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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETAILED ELECTROCHEMICAL BEHAVIOR INVESTIGATION AND DETERMINATION OF ANTIPSYCHOTIC DRUG PALIPERIDONE ON A GLASSY CARBON ELECTRODE

CAMSI KARBON ELEKTROT İLE ANTİPSİKOTİK İLAÇ PALİPERİDONUN AYRINTILI ELEKTROKİMYASAL DAVRANIŞININ ARAŞTIRILMASI VE TAYİNİ

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ABSTRACT

Objective: *A sensitive and cost-effective electrochemical method was developed on a bare glassy carbon electrode (GCE) for the determination of paliperidone (PAL), an antipsychotic drug used in the primary schizophrenia treatment affecting the whole world.*
Material and Method: *The oxidation studies carried out in pH 8 phosphate buffer solution (PBS) by cyclic voltammetry (CV) showed that the oxidation reaction of PAL is a process including the same number of electrons and protons. The electrochemical detection of PAL was carried out by differential pulse voltammetry (DPV).*
Result and Discussion: *The linearity range was between 1 µM and 100 µM. The limit of detection (LOD) and quantification (LOQ) values were calculated as $2.41x10^{-7}$ M and $8.033x10^{-7}$ M, respectively. The applicability of the developed method was confirmed by using it on synthetic human serum. The relative standard deviation (RSD) values were less than 2%. The selectivity of the analysis was demonstrated over against interfering substances such as ascorbic acid, KNO_3, $MgCl_2$, paracetamol, dopamine, Na_2SO_4, and uric acid with recovery% and RSD% values in the range 98.32%-101.56% and 0.15%-1.99%, respectively. The proposed method provided high sensitivity for PAL and is the first reported method for the electroanalysis of PAL.*
Keywords: *Differential pulse voltammetry, electrochemistry, glassy carbon electrode, paliperidone*

ÖZ

Amaç: *Tüm dünyayı etkileyen şizofreninin birincil tedavisinde kullanılan antipsikotik ilaç olan paliperidonun (PAL) tayini için yalın camsı karbon elektrot (CKE) kullanılarak hassas ve uygun maliyetli bir elektrokimyasal yöntem geliştirildi.*
Gereç ve Yöntem: *pH 8 fosfat tampon çözeltisinde dönüşümlü voltametri (DV) ile gerçekleştirilen oksidasyon çalışmaları, PAL'ın oksidasyon reaksiyonunun iki elektron ve iki protonlu bir süreç olduğunu gösterdi. PAL'ın elektrokimyasal tespiti diferansiyel puls voltametrisi (DPV) ile gerçekleştirildi.*
Sonuç ve Tartışma: *Doğrusal aralık $1x10^{-6}$ M ile $1x10^{-4}$ M arasında bulundu. Teşhis sınırı (TS) ve tayin alt sınırı (TAS) değerleri sırasıyla $2.41x10^{-7}$ M ve $8.033x10^{-7}$ M olarak hesaplandı. Geliştirilen yöntemin uygulanabilirliği sentetik insan serumu üzerinde kullanılarak doğrulandı. Bağıl standart*

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sapma (BSS) değerleri %2'den azdı. Yöntemin seçiciliği, askorbik asit, KNO_3, $MgCl_2$, parasetamol, dopamin, Na_2SO_4 ve ürik asit gibi girişim etkili ajanların varlığında sırasıyla %98.32-%101.56 ve %0.15-%1.99 aralığında %geri kazanım ve %BSS değerleri ile gösterilmiştir. Önerilen yöntem PAL için yüksek hassasiyet sağlamıştır ve PAL'in elektroanalizi için bildirilen ilk yöntemdir.
Anahtar Kelimeler: *Camsı karbon elektrot, diferansiyel darbe voltametrisi, elektrokimya, paliperidon*

INTRODUCTION

Based on the World Health Organization's (WHO) official data in 2022, schizophrenia is a major disease affecting approximately 24 million people worldwide. In recent years, rapid advances in science, particularly neuroscience, have created several research areas to explore the brain neurobiological and neurocognitive processes underlying schizophrenia [1]. The primary treatment of schizophrenia is antipsychotic drugs (APS), and treatment outcomes are monitored by therapeutic drug monitoring (TDM) [2]. Schizophrenia is a chronic disease that requires long-term treatment with APS and often relapses [3].

