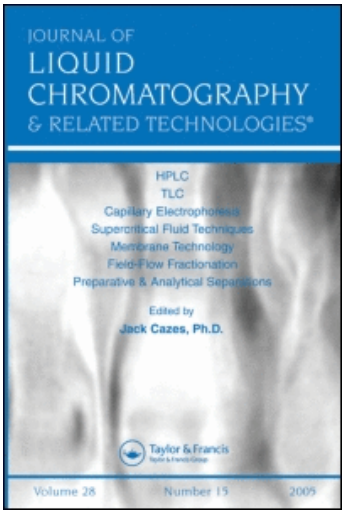

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Application of Genetic Algorithm to Determination of Intrinsic Parameters and Optimization of a Batch Chromatographic Process for 1,3-Propanediol Purification

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Abstract: A recent adaptation of genetic algorithm, NSGA-II-JG, was applied systematically to each key task to be completed for developing an optimal batch chromatographic process for 1,3-propanediol purification. The genetic algorithm was used first in the task of determining intrinsic parameters such as adsorption isotherms and mass transfer coefficient. For such parameters determination, we adopted an inverse method, which is to acquire intrinsic parameters by a least square fitting of the proposed column model to the experimentally measured elution profile. At this stage, the genetic algorithm plays a part in searching the values of intrinsic parameters that lead to the minimum difference between the experimental and the model predicted elution profiles.

In the next stage, the genetic algorithm was applied to optimize a series of operating parameters, which include flow rate, feed loading volume, starting and ending times of product collection, and the time of gap between adjacent two feed injections. Such optimization, which aims for the highest productivity under the constraints of product purity and pressure drop, was repeated by varying adsorbent particle size. The optimization results confirmed that the productivity for small particles was limited by the pressure drop, whereas the productivity

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for large particles was limited by the mass transfer efficiency (or column efficiency). In consequence, the optimal particle size for the maximum productivity falls on the boundary between the two limiting regions.

The results of this study indicate that the application of genetic algorithm is effective in each stage of a batch chromatographic process development, which covers from parameter estimation to process optimization.

Keywords: Batch chromatography, Genetic algorithm, Parameter estimation, Process optimization.

INTRODUCTION

Liquid chromatography (hereafter, "chromatography") has played an important part in the biochemicals and pharmaceuticals industry because of its effective separating power. Various adsorption mechanisms and mild operating conditions make chromatography a flexible and influential separation tool for bioseparation.[1] Several types of operation modes have been applied to the realization of a chromatographic separation. Among the existing operation modes, the most widespread one is a batch elution mode, in which a single chromatographic column is loaded periodically with pulses of feed mixture to be separated.[2]

For such a batch elution chromatography, the recent researches have been focused on the improvement of its process performance, especially when it aims at a preparative or large scale process.[2–6] One of the ways of improving its process performance is to make the most use of a given adsorbent phase,[2–4] which is usually so expensive as to have a major effect on the process economics. The extent of utilizing a given adsorbent phase (or adsorbent utilization) is evaluated mainly by productivity.[2,3] Higher adsorbent utilization leads to higher productivity, resulting in lower separation cost.

To maintain productivity as high as possible, most of batch chromatographic processes are operated under overloaded conditions, which generally make their adsorption behaviors fall into non-linear isotherm regions.[7] Under such a non-linear adsorption condition, it becomes rather difficult and complicated to find out optimal values for a series of design parameters (or operating and system parameters), which are related to the operation of a batch process, the length of a chromatographic column, and the size of adsorbent particle. This necessitates the computer assisted optimization of batch chromatographic processes, particularly at the design stage.[8] In such a scenario, it is more advantageous to use non-traditional optimization methods based on the stochastic search techniques, rather than traditional optimization methods based on the gradient search

techniques.[9,10] The reason is that the former method is much more robust and, thus, more highly efficient in finding out the global optimal solutions. A popular algorithm based on such a non-traditional optimization approach is a genetic algorithm (GA) and its adaptations, which include non-dominated sorting genetic algorithm (NSGA) and NSGA with jumping genes (NSGA-II).[11–15] The concept of the GA (including its adaptations) is based on the principles of genetics and the Darwinian principle of natural selection, i.e., the survival of the fittest.[15] Such principles are embodied in the GA by employing a series of probabilistic operators such as reproduction, crossover, mutation, and jumping gene, all of which are inspired by natural genetics.[10] The GA has been successful in solving engineering optimization problems in many previous studies.[10–16] Recently, the GA has been exploited for the optimizations of several chemical engineering processes including chromatographic separation units,[14–16] which the trend is on the gradual increase.

The first goal of this study is to apply the aforementioned GA to the optimization of a batch chromatographic process aiming at the purification of 1,3-propanediol (1,3-PDO) from a feed mixture containing propanediol isomers (1,3-PDO and 1,2-PDO). This feed mixture comes from the second last step in an existing biotechnological process for the production of 1,3-PDO,[17] which serves as a valuable raw material in the industry of high performance polyester, polyether, and polyurethane productions.

The second goal of this study is to estimate the intrinsic parameters of the feed components (PDO isomers), which are prerequisite to the optimization of the process targeted in the first goal. The intrinsic parameters to be estimated include adsorption isotherms and mass transfer coefficients. Several methods are available for the estimation of such intrinsic parameters.[8,18,19] Among them, the most economical method that requires the least number of experiments is employed in this study. It is an inverse method, which is to acquire the intrinsic parameters by a least square fitting of the proposed column model to the experimentally measured elution profile.[8,19,20] Such a fitting procedure requires a highly efficient and robust optimization technique in order to minimize the least square error between the experimental and the model predicted results. In this study, such a minimization task for the estimation of the intrinsic parameters is performed by the GA technique, which is also to be used in the aforementioned batch process optimization.

The results of this study showed that the adsorption behaviors of the feed components could be well described by the Langmuir isotherm model. The corresponding Langmuir isotherm parameters, together with the mass transfer coefficients (referred to as "intrinsic parameters"

collectively), were successfully determined by the inverse method based on the GA technique. Such intrinsic parameters were then used as input data in the next stage of process optimization, in which all the operating parameters and the adsorbent particle size of the batch chromatographic process were varied to find their optimal value. This optimization aims at the attainment of the highest productivity under the constraints of product purity ($\geq$95%) and pressure drop ($\leq$100 psi). The GA technique was also successful in such a process optimization task.

