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Electroanalytical Investigation of Paracetamol on Glassy Carbon Electrode by Voltammetry

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An electroanalytical method was developed for the direct quantitative determination of paracetamol (or acetaminophen) in tablet dosage forms based on its oxidation behavior. The electrochemical oxidation and determination of paracetamol were easily carried out on glassy carbon electrode (GCE) using a variety of voltammetric techniques. The electrochemical measurements were carried out on GCE in various buffer solutions in the pH range from 0.51 to 12.00 by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. The dependence of pH on the anodic peak current and peak potential was investigated. Acetate buffer (pH 4.51) was selected for analytical purposes. Scan rate studies were also completed. The diffusion controlled nature of the peak was established. A linear calibration curve for DPV analysis was constructed in the paracetamol concentration range from $4x10^{-6}$ mol/L to $1x10^{-4}$ mol/L. Limit of detection (LOD) and limit of quantification (LOQ) were obtained as $3.69x10^{-7}$ mol/L and $1.23x10^{-6}$ mol/L respectively. Validation of applied voltammetric techniques was checked with recovery studies.

Keywords: Voltammetric determination; drug forms; glassy carbon electrode; paracetamol; voltammetry.

1. INTRODUCTION

Paracetamol is also known as acetaminophen (Fig. 1); it is a major ingredient in numerous cold and flu medications and many prescription analgesics [1]. Paracetamol acts as painkiller by inhibiting prostaglandin's synthesis in the central nervous system and relieves fever by sedating the hypothalamic

heat-regulating center [2]. Because of all these properties, it is important to develop for the determine of paracetamol from its pharmaceutical preparations by simple, sensitive electroanalytical methods.

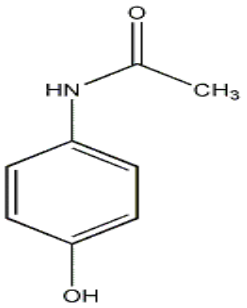


Figure 1. Chemical structure of paracetamol.

So far various techniques have been employed for the detection of paracetamol, including high performance liquid chromatography, spectrophotometry, chemiluminescence, capillary electrophoresis, and titrimetry [3-7]. These methods are tedious, high cost and require pre-treatment of samples. However, electrochemical techniques such as voltammetry offers high sensitivity, precision, low cost and accuracy beside wide linear range. Paracetamol is a well known electro active compound, therefore many papers have been published about the electroanalytical determination of paracetamol based on its oxidation behavior with different electrodes such as modifed glassy carbon electrodes, screen printed electrodes, graphite electrodes, nanotubes, and gold electrodes [8-12].

Electrochemical analytical techniques are powerful and versatile analytical techniques that can easily solve many problems of pharmaceutical interest. Especially, voltammetry is a practical electrochemical analytical technique that offers high sensitivity, selectivity, precision, and accuracy, wide linear range and low-cost instrumentation and time.

The aim of this work was electrochemical investigation of paracetamol and to develop a sensitive electrochemical methodology for direct and fast quantification of paracetamol in its pharmaceutical formulations on solid electrode such as GCE using voltammetric techniques.

Although the oxidation behaviour of paracetamol was studied, there have not been sufficient studies on the determination and electrochemical-oxidation behavior on GCE by voltammetry. So, in this study, electrochemical properties, determination of paracetamol and full validation of applied voltammetric techniques were carried out on GCE.

