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Original Article

Voltammmetric Determination of Captopril Using Multiwall Carbon Nanotubes Paste Electrode in the Presence of Isoproterenol as a Mediator

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Abstract

The electrocatalytic oxidation of captopril (CAP) was studied by modified carbon nanotubes paste electrode in the presence of isoproterenol (ISPT) using cyclic voltammetry (CV), chronoamperometry and square wave voltammetry (SWV). Also, the values of catalytic rate constant (k), and electron transfer coefficient (α) for CAP were calculated. The mechanism of CA electrochemical behavior at the modified electrode surface was analyzed by various electrochemical methods in the presence of mediator. The prepared modified electrode showed voltammetric responses with high sensitivity for CAP, making it very suitable for the detection of CAP at trace levels. Under the optimized conditions, the peak current was linear to CAP concentration over the concentration range of 0.3 to 90 μmol L^{-1} using SWV. The detection limit was 0.1 μmol L^{-1}. The proposed method was successfully applied for the determination of CAP in the urine, tablet and patient urine samples.

Keywords: Captopril; Isoproterenol; Multiwall carbon nanotubes; Sensor; Voltammetry.

Introduction

Electrochemical based techniques using modified electrodes can be considered for the determination of environmental, biological and pharmaceutical compounds as strong alternatives to the other instrumental methods (1-5). The chemically modified electrodes (CMEs) are very interesting and powerful tools for the analysis of many substances at trace level, using very sensitive electroanalytical techniques (6-9). A significant point in CMEs utilization in speciation work is to choose the most convenient modifier for each analyte, because the sensitivity and selectivity of the electroanalytical response depend on the characteristics of the modifier (10-13).

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Since the 'rediscovery' of CNTs by Iijima in 1991, electrochemical sensing based on carbon nanotubes (CNTs) has grown into a fully fledged research field (14). The extraordinary electrochemical features of CNTs make them suitable for use in Faradaic processes. CNTs modified electrodes have many advantages over other forms of carbon electrodes due to their small size, high electrical and thermal conductivity, high chemical stability, high mechanical strength and high specific surface area which make them very promising candidates in a wide range of applications (15-19).

Captopril (Figure 1A) is an antiotebsin-converting enzyme inhibitor (ACE inhibitor) used for the treatment of hypertension and some types of congestive diseases. It was the first ACE inhibitor developed and was considered a breakthrough due to its novel mechanism of action and for the revolutionary development process

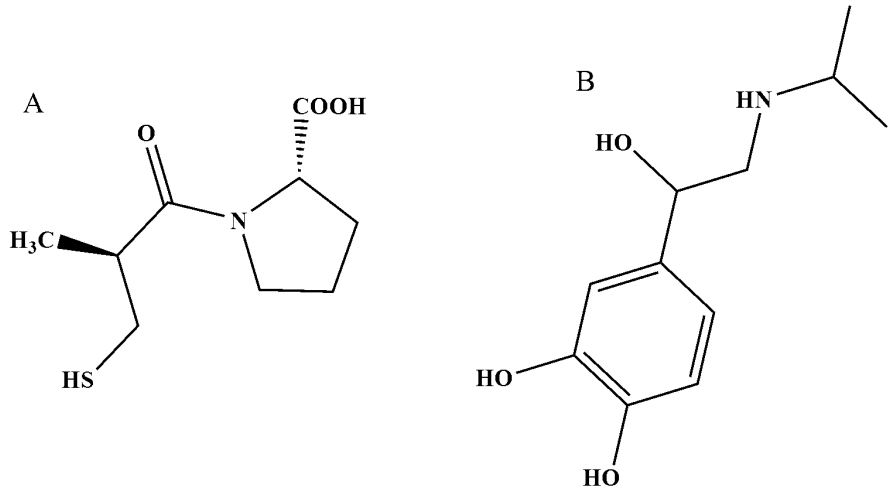

Figure 1. A) Structure of captopril and B) Structure of isoproterenol

(20). Captopril is a unique antihypertensive drug as it is the only one with a thoil-group in its structure. This gives it the ability to act as a scavenger of free radicals in living systems. A further advantage of the pharmaceutical is its antioxidant properties (21). The determination of captopril is important both from a physiological point of view and for quality control purposes.

In this study, we described initially the application of ISPT (Figure 1B) as a suitable mediator in the electrocatalysis and voltammetric determination of CAP in an aqueous buffer solution. In continuous, in order to demonstrate the catalytic ability of the modified electrode in the electrooxidation of CAP in real samples, the method was employed for the voltammetric determination of CAP in urine samples from both patients and healthy subjects on the CAP and tablet sample. Table 1 shows a comparison of the figures of merit of the proposed method with those of recently published voltammetric methods for the determination of CAP. As shown, the selectivity and sensitivity of the proposed method is comparing with other publication papers. On the other hand, application and preparation of this modified electrode is easy.

Experimental

Reagents and apparatus

All chemicals used were of analytical reagent grade and were purchased from Merck (Darmstadt, Germany) unless otherwise stated. Doubly distilled water was used throughout.

A 1.0×10^{-3} mol L^{-1} captopril solution was prepared daily by dissolving 0.022 g captopril in water and the solution was diluted to 100 mL with water in a 100-mL volumetric flask. The solution was kept in a refrigerator at 4 °C in dark. More dilute solutions were prepared by serial dilution with water. Phosphate buffer (sodium dihydrogen phosphate and disodum monohydrogen phophate plus sodium hydroxide, 0.1 mol L^{-1}) solutions with different pH values were used.

Spectrally pure graphite powder (particle size <50 μm) from Merck and multiwall carbon nanotubes (> 90%, MWCNTs, d × l = (90 – 70 nm) × (5 – 9 μm)) from Fluka were used as the substrate for the preparation of the carbon paste electrode. High viscosity paraffin (d = 0.88 kg L^{-1}) from Merck was used as the pasting liquid for the preparation of the paste electrodes.

