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A New Strategy for Determination of Captopril as a Hypertension Drug Using ZnO Nanoparticle Modified Carbon Paste Electrode

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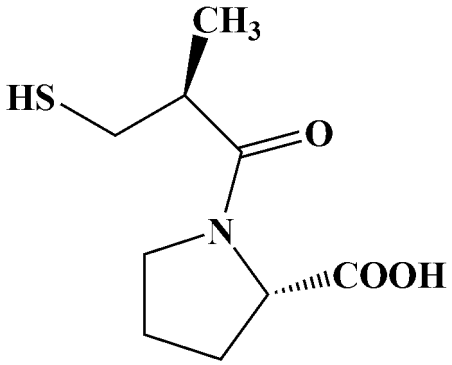
In this study we describe a carbon paste electrode modified with ferrocenecarboxaldehyde and ZnO nanoparticle (ZnO/NPs) for the sensitive and selective voltammetric determination of captopril (CAP) in aqueous solution. The oxidation of CAP at the modified electrode was investigated by cyclic voltammetry (CV), chronoamperommetry, and square wave voltammetry (SWV). The values of the catalytic rate constant (k_h), and diffusion coefficient (D) for CAP were calculated. At the optimum pH of 7.0 in a 0.1 M phosphate buffer solution, the SWV anodic peak currents showed a linear relationship versus CAP concentrations in the range of 0.08–500.0 μM and a detection limit of 0.04 μM. Finally, the proposed method was also examined as a selective, simple and precise electrochemical sensor for the determination of CAP in real samples such as in human patient urine and tablet samples.

Keywords: Captopril, ZnO nanoparticle, Drug analysis, Modified electrode

1. INTRODUCTION

Captopril 1-(3-mercapto-2-d-methyl-1-oxopropyl) proline (Scheme 1) is an important 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 [1]. CAP is an exclusive 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 [2–4]. So, determination of this drug is very important in pharmaceutical and biological samples.



Scheme 1. Structure of captopril

Nanoscience and nanotechnology have become one of the most interesting disciplines in science and technology in the recent years [5-15]. The powerful interest in nanotechnology is being driven by various interesting fields and is leading to a new industrial revolution and pharmaceutical application [16-26]. Nano-materials such as nanoparticles, carbon nanotubes or nanocomposite connected with biomolecules are being used for several bioanalytical applications [27-37].

Electroanalysis is taking advantages from all the possibilities offered by nanomaterials easy to be detected by conventional electrochemical methods [38–48]. Nanoparticle of a variety of shapes, sizes and compositions are changing nowadays the bioanalytical measurement [49-60]. Electroanalytical applications for biological, pharmaceutical and environmental compounds, which utilize chemically modified electrodes (CMEs), should offer a potentially significant efficiency [61-71]. Recently there has been a considerable effort in the investigation of catalytic function of CMEs on the oxidation of environmentally and biologically important compounds [72-82].

In this study, the application of a ferrocenecarboxaldehyde (FCX), as a mediator for the electrocatalytic determination of CAP is investigated using SWV. The suitability of the ferrocenecarboxaldehyde-modified ZnO nanoparticle carbon paste electrode (FCX/ZnO/NPs/CPE) is also studied for the electrocatalytic determination of CAP by voltammetric methods. Finally, 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.

2. EXPERIMENTAL

2.1. Chemicals

All chemicals used were of analytical reagent grade 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 ^{o}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 (PBS) with different pH values were used.

High viscosity paraffin (d = 0.88 Kg L^{-1}) was used as the pasting liquid for the preparation of carbon paste electrode. Spectrally pure graphite powder (particle size<50 μm) and high viscose paraffin oil (density = 0.88 Kg L^{1}) were used for the preparation of the carbon paste electrode (CPE) and the modified electrode.

Captopril tablets (Darou Pakhsh Company, Iran, labeled 50 and 25 mg captopril per tablet) was purchased from Red Cross Drug Store in Sari.

