta_{feed}^{\min} = \Delta^S \equiv (t_e - t_b) - \Delta_{feed} \tag{2}$$

where t_e and t_b are the extinction time and the breakthrough time for a feed batch with an arbitrary size, Δ_{feed}. The length of $\Delta_{feed}^{\min}$ based on eq 2 (Figure3) is related to solute residence time. As explained later, the $\Delta_{feed}^{\min}$ should be larger as solutes stay longer in SMB.

2.2. Batch Integrity in SMB

To maintain batch integrity in SMB, the product stream coming from a certain batch should be collected separately from the product streams coming from the adjacent two batches. The fraction of product in the overlapping region (*FO*) can be derived as a function of Δ_{feed} and $\Delta_{feed}^{\min}$ as follows:

$$FO \equiv \frac{Amount\ of\ product\ in\ the\ overlapping\ region}{Amount\ of\ product\ in\ one\ batch} = \frac{\Delta_{feed}^{\min}}{\Delta_{feed}} \tag{3}$$

Based on eq 4, we define the batch integrity index (*BII*) as follows:

$$BII \equiv 1 - FO = 1 - \frac{\Delta_{feed}^{\min}}{\Delta_{feed}} \tag{4}$$

To improve batch integrity in SMB, one can decrease $\Delta_{feed}^{\min}$ and/or increase Δ_{feed}. Since a shorter residence time leads to smaller $\Delta_{feed}^{\min}$, strategies to reduce residence time in

SMB[13] can also be effective in improving batch integrity (or decreasing *FO* and increasing *BII*).

In order to achieve complete batch integrity (or *BII* = 1) in SMB, one can input eluent between two adjacent batches. However, this method causes a significant decrease in productivity and an increase in solvent consumption as follows:

$$\frac{Prod_G}{Prod} = \frac{\Delta_{feed}}{\Delta_{feed} + \Delta_{gap}} \tag{5}$$

$$\frac{SC_G}{SC} = \frac{\Delta_{feed} + \Delta_{gap}}{\Delta_{feed}} \tag{6}$$

where *Prod* and *SC* stand for productivity and solvent consumption, respectively, and the subscript *G* stands for the placement of an eluent gap between batch injections. Δ_{gap} is the size of the gap in time unit. To minimize loss in productivity and solvent consumption, it is necessary to determine the minimal length of gap that leads to complete batch integrity in the product stream. One can easily proved that the minimal length of gap for complete batch integrity ($\Delta_{gap}^{\min}$) is equal to $\Delta_{feed}^{\min}$. Replacing Δ_{gap} with $\Delta_{feed}^{\min}$ in eqs 5 and 6, one can therefore obtain the highest productivity and the lowest solvent consumption under the condition of complete batch integrity. Furthermore, strategies to shorten residence time in SMB can be applied to decrease $\Delta_{feed}^{\min}$, resulting in a smaller $\Delta_{gap}^{\min}$ as discussed below.

2.3. Effect of Partial Feeding on Batch Integrity

As shown in a previous study,[13] residence time in SMB is a strong function of injection time within one switching period. To decrease $\Delta_{feed}^{\min}$, one can inject feed only during a fraction of the switching period that leads to short residence time for the product of interest. During the rest of the period, eluent is injected into the feed port. These alternating injections are repeated every switching time. This strategy is defined as a partial feeding strategy. The partial feeding increases the amount of time required to complete the injection of one feed batch as follows:

$$\Delta_{feed}^{PF} = \frac{\Delta_{feed}}{h} \tag{7}$$

where *PF* stands for a partial feeding strategy and h is the fraction of feed-injection time over one switching period. Equations 3 and 7 are used to express the *FO* based on the partial feeding strategy.

$$FO_{PF} = \frac{\Delta_{feed}^{PF,\min}}{\Delta_{feed}^{PF}} = h \cdot \left(\frac{\Delta_{feed}^{PF,\min}}{\Delta_{feed}^{\min}} \right) \cdot FO \tag{8}$$

where $\Delta_{feed}^{PF,\min} = (t_e^1 - t_b^1)_{PF} - \Delta_{feed}^{PF}$. Since h is less than unity and $\Delta_{feed}^{PF,\min}$ is smaller than $\Delta_{feed}^{\min}$, the partial feeding strategy always has a lower *FO*, or less amount of product in the overlapping region. As shown in the previous study,[13] a lower h leads to a shorter residence time, which in turn decreases $\Delta_{feed}^{PF,\min}$ and FO_{PF}. However, a lower h results in a lower productivity and a higher solvent consumption as follows:

$$\frac{Prod_{PF}}{Prod} = h \tag{9}$$

$$\frac{SC_{PF}}{SC} = \frac{1}{h} \tag{10}$$

The partial feeding strategy can be employed together with an eluent gap between two adjacent batches to achieve a batch integrity index of unity. The minimal length of gap in the partial feeding strategy ($\Delta_{gap}^{PF,\min}$) is equal to $\Delta_{feed}^{PF,\min}$. Since $\Delta_{feed}^{PF,\min}$ is smaller than $\Delta_{feed}^{\min}$, the partial feeding strategy requires a smaller size of gap to achieve complete batch integrity. The smaller gap results in an increase in productivity. However, the partial feeding itself increases the time needed to process each batch (eq 7), resulting in a decrease in productivity (eq 9). This indicates the importance of determining the optimal h for the highest productivity or the lowest solvent consumption under the condition of complete batch integrity ($FO = 0$).

