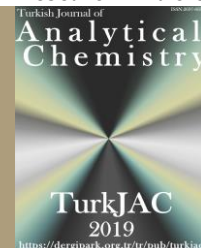




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Electrochemical investigation of buclizine: First mechanistic study of proton-coupled electron transfer at a glassy carbon electrode

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Abstract

This study reports, for the first time, the electrochemical oxidation behavior of buclizine at a glassy carbon electrode using cyclic and differential pulse voltammetry. The effects of solvent composition, methanol content, pH, supporting electrolyte, and scan rate on the oxidation process were systematically examined. Optimal electrochemical signals were obtained in Britton-Robinson buffer at pH 4.0 containing 10% (v/v) methanol. The oxidation peak potential shifted toward more negative values with increasing pH, with slopes close to 59 mV/pH in both voltammetric techniques, indicating that the oxidation involves equal numbers of electrons and protons. Scan rate studies confirmed that the oxidation process proceeds via a single-electron transfer. Based on the experimental findings, an irreversible proton-coupled electron transfer mechanism involving one electron and one proton ($1 e^- / 1 H^+$) was proposed. The findings in this article provide the first experimental information on the electrochemical oxidation pathway of buclizine, offering important data for understanding the chemical stability and pharmaceutical quality of the compound.

Keywords: Buclizine; glassy carbon electrode; irreversible process; oxidation mechanism; proton-coupled electron transfer; voltammetry

1. Introduction

Buclizine is a classical first-generation antihistamine belonging to the piperazine class and characterized by tertiary amine centers within its piperazine ring structure. These basic amines directly affect the degree of ionization, solubility, and bioavailability of the drug, since they can be easily protonated within the physiological and pharmaceutical pH range [1]. They also contribute significantly to the chemical reactivity of buclizine. The presence of these amine functionalities in the molecular structure (Fig. 1) suggests that the molecule is electroactive. Electroanalytical studies on piperazine-containing antihistamines have demonstrated that such compounds can undergo electrochemical oxidation at their nitrogen centers. This indicates that these functional groups are likely involved in the metabolic oxidation and chemical degradation pathways of buclizine as well [2].

The redox sensitivity of amine groups is also related to the general stability of antihistamines. Stability

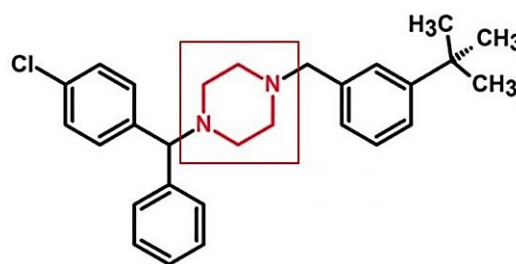


Figure 1. Chemical structure of buclizine

studies conducted under conditions of heat, light, and varying pH have shown that oxidation and dealkylation are the main degradation mechanisms in H₁ antihistamines, and that these processes mainly initiate from side chains containing tertiary amines [3]. In this context, the piperazine nitrogens of buclizine constitute the chemical basis of the molecule's susceptibility to oxidation. This indicates that amine-containing antihistamines need to be carefully evaluated in terms of pharmaceutical quality and shelf life [4,5].

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Electrochemical methods provide powerful tools for mechanism determination by enabling the direct and real-time monitoring of the oxidative behavior of organic and pharmaceutical molecules [6]. Especially for amine-containing pharmaceutical compounds, the electron-transfer processes occurring at the electrode can be clearly observed through oxidation peaks and potential shifts. In this way, the number of electrons involved in the reaction can be evaluated, and it can be determined whether the process proceeds through a single step or successive steps and whether follow-up chemical reactions are involved. Recent studies on piperazine-containing antihistamines have shown that electrochemical techniques directly reveal oxidation occurring at amine centers and provide mechanistic information that cannot be easily obtained by conventional analytical methods [2,6,7].

Cyclic voltammetry (CV) is an electrochemical technique performed by scanning the electrode potential forward and backward over a defined potential range. It provides direct information about whether a reaction is reversible or irreversible, electron-transfer kinetics, and the interactions between the electrode surface and the analyte. Due to these properties, CV is widely used for elucidating oxidation mechanisms [8,9]. Differential pulse voltammetry (DPV) is a highly sensitive technique based on the application of potential pulses. It is particularly useful for improving peak resolution and enabling more accurate determination of peak potentials, thereby assisting in the evaluation of electron and proton involvement. Therefore, DPV is used as a complementary technique in mechanistic studies and supports mechanistic interpretation [10,11].