Paliperidone (PAL; Figure 1) is risperidone's main metabolite, belonging to the second-generation class of antipsychotics and is prescribed for schizophrenia treatment [4]. PAL shows affinity for serotonin and dopamine receptors [5]. It has been approved by the Food and Drug Administration (FDA) for both acute and long-term treatment of schizophrenia since 2006 [6]. The recommended dose of extended-release application of PAL is 6 mg/day. PAL's maximum plasma concentration (C_{max}) after a single dose application is 5.49 ng/ml. Based on the PAL-containing pharmaceutical products, the LD_{50} value (rat, female) is 65 mg/kg [7]. The absolute bioavailability of PAL and its binding to plasma proteins have been reported to be 28% and 74%, respectively. In addition, 59% is excreted directly by the kidneys [8]. The active fraction during treatment is expressed as the sum of risperidone and PAL. In long-term treatments, disadvantages such as adverse reactions, poor drug compliance or tolerance may occur [3]. In order to reduce these side effects, the dose used should be controlled quickly and effectively. PAL is also a frequently encountered antipsychotic agent in suicide cases involving fatal poisoning. In such forensic cases, accurate determination of PAL concentration in the blood is mandatory to prove that PAL intoxication caused death [9].

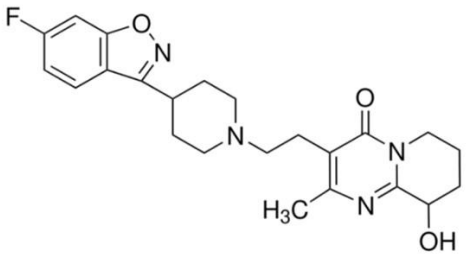

Figure 1. Molecular structure of PAL

As a result of literature reviews, single, double, and triple combination studies of PAL were found. Single studies of PAL in different pharmaceutical formulations by first-derivative spectrophotometric technique [6], pharmaceuticals by high-performance liquid chromatographic (HPLC) method [8], commercial formulations by reversed-phase liquid chromatographic (RP-LC) method [10], by high-performance thin-layer chromatographic (HPTLC) [4,11], pharmaceutical injection forms [5], by ultra-performance liquid chromatography (UPLC), liquid chromatography-quadrupole orbitrap mass spectrometry (LC-Q-Orbitrap-MS) method in human blood [9] and ultra-high performance liquid chromatography-quadrupole orbitrap mass spectrometry (UHPLC-MS/MS) method in beagle dog plasma [3]. Dual and ternary analyses of PAL and risperidone from human plasma and urine by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method [12], and PAL, risperidone and olanzapine from human plasma by LC-MS/MS method [13] were found, respectively.

Only chromatographic methods were noted in the literature, and no electrochemical analyses were performed. Furthermore, the studied methods either require costly instruments or extra sample preparation techniques. Therefore, there is a need for a fast, sensitive, selective, efficient and inexpensive method for PAL analysis in complex matrices.

In this study, PAL was characterized by the cyclic voltammetric method and analyzed from standard solution and commercial sample of human serum by DPV method using a bare glassy carbon electrode (GCE). The electrochemical behavior of PAL was analyzed in terms of pH and scan rate effect. Additionally, the possible oxidation mechanism was evaluated. The proposed method is easy to apply, quick, sensitive, and reproducible for routine analysis.

MATERIAL AND METHOD

Reagents and Chemicals

Active pharmaceutical ingredients of PAL, risperidone (RIS), droperidol (DRO), haloperidol (HAL), and benperidol (BEN) were purchased from Sigma-Aldrich. All other chemicals purchased from Sigma-Aldrich and their intended uses are as follows: Methanol (MeOH; ≥99.8%) to prepare stock drug solutions, acetonitrile (ACN; ≥99.9%) to precipitate serum proteins; sulfuric acid (H_2SO_4; ≥99.99%), acetic acid (≥99.0%), sodium acetate trihydrate (≥99.0%), phosphoric acid (≥99.0%), sodium dihydrogen phosphate dihydrate (≥98.0%), disodium hydrogen phosphate dihydrate (≥99.0%), and sodium hydroxide (≥97.0%) for the preparation of buffer solutions; ascorbic acid, dopamine, uric acid (≥99.0%), paracetamol, magnesium chloride (≥99.0%), sodium sulfate (≥99.0%), potassium nitrate (≥99.0%) for the preparation of interference solutions, drug-free commercial human serum for biological sample application.

10^{-3} M PAL stock solution was prepared in MeOH. Measurement solutions were prepared in desired buffer solutions, keeping the MeOH ratio constant at 20%. Various buffer solutions of H_2SO_4 (pH 0.3, 1.0), phosphate buffer solution (PBS, pH 1.5–8.0), acetate buffer solution (ABS, pH 3.7–5.7), and Britton-Robinson buffer (BRB, pH 2.0–12.0) were used in electrochemical measurements.

Apparatus

A potentiostat by PalmSens BV (Netherlands) using PSTrace 5.9 software was employed for the electrochemical measurements of CV and DPV. A three-electrode cell system consisting of a GCE (diameter=3.0 mm), a reference electrode of Ag/AgCl electrode (3 M KCl), and a counter electrode of platinum wire was connected to the potentiostat. They were all purchased from BASi Inc. (USA). A precision balance from Ohaus Instruments (Shanghai, China) was utilized to weigh solid chemicals. A pH-meter device (pH/ion meter S220) by Mettler-Toledo (Switzerland) was used to measure and adjust the pH values of buffer solutions. J.P. Selecta Corporation (Barcelona, Spain) and ISOLAB Laborgerate GmbH (Germany) provided a vortex mixer and ultrasonic bath.

