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Electrochemical Behavior and Voltammetric Determination of Chlorpheniramine Maleate by Means of Multiwall Carbon Nanotubes-Modified Glassy Carbon Electrode

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Using the cyclic voltammetry as a diagnostic technique, this study describes the electrochemical behavior of Chlorpheniramine maleate, on glassy carbon modified electrode with MWCNTs (MWCNT-GCE). The results indicated that the GCE-MWCNTs remarkably accelerate the electron transfer reactions of CPM. Differential pulse voltammetry of CPM at the modified electrode exhibited a linear calibration curve in the concentration range of CPM of 5–500 μM, with a limit of detection of 1.63μM. The relative standard deviation (R.S.D %) for 5 replicate measurements of CPM (25μM) was 1.86%. The proposed technique was successfully used for the determination of CPM in serum samples.

Keywords: Multiwall carbon nanotubes, Voltammetry, Chlorpheniramine maleate, Differential pulse voltammetry, Determination

1. INTRODUCTION

CPM, Chlorpheniramine maleate or 3-(4-chloro, phenyl)-n, n-dimethyl-3-pyridin-2-yl- propan-1-amine is an antihistamine drug .It has been used for the treatment of common cold and allergic diseases both alone and in combination with other drugs [1].Scheme 1 shows CPM structure. Several analytical techniques have been suggested for the determination of CPM in drug formulations or in biological samples such as spectrophotometry[2],high–performance liquid chromatography[3-6],capillary electrophoresis[7],mass-spectrophotometry[8-9], and chemiluminescence[10] .However, these methods have some disadvantages: The sample preparation process is time-consuming, the analysis takes a long time, the use of solvents is expensive , and they require costly devices and maintenance. Compared to other analytical methods mentioned above, the electrochemical methods on

the basis of chemically modified electrodes are widely used since they are simple, rapid, highly accurate, less expensive, and since they have a wide range of detection.

We have electrochemical methods on the basis of chemically modified electrodes with various types of mediators ,such as the carbon paste electrodes [11-14] which can be modified , and the electrodes which are modified with nanoparticles and Carbon nanotubes [15] .Carbon electrodes (CNT) have been largely used because of high sensitivity, quick response, extremely their high mechanical strength, high electrical conductivity , and compatibility with various types of modifiers[16-17].Since Iijima discovered the carbon nanotubes (CNTs) in 1991 by means of the transmission electron microscopy[18] ,CNTs have received considerable attention in electrochemistry due to their novel structural, magnetic, electronic , optical, and chemical properties [19-20].In recent years, due to its strong antifouling property, high sensitivities, and low detection limits ,the electrode surface modification has been tried with multiwalled carbon nanotubes (MWCNTs) as a means to reduce the overvoltage and facilitate the electron transfer kinetics [21-23].Several studies have used the MWCNTs modified electrodes for the determination of a number of biological species in various analyses [24-27].

The present study uses a simple and rapid method to fabricate the glassy carbon modified electrode with MWCNTs. Moreover, cyclic and differential pulse voltammetric techniques have been used to estimate the electrochemical behavior of chlorpheniramine maleate (CPM) on the modified electrode and for the determination of chlorpheniramine maleate (CPM) in human blood serum samples on glassy carbon modified electrode with MWCNTs (MWCNT-GCE).

2. EXPERIMENTAL

2.1. Apparatus and chemicals

A potentiostat / galvanostat (BHP- 2063, electroanalyzer system, Behpajooh, Iran) was used for carrying out the electrochemical experiments. A three electrode cell was used at 25 ± 1°C. A saturated calomel electrode (SCE), a glassy carbon electrode (GCE), and a platinum wire were used as reference, working and auxiliary electrodes, respectively. All electrodes were obtained from AZAR Electrodes. All the electrochemical studies were performed at 25 ± 1°C. A metrohm model 780 pH/mV meter was also used for pH measurements. All of the solutions were freshly prepared with double-distilled water. Multi-walled carbon nanotubes (MWCNTs) with a purity >95%, an outer diameter of 5-10 nm ,and tube lengths of~ 30 μm were obtained from Shenzhen Nanotech Port Co., Ltd. (Shenzhen, China). SEM (scanning electron microscopy) was used for the investigation of the morphological specification of the modified electrode with the carbon nanotube. Buffer solutions were prepared from acetate buffer solutions (pH_s 4, 5), ortho-phosphoric acid, and its salts (pH_s 6, 6, 7, 8, 9, 10, 11, 12) as supporting electrolytes.

