

An electrochemical acetaminophen sensor based on $\text{La}^{3+}/\text{Co}_3\text{O}_4$ nanoflowers modified graphite screen printed electrode architecture

Iran Sheikhshoae ^{1*}, Fariba Garkani Nejad ¹, Hadi Beitollahi ^{2*}

¹ Department of Chemistry, Shahid Bahonar University, Kerman, Iran.

² Environment Department, Institute of Science and High Technology and Environmental Sciences, Graduate University of Advanced Technology, Kerman, Iran.

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Abstract

In this study, the $\text{La}^{3+}/\text{Co}_3\text{O}_4$ nanoflowers were synthesized by co-precipitation method. The morphology of the $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs were characterized using scanning electron microscopy (SEM), and were further used to modify the graphite screen printed electrode (GSPE). The electrochemical behavior of acetaminophen at $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs/GSPE has been studied in aqueous solutions. Experimental results showed that the $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs modified GSPE possess excellent electrocatalytic activity toward the detection of acetaminophen. Under optimum conditions, the $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs modified electrode exhibited high sensitivity and stability to acetaminophen over a wide linear range of concentrations from 0.5 μM to 250.0 μM , with a detection limit of 0.09 μM . Finally, the proposed sensor was successfully applied to the detection of acetaminophen in real samples.

Keywords: Acetaminophen; Electrocatalytic Activity; Graphite Screen Printed Electrode; $\text{La}^{3+}/\text{Co}_3\text{O}_4$ Nanoflowers; Modified Electrode.

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INTRODUCTION

Recently the design, fabrication and application of novel electroanalytical methods for the analysis of electroactive materials in biological samples have received much interest due to less time consuming, rapid, simple, inexpensive, adequate accuracy and selectivity [1-7]. These features were attained by using modified electrodes as working electrodes in the potentiostatic systems by methods such as voltammetry and amperometry [8-11]. Nowadays, the nanoscale materials have been attracted much attention to modify on the surface of electrodes for electrochemical detection biological compounds due to their unique physical and chemical properties, such as large surface area, plenty active sites, high electronic conductivity and good chemical stability [12-24].

Lanthanides, as f-block-based elements, possess remarkable chemical and physical properties. Lanthanide-based materials have been used as sensing materials in electrode modifiers in voltammetric sensors. In voltammetric sensors, changes in the current produced by the targeted analyte due to redox events are measured as the potential of the working electrode is varied in a controlled way. Because many electroactive species are not able to have a good charge transfer on the electrode surfaces, there is a need to modify the electrode surface with a suitable material. Many Lanthanide-based materials have recently been used as modifiers in voltammetric sensing [25]. Lanthanum (La) is one of the most important lanthanides elements. La ions own relatively low toxicity and extraordinary catalytic properties, thus, those ions can be used to construct environment-friendly sensors [26-28].

* Corresponding Author Email: shoae@uk.ac.ir,
h.beitollahi@yahoo.com

Recently, transition metal oxides such as Co_3O_4 nanoparticles have been explored as the sensing materials for several biologically important analytes detection with satisfactory results due to their biocompatibility, good electrochemical properties, low cost, earth abundance, large surface area, wide availability and good ability of promoting electron transfer reactions [29-32].

Screen printing technology has been evolved for designing feasible disposable chemical sensors, which is involved in the fabrication of screen printed electrodes (SPEs) [33]. The use of screen printed electrodes for the recognition and determination of a variety of analytes is currently undergoing widespread growth. Screen printed electrodes have all the major performance characteristics of sensors: sample preparation is minimal; they are quick, cheap, and easy to use; and they are small and can be miniaturized with new technology [34-38].

