

# SIMULTANEOUS VOLTAMMETRIC DETERMINATION OF PARACETAMOL AND ASCORBIC ACID USING ACTIVATED GLASSY CARBON ELECTRODE: CYCLIC VOLTAMMETRY AND SQUARE WAVE VOLTAMMETRY STUDY

Yared Shewarega<sup>a\*</sup>, Dereje Yenealem<sup>b</sup> and Fikadu Siyum<sup>a</sup>

<sup>a</sup>*Department of Chemistry, College of Natural and Computational Science,  
Kabridahar University, P.O. Box 250, Kebri Dehar, Somali, Ethiopia*

<sup>b</sup>*Department of Chemistry, College of Natural and Computational Sciences,  
University of Gondar, P.O. Box 196, Gondar, Ethiopia*

**Abstract:** Simultaneous voltammetric determination of paracetamol (PA) and ascorbic acid (AA) at activated glassy carbon electrode (aGCE) using cyclic voltammetry (CV) and square wave voltammetry (SWV) was studied. The electrochemical responses of PA and AA were compared at bare (bGCE) and aGCE. The aGCE displayed excellent electrochemical catalytic activities and decreased the over-potential for simultaneous determination of PA and AA. It was found that the redox process at aGCE for both PA and AA is adsorption-controlled process. The linear range, limit of quantification (LOQ) and detection limit (LOD) of PA were found to be 10 to 100  $\mu\text{M}$ ; 0.517  $\mu\text{M}$  and 0.155  $\mu\text{M}$ , respectively. Similarly, the linear range, LOQ and LOD of AA were found to be 0.4 to 0.95 mM, 6.32  $\mu\text{M}$  and 1.89  $\mu\text{M}$ , respectively. The validity of the proposed method was checked by using commercial drug which contain different amount of PA and AA and satisfactory percent recoveries were obtained.

**Keyword:** Ascorbic acid, Paracetamol, simultaneous electrochemical determination, square wave voltammetry.

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\* Yared Shewarega, *e-mail:* shewaregay@gmail.com

## Introduction

Paracetamol (PA), (N-acetyl-p-aminophenol) is an antipyretic and minor analgesic drug that practically has no anti-inflammatory action.<sup>1</sup> It does not exhibit any extreme health effects, because in normal therapeutic dose easily metabolized and completely eliminated in urine. However, the overdoses in some cases can lead to the formation of toxic metabolites.<sup>2</sup> Ascorbic acid (AA) is well known by its high antioxidant activity and clinically used for the treatment and prevention of scurvy, common cold, mental illness, AIDS, and protecting living cells against oxidative injury.<sup>3</sup> It is known for its reductive properties (antioxidant activity). Hence, it represents an important quality indicator that contributes to the antioxidant properties of food.<sup>4</sup> The use of complementary presence of AA intensifies the main favorable effect of PA concomitantly with the compensation of the potential toxicity in the function of the liver.<sup>5</sup> On the other hand, most literature reports about the major interferences between PA and AA, and a great number of chemical species in a variety of matrices.<sup>6</sup> Previously analytical methods have been developed and routinely used for the simultaneous determination of PA and AA. However, some of the methods, such as; chromatography,<sup>7-9</sup> electrophoresis,<sup>10</sup> and spectrophotometry methods,<sup>11</sup> were conducted with some disadvantages like; long analysis time, the need for sample preparation, complicated procedures with high cost of investment and exhibit poor performance.<sup>2</sup> The electrochemical techniques widely used for the determination of electroactive compounds in pharmaceutical forms and physiological fluids.<sup>12</sup>

The voltammetric techniques are often used for determination of pharmaceuticals and represented by solid or carbon electrode materials. They have excellent sensitivity, selectivity, reproducibility and low

detection limit,<sup>13</sup> a wide range of temperature, rapid analysis time, the ability to determine kinetic and mechanistic parameters both in identification and quantification of pharmaceuticals.<sup>14</sup> Glassy carbon electrode (GCE) has higher inertness, very small pores sizes, a small permeability to go and liquid, excellent biocompatibility and extremely low coefficient of thermal expansion.<sup>15-17</sup> Surface pretreatment improve the electrochemical nature of the GCE surface. The electrochemical pretreatment process helps to obtain accurate, definite and reproducible electrochemical signals. The activation of the GCE significantly enhanced the selectivity and the sensitivity of the electrochemical sensors to the analyte of interest by introducing different functional groups on the GCE surface.<sup>18-20</sup>