Quantitative analysis was performed on the drug active substance in tablet dosage form on GCE electrode. It showed excellent electrooxidative activity for paracetamol in acetate buffer (pH 4.51)

2. EXPERIMENTAL

2.1. Apparatus

A Model Metrohm 757 VA Trace Analyzer (Herisau, Switzerland) was used for the voltammetric measurements, with a three-electrode system consisting of glassy carbon working

electrode (GCE; φ = 3 mm, Metrohm), a platinum wire auxiliary electrode and Ag/AgCl (KCl 3 mol/L, Metrohm) reference electrode. The glassy carbon working electrode was polished with alumina (prepared from φ = 0.01 μm aluminum oxide) on an alumina polish pad before each experiment and then rinsed with ultra pure deionized water and ethanol. Then firstly, the deoxygenation process of the supporting electrolyte solutions was carried out with argon gas for 5 min before all experiments. The argon gas was also passed through the solutions for 60 s after the addition of each sample solution in the experiments. In each new experiment, a new bare electrode surface was used. All pH measurements were made with Model Metrohm 744 pH meter (Herisau, Switzerland) at ambient temperature of the laboratory (15 °C to 20 °C).

For the analytical application, the following parameters were employed: pulse amplitude 50 mV; pulse time 0.04 s, voltage step 0.009 V, voltage step time 0.04 , potential step 10 mV (DPV); with the scan rate in the range from 10 mV/s to 1000 mV/s (CV).

2.2. Reagents and materials

Paracetamol was kindly supplied by Atabay (Istanbul, Turkey). A stock solution of $1.0x10^{-2}$ mol/L of paracetamol was prepared by dissolving an accurate mass of the drug in an appropriate volume of methanol kept in the refrigerator. The working solutions for the voltammetric investigations were prepared by dilution of the stock solution. All solutions were protected from light and were used within 24 h to avoid decomposition. 0.5 mol/L H_2SO_4 (pH 0.51) solution, 0.067 mol/L phosphate buffer (pH range of 4.40-7.28), 0.2 mol/L acetate buffer (pH range of 3.51-5.62) and 0.04 mol/L Britton Robinson buffer (pH range of 2.02-12.00) were used for the supporting electrolyte solutions. Ultra pure-deionized water obtained from Sartorius Arium model Ultra Pure Water Systems was used to prepare supporting electrolytes. All chemicals used were of analytical-reagent grade.

2.3. Calibration graph for quantitative determination

The stock solution of paracetamol was diluted with methanol to obtain different paracetamol concentrations. Using the optimum conditions described in the experimental section, a linear calibration curve for DPV analysis was constructed in the paracetamol concentration range from $4x10^{-6}$ mol/L to $1x10^{-4}$ mol/L. The repeatability, accuracy and precision were checked.

2.4. Working voltammetric procedure for spiked tablet dosage forms

Ten tablets were weighed and ground to a fine powder. An adequate amount of this powder, corresponding to a stock solution of concentration $1x10^{-2}$mol/L, was weighed and transferred to a 10 mL calibrated flask and the volume was adjusted with methanol. The contents of the flask were centrifuged for 20 min at 4000 rpm to ensure complete dissolution and then diluted to volume with the same solvent. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquor and diluting with selected supporting electrolyte solutions. Each solution was transferred into

the voltammetric cell. The nominal content of the corresponding regression equations was compared with previously plotted calibration plots.

3. RESULTS AND DISCUSSION

3.1. Electrochemical oxidation behavior of paracetamol

In order to obtain the optimum experimental conditions, some variables affecting the peak current and peak potential, which are pH and the species of supporting electrolyte (pH range of 0.51-12.0), were studied for a paracetamol solution of $5x10^{-5}$mol/L on the GCE by the proposed voltammetric technique (as shown in Fig. 2).

