Differential pulse stripping voltammetric determination of paracetamol in pharmaceutical tablet samples using murexide modified carbon paste electrode

Yonas Beyene Yohannes[1*] and Mohammed Hajole Erba[1]

[1]Department of Chemistry, Bahir Dar University, 79, Bahir Dar, Ethiopia

ABSTRACT

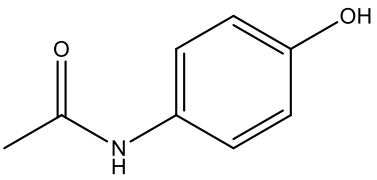
As an acetyl aniline drug, paracetamol (PA) has antipyretic and analgesic functions, which is suitable for the remedy of fever, headache and joint ache. The murexide modified carbon paste electrode was characterized by cyclic voltammetry and electrochemical impedance spectroscopy and compared with bare carbon paste electrode. In this study, murexide-carbon paste electrode (MXCPE) was described for the differential pulse stripping voltammetric determination of paracetamol in pharmaceutical tablet sample. The MXCPE exhibited a better electrocatalytical behavior for the oxidation of PA as evidenced by nearly two folds of current enhancement and a shift of the onset potential by 65 mV in comparison with a bare carbon paste electrode. Differential pulse stripping voltammetry peak currents of PA increased linearly with their concentrations in the ranges of 5-1000 μM with a detection limit of 0.09 μM (S/N = 3). The determination of the analyte in pharmaceutical samples was found in the range 97.6-106.0% of the theoretical values and a recovery result between 94.6 and 96.8% was obtained. For selective determination of PA in the presence of AA was successfully performed.

Keywords: Electrochemical oxidation; Murexide; Paracetamol; Voltammetric determination
DOI: https://dx.doi.org/10.4314/ejst.v14i3.1

INTRODUCTION

As a pain-relieving for home medication for over 50 years, paracetamol (PA) is putative as an effective drug for the respite of pain and fever in adults and children. Paracetamol (N-acetyl-p-aminophenol) (Scheme 1) has been used extensively for the respite of ache associated with a backache, headache, arthritis and post-surgical pain (Anderson, 2008). Hence, PA resides in a sole situation among analgesic drugs (Bertolini *et al.*, 2006). Although PA is regarded as an excellent profile safe medicine taken in a recommended dose, the large-scale therapeutic use of this drug needs the development of simple, sensitive, selective and accurate analytical method for its determination.

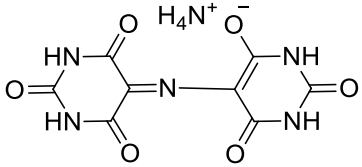
*Corresponding author: yonasb94@gmail.com



Scheme 1. Structure of paracetamol

Numerous analytical techniques including fluorescence (Moreira *et al.*, 2005), high performance liquid chromatography (Shinde *et al.*, 1995; Goyal and Jain, 2007), spectrophotometry (Baptistao *et al.*, 2011), capillary electrophoresis hyphenated to mass spectrometry (Lecoeur *et al.*, 2019), and FTIR and Raman spectrometry (Al-Zoubi *et al.*, 2002) are among the techniques used for the determination of PA in real samples. The aforementioned methods are expensive, time consuming and involve tedious sample pre-treatment procedure, and they are less sensitive and selective making them inappropriate for monotonous analysis (Li *et al.*, 2018). In the past decades, electrochemical methods of analysis have been reported for the determination of PA (Shahmiri *et al.*, 2013; Zhu *et al.*, 2014; Görçay *et al.*, 2016; Foroughi *et al.*, 2019; Meenakshi *et al.*, 2020). Though for the determination of PA many available electrochemical techniques are used, the use of murexide (MX) as a modifier has not been reported.

Murexide (ammonium purpurate) is the ammonium salt of purpuric acid (Scheme 2), which is used in analytical chemistry as indicator for complexometric titrations of Ca, Cu, Ni, Co, Th and rare earth metal ions (Mohran, 2009). Anil Kumar *et al*. (2019) reported electrochemical sensor application of electrodeposited conductive poly(murexide) film on the surface of glassy carbon electrode.



Scheme 2. Structure of murexide (MX)

In this study, we report the application of murexide modified carbon paste electrode (MXCPE) for differential pulse stripping voltammetric determination of paracetamol in pharmaceutical tablet formulation, which to the best of our knowledge is not reported for the same.

MATERIALS AND METHODS

Chemicals and reagents

The chemicals used include paracetamol (99.8%, Merck), potassium phosphate dibasic (K_2HPO_4) (99.0%, Titan Biotech LTD), potassium phosphate monobasic (KH_2PO_4) (99.0%, Titan Biotech LTD), sodium hydroxide (97%, Blulux, India), hydrochloric acid (37%, LobaChemie Pvt. Ltd.), graphite powder (Blulux Laboratories Ltd.), paraffin oil light (BDH, England), murexide (98.8%, Merck).

Apparatus and instruments

All electrochemical experiments were performed with a CHI 760D electrochemical workstation (CH Instruments, USA) connected to a personal computer using a conventional three-electrode system; platinum coil as a counter electrode, Ag/AgCl (3 M KCl) as a reference electrode, and an unmodified carbon paste (CPE) or murexide modified carbon paste electrode (MXCPE) as a working electrode. A pH meter (AD8000, Romania), and an electronic balance (Nimbus, ADAM) were used to measure the pH and mass, respectively. All experiments were performed at room temperature, and the electrode potentials quoted are versus Ag/AgCl electrode.