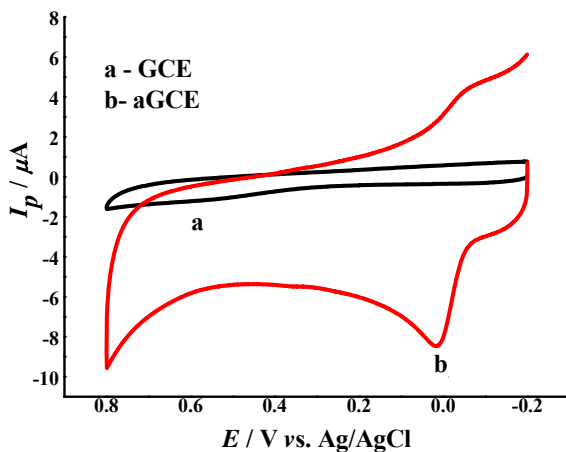
Therefore, in this study the aGCE was used for simultaneous electrochemical determination of PA and AA. The cyclic voltammetric response of PA and AA was studied before and after the activation of GCE. The aGCE exhibit better electrochemical performance than the traditional electrodes. Therefore, the aGCE has been used for the electrochemical investigations of PA and AA.

## **Results and Discussion**

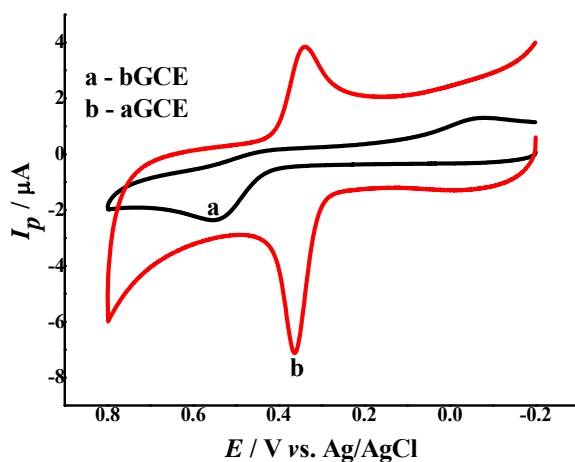
### *Electrochemical behavior of PA and AA*

As can be seen (Figure 1a) no well resolved oxidative and reductive peaks were observed in the potential range from -0.2 to 0.8 V. The broad oxidative peak current is observed without any reductive peak indicating that the electrochemical reaction of AA at bare GCE is totally irreversible, and no reproducible electrode response is obtained due to fouling of the electrode surface by the adsorption of the oxidized product of AA. On the

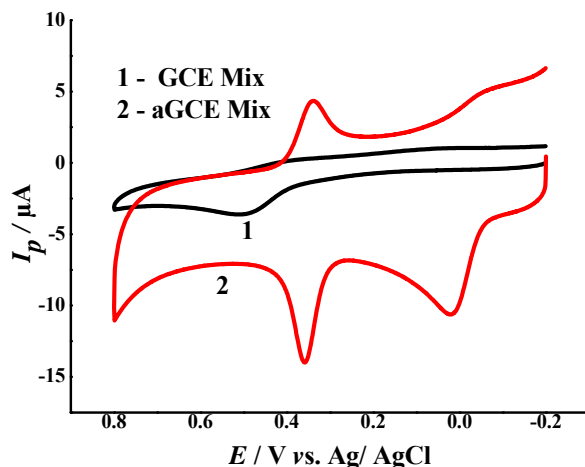
other hand, (Figure 1b) shows that the oxidation of AA on aGCE irreversible. Moreover, the oxidation peak shift to less positive potential shows that much lower over-potential is required for a faster electron transfer reaction. Hence, the faster electron transfer leads to a sharper and better defined peak, as the control of the process passes from the electron transfer to the mass transport.<sup>21</sup> Figure 2a paracetamol shows an oxidative peak potential at  $E_{pa} = 550$  mV and a small cathodic peak potential at  $E_{pc} = -83$  mV, with peak separation between the anodic and cathodic peak potential ( $\Delta E$ ) is 633 mV. Figure 2b at the surface of aGCE a pair of well-defined redox peaks with anodic and cathodic peak potentials at 360 and 340 mV, respectively and the change in potential is 20 mV. On the other hand, the anodic peak potential of PA shifts from 550 mV at the bGCE to 360 mV at the aGCE, and the anodic peak current ( $I_{pa}$ ) is enhanced by approximately 3- fold compared at bare GCE. The decrease of oxidation over potential (190 mV) and the peak current enhancement clearly indicated that activation had great catalytic performance for electrochemical reaction of PA. As shown from Figure 3 (curve 1) the simultaneous determination was difficult due to the oxidation of AA that takes place at a potential close to that of PA, resulting in an overlapped voltammetric response and low currents due to the absence of electro-catalytic behavior of the bare electrode toward PA and AA. On the other hand, at the surface of the aGCE (Figure 3 (curve 2)), the larger separation of the peak potentials, the peak current enhancement and the drop of oxidation over potentials representing an improvement in the reversibility of PA electro-oxidation and suggesting that it was possible to determine both PA and AA simultaneously at activated surface.



