Voltammetric determination of paracetamol at glycine modified carbon paste electrode

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ABSTRACT

The lower body tolerance of paracetamol (PCT) is 50 ppm and if it surpasses; PCT will led to accumulation of toxic metabolites. A carbon paste electrode modified with glycine (GlyCPE) is used for the detection of PCT at relatively low concentrations. In contrast to the bare carbon paste electrode (CPE), an improved onset potential with a shifting of 85 mV and enhancement of anodic peak current at the modified electrode resulted in a the GlyCPE surface with a material that possesses an electroanalytical activity toward the oxidation of PCT. Differential pulse stripping voltammograms (DPSV) of PCT oxidation on the GlyCPE yielded a well-defined oxidation peak of 0.61 V in a 0.1 M phosphate buffer solution of pH 6.0 with a linear calibration from 5.0 to 1000 mM with $R^2 = 0.995$. The DPSV detection limit was projected to be 0.12 mM. In the presence of the interfering ascorbic acid (AA) of 50 and 100 mM, the GlyCPE was able to detect the PCT (100 mM) with a percentage of detection of 100.16 and 97.79, respectively, which did not affect significantly the peak current response of the PCT. Besides, the fabricated GlyCPE accurately measured the amount of PCT in three brand pharmaceutical samples.

Keywords: Paracetamol; Electrochemical oxidation; Glycine-CPE; Differential pulse stripping voltammetry; Pharmaceutical tablets

DOI: https://dx.doi.org/10.4314/ejst.v15i3.5

INTRODUCTION

Drug analysis embarked on all several phases of pharmaceutical development (Berridge, 1993), such as formulation and stability studies, quality control (QC), and toxicology, and pharmacological testing in animals and man (Abo-el-Maali, 2004). Paracetamol (PCT), also known as acetaminophenol, is chemically named N-acetyl-p-aminophenol. It is a commonly used as over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) having actions similar to those of aspirin,

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and it is more suitable for patients who are sensitive to aspirin (Lau *et al.*, 1989; Goyal *et al.*, 2005; Bosch *et al.*, 2006; Kachoosangi *et al.*, 2008; Kang *et al.*, 2010).

Paracetamol does not have any harmful effects for humans, but the abnormal level of paracetamol is found to damage liver and kidney. The lower body tolerance of PCT is 50 ppm (Biswas *et al.*, 2015). If PCT surpasses this level, it will lead to accumulation of toxic metabolites. In pharmaceutical preparations, 4-aminophenol can be found as a degradation product of PCT which can be dangerous and can cause teratogenic effect and nephrotoxicity (Yesilada *et al.*, 1991).

Based on the aforesaid remarks, the development of more efficient analytical techniques, intended to quality control and formulations of the drug, have been utilized for its determination in pure form, formulation, and combination with other substances; mainly polarographic (Walash *et al.*, 1994), amperometric (Felix *et al.*, 2007; Chu *et al.*, 2008; D'Souza *et al.*, 2015), UV-Vis spectrophotometric (Morelli, 1989; Khaskheli *et al.*, 2007; Fatibello-Filho and Vieira, 2008), fluorimetric (Murillo and Garcia, 1996; Moreira *et al.*, 2005), chromatographic (Emre and Özaltın, 2007; Belal *et al.*, 2009; Hadad *et al.*, 2009), and several others.

Carbon and its derivatives, as high-performance material, occupy a special place in electroanalytical methods having its extreme properties. The carbon paste electrode (CPE), which was invented by Adams at the end of the 1950s (Adams, 1958), is composed of an electrically conducting graphite powder and pasting liquid (Kalcher, 1990). CPEs can be easily prepared, regenerated, and modified by mixing with various ligands depending on the application. They further offer a cheap, renewable and modified surface with very low background current interferences (Mojica and Merca, 2005; Somerset *et al.*, 2009).

In the determination of PCT, different voltammetric techniques using modified electrodes have been reported (Boopathi *et al.*, 2004; Kachoosangi *et al.*, 2008; Lu and Tsai, 2011; Khaskheli *et al.*, 2013; Adhikari *et al.*, 2015; Wang *et al.*, 2018; Xu *et al.*, 2018; Amare, 2019; Niedziałkowski *et al.*, 2019). Most voltammetric techniques rely on the use of modified carbon based electrodes such as; a multiwalled carbon nanotube on pyrolytic graphite electrode (Kachoosangi *et al.*, 2008), Fe (III) doped zeolite-graphite composite (Amare, 2019), Bi_2O_3 nanoparticles modified GCE (Zidan *et al.*, 2011), MOF-199 based electrode (Minh *et al.*, 2018), graphene based electrode (Kang *et al.*, 2010), graphitic carbon nitride-electrochemically deposited-poly(3,4-ethylenedioxythiophene) (g-C3N4-E-PEDOT) composite electrode (Xu *et al.*, 2018), graphite oxide film modified electrode (Song *et al.*, 2011), multiwalled carbon nanotubes decorated with Bi (III) oxide electrode (Chipeture *et al.*, 2019), a nanohybrid of palladium-reduced graphene oxide modified with gold nanoparticle electrode (Wang *et al.*, 2018) and platinum nitrogen-doped graphene nanocomposite (Anuar *et al.*, 2018). Recently,

