



# Electrochemical investigation of the voltammetric determination of hydrochlorothiazide using a nickel hydroxide modified nickel electrode

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## ABSTRACT

The preparation and electrochemical characterization of a nickel hydroxide modified nickel electrode as well as its behavior as electrocatalyst toward the oxidation of hydrochlorothiazide (HCTZ) were investigated. The electrochemical behavior of the modified electrode and the electrooxidation of HCTZ were explored using cyclic voltammetry. The voltammetric response of the modified electrode in the detection of HCTZ is based on the electrochemical oxidation of the Ni(II)/Ni(III) and a chemical redox process. The analytical parameters for the electrooxidation of HCTZ by the nickel hydroxide modified nickel electrode were obtained in NaOH solution, in which the linear voltammetric response was in the concentration range from  $1.39 \times 10^{-5}$  to  $1.67 \times 10^{-4}$  mol L<sup>-1</sup> with a limit of detection of  $7.92 \times 10^{-6}$  mol L<sup>-1</sup> and a sensitivity of  $0.138 \mu\text{A L mmol}^{-1}$ . Tafel analysis was used to elucidate the kinetics and mechanism of HCTZ oxidation by the modified electrode.

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## 1. Introduction

Electrochemical methods comprise a collection of extremely useful and versatile measurement tools in biological [1–5], food [6–9] and environmental [10–13] analysis due the high sensitivity, selectivity, accuracy and precision, as well as wide linear dynamic range, with relatively low-cost instrumentation. In the pharmaceutical area [14], the use of electrochemistry is an important approach in drug discovery and research as well as quality control, drug stability, determination of physiological activity and especially in their dosage forms in biological samples.

The diuretics are substances used to increase the production of urine and sodium excretion in order to adjust the volume and composition of body fluids or to eliminate excess of fluids [15]. As therapeutic agents, they are used in the treatment of congestive heart failure, edemas, hypertension, kidney, liver cirrhosis, lung diseases, and prophylaxis of renal failure [15]. According to the World Anti-doping Agency (WADA) the diuretics are on the list of prohibited substances in sports [16] due to their potent ability to remove water from the body and to mask the administration of other doping agents, conditions which promote rapid weight loss that can be required to meet a weight category and reducing their concentration in urine primarily because of an increase in urine volume, respectively [17]. In this manner, it was expected that these substances were not found in biological samples in athletes. Despite this, some athletes misuse diuretics in sports in order to give them competitive advantage.

Among the diuretics, the most common drug detected in the year 2008 by WADA laboratories [17] was hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide – HCTZ). The HCTZ is a benzothiazide diuretic that acts directly on the kidney by increasing the excretion of sodium chloride and water and, to a lesser extent, that of potassium ion [18]. Also, it is a antihypertensive drug which improves the action of other hypotensive substances.

Thus, the development of convenient, rapid, selective and sensitive analytical methods for the determination of illicit diuretics, such as HCTZ, in human urine samples, especially in the urine samples of athletes has gained great importance. The official method recommended by the United States Pharmacopeia [19] for the determination of HCTZ involves the use of high performance liquid chromatography (HPLC). Still, in recent years, different methods have been reported for the detection of HCTZ in pharmaceutical formulations or biological samples, such as capillary electrophoresis [20–22], chemiluminescence [23,24], chemometry [25], conductimetry [26], polarography [27], liquid chromatography/tandem mass spectrometry [28–31] and spectrophotometry [32–34].

Although there are several methods, most of these require large amounts of sample, several time consuming manipulation steps, sophisticated instruments and special training. To minimize these problems and achieve better sensitivity and selectivity, there is the possibility of using electrochemical techniques applying electrochemical sensors. In this way, several electrochemical sensors for HCTZ detection based on unmodified and modified electrodes have been developed (Table 1).

