Ionics (2016) 22:2519–2528
DOI 10.1007/s11581-016-1774-2

ORIGINAL PAPER

Comparative study for voltammetric investigation and trace determination of pramipexole at bare and carbon nanotube-modified glassy carbon electrodes

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Received: 15 April 2016 / Revised: 1 July 2016 / Accepted: 1 July 2016 / Published online: 30 July 2016

Abstract A sensitive, simple, and reproducible method was developed in this study for the determination of pramipexole, and in doing that, a glassy carbon electrode modified with –COOH-functionalized multi-walled carbon nanotube was utilized. The modified electrode was compared with a bare glassy carbon electrode in order to prove the sensitivity of the developed sensor. Cyclic, differential pulse, and adsorptive stripping differential pulse voltammetric techniques were used to investigate the oxidation behavior and stripping techniques were used for the determination of pramipexole. Based on optimum experimental conditions, calibration and partial validation studies were realized for bare and modified electrodes. As a result, the values of limit of detection and quantification were determined as be 2.38×10^{-10} and 7.93×10^{-10} M for bare and 1.06×10^{-10} and 3.52×10^{-10} M for modified glassy carbon electrodes, respectively. The applicability of the bare and modified electrodes was demonstrated for the determination of pramipexole in pharmaceutical dosage forms. The selectivity of the developed method was considered in the presence of Ca^{2+}, Na^{+}, K^{+}, and glucose, ascorbic acid, uric acid, and dopamine. Interfering agents except uric acid did not affect pramipexole determination considerably.

Keywords Pramipexole · Multi-walled carbon nanotube · Voltammetry · Determination · Modified glassy carbon electrode

Introduction

One of the most widely seen chronic as well as progressive neurodegenerative disorders is the Parkinson's disease which had first been identified as "paralysis agitans" by James Parkinson in 1817 [1]. The basic cause of this disease is the absence of dopamine neurotransmitter, which is responsible for the beginning and controlling of movement [2]. The first symptom of the Parkinson's disease is postural instability; however, these problems can also be seen because of tiredness and decrease of energy in old ages. That is why all postural problems could not be perceived as a symptom of this particular disease. Other symptoms include tremor, rigidity, and akinesia (or bradikinesia) [3–5]. What really cause the absence of dopamine neurotransmitter has not been clearly known yet; therefore, the therapy for the disease is focused on the symptoms. The basic target of the therapy is the elimination of the absence of dopamine. Pramipexole (PRM) (Scheme 1) is one of the dopamine agonists and a synthetic amino benzothiazole derivative, which has been used for the treatment of early and later stages of the Parkinson's disease [6].

According to the literature there were spectrophotometric [7–12]; spectrofluorometric [9]; high-performance liquid chromatographic with UV detection [13–17], with tandem mass detection [18–20], and with electrochemical detection [14]; ultra-performance liquid chromatographic with tandem mass detection [20]; high-performance thin layer chromatographic [21]; capillary electrophoretic [22]; gas chromatographic with mass detection [23]; and chemometric [24–26] methods for the determination of PRM. Some of these studies

Electronic supplementary material The online version of this article (doi:10.1007/s11581-016-1774-2) contains supplementary material, which is available to authorized users.

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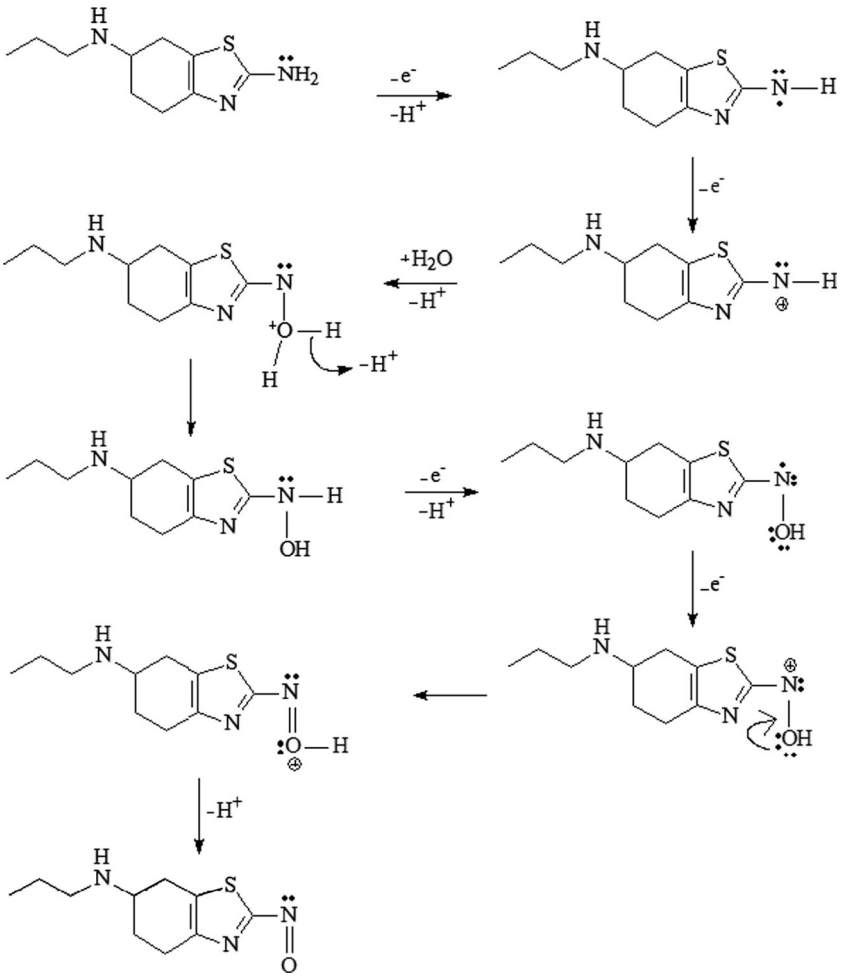
Scheme 1 Possible oxidation mechanism of PRM



