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SELECTIVE SEPARATION OF ACETAMINOPHEN FROM PHARMACEUTICAL FORMULATIONS THROUGH MEMBRANE TECHNIQUES

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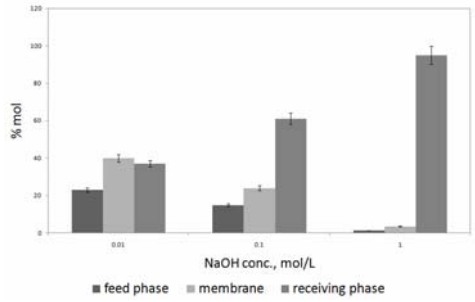
The transport of various chemical species through liquid membrane represents a viable method for several applications in analytical and technological field**.** The behavior at the transport through a chloroform membrane of a synthetic mixture codeine phosphate and acetaminophen was studied. The influence of transport parameters such as: concentration of tributyl phosphate, used as carrier, from the bulk liquid membrane and the NaOH concentration from stripping phase were studied. As an application of optimized membrane system the separation of acetaminophen from codeine phosphate was realized.



INTRODUCTION

N-(4-hydroxyphenyl) acetamide or acetaminophen, also known commonly as paracetamol was firstly introduced in medicine[1] by von Mering in 1893. Acetaminophen is a synthetic compound that derives from *p*-aminophenol[2,3] (Fig.1a) and it is used as an analgesic or antipyretic drug solely or in various mixtures. One of the compounds with which is combined is codeine. Medline Plus, a service provided by the US National Library of Medicine and National Institutes of Health, specifies that codeine and acetaminophen can be purchased in pharmaceutical formulations with brand names such as: Codrix, Tylenol, Papadeine or co-codamol.[4] Codeine or (5α, 6α)-7, 8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol (Fig 1b) is a natural alkaloid from poppy or prepared from morphine.[5] Codeine has antitussive and antipyretic properties.[6] In order to determine these compounds several methods have been proposed such as electrochemical,[7] high performance liquid chromatography (HPLC) with ultraviolet (UV) detection[8] or capillary electrophoresis.[2] The majority of these methods require a separation before. An alternative is membrane separation.

The transport of various chemical species through liquid membrane represents a viable method for several applications in analytical and technological field. The large area of membrane processes applicability is closely correlated with

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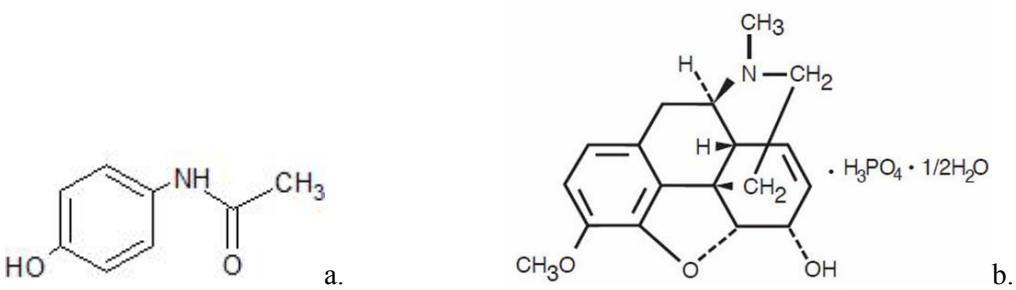

Fig. 1 – Structural formula
a) Acetaminophen, b) codeine phosphate hemihidrated.

their selectivity, with the ability of these systems to carry certain compounds of interest from complex samples.[9-15] Previous studies reported the transport of acetaminophen through liquid membranes, namely emulsion liquid membranes and supported liquid membranes, both using as carrier Aliquat 336. The efficiencies are over 90% after the proper experimental conditions were established.[16,17] Solid membranes can be used to separate acetaminophen from another anti-pyretic and anti-inflammatory drug, namely aspirin. The membranes used are molecularly imprinted polymers by using supercritical fluid technology.[18]

In the present paper were studied some operational parameters that can influence the transport process of acetaminophen through bulk liquid membranes.

