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ORIGINAL ARTICLE

Adsorptive stripping voltammetric methods for determination of aripiprazole

Derya Aşangil[a], İbrahim Hüdai Taşdemir[b,*], Esma Kılıç[a]

[a]*Ankara University, Faculty of Science, Department of Chemistry, 06100 Ankara, Turkey*
[b]*Amasya University, Faculty of Arts and Science, Department of Chemistry, 05100 Amasya, Turkey*

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Abstract Anodic behavior of aripiprazole (ARP) was studied using electrochemical methods. Charge transfer, diffusion and surface coverage coefficients of adsorbed molecules and the number of electrons transferred in electrode mechanisms were calculated for quasi-reversible and adsorption-controlled electrochemical oxidation of ARP at 1.15 V versus Ag/AgCl at pH 4.0 in Britton–Robinson buffer (BR) on glassy carbon electrode. Voltammetric methods for direct determination of ARP in pharmaceutical dosage forms and biological samples were developed. Linearity range is found as from 11.4 μM (5.11 mg/L) to 157 μM (70.41 mg/L) without stripping mode and it is found as from 0.221 μM (0.10 mg/L) to 13.6 μM (6.10 mg/L) with stripping mode. Limit of detection (LOD) was found to be 0.11 μM (0.05 mg/L) in stripping voltammetry. Methods were successfully applied to assay the drug in tablets, human serum and human urine with good recoveries between 95.0% and 104.6% with relative standard deviation less than 10%.

1. Introduction

Aripiprazole (ARP), chemically known as 7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one (Fig. 1), is an atypical antipsychotic and antidepressant used in the treatment of schizophrenia, bipolar disorder and clinical depression. ARP represents a well-tolerated and effective addition to the antipsychotic armamentarium; it acts as a potent partial agonist at dopamine D_2 receptors and serotonin 5-HT1A receptors. ARP is rapidly absorbed after oral administration and the bioavailability of the drug is approximately 87% [1–3].

Only a few analytical techniques including HPLC with UV detection [4], LC–MS/MS [5,6], HPLC with tandem mass spectrometry [7], UPLC with tandem mass spectrometry [8], HPLC–MS [9], column switching HPLC [10] and capillary electrophoresis [11] have been devised for the determination of ARP in pharmaceutical samples or biological fluids. These methods are sufficiently sensitive but are also tedious and require highly sophisticated instrumentation for routine analysis. Although ARP is an electroactive molecule on different

*Corresponding author. Tel.: +90 358 2421613/4684; fax: +90 358 2421616.
E-mail address: ihudai@hacettepe.edu.tr (İ.H. Taşdemir).

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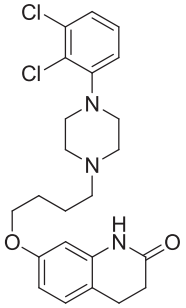

Figure 1 Chemical structure of ARP.

electrodes, there is no study dealing with electrochemical behavior of ARP based on its oxidation or reduction up to date.

Voltammetric techniques, such as cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square-wave voltammetry (SWV), have been proved to be very sensitive for the determination of organic molecules including drugs and related molecules in pharmaceutical dosage forms and biological fluids [12,13]. These methods are faster, easier to be operated and more economic than spectroscopic and chromatographic methods. The sensitivity could be increased drastically when the stripping voltammetry is applied. Adsorptive stripping voltammetry (AdSV) has been shown to be an efficient technique for assay of trace amount of a wide range of species which have interfacial adsorptive character onto the working electrode surface [14].

One aim of the present study was the investigation of electrochemical oxidation behaviors of ARP using voltammetric methods. Development of new validated direct and stripping voltammetric determination methods for the assay of ARP in different samples including pharmaceutical preparations, human serum and human urine was another objective of present study.

