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ORIGINAL ARTICLE

Glassy carbon electrode modified with multi-walled carbon nanotubes sensor for the quantification of antihistamine drug pheniramine in solubilized systems

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Solubilized systems;
Voltammetric quantification

Abstract A sensitive electroanalytical method for quantification of pheniramine in pharmaceutical formulation has been investigated on the basis of the enhanced electrochemical response at glassy carbon electrode modified with multi-walled carbon nanotubes in the presence of sodium lauryl sulfate. The experimental results suggest that the pheniramine in anionic surfactant solution exhibits electrocatalytic effect resulting in a marked enhancement of the peak current response. Peak current response is linearly dependent on the concentration of pheniramine in the range 200–1500 μg/mL with correlation coefficient 0.9987. The limit of detection is 58.31 μg/mL. The modified electrode shows good sensitivity and repeatability.

1. Introduction

Pheniramine (as maleate salt) is a member of alkylamine class of H_1 receptor antagonists. Its chemical name is N,N-dimethyl-3-phenyl-3-(pyridin-3-yl)propan-1-amine (Fig. 1). It is one of the most significant antihistamine used in the treatment of allergic conditions including urticaria and angioedema [1–3].

Surfactants play an important role in micelles formation, which leads to solubilization. It was shown that cationic, anionic and non-ionic surfactants could also be used to improve the accumulation of some electro-active organic molecules at electrodes. It has been seen that surfactants have great significance in electrode reactions, not only in solubilizing organic compounds but also by providing specific orientation of the molecules at the electrode surface [4] and are widely used in electrochemical investigations [5–8]. Recently, nanoparticles have been used as modifier in chemically modified electrode for analysis of drug molecules, metals and ions. Carbon nanotubes (CNTs) are most important nanomaterials due to their high mechanical strength [9], high surface area [10] and high

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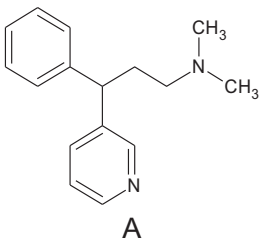

Figure 1 Chemical structure of pheniramine.

chemical stability [11]. Multi-walled carbon nanotubes (MWCNTs) are now considered important modifiers due to their ability to promote electron transfer in electrochemical reactions, improve sensitivity and chemical inertness [12–19], other modifier and different types of surfactants are also used for electrochemical studies [20–25]. In this study, glassy carbon electrode modified with multi-walled carbon nanotubes (GCE-MWCNTs) was fabricated to improve the limit of detection. The resulting GCE-MWCNTs prepared by solution evaporation method in the presence of sodium lauryl sulfate (SLS), exhibited good performance for electrochemical reduction of pheniramine.

2. Materials and methods

2.1. Reagents and chemicals

Pheniramine standard (99% purity) was obtained as a gift from Veeda Clinical Research Pvt. Ltd. (India). Tablets containing pheniramine maleate (Avil® 50) manufactured by Aventis pharma limited in India, labeled 50 mg were obtained from commercial sources. Ultra pure water, obtained from Milli-Q purification system (Millipore Corp., Milford, MA, USA) and double distilled water from distillation assembly, was used throughout the studies. MWCNTs were obtained from Aldrich with o.d. = 10–20 nm, i.d. = 5–10 nm, 0.5–50 μm tube length and purity was 95%. Other chemicals were of analytical grade, and were used as received. All of the procedures were carried out at room temperature.

2.2. Instrumental conditions

Electrochemical measurements were performed using a μ Autolab Type III (Eco-Chemie B.V., Utrecht, The Netherlands) potentiostat–galvanostat with 757 VA computrace software. The utilized electrodes were GCE-MWCNTs as working electrode, a saturated calomel electrode (SCE) as a reference electrode, and a platinum electrode as an auxiliary electrode. All pH measurements were made on a Decible DB-1011 digital pH meter fitted with a glass electrode and a saturated calomel electrode as reference, which was previously standardized with buffers of known pH. All the solutions were purged by high purity nitrogen gas for deaeration and electrochemical cell was kept under nitrogen throughout the experiments.