2.2. Apparatus

Cyclic voltammetry (CV), chronoamperomtry and SWV were performed in an analytical system, Micro-Autolab, potentiostat/galvanostat connected to a three-electrode cell, Metrohm Model 663 VA stand, linked with a computer (Pentium IV, 1200 MHz) and with micro-Autolab software. A conventional three-electrode cell assembly consisting of a platinum wire as an auxiliary electrode and an Ag/AgCl (KCl_{sat}) electrode as a reference electrode was used. The working electrode was either a carbon paste electrode (CPE) or FCX/ZnO/NPs/CPE. X-ray powder diffraction studies were carried out using a STOE diffractometer with Cu-Ka radiation (k = 1.54 Å). Samples for transmission electron microscopy (TEM) analysis were prepared by evaporating a hexane solution of dispersed particles on amorphous carbon coated copper grids.

A pH-meter (Corning, Model 140) with a double junction glass electrode was used to check the pH of the solutions.

2.3. Synthesis of ZnO nanoparticle

To prepare of ZnO/NPs, in a typical experiment, a 0.25M aqueous solution of zinc nitrate ($Zn(NO_3)_2 \cdot 4H_2O$) and 0.5 M aqueous solution of sodium hydroxide (NaOH) were prepared in distilled water. Then, the beaker containing NaOH solution was heated at the temperature of about 55°C. The $Zn(NO_3)_2$ solution was added drop wise (slowly for 1.5 h) to the above-heated solution under high-speed stirring. The beaker was sealed at this condition for 2 h. The precipitated ZnO/NPs were cleaned with deionized water and ethanol then calcined at 200 °C for 2 hours.

2.4. Preparation of the modified electrode

15.0 mg of ferrocenecarboxaldehyde was hand mixed with 885 mg of graphite powder and 100 mg of ZnO/NPs in a mortar and pestle. Using a syringe, 0.45 g of paraffin was added to the mixture

and mixed well for 75 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. The unmodified carbon paste electrode was prepared in the same way without adding mediator and ZnO/NPs to the mixture.

2.5. 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 7.0) 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 20 min at 2000 rpm. The supernatant was filtered using a 0.45 μm filter and then diluted 5–times with PBS (pH 7.0). The solution was transferred into the voltammetric cell to be analyzed without any further pretreatment. The standard addition method was used for the determination of captopril in real samples.

3. RESULT AND DISCUSSION

3.1. X-Ray diffraction of ZnO nanoparticles

The XRD patterns of the ZnO/NPs showed diffraction peaks being absorbed at 2θ values (not shown). The prominent peaks were used to calculate the grain size via the Scherrer equation, expressed as follows:

$$D=K\lambda/(\beta \cos\theta) \quad (1)$$

Where λ is the wavelength (λ = 1.542 Å) (CuKα), β is the full width at half maximum (FWHM) of the line, and θ is the diffraction angle. The grain size of the ZnO nanostructure was 20 nm, and the peaks were observed at the (100), (002), (101), (102), (110), (103), (200), (112), (201), (004) and (202) planes. These peaks correspond to ZnO NPs.

3.2. Electron microscopic investigation of ZnO nanoparticles

The morphology of the as-grown nanostructures was characterized by TEM techniques. Figure 1 shows the TEM images of the synthesized product. It is clear that in this case, a ZnO nanoparticle was successfully prepared.

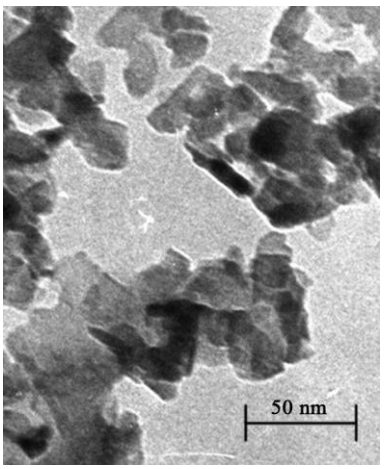


Figure 1. TEM image of ZnO/NPs.

