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Mathematical Modeling of Penicillin G Extraction by a Bifunctional Surfactant in a Continuous Extraction Column

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Abstract−A bifunctional surfactant was used as a carrier of penicillin G for its continuous extraction by an emulsion liquid membrane without an extractant in a countercurrent extraction column of Oldshue-Rushton type. A permeation model was presented to describe transport mechanism of penicillin G in the continuous extraction system, including an axial dispersion model for the continuous phase and a mass transfer model for the dispersed emulsion phase. The mass transfer model describes the external mass transfer around the emulsion drop, the reaction at the external interface, the diffusion as well as the reaction equilibrium within the w/o emulsion drop, and the pH change of internal aqueous phase. Here, we considered three experimental variables: penicillin G concentration, pH of continuous phase and surfactant concentration. The calculated results from the permeation model fitted the experimental data well.

Key words: Penicillin G, Emulsion Liquid Membrane, Mass Transfer Model, Continuous Extraction, Extraction Column

INTRODUCTION

Penicillin G has been successfully extracted by emulsion liquid membranes (ELMs) with Amberlite LA-2 as an extractant and ECA 4360J as a surfactant in previous batch and continuous extraction systems [Lee and Lee, 1992; Lee et al., 1997]; however, there are still a few drawbacks before it can be applied commercially. According to the studies, a polyamine type of surfactant, i.e., ECA 4360J was more effective than Span 80 for the extraction of penicillin G. In other words, more stable emulsion formed by ECA 4360J resulted in less emulsion swelling and membrane breakage, with which a higher degree of extraction as well as a higher concentration rate of penicillin G in the internal phase could be obtained.

ECA 4360J is a surface-active agent, but it happened to act as a carrier of penicillin G in the previous ELM systems. Therefore, two carriers should be considered to exist in the organic phase whenever a permeation model for the extraction of penicillin G in the ELM systems is developed. For this, reaction kinetics of penicillin G with each carrier is preferentially required.

The reaction kinetics of penicillin G with ECA 4360J was already obtained through mathematical modeling for transport mechanism of penicillin G in the batch ELM system containing only a single carrier, that is, ECA 4360J [Lee et al., 1998]. In this work, we will confirm that the kinetic reaction expression is available to develop a permeation model in the continuous ELM system containing the single carrier, which will be helpful to explain the extraction of penicillin G in the continuous ELM system with two carriers, ECA 4360J and Amberlite LA-2 in the future.

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‡This paper is dedicated to Dr. Youn Yong Lee on the occasion of his retirement from Korea Institute of Science and Technology.

THEORETICAL BACKGROUND

1. Transport Mechanism

An equilibrium description of reaction between penicillin G and ECA 4360J is given by Lee et al. [1998] as follows:

$$A(org.)+0.5H^+(aq.)+0.5P^-(aq.) \Leftrightarrow A(HP)_{0.5}(org.) \quad (1)$$

The equilibrium constant of the reaction is defined as

$$K_{eq}=\frac{C_{A(HP)_{0.5}}}{C_A C_H^{0.5} C_P^{0.5}} \text{ or } \frac{C_C}{C_A C_H^{0.5} C_P^{0.5}} \quad (2)$$

where C_A, C_H, C_P and $C_{A(HP)0.5}$ (or C_C) denote the concentrations of ECA 4360J, hydrogen ion, penicillin acid anion and ECA 4360J-penicillin G complex, respectively. The value of the equilibrium constant has been known as 3.720×10^3 dm^3/mol.

The reaction of Eq. (1) occurs at the external interface between the external and the membrane phases to form the complex $A(HP)_{0.5}$. The complex then diffuses through the membrane phase to the internal interface between the membrane and the internal phases, where

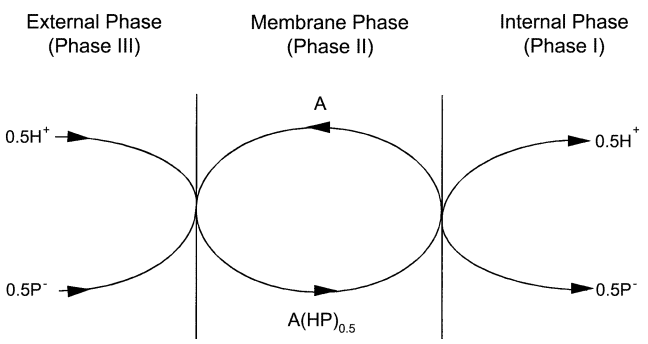

Fig. 1. Transport mechanism of penicillin G across the liquid membrane containing ECA 4360J as a single carrier.