2.3. Pharmaceutical preparation

Twenty tablets were weighed and the average mass per tablet was determined and crushed using mortar pestle to a fine powder. Sufficient amount of powder for the preparation of a stock solution was weighed and transferred in 200 mL beaker containing 100 mL solvents or surfactants solution. It is then mixed using a magnetic stirrer. Solution was sonicated for 15 min and again transferred in conical tubes for centrifugation at 3500 rpm for 5 min. An aliquot of the solution was then analyzed according to the proposed voltammetric procedure.

2.4. Preparation of MWCNTs suspension and modified glassy carbon electrode

10 mg MWCNTs was dispersed in 10 mL N,N-dimethylformamide (DMF) and sonicated in an ultrasonic bath for 30 min to obtain a stable suspension. Glassy carbon electrode (GCE) surface was cleaned mechanically by polishing with 0.3–0.05 μm alumina in water slurry on microcloth pads. Adherent Al_2O_3 particles were removed from the electrode surface by rinsing with double distilled water. It is then sonicated in methanol:water (50:50, v/v) solution and further rinsed with double distilled water and dried the GCE surface in a stream of hot air (40 °C). The GCE-MWCNTs was prepared by coating of 8 μL MWCNTs suspension on the GCE using a micropipette and left to dry at room temperature.

3. Results and discussion

Electrochemical behavior of pheniramine at GCE-MWCNTs was studied using square-wave (SW) and cyclic voltammetry (CV). In the present studies pheniramine gave one well-defined cathodic peak in surfactant media, which may be assigned to the reduction of –C=N– bond of the pyridine ring at GCE-MWCNTs.

3.1. Surface characterization of GCE-MWCNTs

The morphological studies of the GCE-MWCNTs were carried out by scanning electron microscopy (SEM) using Philips SCI

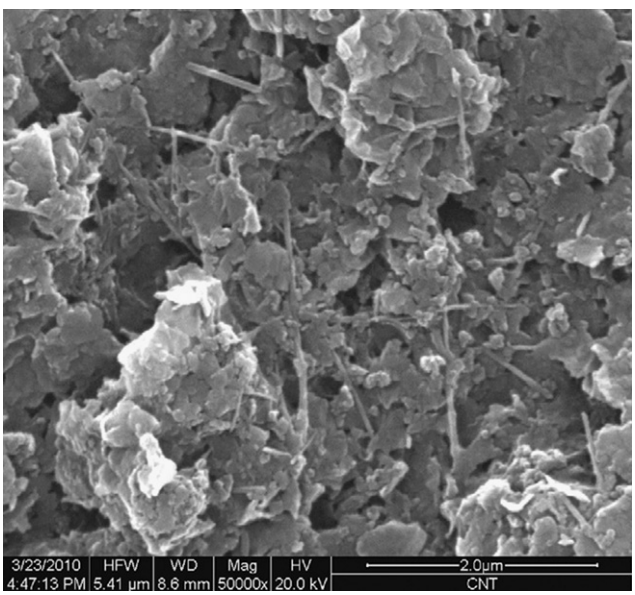

Figure 2 Scanning electron micrograph of GCE-MWCNTs.

quanta 400 instrument. Scanning electron micrograph is shown in Fig. 2. In the figure MWCNTs could be seen in the form of tubes some of which twisted together. MWCNTs with an average diameter of approximately to 200 nm were observed on the GCE-MWCNTs surface. The modification of glassy carbon electrode using multi-walled carbon nanotubes not only enlarges the ratio surface area of the electrode surface but also improves the electron transfer rate between the electrode surface and the bulk solution.

3.2. *Response enhancement effect in different types of solubilized system*

Comparative voltammetric response of pheniramine in organic solvents (ethanol, methanol, DMF and Dioxane), water and in different surfactants such as cetyltrimethyl ammonium bromide (CTAB), Sodium lauryl sulfate (SLS) and Tween-20 is depicted in Fig. 3. It is clear from the Fig. 4 that the square-wave voltammetric peak current response of pheniramine is maximum in anionic surfactant (SLS). It is also observed that the critical micelle concentration (CMC) reached at concentration 950 μg/mL of SLS.

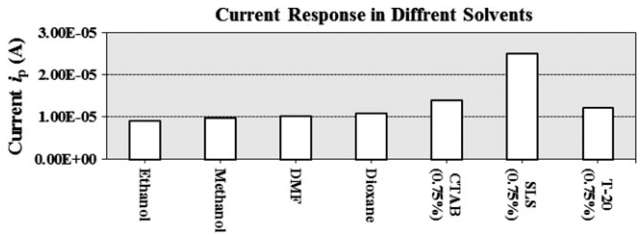

Figure 3 Peak current response i_p (A) comparison of pheniramine (950 μg/mL) in different media (ethanol, methanol, DMF, Dioxane, 0.75% CTAB, 0.75% SLS, and 0.75% Tween-20).