**Figure 1.** CVs of 0.5 mM AA at the bGCE (a) and aGCE (b) respectively in 0.1 M PBS pH 7.0 scan rate;  $100 \text{ mV s}^{-1}$ .



**Figure 2.** CVs recorded 0.1 mM PA at the bGCE (a) and aGCE (b) respectively, other conditions as Figure 1.

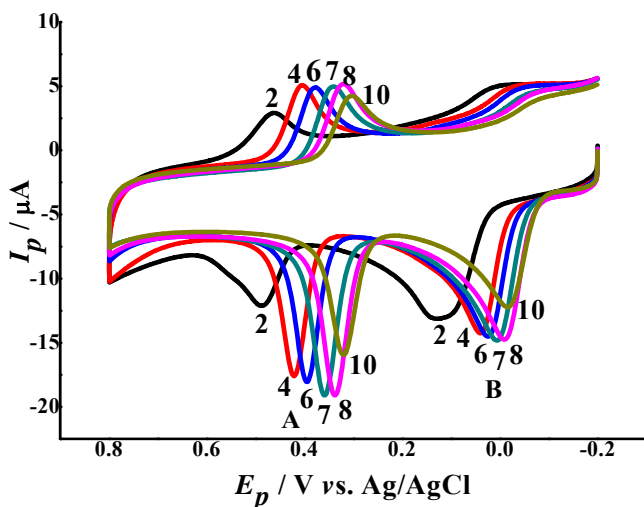


**Figure 3.** CVs recorded at a mixture solution of PA and AA at bare (1) and aGCE (2) respectively, other conditions as Figure 1.