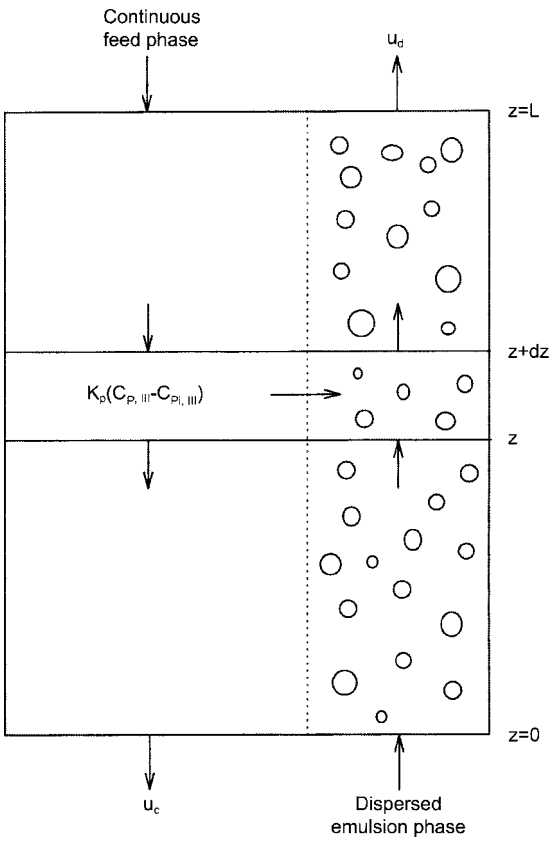

Fig. 2. Mass transfer model in the column.

hydrogen ion and penicillin acid anion are stripped into the internal phase by reaction with sodium carbonate and the uncharged ECA 4360J diffuses back. The overall extraction process is portrayed in Fig. 1.

2. Model Development

Fig. 2 displays mass transfer of penicillin G in the continuous aqueous feed phase within a differential length, dz, of a continuous countercurrent extraction column. When an axial dispersion model is available, the mass balance of penicillin G in the continuous phase can be set at an axial distance from the bottom of the column, z, as follows [Kataoka et al., 1992; Cho et al., 2000]:

$$E_c\frac{d^2C_{p,III}}{dz^2}+u_c\frac{dC_{p,III}}{dz}-k_pa(C_{p,III}-C_{pi,III})=0 \tag{3}$$

where E_c is the axial dispersion coefficient, k_p is the mass transfer coefficient in the continuous aqueous film, a is the specific interfacial area between the continuous and the dispersed phases, and the subscripts i and III denote the interface and the continuous aqueous phase, respectively. Also, the mean superficial velocities of the continuous and the dispersed phases in the extraction column are denoted by u_c and u_d, respectively. Eq. (3) does not include a term of membrane breakage which occurred to a small extent. On the other hand, the mass balance of hydrogen ion in the continuous phase is useless because a high diffusion coefficient of hydrogen ion and the use of buffer solution maintain almost constant hydrogen ion concentration independent of space of the column.

A permeation model has been developed in order to describe transport of penicillin G into the dispersed emulsion phase, shown in Fig. 3, which was already proposed in our previous work on batch extraction of penicillin G [Lee et al., 1998]. The w/o emulsion drop is assumed to be a rigid sphere of radius R. The inner core of the emulsion drop for $0\le r\le R_f$ is composed of aqueous and oil phases, while the outer peripheral thin layer for $R_f\le r\le R$ is composed of only the oil phase. Penicillin G permeates from the continuous phase (III) to the internal aqueous phase (I) through the six steps described in the figure.

