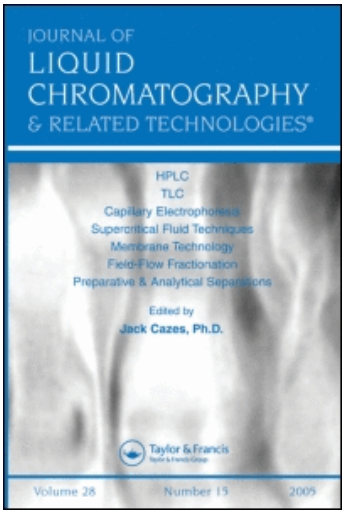

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Abstract: The performance of silica gel as an adsorbent for a chromatographic separation has been recently improved by a special surface processing, in which high purity silica was prepared and then coated with silicone polymer. The superiority of such a polymer coated silica gel over conventional silica gels has been demonstrated previously. In this study, the polymer coated silica gel was applied to a simulated moving bed (SMB) chromatography for amino acid separation. Since the productivity of SMB is largely affected by the size of adsorbent particle, the determination of an optimal particle size for the polymer coated (P-C) silica gel is of importance. Thus, a systematic method of particle size optimization in the SMB for amino acid separation was developed. Based on the developed method, the optimal P-C silica size was determined for the SMBs with different pressure ratings. The results showed that the optimal P-C silica size occurred at the boundary between the pressure limiting and the mass transfer limiting regions. More importantly, the optimal P-C silica size was found to become smaller as the SMB with a higher pressure rating was employed. The results of this study can play an important role in tailoring the P-C silica gel to the SMB process for amino acid separation.

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Keywords: Detailed model, Particle size optimization, Polymer coated silica gel, Pressure drop, Productivity, SMB chromatography

INTRODUCTION

Silica packing materials, represented by octadecylsilylated (ODS) silica gels, have been widely used in the field as an analytical tool or a separation process because of its high performance in separating a biochemical mixture into different pure fractions.[1] However, as the scope of a separation system and process has been expanded, several problems have arisen in the aspects of peak spreading, selectivity, chemical stability, durability, and operational flexibility.[2,3] The manufacture of a new ceramic material or an improved silica gel that can overcome such problems has been the center of attention in the area of an economical separation process development.

Recently, Ohtsu et al.[2] succeeded in preparing an improved silica gel through a special surface processing, which was to coat high purity silica gel with a silicon polymer using vapor deposition method. Such a polymer coated silica gel was found to be much more effective in separating a variety of biochemicals than conventional silica gels. Furthermore, the polymer coated silica gels did not show the aforementioned problems occurring in conventional silica gels. Due to these advantages, the polymer coated silica gel was commercialized by Shiseido Co., in Japan, attracting considerable attention as a potential adsorbent in many separation processes.

One of the highly efficient separation processes in a preparative or an industrial scale is a simulated moving bed (SMB) chromatography (Figure 1), which has been reported to surpass conventional batch chromatographic processes in every performance criterion.[4,5] Particularly, an SMB process has been known for its high productivity, which is regarded as the most important performance criterion influencing overall separation cost.[6] To maintain such a process merit in SMB for a long term period, the choice of a proper adsorbent is of importance. It is expected that the aforementioned polymer coated silica gel can serve as a promising adsorbent in the SMB process.

An important issue in the application of the polymer coated (P-C) silica gel to the SMB process is the determination of its optimal particle size, because the performance criteria of SMB are largely affected by the size of adsorbent particle. No previous studies have addressed the issue of determining the optimal P-C silica size for the purpose of enhancing an SMB performance.

The goal of this study is to develop a systematic method of determining an optimal adsorbent particle size for the highest productivity

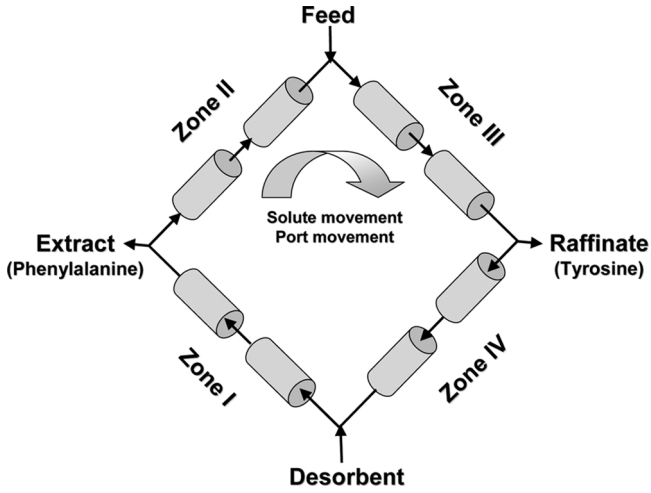


Figure 1. Schematic diagram of a four-zone SMB chromatography for the separation of an amino acid mixture containing tyrosine and phenylalanine.

in SMB. Based on the developed method, we will find out the optimal P-C silica size that leads to the highest productivity regarding an SMB for the separation of two amino acids, tyrosine and phenylalanine. Furthermore, the effect of the P-C silica size on the productivity of the SMB for amino acid separation will be analyzed in detail. Based on such an analysis, it will be investigated which factors are related to the occurrence of an optimal particle size. Finally, we will examine how SMB hardware strength and capacity affect the determination of an optimal particle size.

