



# Simultaneous determination of captopril and hydrochlorothiazide by using a carbon ionic liquid electrode modified with copper hydroxide nanoparticles

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## Abstract

A carbon electrode modified with the ionic liquid octylpyridinium hexafluorophosphate and copper hydroxide nanoparticles was employed in an electrochemical assay for simultaneous determination of captopril (CPT) and hydrochlorothiazide (HCT). The electrode showed two well-defined oxidation peaks for CPT (at 0.22 V) and HCT (at 0.73 V, both vs. Ag/AgCl) at pH 8.0 using square wave voltammetry. Calibration plots are linear in the concentration ranges of 0.7–70  $\mu\text{M}$  (CPT) and 3–600  $\mu\text{M}$  (HCT), with detection limits of 12 and 60 nM, respectively. The electrode was repeatedly applied to simultaneous determination of CPT and HCT in pharmaceutical formulation without showing any fouling.

**Keywords** Cyclic voltammetry · Electrochemical assay · Electrochemical determination · Nanomaterial · Octyl pyridinium hexafluorophosphate · Pharmaceutical dosage · Square wave voltammetry · Tablet analysis · TEM · XRD

## Introduction

Capozide, a tablet of combination of captopril (CPT) and hydrochlorothiazide (HCT), is used in the treatment of high blood pressure. Captopril (Scheme 1a), is a traditional active inhibitor of the angiotensin-converting enzyme (ACE) and has widely served as orally antihypertensive drug [1]. It is also used to moderate cardiovascular problems and decrease high blood pressure caused by blood vessels in the kidneys and symptoms of cystinuria. It is useful in reducing rheumatoid arthritis symptoms, treating Raynaud's phenomena and progression of kidney disease in peoples with diabetes [2]. Unfortunately, CPT can cause some undesirable side effects, such as increasing blood potassium levels, zinc deficiency, constipation, diarrhea,

headache, loss of appetite, nausea, and easy bleeding. Chest pain, difficulty breathing, severe dizziness, fever, tingling in hands or feet, rash, and swollen throat have also been reported [2].

HCT (Scheme 1b) is the prototype of thiazide drugs [3] that increases the excretion of NaCl and water and, to a lesser extent, potassium ions by kidney [4]. The depletion of NaCl stores in the body reduces blood pressure and cardiac output. It also reduces the loss of calcium and the levels of chloride, bicarbonate, phosphate and magnesium. HCT has been used in monotherapy or in combination with other drugs such as CPT [5].

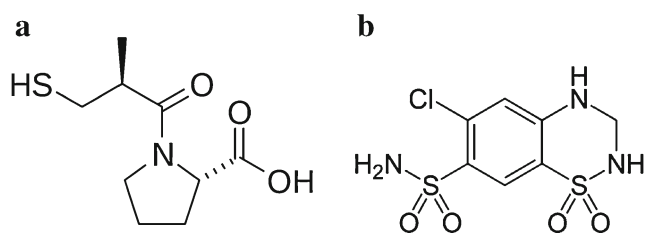
In pharmaceutical industries, CPT is commercialized with HCT as it can improve the action of hypotensive substances preventing possible secondary effects [6]. Therefore, simultaneous determination of CPT and HCT in pharmaceutical drug is extremely important and demanded.

Up to now, HPLC [7–9], microchip-photothermal lens microscopy [10] and spectrophotometry [11] have been used for measurement of CPT and HCT. However, CPT lacks functional groups and thus derivatization procedures are required [7–9, 11]. This functionalization step leads to complicate the procedure along with increasing cost and time of analysis. To overcome this, electrochemical methods are attractive alternatives due to simplicity, remarkable sensitivity, low cost, fast and ease of miniaturization [12, 13].

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**Scheme 1** Chemical structures of (A) Captopril and (B) Hydrochlorothiazide

To the best of our knowledge, graphene/ferrocene composite carbon paste electrode [14], boron-doped diamond electrode [15] and tantalum electrode coated with graphene nanowalls [16] have been used for electrochemical determination of CPT and HCT. However, HCT can be oxidized at the surface of solid electrodes such as glassy carbon (GC) electrode [4]. The electrochemical oxidation of CPT [17–19] is kinetically limited [20]. Therefore, for simultaneous electrochemical determination of CPT and HCT, a carbon electrode must be properly modified.

