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Development of electrochemical sensor based on carbon paste electrode modified with ZnO nanoparticles for determination of chlorpheniramine maleate

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ABSTRACT

Zinc oxide (ZnO) nanoparticles with an average size of 60 nm have been successfully prepared by microwave irradiation. Carbon paste electrode (CPE) was modified with ZnO nanoparticles and used for the electrochemical oxidation of chlorpheniramine maleate (CPM). Cyclic voltammetry (CV) study of the modified electrode indicated that the oxidation potential shifted towards a lower potential by approximately 106 mV and the peak current was enhanced by 2 fold in comparison to the bare CPE (ZnO/CPE-CV). The electrochemical behaviour was further described by characterization studies of scan rate, pH and concentration of CPM. Under the optimal conditions the peak current was proportional to CPM concentration in the range of 8.0×10^{-7} to 1.0×10^{-3} mol L^{-1} with a detection limit of 5.0×10^{-7} mol L^{-1} by differential pulse voltammetry (DPV). The peak current of CPM is linear in the concentration range of 0.8 - 1000 µM (R^2=0.998). The ZnO/CPE has a good reproducibility and high stability for the determination of CPM using this electrode. The proposed method was successfully applied to the determination of CPM in pharmaceutical samples. In addition, the important analytical parameters were compared with other methods which show that ZnO/CPE-CV procedure are comparable to recently reported methods.

1. Introduction

Antihistamines are a class of drugs commonly used to treat symptoms of allergies. These drugs help treat conditions caused by too much histamine, a chemical created by your body's immune system. Chlorpheniramine maleate [*3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine*, CPM] is an alkyl amine antihistamine. For more than 30 years, the CPM as a H_1-receptor antagonist has been used to treat allergies such as hay fever, and other respiratory tract allergies [1]. The common side effects of chlorpheniramine (CPM, CP) include sleepiness, restlessness, and weakness dry mouth and wheeziness. CPM/CP is often combined with phenylpropanolamine to form an allergy medication with both antihistamine and decongestant properties,CPM/CPisapartofaseriesof antihistamines including pheniramine (Naphcon). As previous work, the CPM/CP synthesized through pyridine based on alkylation by 4-chlorophenylacetonitrile. The CPM generated by alkylating with 2-dimethylaminoethylchloride in

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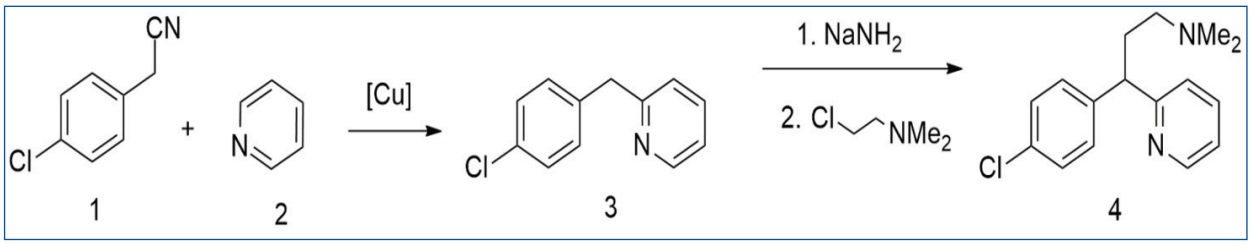

Schema 1. Synthesis of CPM/CP based on alkylation by pyridine

the presence of sodium amide (Schema 1). Several methods have been reported for the determination of CPM maleate including, spectrophotometry [2], liquid chromatography [3], liquid chromatography-mass spectrometry [4], gas chromatography [5], high performance liquid chromatography [6]. However, these instrumental methods have suffered some disadvantages such as time consuming, solvent-usage intensive and requires expensive devices and maintenance [7]. The electrochemical methods using chemically modified electrode have been widely used in sensitive and selective analytical methods for the detection of the trace amounts of biologically important compounds. Electrode surface may be changed with metal nanoparticles and such surfaces have found various applications within the sector of bio electrochemistry, particularly in biosensors. it's also been observed that nanoparticles can act as conductivity centers facilitating the transfer of electrons. Additionally, they provide large catalytic area. Several types of nanoparticles, including metal nanoparticles [8-10], oxide nanoparticles [11-13], semiconductor nanoparticles and even composite nanoparticles [14-16] are widely utilized in electrochemical sensors and bio sensors [17]. Some electrochemical methods are also reported for the determination of CPM by voltammetry [18-21]. Electrochemical sensors satisfy many of the requirements for such tasks particularly owing to their inherent specificity, rapid response, sensitivity and simplicity of preparation [18]. To our knowledge, no study has reported the electrocatalytic oxidation of CPM by using ZnO modified carbon paste electrode. Thus, in the present work, the ZnO nanoparticle have been synthesized using microwave irradiation process and a modified carbon paste electrode is fabricated by using ZnO nanoparticles for the determination of CPM. All results were validated by spiking samples and compared to other methods.