All the voltammetric measurements were performed using an Autolab PGSTAT 302N, potentiostat/galvanostat (Utrecht, The Netherlands) connected to a three-electrode cell, Metrohm (Herisau, Switzerland) Model 663 VA stand, linked with a computer (Pentium IV, 1,200 MHz) and with Autolab software. A platinum wire was used as the auxiliary electrode. Multiwall carbon nanotubes paste electrode (MWCNTPE) and $Ag/AgCl/KCl_{sat}$ were used as the working and reference electrodes, respectively. A digital

Table 1. Comparison of figures of merit of the proposed method with recently published voltammetric methods for the determination of CAP.

Electrode	Method	LOD[a] µmol L^{-1}	LDR[b] µmol L^{-1}	Catalytic Potential mV	Sensitivity/ µA µmol^{-1} L	Ref.
GC [c]	DPV [d]	4.8	8-1000	625	14.272	(22)
CPE [e]	SWV [f]	0.08	0.2-400	430	0.1091	(23)
CPE	DPV	0.007	0.2-800	220	0.216	(24)
CPE	LSV [g]	0.009	0.3-300	750	0.1108	(25)
CPE	DPV	0.87	1.0-430	≈380	0.156	(26)
CPE	SWV	0.1	0.3-90	525	0.0252	This work

[a] LOD Limit of detection; [b] LDR Linear dynamic range; [c] Glassy carbon electrode; [d] Differential pulse voltammetry; [e] Carbon paste electrode; [f] Square wave voltammetry; [g] Linear sweep voltammetry

pH/mV-meter (Metrohm model 710) was applied for pH measurements.

Preparation of the electrode

To eliminate any metal oxide catalysts within the nanotubes, multiwall carbon nanotubes were refluxed in the 2.0 M HNO_3 for 12 h, and then washed with twice-distilled water and dried at room temperature. To obtain the best conditions in the preparation of the modified electrode, we optimized the ratio of MWCNTs. The results showed that the better CV shape and current were achieved with 10.0% (w/w) MWCNTs and 90.0% (w/w) graphite.

According to above points, graphite powder (0.900 g) was dissolved in diethyl ether and hand mixed with 0.100 g carbon nanotubes in a mortar and pestle. The solvent was evaporated by stirring. A syringe was used to add paraffin to the mixture, which was mixed well for 50 min until a uniformly wetted paste, was obtained. The paste was then packed into a glass tube. Electrical contact was made by pushing a copper wire down the glass tube into the back of the mixture. When necessary, a new surface was obtained by pushing an excess of the paste out of the tube and polishing it on a weighing paper.

Preparation of real samples

The tablet solution was prepared by completely grinding and homogenizing ten tablets of captopril, labeled 25 and/or 50 mg per tablet. Then, 10 mg of each tablet powder was accurately weighed and dissolved in 100 mL water by ultrasonication. After mixing completely, the mixture was filtered on an ordinary filter paper, 10 mL of which was subsequently transferred into a 100–mL volumetric flask and diluted to the mark with water. Then, 1.0 mL of the solution plus 4.5 mL of the buffer (pH 4.0) was used for analysis using the standard addition method.

The urine samples were stored in a refrigerator immediately after collection. Ten milliliters of the sample was centrifuged for 15 min at 1500 rpm. The supernatant was filtered using a 0.45 µm filter and then diluted 5–times with PBS (pH 4.0). The solution was transferred into the voltammetric cell to be analyzed without any further pretreatment.

Optimization of ISPT concentration

The influence of ISPT concentration on the electrocatalytic oxidation peak current was studied at three different concentrations of CAP at pH 4.0, and in the range of 100.0 to 700 µmol L^{-1} ISPT. The results showed that by increasing the concentration of ISPT up to 500 µmol L^{-1} the peak current increased, whereas higher concentrations of ISPT caused a slight decrease on the magnitude of peak current, which may be due to the formation of ISPT aggregates. Therefore, 500 µmol L^{-1} ISPT concentrations were selected for further studies.

Results and discussion

Electrochemistry of ISPT

The electrochemical behavior of the ISPT was characterized by cyclic voltammetry. Figure 2 (inset) shows the cyclic voltammograms of ISPT at MWCNTPE in the PBS (pH 4.0) at various scan rates. The experimental results showed well defined and reproducible anodic and cathodic peaks related to $ISPT_{(red)}$/ $ISPT_{(ox)}$

