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Cation transfer across a hydrogel/organic phase: Effect of cation size, hydrophobicity and acid–base properties

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ABSTRACT

The transfers of tetraethylammonium (TEA^+) and protonated trifluprom azine ($HTFP^+$) through a hydrogel/liquid interface (g/o) and a liquid/liquid interface (w/o) were compared using cyclic voltammetry. After the two phases were put in contact, the behavior of each molecule was analyzed at different pH values and at different time points. The gel induces hydrophobic and electrostatic interactions with TEA^+ and $HTFP^+$, shifting the peak potentials to more positive values. The diffusion coefficients, *D*, in both phases (g and w) at different pH values were calculated. In the case of TEA^+, the *D* value remains constant in both systems. However, the *D* value of $HTFP^+$ is lower in the gel phase than in the liquid phase.

$HTFP^+$ is transferred from the aqueous phase to the organic phase via a direct mechanism that involves coupled acid–base and partition processes. At the g/o interface, the coupled chemical reactions of $HTFP^+$ were inhibited by the drug/gel interaction. The results demonstrate that the g/o system could be used as a model to study the controlled release of charged drugs.

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1. Introduction

The use of voltammetry at liquid/liquid (w/o) interfaces has proven to be a valuable tool for obtaining thermodynamic [1–12] and kinetic [2,13–18] transport data for various drugs and for determining partition coefficients from the transfer potential; this type of data is very useful in many chemical and biological applications [19–21]. In the last past years, interesting modifications in the liquid/liquid interface design were introduced to overcome the instability that is inherent to the liquid/liquid interface [22–26]. One approach involved solidifying the interface by adding a gelling agent to either the aqueous phase or the organic phase.

Hydrogels are robust, three-dimensional, cross-linked structures that swell in water, and these materials have many potential applications [27–37]. These applications are closely related to the intrinsic properties of the polymeric networks [29,31–37], and two main characteristics of hydrogels should be emphasized: their chemical structures and the morphology of their networks. The former affects the hydrophilic/hydrophobic ratio of the gel, and consequently, its water retention and absorption capacity. In general, monomers and cross-linking agents with polar functional groups increase the hydrophilic nature of the gel. On the other hand, the morphology of the network exerts an influence on the mechanical and rheological properties because these properties are affected both by the stiffness or flexibility of segments between cross-links and by the density of the cross-links. When the gels are very hydrophilic, they typically contain a larger proportion of free and bound water, and the presence of this water can affect significantly the transport behavior inside the hydrogel [30,38].

Fantini et al. studied the transfer of β-blocker compounds across the water–agarose/1,2-dichloroethane interface and compared these results with those obtained across a conventional water/1,2-dichloroethane interface [22]. Tong et al. used a ligand in an organic phase to facilitate the transfer of K^+, and this research was directed towards microelectrodes applications [23]. Mareček et al. studied charge transfer across polymer gel/liquid interfaces for various applications [39–42] and evaluated the transfer of cations and anions across a poly(vinylchloride) and nitrobenzene gel/water interface using cyclic voltammetry. A shift of the half-wave potential was observed for the ion transfer in the presence of the gel, and the authors concluded that this shift was caused by a change in the diffusion coefficient of the ions in the gel phase [39]. In addition, Mareček et al. proposed that the concentration of ionophores in the organic phase could be determined quantitatively from the ion transfer current at an agar gel/nitrobenzene electrolyte interface [40]. Dvořák et al. investigated the transfer of different ions across a gel/liquid interface as a function of polymer concentration by cyclic voltammetry and equilibrium faradaic impedance measurements. Ion transfer rates were measured, and from these values, the authors were able to predict a decrease in the

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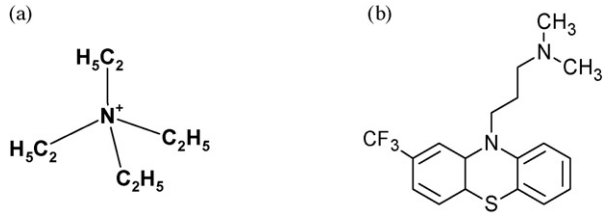

