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Original scientific paper

Electrochemical study of olanzapine transfer across the water/1,2-dichloroethane interface

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Abstract

This study investigates the electrochemical transfer of olanzapine (OLP) across the interface between two immiscible electrolyte solutions using a water/1,2-dichloroethane system. Electrochemical experiments were performed using cyclic voltammetry and square-wave voltammetry analysis in a four-electrode electrochemical cell. The results revealed a reversible ion-transfer process of the protonated species OLPH⁺, with a half-wave transfer potential of 0.184 V on the Galvani potential scale. Voltammetric analysis demonstrated that the ion-transfer process was diffusion-controlled, as evidenced by the linear dependence of the peak current on both the square root of the scan rate and the OLP concentration. Based on the experimental data, the formal Gibbs energy of transfer was determined to be 17.75 kJ mol⁻¹, and the ionic partition coefficient was calculated to be -3.11, indicating the semihydrophobic character of the drug. Furthermore, capacitance studies showed that the breakdown of the electrical double layer occurs at the same transfer potential as that determined by voltammetric techniques, confirming the faradaic nature of the ion-transfer process.

Keywords

Thienobenzodiazepine derivative; immiscible electrolyte solutions (ITIES); voltammetry techniques; ion transfer; ionic partition coefficient; Galvani transfer potential

Introduction

The interface between two immiscible electrolyte solutions (ITIES), also known as the liquid/liquid or water/oil interface, consists of two solvents with limited mutual miscibility, typically an aqueous phase and an organic phase with moderate-to-high dielectric permittivity [1]. Owing to its unique physicochemical properties, the ITIES has become an important electrochemical platform

for investigating ion-transfer processes and for the analytical determination of a broad range of species, including metal ions, proteins, neurotransmitters, and pharmaceutical compounds [2].

Unlike conventional metal/electrolyte (M/E) systems, where electrochemical reactions occur at solid electrode surfaces and frequently require electrode modification to improve analytical performance, ITIES enables the direct investigation of ion transfer across the liquid/liquid interface without chemical modification of the sensing interface. The fundamental faradaic processes at the ITIES involve either ion transfer between the two liquid phases or electron transfer between the redox couples dissolved in each phase, providing mechanistic information complementary to that obtained using conventional solid electrodes [1,3].

The transfer of ionic species across the ITIES is commonly interpreted using Marcus' theory, in which an ion undergoes partial desolvation as it approaches the interface, followed by concerted resolution in the adjacent phase [3]. The energetics and kinetics of this process are governed by the chemical nature of the transferring ion, the interfacial Galvani potential difference, and the relative solvation energies in both phases. Consequently, the ITIES has become an attractive model system for studying the fundamental aspects of ionic transport, while also providing valuable insights into biological membrane transport, solvent extraction, phase-transfer catalysis, and electroanalytical sensing [4].

The first studies involving immiscible liquid interfaces were reported by Nernst and Riesenfeld in 1902, who investigated the transport of coloured salts across a water/phenol/water interface [5]. Since then, significant advances have been made in experimental methodologies, particularly in the development of potentiostatically controlled three- and four-electrode cells. The four-electrode configuration introduced by Samec *et al.* [6] enabled accurate control of the Galvani potential difference across the ITIES, greatly improving the precision, reproducibility, and quantitative interpretation of ion-transfer measurements [7,8].

Electrochemical investigations of pharmaceutical compounds have traditionally focused on the oxidation and reduction processes occurring at solid electrodes, yielding valuable information on the reaction mechanisms, structure-activity relationships, mass transport, and electrocatalytic behaviour [9]. By contrast, studies performed at the ITIES provide direct information on the partitioning and transfer of ionisable drugs between aqueous and organic media, making this approach particularly relevant as a biomimetic model for biological membranes. Numerous pharmacologically and environmentally relevant compounds have been investigated using ITIES, including trimetazidine [10], opioids [11], cocaine metabolites [12], quinine [13], clozapine [14] and other benzodiazepine drugs [15], acetylcholine and cephalosporins [16,17]. Electroanalytical methods for the rapid detection of drugs associated with sexual assaults have recently been reviewed [18].

Olanzapine (OLP), an atypical antipsychotic belonging to the thienobenzodiazepine family, is widely used in the treatment of schizophrenia, bipolar disorder, and other psychotic illnesses (Figure 1). Its pharmacological activity is primarily associated with its high affinity for serotonin (5-HT₂) and dopamine (D₂) receptors, exhibiting a serotonin-to-dopamine receptor binding ratio that distinguishes it from many other antipsychotic agents. Chemically, olanzapine is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-*b*][1,5]benzodiazepine (C₁₇H₂₀N₄S; molecular weight 312.44 g mol⁻¹) [19]. Because OLP is a weakly basic compound, its protonation state strongly influences its lipophilicity and transport across biological membranes, making it an excellent candidate for charge-transfer studies at the ITIES.

