Materials Sciences and Application, 2011, 2, 957-963
doi:10.4236/msa.2011.28128 Published Online August 2011 (http://www.SciRP.org/journal/msa)

A Study on Preparation and Use of Nano Poly Pyrrole and Nano Poly (3,4-Ethylenedioxythiophene) Coated Glassy Carbon Electrode for the Determination of Antihistamine in Pharmaceutical and Urine Sample

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Received September 25th, 2010; revised December 30th, 2010; accepted May 17th, 2011.

ABSTRACT

Pheniramine maleate (*PA*), *an antihistamine, was determined by Differential Pulse Stripping voltammetry using nano polypyrrole* (*Ppy*) *and nano poly* (3,4-*ethylenedioxythiophene*) (*PEDOT*) *modified glassy carbon electrodes. The cyclic voltammetric behavior of pheniramine was studied in aqueous acidic, neutral and alkaline conditions. One well-defined oxidation peak was observed in the cyclic voltammograms at all pHs. The influence of pH, scan rate and concentration revealed irreversible electron transfer and the oxidation was diffusion controlled adsorption. The SEM analysis confirmed good accumulation of PA on the electrode surface. A systematic study of influence of various experimental parameters that affect the stripping voltammetric response was carried out and the maximum peak current conditions were arrived at. Calibration was made under maximum peak current conditions. The range of study was* 0.05 *to* 0.4 *μg/mL on Ppy/GCE and* 0.025 *to* 0.4 *μg/mL on PEDOT/GCE and the lower limit of determination were* 0.035 *μg/mL on Ppy/GCE and* 0.016 *μg/mL on PEDOT/GCE. The suitability of the method for the determination of PA in pharmaceutical preparations and urine samples was also ascertained.*

Keywords: *Pheniramine maleate*, *Cyclic voltammetry*, *Stripping voltammetry*, *Nano polypyrrole*, *Nano poly* (3,4-*ethylenedioxythiophene*)

1. Introduction

Pheniramine maleate (PA), an antihistamine used to treat allergic conditions such as hay fever or urticaria, has relatively strong sedative effects. Because of this, the determination of PA becomes important. High-performance liquid chromatographic method for the quantitative determination of PA in plasma has been developed and validated by El-Sayed *et al.* [1]. Stability tests showed that PA was stable for at least 3 weeks in plasma after freezing. The chromatographic determination of antihistaminic drugs, loratadine and PA from human serum was also developed [2]. Thin-layer chromatography densitometry was used to separate, identify and quant ate chlorpheniramine maleate and PA when present in combination with other drugs in pharmaceutical preparations of tablets, syrups, eye and ear drops, etc. [3]. A new chemiluminescence method, using flow injection, was described for the determination of diphenhydramine hydrochloride and chlorpheniramine maleate [4].

Several high performance liquid chromatographic procedures have been developed for the determination of chloropheniramine maleate in commercial pharmaceutical preparations [5-7] and derivative spectrophotometry

[7-9]. A micellar electrokinetic chromatographic method has also been described for simultaneous determination of paracetamol and chlorpheniramine maleate [10]. High-pressure liquid chromatograph using an intermediate polarity column was reported for the determination of four antihistamines such as brompheniramine maleate, chlorpheniramine maleate, PA and pyrilamine maleate in combination has been discussed. The potentiation of apomorphine-induced gnawing by antihistamines might depend upon the reciprocal balance between dopaminergic and cholinergic systems. High-pressure liquid chromatographic determination of methscopolamine nitrate, phenylpropanolamine hydrochloride, pyrilamine maleate, and pheniramine maleate in tablets was also developed. Enantioselective determination of PA in pharmaceuticals by capillary electrophoresis with charged cyclodextrin was studied by Peter Mikus *et al*. [11]. Analysis of enantiomers in biological matrices by charged cyclodextrin-mediated capillary zone electrophoresis in column-arrangement with capillary sotachophoresis has been discussed [12]. Cyclodextrin-mediated capillary isotachophoresis in cationic regime of the separation has also been developed for the separation and quantitation of alkylamine antihistamine dimethindene and pheniramine enantiomers in various pharmaceutical preparations [13]. Simultaneous determination of pseudoephdrine, pheniramine, guaifenisin, pyrilamine, chlorpheniramine and dextromethorphan in cough and cold medicines by high performance liquid chromatography has been reported [14]. Recently acetaminophen, caffeine and chlorpheniramine maleate in tablet formulations has been simultaneously determined by simple HPLC method [15].