Fig. 1. The chemical structure of the molecules studied. (a) TEA^+ and (b) TFP.

amount of electrolyte present in the solution phase; the remaining electrolyte likely occupied sub-micrometer pores in the polymer matrix, either on the surface or in the bulk polymer. Dvořák et al. concluded that the ion transfer across a polymer gel/liquid boundary is as fast as that across a liquid/liquid boundary [43]. Other studies have focused on the transfer of several anions and cations through PVC membranes and have determined the diffusion coefficients and transfer potentials for these species [44].

Although several authors [22,23,33,43] have mentioned that the aqueous gel exerts no significant influence on the transport of drug at the gel/organic interface, a careful study of the nature of the drug in relation to the structure of the gel needs to be performed.

The aim of this paper is to study the effect of a hydrogel on the transport properties of TEA^+ and $HTFP^+$ through a hydrogel/1,2-dichloroethane (DCE) interface. These particular compounds were chosen for their molecular sizes and acid–base behaviors. Tetraethylammonium (TEA^+) carries a permanent positive charge, whereas triflupromazine (TFP) exhibits acid–base properties due to an amino group that has a pK_a value of 9.40 (Fig. 1). The electrochemical response of each of these compounds was compared to that obtained at a conventional water/1,2-DCE interface. The results of these studies will be informative for future research that involves using hydrogels as carriers for the controlled release of pharmaceutical drugs. Cyclic voltammetry enabled us to study the effect of the structural properties of the gel on the transport of the charged drugs in an easy and reliable manner.

2. Experimental

Voltammetric experiments at w/o or g/o interfaces were performed in a four-electrode system using a conventional glass cell with a 0.12 cm^2 interfacial area. Two platinum wires were used as counter-electrodes, and the reference electrodes were Ag/AgCl. The reference electrode in contact with the organic solution was immersed in an aqueous solution of 1×10^{-2} M tetraphenyl arsonium chloride (TPhAsCl) (Sigma).

The base electrolyte solutions were 1×10^{-2} M LiCl (Merck p.a.) in ultrapure water and 1×10^{-2} M tetraphenyl arsonium dicarbollyl cobaltate (TPhAsDCC) in 1,2-dichloroethane (1,2-DCE, Dorwil p.a.). The aqueous gel phase was prepared from poly(sodium acrylate – co-acrylic acid – co-vinyl alcohol), which was kindly supplied by PROMEDON S.A. The xerogel was swollen for 48 h in an aqueous solution that contained the base electrolyte and either TEA^+ or $HTFP^+$. The extended time period ensures maximum swelling of the gel. Thus, two different interfaces (w/o and g/o) were generated and compared.

TPhAsDCC was prepared by metathesis of tetraphenyl arsonium chloride (TPhAsCl, Sigma) and cesium dicarbollyl cobaltate (CsDCC, Lachema p.a.). The precipitate was recrystallized from a water–acetone mixture and then was dried in an oven at 30 °C for 2 days.

The pH of the aqueous or gel phase was adjusted within the range of 1.8–6.3 using different solutions: pH 1.8 (HCl), pH 3.6 ($HCOOH/HCOO^-$), pH 5.0 (H_3CCOOH/H_3CCOO^-) and pH 6.3 ($H_2PO_4^-/HPO_4^{2-}$).

The equilibrium volume swelling ratios, q_v, were determined by calculating the ratio between the volumes of samples in the swelling equilibrium state (v_{sw}) and in the dry state (v_{dry}). The q_v values were obtained with graded tubes after the samples had been soaked for 48 h in different buffer solutions.

Analytical grade tetraethylammonium chloride (TEACl) and triflupromazine hydrochloride (HTFPCl) were used as received from Sigma and were dissolved in an aqueous phase to a final concentration of 5×10^{-4} M. All experiments were performed at room temperature.