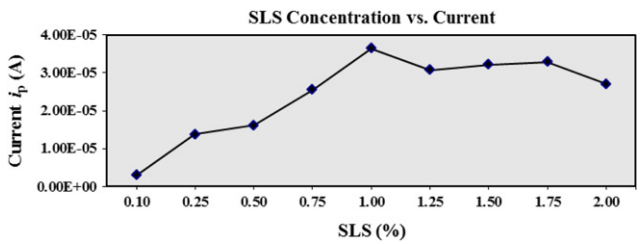

Figure 4 Effect of SLS concentration on square-wave peak current response of 950 μg/mL pheniramine.

3.3. *Electrocatalytic reduction of pheniramine at GCE-MWCNTs*

The electrochemical responses of cyclic (CV) and square-wave voltammograms (SWV) of pheniramine at bare GCE and GCE-MWCNTs in phosphate buffer solution of pH 5.3 are shown in Fig. 5. Reduction peaks were observed at −1.49 V and −1.54 V and at −1.46 V and −1.51 V, for bare GCE and GCE-MWCNTs, respectively. It is observed that the peak current response of the pheniramine improved at the GCE-MWCNTs with a shift in the peak potential by about 300 mV towards the positive values and an improvement in the peak current as compared with that at a bare GCE. On the basis of these observations, it is clear that addition of MWCNTs exerts a significant catalytic effect on the electrochemical reduction of pheniramine leading to decrease of overpotential in the process and enhancement of the peak current is observed. The reason for the better performance of the GCE-MWCNTs is due to the nanometer dimensions of the MWCNTs, electronic structure and topological effects of MWCNTs surface [26]. Comparison of peak current response and peak potential at both electrodes is shown in Table 1. A similar experiment was carried out using acetate buffer or Britton–Robinson buffer. But the background current of GCE-MWCNTs in acetate buffer or Britton–Robinson buffer was large. Therefore, phosphate buffer solution of pH 5.3 was selected.

3.4. *Effect of varying volume of MWCNTs*

The previous studies on the electrochemical behavior of MWCNTs-GCE also support the observation that the kinetics of the electrode processes and sensitivity of the measurements improves on this electrode [27,28]. The effect of varying volume of saturated MWCNTs coated GCE surface ranging from 4.0 to 12.0 μL was studied. Fig. 6 shows that the use of increasing MWCNTs volume is associated with an increasing reduction peak current of pheniramine up to 8 μL and after that peak current decreases inversely due to large background current. This is related to the thickness of the film. If the film is too thin,

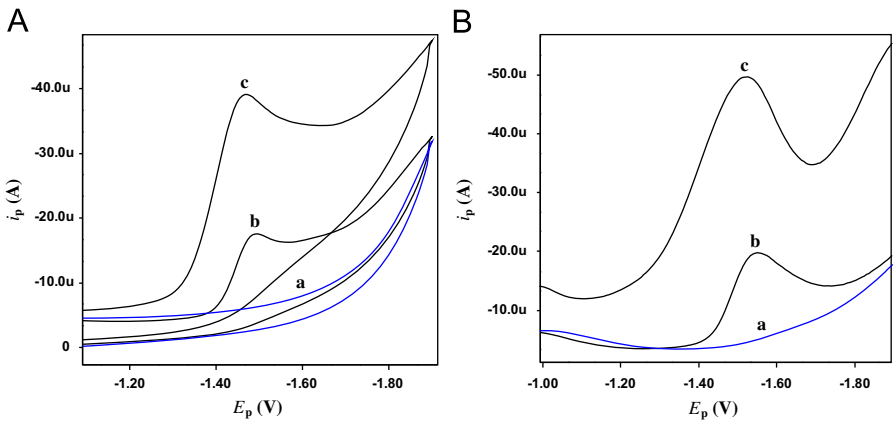

Figure 5 Electrocatalytic effect of GCE-MWCNTs on 200 μg/mL pheniramine voltammograms (A) CV and (B) SWV; in 1% SLS (pH 5.3); scan rate 100 mV/s; at: (a) Blank, (b) GCE, and (c) GCE-MWCNTs.