(Amayreh *et al.*, 2021; Kassem *et al.*, 2022) reported the voltammetry determination of PCT using modified iodine-coated polycrystalline platinum electrode and the use of Cu-nanoparticles on glassy carbon electrode. In the present work, we report the application of glycine modified carbon paste electrodes (GlyCPE) for the sensitive detection of PCT in tablet formulation using cyclic voltammetric and differential pulse stripping voltammetric techniques.

MATERIALS AND METHODS

All chemicals that have been used in this experiment were of analytical grade. Graphite powder (Blulux), paraffin oil (BDH), paracetamol (99.8%, Merk), K_2HPO_4 (98–100%, BDH, England), KH_2PO_4 (Titar, India), NaOH (Blulux, India), HCl (85%, India), glycine (98.8%, India) are the chemicals used. Distilled water was used for solution preparation. For the detection of PCT in 0.1 M phosphate buffer solution (PBS), (pH = 6.0) cyclic voltammetry (CV) and differential pulse stripping voltammetry (DPSV) were carried out. CHI 760d Electrochemical Workstation (Austin, Texas, USA) connected to a personal computer with a three-electrode system unmodified carbon paste or glycine modified carbon paste electrode as a working electrode, platinum coil as a counter electrode, and Ag/AgCl as a reference electrode was used for voltammetric measurements. A pH meter (AD8000) and Romania electronic balance (Nimbus, ADAM) were used to measure the pH and mass, respectively. The experiments were performed at room temperature, and the electrode potentials quoted are versus an Ag/AgCl electrode.

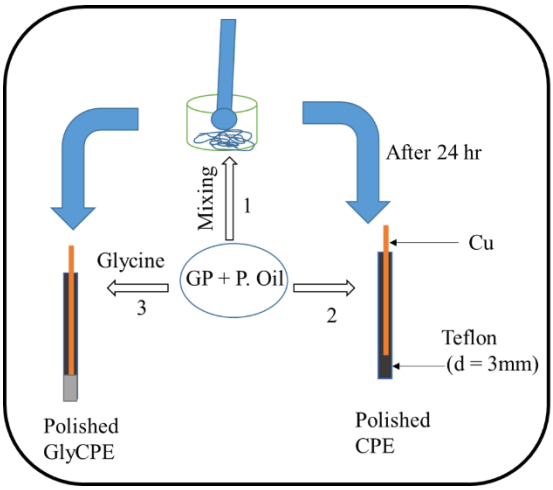
Preparation of bare carbon paste and glycine modified carbon paste electrodes

The glycine modified carbon paste electrode (GlyCPE) was prepared as follows 5-25% (w/w) of glycine mixed with 1 g graphite powder and 30% (0.4 mL) paraffin oil using a mortar and pestle. As reported before (Cao *et al.*, 2008; Salih *et al.*, 2017) the paste was 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 and finally smoothed on a weighing paper. The bare carbon paste electrode (CPE) was fabricated with the same way without addition of the modifier glycine as shown in the scheme (Scheme 1).

Electrochemical Measurement

While cyclic voltammetry (scan rate of 50 mVs^{-1} and potential window of -0.2 to 1.0 V) was used to investigate the electrochemical behavior of PCT at the modified and unmodified carbon paste electrodes, the effect of scan rate on oxidative peak

current, and the dependence of both the oxidative peak current and peak potential of PCT at the surface of the modified carbon paste electrode and the differential pulse stripping voltammetry under optimized parameters (amplitude 25 mV, step potential 4 mV, and frequency 25 Hz) was employed for the quantitative analyses of PCT in PCT tablet designs of different brands. Cyclic voltammetric (CV) measurements were performed in a PBS (pH = 6.0) at a scan rate of 100 mVs^{-1} with the potential range of -0.2 to 1.0 V. The differential pulse stripping voltammogram (DPSV) was performed under optimized parameters as follow: pulse amplitude, 0.05 V; pulse width, 0.025 s; accumulation potential, 0.5 V; accumulation time, 5 s; pulse period of 0.05 s.



Scheme 1. Steps in the making of the working electrode CPE and GlyCPE.