2. Materials and methods

2.1. Apparatus

All voltammetric measurements such as CV, SWV, DPV, bulk electrolysis (BE), differential pulse anodic adsorptive stripping voltammetry (DPAAdSV) and square-wave anodic adsorptive stripping voltammetry (SWAAdSV) were carried out using a CH-instrument electrochemical analyzer (CHI 760). A three electrode cell system incorporating the glassy carbon electrode (GCE) (BAS MF-2012) as working electrode, platinum wire as an auxiliary electrode (BAS MW-1034) and a Ag/AgCl reference electrode stored in 3.0 M KCl solution (MF-2052 RE-5B) was used in all experiments.

A three electrode combination system for bulk electrolysis consisting of reticulated vitreous carbon (BAS MF 2077) as working electrode, coiled platinum wire as an auxiliary electrode (23 cm) (BAS MW-1033) and a Ag/AgCl (in 3.0 M KCl) reference electrode (BAS MF-2052 RE-5B) was used.

All pH measurements were made with Thermo Orion Model 720A pH ion meter having an Orion combined glass pH electrode (912600).

Double-distilled deionized water was supplied from Human Power I^+, ultra pure water system (Produced by ELGA as PURELAB Option-S). All data were obtained at ambient temperature.

2.2. Reagents and solutions

Standard sample of ARP (99.0%, from Bristol Myers Squibb) was used to prepare the stock solution of ARP. This solution was prepared by dissolution of precisely weighed amounts of ARP in methanol in order to have the ARP concentration of 5.0×10^{-3} M (2.24 g/L). Calibration solutions were prepared by diluting the stock solution with Britton–Robinson buffer (BR) and pH value of these solutions was adjusted using 0.2 M NaOH or 0.2 M HCl solutions.

Abilify tablets (from Bristol Myers Squibb) each containing 5 mg ARP were used as pharmaceutical preparation.

All chemicals used in preparation of BR solution, such as phosphoric acid (Riedel), boric acid (Riedel), acetic acid (Merck), and the chemicals to adjust the pH of supporting electrolyte were of analytical reagent grade. Double-distilled deionized water was used in preparations of all the solutions.

All ARP solutions were protected from light and were used within the same day to avoid decomposition.

2.3. Preparation and analysis of samples

To prepare the solutions of tablets, the drug content of ten tablets was weighed initially, finely powdered and mixed in order to get homogeneous powder. The average mass per tablet was determined. A powder sample equivalent to one tablet was weighed and transferred into a 50.0 mL calibrated flask and then 25–30 mL of methanol was added. The contents of the flask were sonicated for 30 min to achieve complete dissolution of ARP. Following the solution step, the content of flask was completed to mark with methanol and centrifuged for 30 min at 1500 rpm after sufficient shaking. 10.0 mL of sample from the clear supernatant liquor was withdrawn and quantitatively diluted to 100.0 mL with BR buffer and pH was adjusted to desired value. This solution was kept at +4.0 °C in dark. Sufficient volumes from this solution were transferred into a calibrated volumetric flask of 10.0 mL, pH was controlled and volume was completed to mark with BR buffer, then content of flask was transferred to electrochemical cell and voltammetric measurements were performed.

Similarly, spiked human serum and urine samples were analyzed. Serum and urine samples obtained from healthy individuals were stored frozen until assay. After gentle thawing, 1.0 mL aliquot volume of serum (or urine) was added to electrochemical cell containing 9.0 mL of BR buffer and then sufficient volumes from stock tablet solution were transferred, after deaeration with argon, measurements were performed to determine ARP content of cell using direct calibration methods.

2.4. Voltammetric procedure

In all voltammetric studies (CV, DPV, SWV, DPAAdSV, SWAAdSV) 10.0 mL of ARP solution in BR was placed into the electrochemical cell for each time. Electrode connections were adjusted and then cell content was deoxygenated with purified argon (99.99% purity) for 15 min before the first running and 30 s between all individual successful runnings. After 2 s equilibration time voltammograms were recorded by applying a positive-going scan.