The glassy carbon electrode (GCE) is widely used for investigating the oxidative behavior of organic and pharmaceutical molecules due to its wide potential window, chemical inertness, and low background current. In this study, a bare GCE was employed to ensure that the observed electrochemical responses reflect the intrinsic redox behavior of buclizine without interference from electrode modifiers. Although modified electrodes, such as those incorporating carbon nanotubes or metal nanoparticles, may enhance sensitivity or reduce the oxidation overpotential, they can also introduce additional surface interactions that complicate mechanistic interpretation. Therefore, the wide potential window and low background current of GCE allow voltammetric responses to be attributed primarily to the intrinsic redox behavior of the analyte. This is particularly advantageous for amine-containing compounds, for which the relatively inert surface of GCE helps minimize electrode-related interactions [12,13]. In addition, the combined use of CV and DPV provides valuable information on electron-transfer reversibility,

possible proton and electron involvement, and surface-related effects, thereby contributing to the elucidation of the oxidation mechanism of pharmaceutical molecules.

In the literature, several studies based on different analytical methods have been reported for buclizine [14–18]. These studies have primarily focused on the determination of the compound, purity control, or the identification of degradation products. In contrast, the electrochemical oxidation behavior of buclizine, the pH dependence of its oxidation peak potential (E_p) and mechanistic evaluations based on the number of electrons and protons involved in the reaction have not been systematically addressed in the literature. In particular, there is a lack of information regarding whether the oxidation process occurring on a GCE is reversible, whether it involves proton-coupled electron transfer, and how this process can be explained within a mechanistic framework supported by experimental evidence. These limitations highlight the need for a detailed investigation of the electrochemical oxidation of buclizine and the elucidation of its underlying mechanism.

In this study, the electrochemical oxidation behavior of buclizine was investigated for the first time at a GCE using CV and DPV. The effects of pH, solvent composition, and scan rate on the oxidation process were systematically examined. Based on the experimental findings, an oxidation mechanism involving one electron and one proton was proposed and supported by experimental electrochemical evidence.

2. Materials and methods

2.1. Chemicals and reagents

Buclizine was obtained from Sigma-Aldrich (St. Louis, MO, USA). Methanol and ethanol (HPLC grade) were purchased from Isolab (Eschau, Germany). Dimethyl sulfoxide (DMSO) was of analytical grade and used without further purification. 0.04 M Britton-Robinson buffer (BRB), 0.1 M acetate buffer (AcB), and 0.1 M sulfuric acid (H_2SO_4) were used for the preparation of supporting electrolytes and buffer solutions. Ultrapure water (18.2 M Ω -cm) was used for the preparation and dilution of solutions.

2.2. Instrumentation and electrochemical measurements

Electrochemical measurements were carried out using an Autolab IMP potentiostat/galvanostat (Metrohm Autolab B.V., Utrecht, The Netherlands) controlled by NOVA 2.1.8. software. A three-electrode system consisting of a GCE (BASi, 3 mm diameter) as the working electrode, an Ag/AgCl (BASi, 3.0 M NaCl) electrode as the reference electrode, and a platinum wire (BASi) as the auxiliary electrode was used. Prior to each

measurement, the surface of the GCE was polished with 0.3 μm alumina slurry and rinsed with distilled water.

The electrochemical behavior of buclizine was investigated by CV and DPV within the potential range of 0.0–1.5 V. CV measurements were performed at scan rates between 50 and 200 mV/s. DPV measurements were carried out using optimized instrumental parameters to obtain a high signal-to-noise ratio and reproducible responses. The DPV parameters were set as follows: step potential 0.003 V, modulation amplitude 0.05 V, modulation time 0.05 s, and interval time 0.2 s.

2.3. Preparation of standard and working solutions

Stock solutions of buclizine (1.0×10^{-3} M) were prepared separately in methanol, ethanol, and DMSO to investigate the effect of solvent composition. For optimization of methanol content, buffer media containing different percentages of methanol (10, 20, 30, and 40%, v/v) were prepared. Working solutions were prepared by appropriate dilution of the stock solutions with suitable buffer and supporting electrolyte solutions. In all cases, the final concentration of buclizine in the working solutions was adjusted to 6.0×10^{-5} M for electrochemical measurements.

