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Sensitive detection of hydrochlorothiazide using Ce³⁺/NiO hexagonal nanoparticles modified glassy carbon electrode

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The present research presented a novel modification approach for modifying a glassy carbon electrode on the basis of the Ce³⁺/NiO hexagonal nanoparticles (Ce³⁺/NiO hexagonal NPs/GCE). In so doing, we devised the new modified electrode for using as one of the sensitive sensors for detecting the trace amounts of hydrochlorothiazide. Moreover, it is an acceptable electrocatalyst for catalytic oxidation of hydrochlorothiazide by shifting the overpotential toward less positive potential and enhancing catalytic current in comparison to the bare GCE. In a concentration range 0.1 to 700.0 µM in a phosphate buffer solution (PBS) at a pH of 7.0, the responses were linear and hydrochlorothiazide detection limit for this method was 0.03 µM (S/N=3). Furthermore, this sensor successfully detected hydrochlorothiazide in hydrochlorothiazide tablets and urine samples with satisfactory recovery ranges, indicating a promising application in biological samples, pharmaceutical compounds analysis and clinical diagnosis.

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Introduction

Hypertension is another name for high blood pressure. The prolonged increased blood pressure has been identified as one of the main risk factors for stroke, kidney failure and heart attacks [1,2]. These problems may be less likely to occur if blood pressure is controlled. Therefore, the first-line medication for hyper-tension contains thiazide-diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blocker as well as calcium channel blockers [3].

Researchers consider hydro-chlorothiazide (i.e., 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide) as one of the thiazide diuretics [4]. Hydrochlorothiazide has been proposed as one of the drugs with the widespread utilizations worldwide to treat the high blood pressure since the advent of chlorothiazide in 1957. Hydrochlorothiazide functions on the kidney and inhibits sodium and chloride ions re-absorption into the nephron-contoured tubules. Moreover, it prevents water re-absorption and decreases the blood pressure. Additionally, hydrochlorothiazide has uses in curing the renal tubular acidosis, edema, diabetes insipiddus and preventing the kidney stone [5,6]. Notably, half-life of hydrochlorothiazide is variable from 6-15 h and approximately 50% to 60% of the oral administration of the drug excreted via urine [7]. An over-dose of hydrochlorothiazide of the patients' loss fluid and electrolyte and the reported symptoms have been dizziness,

sedation or impaired consciousness, hypo-tension as well as cramps in the muscles [8]. Hence, the determination of hydrochlorothiazide in human fluids and pharmaceutical compounds is very important.

Numerous methods have been designed to detect hydrochlorothiazide, including HPLC [9], liquid chromatography tandem mass spectrometry [10], ultraviolet spectrophotometry [11], and electrochemistry [12]. Although such methods are sensitive, there are restrictions such as high costs and complex analysis processes which are cumbersome for analysis. In contrast, electrochemical methods have become prominent in analyte detection because of their low cost, rapid response time, high sensitivity, simplicity and selectivity [13-24].

According to the studies, electro-chemical procedures with the use of the chemically modified electrodes (CMEs) have a widespread utilization as the selective and sensitive analytical techniques to determine trace amount of electroactive prominent compounds [25-35]. However, a major feature of CMEs is their capability of catalyzing the electrode procedure through considerable decline in the over-potential on the basis of the un-modified electrodes. Consequently, choosing materials for constructing diverse modified electrodes to detectanalyte is of high importance.

Recently, nanomaterials have been widely used as modifier in electrochemical detection due to their very good electrical conductivity, larger surface areas [36-43]. In addition, nickel oxide (NiO) that is one of the p-type semiconductors with the broad band gap equal to 3.7 eV in the room temperature and the increased isoelectric point (IEP) of ~10.7, is of particular interest in the environmental, energy as well as biological researches because of their effective electro-catalytic features, acceptable oxygen-ion conductivity, non-toxicity, bio-compatibility, specific capacity equal to 2785 Fg^{-1} and porosity features [44-49]. Nevertheless, for electrochemical applications, the increased conductivity has been proposed as one of the prime parameters for improving its electrochemical functions. Therefore, for improvements in the electrical features of metal oxides, researchers typically run heteroatom doping. Conventionally, metallic dopants have entered the lattice of metal oxides for elevating its electrocatalytic behaviors [50]. As an instance, in the published investigations, some researches confirmed doping heteroatoms like Li^+, La^{3+}, Co^{3+} as well as Y^{3+} for improving its electro catalytic behaviors for diverse utilizations [51-54]. Herein, we used rare earth ions (Ce^{3+}) doping to improve the electrocatalytic performance of NiO nanostructures.

