

# Voltammetric Simultaneous Determination of Ascorbic Acid and Acetaminophen Based on Graphite Screen Printed Electrode Modified with a $\text{La}^{3+}$ -Doped ZnO Nanoflowers

**Rezaei, Rasoul; Foroughi, Mohammad Mehdi\*<sup>+</sup>**

*Department of Chemistry, Kerman Branch, Islamic Azad University, Kerman, I.R. IRAN*

**Beitollahi, Hadi\***

*Environment Department, Institute of Science and High Technology and Environmental Sciences, Graduate University of Advanced Technology, Kerman, I.R. IRAN*

**Jahani, Shohreh; Tajik, Somayeh**

*NanoBioElectrochemistry Research Center, Bam University of Medical Sciences, Bam, I.R. IRAN*

**ABSTRACT:** *In this work, an easy method was employed to successfully develop  $\text{La}^{3+}$ -doped ZnO nanoflowers and Guar-Gum (GG) modified screen printed electrode ( $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$ ), and  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  was applied for the electrochemical detection of Ascorbic Acid (AA). The electrochemical methods, such as Cyclic Voltammetry (CV), chronoamperometry (CHA), and Differential Pulse Voltammetry (DPV) were used to evaluate the electrochemical performances toward ascorbic acid on the  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$ . Good linear-ship was observed for ascorbic acid in the ranges of 1.0–700.0  $\mu\text{M}$ , with the detection limits of 0.03  $\mu\text{M}$ . Moreover, this sensor proved favorable to simultaneously determine ascorbic acid and acetaminophen. Finally, the modified electrode has fairly good performance during the employment of real sample analysis to determine the content of ascorbic acid. These results indicate that the  $\text{La}^{3+}$ -doped ZnO nanoflowers are supposed to be a promising material in the electrochemical determination of ascorbic acid and acetaminophen in real samples.*

**KEYWORDS:** *Ascorbic acid; Acetaminophen;  $\text{La}^{3+}/\text{ZnO}$  nanoflowers; Graphite screen printed electrode; Voltammetry.*

## INTRODUCTION

The quantitative detection of drug content constitutes a permanent preoccupation for research in various fields [1]. It is well-established that Ascorbic Acid (AA) and

acetaminophen (AP) is widely used in the food, pharmaceutical industry, and clinical medicine [2]. Ascorbic acid is an important antioxidant widely present

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\* To whom correspondence should be addressed.

+ E-mail: Foroughi@iauk.ac.ir

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in biological systems, which is an essential substance to maintain normal physiological function of the human body. Abnormal contents of ascorbic acid may cause several symptoms, including fatigue, infertility, and scurvy [3]. Acetaminophen is one of the main components of analgesic and antipyretic medicine. However, overdoses of acetaminophen would lead to severe damage to the liver and kidney [4]. In addition, ascorbic acid and acetaminophen usually coexist in the human body, playing an important role in multifarious biological processes [5]. Therefore, it is imperative to develop a fast and sensitive analysis approach for ascorbic acid and acetaminophen quantitative determination.

Various analytical methods for individual or simultaneous determination of ascorbic acid and acetaminophen have been reported, such as titrimetry, spectrophotometry, fluorimetry, infrared spectroscopy, and chromatography [6,12].

Despite the successful detection results, most of these methods suffer from obstacles such as the requirement for sophisticated equipment, skilled technicians, complicated sample pretreatment, or high-cost biological reagents [13-16]. Among them, electrochemical techniques have been considered as a simple, fast response, sensitive, and stable approach. However, due to the drawbacks such as the inability to detect the required low-level concentrations of analytes, fouling of electrodes, and overlapping of their oxidation potential, individual, as well as simultaneous electrochemical detection in commercial electrodes, is very difficult [17-32]. To address these issues, various chemically modified electrode materials have been proposed [33-47].

Nanomaterials, owing to their specific properties, have acted in increasingly important roles in various fields such as environmental protection, domestic appliances, textile industry, engineering industry, new-energy resources, and medical care in modern society and they also have been applied as nanocatalysts, nano-semiconductors, biomedicine, nanotubes, fine chemicals, sensors, etc. [48-51].

