The 2016 World Congress on
Advances in Civil, Environmental, and Materials Research (ACEM16)
Jeju Island, Korea, August 28-September 1, 2016

An Efficient Supported Liquid Membrane Containing the Methyl Cholate Extractive Agent for an Oriented Process Related to the Facilitated Extraction of the Active Ingredient Acetaminophen (Paracetamol)

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ABSTRACT

A supported liquid membrane (**SLM**) containing a lipophilic compound **methyl cholate (MC**) as extractive agent, previously used for extraction of carbohydrates, has been used to facilitated extraction of active ingredient paracetamol (acetaminophen), from concentrated solutions (0,08 - 0,01 M) at different acidities and temperatures. Substrate acetaminophen is the active ingredient of a number of drugs in the class of antipyretic analgesics; therefore, its recovery as a pure compound is very useful for pharmaceutical industry. In this work, the adopted SLM is made of a micro porous poly(vinylidenedifluoride) film **PVDF**, impregnated with 0,01M solution of the carrier agent in Toluene. The experiments relating to the facilitated extraction process of paracetamol substrate, were performed at different temperatures (293, 298, 303 and 308 °K) and varying acidity (pH = 1, 2, 2.5 and 3). The **macroscopic parameters**, permeability(P) and initial fluxes(J0) on the facilitated extraction of substrate by SLM were determined. The study of the relationship between the flux and initial concentrations of extractive agent and extracted substrate, indicates that the rate-determining step on the extraction mechanism is the migration of the complex (extractive agent – substrate) (**S-T**) in the membrane organic phase. The initial flux of extracted substrate is related to the initial concentration of this compound by a saturation law, which allowed the determination of the **microscopic parameters**, apparent diffusion coefficient **D*** and association constant $\mathbf{K_{ass}}$of formed complex (methyl cholate-paracetamol).

The results show a clear influence of temperature and acidity factors on the evolution of the parameters and membrane performance to the studied process. The low stability of formed entity decreases with temperature and acidity factors, while the apparent diffusion coefficient of substrate varies inversely, which explains the high permeability of adopted MLS. The activation parameters ($\boldsymbol{E_a}$, $\boldsymbol{\Delta H^{\#}}et\boldsymbol{\Delta S^{\#}}$) were determined and the values indicate that the high performance of this membrane type is certainly related to the nature of substrate movement in the organic phase, and structures of substrate and extractive agent.

Keywords : supported liquid membrane, oriented process, facilitated extraction, permeability, flux, apparent diffusion coefficient, association constant, activation parameters.

Nomenclature

A	slope of the plot _ln(C_0 - 2Cr) = f(t)
C_0	initial concentration of chromate ions in the feed phase (mol L^{-1})
Cr	concentration of transported chromate ions in the receiving phase (mol L^{-1})
Cs	concentration of chromate ions in the feed phase (mol L^{-1})
P	the permeability of the SLM for chromate ions (cm^2 s^{-1})
J_0	initial flux on the facilitated transport of substrate (mmol cm^{-2} s^{-1})
D*	apparent diffusion coefficient of the complex (TS) (cm^2 s^{-1})
K_{ass}	association constant on the formation of the complex (TS)
l	the membrane thickness (mm)
S	the membrane area (cm^2)
$[T]_0$	concentration of carrier in the membrane (mol L^{-1})
[TS]	concentration of the complex in the organic phase (mol L^{-1})
T	temperature (°K)
T	time (s)
V	volume of the receiving compartment (cm^3)

1- Introduction :

Today, the discharges of fine chemical industry, pharmaceutical industry and health care facilities, depending on the number of patients treated, the quantity and variety of drugs including anticancer drugs, anesthetics, antibiotics, analgesics, anti-inflammatory and psychotropic drugs, represent a source of emission of several toxic and highly polluting substances to the aquatic environment and water resources, this influences the ecological balance in the environment and threatens marine life and human health in particular (MEDDTL and J.P Besse). Indeed, the treatment of these discharges is a concern for the modern pharmaceutical industry; in order to meet environmental challenges through the development of efficient less expensive separation and extraction technologies, allowing the recovery of value-added molecules and valorization of medical discharges.

Currently, membrane processes are among the most promising extraction, separation and recovery technologies, in various areas of modern industries, thanks to their advantages over other techniques. In fact these processes are now the subject of several research topics, including supported liquid membranes (SLMs) which have shown high performances.