The electrochemical cell that was used is depicted below:

$$|Ag|AgCl|TPhAsCl1 \times 10^{-2}\,M(w)|TPhAsDCC1 \times 10^{-2}\,M(o)|LiCl1 \times 10^{-2}\,MTEA^+/HTFP^+5 \times 10^{-4}\,M(worg)|AgCl|Ag|$$

Cyclic voltammograms were recorded using a potentiostat, which eliminates the *iR* drop automatically by means of periodic current-interruption technique, and LyP Electronica Argentina waveform-generator. Voltammograms were recorded with a 10-bit computer board acquisition card that was connected to a personal computer. IR spectra were recorded on a FT-IR Nicolet 5-SXC.

3. Results and discussion

3.1. Gel-phase structural properties

As expected, the IR spectrum of the poly(sodium acrylate – co-acrylic acid – co-vinyl alcohol) showed the presence of carboxyl and hydroxyl groups. The q_v values were determined in aqueous solutions of different pHs in the presence and absence of LiCl to compare the changes in swelling when the base electrolyte (required for the electrochemical measurements) was added. Table 1 shows the q_v values that were obtained. In the absence of LiCl, the q_v values increased with increasing pH; this result is due to the progressive ionization of the carboxylic acid groups in the polymeric network. In the presence of LiCl, the q_v values remained almost invariant with pH. From these results, it is clear that the swelling behavior is strongly affected by both the pH (Table 1, entry a) and the ionic strength (Table 1, entry b) [45,46]. The latter phenomenon is commonly found in ionic hydrogels and is often attributed to a screening effect exerted by the counter ions; this screening effect limits the extent of swelling. At high and low pHs, the high ion concentrations result in high ionic strengths. When the ionic strength of the solution is increased, the difference in osmotic pressure between the hydrogel and the medium decreases, and thus, the swelling capacity of the hydrogel decreases [45].

Therefore, in these experiments, the capacity for water retention was considered to be high and constant at the three pH values. This factor is important because the transport mechanisms are dependent on the presence of free and bound water in the gel.

3.2. TEA^+ transfer through w/o and g/o interfaces

The transfer of TEA^+ across the w/o interface has been studied extensively, and it occurs through a direct, reversible and diffusion-controlled mechanism without any coupled reactions (Eq. (1)):

$$TEA^+_{(w)} \rightleftarrows TEA^+_{(o)} \quad (1)$$

Table 1
Swelling ratio values of poly(acrylate – acrylic acid – vinyl alcohol) at different pH.

	q_v		
pH	1.8	3.6	5.0
(a) Buffer (C_a: 1×10^{-2} M)	85.0	100.0	110.0
(b) Buffer + LiCl (C_a: 1×10^{-2} M + C_{LiCl}: 1×10^{-2} M)	85.0	85.0	80.0

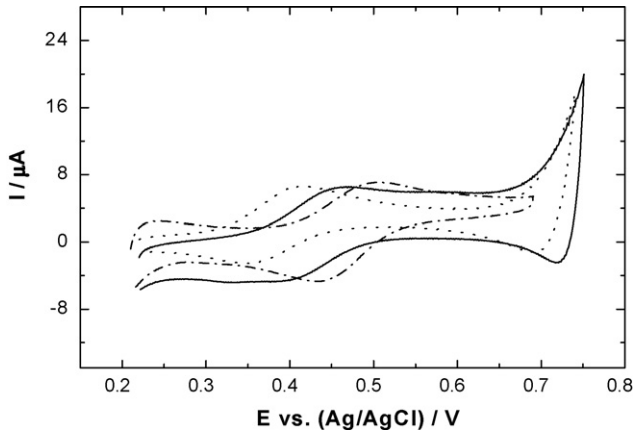

Fig. 2. The cyclic voltammogram of the TEA^+ transfer in g/o and w/o systems. Aqueous phase composition (Apc): (. . .) TEA 5×10^{-4} M, LiCl 1×10^{-2} M, pH 1.8; (–) hydrogel, TEA 5×10^{-4} M, LiCl 1×10^{-2} M, pH 1.8; (- -) hydrogel, TEA 5×10^{-4} M, LiCl 1×10^{-2} M, pH 5.0. Organic phase composition (Opc): TPhAsDCC 1×10^{-2} M. $\nu = 0.025\,V\,s^{-1}$.