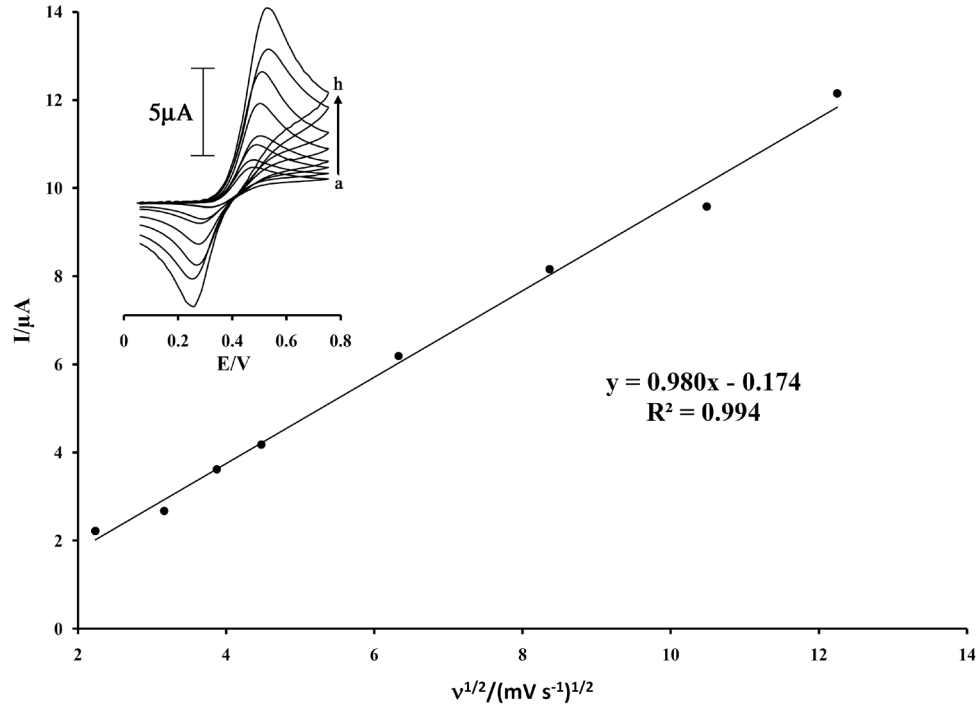

Figure 2 Plot of I_{pa} versus $\nu^{1/2}$ for the oxidation of 200 µmol L^{-1} ISPT at a surface of MWCNTPE. Insert cyclic voltammograms of at various scan rates: (a) 5; (b) 10; (c) 15; (d) 20; (e) 40; (f) 70; (g) 110; and (h) 150 mV s^{-1} in 0.1 mol L^{-1} PBS (pH 4.0).

redox coupled with a quasi reversible behavior and with a peak separation potential of $\Delta E_p(E_{pa} - E_{pc})$=205 mV. These cyclic voltammograms were used to examine the variation of the peak currents vs. the square root of potential scan rates. The plot of the anodic peak current was linearly dependent on $\nu^{1/2}$ with a correlation coefficient of 0.994 at all scan rates (Figure 2).

The active surface areas of the modified electrodes are estimated according to the slope of the I_p vs. $\nu^{1/2}$ plot for a known concentration of $K_4Fe(CN)_6$, based on the Randles–Sevcik equation:

$$I_p = 269000n^{3/2}AD_R^{1/2}\nu^{1/2}C_0 \qquad (1)$$

where I_{pa} refers to the anodic peak current, n the electron transfer number, A the surface area of the electrode, D_R the diffusion coefficient, C_0 the concentration of $K_4Fe(CN)_6$ and ν is the scan rate. For 1.0 mmol L^{-1} $K_4Fe(CN)_6$ in 0.10 mol L^{-1} KCl electrolyte with n=1 and D_R = 7.6×10^{-6} cm^2 s^{-1} and from the slope of the I_{pa}–$\nu^{1/2}$ relation, the microscopic areas were calculated. The active surface areas were equal to 0.09 and 0.18 cm^2 for carbon paste electrode (CPE) and MWCNTPE, respectively. The result shows that the presences of MWCNTPE cause increasing the active surface of the electrode.

Catalytic effect

Figure 3 shows the electrocatalytic oxidation of CAP in the absence or presence of ISPT at a MWCNTPE surface. As is obvious, at the potential range studied (0.05–1.05 V), CAP was not electroactive in the absence of mediator at a surface of MWCNTPE and CPE (Figure 3(e and f)), respectively. On the other hand, the anodic current of ISPT was increased substantially in the presence of low concentrations of CAP at a surface of MWCNTPE and CPE (Figures 3(c) and 3b)), respectively. This observation is an evidence for electrocatalytic oxidation of CAP by ISPT. Similarly, when we compared the oxidation of CAP at the surface of MWCNTPE (curve c) and at CPE (curve b) in the presence of mediator, a dramatic enhancement was observed in the anodic peak current at

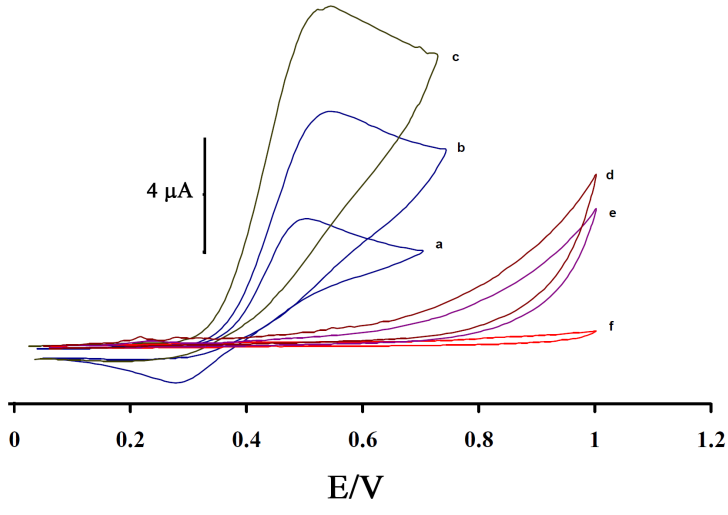

Figure 3. Cyclic voltammograms of (a) the 200 µmol L^{-1} ISPT at the surface of MWCNTPE in 0.1 mol L^{-1} PBS (pH 4.0); (b) 200 µmol L^{-1} ISPT +100 µmol L^{-1} CAP at the surface of carbon paste electrode; (c) 200 µmol L^{-1} ISPT +100 µmol L^{-1} CAP at the surface of MWCNTPE; (d) 100 µmol L^{-1} CAP at the surface of MWCNTPE; (e) 100 µmol L^{-1} CAP at the surface of carbon paste electrode, (f) For the buffer solution at the surface of unmodified electrode (carbon paste electrode); scan rate of 20 mV s^{-1}.