In this work, a supported liquid membrane (SLM),with PVDF as support and methyl cholate as extractive agent are adopted to study the facilitated extraction of paracetamol from acidic solutions (pH = 1, 2, 2.5 and 3) at different temperatures (293, 298, 303 and 308 ° K) in order to determine the macroscopic parameters (permeability ***P*** and initial flux J_0) and microscopic parameters (apparent diffusion coefficient ***D**** and association constant K_{ass}) as well as the activation parameters relating to the process of facilitated extraction of paracetamol through this type of membranes.

The results show that the SLM is effective for the facilitated extraction of paracetamol and that the transport process is governed by the type of interaction established between the functional groups of paracetamol substrate and those of methyl chlorate extractive agent.

2. Method and operating principle of the SLM

The SLM is composed of an organic solvent immobilized by capillary forces in the pores of a support, separating the source phase and the receiving phase. The support of these membranes is in general an inert micro porous hydrophobic polymer and is characterized by a small thickness in the order of 25 to 100 µm and the pore diameter from 0.12 to 1 µm. The passage of species through these membranes is an interfacial phenomenon. The use of a polymer support with high porosity is necessary.

This transport through the SLMs is a cyclical process that takes place in five consecutive steps:

1 - Diffusion of the substrate (S) in the source phase to the membrane interface.

2 - The association substrate-carrier (ST) at the interface of the membrane with the source phase.

3 - Diffusion of the complex (ST) through the organic phase of the membrane to the membrane interface with the receiving phase.

4 - Dissociation of the complex (ST) at the membrane interface with the receiving phase.

5 - Diffusion of free substrate (S) in the receiving phase and the carrier (T) in the organic phase of the membrane, to resume the complexation cycle.

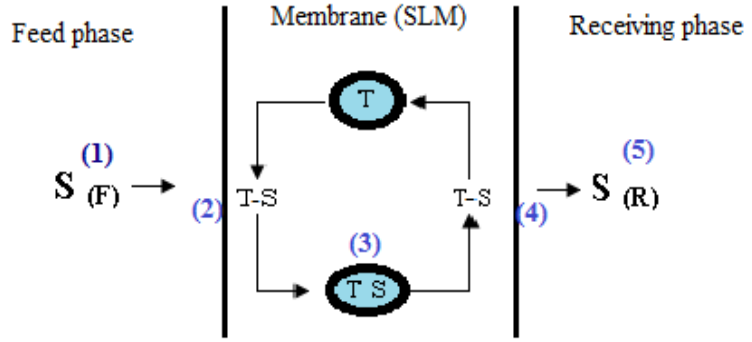

Fig.1: Simplified representation of facilitated transport mechanism through a SLM.

3. Experimental and theoretical models

3-1 Transport cell

The transport experiments were performed in the cell given in Figure 2. This cell consists of two glass compartments, with a volume of 90 ml each, separated by the micro porous membrane (SLM). The cell is immersed in a thermostatic bath (TB). A multi-stirrer ensures the agitation of the two compartment solutions (H. Hassoune).

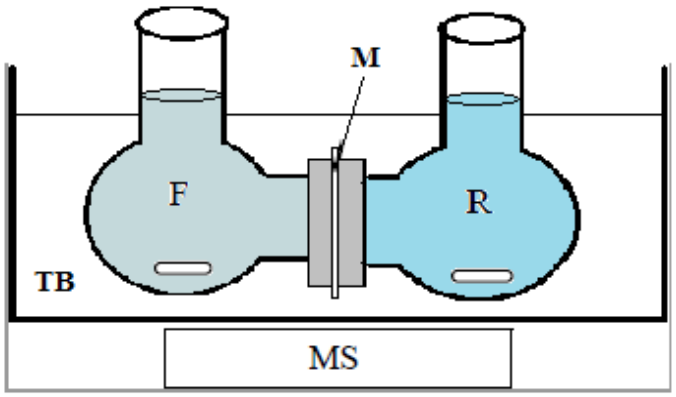

Fig.2: The cell for the facilitated transport through an SLM
M: SLM. F: feed phase. R: receiving phase. TB: thermostatic bath. MS: multi-magnetic stirrer

3-2. Calculation of the macroscopic and microscopic parameters:

a) Permeability *P* and flux *J*:

The membrane is placed between two compartments of the cell. A known volume of the substrate solution S with an initial concentration C_0, is introduced into the

source compartment and the same water volume is placed in the receiving phase compartment. We made several samples in the receiving phase at known time intervals. C_r is the substrate concentration in the receiving phase at time t, the concentration of substrate in the source phase at this time is $C_s = C_0 - C_r$. The equation that relates the flux J to C_r concentration of substrate S, is given by the relationship:

$$dCr/dt = J \times S/V \quad (1)$$

with S the membrane surface in contact with the source phase solution, V the receiving phase volume.

