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Scientific paper

A Reliable Voltammetric Method Utilizing the Effect of an Anionic Surfactant for the Determination of Leuprolide

Begüm Evranos Aksöz[1] and Burcu Dogan Topal[2,*]

[1] *Suleyman Demirel University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Isparta, Turkey*

[2] *Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, Tandogan, Ankara, Turkey*

* *Corresponding author: E-mail: doganb@ankara.edu.tr*

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Abstract

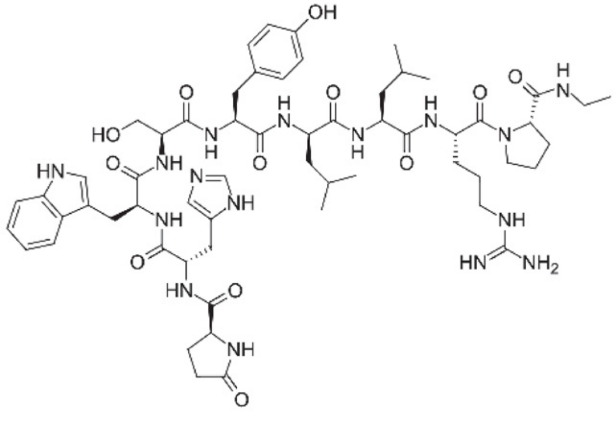
Leuprolide acetate is a synthetic gonadotropin-releasing hormone agonist used in the treatment of central precocious puberty, uterine fibroids, endometriosis, and prostate cancer. In this study, the rapid, simple, environmentally friendly, and sensitive voltammetric method was developed for the quantification of leuprolide acetate in the presence of an anionic surfactant on a glassy carbon electrode. The effect of surfactant types, pH, and scan rate on the voltammetric response of leuprolide acetate were evaluated. Using square wave voltammetry, two anodic peaks were observed at 0.81V and 1.26 V for the glassy carbon electrodes at pH 3.70 (acetate buffer solution). The oxidation peak currents of leuprolide acetate were enhanced in the presence of 8.0×10^{-2} mM sodium dodecyl sulfate. The sodium dodecyl sulfate monomer can be drawn to amino moieties in the drug structure through electrostatic interaction. The voltammetric behavior of leuprolide acetate exhibited irreversible and diffusion-adsorption mix-controlled processes by cyclic voltammetry. All stripping conditions and square wave voltammetric parameters were optimized at pH 3.21 (phosphate buffer). Under optimized conditions, the proposed method exhibits linearity in the concentration range of 3.64×10^{-6}–2.00×10^{-4} mM with a nano-level detection limit of 4.70×10^{-7} mM by square wave adsorptive stripping voltammetry. The developed method was applied for the determination of leuprolide acetate in a pharmaceutical dosage form with a satisfactory recovery of 97.72%.

Keywords: Leuprolide acetate, voltammetry, determination, sodium dodecyl sulfate, validation

1. Introduction

Leuprolide acetate (LPA) in nonapeptide structure known by the chemical name 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (Scheme 1) is a synthetic gonadotropin-releasing hormone agonist[1]. It is more potent and durable to peptidases than the native hormone[1,2]. LPA received its first FDA approval in 1985 for the symptomatic treatment of advanced prostate cancer. LPA acts to stimulates luteinizing hormone (LH) initially[2]. But continuous utilization of LPA decreases gonadotropin-releasing hormone receptors' activity in the pituitary gland and causes complete suppression of LH, follicle-stimulating hormone and gonadal steroids. LPA is used in the treatment of central precocious puberty, uterine fibroids, endometriosis, in vitro fertilization and prostate cancer.

The elimination half-life of 1 mg LPA is 2.9 hours and 3.6 hours for intravenous injection and subcutaneous injection, respectively. While the mean areas below the concentration-time curve are similar for short-acting leuprorelin subcutaneous or intravenous injection, a



Scheme 1: Structure of LPA

dose-dependent increase in the concentration-time curve was detected between 0 and 35 days after depot injection[3]. LPA binds to human plasma proteins at 43–49%. The maximum concentration of LPA is typically achieved 4–5 hours after injection regardless of the formulation and starting dose and varies widely in the range of 4.6–212.0 ng/mL. After administration of 3.75 mg of LPA depot suspension to 3 patients, less than 5% of LPA is excreted unchanged or as the pentapeptide metabolite in the urine.

The quantification of LPA has primarily been performed using methods based on liquid chromatography (LC) combined with mass spectrometry (MS)[4–6]. A voltammetric method for the determination of LPA was developed by our group and the possible electrochemical mechanism of LPA was discussed[7]. The results revealed that the first oxidation process of LPA may occur on the hydroxyl group of the benzene ring of the molecule. It was concluded that a second oxidation step may occur on the nitrogen atom in the indole ring of the molecule leading finally to hydroxylation of the benzene ring.