3.3. Electrocatalytic oxidation of captopril

One objective of the present work was to develop a modified electrode capable of electrocatalytic oxidation of CAP. The cyclic voltammetric responses for the electrochemical oxidation of 300 μM of CAP at the FCX/ZnO/NPs/CPE are shown in curve c (Fig. 2) and those at the FCX carbon paste electrode (FCX/CPE) in curve b (Fig. 2). Curves d (Fig. 2) are the same as curves c (Fig. 2), respectively, but only without the mediator. Curve a (Fig. 2) shows a cyclic voltammogram of the buffer solution (pH 7.0) at the surface of the FCX/ZnO/NPs/CPE. As can be seen, the anodic peak potentials for the oxidation of captopril at both the FCX/ZnO/NPs/CPE and the FCX/CPE (curves c and b) are about 480 mV. On the other hand, captopril oxidation (without the mediator) does not take place at the surface of ZnO/NPs/CPE and/or CPE up to +1.0 V.

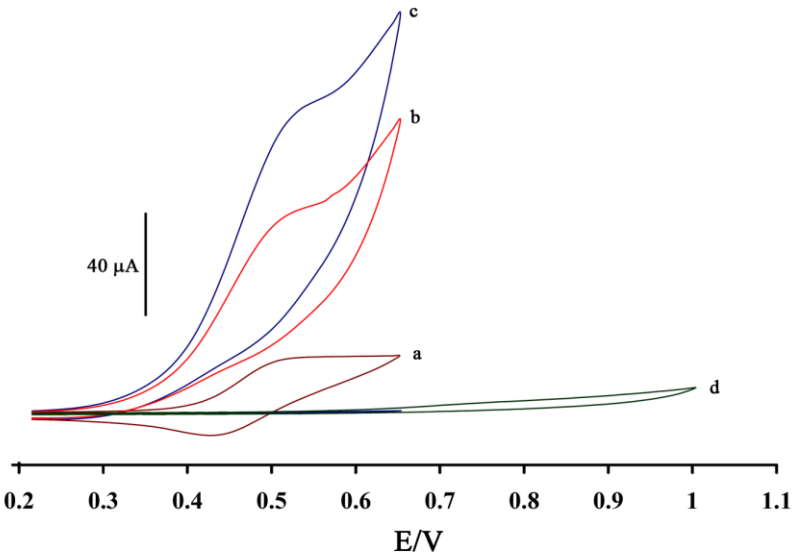
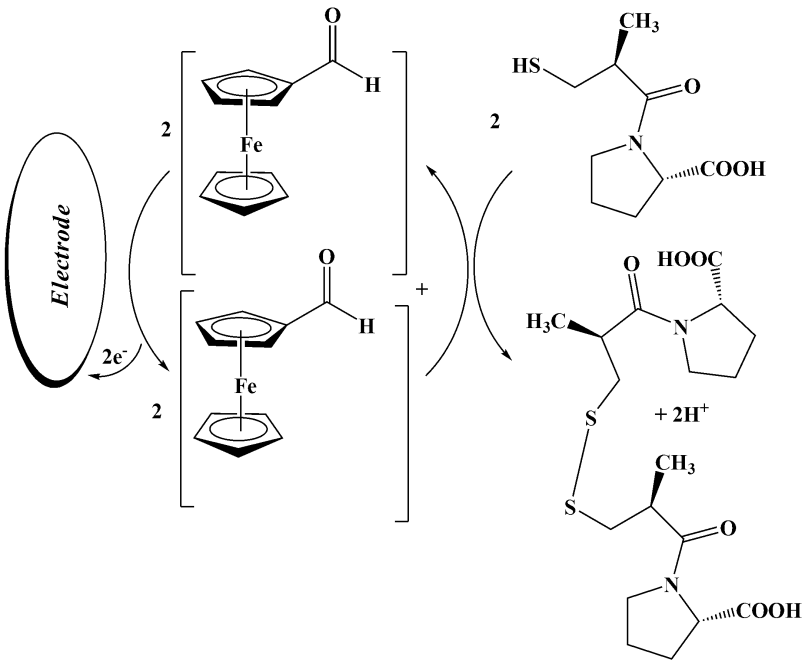