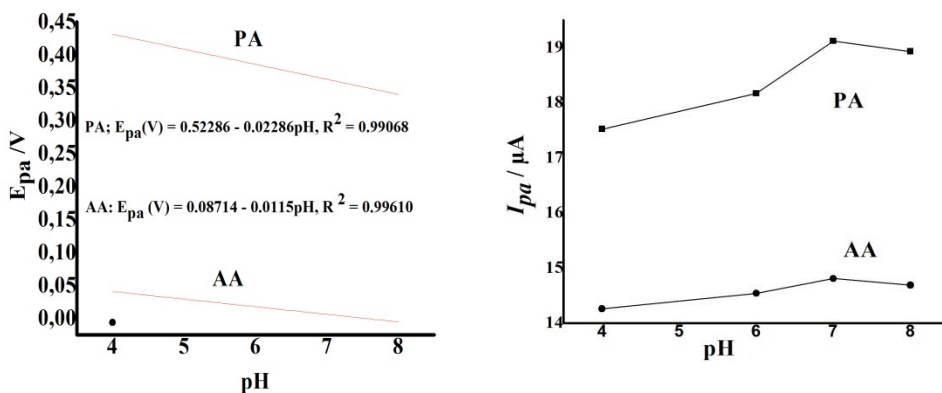
### *Effects of pH and scan rate*

#### Effect of pH

As shown, (Figure 4) the peak potentials shifted towards negative values as the pH increased due to proton involved in electrochemical reaction of PA and AA.<sup>22</sup> The deviation at higher pH, indicating that deprotonation or no longer an equal number of protons and electrons process and, suggesting that oxidation reactions of PA and AA are kinetically less favorable at higher pH. As shown, (Figure 5) the oxidative peak potentials of 0.1 mM PA (upper line) and 0.5 mM AA (lower line) shifted negatively in a linear range of pH (4.0 to 8.0) with a linear regression equation of  $E_{pa}$  (V) = -0.02286pH + 0.52286, ( $R^2 = 0.99068$ ), and  $E_{pa}$  (V) = -0.01150 pH + 0.08714, ( $R^2 = 0.99610$ ), respectively and suggesting that equal number of protons and electrons were involved in the redox reactions of PA and AA. In addition, (Figure 6) shows the oxidation peak current of PA and AA increased up to optimum pH 7.0 and decreased. Based on these observations and in order to obtain high selectivity and sensitivity PBS at pH 7.0 was chosen as optimum supporting electrolyte and used in further experiments.



**Figure 4.** CVs of pH values on the peak current ( $I_p$ ) and peak potential ( $E_p$ ) of 0.1 mM PA (A) and 0.5 mM AA (B) at aGCE, Sensitivity; 100  $\mu\text{A}/\text{V}$ .

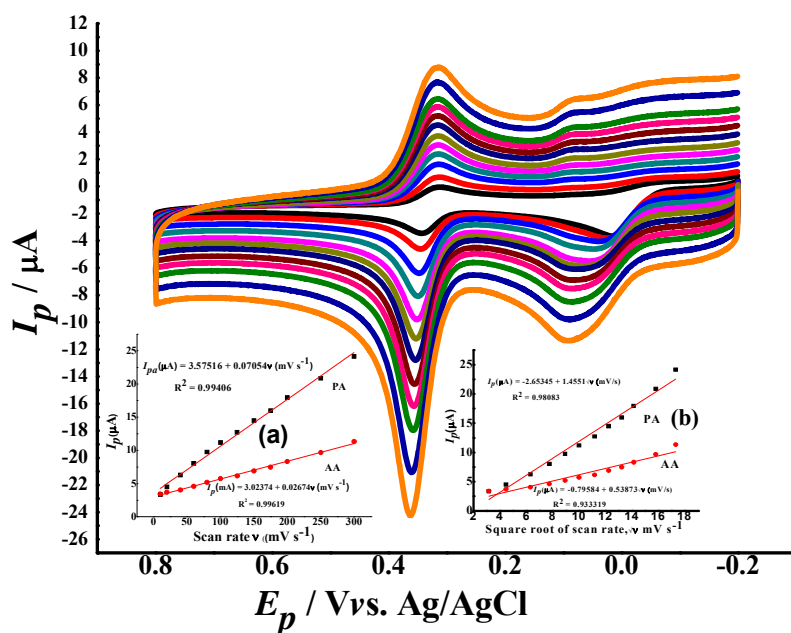


**Figure 5.** Effect of  $\text{pH}$  on the peak potential ( $E_p$ ), Figure 6. Effect of  $\text{pH}$  on the peak current ( $I_p$ ), other conditions as Figure 4.

### *Effect of scan rate*

As shown (Figure 7) the shifting of the peak potentials to more positive values and the proportionality of the peak currents as the scan rate

increased, indicating that the catalytic reaction was controlled by adsorption process. As Figure 7a and Figure 7b the peak currents ( $I_p$ ) of PA and AA increased in a scan rate ( $\nu$ ) changes from 10 - 300 mV/s and the square root of the scan rate ( $\sqrt{\nu}$ ) changes from  $\sqrt{10}$  -  $\sqrt{300}$  mV s<sup>-1</sup> respectively. However, the linear relationship between the peak current ( $I_p$ ) versus scan rate 10 to 300 mV s<sup>-1</sup> (Figure 7 a) with a correlation coefficient of 0.99406 for PA and 0.99619 for AA, indicating that the catalytic reactions were controlled by adsorption process.