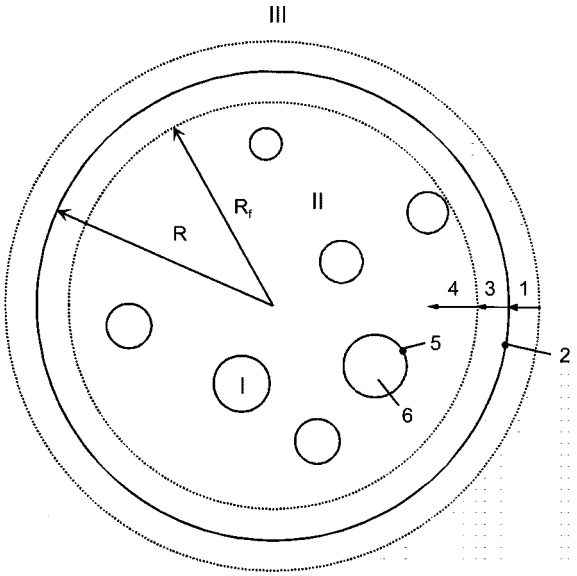

Fig. 3. Permeation model of penicillin G by an emulsion liquid membrane: 1, mass transfer in the external aqueous film; 2, extraction reaction at the external interface; 3, diffusion in thin oil layer; 4, diffusion in w/o emulsion phase; 5, stripping reaction at the internal interface; 6, acid-base reaction in the internal phase.

The mass balance of penicillin G in the region of $0\le r\le R_f$ within the emulsion drop is represented by using the effective diffusivity of complex D_{eC} as follows:

$$\frac{u_d}{\Phi}\left(\frac{1-\phi'}{2}\frac{\partial C_C}{\partial z}+\phi'\frac{\partial C_{P,I}}{\partial z}\right)=\frac{1}{2r^2}\left(\frac{\partial}{\partial r}D_{eC}r^2\frac{\partial C_C}{\partial r}\right) \tag{4}$$

where ϕ' is equal to $\phi/(1-\beta)^3$, ϕ is the volume fraction of internal droplets in the emulsion drop, $V_I/(V_I+V_{II})$, and Φ is holdup of the dispersed phase. The subscripts I and II denote the internal and the membrane phases, respectively, and β is a parameter for the thickness of the thin oil layer given by the following equation:

$$\beta=1-R_f/R \tag{5}$$

Eq. (4) is derived under the assumption that the sizes of emulsion drops and internal droplets are uniform and the internal droplets are immobile [Lee et al., 1996; Ho et al., 1982].

Also, the mass balance of carrier (ECA 4360J) in the region of $0\le r\le R_f$ within the emulsion drop is represented by using the effective diffusivity of carrier D_{eA} as follows:

$$(1-\phi')\frac{u_d}{\Phi}\left(\frac{\partial C_A}{\partial z}+\frac{\partial C_C}{\partial z}\right)=\frac{1}{r^2}\left(\frac{\partial}{\partial r}D_{eA}r^2\frac{\partial C_A}{\partial r}+\frac{\partial}{\partial r}D_{eC}r^2\frac{\partial C_C}{\partial r}\right) \tag{6}$$

When local reaction equilibrium is assumed to exist at the internal interface, the equilibrium description is written by:

$$K_{eq}=\frac{C_C}{C_A C_{H,I}^{0.5} C_{P,I}^{0.5}} \tag{7}$$

When the two terms squared in Eq. (7) are only differentiable for a length variable z, it can be transformed as follows:

$$2C_C\frac{\partial C_C}{\partial z}=K_{eq}^2\left[2C_A C_{H,I} C_{P,I}\frac{\partial C_A}{\partial z}+C_A^2\left(C_{P,I}\frac{\partial C_{H,I}}{\partial z}+C_{H,I}\frac{\partial C_{P,I}}{\partial z}\right)\right] \tag{8}$$

In addition, if acid-base reaction equilibrium exists in the internal aqueous phase, the hydrogen ion concentration, $C_{H,I}$, in the internal phase containing Na_2CO_3 can be calculated with a given amount of penicillin G transported into the internal phase. When the initial concentration of Na_2CO_3 in the solution is C_b and the concentration of penicillin G in the internal phase at any height z is C_a, the following fifth-degree polynomial for $C_{H,I}$ can be obtained as a function of C_a and C_b as in the previous work [Lee et al., 1998]:

$$\begin{aligned}&C_{H,I}^5+C_{H,I}^4(K_1+K_a+2C_b)+C_{H,I}^3(K_1K_2+K_1K_a+K_1C_b+2K_aC_b-K_w-K_aC_{P,I})\\&+C_{H,I}^2(K_1K_2K_a+K_1K_aC_b-K_1K_w-K_aK_w-K_1K_aC_{P,I})\\&-C_{H,I}(K_1K_aK_w+K_1K_2K_w+K_1K_2K_aC_{P,I})-K_1K_2K_aK_w=0\end{aligned} \tag{9}$$

where K_w is the ionic product of water, and K_1 and K_2 are the first and the second dissociation constants of carbonic acid, respectively.