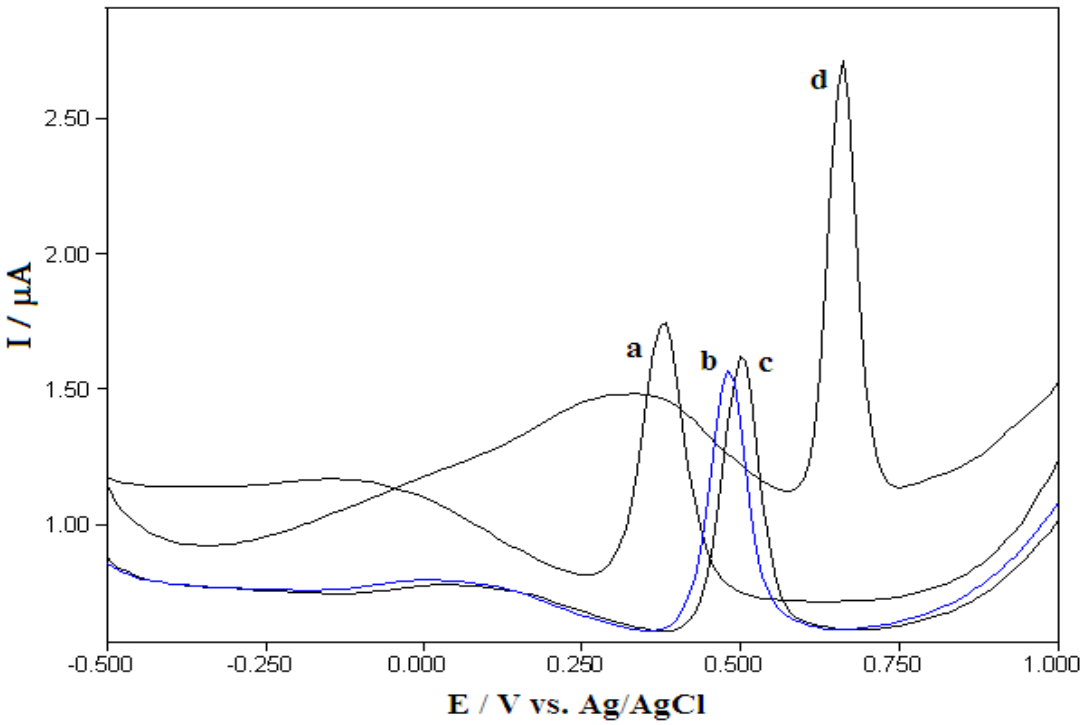


Figure 2. DPV voltammograms of a GCE in different electrolytes containing $5x10^{-5}$ mol/L Paracetamol; a) 0.067 mol/L phosphate buffer at pH 5.45, b) 0.2 mol L^{-1} acetate buffer at pH 4.51, c) 0.04 mol/L BR buffer at pH 4.01, d) 0.5 mol/L sulfuric acid at pH 0.51

When studied the effect of pH on the peak current, the high peak current and shape peak was observed at pH 4.51 in 0.2 M acetate buffer despite the highest peak current was measured in 0.5 mol/L H_2SO_4 (pH 0.51) solution. Therefore, pH 4.51 in 0.2 M acetate buffer were chosen for the electroanalytical studies (as shown in Fig. 3).

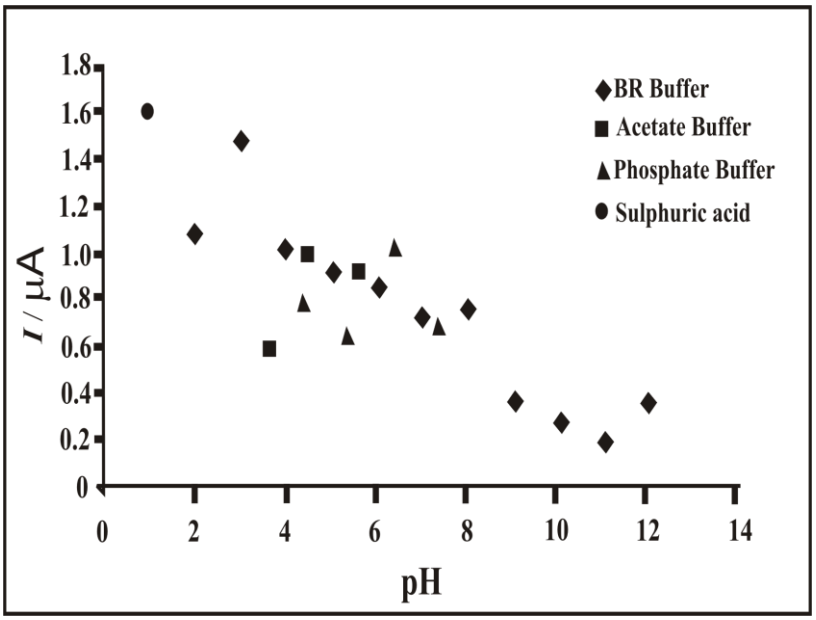


Figure 3. The change in pH on the peak current of $5x10^{-5}$ mol/L paracetamol in different buffer solutions by DPV voltammograms.