Carbon ionic liquid electrodes (CILE) offer wide potential window, low background current, renewable surface possibility, resistivity toward biomolecules fouling, and rapid electron transfer ability [21, 22]. Due to these favorable features, CILEs have been widely used as high-performance electrochemical assays for the determination of variety of analytes [12, 23–26].

Copper nanoparticles have been widely studied due to their unusual properties and potential applications. The evidence implicates that the antioxidant effect of CPT is promoted when it interacts with  $\text{Cu}^{2+}$  ions [20]. This ability is provided due to the presence of thiol moiety in CPT which directly interacts with  $\text{Cu}^{2+}$  ions. Copper-based chemically modified electrodes (CME) do not require pulsed potential waveform for stable long-term detection. Moreover, they are operable, oxidizable and commercially available. Due to these mentioned facts [20, 27–33],  $\text{Cu}(\text{OH})_2$  nanoparticles ( $\text{Cu}(\text{OH})_2\text{NP}$ ) were used to modify a CILE. The modified electrode ( $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$ ) have been optimized and characterized for simultaneous voltammetry of CPT and HCT. The results, as will be discussed, indicated that the detection limits and oxidation overpotentials of both analytes have been improved compared to previously reports [14, 15].

## Experimental

### Apparatus

Voltammetric measurements were performed using an Autolab electrochemical system (Eco-Chemie, Utrecht, The Netherlands, [www.metrohm-autolab.com](http://www.metrohm-autolab.com)) equipped with PGSTAT-12 and GPES software (Eco-Chemie) and a three-electrode electrochemical cell; an  $\text{Ag}/\text{AgCl}/\text{KCl}$  (3.

0 M) as a reference electrode (Metrohm) and a platinum disk as a counter electrode. Working electrodes including carbon paste electrode (CPE), CILE and  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  (2.5 mm diameter) were used. The pH measurements were carried out using a Metrohm pH meter (model 780, [www.metrohm.com](http://www.metrohm.com)) with a combined pH glass electrode calibrated against standard buffers at pH 4.0 and 7.0. The results of XRD were acquired employing Rigaku D/max-3C (Japan, [www.rigaku.com/en](http://www.rigaku.com/en)) with  $\text{Cu-K}\alpha$  ( $\lambda = 1.54$  nm) radiation powder. The XRD pattern was drawn in 0.05 step per second. Transmission electron micrograph (TEM) was taken with an electronic microscope (CM10-Philips, 100 KV, [www.fei.com](http://www.fei.com)). The scanning electron microscope (SEM) images were carried out by a VEGA3-TESCAN (20 KV, [www.tescan.com](http://www.tescan.com)) instrument. An MIRA3-TESCAN (15 KV, [www.tescan.com](http://www.tescan.com)) electronic microscope was used for performing energy-dispersive X-ray spectroscopy (EDS) and field emission scanning electron microscopy (FESEM).

### Materials

Phosphoric acid, 1-bromooctane (98%), pyridine, ethanol, paraffin oil, graphite powder (mesh size  $<100$   $\mu\text{M}$ ), all chloride salts, sodium sulfate, cobalt (II) sulfate, sodium nitrate, sodium perchlorate, leucine, alanine, methionine, cysteine, glucose, and citric acid were purchased from Merck ([www.merck.com](http://www.merck.com)). Pure CPT and HCT were supplied by Daroo-Pakhsh pharmaceutical Co. (Iran, [www.dppcco.com](http://www.dppcco.com)) and tablets of the drugs were obtained from Iran-Daroo Co. (Iran, [www.irandaruo.com](http://www.irandaruo.com)). Copper (II) sulfate, lactose and sucrose were obtained from Fluka ([www.sigmaaldrich.com](http://www.sigmaaldrich.com)). Ammonia (25%) was purchased from Arman Sina (Iran). Phosphate buffer was used as the supporting electrolyte. The ionic liquid (IL), octyl pyridinium hexafluorophosphate (OPFP), was synthesized as described elsewhere [34].

