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Electro-Oxidation Mechanism and Direct Square-Wave Voltammetric Determination of Lidocaine With a Carbon-Paste Electrode

Nadereh Rahbar [1,2,*]; Zahra Ramezani [1,2]; Ahmad Babapour [2]

[1]Nanotechnology Research Center, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran
[2]Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

*Corresponding author: Nadereh Rahbar, Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran. Tel: +98-6133738378, E-mail: n_rahbar2010@ajums.ac.ir

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Background: Lidocaine hydrochloride (LH) is one of the most extensively used local anesthetics and peripheral analgesics. Availability of a simple and sensitive assay method for this analyte in pharmaceutical preparations as well as development of new voltammetric detectors that can be applied in chromatographic systems for determination of this analyte in biological samples are of great importance.
Objectives: In this study, a square-wave voltammetric (SWV) determination of LH at a bare carbon-paste electrode (CPE) was reported. Moreover, the oxidation mechanism for LH molecule at this electrode was investigated.
Materials and Methods: The SW voltammogram of LH solution at CPE showed a well-defined peak between +0.80 and +0.88 V depending on a scan rate in potassium nitrate (KNO_3) solution. Different chemical and instrumental parameters influencing the voltammetric response, such as the pH level and scan rate were optimized for LH determination.
Results: A linear range of 8.0 -1000.0 μmol L^{-1} ($r^2 = 0.999$) was obtained. The limit of detection (LOD) was 0.29 μmol L^{-1}. The relative standard deviations of 2.1% obtained for 0.8 800 μmol L^{-1} solution of LH indicated a reasonable reproducibility of the method.
Conclusions: The results of this study show that LH in different pharmaceutical preparations could be determined with good reliability. In addition, the results reveal that the equal numbers of electrons and protons are involved in the oxidation of LH and the irreversible oxidation of an analyte was performed via amine groups of LH molecule.

Keywords: Lidocaine; Anesthetic; Square Wave Voltammetry; Carbon Paste Electrode

1. Background

Direct electro-oxidation of lidocaine hydrochloride (LH) is important for fast and sensitive determination of this compound in pharmaceutical preparations as well as for the development of voltammetric detectors coupled to flow techniques or chromatographic methods. Figure 1 indicates the chemical structure of LH (2-(diethylamino)-N-(2, 6-dimethylphenyl)-acetamide). It belongs to a group of aromatic amides extensively used as a local anesthetic drug with a pronounced antiarythmic and anticonvulsant effect (1).

This latter capacity of LH makes it suitable as a therapeutic agent in the treatment of cardiac disorders. Analysis of pharmaceutical preparations is of the most important and attractive branches in applied analytical chemistry. A variety of the methods are available for the determination of LH. To date, the most frequently method for LH determination is the high-performance liquid chromatography (HPLC) due to its high sensitivity and excellent selectivity (1-7). Other methods such as gas chromatography (8), electrophoresis (9-11), spectrophotometry (12, 13), and atomic absorption spectrometry (indirect method) (14) have also been developed. Most of these methods are expensive, time consuming, suffer from extensive pretreatment steps and use toxic solvents and reagents. However, electrochemical techniques are useful alternative methods, having important advantages including simplicity, reliability, sensitivity and selectivity and more often are used in the analysis of pharmaceutical preparations and biomedical compounds (15-18). A few published articles are available for the electrochemical determination of LH and related compounds.

