Anal. Bioanal. Electrochem., Vol. 3, No. 1, 2011, 38-50

Analytical & Bioanalytical Electrochemistry

www.abechem.com

Full Paper

Voltammetric Determination of Paracetamol with Poly(3,4-Ethylenedioxythiophene) Modified Glassy Carbon Electrode

Solomon Mehretie, Shimelis Admassie*, Merid Tessema and Theodros Solomon

Department of Chemistry, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia

* Corresponding Author; Tel.: +251-111-239466; Fax: +251-111-234296

E-Mails: shimadm@chem.aau.edu.et; shimadm09@gmail.com

Received: 6 November 2010 / Accepted: 27 January 2011 / Published online: 28 February 2011

Abstract- This study describes the preparation and application of a poly(3,4-ethylenedioxythiophene) (PEDOT) modified glassy carbon electrode for paracetamol determination in pharmaceutical samples. The PEDOT modified electrode was prepared by electropolymerizing 3,4-ethylenedioxythiophene (EDOT) on a glassy carbon electrode in a non-aqueous medium. The best performance of the PEDOT modified electrode in 0.1 mol L^{-1} phosphate buffer obtained at pH 7.0. Under these conditions, an oxidation potential of paracetamol was observed at 0.37 V versus Ag/AgCl/sat'd KCl. The cyclic voltammetric study indicates that the PEDOT modified electrode shows a very good electrocatalytic activity by reducing the overpotential by 200 mV for paracetamol oxidation. The modified electrode showed a linear response range between 2.5 and 150 µmol L^{-1}, a sensitivity of 90.03 µA/mmol L^{-1}, quantification and detection limits of 2.5 µmol L^{-1} and 1.13 µmol L^{-1}, respectively. Finally, the proposed method was applied for paracetamol determination in commercial tablets with a mean recovery of (101±6) %.

Keywords- Paracetamol, PEDOT, Glassy Carbon (GC), Differential Pulse Voltammetry

---

1. INTRODUCTION

Paracetamol, N-acetyl-*p*-aminophenol or acetaminophen, is one of the most commonly used drugs in the world. It is the preferred alternative analgesic and antipyretic to aspirin, to patients who cannot tolerate aspirin [1,2]. Paracetamol is an acylated aromatic amide that was first introduced in medicine by Von Mering in 1893, has been in use as an analgesic for home medication for over 50 years, and is accepted as an effective drug for the relief of pain and fever in adults and children [3].

Standard usage of paracetamol has no any detrimental effect on the human body but overusage of the drug could lead to some serious side effects, such as liver disorders, skin rashes and inflammation of the pancreases [4]. Besides, p-aminophenol, the primary hydrolytic degradation product of paracetamol, can be present in pharmaceutical preparations as a synthetic intermediate or as a degradation product of paracetamol that can cause serious nephrotoxocity and tetragenic effects [5,6].

Nevertheless, paracetamol is being increasingly used for therapeutic purposes. The development of a simple, precise and accurate method for the determination of paracetamol is therefore very important. The various methods reported for the determination of paracetamol in body fluids and pharmaceutical preparations include spectroscopy [7,8], liquid chromatography [9,10], capillary electrophoresis [11-13] and enzyme based assay methods [14]. However, these methods usually involve the hydrolysis of paracetamol sample to 4-aminophenol, which then required the formation of a colored complex using an appropriate reagent, which takes a long time to perform.

Electrochemical methods based on chemically modified electrodes have attracted much attention because of quick response, high sensitivity, and selectivity in the determination of trace level analytes. The slow electron transfer kinetics on bare (unmodified) electrode is substantially changed by modifying the surface of the bare electrode which speeds up the electron transfer kinetics [15-25].

Conjugated polymers (CPs) have widely been used for surface modification of electrodes. CPs have π-conjugated structures that are characterized by a high electrical conductivity. This offers a good electrocatalytic behavior, which explains their use as transducers in the preparation of efficient electrochemical sensors [19,26].

Thin films of CPs can be easily synthesized onto the electrode surface by chemical or electrochemical methods. Their physico-chemical properties strongly depend on the electropolymerization conditions such as solvent type, supporting electrolyte, electrode material, polymerization potential, and electropolymerization method [27]. The formation of charge carriers on the conjugated backbone is realized by oxidation (p-doping) or reduction (n-doping) that allows the appearance of a metal-like intrinsic conductivity. In the case of p-doping of polymers such as polypyrrol or polythiophene, the cationic charges carried by the polymer backbones are counter balanced by negative charges carried by anions [28,29].