The GCE surface cleaning was performed in two steps: Firstly, it was immersed in double distilled water:MeOH (1:1, v/v) mixture and kept in an ultrasonic bath for 15 min. After that, it was polished using a polish pad and alumina slurry. It was washed using distilled water and dried at 25°C.

The optimum measurement conditions for CV are as follows: Potential range: -0.2 V–1.2 V, step potential: 0.01 V, scan rate: 0.1 V/s. The optimum measurement conditions for DPV are as follows: Potential range: -0.2 V–1.0 V, step potential: 0.008V, pulse potential: 0.2 V, pulse time: 0.02 s, scan rate: 0.1 V/s.

Preparation Procedure of Commercial Human Serum Sample

$5x10^{-4}$ M serum stock solution was prepared using 1000 µl of $5x10^{-3}$ M PAL solution, 3600 µl of drug-free commercial human serum, and 5400 µl of ACN. In order for the serum proteins to completely precipitate and separate, this prepared mixture was placed in a centrifuge tube and centrifuged (5000 rpm, 20 min). The resulting supernatant was used to prepare measurement solutions with the necessary dilutions. While preparing these solutions, the optimum buffer solution was used by keeping the MeOH ratio constant at 20%. Then, recovery studies were carried out by spiking standard PAL solutions at two different known concentrations.

RESULT AND DISCUSSION

PAL's Electrochemical Behavior on Bare GCE

In electrochemical analysis studies, a detailed examination of the electrochemical behavior of the studied electroactive drug is fundamental. For this purpose, the oxidative behavior of PAL was examined in pH 8 PBS, which is the optimum electrolyte environment. According to the CV voltammograms displayed in Figure 2, it is observed that PAL has two oxidation peaks that are not completely separated from each other in pH 8 PBS. The first peak is located at 0.79 V, and the other one is at 0.92 V. Despite this visible distinction in CV voltammograms, it appears as a merged peak in DPV voltammograms.

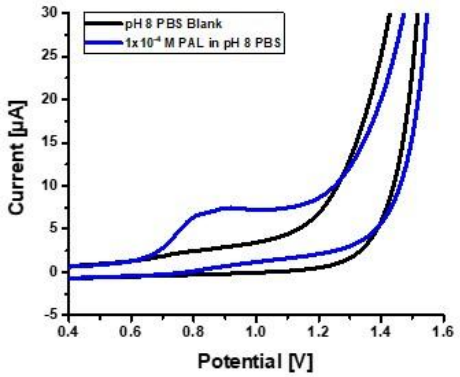

Figure 2. CV voltammograms of pH 8 PBS (black line) and $1x10^{-4}$ M PAL in pH 8 PBS (blue line)

Effect of pH

Analyzing how the target drug's electrochemical behavior is affected by the changes in the pH of the supporting electrolyte solution is an essential aspect of electrochemical analysis. For this purpose, the electrooxidation behavior of $1x10^{-4}$ M PAL was examined in various buffer solutions ranging from pH 0.3 to 12 on bare GCE. Peak potentials (E_p) and currents (I_p) of PAL were evaluated by making DPV measurements at changing pHs (Figure 3A and 3B). Accordingly, it is seen that with increasing pH values towards more basic pH, the PAL peak shifts towards lower potential and increases. As a result, pH 8 PBS, the environment where the highest peak was obtained, and the potential was at lower values (easier oxidation), was chosen as optimum. The relationship of E_p versus pH (Figure 3C) is explained with the equation below:

$$Ep\ (V) = -0.0702\ pH + 1.2334;\ r=0.977\ (pH\ 0.3 – 12)$$

The fact that this equation's slope has a close value to 59 mV/pH (theoretically calculated value) suggests that the oxidation process involves the same amount of protons and electrons of PAL on GCE [14].

Effect of Scan Rate

Observing the effect of changes in scan rate (υ) on the electrochemical behavior of substances makes it possible to enlighten the oxidation mechanism and the number of electrons transferred. In order to observe the effect of υ, cyclic voltammetric responses of $1x10^{-4}$ M PAL were evaluated in the range of 5 to 1000 mV/s in pH 8 PBS on GCE. The I_p versus $\upsilon^{1/2}$ (Figure 4A) and $\log I_p$ versus $\log\upsilon$ (Figure 4B) relations are expressed in the following equations:

$$I_p\ (\mu A) = 0.3105\ \upsilon^{1/2} – 0.04707;\ r = 0.994$$

$$\log I_p\ (\mu A) = 0.5418\ \log\upsilon – 0.6734;\ r = 0.997$$

$$I_p\ (\mu A) = 0.0096\ \upsilon + 1.1718;\ r = 0.973$$

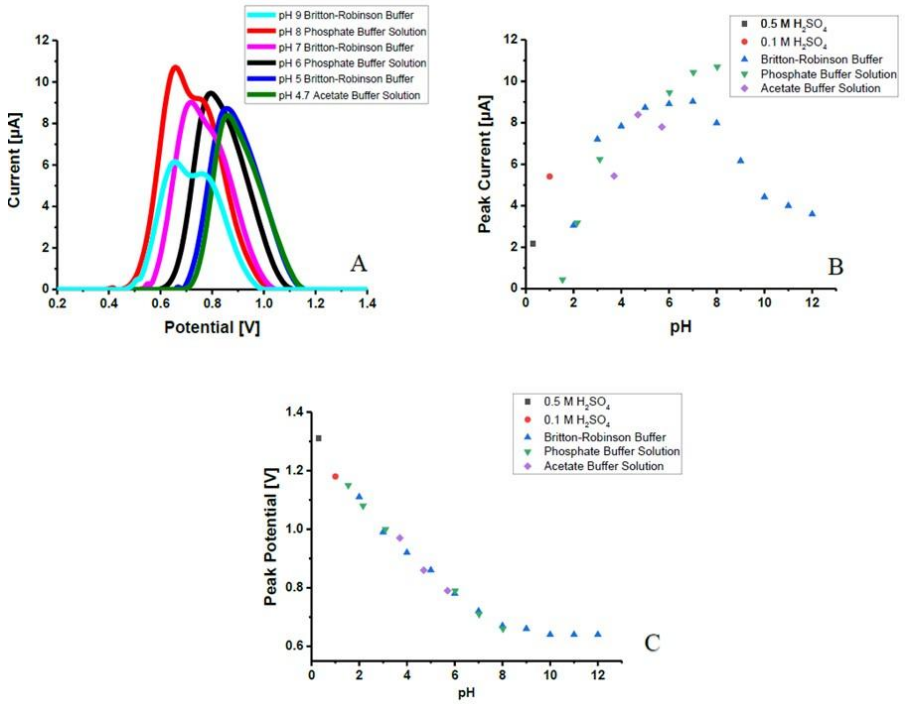

Figure 3. A) DPV voltammograms of 1x10^{-4} M PAL on GCE in pH 4.7 ABS, pH 5, 7, and 9 BRB, and pH 6 and 8 PBS; the plots of B) I_p versus pH and C) E_p versus pH (The measurements are performed in 1x10^{-4} M PAL, pH range is 0.3 – 12.0)

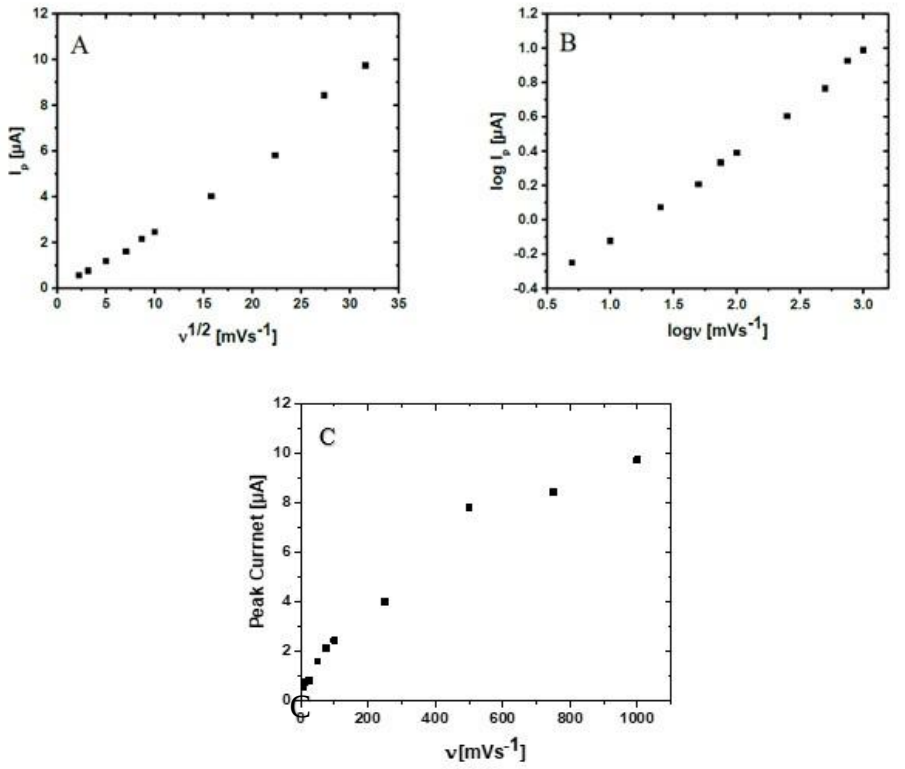

Figure 4. The plots of A) I_p versus $\upsilon^{1/2}$, B) logI_p versus logυ, and C) I_p versus υ in pH 8 PBS on GCE (The measurements are performed in 1x10^{-4} M PAL)