THEORY

Mathematical Model for Chromatographic Column

Solute bands migrating through a chromatographic column are usually affected by several mass transfer mechanisms such as axial dispersion, film mass transfer, and intra-particle diffusion. Such dynamic behaviors of chromatographic columns have been described using well grounded mathematical models in many of the previous studies.[21] Among the models, the most accurate one is the general rate model, which takes into account most of the details of mass transfer phenomena occurring in the inter-particle void, the intra-particle void, and the film region between mobile and stationary phases. Such a detailed consideration, however, causes much more equations to be involved, which makes the general rate model computationally inefficient.[8,21] A good contrast to the general rate model is the ideal equilibrium model, which neglects all the dispersion and diffusion phenomena occurring in the entire void space. Although such an excessive assumption allows an easy and quick calculation, it is virtually too unrealistic for the application to most preparative chromatographic systems.

As mentioned in the introduction section, the major works in this study are to determine intrinsic parameters using the inverse method and to optimize a batch chromatography process. Since these two works require a huge number of numerical simulations, the reduction of computation time by using less complicated model equations can be an important issue. At the same time, a reasonable accuracy is also to be maintained. One of the models to compromise such two requirements is either the equilibrium dispersive (ED) model or the lumped mass transfer (LMT) model.[21,22] In these two models, several different mass transfer phenomena are treated collectively for the purpose of reducing the number of equations involved and, thus, computation time. In case of the ED model, all the mass transfer effects are accounted for by only one collective parameter. By contrast, the LMT model employs two parameters, one of which accounts for axial dispersion and the other

for film mass transfer and intra-particle diffusion in a lump. Since the LMT model has one more parameter for the description of mass transfer phenomena, a higher accuracy is usually obtained from the LMT model rather than from the ED model. Also, the LMT model is more efficient than the general rate model in terms of computation time. For these reasons, the LMT model is employed here as a simulation model for the purification system of our interest.

The LMT model consists of unsteady state mass balance and mass transfer equations for each component i in the mobile and pore phases.[22] For the mobile phase, the model equation is given by:

$$\frac{\partial C_{b,i}}{\partial t} + P \cdot \varepsilon_p \cdot \frac{\partial C_i^*}{\partial t} + P \cdot (1 - \varepsilon_p) \cdot \frac{\partial q_i}{\partial t} + u_0 \frac{\partial C_{b,i}}{\partial z} - E_{b,i} \cdot \frac{\partial^2 C_{b,i}}{\partial z^2} = 0 \quad (1)$$

where C_b is the mobile phase concentration; C^* is the average pore phase concentration; q is the solid phase concentration; P is the phase ratio, defined as $(1 - \varepsilon_b)/\varepsilon_b$, where ε_b is the inter-particle void fraction; u_0 is the mobile phase interstitial velocity; ε_p is the intra-particle void fraction; and E_b is the axial dispersion coefficient. The E_b value, which is a function of mobile phase velocity, was calculated from the Chung and Wen correlation[23] in this study. Higher mobile phase velocity (or higher flow rate under a given column diameter) increase the E_b value, which makes a solute band more dispersed, leading to a decrease in column efficiency.

The model equation for the pore phase is expressed as follows:

$$\varepsilon_p \frac{\partial C_i^*}{\partial t} + (1 - \varepsilon_p) \frac{\partial q}{\partial t} = k_{m,i}\, a_p (C_{b,i} - C_i^*) \quad (2)$$

where k_m is the overall mass transfer coefficient, $a_p = 3/R_p$ for spherical particles, and R_p is the radius of adsorbent particle. As indicated by the above equation, a larger size of adsorbent particle decreases mass transfer rate and, thus, enlarges mass transfer resistances, which can be one of the reasons for lowering column efficiency.

To solve the aforementioned model equations, a biased upwind differencing scheme (BUDS) was employed in conjunction with Gear integration having a step size of 0.005. The number of nodes in each column was set at 120. All of these numerical computations were carried out in Aspen Chromatography 2004.1. simulator, which has been validated in several previous studies.[16,24,25]

Inverse Method for Parameter Determination

In order to characterize the adsorption behavior of the feed components, a series of pulse chromatograms of the propanediol isomers have been

measured. The measured chromatograms showed that the retention times of the peak maxima decreased when the feed concentration increased. Such retention behavior is one of the typical phenomena occurring in nonlinear adsorption systems with convex upward isotherm curves. There are plenty of isotherm models that have been suggested for such types of adsorption systems.[18] Among these isotherm models, the classical Langmuir model has been reported to successfully describe many of the systems relevant in the field of preparative liquid chromatography.[26] The Langmuir model equation for a binary mixture, which comprises components A and B, is expressed as follows:

$$q_A = \frac{a_A C_A}{1 + b_A C_A + b_B C_B} \tag{3a}$$

$$q_B = \frac{a_B C_B}{1 + b_A C_A + b_B C_B} \tag{3b}$$

where C_i and q_i are the concentrations of component i in the mobile phase and on the solid phase, respectively. The other variables, a_i and b_i, correspond to the Langmuir isotherm parameters of component i, which need to be determined before the optimization of a batch chromatographic process.

Besides the above isotherm model, the LMT model in the previous section has one additional parameter to be determined before the batch process optimization. It is the overall mass transfer coefficient ($k_{m,i}$), which relates the rate of concentration variation in the pore phase to the difference between the equilibrium and the actual concentrations in the mobile phase. Therefore, the first half of the present study will be devoted to determining a total of three parameters including a_i, b_i, and $k_{m,i}$ for each component i.

Inverse method is employed here for the aforementioned parameter determination task. In this method, only a few overloaded band profiles of each component are measured from a series of pulse injection experiments. The measured band profiles are then compared with the calculated band profiles, which are based on the LMT and the isotherm models with the assumed values of the unknown parameters (a_i, b_i, and $k_{m,i}$). The band profile calculations are continued until the calculated band profiles match the measured ones the most closely. During these calculation processes, the values of the three key parameters for each component in the model equations are tuned such that the sum $\sum(C_{j,\mathrm{exp}} - C_{j,cal})^2$ are minimized. To facilitate such a minimization task, the use of a robust optimization algorithm with high efficiency and accuracy is essential.