2.4. Relationship Between $\Delta_{feed}^{\min}$ and Residence Time

As an example, the relationship between $\Delta_{feed}^{\min}$ and residence time ($t_{0.99}$) is investigated for the second ring in a tandem SMB for insulin purification.[11] The relationship between the two is presented in Figure 4, in which a partial feeding method with a different throughput is applied to vary the residence time of insulin.[13] One can see that the magnitude of $\Delta_{feed}^{\min}$ increases with increasing residence time.

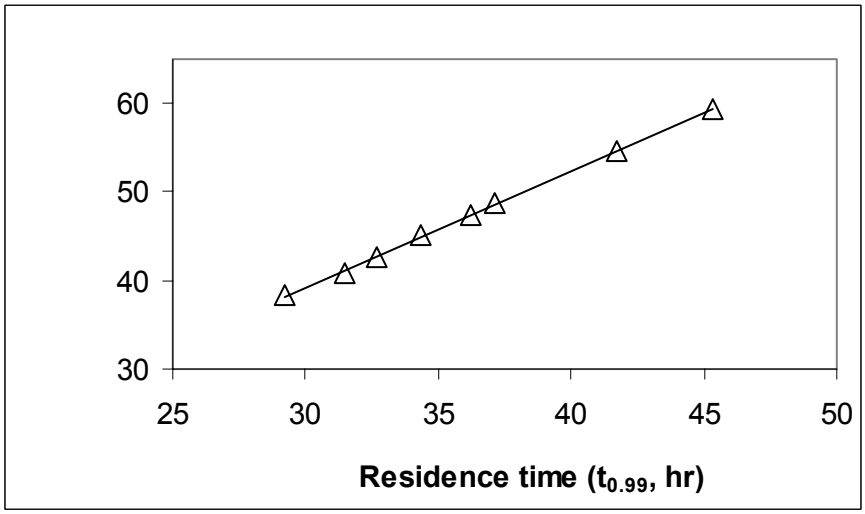

Figure 4. Correlation between $t_{0.99}$ and $\Delta_{feed}^{\min}$ in the second ring of a tandem SMB for insulin purification. $t_{0.99}$ is the time that 99% of insulin have left the SMB when the feed is injected during one switching period. The y-axis is normalized by the switching time (t_s = 36.2 min).

2.5. Effect of Pinched Wave Design on Batch Integrity

In the standing wave design (SWD),[10,17] the flow rates in the four zones are chosen so that the four waves are standing in the appropriate zones in a time-averaged

sense. In this case, the velocities of a fast-moving solute in zone II and a slow-moving solute in zone III relative to the port velocity are minimized to achieve the maximum throughput. However, this leads to a significant increase in the residence times of the solutes. For this reason, a pinched wave design (PWD), in which the concentration wave in zone II or zone III is no longer "standing" but "stuck" or "pinched" between zone II and zone III, can shorten the residence time of the key-component in SMB.[13] The zone III flow rate is decreased to shorten the residence time of the slow-moving solute whereas the zone II flow rate is increased to shorten the residence time of the fast-moving solute.[13] Both cases result in a decrease in the feed flow rate as follows.

$$F_{feed,PW} = f \cdot F_{feed} \tag{11}$$

where PW stands for a pinched wave design and f is the ratio of the feed flow rate in PWD ($F_{feed,PW}$) to the feed flow rate in SWD (F_{feed}). The decrease in the feed flow rate increases the time required to complete the injection of one batch (or batch size in time unit) as follows:

$$\Delta_{feed}^{PW} = \frac{\Delta_{feed}}{f} \tag{12}$$

The shortened residence time and the increased batch size in time unit are both effective in improving batch integrity as shown in the following:

$$FO_{PW} = \frac{\Delta_{feed}^{PW,\min}}{\Delta_{feed}^{PW}} = f \cdot \left(\frac{\Delta_{feed}^{PW,\min}}{\Delta_{feed}^{\min}} \right) \cdot FO \tag{13}$$

where $\Delta_{feed}^{PW,\min} = (t_e^1 - t_b^1)_{PW} - \Delta_{feed}^{PW}$. As shown in eq 13, the amount of product in the overlapping region can be substantially reduced by decreasing f. However, a lower f decreases productivity and increases solvent consumption as follows:

$$\frac{Prod_{PW}}{Prod} = f \tag{14}$$

$$\frac{SC_{PW}}{SC} = \frac{1}{f} \cdot \left(\frac{F_{eluent} + f \cdot F_{feed}}{F_{eluent} + F_{feed}} \right) \tag{15}$$

where F_{eluent} is the eluent flow rate into the eluent port.

