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Modeling of Size Exclusion Parametric Pumping

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Abstract

Sephadex G and Biogel P, well-known gels in size exclusion chromatography, show a large change in their elution behaviors as temperature changes. These phenomena were exploited to separate the binary model solutes Blue Dextran 2000 and nickel nitrate. A series of batch size exclusion parametric pumping experiments in the direct thermal mode was carried out previously to separate binary mixtures. In this paper the experimental separations in batch size exclusion parametric pumping are compared with the predictions of both a local equilibrium model and a dispersion model. The dispersion model, which includes an axial dispersion term, gives a better fit of the experimental data. Experimentally obtained adsorption isotherms are used in the dispersion model to predict the separation performance of nickel nitrate in the Sephadex gel column. The resulting simultaneous partial differential equations are solved by quasilinearization of the equations followed by numerical integration. For both models, all parameters were estimated independently.

INTRODUCTION

Size exclusion chromatography (SEC) is a chromatographic technique utilizing the molecular sieving properties of porous gel particles. On a bed of gel particles, in equilibrium with a suitable solvent, large solute molecules will pass through the interstitial spaces while small solute molecules will distribute equally inside and outside the gel granules and pass through the bed at a slower rate. Separation behaviors of solutes in many gels such as Sephadex G and Biogel P are influenced by

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temperature changes (*1*), mainly because of structural change of the gel networks.

The parametric pumping (PP) apparatus is shown in Fig. 1. This apparatus is very similar to other parametric pumps (*2*, *3*), except the reason for separation differs. In PP with SEC gels the reason for separation is changes in porosity as the bed is heated or cooled. To avoid void spaces in the bed, the bed is initially compressed. The degree of compression ξ is defined as

$$\xi = \frac{\text{column length while compressed}}{\text{column length for gravity settled}} \leqslant 1.0 \qquad (1)$$

Experimental methods and results were presented earlier (*1*, *4*) for the separation of nickel nitrate and Blue Dextran 2000. This mixture was chosen as a model system for desalting proteins.

The major objective of this study was to investigate the influence of temperature on the separation behavior in SEC and to apply the results to the practical separation of solutes through a cyclic separation scheme. The previous experimental results of PP separations (*1*, *4*) are compared with theoretical predictions from the local equilibrium and the dispersion models.

MATHEMATICAL MODELING

Local Equilibrium Model

The local equilibrium model is the most commonly used theory for PP and is useful for visualizing the separation and as a conceptual tool in

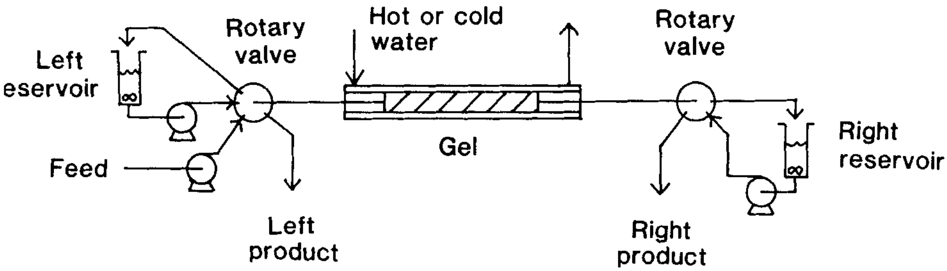

FIG. 1. Schematic diagram for parametric pumping system.

developing new cycles. Pigford et al. (*5*) and Baker and Pigford (*6*) developed the local equilibrium model to theoretically explain cyclic adsorption processes. Since this model is well known and has been extensively reviewed (*2*, *3*), a very brief presentation will be given. The mass balance is

$$\frac{\partial C}{\partial t} + \frac{(1-\varepsilon)\gamma}{\varepsilon} K_d \frac{\partial C_s}{\partial t} + \rho_s \frac{(1-\varepsilon)(1-\gamma)}{\varepsilon} \frac{\partial N}{\partial t} + v \frac{\partial C}{\partial z} - (E_D + D_M) \frac{\partial^2 C}{\partial z^2} = 0 \tag{2}$$

The first term is the accumulation of solute in the mobile phase. The second term is the accumulation of solute in the stationary liquid trapped in the pores of the solid adsorbent, and the third term represents the accumulation of solute in the solid stationary phase. The fourth term depicts convective mass transfer and the fifth represents mass transfer due to axial dispersion and diffusion.