For a quasi-static state, the flux is related to the difference in concentrations of the two compartments.

$$J = P \times \Delta C / l \quad (2)$$

With, P membrane permeability and l the membrane thickness.

The slope (***a***) of the line $- \ln (C_0 - 2C_r) = f(t)$, gives the permeability P according to equation (3) (H. Hassoune)..

$$P = \boldsymbol{a} \times V \times l / 2S \quad (3)$$

b) Apparent diffusion coefficient *D and association constant K_{ass}.**

The facilitated transport of substrate S depends on the formation and dissociation of the substrate-carrier complex (TS) at the membrane-solution interfaces. The carrier T is insoluble in the aqueous phase while the substrate S is not soluble in the membrane organic phase.

We find that the macroscopic parameters ***P*** and $\boldsymbol{J_0}$ are proportional to the substrate initial concentration C_0, and have a Michaelis-Menten evolution, since for high substrate concentrations both parameters tend to limit values. In order to determine the microscopic parameters ***D**** and $\boldsymbol{K_{ass}}$, we use the Lineweaver-Burk method to linearize the expression of equation according to equation and draw the linear representation $1/J_0 = f(1 / C_0)$.

$$1/ J_0 = (l /D^*) \times [(1 / [T]_0 \times Kass) \times (1 / C_0) + (1 / [T]_0)] \quad (4)$$

$$\text{with: } K_{ass} = \text{intercept (OO)} / \text{slope (p)} \text{ and } D^* = (l / OO) * (1 / [T]_0) \quad (5)$$

3-3 Determination of activation parameters:

The flux ***J*** of the substrate S through the SLM, is related to the change in the source phase C_r concentration equation (1), this parameter varies with the temperature according to the Arrhenius relationship (D.J. Speed) given by equation (6) .

$$J_{(T)} = A_j \exp(-E_a/RT) \quad (6)$$

R is the gas constant (8.314 $J.mol^{-1}.K^{-1}$), A_J a constant (pre-exponential factor) whose value is proportional to the number of favourable interaction faces between the substrate and extractive agent (carrier), and $\boldsymbol{E_a}$ is the transition state activation energy

on the formation-dissociation reaction of complex (TS) at the membrane interfaces and in the SLM organic phase. After linearization we obtain:

$$\ln J_0 = -E_a / R * (1/T) + \ln A_j \qquad (7)$$

From the slope of the line ($\ln J_0 = f(1/T)$), we determine the E_a value. On the other hand, it is known from the activated complex theory, that $\boldsymbol{E_a}$ is related to the activation enthalpy ($\boldsymbol{\Delta H^{\#}}$) by the relation:

$$\boldsymbol{\Delta H^{\#}} = E_a - 2500 \quad (J.mol^{-1}) \text{ at } 298\ K \qquad (8)$$

While the activation entropy ($\boldsymbol{\Delta S^{\#}}$), is related to A_J constant by the equation:

$$\boldsymbol{\Delta S^{\#}} = R\,(\ln A_J - 30.46) \quad (J.K^{-1}.mol^{-1}) \text{ at } 298\ K \qquad (9)$$

4. Results and Discussions

4-1. Influence of the source phase acidity

a) Determination of the parameters: permeability *P* and the initial flux J_0:

Under the same experimental conditions, using the same SLM with the same carrier (methyl cholate), paracetamol transport was performed at different C_0 concentrations (C_0= 0.08M, 0.04M, 0.02M et 0.01M) of paracetamol in source phase, and for different acidities, pH = 1, 2, 2.5 or 3 (HCl). The experimental results verify the kinetic proposed model for this facilitated extraction process, and line segments represented by the graph of figure 3, shows the linear evolution of - ln ($C_0 - 2C_r$) terms versus time, provided by this model (H. Hassoune)