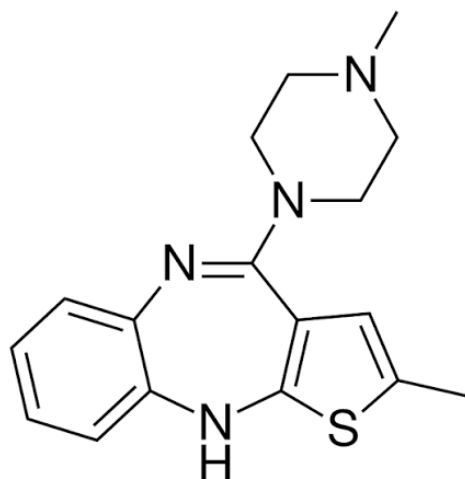


Figure 1. Chemical structure of OLP

Despite the extensive pharmacological importance of OLP and the numerous electrochemical studies performed on solid electrodes, its charge transfer behaviour at the ITIES has received little attention. A quantitative understanding of its interfacial transfer thermodynamics and electrochemical characteristics is essential for elucidating its partitioning behaviour and expanding the application of ITIES-based methodologies in pharmaceutical analysis. In this study, the electrochemical transfer of protonated OLP across a water/1,2-dichloroethane (1,2-DCE) interface was investigated by cyclic voltammetry (CV), square-wave voltammetry (SWV), and capacitance analysis using a four-electrode electrochemical cell. The formal transfer potential, Gibbs energy of transfer, ionic partition coefficient, and interfacial capacitance were determined to establish the thermodynamic and kinetic characteristics of ion transfer at the water/1, 2-DCE interface.

Experimental

All reagents were of analytical grade. Spectrophotometric-grade 1,2-DCE (Sigma-Aldrich, 99%) and triple-distilled water (Jalmek, Mexico) were used as solvents. Tetraphenylarsonium tetrakis(4-chlorophenyl)borate (TPAsTPBCl, Sigma-Aldrich) was used as the supporting electrolyte in the organic phase, and hydrochloric acid (Sigma-Aldrich) was employed in the aqueous phase. Tetraphenylarsonium chloride (TPAsCl; Sigma-Aldrich) was used as the reference electrolyte for the organic phase. Olanzapine (99 % purity) was purchased from Sigma-Aldrich.

TPAsTPBCl was prepared by precipitation of equimolar solutions of potassium tetrakis(4-chlorophenyl)borate (KTPBCl) and TPAsCl. KTPBCl was dissolved in acetone, and TPAsCl was dissolved in water. The two solutions were mixed to produce a colourless precipitate, which was subsequently filtered and dried to obtain TPAsTPBCl as the supporting electrolyte.

Electrochemical measurements were performed in a four-electrode electrochemical cell using two platinum counter electrodes (99.99 % purity, Sigma-Aldrich) and two Ag/AgCl reference electrodes. CV, SWV and capacitance studies were performed using a Reference 620 potentiostat/galvanostat (Gamry Instruments, USA), and data acquisition was performed using Gamry Framework software. All experiments were conducted in Faraday cages at room temperature (25 °C).

The cell configuration is shown in Figure 2, where Ag/AgCl₁ and Ag/AgCl₂ are the reference electrodes located in the organic and aqueous phases, respectively; α denotes the liquid-liquid interface of interest and @ represents the concentration of OLP. The contact area between the two liquids was 0.35 cm².

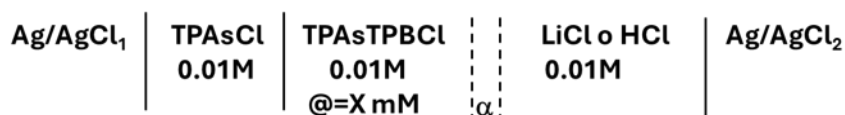


Figure 2. Schematic representation of the cell configuration

The Galvani potential differences ($\Delta_o^w \phi$) across the water/organic solvent (water/1,2-DCE) interface were determined according to Equation (1):

$$\Delta_o^w \phi = E + \Delta_o^w \phi_{\text{TPAs}^+} \quad (1)$$

where E denotes the potential applied by the potentiostat and $\Delta_o^w \phi_{\text{TPAs}^+}$ is the Galvani transfer potential of TPAs⁺ across the water/1,2-DCE interface, and the calculated value is 0.394 V.

Results and discussion

As shown in Figure 2, the dashed trace represents the baseline response of the supporting electrolyte. A wide potential window, extending from -0.35 to 0.55 V on the Galvani potential scale, was obtained. Within this potential range, an ideal polarisable region was observed. This potential window was primarily governed by the presence of TPAsTPBCl in the 1,2-DCE phase and HCl in the aqueous phase.

In the organic phase, TPAsTPBCl dissociates as follows at Equation (2):



where TPAs⁺ and TPBCl⁻ are the cation tetraphenylarsonium and anion tetrakis(4-chlorophenyl)-borate, respectively, and Equation (3) occurs in the aqueous phase:



As the potential scan shifted toward more positive values, the aqueous phase became more positive than the organic phase. Consequently, the current observed at the positive limit of the potential window is attributed to the transfer of TPBCl⁻ (0.44 V) from the organic phase to the aqueous phase. Simultaneously, although unresolved in the voltammogram, H⁺ (approximately 0.48 V) is transferred from the aqueous phase to the organic phase. Upon reversal of the potential scan toward less positive potentials, both ions return to their original phases. As the potential scan reaches more negative values, the voltammogram exhibits a current response associated with the transfer of TPAs⁺ (-0.22 V) from the organic phase to the aqueous phase, as the aqueous phase becomes more negative relative to the organic phase. Likewise, Cl⁻ (approximately -0.26 V) is transferred from the aqueous phase to the organic phase.

When OLP was added to the organic phase after 20 min of equilibration, its pK_a was assumed to be 7.8 [20]. Therefore, at pH 2.0, OLP is expected to be quantitatively protonated. In addition, the equilibrium established in the water/1,2-DCE system is described by Equation (4):



where OLP_o and OLP_w denote the neutral forms of OLP in the organic and aqueous phases, respectively. Similarly, OLPH_w⁺ and OLPH_o⁺ represent the protonated forms of OLP in the aqueous and organic phases, respectively, and H_w⁺ is a proton in the aqueous phase. Upon polarisation of the system, as shown by the solid trace in Figure 3, a positive current peak appears at 0.210 V, approximately in the middle of the potential window, indicating the transfer of OLPH⁺ from the aqueous phase to the organic phase. As can be seen, the OLPH⁺ transfer process is well resolved from the response of the supporting electrolyte (baseline). When the potential scan is reversed, a corresponding negative current peak is observed at 0.159 V, indicating the back-transfer of OLPH⁺ from the organic to the aqueous phase.