First, mass and energy transfer rates are assumed to be very high; thus, liquids in the mobile and stationary phases are in equilibrium (i.e., $C = C_s$). Second, the solid phase concentration is assumed to be a function of temperature and concentration only. Third, the dispersive and diffusive terms are neglected. Finally, the isotherm is assumed to be linear ($N = AC_s$). The simplified result is solutes move in waves with a constant solute velocity U.

$$U = \frac{\varepsilon v}{\varepsilon + (1-\varepsilon)\gamma K_d + (1-\varepsilon)(1-\gamma)\rho_s A} \tag{3}$$

Unless there is a sizable interaction between the solute molecule and the gel material, such as electrostatic interaction, the concentration of a solute in the mobile phase is equal to that in the permeable stationary liquid phase. The distribution coefficient $K_d = 1.0$ for very small molecules and $K_d = 0$ for very large molecules. Usually adsorption on the gel is negligible and A in Eq. (3) is zero. Then Eq. (3) simplifies to

$$U = \frac{\varepsilon v}{\varepsilon + K_d(1-\varepsilon)\gamma} \tag{4}$$

In SEC, ε and γ and possibly K_d are functions of temperature.

The performance of batch PP was predicted by a semiempirical model.

From preliminary experiments with Sephadex G-25, the values of the retention volume of Blue Dextran and nickel nitrate at 5 and 45°C were observed to be in the order $V_B^C < V_B^H < V_N^H < V_N^C$ where B and N represent Blue Dextran and nickel nitrate, and C and H represent cold and hot, respectively. From these retention volumes the solute velocities during the hot and cold portions of the cycle are easily calculated, and characteristic diagrams can be plotted as shown in Fig. 2. Displacement volume, V_D, is defined as the amount of eluent pumped during a half cycle. Each line in Fig. 2 has a slope U given by Eq. (4). During the delay period between each half cycle, solute concentration in the column changes as temperature changes. The concentrations of Blue Dextran

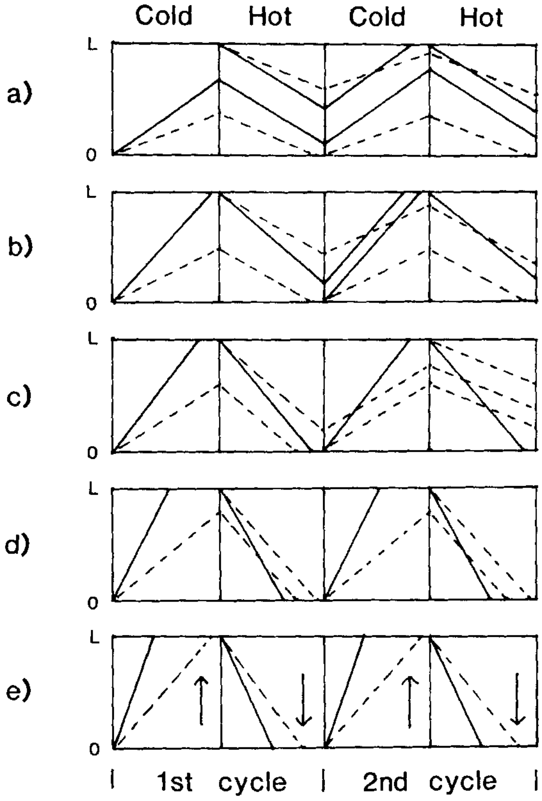

FIG. 2. Characteristic diagrams for Blue Dextran and nickel nitrate for the first and second cycles: (——) Blue Dextran 2000; (- -) nickel nitrate; a) $V_D < V_B^C$, b) $V_B^C < V_D < V_B^H$, c) $V_B^H < V_D < V_N^H$, d) $V_N < V_D < V_N^C$, e) $V_N^C < V_D$.

and nickel nitrate in each reservoir after a given number of cycles are calculated from Fig. 2 and mass balances around the column (*4*).