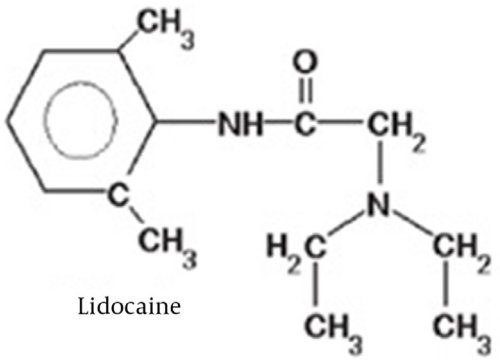

Figure 1. Chemical Structure of Lidocaine

In a study (19), an indirect voltammetric method for the determination of some weak bases (e.g. LH), based on the oxidation of alpha-tocopherol was investigated by the linear sweep voltammetry. In another study, a SWV procedure for the LH determination using boron-doped electrodes was described by another researcher (20). The potentiometric determination of LH using the ion-selective electrodes has also been reported by Giahi et al. (21). A solid - state electrochemiluminescence (ECL) detector making of Tris (2, 2-bipyridyl) ruthenium (II) ($Ru(bpy)_3^{2+}$)-Zirconia - Nafion composite modified glassy carbon disk electrode for determination of LH in injection preparations and biological fluids was also proposed (22). In the other work, Fourier-transform cyclic voltammetry at Au microelectrodes for indirect assay of LH was proposed (23). The capsaicin modified carbon nano-tube modified electrode and pchloranil modified carbon-paste electrodes (CPEs) were prepared for the determination of benzocaine and LH as a model pharmaceuticals (24). However, these methods are sophisticated and time-consuming.

In voltammetric methods, CPEs show interesting properties such as a wide potential range, low- reduction peak of oxygen, ease of fabrication, renewability and compatibility with various types of modifiers. In addition, these electrodes are cheap and harmless from an environmental point of view (25-27).

2. Objectives

To the best of our knowledge, the electrochemical mechanism and determination of LH at a bare CPE have not yet been reported. Therefore, this work is designed to investigate the LH oxidation mechanism, and also to develop a fast, simple, sensitive and cheap method for the determination of LH in pure and pharmaceutical products using SWV at a bare CPE, and introduce the application potential of this method as a detector in chromatographic and flow systems.

3. Materials and Methods

3.1. Reagents and Materials

All chemicals were of analytical grade and obtained from Merck (Darmstadt, Hesse, Germany). Lidocaine hydrochloride, paraffin and graphite powder (100 μm) were purchased from Fluka (Milwaukee, USA).

The LH stock solution (0.01 M) was prepared by dissolving 0.2886 g of LH in distilled water and diluting to the mark in a 100-mL volumetric flask. Working solutions were prepared by an appropriate dilution of the stock solution. Double-distilled water was used throughout this study.

3.2. Apparatus

All voltammetric measurements were performed on a Metrohm (AUTOLAB, model PGSTAT302N) electrochemical device. A three-electrode arrangement was used throughout. A CPE acts as a working electrode and a platinum wire was used as an auxiliary electrode together with an Ag/AgCl reference electrode, using 3M KCl as an electrolyte with a porous membrane. The adjustment of pH was carried out using a pH-meter (JENWAY model 3320-UK).

3.3. Carbon-Paste Electrode Preparation

To prepare a CPE, 0.7 g graphite powder was mixed with 0.3 g paraffin oil for 15 minutes (ratio of C:Paraffin, 70:30, w/w) (28). Preliminary experiments showed that the best SW voltammogram due to the peak shape and current can be observed for LH at this composition. The paste was packed into an insulin syringe and a copper wire was put in contact with it for its external electric contact. The electrode surface was rubbed against a weighing paper to obtain a smooth electrode surface for further use.

3.4. Voltammetric Determination of LH

In this research, cyclic voltammetry (CV) and SWV were used as electrochemical tools for investigation of the LH oxidation mechanism and determination in pharmaceutical formulations. The SWV method is chosen to determine LH due to its sensitivity and speed. Preliminary CV experiments in a potassium nitrate (KNO_3) solution showed a well-defined irreversible peak related to oxidation of LH. Likewise, the general procedure performed in obtaining square-wave voltammograms of LH was as follows: the appropriate amount of standard LH solution and 4 mL of 1M KNO3 solution were added into a 25-mL volumetric flask and diluted to the mark with distilled water. This solution was transferred into the electrochemical cell. After an accumulation time of 120 seconds on an open-circuit, the cyclic voltammograms were recorded from +0.2 to +1.0 V at the scan rate of 0.10 $V\ s^{-1}$. Square-wave voltammograms were recorded by applying a positive-going scan of +0.5 to +1.2 V with a scan rate of 0.125 Vs^{-1}. To regenerate a new and fresh surface on the CPE, the tip of the electrode was polished against a weighing paper.