### Synthesis of $\text{Cu}(\text{OH})_2$ nanoparticles

Copper hydroxide nanoparticles were synthesized according to a previously reported procedure through a simple precipitation process [32]. Briefly, a dark blue copper hexamine complex was obtained by mixing 10 mL aqueous ammonia solution (25%) with 10 mL copper sulfate solution (1.0 M). The resulting solution was diluted by adding 100 mL deionized water. The reaction was carried out under stirring at 70 °C for 1 h. The final product, a pale blue precipitate was centrifuged and washed with deionized water and ethanol for three times and dried in a vacuum oven for 12 h at 80 °C.

### Preparation of the working electrode

$\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  was prepared by hand mixing of graphite powder, IL and  $\text{Cu}(\text{OH})_2\text{NP}$  with a weight ratio of 48/47/5,

respectively. The resulting uniform paste was packed firmly into the cavity (2.5 mm diameter) of a Teflon holder. To achieve an electrode with a highly uniform surface as well as a lower background current, it was heated in an oven for 2 min at 80 °C. The electrode was used after being cooled at ambient temperature. The electrical contact was established via a stainless-steel handle. The CILE was prepared by the same procedure without adding Cu(OH)<sub>2</sub>NP. The graphite powder and IL were used with a weight ratio of 50/50 in the CILE. Carbon paste electrode (CPE) was prepared by mixing graphite powder and Nujol with a weight ratio of 70/30. Cu(OH)<sub>2</sub>/CPE was prepared by mixing graphite powder, Cu(OH)<sub>2</sub>NP and Nujol with a weight ratio of 65/5/30. A new surface was obtained by rubbing the electrode surface against the smooth surface of a grease proof paper.

## Results and discussion

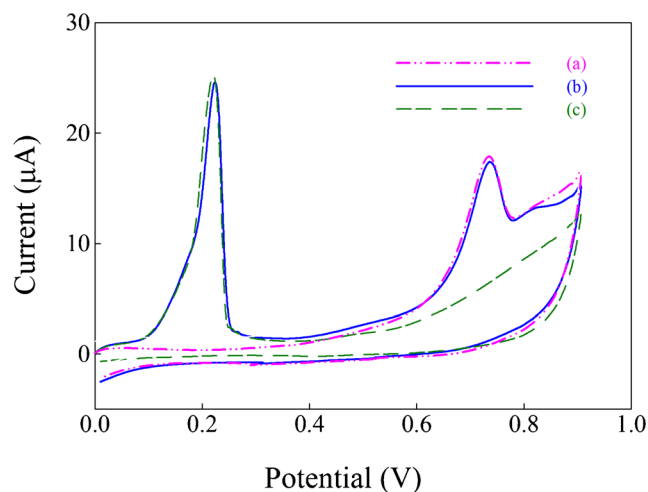
Octylpyridinium hexafluorophosphate (OPFP) is the best IL for using as a binder due to this fact that it produces the lowest background current [21]. Hence, in the current work, OPFP has been chosen as a binder electrode. The advantages of using OPFP as a binder will be discussed in the following. For simultaneous electrochemical determinations of CPT and HCT, separation of the redox peaks is the most important factor. Using a proper modifier can significantly improve the separation process. As reported in literature [31], Cu (II) can successfully bind to thiol groups for complex formation. Since CPT has a thiol group, Cu(OH)<sub>2</sub> is a good and cost-effective choice as modifier in CILE to improve the electrochemical response of the electrode. As reported [21], a 50:50 ratio of graphite to ionic liquid is the optimized composition of CILE as it produced the lowest background current. Hence, in the current work, this ratio was used for CILE composition and subsequently the percentage of the electrode modifier (Cu(OH)<sub>2</sub>NP) was optimized.