Calculated results based on the semiempirical application of the local equilibrium model detailed above are shown in Figs. 3 and 4. Experimental results are from Koo and Wankat (*1*). Calculated results predict the tendencies of the experimental data fairly well for Blue Dextran (Fig. 3). Deviation between theory and experiment increases as the experiment proceeds as a result of the accumulating dispersion effect. Exact agreement is not expected since the local equilibrium model does not include mass transfer or dispersion effects. Large discrepancies between the preditions and the experimental results for nickel nitrate (Fig. 4) are caused by the failure of the local equilibrium model to include the effect of dispersion in the mobile phase and mass transfer resistances in the stationary phase. As the displacement volume increases, these effects have more influence on the separation behavior in PP.

Dispersion Model

The local equilibrium model is useful in acquiring a qualitative picture of the elution behavior in the column, but is unable to include mass transfer and dispersion effects. A more realistic prediction of elution curves in SEC can be made on the basis of mass balances which include diffusion in the stagnant liquid and axial dispersion in the column. The dispersion model (*7–10*) is based on the concept that chromatography has two phases: 1) the stationary phase consisting of liquid within the gel particle, and 2) the mobile phase consisting of liquid in the interstitial volume between the particles.

The dispersion coefficient, *D*, was calculated utilizing the prediction of Chung and Wen (*11*). They expressed the Peclet number in terms of the axial Reynolds number as follows:

$$\varepsilon N'_{\mathrm{Pe}} = 0.2 + 0.011 N_{\mathrm{Re}}^{0.48} \tag{5}$$

Dispersion coefficients were calculated from Eq. (5) to be 8.62 × 10^{-4} and 8.47 × 10^{-4} cm^2/s at 5 and 45°C, respectively, for the conditions of the PP runs.

Blue Dextran is totally excluded from the pores of the Sephadex G-25 gel. This simplifies the calculations drastically. The assumption of nonadsorption of Blue Dextran onto the Sephadex G gels appears to be valid. The dispersion equation for an excluded solute reduces to

