Modeling of Extraction Behavior of Docosahexaenoic Acid Ethyl Ester by Utilizing Slug Flow Prepared by Microreactor

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The liquid–liquid extraction dynamics of an ethyl ester of docosahexaenoic acid (DHA-Et) with silver ion was investigated. The kinetic model was derived according to the following stepwise processes: Diffusion of DHA-Et across the organic film, complex-formation between DHA-Et and silver ion at the interface, and diffusion of extracted complex across the aqueous film. The kinetic parameters for the complex-formation reaction were determined from the investigation with the stirred transfer cell. With the proposed model and determined parameters, we predicted the uptakes of DHA-Et for the extraction system utilizing a slug flow prepared by a microchip. The calculated uptakes showed good correlation to the experimental data. The theoretical investigation suggested that the fast equilibration realized for the slug flow extraction system was due to the large specific interfacial area of the slug caused by the presence of wall film and the thin liquid film caused by the internal circulation. © 2009 American Institute of Chemical Engineers *AIChE J,* 56: 2163–2172, 2010
Keywords: microreactor, slug flow, liquid–liquid extraction, docosahexaenoic acid, silver ion

Introduction

With growing public interests in a considerable impact on health of N-3 polyunsaturated fatty acids (PUFAs),[1–3] various products such as food additives and medical supplies have been developed. In the products, purified and concentrated N-3 PUFA, which is separated from the other PUFAs and saturated fatty acids, has to be used. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the representative N-3 PUFA. They are contained in fish oils with many other fatty acids. Therefore, there is a great demand for development of an effective separation and purification technique of PUFAs. For the last several decades, some techniques for separation and purification of PUFAs were proposed, studied, and developed.[4–13] Among the techniques, the separation method of PUFA ethyl esters (PUFA-Ets) utilizing liquid–liquid extraction with silver ion[8] has attracted attention as an effective method and has been expanded into more effective techniques using supported liquid membrane (SLM),[9,10] emulsion liquid membrane (ELM),[11,12] and slug flow prepared by microchip.[13] Above all, we have directed our attention to utilizing slug flow prepared by microchip. In the previous article, we investigated the extraction of DHA-Et and EPA-Et with the slug flow prepared by T-shape microchip and achieved fast and effective extraction of them.[13]

In general, a microreactor has the advantages of continuous processing over batch processing. Continuous processing allows steady-state operation, so that large production is given by parallelization of microreactors; so-called numbering-up, instead of scaled-up. Especially, our proposing extraction process using slug flow is suit to numbering-up because the most important unit of the process is the channel

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Additional Supporting Information may be found in the online version of this article.

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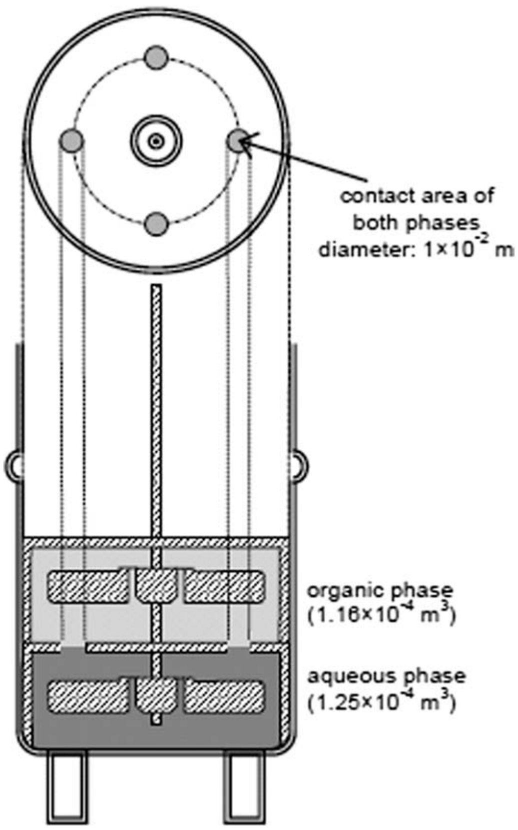

Figure 1. Illustration of the stirred transfer cell.

in the PTFE tube connected to exit of the T-shape microchip. We can easily achieve numbering-up by using module of the PTFE tube. The PTFE tube for the process is very thin so that the size of the module becomes small. In addition, such thin channel allows rapid and exact control of operation temperature[13] and should realize an energy saving process.

So far, with regard to the extraction of PUFA-Ets with silver ion, many investigations into the extraction equilibria and the separation have been carried out. With knowledge of the extraction equilibrium, it is possible to estimate the number of separation stages for required separation efficiency. On the other hand, to design an extraction process, knowledge of extraction kinetics is advantageous. However, to our knowledge, little attention has been paid to the extraction kinetics of PUFA-Ets. With regard to the kinetics of a reactive liquid–liquid extraction, the fundamental processes concerning to the overall extraction rate are as follows; diffusion of chemicals through both of organic and aqueous films and complex-formation reaction between extractant and solute. Over the last several decades, the method of estimating extraction kinetics was developed for metal extraction.[14] A stirred transfer cell, so called Lewis cell, was often used to evaluate the extraction rate.[15–17] From an uptake curve obtained by using a stirred transfer cell, an appropriate rate constant of the complex-formation reaction between an extractant and a solute can be determined. With the determined rate constant, we can elucidate the uptake curves for the extraction systems utilizing SLM, ELM and a slug flow as well as for the conventional liquid–liquid extraction system.

In this study, we carried out a kinetic investigation of DHA-Et extraction with silver ion for the conventional liquid–liquid extraction system and the slug flow system. We had two purposes in this study; one is to determine the kinetic parameters of the DHA-Et extraction and another is modeling the extraction of DHA-Et with slug flow. We used a stirred transfer cell to determine the kinetic parameters of the DHA-Et extraction. The effects of stirring speed, DHA-Et concentration, silver ion concentration, and temperature on the initial extraction rate of DHA-Et were measured. From the experimental results, we determined the kinetic parameters for complex-formation reaction between DHA-Et and silver ion. In addition, the overall rate equation considering diffusion of chemicals in the liquid films as well as complex-formation reaction was proposed. With the proposed kinetic model, the uptake curves of DHA-Et for the slug flow system were predicted. Comparing the calculated and experimental uptakes, we discussed the characteristics of the slug flow extraction.

