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ASPECTS OF THE DIFFUSIVE TRANSPORT OF ACETAMINOPHEN THROUGH BULK LIQUID MEMBRANES

Ioana DIACONU,[a] Hassan Y. ABOUL-ENEIN,[b,*] Andrei A. BUNACIU,[c] Elena RUSE,[a] Cristina MIREA[a,d] and Gheorghe NECHIFOR[a]

[a] University Politehnica Bucharest, Faculty of Applied Chemistry and Materials Science, Department of Analytical Chemistry and Environmental Engineering, 1-7 Polizu Street, 011061, Bucharest, Roumania
[b] National Research Centre, Department of Pharmaceutical and Medicinal Chemistry, Pharmaceutical and Drug Industries Research Division, Dokki, Giza, 12622, Egypt
[c] SCIENT – Research Center for Instrumental Analysis, CROMATEC_PLUS S.R.L., 18 Sos. Cotroceni, Bucharest – 060114, Roumania, 060114
[d] Arcuda Laboratory, Water Quality Service, Joita, Giurgiu, Roumania

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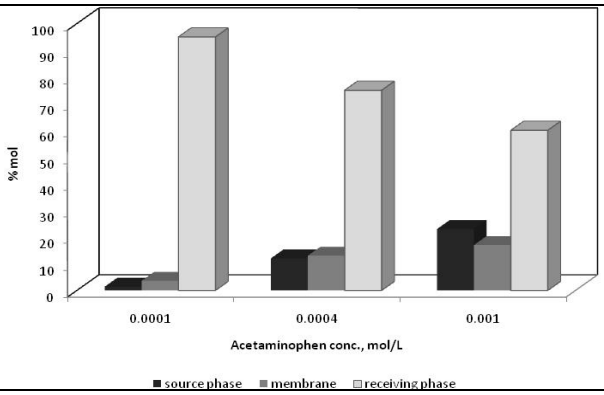
The technique of liquid membranes is frequently used for the transport of various drugs due to several advantages. In the present paper the transport of acetaminophen through bulk liquid membrane using as carrier tributyl phosphate was realized. The influence of the source phase concentration upon the transport efficiency is studied. A diffusive mathematical model was proposed and the extraction constant and diffusion coefficient of the formed complex were calculated.



INTRODUCTION

The transport through liquid represents a versatile method of pre-concentration and separation of some organic and inorganic chemical species such as cations,[1,2] anions,[3] organic acids,[4,5] amino acids,[6-9] phenols and derivatives,[10-13] amines,[14-15] or drugs.[16-18]

In the particular case the bulk liquid membrane represents one of the simplest designs to investigate the transport properties of various compounds.[19]

In the present paper the transport of acetaminophen (*N*-(4-hydroxyphenyl) acetamide) through bulk liquid membrane using as carrier tributyl phosphate was realized.

EXPERIMENTAL

All the reagents used were analytically grade and were used without further purification. Acetaminophen was purchased from Hebei Jiheng (Group) Pharmacy Co., Ltd.-China. Chloroform and tributhyl phosphate was purchased from Merck while NaOH was purchased from Fluka. Chloroform used to prepare the organic membrane was previously saturated with distilled water. The distilled water used to prepare the aqueous phases was previously saturated with chloroform. The transport cell used was a tube in tube transport cell presented in previous papers.[20-22] For the effect of acetaminophen concentration from the source phase the experimental conditions were a source phase formed from acetaminophen solution in the concentration range 10^{-4}–10^{-3} mol/L, a membrane formed from a solution of tributyl phosphate 10^{-2} mol/L in chloroform and as receiving phase

* Corresponding author: haboulenein@yahoo.com, tel.: + 201003678948, fax: +20233370931

1mol/L NaOH solution. All the experiments were realized at a stirring speed of 180 rot/min and the transport time was of 24 hours.