The boundary conditions are as follows:

$$dC_{P,III}/dz=0 \quad \text{for } z=0 \tag{10}$$

$$C_{P,III}=C_{P,III}^0 \quad \text{for } z=L \tag{11}$$

$$C_A=C_A^0,\ C_C=0,\ C_{P,I}=0 \quad \text{for } z=0, \text{ all } r \tag{12}$$

$$\partial C_A/\partial r=\partial C_C/\partial r=\partial C_{P,I}/\partial r=0, \quad \text{for } r=0, \text{ all } z \tag{13}$$

$$\begin{aligned}&k_P(C_{P,III}-C_{Pi,III})\\&=k_f\left(C_{H,III}^{0.32}C_{Pi,III}^{1.37}C_{Ai}^{0.79}-\frac{1}{K_{eq}}C_{H,III}^{-0.18}C_{Pi,III}^{0.87}C_{Ai}^{-0.21}C_{Ci}\right) \quad \text{for } r=R, \text{ all } z\\&=\frac{k_A}{2}(C_A|_{r=R_f}-C_{Ai})=\frac{k_C}{2}(C_{Ci}-C_C|_{r=R_f})=-\frac{D_{eA}}{2}\frac{\partial C_A}{\partial r}=\frac{D_{eC}}{2}\frac{\partial C_C}{\partial}\end{aligned} \tag{14}$$

where k_f is the forward reaction rate constant at the external interface, and k_A and k_C are the mass transfer coefficients of carrier and complex in the peripheral thin oil layer, respectively.

The above ordinary and partial differential equations were converted to nonlinear algebraic equations by using the method of double collocation [Gong, 1990; Lee et al., 1997]. The nonlinear algebraic equations were solved with the boundary conditions by the FORTRAN subroutine DNEQNF available from IMSL MATH/LIBRARY.

3. Estimation of Parameters

Most of the model parameters (K_{eq}, k_f, D_P, D_A, D_C) were already reported in our previous work [Lee et al., 1998], which carries development of a permeation model for extraction of penicillin G in a batch system.

The mass transfer coefficient of penicillin acid anion in the external aqueous film (k_P) was estimated from a correlation for mass transfer in a stirred vessel [Skelland and Moeti, 1990]. For convenience's sake, a compartment of the column was considered as the stirred vessel.

$$\begin{aligned}\frac{k_P d_p}{D_P}&=1.237\times10^{-5}\left(\frac{\mu_c}{\rho_c D_P}\right)^{1/3}\left(\frac{D_R^2 n_R \rho_c}{\mu_c}\right)^{2/3}\left(\frac{D_R n_R^2}{g}\right)^{5/12}\\&\times\left(\frac{D_R}{d_p}\right)^2\left(\frac{d_p}{D_T}\right)^{1/2}\left(\frac{\rho_d d_p^2 g}{\sigma}\right)^{5/4}\Phi^{-1/2}\end{aligned} \tag{15}$$

where d_p is the emulsion drop diameter, μ_c is the viscosity of continuous phase, ρ_c is the density of continuous phase, D_R is the impeller diameter, n_R is the impeller speed, g is the acceleration due to gravity, D_T is the inner diameter of the column, ρ_d is the density of emulsion drop, σ is the interfacial tension and Φ is the holdup of emulsion phase.

The effective diffusivity of the complex (D_{eC}) was derived by modification of Teramoto's mass transfer model in w/o emulsion phase [Teramoto et al., 1992]. With the assumption that the ratio D_{eC}/D_{eA} is equal to the molecular diffusivity ratio D_C/D_A, the effective diffusivity of the carrier D_{eA} is obtained by

$$D_{eA}=D_{eC}\frac{D_A}{D_C} \tag{16}$$

The mass transfer coefficients k_C and k_A in the thin oil layer are given by

$$k_C=\frac{D_C}{\delta},\ k_A=\frac{D_B}{\delta} \tag{17}$$

where δ is the thickness of the thin oil layer. A more detailed explanation for parameter estimation is given in the previous work [Lee et al., 1998]. The size distribution of the w/o emulsion drops and the internal aqueous droplets were measured by the photographic method and Horiba CAPA-300 particle size analyzer, respectively.