MWCNTPE vs. the value obtained with CPE. In other words, the data obtained clearly show that the combination of MWNTs and the mediator definitely improve the characteristics of the electrode for the oxidation of CAP. The ISPT at a surface of MWCNTPE, in 0.1 mol L^{-1} PBS (pH 4.0) and without CAP in solution, exhibited a well-behaved redox reaction (curve a). The process corresponds to an EC' (catalytic) mechanism (see scheme 1) (27-30), where the electrochemically formed $ISPT_{(Ox)}$ reacts chemically with CAP diffused toward the electrode surface, while the simultaneous oxidation of the regenerated $ISPT_{(Red)}$ causes an increase in the anodic current. For the same reason, the cathodic current of the modified electrode is smaller in the presence of CAP.

Since CAP has a thiol moiety, we anticipated that the oxidation of CAP would be pH dependent. In order to ascertain this, the voltammetric response of CAP at a surface of MWCNTPE in the presence mediator was obtained in solutions with varying pH. Result shows that the maximum value of the peak current was appeared at pH 4.0, so this value was selected throughout the experiments (Not shown).

The effects of scan rate (υ) on the oxidation current of CAP were also examined (Figure 4). The peak current increased linearly with the increasing the square root of scan rate that ranged from 2 to 20 mV s^{-1} and it can be expressed as follows:

$$I_p = 1.3454\ \nu^{1/2} + 0.9675\ (r^2 = 0.9967,\ I \text{ in } \mu A,\ \nu \text{ in } mV\ s^{-1}) \qquad (2)$$

This result shows that the electrode process is controlled under the diffusion step.

To obtain information about the rate-determining step, the Tafel plot was drawn, as derived from points in the Tafel region of the cyclic voltammogram (Figure 5). **"Here Figure 5"**

The slope of the Tafel plot was equal to n (1−α) F/2.3RT, which came up to 7.8148 V^{-1} decade. Therefore, we obtained the value of α equal to 0.54.

Figure 6A shows the current–time curves of MWCNTPE in the presence of mediator by setting the electrode potential at 0.2 mV (first step) and 70 mV (second step) for different CAP concentrations. As can be seen, there is no net anodic current corresponding to the

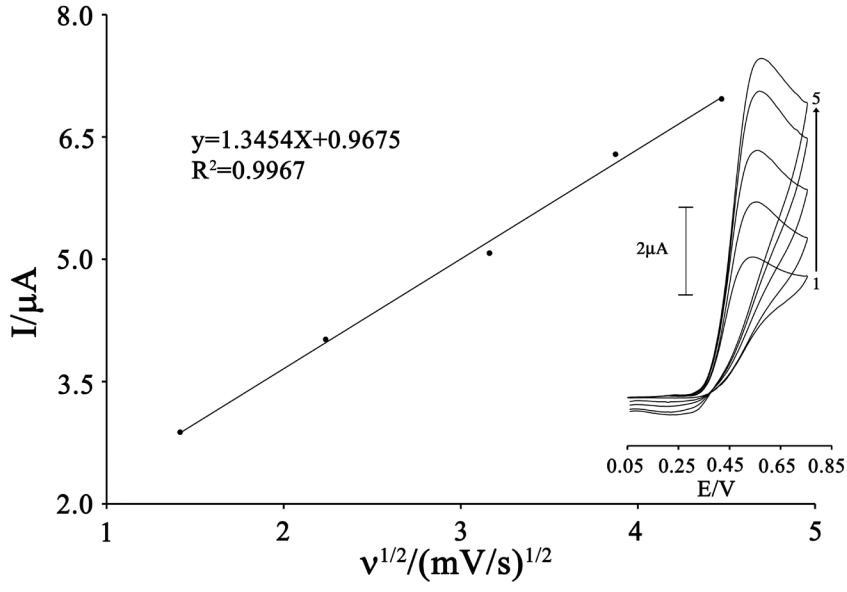

Figure 4. Plot of I_{pa} versus $\nu^{1/2}$ for the oxidation of 80 μmol L^{-1} CAP in the presence 200 μmol L^{-1} ISPT at the surface of MWCNTPE. Inset) Cyclic voltammograms of 80 μmol L^{-1} CAP in the presence 200 μmol L^{-1} ISPT at various scan rates as (a) 2, (b) 5, (c) 10; (d) 15 and e) 20 mV s^{-1} in 0.1 mol L^{-1} buffer solution (pH 4.0).

oxidation of the mediator in the presence of CAP.

On the other hand, the forward and backward potential step chronoamperometry for the mediator in the absence of CAP shows symmetrical chronoamperogram with an equal charge consumed for the reduction and oxidation of the mediator at the surface of MWCNTPE (Figure 6B, a/). On the other hand, the charge value associated with forward chronoamperometry in the presence of CAP is significantly greater than that observed for backward chronoamperometry (Figure 6B, b/).

The rate constant for the chemical reaction between ISPT and CAP (k_h) is determined according to the method of Galus (31)

