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Original article

CuO-nanoparticles modified carbon paste electrode for square wave voltammetric determination of lidocaine: Comparing classical and Box–Behnken optimization methodologies

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ABSTRACT

In this research, copper oxide nanoparticles modified carbon paste electrode was developed for the voltammetric determination of lidocaine. The square wave voltammogram of lidocaine solution showed a well-defined peak between +0.5 and +1.5 V. Instrumental and chemical parameters influencing voltammetric response were optimized by both one at a time and Box–Behnken model of response surface methodology. The results revealed that there was no significant difference between two methods of optimization. The linear range was 1–2500 μmol L^{-1} ($I_p = 0.11C_{LH} + 17.38$, $R^2 = 0.999$). The LOD and LOQ based on three and ten times of the signal to noise (S/N) were 0.39 and 1.3 μmol L^{-1} ($n = 10$), respectively. The precision of the method was assessed for 10 replicate square wave voltammetry (SWV) determinations each of 0.05, 0.5 and 1 mmol L^{-1} of lidocaine showing relative standard deviations 4.1%, 3.7% and 2.1%, respectively. The reliability of the proposed method was established by application of the method for the determination of lidocaine in two pharmaceutical preparations, namely injection and gel.

1. Introduction

Lidocaine (LH) is chemically designated as acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl) and is the common name of an important member of a category of drugs extensively used as local anesthetics. This drug is also widely used as anti-arrhythmic agent. Analysis of pharmaceutical preparations is one of the most important and attractive branches in analytical chemistry. Different methods have been proposed for the determination of LH in the literature. To date chromatographic methods such as high performance liquid chromatography (HPLC) [1–8], gas chromatography [9–12] and electrophoresis [13–16] are most frequently employed for LH determination due to their high sensitivity and excellent selectivity. Spectrophotometric assay [17,18] and the indirect atomic absorption spectrometric determination have also been studied [19]. Most of these methods suffer from limitations. They are expensive, time consuming or need extensive pre-treatment steps and using toxic solvent and reagents.

Electrochemical techniques are useful alternative methods, having important advantages including simplicity, reliability, sensitivity and selectivity. These techniques are more often used in pharmaceutical preparations and biomedical analysis. Little published data are available for electrochemical determination of LH and related compounds [20–24]. Investigation of direct oxidation of LH in order to find a fast, sensitive and reliable electrochemical method for determination of this compound in pharmaceuticals, as well as for the development of lidocaine voltammetric detectors coupled to flow techniques or chromatographic measurements is important. Recently, many studies have been focused on the application of nano-materials in fabrication and modification of different conventional electrodes to improve their sensitivity and selectivity [20,25,26]. Undoubtedly, carbon paste electrodes represent the most convenient working electrode for modification by mixing with a suitable modifier [26,27].

Application of chemometrics in the optimization of analytical parameters has some advantages including: reduction in the number of experiments, lower reagent consumption and considerably less laboratory work. Thus they are faster and more cost effective than classical univariate approaches. These methods enable us to study several parameters simultaneously. In addition

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they can develop mathematical models that interpret the relevance and statistical significance of different factors in an analytical method [28]. Nowadays, response surface methodology (RSM) with a Box–Behnken design (BBD) is widely used for the optimization of analytical factors through a relatively small number of experiments [29–34]. Experimental design methodology has been extensively used in optimization of parameters in analytical chemistry. But, a few reports are available regarding their applications in electrochemical optimization [35,36]. In this work, a laboratory constructed CuO nanoparticle carbon paste electrode (CNCPE) has been introduced for voltammetric determination of LH in pharmaceutical preparations. In addition, RSM with Box–Behnken design and traditional "one factor at a time" optimization protocols were used to identify chemical and instrumental parameters affecting the electrochemical response and their reliability were compared.

2. Experimental

2.1. Chemicals

All common chemicals such as HCl, NaOH and KNO_3 were of analytical grade and obtained from Merck (Darmstadt, Hesse, from Fluka (Milwaukee, USA). Copper oxide nanoparticle powder (40–80 nm) was obtained from Inframat Advanced Material (Farmington, CT, USA).