were for PRM and its impurities [15, 24, 26]; one of them was for PRM and its degradation products [16]; one was for PRM and dexpramipexole [18] and for PRM enantiomers [17]. There were also potentiometric [27], amperometric [28], and voltammetric [28–31] studies for the determination of PRM. These voltammetric studies were summarized in Table 1 for a comparison with the results of this study in terms of linearity range and sensitivity.

There is a recent trend for developing electrochemical sensing devices to be used extensively in clinical assays. In the field of electrochemical sensing, electrode surface modification is quite important because there are multiple possibilities for designing and applying modified electrodes for various purposes [32]. Carbon nanotubes, first discovered in 1991, have been widely preferred in electrochemical sensing thanks to their unique physicochemical properties. They have a large

Table 1 Comparison of this study with other voltammetric studies in the literature

Method	Electrode	Linearity range (M)	LOD (M)	Reference
CV	*f*MWCNT/GCE	12.5×10^{-6}–313×10^{-6}	2.2×10^{-7}	[28]
DPV	ERGONR/GCE[a]	1.0×10^{-8}–1.5×10^{-5}	2.8×10^{-9}	[29]
SWV	GR/GCE[b]	1.9×10^{-7}–1.4×10^{-6}	5.8×10^{-8}	[30]
SWV	PANI-Bi_2O_3/GCE[c]	1.2×10^{-5}–9.6×10^{-5}	6.6×10^{-6}	[31]
AdSDPV	GCE	8.0×10^{-9}–4.0×10^{-7}	2.38×10^{-10}	This work
AdSDPV	*f*MWCNT/GCE	1.32×10^{-8}–6.60×10^{-7}	1.06×10^{-10}	This work

[a] Electrochemically reduced graphene oxide nanoribbon modified glassy carbon electrode

[b] Graphene modified glassy carbon electrode

[c] Polyaniline–bismuth oxide nanocomposite modified glassy carbon electrode

surface area; their chemical stability, bio-compatibility, conductance, and tensile strength are higher than most of other materials and their electron transfer rate is faster. Moreover, they are preferred for their electrocatalytic qualities towards several biomolecules [33, 34]. As a result of these valuable features, carbon nanotubes have been utilized in electrochemical sensor and biosensor design for making these sensing devices more effective, less expensive, and environment friendly [34]. One kind of carbon nanotubes, known as the multi-walled carbon nanotubes (MWCNTs), is preferred in the fabrication of new generation electrochemical sensors based on nanostructures. The advantages of MWCNTs follow as their smaller size, significant electrical and thermal conductivity, a considerable degree of chemical stability, mechanical strength, and wider surface area. These advantages make these nanomaterials very promising for a variety of applications. The ability of these nanomaterials in promoting electron transfer reactions and their electrochemically accessible surface area contribute to their use as a supporting material for several catalysts. All in all, the electrodes modified with MWCNTs have significant advantages over other types of carbon electrodes [34–38].

Voltammetric techniques, which are also used in this study, are preferred for their simplicity, for being economic and environment friendly since they require lesser amounts of solvents. Moreover, they do not necessitate extraction, filtration, or centrifuge and therefore, they require a lower time span [34–38].

In this study, first, through using a bare glassy carbon electrode (GCE), a lower detection limit was provided for the determination of PRM. This outcome led us to think if it is possible to fabricate a more sensitive sensor for PRM determination and as a result, a –COOH-functionalized MWCNT-modified GCE (*f*MWCNT/GCE) was developed. Then, the oxidation behavior of PRM at the bare and modified GCE was investigated. When the two electrodes were compared, it was noted that the electrode demonstrating more sensitive results for PRM with good recovery and reproducibility was the modified one.