Table 1 Comparison of square-wave and cyclic voltammetric response of pheniramine in 200 μg/mL SLS solution and GCE-MWCNTs.

Electrodes	SWV		CV	
	Peak current (i_p, μA)	Peak potential (E_p, V) vs. Ag/AgCl	Peak current (i_p, μA)	Peak potential (E_p, V) vs. Ag/AgCl
Bare GCE	1.75	–1.54	0.85	–1.49
GCE-MWCNTs	4.71	–1.51	3.52	–1.46

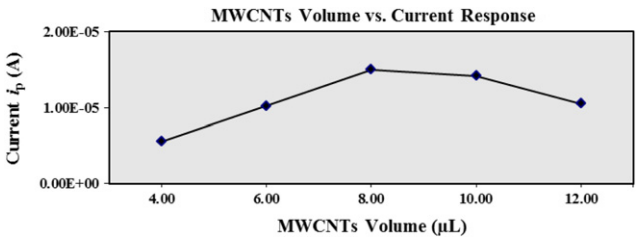

Figure 6 Effect of accumulation volumes of MWCNTs on peak current response of 470 μg/mL pheniramine.

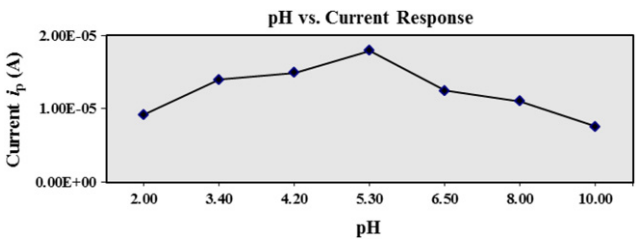

Figure 7 Effect of pH on peak current response of 470 μg/mL pheniramine in phosphate buffer (pH 2.0–10).

the amount of pheniramine adsorbed is small, resulting in a small peak current. When it is too thick, the film conductivity gets reduced and the film becomes unstable as MWCNTs could leave off the electrode surface. Thus, it blocks the electrode surface and hence the peak current decreases. Therefore, 8 μL MWCNTs volume is the optimized experimental condition in the present study.

3.5. *Effect of pH*

The peak potential and peak current of mentioned peaks closely depend on the pH of the buffer solution. The pH of phosphate buffer has a significant influence on the reduction of pheniramine. The pH effect was studied in the range 2.0–10 at scan rate of 100 mV/s (Fig. 7). The cathodic peak current (i_p) reaches maximum value at pH 5.3, after that it decreases.

3.6. *Effect of scan rate*

The voltammetric investigations at various scan rates for pheniramine determination were performed under the optimum conditions. As the scan rate increases gradually from the range 10 to 120 mV/s at fixed concentration of pheniramine, the background signal increases and peak potential is shifted towards a more negative value with increase in current confirming the irreversible nature of the reduction process [29]. The signal-to-noise ratio was maximum at scan rate of 100 mV/s. Therefore, 100 mV/s was chosen in the present study.

3.7. *Repeatability of GCE-MWCNTs*

The repeatability of the modified electrode was investigated by replicate recordings of voltammogram at a fixed pheniramine concentration of 470 μg/mL. The coefficient of variance (%CV) for the peak currents in SWV based on six replicates is 1.29%, indicating an excellent repeatability of the response at GCE-MWCNTs. Also, inter-day variation of same concentration of pheniramine was analyzed for three consecutive days by performing six measurements on each day. The average %CV value is 1.98%, which demonstrates good repeatability of the method at modified electrode (Table 2).

3.8. *Calibration curve and detection limit*

In order to develop a voltammetric method for determining the drug, square-wave voltammetric method was selected, because the peaks are better defined at low concentration. The square-wave peak current at modified electrode significantly increased accompanied with a decrease in potential in its reduction peak. The relationship between the reduction peak current and the concentration of pheniramine was examined at the surface of GCE-MWCNTs by least square regression method [30]. Under the previous mentioned optimum conditions, the reduction peak currents were proportional to the pheniramine concentrations over two intervals in the range of 200–1500 μg/mL in phosphate buffer solution of pH 5.3 (Fig. 8). The linear regression equation was obtained as $i_p = 0.0423 \times -2.6763$ ($r^2 = 0.9987$). The detection limit (LOD) ($3\sigma/s$, where σ is the standard deviation of the intercept and s is the slope of the calibration curve) observed for the pheniramine is 58.31 μg/mL.