The separation between the anodic and cathodic peak potentials was 0.057 V, which, according to the Nernst equation, is consistent with the transfer of a single positive charge. This value is in close agreement with the theoretical value of 0.059 V predicted using the Nernst equation. Furthermore, the ion-transfer process is characterised by a formal half-wave transfer potential $\Delta_o^w \phi_{1/2}$ of 0.184 V at the water/1,2-DCE interface.

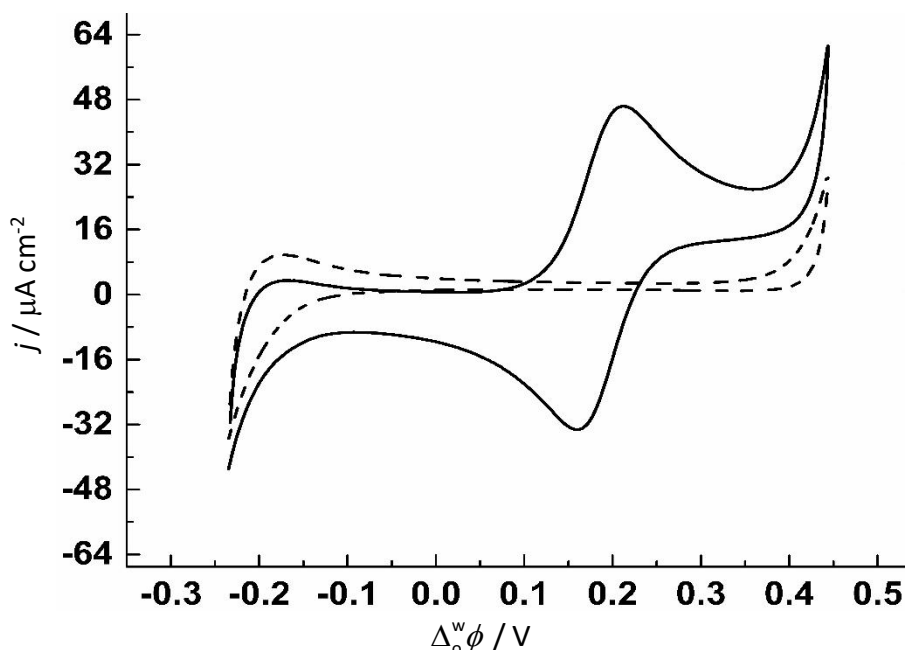


Figure 3. CV of the transfer of OLP (0.05 mM) across the water-1,2-DCE interface. The baseline corresponds to a solution containing 0.01 M TPAsTPBCl in the organic phase and 0.01 M HCl in the aqueous phase. Scan rate: 50 mV s⁻¹

The value of $\Delta_o^w \phi_{1/2}$ obtained from the CV experiments was used to calculate the formal Gibbs energy of transfer ($\Delta_o^w G_{tr,OLPH^+}^{\theta,w \rightarrow o}$) of OLP⁺ at the water/organic interface. This approach is based on the equilibrium established for ion transfer across the liquid-liquid interface as described in Equation (5) [21]:

$$\Delta_o^w \phi_{1/2} = \Delta_o^w \phi^\theta + \frac{RT}{zF} \ln \frac{a_{OLPH^+}^o}{a_{OLPH^+}^w} = \Delta_o^w \phi_{OLPH^+}^\theta + \frac{RT}{zF} \ln \frac{c_{OLPH^+}^o}{c_{OLPH^+}^w} \quad (5)$$

where $\Delta_o^w \phi^\theta$ is the standard Galvani potential difference at the water/1,2-DCE interface; $c_{OLPH^+}^w$ and $c_{OLPH^+}^o$ are the activities of OLP⁺ in the aqueous and organic phases, respectively; and $z = 1$. In addition, $\Delta_o^w \phi_{OLPH^+}^\theta$ is the formal transfer potential at the water/1,2-DCE interface, while $c_{OLPH^+}^w$ and $c_{OLPH^+}^o$ are the concentrations of OLP⁺ in the aqueous and organic phases, respectively.

Under equilibrium conditions, the relationship can be expressed by Equation (6):

$$\Delta_o^w \phi_{1/2} = \Delta_o^w \phi_{OLPH^+}^\theta \quad (6)$$

Consequently, the formal Gibbs energy of transfer can be determined using equation (7):

$$\Delta_o^w G_{tr,OLPH^+}^{\theta,w \rightarrow o} = zF \Delta_o^w \phi_{OLPH^+}^\theta \quad (7)$$

where z is the ion charge and F is the Faraday constant.

$\Delta_o^w G_{tr,OLPH^+}^{\theta,w \rightarrow o}$ represents the degree of hydrophobicity of the ionic species in the ITIES system. In this case, the formal Gibbs energy of transfer was calculated as 17.75 kJ mol⁻¹. Therefore, OLP⁺ is a hydrophobic drug requiring considerable energy for ion transfer. This behaviour was expected owing to the high octanol-water partition coefficient ($\log P = 3.0$) [20]. In comparison with other compounds studied at the water|1,2-DCE interface, such as atrazine (19.87 kJ mol⁻¹), ametryn

(6.17 kJ mol⁻¹), and terbutryne (2.70 kJ mol⁻¹), OLPH⁺ exhibits a significantly higher Gibbs energy of transfer [22]. A comparison with other compounds previously studied at the water|1,2-DCE interface showed that OLPH⁺ exhibited a relatively high standard Gibbs energy of transfer, indicating that a significant amount of energy is required for its transfer from the aqueous phase to the organic phase. Among the compounds considered, only atrazine presented a higher Gibbs energy transfer, whereas ametryn and terbutryne showed lower values. Although OLP is a more hydrophobic molecule according to its log *P*, the transfer of ionic species in ITIES is governed by not only hydrophobicity but also factors such as ion desolvation, charge distribution, molecular size, and specific solute-solvent interactions. The higher Gibbs transfer energy of atrazine is consistent with its lower hydrophobicity and smaller molecular structure.