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 and codeine phosphate was purchased from Matthay MacFarlan Smith. 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.[19-22] When studying the effect of NaOH concentration from the stripping phase we have used a feed phase of 10^{-4} mol/L acetaminophen, a membrane formed from a solution of tributyl phosphate 10^{-2} mol/L in chloroform and the stripping phase formed from NaOH solution in the concentration range 10^{-2} -1 mol/L. The effect of carrier concentration was studied using a feed phase: 10^{-4} mol/L acetaminophen, a membrane formed from a solution of tributyl phosphate 10^{-3}- 10^{-1} mol/L in chloroform and a stripping phase NaOH solution 1mol/L. The separation of acetaminophen from a synthetic mixture of active substances from a mixture of acetaminophen and codeine phosphate was realized with a feed phase: 10^{-4} mol/L acetaminophen, 10^{-4} mol/L codeine phosphate and a membrane: solution of tributyl phosphate 10^{-2} mol/L in chloroform and stripping phase: NaOH solution in the concentration 1 mol/L. All the experiments were realized at a stirring speed 180 rot/min and the transport time was 24 hours.

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

RESULTS AND DISCUSSION

The aim of this study was the separation of acetaminophen from the mixture acetaminophen-codeine phosphate using the technique of bulk liquid membrane. Thus we have sought to improve the analytical performances of spectrophotometric methods in analyzing pharmaceutical methods. The following parameters were taken into account: the effect of sodium hydroxide concentration from the stripping phase, the effect of carrier concentration and as an application the separation of acetaminophen from a mixture of codeine and acetaminophen. The assay of the transport process was realized by determining the composition of the membrane system in molar percentage. Equations (1) and (2) describe the relationship for the transport efficiency and respectively for the molar composition of the phases.

$$\eta\% = \frac{V_r \cdot C_r}{V_s \cdot C_{s_0}} \cdot 100 \qquad (1)$$

where: V_r = volume of stripping phase
C_r = concentration of stripping phase
V_s = volume of feed phase
C_{s_0} = initial concentration of feed phase

$$C\% = \frac{V_w \cdot C_w}{V_s \cdot C_{s_0}} \cdot 100 \qquad (2)$$

where: C% = molar percent
V_w = volume of aqueous phase
C_w = concentration of aqueous phase
C_{s_0} = initial concentration of feed phase

The membrane composition was determined from the mass balance of the membrane system.

1. The effect of NaOH concentration from the stripping phase

The NaOH concentration from the stripping phase was varied in the range 10^{-2} - 1 mol/L.

The experimental data were obtained at different concentration of NaOH in the stripping phase with a concentration of acetaminophen in the feed of 10^{-4} mol/L, the carrier concentration was 10^{-2} mol/L and the transport time was 24 hours. The results are represented in Fig. 2.

The transport efficiency increases with the increasing of the NaOH concentration from the stripping phase. A higher concentration of NaOH ensures a higher neutralization degree of acetaminophen at the interface membrane stripping phase.

2. The effect of carrier concentration

We also investigated the tributyl phosphate concentration in the membrane upon the transport of acetaminophen in the range of 10^{-3}- 10^{-1} mol/L. The experimental data are presented in Fig. 3. The experimental data were obtained when the acetaminophen concentration in the feed phase was of 10^{-4} mol/L. The NaOH concentration in stripping phase was 1 mol/L and the transport time 24 hours.

The increase of tributyl phosphate concentration over 10^{-2} mol/L will not contribute to a major increase of efficiency. A similar study[19] showed that higher concentration of carrier will increase the membrane viscosity and that will influence negatively the transport efficiency.