The chromatographic studies need high volumes of organic solvents and time-consuming sample preparation procedures. Also, both LC and MS devices are expensive compared to electroanalytical instruments. The other advantages of electroanalytical methods include low sensitivity, low cost, environmentally friendly and short analysis time. The glassy carbon electrodes known for long-term stability can be used in drug analysis using electroanalytical methods. The surfactants that may provide significant enhancement of the response of drugs (even in trace quantities) were extensively utilized for various electroanalytical applications[8–16] The most valuable properties of surfactants in electrochemistry are the adsorption at interfaces and the aggregation into supramolecular structures. For such properties, sodium dodecyl sulfate (SDS) is often employed, representing an anionic surfactant that contains a 12-carbon tail attached to a sulfate group.

The aim of this study was to develop the square wave adsorptive stripping (SWAdS) voltammetric method for the sensitive determination of LPA in the presence of SDS on a glassy carbon electrode (GCE). In addition, the proposed method was utilized for the quantification of LPA in pharmaceutical dosage forms.

2. Experimental

2. 1. Apparatus and Electrochemical Procedure

PalmSens equipment (PSTrace 5.7) was used for electrochemical measurements. A GCE with a 3 mm diameter (working electrode, BAS MF-2012), a platinum wire (counter electrode, BAS MW-1032), and an Ag/AgCl (300 mM NaCl) (reference electrode, BAS MF-2052) were used in the electrochemical cell. Experiments were implemented at room temperature. The GCE was polished with aluminium oxide slurry on a damp smooth polishing pad. A Model 538 (WTW, Austria) pH meter was used for all pH measurements.

Potential step was set at 5 mV, and the scan rate was set to 0.1 V/s for cyclic voltammetry. Differential pulse voltammetry (DPV) parameters were as follows: potential step: 5 mV; potential pulse: 20 mV; pulse time: 0.07s; scan rate 0.02V s^{-1}. Square wave voltammetry (SWV) parameters were potential step: 10 mV, amplitude: 0.1 V, frequency: 20 Hz.

The optimum conditions of square wave adsorptive stripping (SWAdS) voltammetry were found as a step potential of 18 mV; an amplitude of 100 mV; a frequency of 100 Hz; an accumulation potential of 200 mV, and an accumulation time of 180 s.

2. 2. Chemicals

LPA was kindly supplied by Abbott Pharmaceutical Company (İstanbul, Turkey). Its pharmaceutical dosage form lucrin (5mg/mL), was purchased from a pharmacy. Cetyltrimethylammonium bromide (CTAB) (≥98%), SDS (≥99%), benzalkonium chloride (BAC) (≥95%), triton-X 100, tween 20, methanol, sulphuric acid, acetic acid, boric acid, phosphoric acid, sodium hydroxide and ultra-pure water were purchased from Merck (Darmstadt, Germany).

2. 3. Preparation of Solutions

The stock solutions of 1.0×10^{-3} M SDS, BAC, triton-X 100, and tween 20 were freshly prepared in ultra-pure water and 1.0×10^{-3} M CTAB was prepared in methanol. Acetate buffer (pH 3.6–5.6), phosphate buffer (pH 2.0, 3.0, and pH 6.0–8.0), Britton-Robinson buffer solutions (BR, 0.4 M, pH 2.0–10.0), and 0.1 M sulphuric acid supporting electrolyte were prepared. All solutions were kept at 4 °C.

The stock solution of 1.0×10^{-3} M LPA was prepared in methanol. The working solutions of LPA (1.0×10^{-2} mM) were prepared by diluting the stock solution of LPA with buffer solution and 8.0×10^{-2} mM *SDS* containing 20% of methanol (v/v).

2. 4. Analysis of LPA in Pharmaceutical Dosage Form

Adequate amount of lucrin injection solution (contain 5 mg LPA per mL of the solution) was dissolved in methanol to prepare the stock solution of 1.0×10^{-3} M injection solution.

The working solutions were prepared by diluting the stock solution of 1.0×10^{-3} M lucrin with pH 3.21 phosphate buffer solution and *SDS* containing 20% of methanol (v/v).

The nominal substance content in the pharmaceutical dosage form was determined using the regression data obtained from the calibration curve in concentration range from 3.64×10^{-6} to 2.00×10^{-4} mM. For recovery experiments, 2 mg of pure drug was added to the pharmaceutical dosage form, and % recovery was determined using the calibration regression data (More details are given in Section 3.5).