The axial dispersion coefficient was estimated by using the following correlation available for a mechanically agitated extraction column [Matsumoto et al., 1990]:

$$E_c=\frac{u_c z_c}{1-\Phi}\left\{0.0268\frac{n_R D_R(1-\Phi)}{u_c}-0.14\right\} \tag{18}$$

where z_c is the height of each compartment. The values of parameters for a typical experimental condition are listed in Table 1.

EXPERIMENTAL

Aqueous feed solution (continuous phase) was prepared by dissolving penicillin G potassium salt in a citrate buffer solution of 0.408 mol/dm^3 which was used to prevent swelling and maintain constant pH throughout the experiments. Organic solution was prepared by dissolving ECA 4360J (nonionic polyamine, average molecular weight: 634.8, Exxon Chemical Eastern Inc.) as a bifunctional surfactant in kerosene. Internal aqueous solution was prepared by dissolving sodium carbonate (Junsei Chemical Co.) in deionized water. A water-in-oil (w/o) emulsion (dispersed phase) was made

Table 1. Values of parameters for a typical condition

E_C: 1.917×10^{-4} m^2/s	k_P: 7.416×10^{-8} m/s
k_A: 8.272×10^{-5} m/s	k_C: 6.789×10^{-5} m/s
R: 3.990×10^{-4} m	δ: 1.968×10^{-6} m
u_c: 2.139×10^{-4} m/s	u_d: 5.347×10^{-5} m/s
Φ: 0.118	

by slow addition of the internal aqueous solution to the organic solution with mixing provided by a homogenizer (High Speed Generator; Tekmar Co.), which was operated at 12,000 rpm for ten minutes.

The experiments for continuous extraction of penicillin G were carried out in a multistage mixer column of the Oldshue-Rushton type. The column was made of an acrylic tube of 6.3 cm inner diameter and 60.6 cm long. It consisted of nine compartments each 4.6 cm high. The diameter of the four-flat blade impellers, located centrally in each stage, is 2.85 cm and that of the stator openings is 3.3 cm. Four acrylic tubes of 1 cm diameter and 60 cm length were installed through holes drilled symmetrically into the stator plates to support ten stators and to act as baffles. The experimental procedure is described in detail by Lee et al. [1997]. Samples were taken from four sampling ports and the bottom of the column at a steady state which was reached in 120 minutes. After the continuous phase was separated from the dispersed phase by filtration using a filter paper, the concentrations of penicillin G in the continuous phase were analyzed by a UV spectrophotometer (PU8715, Phillips) at 247 nm. Average holdup of the dispersed phase was determined by measuring the volume of w/o emulsion phase in the column after inlet and outlet flows of the continuous and the dispersed phases were simultaneously stopped. Experiments were carried out with varying penicillin G concentration in the external phase (20 mmol/dm^3), pH of the citrate buffer solution (5.0) and ECA 4360J concentration in the membrane phase (8 wt%, 114.8 mmol/dm^3). The experimental variables were changed one by one and the typical values of the variables are expressed in parentheses right above. The other experimental parameters are given in Table 2.

Table 2. Experimental condition

Parameters	Values
Stirrer speed	330 rpm
Na_2CO_3 concentration in the internal phase	0.2 mol/dm^3
Flow rate of continuous phase	40 cm^3/min
Flow rate of dispersed phase	10 cm^3/min
Volume ratio of internal phase to memberane phase	1/2

RESULTS AND DISCUSSION

Fig. 4 displays the effect of initial penicillin G concentration on the dimensionless concentration profile of penicillin G in the continuous phase along the column. Here, the calculated results from the mass balance equations of the permeation model are represented by the three different lines. As the initial penicillin G concentration was higher, the concentration gradient of penicillin G in the continuous phase along the column at the top of the column was higher. This extraction tendency supports that the reaction at the external interface between the external aqueous and the membrane phases functions as one of the most dominant rate controlling steps in the continuous ELM system, which was illustrated in the previous ELM work for mathematical modeling of penicillin G extraction in a batch system containing ECA 4360J in the membrane phase without any extractant [Lee et al., 1998]. A comparison between the experimental data and the calculated results for the dimensionless concentration of penicillin G in the continuous phase along the column is depicted in Fig. 5 for two pH values of the external phase. Since pH gradient between the external and the internal phases is the driving force for extraction of penicillin G, a higher concentration gradient along the column was obtained at the lower pH of the external phase. The variation in the concentration profile of penicillin G in the continuous phase is shown in Fig. 6 as a function of the concentration of ECA 4360J in the membrane phase. The concentration gradient of penicillin G at the top of the column was still higher at the higher