Complete batch integrity ($FO_{PW} = 0$) cannot be achieved using only a PWD method. An eluent gap is needed between batch injections to achieve complete batch integrity. Similar to the case of a partial feeding method, the minimal length of gap needed in the PWD method, $\Delta_{gap}^{PW,\min}$, is equal to $\Delta_{feed}^{PW,\min}$. Since $\Delta_{feed}^{PW,\min}$ decreases with decreasing f, a lower f results in a smaller $\Delta_{gap}^{PW,\min}$ and thus has a desirable effect on productivity and solvent consumption. However, a lower f decreases the feed flow rate, resulting in a lower productivity and a higher solvent consumption. For these reasons, there exists an optimal f to achieve either the highest productivity or the lowest solvent consumption while maintaining complete batch integrity.

2.6. Approach

In each case, Δ_{feed}^{min} is calculated to estimate *FO* or Δ_{gap}^{min}. Only one effluent history from a batch with an arbitrary size is required for a quick determination of Δ_{feed}^{min}. The effluent history is generated from rate model simulations. The simulations are carried out using VERSE, which has been validated in several previous studies.[11,18-21]

The second ring of a tandem SMB for insulin purification[11] is the focus of this study. The operating conditions of the SMB were determined from the standing wave design.[10,17] The intrinsic parameters used in the standing wave design and the simulations have been reported by Xie et al.[11] The resulting zone linear velocities and switching time (t_s) are listed in Table 1 and are used in the batch integrity analysis. The volume of each feed batch injected into the SMB is fixed and its size in time unit corresponds to $60\,t_s$.

Table 1. Operating conditions of the SMB (Ring II) used in the analysis of batch integrity

Zone linear velocities† (cm/min)	Zone I	1.0972	Inlet and outlet linear velocities† (cm/min)	Feed	0.1591
	Zone II	0.9299		Eluent	0.1892
	Zone III	1.0890		Raffinate	0.1810
	Zone IV	0.9080		Extract	0.1673
Zone configuration		2 – 3 – 3 – 2	Switching time (min)		36.20

* Single column length = 15 cm.

† $u_0 = F/(\varepsilon_b S)$, where F and S are the flow rate and the column cross-sectional area, respectively.

3. Results and Discussion

First, batch integrity is investigated for the standard case, in which a series of batches are injected without any eluent gap and the operating conditions are based on the standing wave design and the full feeding. The strategies that can reduce residence time[13] are then applied to control batch integrity. Furthermore, the methods to achieve complete batch integrity with the highest productivity or the lowest solvent consumption are developed. In all the methods, the threshold concentration is set to be 1%.

3.1. Batch Integrity for the Standard Case

In the SMB, insulin is recovered from the raffinate port. From eq 2, the Δ_{feed}^{min} is found to be about $59\,t_s$. Since Δ_{feed} is larger than Δ_{feed}^{min}, the SMB has no overlap between the n^{th} batch and the $(n+2)^{th}$ batch at the raffinate port (Figure 5). However, the difference between Δ_{feed} and Δ_{feed}^{min} is too small, resulting in a short interval between the n^{th} batch

and the $(n+2)^{th}$ batch in the effluent history (Figure 5). Both Δ_{feed} and Δ_{feed}^{min} are used to calculate the *FO* as follows:

$$FO = \frac{\Delta_{feed}^{min}}{\Delta_{feed}} = \frac{59t_s}{60t_s} = 0.98$$

The resulting *FO* means that 98% of the insulin in the raffinate comes from multiple batch sources.

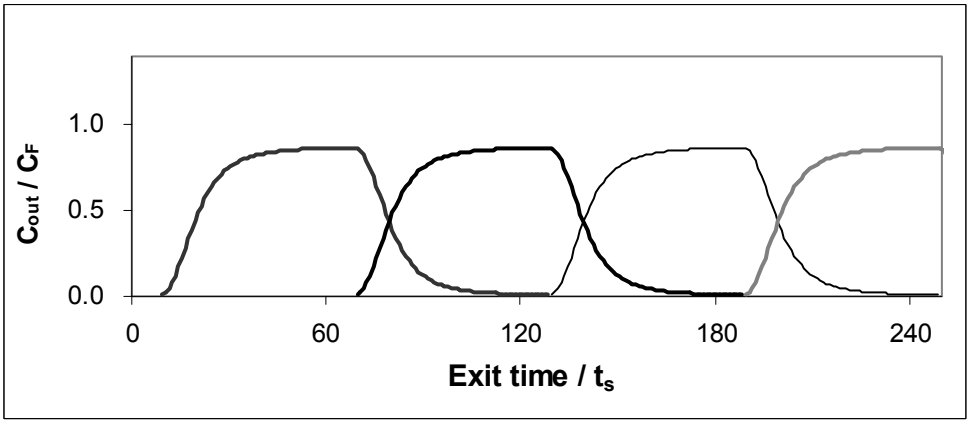

Figure 5. Effluent history of insulin from the injections of a series of batches with a size of $60\,t_s$ in Ring II. Concentrations in the effluent history are averaged over one switching period.

3.2. Strategies to Reduce Overlapping Region without an Eluent Gap

In the previous sections, it was found that a high *FO* (or low batch integrity index) in the SMB is caused by the long residence time of insulin. Since a partial feeding strategy and a PWD method can reduce residence time,[13] these methods can be applied to reduce the overlapping region and increase batch integrity index in the SMB.