ZnO is considered one of the most important and functional metal oxide semiconductor materials due to its various fascinating properties and high technological applications [52-54]. Because of several interesting properties such as wide band gap (3.37 eV), large exciton binding energy (60 meV) at room temperature, larger than several other important semiconductors such as GaN and ZnSe, thermal and mechanical stabilities, piezoelectric and

pyroelectric properties, electrochemical and optoelectronic properties, biocompatibility, and so on [55, 56]. Due to various interesting properties, ZnO is widely used for a variety of applications. Therefore, the excellent properties and wide applications, a variety of ZnO nanomaterials such as nanorods, nanowires, nanobelts, nanoflowers, nanodisks, nanosheets, nanospirals, nanotubes, and so on were prepared via several techniques and reported in the literature [57-63].

According to the previous points, it is important to create suitable conditions for the analysis of ascorbic acid in biological fluids. In this study, La<sup>3+</sup>/ZnO nanoflowers were used to improve the sensitivity of sensors for voltammetric determination of ascorbic acid. The proposed sensor showed good electrocatalytic and accumulative effects on ascorbic acid. Eventually, we evaluate the analytical performance of the suggestion sensor for ascorbic acid determination in real samples.

## EXPERIMENTAL SECTION

### *Apparatus and chemicals*

The electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands). The experimental conditions were controlled with General Purpose Electrochemical System (GPES) software. The screen-printed electrode (DropSens, DRP-110, Spain) consists of three main parts which are a graphite counter electrode, a silver pseudo-reference electrode, and a graphite working electrode, unmodified.

All solutions were freshly prepared with double distilled water. Ascorbic acid and all other reagents were of analytical grade and were obtained 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.

### *Preparation of La<sup>3+</sup>-doped ZnO nanoflowers*

All the chemicals used for the preparation of the nano-powders, namely zinc acetate (Zn(CH<sub>3</sub>COO)<sub>2</sub>·2H<sub>2</sub>O), lanthanum nitrate (La(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O), thiourea ((NH<sub>2</sub>)<sub>2</sub>CS) and ammonia (25% NH<sub>3</sub>), 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 ZnO nanostructures were prepared by dissolving 0.46 mol of zinc 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 deionised water. The number of solutions of zinc acetate, thiourea, and ammonia was held constant at a ratio of 1:1:1. Then the zinc acetate solution was added to 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 La<sup>3+</sup>-doped ZnO nanoflowers is shown in Fig. 1.

#### Preparation of modified electrode

The bare screen-printed electrode was coated with La<sup>3+</sup>/ZnO nanoflowers as follows. 30 mg of La<sup>3+</sup>/ZnO nanoflowers were dispersed into 5 mL of guar-gum (GG) solution with vigorous sonication for 2 h to get a viscous guar-gum solution with uniformly dispersed guar-gum. Then 5 µL aliquot of the hybrid suspension solution was cast on the carbon working electrodes, and waiting until the solvent was evaporated at room temperature.

#### Preparation of real samples

One milliliter of a Vitamin C ampoule (Darou Pakhsh Company, Iran, contained 1 mg/mL of ascorbic acid) was diluted to 10 mL with 0.1 M PBS (pH 7.0); then, a different volume of the diluted solution was transferred into each of a series of 25 mL volumetric flasks and diluted to the mark with PBS. The ascorbic acid content was analyzed by the proposed method using the standard addition method.

Five Vitamin C tablets (labeled 250 mg per tablet, Osvah Pharmaceutical Company, Iran) were grinding. Then, the tablet solution was prepared by dissolving 250 mg of the powder in 25 mL water by ultrasonication. Then, different volume of the diluted solution was transferred into a 25 mL volumetric flask and diluted to the mark with PBS (pH 7.0). The ascorbic acid content was analyzed by the proposed method using the standard addition method.

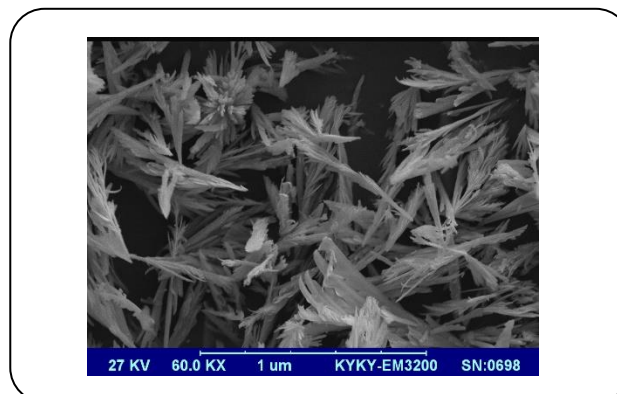


Fig. 1: SEM images of La<sup>3+</sup>-doped ZnO nanoflowers.