The analytical control was realized using a LAMDA UV-VIS-NIR (Perkin Elmer Life and Analytical Sciences) spectrophotometer at acetaminophen specific wavelength: at 241 nm-for source phase and 256 nm-for receiving phase and at codeine phosphate specific wavelength: at 284 nm-for source phase and for the receiving phase.

RESULTS AND DISCUSSION

Acetaminophen is an organic compound slightly dissociated (pKa = 9.50), practically a neutral molecule active for bulk liquid membrane transport.

Neutral molecules transport through bulk liquid membranes is the result of certain processes that take place at the interfaces of the membrane. Thus the fo bllowing equilibriums are established:

$$(A)_w \rightleftharpoons (A)_m \quad (1)$$

$$(A)_w + (L)_w \rightleftharpoons (AL)_w \quad (2)$$

$$(A)_m + (L)_m \rightleftharpoons (AL)_m \quad (3)$$

$$(AL)_w \rightleftharpoons (AL)_m \quad (4)$$

where A = acetaminophen subject to transport, L = carrier (ligand - tributyl phosphate), AL = carrier-acetaminophen complex, w-water, m-membrane

At the interfaces of the membrane system there is a diffusion boundary layer where the organic substrate transport is realized only though diffusion processes.

The diffusive transport of the solute is described through the first law of Fick:

$$J_i = -D_i \frac{dc_i}{dx} \quad (5)$$

where: J_i = flux, D_i = diffusion coefficient of solute "i", dc_i = concentration variation of solute "i", dx = thickness of diffusion layer.

The total flux transported through the membrane (J_{tot}) can be written as a sum of the flux of the solute in the absence of the carrier (J_0) and the flux of the same compound in the presence of the carrier (J_{as}).

$$J_{tot} = J_{as} + J_0 = D_c d^{-1}[AL]_m + D_A d^{-1}[A]_m \quad (6)$$

Based on the equilibriums that take place at the interface source phase-membrane the following constants can be defined:

$$K_{as} = \frac{[AL]_m}{[A]_m [L]_m} \quad (7)$$

K_{as} = association constant for the complex formed by the solute and carrier in the diffusion boundary layer in the membrane

$$K_w = \frac{[AL]_w}{[A]_w [L]_w} \quad (8)$$

K_w = association constant for the complex formed by the neutral solute and carrier in the diffusion boundary layer in the source phase.

$$R_L = \frac{[L]_m}{[L]_w} \quad (9)$$

R_L= the repartition constant of the carrier between the two phases: source phase and the membrane

$$R_A = \frac{[A]_m}{[A]_w} \quad (10)$$

$R_A = R_L$= the repartition constant of the solute between the two phases: source phase and the membrane

The extraction constant of the solute is given by the relationship:

$$K_{ex} = \frac{[AL]_m}{[A]_w [L]_w} \quad (11)$$

By expressing $[AL]_m$ from equation 7 and $[A]_w$ from relationship 10 and replacing them in equation 11 we obtain:

$$K_{ex} = K_{as} \times R_A \quad (12)$$

The extraction constant is equal with the product between association constant (K_{as}) characteristic to the complex formed by the solute and the carrier and the repartition constant (R_A) of the solute between the source phase and the membrane.

When we realize the mass balance we obtain:

$$V_m[L]^\circ = V_m\{[L]_{m,s} + [AL]_{m,s} + [L[_{m,r} + [AL]_{m,r}\} + V_s\{[L]_{w,s} + [AL]_{w,s}\} + V_r\{[L]_{w,r} + [AL]_{w,r}\} \quad (13)$$

where:

V_m = membrane volume, V_s = source phase volume, V_r = receiving phase volume, $[L]^\circ$ = total concentration of carrier, $[L]_{m,s}$ = carrier concentration in membrane at the interface source

phase |membrane, $[AL]_{m,s}$ = complex concentration in membrane at the interface source phase |membrane, $[L]_{m,r}$ = carrier concentration at the interface membrane| receiving phase, $[AL]_{m,r}$ = complex concentration in membrane at de complex the interface membrane| receiving phase, $[L]_{w,s}$ = carrier concentration in aqueous source phase, $[AL]_{w,s}$ = complex concentration in aqueous source phase, $[L]_{w,r}$ = carrier concentration in receiving phase, $[AL]_{w,r}$ = complex concentration in aqueous source phase.

