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BIOPRODUCT ADSORPTION IN IMMOBILIZED ADSORBENT: LOCAL THERMODYNAMIC EQUILIBRIUM MODEL

Jeong-Woo CHOI*

Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, New Brunswick, NJ 08855

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Abstract—A mathematical model using local thermodynamic equilibrium isotherms for adsorption on immobilized adsorbents is proposed in order to optimize the design parameters in *in situ* bioproduct separation process. The model accurately follows the experimental data on the adsorption of berberine, secondary metabolite produced in plant cell culture. The result shows that the lower loading capacity in immobilized adsorbents is due to the decrease in the maximum solid phase concentration and the isotherm equilibrium constant, not the effective diffusivity. Design parameters in *in situ* bioproduct separation process, such as the size of the beads, the ratio of beads to bulk volume and the adsorbent content of the bead, are evaluated by using the model. The decrease of bead size is the most effective parameter for adsorption of berberine in immobilized adsorbent due to a reduction in the overall diffusional resistance.

INTRODUCTION

To enhance process economics through improvements in the primary recovery stages, it is necessary to develop a separation technique which can concentrate the bioproduct, often with some degree of selectivity for the product of interest, and be economical from both capital and operation cost standpoints in large scale cell culture. In addition to the above mentioned advantages, product separation can enhance the production of secondary metabolites by removing feedback regulation mechanisms and nonspecific inhibitors in plant cell culture [1,2]. For *in situ* product separation of plant cell culture, liquid-solid culture systems for plant cells consisting of an aqueous nutrient phase and of solid polar adsorbents, have been preferred because many products of plant cells are expected to be of polar character and bound weakly to the lipophilic phase of liquid-liquid systems. The differences in acid-base properties and sorption characteristics of alkaloids further offers the potential for selectively absorbing specific alkaloids from a mixture [3].

Polycarboxylic ester resin, XAD-7, was investigated to adsorb berberine, secondary metabolite from immobilized *T. rugosum* cells, secreted in permeabilization process and immobilized XAD-7 was developed for *in situ* product separation process in an airlift fermenter [4]. The advantages of immobilized XAD-7 were easy to use in bioreactor operation, prevention of surface fouling, and easy separation of adsorbents from cells for the repeated use of cells and adsorbents [4]. The adsorption of bioproduct on immobilized adsorbent was dependent on a number of design parameters. The performance of the immobilized adsorbent in *in situ* product separation process could be evaluated by judging the adsorption rate for target product. The adsorption behavior of bioproduct was controlled by various diffusional resistances in addition to intrinsic binding characteristics of the free adsorbent particles. Diffusional characteristics were influenced by design parameters such as size of beads, adsorbent content of bead, amount of beads to bulk volume and the type of hydrogel used.

The design and optimization of *in situ* bioproduct separation process using immobilized adsorbent required a detailed mathematical model. Because the effects of various design parameters and process variables were coupled, it was relatively difficult to achieve an optimal design based on purely emperical correlations. In this study, development of a mathematical model to describe diffusion and adsorption in immobilized adsorbent is investigated. The purpose of this study is to investigate the feasibility of using a

*Present Address: Department of Chemical Engineering, Sogang University, Seoul, Korea

mathematical model for an optimal design on bioproduct separation using immobilized adsorbents.

Mathematical models for immobilized adsorbents have been investigated by using simple Langmuir or Freundlich isotherm and solved by finite difference technique with assumed effective diffusivity of solute in XAD-4 adsorbent for cyclohexamide adsorption system [5] and in DEAE-trisacryl adsorbent for enzyme adsorption system [6]. The local thermodynamic equilibrium model could predict the adsorbed enzyme amount in suspended porous supports, Duolite S-761, more accurately than other models [7]. Since diffusion through the pores of the carrier or adsorbent occurs far slower than adsorption, the assumption that all points within the carrier or adsorbent remain in local thermodynamic equilibrium can be permitted. Orthogonal collocation technique was clearly superior to solve the equations for adsorption column system than finite difference technique which was found to be stable only for certain parameter values and converged very slowly [8]. In this work, the model equations are developed based on reversible binding with local thermodynamic equilibrium assumptions for adsorption of bioproduct on immobilized adsorbents. The model equations are solved by orthogonal collocation technique with parameter estimation to minimize computational effort and to develop some simple lumped approximations easily. Results are compared with experimental data using berberine as a target bioproduct and alginate-entrapped XAD-7 as immobilized adsorbents. Design parameters for an optimal design of *in situ* bioproduct separation process are evaluated with the proposed model.

MATERIAL AND METHODS

1. Materials

Berberine standards were supplied by Eastman Kodak company (Rochester, NY). The neutral polymeric resin, XAD-7 was obtained from Supelco Inc. (Bellefonte, PA). All other reagents were analytical grade and purchased from Fisher Scientific (Rochester, NY).

2. Preparation of adsorbent

Prior to use, the resins, XAD-7, were soaked in methanol for 24 hour and then washed with 2 liter distilled water. The washed resins were air dried on the filter paper by pulling a vacuum in the filter flask. Sieve the resin through the nylon nets (mesh size: 250 μm and 500 μm) to get suitable size distribution.