3. Results and Discussion

3. 1. The Effect of Surfactant on Voltammetric Behaviour of LPA

Pulse techniques (DPV and SWV) were used to obtain the distinctive information on the voltammetric response of LPA. Due to the repeatable results, DPV was preferred to assess the effect of surfactant types on the electrochemical response of LPA on GCE. In acetate buffer (pH 3.70), LPA showed two anodic peak responses, namely, a first peak (Ep_1, ip_1) and second peak (Ep_2, ip_2) on bare GCE as seen in Table 1. The voltammetric behavior of 1.0×10^{-2} mM LPA was evaluated in the presence of 1.0×10^{-2} mM SDS, BAC, CTAB, Triton-X 100, and Tween 20 in acetate buffer (pH 3.70) (randomly selected) as seen in Table 1. The higher anodic peak currents of LPA were obtained in the presence of SDS. As a result of this study, SDS was chosen for all subsequent experiments. Table 1 shows that first peak current (ip_1) was significantly higher than the second peak current (ip_2) of LPA.

Table 1: The effect of surfactants on the voltammetric peak potentials and currents of LPA on GCE by DPV in acetate buffer (pH 3.70)

Surfactant types	E_{p1} (mV)	i_{p1} (μA)	E_{p2} (mV)	i_{p2} (μA)
–	0.821	0.083	1.249	0.035
SDS	0.806	0.192	1.310	0.048
Tween 20	0.816	0.115	–	–
Triton X-100	0.831	0.107	1.224	0.016
CTAB	0.831	0.114	1.284	0.006
BAC	0.841	0.074	–	–

3. 2. The Effect of SDS Concentration on Voltammetric Response of LPA

The effect of SDS concentration on voltammetric responses of 1.0×10^{-2} mM LPA was performed in the range of 1.0×10^{-4} – 2.0×10^{-1} mM in acetate buffer (pH 3.70) using DPV and SWV. The critical micelle concentration of SDS is 8.2 mM. Once the concentration is lower than 8.2 mM, SDS is randomly dispersed as monomers in the aqueous solution[19]. Because of the higher peak current, SWV was selected to assess the effect of SDS concentration. As shown in Fig. 1, the ip_1 of LPA enhanced with increasing concentration of SDS up to 8.0×10^{-2} mM and then ip_1 was rather small. The high value of ip_1 was obtained in the presence of 8.0×10^{-2} mM *SDS*, which was selected as the optimal concentration for subsequent experiments.

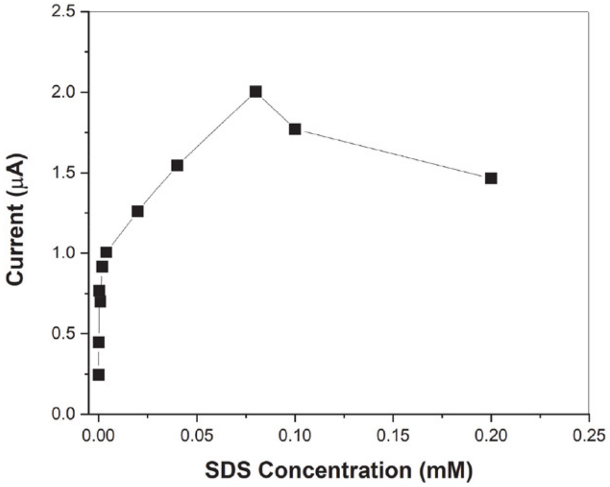


Figure 1: Effect of SDS concentration on ip_1 of LPA (1.0×10^{-2} mM) in acetate buffer (pH 3.70) by SWV.

Fig. 2 depicts the effect of 8.0×10^{-2} mM SDS on the voltammograms of 1.0×10^{-2} mM LPA in acetate buffer (pH 3.70) by SWV. The ip_1 of LPA was enhanced, and its peak potential (Ep_1) slightly shifted to a less positive potential, while the ip_2 of LPA also slightly increased and its peak potential shifted (Ep_2) to a more positive potential (Fig. 2). It was concluded that the negatively charged SDS monomers can be attracted to the amino moiety on the LPA structure via electrostatic interaction[17]. Because of this interaction, more LPA molecules can rapidly reach the GCE surface, increasing the peak currents.