LH stock solution (0.01 mol L^{-1}) 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 appropriate dilution of the stock solution. Doubled distilled water was used throughout this study.

2.2. Apparatus

For voltammetric measurements, a Metrohm (AUTOLAB, model PGSTAT302N) electrochemical device was employed. A three-electrode arrangement was applied throughout. CuO nanoparticles modified carbon paste electrode as a working electrode and a platinum wire as an auxiliary electrode together with an Ag/AgCl reference electrode were used. Adjustment of pH was carried out using a pH-meter (JENWAY model 3320 – UK).

2.3. Fabrication of CNCPE

CNCPE was prepared by mixing graphite powder with paraffin oil and an appropriate amount of CuO nanoparticles for 15 min as cited elsewhere [26]. The paste was then 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 on waxed paper to obtain a smooth electrode surface.

2.4. Voltammetric determination of LH

In order to investigate the oxidation mechanism of LH at CNCPE, cyclic voltammetry (CV) was used. Square wave voltammography (SWV) was chosen as electrochemical tool to determine LH due to its sensitivity and speed. Preliminary CV experiments showed a well-defined irreversible peak related to oxidation of LH. Likewise, the general procedure adopted for obtaining cyclic and square wave voltammograms of LH was as follows: an appropriate amounts of standard LH solution and 5 mL of KNO_3 (1 mol L^{-1}) were added to a 25 mL volumetric flask and diluted to the mark with distilled water. This solution was transferred into the electrochemical cell. The cyclic voltammograms were recorded from +0.5 to +1.4 V at scan rate of 0.10 V s^{-1}. Square wave voltammograms were recorded by scanning the potential in the range of +0.5 to +1.5 V with a scan rate of 0.125 V s^{-1}. In order to regenerate a new and fresh surface on CNCPE, the tip of the electrode was polished on waxed paper.

2.5. Experimental design

A three-level, three-factor Box–Behnken experimental design was used to determine optimum levels for pH (8–12), scan rate (0.2–0.3 V s^{-1}) and percent of CuO nanoparticles (5%–20%) in CNCPE as important parameters affecting the performance of the method. The three selected levels of the variables for the BBD are shown in Table 1. The peak current of the SWV was taken as the response of the system.

To design the experiments, Minitab 15 software was employed. Table 2 shows the experimental design derived from BBD along with their obtained and predicted results, including three center points. Each experiment was performed in triplicate to verify reproducibility. The results were used to calculate the 10 coefficients of the second-order polynomial equation. This equation shows the relation between the desired response and the independent variables (pH, scan rate and CuO nanoparticle percent). Considering all linear, square, and linear-by-linear interaction terms, the second-order polynomial equation can be described as:

$$Y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 \quad (1)$$

where Y is the response (peak current of LH); b_0 is the offset term; b_1, b_2, and b_3 are the linear coefficients; b_{11}, b_{22}, and b_{33} are the quadratic coefficients, and b_{12}, b_{13} and b_{23} are the coefficients of the linear-by-linear interaction effect between independent variables x_1 (pH), x_2 (scan rate), and x_3 (CuO nanoparticle per cent) [37]. The model suitability of fit was assessed using a coefficient of regression (R^2) and analysis of variance (ANOVA).

Table 1
Experimental range and level of independent variables.

Factors range and levels (coded)	−1	0	1
Scan rate (V s^{-1})	0.2	0.25	0.3
pH	8	10	12
CuO% (w/w)	5	10	20

Table 2
Box–Behnken design matrix for three variables-three levels together with observed and predicted values (concentration of LH: 0.4 mmol L^{-1}).