3. Immobilized adsorbent

The neutral resin, XAD-7, was sieved through the nylon nets (mesh size: 250 μm and 500 μm). 2g alginic acid IV was dissolved in water (98 m*l*) by heating under stirring. XAD-7 20g is mixed with alginate solution (80g) at room temperature. Alginate beads of 4.35 mm in diameter were made by dropping alginate/resin suspension into 1% $CaCl_2$ solution under continuous stirring. The beads were allowed to form for 30 min and then collected by filtration. Beads were washed with distilled water and then were autoclaved in 0.5% $CaCl_2$ solution to maintain the integrity for 15 min at 121°C. The sterilized beads were stored in sterilized water.

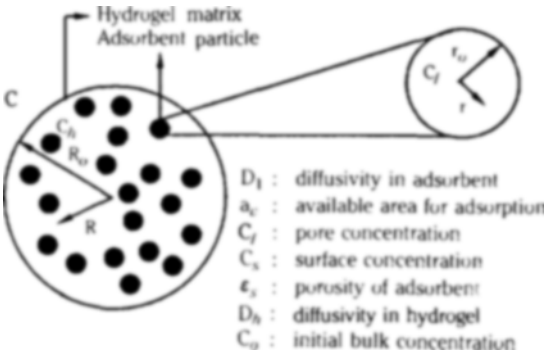

Fig. 1. Schematic diagram of an immobilized adsorbent.

4. Adsorber unit

A 500 m*l* slow speed stirring vessel system, (Corning Co., Corning, NY) was used for a adsorber unit. The working volumes for immobilized adsorbent test were 200 m*l* at 180 agitation rpm. Experiments were conducted by distributing solution of known berberine concentration into adsorber unit. Immobilized resin was added to the adsorber unit. Sample solution was taken from the adsorber unit by the pipet with the cotton filter at various time throughout the experiments. After measuring the UV absorbance of sample solution at 265 nm with a Gilford spectrophotometer, Stasar II Model, the sample solution returned to the adsorber unit. Absorbance was converted into berberine concentration with a standard curve of berberine concentration versus absorbance. All experiments were conducted at 20°C.

THEORETICAL MODEL

1. Model equations

The physical system and the associated notation are depicted in Figure 1. The assumption for mathematical model are as follows:

- Adsorbent particle and hydrogel are sphere.
- Adsorbent particles are distributed uniformly inside the hydrogel bead.

- Each diffusivity in the hydrogel and adsorbent particles is constant.

Volume averaged homogeneous conservation equation for product adsorption in the adsorbent particle is

$$\frac{\partial C_T}{\partial t}=D_l\frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial C_l}{\partial r}\right] \tag{1}$$

where C_T is the total product concentration in the adsorbent particle, given by

$$C_T=C_l+ma_vC_s \tag{2}$$

where C_l and C_s are the liquid (pore) and solid (surface) phase concentrations, respectively, and a_v is the solid area available for product adsorption per unit volume. The product diffusivity in the adsorbent is D_l, the void fraction is ε_s and the parameter m is

$$m=\frac{1-\varepsilon_s}{\varepsilon_s}. \tag{3}$$

Volume averaged homogeneous conservation equation for the hydrogel is

$$\frac{D_h}{R^2}\frac{\partial}{\partial R}\left[R^2\frac{\partial C_h}{\partial R}\right]-\frac{3N_sD_lr_o^2}{R_o^3}\frac{\partial C_l}{\partial r}=\frac{\partial C_h}{\partial t} \tag{4}$$

where C_h is the product concentration and D_h is the product diffusivity in the hydrogel. And N_s is the total number of adsorbent particle per hydrogel bead.

Since the bath (bulk) phases is finite, the product depletion in bulk phase is

$$\frac{\partial C}{\partial t}=\frac{-4\pi N_hR_o^2D_h}{V_B}\left|\frac{\partial C_h}{\partial R}\right|_{R=R_o} \tag{5}$$

where V_B is the bath volume. The concentration of product in the bath, C is the only observable dependent variable under typical experimental conditions. N_h is the total number of hydrogel bead in the bath.

The initial conditions at time (t = 0) are

$$C_h=C_l=C_s=C_T=0 \tag{6}$$

$$C=C_o. \tag{7}$$

The associated boundary conditions are

$$R=0;\ \frac{\partial C_h}{\partial R}=0 \tag{8}$$

$$R=R_o;\ C_h=C \tag{9}$$

$$r=0;\ \frac{\partial C_l}{\partial r}=0 \tag{10}$$

$$r=r_o;\ C_l=C_h. \tag{11}$$

These equations are supplemented by an equilibrium relation for solid-phase and local liquid phase concentrations. Langmuir adsorption isotherm is chosen [4]

$$C_s=\frac{C_{sm}C_l}{K_s+C_l}. \tag{12}$$

The isotherm parameters C_{sm} and K_s are function of the support material as well as bioproduct. If the local thermodynamic equilibrium is relaxed, the above equation is replaced by

$$\frac{dC_s}{dt}=k_a(C_{sm}-C_s)C_l-k_dC_s \tag{13}$$

that must be solved for all local values of C_l. The equilibrium parameter $K_s=k_d/k_a$ and eq. (12) is recovered if local equilibrium is assumed so that the surface concentration tracks the local liquid phase concentration. Furthermore, if external diffusion is important, then eq. (10) becomes

$$D_h\left|\frac{\partial C_h}{\partial R}\right|_{R=R_o}=-k_L(C_h-C) \tag{14}$$

where k_L is the mass transfer coefficient.