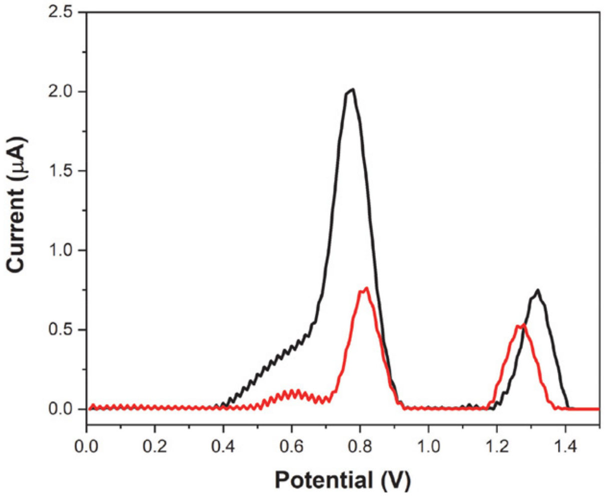


Figure 2: The SW voltammograms of LPA (1.0×10^{-2} mM) in the absence of SDS (red) and the presence (black) of SDS (8.0×10^{-2} mM) in acetate buffer (pH 3.70).

3. 3. The Influence of pH and Scan Rate on Voltametric Response of LPA

The impact of pH on LPA response is significant for enlightening the voltammetric behaviour of LPA. The voltammetric responses of 1.0×10^{-2} mM LPA in the presence of 8.0×10^{-2} mM SDS in the pH range of 1.0–11.0 using acetate buffer, phosphate buffer, Britton-Robinson buffer solutions, and 0.1 M sulphuric acid supporting electrolyte were assessed by cyclic voltammetry, DPV, and SWV. Higher peak current was obtained using SWV, which was selected for further method development studies.

Fig. 3A exhibited the SW voltammograms of 1.0×10^{-2} mM LPA in the presence of 8.0×10^{-2} mM *SDS* in various pH values. The maximum *ip* values were obtained in phosphate buffer with pH 3.21 (Fig. 3B), in which LPA showed two well-defined anodic peaks at 0.80 V (Ep_1) and 1.35 V (Ep_2) (Fig. 3A). The ip_1 of LPA was significantly higher than ip_2 (Fig. 3A), which was selected for further method development studies.

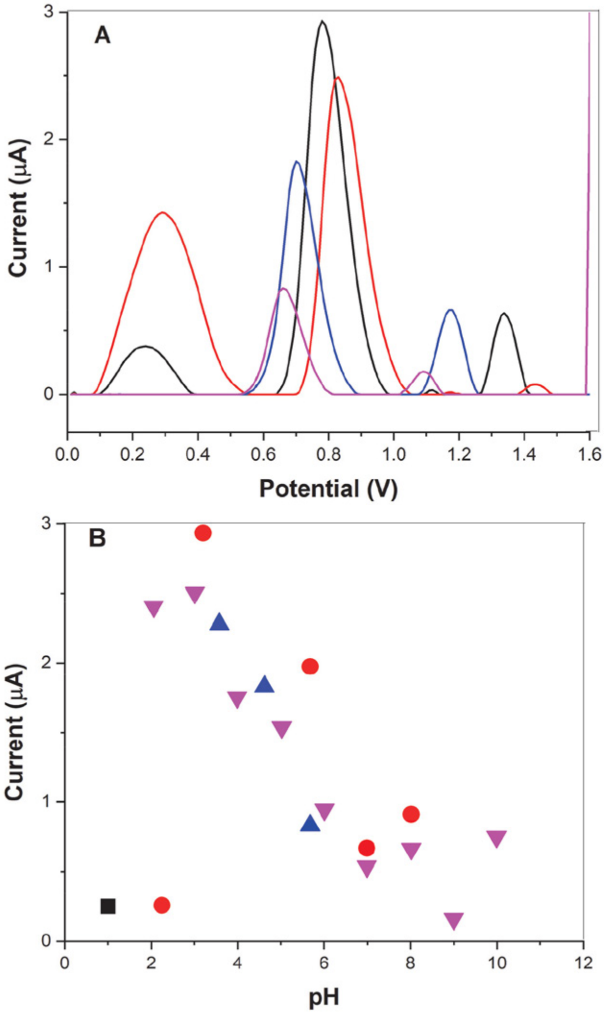


Figure 3: A: SW voltammograms of LPA (1.0×10^{-2} mM) in the presence of *SDS* (8.0×10^{-2} mM) on GCE at different pH values (pH 2.00 BR buffer (red), pH 3.21 phosphate buffer (black), pH 4.62 acetate buffer (blue), pH 5.68 acetate buffer (pink)). **B:** The effect of various supporting electrolyte and pH (▲: acetate buffer, ●: phosphate buffer, ▼: BR buffer, ■: 0.1M H_2SO_4) on ip_1 (1.0×10^{-2} mM LPA).