Procedure

Preparation of the working electrode (bare CPE and MXCPE)

The bare carbon paste electrode (CPE) was prepared by homogeneous mixing of 70% graphite powder and 30% paraffin oil (as binding agent) (Shahmiri *et al.*, 2013). The modified murexide carbon paste electrode (MXCPE) was prepared by substituting corresponding amounts of graphite powder (5, 10, 15, 20, and 25% w/w ratio of the modifier (MX) relative to the graphite powder) and paraffin oil (30 %) and manually homogenizing the mixture using mortar and pestle. Both the bare and modified active pastes were then left for 24 hours and packed into a cavity of plastic tube (d = 3 mm) by tapping and using copper wire (d = 1 mm) to make electric contact. The electrode surface was polished on a clean paper until it had a shiny surface.

Analytical procedures

For voltammetric experiments, the working electrode (either unmodified CPE or MXCPE) was placed in 0.1 M pH 7.0 PBS containing anticipated concentration of PA. CV and DPSV techniques were used for the determination of PA. For CV the measurement was taken in the potential window from –0.2 to +1.0 V at a scan rate of 50 mV s^{-1}. DPSV under optimized parameters (accumulation potential of 0.5 V and accumulation time of 30 s) and default parameters (amplitude 25 mV, step potential 4 mV, sample width 20 ms and pulse width 25 ms) was employed for the quantitative analyses of PA in PA tablet formulations of different brands.

Electrochemical impedance spectroscopy (EIS) measurements were carried out in the frequency range from 100 kHz to 0.01 Hz. A 0.1 M of phosphate buffer solution (PBS) was prepared from equimolar (0.1 M) stock solution of K_2HPO_4 and KH_2PO_4 and employed as supporting electrolyte. All solutions were prepared in double distilled water.

Sample preparation

Commercial pharmaceutical tablet samples (Adol Julphar (Ethiopia), Panadol Adva (Kenya), and Para-Denk (Germany) all labelled 500 mg PA/tablet were inspected for the determination of the content of PA. A stock solution of each brand of tablet with 0.5 mM PA concentration in pH 7.0 PBS was prepared by dissolving an adequately weighed 0.1 g powder PA of each brand transferred in to a 250 mL volumetric flask (Barsan *et al.*, 2015).

RESULTS AND DISCUSSION

Characterization of MXCPE

The characterization of MXCPE was performed by cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). Comparative electrocatalytic properties of the electrodes were studied using $[Fe(CN)_6]^{-3}/[Fe(CN)_6]^{-4}$ as a probe. The cyclic voltammograms obtained for 5 mM $Fe(CN)_6^{3-/4-}$ redox probe using bare CPE and MXCPE electrodes are presented in Figure 1(A). It is clearly seen that, the current response at MXCPE was largely increased, indicating that the electrochemical active sites of the bare CPE increased by MX surface modification. And the peak potential separation (ΔE_p) at MXCPE and bare CPE was found to be 137 mV and 510 mV, respectively. It is perceived that the electron transfer rate increases with a decrease in the value of ΔE_p (Bard and Faulkner, 2001). The redox peak current is also higher in the case of MXCPE which is an indicator of increasing surface area of the electrode. In addition the Randles-Sevcik equation (Kissinger and Heineman, 1983) was utilized to measure the effective surface area by:

$$I_p = 2.69 \times 10^5 A D^{1/2} n^{3/2} \nu^{1/2} C \quad (1)$$

where I_p refers to the peak current (A), n is the number of electrons transferred, A is effective electrode area (cm^2), ν is the scan rate (Vs^{-1}), C_0 and D_0 the molar concentration ($molcm^{-3}$) and diffusion coefficient (cm^2s^{-1}) of $[Fe(CN)_6]^{4-}$, respectively. Under the measured conditions (T = 298 K, ν = 50 mVs^{-1}, C_0 = 5.0 mM, $D_0 = 7.6 \times 10^{-6}$ cm^2s^{-1}) (Zheng *et al.*, 2013) the effective surface area was estimated to be 0.012 cm^2 and 0.038 cm^2 for bare CPE and MXCPE, respectively. As a result, current response for the redox couple $[Fe(CN)_6]^{3-/4-}$ increased with rise in the effective surface area of the murexide modified electrode. To evaluate the electrical conductivity of the electrodes, EIS analysis was performed on the redox probe of 5 mM $Fe(CN)_6^{3-/4-}$ as shown in Figure 1(B). The bare CPE has displayed an

enlargement with an electron transfer resistance while the Nyquist plot of MXCPE shows almost a straight line which suggested its lower electron transfer. Generally, almost a straight line plots at high frequencies imply that the electrode processes are mass transfer-controlled (Ghadimi *et al.*, 2016). These results were in a good agreement with the results obtained with CV proving the electrocatalytical behavior of MXCPE.