### Characterization of Cu(OH)<sub>2</sub> nanoparticles and the modified electrode

The characterization of Cu(OH)<sub>2</sub>NP and the modified electrode have been carried out by means of XRD pattern, TEM, FESEM images and EDS spectra. The corresponding data and figures are available in the Electronic Supporting Materials (ESM).

### Electrocatalytic Oxidation of CPT and HCT

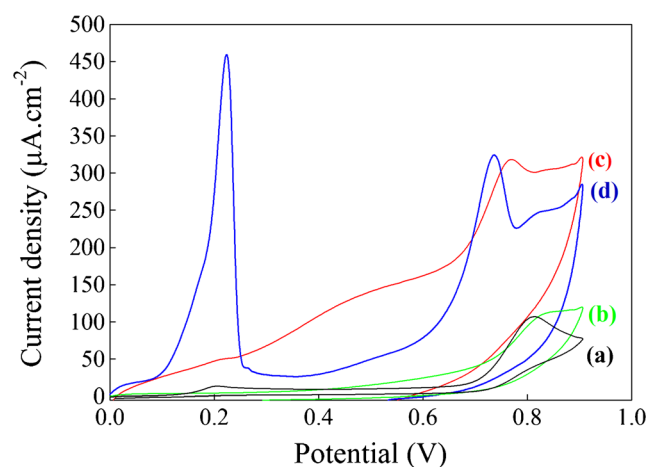
The electrochemical behaviors of CPT and HCT were studied by cyclic voltammetry at Cu(OH)<sub>2</sub>NP/CILE in phosphate buffer (pH = 8.0). Cyclic voltammograms of individual 100 μM CPT (Fig. 1a) and 100 μM HCT (Fig. 1c) as well



**Fig. 1** Cyclic voltammograms of 100 μM of **a)** HCT; **c)** CPT; **b)** HCT and CPT mixture in 0.20 M phosphate buffer (pH = 8.0) at scan rate of 100 mV.s<sup>-1</sup> and an accumulation time of 15 min in the open-circuit potential. All peaks were subtracted from the baseline

as their mixture at same concentration levels (Fig. 1b) are shown in Fig. 1. As shown in Figs. 1a and c, sharp oxidation peaks were observed for CPT in 0.22 V and for HCT in 0.73 V. The remarkable  $\Delta E_p$  (0.51 V) validates the applicability of the Cu(OH)<sub>2</sub>NP/CILE for simultaneous voltammetric determination of CPT and HCT (Fig. 1b).

The electrochemical behaviors of CPT and HCT by cyclic voltammetry at CPE, CILE, Cu(OH)<sub>2</sub>NP/CPE, Cu(OH)<sub>2</sub>NP/CILE in 0.20 M phosphate buffer (pH = 8.0) are compared in Fig. 2. The CPE did not show any oxidation peak for CPT and a weak oxidation peak was observed at 0.82 V (vs. Ag/AgCl) for HCT (Fig. 2b). The broad oxidation peaks of CPT (0.46 V) and HCT (0.76 V), at CILE (Fig. 2c), were 250 and 30 mV more positive, respectively, compared to those observed at Cu(OH)<sub>2</sub>NP/CILE (Fig. 2d). Also, the oxidation currents of



**Fig. 2** Cyclic voltammograms of 100 μM CPT and 100 μM HCT in 0.20 M phosphate buffer (pH = 8.0) at **a)** Cu(OH)<sub>2</sub>NP/CPE; **b)** CPE; **c)** CILE; **d)** Cu(OH)<sub>2</sub>NP/CILE at scan rate of 100 mV.s<sup>-1</sup> and an accumulation time of 15 min in the open-circuit potential. The peaks were subtracted from the base line

CPT and HCT were significantly lower than those at Cu(OH)<sub>2</sub>NP/CILE, Fig. 2d. At Cu(OH)<sub>2</sub>NP/CPE (Fig. 2a), the oxidation peaks of CPT and HCT were, respectively, appeared at 0.22 and 0.80 V (vs. Ag/AgCl) with lower oxidation currents than those observed at Cu(OH)<sub>2</sub>NP/CILE.