3. Results and discussion

3.1. Effect of organic solvent on the electrochemical response of buclizine

In electrochemical systems, the solvent directly affects the solubility of the analyte, its mass transport to the electrode surface, and the symmetry of the oxidation peak. Therefore, the selection of an appropriate solvent is critical for the sensitivity and reproducibility of the method. The solvent optimization was carried out in AcB (pH 3.5) based on preliminary solubility studies of buclizine in different buffer systems. The solubility of buclizine was examined in acidic (AcB, pH 3.5), neutral (PB, pH 7.0), and basic (BRB, pH 9.0) media. Buclizine exhibited precipitation under neutral and basic conditions, whereas it remained sufficiently soluble in the acidic medium. Therefore, all optimization studies were conducted in this medium to ensure reliable and reproducible electrochemical measurements. Subsequently, the effect of organic solvents on the electrochemical oxidation behavior of buclizine was investigated under identical experimental conditions at a fixed analyte concentration (6.0×10^{-5} M) using CV and DPV in AcB (pH 3.5) containing 10% (v/v) ethanol, methanol, or DMSO (Fig. 2).

Evaluation of the voltammograms presented in Fig. 2 shows that the anodic peaks corresponding to the oxidation of buclizine are strongly dependent on the solvent type. In methanol, higher peak currents and

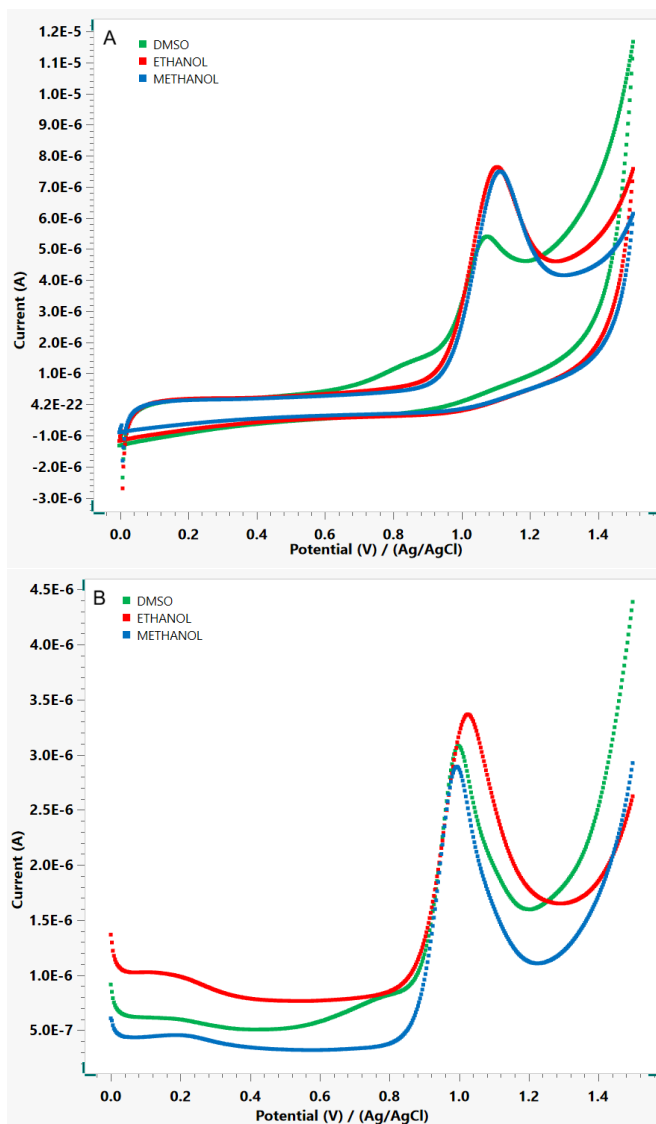


Figure 2. (A) Cyclic and (B) differential pulse voltammograms of 6.0×10^{-5} M buclizine recorded in AcB (pH 3.5) containing 10% (v/v) ethanol, methanol, or DMSO. Scan rate: 100 mV/s

more well-defined, symmetric oxidation peaks were obtained in both CV and DPV measurements. In ethanol, similar peak shapes were observed, but with lower current responses. In contrast, in the presence of DMSO, the oxidation peak became broadened, and the current response was unstable, indicating that the charge-transfer processes at the electrode surface were adversely affected.

The better performance observed in methanol can be attributed to the improved solubility of buclizine, the preservation of the conductivity of the buffer solution, and more efficient mass transport to the electrode surface. In contrast, the higher viscosity and different dielectric properties of ethanol and DMSO negatively affect charge-transfer kinetics and peak symmetry. Based on these results, methanol was selected as the organic solvent for subsequent electrochemical studies.