4. Results

4.1. Electrochemical Characteristics of Lidocaine Hydrochloride on a Carbone Paste Electrode

Direct determination of amines by electrochemical methods at surface of unmodified electrodes is often impractical because of the formation of polymeric films on the electrode surface. Early CV studies on electrochemical behavior of $1.2 \times 10 - 4$ M LH (pH 10) on different electrodes such as platinum, gold disk and glassy-carbon electrodes showed unsuitable voltammograms of LH. The results revealed that time-consuming and tedious steps of the

electrode surface polishing are required to obtain the reproducible peaks. These behaviors are agreed with those of previous studies mentioned (24). However, Figure 2A and 2B illustrate the cyclic voltammogram and a sharp and well-shaped SW voltammogram peak of LH at CPE. To obtain a well-defined SW voltammogram with possible maximum peak current for the determination of trace amounts of LH, different instrumental and chemical parameters such as pH, scan rate, accumulation time and potential, electrolyte type and volume were optimized.

4.2. Effect of pH

The effect of pH on the peak current (Ip) and peak potential (EP) was investigated by applying different pH values ranging from 1 to 12. Figure 3A shows the SW voltammograms of 0.4 mM for LH solution at different pH values (pH 1 - 10). No oxidation peaks were found between pH 1 - 3. At higher pH values between 4 and 8, the peak currents increased rapidly and remained almost constant above pH 8. This implies the presence of hydrogen ions in the electrochemical reaction. In the pH range of 4 to 8, LH peak current increases linearly with slope equal to 0.603 (Figure 3B). These results revealed that the oxidation of LH in higher pH levels is more favorable. On the other hand, considering the relationships between the peak current and rate of electrochemical reaction (17), it can be concluded that the rate of oxidation of LH increases with increasing pH and reaches to its maximum value at pH 8. This might be due to the fact that pK_a of LH is about 8 (19, 20) and above pH 8, the main fraction of LH molecules may be in their deprotonated form. The the linear relationship between peak current and pH is as follwoing equation:

$Ip\ (\mu A) = 0.603\ pH + 1.762\ (r^2 = 0.993)$ (Equation 1)

Moreover, as pH increases, the SW peak potential is shifted towards negative potentials; a 1-unit change in pH can change the SW peak potential about 60 mV (Figure 3C). It can be concluded that the hydrogen ion participates in oxidation processes and the electrochemical reaction involves the proton-transfer steps (29). On the other hand, a change in slope of the Ep - pH curve at pH = pKa indicates the electrode process in which a weak acid or base is involved. In this study, a value of 8.0 was obtained using the intersection of the two linear curves observed in Figure 3C which is very close to literature value of 8.03 (20).

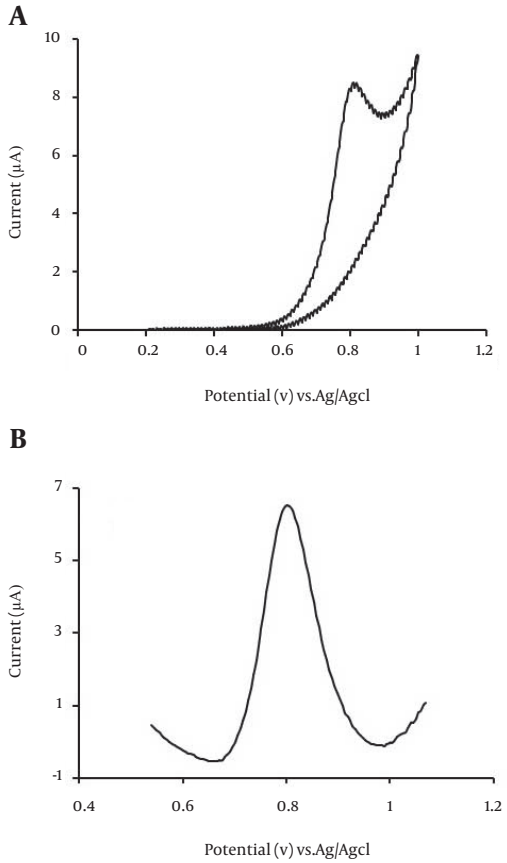

Figure 2. A) The cyclic voltammogram of LH on unmodified CPE. [Conditions: concentration of LH: 0.4 mM; pH = 10.0; accumulation time: 120 s; scan rate: 0.125 V s-1]. B) The SW voltammogram of LH on unmodified CPE. [Conditions: concentration of LH: 0.4 mM; pH = 10.0; accumulation time: 120 s; scan rate: 0.125 V s-1]