The chlorpheniramine maleate was of analytical grade (Fluka). A 1.0×10^{-2} mol L^{-1} stock solution was freshly prepared by dissolving the appropriate, accurate amount of chlorpheniramine

maleate. Other solutions were freshly prepared by sequential dilution of the appropriate stock solution with double distilled water.

2.2. Preparation of MWCNT suspension and modified GCE

The GCE was polished with an alumina fine powder (0.05 μm) in water slurry with a polishing cloth, and then it was washed ultrasonically in ethanol and water in a sequential order.

Briefly speaking, the MWCNTs were added to 5 mL of nitric acid (wt. 65%), the mixture was sonicated for about 3 h so that it can obtain a relative stable suspension. and then they were washed with twice-distilled water and dried at room temperature. The purified MWCNTs were dispersed in N, N-dimethylformamide (0.2 mg mL^{-1}) by means of ultrasonic agitation so that a relative stable suspension can be obtained. The cleaned GCE was coated by casting 40μL of the black suspension of MWCNTs and dried in oven at 60 ◦C as reported in the literature [26-27].The microscopic areas of the bare GCE and the MWCNT-modified GCE were evaluated by cyclic voltammetry by 1mM K_3 Fe $(CN)_6$ solution in 0.1 M KCl as a probe at different scan rates [27].For a reversible process, the Randles- Sevcik equation is used:

$$i_{pa} = 2.69 \times 10^5 n^{3/2} A C_0 D_R^{1/2} v^{1/2} \quad (1)$$

Where i_{pa} refers to the anodic peak current, A is the surface area of the electrode, n is the electron transfer number, D_R is the diffusion coefficient, C_0 is the concentration of K_3 Fe $(CN)_6$, and v is the scan rate. For 1mM K_3 Fe$(CN)_6$ in the 0.1 M KCl electrolyte, n =1,D_R =7.6 × 10^{-6} cm^2 s^{-1} , from the slope of the i_{pa} –$v^{1/2}$ relation, the surface area of electrodes can be calculated.

In bare GCE, the electrode surface was 0.0314 cm^2, and in MWNT-modified GCE the surface was 4.3 times greater.

2.3 Analytical procedure

The MWCNT-modified GCE was first activated in phosphate buffer (pH 10.0) by cyclic voltammetric sweeps from +0.3 to +1.2 V until a stable cyclic voltammogram was obtained. Then, in a typical experiment, the electrodes were immersed in a solution containing CPM and buffer (pH 10.0). The potential was swept from +0.3 to +1.2V versus SCE with a scan rate of 50mVs^{-1}. The experiment was repeated in the presence of CPM as the sample solution.

2.4 Preparation of real samples

The amount of chlorpheniramine maleate (2 mL, 0.01 mol L^{-1}) spiked in the blood serum sample was centrifuged and the supernatant was diluted 50 times with water without any further pretreatment. Then, 2.0 mL of the solution plus 17.0 mL of the buffer (pH 10.0) were used for the analysis with standard addition method. Quantitations were performed by means of the calibration curve method from the related calibration equations.

3. RESULTS AND DISCUSSION

3.1. Electrochemical behavior of chlorpheniramine maleate on GCE and MWCNT modified electrode

Figure 1 shows the morphology of the MWCNT-modified GCE. As it can be seen, a uniform film of the MWCNT was immobilized on the surface of glassy carbon, and most of them were in the form of small bundles or single tubes. Moreover the SEM image reveals that the porous MWCNT film has a large surface area.