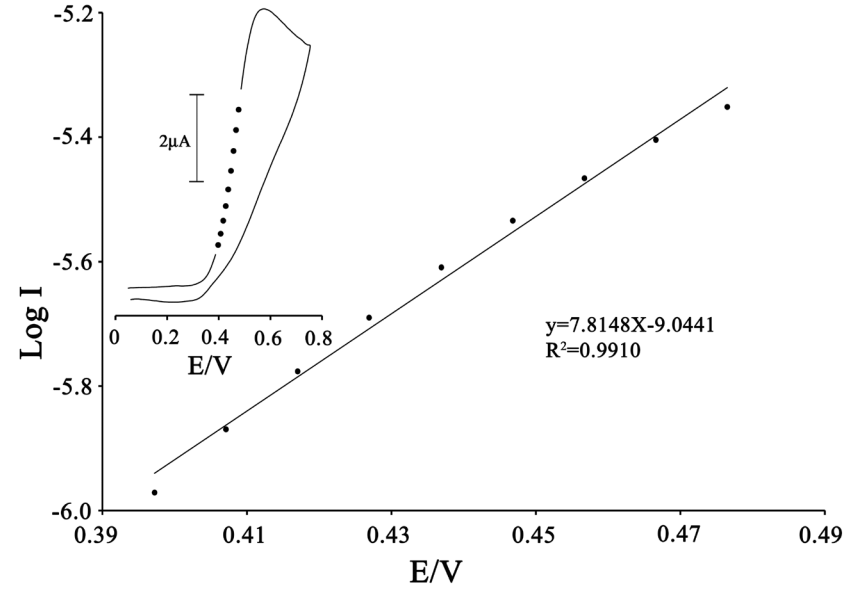

Figure 5. Tafel plot 200 μmol L^{-1} ISPT at the surface of MWCNTPE in 0.1 mol L^{-1} PBS (pH 4.0) at a scan rate of 20 mV s^{-1} in the presence of 100 μmol L^{-1} CAP.

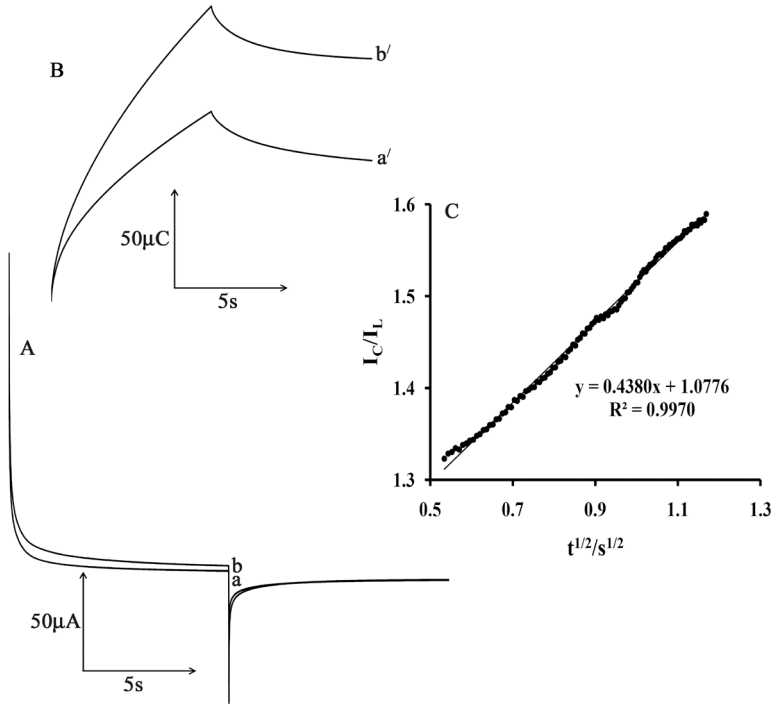

Figure 6 A) Chronoamperograms obtained at the MWCNTPE in the absence a) and in the presence of b) 200 μmol L^{-1} CAP in a buffer solution (pH 4.0). B) The charge-time curves a') for curve (a); and b') for curve (b). C) Dependence of I_c/I_L on the $t^{1/2}$ derived from the chronoamperogram data.

$$I_C/I_L = \pi^{1/2}\,\gamma^{1/2} = \pi^{1/2}(k_h t)^{1/2} \qquad (3)$$

where I_C is the catalytic current of ISPT in the presence of CA and I_L is the limiting current in the absence of CA. From the slope of I_C/I_L versus $t^{1/2}$ for five different concentrations of CAP, the average value of k_h was calculated to be 3.01×10^3 M^{-1} sec^{-1} (Figure 6C). This value of rate constant explains the sharp catalytic peak observed for the oxidation of CAP at the surface of MWCNTPE in the presence of mediator.

Dynamic range and limit of detection

Square wave voltammetry (with amplitude potential of 50 mV and frequency of 12 Hz) was used to determine the concentration of CAP because SWV, had a much higher current sensitivity and better resolution than cyclic voltammetry, which was used to estimate the lower limit of detection of CAP (Figure 7). Responses were linear with CAP concentrations ranging from 0.3-90 μM and a current sensitivity of 0.0252 μA/(μmol/L). The detection limit was determined at 0.1 μM CAP according to the definition of $Y_{LOD}=Y_B+3\sigma$.

Interference study

In order to evaluate the selectivity of the proposed sensor for the determination of CAP, the influence of various foreign species on the determination of 5.0 μmol L^{-1} CAP was investigated. The tolerance limit was taken as the maximum concentration of the foreign substances, which caused an approximately ±5% relative error in the determination.

The results after the experiments revealed that neither 950–fold of K^+, Li^+, Mg^{2+}, Br^-, NO_3^-, ClO_4^-, SO_4^{2-},F^-, glucose, sucrose, lactose, fructose, glycine, urea, histidine, SCN^-, methionine, alanine, and phenylalanine; nor 700–fold of tryptophan, urea, thiourea, ampicillin and tyrosine; nor 300–fold of uric acid, ascorbic acid, aspirin, hydrochlorothiazide, atenolo, amoxicillin (after addition of 1 mM ascorbic oxidaze) and nor saturation of starch solution affected the selectivity. Also, nor 2–fold glutathione and N-actylcusteine affected the