Acetaminophen (N-acetyl-p-aminophenol or Paracetamol) (Fig. 1), is the most widely used analgesic and antipyretic drug in the world [39-40]. When it is used as an analgesic drug it reduces mild-moderate pain associated with headache, backache, muscular aches, toothache, migraine and postoperative pain. As an antipyretic agent it reduces fevers of viral and bacterial origin [41-42]. Limited use of acetaminophen does not exhibit any harmful side effects, while overdoses of acetaminophen will damage liver and kidney [43-44]. Thus, the development of efficient, sensitive, and simple analytical techniques for the determination of acetaminophen is important. A great number of analytical methods such as: high performance liquid chromatography (HPLC) [45], spectrofluorimetry [46], spectrophotometry [47], and electrochemical methods [48-51] have been developed for the determination of acetaminophen. The aim of this study is to develop a novel, simple, reliable electrochemical sensor for the determination of acetaminophen

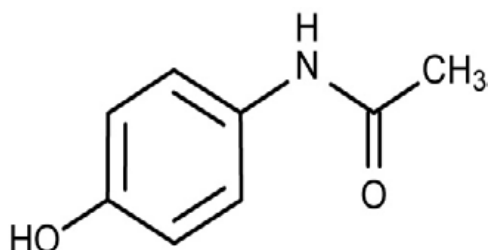


Fig. 1. Chemical structure of acetaminophen.

based on the co-precipitation synthesized $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs modified graphite screen printed electrode (GSPE). The $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs modified GSPE showed a better electrocatalytic redox behavior compared with unmodified GSPE. The prepared modified electrode ($\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs/GSPE) showed a good sensitivity and reproducibility. The proposed sensor was successfully applied to the determination of acetaminophen in acetaminophen tablet and urine samples.

EXPERIMENTAL

Chemicals and Apparatus

Electrochemical measurements were done by an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands). Experimental conditions were controlled through General Purpose Electrochemical System (GPES) software. The screen printed electrode (DropSens, DRP-110, Spain) consists of three conventional electrodes: graphite counter electrode, a silver pseudo-reference electrode and an unmodified graphite working electrode. A Metrohm 710 pH meter was employed for pH measurements. $\text{La}^{3+}/\text{Co}_3\text{O}_4$ NFs were synthesized in our laboratory as described below.

The solutions were freshly prepared with double distilled water. Acetaminophen and all other reagents were of analytical grade and were purchased from Merck chemical company (Darmstadt, Germany). The buffer solutions were prepared from orthophosphoric acid and its salts in the pH range of 2.0-9.0.

Synthesis of $\text{La}^{3+}/\text{Co}_3\text{O}_4$ nanostructures

All the chemicals used for the preparation of the nano-powders, namely cobalt acetate ($\text{Co}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$), lanthanum nitrate ($\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$), thiourea ($(\text{NH}_2)_2\text{CS}$) and ammonia (25% NH_3), were of analytical grade. All the precursors were dissolved in deionized water. During the preparation of the nano-powders, ammonia was used as a complexing agent. The La^{3+} -doped Co_3O_4 nanostructures were prepared by dissolving 0.46 mol of cobalt acetate in 80 mL of deionized water, 0.0046 mol of lanthanum nitrate in 80 mL of deionized water, 0.18 mol of thiourea in 80 mL of deionized water and lastly by adding 19.76 mL of ammonia in 80 mL of deionized water. The amount of solutions of cobalt acetate, thiourea and ammonia was held constant at a ratio of 1 : 1 : 1. Then the cobalt acetate solution was added in

a beaker in the reaction bath, followed by adding thiourea and lanthanum nitrate solution in the same reaction bath and the mixture was stirred for a few seconds. Lastly ammonia solution was added slowly into the mixture, while continuing stirring for 5 min. The temperature of the bath was then allowed to increase up to 80 °C. After that the precipitates were formed and were left overnight and filtered thereafter. The precipitates were then washed with ethanol. The obtained powders were dried at ambient conditions for several days. A typical SEM for synthesized La³⁺-doped Co₃O₄

nanoflowers is shown in Fig. 2.

Preparation of the electrode

The bare graphite screen printed electrode was coated with La³⁺/Co₃O₄ according to the following simple procedure. 1 mg La³⁺/Co₃O₄ was dispersed in 1 mL aqueous solution within 45 min ultrasonication. Then, 5 µl of the prepared suspension was dropped on the surface of carbon working electrodes. It remains at room temperature until becomes dry.