The electrochemical determination of paracetamol using square-wave voltammetry (SWV) at a polyaniline-multi-walled carbon nanotubes composite modified glassy carbon (GC) electrode has been reported [19]. The oxidation peak current at this electrode was linear for paracetamol concentration in the range 1×10^{-6}-2×10^{-3} mol L^{-1} with a detection limit of 2.5×10^{-7} mol L^{-1}.

To our knowledge, no work has so far been reported on the redox behavior of paracetamol at poly (3,4-ethylenedioxythiophene) (PEDOT) modified GC electrode. In this paper, we report the preparation, and electrocatalytic application of the modified GC electrode. The method is based on modifying a GC electrode with PEDOT using electropolymerization of 3,4-ethylenedioxythiophene monomer and then study its electrocatalytic activity towards the electrochemical oxidation of paracetamol. The method developed was applied for the determination of paracetamol in commercial tablet samples.

2. EXPERIMENTAL

2.1. Apparatus

The voltammetric experiments were carried out using BAS 100A, electrochemical analyzer [Bioanalytical systems (BAS), USA] controlled by a Dell computer with conventional three-electrode configuration. The PEDOT modified glassy carbon electrode was used as the working electrode, a platinum electrode served as the counter electrode with Ag /AgCl/sat'd KCl as the reference electrode. The pH of the buffer solutions was measured with a JENWAY model 3510 pH meter.

2.2. Chemicals and reagents

Paracetamol (Sigma, Germany) tetrabutylammonium tetrafluoroborate (Sigma-Aldrich, Germany), acetonitrile (Scharlau Chemie, Spain), disodium hydrogen phosphate (Techno Pharmchem, India), sodium dihydrogen phosphate (BDH, England), hydrochloric acid (Riedel-deHaen, Germany), and sodium hydroxide (BDH, England) were used without further purification. 3,4-ethyleneoxythiophene (EDOT) was distilled repeatedly under vacuum until a colorless liquid was obtained and was kept in the dark. Stock solutions of paracetamol and phosphate buffer solutions (0.1 mol L^{-1} NaH_2PO_4 and 0.1 mol L^{-1} Na_2HPO_4) were prepared by using deionized water. The pH of the phosphate buffer solution was adjusted by adding drops of concentrated hydrochloric acid and sodium hydroxide.

2.3. Preparation of the modified electrode

Before modification, the GC electrode was polished with 0.05 μm alumina slurry and then cleaned with deionized water. A 0.01 mol L^{-1} EDOT monomer was dissolved in a 0.1 mol L^{-1} tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) in acetonitrile as the solvent. The EDOT was electropolymerized on the dried GC by running cyclic voltammetry from 0.0 to

1.3 V for ten cycles. Then the modified electrode was cycled 15 times in 0.1 mol L^{-1} Bu_4NBF_4/acetonitrile solution for stabilization. After electropolymerization, the PEDOT modified GC electrode was carefully washed with acetonitrile.

2.4. Sample preparation

Five tablets obtained from commercial available drug houses (500 mg paracetamol per tablet) were accurately weighed and finely powdered in a mortar. An adequate amount of the powder was weighed and transferred to 100 mL flask containing 30 mL of 0.1 mol L^{-1} phosphate buffer (pH 7.0). The flask was thoroughly shaken until most of the sample dissolved and the mixture was centrifuged. Finally, the clear solution was filtered through a Whatman 41 filter paper and the pH of the supernatant was adjusted to 7.0.

2.5. Electrochemical measurements

The electrochemical behavior of paracetamol at PEDOT modified GC electrode was investigated using cyclic voltammetry. The determination of paracetamol was carried out by using differential pulse voltammetry (DPV). DPVs were obtained by scanning the potential in the range from +0.20 to +0.50 V at frequency amplitude of 25 Hz. Before each experiment, the modified electrode was transferred in 0.1 mol L^{-1} phosphate buffer solution (pH=7.0), for updating by cycling the potential between 0.0 V and 0.8 V with a scan rate 0.1 Vs^{-1} until the peak of paracetamol disappeared. The paracetamol concentrations were obtained by measuring the heights of the oxidative peak currents. The detection limit was calculated as three times of the standard deviation for 10 nmol L^{-1} of paracetamol divided by the slope of the calibration curve.

3. RESULTS AND DISCUSSION

3.1. Investigation of the electrochemical behavior of the modified GCE

The PEDOT film was made potentiodynamically by cycling the potential between 0.0 V and 1.3 V versus $Ag/AgCl/Cl^-$ standard reference electrode in 0.1 mol L^{-1} Bu4NBF4/acetonitrile solution. The thickness of the film was controlled by the number cycles (10) as shown in Fig. 1. The inset in Fig. 1 depicts the cyclic voltammetry of the PEDOT modified electrode in the phosphate buffer solution without paracetamol.