The calculated slope value of the $\log I_p$ versus $\log \upsilon$ equation was found to be close to the theoretical value of 0.5, indicating that the oxidation process of PAL is diffusion-controlled. Additionally, the non-linear response of I_p versus υ (Figure 4C) confirmed the diffusion-controlled process. Furthermore, the slope value of the E_p versus $\log \upsilon$ equation $= \frac{2.3RT}{2(1-\alpha)nF}$ formula was used to calculate the number of transferred electrons for PAL in pH 8 PBS on GCE. When the necessary calculations were made, n was found to be approximately 2. The parameters in the formula above are:

R: Universal gas constant
T: Absolute temperature
α: Transfer coefficient (If it is an irreversible oxidation reaction, it is calculated as 0.5)
n: Number of electrons
F: Faraday constant

Evaluation of Possible Oxidation Mechanism

CV is a valuable technique that enlightens the electrooxidation behavior of electroactive compounds. In order to elucidate the oxidation mechanism of PAL, molecules with similar structures to PAL, risperidone (RIS), droperidol (DRO), haloperidol (HAL), and benperidol (BEN) were selected (Figure 5). The oxidation peaks of each molecule were examined on bare GCE in three different electrolyte media (pH 4.7 ABS, pH 8 PBS, and pH 9 BRB) by the CV method (Figure 6). As it was given in effect of scan rate section, the number of transferred electrons for PAL was found to be 2. Additionally, the results in effect of pH section indicated that equal numbers of electrons and protons are involved in the oxidation process of PAL. Hence, it is shown that PAL's oxidation reaction is a two-electron and two-proton process. As it was reported in a study by Arvand et al. [15], the oxidation of RIS occurs via nitrogen in the piperidine ring in its structure. This piperidine ring is the mutual structure of PAL, DRO, HAL, and BEN. Therefore, it can be suggested that the oxidation of PAL occurs at its piperidine ring (Figure 7). This suggestion is supported by the fact that the oxidation peaks in Figure 6 are located at approximately the same potential.