The peak potential of the oxidation peak shifted from 0.7 V to 0.1 V values with increasing pH (Fig.4). This indicate that, the voltammetric response was strongly pH dependent. These can also be explained by changes in protonation of the acid-base functions in the paracetamol molecules (Scheme 1) . In other word, proton takes part in the electrochemical reactions of paracetamol [13-23].

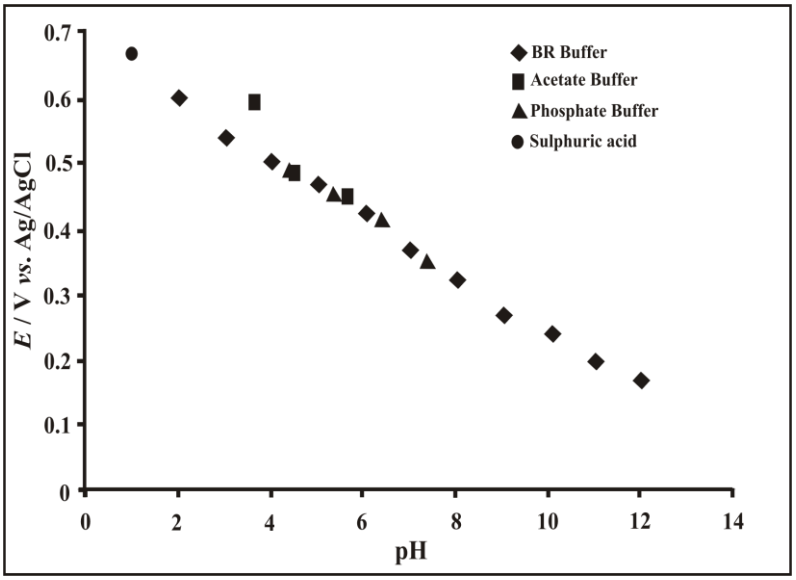


Figure 4. The change in pH on peak potential of $5x10^{-5}$ mol/L paracetamol in different buffer solutions by DPV voltammograms.

The effects of the scan rate from10 mV/s to 1000 mV/s on the peak potential and the paracetamol peak current were evaluated. With increasing scan rate, the anodic peak current increased (as shown in Fig. 5).

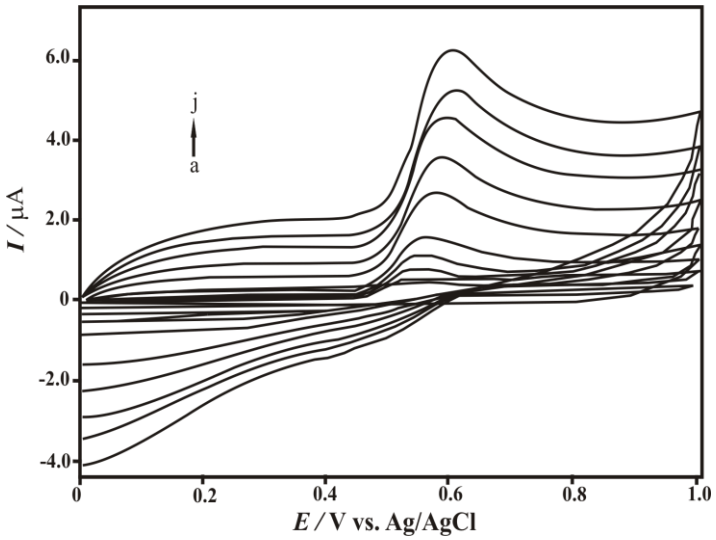


Figure 5. The cyclic voltammograms of $1x10^{-4}$ mol/L paracetamol in 0.2 mol/L acetate buffer (pH 4.51) on a GCE. Scan rate, mV/s) blank b) 10 c) 25 d) 50 e) 100 f) 250 g) 400 h) 600 i) 750 j) 1000 (mV/s).