Among the wide range of chemical modifier compounds, the nickel hydroxide has gained notoriety due its ease in construction of modified

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**Table 1**

A brief review of electrochemical sensors for HCTZ.

| Material   | Ref. |
|--|------|
| 5-Amino-20-ethyl-biphenyl-2-ol modified carbon paste electrode | [41] |
| Benzoylferrocene-modified carbon nanotube paste electrode      | [37] |
| Boron-doped diamond electrode                                  | [38] |
| Carbon nanotube/polypyrrole film                               | [42] |
| Carbon nanotubes/silicone rubber composite electrode           | [43] |
| Ferrocenedicarboxylic acid modified carbon paste electrode     | [44] |
| Glassy carbon electrode  | [39] |
| Graphene/ferrocene composite carbon paste electrode            | [45] |
| Multiwalled carbon nanotubes modified electrode                | [46] |

electrodes both in the form of thin films and micro/macro-scale, in addition to the presence of sites of Ni(II), especially in its oxidized form Ni(III), which have excellent properties in the electrochemical oxidation of various organic molecules [35]. Therefore, in this manuscript, the preparation and electrochemical characterization of a nickel hydroxide modified nickel electrode, as well as, its behavior as electrocatalyst toward the oxidation of hydrochlorothiazide were investigated.

## 2. Material and methods

### 2.1. Apparatus

Cyclic voltammetry measurements were carried out with a micro-Autolab (Metrohm) controlled by a microcomputer using de GPES 4.9 software in a thermostatic electrochemical cell containing three electrodes: nickel hydroxide modified nickel electrode (NMN) as the working electrode, platinum wire as the auxiliary electrode and saturated calomel electrode (SCE) as the reference electrode.

### 2.2. Reagents and solutions

All the chemicals were of analytical high-purity and all solutions were prepared using Millipore Milli-Q deionized water. The supporting electrolyte used for all experiments was 0.5 mol L<sup>-1</sup> NaOH (Sigma-Aldrich). The analyte solution was prepared by the addition of HCTZ (Sigma-Aldrich) in 0.5 mol L<sup>-1</sup> NaOH.

### 2.3. Preparation of nickel and nickel hydroxide-modified nickel (NMN) electrode

A nickel (100% purity) rod with a diameter of 6.24 mm and length of 10.0 cm was introduced in a glass cylinder with inner diameter of 8.0 mm and was wrapped with epoxy resin. This electrode stayed for 24 h in room temperature to dry. The electrode surface was polished using 400 and 600 mesh emery paper and thoroughly rinsed with distilled water. The modification of the working electrode was carried out by cyclic voltammetry in a range of potential from 0.25 V to 0.50 V with fifty potential cycles in 0.5 mol L<sup>-1</sup> NaOH solution.

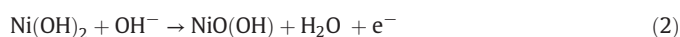
### 2.4. Performance of the modified nickel electrode as electrochemical sensor for HCTZ

The HCTZ determination was made by the application of potentials via linear voltammetry using a potential range from 0.25 V to 0.45 V vs. SCE at a scan rate of 25 mV s<sup>-1</sup>. The modified nickel electrode was submitted to potential scans in 25 mL of 0.5 mol L<sup>-1</sup> NaOH. The evaluation of the electrochemical performance of sensor for HCTZ was conducted by the addition of the analyte (1.0 mmol L<sup>-1</sup>) in the electrochemical cell.

## 3. Results and discussion

### 3.1. Activation of nickel modified electrode

The chemical modification on the nickel electrode surface was made applying 50 potential cycles in a potential range from 0.25 V to 0.50 V vs. SCE at a scan rate of 25 mV s<sup>-1</sup> in 0.5 mol L<sup>-1</sup> NaOH solution. Cyclic voltammograms (Fig. 1) obtained show that consecutive potential scans lead to a progressive increase of anodic and cathodic peak current values, indicating the formation of the Ni(OH)<sub>2</sub> in surface electrode. The electrode becomes derivatized to the oxide species quantitatively in surface. The electrochemical reactions may be described as follows [35]:



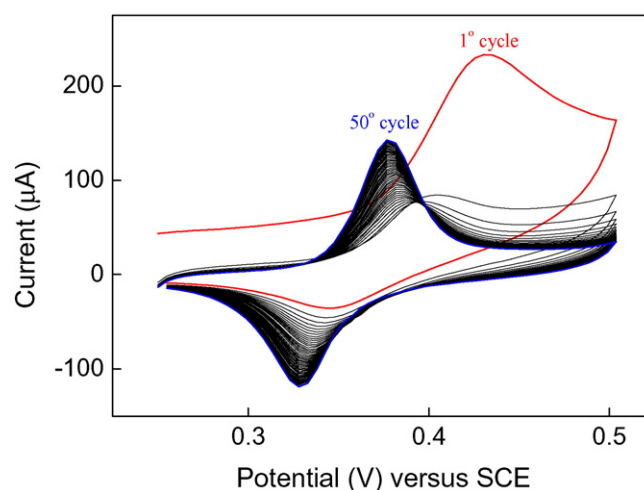
The shift of the peaks due to the number of scan is due changes in crystal structures of the nickel hydroxide and nickel oxyhydroxide on electrode surface.

### 3.2. Electrochemical properties of the nickel hydroxide modified nickel electrode

After the activation of the electrode, the electrochemical behavior of the modified nickel electrode was studied by cyclic voltammetry in 0.5 mol L<sup>-1</sup> NaOH solution. The electrochemical processes related to the modified electrode were stabilized after fifteen potential cycles. It is further observed an increase the reversibility of the redox system. From the second potential scan, both currents slightly increased and the distance between the peak potentials decreased to stabilize after fifteen cycles (Supplementary material).

The cyclic voltammogram obtained after stabilization for the modified electrode (Supplementary material) revealed a reversible system with only one redox couple ( $E_{pc} = 0.330$  and  $E_{pa} = 0.396$  V vs. SCE for scan rate of 25 mV s<sup>-1</sup>) which is attributed to the redox process of Ni(II)/Ni(III), peak-to-peak separation ( $\Delta E_p$ ) of 0.066 V and half potential ( $E_{p/2}$ ) of 0.363 V versus SCE, according to Eq. (2).

The effect of the potential scan rates (5 to 150 mV s<sup>-1</sup>) on the voltammetric response for the modified electrode in 0.5 mol L<sup>-1</sup> NaOH solution was investigated. The recorded cyclic voltammograms



**Fig. 1.** Cyclic voltammograms for deposition of nickel hydroxide on the nickel electrode surface applying 50 potential cycles in a potential range from 0.25 to 0.50 (V) vs. SCE at scan rate of 25 mV s<sup>-1</sup> in 0.5 mol L<sup>-1</sup> NaOH solution. Red line = 1st cycle; blue line = 50th cycle.

exhibit an increase of the anodic and cathodic peak current in function of scan rate (Supplementary material). This behavior suggests that the redox process follows adsorptive-controlled mechanism, in which the electron transfer occurs in the thin layer on the surface of the electrode. The concentration of electroactive species was calculated from the slope of the linear relation of peak current as a function of the scan rate, as represented by Eq. (3) [36]:

$$I_p = \frac{n^2 F^2}{4 RT} Av\Gamma \quad (3)$$

in which  $I_p$  is the peak current (ampere),  $n$  is the number of electrons,  $F$  is the Faraday constant ( $C \text{ mol}^{-1}$ ),  $A$  is the area of the electrode surface ( $1.22 \text{ cm}^2$ ),  $\Gamma$  is the concentration of electroactive species ( $\text{mol cm}^{-2}$ ),  $R$  is the gas constant ( $C \text{ K}^{-1} \text{ mol}^{-1}$ ),  $T$  is the temperature (K) and  $v$  is the scan rate ( $V \text{ s}^{-1}$ ). Using the relation of peak current as a function of the scan rate ( $\leq 100 \text{ mV s}^{-1}$ ), it was possible to obtain the concentration of electroactive species on the electrode surface, i. e.,  $3.83 \times 10^{-9} \text{ mol cm}^{-2}$ .