3.2.1. Method I: Partial Feeding Strategy. In the SMB, insulin molecules injected earlier in a switching period have a shorter residence time.[13] Thus, the feed should be injected during the initial part of the switching time to shorten insulin residence time. As the fraction of feed-injection time during one switching period (*h*) is decreased, the residence time of insulin is reduced (Figure 6a). For this reason, the *FO* of Ring II decreases with decreasing *h* as shown in Figure 6b.

The *FO* for full feeding (or $h = 1$) is 0.98. If the feed is injected only during the first half of the switching period (or $h = 0.5$), the *FO* is reduced to 0.32, resulting in 67 % decrease in the amount of insulin in the overlapping region. Effluent history of insulin from the partial feeding ($h = 0.5$) is presented in Figure 7a. One can see that more insulin in the product stream comes from the same feed batch compared to the standard case (Figure 5).

Comparison of Figures 6a and 6b reveals that as *h* decreases, both residence time and *FO* decrease. Below $h = 0.85$, a smaller *h* results in a slight reduction in the residence

time but still a significant reduction in the *FO*. This is due to the effect of *h* on batch size (Δ_{feed}). A small *h* increases the amount of time needed for processing one batch with a fixed volume, resulting in a large Δ_{feed} and small *FO*. Therefore, if *h* is below 0.85, increased Δ_{feed} is the main reason for reduced *FO*. However, for a value of *h* slightly less than 1.0, shortened residence time is the main reason for the reduced *FO*.

3.2.2. Method II: PWD Method. In the SMB, insulin is collected at the raffinate port. The trailing wave of insulin is standing in zone II. In this standing wave condition, insulin in zone II takes a long time to reach the raffinate port, resulting in a long residence time and a low batch integrity index. To shorten the residence time of insulin, one can use pinched wave operating conditions, in which the zone II flow rate is maintained higher than the standing wave value.[13] As the zone II flow rate is increased by decreasing the extract flow rate, the feed flow rate should be decreased accordingly in order to maintain the standing wave of the slow-moving solute in zone III.

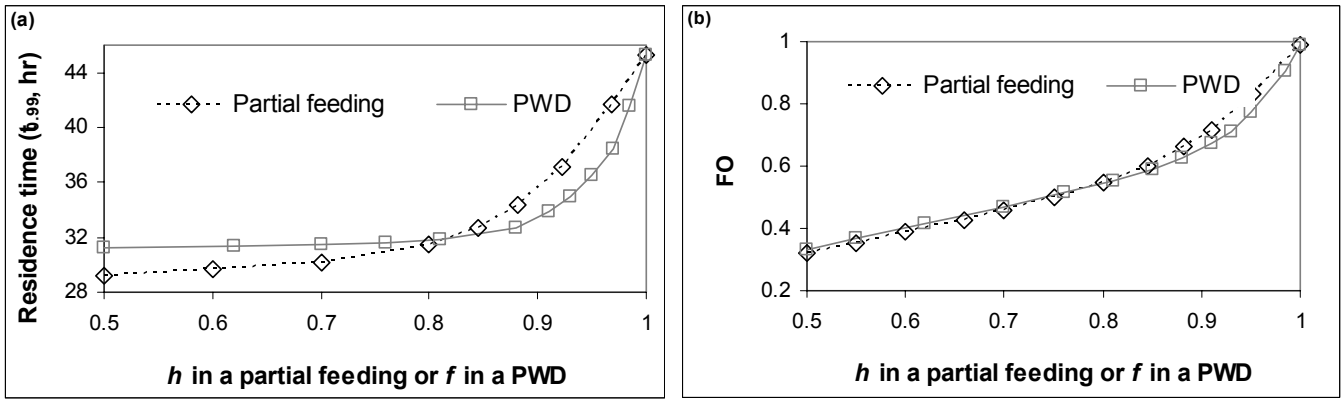

Figure 6. Partial feeding strategy and PWD method for reducing *FO* in Ring II. No gap is put between batch injections. (a) Effect of *h* or *f* on the residence time ($t_{0.99}$) of insulin; (b) Effect of *h* or *f* on *FO*.

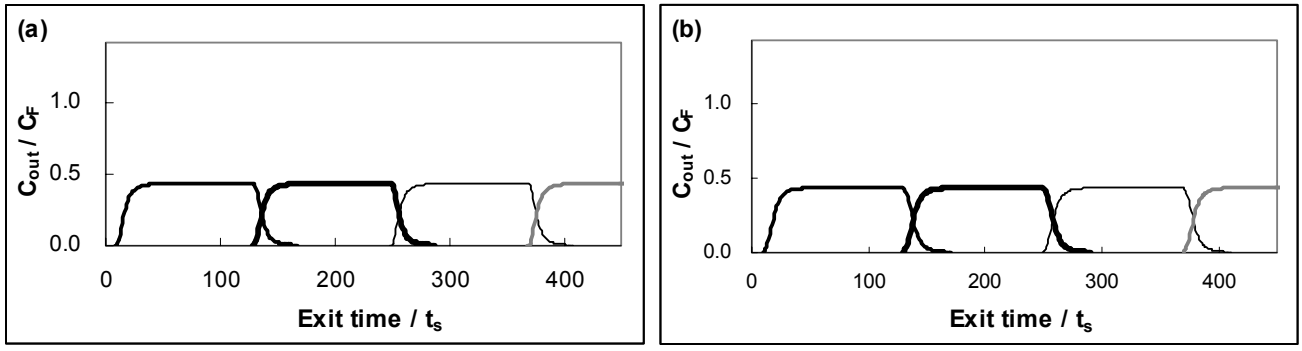

Figure 7. Effluent histories of insulin from the strategies to reduce *FO* in Ring II. (a) Partial feeding (*h* = 0.5) without a gap; (b) PWD (*f* = 0.5) without a gap