3.2. Optimization of methanol content

To evaluate the effect of methanol content on the electrochemical behavior of buclizine, CV and DPV measurements were performed by varying the organic solvent percentage in the range of 10–40% (v/v). The obtained data are presented in Table 1. As shown in Table 1, a decrease in the oxidation peak current and a shift of the peak potential toward more negative values were observed in both CV and DPV measurements with increasing methanol percentage. In the medium containing 10% (v/v) methanol, the highest and most well-defined oxidation peaks were obtained in both CV and DPV measurements. Increasing the methanol content in the range of 20–40% led to a decrease in peak current and a deterioration of the peak shape. These results indicate that the electrochemical response of buclizine is sensitive to the methanol content and that the most suitable experimental conditions are provided in the medium containing 10% (v/v) methanol. Therefore, the methanol content was fixed at 10% (v/v) for all subsequent experiments.

Table 1. Electrochemical data obtained for 6.0×10^{-5} M buclizine in AcB (pH 3.5) containing 10, 20, 30, and 40% (v/v) methanol

Methanol (% v/v)	CV		DPV	
	Peak current (μ A)	Peak potential (mV)	Peak current (μ A)	Peak potential (mV)
10	5.23	1106	2.17	1022
20	3.20	1087	1.85	977
30	3.33	1062	1.63	964
40	2.19	1048	1.16	952

3.3. Effect of pH and supporting electrolyte

To evaluate the effect of pH and supporting electrolyte on the electrochemical behavior of buclizine, CV and DPV measurements were performed in different acidic media. In this context, measurements were carried out in H_2SO_4 , AcB, and BRB within the pH range of 1.0–4.0. As shown in Fig. 3, the oxidation peak current and peak symmetry were strongly dependent on the supporting electrolyte and pH. In particular, in BRB at pH 4.0, sharper and more symmetric oxidation peaks were obtained in both CV and DPV measurements. At lower pH values, a decrease in peak current and a deterioration of the peak shape were observed. At pH values of 4.5 and above, precipitation of buclizine was observed, and therefore electrochemical measurements could not be performed at higher pH values. These results indicate that the solubility and electrochemical stability of buclizine are limited at higher pH values.