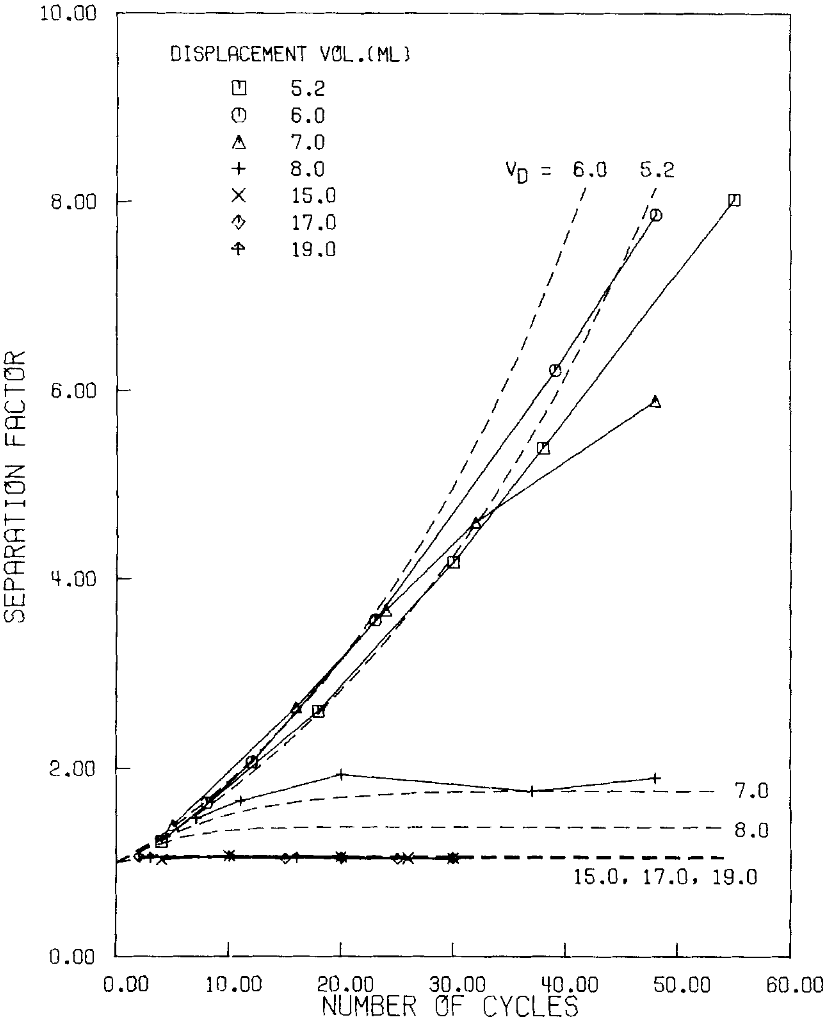

FIG. 3. Separation factors for Blue Dextran with displacement volume as a parameter in batch parametric pumping: Sephadex G-25 (50–150 μm), ξ = 0.818 (= 26.0/31.8), V_L = 20 mL, V_R = 10 mL; (——) experimental data; (- -) calculated results from the local equilibrium model.

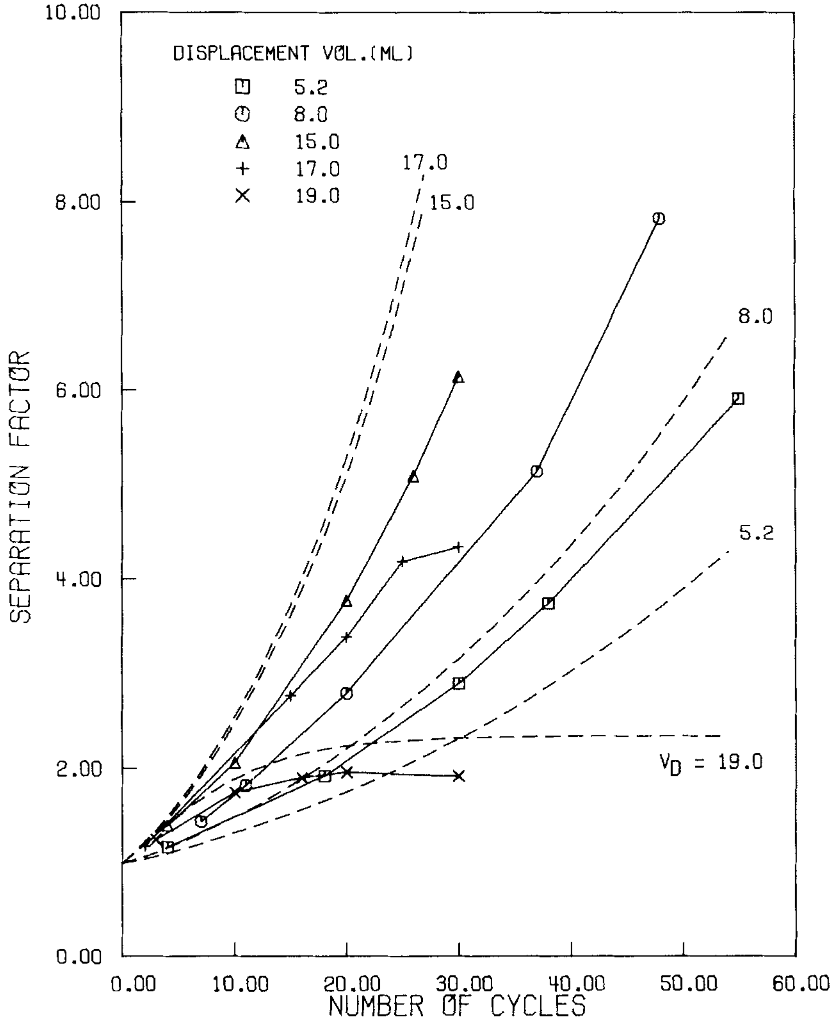

FIG. 4. Separation factors for nickel nitrate with displacement volume as a parameter in batch parametric pumping: Sephadex G-25 (50–150 μm), $\xi = 0.818$ (= 26.0/31.8), $V_L = 20$ mL, $V_R = 10$ mL; (——) experimental datat; (- -) calculated results from the local equilibrium model.

$$D \frac{\partial^2 C}{\partial z^2} = v \frac{\partial C}{\partial z} + \frac{\partial C}{\partial t} \tag{6}$$

with the following initial and boundary conditions.