In this study, an adaptation of the state of them art optimization method, non-dominated sorting genetic algorithm with jumping genes

(NSGA-II-JG)[13] was employed in combination with Excel VBA (Visual Basic Application), which functions as calling and running Aspen Chromatography for band profile calculations each time. The GA optimization begins with the specification of several GA parameters such as population size, length of chromosome, length of substring, number of generations, crossover probability, mutation probability, and jumping gene probability.

Table 1 lists the GA parameters used in the determination of the three intrinsic parameters for each PDO component. Considering both accuracy and calculation time, we chose 50 chromosomes and stopped the iteration after 50 generations. In order to ensure that the global optimum was obtained, three optimization runs based on different sets of initial pool of chromosomes were performed for each of the experimental chromatograms.

Optimization of Productivity in a Batch Chromatographic Process

In a classical batch chromatographic process, a feed mixture is periodically injected into a chromatographic bed instead of being loaded continuously. During the time of gap between the adjacent two feed injections, a mobile phase is introduced into the bed. This is to prevent an excessive overlap between the solute bands coming from different feed injections, which usually occurs as a result of mass transfer spreading.

The application of the aforementioned operation mode to the purification of 1,3-PDO is depicted in Figure 1. Two pumps are placed ahead of the feed loading position. One of the pumps is used to deliver a stream of the feed solution, which is the mixture of 1,3-PDO and 1,2-PDO dissolved in the mobile phase. The other pump is used to deliver the mobile phase during the gap time between the adjacent feed injections. In addition, two reservoirs are placed behind the column outlet. One of the reservoirs is used to collect a stream of the purified product of 1,3-PDO, while the other deals with a waste stream. Under such arrangements of pumps and reservoirs, three sequential operations such as feed injections, mobile phase elution, and product collections are repeated cyclically. To facilitate the analysis of such a cyclic operation scheme, several terms are introduced here. As shown in Figure 2a, the time that the 1st feed injection begins is defined as t_1^{feed}, which is usually set to zero. The time that the nth feed injection begins (t_n^{feed}) can thus be expressed as follows:

$$t_n^{\text{feed}} = (n-1) \cdot (\Delta_{\text{feed}} + \Delta_{\text{gap}}) \tag{4}$$

where Δ_{feed} and Δ_{gap} are the feed and gap sizes in time unit, respectively. In this situation, the starting time and the ending time of the nth product

Table 1. GA parameters used in the determination of intrinsic parameters and the optimization of batch chromatographic process for 1,3-propanediol purification

	Determination of intrinsic parameters		Optimization of batch chromatographic process	
Population size	50		50	
Number of generations	50		80	
Length of chromosome	30 bits		105 bits	
Length of substring	Langmuir isotherm parameter, a	10 bits	Flow rate	15 bits
	Langmuir isotherm parameter, b	10 bits	Feed loading volume	15 bits
	Overall mass transfer coefficient, k_m	10 bits	Gap size in time unit	15 bits
			Starting time of product collection	30 bits
			Ending time of product collection	30 bits
Crossover probability	0.9		0.9	
Jumping gene probability	0.6		0.7	
Mutation probability	1/(length of chromosome)		1/(length of chromosome)	

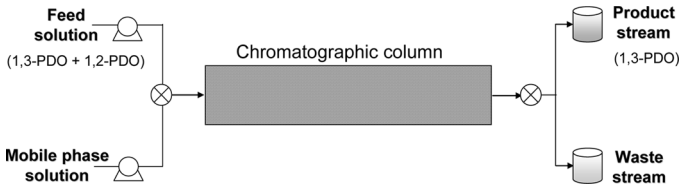

Figure 1. Schematic diagram of a batch chromatographic process for 1,3-PDO purification.

collection (denoted as $t_{n,\text{start}}^{\text{collect}}$ and $t_{n,\text{end}}^{\text{collect}}$, respectively), which are illustrated in Figure 2b, can be related to Δ_{feed} and Δ_{gap} by the following equation.

$$t_{n,\text{start}}^{\text{collect}} = (n-1)\cdot(\Delta_{\text{feed}} + \Delta_{\text{gap}}) + t_{1,\text{start}}^{\text{collect}} \tag{5a}$$

$$t_{n,\text{end}}^{\text{collect}} = (n-1)\cdot(\Delta_{\text{feed}} + \Delta_{\text{gap}}) + t_{1,\text{end}}^{\text{collect}} \tag{5b}$$

where $t_{1,\text{start}}^{\text{collect}}$ and $t_{1,\text{end}}^{\text{collect}}$ are the starting time and the ending time of the 1st product collection, respectively.

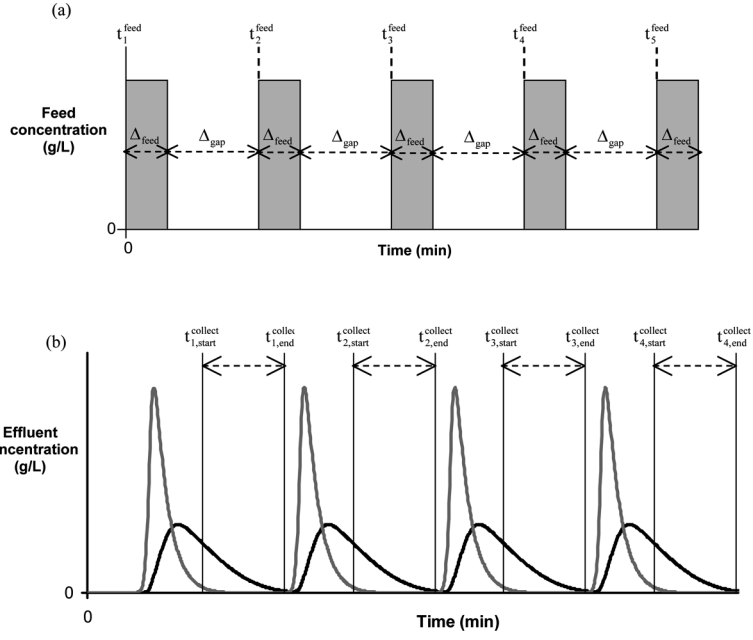

Figure 2. Patterns of feed loading and product collection in a batch chromatographic process. (a) Periodic feed injection (Δ_{feed}) and mobile phase elution (Δ_{gap}), (b) Periodic product collection.: 1,2-PDO,: 1,3-PDO (product).