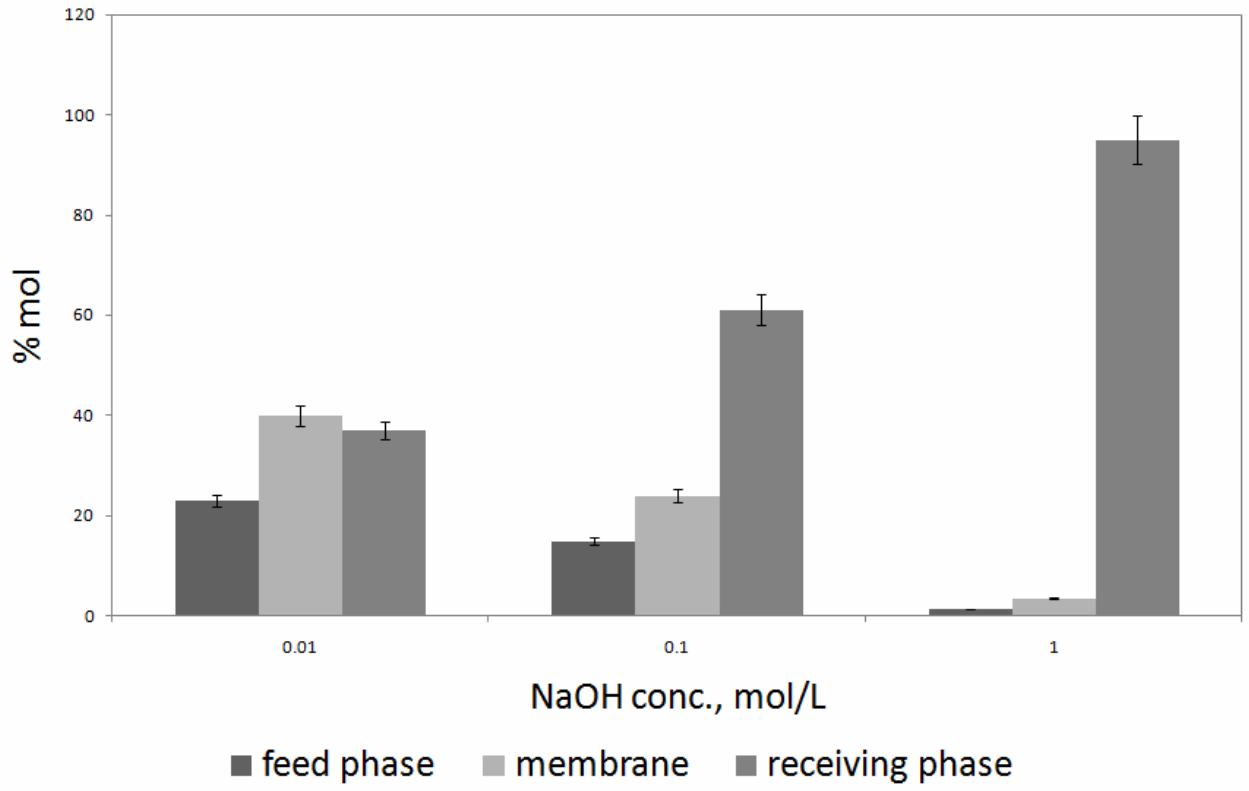

Fig. 2 – The effect of NaOH concentration from the stripping phase.
Experimental conditions: feed phase: 10^{-4} mol/L acetaminophen, membrane: solution of tributyl phosphate 10^{-2} mol/L in chloroform, stripping phase: NaOH solution in the concentration range 10^{-2} -1mol/L, transport time was of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