3. Results and discussion

3.1. Voltammetric behavior of ARP

Anodic behavior of ARP was investigated using CV and SWV. In CV studies, ARP exhibited one distinct and well-defined oxidation peak at about 1.15 V (vs. Ag/AgCl) when the potential was scanned between 0.0 V and 1.3 V (Fig. 2), and intensity of the peak was found to increase with increasing concentration of ARP (Fig. 2, inset), also a reduction peak at about 0.8 V at reverse scan appeared, but existence of this peak depend on the concentration of ARP indicating quasi-reversibility of electrode mechanism.

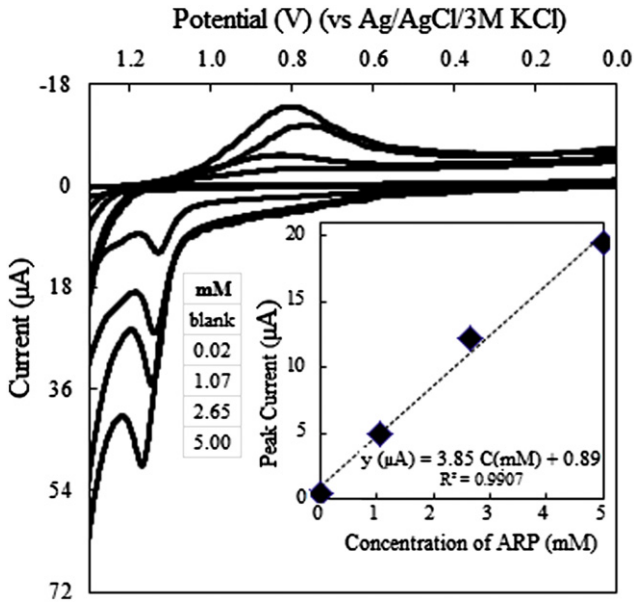

Figure 2 Cyclic voltammograms of solutions with different ARP concentrations in BR buffer of pH 4.0, scan rate 0.100 V/s (inset: graph for peak current vs. concentration).

More detailed experimental studies were carried out about characteristic of oxidation. First of all, influences of potential scan rate on peak potential and peak current were studied. As could be seen in Fig. 3, peak potential shifts to more anodic values with increasing scan rate confirming and supporting the irreversibility or quasi-reversibility of oxidation under investigation. For this kind of mechanism, the relationship between the peak potential (E_p) and logarithm of scan rate is expressed as [15]

$$E_p = k + \frac{RT}{(\beta n)F}\ln V \tag{3.1}$$

Here, E_p is peak potential in V, R is ideal gas constant, T is absolute temperature, F is Faraday's constant, n is number of electrons transferred in mechanism, β is anodic charge transfer coefficient and V is scan rate in V/s.

A straight line was observed when E_p was plotted against log V at a particular concentration and at pH 4.0. As could be seen in Fig. 3 inset **a**, this line could be expressed as: E_p $(V) = 0.062\,\log V + 1.19$ with $R^2 = 0.9973$. Using the slope value of this straight line, βn was calculated to be 0.95.

Same parameter (βn) was calculated from Eq. (3.2) in which the difference between peak potential and half-peak potential