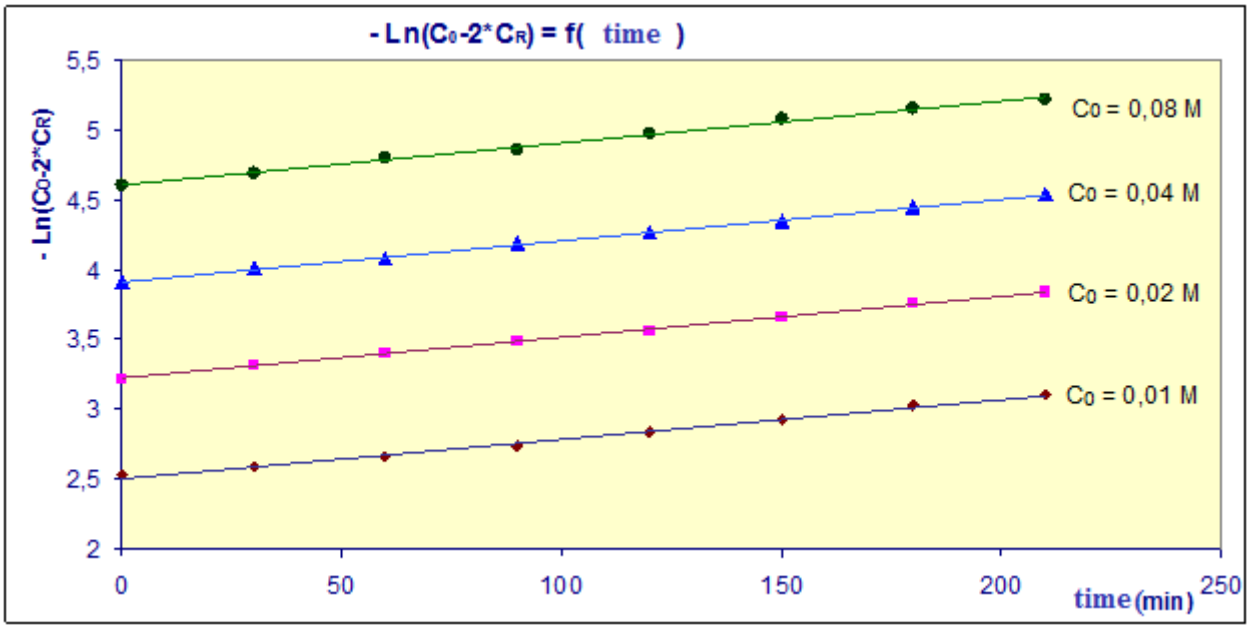

Fig 3: Representation of the straight -ln (C_0-$2C_r$) = f (time) paracetamol transport through the PVDF MLS and methyl cholate as a carrier to pH = 2 and T = 25°C

The slopes calculated from Fig. 3, according to equation 3, allow the determination of the permeability coefficients ***P*** and the initial flux $\boldsymbol{J_0}$.

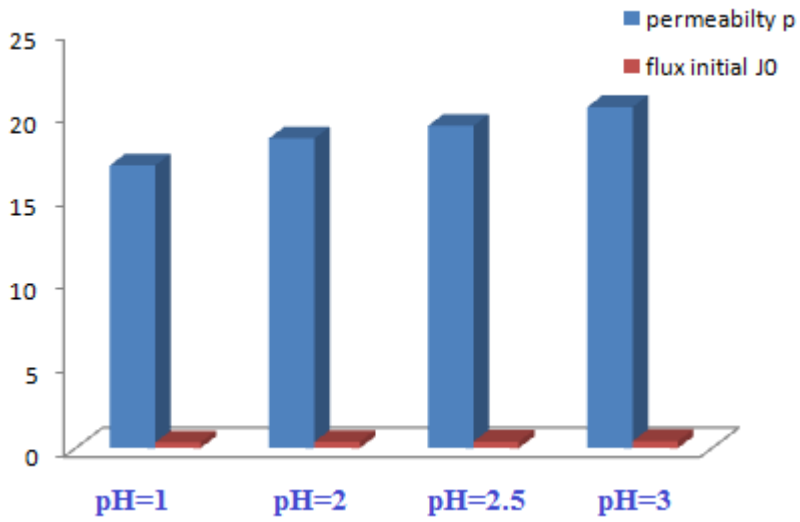

Fig 4 : permeabilty P and initial flux J_0

b) Determination of the macroscopic parameters:

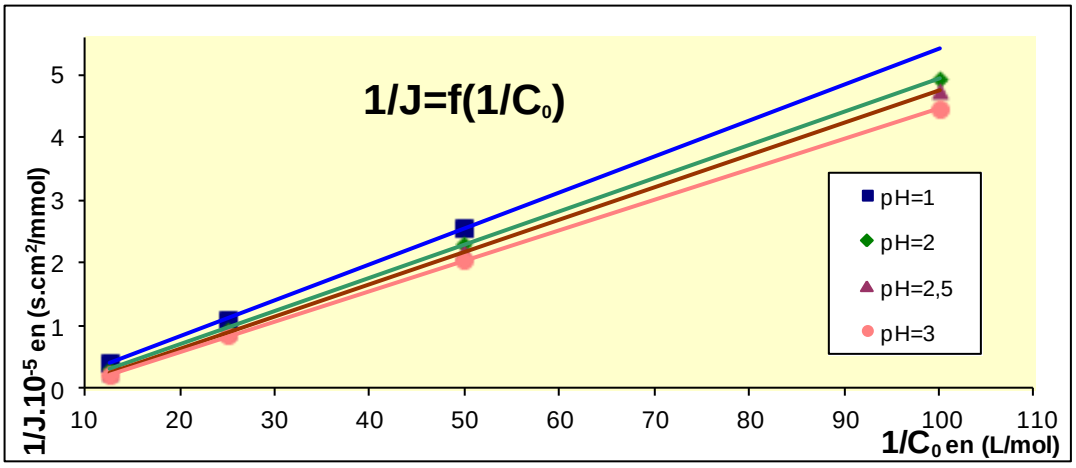

Fig. 5: The Lineweaver-Burk representation for the facilitated transport of pracetamol through the SLM, [MC] = 0.01 M, toluene phase and T = 298 K.

From these line segments (Fig. 5), slopes (*p*) and intercepts (*oo*) were calculated and using equation (5), the parameters ***D**** and K_{ass} were determined.

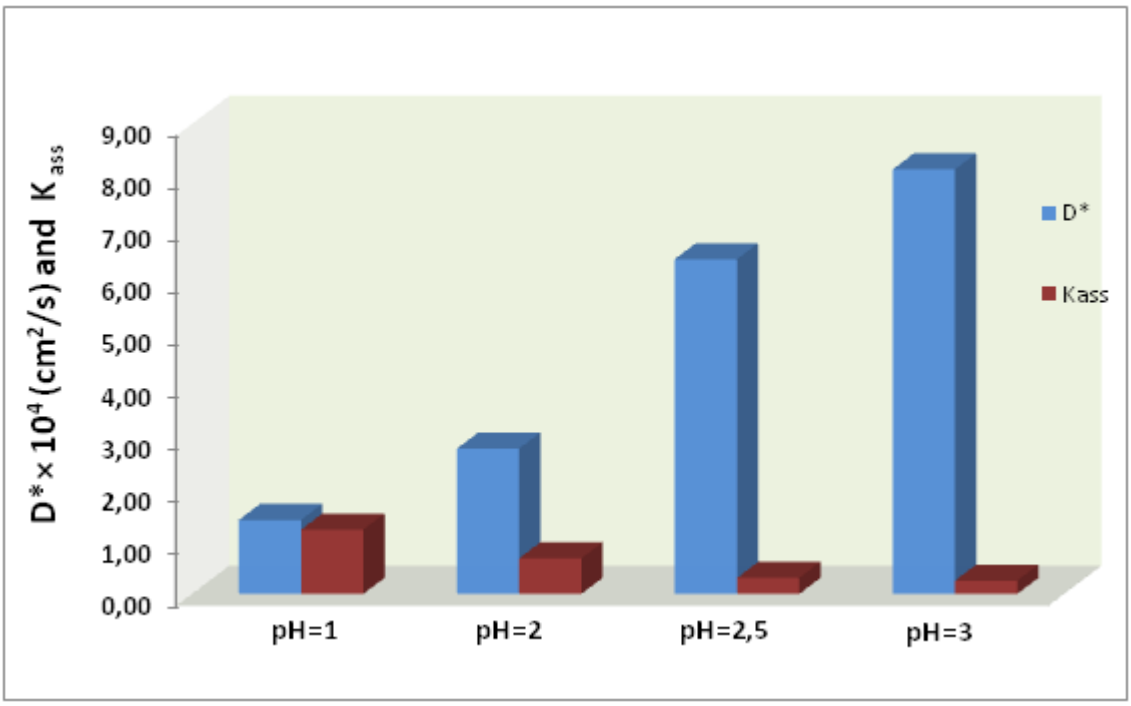

Fig (6): The representation of the evolution of microscopic parameters; the apparent diffusion coefficient ***D**** and the association constant K_{ass} to pH studied.