In dimensionless form, eqs. (1) to (11) are reduced to

$$\Gamma(\phi_l)\frac{\partial\phi_l}{\partial\theta}=\alpha\frac{1}{\xi^2}\frac{1}{\partial\xi}\left(\xi^2\frac{\partial\phi_l}{\partial\xi}\right) \tag{15}$$

where

$$\Gamma(\phi_l)=1+m\frac{\phi_{sm}\omega}{(\omega+\phi_l)^2}=1+m\frac{d\phi_l'}{d\phi_l} \tag{16}$$

$$\frac{1}{\chi^2}\frac{1}{\partial\chi}\left(\chi^2\frac{\partial\phi_h}{\partial\chi}\right)=3N_s\alpha\sqrt{\beta}\left|\frac{\partial\phi_l}{\partial\xi}\right|_{\xi=1}+\frac{1}{\beta}\frac{\partial\phi_h}{\partial\theta} \tag{17}$$

$$\frac{\partial\phi}{\partial\theta}=-3\beta N_k\left|\frac{\partial\phi_h}{\partial\chi}\right|_{\chi=1}. \tag{18}$$

The initial conditions become

$$\phi_l(0,\xi)=0 \tag{19}$$

$$\phi_h(0,\chi)=0 \tag{20}$$

$$\phi(0)=1. \tag{21}$$

The boundary condition become

$$|\phi_l|_{\xi=1}=\phi_h \tag{22}$$

$$\left|\frac{\partial\phi_l}{\partial\xi}\right|_{\xi=0}=0 \tag{23}$$

$$|\phi_h|_{\chi=1}=1 \tag{24}$$

$$\left|\frac{\partial\phi_h}{\partial\chi}\right|_{\chi=0}=0. \tag{25}$$

The dimensionless variables ϕ are introduced by normalizing the corresponding concentration C to the initial concentration C_o. The other dimensionless groups

are defined as

$$\theta = \frac{D_h t}{r_o^2} \tag{26}$$

$$\xi = \frac{r}{r_o} \tag{27}$$

$$\chi = \frac{R}{R_o} \tag{28}$$

$$N_R = \frac{N_h 4/3\pi R_o^3}{V_H} = \frac{N_h V_H}{V_H} \tag{29}$$

$$\beta = \frac{r_o^2}{R_o^2} \tag{30}$$

where V_H is the total volume of hydrogel bead.

The dimensionless groups of parameters that define the particular problems are

$$\alpha = \frac{D_l}{D_h} \tag{31}$$

$$m\phi_{sm} = m\frac{C_{sm} a_v}{C_o} \tag{32}$$

$$\omega = \frac{K_s}{C_o}. \tag{33}$$

The parameters to be estimated are D_l, C_{sm} and K_s. The model is reduced to the functional form $\phi = \phi(\theta; \alpha, m\phi_{sm}, \omega)$.

2. Numerical techniques

For immobilized adsorbent, it is convenient to introduce the transformation $\zeta = \xi^2$ and $\Psi = \chi^2$ to eliminate eq. (23) and eq. (25), and the two-point nature of the boundary conditions. Thus, the governing equations are further reduced to

$$\frac{\partial \phi}{\partial \theta} = -6\beta N_R \left|\frac{\partial \phi_h}{\partial \Psi}\right|_{\Psi=1} \tag{32}$$

$$\Gamma(\phi_l)\frac{\partial \phi_l}{\partial \theta} = \alpha\left(6\frac{\partial \phi_l}{\partial \zeta} + 4\zeta\frac{\partial^2 \phi_l}{\partial \zeta^2}\right) \tag{33}$$

$$6N_s\alpha\sqrt{\beta}\left|\frac{\partial \phi_l}{\partial \zeta}\right|_{\zeta=1} + \frac{1}{\beta}\frac{\partial \phi_l}{\partial \theta} = 6\frac{\partial \phi_h}{\partial \Psi} + 4\zeta\frac{\partial^2 \phi_h}{\partial \Psi^2} \tag{34}$$

and the boundary conditions given in eqs. (19), (20), (21), (22) and (24). These equations may be solved using the method of orthogonal collocation [9].

For the product concentration in the adsorbent particle, let

$$\frac{\partial \phi_{li}}{\partial \zeta} = \sum_{j=1}^{N+1} A_{ij}\phi_{lj} \tag{35}$$

$$\frac{\partial^2 \phi_{li}}{\partial \zeta^2} = \sum_{j=1}^{N+1} B_{ij}\phi_{lj} \tag{36}$$

be approximations to the corresponding derivatives at the locations ζ_i that are the roots of an Nth-order Jacobi polynominal. The semidiscretization elements A_{ij} and B_{ij} that are used to approximate the first and second derivatives, respectively, depend on particular polynominal used.