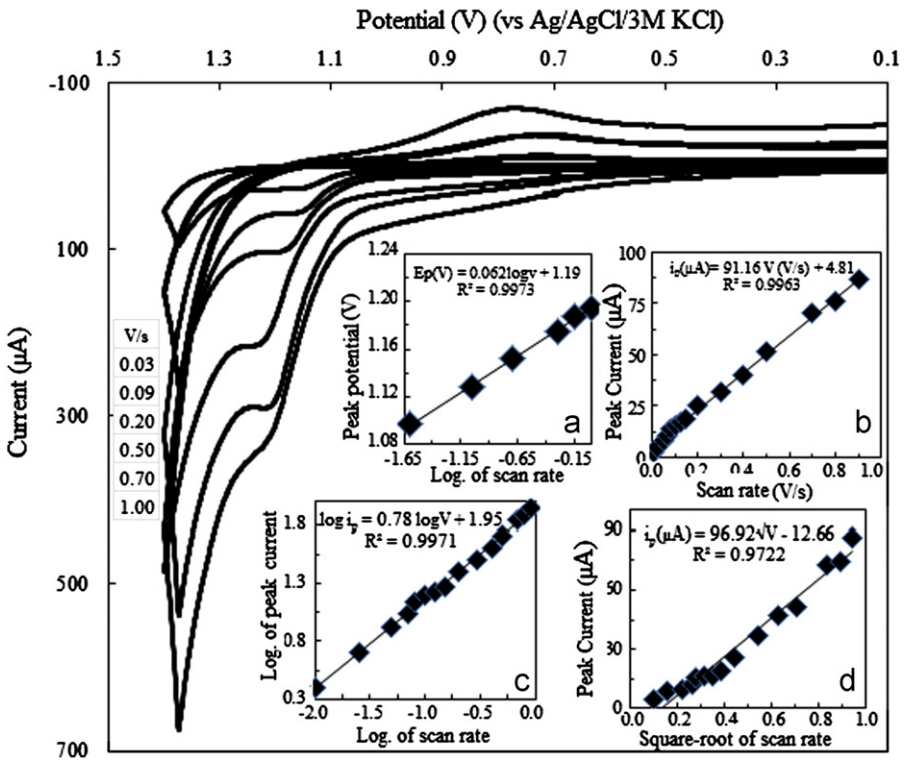

Figure 3 Effect of scan rate on peak parameters in BR buffer of pH 4.0 when concentration of ARP is 8 mM (inset (**a**) variation of peak potential with logarithm of scan rate, (**b**) graph of peak current vs. scan rate, (**c**) graph of logarithm of peak current vs. logarithm of scan rate, (**d**) graph of peak current vs. square root of scan rate).

is expressed [16] for cyclic voltammograms and it was calculated to be 1.17.

$$|E_p - E_{p,h}| = \frac{1.857RT}{\beta nF}, \text{ and at } 25\,^{\circ}\text{C} \; |E_p - E_{p,h}| = \frac{47.7}{\beta n} \qquad (3.2)$$

In this equation, $E_{p,h}$ is half peak potential in V and other abbreviations have the same meaning as in Eq. (3.1).

In order to confirm these two values for βn, frequency studies were carried out in SWV and relationship between frequency and peak potential [14] was used to calculate βn, and it was found as 1.21. When these three results and the limiting values for the charge transfer coefficient (between 0 and 1.0) [16–18] were coevaluated, the number of electrons in electrode process could be predicted as 2.

Effects of scan rate on peak current were also investigated. As scan rate increased from 0.03 V/s to 1.00 V/s at fixed concentration of ARP, peak current was found to be changed linearly with scan rate (Fig. 3(**b**)), indicating the effect of adsorption on mechanism [16–18]. When the linear line given in Fig. 3(**c**) is analyzed, it will be noticed that the logarithm of peak current changed linearly with the logarithm of scan rate with a slope value of 0.78 and this slope is midway between 0.5 and 1.0 for ideal diffusion controlled and adsorption-controlled charge transfer mechanism, respectively [14–18]. Relation between peak current and square root of scan rate is not linear at whole range but linear at relatively higher scan rates as depicted in Fig. 3(**d**). This behavior may show the inefficient effect of diffusion to mechanism.

The surface coverage of adsorbed substance (Γ) was calculated from the slope of the curve of peak current (A) versus scan rate (Vs^{-1}) according to equation given in literature [13–18] and it was found as $(3.4 \pm 0.3) \times 10^{-10}$ mol/cm^2 for scan rates between 0.030 V/s and 1.00 V/s.

The following equation for diffusion coefficient which expresses adsorption phenomena validated by Garrido [19] was used to calculate the diffusion coefficient of ARP:

$$i_p = 1.06 \times 10^6 n^2 ACV\sqrt{Dt_p} \qquad (3.3)$$

where, A is the area of electrode surface in cm^2, C is the analytical concentration of diffuses species in mol/cm^3, D is diffusion coefficient in cm^2/s, t_p is time required to reach peak potential from the beginning of potential scan and others are known from early equations. The mean of the diffusion coefficient calculated from this equation was obtained as $(3.7 \pm 0.05) \times 10^{-7}$ cm^2/s.