The performance of the above process is usually evaluated by its productivity. In this study, productivity (Prod) was defined as the amount of 1,3-PDO product collected per unit time, per unit bed volume (BV) as follows:

$$\text{Prod} = \frac{C_A^{\text{feed}} \cdot Q \cdot \Delta_{\text{feed}} \cdot \text{Yield}_A}{\text{BV} \cdot (\Delta_{\text{feed}} + \Delta_{\text{gap}})} = \frac{C_A^{\text{feed}} \cdot V_F \cdot \text{Yield}_A}{\text{BV} \cdot (\Delta_{\text{feed}} + \Delta_{\text{gap}})} \tag{6}$$

where the subscript A indicates 1,3-PDO component; C_A^{feed} is the concentration of 1,3-PDO in the feed; V_F is the feed loading volume; and Q is the volumetric flow rate. Such a productivity of a batch chromatographic process is generally governed by several operating and system parameters, which are associated with the conditions of a batch process operation and the specifications of a chromatographic bed, respectively. The former includes flow rate, feed loading volume, gap size in time unit, and the starting time and the ending time of the product collection, while the latter the length of a chromatographic bed and the size of adsorbent particle.

Among these parameters, only the length and diameter of the chromatographic bed were fixed in this study. All the other parameters were taken into consideration as the variables to be optimized for the maximization of productivity. In addition, the following two constraints were taken into account. First, the purity of 1,3-PDO in the collected product stream should be higher than 95%. Secondly, the pressure drop through the chromatographic bed must not exceed 100 psi, which is a general criterion for a low pressure chromatographic purification process. Such an optimization problem can be represented mathematically as follows:

$$\text{Max} \qquad J = \text{Prod}\left[Q, V_F, \Delta_{\text{gap}}, t_{1,\text{start}}^{\text{collect}}, t_{1,\text{end}}^{\text{collect}}\right] \tag{7a}$$

$$\text{Subject to} \qquad \text{PurA} \geq 95\% \tag{7b}$$

$$\Delta P \leq 100\,\text{psi} \tag{7c}$$

$$\text{Dependent variables} \qquad \Delta_{\text{feed}}, t_n^{\text{feed}}, t_{n,\text{start}}^{\text{collect}}, t_{n,\text{end}}^{\text{collect}} \tag{7d}$$

$$\text{Fixed variables} \qquad L_c = 30\,\text{cm}, d_c = 2\,\text{cm} \tag{7e}$$

where PurA is the purity of 1,3-PDO product; ΔP is the pressure drop; and L_c and d_c are the length and diameter of the chromatographic bed, respectively. For the four dependent variables in Equation 7d, $\Delta_{\text{feed}} = V_F/Q$ and the other three variables (t_n^{feed}, $t_{n,\text{start}}^{\text{collect}}$, $t_{n,\text{end}}^{\text{collect}}$) are related to the decision variables (or the variables to be optimized) by Equations (4) and (5). To reduce the computation time, the adsorbent particle size was not directly included as the variables to be optimized, as can be seen in Equation (7a). Instead, the adsorbent particle size was changed in a

discrete manner and for each step the five decision variables (Q, V_F, Δ_{gap}, $t_{1,start}^{collect}$, $t_{1,end}^{collect}$) were optimized.

One of the difficulties in the above optimization task was that its objective function (Equation (7a)) was subject to the inequality constraint on product purity (Equation (7b)), which correspond to the output from numerical simulations. To facilitate such type of optimization task, the inequality constraint, namely, the purity constraint (Equation (7b)) were incorporated into the objective function using a penalty function as described by Zhang et al.[27] and Subramani et al.[28] The objective function modified in this fashion is given by:

$$\text{Min } I = \frac{1}{1+J} + w\{(\text{PurA} - 95.0) - |(\text{PurA} - 95.0)|\}^2 \qquad (8)$$

where a large weighting factor, w ($= 10^4$) was used to meet the purity constraint (PurA $\geq$95.0%), while maximizing the original objective function J.

The above optimization problem was handled with the same optimization tool as used in the previous section for the parameter determination task. As stated previously, the optimization tool is based on the recent adaptation of genetic algorithm, NSGA-II-JG,[13] in combination with Excel VBA (Visual Basic Application) and Aspen Chromatography simulator. The GA parameters used in such an optimization for the batch chromatographic process are listed in Table 1. Note that the length of substring used in such a case is markedly larger compared to that in the case of parameter determination task. This is to ensure high accuracy of the process optimization. For the case of the batch process optimization, the collection time usually has more a significant effect on productivity than the other operating parameters. For this reason, the length of substring for the collection time is set larger than those for the other decision variables.

EXPERIMENTAL

Materials

Two propanediol isomers, 1,3-propanediol (1,3-PDO, 98%) and 1,2-propanediol (1,2-PDO, 99%), were purchased from Acros organics (Morris Plains, NJ). HPLC grade hexane, which was used as a non-retained tracer, was obtained from Mallinckrodt Baker Inc. (Phillipsburg, NJ). HPLC grade ethyl acetate and methanol, which were purchased from Fisher Scientific (Fairlawn, NJ), were mixed in a ratio of 98:2 (v/v) and used as a mobile phase.

Silica gel 60 was purchased from Merck Co. (Dormstadt, Germany) and used as the adsorbent in this study. Its average particle size is 25.75 μm and its surface area is $480 \sim 540\,m^2/g$ according to the manufacturer's information. The chromatographic column employed in the task of determining the intrinsic parameters has a dimension of 30 cm in length and 0.65 cm in diameter.

Equipment

A Waters HPLC system (Milford, MA) was used for a series of batch chromatography experiments. As shown in Figure 3, the HPLC system consists of a solvent delivery pump (Waters 400), a refractive index detector (Waters 410), and a Rheodyne 7010 injector. The Waters Millennium software operating in the Windows environment was used to control the HPLC system and acquire experimental data. To maintain the temperature of the batch column at 35°C, a column heater module (Waters UL STD 3101-1) was installed in the HPLC system. The mobile phase reservoir was immersed in a Jeio-Tech water bath (model UC-10) in order to heat the mobile phase prior to entering the column.