Exp. run	Scan rate (V s^{-1})	pH	CuO% (w/w)	Current (μA)	Predicted current
1	0.3	10	20	20.49	21.798
2	0.3	8	10	6.64	5.566
3	0.25	10	10	14.90	14.900
4	0.2	10	5	8.78	7.241
5	0.2	8	10	4.50	4.120
6	0.25	12	20	55.92	54.359
7	0.3	10	5	10.81	10.196
8	0.25	12	5	22.10	22.207
9	0.3	12	10	29.42	29.800
10	0.2	10	20	16.12	16.965
11	0.25	8	5	12.39	14.435
12	0.25	10	10	14.90	14.900
13	0.2	12	10	23.01	24.084
14	0.25	10	10	14.90	14.900
15	0.25	8	20	4.20	3.608

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3. Results and discussion

3.1. Electrochemical characteristics of LH on CNCPE

Preliminary cyclic voltammetry studies on the electrochemical behavior of 0.4 mmol L^{-1} LH solution in KNO_3 at pH 8 were performed on both CNCPE and non-modified carbon paste electrode (CPE), revealed that the voltammograms of LH on these two electrode surfaces differ significantly (Fig. 1a and 1b). It can be seen that CPE shows low sensitivity with respect to LH in comparison to that of CNCPE. The irreversible oxidation peak at +0.90 V might be due to the oxidation of the amine group in LH molecule. Fig. 2a and 2b illustrate square wave voltammograms of LH at CNCPE and CPE. The higher oxidation peak current of LH at CNCPE shows that this modified electrode is more sensitive than CPE. The above mentioned parameters (Table 1) were optimized by both classical and BBD methodologies in order to obtain a well-defined square wave voltammogram with maximum peak current for the determination of traces of LH.

3.2. Classical optimization methodology

3.2.1. Effect of pH

The effect of pH on peak current (I_p) and potential were investigated by applying different pH values ranging from 3 to 12. No oxidation peaks were found before pH 3. Fig. 3a shows two oxidation peaks at low pH. This is due to the presence of both protonated (LH) and deprotonated (L) form of lidocaene. At pH 8 and higher L form is predominant. Then, L can be accumulated on the surface of the electrode through N-Cu interaction. So, the corresponding peak current increases. As shown in Fig. 3b, in these pH ranges, LH peak current increases linearly and implies the participation of hydrogen ions in the electrochemical reaction [27]. This result revealed more favorable oxidation of LH at higher pHs. Also considering the relationships between current and rate of electrochemical reaction [38], it can be concluded that the rate of oxidation of LH increases with increasing pH and reaches its maximum value and levels off at pHs 11–12. This might be due to the fact that pk_a of LH is about 8 and above pH 8 the main fraction of LH molecules may be in their de-protonated form [21,24]. However, above pH 12, the shape of LH voltammogram became undesirable and its shape degraded. The linear dependency between I_p and pH can be concluded by the regression Eq. (2):

$$I_p\ (\mu A) = 3.960\,pH - 9.274\ \ (r^2 = 0.995) \qquad (2)$$

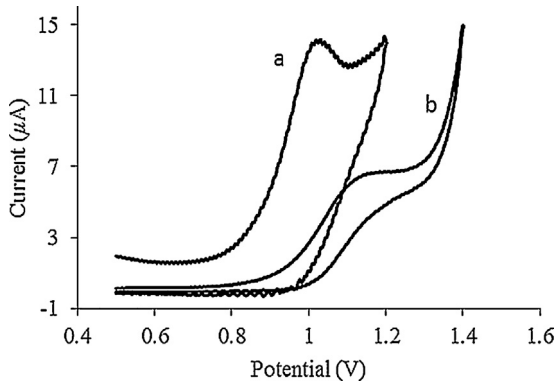

Fig. 1. The cyclic voltammogram of LH at (a) CNCPE and (b) CPE (concentration of LH: 0.4 mmol L^{-1}; pH = 10.0; scan rate: 0.125 V s^{-1}; CuO%: 10).