Experimental

Apparatus

The basic apparatus for the electrochemical measurements was AUTOLAB-PGSTAT302 (Eco Chemie, Utrecht, The Netherlands) electrochemical and electroanalytical instrument, on which the General Purpose Electrochemical Software (GPES) 4.9 was loaded. Cyclic (CV), differential pulse (DPV), and adsorptive stripping differential pulse voltammetry (AdSDPV) were preferred as electroanalytical techniques in this study. A three-electrode system based on a bare GCE and *f*MWCNT/GCE as the working electrodes, a platinum wire (BASi) as the auxiliary electrode, and an Ag/AgCl (BASi; 3 M NaCl) as the reference electrode was used.

The pH meter used for all pH measurements was Model 526 (WTW, Austria) with a combined electrode (glass electrode–reference electrode).

DPV conditions were used as such: The step potential, modulation amplitude, modulation time, and interval time were set as 0.00795 V, 0.0505 V, 0.050 s and 0.500 s, respectively. Considering the AdSDPV conditions, accumulation potential (E_{acc}) and accumulation time (t_{acc}) were optimized as 0.0 V and 60 s for bare GCE and 0.1 V and 150 s for *f*MWCNT/GCE. The "peak width" for average baseline correction was 0.01 V.

Reagents and chemicals

Deva (Istanbul, Turkey) company supplied us with PRM dihydrochloride monohydrate and Ramipex® tablets each of which includes 1-mg PRM. The standard solution of PRM was prepared in distilled water and put into a refrigerator for storage. *f*MWCNT were bought from DropSens and dimethylformamide (DMF) from Merck.

To be used in electrochemical measurement, the following supporting electrolytes were prepared: 0.1 M H_2SO_4, 0.5 M H_2SO_4, acetate (1.0 M CH_3COOH; pH 3.7–5.7), phosphate (0.2 M H_3PO_4; 0.2 M $NaH_2PO_4{\cdot}2H_2O$; pH 2.0–8.0), borate (0.2 M H_3BO_3; pH 9.0–10.0), and Britton-Robinson (BR) (0.04 M, pH 2.0–12.0) buffers. Other reagents, which were of analytical grade, were prepared in distilled water. CH_3COOH and H_3PO_4 were purchased from Sigma-Aldrich, H_3BO_3 from Pancreac, and $NaH_2PO_4{\cdot}2H_2O$ and Na_2HPO_4 from Riedel-de Haen.

Preparation of *f*MWCNT/GCE

In order to prepare *f*MWCNT/GCE, first 0.5 mg *f*MWCNT was suspended in 1.0 mL DMF. Second, in order to obtain a homogenous and stable suspension of 0.5 mg mL^{-1} *f*MWCNT, the suspension was sonicated in an ultrasonic bath for 2 h. Third, 4.0–12.0 μL *f*MWCNT was dropped on a bare electrode surface by using a micropipette. The modified electrode was left drying for approximately 15 h. The measurements were made in pH 2.0 phosphate buffer solutions (PBS). The optimized volume of *f*MWCNT was determined as 4.0 μL. Then, the modified electrode was cleaned electrochemically by using cyclic voltammetry before each measurement.

Tablet assay procedure and recovery experiments from tablets

Ten Ramipex® tablets were powdered in a mortar. A certain amount of this powder was weighed in a way to correspond to stock solutions with concentrations of 1×10^{-3} and 3.3×10^{-3} M and put into 25.0-mL flasks separately. Then, the flasks were filled with pH 2.0 BR buffer (bare GCE) and pH 3.0 PBS (modified GCE) and sonicated for 30 min. Aliquots were taken from the stock solution, which are diluted with the pH 2.0 BR buffer (bare GCE) and pH 3.0 PBS (modified GCE), and analyzed solutions were prepared accordingly. Known amounts of the pure drug were added into the tablet formulation in order to examine the interferences of the excipients before the analysis. Five parallel analyses were performed for the determination of the recovery results.

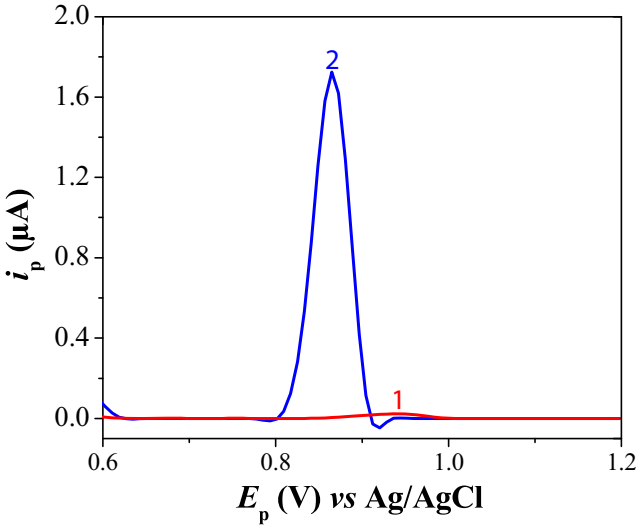


Fig. 1 AdSDP voltammograms 1.65×10^{-6} M PRM in pH 2.0 PBS at bare GCE (*1*) and *f*MWCNT/GCE (*2*). $t_{acc} = 60$ s and $E_{acc} = 0$ V

Results and discussion

Voltammetric behavior of PRM

In this study, PRM signal was aimed to search with bare and modified GCE and it was noted that an irreversible oxidation behavior was observed for the PRM at both electrodes. Figure 1 shows the differences between bare and modified electrodes. The increase of PRM peak current at modified electrode and catalytic effect of *f*MWCNT towards the PRM oxidation can be clearly seen from the figure.