Figures 6a and 6b show the effects of the pinched wave operating conditions on the insulin residence time and *FO*. A decrease in the feed flow rate (or a decrease in *f*), which results from an increase in the zone II flow rate, leads to a shorter residence time of insulin (fast-moving solute) and a smaller *FO*. VERSE simulations are used to generate the effluent history resulting from the PWD based on 50% decrease in the feed flow rate (Figure 7b). One can see that the overlapping region between two adjacent batches is much smaller than that of the standard case (Figure 5). The use of PWD with f = 0.5 results in a reduction of insulin in the overlapping region by 66%.

3.3. Strategies to Maintain Complete Batch Integrity (*BII* = 1)

The first step to achieve complete batch integrity (or *FO* = 0) is to determine the minimal eluent gap between adjacent feed batches. Since $\Delta_{feed}^{\min}$ was estimated to be $59\,t_s$, the $\Delta_{gap}^{\min}$ should also be $59\,t_s$ as explained in the theory section. However, this causes 50% decrease in productivity and 98% increase in solvent consumption compared to the standard case. To achieve complete batch integrity with a higher productivity or a lower solvent consumption, one can use a partial feeding or a PWD together with a minimal eluent gap between batch injections as discussed below.

3.3.1. Partial Feeding Strategy for Complete Batch Integrity. The productivity of the partial feeding with a minimal eluent gap is shown as a function of *h* in Figure 8a. The y-axis is normalized by the productivity for a full feeding with the minimal eluent gap. For a full feeding (*h* = 1), the minimal size of gap needed for complete batch integrity should be $59\,t_s$. As *h* is decreased, the amount of time needed for processing one batch increases accordingly. On the other hand, a decrease in *h* leads to a reduction in the residence time, which in turn decreases the required minimal gap size to below $59\,t_s$. Since the residence time is reduced sharply between *h* = 0.88 and *h* = 1 (Figure 8a), the productivity keeps increasing until *h* is reduced to 0.88 (Figure 8a). In this case, the productivity is mainly governed by the size of the gap. However, if *h* is less than 0.88, the residence time is reduced slowly (Figure 8a) and its effect on the gap size becomes negligible. In this case, the productivity decreases as *h* decreases because of the corresponding increase in batch processing time. As a result, the productivity is maximum at *h* = 0.88 (Figure 8a). For the same reason, the solvent consumption is minimum at *h* = 0.88 (Figure 8b). The results indicate that partial feeding with the optimal *h* (0.88) is more effective in maintaining complete batch integrity than a full feeding.

3.3.2. PWD Method for Complete Batch Integrity. The productivity of the PWD with a minimal eluent gap is shown as a function of f in Figure 8a. The productivity of the SWD (f = 1) with the minimal eluent gap is set to be unity. As shown in Figure 8a, the productivity keeps increasing until f is reduced to 0.91. This is because the residence time has a sharp reduction between f = 0.91 and f = 1 (Figure 8a), resulting in a sharp decrease in the size of the eluent gap required for complete batch integrity. As a result, a maximum in the productivity is obtained at f = 0.91. The maximum productivity is about 9% higher than the productivity of the SWD with an eluent gap. The results indicate that

PWD with the optimal f (0.91) is more effective in achieving complete batch integrity than SWD.

The PWD also has lower solvent consumption than the SWD as shown in Figure 8b. If the feed flow rate is decreased by 15% in the PWD (f = 0.85), it results in 12% savings in solvent consumption compared to the SWD. In addition, the solvent consumption of the PWD method is much lower than that of the partial feeding strategy (Figure 8b). This is because an additional decrease in the feed flow rate during a batch injection and a gap also contributes to a substantial reduction in the solvent usage of the PWD method. Since the maximum productivity of the PWD method is also higher than that of the partial feeding strategy (Figure 8a), the PWD method is preferred for achieving complete batch integrity in SMB.