THEORY

Systematic Method of Determining an Optimal Particle Size in the SMB for Amino Acid Separation

A systematic method of determining the optimal P-C silica size in the SMB for amino acid separation is proposed (Figure 2). This method significantly reduces trial and error in the numerical calculation and the number of experiments required for particle size determination. In this method, a series of multiple frontal tests are first applied to obtain the intrinsic parameters that are independent of the scale or the operating condition of the system. Such parameters include adsorption isotherm and mass-transfer parameters. These intrinsic parameters are used in the optimal SMB design tool to determine the optimal P-C silica size

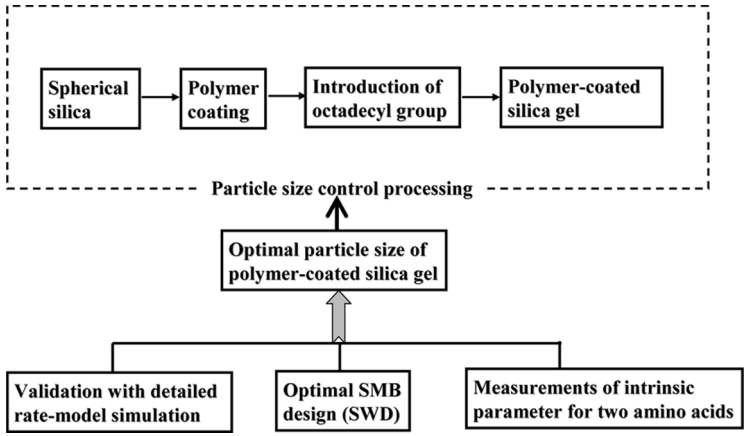


Figure 2. Systematic method of optimizing the P-C silica size for the SMB aiming at amino acid separation.

as well as the optimal operating conditions. The objective function employed in such an optimal design is the productivity, which is defined as the amount of feed that can be processed per unit time per unit volume of adsorbent while meeting the requirements for product purities.

Then, the separation performance of the SMB based on the optimal P-C silica size and the optimal operating conditions is verified using detailed rate model simulations. Once verified, the optimal particle size serves as a target specification in the manufacture of the P-C silica gel (Figure 2).

Optimal SMB Design Based on Concentration Wave Formation

Several SMB design methods were reported in previous studies.[7–9] Among them, the standing wave design (SWD) method[9] has been regarded as the most efficient and accurate one that can ensure the highest productivity for a given SMB system. Furthermore, the design equations associated with the SWD includes the term of adsorbent particle size, which means that the SWD has the great advantage in finding out the optimal adsorbent particle size for the highest SMB productivity. For this reason, the SWD was adopted in this study as a tool of determining the optimal particle size of the P-C silica gel in the SMB of interest.

The basic principle of the SWD is to select the four zone linear velocities and step time, such that each concentration wave can be made standing in its respective zone on the time averaged sense (Figure 3).[9] The main idea of realizing this principle is to match the migration velocity

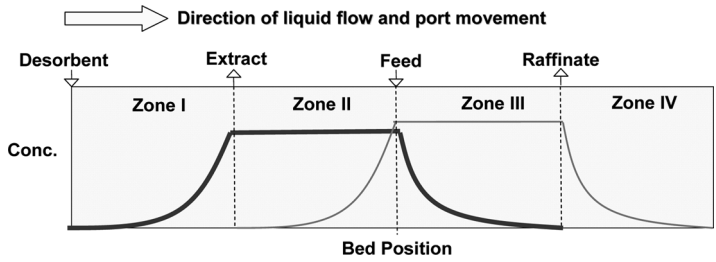


Figure 3. Formation of concentration waves based on the SWD in SMB for a binary separation. The thick and thin lines indicate the slow-migrating (high-affinity) and the fast-migrating (low-affinity) components, respectively.