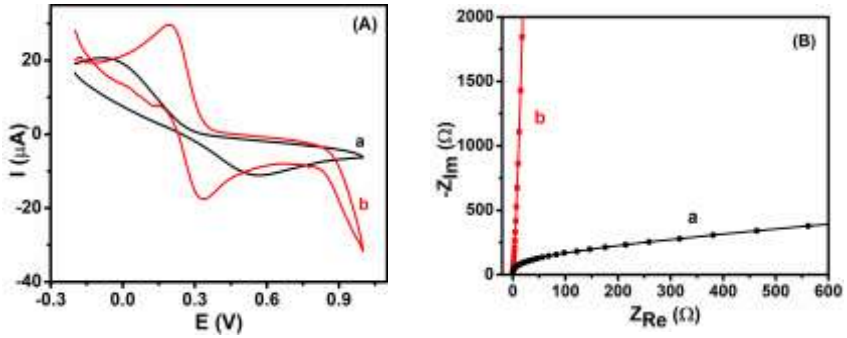


Figure 1. (A) Cyclic voltammograms, and (B) Nyquist diagrams of bare CPE (a) and MXCPE (b) of 5 mM $Fe(CN)_6^{3-/4-}$ in 0.1 M KCl redox probe (scan rate for CV: 50 mVs^{-1}, frequency range for EIS: 10^{-2} to 10^5 Hz at 0.40 V).

Electrochemical Behavior of Paracetamol at MXCPE

The CVs of the bare CPE and MXCPE recorded in pH 7.0 PBS at scan rate of 50 mV s^{-1} in the presence and absence of 0.5 mM PA were shown in Figure 2. As predictable, no anodic or cathodic peaks appeared at either bare CPE or MXCPE in PBS in the absence of PA. However, well-defined oxidation peak was observed for 0.5 mM PA in pH 7.0 PBS around 0.68 V and 0.60 V at bare CPE and MXCPE, respectively while no peak was observed in the reverse scan direction suggesting that PA undergoes oxidation irreversibly at both electrodes (Figure 2), which agrees with previous reports (Khaskheli *et al.*, 2013; Bharathi *et al.*, 2018).

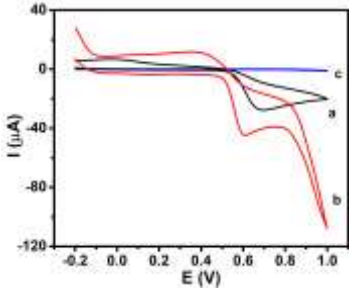


Figure 2. Cyclic voltammograms of a) bare CPE, b) MXCPE, and c) MXCPE in pH 7.0 PBS containing (a and b) 0.5 mM PA and no PA (c) at scan rate of 50 mV s^{-1}.

In contrast to the bare CPE, an oxidation peak with enhanced current at the MXCPE (Figure 2, curve b) with an onset potential of 65 mV to more negative region confirmed the electrocatalytic ability of the MXCPE towards PA.

Effect of murexide/graphite ratio on peak current of PA

The effects of the proportion of MX in the carbon paste on cyclic voltammetric responses of the modified electrode for 0.5 mM PA in pH 7.0 PBS was examined by varying the amount of murexide (MX) from 5 to 25%. As can be seen from the Inset of Figure 3, the oxidative current response of the modified electrode for PA increased with the amount of MX up to 15% and then decreased dramatically at MX amount above 15%. Hence, 15% of MX modified CPE was chosen as the optimum for the study of all other parameters.

Potential scan rate effect

The effect of scan rate on the oxidation peak potential (E_{pa}) and peak current (I_{pa}) of PA at MXCPE was examined in the scan rate range 10-200 mV s^{-1}. As depicted in Figure 4(A), the peak potential shift in the positive direction observed with increasing scan rate for 0.5 mM PA in pH 7.0 PBS solution further confirmed the irreversibility of the oxidation of PA at the MXCPE. As can be inferred from the inset of Figure 4(A), there is a linear relationship between Log I_{pa} and Log ν, with a slope of 0.39. The obtained slope value acquired for PA is close to the theoretical value (0.50) predictable for electrochemical process controlled by diffusion which received a good support from the literature (Meenakshi *et al.*, 2020).

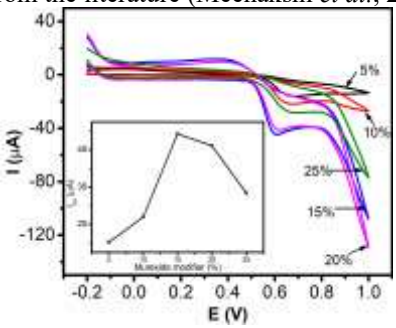


Figure 3. CVs 0.5 mM PA in pH 7.0 PBS at CPE modified with MX of various amounts (5-25%). Inset: the plot of anodic peak current of PA versus amount of MX added as modifier.