The electrochemical behavior of paracetamol at bare and modified GC electrode was studied by using cyclic voltammetry at a scan rate of 0.1 Vs^{-1}. Cyclic voltammograms obtained in 0.1 mol L^{-1} phosphate buffer solutions are shown in Figure 2a. At bare GC electrode, paracetamol shows quasi-irreversible behavior with a peak-to-peak potential separation (ΔE_p) of 0.58 V (Fig. 2b). In contrast, the peak for paracetamol oxidation at the PEDOT modified GC electrode shows a substantial shift to the negative potential (overpotential reduced by 200 mV) and a large increment in both anodic and cathodic

currents (Fig. 2c). The peak-to-peak potential separation of the modified electrode (ΔE_p=0.07 V) is much smaller than that of the bare electrode. This indicates that the modified electrode displays very good electrocatalytic property for the redox reaction of paracetamol.

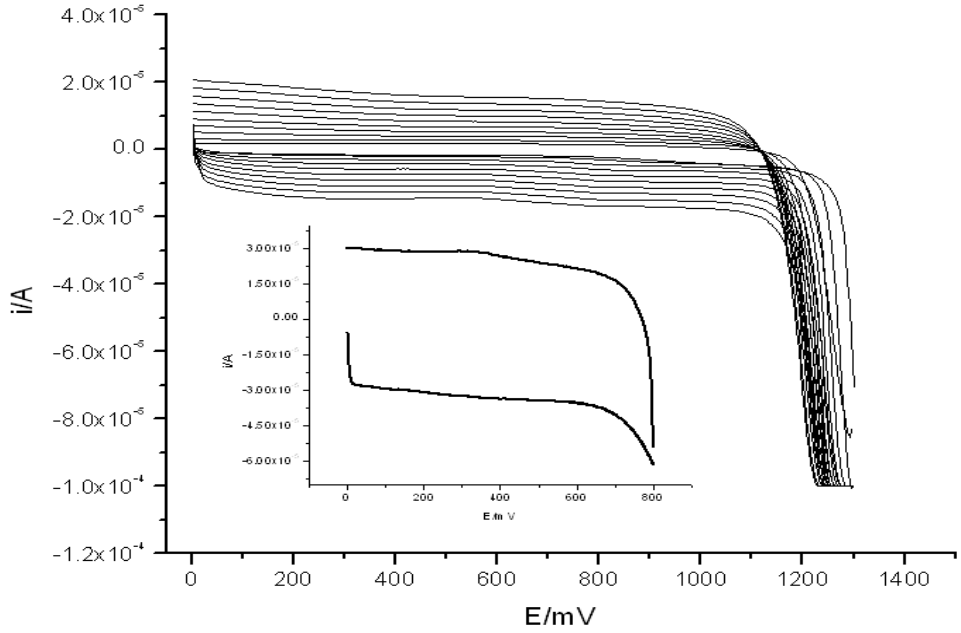

Fig. 1. Formation of PEDOT film onto GC electrode. The inset is the cyclic voltammetry of the PEDOT modified electrode in phosphate buffer solution

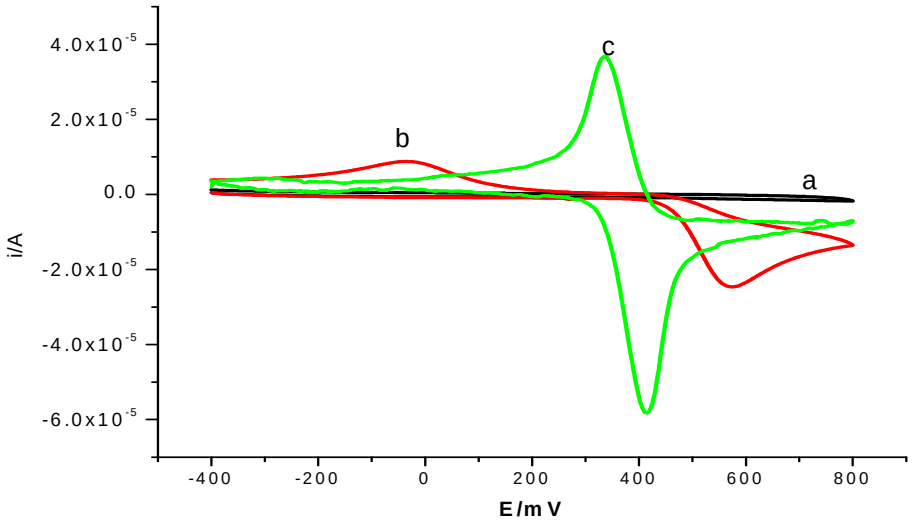

Fig. 2. Cyclic voltammogram (CV) at scan rate of 0.1 Vs^{-1} obtained at: (a) GC electrode for 0.1 mol L^{-1} phosphate buffer supporting electrolyte, (b) bare GC with 1 mmol L^{-1} paracetamol in phosphate buffer and (c) PEDOT modified GC electrode with 1 mmol L^{-1} paracetamol in phosphate buffer (Background subtracted)