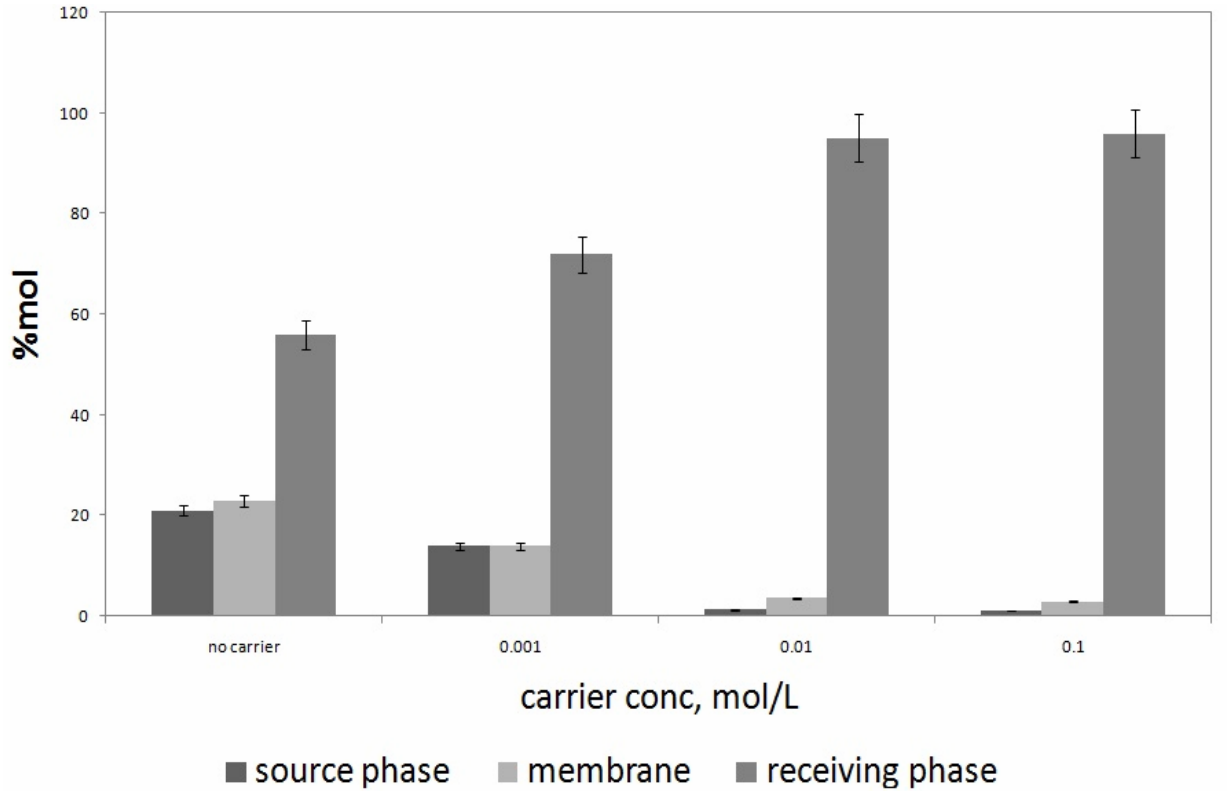

Fig. 3 – The effect of carrier concentration.
Experimental conditions: source phase: 10^{-4} mol/L acetaminophen, membrane: solution of tributyl phosphate 10^{-3}- 10^{-1} mol/L in chloroform, stripping phase: NaOH solution 1mol/L, transport time: 24 hours, stirring speed: 180 rot/min.

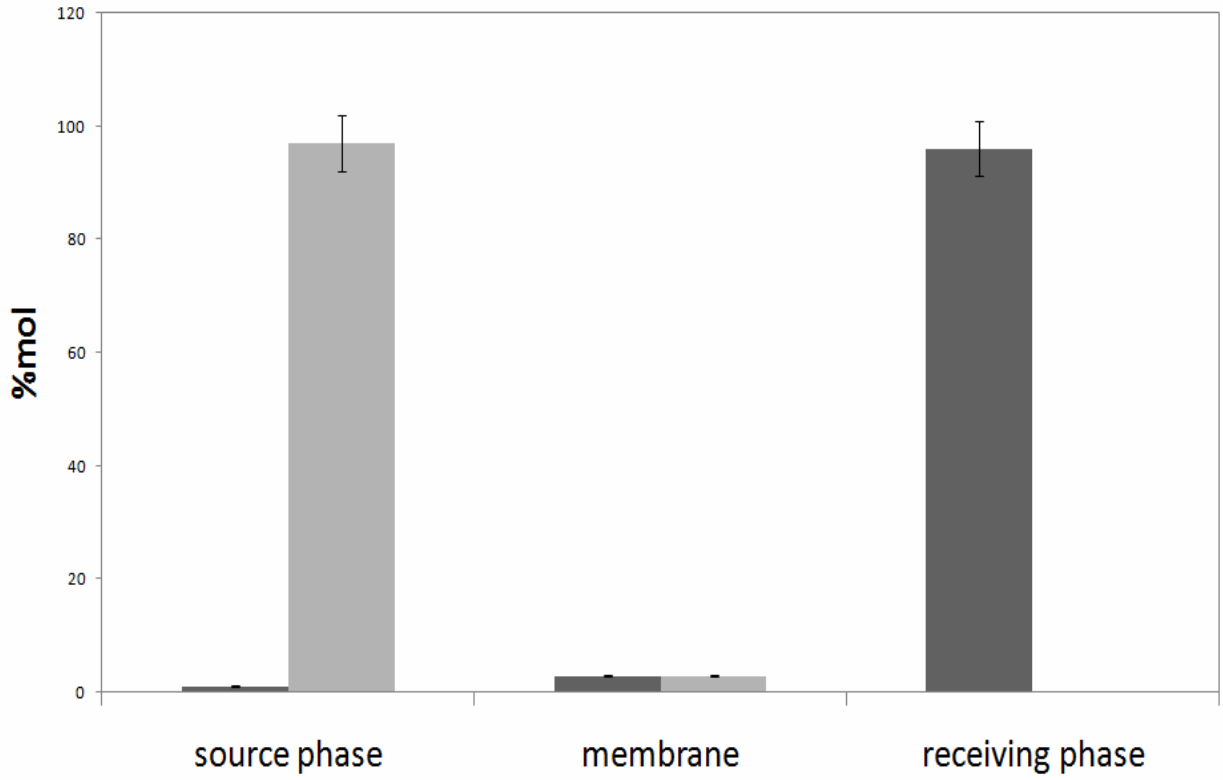

Fig. 4 – Separation of acetaminophen from a mixture of codeine and acetaminophen. The experimental conditions: source phase: 10^{-4} mol/L acetaminophen, 10^{-4} mol/L codeine phosphate, membrane: solution of tributyl phosphate 10^{-2} mol/L in chloroform, stripping phase: NaOH solution in the concentration 1 mol/L, transport time- 24 hours, stirring speed: 180 rot/min.