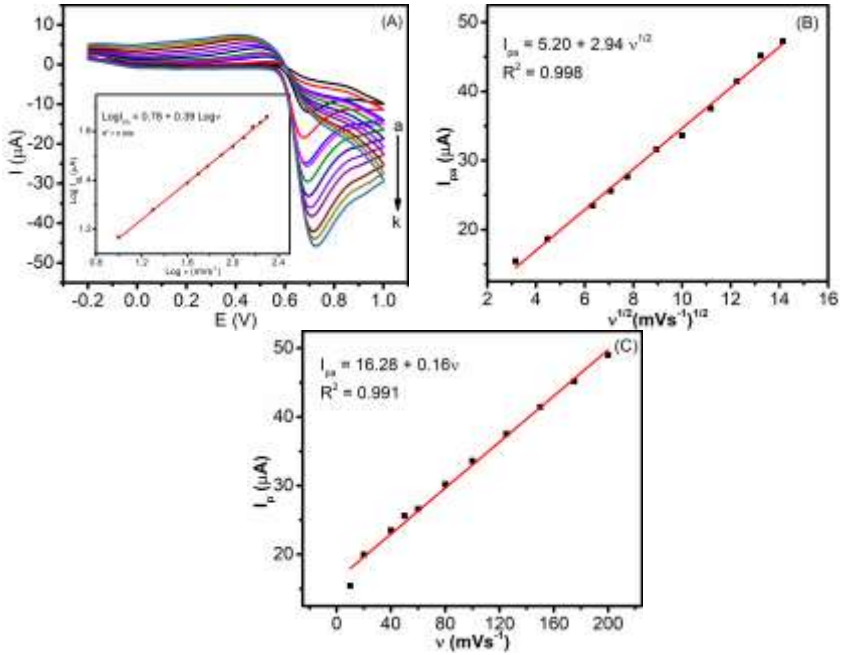


Figure 4. (A) Cyclic voltammograms of MXCPE in PBS pH 7.0 containing 0.5 mM PA at various scan rates (a–k: 10, 20, 40, 50, 60, 80, 100, 125, 150, 175, and 200 mV s^{-1}, respectively), (B) plot of oxidative peak current versus square root of scan rate, and (C) plot of oxidative peak current versus scan rate. Inset: plot of log of oxidative peak current versus log of scan rate.

Further evidence for non-adsorptive behavior of PA was obtained as shown in Figure 4(B), the peak current of PA showed linear dependence on the square root of scan rate with the regression equation of I_{pa} (μA) = 5.20 + 2.94 $\nu^{1/2}$ (R^2 = 0.998) in comparison to the plot of oxidative peak current versus scan rate (Figure 4(C)) with regression equation of I_{pa} (μA) = 16.28 + 0.16ν (R^2 = 0.991). With increasing scan rate (Figure 5), anodic peak potentials shifted to more positive values (Filik *et al.*, 2014). Figure 5 shows the relationship between E_{pa} (V) and ln (ν) for scan rates of 10 to 200 mVs^{-1} produces a linear regression equation of E_{pa} = 0.023 ln (ν) + 0.59 (R^2 = 0.999). Based on the Laviron theory (Laviron, 1979), the slope of the line is equal to $RT/\alpha nF$. Hence the charge transfer coefficient (α) and the electron transfer number (n) are calculated to be 0.55 and 2.05, respectively. Incorporating the value of α in Eq. (2), the standard heterogeneous reaction rate constant; K_s (s^{-1}) is predicted to be 2.24 s^{-1}. On the surface of MXCPE the adsorbed amount of PA was further calculated by the following equation: $I_p = {n^2F^2A\Gamma\nu}/{4RT}$ (Laviron, 1979). Using the association of i_{pa} with ν, (slope = 0.17) the value of the surface

concentration of PA (Γ) 2.34 × 10^{-6} mol/cm^2 was obtained. This high surface concentration can be credited to the MX modifier. This behavior has a good support from literature (Bouabi *et al.*, 2016; Meenakshi *et al.*, 2020).

$$logK_s = \alpha \log(1-\alpha) + (1-\alpha)log\alpha - log\left(\frac{RT}{nF\nu}\right) - \alpha(1-\alpha)\frac{nFE}{2.3RT} \quad (2)$$

where R, F, T, and ν are the usual meaning of universal gas constant ($JK^{-1}mol^{-1}$), Faraday constant ($Cmol^{-1}$), absolute temperature (K), and scan rate (mVs^{-1}).

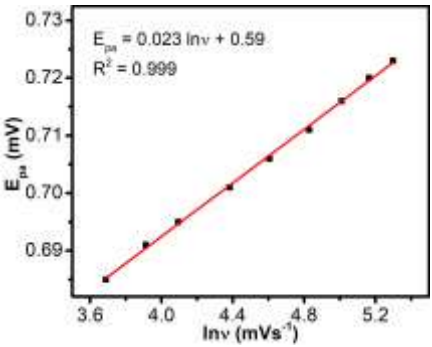


Figure 5. Plot of E_{pa} *vs*. lnν of 0.5 mM PA in PBS of pH 7.0 on MXCPE.

Influence of pH on PA oxidation

The effect of pH on the electrochemical response of PA on the surface of MXCPE in PBS was investigated in the pH range 4.0 – 9.0. Figure 6(A) represents CVs of 0.5 mM PA at MXCPE in different pH range. The anodic peak potential (E_{pa}) of PA was found to be dependent on pH and shifted to less positive potential with increasing pH, suggesting the involvement of protons in the oxidation reaction of PA (Figure 6). Similar trends have been reported (Gowda *et al.*, 2015; Chipeture *et al.*, 2019). From the plot of E_{pa} vs. pH (Figure 6(B)), it is clearly observed that the oxidation peak potential of PA shifted in the negative potential direction with increasing pH. A linear relationship between oxidation peak potential and pH was observed with a regression equation:

$$E_{pa}\ (V) = 0.826 - 0.037\ pH \quad (R^2 = 0.997).$$

The slope of the graph should be equal to -59 mV p/n where p is the number of protons involved in the electrode reaction, n is the number of electrons transferred and the rest are commonly known constants (Shah *et al.*, 2014). In this study using MXCPE, the p/n value for PA is calculated to be 0.61 which infers an unequal number of protons and electros are involved in the oxidation process. Hence for PA, a slope of -37.4 mV per pH unit indicates that the electrode process is more complex and the ratio of proton and transferred electrons is predicted to be 1:2. Li *et al*. reported a non-equal number of two electrons and one proton transfer process with a slope value of -38 mV/pH (Li *et al.*, 2018). The possible oxidation mechanism of paracetamol on the surface of MXCPE was illustrated in Scheme 3.

The anodic oxidation peak currents decreased and increased with an increase in pH from 4.0 and then maximum was reached at 7.0 (Figure 6(B)) and pH 7.0 was opted for further studies.