Experimental Methods

Pulse Tests

All experiments were carried out at 35°C. For pulse tests, the HPLC system described in Figure 3 was used. Effluent from the column was monitored with a refractive index detector, which was calibrated before experiments so that its responses were linearly proportional to the concentrations.

To perform pulse tests, a 500 μL loop was connected to the injector. In the load position, the loop was filled with a feed solution. To start the injection of a feed solution into the batch column,

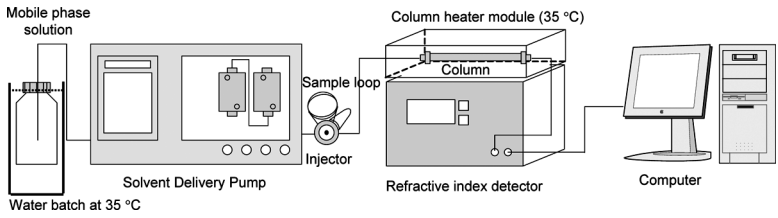

Figure 3. Schematic diagram of HPLC system.

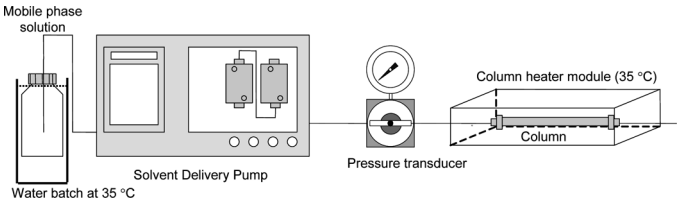

Figure 4. Schematic diagram of the experimental system for measuring pressure drop through the packed column.

the injector was switched to the inject position. Data recording was started simultaneously. All pulse tests were performed at a flow rate of 1.0 mL/min.

Pressure Drop Testing

The pressure drop testing experiments were carried out to measure the effect of flow rate on the pressure drop across the packed column, which allows for a quick determination of the inter-particle void fraction as will be explained in the next section. For such experiments, a pressure transducer (FMI Pulse Dampener PD-60-LF) was installed before the column inlet to monitor the inlet pressure (Figure 4). The pressure drop was measured after flowing the mobile phase at a fixed flow rate for 30 min or longer. The experiment was then repeated at different flow rates. All the pressure drop experiments were carried out at 35°C.

RESULTS AND DISCUSSION

Column Characterization

The characterization of a packed column, which is to measure column void fraction such as inter-particle (ε_b) and intra-particle void fractions (ε_p), is a prerequisite to the determinations of adsorption isotherm parameters because the void fraction is one of the factors affecting the values of isotherm parameters. Between the two types of void fractions, the inter-particle void fraction was estimated first from a series of measurements of pressure drops through the packed column at five different flow rates. The experimentally measured pressure drop data were then correlated with the following Ergun equation,[29] which is a function of inter-particle void fraction.

$$\Delta P = \left(\frac{150\,\mu u_0 L_c}{d_p^2} \left(\frac{1-\varepsilon_b}{\varepsilon_b} \right)^2 \frac{10^6}{6} + \frac{1.75\,\rho (u_0)^2 L_c}{d_p} \frac{1-\varepsilon_b}{\varepsilon_b} \frac{1}{3.6} \right) \frac{14.7}{1.013 \times 10^5} \tag{9}$$

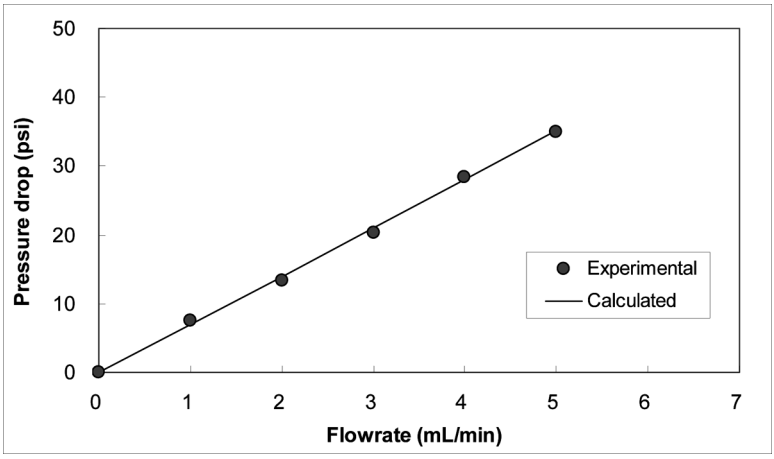

Figure 5. Comparison of the experimental measurements and the calculated values from the Ergun equation in a pressure drop testing using the column packed with the silica gel.

where ΔP is the pressure drop through the packed column, d_p is the diameter of adsorbent particle, and μ is the viscosity of mobile phase. From the best fitting of the experimental pressure drop data (Figure 5), the inter-particle void fraction of the packed column was found to be 0.321.

For the estimation of intra-particle void fraction (ε_p), a pulse test was conducted with hexane, which serves as a non-retained tracer under the mobile and stationary phases employed. The hexane chromatogram resulting from the pulse test allowed the measurement of its retention time, which was then used to check the total void fraction (ε_t) of the packed column. The resulting total void fraction, combined with the inter-particle void fraction estimated above, can be used to calculate the intra-particle void fraction (ε_p) from the following equation.

$$\varepsilon_p = \frac{\varepsilon_t - \varepsilon_b}{1 - \varepsilon_b} \tag{10}$$

From the above equation, the intra-particle void fraction was calculated to be 0.635.

Determination of Langmuir Isotherms and Overall Mass Transfer Coefficient Using the Inverse Method

In order to apply the inverse method to determining the parameters of our interest, one or a few chromatograms are to be acquired under

overloaded conditions. In this study, two overloaded chromatograms were obtained for each PDO component through a series of pulse injection experiments, one of which was based on the higher feed concentration (14 g/L) and the other on the lower feed concentration (6 g/L).