Preparation of PCT standard solutions and pharmaceutical tablet samples

33 mM standard stock solution of PCT was prepared in 100 mL of pH 6.0 PBS. PCT working solutions were prepared by a serial dilution of the stock solution with PBS of the required pH. Paracetamol tablets of three brands; Adol Julphar (Ethiopia), Panadol Adva (Kenya), and Para-Denk (Germany) all labeled 500 mg PCT/tablet were purchased from a local pharmacy store. Tablets were finely powdered in a mortar and pestle separately. Calculated amount of the tablets required for 0.5 mM of working tablet solutions were transferred into volumetric flasks in PBS pH 6.0 and kept in a refrigerator for PCT content analysis (Amare, 2019). To further validate the applicability of the developed method, interference tests for Germany brand tablet sample solutions nominated as; Germany tablet sample, spiked with 50 μM AA, and spiked with 100 μM AA were prepared in PBS pH 6.0.

RESULTS AND DISCUSSION

Electrochemical activities of paracetamol at Glycine/CPE

Cyclic voltammetric behavior of 0.5 mM PCT at bare CPE and GlyCPE were studied in 0.1 M PBS, pH 6.0 at a scan rate of 50 mVs^{-1} (Figure 1). At the bare CPE (Figure 1a), a PCT exhibit an irreversible behavior with peak at E_{pa} (anodic peak potential) = 0.691 V. However, at GlyCPE (Figure 1b), PCT exhibits a peak with E_{pa} = 0.630 V and an improved onset potential which becomes lower than that on the bare CPE with a shifting of 85 mV. Besides, an enhancement of anodic current at the modified electrode confirmed the modification of the electrode surface with a material that possesses electrocatalytic activity towards the oxidation of PCT (Kang *et al*., 2010; Li *et al.*, 2018). Therefore, the addition of glycine in the carbon paste electrode enhanced the electrochemical performance of the electrode.

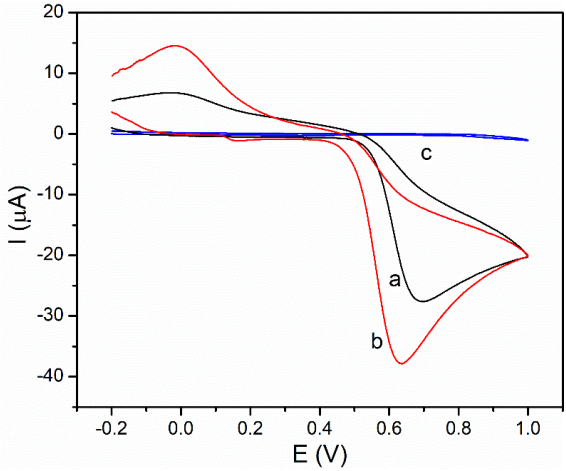


Figure 1. CVs recorded at a bare CPE (a); GlyCPE(b) with 0.5 mM PCT and without PCT (c) in the buffer of 0.1 M PBS, pH 6.0, scan rate: 50mVs^{-1}.

Effect of glycine (Gly) as a modifier

Glycine is the smallest amino acid and has an H atom as its R-group. It is the only α-amino acid that is not optically active. The characterization of GlyCPE was investigated by using cyclic voltammetric technique. GlyCPE was prepared with different ratios by adding different amounts of Gly in milligrams. By increasing the amount of Gly from 5 to 25% in the carbon paste electrode, using 0.1 M PBS as supporting electrolyte, the electrochemical redox peak current of 0.5 mM PCT goes on increasing. The graph of anodic peak current versus the different amount of Gly

in carbon paste electrode was plotted and shown in Figure 2. The 15% GlyCPE shows a maximum current signal and, so we have chosen 15% Gly as an optimum amount for the study of all the other parameters.

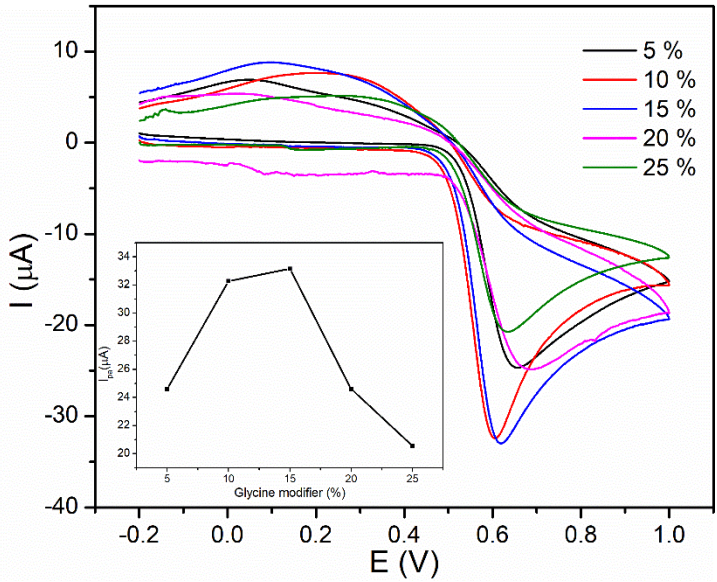


Figure 2. CVs acquired on CPE with 0.5 mM PCT with a different amount of Gly modifier (5-25%) in 0.1 M PBS. Inset is the plot of anodic peak current of PCT versus amount of Gly modifier.