All these results pointed out the co-contribution of adsorption and diffusion on electrode mechanism.

Effect of pH on peak parameters was also analyzed. As shown in Fig. 4, peak potential shifts to smaller values (less anodic values) with increasing pH from 2.0 to 5.0, and pH independent at higher pH values after 5.0. In medium having pH higher than 6.0, solubility of ARP decreases sharply and formation of precipitation occurs, hence at higher pH, electrochemical behavior of ARP was not studied.

Shifting in peak potential with pH was considered as existence of protons in oxidation mechanism. As could be seen in inset graph in Fig. 4, linear relation between peak potential and pH could be expressed as: E_p (V) $= -0.09$ pH $+1.40$ (with $R^2 = 0.9918$) between the pH values of 2.0 and 5.0. When the slope of this relation was evaluated in Eq. (3.4) [20], the ratio of proton to electron participated in

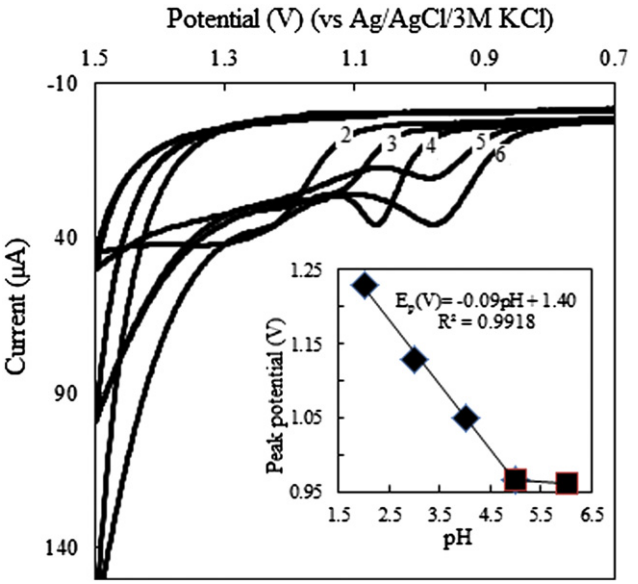

Figure 4 Cyclic voltammograms of 2.65 mM ARP solution on different pH values with scan rate of 0.100 V/s (inset: variation of peak potential with pH).

mechanism was calculated as 1.52:

$$E_p = E^o - \frac{RT}{nF}\ln\frac{[\text{Ox}]}{[\text{Red}]} \pm \frac{2.303\partial RT}{nF}\text{pH} \qquad (3.4)$$

Here, E^o is standard peak potential in V; [Ox] and [Red] are equilibrium concentrations of oxidized and reduced species, respectively and ∂ is number of proton participated in mechanism and others are common abbreviations.

Shifting in peak potential to less anodic potential with increasing pH may be concluded as the deprotonation step before electron transfer step.

Although the exact electrode mechanism was not determined, some conclusions about the electroactive centers under the working conditions could be evaluated. Taking into consideration all the experimental studies performed, it could be thought that the electrode reaction is the oxidation of nitrogen in the dihydroquinolin moiety in the ARP molecule.

3.2. *Application of voltammetric methods to ARP determination*

3.2.1. *Optimization of experimental conditions*

Voltammetric response depends markedly on instrumental conditions. To obtain a much more sensitive peak current, the optimum instrumental conditions, such as pulse amplitude, E_a, scan increment, E_s and frequency, f, were studied for 3.0×10^{-6} M ARP solution. The f was varied from 5 to 500 Hz. Although the response to ARP increased with f, above 500 Hz the peak shape was distorted by a large residual current. When E_a was varied in the range of 5–100 mV, the peak current increased with increasing E_a. Analysis of the data showed a linear increase in the peak current for $E_a \leq 65$ mV. When E_a was greater than 50 mV the peak width increased at the same time. Hence, the best peak definition was recorded when using 25 Hz square-wave frequency, 50 mV pulse amplitude and 3 mV scan increment in SWV and 5 mV in DPV.