The standard ionic partition coefficient ($\log p^{\theta}_{\text{OLPH}^+}$) at the water/1,2-DCE interface can be calculated using Equation (7):

$$\log p^{\theta}_{\text{OLPH}^+} = -\frac{\Delta_o^w G^{\theta, w \rightarrow o}_{\text{tr,OLPH}^+}}{2.3RT} \quad (7)$$

The calculated result (-3.1) indicates that the OLPH⁺ shows an intermediate affinity for the organic phase. Although the ionic partition coefficient remained negative, it was considerably higher than those reported for other compounds such as amines and amino acids, reflecting the relatively hydrophobic nature of OLPH⁺. This behaviour is due to the presence of aromatic and hydrophobic moieties in the OLP structure, which enhance its tendency to partition into the organic phase, despite its positive charge [23,24].

Figure 4 shows the transfer of OLPH⁺ at a constant concentration (0.2 mM) recorded at varying scan rates. Both positive and negative peak currents, corresponding to the transfer of OLPH⁺ across the interface, remained at the same peak potential over the entire range of scan rates investigated. This behaviour indicates that OLPH⁺ remains electrochemically stable during the transfer process and that no coupled chemical reaction occurs within the experimental time scale. Furthermore, these results demonstrate that the observed currents were controlled by the diffusion of the electroactive species.

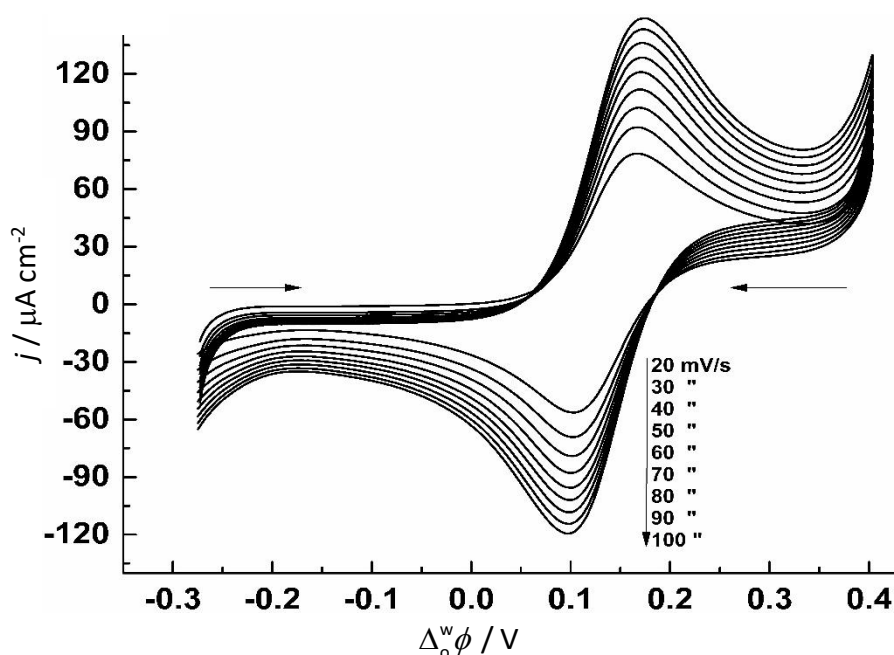


Figure 4. CV of OLPH⁺ transfer at different scan rates across the water-1,2-DCE interface

The Randles-Ševčík analysis of the peak currents plotted against the square root of the scan rate (Figure 5) showed an excellent linear relationship. This result confirmed that the transfer process

was diffusion-controlled, with the observed currents being limited by the diffusion of OLPH⁺ to the water|1,2-DCE interface.

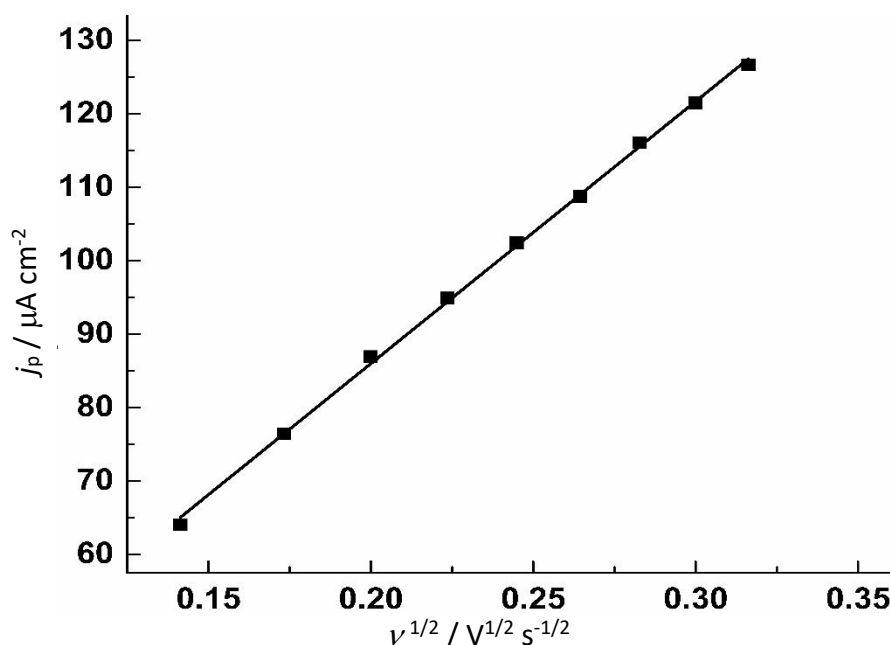


Figure 5. The Randles-Ševčík analysis for the OLPH⁺ (0.2 mM) transfer across the water-1,2-DCE interface