The electrochemical behavior of CPM on a bare glassy carbon electrode and the MWCNT-modified GCE were examined in the absence (curve a, c) and presence of (curve b, d) 0.5mM CPM (pH 10), respectively by means of cyclic voltammetry. Figure 2 shows no oxidation peak neither on a bare glassy carbon electrode nor on the MWNT-modified GCE in the absence of CPM (the curves a and b), but the curves (c) and (d) can exhibit the voltammetry response of the two anodic peaks observed in the presence of CPM. It can be seen that the increase in the peak current at the modified electrode due to the presence of MWCNT on the glassy carbon electrode speeds up the electron transfer between CPM and the modified electrode.

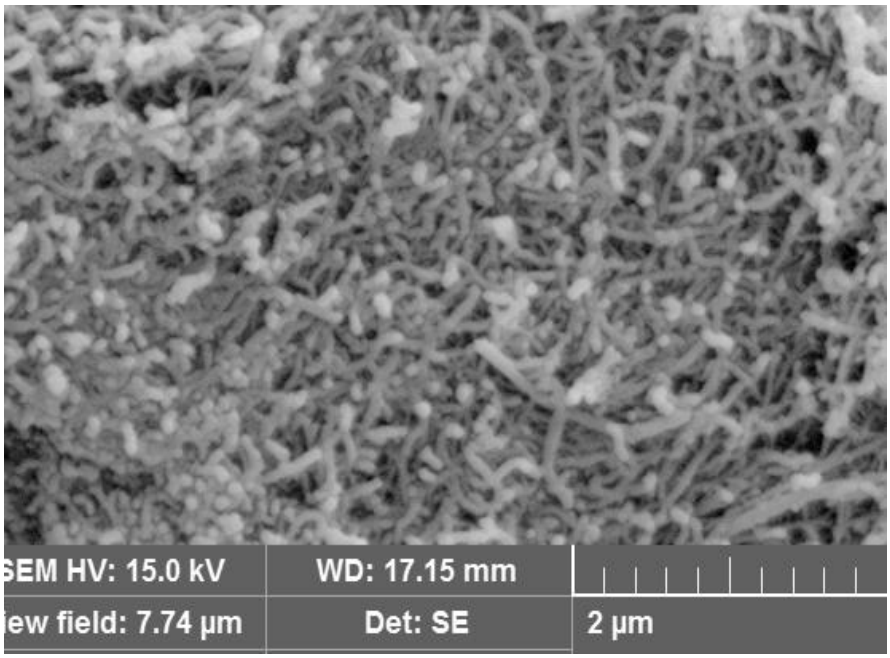

Figure 1. SEM image of the MWCNT-film modified electrode

The effect of scan rate (υ) on the electrochemical response of 0.5mM CPM at the MWCNT-modified GCE in a buffered solution of pH 10.0 at different potential sweep rates was also studied by the cyclic voltammetry (Fig. 3A). The plot of square root of scan rate ($\upsilon^{1/2}$) versus peak current in the range of 10 to 100 mVs^{-1} indicated a linear relationship, which is a characteristic of a diffusion-controlled process, and the corresponding equation can be expressed as:

$$I\ (\mu A) = 24.905\ \upsilon^{1/2}\ (mV\ s^{-1}) - 55.475\ (R^2 = 0.9915)$$

(Fig. 3B). Moreover, it can be seen that, by increasing the scan rate, the anodic peak potential shifts toward positive potentials, suggesting a kinetic limitation in the reaction between redox sites of the MWCNT-modified GCE and CPM.