For the porduct concentration in the hydrogel bead, let

$$\frac{\partial \phi_{hp}}{\partial \Psi} = \sum_{q=1}^{M+1} C_{pq}\phi_{hq} \tag{37}$$

$$\frac{\partial^2 \phi_{hp}}{\partial \Psi^2} = \sum_{q=1}^{M+1} D_{pq}\phi_{hq} \tag{38}$$

be approximations to the corresponding derivatives at the location Ψ_i that are the roots of an Mth-order Jacobi polynominal. The semidiscretization elements C_{pq} and D_{pq} that are used to approximate the first and second derivatives, respectively, depend on particular polynominal used.

The evaluation of these elements (A_{ij}, B_{ij}, C_{pq} and D_{pq}) and the underlying theoretical support for the method can be found in Villadsen and Michelsen [9] who also provides subroutine listings that used in this study. The boundary condition for the adsorbent particle is $\phi_{l,N+1} = \phi_h$, where N is the number of internal collocation points that corresponds to a particular Nth-order polynominal approximation. The boundary condition for the hydrogel beads is $\phi_{h,M+1} = \phi$ where M is the number of internal collocation points the corresponds to a particular Mth-order polynominal approximation. Since the boundary conditions for the adsorbent particle and hydrogel beads are coupled, the boundary condition for the hydrogel beads can be expressed as $\phi = \phi_{h,M+1} = (\phi_{l,N+1})_{M+1}$. Substituting the above relationships into a diffusion equations yield a set of first-order differential equations:

$$\frac{d\phi_{li}}{d\theta} = \frac{\alpha}{\Gamma(\phi_l)}\sum_{j=1}^{N+1} E_{ij}\phi_{lj}; \quad i = 1, 2, \cdots, N \tag{39}$$

where

$$E_{ij} = 4\zeta_i B_{ij} + 6A_{ij} \tag{40}$$

$$6N_s\alpha\sqrt{\beta}\sum_{j=1}^{N+1} A_{ij}\phi_{lj} + \frac{1}{\beta}\frac{d(\phi_{l,N+1})_q}{d\theta} = \sum_{q=1}^{M+1} F_{pq}(\phi_{l,N+1})_q; \quad i = 1\sim N \text{ and } p = 1\sim M \tag{41}$$

where

$$F_{pq} = 4\Psi_i C_{pq} + 6D_{pq} \tag{42}$$

$$\frac{\partial \phi}{\partial \theta} = \frac{d\phi_{h,M+1}}{d\theta} = \frac{d(\phi_{l,N+1})_{M+1}}{d\theta} = -6\beta N_R\sum_{q=1}^{M+1} C_{pq}(\phi_{l,N+1})_q \tag{43}$$

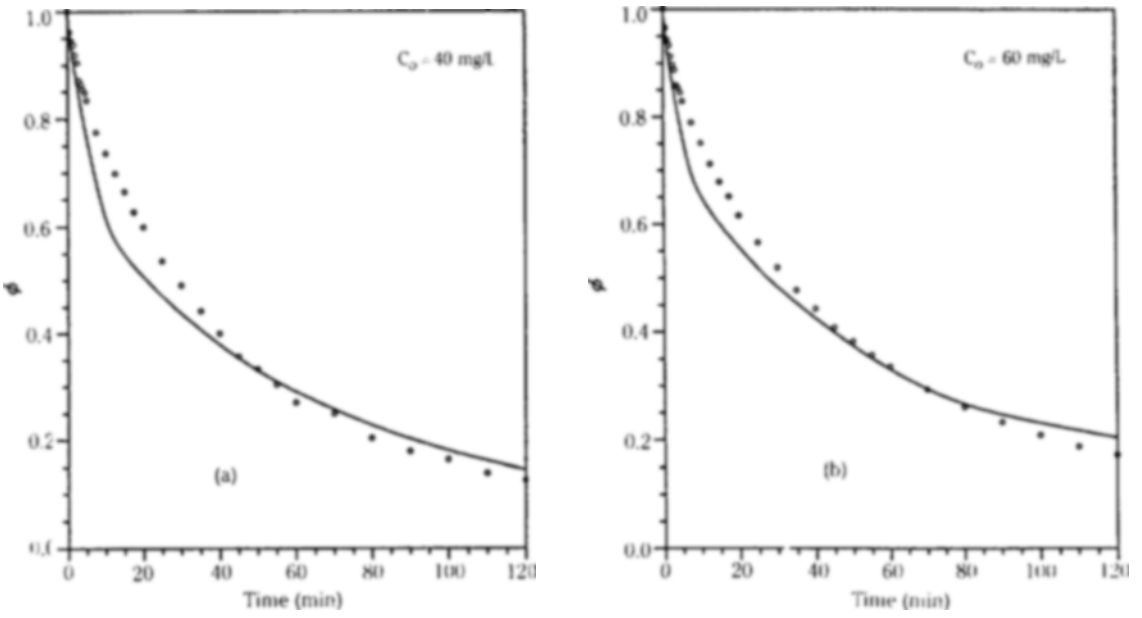

Fig. 2. Experimental (circle) and theoretical (solid line) results for adsorption of berberine on immobilized adsorbents at two different initial berberine concentration (a) 40 mg/L (b) 60 mg/L.

that are easily integrated by an explicit Runge-Kutta type method (10) or similar technique with the initial conditions $\phi_h(0)=0$, $\phi_{hp}(0)=0$ and $\phi(0)=1$.