2. Experimental

2.1. Chemicals and Reagents

Pure CPM, sodium dihydrogen ortho phosphate (NaH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4), sodium phosphate (Na_3PO_4), orthophosphoric acid ($H_3PO_{4)}$, sodium hydroxide (NaOH), hydrochloric acid (HCl), $Zn(NO_3)_2.4H_2O$ and graphite powder were obtained from Merck. The buffer solutions were prepared from orthophosphoric acid and its salts in the pH range of 8 to 11. All the aqueous solutions were prepared by using double distilled water. High viscosity paraffin (d =0.88 kg L^{-1}) from Merck was used as the pasting liquid for the preparation of the carbon paste electrodes.

2.2. Apparatus

Electrochemical studies were performed using a Metrohm polarograph potentiostat-galvanostat (Metrohm Computrace 797-VA). The 797 VA is a voltammetric measuring stand that is connected to a PC. The computer software provided controls the measurement, records the measured data and evaluates it. Operation is most straightforward due to the well-laid-out structure of the program. The integrated potentiostat with galvanostat guarantees the highest sensitivity with reduced noise. Voltammetry system for the determination of organic additives in electroplating baths with

cyclic voltammetric stripping (CVS). Complete accessories with VA Computrace software and all electrodes for a complete measurement system: Rotating platinum disk electrode (RDE), Ag/AgCl reference electrode and Pt auxiliary electrode. Three-electrode system consisted of a bare CP and ZnO/CPE electrode as the working electrode, Ag/AgCl (3M KCl) as the reference electrode and a platinum wire as the auxiliary electrode. A Metrohm 691 pH/Ion meter was used for pH measurements. Solutions were degassed with nitrogen for ten minutes prior to recording of the voltammogram. X-ray diffraction (XRD) patterns were recorded by a Philips-X'pertpro, X-ray diffractometer using Ni-filtered Cu Ka radiation in University of Kashan-Iran. Scanning electron microscopy (SEM) images were obtained from LEO instrument model 1455VP.

2.3. Synthesis of ZnO nanoparticles

In this work, zinc acetate and graphene powders were used as the starting reagent. 0.41 mol of $Zn(NO_3)_2.4H_2O$ was dissolved in 50 ml of deionized water under vigorous stirring. 1 ml of NaOH (1 M) was then added dropwise to the solution. Afterward, the solution was exposed by microwave irradiation with different powers and times. The microwave oven followed a working cycle of 30 s on and 70 s off (30 % power). After reaction in microwave the samples were cooled to room temperature naturally. Precipitates were washed with deionized water and ethanol, and air-dried at room temperature.

2.4. Preparation of bare carbon paste electrode and modified carbon paste electrode

The modified carbon paste electrode was prepared by hand mixing 0.1 g of ZnO nanoparticles with 0.9 g graphite powder with a mortar and pestle. Then paraffin was added to the above mixture and mixed for 30 min until a uniformly wetted paste was obtained. This paste was then packed into the end of a glass tube (ca. 3.35 mm i.d. and 10 cm long). Electrical contact was made by forcing a copper wire down into the tube. When necessary, a new surface was obtained by pushing out an excess of paste and polishing it on weighing paper. Unmodified CPE was prepared in the same way without adding of ZnO nanoparticles.

2.5. Procedure and sample preparation

20 pieces of CPM tablet (Daro pakhsh. Iran) were powdered in a mortar. A portion equivalent to a stock solution of a concentration of about 0.01 M was accurately weighed and transferred into a 100 mL calibrated flask and completed to the volume with double distilled water. The contents of the flask were sonicated for 10 min to affect complete dissolution. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquid and diluting them with the phosphate buffer solutions. Also, 0.5 ml of an ampoule of CPM, according to its specifications, each ml of which contains 10 mg of the drug, was placed in a 25 ml calibrated flask and completed with a buffer at pH=10 and voltammetry was performed on it. The differential pulse voltammograms (DPV) were recorded between 0.4 and 1.2 V. The oxidation peak current of CPM was measured. The parameters for DPV were pulse width of 0.05 s, pulse increment of 4 mV, pulse period of 0.2 s, pulse amplitude of 50 mV and scan rate of 50 mVs^{-1}.