Experimental Section

Reagents

DHA-Et was kindly supplied from Bizen Chemical Co. (Okayama, Japan). The purity was above 98%. Other chemicals, such as silver nitrate, sodium nitrate, and n-heptane were of guaranteed grade. They were purchased from Wako Pure Chemical Industries Co. (Osaka, Japan). The organic phase was prepared by dissolving DHA-Et in n-heptane. Aqueous phase was prepared by dissolving desired amount of silver nitrate in ultrapure water. The ionic strength of aqueous phase was adjusted to 4.0×10^3 mol m^{-3} by adding sodium nitrate.

Interfacial tension measurement

The interfacial tensions of the organic solution having various concentrations of DHA-Et were measured with Wilhelmy plate interfacial tension meter (CBVP-A3, Kyowa interface science Co.). In the measurement of interfacial tension, 4.0×10^3 mol m^{-3} $NaNO_3$ aqueous solution was used as an aqueous solution and n-heptane was used as an organic solvent. Experiments were carried out at 293 K.

Measurement of extraction rate with stirred transfer cell

The initial liquid–liquid extraction rate was measured by using the stirred transfer cell as described in Figure 1. The volume of aqueous and organic phases was 1.25×10^{-4} m^3 and 1.16×10^{-4} m^3, respectively. The interfacial area was 3.14×10^{-4} m^2. The cell was soaked in a water bath which equipped a temperature controller to keep the temperature constant. A 1.25×10^{-4} m^3 of an aqueous phase was first introduced into the cell, and then 1.16×10^{-4} m^3 of an organic phase was quickly but carefully introduced in the cell to maintain a quiescent interface. Then the solutions in the cell were immediately stirred by four flat-blade stirrers without disturbing the interface. About 3.5×10^{-7} m^3 of the

Table 1. Standard Experimental Condition for Measurement of Initial Extraction Rate with the Stirred Transfer Cell

Stirring speed	1.0 s^{-1}
Initial DHA-Et concentration	10 mol m^{-3}
Initial silver ion concentration	2700 mol m^{-3}
Volume of the aqueous phase	1.25×10^{-4} m^3
Volume of the organic phase	1.16×10^{-4} m^3
Interfacial area	3.14×10^{-4} m^2
Temperature	298 K

organic sample was taken at desired intervals. The DHA-Et concentration in the sample was measured by using a gas chromatograph equipped with a flame ionization detector (GC-14A, Shimadzu Co.). The initial extraction rates were measured under various experimental conditions: Stirring speed at 0.583–1.083 s^{-1}, DHA-Et concentration at 5–50 mol m^{-3}, and silver ion concentration at 1.4×10^3 to 2.9×10^3 mol m^{-3}. We also measured the temperature dependence of the initial extraction rate to determine the activation energy and frequency factor from Arrhenius plot. Temperature was changed in the range of 278–313 K. The standard experimental condition is shown in Table 1.

Extraction of DHA-Et with slug flow prepared with a microreactor

The experimental setup for DHA-Et extraction with slug flow is shown in Figure 2a. In this study, a glass chip having T-shape microchannel (MP4B-15, Tosoh Co.) was used to prepare a slug flow. The inlets of the glass chip were connected to syringe pumps (BS-MD1001, Bioanalytical Systems) with poly(tetrafluoroethylene) (PTFE) tube of i.d. 5×10^{-4} m. From these syringe pumps, the aqueous and organic phases were fed at the same flow rate of 1.67×10^{-9} m^3 s^{-1}, respectively. Behind the glass chip, a PTFE tube of i.d. 5×10^{-4} m was connected. A slug flow created in the glass chip was fed into the PTFE tube. During the slugs passed through the PTFE tube, DHA-Et was extracted from the organic phase to the aqueous phase. In the early periods of operation, the solutions flew out through the PTFE tube of i.d. 2×10^{-3} m for 120 s to reach the steady flow. After 120 s, the PTFE tube of i.d. 2×10^{-3} m was closed, and the stream was changed to flow into a syringe through a poly(ether-ether-ketone) (PEEK) tube of i.d. 1.3×10^{-4} m. Because the inner diameter, i.e., the inner volume, of PEEK tube was small, the residence time in the PEEK tube was very short. Therefore, it can be considered that little amount of DHA-Et was extracted in the PEEK tube. In the syringe, both organic and aqueous phases were quickly separated each other and the aqueous phase was continuously removed from the syringe with a HPLC pump at the same flow rate as the aqueous inlet. Therefore, the extracted amount of DHA-Et in the syringe was regarded as quite small. After a desired time passed, 5×10^{-7} m^3 of the organic phase was collected and the concentration of DHA-Et was measured by using a gas chromatograph. In this study, all experiments were carried out twice and the reproducibility was confirmed.

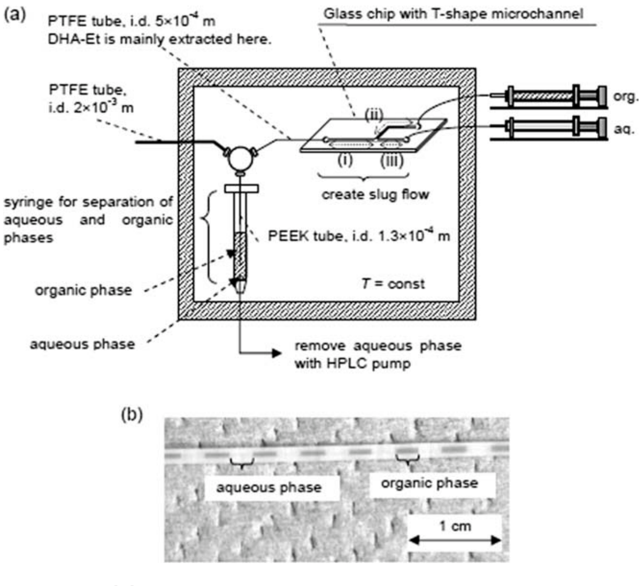

Figure 2. (a) Illustration of experimental setup for extraction of DHA-Et using slug flow prepared by glass chip with T-shape microchannel. Channel width: (i) 1.33×10^{-4} m, (ii) 9.8 $\times$ 10^{-5} m, and (iii) 1.31×10^{-4} m. Channel depth: 4.7×10^{-5} m. (b) Typical slug flow passing through the PTFE tube connected to the exit of T-shape microchannel.

The glass chip, the PTFE tube connected behind the glass chip, the PEEK tube and the syringe were set in a constant temperature chamber (SU-261, ESPEC Co.). The residence time was controlled by changing the length of the PTFE tube connected behind the glass chip.