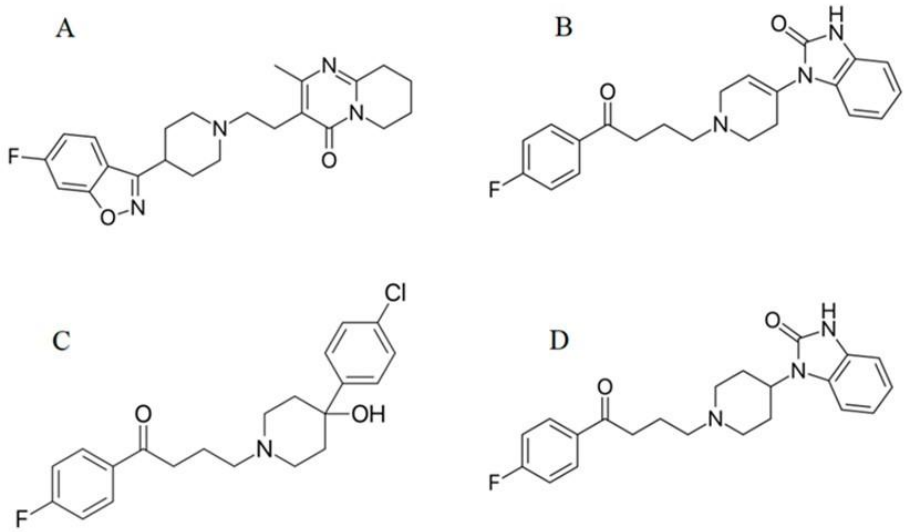

Figure 5. Chemical structures of A) RIS, B) DRO, C) HAL, and D) BEN

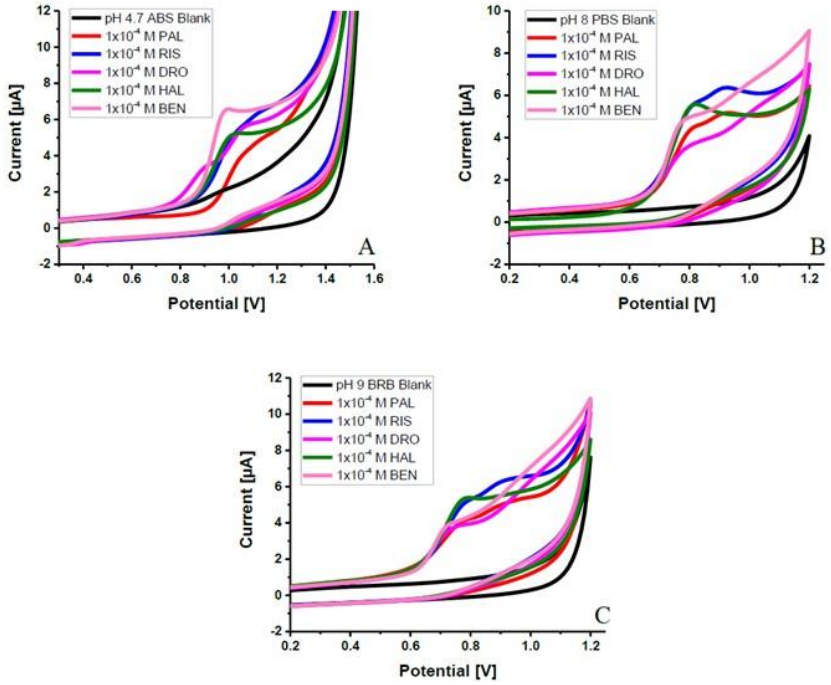

Figure 6. Cyclic voltammograms of $1x10^{-4}$ M PAL, RIS, DRO, HAL, and BEN in A) pH 4.7 ABS, B) pH 8 PBS, and C) pH 9 BRB on GCE

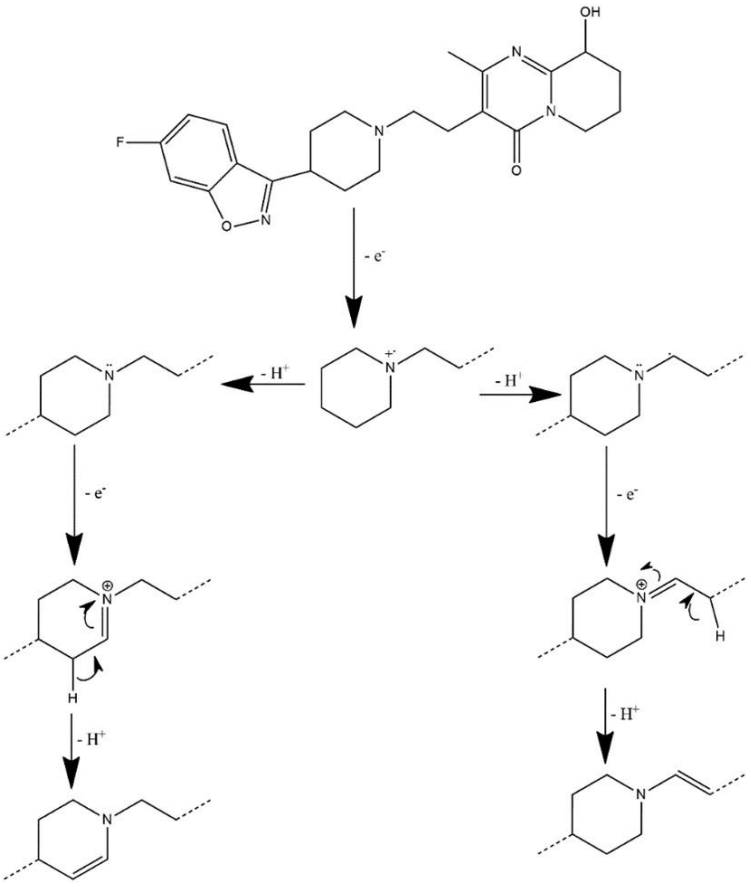

Figure 7. Possible oxidation mechanism of PAL

PAL Determination on Bare GCE

Determination of PAL on bare GCE was assessed using the DPV technique in pH 8 PBS. The obtained I_p values were plotted against varying concentrations of PAL to create the calibration curve. Bare GCE gave a linear response for PAL determination in a wide concentration range between $1x10^{-6}$ M and $1x10^{-4}$ M (Figure 8A). The related regression equation was found as I_p (µA) = 77.744×10^3 (µA/M) × C (M) + 0.394 (r = 0.999). The obtained DPV voltammograms for each PAL concentration are shown in Figure 8B. The formulas below, which are given in ICH guidelines, were used to calculate LOD and LOQ as $2.410x10^{-7}$ M and $8.033x10^{-7}$ M, respectively [16]. The other regression data are given in Table 1. Table 2 overviews the other studies performed for PAL analysis in the literature.