Investigation of the effect of scan rate on the electrochemical oxidation of paracetamol at the PEDOT modified GC electrode showed the oxidation peak current of paracetamol increased linearly with scan rates in the range 0.01-0.15 Vs^{-1}, with a correlation coefficient of 0.9992 (Fig. 3). This suggests that the process of the electrode reaction is controlled by adsorption process [30].

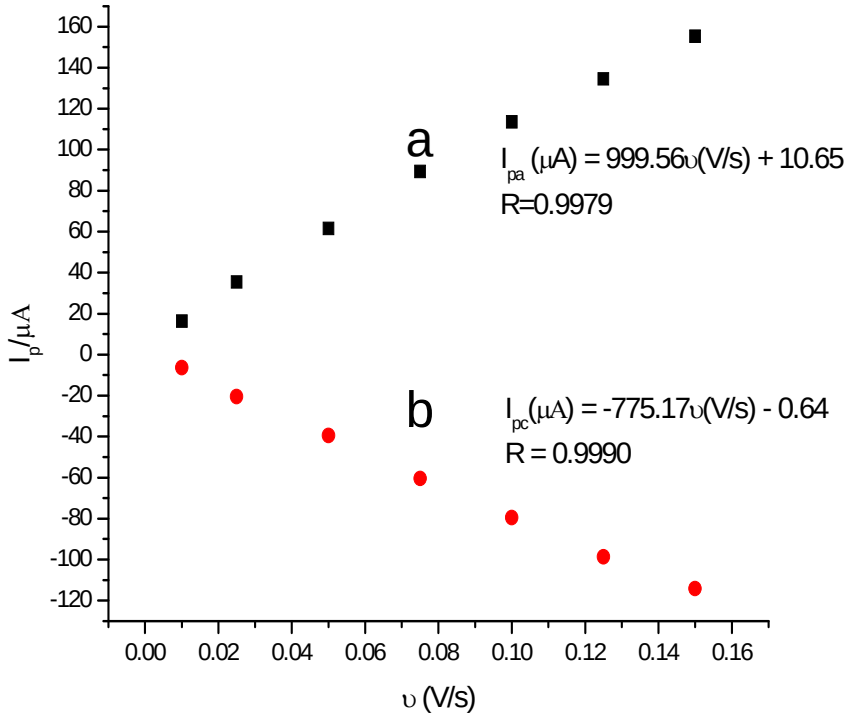

Fig. 3. Plot of peak current versus scan rate for the electrochemical oxidation of paracetamol at the PEDOT modified GC electrode: (a) anodic current peak and (b) cathodic current peak

3.2. Effect of pH

In order to optimize the responses of the PEDOT modified GC electrode for paracetamol oxidation, the effect of pH on the electrochemical oxidation was investigated using DPV. Fig. 3A illustrates the peak current response of paracetamol (1.0 mmol L^{-1}) at different pH, from pH 3.0 to 9.0. It can be seen that the response of the modified electrode was highest at neutral pH 7 and lower for low and high pH values. At lower pHs, the low response can be attributed to hydrogen ion which is one of the products formed in the oxidation of paracetamol. The high concentration of H^+ hinders the electrochemical oxidation of paracetamol due to common ion effect, thus producing a weaker response. A significant increase in the oxidation current peak was found with increasing pH but decrease in the response was observed after pH 7.0 which is the result of hydroxylation of the mediator at higher pH [31]. The decrease in the current response is accounted by the electrochemical

inactivity of the hydroxylated mediator. Therefore, 0.1 mol L^{-1} phosphate buffer of pH 7.0 was chosen for further experiment