of a key concentration wave in each zone with the time averaged port velocity. The mathematical expression for such an idea is given in the following:[9]

$$u_0^I = [1 + P \cdot \delta_A] \cdot \nu + \frac{\beta_A^I}{N_c^I \cdot L_c}\left[E_{b,A}^I + \frac{P \cdot (\delta_A \cdot \nu)^2}{K_{f,A}^I}\right] \tag{1a}$$

$$u_0^{II} = [1 + P \cdot \delta_B] \cdot \nu + \frac{\beta_B^{II}}{N_c^{II} \cdot L_c}\left[E_{b,B}^{II} + \frac{P \cdot (\delta_B \cdot \nu)^2}{K_{f,B}^{II}}\right] \tag{1b}$$

$$u_0^{III} = [1 + P \cdot \delta_A] \cdot \nu - \frac{\beta_A^{III}}{N_c^{III} \cdot L_c}\left[E_{b,A}^{III} + \frac{P \cdot (\delta_A \cdot \nu)^2}{K_{f,A}^{III}}\right] \tag{1c}$$

$$u_0^{IV} = [1 + P \cdot \delta_B] \cdot \nu - \frac{\beta_B^{IV}}{N_c^{IV} \cdot L_c}\left[E_{b,B}^{IV} + \frac{P \cdot (\delta_B \cdot \nu)^2}{K_{f,B}^{IV}}\right] \tag{1d}$$

where the superscripts I to IV stand for zone number; the subscripts A and B indicate the slow migrating (or high affinity) and the fast migrating (or low affinity) solutes respectively; u_0^j is the linear velocity in zone j; ν is the port velocity (=single column length (L_c)/step time (t_s)); ε_b is the inter-particle void fraction; δ_i is defined as $\varepsilon_p + (1-\varepsilon_p)\cdot a_i$, where ε_p is the intra-particle void fraction and a_i is the linear isotherm parameter of solute i; N_c^j is the number of columns in zone j; P is the phase ratio, defined as $(1-\varepsilon_b)/\varepsilon_b$; E_b is the axial dispersion coefficient; and β is a decay factor that is related to yield and zone linear velocity. If the yield of each component is given, the β values are determined from component mass balance equations.[10] The lumped mass transfer coefficient (K_f) can be

estimated from the following Equation:[9]

$$\frac{1}{K_f} = \frac{(d_p/2)^2}{15\varepsilon_p D_p} + \frac{(d_p/2)}{3k_f} \tag{2}$$

where d_p is the diameter of adsorbent particle; D_p is the intra-particle diffusivity; and k_f is the film mass-transfer coefficient.

If the SMB under consideration is operated on the basis of the aforementioned SWD conditions, it will give the highest productivity for a given size of P-C silica gel. Since the SWD is a strong function of adsorbent particle size (Eqs. (1) and (2)), the productivity of the SMB under consideration can be improved further by using the P-C silica gel that goes through a special processing to maintain a proper particle size.

One of the important considerations in determining the particle size of P-C silica gel is that the particle size has a direct effect on the pressure drop through an SMB unit, which is usually estimated from the following Ergun Equation.[11,12]

$$\Delta P = \sum_{j=I}^{IV} \Delta P^j = \sum_{j=I}^{IV} N_c^j \left(\frac{150\mu \cdot u_0^j \cdot L_c}{d_p^2} \left(\frac{1-\varepsilon_b}{\varepsilon_b} \right)^2 \frac{10^6}{6} + \frac{1.75\rho (u_0^j)^2 L_c}{d_p} \left(\frac{1-\varepsilon_b}{\varepsilon_b} \right) \frac{1}{3.6} \right) \frac{14.7}{1.013 \times 10^5} \tag{3}$$

where ΔP is the total pressure drop through an SMB unit; ρ is the mobile phase density; and μ is the mobile phase viscosity. In general, any SMB system has its own pressure rating (or maximum allowable pressure drop) due to the finite strength of equipment materials and other hardware conditions. Thus, the particle size resulting in a higher pressure drop than the maximum allowable one should be avoided. This issue will be taken into account in the following SMB optimization study.

Simulation Model

A lumped mass transfer model[9] was employed in this study as a model for detailed simulation, which served as a verification procedure for the separation performance of an optimized SMB. The lumped mass transfer model, which is one of the well established rate models in the literature, is based on differential mass balance equations for both the mobile phase and the stationary phase. The model equations consider convection, axial dispersion, film mass transfer, intra-particle diffusion, and adsorption. The details of the model equations can be found elsewhere.[9]

To solve the model equations, a biased upwind differencing scheme (BUDS) was used in conjunction with Gear integration having a step size of 0.05. All of these numerical computations are carried out in an Aspen simulator, which has been validated in several previous studies.[13–15]

EXPERIMENTAL

The amino acids under investigation included tyrosine (99%) and phenylalanine (99%), both of which were purchased from Sigma-Aldrich Co., (St. Louis, MO). Methanol was obtained from Mallinckrodt Baker Inc. (Paris, KY) and used as an organic solvent in the mobile phase employed. The mobile phase was prepared by mixing methanol and deionized distilled water (DDW) in the ratio of 3 to 7.