Effect of scan rate

The effect of the potential scan rate on the PCT electrochemical responses was investigated using the CV technique, varying the potential scan rate from 10 to 200 mVs^{-1}. The cyclic voltammograms obtained in this study using the GlyCPE for 0.5 mM PCT in a 0.1 M phosphate buffer (pH 6.0) can be seen in Figure 3(a). As can be inferred from the inset of Figure 3(a), there is a linear relationship between Log I_{pa} and Log ν, with a slope of 0.45. The value obtained is close to the theoretical value (0.50) expected for electrochemical processes controlled by diffusion (Bard and Faulkner, 2001; Engin *et al.*, 2015; Chitravathi and Munichandraiah, 2016; Deroco *et al.*, 2018).

As shown in Figure 3(a), the observed peak potential shift in the positive direction with increasing scan rate confirms irreversibility of the oxidation reaction of paracetamol at the modified electrode with increasing scan rate. For the dependence of the peak current with the scan rate shown in Figure 3(b), the high correlation

coefficients (R^2 = 0.998) for the dependence of the anodic peak current on the square root of scan rate indicates the involvement of diffusion mode transport.

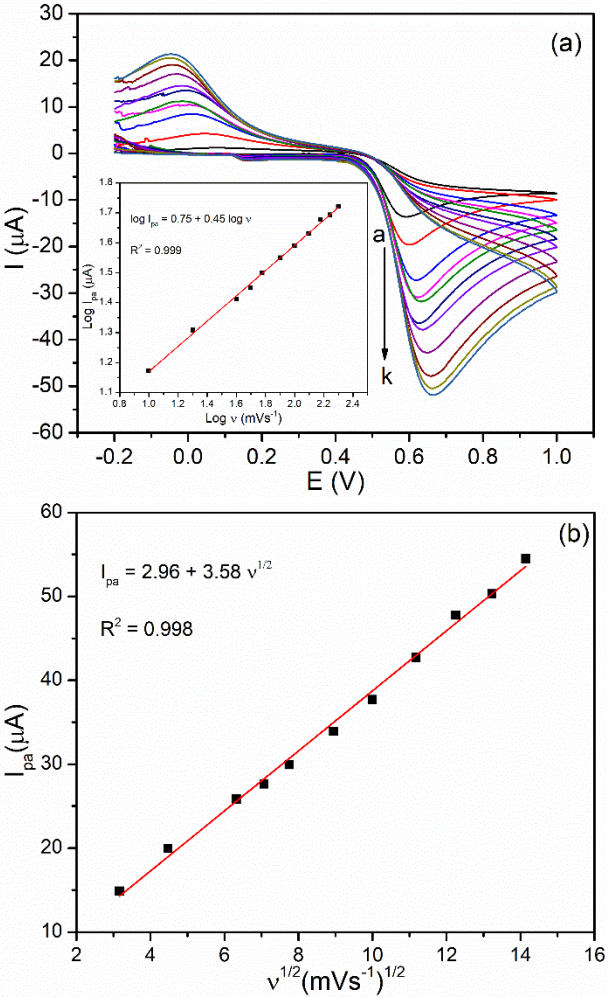


Figure 3. (a) CVs acquired on GlyCPE with 0.5 mM paracetamol in the buffer of PBS (0.1M, pH 6.0) at different scan rates from (a-k): 10 to 200mVs^{-1}, (b) plot of oxidative peak current versus square root of scan rate. Inset is the respective linear relationship of Log I_{pa}*vs.* Log ν.

Also, the plot of peak potential (E_{pa}) vs. logarithm of scan rate (Figure 4) produces a straight line with linear regression equation as: E_{pa} = 0.530 + 0.053Logν (R^2 = 0.998). According to Laviron's equation (Laviron, 1979), the slope of the line is equal to 2.3RT/(1 - α) nF. Hence, according to the document (Wangfuengkanagul and Chailapakul, 2002; Li and Jing, 2007), the electron transfer number (n) of PCT oxidation is 2. Therefore, the value of the electron transfer coefficient (α) is calculated to be 0.46, which also indicates an irreversible process (Fotouhi *et al.*, 2012). Moreover, the behavior for the PCT oxidation was reliable with the EC nature of the reaction in which the electrode reaction is coupled with an irreversible follow-up chemical step (Goyal *et al.*, 2006; Fotouhi *et al*., 2012).