Five Vitamin C effervescent tablets (labeled 500 mg per tablet, Hakim Pharmaceutical Company, Iran) were ground. Then, the tablet solution was prepared by dissolving 500 mg of the powder in 25 mL water by ultrasonication. Then, different volume of the diluted solution was transferred into a 25 mL volumetric flask and diluted to the mark with PBS (pH 7.0). The ascorbic acid content was analyzed by the proposed method using the standard addition method.

## RESULTS AND DISCUSSION

### Electrocatalytic oxidation of ascorbic acid at a La<sup>3+</sup>/ZnO/GG/SPE

The electrochemical behavior of ascorbic acid is dependent on the pH value of the aqueous solution. Therefore, pH optimization of the solution seems to be necessary in order to obtain the electrocatalytic oxidation of ascorbic acid. Thus the electrochemical behavior of ascorbic acid was studied in 0.1 M PBS in different pH values (2.0 < pH < 9.0) at the surface of La<sup>3+</sup>/ZnO/GG/SPE by CV. It was found that the electro-oxidation of ascorbic acid at the surface of La<sup>3+</sup>/ZnO/GG/SPE was more favored under neutral conditions than in acidic or basic medium. Thus, pH 7.0 was chosen as the optimum pH for electrocatalysis of ascorbic acid oxidation at the surface of La<sup>3+</sup>/ZnO/GG/SPE.

Fig. 2 depicts the cyclic voltammetric responses for the electrochemical oxidation of 700.0 µM ascorbic acid at La<sup>3+</sup>/ZnO/GG/SPE (curve a) and bare SPE (curve b). The anodic peak potential for the oxidation of ascorbic acid at La<sup>3+</sup>/ZnO/GG/SPE (curve a) is about 340.0 mV compared with 240.0 mV for that on the bare SPE (curve b). Similarly, when the oxidation of ascorbic

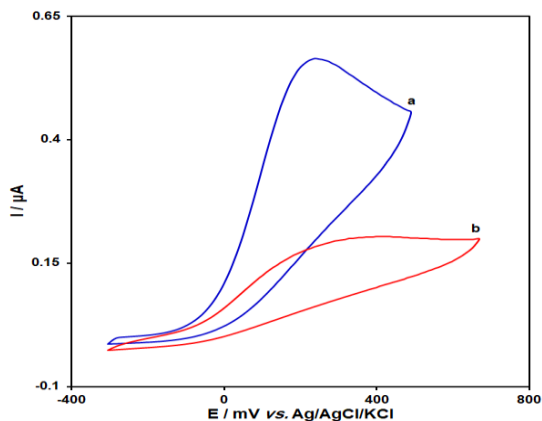


Fig. 2: Cyclic voltammograms of (a)  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  and (b) bare SPE in 0.1 M PBS (pH 7.0) in the presence of 700.0  $\mu\text{M}$  ascorbic acid at the scan rate 50  $\text{mVs}^{-1}$ .

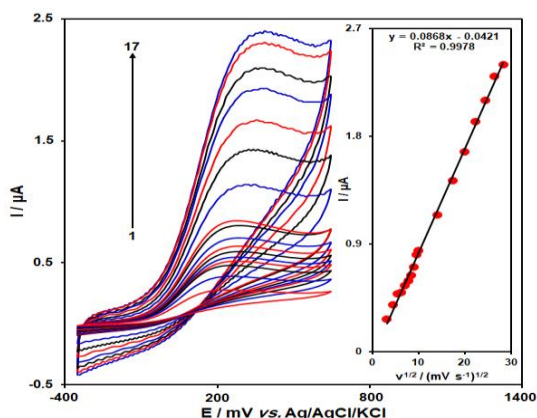


Fig. 3: CVs of  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  in 0.1 M PBS (pH 7.0) containing 700.0  $\mu\text{M}$  ascorbic acid at various scan rates; numbers 1-17 correspond to 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700 and 800  $\text{mVs}$ , respectively. Inset: variation of anodic peak current vs.  $v^{1/2}$ .

acid at the  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  (curve a) and bare SPE (curve b) are compared, an extensive enhancement of the anodic peak current at  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  relative to the value obtained at the bare SPE (curve b) is observed. In other words, the results clearly indicate that the  $\text{La}^{3+}/\text{ZnO}$  nanoflowers improve the ascorbic acid oxidation signal.