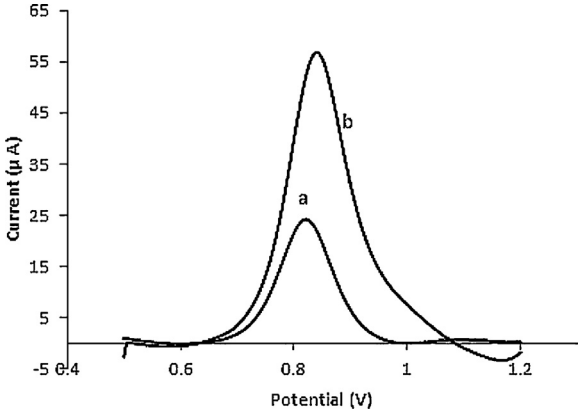

Fig. 2. The SW voltammogram of LH at (a) CPE and (b) CNCPE (concentration of LH: 0.4 mmol L^{-1}; pH = 10.0; scan rate: 0.125 V s^{-1}; CuO%: 10).

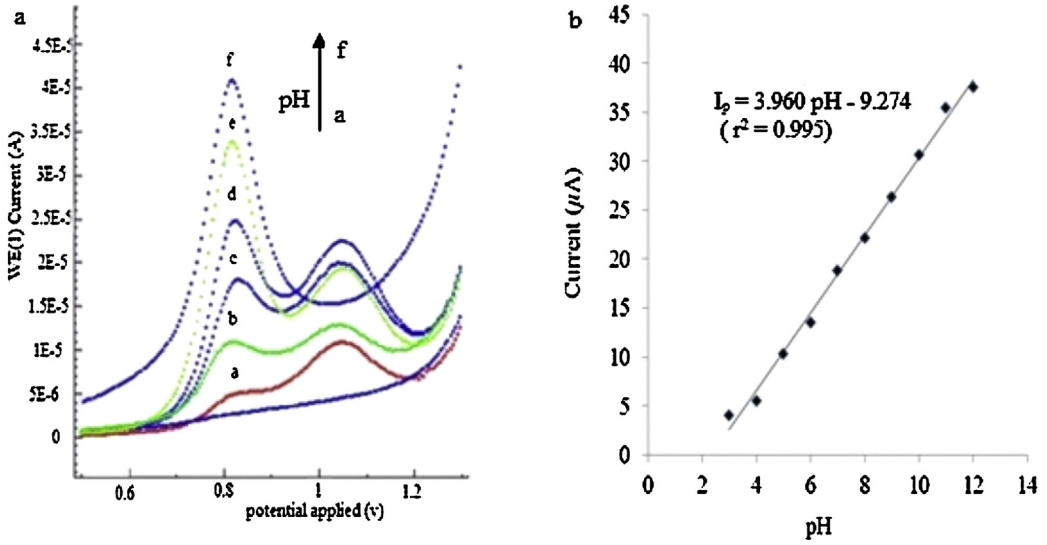

Fig. 3. (a) SW voltammogram and (b) plot of peak currents *vs.* pH (concentration of LH: 0.4 mmol L^{-1}; scan rate: 0.25 V s^{-1}; CuO%: 10).

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3.2.2. Potential scan rate effect

A study of the effect of potential sweep rate (ν) on the peak current helps to identify that the oxidation of LH at CNCPE is diffusion or surface controlled. However, the plot of peak current *vs.* square root of scan rate (Fig. 4) exhibited linear relationship and suggests that the process is controlled by the diffusion of analyte in the interfacial reaction zone of CPE surface [27]. The linear regression equation is:

$$I_p\ (\mu A) = 33.53\nu^{1/2}\ (V\,s^{-1}) + 6.102 \quad (r^2 = 0.990) \tag{3}$$

Furthermore, an increase in scan rate causes peak potential shifts to more positive values; this positive shift confirms the irreversibility of the oxidation reaction [39,40].

3.2.3. Influence of CuO-nanoparticle amount in CNCPE

The best weight ratio of C: paraffin for preparation of carbon paste, 70: 30 (w/w), has been reported elsewhere [26]. However in order to achieve the most sensitive electrode, different amounts of CuO nanoparticles were added to the paste and mixed thoroughly in a mortar to prepare a modified carbon paste. Highest peak current intensities were obtained at CuO:C:paraffin weight ratio of 20:60:30 (Fig. 5) and this composition was used in further work. Complex formation between copper ion and amines is well known. However, copper ion in the paste can attract amine group of LH. This tendency increase LH concentration at the surface of the electrode and causes shift in oxidation potential and increase in the current, consequently. At higher amounts of nanoparticles, the background intensity was increased and caused a lowering in peak current of analyte. It may be due to the existence of copper oxide in the electrode originally causing an increase in the baseline of the CNCPE. So at higher amounts of modifier the sensitivity of the modified electrode is diminished.