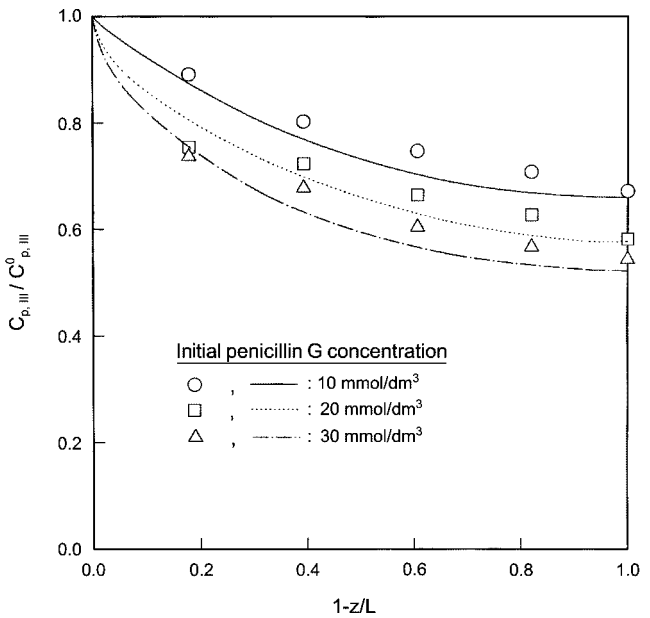

Fig. 4. Comparison of the experimental data with the calculated results for the dimensionless concentration of penicillin G in the continuous phase along the column as a function of initial concentration of penicillin G in the external phase.

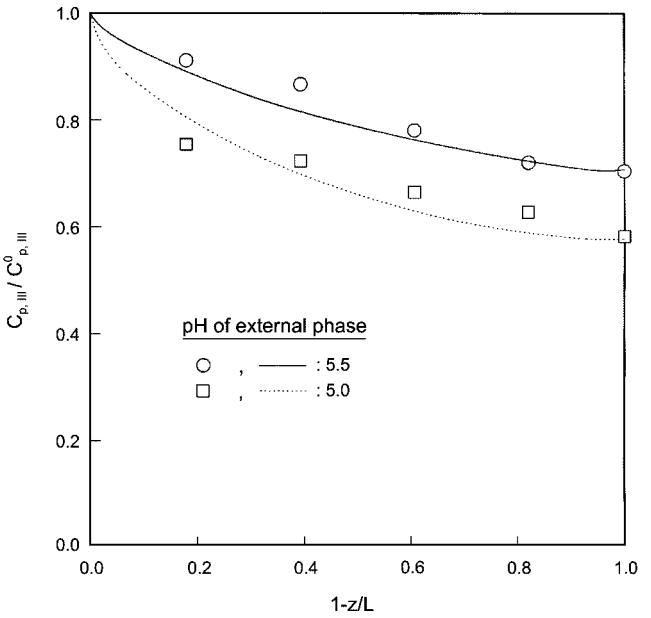

Fig. 5. Comparison of the experimental data with calculated results for the dimensionless concentration of penicillin G in the continuous phase along the column as a function of pH of the external phase.

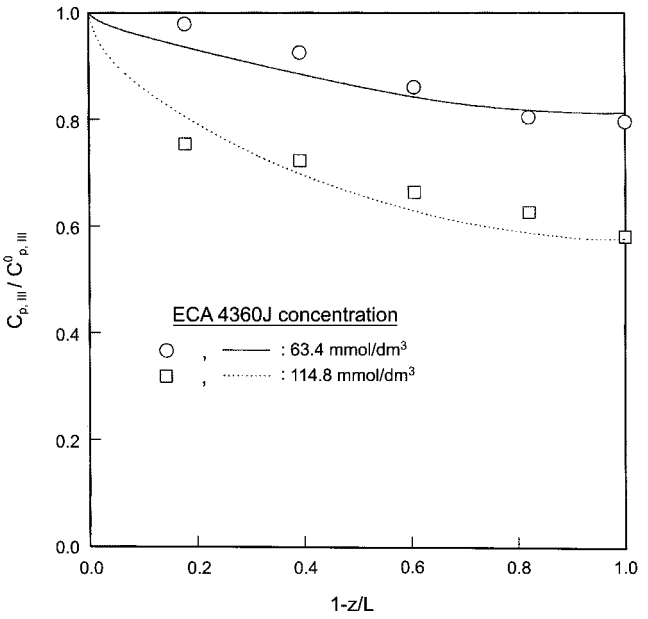

Fig. 6. Comparison of the experimental data with the calculated results for the dimensionless concentration of penicillin G in the continuous phase along the column as a function of initial concentration of ECA 4360J in the membrane phase.