The present work aimed at employing the electrochemical method for determination of hydrochlorothiazide at the synthesized Ce^{3+}/NiO hexagonal NPs modified GCE. An excellent electrocatalytic activity was observed regarding hydrochlorothiazide oxidation with the increased oxidation peak current and decrease of overpotential. Also, using this developed sensor, the determination of hydrochlorothiazide was carried out in tablets and urine samples.

Experimental section

Instruments and chemicals

An Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands) was utilized to measure electrochemicals. A platinum wire as the auxiliary electrode, CuO NFs/GCE as the working electrode and an Ag/AgCl/KCl (3.0 M) as reference electrode were used for electrochemical measurements. The ortho-phosphoric acid as well as the respective salts (KH_2PO_4, K_2HPO_4, K_3PO_4) with a pH ranging between 2.0 and 9.0 were utilized to procure buffer solution. The pH values were measured using a pH-meter (Metrohm 692 model, Herisau, Switzerland).

Hydrochlorothiazide and all other reagents were of the analytical grade, and were obtained from Merck (Darmstadt, Germany). The phosphate buffer solution (PBS) was produced from concentrate phosphoric acid and its salts.

Preparation of electrode

The GCE was modified with Ce^{3+}/NiO hexagonal NPs using a simple drop-casting method. To prepare the CuO NF stock solution in 1 mL of aqueous solution, the Ce^{3+}/NiO hexagonal NPs (1 mg) was distributed by 30-minute ultrasonication. After that, a 5 μL Ce^{3+}/NiO hexagonal NPs suspension was dropped on the glassy carbon working electrode surface. Then, the solvent was evaporated at an ambient temperature. The surface areas of the Ce^{3+}/NiO hexagonal NPs/GCE and the bare GCE were obtained by CV using 1mM $K_3Fe(CN)_6$ at different scan rates. Using Randles-Sevcik formula [55] in Ce^{3+}/NiO hexagonal NPs/GCE, the electrode surface was found 0.156 cm^2 which was about 4.96 times greater than bare GCE.

Results and discussion

Electrochemical behaviours of hydrochlorothiazide on the various surface of electrodes

For studying electrochemical behaviours of *hydrochlorothiazide* based on pH, providing an optimized pH-value could be of high significance to obtain acceptable outputs. Hence, the modified electrode was used for running experimentations under different pH amount ranging from 2.0 to 9.0 (Figure 1). In the last step, the most promising results were seen in the case of electrooxidation of hydrochlorothiazide at the pH equal to 7.0.
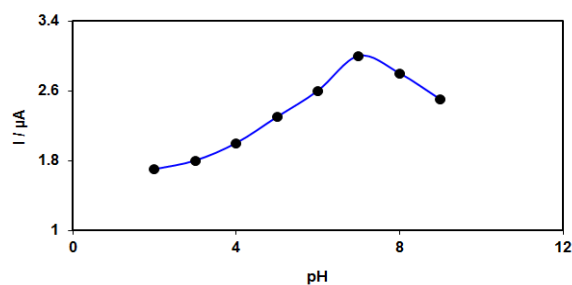

FIGURE 1 Plot of Ip vs. pH obtained from DPVs of Ce^{3+}/NiO hexagonal NPs/GCE in a solution containing 100.0 μM of hydrochlorothiazide in 0.1 PBS with different pHs (2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0)