Figure 2. Cyclic voltammograms of: (a) FCX/ZnO/NPs/CPE in 0.1 mol L^{-1} PBS (pH 7.0); (b) cylic voltammograms of FCX/CPE in 0.1 mol L^{-1} PBS (pH 7.0) in the presence of 300 μM captopril; (c) is as (b) at FCX/ZnO/NPs/CPE; (d) is as (c) at ZnO/NPs/CPE, respectively; Condition: scan rate of 20 mV s^{-1}.

Similarly, when we compared the oxidation of CAP at the surface of the FCX/ZnO/NPs/CPE (Fig. 2c) and at the FCX/CPE (Fig. 2b), an enhancement of the anodic peak current was found to occur at the FCX/ZnO/NPs/CPE. In other words, the data obtained clearly show that the combination of ZnO/NPs and the mediator definitely improve the characteristics of the electrode for the oxidation of CAP. Based on these results, the following catalytic diagram (EC, catalytic mechanism) describes the voltammetric response of the electrochemical oxidation of CAP at the FCX/ZnO/NPs/CPE (Scheme 2) [83-89].



Scheme 2. Electrocatalytic mechanism for this work.

The effect of scan rate on the electrocatalytic oxidation of CAP at the FCX/ZnO/NPs/CPE was investigated by cyclic voltammetry. Result shows, the oxidation peak potential shifted towards a more positive potential with increasing scan rate, confirming the kinetic limitation of the electrochemical reaction [90-93]. In addition, a plot of peak height (I_p) against square root of scan rate ($v^{1/2}$) was constructed which was found to be linear, suggesting that, at sufficient overpotential, the process is diffusion rather than surface controlled. In order to obtain information about the rate-determining step, Tafel plots (plots of logI *vs.* potential) were drawn (Fig. 3) which were derived from points of the Tafel region of the cyclic voltammogram in Fig. 3 (insert). The results of the polarization studies for electro-oxidation of CAP at the FCX/ZnO/NPs/CPE showed that for all potential sweep rates, the average Tafel slope was 0.1496 V^{-1}. The slope of the Tafel plot was equal to $n(1 - \alpha)F/2.3RT$. We obtained $n\alpha$ equal to 0.6. Assuming n = 1, then $\alpha = 0.6$.