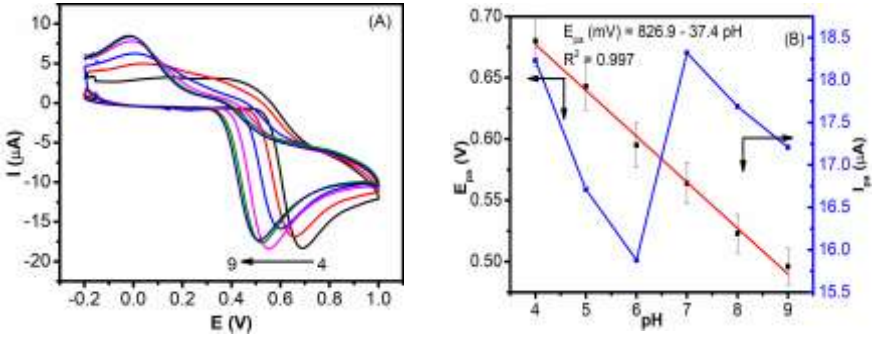
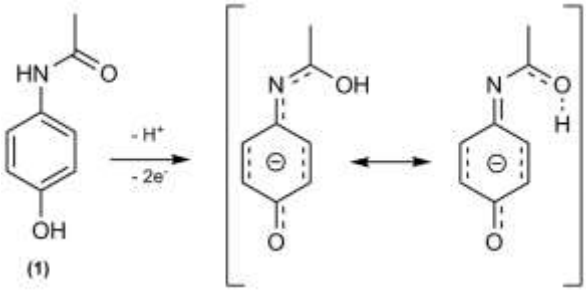


Figure 6. (A) Cyclic voltammograms of MXCPE in PBS of various pHs (4.0, 5.0, 6.0, 7.0, 8.0, 9.0, respectively) containing 0.5 mM PA, and (B) plot of oxidative peak potential (red curve) and peak current (blue curve) as a function of pH in the entire range (4.0–9.0).



Scheme 3. Electrochemical oxidation of PA (1).

Differential pulse stripping Voltammetric behavior of PA at the MXCPE

Effect of accumulation potential and time

Because of the oxidation of PA, the accumulation step could increase to make the peak currents increased. The accumulation potential (E_{acc}) and accumulation time (t_{acc}) with stripping voltammetry technique are shown in Figure 7.

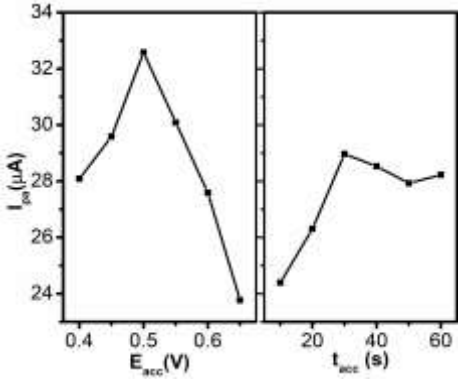


Figure 7. Effect of accumulation potential (left) and accumulation time (right) on peak currents of PA (0.5 mM).

It can be seen from Figure 7 (left panel) that in the accumulation potential range from 0.4 V to 0.65 V, the peak currents increased between 0.4 V to 0.5 V, and then decreased to 0.65 V. Thus, 0.5 V was chosen as optimal accumulation potential for the further voltammetric studies of PA with DPSV. Accumulation time was also tested over the range of 10 to 60 s (Figure 7, right panel). It is observed that oxidation peak current was increased rapidly and reached maximum at 30 s, then decreased until 60 s accumulation time. It is suggested that the adsorption quantity of PA on the MXCPE reached saturation. In reflection of both compassion of the examination and working efficiency, 30 s was nominated as the optimal accumulation time.

Dependence of the oxidative current on the concentration of PA

Under the optimized accumulation potential and time, the made-up MXCPE sensor carried out for the quantitative analysis of PA. Differential pulse stripping voltammetry (DPSV) was applied in this examination because its charging current to the background current is quite low compared to the cyclic voltammetry. Figure 8 shows the dependence of the DPSV oxidation peak current with different concentrations of PA. The relation between the oxidative peak current and concentration of PA ([PA]) showed a linear dependence in the range of 5.0 – 1000 μM with a regression equation of I_{pa} (μA) = 4.45 + 0.047 [PA] μM (R^2 = 0.996).

The limit of detection (LOD) of MXCPE was calculated to be 0.09 μM PA according to the equation 3S/M, where M is the slope of the calibration graph and S is standard deviation of the blank solution (n = 8) (Miller and Miller, 2018). The obtained LOD value is compared with other reported modified electrodes (Table 1).

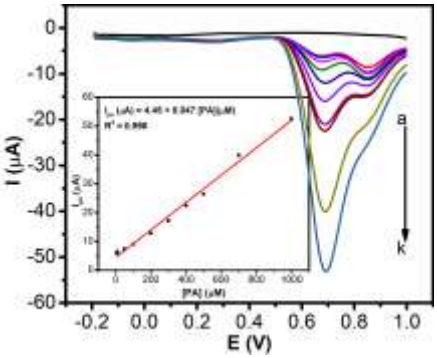


Figure 8. DPSVs of different concentrations (b → k): 5, 10, 50, 100, 200, 300, 400, 500, 700, and 1000 μM PA in PBS pH 7.0 on MXCPE and curve (a) is the blank. Inset: Plot of I_{pa} versus concentrations of PA.