The decrease in CPT oxidation overpotential on Cu(OH)<sub>2</sub>NP/CILE and Cu(OH)<sub>2</sub>NP/CPE may be due to complex formation between copper (II) ions (existing at the electrode surface) and the thiol groups of CPT [31]. The better electrochemical performances of CILE and Cu(OH)<sub>2</sub>NP/CILE, compared to CPE and Cu(OH)<sub>2</sub>NP/CPE, revealed superiority of OPFP over paraffin oil as binder. The OPFP improved the rate of heterogeneous electron-transfer processes in CILE by forming an excellent charge-transfer bridge in the electrode [21]. But paraffin oil is nonconductive and can block the electrocatalytic activated sites in CPE [21]. Eventually, the results confirmed that Cu(OH)<sub>2</sub>NP/CILE was more suitable electrode for simultaneous electrochemical determination of CPT and HCT than CPE, CILE and Cu(OH)<sub>2</sub>NP/CPE.

### Optimization of the experimental conditions

The square wave voltammetry (SWV) was chosen for the quantifications of CPT and HCT because it offers good resolution and higher sensitivity. The peak current in SWV depends on various instrumental parameters such as SW frequency ( $f_{sw}$ ), step potential ( $\Delta s$ ) and SW amplitude ( $E_{sw}$ ). Each optimization run was performed in 0.20 M phosphate buffer (pH = 8.0) containing 50  $\mu$ M CPT and 50  $\mu$ M HCT. The results showed that the  $\Delta s$  of 10 mV,  $E_{sw}$  of 50 mV and  $f_{sw}$  of 10 Hz were the optimized values for further investigations.

Influential experimental parameters, for achieving better analytical performance, were investigated through one-factor-at-a-time optimization strategy. In this regard, the effects of supporting electrolyte pH, type and concentration, as well as scan rate, accumulation time and potential were investigated. The optimal conditions were found to be: 0.20 M phosphate buffer, pH = 8.0, scan rate of 100 mV.s<sup>-1</sup> and 15 min accumulation time in the open-circuit potential. Moreover, the weight percent of Cu(OH)<sub>2</sub>NP in the modified electrode was evaluated and 5% was utilized as its optimal value. Some data and figures corresponding to the optimization procedure are provided in the ESM.

### Fouling effect investigation

The fouling effect of the electrode was investigated by recording sequential cyclic voltammograms of analytes at Cu(OH)<sub>2</sub>NP/CILE. The results depicted in Figs. S4 (A) and (B) show replicated voltammograms, recorded at scan rate of 100 mV.s<sup>-1</sup>, for a solution containing 100  $\mu$ M CPT and 100  $\mu$ M HCT. After the first scan, the oxidation peak height decreased due to decrease of diffusion layer. By stirring the

solution for a few seconds, the heights of the oxidation peaks increased showing that the analytes were adsorbed on the electrode surface. These results revealed that the oxidation products of CPT and HCT did not foul the electrode surface. This is obviously resulting from the nature of CILEs [21].