The impact of pH on the peak potentials and peak currents

It was understood from the results that the change in pH affected the peak currents and potentials for both electrodes. The cyclic and DP voltammograms of PRM in different types of buffer solutions, whose pH varied between 0.3–12.0 for bare GCE and between 2.0–10.0 for *f*MWCNT/GCE, were recorded. Figure 2 showed the DP and AdSDP voltammograms, which were obtained in different pH values for bare and modified GCEs, respectively. The best peak shapes and reproducible results were obtained in pH 2.0 BR buffer at bare and pH 3.0 PBS at modified electrode. Although it seems from Fig. 2b that the best response at modified GCE is recorded at pH 6.0 for the working concentration (1.65×10^{-6} M) of PRM, the voltammogram which was obtained in pH 6.0 did not give a good shape and reproducible results. Therefore, this pH was not preferred.

The DP voltammograms figure out that the pH increase shifted the peak potentials (E_p) negatively at both electrodes. E_p versus pH response was linear with slopes of −60.99 and −60.35 mV/pH for bare GCE (Suppl. 1) and *f*MWCNT/GCE (Suppl. 2), respectively. The slope values were close to −59 mV/pH; as a result of this, it was inferred that electron and proton numbers, which are transferred throughout the reaction were equal. Related equations were as follows:

$$E_p(\text{mV}) = -60.99\ \text{pH} + 972.3\ ;\ r = 0.998\ (n = 13)\ (\text{pH}\,1.0\text{–}12.0)\ \text{with DPV for bare GCE}$$
$$E_p(\text{mV}) = -60.35\,\text{pH} + 982.5; r = 0.999 (n = 14) (\text{pH}\,2.0\text{–}10.0)\ \text{with AdSDPV for}\ f\text{MWCNT}/\text{GCE}$$

Effect of the scan rate

The electrochemical mechanism for PRM was tried to be understood, and in doing that, the relationship between the scan rate (v) and peak current (i_p) was proved to be useful. The electrochemical behavior of 1.0×10^{-5} M (in pH 2.0 BR buffer) and 3.3×10^{-4} M PRM (in pH 3.0 PBS) were investigated at different scan rates ranging from 5 to 500 mV s^{-1} by CV. The outcome of the logarithm of i_p versus the logarithm of v plot was observed as