3. Results and discussion

3.1. XRD analysis

The phase type, crystal structure and purity of the product obtained are determined by the XRD method. The XRD pattern of the as obtained ZnO nanoparticles as sample number 1 was shown in Figure 1. Peaks in this pattern are reported in the range of 2Θ from 20 to 80 degrees. Patterns of the samples were indexed as a cubic phase. The XRD results proved the high crystallinity and purity of the products synthesized by microwave method. According to XRD data, the crystalline size (D_c) of ZnO nanoparticles can be determined by using Debye- Scherrer formula. The obtained average particle size was found to be 60 nm.

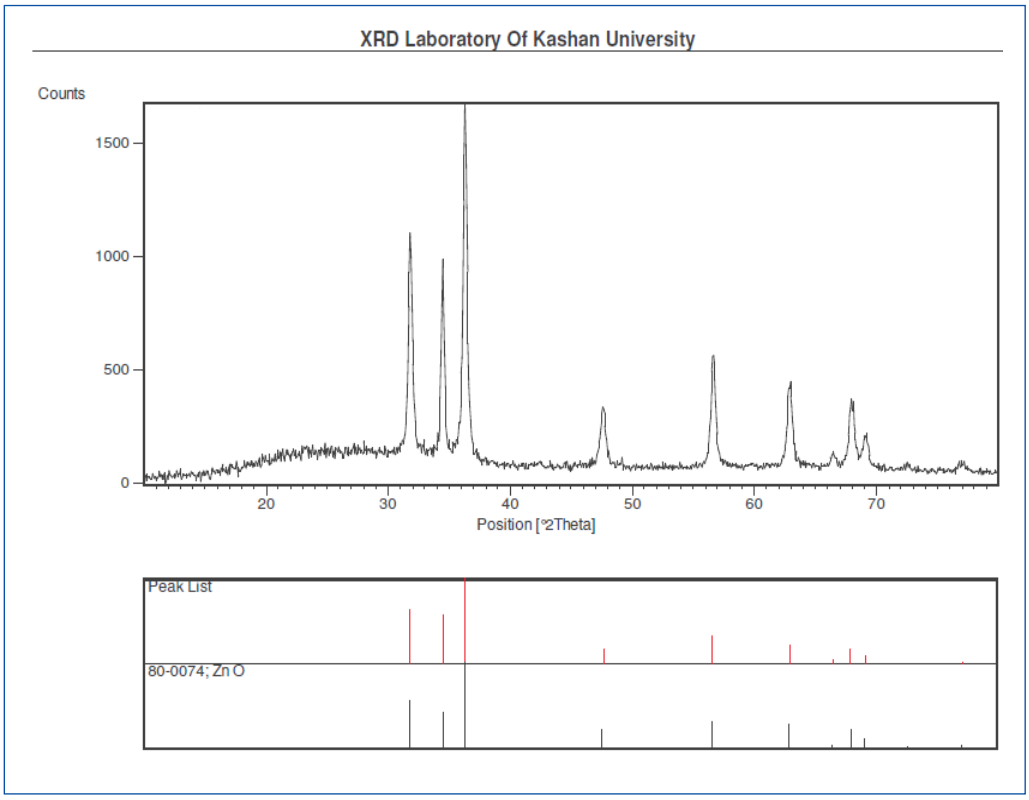

Fig. 1. XRD patterns of ZnO nanoparticles sample 1

3.2. Scanning electron microscopy

In Figure 2 shows SEM image of ZnO powder obtained at 4 min and 360 W (sample no 1), at 540 W (sample no 2) and 750 W (sample no 3). As can be seen from SEM images, at 360 power, the reaction is faster due to the generation of more free radicals in solution and increased heat production due to the rotation of these active species. The formed nanoparticles have relatively smaller sizes and better distribution. At 540 and 720 W, due to the very high energy produced in these powers, the nucleation of the particles is increased, and since the particles have a very active surface, large and cohesive masses are obtained in all test conditions. Therefore, the sample prepared in 360 W power and 4 min time due to the creation of nanoparticles in nanometer size according to the scale of images and homogeneous distribution is an optimized condition for time and power consumption to make ZnO nanoparticles. The produced ZnO nanoparticles have mean diameters of approximately 40-80 nm.