Preparation of real samples

Five acetaminophen tablets (labeled 300 mg per tablet, Amin Company, Iran) were grinding and homogenizing. Then, the tablet solution was prepared by dissolving 300 mg of the powder in 25 ml water by ultrasonication. Then, different volumes of the diluted solution were transferred into a 25 ml volumetric flask and diluted to the mark with PBS (pH 7.0). The acetaminophen content was analyzed by the proposed method using the standard addition method.

Urine samples were stored in a refrigerator immediately after collection. 10 ml of the sample was centrifuged for 15 min at 2000 rpm. The supernatant was filtered out using a 0.45 µm

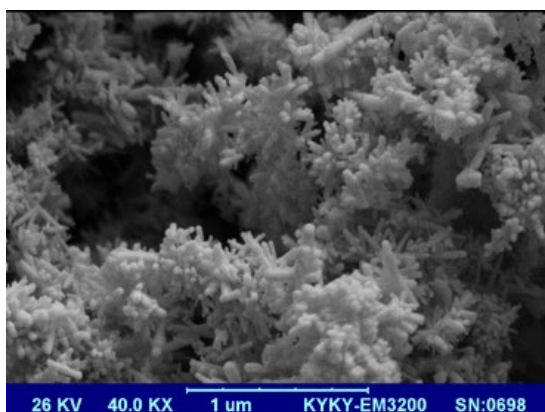


Fig. 2. SEM image of La³⁺/Co₃O₄ nanoflowers.

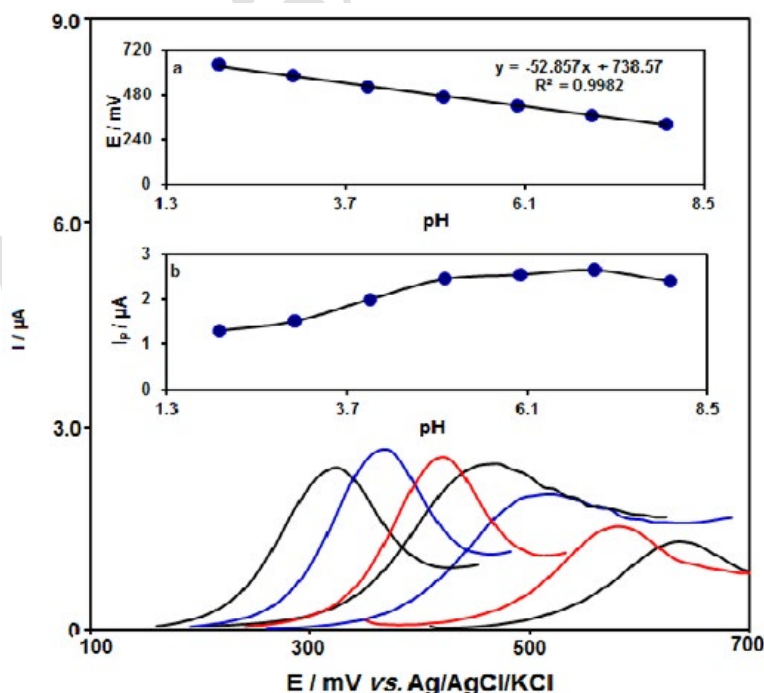


Fig. 3. DPVs (at 50 mV s⁻¹) of La³⁺/Co₃O₄/GSPE at various buffered pHs (2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 9.0). Insets: (a) Plot of E vs. pH and (b) Plot of I_p vs. pH.

filter. Then, different volumes of the solution were transferred into a 25 ml volumetric flask and diluted to the mark with PBS (pH 7.0). The diluted urine sample was spiked with different amounts of acetaminophen.

RESULT AND DISCUSSION

Electrochemical behavior of acetaminophen on the $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$

The electrochemical behavior of acetaminophen is dependent on the pH value of the aqueous solution.