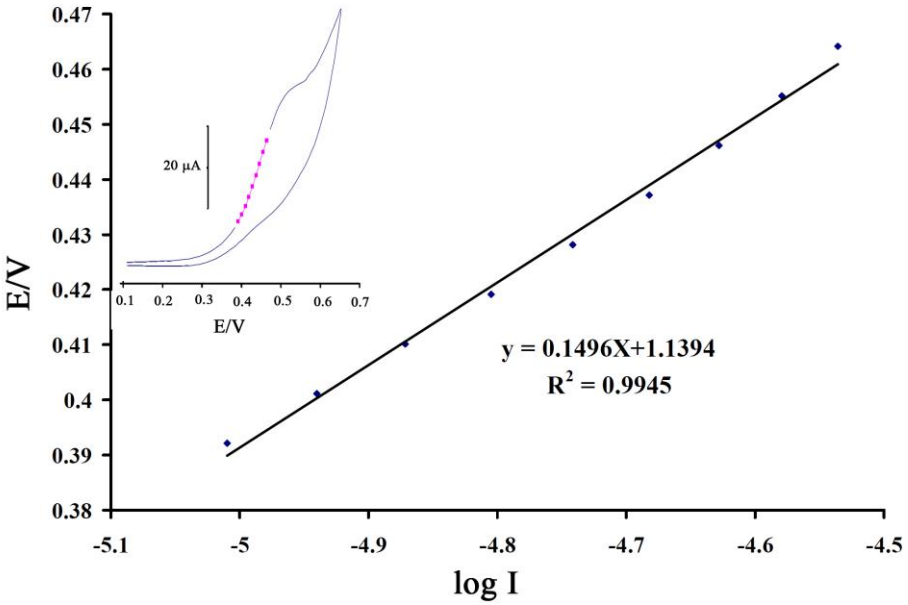


Figure 3. Tafel plot for FCX/ZnO/NPs/CPE in 0.1 mol L^{-1} PBS (pH 7.0) with a scan rate of 20 mV s^{-1} in the presence of 200 μM captopril.

3.4. Chronoamperometric study

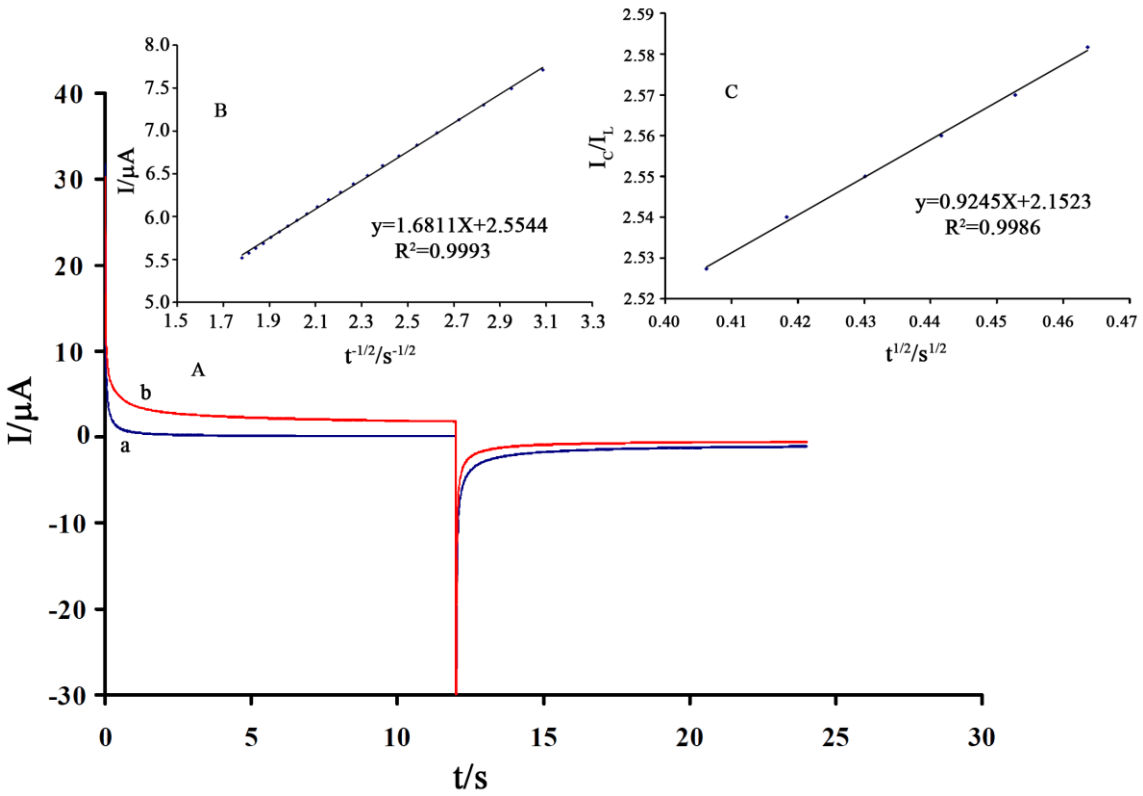


Figure 4. (A) Chronoamperograms obtained at FCX/ZnO/NPs/CPE (a) in the absence, and in the presence of (b) 300 μM captopril at pH 7.0. (B) Cottrell's plot for the data from the chronoamperograms. (C) Dependence of I_c/I_L on the $t^{1/2}$ derived from the chronoamperogram data.