3. Parameter estimation

Under the conditions where the relative volumes are known and the diffusion coefficient in hydrogel can be estimated *a priori,* the parameters to work with are α, $m\phi_{sm}$ and ω. The diffusion coefficient of berberine in hydrogel bead, alginate in this experiment, is estimated using the method described by Tanaka et al. [11]. $D_h=2.831\times10^{-1}cm^2/min$ is obtained for diffusion of berberine into alginate bead [4].

The solution to eqs. (39), (41) and (43) depends on the choice of N and the Jacobi polynominal used for the basic functions. The Jacobi polynominal used in all numerical approximations is characterized by the weighting factor $\Psi^{1/2}(1-\Psi)$ over the interval $0<\Psi<1$ and $\zeta^{1/2}(1-\zeta)$ over the interval $0<\zeta<1$. N=4 for the adsorbent particle and M=4 for the hydrogel beads are chosen as the number of internal collocation points, which represent a compromise between extreme accuracy and computational speed.

The experimental data, C vs. θ, are compared to the model predictions by choosing parameters α, $m\phi_{sm}$, ω that give a best fit of the model to the data. A nonlinear parameter estimation technique is used [12, 13] that uses a weighting factor for the residuals proportional to ϕ^{-2} so that the information near equilibrium conditions is highlightened.

Table 1. Experimental values in simulation for the adsorption of berberine on immobilized adsorbents

r_o = 0.025 cm	R_o = 0.435 cm
ε_s = 0.532	a_v = 445 m^2/g XAD-7
N_h = 377	N_s = 356
$D_h=2.831\times10^{-4}$ cm^2/min	
C_o = 60 mg/L	V_B = 200 mL

RESULTS AND DISCUSSION

1. Berberine adsorption

For the immobilized adsorbent, the experimental concentration-time curves for berberine adsorption are shown in Figure 2 for two different initial berberine concentrations. Table 1 shows the experimental values to be used for simulation. Void fraction, ε_s, and available surface area, a_v, for XAD-7 was reported by Paleos [14]. The experimental data shown were used in the parameter estimation routine to find isotherm parameters and diffusivity coefficient of berberine in the adsorbent particle, which decide the loading capacity in immobilized adsorbents. The model results with these estimates are shown as smooth, soild curve in Figure 2. The corresponding estimates of parame-

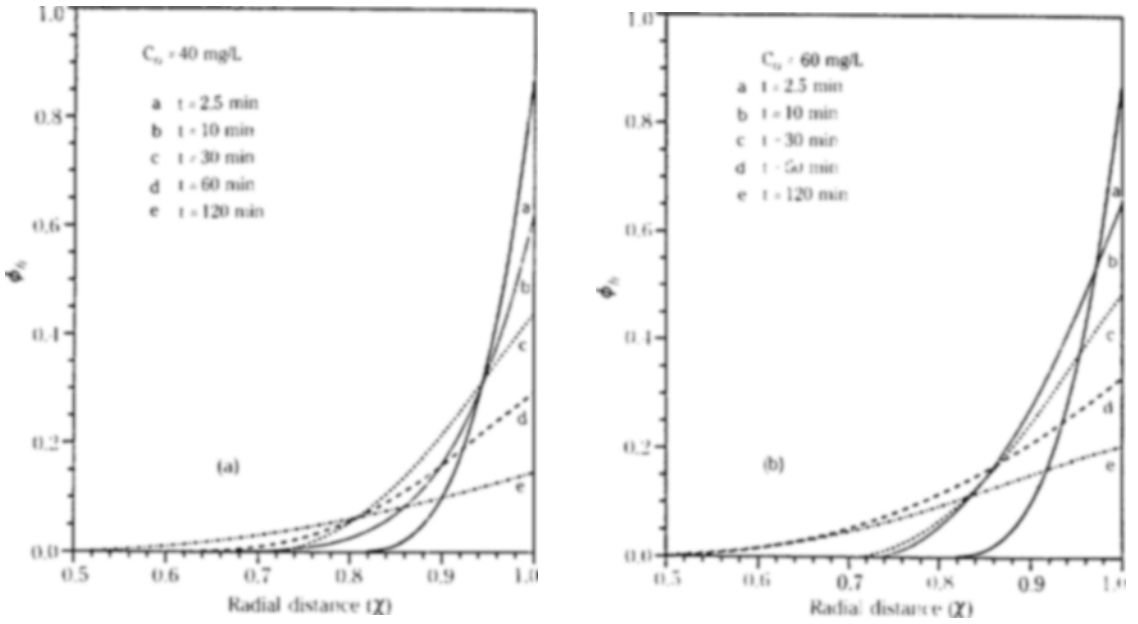

Fig. 3. Berberine concentration profile in immobilized adsorbents at two different initial berberine concentration and at five different times (a) 40 mg/L (b) 60 mg/L.

ters are found to be

$$C_{sm} = 0.2679\,g/L \quad (44)$$

$$K_s = 0.4099\ g/L \quad (45)$$

$$D_l = 7.796 \times 10^{-5}\,cm^2/min. \quad (46)$$

The average correlation coefficient for all curves are r = 0.988. The average correlation between parameters is found to be 0.2411, which means that resulting parameters are reliable due to low correlation coefficient linking. It is seen that the model is quite consistent over the range of initial berberine concentrations investigated and is able to approximate all the experimental data fairly well.