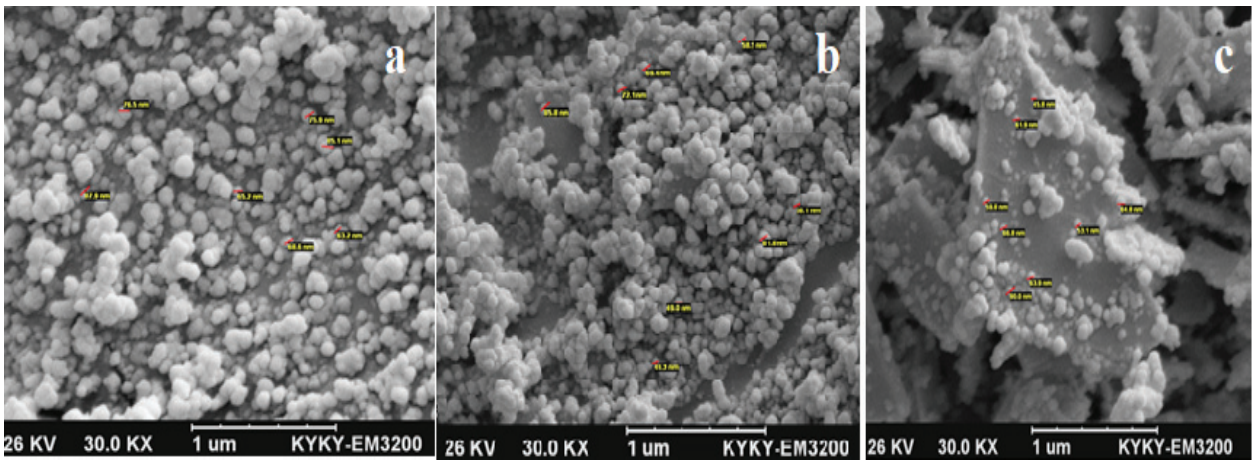

Fig. 2. SEM images of the ZnO nanoparticles for **a)** sample no. 1**, b)** sample no. 2, **c)** sample no. 3

3.3. Electrochemical behavior of CPM at the ZnO/CPE

The electrochemical behavior of CPM has been studied in two electrodes. Cyclic voltammetry (CV) was applied to investigate the electrochemical behavior of 0.4 mM CPM in 0.1 M phosphate buffer at pH 10 with a bare CPE and ZnO/CPE. Figure 3 shows the cyclic voltammograms in the CPE and ZnO/CPE electrode. As shown in this figure, in the presence of CPM, an irreversible oxidation peak at 1.093 V on the bare CPE attributed to the electrochemical oxidation of CPM. In the case of the ZnO /CPE, the oxidation peak of CPM decreased to 0.987 V and the peak current increased by 2.0 times compared with that for the bare CPE. These results suggested that ZnO obviously accelerate the electron transfer at the electrode surface and improve the electrochemical performance accordingly.

3.4. Effect of pH

The effect of pH of the solution on the electrochemical response of CPM was investigated from pH 8 to 11 (although lower pH was also examined in which the peak did not appear well). As can be seen in the Figure 4, with increasing pH, the anodic potential shifts to more negative potentials, which indicates better oxidation of the material at the electrode surface and the electrocatalytic effect. A linear relationship existed between the potential and pH in the range 8 to 11 (Fig. 5). The linear regression equation was E= -60.5pH+1582 (R^2=0.991). The slope of 59 mV/pH suggests that an equal number of protons and electrons are involved in the oxidation process. Also, with increasing pH, the peak current increases to 10 and at pH = 11, the current decreases, so pH = 10 is chosen as the optimal point.