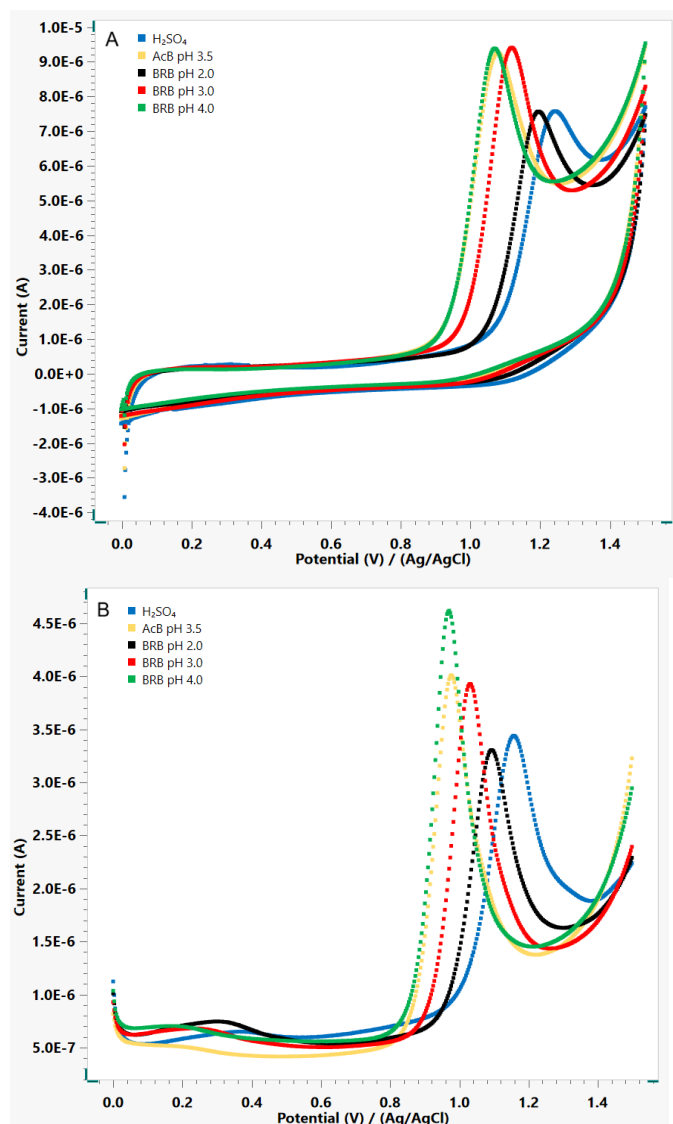


Figure 3. (A) Cyclic and (B) differential pulse voltammograms of 6.0×10^{-5} M buclizine in a supporting electrolyte and buffer solutions obtained at the GCE. Scan rate: 100 mV/s

In Fig. 3A, a clear anodic peak was observed, while the absence of a reduction peak in the reverse scan indicated that the oxidation of buclizine at the GCE was irreversible. The decrease in hydrogen ion concentration (increase in pH) resulted in a shift of the E_p toward more negative values. This behavior can be attributed to the deprotonation of the buclizine molecule and indicates that the oxidation process occurs more readily at higher pH values. This behavior was clearly illustrated in Fig. 4, where the relationships between pH and both peak potential and peak current were presented graphically. Based on the obtained results, BRB at pH 4.0 was determined to be the most suitable medium for the electrochemical characterization of buclizine, and all subsequent mechanistic studies were carried out under these optimal conditions.