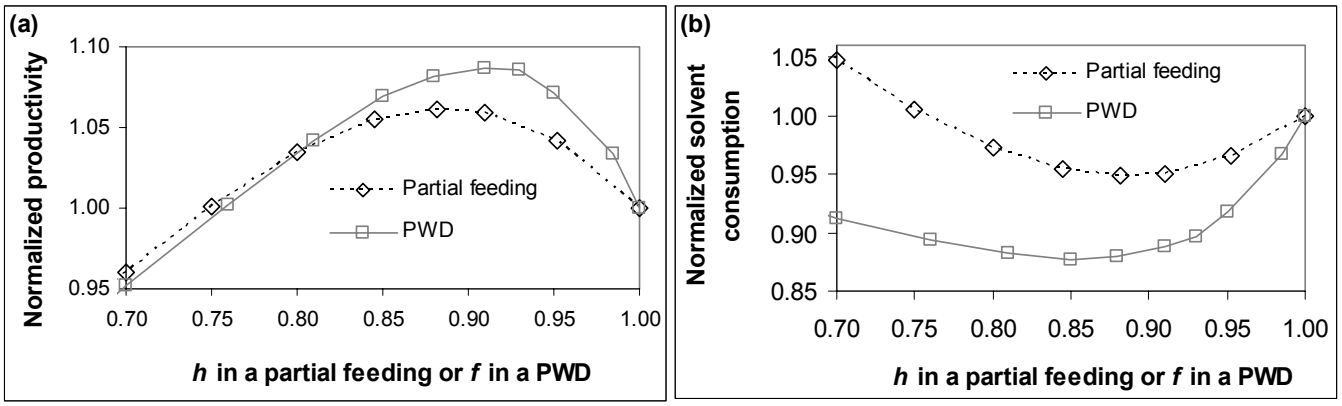

Figure 8. Partial feeding strategy and PWD method for complete batch integrity (FO = 0) in Ring II. A minimal eluent gap is used between batch injections. (a) Effect of h or f on productivity; (b) Effect of h or f on solvent consumption.

3.3.3. Alternate Use of a Four-Zone SMB and a Three-Zone SMB for Complete Batch Integrity. In the two aforementioned methods, the eluent is injected into the feed port between two adjacent batches in order to maintain constant flow rates in all four zones. To reduce solvent consumption, one can increase the zone II flow rate by reducing the extract flow rate and decrease the eluent flow rate into the feed port during the gap period. The residence time of insulin is reduced as a result of the increased zone II flow rate.[13] The decrease in the eluent flow rate into the feed port helps reduce solvent consumption without affecting productivity and batch integrity. The solvent consumption reaches a minimum when there is no eluent flowing into the feed port during the gap period. This case, in fact, corresponds to a three-zone SMB where the zone III flow rate is the same as the zone II flow rate. Therefore, the strategy of running a three-zone SMB to create a gap between different batches and a four-zone SMB during the feed period can completely isolate the different batches while having the lowest solvent consumption, as shown later in an example in Figure 10.

3.3.4. Alternate Use of a PWD and a SWD for Complete Batch Integrity. In most cases, the operating conditions during the latter periods of a batch injection have more impact on batch integrity than the operating conditions during the earlier periods. From this standpoint, a PWD for complete batch integrity needs to be applied only in the latter part of a batch injection. During the rest of the batch injection period, SWD operating conditions can be used to decrease the batch size (or the amount of time needed for processing each batch). This alternate use of PWD and SWD conditions can lead to a higher productivity compared to the case where only a PWD is used to maintain complete batch integrity.

If only a PWD with $f = 0.5$ is used to maintain complete batch integrity, the batch size and the minimal gap size should be $120\,t_s$ and $40\,t_s$, respectively. However, if the SWD is applied from the beginning of a batch injection for a time period of $45\,t_s$ and followed by the PWD, the batch size can be reduced to $75\,t_s$. In this case, the gap size for complete batch integrity can be maintained the same as in the case where only the PWD with $f = 0.5$ is used. On the basis of the two aforementioned methods, the effluent histories are obtained from VERSE simulations and compared in Figure 9. It is easily seen that a larger number of batches can be processed by the alternate use of PWD and SWD. In addition, the eluent gap with a size of $40\,t_s$ is sufficient to maintain complete batch integrity. Overall, the alternate use of the PWD ($f = 0.5$) and the SWD results in 39% increase in productivity compared to the case where only the PWD ($f = 0.5$) is used.

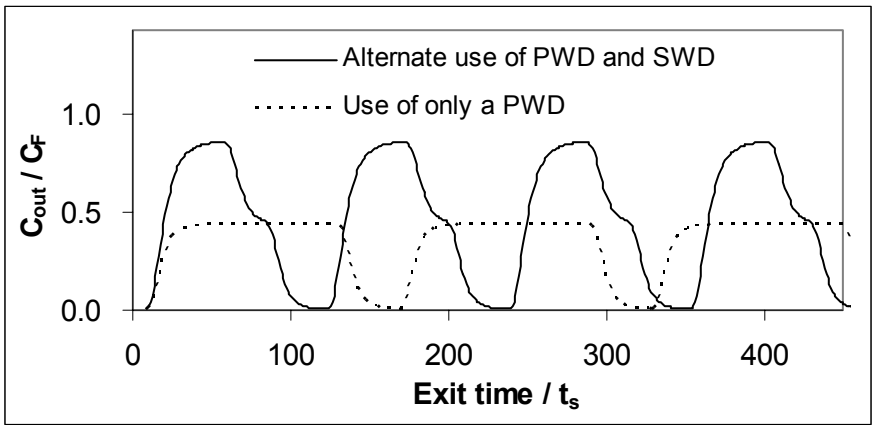

Figure 9. Comparison of the effluent histories of insulin in Ring II from the alternate use of PWD ($f = 0.5$) & SWD and the use of only PWD ($f = 0.5$). An eluent gap with a size of $40\,t_s$ is injected between two adjacent batches.