$$C = C_i(z); \qquad t = 0, z > 0 \tag{7}$$

$$C = C_f(t); \qquad z = 0, t > 0 \tag{8}$$

The analytical solution of Eq. (6) obtained by Lapidus and Amundson (*10*) has the following form:

$$C(z,t) = [f_1(z,t) + f_2(z,t)] \exp\left(\frac{vz}{2D} - \frac{v^2 t}{4D}\right) \tag{9}$$

where

$$f_1(z,t) = \frac{1}{2}\sqrt{\frac{1}{\pi D t}} \int_0^\infty C_i(s)\left[\exp\left(\frac{-vs}{2D}\right)\right]\left[\exp\left(\frac{-(s-z)^2}{4Dt}\right) - \exp\left(\frac{-(s+z)^2}{4Dt}\right)\right] ds \tag{10}$$

$$f_2(z,t) = \frac{z}{2}\sqrt{\frac{1}{\pi D}} \int_0^t C_0(s) \exp\left[\frac{v^2 s}{4D} - \frac{z^2}{4D(t-s)}\right] \frac{ds}{(t-s)^{3/2}} \tag{11}$$

The concentration profile along the length of the column at the end of a half cycle can be obtained from Eq. (9). The effect of the temperature change is determined by multiplying by the ratio of the retention volumes at 5 and 45°C. This gives the initial condition for the next half cycle. The concentration profile as a function of time at the end of the column can be obtained in a similar way. This information is used to calculate the new concentration in the outlet reservoir and is used as a boundary condition for the next half cycle. Computations are repeated following these procedures iteratively as the cycle proceeds.

Results are shown in Fig. 5. Calculated results from the dispersion model fit the experimental data much better than the local equilibrium model. The dispersion model is particularly good in predicting the separation behavior at displacement volumes of 7 and 8 mL where the dispersion effects can cause a large deviation compared to the local equilibrium model. Note that no parameters are fitted in this model.