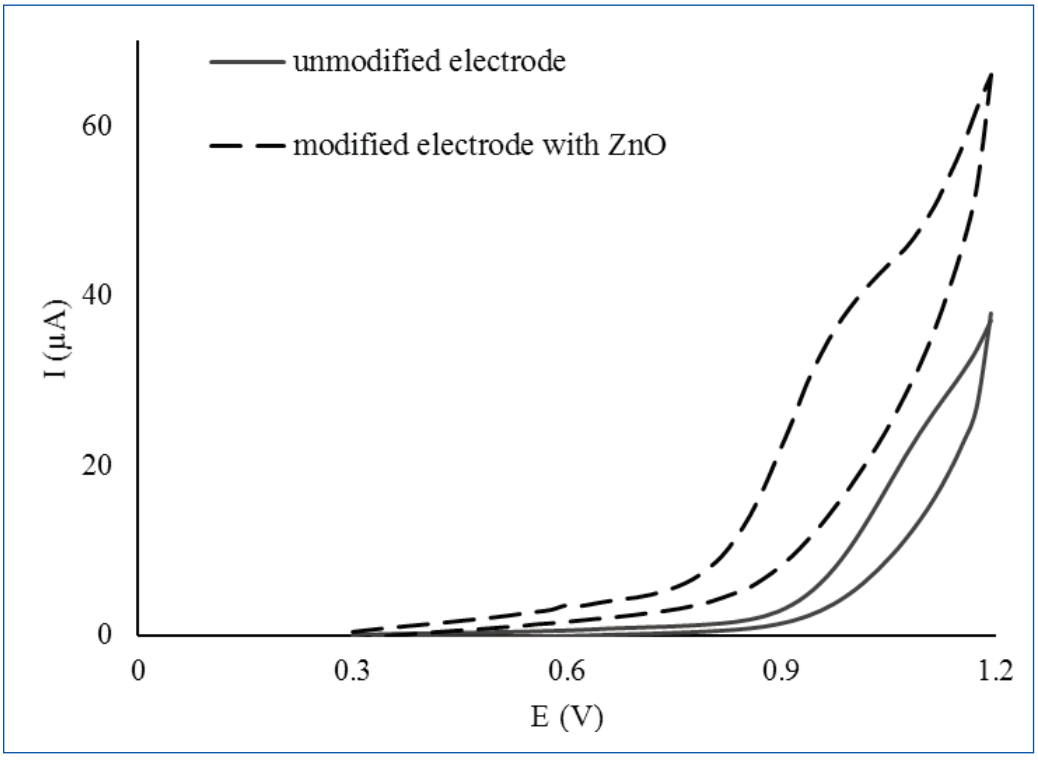

Fig. 3. Cyclic voltammograms of CPE and ZnO/CPE at presence of 0.4 mM CPM in 0.1 phosphate buffer solution (pH 10) at scan rate 50 mVs^{-1}