### Analytical figures of merit

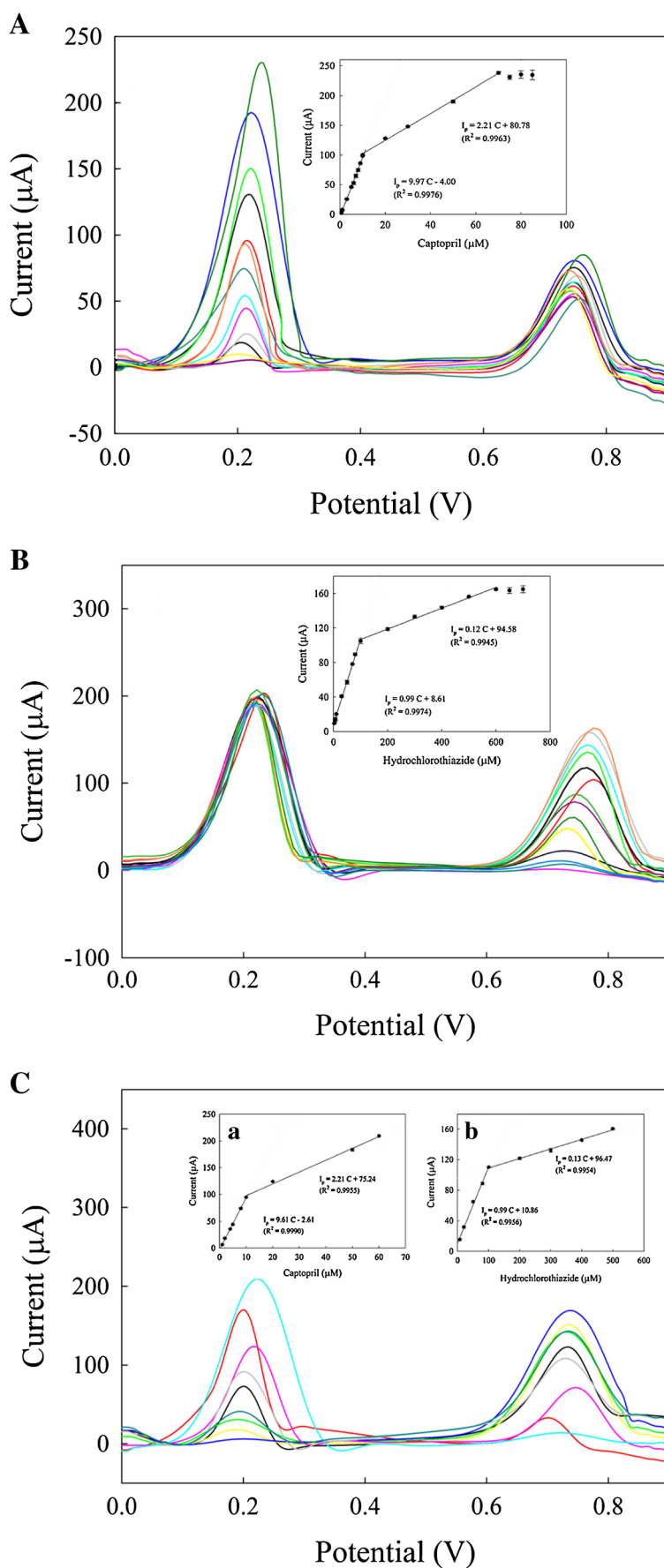
The square wave voltammetry curves for different concentrations of CPT and HCT, at Cu(OH)<sub>2</sub>NP/CILE, under the optimum experimental conditions (0.20 M phosphate buffer, pH = 8.0, 15 min accumulation time in the open-circuit potential, potential window of 0.0–0.9 V, step potential of 10 V, amplitude of 50 mV and frequency of 10 Hz) were performed. The concentration of CPT increased linearly in the presence of a fixed concentration of HCT (Fig. 3A). And, the concentration of HCT was increased linearly in the presence of a fixed concentration of CPT (Fig. 3B). Two linear relationships were established between peak current and CPT concentration in the ranges of 0.7–10.0 and 10.0–70.0  $\mu$ M with correlation coefficients of 0.9976 and 0.9963, respectively. Also, two linear relationships were established between peak current and the concentration of HCT in the ranges of 3.0–100.0 and 100.0–600.0  $\mu$ M with correlation coefficients of 0.9974 and 0.9945, respectively. The detection limits of CPT and HCT were found to be 12.5 and 59.7 nM, at an S/N ratio of 3.

Fig. 3C shows the SWV of binary mixtures of CPT and HCT at their various concentrations. The peak currents of CPT and HCT increased linearly with concentration. Two linear ranges were obtained for CPT having equations of  $I_p = 9.61C - 2.61$  ( $R^2 = 0.999$ ) and  $I_p = 2.21C + 75.24$  ( $R^2 = 0.9955$ ). Two linear ranges were obtained for HCT having equations of  $I_p = 0.99C + 10.86$  ( $R^2 = 0.9956$ ) and  $I_p = 0.13C + 0.96.47$  ( $R^2 = 0.9954$ ). Similarity of the obtained equations and linear ranges with the previous data refers to good electrocatalytic response of Cu(OH)<sub>2</sub>NP/CILE to simultaneous determination of CPT and HCT. The obtained calibration plots had slopes of 185.95 and 18.44  $\mu$ A  $\mu$ M<sup>-1</sup> cm<sup>-2</sup> for CPT and HCT, respectively, which are indications of the offered sensitivities of the modified electrochemical assay toward measuring the analytes.