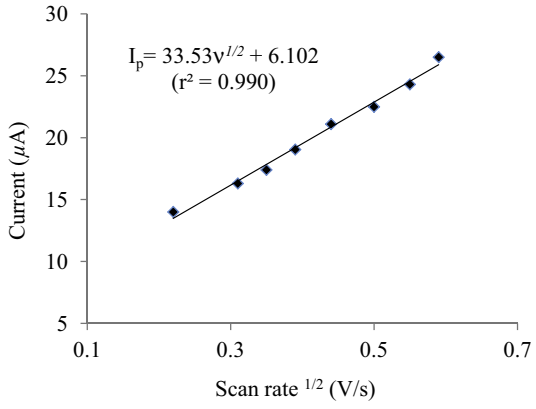

Fig. 4. The plot of peak current *vs.* square root of scan rate (0.4 mmol L^{-1}; pH 11.5; CuO%: 10).

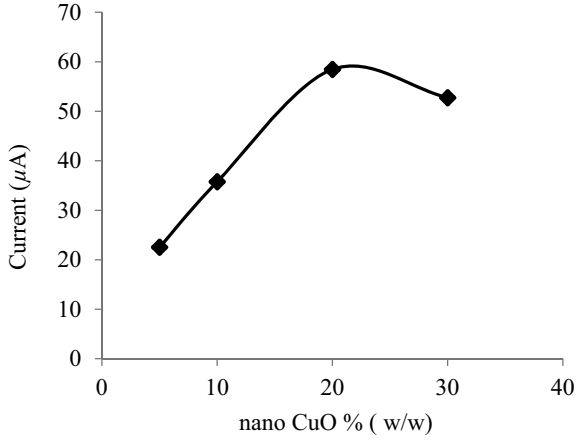

Fig. 5. The plot of peak current *vs.* CuO% in CNCPE (concentration of LH: 0.4 mmol L^{-1}; pH 11.5; scan rate: 0.25 V s^{-1}).

3.3. Box–Behnken optimization method

3.3.1. Statistical analysis of Box–Behnken model

Surface and counter plots of the major influencing parameters (pH, scan rate and the percentage of CuO nanoparticles in CPE) showed their impact in response Y (peak current intensity) in the experimental design. In these plots the function of two parameters was examined while the third factor is held at a constant level. ANOVA and α level of 0.05 (95% confidence) were used to determine the statistical significance of the independent variables. Minitab 15 software was used to obtain the second-order polynomial coefficients and statistical parameters and analyze the results. ANOVA results for the quadratic model for peak current of LH oxidation on CNCPE is shown in Table 3. ANOVA showed that all effects were statistically significant ($P < 0.05$) at 95% confidence interval except for second-order CuO% ($P = 0.127$) and the interaction effects of scan rate with pH and CuO% with P values of 0.269 and 0.599, respectively. Considering all linear, square, and linear-by-linear interaction terms, the second-order polynomial equation can be described as:

$$I = 74.89 + 30.79\,pH + 3.89\,SR + 7.60\,CuO\% + 1.328\,pH^2 - 0.04\,SR^2 + 0.03\,CuO\%^2 + 0.05\,pH \times SR + 0.716\,pH \times CuO\% + 0.01\,SR \times CuO\% \tag{4}$$

where SR is the potential scan rate.