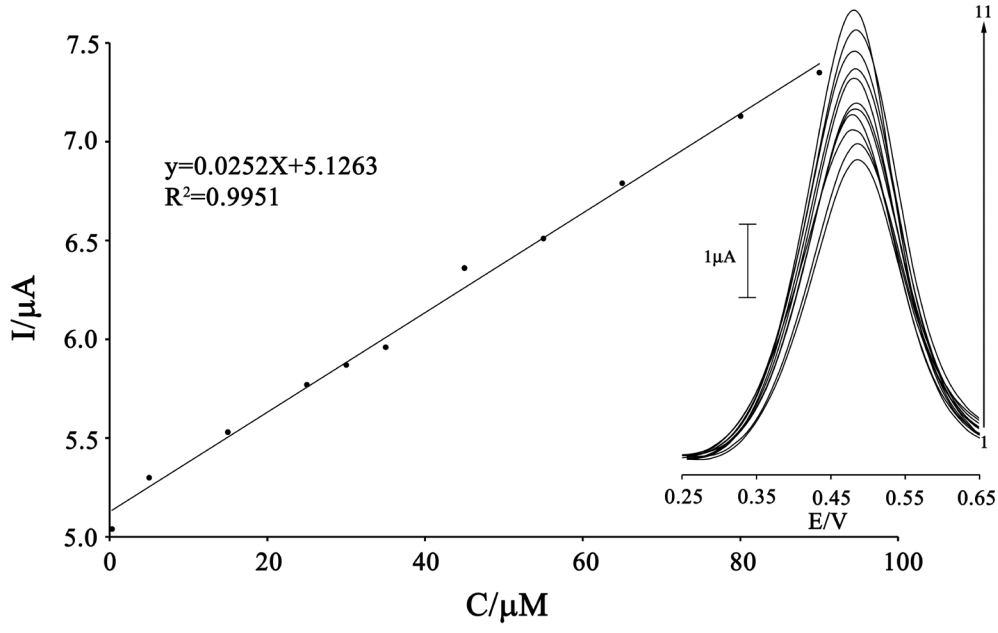

Figure 7. The plots of the electrocatalytic peak current as a function of CAP concentration. Inset shows the SWVs of MWCNTPE in the presence 200 μmol L^{-1} ISPT (pH 4.0) containing different concentrations of CAP. From inner to outer (1–11) correspond to 0.3, 0.5, 15.0, 25.0, 30.0, 35.0, 45.0, 55.0, 65.0, 80.0, and 90.0 μmol L^{-1} of CAP.

selectivity. Those results confirm the suitable selectivity of the proposed sensor for CAP determination.

Determination of CA in real samples

Electrochemical methods have a good sensitivity and selectivity for determination of pharmaceutical and biological sample analysis in real samples.[33-40] In order to evaluate the applicability of the proposed sensor for the determination of CAP in real samples; we have examined the ability of the electrochemical sensor for the determination of CAP in tablet and urine samples using standard addition method. The samples were also analyzed by a standard method including potentiometric titration with potassium iodate.[32] The results for the tablet sample analysis are given in Table 2

In addition, the results obtained for the urine samples by the proposed method were compared with the standard method statistically, using Student's t test (for the accuracy), and variance ratio, F test (for the precision) at 95% confidence level. The results are given in Tables 3. Those results demonstrated the ability of propose sensor for voltammetric determination of CAP in real samples with the good recoveries of the spiked CAP and good reproducibility.

Stability and reproducibility

The repeatability and stability of the MWCNTPE was investigated using square

Table 2. Determination of captopril in tablet and urine samples (n=3).

Sample	Captopril added (μmol L^{-1})	Expected value (μmol L^{-1})	Captopril founded (μmol L^{-1})	Standard Method (μmol L^{-1})
Tablet [a]	—	10.0	10.33 ± 0.35	10.55 ± 0.65
	10.0	20.0	19.88 ± 0.45	20.45 ± 0.69
	20.0	40.0	39.75 ± 0.88	39.84 ± 0.75
Tablet [b]	—	55.0	55.45 ± 0.55	54.92 ± 0.69
	5.0	60.0	59.65 ± 0.75	60.78 ± 1.01
	10.0	70.0	70.84 ± 0.95	70.95 ± 1.11

[a] 50 mg tablet, Darou Pakhsh Company, Iran
[b] 25 mg tablet, Darou Pakhsh Company, Iran

Table 3. Concentration values obtained from the proposed and the reference method for captopril analysis of urine sample using the proposed method under optimum conditions (n=3).

Sample	Proposed method (μmol L^{-1})	Standard method (μmol L^{-1})	F_{ex}	F_{tab}	t_{ex}	$t_{tab(95\%)}$
Urine[a]	4.14 ± 0.25	4.51 ± 0.65	7.5	19	2.1	3.8
Urine[b]	5.25 ± 0.33	5.62 ± 0.82	8.5	19	2.6	3.8
Urine[c]	7.35 ± 0.75	6.95 ± 0.85	8.7	19	3.8	3.8
Urine[d]	4.55 ± 0.37	4.865 ± 0.55	6.1	19	2.4	3.8

[±] Shows the standard deviation.
[a] Sampling was made after 1.5 h from a man who had heart problem and used captopril.
[b] Sampling was made after 2.0 h from a man who had heart problem and used captopril.
[c] Sampling was made after 2.5 h from a man who had heart problem and used captopril.
[d] Sampling was made after 3.0 h from a man who had heart problem and used captopril.

wave voltammetric measurements of 20.0 μmol L^{-1} CAP in the presence of mediator. The relative standard deviation (RSD%) for seven successive assays of CAP was 2.1%. When using six different electrodes, the RSD% for seven measurements of 20.0 μmol L^{-1} CAP was 2.9%. When the modified electrode stored in the laboratory, the response of the modified electrode retained 97% of its initial response value after two week and 92% after 35 days. These results indicate that MWCNTPE has good stability and reproducibility.

Conclusion

This study demonstrates the construction of a chemically modified carbon paste electrode by incorporation of carbon nanotubes as a suitable electrochemical sensor in the presence of ISPT as a homogeneous mediator for CAP determination at trace level. The new voltammetric sensor for the determination of CAP is very rapid, reproducible, selective and sensitive, and can be used for real sample analysis. The proposed method is a selective, simple and precise method for voltammetric determination of CAP in real samples such as drug and patient urine, as low as 0.1 μmol L^{-1} CAP. In addition, the kinetic parameters of the system have been calculated from the experimental results.