The experiments were conducted with the HPLC system (Figure 4), which consisted of two HPLC pumps (Waters 515), a PDA detector (Waters 996), and an injector (Rheodyne 9725i). The adsorbent used was the polymer coated silica gel, which has an average particle size of 20μm. The column containing the adsorbent has a length of 250 mm and a diameter of 10 mm, and it was pre-packed by the manufacturer (Shiseido Co., in Japan). The inter-particle and intra-particle porosities of the pre-packed column were 0.3 and 0.5, respectively, which were obtained from a series of tracer molecule pulse tests. A Milli-Q system by Millipore (Bedford, MA) was used to obtain DDW.

For multiple frontal experiments, both HPLC pumps were used (Figure 4). One pump delivered mobile phase solution and the other feed solution (amino acid solution). The two streams were mixed before entering the column. Such a mixing process was facilitated using a Dynamax dual chamber mixer (Varian 0.6 ML SS), which enabled the two streams to attain the state of a perfect mixing before entering the column. The total flow rate for the mixed stream was kept constant at 2 mL/min. Various feed compositions (25%, 50%, 75%, and 100%) were obtained

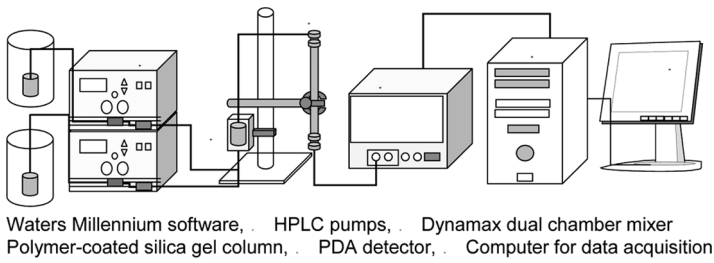


Figure 4. Experimental system for multiple frontal tests.

by changing the ratio of the two streams. The ratio was changed only after a concentration plateau was fully developed at the column outlet. The column effluent was monitored at the wavelengths of 260 nm for tyrosine and 254 nm for phenylalanine using the PDA detector.

RESULTS AND DISCUSSION

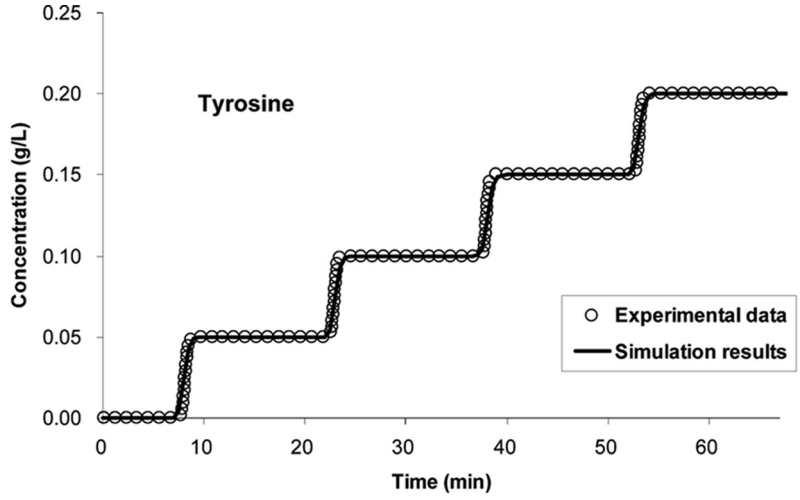
Intrinsic Parameters of Amino Acids on the P-C Silica Gel

Intrinsic parameter estimation for the feed components (tyrosine and phenylalanine) is a prerequisite to optimal determination of the P-C silica gel size, because the intrinsic parameters correspond to input data of the optimal SMB design equations, i.e., the SWD. The intrinsic parameters to be estimated include adsorption isotherm and mass transfer parameters for each amino acid component.

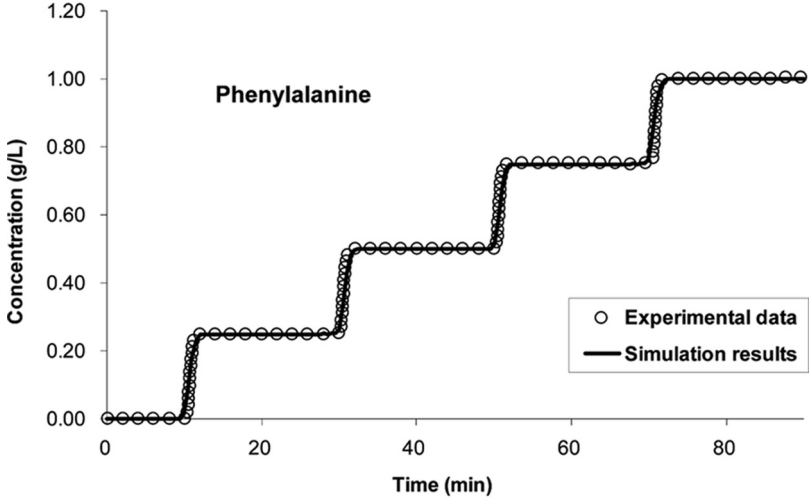
First, the adsorption equilibrium data of tyrosine and phenylalanine on the P-C silica gel were measured using multiple frontal experiments. The resulting chromatograms are presented for each amino acid in Figure 5. Note that such chromatogram data has several plateau concentration regions. In each plateau region, the solid phase concentration (i.e., the mass of amino acid adsorbed per unit volume of the P-C silica gel) is maintained at the one in equilibrium with the liquid phase concentration (i.e., the concentration of amino acid in the mobile phase solution).