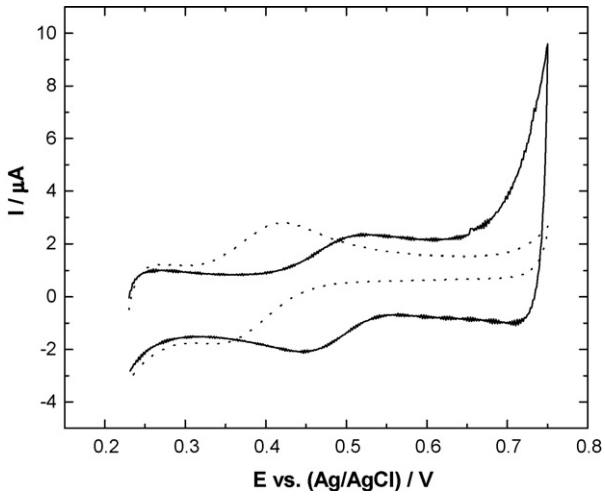

Fig. 3. The cyclic voltammogram of the $HTFP^+$ transfers in g/o and w/o systems. Apc: (. . .) $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M, pH 3.6 and (–) hydrogel, $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M, pH 3.6. Opc: TPhAsDCC 1×10^{-2} M. $\nu = 0.050\,V\,s^{-1}$.

Fig. 2 shows typical voltammograms that correspond to the transfer of TEA^+ across the w/o and g/o interfaces at different pH values. In the case of the w/o system, the peak potential (0.410 V) is constant within the whole pH range studied, and the peak current is proportional to the TEA^+ concentration. In the g/o system, the peak potential shifts towards more positive values. This shift is more pronounced at high pH values ($E_p^+ = 0.463$ V at pH = 1.8, and $E_p^+ = 0.507$ V at pH = 5.0). This shift indicates that the interactions between TEA^+ and the gel phase become stronger as the pH increases. Two different driving forces for the attraction or repulsion between the compounds and the gel phase have been proposed: hydrophobic interactions and electrostatic interactions. The former are always present, but the latter are stronger at higher pH since the carboxylic groups of the acrylic acid co-monomer are negatively charged (pK_a = 4–4.5 [47]), which increases the attractive forces with the positively charged TEA^+ molecules.

By analyzing the variation of the voltammetric parameters (I_P^+, ΔE_p and E_p^+) with the sweep rate, it was possible to establish that the transfer process is reversible and diffusion-controlled for both systems. The diffusion coefficient calculated from plots of I_P^+ versus $\nu^{1/2}$ [48] was equal to $7.20 \times 10^{-6}\,cm^2\,s^{-1}$ for both interfaces (Table 2); this value is in good agreement with reported values [49–51]. Therefore, we conclude that the gel does not affect the diffusion rate of TEA^+, but the attractive electrostatic interactions affects the Gibbs energy of transfer.

3.3. $HTFP^+$ transfer through w/o and g/o interfaces

Triflupromazine is a weak base (pK_a = 9.40) with a high partition coefficient ($\log P_{neutral} = 2.24$; $\log P_{ionized} = 0.54$) [20], and therefore, it is a fairly hydrophobic molecule. This drug undergoes a protonation reaction in the aqueous phase prior to the transfer across the interface (Eqs. (2) and (3)):

$$TFP_{(w)} + H^+_{(w)} \rightleftarrows HTFP^+_{(w)} \quad (2)$$

$$HTFP^+_{(w)} \rightleftarrows HTFP^+_{(o)} \quad (3)$$

Fig. 3 shows the voltammograms for the $HTFP^+$ transfer through w/o and g/o interfaces at pH 3.6. In this case, a positive shift in potential was observed when the gel was used in place of the aqueous phase.