Figure 2 depicts CVs for hydrochlorothiazide oxidation, at bare GCE (a), and Ce^{3+}/NiO hexagonal NPs/GCE (b) in 0.1 M PBS (pH of 7.0) solution containing 100.0 μM hydrochlorothiazide at scan rate of 50 mV s^{-1}. The anodic peak potential for hydrochlorothiazide oxidation on the bare GCE was about 1150 mV, while on the Ce^{3+}/NiO hexagonal NPs/GCE, the peak potential was around 800 mV. This reduction of around 350 mV proposes that the Ce^{3+}/NiO hexagonal NPs possesses highly efficient electrocatalytic activity considering the oxidation of hydrochlorothiazide.
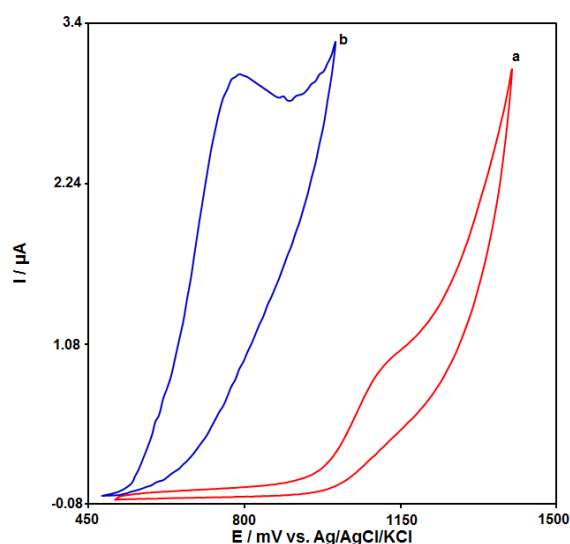

FIGURE 2 CVs of (a) bare GCE and (b) CuO NFs/GCE in the presence of 100.0 μM hydrochlorothiazide. Scan rate was 50 mVs $^{-1}$

Effect of scan rate on the results

The relationship between scan rate and peak current shows promising data with respect to electrochemical mechanisms. Hence, the influence of scan rate onto the peak current of hydrochlorothiazide was studied by LSV (Figure 3). The electrode response of hydrochlorothiazide was a diffusion-controlled process since the peak current of oxidation was proportional to the square root of the scan rate (Figure 3, inset).
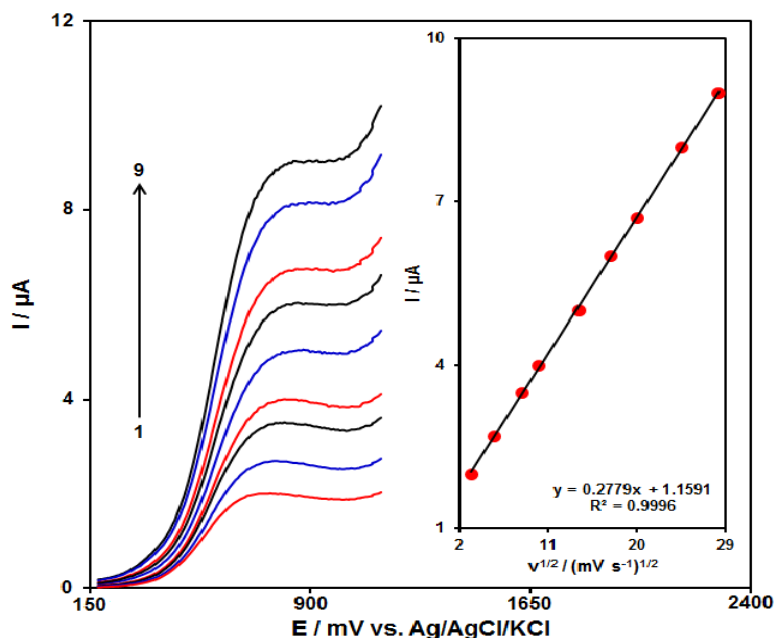

FIGURE 3 CVs of Ce^{3+}/NiO hexagonal NPs/GCE in 100.0 µM of hydrochlorothiazide at different scan rates; (10, 30, 70, 100, 200, 300, 400, 600 and 800 mV s^{-1}). Inset: Variation in the peak current *vs.* v$^{1/2}$

Chronoamperometric analyse

Chronoamperometric study was used to calculate the diffusion coefficient (D) of methionine on the surface Ce^{3+}/NiO hexagonal NPs/GCE at an optimum condition. Figure 4 displays chronoamperometric results of diverse concentrations of the hydrochlorothiazide sample in PBS considering pH of 7.0. In addition, Cottrell equation is proposed in the case of the chronoamperometric analyses of electroactive moiety in the basis of the mass transfer restricted states [55]. Hence, D mean value equaled to 2.4 × 10^{-5} cm^2 s^{-1}.