LOD = 3 x standard deviation/slope

LOQ = 10 x standard deviation/slope

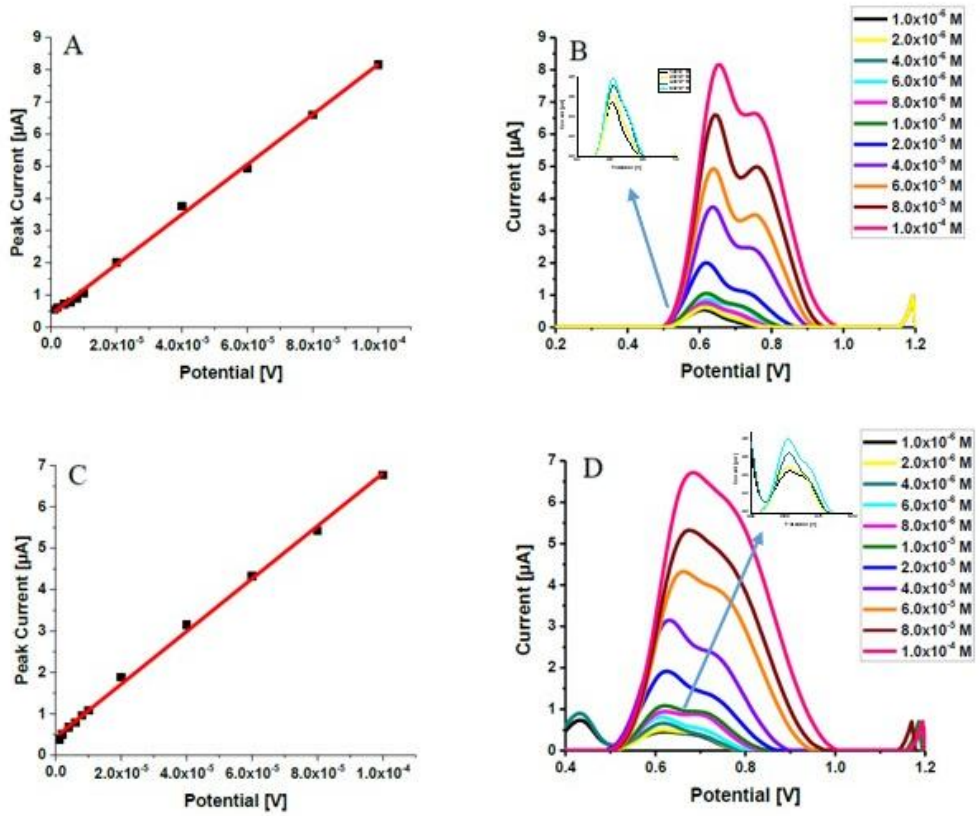

Figure 8. Calibration curves of PAL determination on GCE A) in pH 8 PBS; C) in commercial sample of human serum; DPV voltammograms of various PAL concentrations B) in pH 8 PBS; D) in commercial human serum sample

Analytical Performance in the Biological Media

The next stage in the analytical performance examination is to assess the determination of PAL in biological media. For this purpose, PAL was determined in the sample of commercial human serum that was prepared based on the procedure described in preparation procedure of commercial human serum sample section on GCE using the DPV technique. The linear range was obtained between $1x10^{-6}$ M and $1x10^{-4}$ M as in the standard solution with the regression equation of I_p (µA) = 63.730×10^3 (µA/M) × C (M) + 0.438 (r = 0.999) (Figure 8C). Associated DPV voltammograms for PAL determination are displayed in Figure 8D. The LOD and LOQ values were found to be $2.94x10^{-7}$ M and $9.799x10^{-7}$ M, respectively. The regression data parameters are given in Table 1.

Following this, the recovery assay was realized by spiking two known concentrations of standard PAL solution to the sample of commercial human serum. The acquired average recovery% and RSD% values in Table 3 confirmed the accuracy and feasibility in biological samples.

Table 1. Regression data of the calibration line for PAL on GCE in standard solution and commercial human serum sample

	Standard solution	**Commercial human serum sample**
Linear range (M)	$1.0 \times 10^{-6} – 1.0 \times 10^{-4}$	$1.0 \times 10^{-6} – 1.0 \times 10^{-4}$
Slope (µA/M)	77.744×10^{3}	63.730×10^{3}
Standard error of slope (µA/M)	1.107×10^{3}	0.933×10^{3}
Intercept (µA)	0.394	0.438
Standard error of intercept (µA)	0.049	0.042
Correlation coefficient (*r*)	0.999	0.999
LOD (M)	2.410×10^{-7}	2.940×10^{-7}
LOQ (M)	8.033×10^{-7}	9.799×10^{-7}
Repeatability of peak current (RSD%)*	0.682	1.779
Reproducibility of peak current (RSD%)*	1.771	1.994
Repeatability of peak potential (RSD%)*	0.072	0.081
Reproducibility of peak potential (RSD%)*	0.075	0.143

* Each value is the mean of five experiments.