In the past decades, conducting polymer modified electrodes have received great attention due to their excellent characteristics, including high stability and selectivity, good reproducibility and conductivity, more active sites and good homogeneity [16-18]. They are widely applied in many areas, such as molecule or ion recognition [16], electrocatalysis [19], electron transfer [20]. The modified electrode was characterized by electrochemical method [21] and the method proposed was successfully applied to the determination of phenylephrine and chlorprothixene in drug injections or tablets and proved to be reliable compared with ultraviolet spectrophotometry. The application of conjugated polymers as sensor has been exploited as active sensing elements by coupling ligands to the backbone. Here, the binding of an analyte results in physical distortion or changes in electron density, there by altering conductivity [22].

Nanomaterials of conjugated polymers are found to have superior performance relative to conventional materials due to their much larger exposed surface area [23]. Shamsipur *et al.* has been studied nano-structured conducting polymer and its application to the design of reliable scaffolds for impedimetric biosensors [24]. Advancement of in the design of innovative microbicide nanocarriers and nano-enabled microbicides has also been discussed [25].

Electrochemical methods have proved to be highly sensitive for the analysis of drugs in pharmaceutical formulations and human body fluids owing to the simplicity, low cost and relatively short analysis time as compared to the other routine analytical techniques including chromatography. Perusal of literature reveals that there are no publications concerning the electroanalytical determination of pheniramine maleate in pharmaceutical formulations. Therefore, the aim of the present investigation is to investigate the voltammetric behavior of pheniramine maleate in an attempt to develop a simple and reliable electrochemical method for its determination in pharmaceutical formulations and human urine.

2. Experimental

2.1. Apparatus and Reagents

EG&G M 273A Electrochemical Analyzer—Princenton Applied Research Corporation (PARC) was employed mainly for carrying out electroanalytical studies. The pheniramine (PA) was purchased from SIGMA and used. The stock solution was made up in double distilled TKA-LAB purified water. For the electrochemical studies, Britton Robinson buffers, 0.1 mol·dm^{-3} KOH, KCl and H_2SO_4 were used as the medium for the analysis. 3, 4-Ethylenedioxythiophene (Bayer), Pyrrole (AR-Merck) and tetra butyl ammonium perchlorate (Sigma) were used for electropolymerisation.

2.2. Procedure

Purging of nitrogen was done for analyte solution placed in the electrochemical cell of 15 ml capacity for 20 minutes under stirred conditions. Various voltammograms were recorded while nitrogen gas was blanketed. To get reproducible results, great care was taken in the electrode pretreatment. The glassy carbon electrode was pretreated in two ways: mechanical polishing over a velvet micro-cloth with an alumina suspension and electrochemical treatment by applying a potential of 1.5 V for 2 seconds.

2.3. Preparation of Nano Polypyrrole Coated Glassy Carbon Electrode (Ppy/GCE)

Polypyrrole films were deposited on GCE by the electrooxidation of 0.1 M pyrrole in acetonitrile containing 0.1 M tetrabutyl ammonium perchlorate at 0.0 to 0.90 V

(vs. Ag/AgCl) applied potential [26,27]. Thickness of the films was controlled by number of cycles and 0.1. thick films were used in all cases.

2.4. Preparation of Nano Poly (3,4-ethylenedioxythiophene) Coated Glassy Carbon Electrode (PEDOT/GCE)

Poly (3,4-ethylenedioxythiophene) films were deposited on GCE by the electrooxidation of 0.01 M 3,4-ethylene-dioxythiophene in acetonitrile containing 0.1M tetrabutyl ammonium perchlorate (TBAP). The polymerisation of this monomer was carried out voltammetrically by giving multi cycle in the potential range between –0.2 and 1.2 V at 50 mV/s using Ag/AgCl reference electrode [28]. Thickness of the film was controlled colulometrically and 0.1 thick films were used in all cases. The SEM photograph reveals the deposition of nano size (100 nm) PEDOT on GCE.

Care was taken to remove the coating and clean the glassy carbon electrode after every experiment in 1:1 HCl/water and 1:1 H_2O_2/acetic acid mixture before usual surface treatment. Nitric acid (6 M) solution was used to clean the cell.

The electrode stability of polypyrrole, PEDOT modified electrode is of prime importance in these studies. The electrode was prepared quickly and found to be stable in the medium. It showed slight decrease in peak current after 15 days of its preparation and thus it is recommended that it should not be used after 15 days because the peak current values start decreasing. The response time of the electrode was very fast and all measurements were carried out easily and quickly.