Following the procedure described by Ma et al.,[16] the multiple frontal data in Figure 5 can be used to calculate the equilibrium solid phase concentration (q) associated with each plateau concentration (C). The resulting adsorption data (q and C) for each amino acid are plotted in Figure 6. It is easily seen that the adsorption pattern of each amino acid component follows a linear isotherm relation. The isotherm parameter, which is the ratio of solid phase concentration (q) to liquid phase concentration (C) at equilibrium, was obtained for each amino acid by using linear regression based on a least square analysis, and the resultant value is listed in Table 1.

Besides the aforementioned isotherm parameters, the mass transfer parameters are also needed in the determination of the optimal P-C silica size. The required mass transfer parameters include axial dispersion coefficient (E_b), film mass transfer coefficient (k_f), Brownian diffusivity (D_∞), and intra-particle diffusivity (D_p). All of these four mass-transfer parameters were obtained from the literature correlation equations,[17–20] which were established previously on the basis of a theoretical or a semi-empirical background. The axial dispersion and the film mass transfer coefficients were calculated from the Chung & Wen correlation[17] and the Wilson & Geankoplis correlation,[18] respectively. The Brownian and



(a)

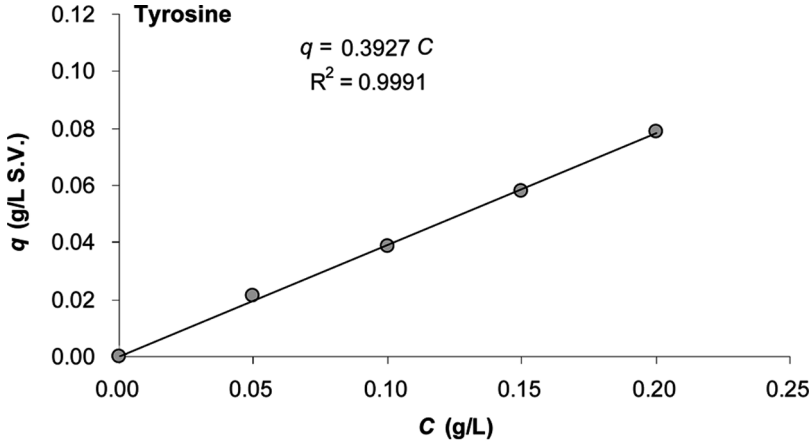


(b)

Figure 5. Experimental data and simulation results of the multiple frontal test. (a) Tyrosine, (b) Phenylalanine.

the intra-particle diffusivities were estimated from the Wilke & Chang correlation[19] and the Mackie & Mears correlation,[20] respectively. The resulting mass transfer parameter values are summarized in Table 1.

Detailed rate model simulations with the intrinsic parameters estimated above were carried out to check against the experimentally



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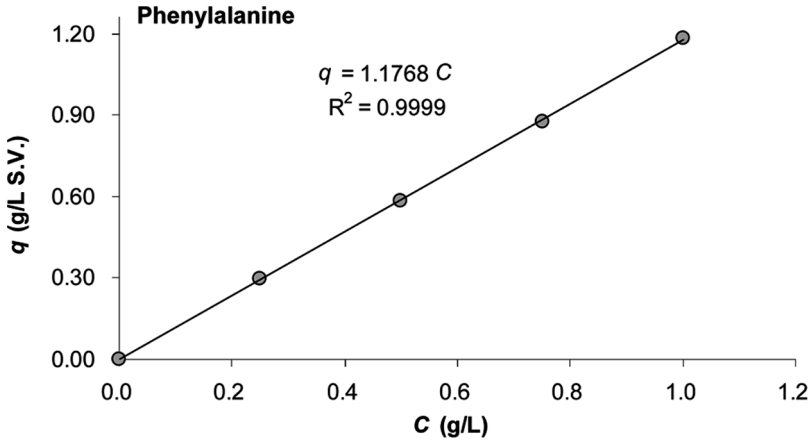


(b)

Figure 6. Plot of adsorption isotherm data. (a) Tyrosine, (b) Phenylalanine.