The intraparticle berberine concentrations have been calculated using the estimated model parameters and the results are shown in Figure 3 for two different initial berberine concentrations at the five different times. The solid curves represent the dependent variable used in the model that is approximated by a polynomial in χ and ξ. As time increased, the penetration distance of berberine increased because berberine adsorption onto the adsorbent particle near the surface become equilibriated. It is also seen that a parabolic profile would be good approximation.

For the suspended adsorbent, the same technique is used [4] and the corresponding estimates of parameters are found to be

$$C_{sm} = 1.3830\ g/L \quad (47)$$

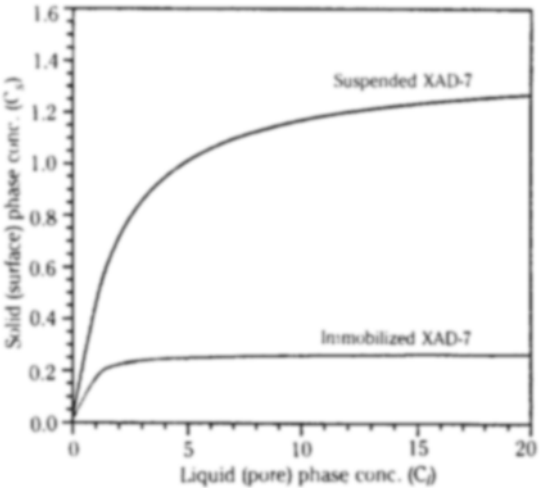

Fig. 4. Adsorption isotherm for the solid (pore) phase and local liquid (surface) phase concentration is suspended and immobilized adsorbents.

$$K_s = 1.8700\ g/L \quad (48)$$

$$D_l = 9.603 \times 10^{-5}\,cm^2/min. \quad (49)$$

Figure 4 shows the adsorption isotherm curve with the estimated solid (pore) phase and local liquid (surface) phase concentration in suspended and immobilized adsorbent. Though the effective diffusivity in immobilized adsorbent particle decreases 19% com-

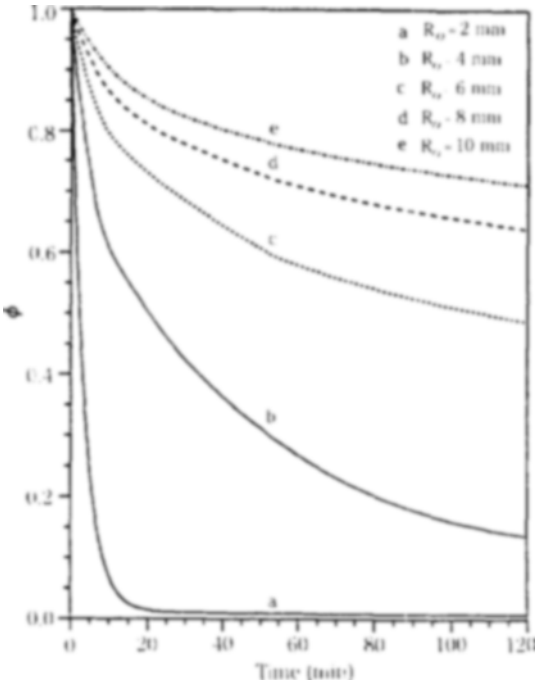

Fig. 5. Simulated bulk concentration profiles for the adsorption of berberine on immobilized adsorbents by changing the size of bead.

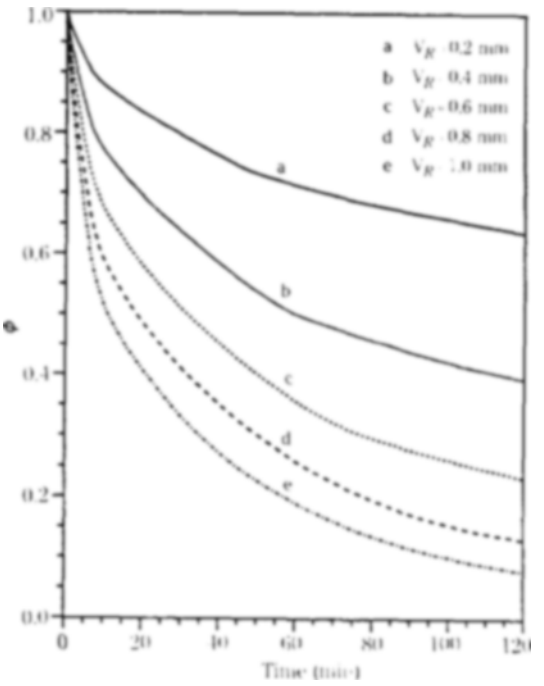

Fig. 6. Simulated bulk concentration profiles for the adsorption of berberine on immobilized adsorbents by changing the volume ratio of bead to bulk solution.