Table 1. Comparison of the effectiveness of some modified electrodes for the detection of PA.

Electrodes	**Techniques**	**Detection limit (μM)**	**References**
Graphene chitosan (GR–CS) nanocomposite/GCE	DPV	0.3	(Zheng *et al*., 2013)
Ethynylferrocene (EF) and NiO/MWCNT nanocomposite/CPE	SWV	0.5	(Shahmiri *et al*., 2013)
Nanosheet- assembled lindgrenite microflowers/GCE	DPV	0.01	(Fu *et al*., 2020)
MWCNTs/ZnO nanoparticles/GPE	DPV	0.0033	(Patil *et al*., 2019)
Phosphorus-doped graphene/GCE	DPV	0.36	(Zhang *et al*., 2018)
Murexide/CPE	DPSV	0.09	This work

Analytical application

DPSV technique was used to determine PA in three tablet samples. In the study, Panadol Adva (Kenya), Para Denk (Germany), and Julphar Aldol (Ethiopia) brand tablets accessible at local pharmacies were used. The tablet samples were precisely weighed and finely ground in a mortar. A chosen amount of powder (tablet sample) is mixed with a prepared solution of PBS. Afterward, a 20 mL prepared solution was transferred to the cell and the current response was noticed. As shown in Figure 9, the results confirm the consistent sensitivity of the MXCPE electrochemical response. The results were summarized in Table 2. The calculated relative errors indicated that the accuracy of this analytical method was assessed to be ≤ 5.60%.

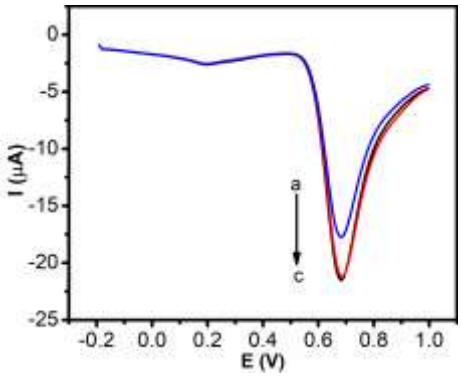


Figure 9. DPSVs of MXCPE in PBS of pH 7.0 containing PA tablet samples of different brands (a → c; Kenya, Germany, and Ethiopia).

Table 2. Determination of PA in pharmaceutical tablet samples.

Tablet sample	Declared PA content (mg/tablet)	Detected PA by this method		PA found (%)	Relative error (%) *
		μM	mg/tablet		
Pandol Adva (Kenya)	500	53.69	488	97.6	2.45
Para Denk (Germany)	500	56.0	508	100.1	1.57
Adol Julphar (Ethiopia)	500	58.40	530	106.0	5.60

*Relative error = 100% × (detected value − declared value)/detected value

The determination of PA on the sensing performance in real pharmaceutical samples using the developed method was investigated by using the standard addition method. The results are listed in Table 3. Upon addition of certain amounts of PA, excellent recovery results (94.6-96.8 %) are obtained. These results confirm that the MXCPE is a promising electrode material for the sensitive and selective detection of PA in real pharmaceutical tablets.

Table 3. Summary of recovery results of 110.0 μM PA from tablet solutions.

Tablet sample	Spiked PA (μM)	Detected PA (μM)	Recovery (%)
Julphar aldol (Ethiopia)	66	166.50	94.60
Para Denk (Germany)	66	168.43	95.69
Panadol Adava (Kenya)	66	170.50	96.87

Interference study

An accuracy of the analysis can be pretentious by the limitation of analytical selectivity. For the proposed method in the determination of PA the selectivity of

the method was evaluated in the presence of foreign species. For the interference study different amount of ascorbic acid (AA) was used. Under optimized conditions, a comment interferent of 50 µM and 100 µM AA was added into 100 µM and then the alteration of the peak current was checked. As can be seen from Figure 10, there was no change in the peak current and peak potential occurred for PA. From Table 4, the change in signal indicates almost no influence on the detection of PA, since the peak current varied approximately below 5% which discloses that the MXCPE sensor has good sensitivity for PA determination.

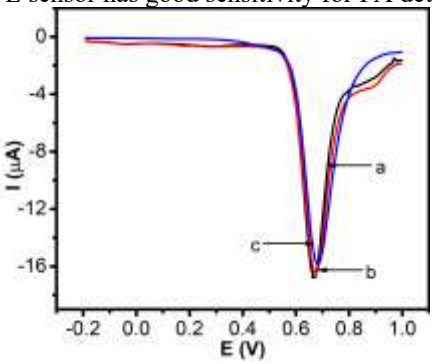


Figure 10. DPSVs in PBS of pH 7.0 containing (a) Ethiopian PA tablet solution, (b) a + 50 µM AA and (c) a + 100 µM AA.

Table 4. Effect of AA interferent on the DPSV response of 50 µM PA at MXCPE.

Tablet	**PA (µM)**	**Added AA (µM)**	**Recorded I_{pa} (µA)**	**% Error**
Julphar Aldol	100	-------	16.86	-----
(Ethiopia)	100	50	16.58	1.68
	100	100	15.88	5.81

CONCLUSION

A modified electrode, MXCPE, was fabricated by modifying the CPE by using murexide and subsequent mixing with graphite and paraffin oil. The MXCPE exhibits an excellent electrocatalytic oxidation activity towards paracetamol. The response for the oxidation of paracetamol at MXCPE shows an improved onset potential shift by 65 mV when equated to CPE. For the experimental conditions, the effect of scan rate, pH, accumulation potentials and time were studied. The scan rate studies indicated that paracetamol undergoes a diffusion process on the modified electrode. Furthermore, the common analytical interfering, ascorbic acid introduced did not affect the peak positions of paracetamol in pharmaceutical samples.