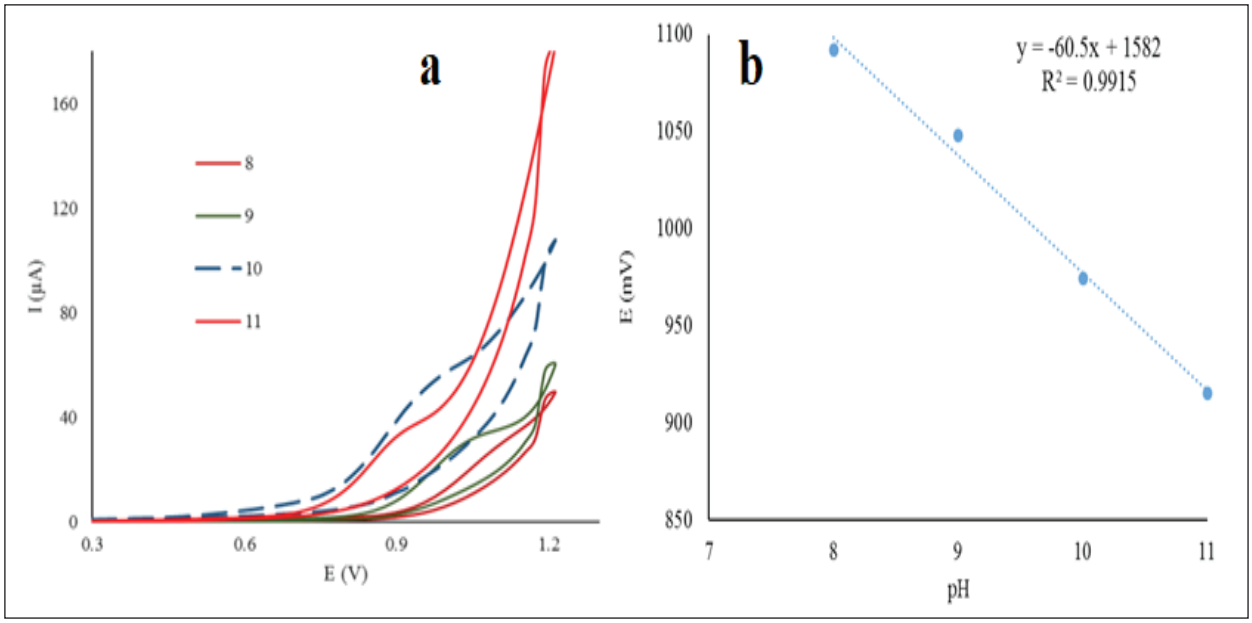

Fig.4. a) Cyclic voltamogram of CPM at different pH b) Relationship between the peak potential of CPM and pH.

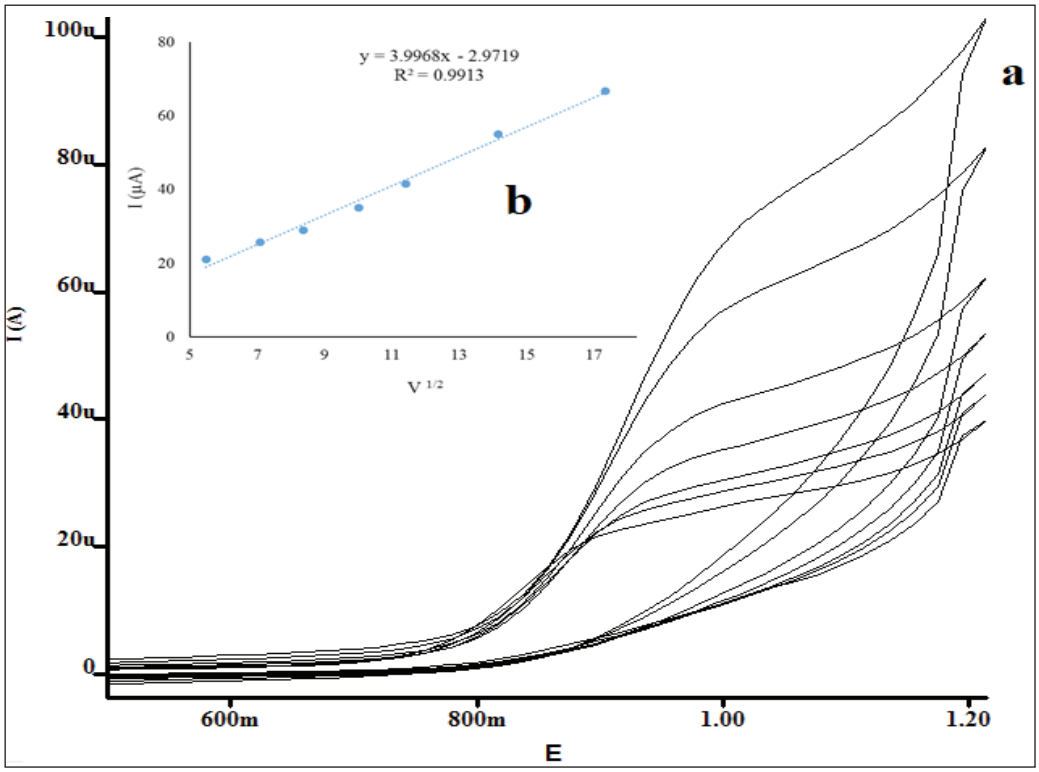

Fig. 5. Cyclic voltammograms of ZnO/CPE in the presence of 0.2 mM of CPM in 0.1 phosphate buffer solution (pH 10) at different scan rates (from inner to outer): 30, 50, 70, 100, 130, 200 and 300 mV s^{-1}. Insets: b, peak current vs. square root of scan rate ($v^{1/2}$)

3.5. Effect of scan rate

The effect of scan rate on the electrocatalytic oxidation of CPM at the ZnO /CPE was investigated by cyclic voltammetry. As can be seen in the Figure 5a, the scanning potential increases the peak CPM oxidation shifts to more positive potentials, which imposes a kinetic constraint on the electrochemical reaction. Figure 5b illustrates that a linear relationship existed between the oxidation peak currents of CPM and the square root ($v^{1/2}$) of the scan rate in the range from 30 to 300 mVs^{-1}, indicating a diffusion-controlled process. The linear regression equation was expressed as $I_{(\mu A)} = 24.597v^{1/2} - 2.942$ ($R^2 = 0.991$).