The two chromatograms obtained for each PDO component were then fitted simultaneously by tuning the Langmuir isotherm parameters and the overall mass transfer coefficient in the corresponding model equations (Equations (1) to (3)). Such a tuning process was facilitated by employing the robust optimization algorithm, which was explained in detail in the previous section. In each optimization run, the initial guesses of the isotherm parameters were set on the basis of the retention times of the acquired chromatograms. By contrast, it is not straightforward to predict the initial guess of the overall mass transfer coefficient. Thus, a wide range was first adopted for the searching region of the overall mass transfer coefficient, followed by narrowing down the searching region in stages.

The optimization results, i.e., the values of the three parameters for each PDO component are listed in Table 2. Based on these parameter values, the model predicted elution profiles were generated and they are compared with the experimental chromatogram data in Figures 6 and 7. A close agreement between the experimental and the model predicted profiles is observed, indicating that the Langmuir isotherm can account for the retention mechanisms of 1,3-PDO and 1,2-PDO on the silica gel quite well.

To check the validity of the parameter values determined above (Table 2), other pulse tests were carried out with a different feed concentration (10 g/L). The chromatograms resulting from these pulse tests were compared with the model predicted elution profiles, which were obtained on the basis of the parameter values in Table 2 and the feed concentration of 10 g/L. As shown in Figures 8 and 9, the model prediction results fit well with the experimental data, which verifies the validity of the parameter values obtained from the inverse method.

Table 2. Intrinsic parameter values determined from the inverse method based on the genetic algorithm (NSGA-II-JG)

	1,3-PDO	1,2-PDO
Langmuir isotherm parameter, a (L/L S.V.)	10.589	6.172
Langmuir isotherm parameter, b (L/g)	0.11021	0.07411
Overall mass transfer coefficient, k_m (cm/min)	0.03657	0.03686

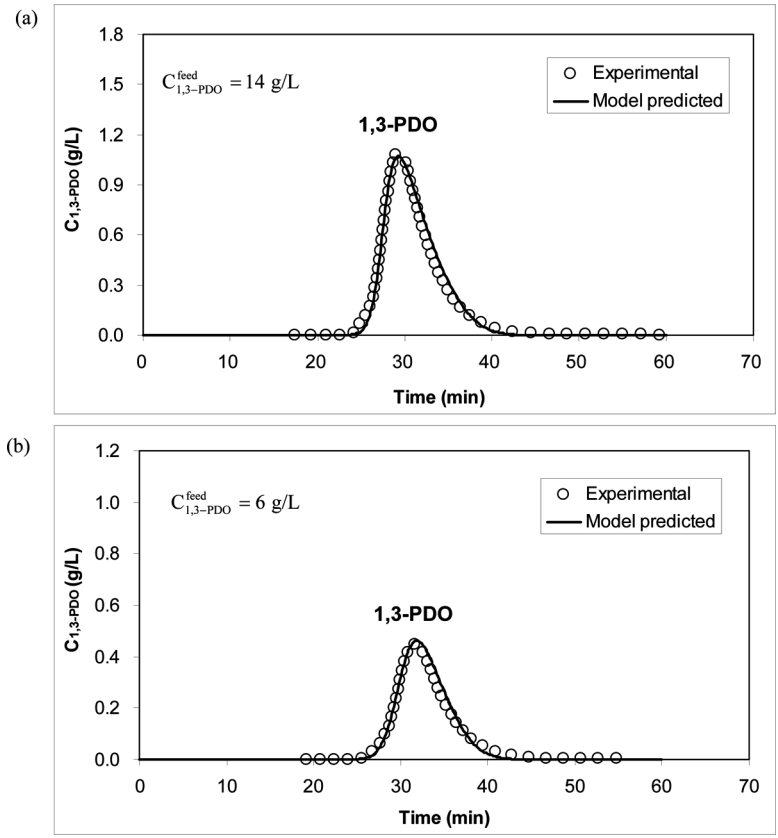

Figure 6. Experimental data and model predicted elution profile for the pulse test based on the injection of 1,3-PDO. (a) Concentration of 1,3-PDO in the feed = 14 g/L, (b) Concentration of 1,3-PDO in the feed = 6 g/L.

Optimization of the Batch Chromatographic Process for the Purification of 1,3-PDO

The isotherm parameters and the overall mass transfer coefficient were determined for each feed component in the previous section. Based on these parameter values, the batch chromatographic process for the purification of 1,3-PDO was optimized in this section to achieve the highest productivity under the following two constraints; (1) purity of 1,3-PDO$\geq$95% and (2) pressure drop through the chromatographic bed $\leq$ 100 psi. In addition, the feed concentration was set at 10 g/L for each PDO component.

In the aforementioned optimization, a series of parameters related to batch chromatographic operations (or operating parameters) were

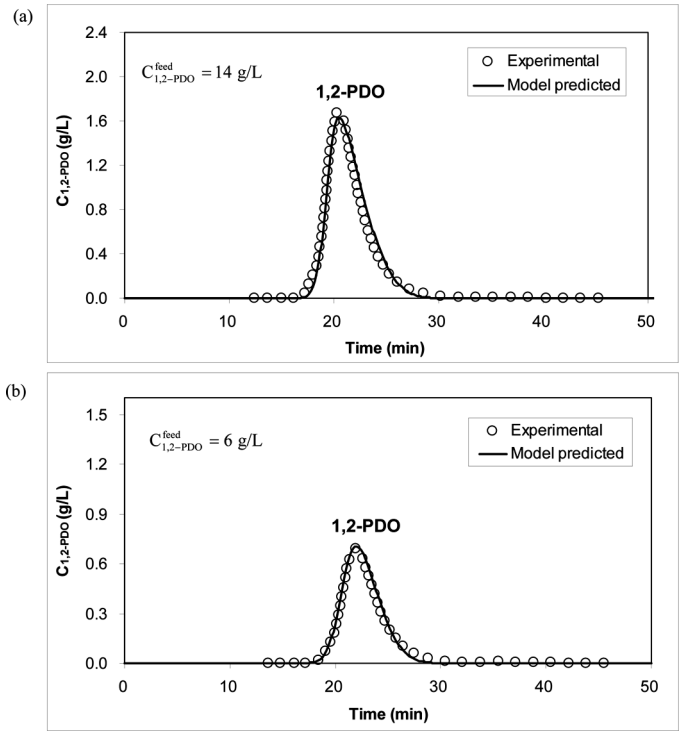

Figure 7. Experimental data and model predicted elution profile for the pulse test based on the injection of 1,2-PDO. (a) Concentration of 1,2-PDO in the feed = 14 g/L, (b) Concentration of 1,2-PDO in the feed = 6 g/L.