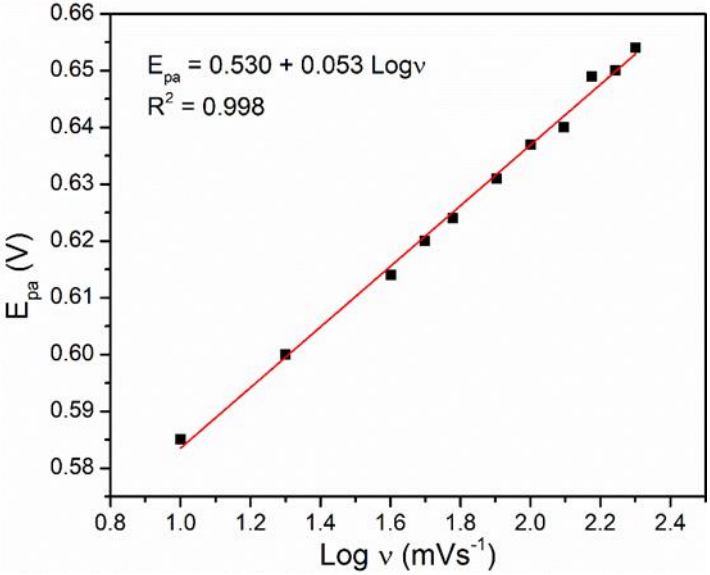


Figure 4. Plot of E_{pa} *vs.* logarithm of sweep rate of 0.5 mM PCT at pH 6.0 using 0.1 M PBS.

Effect of pH on the oxidation of PCT

For the development of the analytical method, the influence of the pH (hydrogen ion concentration) of the supporting electrolyte on the oxidation response of PCT (0.5 mM) was evaluated by the CV technique using the GlyCPE. The effect of pH on the oxidation peak currents of 0.5mM PCT was studied in PBS in the range of pH 2.0 - 9.0, by CV technique to find the optimum pH of supporting electrolyte, which is best suited for the determination of PCT and also the ratio of electrons and protons involved by employing GlyCPE. As depicted in Figure 5(a) and Figure 5(b), the anodic peak current of PCT initially increases from pH 2.0 to 3.0 and is stable till 4.0 and decreases from pH 4.0 to 5.0 then increases till pH 6.0 and

decreases afterward. The better sensitivity at a pH value of 6.0 in the buffer solution was chosen as the optimum value.

The anodic peak potential (E_{pa}) of PCT was found to be dependent on pH and shifted to a less positive potential with increasing pH, suggesting the involvement of protons in the oxidation reaction of PCT (Goyal *et al*., 2005; Fan *et al.*, 2011; Habibi *et al.*, 2011). As perceived from the plot of E_{pa} *vs.* pH (Figure 5(b)), it is clear that the oxidation peak potential varies linearly with pH and shifts to more negative by 0.035 V/pH expressed by the following regression equation:
E_{pa} (V) = 0.803 – 0.035 pH (R^2 = 0.998).

This equation indicates a 35 mV/pH gradient. Based on the equation dE_{pa}/dpH = 2.303mRT/nF (m: number of protons involved in the electrochemical reaction; n: number of electrons; R: ideal gas constant; T: absolute temperature; F: Faraday constant), m/n was calculated to be 0.5. This result suggests that the oxidation of PCT involves a two-electron, one-proton process as shown in scheme 2. This result is consistent with other reports (Kang *et al*., 2010).

Optimization of deposition potential and time of DPSV

The effect of accumulation potential and time on the magnitude of peak current response of GlyCPE for 0.5 mM paracetamol was investigated. The effect of accumulation potential (E_{acc}) over the potential range of 0.4 to 0.65 V on the oxidative peak current of PCT at a constant accumulation time of 30 s is investigated. As can be seen from Figure 6a, the peak current increased with increasing the accumulation potential from 0.4 to 0.5V. A peak current decrease was observed at accumulation potentials higher than 0.5V, and hence, a preconcentration potential of 0.5V was taken as the optimum accumulation potential throughout the present work.

The effect of accumulation time on the peak current of 0.5 mM paracetamol in pH 6 PBS using GlyCPE is studied by varying the time from 3 to 50 s at accumulation potential 0.5V, pulse amplitude 50 mV and scan rate 50 mVs^{-1}.

As can be seen from Figure 6(b), the peak current increased with increasing the accumulation (deposition) time until it reached its maximum at 5 s. An accumulation time longer than 5 s, the peak current decreased. This could be ascribed to the saturation of the electrode surface. Thus, an accumulation time of 5 s was selected as an optimum (deposition) time for this work.