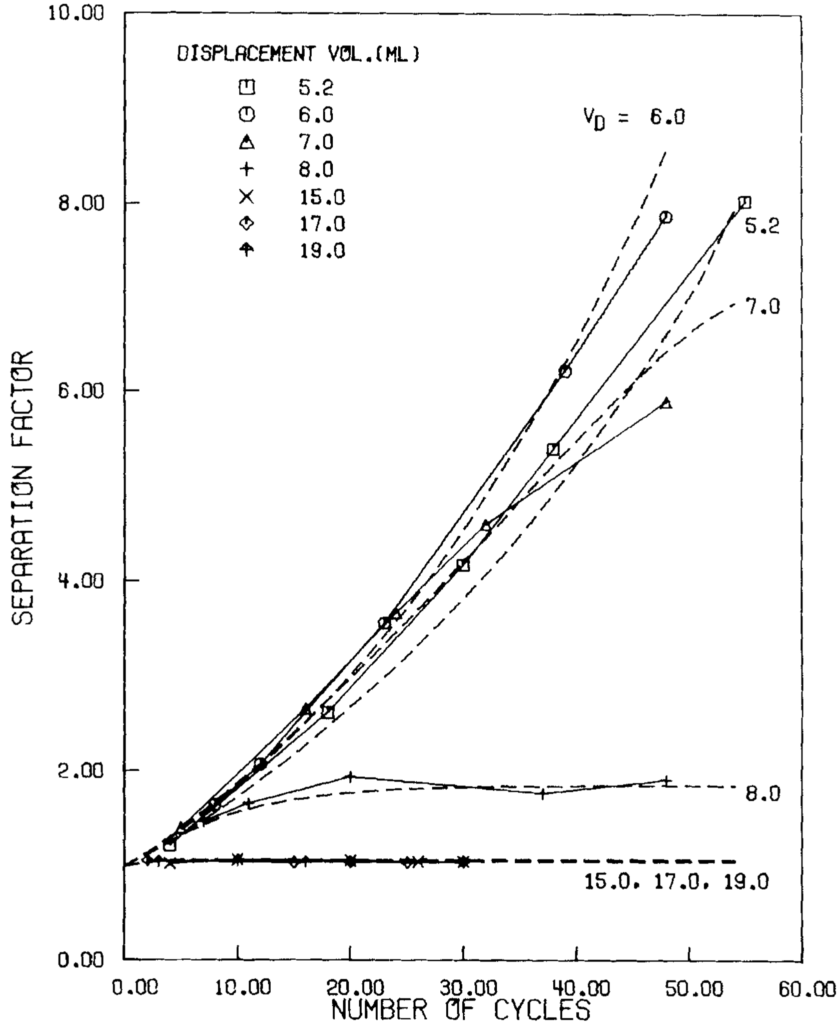

FIG. 5. Separation factors for Blue Dextran with displacement volume as a parameter in batch parametric pumping: Sephadex G-25 (50–150 μm), $\xi = 0.818$ (= 26.0/31.8), $V_L = 20$ mL, $V_R = 10$ mL; (——) experimental data; (- -) calculated results from the dispersion model.

The dispersion model to predict the elution of nickel nitrate is more complicated since nickel nitrate is able to penetrate into the intrastitial pores and adsorb onto the gel. Therefore, reliable data for the intrastitial porosity and the adsorption isotherm of nickel nitrate in addition to the dispersion coefficient are required for a good description of the system.

Adsorption isotherms were measured for nickel nitrate in a batch experiment (*4*). Aqueous nickel nitrate solution of known volume and concentration was added to the pure solvent containing swollen gel of known volume. The amount of nickel nitrate adsorbed onto the gel was calculated from the measured concentration in the supernatant. An atomic absorption spectrophotometer was used to measure solute concentration. The isotherms are shown in Fig. 6. Data points are rather scattered, since it is difficult to obtain good reproducibility at these very low solute concentrations. Experimental points were curve fitted by the least-squares method used to fit Langmuir-type isotherms. Adsorption isotherms of nickel nitrate on Sephadex G-25 were determined as

$$N = \frac{9.18C_s}{(1 + 139.74C_s)} \text{ at } 5\,^\circ\text{C} \tag{12}$$

$$= \frac{14.56C_s}{(1 + 290.29C_s)} \text{ at } 45\,^\circ\text{C} \tag{13}$$

where N is the concentration of nickel nitrate adsorbed based on the volume occupied by the gel, and C_s is the concentration of nickel nitrate.

Since the retention volume of nickel nitrate in a gel column reflects the combined effects of Donnan ion exclusion, adsorption, and steric exclusion, the intrastitial porosity of the gel is not readily obtainable from the elution data. However, the solute concentration change in the liquid phase due to adsorption was calculated to be less than 2% of the total when the solute concentration was higher than 0.5 w/v%. Concentrations were above this level in the batch PP separation of nickel nitrate. Therefore, the elution volume of nickel nitrate in 0.01 M nickel nitrate solution was used to calculate the intrastitial porosity in the Sephadex G-25 gel column. At 5°C the estimated dispersion coefficient for nickel nitrate is 8.62×10^{-4} cm^2/s while at 45°C the value is 8.47×10^{-4} cm^2/s. The intrastitial void fraction γ was estimated as 0.831 and 0.751 at 5 and 45°C, respectively.

In the dispersion model a solute penetrates into the intrastitial pores of a gel particle, but the mass transfer resistance in the pores is assumed to