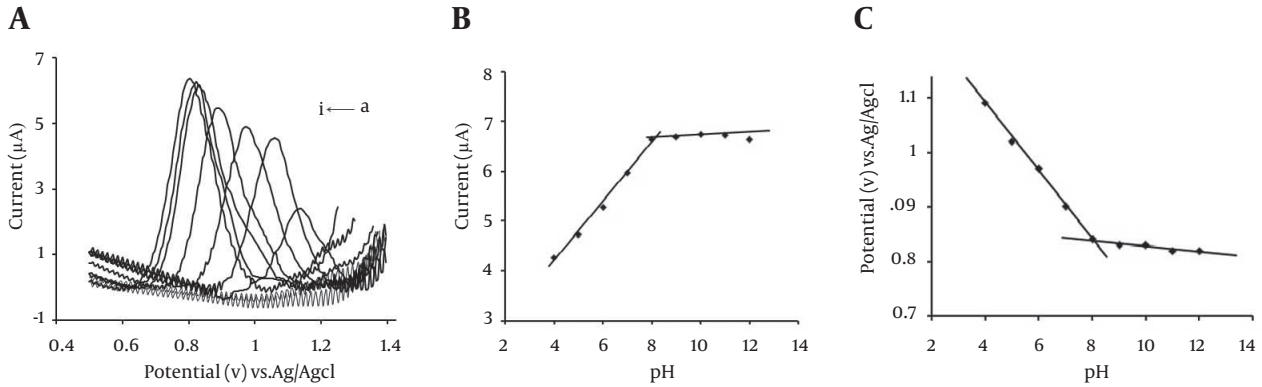

Figure 3. A) SW voltammograms of LH solution at different pH values of (a) 2, (b) 3, (c) 4, (d) 5, (e) 6, (f) 7, (g) 8, (h) 9, (i) 10. B) Plot of peak currents vs. pH (4-12). C) Plot of peak potential vs. pH. [Conditions: concentration of LH: 150 μM; accumulation time: 120 s; scan rate: 0.125 V s-1]

The linear relationship between pH and peak potential in the pH range of 4.0-8.0 was observed. The regression equation is as:

Ep (V) = 1.336 - 0.062 pH (r^2 = 0.997) (Equation 2)

The slope value of 62 mV per pH unit suggests that equal numbers of electron and protons are involved in the oxidation of LH. That is 0.0592(h/n) V/pH, where h and n are the number of protons and electrons participate in electrochemical processes, respectively (15, 17). It may be assumed that the electro-active centers in the LH molecule are either tertiary aliphatic amine or amide group (30). According to the previous studies, an oxidation process of amide function in the presence of nucleophiles such as water involves two electrons and one proton (31, 32). However, the oxidation mechanism of tertiary aliphatic amines has been investigated previously and the results suggest a two-electron/two-proton process. The obtained results in that research showed that the oxidation products of tertiary aliphatic amines in aqueous alkaline solution are secondary amines and aldehydes (33, 34). This agrees with slope obtained from linear relationship between pH and peak potential (62 mV/pH). Moreover, the existence of aromatic electron withdrawing group in the next of amide function hinders the oxidation of this group in comparison with amine group in LH molecule. Meanwhile, the electron donating groups (ethyl groups) provide more facility for oxidation of amine center of this molecule. Therefore, it can be concluded that the oxidation of amine group of LH molecule is more probable than the amide oxidation mechanism and oxidation products might be the secondary amine and an aldehyde. In the light of these findings, the reaction that is shown in Figure 4 can be suggested for the LH oxidation at CPE. However, more investigations are in progress to establish the real mechanism of LH oxidation. In the pH range of 8 to 12, peak potentials keep almost unchanged; therefore, it can be concluded that in these pH levels the rate of the LH oxidation reaction rises to its maximum value.