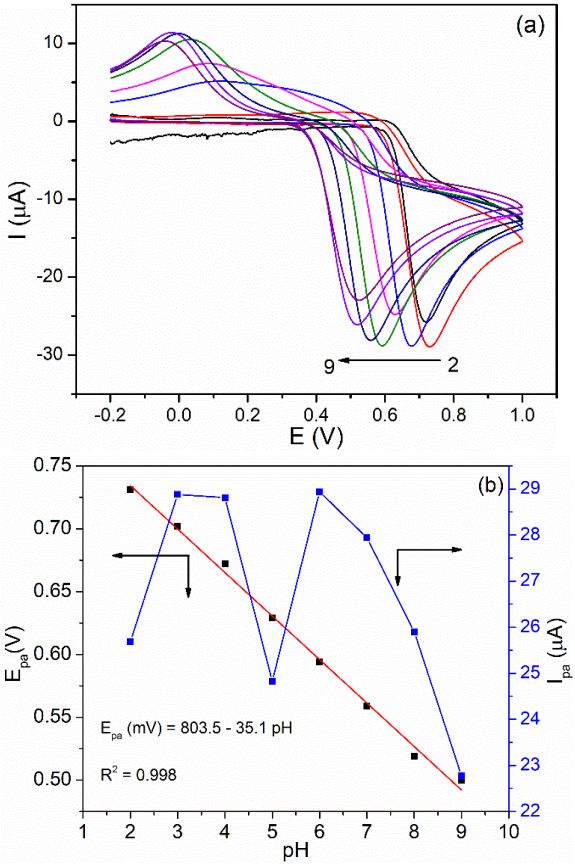
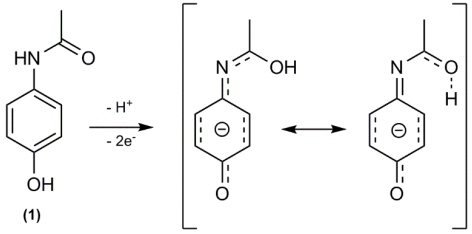


Figure 5. (a) CV obtained at GlyCPE with 0.5 mM PCT in PBS of various pHs (2-9), and (b) plot of oxidative peak potential and current as a function of pH.



Scheme 2. Electrochemical oxidation of PCT (1).

Generally considering the higher current sensitivity of the molecules and may have an absence of background current are measured by Differential Pulse Stripping Voltammetry (DPSV) is the accurate method. DPSV technique was frequently employed for the determination of low concentration of analytes.

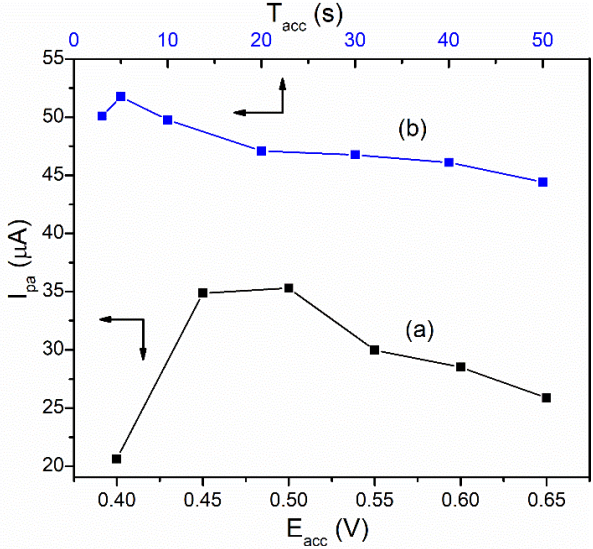


Figure 6. Plot of oxidative peak current of 0.5 mM PCT solution versus (a) accumulation potential and (b) accumulation time. Scan rate: 50 mV/s and pulse amplitude: 50 mV

As can be seen from Figure 7, under the optimal experimental conditions (pH, accumulation potential (E_{acc}), accumulation time (t_{acc}), pulse width, amplitude, and pulse period of 6.0, 0.5 V, 5 s, 0.025 s, 0.05 V, and 0.05 s respectively), the dependence of oxidative peak current on the concentration of PCT and the inherited sensitivity of the method was investigated in the concentration range of 5-1000 μM. The peak current of PCT linearly increased while increasing the concentration of PCT. A plot between PCT oxidation peak current against concentration gives linearity with a correlation coefficient of 0.995 and the detection limit was found to be 1.2×10^{-7} M (S/N = 3). The obtained linear range and detection limit of PCT were compared with the reported papers and are given in Table 1.