ECA 4360J concentration, because ECA 4360J functioned as a carrier as well as a surfactant [Lee and Lee, 1992; Lee et al., 1998]. All the experimental data for three different experimental parameters were well fitted with the calculated results from the present model, which supports the validity of the diffusion model describing axial mixing [Ingham, 1972].

CONCLUSIONS

Continuous extraction of penicillin G was performed by an emulsion liquid membrane without an extractant in a countercurrent extraction column. A bifunctional surfactant functioned not only as an emulsion-stabilizing agent, but also as a carrier of penicillin G. A permeation model of the continuous extraction was proposed to describe the transport mechanism of penicillin G in the continuous system. The permeation model was developed with the help of mathematical modeling of the previous batch extraction of penicillin G. The experimental data on the extraction of penicillin G by the ELM process using the bifunctional surfactant were satisfactorily simulated by the proposed permeation model. Also, the permeation model in the continuous ELM system without an extractant seems to be able to be extended to development of the model to describe the continuous ELM system with an extractant such as Amberlite LA-2.

NOMENCLATURE

A : ECA 4360J
a : specific surface area of dispersed emulsion drops [1/m]
$A(HP)_{0.5}$: ECA 4360J-penicillin G complex
aq. : aqueous phase
C : concentration [mol/dm^3]
D : molecular diffusivity [m^2/s]
D_e : effective diffusivity [m^2/s]
d_p : sauter mean diameter of emulsion drops [m]
D_R : impeller diameter [m]
D_T : inner diameter of extraction column [m]
E_c : axial dispersion coefficient [m^2/s]
g : acceleration due to gravity [m/s^2]
k_A : mass transfer coefficient of carrier in the peripheral thin oil layer [m/s]
K_a : acid dissociation constant of penicillin G [mol/dm^3]
k_C : mass transfer coefficient of complex in the peripheral thin oil layer [m/s]
K_{eq} : equilibrium constant defined by Eq. (2) [dm^3/mol]
k_f : forward reaction rate constant given by Eq. (14) [$(dm^3/mol)^{1.48} \cdot m/s$]
k_P : mass transfer coefficient of penicillin acid anion in the external aqueous film [m/s]
K_w : ionic product of water [mol^2/dm^6]
K_1 : first dissociation constant of carbonic acid [mol/dm^3]
K_2 : second dissociation constant of carbonic acid [mol/dm^3]
L : active column length [m]
n_R : stirrer speed [rev/s]
org. : organic phase
P^- : penicillin acid anion
r : radius [m]
R : sauter mean radius of emulsion drops [m]
R_f : radius of inner core of w/o emulsion drop [m]
u_c : mean superficial velocity of continuous aqueous phase [m/s]
u_d : mean superficial velocity of dispersed emulsion phase [m/s]
V : volume [m^3]
z : axial distance from the bottom of the column [m]
z_c : height of each compartment [m]

Greek Letters

β : parameter for the thickness of the thin oil layer defined by Eq. (5)
δ : thickness of thin oil layer [m]
ϕ : volume fraction of internal droplets in the emulsion
Φ : holdup of dispersed phase in the column
ϕ' : $\phi/(1-\beta)^3$
μ : viscosity of continuous aqueous phase [$N \cdot s/m^2$]
ρ : density [kg/m^3]
σ : interfacial tension [N/m]

Superscript

0 : initial value

Subscripts

A : ECA 4360J
a : penicillin G
$A(HP)_{0.5}$: ECA 4360J-penicillin G complex
b : Na_2CO_3
C : ECA 4360J-penicillin G complex
c : continuous aqueous phase
d : dispersed emulsion phase
H : hydrogen ion

i : interface
P : penicillin acid anion
I : internal aqueous phase
II : membrane phase
III : external aqueous phase

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