The Randles-Ševčík Equation (8) is expressed as follows [25]:

$$i_p = 2.69 \times 10^5 n^{3/2} A c D^{1/2} \nu^{1/2} \quad (8)$$

where n is the ionic charge number ($n = 1$ for OLPH⁺), A / cm^2 is the interfacial area between the two liquid phases, $c / mol cm^{-3}$ is the concentration, $D / cm^2 s^{-1}$ is the diffusion coefficient, and $\nu / V s^{-1}$ is the potential scan rate.

Using this approach, the diffusion coefficient of OLPH⁺ ($D_{OLPH^+}^w$) in the aqueous phase was determined to be $1.17 \times 10^{-5} cm^2 s^{-1}$. The diffusion coefficient in the organic phase ($D_{OLPH^+}^o$) was estimated from the ratio D^o/D^w , obtained using the Walden rule, $D^o/D^w = \eta^w / \eta^o$, where η^o and η^w are the viscosities of the organic and aqueous solvents, respectively [21]. Considering the viscosity values of 0.890 and 0.779 mPa s for the aqueous and 1,2-DCE phases, respectively, the (D^o/D^w) ratio was estimated to be 1.14. Accordingly, the diffusion coefficient of OLPH⁺ in the organic phase was estimated to be $1.34 \times 10^{-5} cm^2 s^{-1}$. These values are within the range reported for the transfer of structurally related organic molecules across a water|1,2-DCE interface [26].

Figure 6 shows the logarithmic relationship between peak current ($\log i_p$) and scan rate ($\log \nu$). This relationship can be expressed by the following linear Equation (9):

$$\log i_p = 2.52 + 0.42 \log \nu \quad (9)$$

An excellent linear relationship was observed ($R^2 = 0.999$), yielding a slope of 0.42. This value is close to the theoretical value of 0.5 expected for a diffusion-controlled process, indicating that OLPH⁺ transfer across the water-1,2-dichloroethane interface is predominantly diffusion-controlled. This result is consistent with the previous Randles-Ševčík analysis, in which the peak current was plotted against the square root of the scan rate.

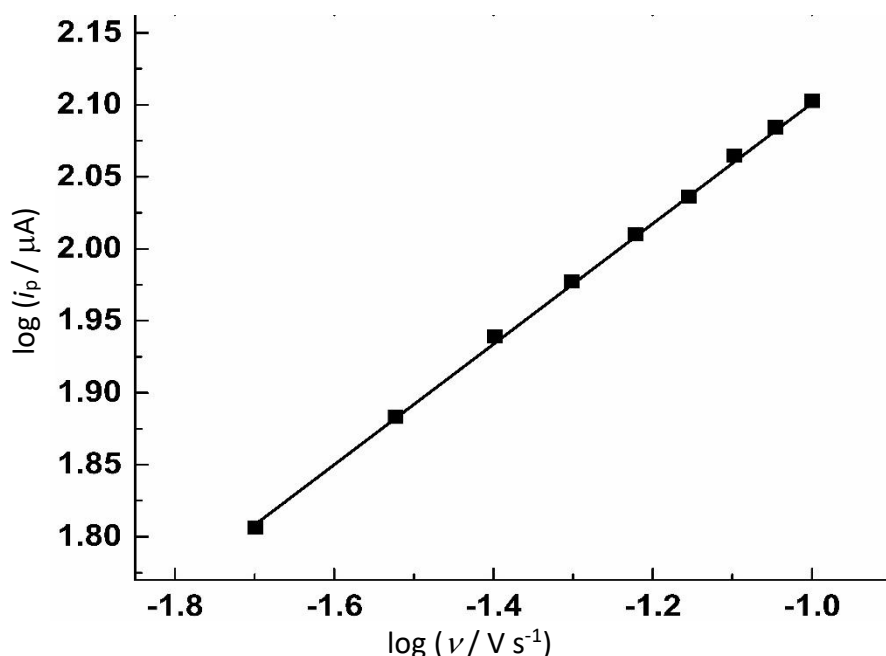


Figure 6. Logarithmic plot of the peak current vs. scan rate for OLP (0.2 mM) transfer across the water-1,2-DCE interface

Experiments were also performed by varying the concentration of OLP in the organic phase, as shown in Figure 7. As the OLP concentration increased while maintaining a constant scan rate of 50 mV s^{-1} , the ion-transfer peak current increased significantly, whereas the peak potential remained essentially unchanged. Furthermore, the voltammetric response remained reversible over the entire concentration range investigated. The peak-to-peak potential separation (Δp) was approximately 57 mV throughout the experiments, indicating that the ion-transfer process of OLPH^+ across the liquid-liquid interface was electrochemically reversible and not subject to significant kinetic limitations.

Similarly, $\Delta_o^w \phi_{1/2}$ remained essentially constant over the OLP concentration range of 0.025 to 0.125 mM (Figure 8), with a value of 0.184 V. By contrast, the peak current increased proportionally with OLP concentration, demonstrating a direct concentration-current relationship. These results highlight the potential of the ITIES as the basis for an electroanalytical method for the quantitative determination of OLPH^+ .