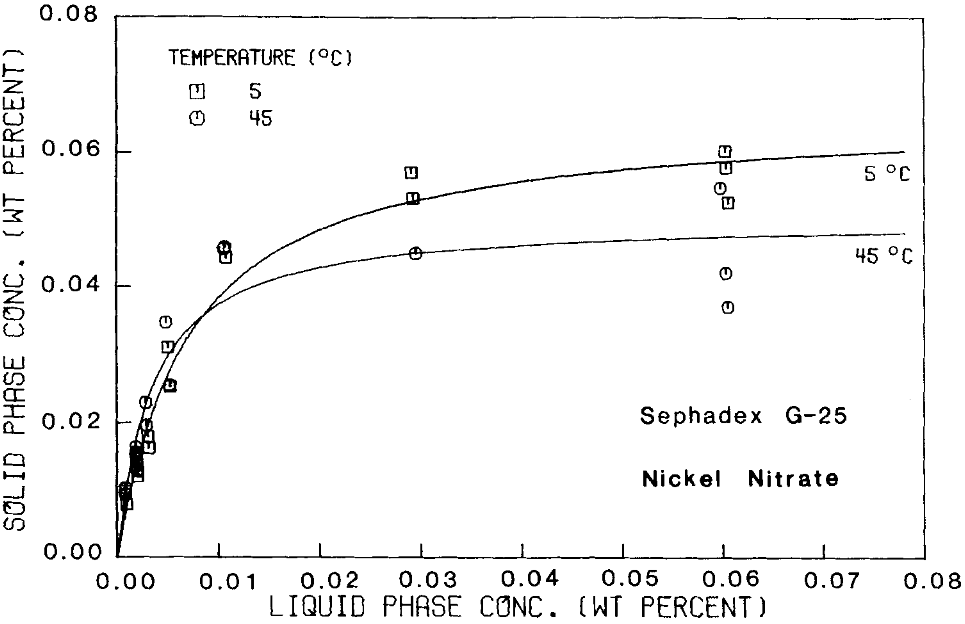

FIG. 6. Adsorption isotherms for nickel nitrate on Sephadex G-25 (50–150 μm).

be negligible. This allows the solute concentration at the various points in the pores to be uniform and equal to the solute concentration in the mobile phase near the gel particle. The mass balance equation of a penetrating solute is expressed as follows:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial z^2} - v\frac{\partial C}{\partial z} - \frac{1-\varepsilon}{\varepsilon}\frac{\partial C_s}{\partial t} - \frac{(1-\varepsilon)(1-\gamma)}{\varepsilon}\frac{\partial N}{\partial t} \tag{14}$$

The initial condition is

$$z \geqslant 0, t = 0; \qquad C = 0 \tag{15}$$

while the boundary conditions are

$$z = 0, t_0 \geqslant t \geqslant 0; \qquad C_f = C_0 \tag{16}$$

$$z = 0, t \geqslant t_0; \qquad C_f = 0 \tag{17}$$

$$N_{\mathrm{Pe}}C - \frac{\partial C}{\partial z} = N_{\mathrm{Pe}}C_f \tag{18}$$

$$z = L, t \geqslant 0; \qquad \frac{\partial C}{\partial z} = 0 \tag{19}$$

For convenience, the unit of the solute concentration adsorbed onto the gel substances (N) is chosen to be the mass of the adsorbed solute per volume of the gel substance. The column is initially empty of solute and there is a pulse input of a feed solution (concentration C_0) from $t = 0$ to t_0. The Danckwert's boundary condition, Eq. (18), is applied at the inlet of the column. The solute concentration, N, was determined from Eqs. (12) and (13). As C_s is equal to γC, Eq. (14) is rearranged to

$$\frac{\partial C}{\partial t} = \frac{1}{A_1}\left(\frac{1}{N_{\mathrm{Pe}}}\frac{\partial^2 C}{\partial z^2} - \frac{\partial C}{\partial z} - A_2\frac{\partial N}{\partial t}\right) \tag{20}$$

where

$$A_1 = 1 + \frac{(1-\varepsilon)\gamma}{\varepsilon}, \qquad A_2 = \frac{(1-\varepsilon)(1-\gamma)}{\varepsilon} \tag{21}$$

Since only the term $\partial N/\partial\tau$ is nonlinear and all the differentials appear linearly, Eq. (20) is a quasilinear partial differential equation. After putting Eqs. (15) to (20) in dimensionless form, the equation was linearized using the Newton-Raphson method. The resulting linear equation was solved by a finite difference method using an implicit forward difference formula. A computer program (*4*) was written to calculate the solute concentration along the length of a column using this dispersion model. The concentration at each time step obtained by the computer calculation met the mass balance within a 5% error limit.

Following procedures similar to the previous section, we obtained the separation factors for nickel nitrate in batch PP in a Sephadex G-25 column. Calculation of the concentration change in the column with changing temperature was based on the solute mass balance involving the interstitial porosity, the intrastitial porosity, and the adsorption. Computational results are shown in Fig. 7. Again, no parameters were fit by using the PP experiments. The prediction by the dispersion model fitted the experimental data better than the local equilibrium model predictions shown in Fig. 4. However, the dispersion model predicts better separation than the actual experiments. As mentioned earlier, this probably occurs because mass transfer resistances are not included.