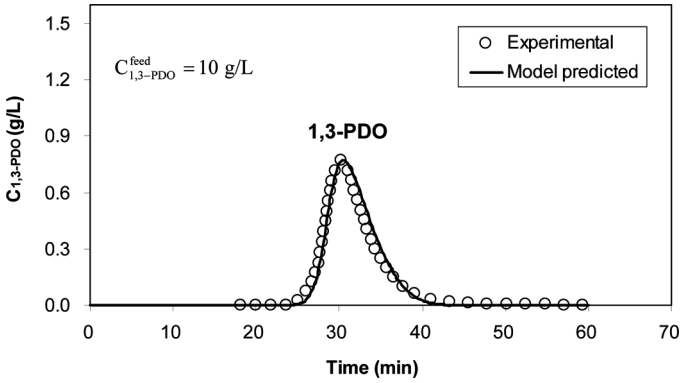

Figure 8. Comparison of experimental data and model predicted elution profile for the pulse test based on the injection of 1,3-PDO with a feed concentration of 10 g/L.

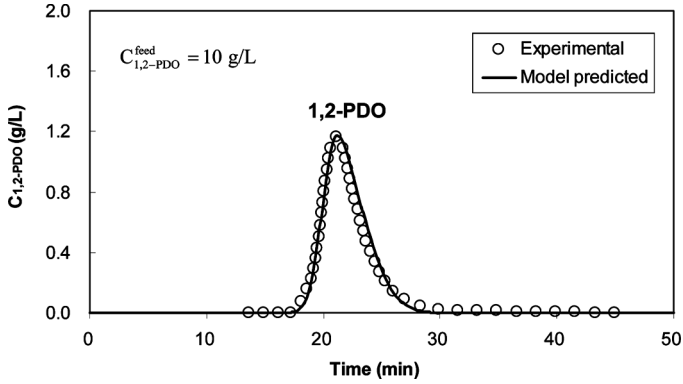

Figure 9. Comparison of experimental data and model predicted elution profile for the pulse test based on the injection of 1,2-PDO with a feed concentration of 10 g/L.

included as the decision variables while fixing the length and diameter of the batch column at 30 cm and 2 cm, respectively. Such an optimization task was performed in series while varying the adsorbent particle size at the intervals of 5 μm. The results are presented in Figure 10, where the productivity of the optimized batch process at each particle size was plotted with respect to the particle size. As expected, the productivity is largely affected by the size of particle. In the region of small particles (<35 μm), the productivity increases rapidly as the particle size increases.

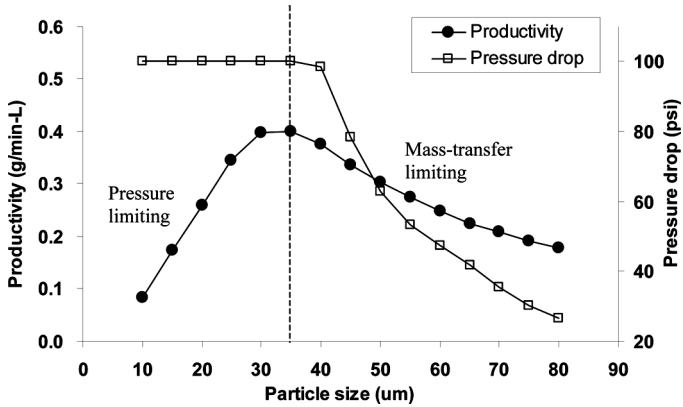

Figure 10. Effect of the adsorbent particle size on productivity and pressure drop for the optimized batch chromatographic process for 1,3-PDO purification. The pressure drop at each particle size was calculated from the Ergun equation.

Table 3. Optimal operating parameters of the batch chromatographic process for 1,3-PDO purification with the adsorbent particle size of 35 μm leading to the maximum productivity

Decision variables (or optimization variables)		Dependent variables	
Q (mL/min)	62.367	Δ_{feed} (min)	0.642
V_F (mL)	40.042	t_n^{feed} (min)[a]	$(n-1)\times 4.110$
Δ_{gap} (min)	3.468	$t_{n,start}^{collect}$ (min)[a]	$(n-1)\times 4.110 + 3.913$
$t_{1,start}^{collect}$ (min)	3.913	$t_{n,end}^{collect}$ (min)[a]	$(n-1)\times 4.110 + 5.952$
$t_{1,end}^{collect}$ (min)	5.952	Cycle time (min)[b]	4.110

[a]The letter "n" stands for the number of cycles.
[b]Each cycle consists of feed injection (for Δ_{feed}) and mobile phase elution (for Δ_{gap}).

Such a trend is continued until the particle size reaches 35 μm, beyond which the productivity rather shows a reduction with an increase in the particle size. As a result, a maximum in the productivity occurs at the particle size of 35 μm (Figure 10). For such a particle size (35 μm), the optimal operating parameter values of the corresponding batch process are summarized in Table 3.

To examine the reason for the aforementioned phenomenon, the pressure drop of each batch process with different particle size was calculated from the Ergun equation (Equation (9)). The calculated pressure drops are presented as a function of particle size in Figure 10. It is easily seen that the pressure drop is maintained at its upper limit (100 psi) while the particle size is kept below 35 μm. This result indicates that the productivity of the batch process with small particles (<35 μm) is virtually limited by the pressure drop. In such a pressure limiting region, the batch process is operated at its maximum allowable flow rate (Figure 11), whose value varies according to the size of particle. According to the Ergun equation, the maximum flow rate increases if the size of the particle is larger under a fixed pressure drop. Therefore, the productivity, if limited by the pressure drop, has an increasing trend as the particle size increases (Figure 10).