3.3.5. Alternate Use of a Full Feeding Followed by a Partial Feeding for Complete Batch Integrity. Similarly, a partial feeding and a full feeding can also be applied alternately to increase productivity while maintaining complete batch integrity. In this case, alternate partial feeding and full feeding give similar results as alternate PWD and SWD operating conditions mentioned previously.

3.3.6. Alternate Use of a Four-Zone SMB, a Three-Zone SMB, a PWD (or Partial Feeding), and a SWD (or Full Feeding) for Complete Batch Integrity. In the previous sections, it was found that the alternate use of a four-zone SMB and a three-zone SMB requires less eluent to achieve complete batch integrity than the use of only a four-zone SMB. In addition, the alternate use of a PWD (or partial feeding) and a SWD (or full feeding) was found to decrease the time for processing each feed batch, resulting in a higher productivity than the use of only a PWD (or partial feeding). Therefore, one can combine the two methods to have the highest productivity and the lowest eluent consumption while maintaining complete batch integrity. In this case, the SWD (or full feeding) is followed by the PWD (or partial feeding) during each batch injection under the four-zone SMB. After the batch injection is completed, the feed port is closed in order to operate as a three-zone SMB, which is maintained until the next feed batch injection.

Figure 10a shows an example of applying a four-zone SMB, a three-zone SMB, PWD, and SWD alternately. The effluent history resulting from the application is shown in Figure 10b, where complete batch integrity is confirmed. This application has an 13% increase in the productivity, a 29% reduction in the solvent consumption, and a 13% increase in the average product concentration, compared to the method of using only SWD and four-zone SMB with the minimal eluent gap.

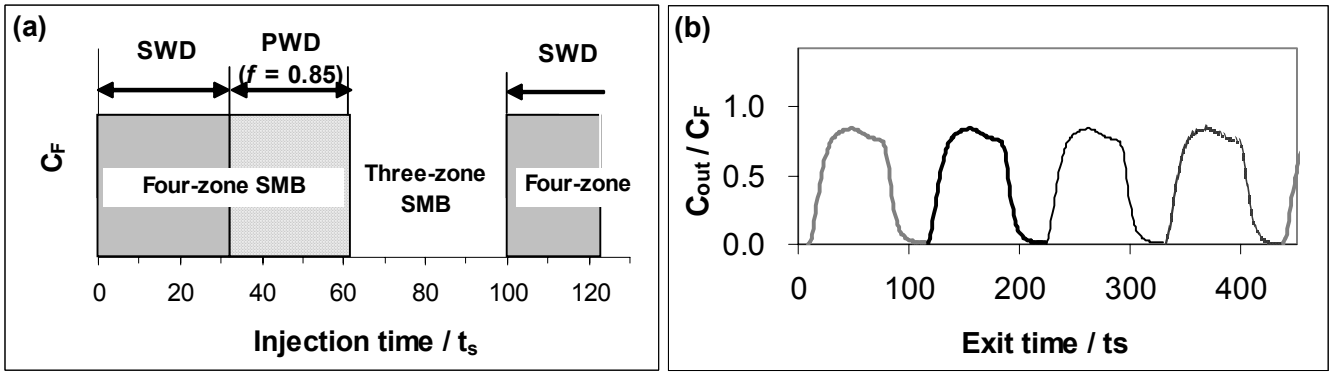

Figure 10. Alternate use of PWD (f = 0.85), SWD, a four-zone SMB, and a three-zone SMB for complete batch integrity in Ring II. (a) Change in operation mode; (b) Effluent history of insulin at the raffinate port.

4. Conclusion

Batch integrity in SMB was analyzed based on the assumption that all the feed batches have the same volume and concentration, and the system of interest is linear and non-interacting. The results show that batch integrity in SMB strongly depends on the following two factors: (1) Δ_{feed} (batch size in time unit) and (2) $\Delta_{feed}^{\min}$, which is closely related to the residence time of a solute in SMB. $\Delta_{feed}^{\min}$ corresponds to the difference between the total elution time and the Δ_{feed} for a batch. Only one effluent history obtained from the rate model simulation is needed to estimate $\Delta_{feed}^{\min}$.

To reduce the overlap between the products from two adjacent batches, one should increase feed size or shorten the residence time of the solute of interest by applying a partial feeding strategy or pinched wave operating conditions (PWD).

To achieve complete control of batch integrity in SMB, one should have an eluent gap between batch injections. In this method, the full feeding or standing wave design (SWD) has a significantly higher solvent consumption and lower productivity than the partial feeding method or the PWD method with the minimal eluent gap. To reduce the solvent consumption further, one can use a three-zone SMB without feed during the gap period and a four-zone SMB during the feed batch injection (A). To increase the productivity further, one can use alternating partial feeding and full feeding or use alternating PWD and SWD conditions (B). Therefore, the most effective method in achieving complete batch integrity is to combine the two methods (A) and (B). In this case, the SWD (or full feeding) is followed by the PWD (or partial feeding) during each batch injection under the four-zone SMB. Each time the batch injection is completed, the feed port is closed in order to operate as a three-zone SMB, which is maintained until the next feed batch injection. This application results in a 13% (or 12%) increase in the productivity and a 29% (or 26%) reduction in the solvent consumption, compared to the use of only SWD (or full feeding) and four-zone SMB.