3.6. Calibration curve

In order to develop a voltammetric method for determination of the drug, the DPV mode is selected, because the peaks are sharper and better defined at lower concentration of CPM than those obtained by cyclic voltammetry, with a lower background current, resulting in improved resolution. According to the obtained results, it was possible to apply this technique to the quantitative analysis of CPM. The phosphate buffer solution of pH 10 was selected as the supporting electrolyte for the quantification of CPM as it gave maximum peak current at pH 10. DPV obtained with increasing amounts of CPM showed that the peak current increased linearly with increasing concentration, as shown in Figure 6**.** Using the optimum conditions described previously, linear calibration curves were obtained for CPM in the range of in range of 8×10^{-7} to 1×10^{-3} M. (Fig. 6 Inset). The linear equation I=0.159x+6.99 (R^2=0.994).

3.7. The repeatability and stability of the ZnO/CPE

Repeatability of the ZnO/CPE was examined by the determination of 0.5 mM of CPM in 0.1 M phosphate buffer solution at pH=10 with the same electrode 5 times. A relative standard deviation (RSD) value of 2.76% was observed, that indicating a good reproducibility of ZnO/CPE for CPM determination. Furthermore, the operational stability of ZnO/CPE was investigated by CV method every 2 days in 2 weeks. Only a small decrease of current (about 3.5%) for 2 mM CPM was observed, which can be attributed to the good stability of the modified electrode.

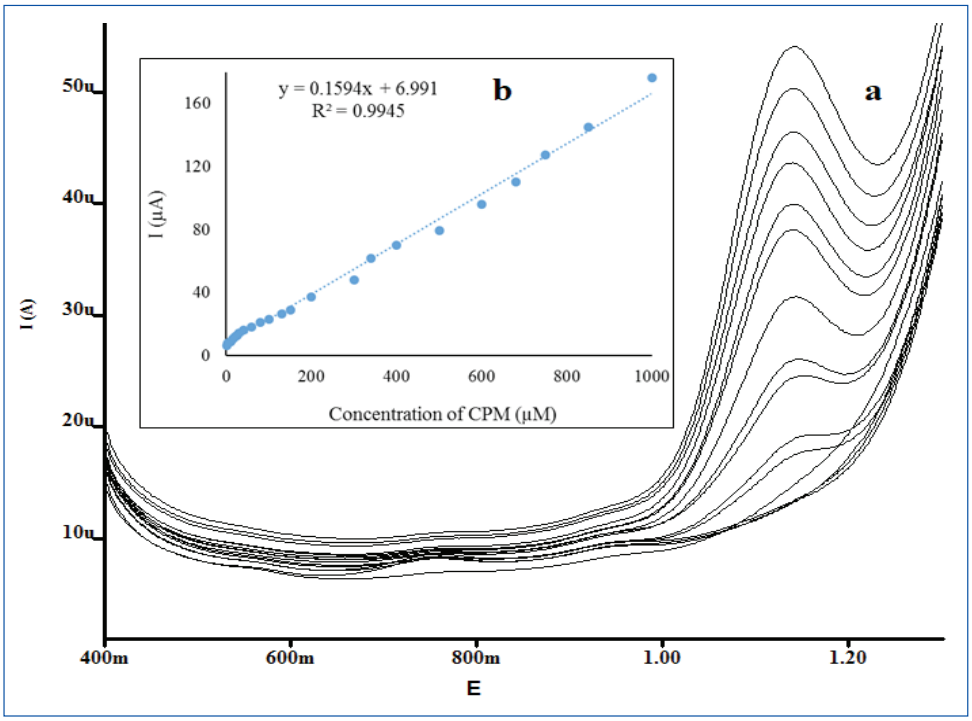

Fig. 6. DPV obtained at a ZnO/CPE for different concentrations of CPM (0.8 to 1000 µM). Inset: linear relationship between the peak current and concentration of CPM, scan rate: 50 mV s^{-1}

3.8. Analysis of real samples

In order to evaluate the applicability of the proposed method in the real sample analysis, it was used to detect CPM in tablets and ampoule (4 mg per tablet and 10 mg/mL for ampoule) (Fig. 7). The results are in good agreement with the content marked in the label. The detected content was 4.06 mg per tablet with 95% recovery and 9.76 mg/mL with 101 %recovery for ampoule. Recovery studies were carried out after the addition of known amounts of the drug to various preanalyzed formulations of CPM. The results are listed in Table 1**.** Analytical parameters obtained here were compared with results obtained by other methods which show that they are comparable or better than the values reported by other groups (Table 2).