3. Results and Discussions

3.1. Effect of pH

Effect of pH was studied in detail by choosing thirteen different pH conditions between 1.0 to 13.0. The pH of the supporting electrolyte has a significant influence on the electrooxidation of pheniramine at the modified electrodes. The peak potential and the current were measured by recording cyclic voltammograms at different pHs at a sweep rate, 100 mV/s on nano Ppy/GCE and PEDOT/GCE. The peak potentials showed decreasing trend with pH (**Figure 1**) while the peak current showed increasing trend with pH (**Figure 2**). Since the protonated substrate is oxidised at basic media, the maximum peak current was observed only at pH 13.0. Because of the low energy requirement and high electron transfer rate at pH 13.0, it was considered as the most suitable pH for the electroanalytical studies of pheniramine.

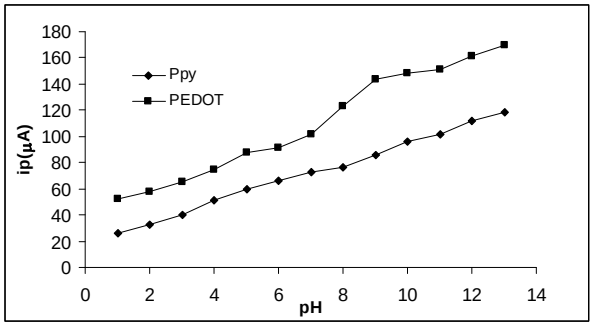

Figure 1. Plot of peak current vs. pH on two different electrodes.

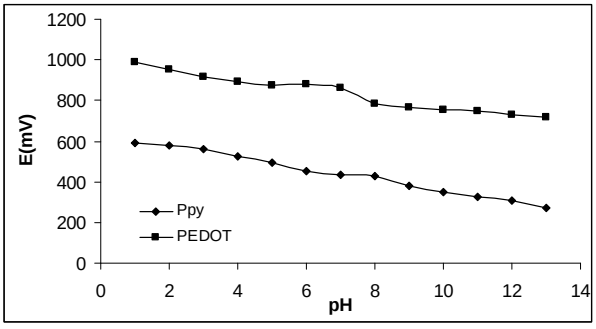

Figure 2. Plot of peak potential vs. pH on two different electrodes.

3.2. Electrochemical Studies of Drug on Modified Electrode

A representative cyclic voltammogram is presented in **Figure 3** on polymer modified GCE. The plot of peak current vs scan rate (showed linear relationship. A straight line with better correlation coefficient was obtained when plotting i_p vs square root of suggesting diffusion-controlled adsorption of PA on both electrodes. Another correlation of log peak current with log scan rate resulted in straight line and slope value obtained is 0.4817 for Ppy and 0.4833 for PEDOT. These values are closer to 0.5 confirming diffusion controlled adsorption. There was no counter peak in the reverse scan and αn value was fractional. Increase in the concentration of PA showed increased peak current and gradual increase in peak potential. The plot of i_p vs. C was also linear. All these studies reveal that the electron transfer taking place in the redox process is irreversible and the oxidation is diffusion-controlled adsorption. Among the two modified systems, the PEDOT/GCE was selected as a better electrode system for the electroanalytical determination of PA due to higher peak current.

3.3. Rate Constant

The standard rate constant k_s was calculated from the

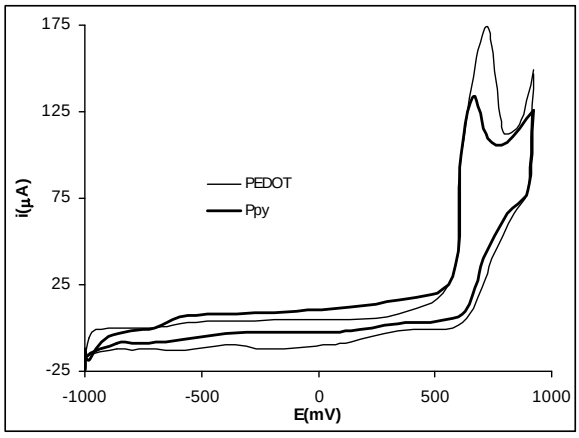

Figure 3. Cyclic voltammogram of 250 mg/mL PA on different electrode at pH 13.0; scan rate 100 mV/s.

slope of log i_p vs $E - E_i$ plot by employing the following equation.

$$i_p = nFACk_s \exp [-\alpha n/RT(E - E_i)]$$

where i_p = peak current in A, n = number of electrons transferred, F = Faraday constant, 96487 C, A = area of the electrode in cm^2, C = concentration of the analyte, moles/cm^3, k_s = standard rate constant, cm/s, α = transfer coefficient, R = gas constant (8.314), T = temperature in K, E = peak potential in V, E_i = potential at the foot of the response in V.