A typical slug flow created by introducing both ultrapure water and n-heptane was shown in Figure 2b. It should be noted that a blue dye (oil blue N) was dissolved in only the organic phase shown in Figure 2b to clearly observe each phase of the slug flow although all experiments of DHA-Et extraction was performed without oil blue N. The average length of each phase was 2.54×10^{-3} m. Their coefficient of variance (CV) for aqueous and organic phases was 7.85 and 5.28%, respectively.

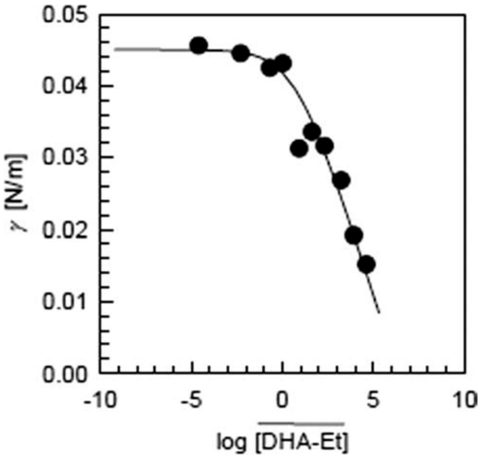

Figure 3. Relation between interfacial tension and the concentration of DHA-Et.

Theoretical Section

To analyze the uptake curves, we have to consider where DHA-Et and silver ion react. Teramoto et al. considered that DHA-Et reacts with silver ion in an aqueous bulk.[8] However, we cannot easily accept it because DHA-Et would adsorb on oil/water interface. Figure 3 shows the relationship between interfacial tension and DHA-Et concentration in the organic phase. As shown in Figure 3, the interfacial tension decreased with increasing the DHA-Et concentration. This fact indicates that DHA-Et adsorbs on the liquid–liquid interface. Because DHA-Et adsorbs on the interface, there is every possibility that DHA-Et reacts with silver ion at the liquid–liquid interface. Therefore, we derived two theoretical models; one was derived from the interfacial reaction and another was derived from the reaction occurred in the aqueous bulk. We conducted calculations with the theoretical models and concluded that the model derived for the interfacial reaction was suitable. The derivation of the interfacial reaction model is written later. The derivation and evaluation of the model for the reaction in an aqueous bulk is shown in Supporting Information (I).

Derivation of the theoretical model for the slug flow system

According to the investigations by Burns and Ramshaw[18] and Kashid et al.,[19,20] a circulation is generated within the aqueous and organic phases of a slug flow. Therefore, it would be considered that the liquid film thickness of both phases is thinner than that under stationary condition. However, the actual liquid film thickness is not clear, so that the diffusion as well as complex-formation reaction may affect the overall extraction rate. Therefore, to predict the uptakes for the slug flow system, we derived the theoretical model considering the following stepwise processes: (I) diffusion of DHA-Et from the organic bulk to the interface across the organic film, (II) complex-formation reaction between DHA-Et and silver ion at the interface, and (III) diffusion of extracted complex from the interface to the aqueous bulk across the aqueous film.

Diffusion of DHA-Et through the organic film to the interface

With a linear driving force approximation, the mass transfer rate of DHA-Et through the organic film, W_{org}, can be expressed as the product of an interfacial area, A, and the molar flux of DHA-Et in the organic film, $R_{\mathrm{A,org}}$.

$$W_{\mathrm{org}} = A \times R_{\mathrm{A,org}} = A\frac{D_{\mathrm{org}}}{\delta_{\mathrm{org}}}\left(\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{b}} - \overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{i}}\right) \quad (1)$$

where D_{org} and δ_{org} mean the diffusion coefficient of DHA-Et in the organic film and the thickness of the organic film, respectively. Subscripts "b" and "i" denote the bulk phase and near the interface, respectively. Overbar denotes the organic phase.

Complex-formation reaction of DHA-Et with silver ion near the interface

Considering stepwise complex-formation reactions, the reaction rate of DHA-Et with silver ion near the interface, W_{com}, can be written as follows.

$$W_{\mathrm{com}} = A\left(k_1\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{i}}[\mathrm{Ag}^+]_{\mathrm{i}}^{m} - k_2[\mathrm{com}]_{\mathrm{i}}\right) \quad (2)$$

where "com" denotes the extracted complex. m is the apparent reaction order. k_1 and k_2 are the apparent forward and reverse reaction rate constants, respectively. The derivation of Eq. 2 is written in Supporting Information (II). Regarding the silver ion concentration, the concentration of silver ion gradually decreased until the reaction reached equilibrium. However, it could be considered as a constant because the amount of silver ion was significantly larger than those of DHA-Et and the intermediate complex under all of the experimental conditions in this study. That is, $[\mathrm{Ag}^+]_{\mathrm{i}} = [\mathrm{Ag}^+]_{\mathrm{i,eq}} = [\mathrm{Ag}^+]_{\mathrm{b,0}}$, where subscripts "eq" and "0" denote the equilibrium and initial state, respectively.

Now, we consider the extraction equilibrium state. The concentrations of chemicals near the interface at equilibrium state ought to be same as those in the bulk phases. In addition, W_{com} is zero. Hence from Eq. 2,

$$k_2 = \frac{k_1\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{b,eq}}[\mathrm{Ag}^+]_{\mathrm{b,0}}^{m}}{[\mathrm{com}]_{\mathrm{b,eq}}} \quad (3)$$

The $[\mathrm{com}]_{\mathrm{b,eq}}$ in Eq. 3 can be expressed by $\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{b,eq}}$ and $[\mathrm{Ag}^+]_{\mathrm{b,0}}$ with the extraction equilibrium constant of DHA-Et with silver ion. Here, we consider the extraction equilibrium relationship as the following;

$$\overline{\mathrm{DHA\text{-}Et}} + n\mathrm{Ag}^+ \rightleftarrows \mathrm{com}; K_{\mathrm{ex}} \quad (4)$$

$$K_{\mathrm{ex}} = \frac{[\mathrm{com}]_{\mathrm{b,eq}}}{\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{b,eq}}[\mathrm{Ag}^+]_{\mathrm{b,0}}^{n}} \quad (5)$$

where K_{ex} is the extraction equilibrium constant based on Eq. 4 and n is the number of Ag^+ coordinated with a DHA-Et, which was determined in our previous study as 6 and was corresponding to the number of unsaturated double bonds of DHA-Et.[13] Substituting Eqs. 3 and 5 into Eq. 2, W_{com} is rewritten as follows:

$$W_{\mathrm{com}} = Ak_1[\mathrm{Ag}^+]_{\mathrm{b,0}}^{m}\left(\overline{[\mathrm{DHA\text{-}Et}]}_{\mathrm{i}} - \frac{[\mathrm{com}]_{\mathrm{i}}}{K_{\mathrm{ex}}[\mathrm{Ag}^+]_{\mathrm{b,0}}^{n}}\right) \quad (6)$$

Diffusion of extracted complex through the aqueous film to the aqueous bulk

The mass transfer rate of extracted complex through the aqueous film, W_{aq}, can be expressed with a linear driving force approximation.

$$W_{\mathrm{aq}} = A \times R_{\mathrm{A,aq}} = A\frac{D_{\mathrm{aq}}}{\delta_{\mathrm{aq}}}\left([\mathrm{com}]_{\mathrm{i}} - [\mathrm{com}]_{\mathrm{b}}\right) \quad (7)$$

where $R_{A,aq}$ is the molar flux of extracted complex in the aqueous film. D_{aq} and δ_{aq} mean the diffusion coefficient of extracted complex and the thickness of the aqueous film, respectively.