Therefore, pH optimization of the solution is necessary in order to obtain the best results for electro-oxidation of acetaminophen. Thus the electrochemical behavior of acetaminophen was studied in 0.1 M PBS in different pH values (2.0-9.0) at the surface of $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ by voltammetry (Fig. 3). It was found that the electro-oxidation of acetaminophen at the surface of $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ was more favored under neutral conditions than in acidic or basic medium (Fig. 3 inset b). Thus, the pH 7.0 was chosen as the optimum pH for electro-

oxidation of acetaminophen at the surface of $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$. The mechanism for oxidation of acetaminophen is shown in Fig. 4.

In addition, the long-term stability of the $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ was tested over a three-week period. When CVs were recorded after the modified electrode was stored in atmosphere at an ambient temperature, the peak potentials for acetaminophen oxidation were unchanged and the current signals showed less than 2.5% decrease relative to the initial response. The antifouling properties of the modified electrode toward acetaminophen and its oxidation product were investigated by recording the CVs of the modified electrode before and after use in the presence of acetaminophen. CVs were recorded in the presence of acetaminophen after having cycled the potential 20 times at a scan rate of 50 mV s^{-1} . The peak potentials were unchanged and the currents decreased by less than 2.4%. Therefore, at the surface of $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$, not only the sensitivity increases, but the fouling effect of the analyte and its oxidation product also decreases.

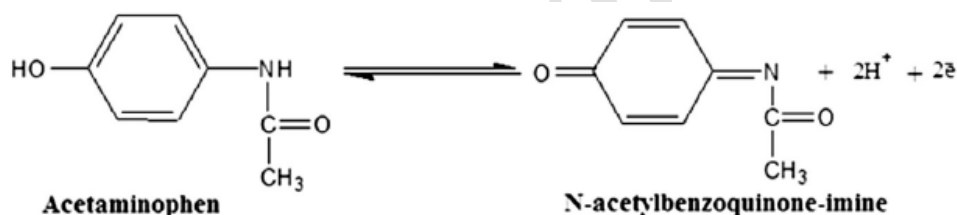


Fig. 4. Probable oxidation mechanism for acetaminophen.

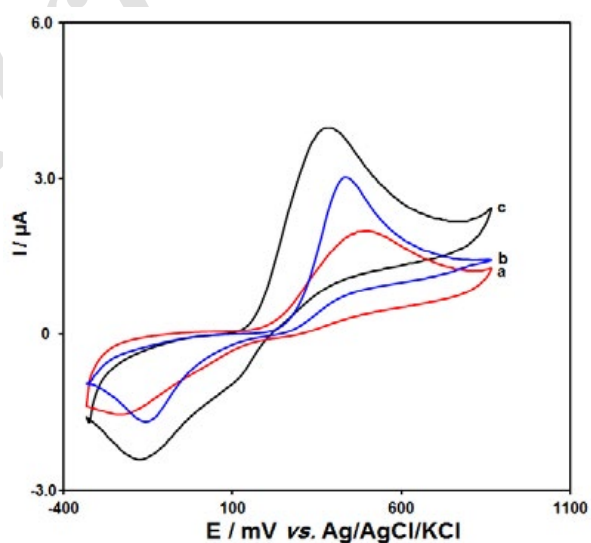


Fig. 5. CVs of a) bare GSPE, b) $\text{Co}_3\text{O}_4/\text{GSPE}$ and c) $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ in the presence of $150.0 \mu\text{M}$ acetaminophen at a pH 7.0. In all cases the scan rate was 50 mV s^{-1} .

Fig. 5. depicts the CV responses for the electro-oxidation of 150.0 μ M acetaminophen at an unmodified GSPE (curve a), Co₃O₄/GSPE (curve b), and La³⁺/Co₃O₄/GSPE (curve c). The peak potential due to the oxidation of acetaminophen at the surface of La³⁺/Co₃O₄/GSPE (curve c) occurs at 390 mV, which is about 50 and 110 mV more negative than Co₃O₄/GSPE (curve b) and unmodified GSPE (curve a) respectively. Also, La³⁺/Co₃O₄/GSPE shows much higher anodic peak current for the oxidation of acetaminophen (4 μ A) compared to Co₃O₄/GSPE (3 μ A) and unmodified GSPE (2 μ A), indicating that the modification of unmodified GSPE with La³⁺/Co₃O₄NFs has significantly improved the performance of the electrode toward acetaminophen oxidation.