3.9. *Recovery*

To check the interference from excipients present in pharmaceutical formulation, recovery experiments were carried out in the presence of some common excipients (e.g., starch, lactose, cellulose and magnesium stearate) added in the same ratio as in pharmaceutical preparation [31]. The recovery study was performed in the concentration range 200–1500 μg/mL as per experimental conditions. The recoveries vary in the range 97–99.6% and the cofficient of variance (%CV) is ±1.72%. The data showed that there was no interference of excipients in the analysis of pheniramine in pharmaceutical formulation.

Table 2 Repeatability experiment at GCE-MWCNTs with 200 μg/mL pheniramine.

Time	Inter-day repeatability		Intra-day repeatability	
	Average current (i_p, μA)	Coefficient of variance (% CV)	Average current (i_p, μA)	Coefficient of variance (% CV)
Day 1	5.52[a]	1.29	5.52[a]	1.29
Day 2	5.20[a]	1.84		
Day 3	4.74[a]	2.80		
Average	**5.15**[b]	**1.98**[b]		

[a]Average of six replicates readings.
[b]Average of three consecutive days readings.

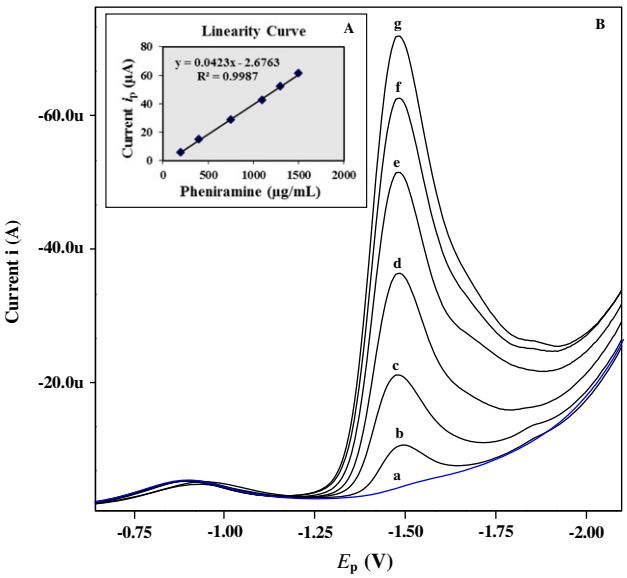

Figure 8 (A) Plot of current vs. different concentrations of pheniramine in 1% SLS (pH 5.3). (B) Calibration of square-wave voltammetric peak current response of pheniramine at different concentrations in 1% SLS (pH 5.3); (a) Blank, (b) 200 μg/mL, (c) 400 μg/mL, (d) 750 μg/mL, (e) 1100 μg/mL, (f) 1300 μg/mL and (g) 1500 μg/mL.

3.10. Application of the proposed method for quantification of pheniramine in pharmaceutical formulation

The developed procedure could be applied successfully for the quantification of pheniramine in commercial pharmaceutical dosage forms (Avil® 50) at GCE-MWCNTs. Voltammograms of pheniramine in SLS exhibit very well-defined cathodic peak. The quantitative analysis of the drug was based on the dependence of the cathodic peak current on the concentration of pheniramine. The current is proportional to the concentration over a convenient range (200–1500 μg/mL) with good correlation coefficient (r^2=0.9987).

4. Conclusion

The surface modification of the electrode alters its characteristics in such a way that the electrode performance gets improved. GCE-MWCNTs shows electrocatalytic nature and this behavior is attributed to higher surface activity of MWCNTs because of the presence of more surface area in comparison to regular size material. In the present work, the modified electrode showed an excellent electrocatalytic activity in lowering the cathodic over-potential and remarkable enhancement of cathodic current of pheniramine in SLS as compared with electrochemical performances obtained at bare GCE. The modified electrode has good operating characteristics like sensitivity, repeatability, low detection limit and wide linearity range. Hence, an excellent approach towards the development of GCE-MWCNTs has been presented for determination of pheniramine in the presence of solubilized system. In this case, a low current cathodic peak was observed at bare GCE. However, at the modified electrode the peak current gives significant increase accompanied with a positive shift in its reduction peak potential approximate to 300 mV.

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