Rate equation for overall process

By assuming a quasi-steady-state for the overall process of the DHA-Et extraction, it is considered that Eqs. 1, 6, and 7 are equal to the reaction rate of DHA-Et, $-r_{\text{DHA-Et}}$.

$$\begin{aligned} -r_{\text{DHA-Et}} &= A\frac{D_{\text{org}}}{\delta_{\text{org}}}\left(\overline{[\text{DHA-Et}]}_{\text{b}} - \overline{[\text{DHA-Et}]}_{\text{i}}\right) \\ &= Ak_1[\text{Ag}^+]^m_{\text{b},0}\left(\overline{[\text{DHA-Et}]}_{\text{i}} - \frac{[\text{com}]_{\text{i}}}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}\right) \\ &= A\frac{D_{\text{aq}}}{\delta_{\text{aq}}}\left([\text{com}]_{\text{i}} - [\text{com}]_{\text{b}}\right) \end{aligned} \quad (8)$$

Equation 8 can subsequently be rewritten to Eq. 9:

$$\begin{aligned} -r_{\text{DHA-Et}} &= \frac{\overline{[\text{DHA-Et}]}_{\text{b}} - \overline{[\text{DHA-Et}]}_{\text{i}}}{\delta_{\text{org}}/(AD_{\text{org}})} \\ &= \frac{\overline{[\text{DHA-Et}]}_{\text{i}} - \frac{[\text{com}]_{\text{i}}}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}}{1\Big/\left(Ak_1[\text{Ag}^+]^m_{\text{b},0}\right)} = \frac{\frac{[\text{com}]_{\text{i}}}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}} - \frac{[\text{com}]_{\text{b}}}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}}{\frac{\delta_{\text{aq}}}{AD_{\text{aq}}}\frac{1}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}} \end{aligned} \quad (9)$$

By adding the denominator of the second, third, and fourth terms together and also adding the numerator of the second, third, and fourth terms together, Eq. 9 can be rewritten as follows:

$$-r_{\text{DHA-Et}} = \frac{\overline{[\text{DHA-Et}]}_{\text{b}} - \frac{[\text{com}]_{\text{b}}}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}}{\frac{\delta_{\text{org}}}{AD_{\text{org}}} + \frac{1}{Ak_1[\text{Ag}^+]^m_{\text{b},0}} + \frac{\delta_{\text{aq}}}{AD_{\text{aq}}}\frac{1}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}} \quad (10)$$

Here, we consider the mass balance of DHA-Et. The mass balance of DHA-Et can be written as follows:

$$\begin{aligned} \overline{[\text{DHA-Et}]}_{\text{b},0}V_{\text{org}} &= \overline{[\text{DHA-Et}]}_{\text{b}}V_{\text{org}} + \Gamma_{\text{DHA-Et}}A \\ &\quad + [\text{DHA-Et}]_{\text{b}}V_{\text{aq}} + [\text{com}]_{\text{b}}V_{\text{aq}} \end{aligned} \quad (11)$$

where V_{org} and V_{aq} are the volume of organic and aqueous phases, respectively. $\Gamma_{\text{DHA-Et}}$ is interfacial adsorption amount of DHA-Et for unit interface. Because the amount of DHA-Et distributed in an aqueous phase and that adsorbed on the interface are much smaller than the amount of DHA-Et in an organic phase and the amount of extracted complex, $[\text{DHA-Et}]_{\text{b}}V_{\text{aq}}$ and $\Gamma_{\text{DHA-Et}}A$ can be regarded as zero. Therefore, Eq. 11 can be rewritten as follows.

$$[\text{com}]_{\text{b}} = \left(\overline{[\text{DHA-Et}]}_{\text{b},0} - \overline{[\text{DHA-Et}]}_{\text{b}}\right)\frac{V_{\text{org}}}{V_{\text{aq}}} \quad (12)$$

By substituting Eq. 12 into Eq. 10, $-r_{\text{DHA-Et}}$ can be expressed as follows:

$$\begin{aligned} -r_{\text{DHA-Et}} &= -V_{\text{org}}\frac{d\overline{[\text{DHA-Et}]}_{\text{b}}}{dt} \\ &= \frac{(1+\beta)\overline{[\text{DHA-Et}]}_{\text{b}} - \beta\overline{[\text{DHA-Et}]}_{\text{b},0}}{\alpha} \end{aligned} \quad (13)$$

where

$$\begin{aligned} \alpha &= \frac{\delta_{\text{org}}}{AD_{\text{org}}} + \frac{1}{Ak_1[\text{Ag}^+]^m_{\text{b},0}} + \frac{\delta_{\text{aq}}}{AD_{\text{aq}}}\frac{1}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}} \\ \beta &= \frac{1}{K_{\text{ex}}[\text{Ag}^+]^n_{\text{b},0}}\frac{V_{\text{org}}}{V_{\text{aq}}} \end{aligned} \quad (14)$$

Integrating Eq. 13 under the initial condition; $\overline{[\text{DHA-Et}]}_{\text{b}} = \overline{[\text{DHA-Et}]}_{\text{b},0}$ at $t = 0$, the following equation is led.

$$\overline{[\text{DHA-Et}]}_{\text{b}} = \frac{\beta + \exp\{-(1+\beta)t/(\alpha \times V_{\text{org}})\}}{1+\beta}\overline{[\text{DHA-Et}]}_{\text{b},0} \quad (15)$$