The final mathematical model in terms of significant actual factors affecting in peak current (I) of LH, determined by Minitab 15 software is:

$$I = 74.89 + 30.79\,pH + 3.89\,SR + 7.60\,CuO\% + 1.328\,pH^2 - 0.04\,SR^2 + 0.718\,pH \times CuO\% \tag{5}$$

From Eq. (5), it can be concluded that the first order main effects (pH, SR and CuO%) all had significant effect on LH peak current. The ANOVA results (Table 3) show that first-order effect of the main factors were more significant than their quadratic and interaction effect. Moreover, of all model components, the interaction effect of SR and CuO% showed the least effect on response ($P = 0.599$). The adjusted R^2 of 0.9821 indicates the significance and goodness of fit of the model and that only about 2% of variations could not be interpreted by the model. This high value of regression coefficient of the model showed a good correlation between experimental results and predicted responses.

Table 3
ANOVA for response surface reduced quadratic model.

Term	Coef.	SE Coef.	T	P
Constant	74.8873	40.1149	1.867	0.121
Frequency	3.8877	1.0011	3.883	0.012
pH	30.7948	5.0056	−6.152	0.002
CuO%	7.6042	0.9239	−8.231	0.000
Frequency*Frequency	−0.0430	0.0089	−4.817	0.005
pH*pH	1.3244	0.2234	5.928	0.002
CuO%*CuO%	0.0336	0.0183	1.831	0.127
Frequency*pH	0.0534	0.0429	1.243	0.269
Frequency*CuO%	0.0063	0.0111	0.562	0.599
pH*CuO%	0.7163	0.0557	12.858	0.000

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3.3.2. Effect of pH

The pH values ranged from 8 to 12. Based on ANOVA analysis, initial pH had the greatest positive effect on peak current. Increasing pH raised the peak current to maximum value. Figs. S1a and S1b (see Supporting information) represent the interaction effects of pH by scan rate (frequency) and CuO%, respectively, on LH the peak current as analyzed by BBD. In each graph the third factor was kept constant. According to these figures, pH increased from 8 to 12, the LH peak current increased linearly. The BBD model predicted that the highest peak current should be at pH = 12 as the optimum value. The results of this section agree with those obtained from Section 3.2.1.

3.3.3. Effect of potential scan rate

As seen in Eq. (4), predicted correlation coefficient of scan rate is 3.89 that show the important effect of this factor on LH peak current. Figs. S1a and S1c (see Supporting information) represent the results analyzed by BBD in interactive effects between the scan rate (frequency) and pH (CuO% being constant) and CuO% (pH value being constant). These results reveal that peak current rises as scan rate or frequency becomes higher and reaches its maximum level at 0.25 V s^{-1} (frequency = 50 Hz) and then falls at high scan rate (0.35 V s^{-1}). This found optimum value (0.25 V s^{-1}) for potential scan rate is in good agreement with that of the result in Section 3.2.2. However, as stated in Section 3.3.1, *P* values show insignificant interaction effects of scan rate with pH and CuO% and Fig. 6a and c are consistent with those results.

3.3.4. Effect of CuO-nanoparticle percent in CNCPE

The correlation coefficient of 7.60 (Eq. (4)) for this factor, indicates that the amount of CuO has important effect on the response. This also can be concluded from Figs. S1b and S1c (see Supporting information). The inherent attraction between the amine group in LH and Cu, and increased conductivity in electrode due to existence of nanoparticles could be responsible for this finding. However, as mentioned before, according to the ANOVA analysis results, only the correlation between CuO% and pH is significant. Furthermore, this significant positive correlation is confirmed by increased peak currents in higher values of both of these factors. In the light of findings from both optimization methodologies, it can be concluded that they present similar results.

3.4. Analytical performance and method validation

The analytical features such as the dynamic range of the calibration curve, LOD, LOQ, accuracy and precision were examined to establish validity of the proposed method. As illustrated in Fig. 6

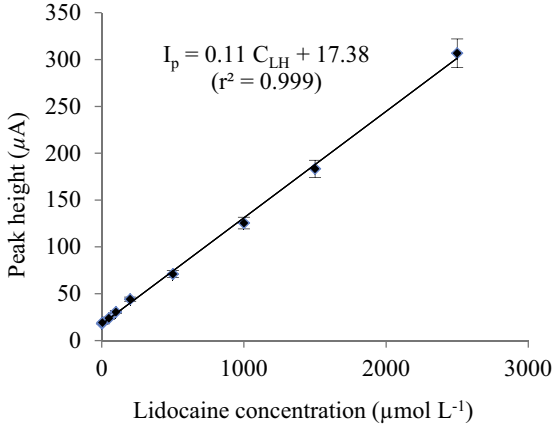

Fig. 6. The plot of the peak current *vs.* concentration of LH under optimum conditions range.