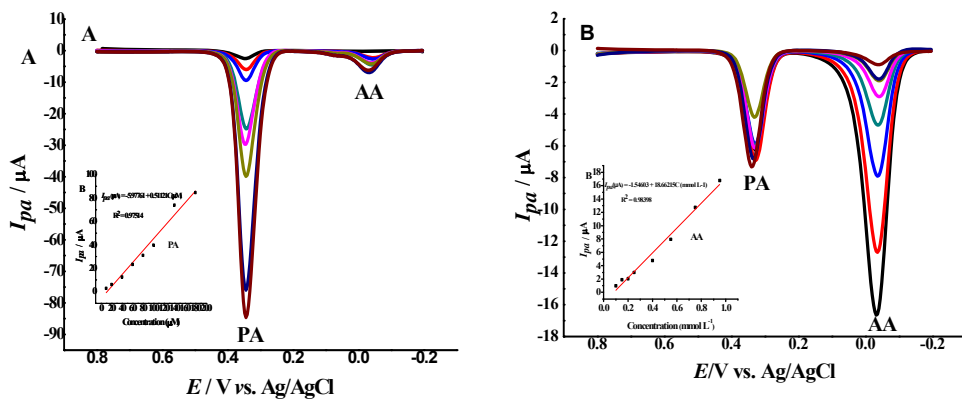


**Figure 7.** CVs of (0.1mM) PA and (0.5mM) AA in (0.1 M PBS (pH 7.0), at various scan rates from inner to outer, 10 to 300 mV/s at aGCE. Insets: (a) the plots of peak current ( $I_p$ ) vs. scan rates ( $\nu$ ), and (b)  $I_p$  vs. the square root of the scan rate ( $\sqrt{\nu}$ ).

#### *Square wave voltammetric behavior of PA and AA*

As can be seen from (Figure 8A & B), the electro-oxidation processes of PA and AA in mixtures were investigated when the concentration of one species changed and the other was kept constant. The

results show that the peak currents increased linearly with increasing the concentration of one species by keeping the other constant and addition of one species does not affect the determination of the other at the activated surface. The regression equation shows a linear characteristic in the concentration range of PA from 10 to 100  $\mu\text{M}$  and in concentration range of AA from 0.4 – 0.95 mM respectively, suggesting that activated GCE effectively catalyze the determination of the species simultaneously. The detection limit was calculated using the formula  $3\delta/M$ , where  $\delta$  is the standard deviation of the blank under the same conditions as for the standard sample analysis which was taken from eight repeats ( $n = 8$ ) and  $M$  is the slope obtained from the calibration plot. The detection limit of PA was 0.155  $\mu\text{M}$ , standard deviation (0.02642  $\mu\text{A}$ ) and slope from the calibration plot was (0.51121  $\mu\text{A} / \mu\text{M}$ ). Similarly, the detection limit of AA was 1.89  $\mu\text{M}$ , standard deviation (0.0118  $\mu\text{A}$ ) and slope (18.66215  $\mu\text{A} / \text{mM}$ ). The limit of quantification was also calculated by the relationship  $10\delta/M$ . The quantification limit of PA was 0.517  $\mu\text{M}$  and 6.32  $\mu\text{M}$  for AA.



**Figure 8.** SWV at aGCE for different concentrations of PA (10  $\mu\text{M}$  to 180  $\mu\text{M}$ ) in the presence of 0.55 mM AA (from 0.1 mM to 0.65 mM) in the presence of 10  $\mu\text{M}$  PA, (Inset: the corresponding calibration curves).

### *Real sample analysis*

aGCE was applied to detect PA and AA in paracetamol + vitamin C (500 mg PA/300 mg AA). The standard addition method was used to evaluate the percent recoveries and the results showed that the recovery tests of PA and AA were 101.5% and 95%, respectively, indicating that the method developed in this work had excellent sensitivity and selectivity for detecting PA and AA in commercial drug formulation. In addition, the recovery studies show that the drug excipients do not significantly interfere with the proposed method.

### *Interference study*

There are several possible interferes which affect the selectivity of aGCE for the simultaneous electrochemical detection of PA and AA. Different interfering substances were added as an interferent into a solution containing PA and AA. Equimolar amounts of glucose (GL),  $K^+$ ,  $Na^+$ ,  $Cl^+$ , and  $NO_3^-$  did not show interference in determination of PA and AA.