The k_s value for the electrooxidation of PA was 6.451 × 10^{-6} cm/s on Ppy/GCE and 3.76 × 110^{-5} cm/s on PEDOT/GCE. The lower value of rate constant k_s confirms that electron transfer is irreversible.

3.4. Differential Pulse Stripping Analysis of Drugs (DPSV)

Adsorptive stripping voltammetry involves two steps in which the first step is accumulation of the substrate on the electrode and the second step involves stripping. Cyclic voltammetric results revealed the good accumulation of the substrate on electrode at pH 13.0 and hence adsorptive stripping voltammetric studies performed well in the determination of drug.

The pH, accumulation potential and time were varied independently at default experimental conditions and maximum peak current parameters were found out. The solution was stirred throughout the accumulation period. The accumulation of the drug on the modified electrode surface under the optimum accumulation conditions was confirmed from the changes in the electrode surface before and after accumulation. SEM was employed to study the surface morphology of the accumulated PA on nano coated glassy carbon electrodes. **Figure 4(a)** and **4(b)** shows the small uniform granular nano Ppy and irregular granular nano PEDOT surface. The drug PA adsorbed on nano Ppy electrode during accumulation and exhibited sponge like structure (**Figure 4(c)**) and nano PEDOT exhibited broken leaves structure (**Figure 4(d)**).

The stripping parameters were varied and optimized. The range of study and optimized values are presented in **Table 1**. Under optimum experimental conditions, the influence of concentration on the stripping signal was studied. The experimental results showed that the peak current increased with the increase in the concentration of PA. A representative differential stripping voltammogram is presented in **Figure 5**. Calibration was made and the straight line plot is presented in **Figure 6**. The lower limit of detection (LOD) determined from the peak current obtained using nano Ppy is 0.035 g/mL and it is 0.016 g/mL using nano PEDOT (**Table 2**). The reproducibility of the stripping signal was understood from the relative standard derivation (2.8%) calculated for five identical measurements at a concentration level of 0.2 g/mL. The LOD values obtained from this study for the

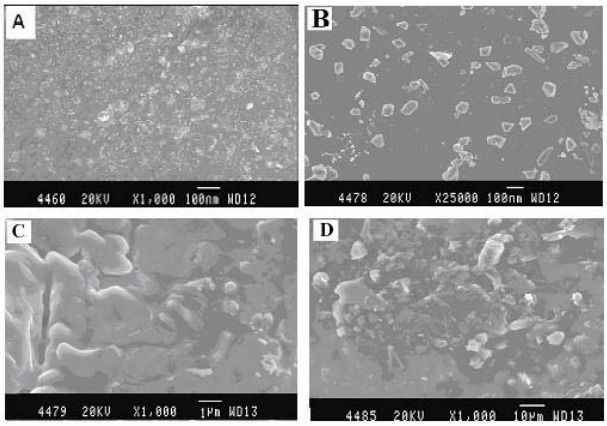

Figure 4. SEM photographs of (a) Nano Ppy (b) Nano PEDOT (c) PA on Nano Ppy and (d) PA on Nano PEDOT.

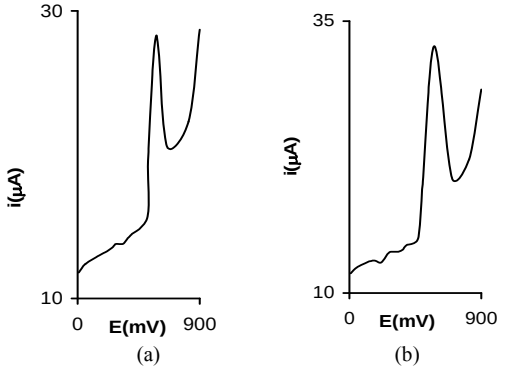

Figure 5. DPSV behaviour of 0.2 μg/mL PA on (a) Ppy and (b) PEDOT.

Table 1. Optimum parameters condition of stripping voltammetry of pheniramine on modified glassy carbon electrode.