3. Separation of acetaminophen from a mixture of acetaminophen and codeine phosphate

A number of phenolic compounds are active ingredients for a wide range of drugs. For example cocodamol composition has as active substances codeine phosphate and acetaminophen.

The separation of active principles is realized in analytical purpose. The results are represented in Fig. 4.

Codeine phosphate is an ionic structure inactive for the transport through an organic membrane, while acetaminophen is a phenolic compound slightly dissociated, active for transport through an organic membrane from an aqueous phase.

Codeine phosphate remains in the feed phase while acetaminophen is recovered in the stripping phase with efficiency of over 95%.

CONCLUSIONS

In the present paper acetaminophen operational transport parameters were studied through bulk liquid membranes (tributyl phosphate concentration in chloroform membrane, NaOH concentration in stripping phase). The optimum transport conditions for acetaminophen transport through bulk liquid membrane were established: membrane – carrier tributyl phosphate (10^{-2} mol/L in chloroform), stripping phase- NaOH solution 1 mol/L, transport time 24 hours. In these optimal transport conditions the separation of acetaminophen from a synthetic mixture of acetaminophen and codeine phosphate with efficiency of over 95%.

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REFERENCES

1. M. Khanmohammadi, M. Soleimani, F. Morovvat, A. Bagheri Garmarudi, M. Khalafbeigi and K.Ghasemi, *Thermochim. Acta*, **2012**, *530*, 128.
2. M-E. Capella-Peiró, D. Bose, M. F. Rubert and J. Esteve-Romero, *J.Chromatogr. B*, **2006**, *839*, 95.
3. M. K. Ea. Al-Shwaiyat, *Jordan J. Chem.*, **2013**, *8*, 79.
4. M. Bhandari, A. Bhandari1 and A. Bhandari, *Pharm. Methods*, **2011**, *2*, 3.
5. L. Švorc, J. Sochr, J. Svítková, M. Rievaj and D. Bustin, *Electrochim. Acta*, **2013**, *87*, 503.
6. Y. Li, K. Li, G. Song, J. Liu, K. Zhang and B. Ye,. *Sensor. Actuat. B-Chem.*, **2013**, *182*, 401.
7. M. H. Mashhadizadeh and F. Rasouli, *Electroanalysis*, **2014**, *26*, 2033.
8. V. Maslarska and J. Tencheva,*J. Pharm. Sci.*, **2013**, *5*, 417.
9. C. Olteanu, P. Szczepanski, C. Orbeci, C. G. Lica, L. Costache and I. Diaconu, *Rev. Chim. (Bucharest)*, **2013**, *64*, 925.
10. I. Zaharia, I. Diaconu, E. Ruse and G. Nechifor, *Dig. J. Nanomater. Bios.*, **2012**, *7*, 1303.
11. I. Zaharia, I. Diaconu, E. Ruse and G. Nechifor, *UPB Sci. Bull.,B: Chem. Mat.Sci.*, **2012**, *74*, 61.
12. P. Szczepański and I. Diaconu, *Separ. Sci. Technol.*, **2012**, *47*, 1725.
13. I. Diaconu, I. Zaharia, E. Ruse and D. A. Radu, *Rev. Chim. (Bucharest)*, **2012**, *63*, 153.
14. I. Diaconu, R. Gîrdea, C. Cristea, G. Nechifor, E. Ruse and E. E. Totu, *Rom. Biotech. Lett*, **2010**, *15*, 5702.
15. I. Diaconu, E. Ruse, E. E. Totu and G. Nechifor, *Rev. Chim.*, **2010**, *61*, 718.
16. S. Chaouchi and H. Oualid, *Sep. Purif. Technol.*, **2014**, *129*, 32.
17. N. Kouki, R. Tayeb and M. Dhahbi, *Chem. Pap.*, **2014**, *68*, 457.
18. S. D. Yoon and H. S Byun, *Chem. Eng. J.*, **2013**, *226*, 171.
19. W. Zhang, J. Liu, Z. Ren, S. Wang, C. Du and J. Ma, C*hem. Eng. J.*, **2009**, *150*, 83.
20. I. Diaconu, H. Y. Aboul-Enein, M. A. Al-Omar, G. Nechifor, E. Ruse, A. A. Bunaciu and E. E Totu., *Arab. J. Chem*., **2011**, *4*, 99.
21. I. Diaconu, G. Nechifor, A. C. Nechifor, E. Ruse and E. E. Totu, *UPB. Sci. Bull. Serries B*, **2009**, *71*, 61.
22. I. Diaconu, G. Nechifor, A. C. Nechifor, E. E. Totu and E. Ruse, *Rev. Chim. (Bucharest)*, **2009**, *60*, 1243.