By contrast, if the particle size is larger than 35 μm, the pressure drop of the corresponding batch process is reduced to below 100 psi as shown in Figure 10. Under such circumstances, the productivity must be limited by other factors than the pressure drop. The factor limiting the productivity for large particles (>35 μm) is the mass transfer efficiency (or column efficiency), which is usually governed by flow rate and particle size. As explained in the theory section, higher flow rate or larger particle size increases the effects of dispersion and mass transfer resistance, thereby causing more significant spreading of

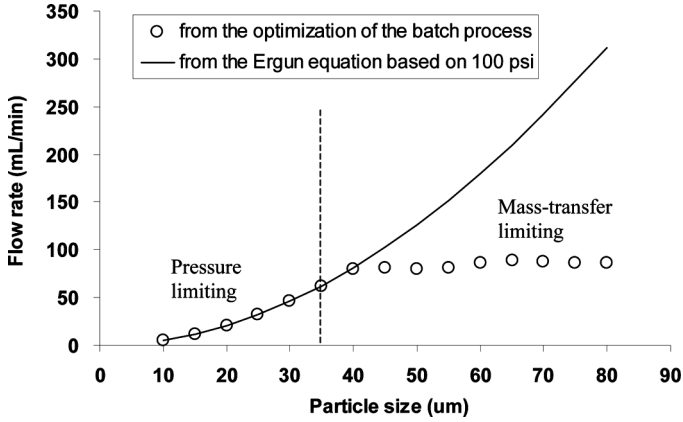

Figure 11. Plot of adsorbent particle size versus operating flow rate of the optimized batch chromatographic process for 1,3-PDO purification. The calculated line corresponds to the maximum allowable flow rate of the batch process at each particle size.

chromatographic bands. This can obviously reduce the product yield, which in turn decreases the productivity. This is why the productivity decreases with increasing the particle size in the region of large particles ($>35\,\mu m$) (Figure 10). In such a situation, the flow rate of the batch process is kept far below its maximum allowable one, leading to the pressure drop limitation (100 psi) as shown in Figure 11. This is mostly because a higher flow rate makes the dispersion effect more severe and, thus, reduces the product yield, especially in the region of large particles.

So far, we have discussed how the productivity of the optimized batch process was affected by the particle size. Putting all the aforementioned analyses together, one can conclude as follows. The productivity for small particles ($<35\,\mu m$) is limited by the pressure drop, whereas the productivity for large particles ($>35\,\mu m$) is limited by the mass transfer efficiency. In the pressure limiting region, the smaller the particles, the smaller is the productivity. As the particle size increases, the productivity first increases in the pressure limiting region and then decreases in the mass transfer limiting region. Therefore, the optimal particle size for the maximum productivity falls on the boundary between the two limiting regions.

CONCLUSIONS

The inverse method was applied to obtain the intrinsic parameters of 1,3-PDO and 1,2-PDO in a chromatographic system where the silica

gel and the mixture of ethyl acetate and methanol (98:2 v/v) were employed as the stationary and mobile phases, respectively. The intrinsic parameters of interest include the Langmuir isotherms and the overall mass transfer coefficient. For such an application of the inverse method, two overloaded chromatograms with different feed concentrations were measured for each PDO component and a highly efficient adaptation of genetic algorithm, NSGA-II-JG, was connected with the lumped mass transfer model equations. The least square fitting of such model equations to the two overloaded experimental chromatograms allowed for a robust determination of the intrinsic parameters. The model predicted elution profiles, which were based on the parameter values resulting from such a least square fitting procedure, were found to match the experimental chromatograms very closely. This indicates the validity of the results from the inverse method based on the optimization algorithm of NSGA-II-JG.

The intrinsic parameters determined in such a manner were used as key input data in the subsequent task, i.e., the optimization of the batch chromatographic process for 1,3-PDO purification, which was also carried out by the use of NSGA-II-JG. The optimization aims at the attainment of the highest productivity while taking into account the following two constraints; (1) purity of 1,3-PDO0$\geq$95% and (2) pressure drop $\leq$100 psi. During such optimization, all the operating parameters and the adsorbent particle size were varied in order to find their optimal values while the column length was fixed at 30 cm. The results showed that the productivity for small particles ($<$35 μm) was limited by the pressure drop, whereas the productivity for large particles ($>$35 μm) was limited by the mass transfer efficiency. Consequently, the optimal particle size for the maximum productivity occurs at 35 μm, which corresponds to the boundary between the pressure and the mass transfer limiting regions.

Overall, the main stream of this study tells that the application of genetic algorithm or its adaptation can make the entire task of developing a batch chromatographic purification process more efficient, which covers from the estimation of intrinsic parameters to the robust optimization of operating and system parameters.

NOMENCLATURE

a_i = Langmuir isotherm parameters of component i based on solid volume, L/L S.V.

b_i = Langmuir isotherm parameters of component i, L/g

BV = bed volume, mL

C_b = mobile phase concentration, g/L

C^* = average pore phase concentration, g/L

C_A^{feed} = concentration of 1,3-PDO in the feed, g/L

d_c = column diameter, cm

d_p = diameter of adsorbent particle, μm

E_b = axial dispersion coefficient, cm^2/min

L_c = column length, cm

$k_{m,i}$ = overall mass transfer coefficient of component i, cm/min

P = phase ratio

Prod = productivity, g/min-L

PurA = purity of 1,3-PDO in the product stream

q = solid phase concentration, g/L S.V.

Q = volumetric flow rate, mL/min

R_p = radius of adsorbent particle, μm

S.V. = solid volume, mL

$t_{n,start}^{\text{collect}}$ = the starting time of the nth product collection, min

$t_{n,\text{end}}^{\text{collect}}$ = the ending time of the nth product collection, min

t_1^{feed} = the time that the 1st feed injection begins, min

t_n^{feed} = the time that the nth feed injection begins, min

u_0 = mobile phase interstitial velocity, cm/min

V_F = feed loading volume, mL

w = weighting factor

Yield_A = yield of 1,3-PDO

ρ = mobile phase density, g/cm^3

μ = mobile phase viscosity, g/cm-sec

ε_b = inter-particle void fraction

ε_p = intra-particle void fraction

ε_t = total void fraction

ΔP = pressure drop through the chromatographic bed, psi

Δ_{feed} = feed size in time unit, min

Δ_{gap} = gap size in time unit, min

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