The effect of potential scan rates on the oxidation current of ascorbic acid has been studied (Fig. 3). The results showed that an increase in the potential scan rate induced an increase in the peak current. In addition, the oxidation process is diffusion-controlled as deduced from the linear

dependence of the anodic peak current ( $I_p$ ) on the square root of the potential scan rate ( $v^{1/2}$ ) over a wide range from 10 to 800  $\text{mVs}$  [64].

### Chronoamperometric measurements

Chronoamperometric measurements of ascorbic acid at  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  were carried out by setting the working electrode potential at 300 mV for the various concentrations of ascorbic acid in PBS (pH 7.0) (Fig. 4). For an electroactive material (ascorbic acid in this case) with a diffusion coefficient of  $D$ , the current observed for the electrochemical reaction at the mass transport limited condition is described by the Cottrell equation [64].

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

Where  $D$  and  $C_b$  are the diffusion coefficient ( $\text{cm}^2/\text{s}$ ) and the bulk concentration ( $\text{mol cm}^{-3}$ ), respectively. Experimental plots of  $I$  vs.  $t^{-1/2}$  were employed, with the best fits for different concentrations of ascorbic acid (Fig. 4A). The slopes of the resulting straight lines were then plotted vs. ascorbic acid concentration (Fig. 4B). From the resulting slope and Cottrell equation the mean value of the  $D$  was found to be  $1.46 \times 10^{-6} \text{ cm}^2/\text{s}$ .

### Calibration plot and limit of detection

The peak current of ascorbic acid oxidation at the surface of the modified electrode can be used for the determination of ascorbic acid in solution. Therefore, differential pulse voltammetry (DPV) experiments were done for different concentrations of ascorbic acid (Fig. 5). The oxidation peak currents of ascorbic acid at the surface of a modified electrode were proportional to the concentration of the ascorbic acid within the ranges 1.0 to 700.0  $\mu\text{M}$ . The detection limit ( $3\sigma$ ) of ascorbic acid was found to be 0.03  $\mu\text{M}$ .

### Simultaneous determination of ascorbic acid and acetaminophen

The electrochemical determination of ascorbic acid using bare electrodes suffers from interference by acetaminophen because the oxidation potential for acetaminophen is fairly close to that of ascorbic acid.

Determination of two compounds was performed by simultaneously changing the concentrations of ascorbic acid and acetaminophen, and recording the DPVs (Fig. 6). The voltammetric results showed well-defined anodic peaks at potentials of 260 and 480 mV, corresponding

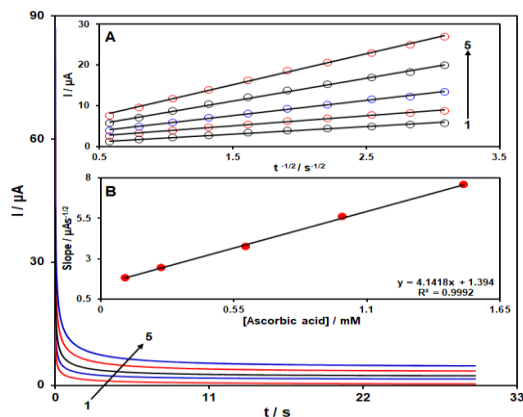


Fig. 4: Chronoamperograms obtained at  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  in 0.1 M PBS (pH 7.0) for different concentrations of ascorbic acid. The numbers 1–5 correspond to 0.1, 0.25, 0.6, 1.0, and 1.5 mM of ascorbic acid. Insets: (A) Plots of  $I$  vs.  $t^{-1/2}$  obtained from chronoamperograms 1–5. (B) Plot of the slope of the straight lines against ascorbic acid concentration.