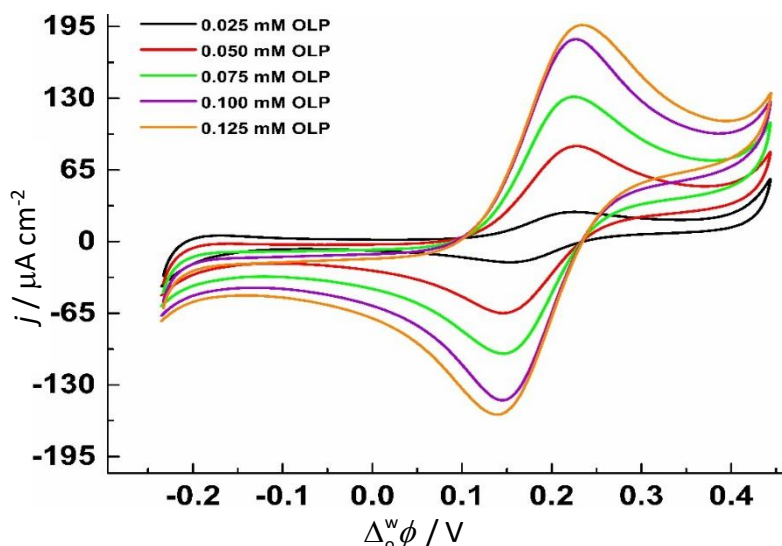


Figure 7. CV for the transfer of OLPH^+ across the water-1,2-DCE interface at different OLP concentrations. Scan rate: 50 mV s^{-1}

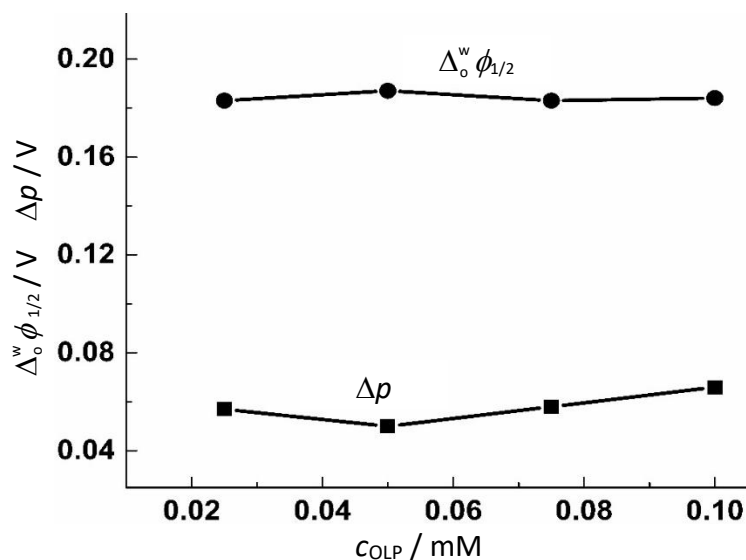


Figure 8. Δp and $\Delta_o^w \phi_{1/2}$ as a function of OLP concentration

The electrochemical response of the $OLPH^+$ is illustrated in Figure 9, which shows the SWV obtained at varying OLP concentrations. Increasing the OLP concentration in the organic phase progressively enhanced the ion-transfer peak current, with a linear correlation between peak current and OLP concentration over the studied range. This concentration-dependent response confirms the applicability of the ion-transfer process for $OLPH^+$ quantification and demonstrates the reproducibility and sensitivity of the ITIES-based electrochemical system.

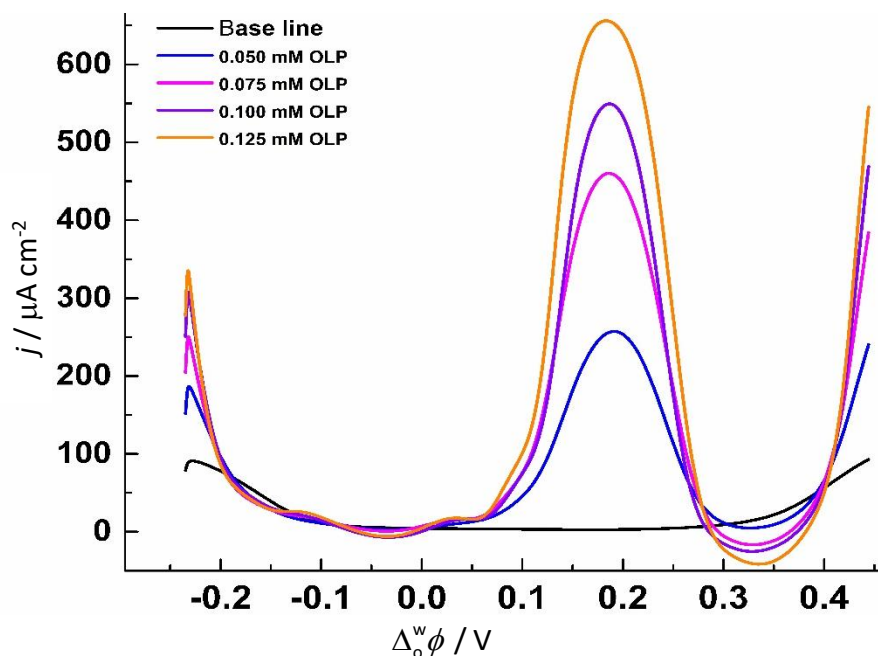


Figure 9. SWVs of $OLPH^+$ transfer across the water/1,2-DCE interface at different OLP concentrations. Pulse amplitude: 30 mV; frequency: 10 Hz

The transfer peak was observed at a potential corresponding to the $\Delta_o^w \phi_{1/2}$ previously determined by CV. In this case, the transfer potential was 0.189 V on the Galvani potential scale, which was in close agreement with the value obtained by CV (0.184 V). The excellent agreement between the two electrochemical techniques supports the reliability of the experimental results. Furthermore, the close similarity between these values indicates that the transfer of $OLPH^+$ across the ITIES remained stable, regardless of the voltammetric technique employed.