Under these conditions, electroanalytical procedures based on ARP oxidation at the GC electrode were developed, involving DPV, SWV, DPAAdSV and SWAAdSV for determination of this substance at low levels. Spontaneous adsorption of ARP could be used as an effective preconcentration step before voltammetric measurement and it is necessary to select the optimum preconcentration parameters. The effect of preconcentration potential on the stripping peak current was evaluated from 0.0 to 0.9 V. A maximum peak current was observed at 0.0 V, so this deposition potential was selected in all subsequent studies. Different voltammograms with increasing accumulation times (between 0 s and 210 s) were recorded for solutions containing ARP at different concentrations (5×10^{-7} and 1×10^{-7} M). The peak current increased linearly up to a maximum at 90 s and then remained constant, indicating surface saturation. The value of 90 s was found to be the optimum accumulation time because it provided the largest peak current in the linearity range.

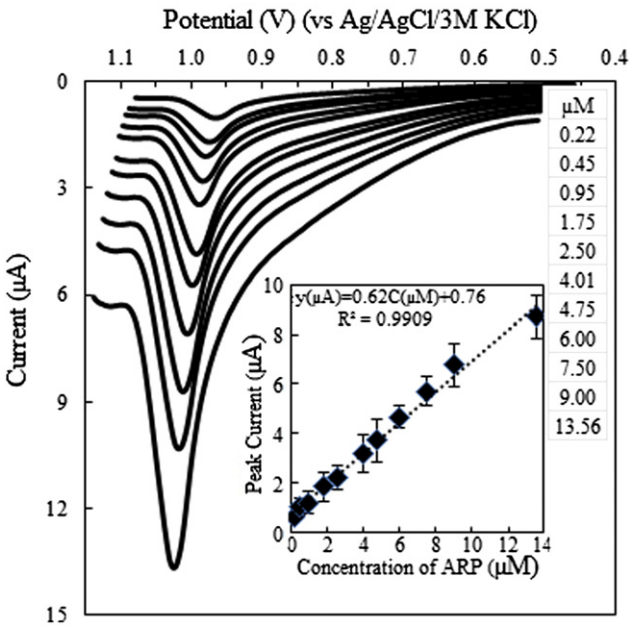

Figure 5 Square-wave anodic adsorptive strippig voltammograms of solutions with different ARP concentrations in BR buffer of pH 4.0, preconcentration time and preconcentration potentials are 90 s and 0.0 V, respectively (inset: variation of peak current with concentration).

3.2.2. *Validation of proposed methods*

When all variables that could affect the performance characteristics of proposed methods were optimized, variation of the peak current with the bulk drug concentration was investigated by recording voltammograms using proposed methods for serial solutions of increasing ARP concentration. In direct voltammetric methods (i.e. without any accumulation step) the response of the oxidation peak was linear in the concentration range 1.14×10^{-5} M (5.11 mg/L) to 1.57×10^{-4} M (70.41 mg/L).

A solution of ARP in BR of pH 4.0 was found to be stable for at least 4 weeks if stored at 4 °C in dark. Using accumulation to the electrode carried out before voltammetric measurement, higher sensitivities could be readily achieved. The relationship between stripping peak current and concentration was found to be linear over the range 2.21×10^{-7} M (0.10 mg/L) to 1.36×10^{-5} M (6.10 mg/L). Calibration voltammograms of SWAAdSV method are given in Fig. 5, and calibration characteristics and the related validation data are given in Table 1.

Limits of detection and quantification of each procedure are also shown in Table 1; they were calculated from the calibration plots using the equations: LOD = $3s_b/m$ and LOQ = $10s_b/m$ (where s_b is the standard deviation of the intercept and m is the slope of the calibration plot) [14]. These values, especially calculated for stripping methods which are in the same order as for therapeutic range [7], confirmed the sensitivity of the proposed methods for ARP determination.