Calibration plot and detection limit

In this step, DPV was applied for determining hydrochlorothiazide content with different concentration gradients at a pH of 7.0 (Figure 5). (Step potential=0.01 V and pulse amplitude=0.025 V). It was found that the peak currents of hydrochlorothiazide oxidation at Ce^{3+}/NiO hexagonal NPs/GCE surface linearly depended on hydrochlorothiazide concentrations above the range of 0.1–700.0 µM. The detection limit was 0.03 µM. The comparison of the results for the detection of hydrochlorothiazide with different modified electrodes in the literatures are listed in Table 1.
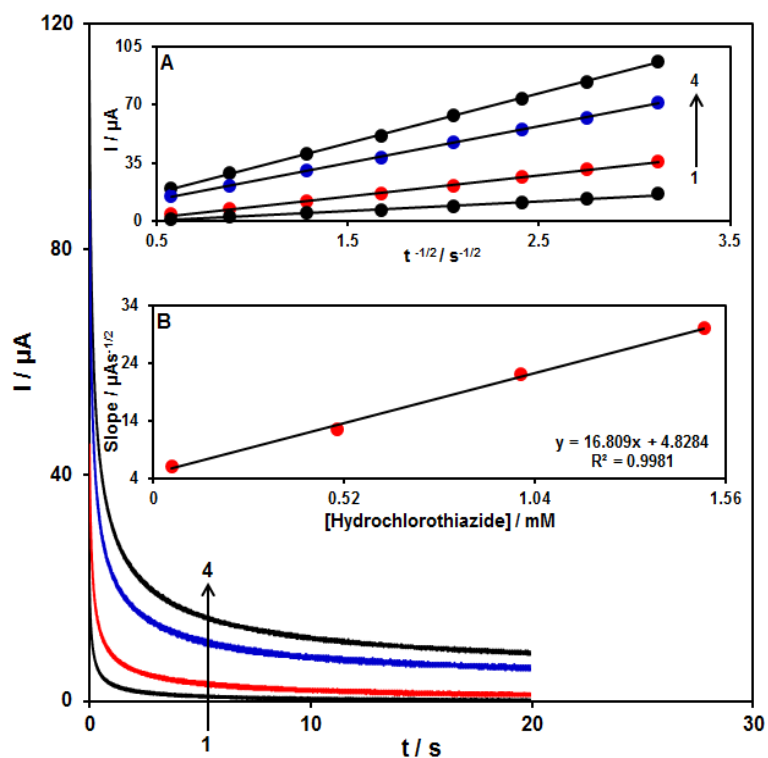
FIGURE 4 Chronoamperograms of Ce^{3+}/NiO hexagonal NPs/GCE in different concentration of hydrochlorothiazide. (0.05, 0.5, 1.0 and 1.5mM) Insets: (A) Plots of I vs. t $^{-1/2}$. (B) Plot of the slope against methionineconcentration