Fig. 4 shows the differences between peak potentials obtained in the g/o and w/o interface ($E^+_{p(g)} - E^+_{p(w)}$), for the $HTFP^+$ and TEA^+ transfers at pH values of 1.8 and 5.0, versus potential sweep rate. The highest shift was obtained for $HTFP^+$ at pH 5.0.

In the pH range that was studied, E_p^+ and ΔE_p were independent of ν, and I_P^+ had a linear relationship with $\nu^{1/2}$, confirming that the transfer process is reversible and diffusion-controlled in both cases.

The diffusion coefficients for all systems are summarized in Table 2. These values were obtained from the slope in plots of I_P^+ versus $\nu^{1/2}$. For $HTFP^+$ in the presence of the gel, the diffusion coefficients were lower compared to the values obtained in water. In contrast, the values are almost constant for TEA^+. This behavior may

Table 2
D values calculated from the slope of I_p versus $\nu^{1/2}$ plots of TEA^+ and $HTFP^+$ in aqueous and gel phase, respectively.

Compound	pH	D in water (D_w) $cm^2\,s^{-1}$	D in gel (D_g) $cm^2\,s^{-1}$	D_w/D_g
TEA^+	1.8	7.25×10^{-6}	7.10×10^{-6}	1.02
	5.0	7.20×10^{-6}	7.20×10^{-6}	1.00
$HTFP^+$	1.8	8.40×10^{-7}	5.50×10^{-7}	1.53
	3.6	8.50×10^{-7}	5.40×10^{-7}	1.57
	5.0	8.50×10^{-7}	5.50×10^{-7}	1.55

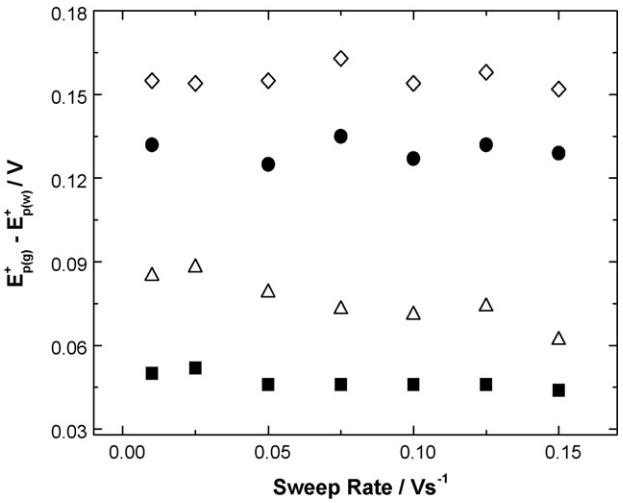

Fig. 4. The differences in E_p^+ in g/o and w/o systems versus potential sweep rate (ν) for TEA^+ and $HTFP^+$ at different pH values: (■) TEA, pH 1.8; (△) TEA, pH 5.0; (●) $HTFP^+$, pH 1.8; (◊) $HTFP^+$, pH 5.0.

be attributed to size differences between the two compounds, as will be discussed below.

Moreover, these results also indicate that the D values remain constant across a broad pH range.