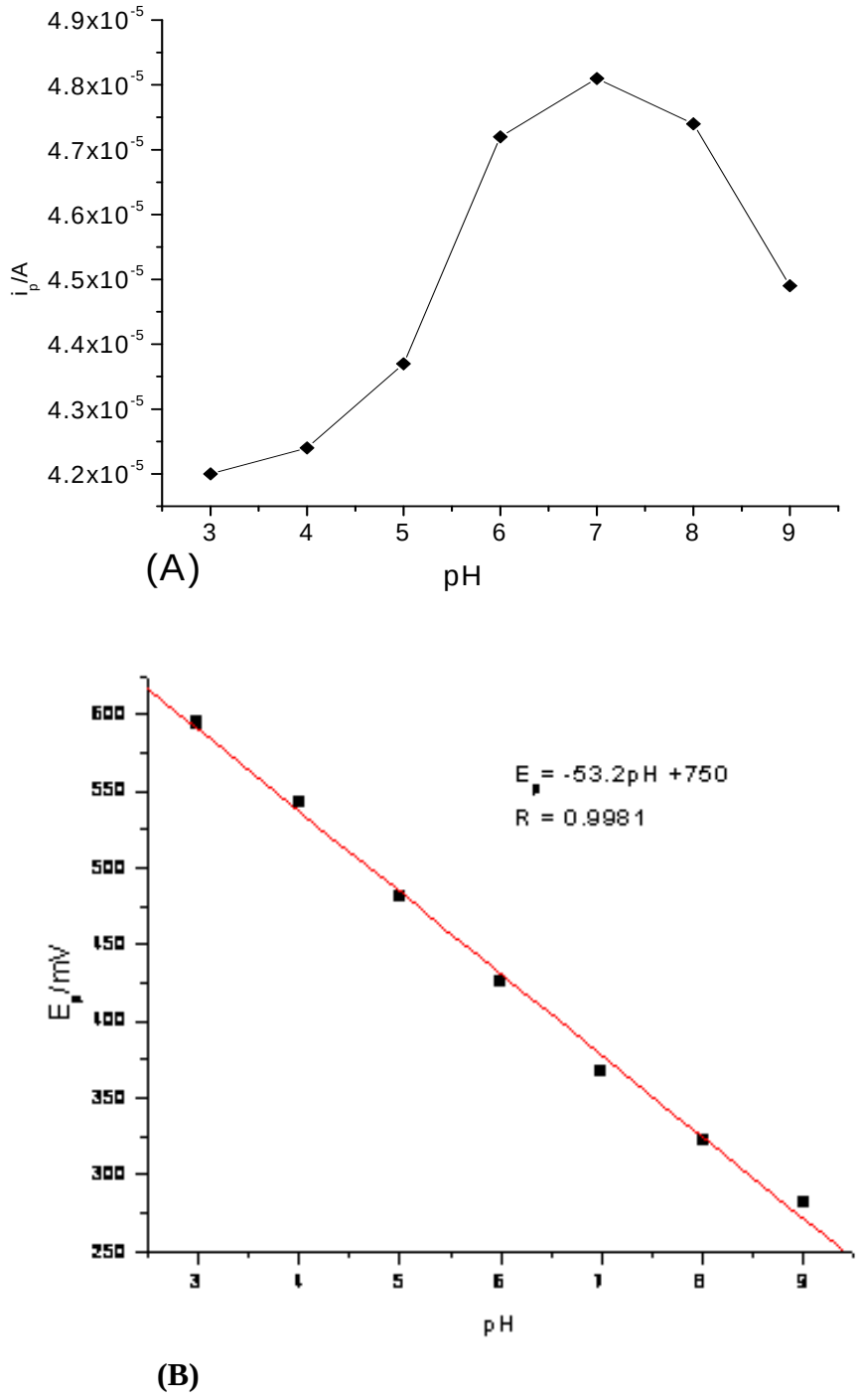

Fig. 4. The relation between (A) peak current I_p and pH, and (B) peak potential E_p and pH. Scan rate 0.1 V s^{-1}

The anodic peak potential (E_{pa}) was plotted versus pH in the range of 3-9 as shown in Fig. 4B and a linear response with a slope of -53.2 mV/pH (R=0.9981) was obtained. The signal for paracetamol shifted to more cathodic potentials as pH increased.The result indicates that the loss of electrons is accompanied by the loss of an equal number of protons which is consistent with literature reports [19] and the probable oxidation reaction [23] of paracetamol in phosphate buffer is shown in Fig. 5.

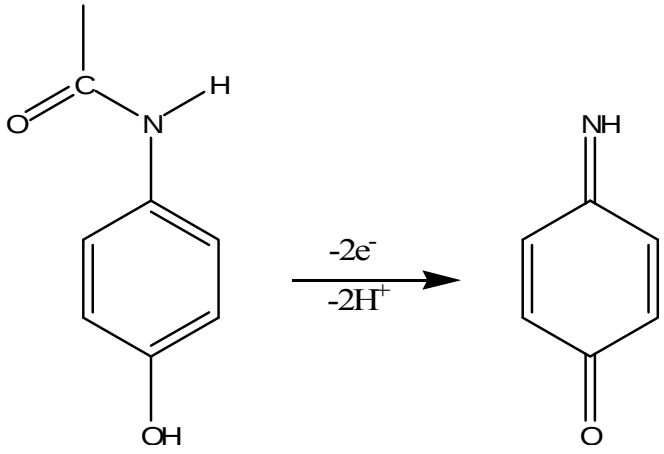

Fig. 5. The oxidation reaction for paracetamol in 0.1 phosphate buffer (pH = 7.0)