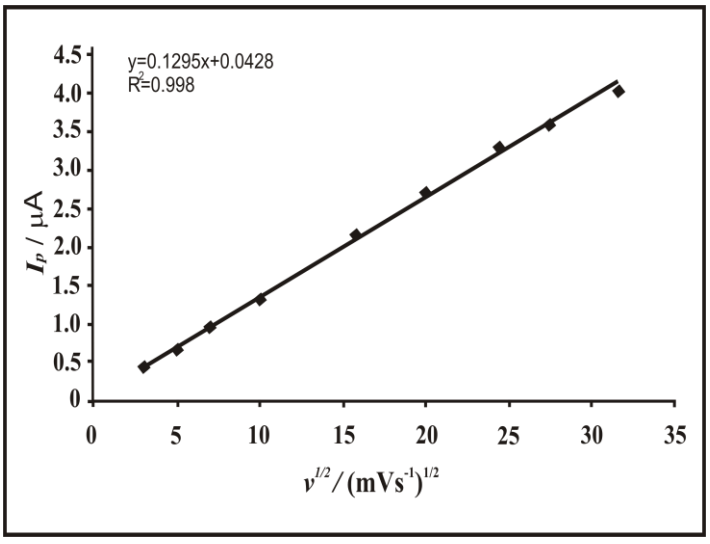


Figure 6. Plot of square root of scan rate versus peak current.

The electrochemical oxidation process was carried out using CV techniques. The CV voltammogram of paracetamol exhibited only one anodic peak, with no peak on the reverse scan, indicating the totally irreversible nature of the electrode reaction. In addition, for an irreversible

oxidation process, the peak potential E_p shifts to less positive values with the increase in scan rate. Therefore, the oxidation process of paracetamol was proved to be irreversible [13-23].

The correlation coefficient of anodic peak current and square root of the scan rate 0.9981 (expected about 1.0) (Ip/μA=0.1295 $\upsilon^{1/2}$+0.0428), and 0.4984 which is almost close to the theoretical value of 0.5 (logIp/μA=0.4984logυ-0.8739) slope of plot of logarithm of peak current versus logarithm of scan rate indicated that the oxidation process is predominantly diffusion-controlled (as shown in Fig. 6 and Fig. 7) [13-23].