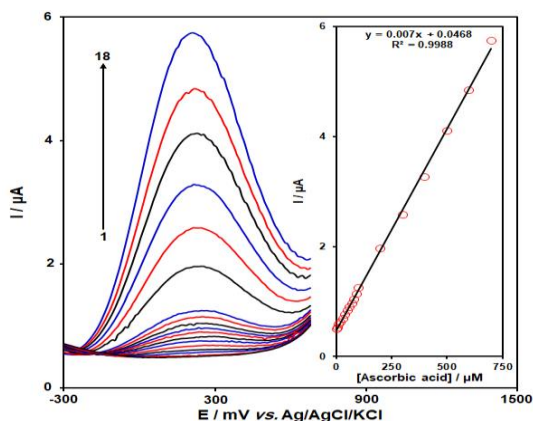


Fig. 5: DPVs of  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  in 0.1 M (pH 7.0) containing different concentrations of ascorbic acid. Numbers 1–18 correspond to 1.0, 5.0, 10.0, 20.0, 30.0, 40.0, 50.0, 60.0, 70.0, 80.0, 90.0, 100.0, 200.0, 300.0, 400.0, 500.0, 600.0 and 700.0  $\mu\text{M}$  of ascorbic acid. Inset: Plot of the electrocatalytic peak current as a function of ascorbic acid concentration in the range of 1.0–700.0  $\mu\text{M}$ .

to the oxidation of ascorbic acid and acetaminophen, respectively, indicating that simultaneous determination of these compounds is feasible at the  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  as shown in Fig. 6.

The sensitivity of the modified electrode towards the oxidation of ascorbic acid was found to be  $0.007 \mu\text{A}/\mu\text{M}$ . This is very close to the value obtained in the absence of acetaminophen ( $0.007 \mu\text{A}/\mu\text{M}$ ), indicating that oxidation

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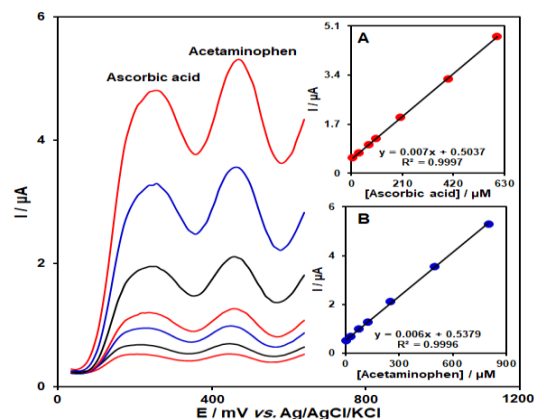


Fig. 6: DPVs of  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  in 0.1 M PBS (pH 7.0) containing different concentrations of ascorbic acid and acetaminophen in  $\mu\text{M}$ , from inner to outer: 5.0+5.0, 30.0+30.0, 70.0+75.0, 100.0+125.0, 200.0+250.0, 400.0+500.0 and 600.0+800.0 respectively. Insets (A) plots of  $I_p$  vs. ascorbic acid concentration in the range of 5.0–600.0  $\mu\text{M}$ , (B) plots of  $I_p$  vs. acetaminophen concentration in the range of 5.0–800.0  $\mu\text{M}$ .

processes of these compounds at the  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  are independent and therefore, simultaneous determination of their mixtures is possible without significant interferences.

#### Real sample analysis

In order to evaluate the analytical applicability of the proposed method, also it was applied to the determination of ascorbic acid in vitamin C tablets, acetaminophen tablets, and urine samples. The results for the determination of ascorbic acid and acetaminophen in real samples are given in Table 1. Satisfactory recovery of the experimental results was found for ascorbic acid and acetaminophen. The reproducibility of the method was demonstrated by the mean Relative Standard Deviation (R.S.D.).