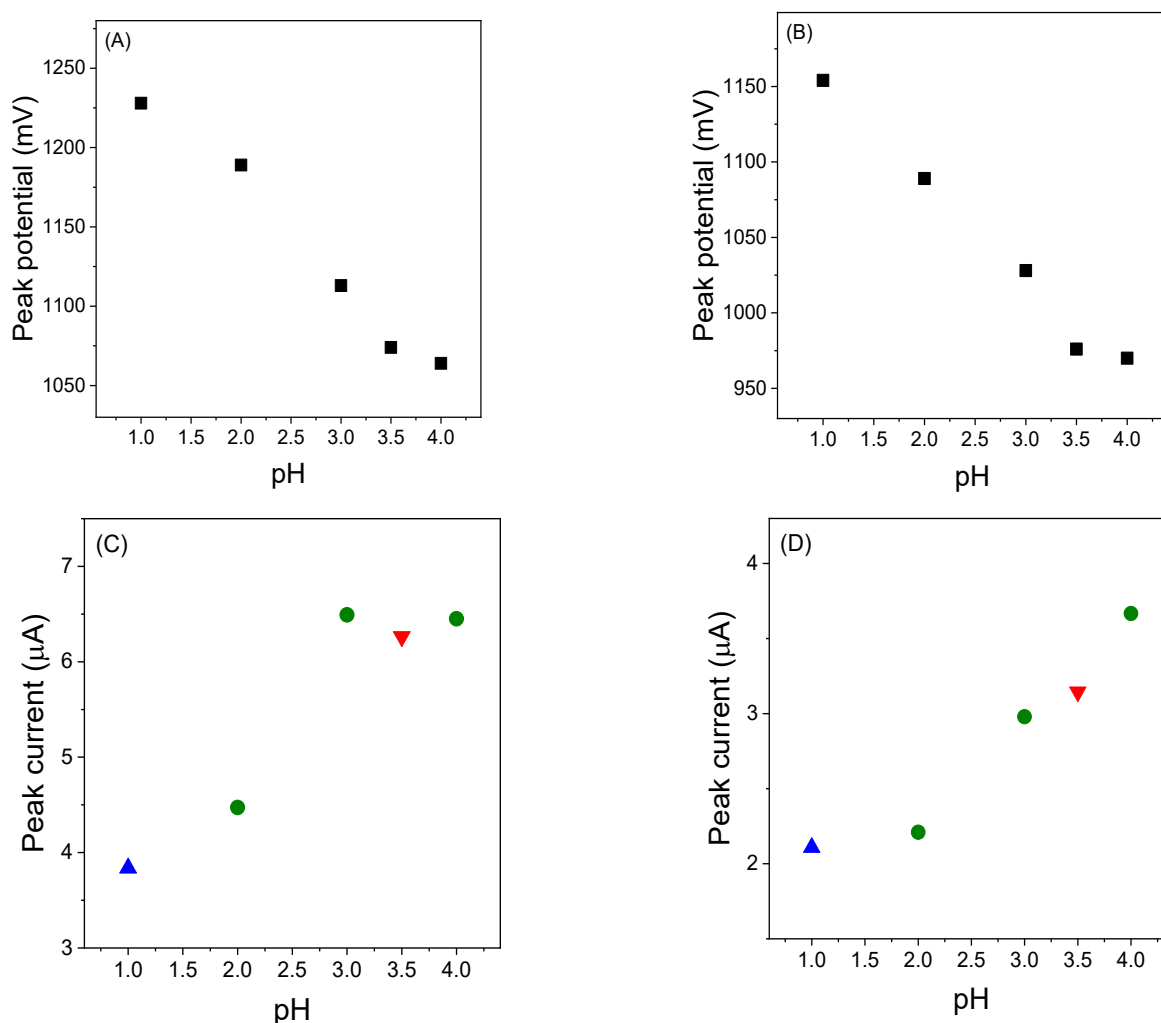


Figure 4. Effect of pH on the peak potential (A, B) and peak current (C, D) of 6.0×10^{-5} M buclizine recorded at the GCE by CV (A, C) and DPV (B, D) in different media within the pH range of 1.0–4.0. ●: BRB, ▼: AcB, ▲: H₂SO₄

3.4. Relationship between peak potential and pH

To evaluate the role of pH and proton involvement in the oxidation of buclizine, the relationship between E_p and pH was investigated. Linear relationships between E_p and pH were obtained for both CV and DPV measurements and are expressed by Eq. (1) and Eq. (2), respectively. In both methods, E_p shifted toward more negative values with increasing pH, indicating that the oxidation process is associated with proton transfer.

$$E_p \text{ (mV)} = 1293.1 - 59.02 \text{ pH} \quad (r = 0.978) \text{ for CV} \quad (1)$$

$$E_p \text{ (mV)} = 1217.3 - 64.33 \text{ pH} \quad (r = 0.986) \text{ for DPV} \quad (2)$$

The slope values are close to the theoretical Nernstian value of 59 mV/pH [19]. In electrochemical systems, such a slope indicates that equal numbers of electrons and protons participate in the electrode oxidation reaction. Accordingly, E_p -pH analysis suggests that the oxidation of buclizine involves a proton–electron coupled process. This result provides important evidence for the involvement of proton transfer in the oxidation mechanism.

3.5. Electrochemical behavior and irreversibility of buclizine oxidation

The electrochemical behavior of buclizine at the GCE indicated that the oxidation process was irreversible. In CV measurements, a well-defined anodic peak was observed in the forward scan, whereas no corresponding reduction peak appeared in the reverse scan, confirming the irreversible nature of the electron transfer process [2,19].

Irreversible electrochemical behavior is commonly observed in systems where the electron transfer is followed by chemical steps. Such behavior suggests that the oxidation process is not limited to a simple electron transfer but involves subsequent chemical transformation [2,19]. These observations provide a basis for further discussion of the oxidation mechanism of buclizine and for proposing a plausible reaction pathway.

3.6. Effect of scan rate and determination of electron transfer number

Variations in peak potential and peak current with scan rate offer valuable insight into the electrochemical

mechanism at the electrode surface, including whether the process is governed by adsorption, diffusion, or electron transfer kinetics. To explore this behavior, cyclic voltammograms of 6.0×10^{-5} M buclizine were recorded over a scan rate range of 75–200 mV/s in BRB (pH 4.0) (Fig. 5). The relationships between scan rate (v) and anodic peak current (I_p), as well as between the square root of scan rate ($v^{1/2}$) and I_p , are expressed in Eqs. (3) and (4), respectively. As seen from these equations, the linear relationship between I_p and v , together with the absence of linearity between I_p and $v^{1/2}$, indicates that the electrochemical process is predominantly adsorption-controlled [20]. Furthermore, with increasing scan rate, E_p shifted toward more positive values, confirming the irreversible nature of the electrode process.

$$I_p (\mu\text{A}) = 0.0026 v (\text{mV/s}) + 1.416 \quad (r = 0.993) \quad (3)$$

$$I_p (\mu\text{A}) = 0.0589 v^{1/2} (\text{mV/s}) + 1.090 \quad (r = 0.985) \quad (4)$$