Acknowledgements

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References

(1) Karimi-Maleh H, Biparva P and Hatami M. A novel modified carbon paste electrode based on NiO/CNTs nanocomposite and (9, 10-dihydro-9, 10-ethanoanthracene-11, 12-dicarboximido)-4-ethylbenzene-1,2-diol as a mediator for simultaneous determination of cysteamine, nicotin amide adenine dinucleotide and folic acid. *Biosens. Bioelect.* (2013) 48: 270-275.

(2) Elyasi M, Khalilzadeh MA and Karimi-Maleh H. High sensitive voltammetric sensor based on Pt/CNTs nanocomposite modified ionic liquid carbon paste electrode for determination of Sudan I in food samples. *Food Chem.* (2013) 141: 4311-4317.

(3) Ensafi AA and Karimi-Maleh H. Modified multiwall carbon nanotubes paste electrode as a sensor for simultaneous determination of 6-thioguanine and folic acid using ferrocenedicarboxylic acid as a mediator. *J. Electroanal. Chem.* (2010) 640: 75-83.

(4) Roodbari Shahmiri M, Bahari A, Karimi-Maleh H, Hosseinzadeh R and Mirnia N. Ethynylferrocene–NiO/MWCNT nanocomposite modified carbon paste electrode as a novel voltammetric sensor for simultaneous determination of glutathione and acetaminophen. *Sens. Actuators B* (2013) 177: 70-77.

(5) Ensafi A, Karimi-Maleh H, Mallakpour S and Rezaei B. Highly sensitive voltammetric sensor based on catechol-derivative-multiwall carbon nanotubes for the catalytic determination of captopril in patient human urine samples. *Coll. Surf. B* (2011) 87: 480-488.

(6) Gupta VK, Jain AK, Singh LP and Khurana U. Porphyrins as carrier in PVC based membrane potentiometric sensors for nickel(II). *Anal. Chim. Acta* (1997) 355: 33-41.

(7) Gupta VK, Mangla R, Khurana U and Kumar P. Determination of uranyl ions using poly(vinyl chloride) based 4-tertbutylcalix[6]arene membrane sensor. *Electroanalysis* (1999) 11: 573-576.

(8) Gupta VK, Prasad R, Kumar P and Mangla R. New nickel (II) selective potentiometric sensor based on 5,7,12,14-tetramethyldibenzotetraazaannulene in a

poly(vinyl chloride) matrix. *Anal. Chim. Acta* (2000) 420:19-27.

(9) Fern´andez L and Carrero H. Electrochemical evaluation of ferrocene carboxylic acids confined on surfactant–clay modified glassy carbon electrodes: oxidation of ascorbic acid and uric acid. *Electrochim. Acta* (2005) 50: 1233-1240.

(10) Beitollahi H, Karimi-Maleh H and Khabazzadeh H. Nanomolar and selective determination of epinephrine in the presence of norepinephrine using carbon paste electrode modified with carbon nanotubes and novel 2-(4-oxo-3-phenyl-3,4-dihydroquinazolinyl)-*N*′-phenyl-hydrazinecarbothioamide. *Anal. Chem.* (2008) 80: 9848-9851.

(11) Ensafi AA, Karimi-Maleh H, Mallakpour S and Hatami M. Simultaneous determination of *N*-acetylcysteine and acetaminophen by voltammetric method using *N*-(3,4-dihydroxyphenethyl)-3,5-dinitrobenzamide modified multiwall carbon nanotubes paste electrode. *Sens. Actuators B* (2011) 155: 464-472.

(12) Tavana T, Khalilzadeh MA, Karimi-Maleh H, Ensafi AA, Beitollahi H and Zareyee D. Sensitive voltammetric determination of epinephrine in the presence of acetaminophen at a novel ionic liquid modified carbon nanotubes paste electrode. *J. Mol. Liq.* (2010) 168: 69-74.

(13) Salmanpour S, Tavana T, Pahlavan A, Khalilzadeh MA, Ensafi AA, Karimi-Maleh H, Beitollahi H, Kowsari E and Zareyee D. Voltammetric determination of norepinephrine in the presence of acetaminophen using a novel ionic liquid/multiwall carbon nanotubes paste electrode. *Mat. Sci. Eng. C* (2012) 32: 1912-1918.

(14) Iijima S. Helical microtubules of graphitic carbon. *Nature* (1991) 354: 56-58.

(15) Shahrokhian S and Zare-Mehrjardi HR. Simultaneous voltammetric determination of uric acid and ascorbic acid using a carbon-paste electrode modified with multi-walled carbon nanotubes/nafion and cobalt(II)-nitrosalophen. *Electroanalysis* (2007) 19: 2234-2242.

(16) Antiochia R and Gorton L. Development of a carbon nanotube paste electrode osmium polymer-mediated biosensor for determination of glucose in alcoholic beverages. *Biosens. Bioelect.* (2007) 22: 2611-2617.

(17) Beitollah H, Goodarzian M, Khalilzadeh MA, Karimi-Maleh H, Hassanzadeh M and Tajbakhsh M. Electrochemical behaviors and determination of carbidopa on carbon nanotubes ionic liquid paste electrode. *J. Mol. Liq.* (2012) 173: 137-143.

(18) Afsharmanesh E, Karimi-Maleh H, Pahlavan A and Vahedi J. Electrochemical behavior of morphine at ZnO/CNT nanocomposite room temperature ionic liquid modified carbon paste electrode and its determination in real samples. *J. Mol. Liq.* (2013) 181: 8-13.

(19) Mokhtari A, Karimi-Maleh H, Ensafi AA and Beitollahi H. Application of modified multiwall carbon nanotubes paste electrode for simultaneous voltammetric determination of morphine and diclofenac in biological and pharmaceutical samples. *Sens. Actuators B* (2012) 169: 96-105.