### 3.3. Electrocatalytic oxidation of HCTZ by NMN electrode

The determination of HCTZ in unmodified electrodes is generally difficult, because it occurs at high potential values [37–39]. Recently, Alghamdi [39] reported the oxidation of HCTZ in Britton–Robinson buffer solution (pH 3.0) using a glassy carbon electrode by anodic stripping voltammetry (ASV) and cyclic voltammetry (CV). Using ASV, the drug gave an increase of anodic peak at  $+1.2 \text{ V}$  vs. Ag/AgCl with a calibration graph for HCTZ obtained from  $4.0 \times 10^{-6}$  to  $4.0 \times 10^{-5} \text{ mol L}^{-1}$  and a limit of detection of  $4.3 \times 10^{-9} \text{ mol L}^{-1}$ . From another point, in evaluating modified electrodes, a significant decrease in the potential of oxidation of the HCTZ was obtained by Beitollahi and Ghorbani [37]. Using a benzoylferrocene modified multi-walled carbon nanotube paste electrode was obtained the electrocatalytic oxidation of HCTZ at  $+0.645 \text{ V}$  versus Ag/AgCl over a linear concentration range from  $6.0 \times 10^{-7}$  to  $3.0 \times 10^{-4} \text{ mol L}^{-1}$  and limit of detection  $9.0 \times 10^{-8} \text{ mol L}^{-1}$ .

In order to evaluate the electrocatalytic activity of the NMN electrode toward HCTZ oxidation, the linear voltammograms were obtained in the absence and presence of HCTZ in  $0.5 \text{ mol L}^{-1} \text{ NaOH}$  solution and the curves are presented in Fig. 2. Upon the addition of  $5.20 \times 10^{-5}$ ,  $1.30 \times 10^{-4}$  and  $3.90 \times 10^{-4}$  of HCTZ, the anodic peak currents increase while the cathodic peak current decreases, indicating that modified electrode exhibits excellent electrocatalytic activity toward the oxidation of

HCTZ. Furthermore, a decrease in the overpotential of  $744 \text{ mV}$  compared to the unmodified electrodes can be observed. These behaviors are consistent with a very strong electrocatalytic effect.

In addition, a kinetic study of HCTZ oxidation reaction by the Tafel region was performed using the conventional method of constructing Tafel plots ( $\log \text{Current (A)}$  vs. overpotential (V)) for each HCTZ concentration to elucidate the kinetics of electron transfer between the active centers in the thin layer and the analyte [36]. The Tafel region represents the kinetics of the electron transfer between HCTZ and nickel hydroxide. In this way, the electron transfer coefficient as a function of the number of electrons involved in the determination step of the redox process can be obtained by the slope (Eq. (4)) of the Tafel relation (see Fig. 3).

According to the values of Tafel slope and  $\alpha_a n$  reported in Table 2, the electron transfer coefficient was dependent of HCTZ concentration indicating a two-electron transfer as determining step.

$$\text{slope} = \frac{2.303 RT}{\alpha_a n F} \quad (4)$$

Seeing that anodic transfer coefficient is 0.5, the electronic transfer number was calculated from slopes ( $0.061 \pm 0.004 \text{ V/decade}$ ), which approaches the theoretical value of 2.

The apparent order of reaction ( $q$ ) for the respective concentrations of HCTZ was determined by the Tafel region with potential fixed based on the linear relation of  $\log \text{Current (A)}$  vs.  $\log$  concentration of HCTZ (Supplementary material), which the apparent order of reaction varied were 0.088, 0.051, 0.021 and 0.017 in relation potential range of the Tafel region ( $0.412 \text{ V}$  to  $0.442 \text{ V}$  versus SCE). Therefore,  $q$  is dependent on the concentration of HCTZ at an applied potential (Supplementary material), where it is defined by:

$$q = \left( \frac{d \log I}{d \log [\text{HCTZ}]} \right)_{E,T} \quad (5)$$

The effect of the potential scan rates ( $5$  to  $200 \text{ mV s}^{-1}$ ) on the voltammetric response of a NMN electrode was investigated in a solution containing  $5.2 \times 10^{-5} \text{ mol L}^{-1}$  HCTZ (Fig. 4A). The anodic peak currents varied linearly with the scan rate (Fig. 4B), suggesting that the HCTZ oxidation follows an irreversible oxidation process and an adsorptive-controlled mechanism. For scan rates above  $150 \text{ mV s}^{-1}$ , a small decrease in the anodic and cathodic peak currents was observed, indicating the existence of kinetic limitation in the reaction between nickel hydroxide and HCTZ for high scan rates. From these results, a scan rate of  $25 \text{ mV s}^{-1}$  was chosen for further studies since it results in voltammograms with better peak definition.

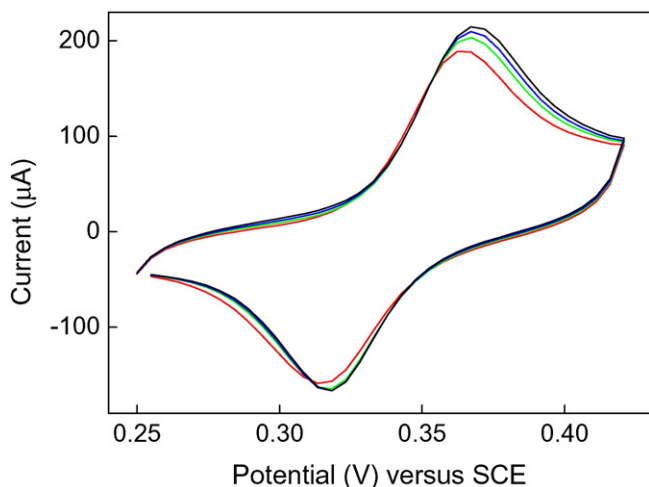


Fig. 2. Cyclic voltammogram for NMN-sensor in  $0.5 \text{ mol L}^{-1} \text{ NaOH}$  solution in absence (red line) and presence of  $5.2 \times 10^{-5}$  (green line);  $1.3 \times 10^{-4}$  (blue line); and  $3.9 \times 10^{-4}$  (black line) HCTZ using a potential range from 0.25 to 0.45 (V) vs. SCE at  $25 \text{ mV s}^{-1}$ .

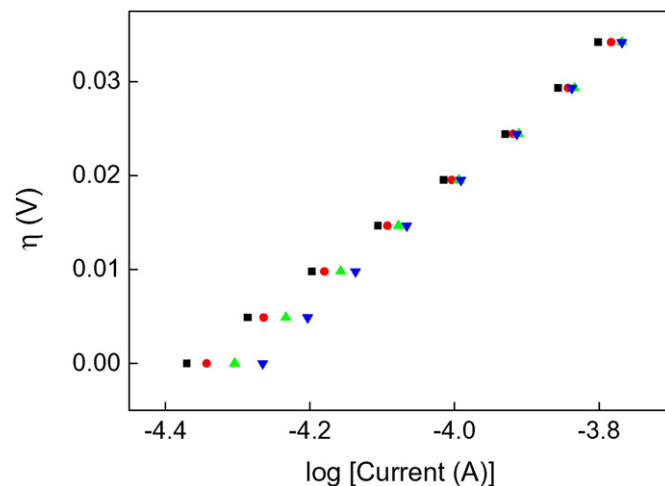


Fig. 3. Tafel relation for the NMN-sensor in presence of  $5.2 \times 10^{-5}$  (■);  $1.3 \times 10^{-4}$  (●);  $3.9 \times 10^{-4}$  (▲); and  $7.5 \times 10^{-4} \text{ mol L}^{-1}$  (▼) of HCTZ.