3.4. Time analysis of $HTFP^+$ and TEA^+ transfers

The results shown above indicate that the nature and physicochemical properties (e.g., size, acidity and hydrophobicity) determine the transport behavior of each compound in the gel phase. The TEA^+ transfer mechanism is the same at w/o and g/o interfaces (Eq. (1)). In addition, the presence of the gel does not affect the diffusion of the drug. On the other hand, $HTFP^+$ suffers an acid–base reaction in the aqueous phase, and the neutral species (TFP) exhibits a high partition coefficient. The w/o partition can occur when both phases (aqueous and organic) are brought into contact before applying the potential sweep:

$$HTFP^+_{(w)} \rightleftarrows TFP_{(w)} + H^+_{(w)} \quad (4)$$

$$TFP_{(w)} \rightleftarrows TFP_{(o)} \quad (5)$$

The deprotonation and partition equilibria compete with the electrochemical transfer process of $HTFP^+$. These coupled reactions become more important as the pH increases. To evaluate the extent of these competitive processes, the voltammograms corresponding to the transfer of $HTFP^+$ from the aqueous (or gel) phase to the organic phase were recorded at pH = 6.3 and were monitored over time (beginning from when the two phases were put in contact). Fig. 5 shows the variation of I_P^+ over time for both systems (w/o and g/o). A current decrease is observed for the transfer of $HTFP^+$ from the aqueous phase to the organic phase. This change could be due to a decrease in the $HTFP^+$ concentration at this pH value, as expected from reactions (4) and (5). It is important to note that this effect is not observed at lower pH values. The figure also indicates that the transfer of $HTFP^+$ changes substantially in the presence of the gel: the decrease in current is delayed when the gel is present. This delay could be ascribed to drug–gel interactions that prevent the partitioning of TFP in the organic phase (Eq. (5)).

In addition, no changes in I_P^+ versus time were observed for the transfer of TEA^+ when either an aqueous or a gel phase was employed (data not shown).

3.5. Dependence of transfer potential with pH

Fig. 6 shows the variation of the peak potential (E_p^+) with pH for the transfer of $HTFP^+$ in g/o and w/o systems. The values of E_p^+ are markedly higher in the presence of the gel, and the values become more positive with increasing pH. This behavior could be associated with a change in the energy required for the transfer of $HTFP^+$ as a consequence of the strong gel–drug interaction.

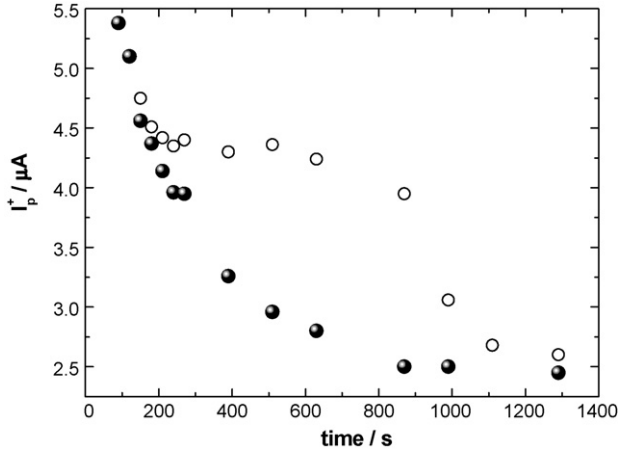

Fig. 5. A plot of I_P^+ versus time for the $HTFP^+$ transfer. Apc: (●) $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M and (○) hydrogel, $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M, pH 6.3. Opc: TPhAsDCC 1×10^{-2} M. $\nu = 0.050\,V\,s^{-1}$.

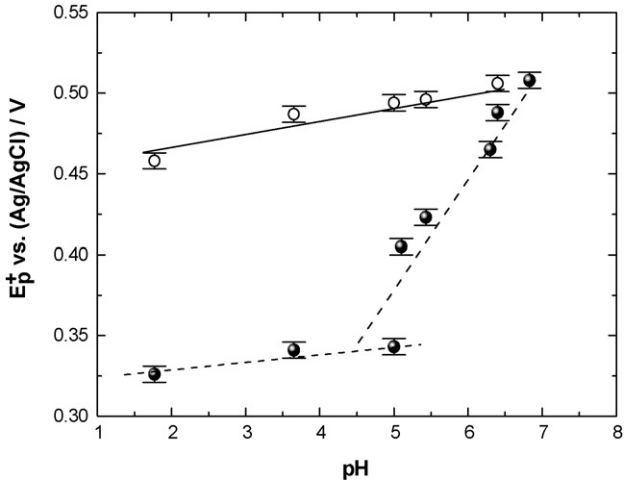

Fig. 6. A plot of E_p^+ versus pH for the $HTFP^+$ transfer. Apc: (●) $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M and (○) hydrogel, $HTFP^+$ 5×10^{-4} M, LiCl 1×10^{-2} M. Opc: TPhAsDCC 1×10^{-2} M.