ACKNOWLEGEMENTS

The authors would like to gratefully acknowldge Department of Chemistry, Bahir Dar University for providing facilities and Prof. Meareg Amare for his support to conduct and complete the study.

REFERENCES

Al-Zoubi, N., Koundourellis, J and Malamataris, S. (2002). Ft-ir and raman spectroscopic methods for identification and quantitation of orthorhombic and monoclinic paracetamol in powder mixes. *Journal of Pharmaceutical and Biomedical Analysis* **29**: 459–467: https://doi.org/10.1016/S0731-7085(02)00098-5.

Anderson, B.J. (2008). Paracetamol (acetaminophen): Mechanisms of action. Pediatric *Anesthesia* **18**: 915–921: https://doi.org/10.1111/j.1460-9592.2008.02764.x.

Baptistao, M., Rocha, W.F.D.C and Poppi, R. J. (2011). Quality control of the paracetamol drug by chemometrics and imaging spectroscopy in the near infrared region. *Journal of Molecular Structure* **1002**: 167–171: https://doi.org/10.1016/j.molstruc.2011.07.019.

Bard, A.J and Faulkner, L.R. (2001). Fundamentals and applications. *Electrochemical Methods* 2: 580–632.

Barsan, M.M., Toledo, C.T and Brett, C.M. (2015). New electrode architectures based on poly (methylene green) and functionalized carbon nanotubes: Characterization and application to detection of acetaminophen and pyridoxine. *Journal of Electroanalytical Chemistry* **736**: 8–15: https://doi.org/10.1016/j.jelechem.2014.10.026.

Bertolini, A., Ferrari, A., Ottani, A., Guerzoni, S., Tacchi, R and Leone, S. (2006). Paracetamol: New vistas of an old drug. *CNS Drug Reviews* **12**: 250–275: https://doi.org/10.1111/j.1527-3458.2006.00250.x.

Bharathi, K., Kumar, S.P., Prasad, P.S and Narayanan, V. (2018). Voltammertic determination of paracetamol by n, n'-bis (salicylaldimine)-benzene-1, 2-diamine chromium (iii) schiff base complex modified gce. *Materials Today: Proceedings* **5**: 8961–8967: https://doi.org/10.1016/j.matpr.2017.12.336.

Bouabi, Y.E., Farahi, A., Achak, M., Zeroual, M., Hnini, K., El Houssame, S., Bakasse, M., Bouzidi, A and El Mhammedi, M. (2016). Electrocatalytic effect of fluoroapatite in reducing paracetamol at carbon paste electrode: Analytical application. *Journal of the Taiwan Institute of Chemical Engineers* **66**: 33–42: https://doi.org/10.1016/j.jtice.2016.06.013.

Chipeture, A.T., Apath, D., Moyo, M and Shumba, M. (2019). Multiwalled carbon nanotubes decorated with bismuth (iii) oxide for electrochemical detection of an antipyretic and analgesic drug paracetamol in biological samples. *Journal of Analytical Science and Technology* **10**: 22: https://10.0.4.162/s40543-019-0181-5.

Filik, H., Avan, A.A., Aydar, S and Çetintaş, G. (2014). Determination of acetaminophen in the presence of ascorbic acid using a glassy carbon electrode modified with poly (caffeic acid). *International Journal of Electrochemical Science* **9**: 148–160: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.661.1673.

Foroughi, M.M., Jahani, S and Hassani Nadiki, H. (2019). Lanthanum doped fern-like cuo nanoleaves/mwcnts modified glassy carbon electrode for simultaneous determination of

tramadol and acetaminophen. *Sensors and Actuators B: Chemical* **285**: 562–570: https://doi.org/10.1016/j.snb.2019.01.069.

Fu, R., Shen, M., Ding, Y., Li, M., Li, L., Ren, Z and Wu, Q. (2020). Electrocatalytic oxidation and sensitive determination of paracetamol based on nanosheets self-assembled lindgrenite microflowers. *Electroanalysis* **32**: 978–985: https://doi.org/10.1002/elan.201900504.

Ghadimi, H., Tehrani, R.M., Basirun, W.J., Ab Aziz, N.J., Mohamed, N and Ab Ghani, S. (2016). Electrochemical determination of aspirin and caffeine at mwcnts-poly-4-vinylpyridine composite modified electrode. *Journal of the Taiwan Institute of Chemical Engineers* **65**: 101–109: https://doi.org/10.1016/j.jtice.2016.05.043.

Görçay, H., Çelik, İ., Yurdakul, E., Şahin, Y and Kökten, Ş. (2016). Highly sensitive electrochemical determination of acetaminophen in pharmaceuticals by poly [2, 5-di (2-thiophenyl)-1-p-(tolyl) pyrrole] modified pencil graphite electrode. *IEEE Sensors Journal* **16**: 2914–2921: https://doi.org/10.1109/JSEN.2016.2526609.

Gowda, J.I., Gunjiganvi, D.G., Sunagar, N.B., Bhat, M.N and Nandibewoor, S. T. (2015). Mwcnt–ctab modified glassy carbon electrode as a sensor for the determination of paracetamol. *RSC Advances* **5**: 49045–49053: https://doi.org/10.1039/C5RA05802C.