4-2 Influence of the temperature factor:

From the representation $Ln(J_0)$ versus 1/T (Figure (7)) we calculated the activation parameters in the facilitate extraction process of paracetamol through this membrane.

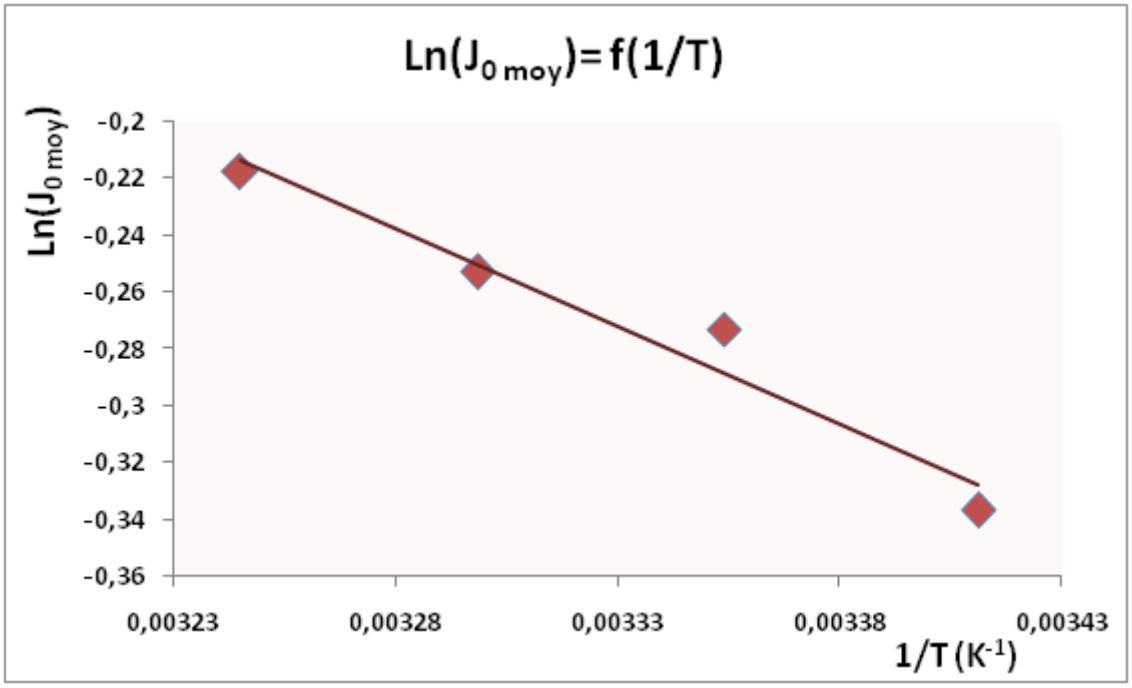

Fig. 7: Dependence of paracetamol fluxes on temperature obtained in facilitated extraction across the SLM**.**

- The activation energy: ***Ea***= 5,69 KJ/mol

-The activation enthalpy: $\Delta H^{\#}$ = 3,215 KJ/ mol

- The activation entropy: $\Delta S^{\#}$ = - 236 $J.mol^{-1}\ K^{-1}$

The low values E_a and $\Delta H^{\#}$ indicate that the transition state on the formation-dissociation reaction of the complex (*ST*) requires low energy. The negative value of $\Delta S^{\#}$ expresses a gain of order and therefore a real association between substrate and carrier in this transition state. (…)

5. Conclusion:

These studies showed that the lipophilic agent methyl cholate is very effective for the facilitated extraction process of paracetamol and the prepared SLM is very permeable for of the substrate for this oriented process (high values of macroscopic parameters ***P*** and J_0). The proposed mechanism allows the determination of the microscopic parameters ***Kass*** and ***D**** relating to the movement of paracetamol substrate through the membrane organic phase.. The obtained values show that the stability and diffusion of the substrate-carrier complex (*ST*) are closely related to the movement nature of the substrate in the organic phase of the SLM. The increase in

temperature rised the values of ***P, J_0*** and ***D****. Furthermore, this study identified the activation parameters (***E_a***, ***$\Delta H^{\#}$*** and ***$\Delta S^{\#}$***) that characterize the formation and the dissociation reactions of the complex (*ST*) at interfaces. The obtained values confirm the high permeability of the SLM and allow the determination of the mechanism of the substrate movement through the organic phase of the membrane. The diffusion of the substrate through the SLM is due to a series of reactions (formation/dissociation) and to successive jumps of substrate molecules from one carrier to another (T. ELJADDI)

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