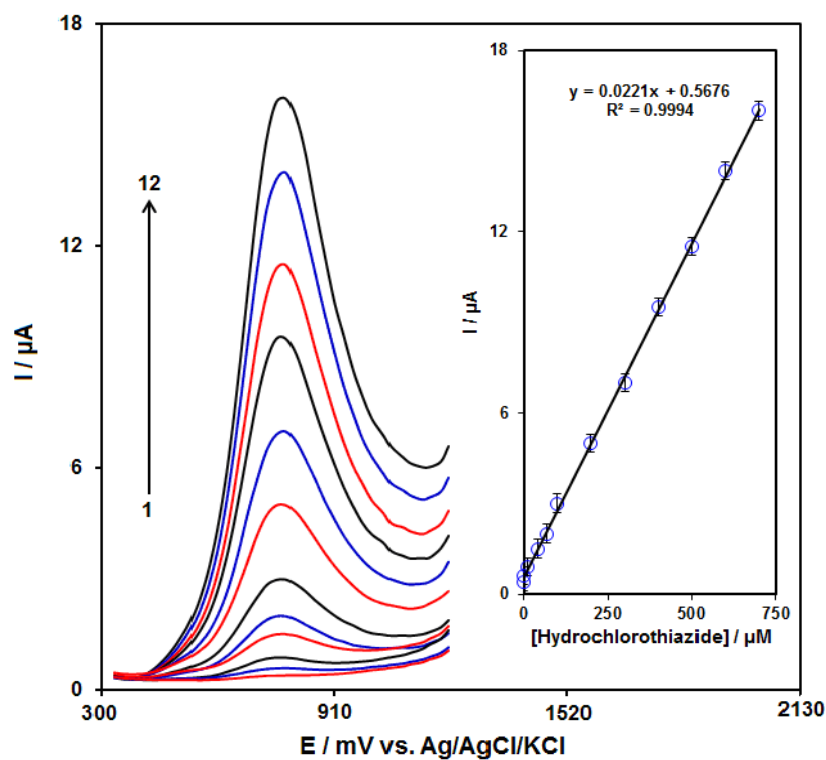**FIGURE 5** DPVs of Ce^{3+}/NiO hexagonal NPs/GCE in different concentrations of hydrochlorothiazide (0.1, 1.0, 10.0, 40.0, 70.0, 100.0, 200.0, 300.0, 400.0, 500.0, 600.0 and 700.0 µM). Inset: plot of the peak current vs. hydrochlorothiazide concentration

TABLE 1 Comparing performance of purposed electrochemical sensor with others for detection of hydrochlorothiazide

Ref.	Limit of Detection (µM)	Linear Range (µM)	Method	Electrochemical Sensor
[56]	21.2 µmol dm^{-3}	0.22–5.82 mmol dm^{-3}	Amperometry	Nickel Nanowrinkles/Carbon Paste Electrode
[57]	2.71 nM	0.01-0.2 µM	Square Wave Voltammetry	Graphene Oxide/GCE
[58]	2.8×10^{-8} M	1.0×10^{-7}-2.0×10^{-5} M	Adsorptive stripping voltammetry	Multi-Walled Carbon Nanotube/GCE
[59]	0.14 µM	1.0–500.0 µM	Square Wave Voltammetry	NiO NPs-Benzoylferrocene/Carbon Paste Electrode
[60]	8.55 µM	28.5-300.0 µM	DPV	Poly L-Glutamic Acid/ Screen-Printed Carbon Electrode
This Work	0.03 µM	0.1-700.0 µM	DPV	Ce^{3+}/NiO Hexagonal NPs/GCE

Analysis of real samples

Finally, the performance of Ce^{3+}/NiO hexagonal NPs/GCE as a new electrochemical sensor for analyzing of hydrochlorothiazide in hydrochlorothiazide tablets and urine samples was evaluated. Table 2 shows obtained data as well as the recovery data proving the ability of Ce^{3+}/NiO hexagonal NPs/GCE as a sensitive sensor in the case of the analysis of hydrochlorothiazide in real samples.

TABLE 2 The application of Ce^{3+}/NiO hexagonal NPs/GCE for determination of hydrochlorothiazide in hydrochlorothiazide tablets and urine samples (n=5)

(%)R.S.D.	Recovery (%)	Found (µM)	Spiked (µM)	Sample
3.2	-	3.0	0	Hydrochlorothiazide Tablets
1.9	98.7	7.9	5.0	
2.8	103.1	13.4	10.0	
2.3	97.2	17.5	15.0	
2.1	100.8	23.2	20.0	
-	-	-	0	Urine
1.9	102.9	7.2	7.0	
2.8	98.3	11.8	12.0	
3.0	102.3	17.4	17.0	
3.1	97.7	21.5	22.0	

Conclusion

This research demonstrated the fabrication of Ce³⁺/NiO hexagonal NPs/GCE and the respective utilization to determine hydrochlorothiazide. The results showed catalysis of hydrochlorothiazide oxidation at a pH of 7.0 and the respective peak potential switched to a less positive potential at the surface of the modified electrode. Finally, this developed sensor can be successfully utilized to analyze hydrochlorothiazide in hydrochlorothiazide tablets and the urine sample. Hence, the sensor can be helpful with the acceptable analytical advancements.

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