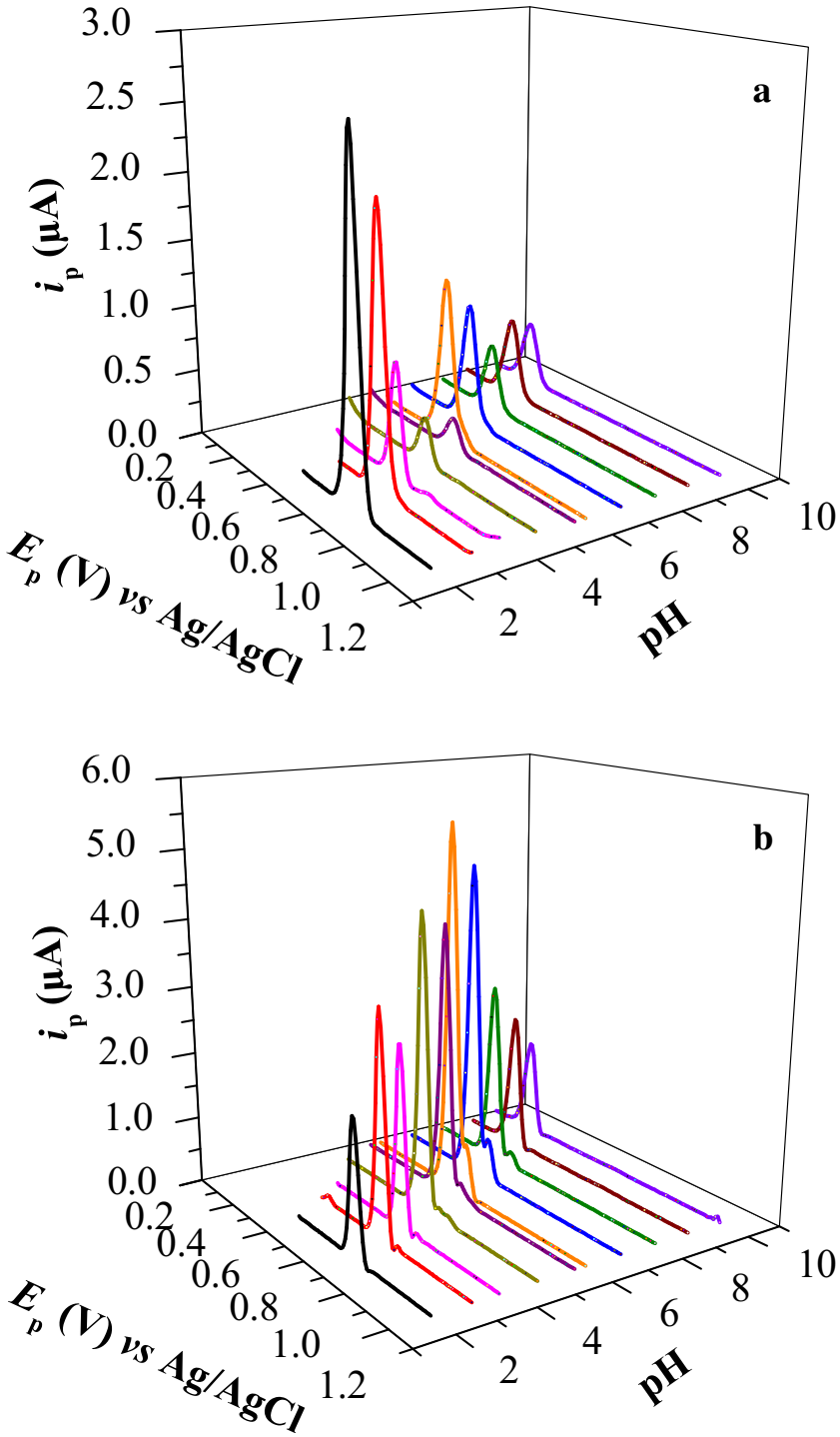


Fig. 2 **a** DPV of 1×10^{-5} M PRM at bare GCE and **b** AdSDPV of 1.65×10^{-6} M PRM at *f*MWCNT/GCE in different pH values

a linear dependence as the equations given suggest as follows:

$$\log i_p(\mu A) = 0.970 \log v\left(\text{mV s}^{-1}\right) - 1.471\, r$$
$$= 0.989 (n = 7) \text{ for the bare GCE } \log i_p\ (\mu A)$$
$$= 0.629 \log v\left(\text{mV s}^{-1}\right) - 0.169\, r$$
$$= 0.993 (n = 11) \text{ for the } f\text{MWCNT/GCE}$$

i_p versus log$v$ plot, a straight line with a slope of 0.970 at bare GCE, was very close to the theoretical value of 1.0. This reveals that the transfer process of PRM to the electrode surface was adsorption controlled. A plot of logi_p versus log$v$, which was also a straight line with a slope of 0.629 at *f*MWCNT/GCE, was meant that the PRM transfer process to the electrode surface was diffusion controlled with adsorption [36].

It was also observed that when the scan rate increased, the E_p values of the anodic peak of PRM shifted positively. The E_p versus log$v$ plots were linear and the correlation coefficients (r) were calculated as 0.998 and 0.996 for the bare and modified GCE, respectively. The E_p–log$v$ equations were given as follows:

$$E_p(\mathrm{mV}) = 32.77\log v\left(\mathrm{mV\ s^{-1}}\right) + 827.31; r = 0.998 (n = 6) \text{ for the bare GCE} E_p\ (\mathrm{mV})$$

$$= 32.81\log v\left(\mathrm{mV\ s^{-1}}\right) + 799.22; r = 0.996 (n = 6) \text{ for the fMWCNT}/\text{GCE}$$

In line with the Laviron equations for an irreversible electrode process [39], E_p is determined through the equation given as follows:

$$E_p = E^{0\prime} - \frac{2.303RT}{\alpha nF}\log\frac{RTk^0}{\alpha nF} + \frac{2.303RT}{\alpha nF}\log v$$

where α, k^0, n, υ $E^{0\prime}$, R (8.314 J K^{-1} mol^{-1}), T (298 K), and F (96.480 C mol^{-1}) are used in their usual meanings. The slopes of E_p–log$v$ plots were also used to calculate the αn values, which were determined as about 1.80 for both electrodes.

For irreversible processes, α is determined as 0.5 [40]; the n values transferred in the oxidation of PRM were calculated as about 3.60 using the results of bare GCE and modified GCE. It means PRM oxidation is 4 (four) electron process.

Possible oxidation pathway

Using the bare and modified GC electrodes, the number of electron was calculated as four for PRM oxidation according to the relationship between E_p–log$v$. When examining the slope of E_p–pH, it can be said that number of electron and proton are equal and the PRX oxidation is a four electron-four proton process. Proposed oxidation mechanism, which is given by the way of 2-amino group of benzothiazole ring, was revealed in Scheme 1.