In this study, we simulated the relationship between $\overline{[\text{DHA-Et}]}_{\text{b}}$ and t for the slug flow system with Eq. 15. The parameters used in the calculation are as follows; $[\text{Ag}^+]_{\text{b},0}$, V_{org}, and V_{aq} are the experimental condition and K_{ex} was calculated from the following equation:

$$\log K_{\text{ex}} = \frac{\Delta S^\circ}{2.303R} - \frac{\Delta H^\circ}{2.303R} \times \frac{1}{T} \quad (16)$$

where R and T are the gas constant and temperature, respectively. ΔS° and ΔH° are entropy and enthalpy of the extraction of DHA-Et with silver ion, respectively. They were determined in the previous article.[13] We took 2.5×10^{-9} m^2 s^{-1} for both of D_{org} and D_{aq}, because the diffusion coefficient of several solutes in several solvent are in the range between 1×10^{-9} m^2 s^{-1} and 4×10^{-9} m^2 s^{-1} as reported by Wilke and Chang.[21] In addition, it was assumed that δ_{org} and δ_{aq} are the same. The calculation of the film thickness is very difficult because the phases are in turbulent flow in a geometry, which is not usually well defined. So we calculated the uptake curves with several δ. The interfacial area, A, is another important parameter to discuss the characteristics of the slug flow. We calculated the uptake curves with two different values of A. One is the columnar area which is equivalent to the surface area of the unit slug, i.e., $A_1 = 2\pi r^2 + 2\pi rL$ where r and L are inner radius of PTFE tube and length of a slug, respectively. Another is the sum of the circular area of both ends of the unit slug, i.e., $A_2 = 2\pi r^2$. The kinetic parameters, m and k_1, were determined from the experimental results of the extraction dynamics obtained by using the stirred transfer cell. The m was determined from the plot concerning to the effect of silver ion concentration on the initial extraction rate. The k_1 was determined from the plot based on the theoretical equation derived in the next section.

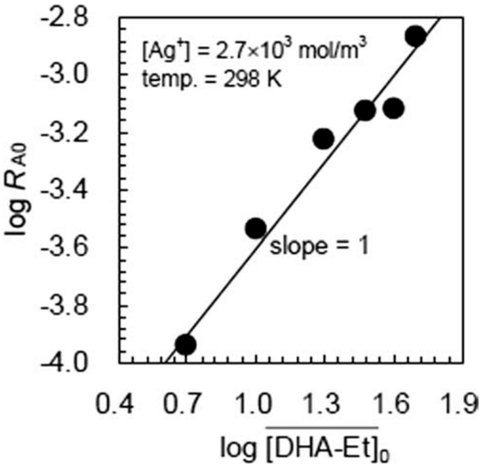

Figure 4. Effect of DHA-Et concentration on initial extraction rate of DHA-Et measured by using the stirred transfer cell.

Determination of the apparent rate constant for complex-formation reaction between DHA-Et and silver ion

Before the modeling of the uptake curves for the slug flow system, we determined k_1 according to the following analysis, which is available when chemical reaction is rate-controlling. Such condition can be realized by using a stirred transfer cell for the extraction. When chemical reaction controls, W_{com} is regarded as the overall mass transfer rate. Therefore, the mass transfer rate based on unit volume, R_V, can be written as follows:

$$R_V = -\frac{d\overline{[\text{DHA-Et}]}_i}{dt} = \frac{A}{V_{\text{org}}}k_1[\text{Ag}^+]^m_{b,0}\left(\overline{[\text{DHA-Et}]}_i - \frac{[\text{com}]_i}{K_{\text{ex}}[\text{Ag}^+]^n_{b,0}}\right) \quad (17)$$

In addition, $\overline{[\text{DHA-Et}]}_i$ and $[\text{com}]_i$ in Eq. 17 can be regarded as those in the bulk.

Therefore, by substituting Eqs. 5 and 12 into Eq. 17 and simplifying, R_V can be rewritten as follows:

$$R_V = -\frac{d\overline{[\text{DHA-Et}]}_b}{dt} = \frac{A}{V_{\text{org}}}\frac{k_1[\text{Ag}^+]^m_{b,0}\overline{[\text{DHA-Et}]}_{b,0}}{\overline{[\text{DHA-Et}]}_{b,0} - \overline{[\text{DHA-Et}]}_{b,\text{eq}}}\left(\overline{[\text{DHA-Et}]}_b - \overline{[\text{DHA-Et}]}_{b,\text{eq}}\right) \quad (18)$$

Integrating Eq. 18 under the initial condition; $\overline{[\text{DHA-Et}]}_b = \overline{[\text{DHA-Et}]}_{b,0}$ at $t = 0$, the following equation is led.

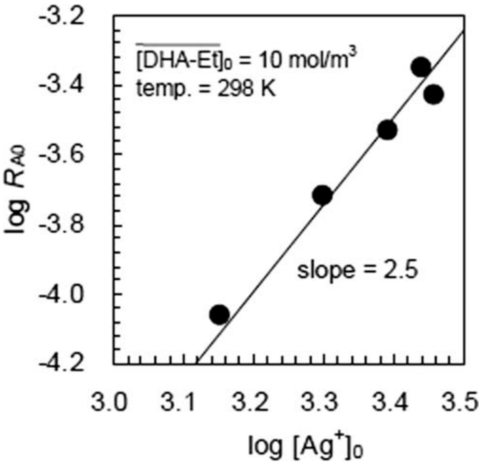

Figure 5. Effect of silver ion concentration on initial extraction rate of DHA-Et measured by using the stirred transfer cell.

$$-\ln\frac{\overline{[\text{DHA-Et}]}_b - \overline{[\text{DHA-Et}]}_{b,\text{eq}}}{\overline{[\text{DHA-Et}]}_{b,0} - \overline{[\text{DHA-Et}]}_{b,\text{eq}}} = \frac{A}{V_{\text{org}}}\frac{k_1[\text{Ag}^+]^m_{b,0}\overline{[\text{DHA-Et}]}_{b,0}}{\overline{[\text{DHA-Et}]}_{b,0} - \overline{[\text{DHA-Et}]}_{b,\text{eq}}}t \quad (19)$$

According to Eq. 19, a plot of $-\ln\frac{\overline{[\text{DHA-Et}]}_b - \overline{[\text{DHA-Et}]}_{b,\text{eq}}}{\overline{[\text{DHA-Et}]}_{b,0} - \overline{[\text{DHA-Et}]}_{b,\text{eq}}}$ versus t gives a proportional relationship and the slope gives k_1.