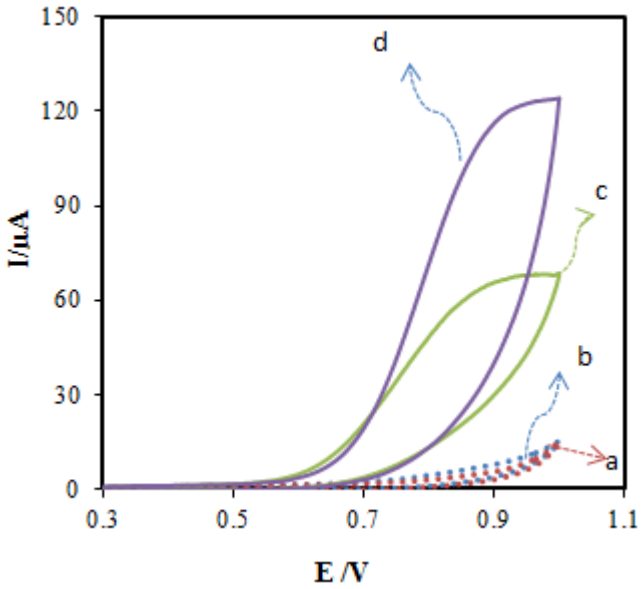

Figure 2. Cyclic voltammogram in the absence (a, b) and in the presence (c, d) of 0.5 mM CPM at the MWCNT-modified GCE in phosphate buffer solution pH 10 at a scan rate of 50mVs^{-1}.

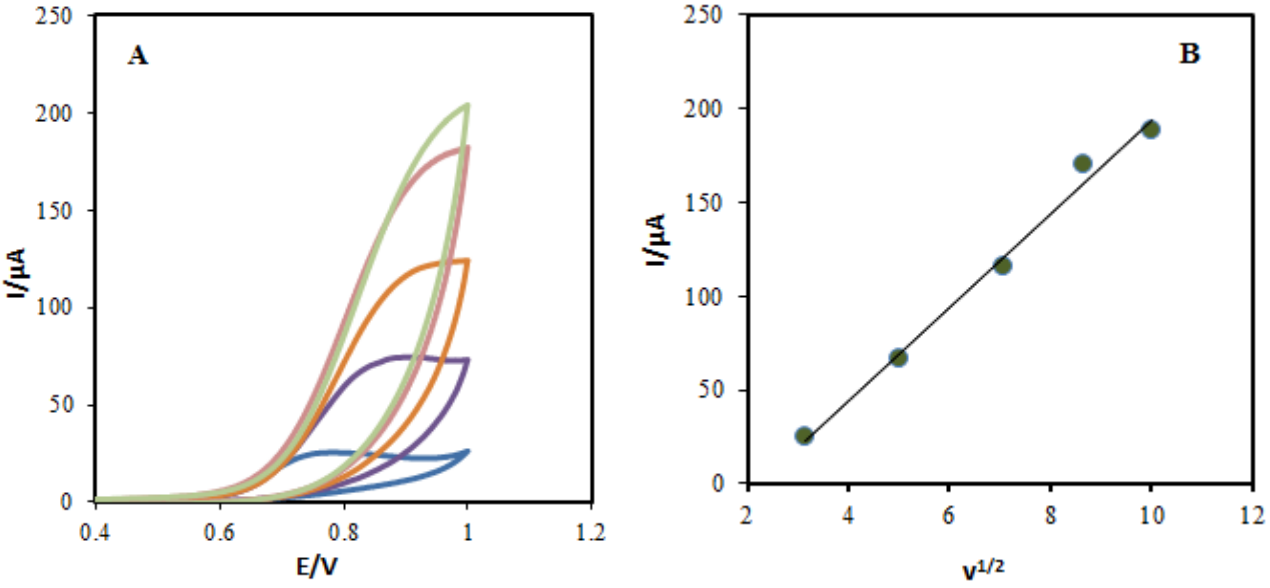

Figure 3. (A) Effect of the scan rates on the cyclic voltammetric responses in buffer solution of pH 10 at the MWNT-modified GCE for 0.5mM CPM at various scan rates (from 10 to 100): 10, 25, 50, 75, and 100 mV s^{-1}. (B) The relationship of anodic peak currents and the scan rate for CPM (0.5mM).

The effect of pH on the current response of a 0. 5 mM CPM at the MWCNT-modified GCE was investigated in the pH range from 6.0 to 11.0 by cyclic voltammetry (Fig. 4A). Fig.4B shows that the anodic peak current (Ipa) increases gradually as pH increases up t o pH = 10.0. Then, the anodic peak current (Ipa) decreases, and for this reason, it was chosen for the determination of the drug. At the same time, the oxidation peak potentials shifted from more positive potential to negative potential as pH increases.