pared to that in suspended adsorbent particle, the maximum solid phase concentration and the isotherm equilibrium constant in immobilized adsorbent particle decreased 81% and 78%, respectively, compared to those in suspended adsorbent particle. The reason for this might be that surface of adsorbents is deactivated or available surface area of adsorbents decreased by the adsorption of ions onto adsorbent during immobilization process. The decrease of effective diffusivity might be due to the filling of alginate solution in the pore of adsorbent particle during immobilization process. These results suggest that the decrease of loading capacity in immobilized adsorbent particle is due to decrease of the maximum solid phase concentration and the isotherm equilibrium constant on surface, not of the effective diffusivity. Thus, the proposed mathematical model for immobilized adsorbent is useful to evaluate the diffusion and adsorption of bioproduct which decide the performance of bioproduct separation.

2. Simulation studies for investigating the disign parameters

The proposed mathematical model for immobilized adsorbent can describe the various diffusional characteristics in addition to intrinsic binding characteristics of the immobilized adsorbent particles. The performance of an immobilized adsorbent in *in situ* product separation process can be evaluated by using the proposed model for the adsorption rate for target product, berberine in this experiment. The performance of immobilized adsorbents is influenced by design parameters such as size of beads, amount of beads to bulk volume and adsorbent content of bead.

The size of alginate entrapped adsorbent bead, R_o, can be varied by using a different nozzle or air flow rate during immobilization process. The batches of alginate-entrapped adsorbent beads prepared using this methodology only vary in size but have similar properties of diffusion and adsorption. But time of adsorption using immobilized adsorbent can be reduced by reducing the size of beads. Figure 5 shows the simulation curves indicating the effect of bead size on adsorption kinetics in immobilized adsorbent. The decrease in the size of immobilized adsorbent bead speeds up the binding kinetics significantly. However, in the practical design the size of bead can be reduced only upon a certain limit because the loading number of adsorbent particles decreases as bead size decreases, to make very small bead is very difficult process if size of the adsorbent particle is not very small, and too small beads are difficult to handle and to be separated

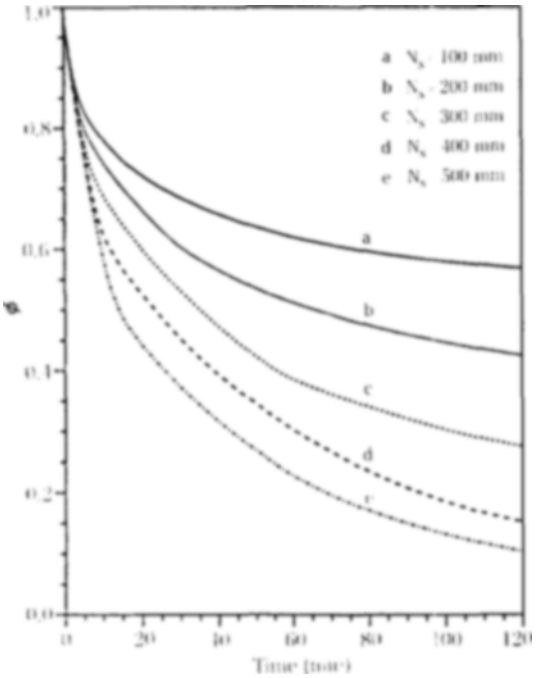

Fig. 7. Simulated bulk concentration profiles for the adsorption of berberine on immobilized adsorbents by changing the adsorbent content per bead.

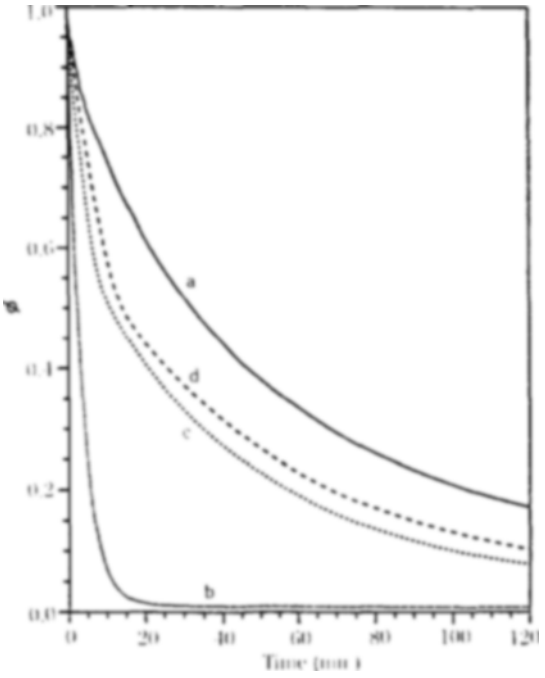

Fig. 8. Comparison of three strategies for the adsorption of berberine on immobilized adsorbents.

(a) $R_o = 0.435$ mm, $V_R = 0.6499$, $N_s = 339$ (Experimental condition), (b) $R_o = 0.200$ mm, $V_R = 0.6499$, $N_s = 339$ (R_o change), (c) $R_o = 0.435$ mm, $V_R = 1.0000$, $N_s = 339$, (V_R change), (d) $R_o = 0.435$ mm, $V_R = 0.6499$, $N_s = 500$ (N_s change)

from culture medium. The optimization of bead size will depend upon specific size of adsorbent and process conditions.