If we consider that in the membrane phase at the two interfaces the complex concentration and carrier concentration are equal we can write:

$$[L]_{m,s} + [AL]_{m,s} = [L]_{m,r} + [AL]_{m,r} = [L]_m + [AL]_m \quad (14)$$

For the initial time of the transport the following hypothesis are valid: $[A]_{w,s} = [A]°_{w,s}$, $[AL]_{m,r} = 0$, $[AL]_{v,r} = 0$
$[L]_{w,r} = 0$

where: $[A]°_{w,s}$ is the initial concentration of neutral compound in the source phase.

In this hypothesis the balance equation of the transport becomes:

$$V_m[L]° = V_m\{[L]_m + [AL]_m\} + V_s\{[L]_{w,s} + [AL]_{w,s}\} + V_r[L]_{w,r} \quad (15)$$

or:

$$[L]° = \{[L]_m + [AL]_m\} + V_s/V_m\{[L]_{w,s} + [AL]_{w,s}\} + V_r/V_m[L]_{w,r} \quad (16)$$

If we write: $P_s = \frac{V_m}{V_s}$ and $P_r = \frac{V_m}{V_r}$ it results:

$$[L]^0 = \{[L]_m + [AL]_m\} + \frac{1}{P_s}\{[L]_{w,s} + [AL]_{w,s}\} + \frac{1}{P_r}[L]_{w,r} \quad (17)$$

Using relationships 8, 9 and 11 it results:

$$[L]^0 = \frac{[AL]_m}{K_{ex}[A]^0_w}\left(1 + \frac{1}{P_s R_L} + \frac{1}{P_r R_L} + \frac{K_w[A]}{P_s}\right) + [AL]_m \quad (18)$$

or:

$$[L]^0_m = [AL]_m + H\frac{[AL]_m}{K_{ex}[A]^0_w} \quad (19)$$

where we have written:

$$H = \left(1 + \frac{1}{P_s R_L} + \frac{1}{P_r R_L} + \frac{K_w[A]}{P_s}\right) \quad (20)$$

If $R_L > 10^5$ we can consider that H=1. Using equation 6 we can obtain:

$$\frac{[L]^0_m}{J_{as} \times d} = \frac{1}{D_{AL}} + H\frac{1}{K_{ex}[A]^0_w D_{AL}} \quad (21)$$

where D_{AL} = diffusion coefficient of the complex

From this relationship we can express the facilitated:

$$J_{as} = \frac{[L]_m D_{AL} K_{ex}[A]^0_w}{d\left(1 + K_{ex}[A]^0_w\right)} \quad (22)$$

If the flux is measured depending on the concentration of the neutral compound, the product $[L]xJ^{-1}_{as}$ can be represented as a function of $[A]^{-1}$. Based on this linear correlation expressed by relationship 21 the diffusion coefficient can be calculated from the intercept at origin and from the slope we can determine the extraction constant K_{ex}.

Therefore, in the experimental study we investigated the acetaminophen concentration in the source phase upon its transport. We realized the assessment of the diffusion coefficient and the extraction constant of the complex formed with tributyl phosphate.

The effect of acetaminophen from the source phase was studied in range of 10^{-4} – 10^{-3} mol/L. The experimental data were obtained using for the receiving phase 1 mol/L NaOH solution. The carrier (tributyl phosphate) concentration was of 10^{-2} mol/L. The transport time was of 24 hours.