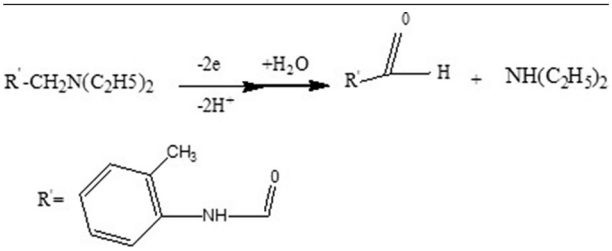

Figure 4. The Proposed Mechanism for Oxidation of Lidocaine Hydrochloride on a Carbon Paste Electrode

4.3. Effect of Potential Scan Rate

A study of the effect of potential sweep rate (ν) on the peak current was investigated. It helps to identify that the oxidation of LH at CPE is diffusion- or surface-controlled. Figure 5A illustrates the SW voltammograms of 150 μM LH at different scan rates within the range of 0.01 - 0.30 V s^{-1}. It shows a linear increase in the peak current with increase in scan rate between 0.05 - 0.20 V s^{-1} as expected for the surface-controlled process. This linear dependency between Ip and ν (Figure 5B) can be concluded by the regression equation:

Ip (μA) = 38.70 ν (V s^{-1}) + 2.754 (r^2 = 0.990) (Equation 3)

Moreover, the plot of logarithm of Ip versus logarithm of ν (Figure 5C) was also linear within 10 to 300 mV s^{-1}. The regression equation is:

log Ip (μA) = 0.631 log ν (V s^{-1}) + 1.428 (r^2 = 0.996) (Equation 4)

These results can be related to the adsorption of the analyte at CPE, indicating that the oxidation of LH is a surface-controlled redox process (17, 18). However, at higher scan rates a decrease in peak currents was observed. On the other hand, a plot of peak current versus square root of scan rate (Figure 5D) exhibited a linear relationship and suggests that the process is controlled by diffusion of analyte in the interfacial reaction zone of CPE surface (29). The Linear regression equation is as:

Ip (μA) = 25.24 ν 1/2 (V s^{-1}) - 1.232 (r^2 = 0.995) (Equation 5)

On the basis of these results and also the slope value of the equation 4 (0.631) that is between 0.5 and 1.0, it can be considered that the electrochemical process has a mixture of diffusion and adsorption mechanisms (29). In addition, the peak potential versus logarithm of scan rate (Figure 5E) also exhibits linear behavior within a range of 0.025 - 0.150 V s^{-1} as indicated in equation 6 and the irreversibility of the oxidation reaction can be concluded. Furthermore, an increase in a scan rate can cause the peak potential shifts to more positive values (0.80 to 0.88 V); this positive shift also confirms the irreversibility of the oxidation reaction (15, 16).

Ep (V) = 0.090 log ν (V s^{-1}) + 0.951 (r^2 = 0.991) (Equation 6)

4.4. Influence of Accumulation Potential and Time

Accumulation potential and time may significantly affect sensitivity of the determination method by altering the amount of the adsorbed species at the electrode surface. Therefore, the effect of the accumulation potential was examined in the range of 0 - 0.6 V on the SWV peak currents of 0.4 μmol L^{-1} of LH solution. The results showed that the peak current of LH is almost independent of this factor. However, the peak current of LH was increased with increasing the accumulation time from 0 to 120 seconds; however, above 120 seconds, the peak current remained almost unchanged indicating that an accumulation or extraction equilibrium is achieved at the electrode/solution surface (26). Thus, the accumulation step was carried out under the open-circuit condition in 120 seconds.

4.5. The Analytical Performance and Method Validation

The square-wave voltammetry was used as a sensitive and rapid electrochemical method for the determination of LH. The analytical figure of merit such as a dynamic range, LOD, LOQ, accuracy and precision were