**Table 2**

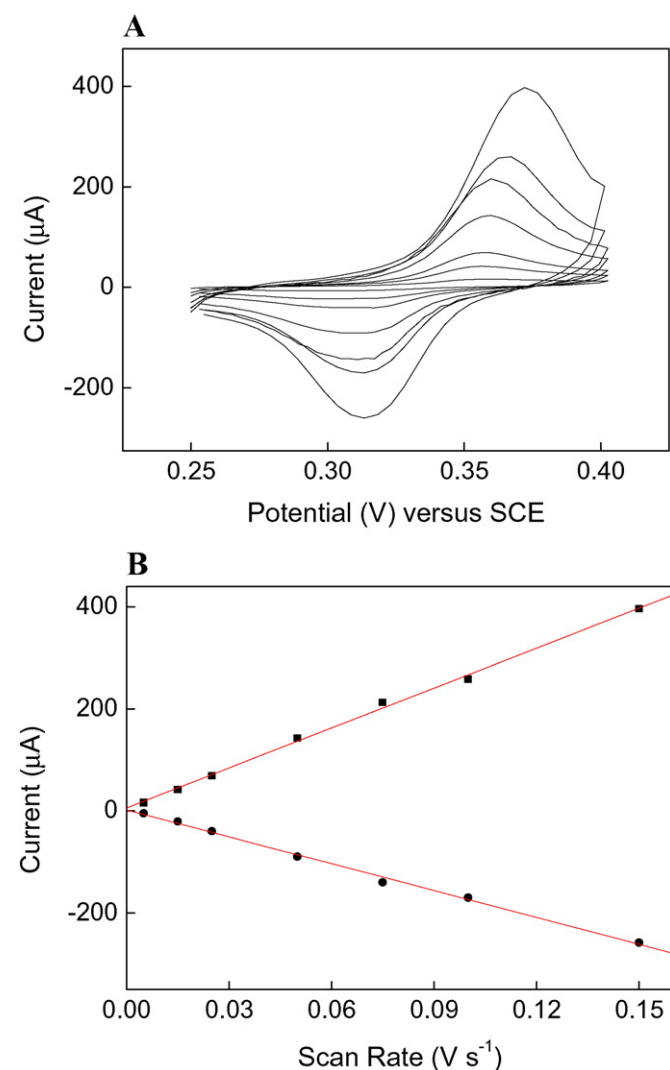
Kinetic parameters for hydrochlorothiazide oxidation at NMN-sensor in different HCTZ concentration in 0.5 mol L<sup>-1</sup> NaOH at 298 K.

| [HCTZ] mol L <sup>-1</sup> | Tafel slope (V dec <sup>-1</sup> ) | $\alpha_a n$ |
|----------------------------|------------------------------------|--------------|
| $5.20 \times 10^{-5}$      | 0.058                              | 1.02         |
| $1.30 \times 10^{-4}$      | 0.059                              | 1.00         |
| $3.90 \times 10^{-4}$      | 0.062                              | 0.95         |
| $7.50 \times 10^{-4}$      | 0.067                              | 0.88         |

On the basis of the reported results, the following mechanism can be proposed for the mediated oxidation of HCTZ on the modified surface, in which the NMN electrode promotes the oxidation of HCTZ through of a catalytic mechanism, making an electrochemical step according to the following equation:



In addition, a chemical step occurs, in which HCTZ is oxidized on modified surface via the following reaction:



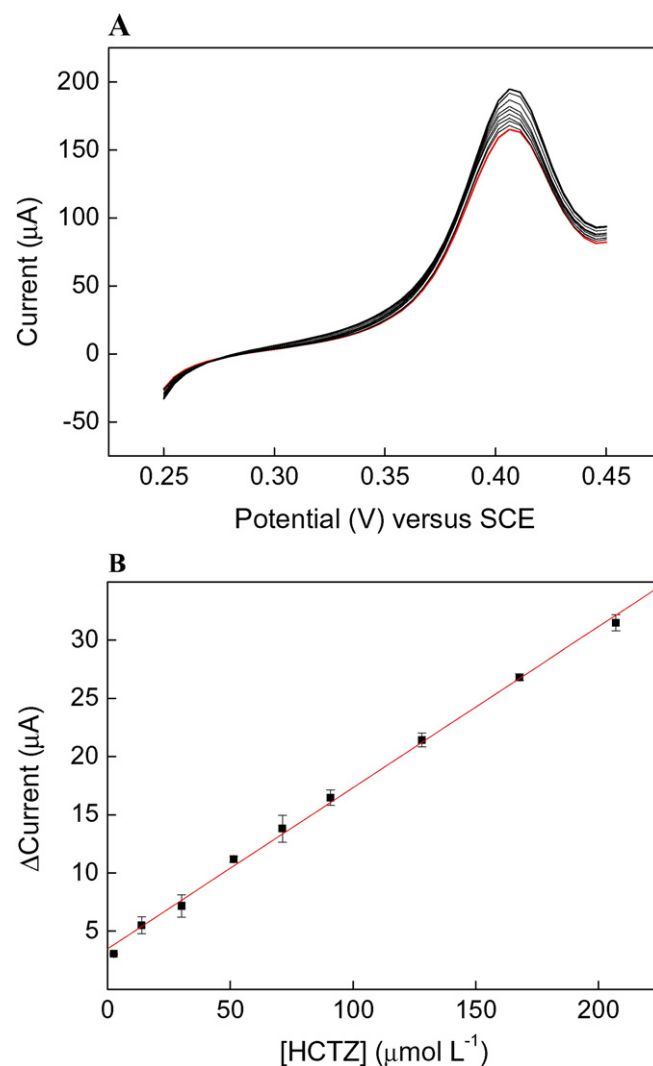
**Fig. 4.** (A) Typical cyclic voltammograms for NMN-sensor in 0.5 mol L<sup>-1</sup> NaOH containing  $5.2 \times 10^{-5}$  mol L<sup>-1</sup> HCTZ in the potential scan rates of 5, 15, 25, 50, 75, 100, 150 and 200 mV s<sup>-1</sup> and (B) linear dependence of anodic and cathodic peak currents to the scan rate values.

Finally, linear sweep voltammetric measurements were carried out with successive additions of HCTZ from  $2.00 \times 10^{-6}$  mol L<sup>-1</sup> to  $2.07 \times 10^{-4}$  mol L<sup>-1</sup> to evaluate the performance of the NMN as electrochemical sensor and to obtain an analytical curve (Fig. 5A). The values of anodic peak current were linearly dependent on the HCTZ concentration range from  $1.39 \times 10^{-5}$  mol L<sup>-1</sup> to  $1.67 \times 10^{-4}$  mol L<sup>-1</sup> with a limit of detection [40] of  $7.92 \times 10^{-6}$  mol L<sup>-1</sup> and a sensitivity of  $0.138 \mu\text{A L mmol}^{-1}$  (Fig. 5B), according to Eq. (8). At concentrations greater than  $1.67 \times 10^{-4}$  mol L<sup>-1</sup>, a saturation of the electrocatalytic sites was observed. This phenomenon can be explained by the adsorption phenomenon of HCTZ and saturation of the electroactive sites of nickel on the electrode surface.

$$I_{\text{pa}} (\mu\text{A}) = 3.48 + 0.138 [\text{HCTZ} (\mu\text{mol L}^{-1})] \quad (8)$$

#### 4. Conclusion

The nickel hydroxide layer chemically deposited at the surface of nickel electrode acts as an active electrocatalyst for the HCTZ oxidation through the mediation by Ni(II)/Ni(III) redox couple in NaOH solution. The oxidation currents are directly proportional to HCTZ concentration



**Fig. 5.** (A) Linear voltammogram for NMN-sensor in 0.5 mol L<sup>-1</sup> NaOH in absence and successive additions of HCTZ using a potential range from 0.25 to 0.45 (V) vs. ECS at scan rate of 25 mV s<sup>-1</sup> and (B) relationship of the current response ( $n = 3$ ) of the NMN electrode with the HCTZ concentration.

in a wide range, which exhibits the potential applications of the sensor for the anodic determination of HCTZ by voltammetric methods. Furthermore, the NMN-sensor showed distinct advantages such as simple preparation, good chemical and mechanical stability, low detection, and high sensibility and offers a promising platform for HCTZ detection in real samples, such as in doping control analysis.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.msec.2015.07.035>.

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