It is worth commenting on the differences observed at pH > 5.0 in Fig. 6. In the w/o system, E_p^+ is constant up to pH 5.0 and, from there, increases sharply with a slope equal to 0.060 V per pH unit. Such behavior could be due to the change in the transfer mechanism from direct (pH ≤ 5.0) to facilitated (pH > 5.0) transfer, as suggested by the ionic partition diagram described by Gobry et al. [52]. In the latter case, after Eqs. (4) and (5) occur, the following process could take place:

$$TFP_{(o)} + H^+_{(w)} \rightleftarrows HTFP^+_{(o)} \quad (6)$$

However, it is important to emphasize that this mechanism does not occur in the presence of the gel because Eqs. (4) and (5) are inhibited by the drug–gel interaction.

4. Conclusions

The results reported in this paper confirm that the gel induces hydrophobic and electrostatic interactions with TEA^+ and $HTFP^+$, thereby increasing the Gibbs energy of transfer. However, the presence of the gel affects the $HTFP^+$ diffusion coefficient, but no changes in D were observed for the smaller molecule TEA^+.

From the analysis of I_P^+ as a function of time, it was possible to conclude that the kinetics of the reaction was not affected by the presence of the gel in the case of the TEA^+ transfer. However, for the $HTFP^+$ transfer, the coupled chemical reactions were inhibited due to strong interactions between $HTFP^+$ and the gel. Similar conclusions can be drawn from the variation of E_p^+ with the pH.

Concerning the effect of the gel on the D values, we must consider the different mechanisms of molecular diffusion within the gel. The diffusion of small molecules can be explained in terms of the pore mechanism, which could occur by solute diffusion via bulk-like water regions that are present in the microchannels or in the pores [27]. This latter mechanism is operative with TEA^+, where the gel exerted no effect on the D values at any pH. Indeed, the swelling ratio values (obtained in a buffer containing LiCl) were not altered by the pH, indicating that both the capacity for water retention and the pore size of the gel are constant. On the other hand, the "partition" or "solution diffusion" mechanism takes place with $HTFP^+$. For this molecule, the diffusion could occur via dissolution and diffusion of the solute into segments of the polymer matrix. In

this case, the interactions between the drug and the polymer would determine the diffusion rate. The analysis of the D values obtained in the presence and absence of the polymer allow us to conclude that significant interactions take place and slow the diffusion process. Nevertheless, similar D values are obtained across a broad pH range. This behavior can be explained taking into account the different interactions at different pH values. At low pH values, the polar groups of the gel are not ionized, so the gel exhibits lipophilic character and a higher affinity for the hydrophobic region of $HTFP^+$. In other words, hydrophobic interactions predominate when the pH is below 5.0. On the contrary, at pH values above 5.0, the gel is negatively charged, and electrostatic interactions with $HTFP^+$ are important. Therefore, both hydrophobic and hydrophilic interactions affect the diffusion rate with similar magnitudes. However, the pore sizes remained constant at the three pH values analyzed, as can be deduced from the q_v values shown in Table 1, suggesting that the constant D values are a result of hydrophobic interactions, hydrophilic interactions, and similar pore sizes.

These results demonstrate that cyclic voltammetry at a g/o interface is an important tool for studying the transfer mechanism of pharmaceutical compounds in a gel network. The types of interactions that are observed are closely related to the chemical structure and behavior of the drug. These interactions affect transfer and diffusion processes, and therefore, they are especially interesting for studying the controlled release of drugs.

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