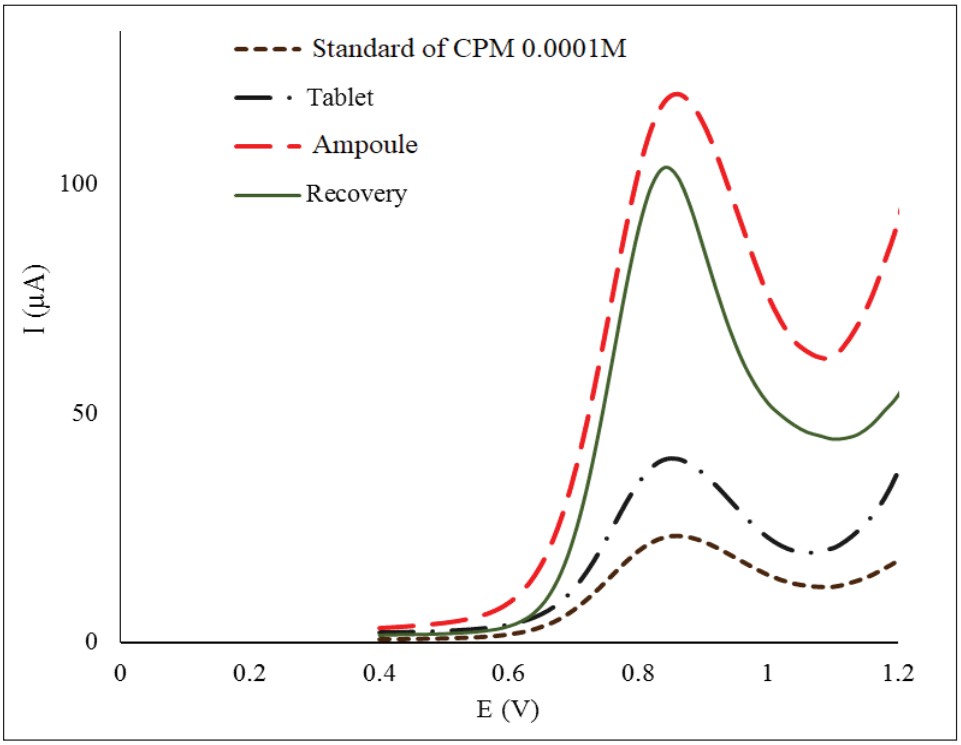

Fig.7. DPV obtained at a ZnO/CPE for standard solution 0.0001M of CPM, tablet, ampoule and standard added with tablet sample.

Table. 1. Determination of CPM in tablet and ampoule sample with ZnO/CPE by DPV method

Sample	Amount CPM in sample (mg)	Found in sample	Added (mg)	Deffected after addition (mg)	Recovery (%)
Tablet	4	4.06±0.08	2.74	2.62±0.1	95.62
Ampoule	10	9.77±0.2	3.5	3.73±0.07	106.3

Table 2. Comparison of analytical parameters for determination of CPM with different analytical methods.

Electrode	Method	LOD(µM)	LR(µM)	Ref
CPE-ion exchanger	PM	0.51	1.2-10000	[18]
CPE-SDS	DPV	1.7	1.0 – 800	[7]
Ru/Pty/GCE	CV	0.338	2.0 -45	[19]
MWCNT-modified GCE	DPV	1.63	5.0-500	[20]
CPE- CO nanostructure	DPV	0.08	0.1-10	[21]
CPE- ZnO Nanoparticle	DPV	0.50	0.8–1000	This work

4. Conclusions

ZnO/CPE was successfully fabricated and has shown electrocatalytic effect on the oxidation of CPM. In Comparison with the bare CPE, the presence of small amounts of ZnO reduced the oxidation peak potential of CPM while increased the current response of CPM. The CPM peak current is linear from a concentration range of 0.8 µM to 1000 µM with excellent R^2 value of 0.998. The detection limit of this modified electrode was found to be 0.5 µM and a good reproducibility, high stability was obtained for the determination CPM using this electrode. The content of CPM in tablet and ampoule samples was successfully determined with ZnO/CPE, which indicated the modified electrode is useable for the determination of CPM concentration in real samples.

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