Table 2. Comparison of analytical methods developed for PAL determination

Method	**Linear Range**	**LOD**	**Sample**	**Recovery (%)**	**Ref.**
HPTLC	100 – 600 ng/ml	NA	Tablet	98.77 – 101.39	[4]
LC-MS/MS	25 – 500 ng/ml	25 ng/ml	NA	NA	[17]
UPLC	0.00005 – 2.25 µg/ml	0.00001 µg/ml	Pharmaceutical injection	87.6 – 106.3	[5]
RP-HPLC	20 – 120 µg/ml	1.25 µg/ml	Tablet	99.80	[18]
Spectrophotometry	40 – 80 µg/ml	0.85 µg/ml	Tablet	101.84 – 102.76	[19]
UHPLC-MS/MS	1 – 1000 ng/ml	1 ng/ml	Beagle dog plasma	NA	[3]
UFLC	2 – 100 µg/ml	0.5 µg/ml	Tablet	98.22 – 102.96	[20]
LC-MS/MS	2.5 – 160 ng/ml	0.25 ng/ml	Serum	NA	[13]
HPLC	0.125 – 100 µg/ml	0.0132 µg/ml	Tablet	98 – 100	[8]
HPTLC	20 – 140 ng/band	1.288 ng/band	Tablet	NA	[11]
LC-MS/MS	1 – 2000 ng/ml	NA	Plasma, urine	90.4 – 105.1	[12]
Spectrophotometry	2.5 – 70 µg/ml	0.316 µg/ml	Tablet	98.94	[6]
Electrochemistry	$1.0 \times 10^{-6} – 1.0 \times 10^{-4}$ M (0.4 – 40 µg/ml)	2.410×10^{-7} M (0.097 µg/ml)	Serum	98.90 – 100.23	This work

HPTLC: high-performance thin-layer chromatography, NA: not available, LC-MS/MS: liquid chromatography tandem mass spectrometry, UPLC: ultra-performance liquid chromatography, RP-HPLC: reverse phase high performance liquid chromatography, UHPLC-MS/MS: ultra-high performance liquid chromatography–tandem mass spectrometry, UFLC: ultrafast liquid chromatography

Table 3. Recovery results of commercial human serum samples for PAL on GCE

	Serum Sample 1	**Serum Sample 2**
Sample concentration (M)	2.00×10^{-5}	4.00×10^{-5}
Spiked amount (M)	4.00×10^{-5}	2.00×10^{-5}
Found amount (M)*	5.89×10^{-5}	5.99×10^{-5}
Confidence interval*	±1.946	±1.157
Average recovery%	98.90	100.23
RSD% of recovery	2.00	1.32
Bias%	-1.10	+0.23

* Each value is the mean of five experiments

Interference Effect Assessment

Interference assay evaluates GCE's ability to determine PAL in the presence of substances found in biological fluids (natural or exogenous) without being affected by their signals. For this purpose, the most known possible interfering agents, ascorbic acid, KNO_3, $MgCl_2$, paracetamol, dopamine, Na_2SO_4, and uric acid, were selected. The recovery% and RSD% values were between 98.32%-101.56% and 0.15% and 1.99%, respectively. The determination performance of GCE and $2x10^{-5}$ M PAL was investigated in the presence of these compounds at 1-, 10-, and 100-times concentrations. As the obtained recovery% results are examined, PAL could be determined in the presence of ascorbic acid, $MgCl_2$, and Na_2SO_4 without any interference effect. On the other hand, an interference effect was observed in the presence of KNO_3 and paracetamol at 100 times and in the presence of dopamine at 10 and 100 times. An interference effect was observed due to the oxidation of uric acid at a very similar potential with PAL in the pH 8 PBS environment.

Conclusion

This work is the first one in the literature to evaluate electrochemical behavior and determination of an antipsychotic drug, PAL, on GCE. Investigation of the electrooxidation characteristics of PAL showed that in pH 8 PBS, PAL has two oxidation peaks located around 0.79 V and 0.92 V, which are not completely separated. As a result of the pH effect investigation, the oxidation peak of PAL shifts towards lower potentials with higher pH values and has the highest value at pH 8 PBS. Additionally, it was found that an equal number of electrons and protons are involved in the PAL oxidation. The effect of scan rate investigation revealed that the number of transferred electrons in the oxidation reaction is 2, and PAL's oxidation process is diffusion-controlled. Furthermore, based on the oxidation behavior of other similarly structured compounds (RIS, DRO, HAL, and BEN), it is suggested that PAL oxidation occurs at the piperidine ring in its structure. Determination of PAL in standard solution has a linear response in the concentration range between $1x10^{-6}$ M and $1x10^{-4}$ M. The LOD and LOQ values are $2.41x10^{-7}$ M and $8.033x10^{-7}$ M, respectively. The determination of PAL in biological media was assessed in the sample of commercial human serum, and the same linear range as in the standard solution was obtained. Recovery studies confirmed the feasibility of PAL determination in biological media. It was also found that PAL could be determined without any interference effect in the presence of ascorbic acid, $MgCl_2$, and Na_2SO_4.

AUTHOR CONTRIBUTIONS

Concept: S.I.K., S.A.O.; Design: S.I.K., S.A.O.; Control: S.I.K., S.A.O.; Sources: N.K.B., S.A.O.; Materials: N.K.B., S.A.O.; Data Collection and/or Processing: S.I.K., E.O.; Analysis and/or Interpretation: S.I.K., E.O.; Literature Review: S.I.K., E.O.; Manuscript Writing: S.I.K., E.O.; Critical Review: S.I.K., N.K.B., S.A.O.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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