Parameters	Ppy		PEDOT	
	Range examined	*Optimized value*	*Range examined*	*Optimized value*
pH	**1.0 to 13.0**	**13.0**	**1.0 to 13.0**	13.0
Accumulation potential (mV)	**450 to 650**	**500**	350 to550	500
Deposit time (sec)	**10 to 60**	**10**	10 to 60	10
Initial scan potential (mV)	**0 to 400**	**0**	–100 to 300	0
Pulse height (mV)	**25 to 125**	**50**	25 to 125	25
Pulse width (msec)	**25 to 125**	**50**	**25 to 125**	50
Scan increment (mV)	**2 to 10**	**4**	**2 to 20**	4
Scan rate (mV/sec)	**10 to 60**	**50**	**10 to 100**	50
Stirring rate (rpm)	**50 to 250**	**250**	**50 to 250**	250
Rest period (Sec)	**2 to 10**	**5**	**2 to 10**	5

Table 2. DPSV behaviour of analgesic drugs on modified GCE.

Electrode	Range studying in μg/mL	LOD in μg/mL	% RSD value
Ppy/GCE	0.05 to 0.4	0.035	3.1
PEDOT/GCE	0.025 to 0.4	0.016	2.3

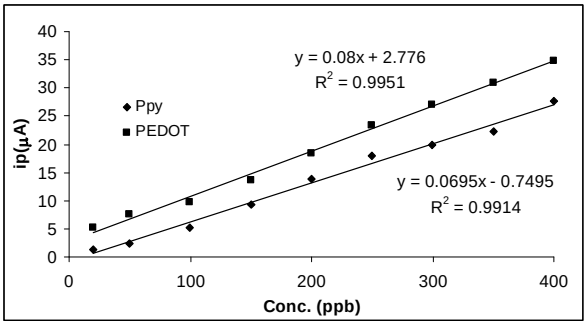

Figure 6. Calibration plot of DPSV.

antihistamine was compared with that reported already and the details are presented in **Table 3**. The table shows that the differential pulse stripping voltammetry (DPSV) method using polypyrrole and poly (3,4-ethylenedioxythiophene) modified electrode for the determination of the analgesics is superior to the already available methods.

3.5. Analysis of Pharmaceutical and Urine Samples

The pharmaceutical samples having PA was collected from medical shops at Karaikudi and analyzed. The tablets were powdered, dissolved and subsequently diluted to a required concentration. DPSV of the drug at pH 13.0 was recorded under optimum experimental conditions. By substituting the peak current in the calibration plot and keeping dilution factor in to consideration, the amount of PA present in the tablet was determined. The amount of PA determined was 47 ± 0.8 mg from nano Ppy/GCE and 49 ± 0.5 mg from nano PEDOT/GCE. These values are in good agreement with the company reported value, 50 mg.

Measurement of PA in urine samples collected after 8 hours of administration was made. 1.0 ml of the urine sample was mixed with pH 13.0. This experiment was repeated for 5 times and the average weight of PA in 1.0 ml of urine sample was determined to be 0.21 g for PA with relative standard deviation 3.2. There is no appreciable interference due to the presence of small amount urine present in the electrolyte hence the same calibration plot was used. There was no degradation of the analyte in solution during experiment. The other matters present in tablets and urine samples are not interfering with the study. This method is simple and suitable for the determination of PA. Repetition rate is found to be high.

4. Conclusions

Pheniramine maleate, an antihistamine, was anodically oxidised irreversibly on glassy carbon electrode in the pH range 1.0 to 13.0 and the oxidation was diffusion controlled adsorption. The standard rate constant was also calculated. Effect of pH leads to the conclusion that pH 13.0 was suitable for analytical studies. Employing DPSV technique, the adsorptive stripping voltammetric studies of PA was carried out. Optimum conditions were arrived at and the influence of concentration was found out. A calibration plot was made and proposed for the determination of PA. This was used to find out the amount of drug present in the pharmaceutical tablet and urine samples. Lower limit of detection was determined and the % of RSD confirmed reproducibility of the method. This method is simple, easy to perform and can very well be used in the determination of PA in real samples. Thus stripping voltammetry provides a better method for the determination of PA over spectral and other methods.

Table 3. Comparison of available methods.

Methods	LOD in $\mu g \cdot mL^{-1}$
Gas chromatography-mass spectrometry [29]	**2**
HPLC method [14]	**5 - 50**
Capillary isotachophoresis [15]	**1,**
Capillary electrophoresis determination[30]	**4 - 28**
Micellar liquid chromatography [31]	**1**
Spectrophotometric determination [32]	**9.75 - 32.5**

5. Acknowledgments

C. Vedhi, gratefully acknowledge DST for financial support through Fast Track Scheme for Young Scientists, New Delhi, India to present this aper.

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