Optimization of method parameters

For both electrodes, accumulation potential (E_{acc}) and accumulation time (t_{acc}) values were optimized for AdSDP voltammetric technique. The relationship between the E_{acc} and the i_p was studied in case of t_{acc} was being 60 s for the PRM concentration of 1.0×10^{-6} and 1.65×10^{-6} M for bare GCE and modified GCE, respectively. The E_{acc} between the ranges of 0–0.8 and 0–0.7 V was investigated; in line with the i_p values, E_{acc} were selected as 0 and 0.1 V with bare GCE (Fig. 3) and modified GCE (Fig. 4), respectively. During the optimization procedure, the interdependence between the i_p and t_{acc} was searched. Significant increases were observed until 60 and 150 s for bare GCE (Fig. 3) and modified GCE (Fig. 4), respectively.

Calibration curve and method validation

In order to determine PRM in pH 2.0 BR buffer and pH 3.0 PBS, AdSDP voltammetric technique was used. When optimum conditions were achieved, PRM's response was linear between i_p and PRM concentration (C) in the range of 8.0×10^{-9}–4.0×10^{-7} M for the bare GCE (Fig. 5) and 1.32×10^{-8}–6.60×10^{-7} M for the *f*MWCNT/GCE (Fig. 6). Equations based on the calibration were given as follows:

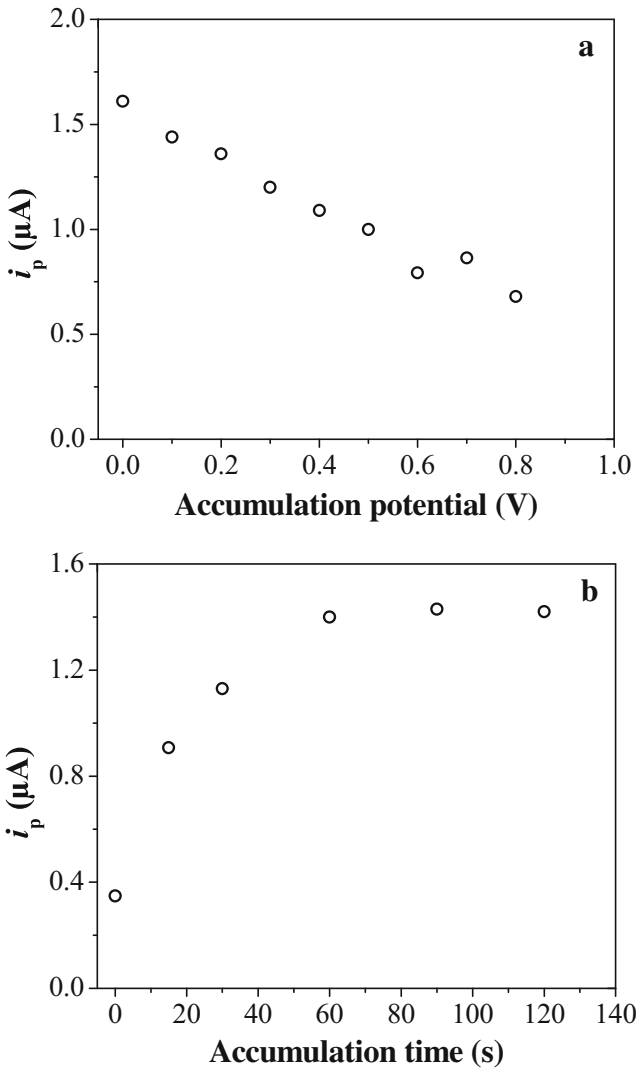


Fig. 3 Influence of E_{acc} (t_{acc}: 60 s) (**a**) and t_{acc} (E_{acc}: 0 V) (**b**) on 1.0×10^{-6} M PRM peak current using AdSDPV in pH 2.0 BR buffer at GCE