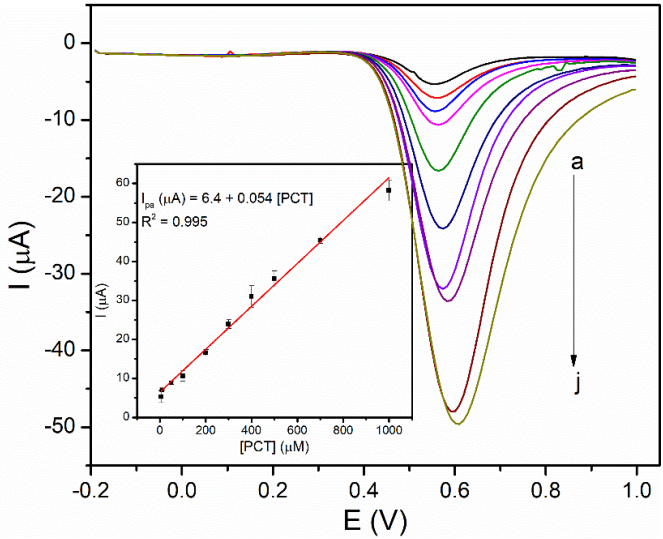


Figure 7. DPSV on GlyCPE for different PCT concentrations (a-j): 5, 10, 50, 100, 200, 300, 400, 500, 700, and 1000 μM in 0.1 M PBS. Inset is the relationship of oxidative current responses to PCT concentration.

Table 1. Comparison of different modified electrodes for the determination of PCT in contrast to the present work.

Electrode	**Linear range (μM)**	**Detection limit (μM)**	**Reference**
C–Ni/GCE	2-232	0.6	(Wang *et al.*, 2007)
Fe_3O_4/rGO	2-150	0.72	(Thu *et al.*, 2018)
NanoBi_2O_3/GC	50-1500	0.2	(Zidan *et al.*, 2011)
Nafion/ ER-GO /GC	0.4-1.0, 1.0-10	0.025	(Filik *et al.*, 2013)
PEDOT/AG/GCE	0.15–5881.09	0.041	(Li *et al.*, 2018)
MWCNT/PPGE	0.1-25	0.045	(Kachoosangi *et al.*, 2008)
Graphene/GCE	0.1-20	0.032	(Kang *et al.*, 2010)
CILE	1.0-2000	0.3	(Shang Guan *et al.*, 2008)
CS-CPE	1.0-0.4 mM, 0.02-0.8	0.5	(Bouabi *et al.*, 2016)
Glycine/CPE	5.0-1000	0.12	Present work

Determination of PCT in pharmaceutical samples

To determine the practical application of the modified glycine/CPE, PCT tablets were used to determine the concentration of PCT content in three brand tablets. The sample preparation followed by acceptable dilution is described in the experimental part. As shown in Figure 8, the voltammograms studied for three tablets and the results are summarized in Table 2.

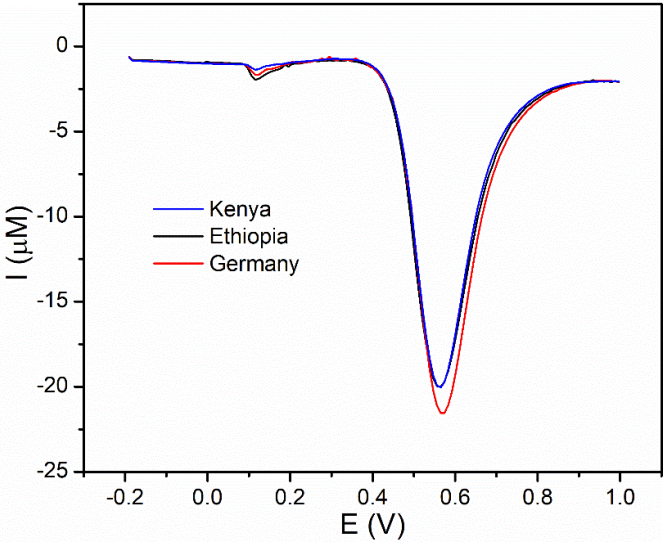


Figure 8. DPSVs of GlyCPE in pH 6.0 PBS containing PCT tablet samples of different brands (Kenya, Ethiopia, and Germany).

Table 2. Summary of detected PCT content per tablet sample using the method compared with expected PCT content.

Tablet sample	**Declared PCT content in mg/tablet**	**Nominal PCT content (μM)**	**Detected PCT by this method**		**PCT found (%)**
			μM	**mg/tablet**	
PandolAdva (Kenya)	500	55	53.69	488	97.6
AdolJulphar (Ethiopia)	500	55	54.30	493	98
Para Denk (Germany)	500	55	57.0	518	103

Recovery and interference studies

Recovery tests for spiked PCT in tablet sample solutions were conducted to evaluate the accuracy of the developed DPSV method for its applicability of PCT in real samples. As shown in the voltammogram (Figure 9) and the summarized results in Table 3, recoveries have been found to lie in the range of 90.0-106%.