Results and Discussion

Determination of kinetic parameters for complex-formation reaction between DHA-Et and silver ion

Experiments were carried out using the stirred transfer cell. As a preliminary test, we investigated the effect of stirring speed of the stirred transfer cell on the initial extraction rate, and found that the initial extraction rate became constant when the stirring speed was over 0.833 s^{-1}. That is, the complex-formation reaction was the rate-controlling step

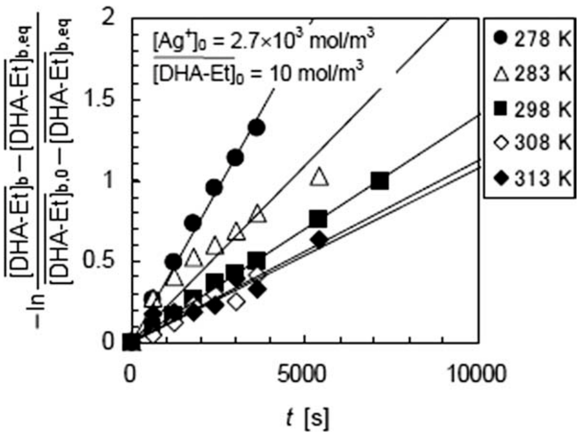

Figure 6. Plots based on Eq. 19 for different temperatures.

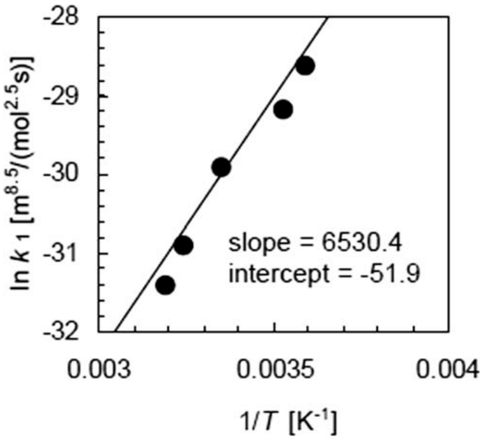

Figure 7. Arrhenius plot of apparent rate constant for complex-formation reaction between DHA-Et and silver ion.

when the stirring speed was faster than 0.833 s^{-1}. Therefore, we carried out the experiments at 1.0 s^{-1} of the stirring speed after this.

When the complex-formation reaction is the rate-controlling, the initial extraction rate based on unit surface, R_{A0}, can be expressed as follows:

$$R_{A0} = -\frac{V_{org}}{A}\frac{d\overline{[\text{DHA-Et}]}_b}{dt}\bigg|_{t=0} = k_1\overline{[\text{DHA-Et}]}_b[\text{Ag}^+]_b^m \qquad (20)$$

where the concentration of extracted complex is regarded as zero because the initial state of extraction is taken up. To confirm the first reaction order for DHA-Et concentration and to determine m, the initial extraction rate was measured for various DHA-Et concentrations and silver ion concentrations. The effects of DHA-Et and silver ion concentration on the initial extraction rate are shown in Figures 4 and 5, respectively. From the result shown in Figure 4, it was confirmed that the reaction order with respect to DHA-Et was 1. In addition, as shown in Figure 5, it was found that the apparent reaction order with respect to silver ion was 2.5.

Subsequently, to determine k_1, we made the plot based on Eq. 19 for different temperatures. The results are shown in Figure 6. As shown in Figure 6, the plots for all investigated temperatures indicated the proportional relationship, and k_1 was determined from the slopes. Figure 7 shows the Arrhenius plot based on Eq. 21.

$$k_1 = k_0 \exp\left(-\frac{E_a}{RT}\right) \qquad (21)$$

where E_a and k_0 are the overall activation energy and frequency factor, respectively. As shown in Figure 7, the plots showed the proportional relationship with a positive slope. This positive slope indicates that the activation energy for the overall extraction process is negative. According to the investigation by Shimomura et al.,[22] negative activation energy was obtained when the reactions occurred sequential and one of the intermediate reactions was rate-controlling one. In the complex formation reaction between DHA-Et and silver ions, the complete complex of $(\text{DHA-Et } 6\text{Ag})^{6+}$ must be formed through sequential reactions. As stated earlier, it was found that the reaction was 2.5th order with respect to silver ion. This fact suggested that the 2nd and/or 3rd of intermediate reactions were the rate-controlling one, and thereby the negative activation energy was obtained.

Table 2. Determined Kinetic Parameters of DHA-Et Extraction with Silver Ion

m	Activation energy	Frequency factor
2.5	-54.29 kJ mol^{-1}	2.88×10^{-23} $m^{8.5}$ mol^{-2} s^{-1}

By using the parameters summarized in Table 2, which were obtained from Figures 5 and 7, we can predict the uptake curves. Substituting the determined parameters and Eq. 21 into Eq. 15, the uptakes obtained by using the stirred transfer cell was calculated for various experimental conditions. Figure 8 shows the examples of the results. The experimental conditions and the parameters used for the calculation are shown in Table 3. In the calculation, δ, which was

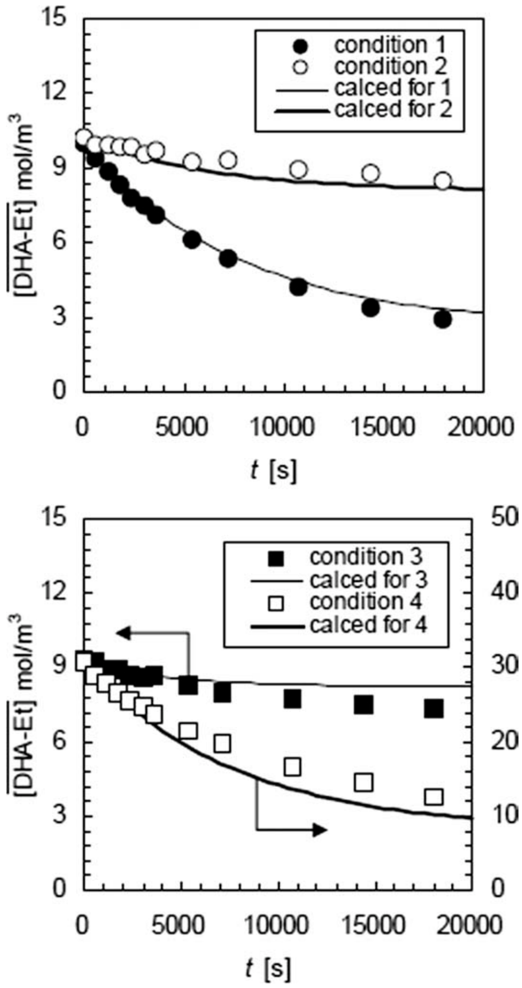

Figure 8. Experimental and predicted uptake curves of DHA-Et extraction measured by using the stirred transfer cell. Plots are the experimental data and lines are the calculated results.