Fig. 4A shows the chronoamperograms of CAP at the FCX/ZnO/NPs/CPE obtained by setting the potential of the working electrode at 300 and 700 mV for various concentrations of CAP. For an electroactive with a diffusion coefficient of D, the current for the electrochemical reaction with a mass transport limited rate is described by the Cottrell equation [94]. Under diffusion control, a plot of I versus $t^{-1/2}$ will be linear, and the value of D can be obtained from the slope. Fig. 4B shows the experimental plots with the best fits for different CAP concentrations employed. The slopes of the resulting straight lines were plotted versus CAP concentration. The value of D was found to be 1.3×10^{-6} cm^2 s^{-1}.

Chronoamperometry can also be employed to evaluate the catalytic rate constant, k, for the reaction between captopril and the FCX/ZnO/NPs/CPE according to the method of Galus [95]:

$$I_C/I_L = \pi^{1/2} \gamma^{1/2} = \pi^{1/2} (kC_b t)^{1/2} \quad (1)$$

where I_C is the catalytic current, I_L is the limited current in the absence of CAP, and C_b is the bulk concentration of CAP. The above equation can be used to calculate the rate constant of the catalytic process. Based on the slope of the I_C/I_L versus $t^{1/2}$ plot, k can be obtained for a given CAP concentration. Such plots obtained from the chronoamperograms in Fig. 4A are shown in Fig. 4C. From the values of the slopes, an average value of k was found to be 9.43×10^2 mol^{-1} L s^{-1}. The value of k explains the sharp feature of the catalytic peak potential for the oxidation of CAP at the surface of FCX/ZnO/NPs/CPE.

3.5. Stability and reproducibility

The repeatability and stability of the FCX/ZnO/NPs/CPE was investigated using cyclic voltammetric measurements of 1.0 and 20.0 μM CAP. The relative standard deviation (*RSD%*) for seven successive assays were 2.0% and 1.2%, respectively. When using four different electrodes, the *RSD%* for five measurements was 2.5%. When the electrode was stored in our laboratory at room temperature, the modified electrode retained 95% of its initial response after 10 days and 91% after 35 days. These results indicate that the FCX/ZnO/NPs/CPE has good stability and reproducibility, and that it could be used for CAP.

4. SQUARE WAVE VOLTAMMETRIC STUDY

Since SWV has a much higher analytical sensitivity and a better resolution than cyclic voltammetry, it was used to estimate the regression equation and limit of detection of CAP. The results showed two linear segments with different slopes for CAP concentration: for 0.08 – 0.5 μM CAP, the regression equation was $I_p(\mu A) = 14.7610\ C_{captopril} + 7.1082$ ($r^2 = 0.9911$, n = 5); and for 0.5 – 500 μM CAP, the regression equation was $I_p(\mu A) = 0.0776\ C_{captopril} + 17.0640$ ($r^2 = 0.9915$, n = 9), where $C_{captopril}$ is μM concentration of captopril.

The detection limit was obtained to be 0.04 μmol L^{-1} captopril according to the definition of $Y_{LOD} = Y_B + 3\sigma$ [96].

5. INTERFERENCE STUDIES

The influence of various substances as potential interfering compounds with the determination of CAP was studied under the optimum conditions with 5.0 μM CAP at pH 7.0. The potentially interfering substances were chosen from the group of substances commonly found with CAP in pharmaceuticals and/or in biological fluids. Tolerance limit was defined as the maximum concentration of the interfering substance that caused an error less than ±5% for the determination of CAP. The results are presented in Table 1.