Table 1. Intrinsic parameter values estimated from the multiple frontal experiments and the literature correlation equations

	Tyrosine	Phenylalanine
Isotherm parameter, a (L/L S.V.)	0.3927	1.1768
Axial dispersion coefficient, E_b (cm^2/min)	0.02537	0.02537
Film mass-transfer coefficient, k_f (cm/min)	1.1425	1.1598
Brownian diffusivity, D_∞(cm^2/min)	2.21×10^{-4}	2.26×10^{-4}
Intra-particle diffusvitiy, D_p (cm^2/min)	4.91×10^{-5}	5.02×10^{-5}

measured chromatogram data. As shown in Figure 5, the simulation results are in good agreement with the experimental data, indicating the validity of the intrinsic parameters estimated.

Optimal Particle Size of P-C Silica Gel Under a Pressure Limit of 400 psi

The intrinsic parameters validated above are used in this section to determine the optimal particle size of P-C silica gel that leads to the highest productivity for the SMB aiming at amino acid separation. In such an SMB system, each zone was allowed to contain two columns, constituting the column configuration of 2 – 2 – 2 – 2. In addition, the length of each column (L_c) in the SMB was kept the same as in the multiple frontal experiments, whereas the diameter of each column (d_c) was set to be larger in order to attain a preparative-scale of SMB.

During the optimization of SMB with the aforementioned specifications, several important issues were taken into account. Since high product purity is an important requirement for biochemicals, the purities of both tyrosine and phenylalanine are set to be higher than 99.5% in the present study. Secondly, the pressure drop through the SMB unit was not allowed to exceed 400 psi, which is a general criterion for a medium pressure chromatographic separation process. Such an optimization problem can be represented mathematically as follows.

$$\text{Max} \qquad \text{J} = \text{Productivity}\,[u_0^I, u_0^{II}, u_0^{III}, u_0^{IV}, t_s] \tag{4a}$$

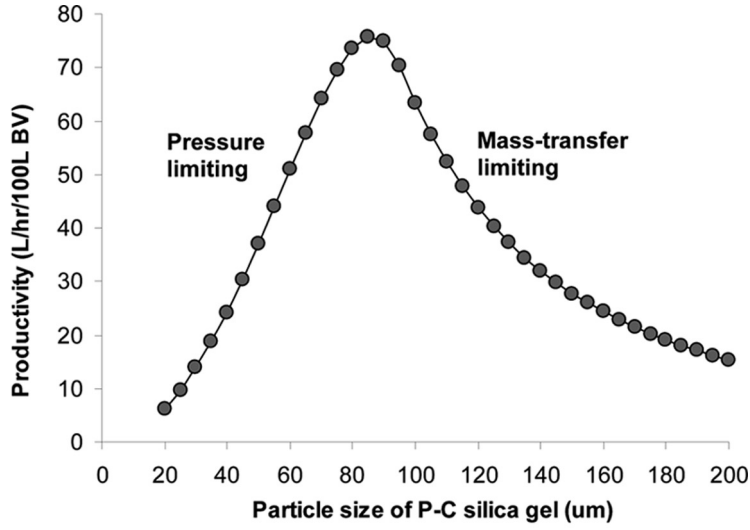
$$\text{Subject to} \qquad \text{Pur}_\text{A} \geq 99.5\%,\ \text{Pur}_\text{B} \geq 99.5\%, \tag{4b}$$

$$\Delta P \leq 400\,\text{psi} \tag{4c}$$

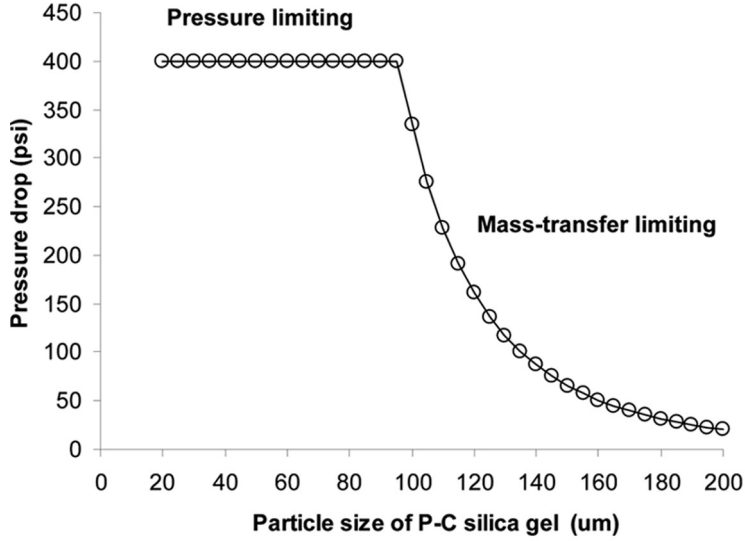
$$\text{Fixed variables} \qquad C_\text{F} = 0.2\,\text{g/L for each component} \tag{4d}$$