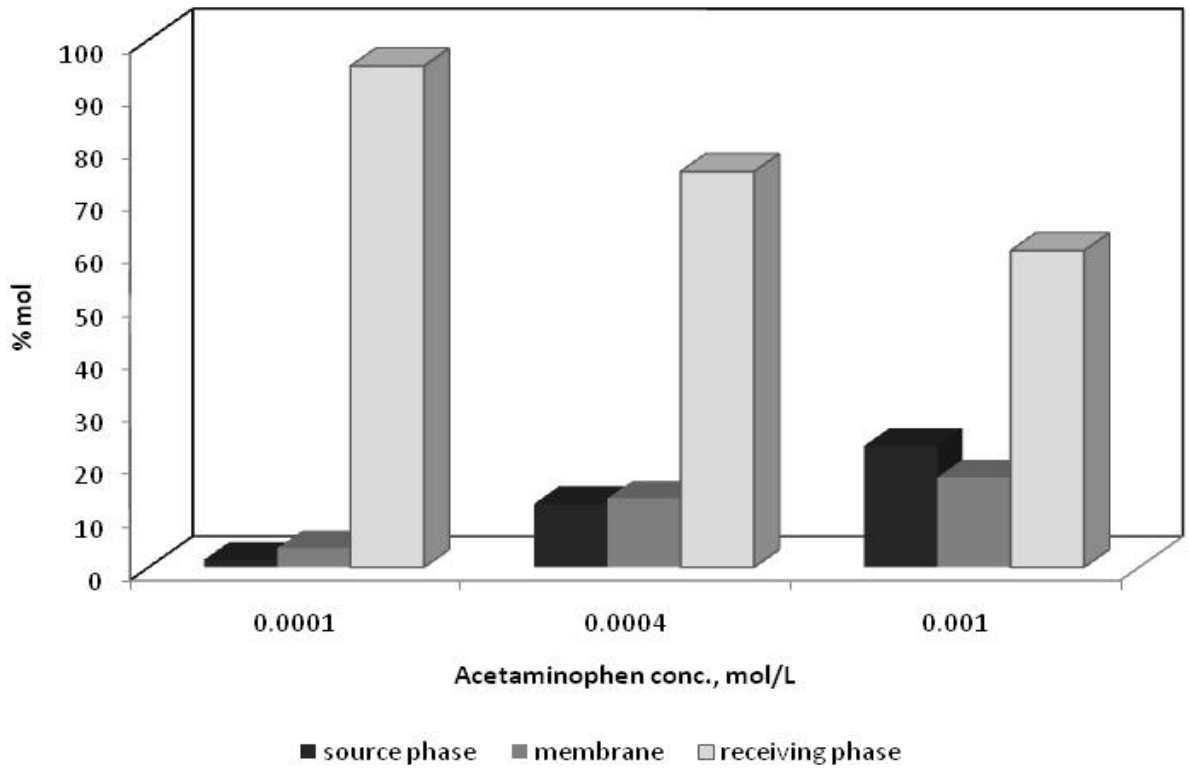


Fig. 1 – The effect of acetaminophen concentration from the source phase. Experimental conditions: source phase: acetaminophen 10^{-4} – 10^{-3} mol/L, membrane: solution of tributyl phosphate 10^{-2} mol/L in chloroform, receiving phase: 1mol/L NaOH solution, transport time 24 hours, stirring speed: 180 rot/min.