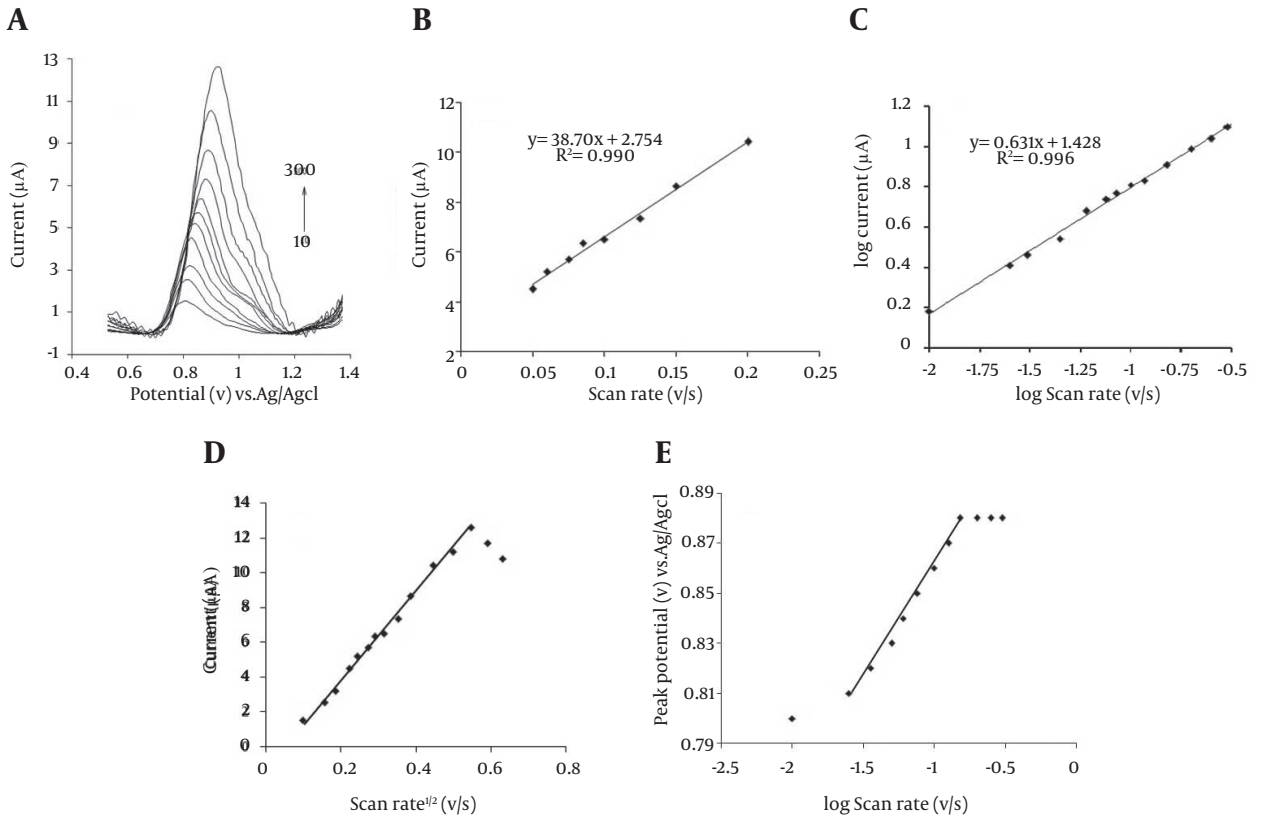

Figure 5. A) SW voltammograms of LH solution at different potential scan rates within the range of 10-300 mV s-1. B) The plot of peak current vs. scan rate. C) The plot of log of peak current vs. log of scan rate. D) The plot of peak current vs. square root of scan rate. E) The plot of peak potential vs. log of scan rate. [Conditions: concentration of LH: 150 µM; pH=10.0; accumulation time: 120 s]

determined to validate the method. Under optimized conditions, the LH calibration curve has a linear range of 8.0 - 1000.0 µM with a regression equation of Ip (µA) = 0.054 CLH (µM) - 0.358 and a correlation coefficient of r^2 = 0.999, indicating that the method can be applied in the LH determination in different samples. The LOD and LOQ for the determination based on three and ten times of the blank standard deviation (3Sb, 10Sb) were 0.29 and 0.96 µM (n = 10), respectively. The precision of the method was assessed for 10 replicate SWV determinations of 0.04, 0.2 and 0.8 µmol L^{-1} of LH. Their corresponding relative standard deviations were 5.1%, 3.7% and 2.1%, respectively.

4.6. Real Sample Analysis

The above-mentioned procedure was applied for a determination of LH in different pharmaceutical preparations. The procedure described in the United States Pharmacopeia (35) that used HPLC for the LH determination was used as an alternative method of analysis to test the reliability and accuracy of the results. As indicated in Table 1, different amounts of LH standard solutions were spiked into the LH injection and gel formulations. Then the spiked samples were subjected to the present determination method. The experiments implied that the same voltammetric behavior of the LH was observed in these pharmaceutical preparations and standard solutions. All experiments were performed in triplet and the recovery efficiencies (Recovery %) were calculated. The excellent recovery results (Table 1) indicate that the constituents in the formulations do not interfere with LH determination. To compare the results with HPLC standard methods reported in USP, the samples were analyzed by two methods. The results indicated a good accuracy obtained by the present method. However, this method can be used as a very reliable and sensitive determination technique for LH in pharmaceutical preparations.