By SWV, in the pH range of 1.0–9.0 (Figure 4), the Ep_1 and Ep_2 of LPA were shifted to lower positive values, which can be expressed by the following equations;

$$Ep_1\ (\text{V}) = -0.032\ pH + 0.872\ (\text{r: } -0.980) \quad (1)$$

$$Ep_2\ (\text{V}) = -0.073\ pH + 1.542\ (\text{r: } -0.989) \quad (2)$$

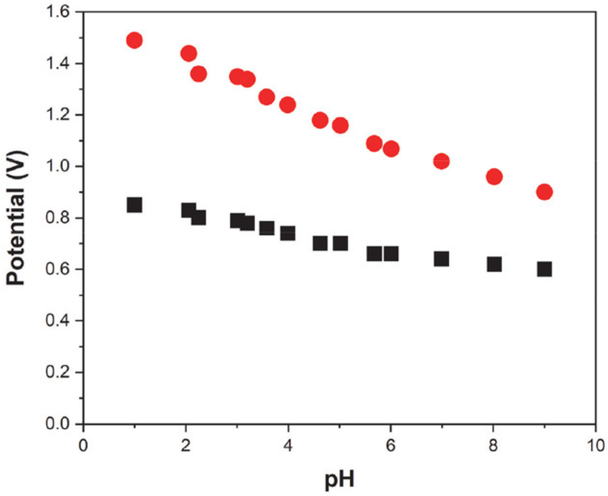


Figure 4: The effect of pH on Ep_1 (■, black color) and Ep_2 (●, red color) for LPA (1.0×10^{-2} mM) in the presence of *SDS* (8.0×10^{-2} mM).

This shifting indicated the changes in the acid-base protonation functions in LPA molecule.

The effect of scan rate on the first peak oxidation process of 4.0×10^{-2} mM LPA was investigated using cyclic voltammetry in the range of 0.005–0.5Vs^{-1} (Figure 5) in phosphate buffer (pH 3.21) in the presence of *SDS* (8.0×10^{-2} mM).

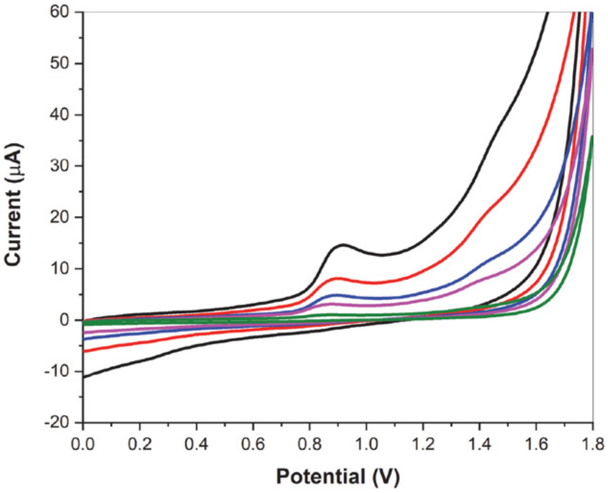


Figure 5: Cyclic voltammograms of LPA (4.0×10^{-2} mM) scanned at the following scan rates (mVs^{-1}); 500 (green), 200 (pink), 100 (blue), 50 (red) and 10 (black).

There was a linear relationship between ip_1 and the scan rate (v) where n: number of data points as seen in the following equation;

$$ip_1\ (\mu A) = 16.29\ v\ (Vs^{-1}) + 0.703\ (r: 0.994;\ n: 9) \qquad (3)$$

A plot of log ip_1-log v gave a straight line where n: number of data points as follows;

$$\log ip_1\ (\mu A) = 0.69 \log v\ (Vs^{-1}) + 1.125\ (r: 0.999;\ n: 9) \qquad (4)$$

The slope was found as 0.69. This suggests the electrochemical process was realized under diffusion-adsorption mixed controlled[21].

3. 4. The Effect of Accumulation Potential/ Time and SWV Parameters on Peak Currents

Given that LPA may be adsorbed at the electrode surface, the influence of deposition potential (E_{acc}) and time (t_{acc}) were evaluated for LPA solution (1.0×10^3 mM) in the presence of *SDS (*8.0×10^{-2} mM) by SWV.

The t_{acc} was constant at 60 s, the effect of E_{acc} on peak currents was studied in the range from 0.0 to 1.5 V (Figure 6A). The 0.2 V was chosen due to the better repeatability and higher peak currents. Then the effect of t_{acc} on peak currents was varied in the range 0–360 s, and t_{acc} of 180 s was selected (Figure 6B). The optimal conditions of SWAdS voltammetric method were E_{acc} of 0.2 V and t_{acc} of 180 s.