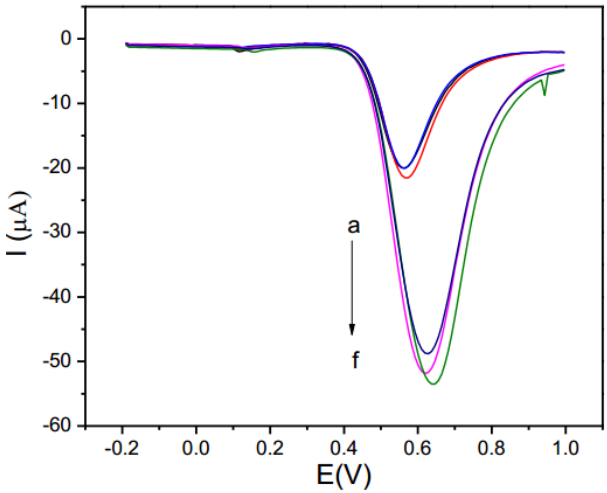


Figure 9. DPSV of pH 6 PBS containing (a) KEN, (b) ETH, (c) GER PCT tablet solution, (d) a + 33 μM, (e) b + 33 μM, and (f) c + 33 μM standard PCT.

Table 3. Percentage recovery of PCT from pharmaceutical tablets using GlyCPE.

Tablet	**Present PCT (μM)**	**Added PCT (μM)**	**Expected PCT (μM)**	**Found PCT (μM)***	**Recovery (%)± RSD**
Pando Adva (Kenya)	142	33	175	172	90 ± 0.86
AdolJulphar (Ethiopia)	142	33	175	176	103 ± 0.52
Para Denk (Germany)	144	33	177	179	106 ± 0.23

*Mean of double measurements.

Interference of other biologically important compounds such as ascorbic acid (AA) which affect the determination of PCT was carried out. The effect of the selected interference was investigated at different concentrations, which are added to 100 μM PCT as shown in Figure 10. The DPSV response of GlyCPE to Para Denk PCT tablet brand of 100 μM generated an anodic peak current of 15 μA as can be seen in Curve "a" of Figure 10. After the addition of the interferents AA (Curve b and c), no obvious change of the peak potential and peak current was observed. The results obtained in the presence of different concentrations of AA were summarized in Table 4. The presence of different concentrations of AA with a fixed concentration of PCT doesn't significantly affect the peak current response of PCT. Thus, the determination of PCT in the presence of AA was achieved.

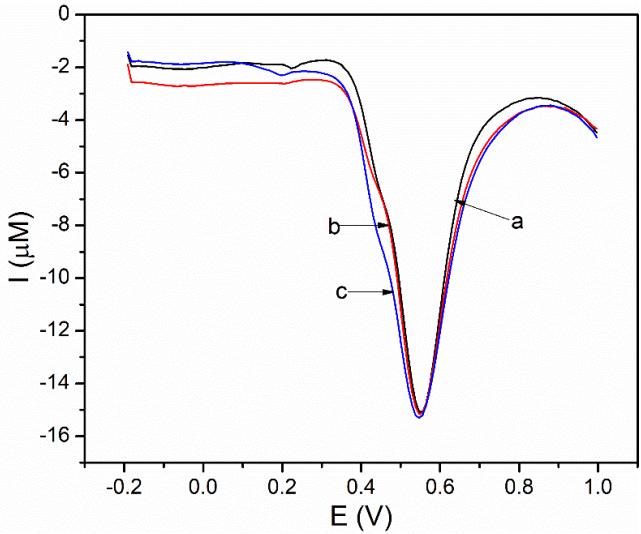


Figure 10. DPSVs of pH 6.0 PBS containing (a) Para Denk (Germany) PCT tablet, (b) a +50 μM AA, and (c) a + 100 μM AA.

Table 4. Interference study of PCT with different concentrations of AA.

Tablet	**Present PCT (μM)**	**Added AA (μM)**	**Expected PCT (μM)**	**Detected PCT (μM)***	**% detected**
Para Denk (Germany)	100	------	100	98.644	------
	100	50	100	100.16	100.16
	100	100	100	97.790	97.79

*Mean of doublet measurement

CONCLUSION

In the present work, cyclic voltammetry was employed for the study of electrochemical oxidation of PCT. An electrochemical method using glycine modified CPE provided a linear association between PCT and the current response was acquired in the concentration range of 5 μM-1 mM with excellent reproducibility of the current. The modified GlyCPE was characterized by cyclic voltammetry and differential pulse stripping voltammetry. Effects of potential sweep rates, pH, accumulation potentials, and time were studied for the experimental conditions. An excellent approach towards the development of glycine-modified CPE was used for application in testing pharmaceutical products and satisfactory results were obtained.

ACKNOWLEDGEMENTS

We are grateful to the Department of Chemistry, Bahir Dar University for providing facilities to conduct and complete this study.

Funding Information

The authors receive no financial support.

Conflict of interest

The author states no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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