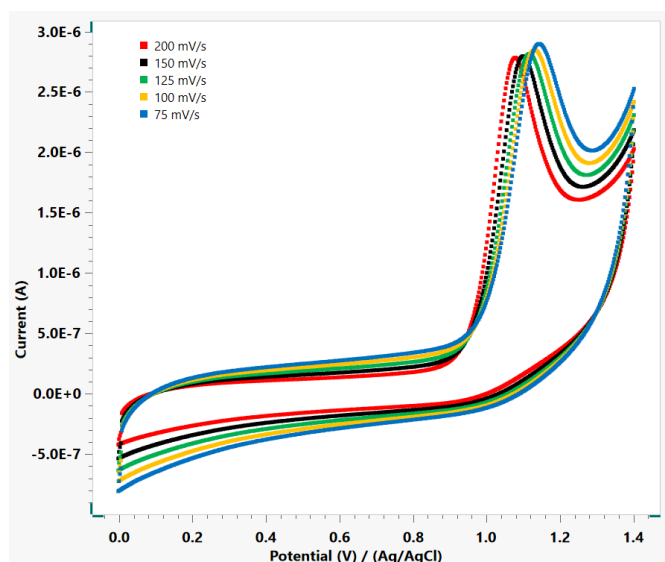


Figure 5. Cyclic voltammograms of 6.0×10^{-5} M buclizine in BRB (pH 4.0) at scan rates of 75, 100, 125, 150, and 200 mV/s

From the CV measurements recorded at a scan rate of 100 mV/s, the number of electrons involved in the

process (n) was determined using the expression $\Delta E_p = E_p - E_{p/2} = 47.7 \text{ mV}/\alpha n$ [21], where E_p and $E_{p/2}$ denote the peak and half-peak potentials, respectively. By assuming the charge transfer coefficient (α) to be 0.5, which is commonly accepted for irreversible systems, the value of n was calculated as 1.1 (≈ 1), indicating that the oxidation process involves one electron. In agreement with this result, the slope of the E_p -pH relationship further supports that the irreversible oxidation of buclizine at the GCE in BRB (pH 4.0) proceeds through the transfer of one electron and one proton.

3.7. Proposed oxidation mechanism of buclizine

In this study, the oxidation of buclizine at the GCE was systematically investigated, and a possible oxidation mechanism is presented in Fig. 6. The proposed mechanism is supported by complementary evidence obtained from pH studies, scan rate experiments, and observations of irreversible behavior. The experimental evidence and the obtained data are discussed step by step below, and their relationship to the proposed mechanism is explained.

- Firstly, a well-defined anodic peak observed in the forward scan and the absence of a corresponding reduction peak in the reverse scan indicate that the oxidation of buclizine at the GCE is irreversible. This behavior suggests that the oxidized species undergoes a rapid chemical transformation following electron transfer and therefore cannot be electrochemically reduced. Similar irreversible oxidation has been widely reported in the literature for nitrogen-containing pharmaceutical compounds, where chemical steps following electron transfer render the process irreversible [22–24].
- Secondly, the pH dependence of the oxidation peak provided important evidence for the proposed mechanism. In the E_p -pH analysis, the slopes obtained