Effect of scan rate on the results

In the next experiment, the scan rate of the method was optimized to consider the response mechanism. Increasing in scan rate leads to enhancement of the oxidation peak current of acetaminophen. According to the obtained results from the study of the effect of potential scan rates on the oxidation currents of acetaminophen, Fig. 6, it can be concluded that there is a linear relationship between I_p and the square root of the

potential scan rate ($v^{1/2}$). This demonstrates that the oxidation procedure of acetaminophen is a kind of diffusion control process.

Chronoamperometric analysis

The analysis of chronoamperometry for acetaminophen samples was performed by use of La³⁺/Co₃O₄/GSPE vs. Ag/AgCl/KCl (3.0 M) at 0.45V. The Chronoamperometric results of different concentration of acetaminophen sample in PBS (pH 7.0) are demonstrated in Fig. 7. The Cottrell equation for chronoamperometric analysis of electroactive moieties under mass transfer limited conditions is as follow [52]:

$$I = nFAD^{1/2}C_b\pi^{-1/2}t^{-1/2}$$

Where D represents the diffusion coefficient (cm² s⁻¹), and C_b is the applied bulk concentration (mol cm⁻³). Experimental results of I vs. $t^{-1/2}$ were plotted in Fig. 6A, with the best fits for different concentrations of acetaminophen. The resulted slopes corresponding to straight lines in Fig. 6A, were then plotted against the concentration of acetaminophen (Fig. 6B). The mean value of D was determined to be 8.6 \times 10⁻⁵cm²/s and according to the resulting slope and Cottrell equation.

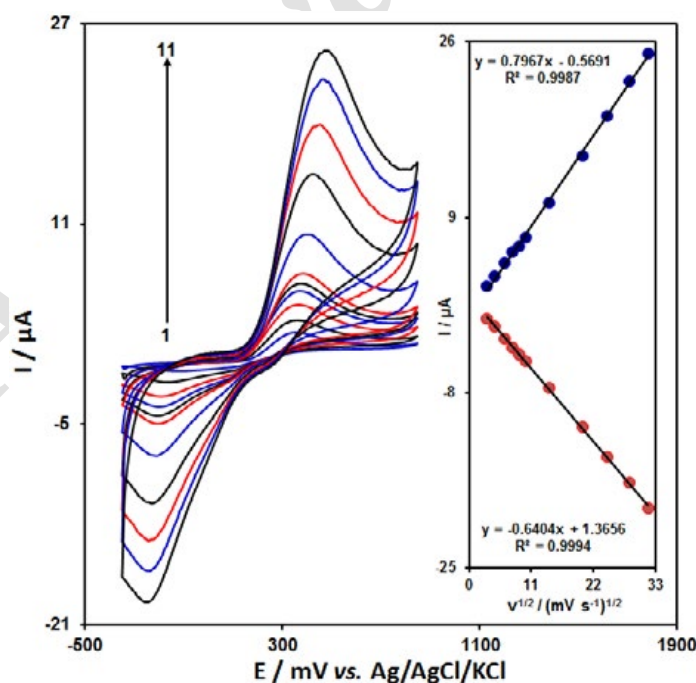


Fig. 6. Cyclic voltammograms of La³⁺/Co₃O₄/GSPE in 0.1 M PBS (pH 7.0) containing 200.0 μ M acetaminophen at various scan rates; numbers 1-11 correspond to 10, 20, 40, 60, 80, 100, 200, 400, 600, 800 and 1000 mV s⁻¹, respectively. Inset: Variation of anodic and cathodic peak current vs. $v^{1/2}$.