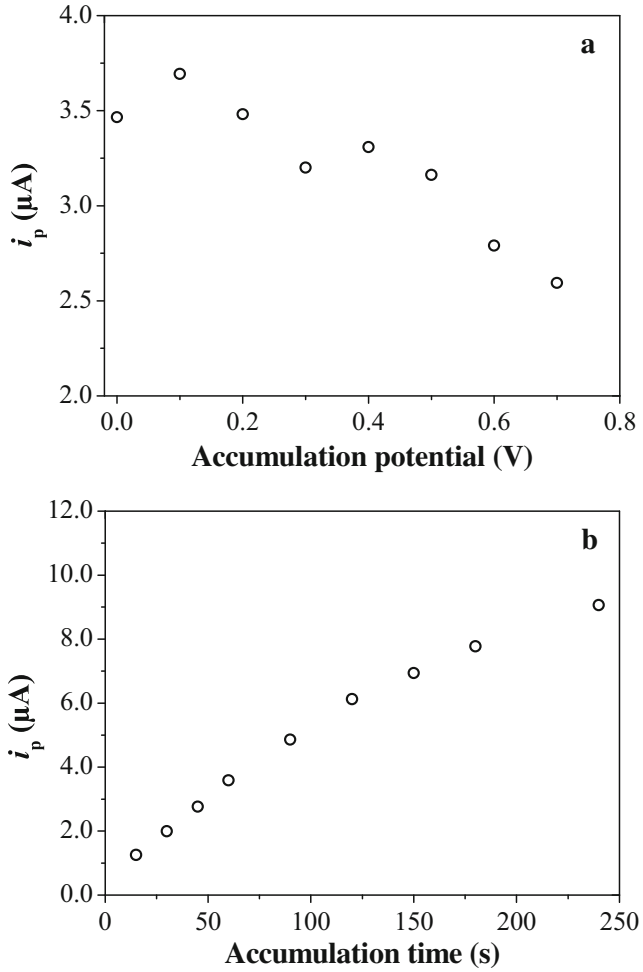


Fig. 4 Influence of E_{acc} (t_{acc}: 60 s) (**a**) and t_{acc} (E_{acc}: 0.1 V) (**b**) on 1.65×10^{-6} M PRM peak current using AdSDPV in pH 3.0 PBS at *f*MWCNT/GCE

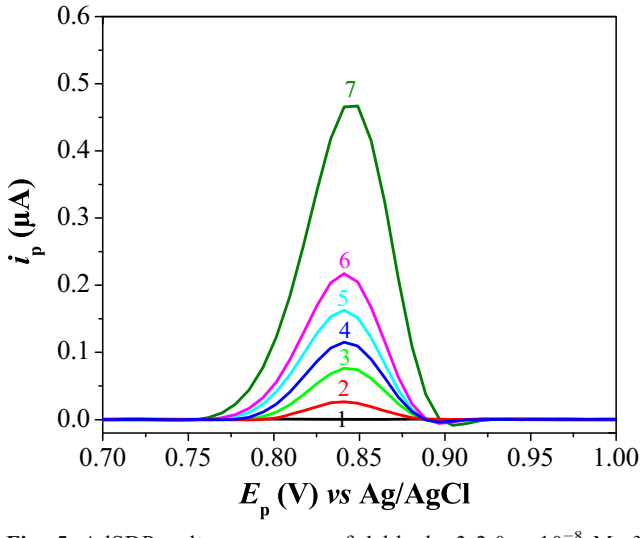


Fig. 5 AdSDP voltammograms of *1* blank, *2* 2.0×10^{-8} M, *3* 4.0×10^{-8} M, *4* 6.0×10^{-8} M, *5* 8.0×10^{-8} M, *6* 1.0×10^{-7} M, and *7* 2.0×10^{-7} M PRM in pH 2.0 BR buffer solution using bare GCE (E_{acc}: 0.0 V and t_{acc}: 60 s)

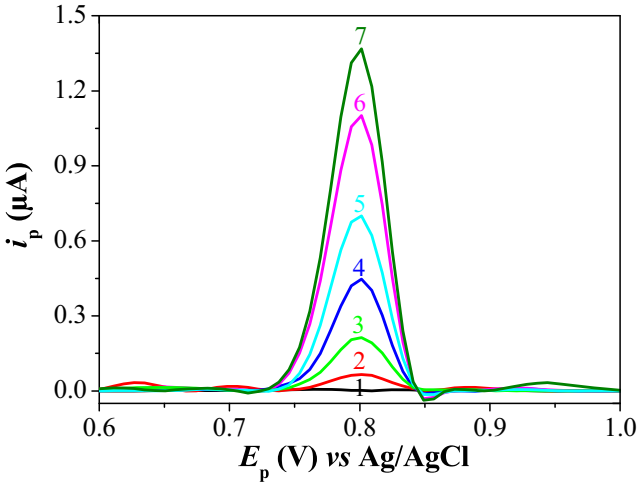


Fig. 6 AdSDP voltammograms of *1* blank, *2* 3.30×10^{-8} M, *3* 6.60×10^{-8} M, *4* 1.32×10^{-7} M, *5* 1.98×10^{-7} M, *6* 2.34×10^{-7} M, and *7* 3.30×10^{-7} M PRM in pH 3.0 PBS using modified GCE (E_{acc}: 0.1 V and t_{acc}: 150 s)

$$i_p(\mu A) = 2.185 \times 10^6 C(M) - 0.0075; r = 0.999 (n = 9) \text{ for bare GCE} i_p\ (\mu A) = 4.34 \times 10^6 C(M) - 0.081; r = 0.999 (n = 10) \text{ for } f\text{MWCNT}/\text{GCE}$$

According to these equations, the limit of detection (LOD) and limit of quantification (LOQ) were calculated as $3s/m$ and $10s/m$, respectively (*s* symbolizes the standard deviation of the response of three repeat measurements of the lowest concentration of linear range and *m* symbolizes the slope of the linear curve). Table 2 summed up these values.

The precision of the developed methods were determined through repeatability studies. 1.0×10^{-7} M (bare GCE) and 6.6×10^{-8} M (modified GCE) PRM was used for within and between day precision. In order to determine relative standard deviation (RSD %) values, five independent data were measured (Table 2). From these results, it can be inferred that the repeatability of the developed methods were good.