Table 3. Experimental Conditions and Parameters Used for Calculation of Uptake Curves of DHA-Et Extraction Shown in Figure 8

	Condition 1	Condition 2	Condition 3	Condition 4	Unit
$[\text{DHA-Et}]_{\text{org},0}$	9.98	10.2	9.25	30.7	mol m^{-3}
$[\text{Ag}^+]_{\text{aq},0}$	2700	2700	1600	2700	mol m^{-3}
T	298	313	298	298	K
ΔH°	−122.0	−122.0	−122.0	−122.0	kJ mol^{-1}
ΔS°	−795.5	−795.5	−795.5	−795.5	J K^{-1} mol^{-1}
D_{aq}	2.5×10^{-9}	2.5×10^{-9}	2.5×10^{-9}	2.5×10^{-9}	m^2 s^{-1}
D_{org}	2.5×10^{-9}	2.5×10^{-9}	2.5×10^{-9}	2.5×10^{-9}	m^2 s^{-1}
δ_{aq}	1×10^{-6}	1×10^{-6}	1×10^{-6}	1×10^{-6}	m
δ_{org}	1×10^{-6}	1×10^{-6}	1×10^{-6}	1×10^{-6}	m

the only unknown parameter, was set to 1×10^{-6} m. As shown in Figure 8, a reasonable agreement of theoretical to experimental data is obtained for all conditions. In addition, we confirmed that the calculated uptake curves hardly changed when δ was set below 5×10^{-6} m (data is not shown). This indicates that the overall extraction process is limited by complex-formation reaction when δ is thinner than 5×10^{-6} m.

Prediction of the uptake curves of DHA-Et for slug flow system

Figures 9 and 10 show the experimental results of DHA-Et extraction for the slug flow system by using the aqueous phases containing 2.0×10^3 and 1.0×10^3 mol m^{-3} of silver ion, respectively. In these experiments, the temperature was set to 298 and 268 K. Because large amount of salts ($AgNO_3$ and $NaNO_3$) were dissolved in an aqueous phase (total concentration of them were 4.0×10^3 mol m^{-3}), the

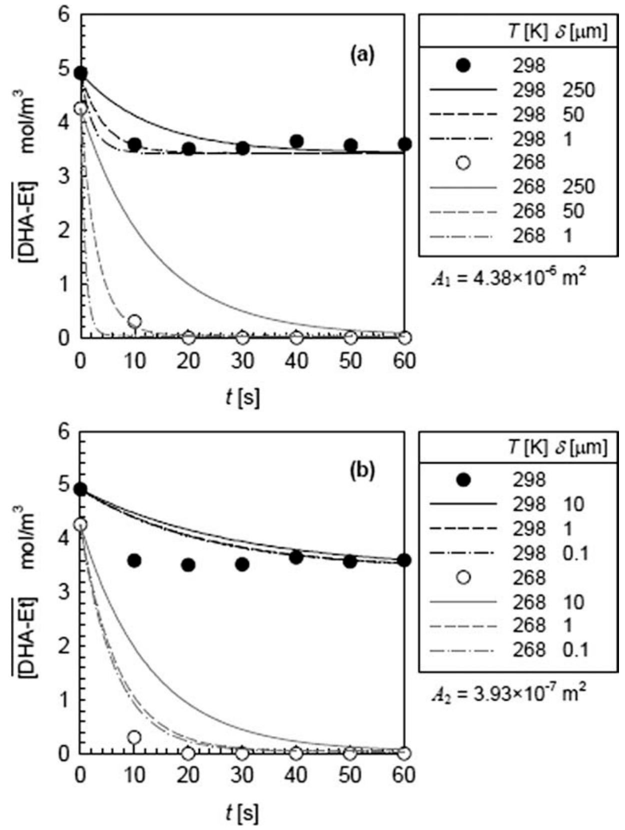

Figure 9. Uptake curves of DHA-Et extraction with the slug flow for $[\text{Ag}^+]_{\text{aq},0}$ = 2000 mol m^{-3}.

Plots are the experimental data. Solid, broken, and dash-dotted lines are the calculated results for different values of δ. Interfacial area: (a) Columnar area which is equivalent to the surface area of the unit slug ($A_1 = 4.38 \times 10^{-6}$ m^2) and (b) sum of the circular area of both ends of the unit slug ($A_2 = 3.93 \times 10^{-7}$ m^2).

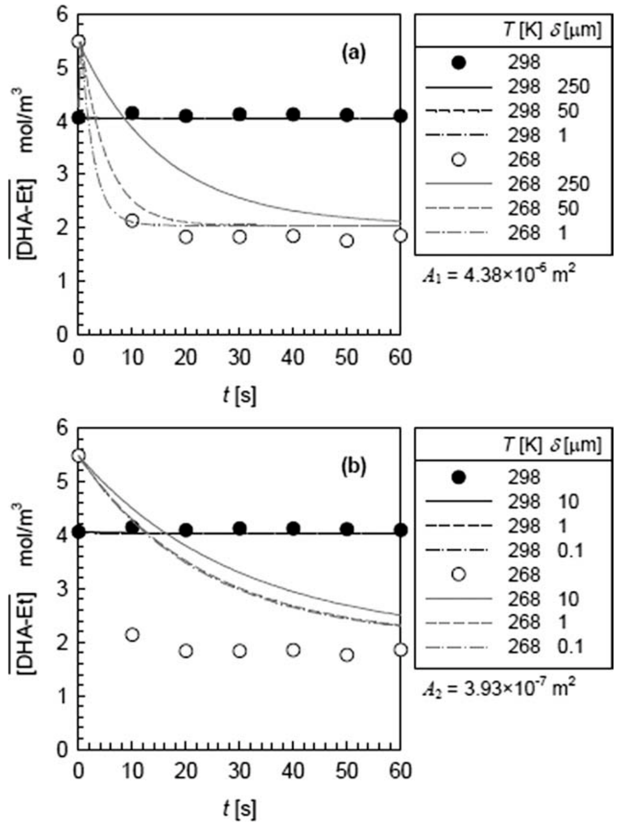

Figure 10. Uptake curves of DHA-Et extraction with the slug flow for $[\text{Ag}^+]_{\text{aq},0}$ = 1000 mol m^{-3}.