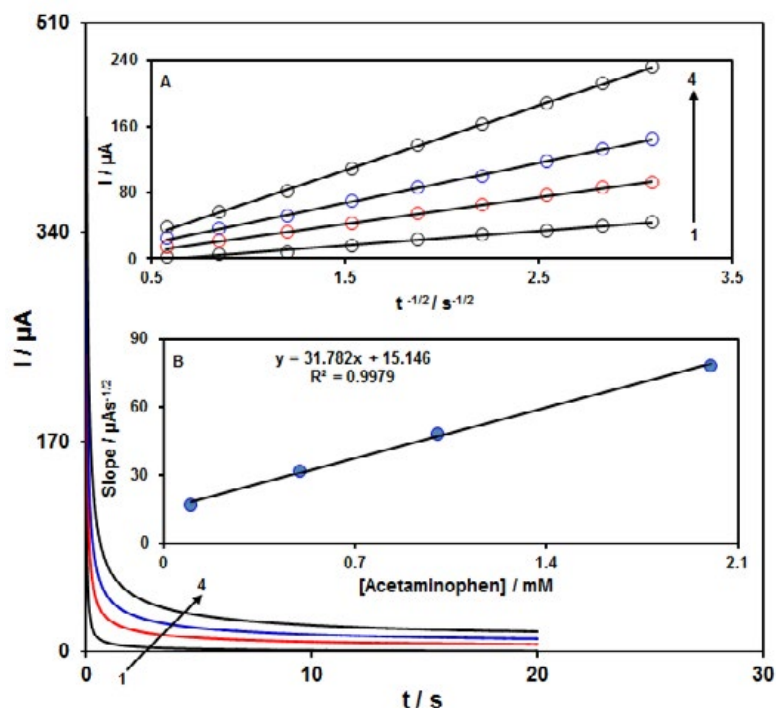


Fig. 7. Chronoamperograms obtained at $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ in 0.1 M PBS (pH 7.0) for different concentration of acetaminophen. The numbers 1–4 correspond to 0.1, 0.5, 1.0 and 2.0 mM of acetaminophen. Insets: (A) Plots of I vs. $t^{-1/2}$ obtained from chronoamperograms 1–4. (B) Plot of the slope of the straight lines against acetaminophen concentration.