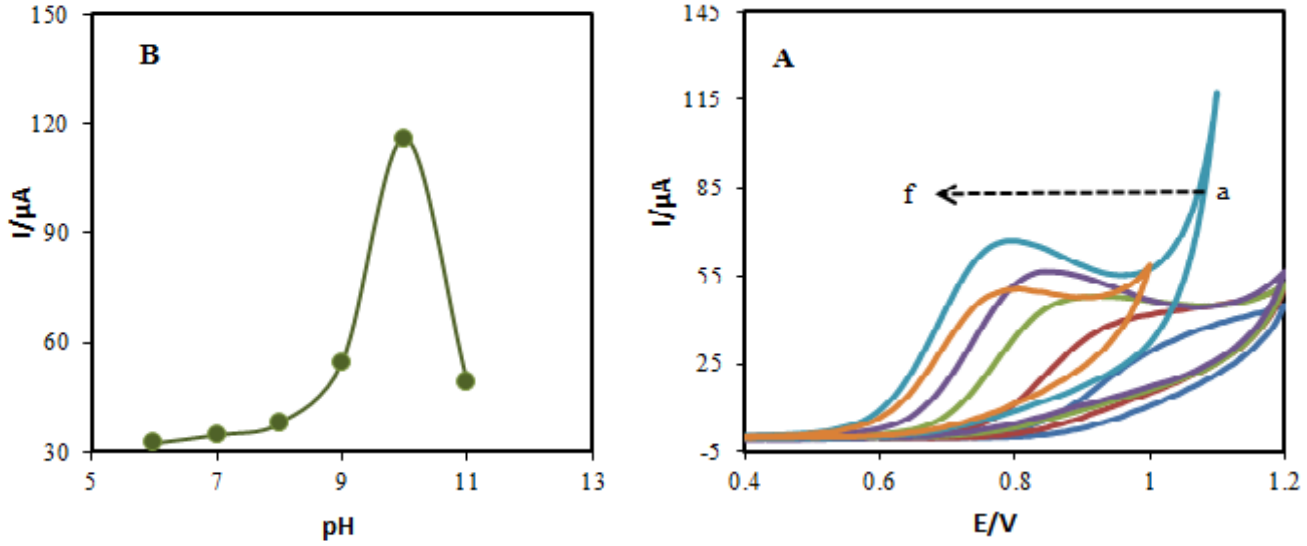

Figure 4. (A) Cyclic voltammograms of 0.5m M CPM at the surface of the MWNT-modified GCE immersed in in phosphate buffer solution PH 6-11, scan rate 50 mV/s; (B) variation of anodic peak potential vs. various pH values in 0.5 mM CPM.

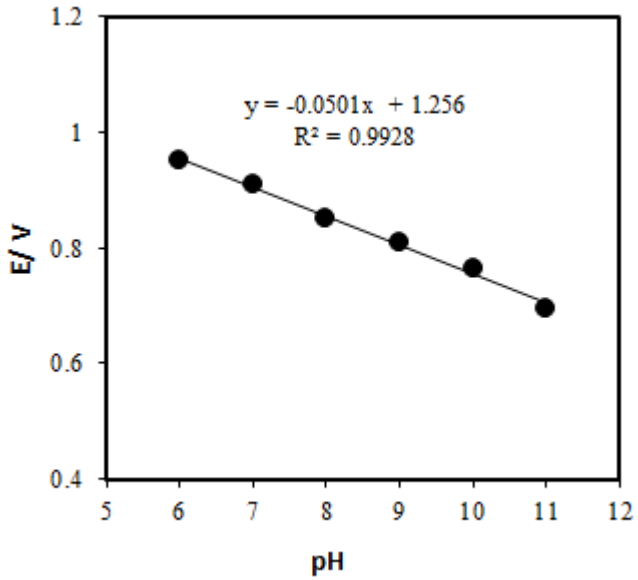

Figure 5. Effect of buffer pH on the oxidation peak potential (Epa). Conditions are the same as in Fig. 4.