References

(1) Broughton, D. B. Molex: Case History of a Process. *Chem. Eng. Prog.* **1968**, *64*, 60.

(2) Broughton, D. B.; Neuzil, R. W.; Pharis, J. M.; Brearley, C. S. The Parex Process for Recovering Paraxylene. *Chem. Eng. Prog.* **1970**, *66*, 70.

(3) Broughton, D. B. Production-Scale Adsorptive Separations of Liquid Mixtures by Simulated Moving Bed Technology. *Sep. Sci. Technol.* **1984**, *19*, 723.

(4) Barker, P. E.; Joshi, K. The Recovery of Frutose from Inverted Sugar Beet Molasses Using Continuous Chromatography. *J. Chem. Technol. Biotechnol.* **1991**, *52*, 93.

(5) Ching, C. B.; Ruthven, D. M.; Hidajat, K. Experimental Study of a Simulated Counter-Current Adsorption System — III. Sorbex Operation. *Chem. Eng. Sci.* **1985**, *40*, 1411.

(6) Nicoud, R. M.; Fuchs, G.; Adam, P.; Bailly, M.; Kusters, E.; Antia, F. D.; Reuille, F.; Schmid, E. Preparative Scale Enantioseparation of a Chiral Epoxide: Comparison of Liquid Chromatography and Simulated Moving Bed Adsorption Technology. *Chirality* **1993**, *5*, 267.

(7) Pais, L. S.; Loureiro, J. M.; Rodrigues, A. E. Separation of 1,1'-bi-2-naphthol Enantiomers by Continuous Chromatography in Simulated Moving Bed. *Chem. Eng. Sci.* **1997**, *52*, 245.

(8) Pedeferri, M.; Zenoni, G.; Mazzotti, M.; Morbidelli, M. Experimental Analysis of a Chiral Separation through Simulated Moving Bed Chromatography. *Chem. Eng. Sci.* **1999**, *54*, 3735.

(9) Lehoucq, S.; Verheve, D.; Wouwer, A. V.; Cavoy, E. SMB Enantioseparation: Process Development, Modeling, and Operating Conditions. *AIChE J.* **2000**, *46*, 247.
(10) Hritzko, B. J.; Xie, Y.; Wooley, R. J.; Wang, N.-H. L. Standing Wave Design of Tandem SMB for Linear Multicomponent Systems. *AIChE J.* **2002**, *48*, 2769.
(11) Xie, Y.; Mun, S.; Kim, J.-H.; Wang, N.-H. L. Standing Wave Design and Experimental Validation of a Tandem Simulated Moving Bed Process for Insulin Purification. *Biotech. Prog.* **2002**, *18*, 1332.
(12) Mun, S.; Xie, Y.; Wang, N.-H. L. Optimal Design of a Size-Exclusion Simulated Moving Bed for Insulin Purification. *Ind. Eng. Chem. Res.* **2003**, *42*, 1977.
(13) Mun, S.; Xie, Y.; Wang, N.-H. L. Residence Time Distribution in a Size-Exclusion SMB for Insulin Purification. *AIChE J.* **2003**, *49*, 2039.
(14) Xie, Y.; Mun, S.; Chin, C.; Wang, N.-H. L. "Simulated Moving Bed Technologies for Producing High Purity Biochemicals and Pharmaceuticals," in *New Frontiers in Biomedical Engineering*; N. H-C. Hwang, Ed.; Kluwer Academic Publishers: New York, 2003.
(15) Zang, Y.; Wankat, P.C. SMB Operation Strategy – Partial Feed. *Ind. Eng. Chem. Res.* **2002**, *41*, 2504.
(16) Mun, S.; Xie, Y.; Wang, N.-H. L. Robust Pinched Wave Design of a Size-Exclusion Simulated Moving Bed Process for Insulin Purification. *Ind. Eng. Chem. Res.* **2003**, *42*, 3129.
(17) Ma, Z.; Wang, N.-H. L. Standing Wave Analysis of SMB Chromatography: Linear Systems. *AIChE J.* **1997**, *43*, 2488.
(18) Whitley, R. D. *Dynamics of Nonlinear Multicomponent Chromatography — Interplay of Mass Transfer, Intrinsic Sorption Kinetics, and Reaction*. PhD's thesis, Purdue University, West Lafayette, IN. 1990.
(19) Berninger, J. A.; Whitley, R. D.; Zhang, X.; Wang, N.-H. L. A Versatile Model for Simulation of Reaction and Nonequilibrium Dynamics in Multicomponent Fixed-Bed Adsorption Processes. *Comp. Chem. Eng.* **1991**, *15*, 749.
(20) Ma, Z.; Tanzil, D; Au, B. W.; Wang, N.-H. L. Estimation of Solvent Modulated Linear Adsorption Parameters of Taxanes from Dilute Plant Tissue Culture Broth. *Biotechnol. Prog.* **1996**, *12*, 810.
(21) Hritzko, B. J., *Design and Dynamic Modeling of Simulated Moving Bed Process for Multicomponent Biochemical Separations,* PhD's thesis, Purdue University, West Lafayette, IN. 2001.