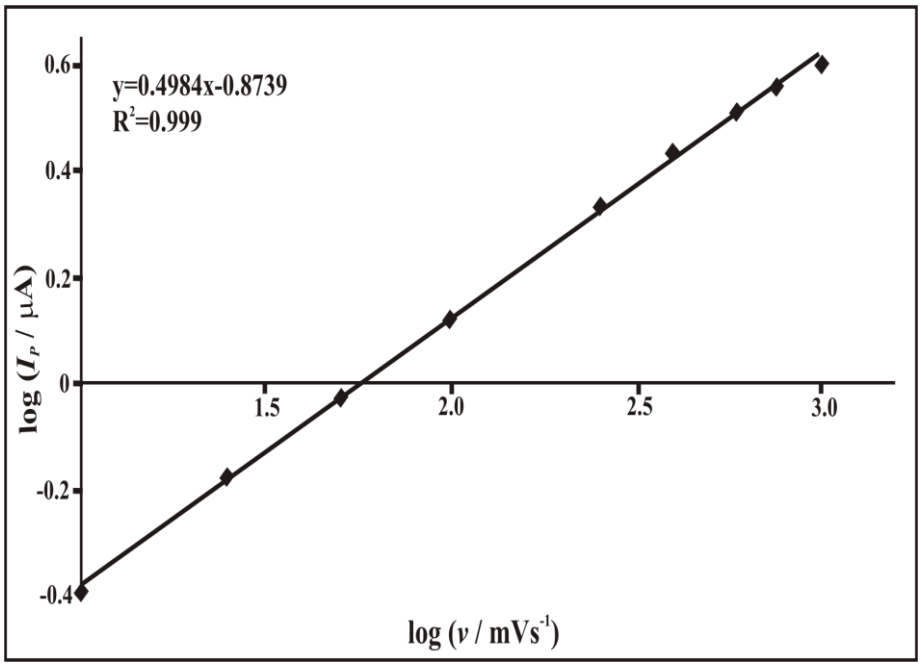
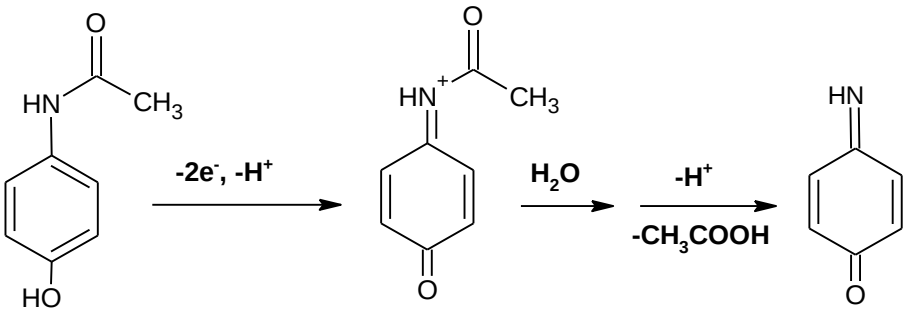


Figure 7. Plot of logarithm of peak current versus logarithm of scan rate.

From this study, approximately two protons were transferred in the reaction. Paracetamol oxidation is a two-electron and two-proton process in Scheme 1 given below. A conclusion that is consistent with that reported in the literature [24-26].



Scheme 1. Suggested oxidation mechanisms of paracetamol on GCE .

3.2. Validation of the proposed voltammetric technique

DPV technique was used to develop a voltammetric methodology for determination of the drug in pharmaceutical form. Under the optimized experimental conditions, a linear relationship between the oxidation peak current of paracetamol at GCE and concentration can be established in the range from $4x10^{-6}$ mol/L to $1x10^{-4}$ mol/L (as shown in Fig. 8).

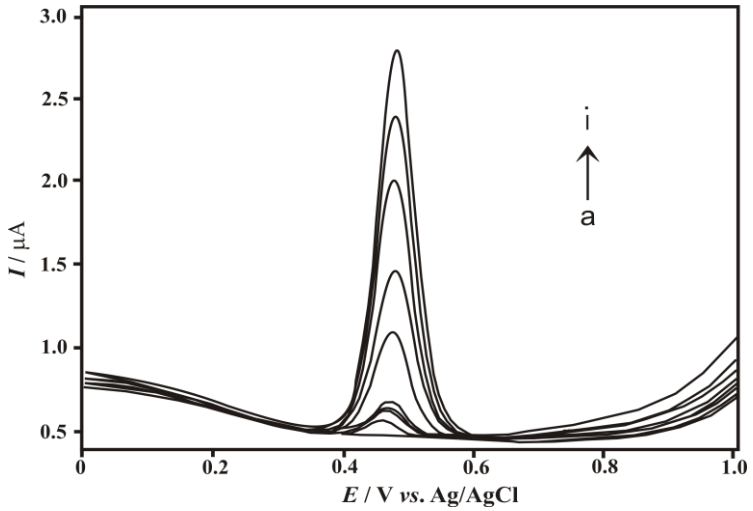


Figure 8. The calibration voltammograms at different concentrations of paracetamol in acetate buffer (pH 4.51) on a GCE by DPV. a) $4x10^{-6}$ b) $6x10^{-6}$ c) $8x10^{-6}$ d) $1x10^{-5}$ e)$3x10^{-5}$ f) $5x10^{-5}$ g) $7x10^{-5}$ h) $9x10^{-5}$ i) $1x10^{-4}$ (mol/L).