Goyal, A and Jain, S. (2007). Simultaneous estimation of paracetamol, chlorzoxazone and diclofenac sodium in pharmaceutical formulation by a novel hplc method. *Acta Pharmaceutica Sciencia* **49**: 147–151: http://www.actapharmsci.com/uploads/pdf/pdf_112.pdf.

Khaskheli, A.R., Fischer, J., Barek, J., Vyskočil, V., Sirajuddin, S. and Bhanger, M.I. (2013). Differential pulse voltammetric determination of paracetamol in tablet and urine samples at a micro-crystalline natural graphite–polystyrene composite film modified electrode. *Electrochimica Acta* **101**: 238–242: https://doi.org/10.1016/j.electacta.2012.09.102.

Kissinger, P.T and Heineman, W.R. (1983). Cyclic voltammetry. *Journal of Chemical Education* **60**: 702–706: https://pubs.acs.org/doi/abs/10.1021/ed060p702.

Laviron, E. (1979). General expression of the linear potential sweep voltammogram in the case of diffusionless electrochemical systems. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **101**: 19–28: https://doi.org/10.1016/S0022-0728(79)80075-3.

Lecoeur, M., Rabenirina, G., Schifano, N., Odou, P., Ethgen, S., Lebuffe, G and Foulon, C. (2019). Determination of acetaminophen and its main metabolites in urine by capillary electrophoresis hyphenated to mass spectrometry. *Talanta* **205**: 120108: https://doi.org/10.1016/j.talanta.2019.07.003.

Li, C., Xu, J., Wu, Y., Zhang, Y., Zhang, C., Lei, W and Hao, Q. (2018). G-c3n4 nanofibers doped poly(3,4-ethylenedioxythiophene) modified electrode for simultaneous determination of ascorbic acid and acetaminophen. *Journal of Electroanalytical Chemistry* **824**: 52–59: https://doi.org/10.1016/j.jelechem.2018.07.025.

Meenakshi, S., Pandian, K and Gopinath, S.C.B. (2020). Quantitative simultaneous determination of pentoxifylline and paracetamol in drug and biological samples at graphene nanoflakes modified electrode. *Journal of the Taiwan Institute of Chemical Engineers* **107**: 15–23: https://doi.org/10.1016/j.jtice.2019.11.011.

Miller, J and Miller, J.C. (2018). *Statistics and chemometrics for analytical chemistry*, Pearson education.

Mohran, H.S. (2009). An electrochemical investigation of the redox properties of murexide in aqueous and non-aqueous media. *American Journal of Applied Sciences* **6**: 964–969: https://doi.org/10.3844/ajassp.2009.964.969.

Moreira, A.B., Oliveira, H.P., Atvars, T.D., Dias, I.L., Neto, G.O., Zagatto, E. A and Kubota, L.T. (2005). Direct determination of paracetamol in powdered pharmaceutical samples by fluorescence spectroscopy. *Analytica Chimica Acta* **539**: 257–261: https://doi.org/10.1016/j.aca.2005.03.012.

Patil, D.S., Shetti, N.P., Nayak, D.S and Revankar, R.S. (2019). Fabrication of multi-walled carbon nanotubes and zno nanoparticles composite electrode as a sensor for paracetamol. *Materials Today: Proceedings* **18**: 1124–1131: https://doi.org/10.1016/j.matpr.2019.06.572.

Shah, A.H., Shah, A., Rana, U.A., Khan, S.U.D., Hussain, H., Khan, S.B., Qureshi, R and Badshah, A. (2014). Redox mechanism and evaluation of kinetic and thermodynamic parameters of 1, 3-dioxolo [4, 5-g] pyrido [2, 3-b] quinoxaline using electrochemical techniques. *Electroanalysis* **26**: 2292–2300: https://doi.org/10.1002/elan.201400324.

Shahmiri, M.R., Bahari, A., Karimi-Maleh, H., Hosseinzadeh, R and Mirnia, N. (2013). Ethynylferrocene–nio/mwcnt nanocomposite modified carbon paste electrode as a novel voltammetric sensor for simultaneous determination of glutathione and acetaminophen. *Sensors and Actuators B: Chemical* **177**: 70–77: https://doi.org/10.1016/j.snb.2012.10.098.

Shinde, V., Desai, B and Tendolkar, N. (1995). Simultaneous determination of paracetamol, diclofenac sodium and chlorzoxazone by hplc from tablet. *Indian Journal of Pharmaceutical Sciences* **57**: 35–37.

Zhang, X., Wang, K.-P., Zhang, L.-N., Zhang, Y.-C and Shen, L. (2018). Phosphorus-doped graphene-based electrochemical sensor for sensitive detection of acetaminophen. *Analytica Chimica Acta* **1036**: 26–32: https://doi.org/10.1016/j.aca.2018.06.079.

Zheng, M., Gao, F., Wang, Q., Cai, X., Jiang, S., Huang, L and Gao, F. (2013). Electrocatalytical oxidation and sensitive determination of acetaminophen on glassy carbon electrode modified with graphene–chitosan composite. *Materials Science and Engineering: C* **33**: 1514–1520: https://doi.org/10.1016/j.msec.2012.12.055.

Zhu, W., Huang, H., Gao, X and Ma, H. (2014). Electrochemical behavior and voltammetric determination of acetaminophen based on glassy carbon electrodes modified with poly (4-aminobenzoic acid)/electrochemically reduced graphene oxide composite films. *Materials Science and Engineering: C* **45**: 21–28: https://doi.org/10.1016/j.msec.2014.08.067.