Therefore, the mechanism of the electrode reaction is dependent on pH. As Fig. 5 shows, the plot of Epa vs. pH has a slope of −0.0501V, which is close to the theoretical value of 59 mV/pH [28], indicating that the number of electrons and protons involved in the reaction mechanism is the same, containing one electron with one proton in the rate determining step, which is consistent with literature reports [11, 13, 29-31].

3.2. Electrochemical determination of chlorpheniramine maleate (CPM)

The differential pulse voltammetry (DPV) technique commonly has a higher sensitivity toward CV.Therfore; it was possible to apply this technique for the quantitative detection of CPM at MWCNT-modified GCE under the optimum conditions with a scan rate of 50 mVs^{-1}. Fig. 6A shows a differential pulse voltammetry (DPV) response to the addition of CPM. Based on the results, a well defined response was observed during the successive addition of CPM. As it can be seen, the response current is linear in the CPM concentration range of 5 µM to 500 µM, with the linear equation Ipa/ µA = 0.3322 [CPM] / µM + 10.127 and R^2 = 0.9921(Fig. 6B).A correlation coefficient of 0.991 was obtained, indicating that the regression line is fitted very well with the experimental data and that the regression equation can be applied in the unknown sample determination.

A detection limit of 1.63 µM was obtained with the calculation based on the definition of LOD = 3sb/m, where sb is the standard deviation of the peak current of the blank (n = 6), and m is the slope of the calibration curve for the determination of CPM.

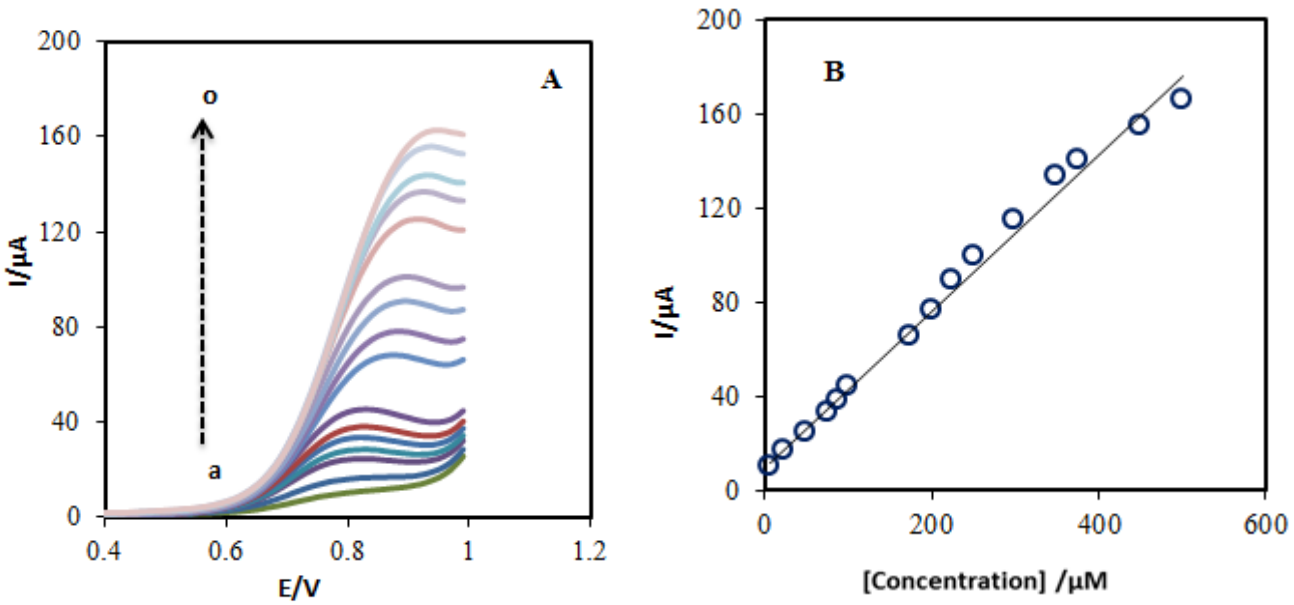

Figure 6 (A) DPVs of 5.0 (a), 23.0 (b), 62.5 (c), 75.0 (d), 87.5 (e), 100.0 (f), 175.0 (g), 200.0 (h), 225.0 (i), 250.0 (j), 300.0 (k), 350.0 (l), 375.0 (m), 450.0 (n) and 500.0 µM CPM on the MWNT-modified GCE under the optimum conditions and a scan rate of 50mVs^{-1}**.** (B) Plot of the peak current in differential pulse voltammetry versus the concentration of CPM.