#### The stability, repeatability, and selectivity of $\text{NiO}/\text{Co}_3\text{O}_4/\text{GCE}$

In order to evaluate  $\text{NiO}/\text{Co}_3\text{O}_4/\text{GCE}$  long-term stability, its functionality was evaluated for a period of 3 weeks. In this regard, the tests were conducted again upon storing the adjusted electrode at room temperature for a period of 3 weeks. Cyclic voltammograms showed that there were no palpable variations in regard to drosidopa oxidation peak potential with the exception of a drop of less than 2.53% in comparison to the primary response. The adjusted electrode oxidation antifouling capacity

**Table 1: The application of  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  for determination of ascorbic acid and acetaminophen in vitamin C tablet, acetaminophen tablet, and urine samples ( $n=5$ ). All concentrations are in  $\mu\text{M}$ .**

Sample	Spiked		Found		Recovery (%)		R.S.D. (%)	
	Ascorbic acid	Acetaminophen	Ascorbic acid	Acetaminophen	Ascorbic acid	Acetaminophen	Ascorbic acid	Acetaminophen
Vitamin C tablet	0	0	7.5	-	-	-	2.4	-
	5.0	12.5	12.7	12.2	101.6	97.6	1.7	2.8
	10.0	17.5	17.3	17.4	98.8	99.4	3.1	2.7
	15.0	22.5	22.8	22.7	101.3	100.8	2.1	1.9
Acetaminophen tablet	0	0	-	10.0	-	-	-	3.1
	15.0	10.0	15.1	19.8	100.6	99.0	3.4	2.6
	25.0	15.0	24.7	25.3	98.8	101.2	2.3	2.1
	35.0	20.0	35.1	29.6	100.2	98.6	1.6	2.4
Urine	0	0	-	-	-	-	-	-
	10.0	15.0	9.8	15.2	98.0	101.3	1.8	3.3
	20.0	20.0	20.6	19.8	103.0	99.0	2.2	2.4
	30.0	25.0	30.3	25.3	101.0	101.2	2.4	3.1

pertaining to droxidopa and relevant oxidation byproducts were examined via CV evaluation.

In the vicinity of ascorbic acid, voltammograms were documented upon potential cycling of 20 repetitions at 50 mV/s scan rate. Based on the outcomes, there were no changes in terms of peak potentials apart from a decrease of less than 2.62%. The results validated the greater sensitivity and decreased fouling impact of  $\text{NiO}/\text{Co}_3\text{O}_4/\text{GCE}$  in regard to ascorbic acid and relevant oxidation byproducts.

The effect of different materials as composites potentially involved in determining ascorbic acid is investigated at optimal circumstances with 20.0  $\mu\text{M}$  ascorbic acid at  $\text{pH} = 7.0$ . The possibly contributing materials were selected among a set of materials typically observed with ascorbic acid within biological and/or pharmaceutical liquids. The limit of tolerance was determined as the maximal concentrations of contributing materials which led to an error that was less than  $\pm 6\%$  in determining ascorbic acid. Based on the findings, urea, saturated starch solution, folic acid (vitamin  $\text{B}_9$ ), glycine, phenylalanine, methionine, alanine,  $\text{Cl}^-$  or  $\text{F}^-$ ,  $\text{Fe}^{3+}$ ,  $\text{CO}_3^{2-}$ ,  $\text{NH}_4^+$ ,  $\text{Fe}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{SO}_4^{2-}$ ,  $\text{Mg}^{2+}$ , ethanol, methanol, citric acid, fructose, lactose, sucrose, and glucose were not involved in determining ascorbic acid.

## CONCLUSIONS

A facile method was developed to prepare  $\text{La}^{3+}$ -doped  $\text{ZnO}$  nanoflowers ( $\text{La}^{3+}/\text{ZnO}$  NF). The prepared nanoflowers were successfully employed to modify the SPE and  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  was applied for the study of the determination of ascorbic acid. The results showed that the  $\text{La}^{3+}/\text{ZnO}$  NF could be successfully employed to detect ascorbic acid under optimum conditions; ascorbic acid under 0.1 M PBS ( $\text{pH} = 7.0$ ) was also electrochemically determined by  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$ . The  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  exhibited the best electrochemical activity, most efficient electron transfer ability, and highest sensitivity toward the electrochemical oxidation of ascorbic acid compared with unmodified electrode. Consequently, the proposed electrode was successfully applied for simultaneous determination of ascorbic acid and acetaminophen. What's more, the as-synthesized  $\text{La}^{3+}/\text{ZnO}/\text{GG}/\text{SPE}$  demonstrated excellent performance in the electrochemical detection of ascorbic acid and acetaminophen in the real sample analysis, suggesting the high practicability of the prepared electrode. This work could inspire us for more applications of  $\text{La}^{3+}/\text{ZnO}$  NF in the electrochemical determination of electroactive materials.

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