3.3. Determination of paracetamol

The PEDOT modified GC electrode showed excellent electrocatalytic behavior facilitating differential pulse voltammetric determination of paracetamol at low applied potentials. The oxidation peak current is dependent on various instrumental parameters, such as pulse amplitude and pulse width. These parameters are interrelated and have a combined effect on the voltammetric response. The optimum values were found to be 25 mV pulse amplitude and 75 ms pulse width.

Fig. 6 shows the differential pulse voltammograms of paracetamol at the modified electrode. The oxidative peak current increases linearly with the concentration of paracetamol in the range of 2.5×10^{-6} to 1.5×10^{-4} mol L^{-1} (inset of Fig. 4). The regression analysis of the plot yields a slope (sensitivity) of 90.03 μA/mmol L^{-1} and a correlation coefficient of 0.9991. The PEDOT modified electrode has a detection limit of 1.13×10^{-6} mol L^{-1} of three times of the standard deviation for 10 nmol L^{-1} of paracetamol.

3.4. Interference Study

The selectivity of the PEDOT modified GC electrode was studied in the presence of different interfering species. Voltammetric responses of paracetamol at the modified electrode were examined in the presence of possible interfering substances such as

acetylsalicylic acid, saccharine, ascorbic acid, citric acid, and sodium carbonate which can be present in pharmaceutical samples. Differential pulse (DP) voltammograms were recorded for the oxidation of paracetamol in the concentration ratios (interferent to paracetamol) of 1:10, 1:1, and 10:1, and the results obtained are given in Table 1. In all cases, there is no substantial change in the current response for 0.075 mmol L^{-1} paracetamol even in the presence of ten-fold excess of interferents except for saccharine which suppresses current response by 26.6%. The interference of the latter may be attributed to the surface adsorption of saccharine on the modified electrode [32] and then blocking the oxidation of paracetamol. Therefore, the response for paracetamol at the modified electrode is not affected by the presence of these species that were suspected to interfere in the determination of paracetamol.