Furthermore, Figure 10 shows the relationship between the peak current density and the OLP concentration, revealing a well-defined linear correlation. This linear dependence suggests that SWV has strong potential as an analytical method for the quantification of OLP in aqueous media owing to its high sensitivity, rapid response, and ability to accurately detect changes in the concentration of this compound.

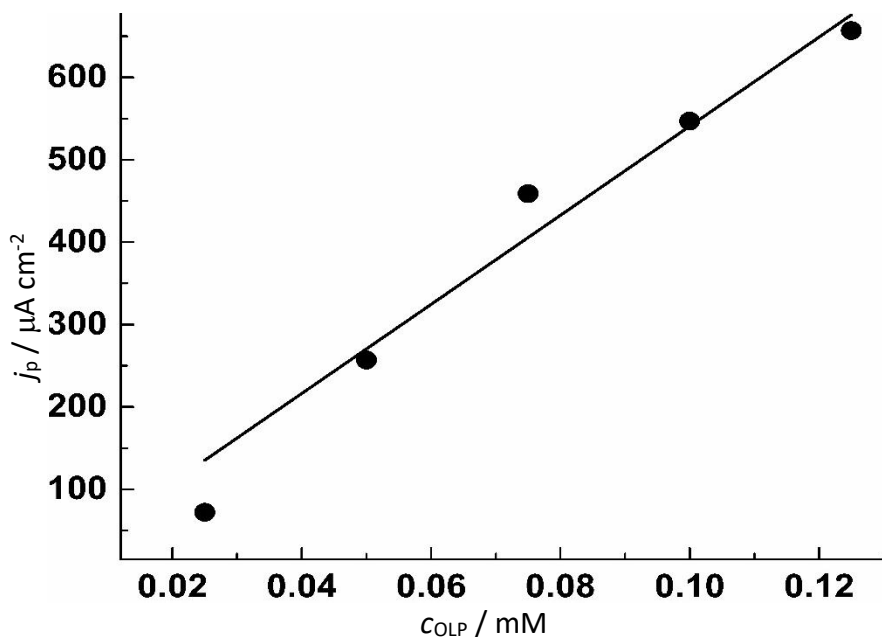


Figure 10. Peak current density as a function of OLP concentration

Capacitance studies

Capacitance studies were performed using the Mott-Schottky analysis to demonstrate charge accumulation (interfacial capacitance) at the boundary between the two immiscible liquids and to monitor the disruption of this interfacial organisation during the transfer of $OLPH^+$. The liquid/liquid interface was perturbed, and the interfacial capacitance was measured as a function of the applied potential at a frequency of 100 Hz. For simplicity, the equivalent circuit describing the interfacial charge storage is represented as a parallel-plate capacitor (Figure 11).

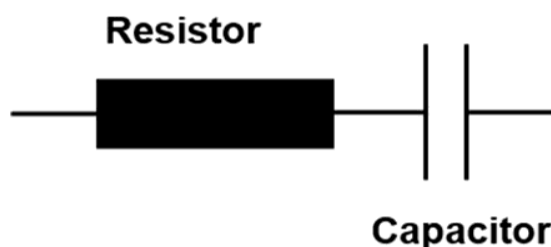


Figure 11. Equivalent circuit describing interfacial charge storage

Figure 12 shows the capacitance curves (expressed as $1/C$) as functions of the applied electrical potential at varying OLP concentrations. The region of high capacitance (black line) corresponding to the baseline response provided by the supporting electrolyte (TPAsTPBCl and HCl) is clearly distinguished. Within the Galvani potential range of -0.125 to 0.341 V, the interfacial charge distribution remains nearly constant, indicating a stable organisation of the electrical double layer on both sides of the liquid-liquid interface. By contrast, at the boundaries of the potential window (-0.232 and 0.440 V), the double-layer structure breaks down owing to the transfer of supporting electrolyte ions between the two phases (Figure 13a).

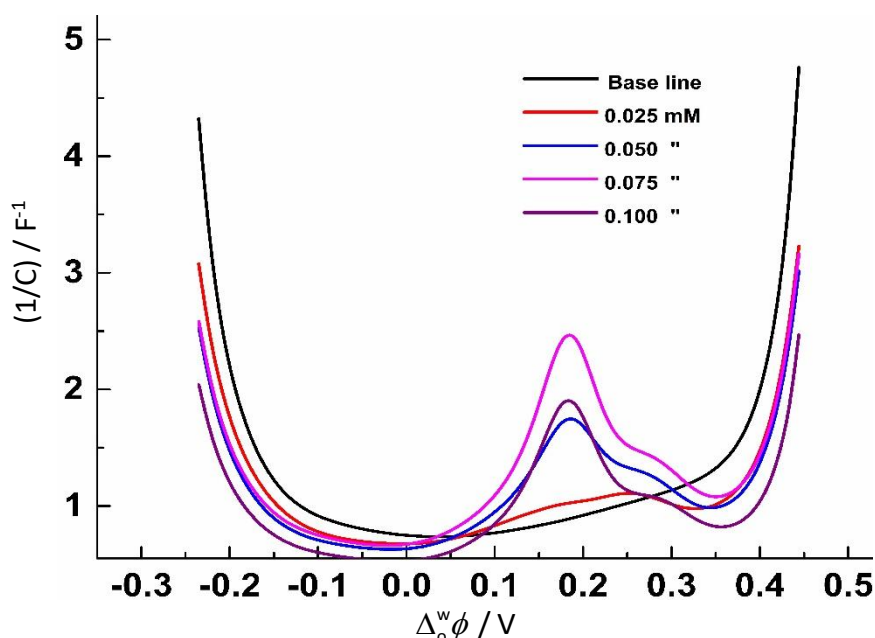


Figure 12. Interfacial capacitance as a function of the Galvani potential for OLP transfer across the water/1,2-DCE interface