$$L_\text{c} = 25\,\text{cm},\ d_\text{c} = 5\,\text{cm}, N_\text{c,total} = 8 \tag{4e}$$

where Pur_A and Pur_B are the purity of tyrosine in the raffinate stream and the purity of phenylalanine in the extract stream, respectively; C_F is the feed concentration; and $N_\text{c,total}$ is the total number of columns used in SMB unit. To reduce computation time, the particle size of P-C silica gel (d_p) was not directly included as the variables to be optimized, as can be seen in Eq. (4a). Instead, the particle size was changed in a discrete manner and for each step the five decision variables (u_0^I, u_0^{II}, u_0^{III}, u_0^{IV}, t_s) were optimized. This approach is advantageous to the analysis of the optimization results, because the effect of the particle size on productivity can be demonstrated while finding out the optimal particle size.



(a)



(b)

Figure 7. Effects of the P-C silica size on (a) productivity, and (b) pressure drop in the SMB for amino acid separation.

Based on the SWD equations, the aforementioned optimization work was conducted in series while varying the particle size at the intervals of 5 μm. The results are presented in Figure 7a, where the SMB productivity

is plotted as a function of the particle size. Notice that the particle size has a marked impact on the productivity. If the particle size is relatively small (<85 μm), the productivity becomes higher as the particle size increases. By contrast, if the particle size is relatively large (>85 μm), the productivity decreases with increasing the particle size. Consequently, a maximum in the productivity occurs at the particle size of 85 μm, which virtually corresponds to the optimal particle size for the P-C silica gel to be used in the SMB for amino acid separation.

The aforementioned phenomenon occurs because the particle size influences both pressure drop and mass transfer efficiency, which are the key factors in productivity. To check this point for the SMB of interest, the pressure drop of the process optimized at each particle size was calculated from the Ergun equation (Eq. (3)) and the results are presented in Figure 7b. Note that in the region of small particles (<85 um), the pressure drop is maintained at its upper limit (400 psi). This implies that the SMB productivity is virtually restricted by the pressure drop limit. In such a pressure limiting region, the flow rate in each zone is kept at its maximum allowable value, which varies in accordance with the particle size. According to the Ergun equation (Eq. (3)), the maximum allowable flow rate increases as the particle size becomes larger under a fixed pressure drop. In general, an increase in the maximum allowable flow rate enables the processing of more amount of feed without affecting adversely the product purities. Hence, the SMB productivity, if limited by the pressure drop, enhances as the particle size increases (Figure 7a).

By contrast, in the region of large particles (>85 um), the pressure drops of the corresponding SMBs are reduced to below 400 psi as shown in Figure 7b. Under such circumstances, the productivity is no longer limited by the pressure drop limit but by the mass transfer efficiency. As can be seen from Eq. (2), a larger particle size lowers the mass transfer efficiency. Obviously, lower mass transfer efficiency causes each solute band to be more spread, making complete separation more difficult. In this situation, the feed flow rate should be decreased to maintain the product purities required. As a result, the productivity, if limited by the mass transfer efficiency, reduces as the particle size increases (Figure 7a).

Putting all the above results together, one can conclude that the particle size at the boundary between the pressure limiting and the mass transfer limiting regions can serve as the optimal P-C silica size for the productivity of the SMB for amino acid separation.

Effect of a Pressure Limit on the Optimal Particle Size of P-C Silica Gel

In the previous section, the SMB of interest was constrained to be operated below a pressure drop of 400 psi. Such a pressure limit,

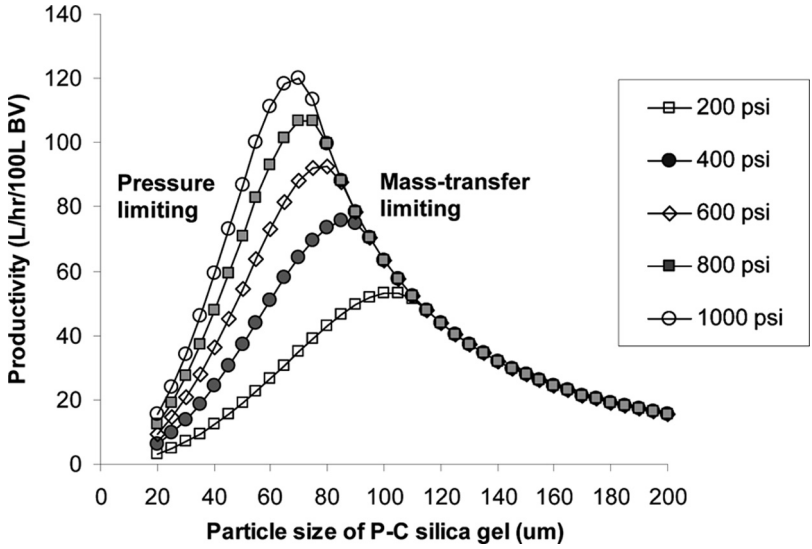


Figure 8. Effect of a pressure limit on the optimal particle size of P-C silica gel in the SMB for amino acid separation.

however, can be varied depending on the equipment materials and pump capacities.