The slopes of three calibration plots, which were attained by using only one electrode, have been used for calculating the corresponding relative standard deviation (RSD%) as a measure of the repeatability of the electrode responses. The obtained RSD% values were 3.89% and 4.23% for CPT and HCT, respectively. The reproducible functioning of the electrode was obtained by using the slopes of three calibration plots constructed for each analyte where three different reproduced electrodes were utilized. The performance of the reproducible electrodes for measurement of CPT and HCT in term of RSD%, respectively, were found to be 4.87% and 5.16%.

To test the stability of Cu(OH)<sub>2</sub>NP/CILE, the peak oxidation currents of analytes only at the medium concentration levels of

**Fig. 3** Acquired square wave voltammograms at Cu(OH)<sub>2</sub>NP/CILE under the optimal experimental conditions (0.20 M phosphate buffer, pH = 8.0, 15 min accumulation time in the open-circuit potential, potential window of 0.0–0.9 V (vs. Ag/AgCl), step potential of 10 V, amplitude of 50 mV, frequency of 10 s<sup>-1</sup> and scan rate of 100 mV.s<sup>-1</sup>) at the: **(A)**, a linear increasing in the concentration of CPT (0.7, 0.9, 1, 3, 5, 6, 7, 8, 9, 10, 20, 30, 50, 70 μM) at a fixed concentration of HCT (50 μM); **(B)**, a linear increasing in the concentration of HCT (3, 5, 7, 10, 30, 50, 70, 80, 100, 200, 300, 400, 500, 600 μM) at fixed a concentration of CPT (50 μM); **(C)**, binary mixtures of CPT and HCT at various concentrations (CPT concentrations: 1, 2, 4, 5, 8, 10, 20, 50, 60 μM and HCT concentrations: 7, 20, 50, 80, 100, 200, 300, 400, 500 μM). Insets represent the calibration plots for the determination of the analytes and the error bars are corresponding to the standard deviations (*n* = 3). The peaks were subtracted from the base line



their corresponding calibrations plots (35  $\mu\text{M}$  for CPT and 300  $\mu\text{M}$  for HCT) were recorded. The electrode was used every 5-day for recording the oxidation currents of analytes until 50 days. The electrode was kept at ambient conditions when was not in use. The results revealed that the electrode responses for CPT and HCT, respectively, retained at about 95.4% and 95.1% of their initial values when were remeasured after 50 days. The results obtained at medium concentrations of analytes show that calibration can be performed with the same electrode over at least 50 days at an accepted confidence limit. It should be noted that all measurements have been performed at the optimum experimental conditions.

The analytical performance of  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  has been compared (Table 1) with three previously reported electrochemical assays for simultaneous determination of CPT and HCT. As can be inferred from Table 1, in contrast to GFCPE [14] and BDE [15],  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  showed much better performance in terms of detection limit (DL) and linear range (LR). Moreover, the oxidation potentials of CPT and HCT, at the surface of  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$ , were much less than those reported for GFCPE and BDE. When compared with  $\text{NiO}/\text{CNTs}/\text{DPID}/\text{CPE}$  [35],  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  provided better DL for HCT but the DL values reported for CPT, by both electrodes, are almost the same. Although  $\text{NiO}/\text{CNTs}/\text{DPID}/\text{CPE}$  has provided a wider LR for determination of CPT, the linear ranges for HCT are almost the same for both electrodes. Unfortunately, the overpotentials corresponding to CPT and HCT have not reported for  $\text{NiO}/\text{CNTs}/\text{DPID}/\text{CPE}$  in order to have a more detailed comparison between these electrodes. However, in terms of DL and LR obtained for simultaneous determination of CPT and HCT, it may be concluded that both electrodes showed almost similar performances.