3.3. Reproducibility and stability of the modified electrode

Repeatability was examined for 5 replicate measurements of 25 μM of CPM and the relative standard deviation (R.S.D.) of 1.86% was obtained. Table 1 shows the comparison of this study and previously reported voltammetric methods for the determination of CPM. As it is seen, the analytical parameters are comparable or better than the results reported for CPM determination at the surface of other modified electrodes.

To evaluate the stability of the MWCNT-modified GCE, it was stored in 0.2 M buffer solution at 4◦C for two weeks. No obvious changes were found in the current response for the same sample concentration. The current responses for the detection of 25 μM of CPM decreased by less than about 5% of the initial response after 1 month. Therefore, the stability of the proposed electrode was good enough for the electrochemical application.

Table 1. Comparison of the results of the proposed method with similar reports

Method	Electrode	Linear range(μmol L^{-1})	Detection limit (μmol L^{-1})	Reference
PM	CPE-ion exchanger	2.0 -12000	0.51	11
DPV	CPE-SDS	1.0 - 800	1.7	13
DPV	CPE-Co nanostructure	0.1-10	0.08	28
SWV	HMDE	0.984 - 9.756	0.984	29
CV	Ru/Pty/GCE*	2 .0-45	0.338	30
DPV	MWCNT-modified GCE	5.0-500	1.63	This work

*PM: Potentiometry, DPV: Differential pulse voltammetry, SWV: Square wave voltammetry, CV: Cyclic voltammetry,

**Sodium dodecyl sulfate

***Ru/Pty/GCE: tris (2, 2’-bipyridyl) Ru (II) complex

3.4. Real sample analysis

Maintaining the same experimental conditions, human blood serum samples were tested by measuring the concentration of CPM. The standard addition technique was used for the determination of CPM in human blood serum samples. The recovery of CPM from human blood serum was measured by the injection of drug with a known amount of CPM. Table 2 shows the results obtained for CPM analysis in human blood serum plasma. These results indicate that the proposed sensor

provides a potential tool for the determination of CPM in real samples with good recoveries and good reproducibility.

Table 2. Determination of Chlorpheniramine maleate in human serum samples under the optimum conditions (n = 5).

Sample concentration	Added (μM)	Found (μM)	Recovery (%)
Plasma	100	98.4 ±0.5	98.4
Plasma	125	120.3 ±0.2	96.0
Plasma	150	150.1 ±0.3	100.0

3.5. Interference study

The present study evaluated the effect of various substances on the determination of 100 μM chlorpheniramine maleate under optimal conditions. The tolerance limit was taken as the maximum concentration of the interfering substance that caused an error of less than 5% for CPM determination .The results indicated that the presence of these coexisting species had no significant interference on the current response of 100 μM CPM (Table 3).

Table 3. Interference of some foreign species on the determination of 100.0 μM CPM under the optimized conditions.

Foreign species	Tolerant limits ($W_{substance}/W_{CAP}$)
Lactose ,sucrose, glucose, sodium benzoate ,fructose	100
starch, citric acid	10

4. CONCLUSION

In summary, we have demonstrated the oxidation behavior of CPM on the MWCNT-modified GCE. This modified electrode significantly improved the electrochemical response of CPM, and it clearly demonstrates the excellent electrocatalytic activity of the MWCNT-GCE toward the oxidation of CPM. Under the optimum conditions, the results indicate that the oxidation peak current was proportional to CPM concentration in the range of 5-500 μM with the detection limit being 1.63 μM. Therefore, the modified electrode was successfully applied to the highly sensitive detection of CPM in the real samples.

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