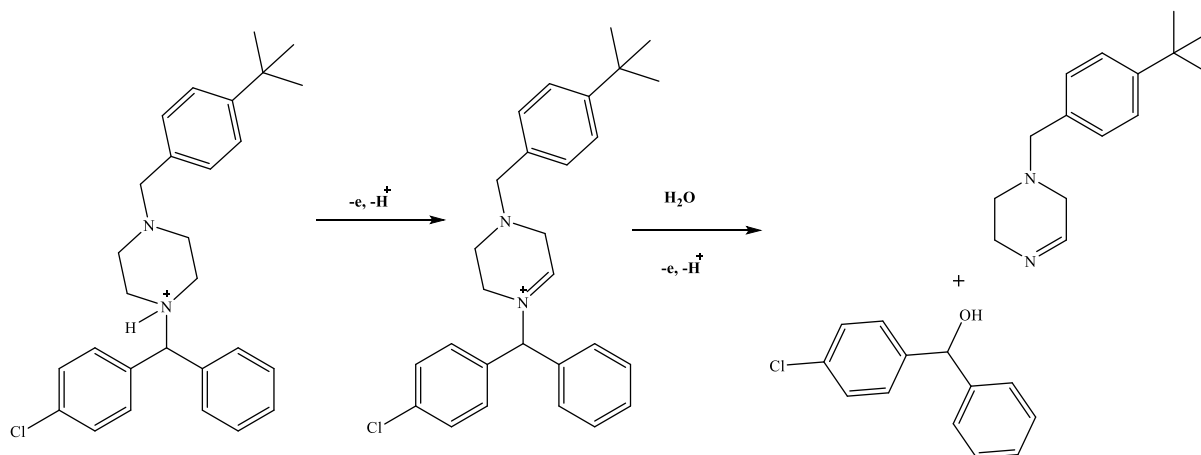


Figure 6. Possible oxidation mechanism of buclizine

from both CV and DPV (≈ 59 mV/pH) indicate that equal numbers of electrons and protons participate in the reaction, confirming the involvement of proton transfer in the oxidation of buclizine. The slightly higher slope obtained by DPV (64.33 mV/pH) can be attributed to technique-related pulse effects. The close agreement of the slopes obtained from both techniques with the theoretical value supports the reliability of the proposed mechanism.

- Thirdly, scan rate analysis provided further evidence for the proposed mechanism. In voltammograms recorded at different scan rates in BRB (pH 4.0), E_p shifted toward more positive values with increasing scan rate, confirming the irreversible nature of the oxidation process. The number of electrons transferred for buclizine was determined using the approach commonly applied to irreversible systems, yielding a value of $n = 1.1$ (≈ 1). This result, together with the electron-proton equivalence obtained from the E_p -pH analysis, indicates that the oxidation of buclizine proceeds via a proton-coupled electron transfer mechanism involving one electron and one proton ($1 e^- / 1 H^+$).

- The structural features of buclizine also support the proposed mechanism. The molecular structure contains basic tertiary amine and heteroatom-containing functional groups. In addition, the carbon in the N-CH(Ph)₂ moiety represents a classical benzhydryl center. Radicals or carbocations formed at this site are effectively stabilized through resonance delocalization over the two phenyl rings. Studies on piperazine derivatives and other tertiary amine-containing pharmaceuticals have shown that oxidation generally occurs at the nitrogen center. Following electron transfer, proton loss leads to the formation of radical or cationic intermediates, which contribute to the irreversible nature of the process [2,3,25]. In addition, E_p -pH slopes close to 59 mV/pH are widely accepted as evidence of proton-coupled electron transfer [20,26]. The results obtained for buclizine are consistent with these observations, suggesting that its oxidation proceeds via a nitrogen-centered step involving coupled electron and proton transfer.

- The results obtained from solvent and medium optimization also support the proposed mechanism. The higher and more symmetric peaks observed in methanol indicate more stable and controlled oxidation conditions. At higher organic solvent contents, the decrease in peak current and the distortion of the peak shape suggest limitations in charge-transfer processes. Furthermore, precipitation observed at pH values above

4.5 indicates that the solution stability of buclizine is strongly pH-dependent, highlighting the importance of appropriate medium conditions for reliable mechanistic evaluation.

When all the evidence described above is considered together, the oxidation of buclizine at the GCE can be described as an irreversible proton-coupled electron transfer process involving one electron and one proton. Accordingly, the mechanism proposed in Fig. 6 suggests that oxidation initiates at the nitrogen center. Similar nitrogen-centered oxidation mechanisms have been reported for structurally related antihistamines, such as meclizine, hydroxyzine, and cetirizine, where the electrochemical process was also characterized as a one-electron/one-proton transfer [25,27].

4. Conclusion

In this study, the electrochemical oxidation behavior of buclizine at the GCE was systematically investigated. The results showed that buclizine undergoes irreversible oxidation at the GCE and that the oxidation process involves a mechanism including one electron and one proton. The oxidation behavior was found to be strongly dependent on both pH and solvent environment. The most suitable electrochemical response was obtained in BRB at pH 4.0 containing 10% (v/v) methanol. Overall, the E_p -pH relationship together with the scan rate analysis supports the proposed oxidation mechanism, which is in agreement with mechanistic observations reported for structurally similar compounds in the literature.

Ethics Statement

Ethics committee approval was not required for this study.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This study received no financial support.

Author Contributions

Ümran Sofu: Conceptualization, methodology, investigation, data curation, writing – original draft.

Gökçe Öztürk: Methodology, investigation, formal analysis, writing – review and editing.

Zehra Üstün: Investigation, formal analysis, validation, writing – review and editing.

Ebru Çubuk Demiralay: Supervision, conceptualization, writing – review and editing.

Use of Generative AI

Generative AI tools were used only for language editing and improving readability. The author reviewed and approved the final version of the manuscript and takes full responsibility for its content.

Data Availability

All data analyzed during the study are included in this article.

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