The equation of the linear regression plots was $I_p/\mu A=2.20x10^4(mol/L)–0.0024$; correlation coefficient, r=0.9989; n=5 repeat measurements. Standard deviations for intercept and slope of the calibration curve are given in Table 1.

Validation of the procedure for the quantitative determination of paracetamol was examined via evaluation of the limit of detection (*LOD*), limit of quantification (*LOQ*), repeatability, reproducibility, recovery, accuracy and precision (Table 1).

Table 1. Analytical parameters of paracetamol obtained in acetate buffer (pH 4.51) by DPV technique

Parameters	**Results**
Measured potential,V	0.418
Linear concentration range, mol L^{-1}	from $4x10^{-6}$ to $1x10^{-4}$
Slope, μA M^{-1}	$2.20x10^4$
SD of slope	133.51
Intercept(nA)	0.0024
SD of intercept	$2.74x10^{-3}$
Correlation coefficient, r	0.9989
LOD, mol L^{-1}	$3.69x10^{-7}$
LOQ, mol L^{-1}	$1.23x10^{-6}$

Repeatibilty of peak current, *RSD* / %	2.33 for $3x10^{-5}$ M and 1.39 for $9x10^{-5}$ M
Repeatibilty of peak potential, *RSD* / %	1.075 for $3x10^{-5}$ M and 1.096 for $9x10^{-5}$ M
Reproducibility of peak current, *RSD* / %	2.33 for $3x10^{-5}$ M and 1.94 for $9x10^{-5}$ M
Reproducibility of peak potential, *RSD* / %	2.38 for $3x10^{-5}$ M and 1.87 for $9x10^{-5}$ M

LOD and *LOQ* were calculated on the oxidation peak current using the following equations: *LOD = 3 s/m*, *LOQ = 10 s /m* (s is the standard deviation of the peak currents five runs, m is the slope of the calibration curve). The *LOD* and *LOQ* were calculated as $3.69x10^{-7}$ mol/Land $1.27x10^{-6}$ mol/L respectively.

A good repeatability and reproducibility of the peak current and potential were calculated from five independent measurements.

3.3. Determination of paracetamol in tablet form by voltammery techniques

The amount of paracetamol in commercial tablets was calculated by reference to the appropriate calibration plots. The results obtained are given in Table 2.

To determine whether excipients in the tablets interfered with the analysis, the accuracy of the proposed methods was evaluated by recovery tests after the addition of a certain amount of pure drug to pre-analyzed formulations of paracetamol. The results showed the validity of the proposed techniques for the quantitative determination of paracetamol in tablets.

Table 2. Application of the DPV technique for the assay of paracetamol in tablet form.

Parameters	**Results**
Labeled paracetamol, mg	500.00
Amountfound, mg	495.71
Relative Standart deviation, *RSD* / %	0.72
Bias, %	0.86
Paracetamol spiked, mg	40.00
Found, mg	39.32
Average recovery, %	98.30
Relative standart deviation of recovery, *RSD* / %	1.70
Bias, %	1.86

4. CONCLUSIONS

A simple, sensitive, selective DPV technique for the quantitative determination of paracetamol based on the electrochemical oxidation at GCE was established. From the CV and DPV measurements, it is understood that the electrode reaction process is irreversible and pH dependent. Paracetamol was successfully determined in acetate buffer (pH 4.51) in tablet doses by DPV technique.