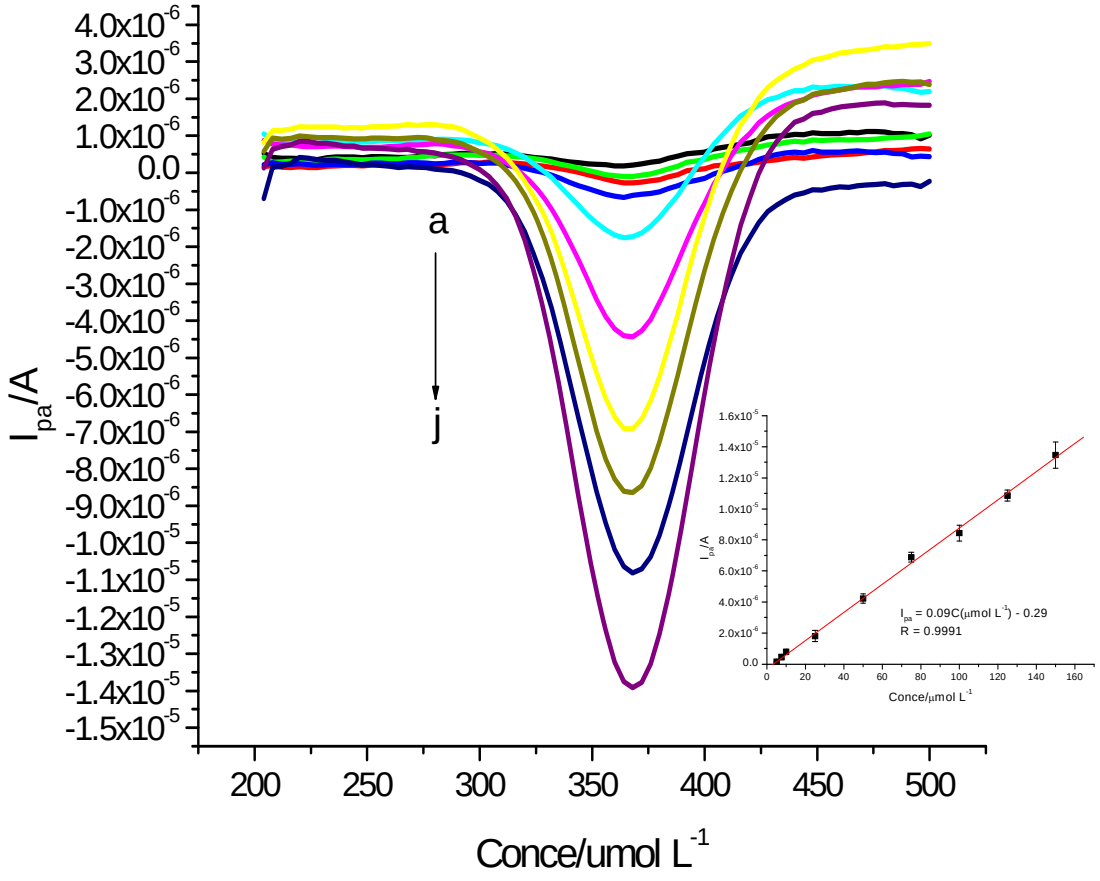

Fig. 6. Differential pulse voltammograms of solution containing (aj) 2.5, 5.0, 7.5, 10, 25, 50, 75, 100, 125 and 150 μmol L^{-1} standard paracetamol. The inset shows the calibration curve for various concentrations of paracetamol. (Background subtracted)

3.5. Application of the modified electrode to pharmaceutical samples

Commercial pharmaceutical samples (tablets) containing paracetamol were analyzed to evaluate the validity of the PEDOT modified GC electrode. Solutions obtained by dissolution of paracetamol tablets were subsequently diluted so that paracetamol concentration lies in the range of the calibration plot. DP voltammograms were then recorded under identical conditions that were employed while recording DP voltammograms for tracing the calibration plot. The results obtained are listed in Table 2.

Recovery study shows average values in the range from 97 to 107% of paracetamol, with an average recovery of (101±6) %. The precision was determined by calculating the relative standard deviation (%R.S.D.) for the replicate measurements of each sample which is less than 2.0%. The recovery study indicates that the PEDOT modified GC electrode can be effectively used for the selective determination of paracetamol in pharmaceutical samples.

Table 1. Effect of interferents on the differential pulse voltammetric response for 0.075 mmol L^{-1} paracetamol at the PEDOT modified GC electrode

Interferents	Concentration ratios (Interferent : Paracetamol)	Percent change in anodic current response for 0.075 mmol L^{-1} paracetamol (%)
Acetylsalicylic	1:10	+4.7
acid	1:1	+2.7
	10:1	-2.5
Saccharin	1:10	+3.4
	1:1	+1.1
	10:1	-26.6
Ascorbic acid	1:10	+3.2
	1:1	+2.0
	10:1	-6.3
Citric acid	1:10	+4.3
	1:1	+5.6
	10:1	+3.2
Na_2CO_3	1:10	+0.7
	1:1	+4.3
	10:1	-2.0

Table 2. Recovery study of three commercial available tablet samples using DPV with the modified electrode

Tablet sample	Amount of paracetamol (mg)		Recovery (%)	R.S.D. (%)
	labeled	Recovered by this method*		
EPHARM	500	484.90	97	1.50
ZNP	500	531.75	107	0.59
GSK	500	495.40	99	1.67

*Each value is the mean of nine measurements (three replicates of samples each prepared from different concentration levels.) (30, 60, and 90 μmol L^{-1})

3.6. Comparison with other methods

The voltammetric determination of paracetamol in this study is compared with other methods as summarized in Table 3. It can be seen that the electrochemical sensor based on PEDOT modified GC electrode provides a reasonable analytical performance but higher detection limit than nanogold modified indium tin oxide (ITO) electrode [3], polyanaline-multiwalled carbon nanotubes (MWCNT) modified electrode [19] and MWCNT basal plane pyrolytic graphite (BPPG) electrode [25]. However, the PEDOT modified electrode offers easy modification with controlled film thickness and rapid electrode preparation compared to the MWCNT modified electrodes.

Table 3. Comparison of electroanalytical data for paracetamol determination obtained using the present method to that reported in the literature

Electrode	Method	Linear (dynamic) range (μmol L^{-1})	Detection limit (μmol L^{-1})	References
Chemically modified electrode	Square wave Voltammetry	5.0-250	1.20	15
Polyanaline-MWCN Modified electrode	Square wave Voltammetry	1.0-200	0.25	19
Nanogold modified ITO electrode	Differential pulse voltammetry	0.2-1500	0.18	3
MWCNT modified BPPG electrode	Adsorptive stripping voltammetric	0.01-20	0.01	25
PEDOT modified electrode	Differential pulse voltammetry	2.5-150	1.13	This method

4. CONCLUSION

The obtained results of the above confirm that PEDOT modified electrode prepared by electropolymerization EDOT on GC electrode proves to be a very good electrochemical sensor for the determination of paracetamol. The modified electrode shows excellent electrocatalytical behavior for paracetamol determination with a dynamic linear range between 2.5×10^{-6} and 1.5×10^{-4} mol L^{-1}, with a detection limit of 1.1×10^{-6} mol L^{-1} and a sensitivity of 90.03 μA/mmol L^{-1}. The real sample analyses reveal that the modified electrode can be suitable for the selective determination of paracetamol in pharmaceutical samples.