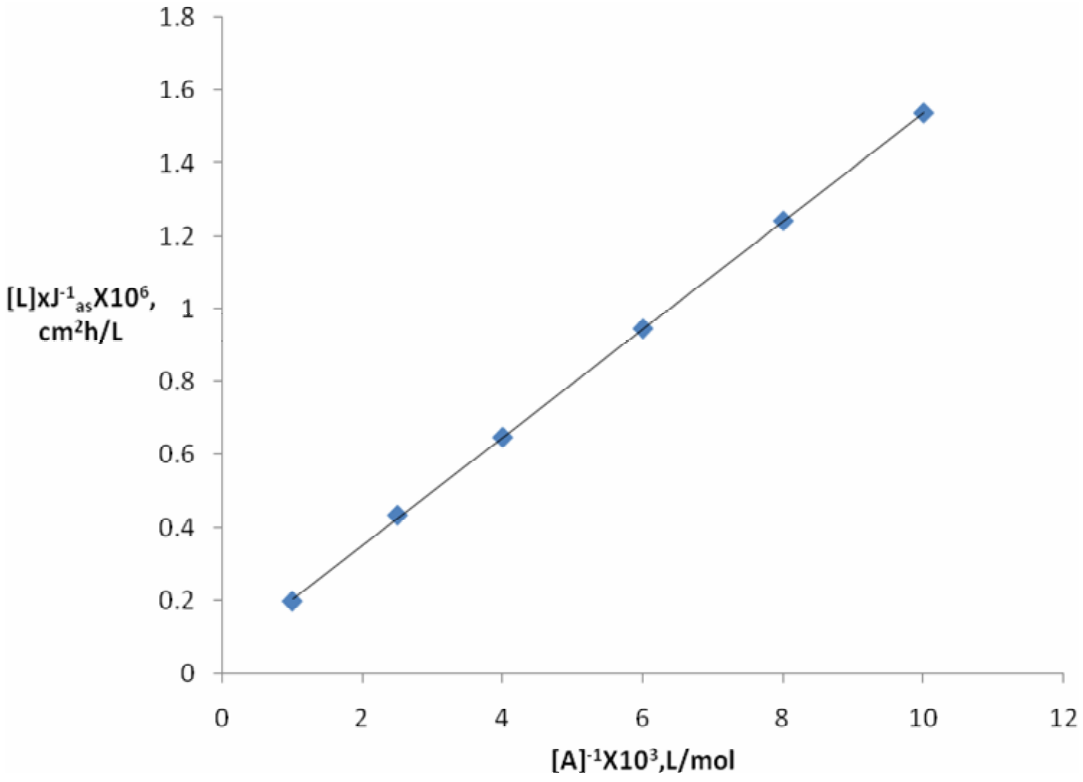


Fig. 2 – Dependence $[L]xJ^{-1}_{as}$ of $[A]^{-1}$.

The maximum efficiency is obtained at a concentration of acetaminophen of 10^{-4} mol/L, as we can observe from Fig. 1. As we increase the concentration of acetaminophen from the source phase we can observe a decrease of the percent of acetaminophen recovered in the receiving phase. This result can be correlated with the transport mechanism in the receiving phase that is based on the reaction of acetaminophen with NaOH. At high concentrations of acetaminophen the neutralization is realized in a lesser extent at the diffusion boundary layer

In order to assess the diffusion coefficient and the extraction constant the transport flux was calculated using the following relationship:[15]

$$J = \frac{V_s \Delta C_s}{At} \quad (23)$$

where: J = membrane entrance flux, mol/cm^2·h

V_s = source phase volume, L

ΔC_s = concentration variation in source phase, mol/L

A = area of the interface source phase |membrane, cm^2

t = time, h

The results are presented in Fig. 2 as the product $[L]xJ^{-1}_{as}$ as a function of $[A]^{-1}$.

We can determine diffusion coefficient from the intercept at origin and we obtain the following value: 1. 81x10^{-4}± 1.12x10^{-5} cm^2/h.

From the slope of the dependence $[L]xJ^{-1}_{as}$ on $[A]^{-1}$ we can determine the extraction constant K_{ex}. The value obtained for the extraction constant 371, 80± 1.48 L/mol.

These values are similar with values obtain by other researches with similar compounds in similar studies.[3,15]

CONCLUSIONS

In the present paper acetaminophen concentration in source phase of the membrane system was studied. Thus the optimum transport conditions from the source phase for acetaminophen transport through bulk liquid membrane were established: source phase a solution of acetaminophen with a concentration of 10^{-4} mol/L, membrane: solution of tributyl phosphate 10^{-2} mol/L in chloroform, receiving phase: 1mol/L NaOH solution, transport time -24 hours, stirring speed: 180 rot/min. Based on experimental data obtained we have developed a mathematical model regarding the diffusive transport of acetaminophen through bulk liquid membrane. The extraction constant and diffusion coefficient of acetaminophen and tributyl phosphate complex were determined.

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