6. REAL SAMPLE ANALYSIS

To investigate the applicability of the proposed sensor for the catalytic determination of CAP in real samples, we selected urine and tablet samples for the analysis of their CAP contents. The urine sample was centrifuged and diluted five-times with buffer solution without any further pretreatment. The standard addition method was used for measuring CAP concentrations in the samples. The proposed method was also compared with a published method [97], the results of which are given in Table 2.

Table 1. Interference study for the determination of 5.0 μM captopril under the optimized conditions.

Species	Tolerante limits ($W_{Substance}/W_{CAP}$)
Glucose , Fructose, Lactose , Sucrose	1000
Tryptophan, Valine, Methionine, Glycine, Lucine, Histidine, Glutamic acid, Alanine , Glycine, Phenylalanine	700
Li^+, Cl^-, CO_3^{2-}, ClO_4^-, SO_4^{2-}, SCN^-, Na^+, Mg^{2+}, K^+, Ca^{+2}	500
Thiourea, urea	300
Starch	Saturation

Table 2. Determination of captopril in tablet sample.

Sample	Captopril added (μM)	Expected value (μM)	Captopril founded (μM)	Standard Method (μM)
Tablet [a]	5.0	5.0	4.83±0.55	5.1±0.33
	5.0	10.0	10.23±0.44	9.9±0.56
Tablet [b]	20.0	20.0	20.55±0.63	20.28±0.72
	10.0	30.0	29.75±0.46	30.78±1.1

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

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

In addition, the amounts of CAP in the urine samples of both patient and healthy subjects on CAP were measured (Table *3*). It was found that excretion of CAP happens from 1–3 h after consumption of the tablet and it will be maximum from 2.5 h onwards [*3*]. It is interesting that the amount of CAP in patient urine samples was maximum 2.5 h after consumption. In addition, the excreted CAP value was higher in the urine samples from healthy subjects than in those from patients under similar conditions.

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 (μM)	Standard method (μM)	F_{ex}	F_{tab}	t_{ex}	$t_{tab(95\%)}$
Urine[a]	5.33±0.65	6.01±0.75	8.5	19	2.2	3.8
Urine[b]	8.67±0.72	8.22±0.72	8.9	19	2.3	3.8
Urine[c]	10.03±0.92	9.95±1.05	9.5	19	2.8	3.8
Urine[d]	9.55±0.75	9.45±0.66	9.2	19	2.7	3.8
Urine[e]	6.34±0.65	6.44±0.79	7.8	19	2.1	3.8

±Shows the standard deviation.
[a] Sampling was made after 1.0 h from a woman who had heart problem and used captopril.
[b] Sampling was made after 2.0 h from a woman who had heart problem and used captopril.
[c] Sampling was made after 2.5 h from a woman who had heart problem and used captopril.
[d] Sampling was made after 2.5 h from a man had heart problem and used captopril.
[e] Sampling was made after 3.0 h from a woman who had heart problem and used captopril.

This showed that higher amounts of CAP are absorbed in the patient body and that, therefore, less amounts are excreted in the urine. A statistical comparison was also made between the proposed method and the standard method, using Student's t test (for accuracy), variance ratio, and F test (for precision) at 95% confidence level. The results demonstrated the capability of the FCX/ZnO/NPs/CPE for voltammetric determination of CAP in real samples with good recoveries of the spiked CAP and good reproducibility.

7. CONCLUSIONS

The electrochemical methods are powerful technique in compare of other methods for investigation and determination of biological and pharmaceutical compounds [98-102]. So, in this study, carbon-paste electrode modified with ferrocenecarboxaldehyde and ZnO/NPs was used for the determination of CAP. The electrochemical investigations showed effective electrocatalytic activity of the modified electrode in lowering the anodic overpotential for the oxidation of CAP. Finally, the modified electrode was also examined as a selective, simple, and precise new electrochemical sensor for the determination of CAP in real samples such as drug and urine. For more investigation, urine samples of sick and healthy people were compared. Interestingly, the results revealed that smaller amounts of CAP are observed in the urine from sick people on the drug than in the urine from healthy subjects taking CAP.

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