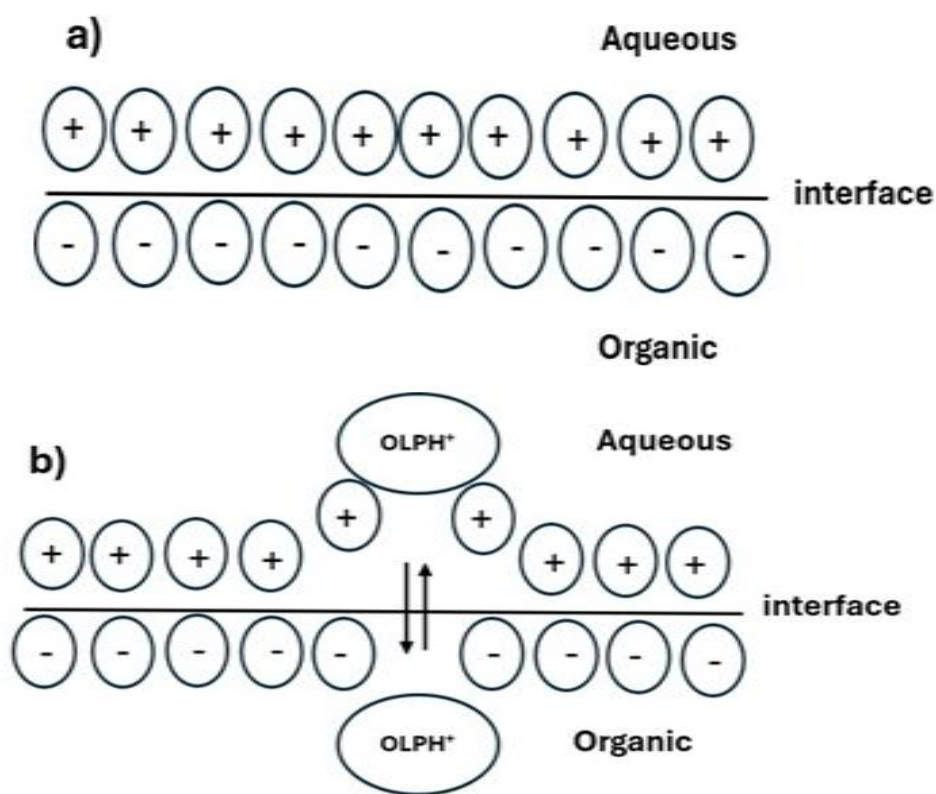


Figure 13. Schematic representation of the charge distribution at the water/1,2-DCE interface: (a) supporting electrolyte; (b) OLPH⁺ transfer across the interface

The behaviour of the electrical double layer in the ITIES was previously investigated through electrocapillary studies. These studies demonstrate the formation of a lipid monolayer at the ITIES, providing evidence of the interfacial organisation of lipid molecules and their influence on the electrochemical properties of the interface [27].

When OLP was added to the organic phase, the organisation of the interfacial electrical double layer was significantly perturbed, as evidenced by the distinct capacitance transition that occurred

at a Galvani potential of 0.184 V. This potential coincided with the formal transfer potential determined independently by both CV and SWV, demonstrating the reproducibility and well-defined nature of the electrochemical process. Moreover, the decrease in capacitance remained centered at the same potential over the entire range of OLP concentrations, indicating that the interfacial response was directly associated with a specific ion-transfer process rather than with a gradual or diffuse reorganisation of the interface. The excellent agreement between the capacitance studies and voltammetric measurements provides strong evidence for a faradaic process involving the transfer of the protonated species $OLPH^+$ across the liquid/liquid interface, accompanied by the structural rearrangement of the electrical double layer (Figure 13b).

Conclusions

This study demonstrates that the electrochemical behaviour of OLP can be investigated at the water/1,2-DCE interface. Voltammetric experiments showed that $OLPH^+$ was transferred within the available potential window, exhibiting a formal transfer potential of 0.184 V on the Galvani potential scale. Under conditions where the molecule is fully protonated, the standard Gibbs energy of transfer was determined to be $17.75 \text{ kJ mol}^{-1}$, corresponding to an ionic partition coefficient of -3.11. These results indicated that protonated OLP exhibited a markedly greater affinity for the aqueous phase than for the organic phase.

The result further demonstrated that the disruption of the electrical double layer occurs at the formal transfer potential, which coincides with the values independently determined by CV and SWV. This confirms that the ion-transfer process is closely associated with the structural reorganisation of the electrical double layer at the liquid/liquid interface.

Overall, the results demonstrate that $OLPH^+$ undergoes a well-defined ion-transfer process across the water/1,2-DCE interface, enabling the determination of thermodynamic parameters related to its ionic partitioning. Furthermore, the methodology presented here provides a valuable electrochemical approach for investigating the interfacial transfer properties of ionisable pharmaceutical compounds, yielding insights into the transport phenomena and membrane permeability in biomimetic systems.

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Conflict of interest: The authors declare that there is no conflict of interest.

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