The influence of parameters including step potential (E_{step}), frequency, and pulse amplitude on peak currents of 1.0×10^{-3} mM LPA in the presence of 8.0×10^{-2} mM *SDS* was evaluated. The step potential was selected in the range of 4 to 22 mV at a constant frequency of 20 Hz, amplitude of 100 mV, E_{acc} of 0.2 V, and t_{acc} of 180 s. The ip_1 and ip_2 increased up to 18 mV, which was chosen as the optimal value (Fig. 7A). The pulse amplitude varied from 10 to 150 mV, and the ip_1 and ip_2 were increasing up to 100 mV (Fig. 7B), which was chosen as the optimum. The effect of the frequency on peak currents was studied between 10–100 Hz and 100 Hz was chosen (Figure 7C).

3. 5. Analytical Method Development and Validation

Considering all the results thus far, due to the higher peak current, ip_1 of LPA was assessed for the development of the analytical method compared to ip_2.

The LPA response improved in the presence of 8.0×10^{-2} mM *SDS* by performing deposition of 180 s at 0.2 V, step potential of 18 mV, pulse amplitude of 100 mV, and frequency of 100 Hz using the SWAdS voltammetric technique.

All analytical method validation parameters containing limit of detection (LOD), limit of quantification (LOQ), linearity, precision, and accuracy were calculated according to ICH guidelines[17].The precision of the proposed method was evaluated in terms of repeatability and reproducibility by calculating the relative standard deviations (RSD %) with five replicates (n = 5). The accuracy of the proposed method was quantitatively given by the use of relative errors (Bias %) with three replicates (n = 3). LOD and LOQ values were calculated based on the following equations:

LOD = 3*s*/m; LOQ = 10*s*/m where "*s*" is the standard deviation of the lowest concentration-response (three replicates) and *m* is the slope of the calibration line.

Using optimized conditions, the SWAdS voltammetric method was developed for the determination of LPA in the presence of *SDS* (8.0×10^{-2} mM) in phosphate buffer

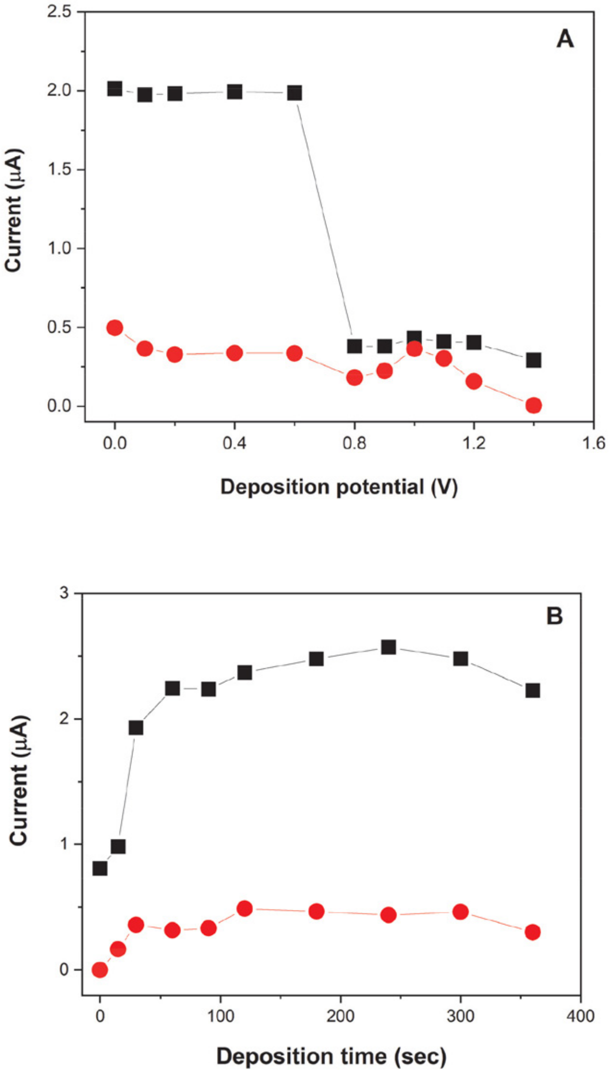


Figure 6: The effect of the E_{acc} (A) and t_{acc} (B) on ip_1 (■, black color) and ip_2 (●, red color) of LPA (1.0×10^{-3} mM) in phosphate buffer (pH 3.21) in the presence of *SDS* (8.0×10^{-2} mM) examined by SWAdV.