The precision of the proposed method was determined by performing five replicate measurements of 2.0×10^{-5} and 5.0×10^{-5} M ARP in solutions by direct voltammetric methods and 8.0×10^{-7} and 5.0×10^{-6} M ARP in solutions by adsorptive stripping voltammetric methods. Relative standard deviation ranged from 5.85% to 8.94% for peak current in intra-day measurements and ranged from 9.07% to 11.17% in inter-day measurements. Same parameter for peak potential was evaluated as ranged from 2.32% to 5.63% for intra-day measurements and ranged from 4.76% to 7.98% for inter-day measurements.

3.2.3. *Determination of ARP from pharmaceuticals and biological samples*

To check the applicability of the proposed methods, a commercial tablet formulation containing ARP was analyzed.

Table 1 Analytical parameters of calibration graph in the determination of ARP by voltammetric methods.

Parameters	DPV	SWV	DPAAdSV	SWAAdSV
Linear range (μM)	11.4–157.0		0.221–13.6	
Slope of calibration (m) (A/M)	0.0073	0.0257	0.18	0.62
Intercept (b) (μA)	0.0284	0.4566	0.11	0.76
Standard deviation (SD) of calibration (s_r) (μA)	0.0094	0.0194	0.0214	0.0106
SD of slope (s_m) (A/M)	0.0009	0.0026	0.0204	0.0151
SD of intercept (s_b) (μA)	0.015	0.047	0.008	0.023
Limit of detection (LOD) (μM)	6.16	5.49	0.14	0.11
Limit of quantification (LOQ) (μM)	20.60	18.30	0.47	0.37
Regression coefficient (R^2)	0.9924	0.9900	0.9918	0.9909
Intra-day repeatability of current, RSD (%)	6.83	5.85	8.94	8.15
Inter-day repeatability of current, RSD (%)	10.47	9.07	11.17	9.76
Intra-day repeatability of potential, RSD (%)	4.37	2.32	5.63	4.23
Inter-day repeatability of potential, RSD (%)	5.56	4.76	7.98	5.56

Because of the high concentration of ARP in its dosage form (5 mg per tablet), no accumulation time was needed and tablet assay was conducted using the direct voltammetric techniques. In such studies, ARP content of commercially available tablets was determined by estimating recoveries at five different concentrations using the corresponding calibration equation. Recoveries of the drug from this type of matrix ranged from 90.0% to 108.0% in DPV with relative standard deviations of 7.4% and ranged from 87.0% to 104.4% in SWV with relative standard deviations of 7.0% (Table 2). To discover whether excipients in the tablet interfered with the analysis, the nominal content of ARP tablets was determined using the standard addition method. The mean concentration obtained was 4.65 mg per tablet with a relative standard deviation of 5.98%, indicating adequate accuracy and precision of the proposed analysis procedures.

To control the applicability of the proposed methods to biological samples, spiked human serum and spiked human urine samples were used. In such applications, known volumes of standard ARP solutions were spiked to human serum and human urine samples in order to have ARP concentration in linear range and its therapeutic range, then voltammetric measurements were performed and recovery values of proposed methods were calculated using related calibration parameters. Because of the low concentration of ARP in biological samples (its therapeutic range is 50–350 μg/L) [7], direct voltammetric methods are not sensitive enough to detect it in such samples. Therefore, in biological samples only anodic adsorptive stripping voltammetric methods were used. The ARP content of spiked samples was determined by estimating recoveries at five different concentrations using the corresponding calibration equation. Recoveries of the drug from this type of matrix ranged from 84.0% to 109.5% for urine samples with relative standard deviations less than 10.0% and ranged from 90.7% to 110.0% for serum samples with relative standard deviations again less than 10.0% (Table 3). To discover whether any possible organic and inorganic species in serum and urine interfered with the analysis, voltammetric base line of ARP-free biological samples was measured and no extra voltammetric signals in the peak potential ranges of ARP were recognized (Fig. 6) and mean recovery values (Table 3) for such samples were good enough indicating the absence of any interfering effect of biological samples.