Plots are the experimental data. Solid, broken, and dash-dotted lines are the calculated results for different values of δ. Interfacial area: (a) Columnar area which is equivalent to the surface area of the unit slug ($A_1 = 4.38 \times 10^{-6}$ m^2) and (b) sum of the circular area of both ends of the unit slug ($A_2 = 3.93 \times 10^{-7}$ m^2).

aqueous phase did not freeze at 268 K. As shown in Figures 9 and 10, the DHA-Et concentration in the organic phase became plateau after 10 s, i.e., equilibration was completed within 10 s. We tried to elucidate the reason why such fast equilibration was achieved by utilizing slug flow with the theoretical calculation based on the proposed model.

The solid, broken, and dash-dotted lines in Figures 9 and 10 are the calculated uptake curves by using Eq. 15 with the determined kinetic parameters. In the calculation, three different values of δ and two different interfacial areas were used to discuss the characteristics of the slug flow. At first, we consider the interfacial area. The panels (a) and (b) in Figures 9 and 10 show the calculated results with the columnar area, A_1, and the sum of the circular area of both ends of the unit slug, A_2, respectively. Regardless of the silver ion concentration and temperature, the calculated uptake curves in panel (a) showed good agreement with the experimental data but those in panel (b) were quite different. These results may be due to the presence of wall film of liquid in the PTFE tube, i.e., oil/water interface exists at the side of the aqueous or organic phase of the slug flow and is available for extraction. This consideration supports the experimental result reported by Kashid et al.[19] They directly observed the organic film between the wall of Teflon tube and the aqueous phase with the fluorescence measurement. Therefore, in our extraction system, an organic film may be present between the aqueous slug and the inner wall of the PTFE tube because of the superior wetting properties. The presence of the wall film significantly enhances the overall extraction rate because the whole interface surrounding aqueous slug takes part in diffusion of chemicals and complex-formation reaction as shown in Eqs. 1, 6, and 7.

Subsequently, we consider the thickness of the liquid film. As shown in panel (a) in Figures 9 and 10, the thinner the liquid film thickness is, the faster the calculated uptake curve reaches equilibrium. Comparing the experimental and calculated results shown in Figures 9a and 10a, it is found that the reasonable liquid film thickness for the slug flow system is thinner than 5×10^{-5} m. Although the experimental data for early periods of extraction are not sufficient to discuss the effect of liquid film thickness, at least we conclude that the liquid film thickness is thinner than half of the inner diameter of the channel (2.5×10^{-4} m), which corresponds to the maximum liquid film thickness in slug created under stillness condition. As proposed by Burns and Ramshaw[18] and Kashid et al.,[19] it is considered that the reduction of the liquid film thickness is due to the internal circulation.

From the earlier discussions, we conclude that the influential parameters in the fast equilibration of slug flow extraction system are the significantly large specific interfacial area caused by the presence of wall film and the reduction of liquid film thickness caused by the internal circulation in the slug.

Conclusions

The extraction dynamics of DHA-Et with silver ion as the extractant was investigated with the stirred transfer cell to determine the kinetic parameters. The DHA-Et extraction was first order with respect to DHA-Et and 2.5th order with respect to silver ion. Based on the proposed model, the apparent rate constant for complex-formation reaction between DHA-Et and silver ion was determined for different temperatures. Negative activation energy was obtained from the Arrhenius plot. The apparent reaction order with respect to silver ion and the negative activation energy indicated that intermediate complex-formation reaction controls the overall complex-formation reaction rate.

The overall rate equation considering diffusion of both of DHA-Et and extracted complex across the liquid film and the complex-formation reaction between DHA-Et and silver ion at the interface was proposed. With the proposed kinetic model and determined kinetic parameters, we predicted the uptake curves of DHA-Et extraction resulted from both systems in which utilizing the stirred transfer cell and the slug flow. The calculated uptake curves corresponded well to the experimental data for both systems. Comparing the calculated and experimental uptake curves for the slug flow system, we investigated the effective interfacial area and the liquid film thickness of the slug flow. As a result, we conclude that the influential parameter in the fast equilibration of the slug flow extraction system is the large specific interfacial area caused by the presence of the organic wall film and the thin liquid film caused by the internal circulation.

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Notation

A = interfacial area between aqueous and organic phases (m^2)
D_{aq} = diffusion coefficient of extracted complex in aqueous film (m^2 s^{-1})
D_{org} = diffusion coefficient of DHA-Et in organic film (m^2 s^{-1})
E_{a} = activation energy for forward reaction of complex-formation (kJ mol^{-1})
$\Delta H°$ = enthalpy for PUFA-Et extraction (J mol^{-1})
K_{ex} = extraction equilibrium constant (m^3 mol^{-1})^6
L = length of unit slug (m)
R = gas constant (J K^{-1} mol^{-1})
R_{A} = extraction rate based on unit interface (mol m^{2}s^{-1})
R_{A0} = initial extraction rate based on unit interface (mol m^{2}s^{-1})
R_{V} = extraction rate based on unit volume (mol m^{3}s^{-1})
$\Delta S°$ = entropy for PUFA-Et extraction (J K^{-1} mol^{-1})
T = temperature (K)
V_{aq} = volume of aqueous phase (m^3)
V_{org} = volume of organic phase (m^3)
W_{aq} = mass transfer rate of extracted complex through the aqueous film (mol s^{-1})
W_{com} = complex-formation rate of DHA-Et and silver ion at the interface (mol s^{-1})
W_{org} = mass transfer rate of DHA-Et through the organic film (mol s^{-1})
com = extracted complex
k_0 = frequency factor for forward reaction of complex-formation (m$^{8.5}$ mol$^{-2.5}$ s^{-1})
k_1 = apparent rate constant for forward reaction of complex-formation (m$^{8.5}$ mol$^{-2.5}$ s^{-1})
k_2 = apparent rate constant for backward reaction of complex-formation (m s^{-1})
m = reaction order with respect to silver ion (–)

n = number of Ag^+ coordinated with a DHA-Et molecule to form extracted complex (−)
r = inner radius of PTFE tube connected to the exit of T-shape microchip (m)
$-r_{\text{DHA-Et}}$ = overall extraction rate of DHA-Et (mol s^{-1})
t = time (s)
v_{aq} = flow rate of the aqueous phase (m^3 s^{-1})
v_{org} = flow rate of the organic phase (m^3 s^{-1})

Subscripts

0 = initial state
b = bulk phase
eq = equilibrium state
i = near interface
org = organic phase

Greek letters

$\Gamma_{\text{DHA-Et}}$ = adsorption amount of DHA-Et on the interface (mol m^{-2})
δ_{aq} = thickness of aqueous film (m)
δ_{org} = thickness of organic film (m)
γ = interfacial tension of DHA-Et between ultrapure water and n-heptane (N m^{-1})

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