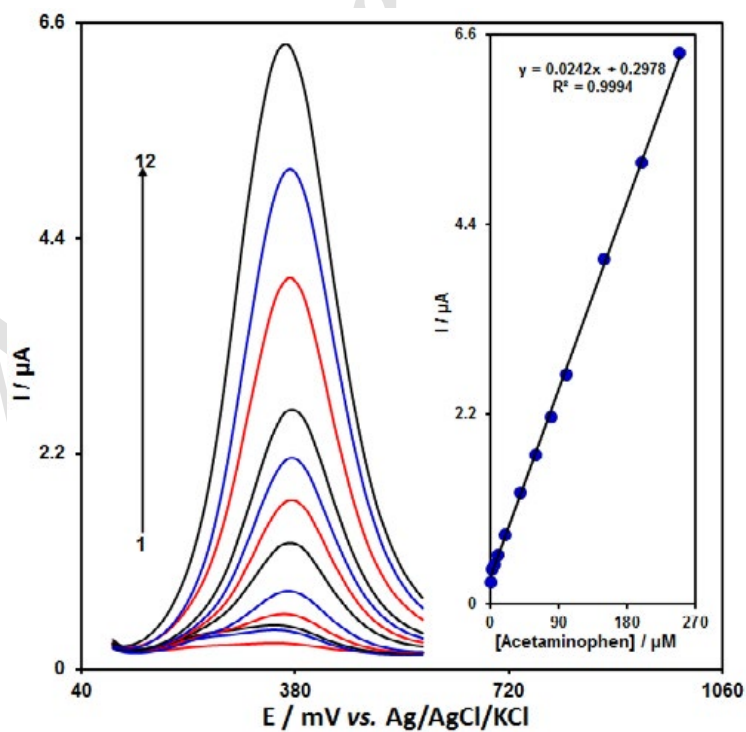


Fig. 8. DPVs of $\text{La}^{3+}/\text{Co}_3\text{O}_4/\text{GSPE}$ in 0.1 M (pH 7.0) are containing different concentrations of acetaminophen. Numbers 1–12 correspond to 0.5, 2.0, 5.0, 10.0, 20.0, 40.0, 60.0, 80.0, 100.0, 150.0, 200.0 and 250.0 μM of acetaminophen. Inset: plot of the peak current as a function of acetaminophen concentration in the range of 0.5–250.0 μM .

Table 1. A comparison of the efficiency of various modified electrodes reported for the detection of acetaminophen.

Electrode	Modifier	Method	LDR (μM)	LOD (μM)	Ref.
Glassy Carbon	Gold nanoparticles/multiwalled carbon nanotube	Voltammetry	0.09–35.0	0.03	8
Glassy Carbon	Multiwalled carbon nanotube-alumina coated silica (MWCNT-ACS) nanocomposite	Voltammetry	2- 0.1	0.05	39
Carbon Paste	Fe(III)-exchanged clinoptilolite nano-particles	Voltammetry	0.0001-10000	0.00099	41
Glassy Carbon	Nickel hydroxide nanoparticles/multi-walled carbon nanotubes c	Voltammetry	0.06–26	0.017	43
Glassy Carbon	Poly(4-amino-3-hydroxynaphthalene sulfonic acid)	Voltammetry	10–125	0.45	44
Glassy Carbon	Graphene/platinum nanoparticles/naion composite	Voltammetry	0.0016-8.2	0.000106	48
Glassy Carbon	zirconium alcoxide porous gels	Voltammetry	19.6-255	0.117	49
Glassy Carbon	Nano-TiO ₂ /polymer	Voltammetry	12.0-120	2.0	50
Glassy Carbon	Carbon-coated nickel magnetic nanoparticles	Voltammetry	7.8 – 110	2.3	51
Graphite screen printed	La ³⁺ /Co ₃ O ₄ nanoflowers	Voltammetry	0.5-250.0	0.09	This Work

Table 2. Determination of acetaminophen in real samples. Concentrations are in μM (n=5).

Sample	Spiked	Found	Recovery (%)	R.S.D. (%)
Acetaminophen Tablet	0	10.0	-	3.2
	2.0	11.8	98.3	1.8
	4.0	14.5	103.6	2.4
Urine	0	-	-	-
	5.0	4.9	98.0	1.8
	10.0	10.2	102.0	2.9

Calibration plot and limit of detection

Fig. 8. showed the differential pulse voltammetric response of acetaminophen at La³⁺/Co₃O₄/GSPE in the phosphate buffer solution with pH=7.0. We found a relationship between the oxidation current of acetaminophen and its concentration within the range 0.5-250 μM . The detection limit (3 σ) of acetaminophen was found to be 0.09 μM .

Table 1. shows a comparison of analytical properties for the detection of acetaminophen at the prepared electrode in this work and some other works.

Analysis of real samples

In order to evaluate the analytical applicability of acetaminophen, the proposed method, also it was applied to the determination of acetaminophen in acetaminophen tablet and urine, using a standard addition method. The results for determination of the acetaminophen in real samples are given in Table 2. Satisfactory recoveries of the experimental results were found for acetaminophen. The reproducibility of the method was demonstrated by the mean relative standard deviation (R.S.D.).

CONCLUSION

In conclusion, La³⁺/Co₃O₄NFs were used to modify the surface of the GSPE. A sensitive and reliable method to determine the acetaminophen in the real samples was firstly elaborated by the obtained La³⁺/Co₃O₄NFs/GSPE. The results indicated that the La³⁺/Co₃O₄NFs/GSPE exhibited a remarkable capacity to the electrochemical oxidation and reduction of the acetaminophen. Moreover, a linear relationship was observed between the response and the concentration in the range of 0.5 to 250.0 μM .

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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