The principal advantage of the DPV technique over the other techniques is that it may be applied directly to the analysis of pharmaceutical dosage form without the need for extensive sample preparation, since there was no interference from the excipients and endogenous substances. Another advantage is that the developed DPV technique is rapid, requiring about 5 min to run any sample and involves no sample preparation other than dissolving, diluting, precipitating, centrifuging and transferring an aliquot to the supporting electrolyte.

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References

1. M. E. Bosch, A. J. R. Sanchez, F. S. Rojas, *J.Pharmaceut Biomed Anal.*, 42 (2006) 291.
2. R. N. Goyal, S. P. Singh, *Electrochim.Acta,* 51 (2006) 3008.
3. A. Marin, E. Garcia, A. Garcia, *J.Pharmaceut. Biomed. Anal.*, 29 (2002) 701.
4. B. Morelli, *J. Pharm Biomed Anal.*, 7 (1989) 577.
5. W. Ruengsitagoon, S. Liawruangrath, A. Townshend,*Talanta*,69 (2006) 976.
6. S. Zhao, W. Bai,H. Yuan,*Anal.Chim.Acta*, 559 (2006)195.
7. G. Burgot, F. Auffret, J. L. Burgot, *Anal.Chim.Acta* 343 (1997) 125.
8. W.Y. Su, S.H. Cheng, *Electroanal.*, 22 (2010) 707.
9. J. M. Zen, Y. S. Ting, *Anal.Chim.Acta*, 342 (1997) 175.
10. R. T. Kachoosangi, G. G. Wildgoose,R. G. Compton, *Anal.Chim.Acta*, 618 (2008) 54.
11. R. N.Goyal, V. K. Gupta, M.Oyama,*Electrochem.Commun.*,7 (2005) 803.
12. S. Cheemalapati, S. Palanisamy, V. Mani,*Talanta*, 117(2013) 297.
13. M. Citak, S. Yilmaz, Y. Dilgin, G. Türker, S. Yagmur, H. Erdugan, N. Erdugan, *Curr. Pharm. Anal.* 3 (2007) 141.
14. S. Skrzypek, W. Ciesielski, A. Sokolowski, S. Yilmaz, D. Kazmierczak, *Talanta*, 66 (2005) 1146.
15. S. Yagmur, S. Yilmaz, M. Sadikoglu, G. Saglikoglu, M. Yildiz, C. Yengin, E. Kilinc, *Int. J. Electrochem. Sci*., 8 (2013) 6818.
16. S. Skrzypek, W. Ciesielski and S. Yilmaz, *Chem. Anal.(Warsaw)* 52 (2007) 1071.
17. S. Yılmaz, S.Skrzypek,Y.Dilgin, S. Yagmur and M. Coskun, *Current Analytical Chemistry*, 3 (2007) 41..
18. S. Yilmaz, M. Sadikoglu, G. Saglikoglu, S. Yagmur and G. Aksin, *Int. J. Electrochem. Sci.*, 3 (2008) 1534..
19. S. Yilmaz, *Colloids and Surfaces, B:Biointerfaces*, 71 (2009) 79.
20. M. Sadikoglu, G. Saglikoglu, S.Yagmur, E. Orta and S. Yilmaz, *Current Analytical Chemistry*, 7 (2011) 130.
21. B.Uslu, S.A.Ozkan, Electrochimica Acta, 49 (2004) 4321.
22. B.Uslu, S.A.Ozkan, Electroanalysis, 17 (2005) 2074.
23. C. Engin, *Çanakkale Onsekiz Mart University, Graduate School of Scince and Engineering Chair for Chemistry, Thesis of Master*, Canakkale, Turkey, 2012.
24. M. Zidan, T.W. Tee , A. Abdullah, Z. Zaina , G. J. Kheng, Int. J. Electrochem. Sci., 6 (2011) 279.
25. M. Zidan, T.W. Tee , A. Abdullah, Z. Zaina , G. J. Kheng, *E-Journal of Chemistry*, 8 (2011) 553.
26. X. S. Guan, H. Zhang, .*Anal Bioanal Chem*, 391 (2008) 1049.