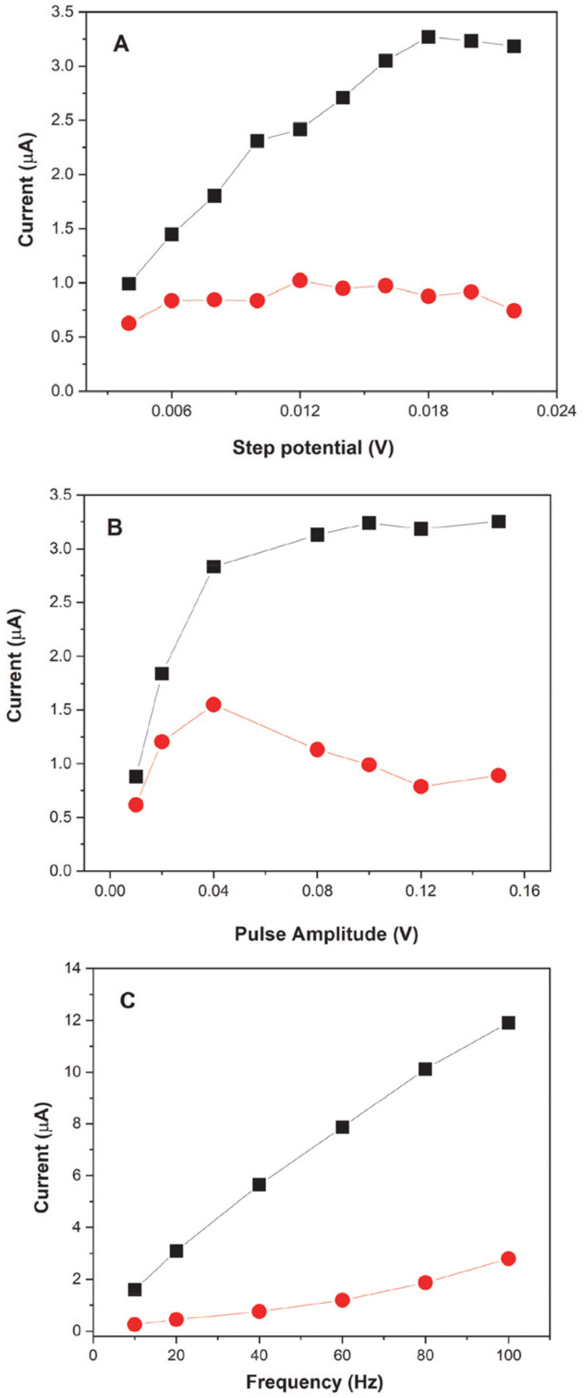


Figure 7: Influence of E_{step} (A), pulse amplitude (B), and frequency (C) on ip_1 (■, black color) and ip_2 (●, red color) of LPA (1.0×10^{-3} mM) in phosphate buffer (pH 3.21) in the presence of *SDS* (8.0×10^{-2} mM) examined by SWAdV.

(pH 3.21). The calibration curves were linear in the range from 3.64×10^{-6}–2.00×10^{-4} mM. Equation for calibration curve was ip (µA) = 4.86×10^7 C (mM) – 0.015 with correlation coefficient of r = 0.9986. Some selected SWAdS voltammograms of calibration curve were given in Fig. 8. LOD was calculated to be 4.70×10^{-7} mM, while LOQ was calculated to be 1.42×10^{-6} mM. The RSD% ±SE values of repeatability and reproducibility of 5.46×10^{-5} mM LPA were 1.86±0.05 and 2.11±0.06, respectively. The precision values suggest that the proposed method is convenient for quantification of LPA in pharmaceutical dosage forms.

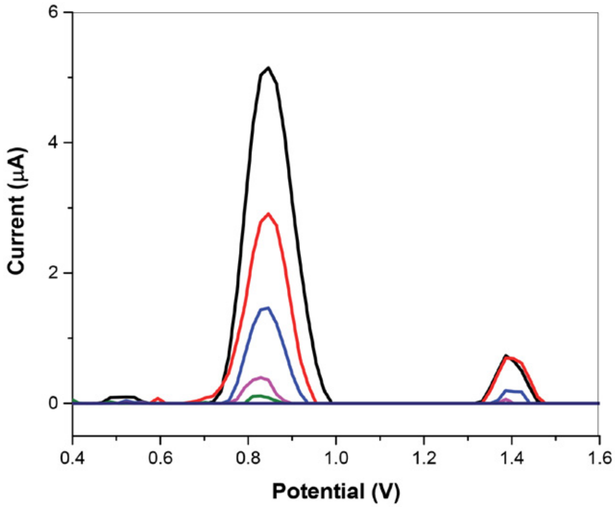


Figure 8: SWAd voltammograms of supporting electrolyte (purple), LPA levels of 1.0×10^{-5} mM (green), 2.0×10^{-5} mM (pink), 4.0×10^{-5} mM (blue), 8.0×10^{-5} mM (red), and 1.0×10^{-4} mM (black) at pH 3.21 (phosphate buffer) in the presence of 8.0×10^{-2} mM *SDS.*