A comparison of these results with other voltammetric studies in the literature in terms of the linearity range and LOD values were given in Table 1, which showed that the electrodes used in this study gave more sensitive results. In comparison of bare and modified electrodes in itself for our work, the modified GCE did not have a great linearity range compared to bare GCE but modified GCE provided lower LOD value and almost two times higher slope value for the calibration curve (Table 2). The slope of the calibration curve is a parameter demonstrating sensitivity. Sensitivity shows how much the change in the concentration of the analyte studied affects the answer. The high slope value obtained by

Table 2 Regression data of the calibration curves and required validation parameters for the determination of PRM by AdSDPV for bare GCE and modified GCE

	Bare GCE	*f*MWCNT/GCE
Measured potential (V)	0.840	0.801
Linear range (M)	8.00×10^{-9}–4.00×10^{-7}	1.32×10^{-8}–6.60×10^{-7}
Slope (μA M^{-1})	2.19×10^{6}	4.34×10^{6}
Intercept (μA)	-7.54×10^{-3}	−0.081
Correlation coefficient (*r*)	0.999	0.999
Standard error of slope	1.52×10^{4}	2.72×10^{4}
Standard error of intercept	2.39×10^{-3}	7.88×10^{-3}
LOD (M)	2.38×10^{-10}	1.06×10^{-10}
LOQ (M)	7.93×10^{-10}	3.52×10^{-10}
Within day precision of current (RSD %)[a]	0.66	1.56
Within day precision of potential (RSD %)[a]	0.26	0.10
Between days precision of current (RSD %)[a]	1.51	1.75
Between days precision of potential (RSD %)[a]	0.05	0.13

$C_{PRM} = 1.0 \times 10^{-7}$ M for bare GCE and $C_{PRM} = 6.6 \times 10^{-8}$ M for modified GCE

[a] Obtained from five measurements

modified GCE shows the sensitivity of this electrode. The LOD value depends on the slope value according to the abovementioned formula; therefore, a lower LOD was obtained by the modified electrode.

Tablet analysis

The methods developed were applied to the pharmaceutical dosage forms (Ramipex® tablets) of PRM as well. Recovery studies were also performed by adding known amounts of pure PRM to the pharmaceutical dosage forms. Five recurrent experiments were held and by using the calibration curve and in line with the results given in Table 3 (in which the results for the determination of PRM in pH 2.0 BR buffer and pH 3.0 PBS, respectively, from Ramipex® tablets and recovery studies are shown) the recovery results were calculated.

Table 3 The results for the determination of PRM in pH 2.0 BR buffer and pH 3.0 PBS, respectively, from Ramipex® tablets and recovery studies obtained for bare and modified GC electrodes using AdSDPV

	Bare GCE	*f*MWCNT/GCE
Labeled claim (mg)	1.00	1.00
Amount found (mg)[a]	1.03	1.01
RSD %	1.10	0.89
Bias %	−3.20	−1.00
Added (mg)	0.500	1.00
Found (mg)[a]	0.504	1.002
Average recovered %	100.84	100.17
RSD %	1.803	1.04
Bias %	−0.838	−0.17

[a] Obtained using five measurements

Interference studies

In order to understand whether some ions and biological compounds situated in the body fluids have an interference impact, interference studies were performed through AdSDPV by using modified GCE. 0.1 μg mL^{-1} (3.3×10^{-7} M) PRM was studied in the presence of tenfold (1.0 μg mL^{-1}) of each interferent. According to the AdSDPV results, it was found that Ca^{2+}, Na^{+}, K^{+}, and glucose, ascorbic acid, and dopamine did not affect the signal of PRM more than 10 %; but uric acid, decreased the i_p of PRM more than 10 %. When the change in the peak current is more than 10 %, then it can be concluded that the substance resulted in an obvious interference. The corresponding concentration was called the tolerance level [41].

Conclusion

In the present study, bare GCE and *f*MWCNT/GCE were compared for the investigation and determination of PRM. The AdSDPV results showed electro catalytic effect, sensitivity, and reproducibility of the voltammetric responses obtained through the developed sensor. The developed sensor was proved very useful for the determination of PRM from tablet formulations thanks to its low detection limit, ease of preparation, and surface regeneration. High percentage of recovery showed that the developed sensor can be used to quantify PRM without interference from other ingredients. Interference studies were also investigated using Ca^{2+}, Na^{+}, K^{+}, and glucose, ascorbic acid, uric acid, and dopamine; it was found that these ions and molecules except uric acid did not affect the response of PRM. The developed method at modified GCE with a detection limit of 1.06×10^{-10} M is more

sensitive for the determination of PRM when compared to bare GCE (used in this study) and other voltammetric methods recorded in literature [28–31]. Thus, due to its sensitivity and accuracy, the developed sensor and method may be an effective alternative to the other literature methods.

Acknowledgments This study owes much to the financial support from Ankara University, Department of Scientific Research Projects (Project No: 13 L3336001) for which the authors are grateful. This work was a product of the PhD dissertation completed by Burçin Bozal-Palabiyik (Ankara University, Health Sciences Institute).

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