Table 2 Result of tablet analysis by DPV and SWV.

Method	Nominal value (mg)	Found (mg)	Mean recovery[a] (%)	RSD (%)
DPV	5.0	4.5, 4.7, 4.9, 5.2, 5.4	98.8±9.1	7.4
SWV	5.0	4.4, 4.8, 4.9, 5.1, 5.2	97.4±8.5	7.0

[a]Mean$\pm ts/\sqrt{N}$, at 95% confidence level, here t is tabulated value of critical t value for 95% of confidence level for $N=5$, and s is the standard deviation of found values.

Table 3 Results of proposed methods to biological samples.

Sample and method	Spiked (mg/L)	Found (mg/L)	Mean recovery[a] (%)	RSD (%)
Urine DPAAdSV	0.35	0.29, 0.34, 0.34, 0.35, 0.37	97.0±9.8	9.2
Serum DPAAdSV	0.35	0.32, 0.33, 0.34, 0.35, 0.37	97.2±6.7	5.7
Serum SWAAdSV	0.35	0.32, 0.33, 0.33, 0.37, 0.39	98.0±10.6	7.9
Urine SWAAdSV	0.35	0.33, 0.33, 0.34, 0.37, 0.38	101.4±8.4	7.5

[a]Mean$\pm ts/\sqrt{N}$, at 95% confidence level, here t is tabulated value of critical t value for 95% of confidence level for $N=5$ and s is the standard deviation of found values.

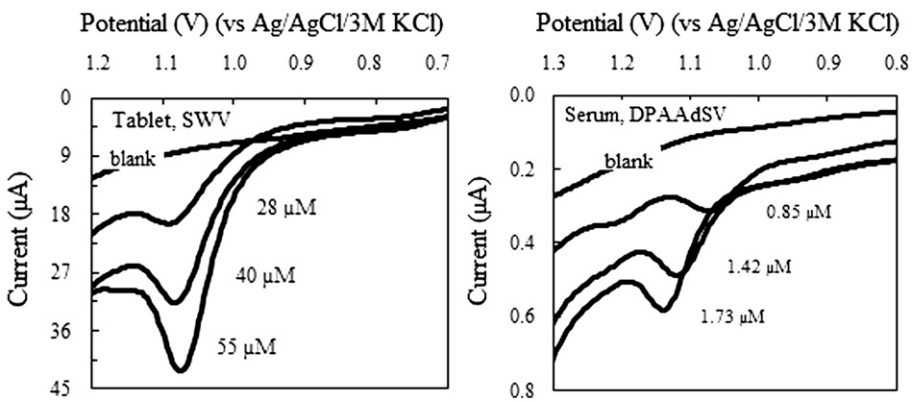

Figure 6 SWV (left) and DPAAdSV (right) measurements of tablet and serum samples for different ARP concentrations in BR buffer of pH 4.0 at optimum conditions.

4. Conclusions

Electrochemical behavior of ARP, atypical antipsychotic and antidepressant, on GCE was investigated for the first time. According to these investigations, ARP was oxidized on GCE by quasi-reversible mechanism with contribution of adsorption and diffusion. These results may be used in investigating the adsorption, distribution and metabolism, pharmacological, toxicological and pharmacokinetic parameters of molecule under investigation. It also could be significant to investigate further studies regarding its side effect, target, related organs, form and way of excreting.

Direct and adsorptive stripping voltammetric methods for direct determination of ARP were proposed. A high percentage of recovery and low RSD values of proposed methods indicate that these methods could be used to quantify ARP without interference from other ingredients. Furthermore, proposed voltammetric methods have distinct advantageous over other existing methods regarding sensitivity, minimum detectability, applicability to biological samples without any pretreatment and time saving. Moreover, no sophisticated instrumentation is required. Consequently, proposed voltammetric methods have the potential for being a good alternative for the assay of ARP in different samples.

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