For accuracy studies the developed method was applied to pharmaceutical dosage forms in the presence of SDS (8.0×10^{-2} mM) in phosphate buffer (pH 3.21). The sample preparation procedure was reported in the experimental part. The developed method was utilised to determine of LPA in pharmaceutical dosage forms (5mg/mL) without any matrix effects using the related linear regression equations of the bulk form. The recovery studies were performed by standard addition methods in which 2 mg of pure LPA solution were added to the pharmaceutical dosage form (Figure 9). The recovery parameters (Table 2) were calculated using the related calibration equations. The recovery value of 97.72% exhibited that the proposed method is free from interferences of the excipients in pharmaceutical dosage forms[17].

Table 2: Analysis LPA in pharmaceutical dosage form and recovery studies.

Labeled claim (mg/mL)	5.00
Amount found[a] (mg/mL)	4.92±0.05
RSD (%)	0.98
Bias (%)	−1.61
Added (mg)	2.00
Found [a] (mg)	1.95±0.09
Average recovery (%)	97.72±4.52
RSD (%) of recovery	4.63
Bias (%)	−2.28

[a] Each value is the mean of three replicates given with standard error value

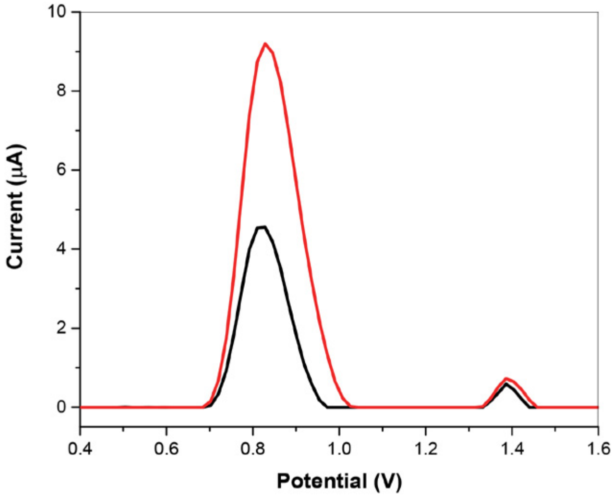


Figure 9: SWAdVs of labeled claim (black) and added amount (red) of LPA levels in pH 3.21 phosphate buffer in the presence of 8.0 × 10^{-2} mM *SDS.*

4. Conclusion

A reliable, sensitive, and low-cost SWAdS voltammetric method has been developed for the quantification of LPA in the presence of SDS on a glassy carbon electrode. The peak currents of LPA demonstrated higher sensitivity in the presence of 8.0 × 10^{-2} mM SDS. The monomer structure of anionic surfactant can be attracted to amino moieties in LPA structure via the electrostatic interaction. The developed method showed excellent analytical performance with nano-level detection limits and good reproducibility. The method enables measurement without time-consuming electrode modifications and sample pre-treatment. The developed method was administered for the determination of LPA in the pharmaceutical dosage form with satisfactory recovery. This simple and rapid electrochemical method may open the way for possible applications in the field of analytical chemistry for direct determination of LPA in pharmaceuticals.

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Povzetek

Leuprolid acetat (LA) je sintetični agonist gonadotropin sproščujočega hormona, ki se uporablja pri zdravljenju centralne prezgodnje pubertete, materničnih fibroidov, endometrioze in raka prostate. V tej študiji je bila razvita hitra, preprosta, okolju prijazna in občutljiva voltametrična metoda za kvantifikacijo LA v prisotnosti anionske površinsko aktivne snovi na elektrodi iz steklastega ogljika. Ovrednoten je bil vpliv površinsko aktivnih snovi, pH in hitrosti skeniranja na voltametrični odziv LA. Pri pH 3,70 (raztopina acetatnega pufra) sta bila z voltametrijo s kvadratnim spreminjanjem potenciala ("*square wave voltammetry*") zaznana dva anodna vrha pri 0,81 V in 1,26 V. S "*square wave*" adsorptivno inverzno voltametrijo ("*square wave adsorptive stripping voltammetry*") je bila pri optimiziranih pogojih umeritvena krivulja za LA linearna v koncentracijskem območju od $3,64 \times 10^{-6}$ do $2,00 \times 10^{-4}$ mM, meja zaznave pa je bila $4,70 \times 10^{-7}$ mM. Razvita metoda je bila uporabljena za določanje LA v farmacevtski obliki.