A change in the pressure limit obviously has a great effect on the optimal P-C silica size for the highest SMB productivity. To investigate this issue, another SMB optimization was conducted in series by setting the pressure limit at a different value. The results are presented in Figure 8. One of the noteworthy phenomena is that the optimal P-C silica size becomes smaller as the pressure limit is set higher. This is mainly because a higher pressure limit narrows down the pressure limiting region while enlarging the mass transfer limiting region (Figure 8), thereby causing the particle size at the boundary between the two limiting regions to be moved toward a smaller one. Since such a particle size at the boundary corresponds to the optimal one as mentioned above, a higher pressure limit eventually leads to a decrease in the optimal P-C silica size.

Another interesting observation is that a maximal productivity occurring at the optimal particle size improves as the pressure limit is set higher. This is due to the following two reasons; a higher pressure limit (1) provides higher operational flexibilities in SMB and (2) simultaneously allows the use of a smaller P-C silica gel, inducing better separation efficiency as a result of higher mass transfer efficiency.

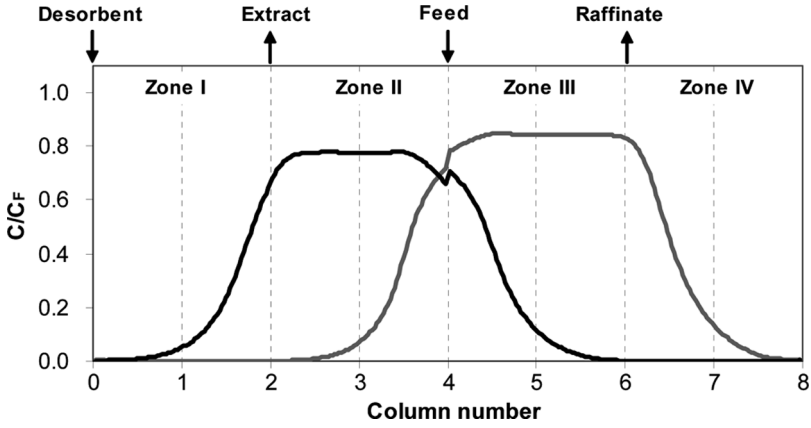


Figure 9. Steady-state internal concentration profiles of tyrosine and phenylalanine from detailed rate-model simulation for the SMB based on the P-C silica gel with an optimal particle size under a pressure limit of 400 psi. The black and gray lines indicate the concentration profiles of phenylalanine and tyrosine, respectively.

Detailed Simulations for the SMB Based on the P-C Silica Gel with an Optimal Particle Size

In the previous section, the optimal particle size of P-C silica gel was determined for the SMB of interest using the optimization tool based on the SWD. To verify the separation performance of such an SMB based on the optimal particle size, the internal concentration profiles of tyrosine and phenylalanine at the cyclic steady state were obtained from the rate model simulation.

Figure 9 presents the resulting profiles. Note that the front and the rear of the phenylalanine band are confined within zones I and III, respectively, while the front and the rear of the tyrosine band are confined within zones II and IV, respectively. This type of a solute band distribution ensures the continuous collection of almost pure phenylalanine and tyrosine through the extract and raffinate product ports, respectively, resulting in 99.5% purity for each amino acid. This indicates that the SWD is effective and robust in determining the optimal P-C silica gel size for the SMB aiming at amino acid separation.

CONCLUSIONS

If the polymer coated (P-C) silica gel is to serve as an adsorbent in the SMB for amino acid separation, its particle size should be controlled

during the entire preparation and processing steps. This is because the particle size of P-C silica gel has a significant impact on the productivity of the SMB. To facilitate such a task, a systematic method of determining an optimal particle size and reflecting it in the manufacturing process for P-C silica gel was proposed. In accordance with the proposed method, a series of multiple frontal experiments were carried out first in order to obtain the adsorption isotherm and mass transfer parameters of tyrosine and phenylalanine. These parameters were then used in the SWD to determine the optimal P-C silica size for the SMB with a pressure limit of 400 psi. It was found that the optimal P-C silica size occurred at 85 μm, which corresponded to the particle size at the boundary between the pressure limiting and the mass transfer limiting regions. In the pressure limiting region, a larger particle size was advantageous for the attainment of higher productivity. By contrast, in the mass transfer limiting region, a smaller particle size led to higher productivity. More importantly, the optimal P-C silica size was found to become smaller as the pressure limit of the SMB increased. The results and methodology in this paper are expected to pave the way for a successful application of P-C silica gels to other SMB processes for the separation of valuable biochemicals.

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