Table 4
CPE and CNCPE figure of merit for LH determination.

Electrode	LR (μmol L^{-1})	LOD	r^2	Slope
CPE	8–1000	2.90	0.999	0.05
CNCPE	1–2500	0.39	0.999	0.11

LR stands for linear range.

Table 5
Determination of LH content and recovery tests in different pharmaceutical formulations with the proposed method ($n = 3$).

Sample	Added (μmol L^{-1})	Found (μmol L^{-1})[a]	Recovery (%)
Gel	–	14.7 ± 0.8 (14.2)	–
	250	263.7 ± 7.3	99.6
	500	520.1 ± 12.9	101.1
Injection 1	–	55.5 ± 2.1 (54.3)	–
	500	528.8 ± 11.7	95.1
	1000	1048.1 ± 23.2	99.3
Injection 2	–	67.1 ± 1.9 (66.7)	–
	500	583.0 ± 10.8	102.8
	1000	1075.3 ± 21.9	100.8

[a] Indicates *x*(average) ± SD ($n = 3$). Data in parenthesis are results obtained by HPLC method reported in USP.

under optimum conditions, peak currents of LH voltammograms show linearity in the concentration range 1–2500 μmol L^{-1}. The regression equation for the obtained calibration graph with a correlation coefficient of 0.999, was I_p (μA) = 0.11 C_{LH} (μmol L^{-1}) + 17.38, where C_{LH} is the concentration of LH and I_p is the peak current intensity. The LOD and LOQ for the determination based on three and ten times of the signal to noise (S/N) were 0.39 and 1.3 μmol L^{-1} ($n = 10$), respectively. The precision of the method was assessed for 10 replicate SWV determinations each of 0.05, 0.5 and 1 mmol L^{-1} of LH. Their corresponding relative standard deviations were 4.1%, 3.7% and 2.1%, respectively.

In order to check the performance of the CNCPE compare to previously reported CPE [41] for LH determination some important parameters in method validation are presented in Table 4. Wider linear rang, lower limit of detection, and higher sensitivity (about two times of CPE) is obtained for LH measurement using CNCPE.

3.4.1. Application to real samples

The above proposed procedure was applied for the determination of LH in different pharmaceutical preparations. In order to test the validity of the method, as indicated in Table 5, 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 (%) were calculated. The excellent recovery results (Table 5) indicate that the constituents in the formulations do not interfere with LH determination. The procedure described in the United States Pharmacopeia (USP) that used HPLC for the LH determination was used as an alternative method of analysis to test the reliability and accuracy of the results [42]. In order to compare the results with HPLC standard method reported in USP, the samples were analyzed by both methods. The results were consistent with those of the standard USP method (Table 5).

4. Conclusion

The methodology presented in this study was simple and economic, especially if more sophisticated techniques such as

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electrophoresis and chromatography are not easily available. The simple fabrication procedure of CNCPE and the short analysis time 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 ones. Some reported LOD values (most of them corresponding to the chromatographic methods) are better than that of the present method, but the chromatographic methods are expensive, require extensive pre-treatment steps as well as consume large amounts of toxic solvents and have a lengthy analysis time. The peak current of present method is linear up to 4 orders of magnitude (1–2500 $\mu mol\ L^{-1}$) of LH concentration. This dynamic range is wider than all reported methods.

Overall, this method is reliable and sensitive determination technique for LH in pharmaceutical preparations and similar amine and amide functionalized drugs. If the present electrode couples to techniques such as HPLC, capillary electrophoresis or flow injection analysis, it can also be applied in the detection of these drugs in biological fluids.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.04.017.

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