To increase the amount of immobilized adsorbent beads used per unit volume of culture medium can enhance the adsorption kinetics. Figure 6 shows the simulation curves indicating the effect of changing the volume ratio of bead to bulk solution, V_R, on the adsorption kinetics. The larger value V_R implies the increase of adsorption at the equilibrium. However, as V_R increases, extent of the effect of V_R on adsorption kinetics decreases. The value of V_R can be increased only up to a certain limit due to maintain appropriate processing conditions and concentration factors.

By increasing the adsorbent contents per bead, N_s, amount of adsorbent used per unit volume of culture medium can be increased with enhancing the binding capacity of beads. Figure 7 shows the simulation curves indicating the effect of adsorbent content on the adsorption kinetics. The larger value N_s implies the increase of the overall adsorption. However, at very large N_s extent of the effect of N_s on adsorption kinetics decreases. In terms of magnitude, the amount of increase is slightly lower compared to the previous strategies of changing R_o and V_R. The value of N_s can be increased only up to a certain limit because mechanical strength of bead decreases and operational difficulty increases in manufacturing increases as N_s increases.

Figure 8 shows a comparison among the mentioned three strategies. Adsorption curve referred as (a) is the experimental result. Adsorption curves for the decrease of R_o, and increase of V_R and N_s are (b), (c) and (d) compared to the experimental condition (a). The kinetic adsorption of berberine is enhanced by using every strategies in terms of rate and the capacity compare to the experimental case. The highest berberine adsorption is observed in set (b), decrease of R_o. This result suggests that the decrease of bead size is compared to the experimental case. The highest berberine in immobilized adsorbent due to reduction of diffusional resistance. However, the size of bead can be decreased only up to a certain limit in practical operation.

Thus, the proposed mathematical model for immobilized adsorbent can be used for an optimal design on

bioproduct separation by evaluating the design parameters. Since the optimization of design parameters depends on specific process condition, it is relatively difficult to achieve an optimal design based on purely emperical correlations. The proposed mathematical model can optimize the design parameters in various process conditions. When there are one or more compounds present in the fermentation broth which may compete for the adsorption site in the adsorbent particle, the proposed model can be used to optimize the design parameters to maximize the purity of desired product by introducing adsorption rate constants of various products.

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NOMENCLATURE

a_v : solid adsorption area/unit volume [cm^2/cm^3]
A_{ij}, B_{ij} : discretization elements for the derivation
C : bulk concentration of solute [mg/mL]
C_o : initial bulk concentration [mg/mL]
C_h : concentration in the hydrogel bead [mg/mL]
C_l : liquid (pore) phase concentration in the adsorbent particle [mg/mL]
C_s : solid (surface) concentration in the adsorbent particle [mg/mL]
C_{sm} : maximum solid phase concentration of solute [mg/mL]
C_T : total concentration in the adsorbent particle [mg/mL]
C_{ij}, D_{ij} : discretization elements for the derivation
D_l : effective diffusivity in the adsorbent particle [cm^2/min]
D_h : effective diffusivity in the hydrogel bead [cm^2/min]
E_{ij}, F_{ij} : discretization elements for the derivation
i, j : counting indexes
k_a, k_d : adsorption, desorption rate constants [mg/mL/s, s^{-1}]
k_L : mass transfer coefficient [cm/s]
K_s : isotherm equilibrium constant [mg/mL]
m : parameter equal to $(1-\epsilon_s)/\epsilon_s$
M : number of internal collocation points in the hydrogel bead
N : number of internal collocation points in the adsorbent particle
N_h : total number of the hydrogel bead per the bulk volume
N_R : capacity factor for the immobilized adsorbent bead [$=N_hV_H/V_B$]
N_s : total number of the adsorbent particle per the hydrogel beads
p, q : counting indexes
r : radial coordinates in the adsorbent particle [cm]
r_o : radius of the adsorbent particle [cm]
R : radial coordintes in the hydrogel bead [cm]
R_o : radius of the hydrogel bead [cm]
t : time [min]
V_B : bulk liquid volume [mL]
V_H : total volume of the hydrogel bead [mL]
V_R : volume ratio of the hydrogel bead to the bulk liquid volume

Greek Letters

Γ : dimensionless bath isotherm defined by eq. (16)
α : dimensionless parameter for effective diffusivity [$=D_l/D_h$]
β : dimensionless parameter for distance [$=r_o^2/R_o^2$]
χ : dimensionless radial coordinates in the hydrogel bead [$=R/R_o$]
ϵ_s : solid void fraction in the adsorbent particle
ϕ : dimensionless solute concentration [C/C_o]
θ : dimensionless time for the immobilized adsorbent bead [$=D_ht/R_o^2$]
ω : dimensionless isotherm parameter [$=K_s/C_o$]
ξ : dimensionless radial coordinates in the adsorbent particle [$=r/r_o$]
Ψ : transformed coordinates [$=\chi^2$]
ζ : transformed coordinates [$=\xi^2$]

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