(20) Khalilzadeh MA, Karimi-Maleh H, Amiri A, Gholami F and Motaghed mazhabi R. Determination of captopril in patient human urine using ferrocenemonocarboxylic acid modified carbon nanotubes paste electrode. *Chin. Chem. Lett.* (2010) 21: 1467-1470.

(21) Ensafi AA, Karimi-Maleh H, Ghiaci M and Arshadi M. Characterization of Mn-nanoparticles decorated organo-functionalized SiO_2–Al_2O_3 mixed-oxide as a novel electrochemical sensor: application for the voltammetric determination of captopril. *J. Mater. Chem.* (2011) 21: 15022-15030.

(22) Ensafi AA and Arabzadeh A. A new sensor for electrochemical determination of captopril using chlorpromazine as a mediator at a glassy carbon electrode. *J. Anal. Chem.* (2012) 67: 486-496.

(23) Ensafi AA, Monsef M, Rezaei B and Karimi-Maleh H. Electrocatalytic oxidation of captopril on a vinylferrocene modified carbon nanotubes paste electrode. *Anal. Methods* (2012) 4: 1332-1338.

(24) Mazloum-Ardakani M, Sheikh-Mohseni MA, Mirjalili BF and Zamani L. Simultaneous determination of captopril, acetaminophen and tryptophan at a modified electrode based on carbon nanotubes. *J. Electroanal. Chem.* (2012) 686: 12-18.

(25) Habibi D, Farajia AR and Gil A. A highly sensitive supported manganese-based voltammetric sensor for the electrocatalytic determination of captopril. *Sens. Actuators B* (2013) 182: 80-86.

(26) Gholivand MB and Khodadadian M. Simultaneous voltammetric determination of captopril and hydrochlorothiazide on a graphene/ferrocene composite carbon paste electrode. *Electroanalysis* (2013) 25: 1263-1270.

(27) Raoof JB, Ojani R and Karimi-Maleh H. Carbon paste electrode incorporating 1-[4-(ferrocenyl ethynyl) phenyl]-1-ethanone for electrocatalytic and voltammetric determination of tryptophan. *Electroanalysis* (2008) 20: 1259-1262.

(28) Keyvanfard M, Sami S, Karimi-Maleh H and Alizad K. Electrocatalytic determination of cysteamine using multiwall carbon nanotube paste electrode in the presence of 3,4-dihydroxycinnamic acid as a homogeneous mediator. *J. Braz. Chem. Soc.* (2013) 24: 32-39.

(29) Moradi R, Sebt SA, Karimi-Maleh H, Sadeghi R, Karimi F, Bahari A and Arabi H. Synthesis and application of FePt/CNTs nanocomposite as a sensor and novel amide ligand as a mediator for simultaneous determination of glutathione, nicotinamide adenine dinucleotide and tryptophan *Phys. Chem. Chem. Phys.* (2013) 15: 5888-5897.

(30) Keyvanfard M, Khosravi V, Karimi-Maleh H, Alizad K and Rezaei B. Voltammetric determination of 6-mercaptopurine using a multiwall carbon nanotubes paste electrode in the presence of isoprenaline as a mediator *J. Mol. Liq.* (2013) 177: 182-189.

(31) Galus Z. Fundumentals of electrochemical analysis. Ellis Horwood, New York. 1976.

(32) The United States Pharmacopeia USP 26 NF 22. Washington, 1, Convention Rockville, MD: National Formulary; 2004.
(33) Nematollahi D, Feyzi Barnaji B and Amani A. Electrochemical synthesis and kinetic evaluation of electrooxidation of acetaminophen in the presence of antidepressant drugs, ServicesIranian *Iran. J. Pharm. Res*. (2015) 14: 1115-1122.
(34) Karimi-Maleh H, Tahernejad-Javazmi F, Gupta VK, Ahmar H and Asadi MH. A novel biosensor for liquid phase determination of glutathione and amoxicillin in biological and pharmaceutical samples using a ZnO/ CNTs nanocomposite/catechol derivative modified electrode. *J. Mol. Liq*. (2014) 196: 258-263.
(35) Karimi-Maleh H, Sanati AL, Gupta VK, Yoosefian M, Asif M and Bahari A. A voltammetric biosensor based on ionic liquid/NiO nanoparticlemodified carbon paste electrode for the determination ofnicotinamide adenine dinucleotide (NADH). *Sens. Actuators B* (2014) 204: 647-654.
(36) Ciltas U, Yilmaz B, Kaban S, Akcay BK, and Nazik G. Square wave voltammetric determination of diclofenac in pharmaceutical preparations and human serum. *Iran. J. Pharm. Res*. (2015) 14: 715-722.
(37) Karimi-Maleh H, Tahernejad-Javazmi F, Atar N, Yola ML, Gupta VK, and Ensafi AA.
(38) A novel DNA biosensor based on a pencil graphite electrode modified with polypyrrole/functionalized multiwalled carbon nanotubes for determination of 6-mercaptopurine anticancer drug. *Ind. Eng. Chem. Res*. (2015) 54, 3634-3639.
(39) Karimi-Maleh H, Tahernejad-Javazmi F, Ensafi AA, Moradi R, Mallakpour S and Beitollahi H. A high sensitive biosensor based on FePt/CNTs nanocomposite /N-(4-hydroxyphenyl)-3, 5-dinitrobenzamide modified carbon paste electrode for simultaneous determination of glutathione and piroxicam. *Biosens Bioelectrs* (2014), 60: 1-7.
(40) Ghorbani-Bidkorbeh F. Electrochemical sensors and biosensors represent very promising tools in pharmaceutical sciences. *Iran. J. Pharm. Res*. (2015) 14: 663-664.

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