## Interference study

Influence of various compounds in simultaneous determination of 50.0  $\mu\text{M}$  CPT and 50.0  $\mu\text{M}$  HCT was studied under the

**Table 2** Simultaneous determination of CPT and HCT in a pharmaceutical sample

Analyte	Expected concentration ( $\mu\text{M}$ )	Found concentration ( $\mu\text{M} \pm \text{SD}^*$ )	Relative error (%)	Mean relative error (%)
CPT	6.4	6.7 ( $\pm 0.1$ )	4.69	4.24
	4.6	4.8 ( $\pm 0.47$ )	4.34	
	2.7	2.8 ( $\pm 0.34$ )	3.7	
HCT	75.00	77.60 ( $\pm 1.17$ )	3.47	3.03
	53.00	52.33 ( $\pm 1.15$ )	-1.26	
	32.00	33.40 ( $\pm 1.36$ )	4.37	

Standard deviations ( $N = 5$ )

optimum experimental conditions. The tolerance limit was defined as the maximum concentration of a possible interfering compound that caused an error less than  $\pm 5\%$ . The results given in Table S1 refer to good selectivity of the constructed electrode.

## Simultaneous determination of CPT and HCT in pharmaceutical preparations

$\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  was used for simultaneous determination of CPT and HCT in pharmaceutical preparations. The CPT tablet (50 mg) and HCT tablet (25 mg) were selected as real samples. Equal amounts of captopril and hydrochlorothiazide tablets were mixed by using a mortar and pestle to obtain a uniform powder sample. A preselected weight of the powdered sample was dissolved in water/methanol (70:30) solution. After adequate dilution by 0.20 M phosphate buffer (pH = 8.0), SWV was performed for monitoring CPT and HCT in the sample. The mean results for five simultaneous determinations of CPT and HCT at  $\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$  are summarized in Table 2. The results of the recovery test revealed that the constructed electrode can be used for simultaneous detection of CPT and HCT in pharmaceutical preparations.

**Table 1** Comparison of different assays for electrochemical determination of CPT and HCT

Electrode	Linear range ( $\mu\text{M}$ )		Detection limit ( $\mu\text{M}$ )		Oxidation overpotential (V)		Reference
	CPT	HCT	CPT	HCT	CPT	HCT	
<sup>a</sup> GFCPE	1-430	0.5-390	0.87	0.38	0.38	1.2	[14]
<sup>b</sup> BDE	27-81	10-30	0.14	0.27	1.8	1.4	[15]
<sup>c</sup> $\text{NiO}/\text{CNT}/\text{DPID}/\text{CPE}$	0.7-200	10-600	0.009	5	-	-	[35]
$\text{Cu}(\text{OH})_2\text{NP}/\text{CILE}$	0.7-70	3-600	0.012	0.060	0.21	0.78	This work

<sup>a</sup> Graphene/Ferrocene composite carbon paste electrode

<sup>b</sup> Boron-doped diamond electrode

<sup>c</sup> Nickel oxide/Carbon nanotubes/2-(3, 4-Dihydroxyphenyl)isoindoline-1, 3-dione/Carbon paste electrode

## Conclusions

Captopril (CPT) and hydrochlorothiazide (HCT) were simultaneously determined by using Cu(OH)<sub>2</sub>NP/CILE as a renewable and inexpensive working electrode. The electrode was easily prepared and showed high resistance toward electrode fouling. Calibration plots were linear in the concentration ranges of 0.7–70 (CPT) and 3–600 μM (HCT) with detection limits of 12 and 60 nM, respectively. It had capability to resolve the CPT and HCT peak potentials with an excellent resolution of  $\Delta E_p = 0.51$  V. The applicability of the electrode was successfully demonstrated for simultaneous determination of CPT and HCT in real tablet samples which is promising for routine pharmaceutical analysis.

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**Compliance with ethical standards** The authors declare that they have no competing interests.

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