REFERENCES

[1] M. E. Bosch, A. J. R. Sanches, F. S. Rojas, and C. B. Ojeda, J. Pharm. Biomed. Anal. 42 (2006) 291.

[2] R. M. De Carvalho, R. S. Freire, S. Rath, and L. T. Kubota, J. Pharm. Biomed. Anal. 34 (2004) 871.

[3] N. R. Goyal, V. K. Gurpta, M. Oyama, and N. Bachheti, Electrochem. Commun. 7 (2005) 803.

[4] S. J. R. Prabakar, and S. S. Narayanan, Talanta 72 (2007) 1818.

[5] J. Forshed, F. O. Andersson, and S. P. Jacobsson, J. Pharm. Biomed. Anal. 29 (2002) 495.

[6] A. Yesilada, H. Erdogan, and M. Ertan, Anal. Lett. 24 (1991) 129.

[7] F. A. Mohamed, M. A. AbdAllah, and S. M. Shammat, Talanta 44 (1997) 61.

[8] M. S. Bloomfield, Talanta 58 (2002) 1301.

[9] A. Marin, E. Garcia, A. Garcia, and C. Barbas, J. Pharm. Biomed. Anal. 29 (2002) 701.

[10] L. A. Shervington, and N. A. Sakhnini, J. Pharm. Biomed. Anal. 24 (2000) 43.

[11] F. Bohnenstengel, H. K. Kroemer, and B. Sperker, J. Chromotogr. B. Biomed. Sci. Appl. 721 (1999) 295.

[12] S. Heitmer, and G. Blaschke, J. Chromotogr. B. Biomed. Sci. Appl. 721 (1999) 93.

[13] L. Suntornsuk, O. Pipitharome, and P. Wilairat, J. Pharm. Biomed. Anal. 33 (2003) 441.

[14] E. Valero, P. Carrion, R. Varon, and F. Garcia-Carmona, Anal. Biochem. 318 (2003) 187.

[15] J. M. Zen, and Y. S. Ting, Anal. Chim. Acta 342 (1997) 175.

[16] F. S. Felix, C. M. A Brett, and L. Angnes, J. Pharm. Biomed. Anal. 43 (2007) 1622.

[17] S. F. Wang, F. Xie, and R. F. Hu, Sens. Actuators B 123 (2007) 495.

[18] R. N. Goyal, and S. P. Singh, Electrochim. Acta 51 (2006) 3008.

[19] M. Li, and L. Jing, Electrochim. Acta 52 (2007) 3250.

[20] A. Gómez-Caballero, M. A. Goicolea, and R. J. Barrio, Analyst 130 (2005) 1012.

[21] F. Y. He, A. L. Liu, and X. H. Xia, Anal. Bioanal. Chem. 379 (2004) 1062.
[22] A. Safavi, N. Maleki, and O. Moradlou, Electroanalysis 20 (2008) 2158.
[23] X. ShangGuan, H. Zhang, and J. Zheng, Anal. Bioanal. Chem. 391 (2008) 1049.
[24] B. C. Lourencao, R. A. Medeiros, R. C. Rocha-Filho, L. H. Mazo, and O. Fatibello-Filho, Talanta 78 (2009) 748.
[25] R. T. Kachoosangi, G. G. Wildgoose, and R. G. Campton, Anal. Chim. Acta 618 (2008) 54.
[26] L. Ozcan, and Y. Sahin, Sens. Actuators B 127 (2007) 362.
[27] S. A. Emr, and A. M. Yacynych, Electroanalysis 7 (1995) 913.
[28] S. Cosnier, and A. Lepellec, Electrochim. Acta 44 (1999) 1833.
[29] M. Hiller, C. Kranz, J. Huber, P. Bauerle, and W. Schuhmann, Adv. Mater. 8 (1996) 219.
[30] D. Pletcher, R. Greef, R. Peat, L. M. Peter, and J. Robinson, Electrochemistry Horwood Publishing, Chichester (2001) 206.
[31] D. Ravishankaran, and S. S. Narayanan, Sens. Actuators B 86 (2002) 180.
[32] T. M. Manhabosco, and I. L. Muller, Surf. Coat. Technol. 202 (2008) 3585.