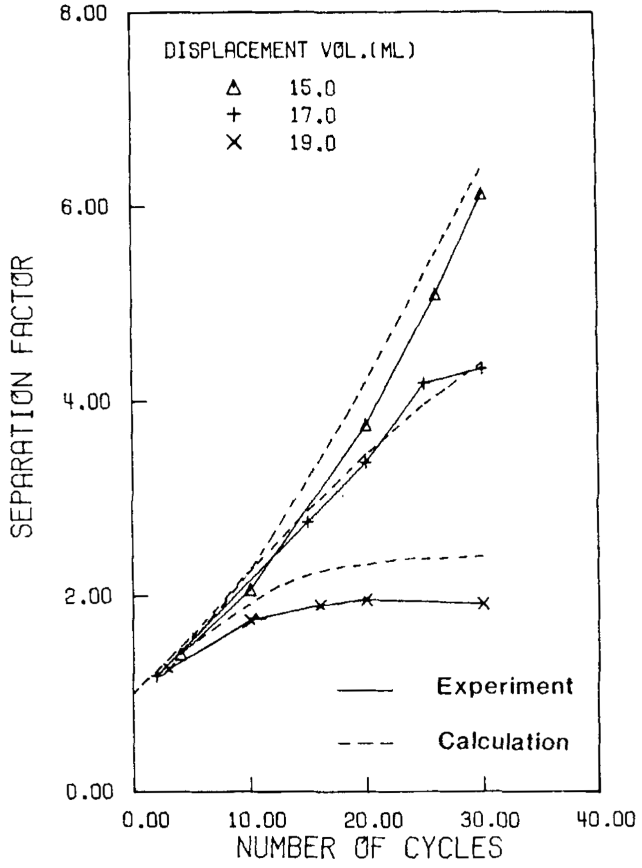

FIG. 7. Separation factors for nickel nitrate in batch parametric pumping: Sephadex G-25 (50–150 μm), $\xi = 0.818$ (= 26.0/31.8), V_L = 20 mL, V_R = 10 mL; (——) experimental data; (- -) calculated results from the dispersion model.

CONCLUSIONS

Local equilibrium and dispersion models were used to simulate parametric pumping SEC separations of the model system Blue Dextran 2000 and nickel nitrate. The local equilibrium model was useful for qualitatively explaining the separations. The dispersion model simplifies to the well-known Lapidus and Amundson solution for the excluded Blue Dextran. Agreement between theory and experiment was good. For nickel nitrate which penetrates the gel, a numerical solution of the dispersion model was required. Agreement was not as good since the dispersion coefficients used did not include mass transfer resistances.

SYMBOLS

A	proportionality constant for linear adsorption isotherm
C	solute concentration in mobile liquid (w/v%)
C_s	solute concentration in stationary liquid (w/v%)
d_p	diameter of a gel particle (cm)
D	effective axial dispersion coefficient (cm^2/s)
D_M	molecular diffusivity (cm^2/s)
E_D	eddy diffusivity (cm^2/s)
k_f	mass transfer coefficient across the mobile-stationary phase interface (cm/s)
K_d	distribution coefficient
L	column length (cm)
N	solute concentration in solid phase (w/v%)
N_{Pe}	axial Peclet number (vL/D)
N'_{Pe}	Peclet number ($d_p v/D$), Eq. (5)
N_{Re}	axial Reynolds number ($d_p U_s \rho/\mu$)
r	radial distance (cm)
R	radius of a gel particle (cm)
t	time (s)
T	temperature (K)
U	solute wave velocity (cm/s)
U_s	superstitial fluid velocity (cm/s)
v	interstitial fluid velocity (cm/s)
V	retention volume (cm^3)
V_D	displacement volume (cm^3)
V_L	left reservoir volume (cm^3)
V_R	right reservoir volume (cm^3)
V_0	excluded volume (cm^3)
V_s	stationary liquid volume (cm^3)
V_t	total bed volume (cm^3)
z	axial distance (cm)

Greek Letters

γ	intrastitial void fraction
ε	interstitial void fraction

μ	viscosity of fluid (g/cm · s)
ξ	degree of compression, Eq. (1)
ρ	density of fluid (g/cm^3)
ρ_s	density of solid phase (g/cm^3)

Subscripts

B	Blue Dextran
N	nickel nitrate
s	stationary liquid

Superscripts

C	cold temperature
H	hot temperature

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