5. Discussion

The methodology presented in this study was simple and economic, especially if more sophisticated techniques such as electrophoresis and chromatography are not easily at hand. A simple fabrication procedure of CPE and the short time of the analysis are other advantages of the proposed method. The detection limit of the proposed method is better than or comparable to some of the previously reported methods. Some reported LOD values (most of them were corresponding to the chromatographic methods) are better than those of the present method; however, they suffer from the expensive and

Table 1. Determination of Lidocaine Hydrochloride Content and Recovery Tests in Different Pharmaceutical Formulations With the Proposed Method

Sample	Added, μmol/L^{-1}	Found, μmol/L^{-1} [a]	Recovery, %
Gel		62.9 ± 3.2	
Gel	100	160.0 ± 2.7	98.0
Gel	200	268.0 ± 2.5	103.0
Injection 1		57.0 ± 2.9	
Injection 1	100	154.9 ± 2.8	97.9
Injection 1	200	256.0 ± 2.4	99.3
Injection 2		46.7 ± 3.3	
Injection 2	100	150.3 ± 2.6	103.0
Injection 2	200	250.0 ± 2.1	101.5

[a] Data are presented as Mean ± SD (n = 3).

Table 2. Comparison of the Proposed Method With Some of the Methods Reported in Literature [a]

Method	Linear range, μg mL^{-1}	LOQ, μg mL^{-1}	LOD, μg mL^{-1}	RSD, %	References
RP-HPLC	0.01-0.1 mg mL^{-1}	15	5	1.9	(1)
HPLC	0.1-10	NR	0.05	5.51	(2)
LC	1.25-80	1.25	0.346	0.95	(4)
LC-MS	0.2-18.0	0.2	NR	6.9	(5)
LC	0.125-500	NR	0.73 ng/20 μL	2	(6)
RP-HPLC	2.5-60	NR	0.05	5.5	(7)
CZE	0.5-10	0.35	0.11	1.8	(10)
CE-ECL	0.1-100	NR	0.02	3.5	(11)
Spect.	160-480	NR	0.14	NR	(13)
SWV-BDDE	24.2-114 μM	34.4 ng mL^{-1}	10	2.6	(20)
SWV-MCPE	10-180	NR	7.2	NR	(24)
SWV-CPE	8-1000 μM	0.96 μM	0.29 μM	2.1	proposed

[a] Abbreviations: BDDE, Boron-doped diamond electrode; CE, capillary electrophoresis; CZE, capillary zone electrophoresis; RP-HPLC- M, reverse phase-high-performance liquid chromatography-mass spectrometry; MCPE, modified carbon-paste electrode; NR, not reported; Spect, spectrophotometry.

extensive pretreatment steps along with a consumption of toxic solvents and lengthy time of analysis. The peak current is linear up to 3 orders of magnitude (8-1000 μM) of LH concentration. This dynamic range is wider than most of the reported methods. Table 2 shows a comparison of the proposed method with other reported methods.

Up to our best knowledge, for the first time, a direct determination of LH was successfully performed at an unmodified CPE with good sensitivity in comparison to other reported results. On the other hand, the mechanism of oxidation of LH and similar drugs in voltammetric methods on the basis of electrochemical evidences was proposed. Although, this developed procedure has been designed for a determination of LH and similar drugs involving amine or amide functional groups in pharmaceutical formulations, it can be considered as a new sensitive and fast method for the detection of these drugs in biological fluids by chromatographic systems, such as HPLC and capillary electrophoresis as well as flow injection methods.

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Authors' Contributions

Nadereh Rahbar: developing the original idea, study concept and design of experiments, acquisition of data, analysis and interpretation of data, writing the manuscript; Zahra Ramezani: consulting in all steps of the research and editing the manuscript; Ahmad Babapour: conducting the experimental section.

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