### *Comparison with results of other studies*

Comparison was made between the linear range and the LOD of PA and AA at aGCE and other electrochemical analysis methods reported for the simultaneous electrochemical detection of PA and AA and shown in Table 1. The experimental results show that aGCE has comparable linear range and LOD as compared with other electrochemical analysis methods for detecting PA and AA.

**Table 1.** Comparison with other electrochemical methods.

Modified electrode	Metho d	Linear range ( $\mu\text{M}$ )	LOD ( $\mu\text{M}$ )	pH	References
SWCNT/CCE	DPV	APAP; 0.2 to 150 AA; 5.0 to 700.0	0.12 3.00	PBS (7)	21
MWCNT/CPE	DPV	APAP; 2.0 to 400 AA; 0.02 to 140	0.80 0.009	PBS (6)	22
Al/Pd	DPV	APAP; 100 to 5000 AA; 100 to 300	5.00 5.00	ABS (6)	23
Au/MWCNT/G CE	DPV	APAP; 0.09 to 35 AA; 1.0 to 150	0.03 0.76	BRBS (6.0)	24
(GCEMWCNT- Polyhistidine)	DPV	APAP; 0.25 to 5.0 AA; 25 $\mu\text{M}$ to 1.50	0.032 0.76	PBS (7.4)	25
(Thionine – MWCNT/CPE)	DPV	APAP; 0.1 to 100 AA; 1.0 to 100	0.05 0.30	ABS (4)	26
AGCE	SWV	APAP: 10 to 100 AA: 400 to 950	0.155 1.890	PBS (7)	<b>This work</b>

## Experimental section

### *Instrumentation*

Voltammetric experiments were carried out using voltammetric analyzer CHI760E (Bioanalytical systems (BAS, USA) equipped with voltammetric interface and driven by software package in conjunction with a three electrode system and a dell desk top computer was employed for data storage and processing. A three electrode cell system composed of silver/silver chloride (Ag/AgCl) (sat.) as the reference electrode, a platinum wire as the counter/auxiliary electrode, and the bare and potentially aGCEs as the working electrodes each 3 mm diameter were used. The pH meter (JENWAY model 3510) and digital balance were used.

### *Chemicals and reagents*

Pure paracetamol (Addis pharmaceutical factory, Ethiopia), pure ascorbic acid (Tarapu MIDC, India), anhydrous di-potassium hydrogen orthophosphate (BDH, England), potassium dihydrogen phosphate (Sigma

Aldrich, Switzerland), hydrochloric acid (Riedel deHaen, Germany), uric acid (LABORT, India), and sodium hydroxide (BDH, England) without any further purification were used.

#### *Preparation of the aGCE*

Before activation, the surface of GCE (3.0 mm diameter) was polished to a mirror with 0.5  $\mu\text{m}$  alumina powder with in a polishing cloth and then cleaned thoroughly with distilled water. The cleanness of the electrode was checked by a 0.5M sulfuric acid by running in cyclic voltammetry with a potential window between -200 mV and 800 mV at the scan rate of 100 mV/s, sensitivity; 100  $\mu\text{A/V}$ . Then, the GCE was activated for 200 s in a time base technique at a potential of 1750 mV, sensitivity; 100  $\mu\text{A/V}$  in 0.1M PBS at pH 7.0. Then cyclic voltammogram of the activated electrode was run between a potential from 0.0 to 700 mV until a stable voltammogram was obtained.

#### *Preparation of stock and standard solutions*

For cyclic voltammetric studies, 1 mM PA and 1 mM AA stock solutions were prepared by dissolving 0.0755 g of PA and 0.0882 g of AA in 500 ml of 0.1M pH 7.0 PBS. From the stock solutions, 0.1 mM solution of PA, 0.5 mM solution of AA and a mixture (0.1 mM PA and 0.5 mM AA) were used for the voltammetric investigation at the bare and the aGCE. The working solutions of different concentrations of PAP (10, 20, 40, 60, 80, 100, 140 and 180  $\mu\text{M}$ ) and AA (0.1, 0.15, 0.2, 0.25, 0.4, 0.55, 0.75 and 0.95 mM) in pH 7.0 PBS were prepared from the stock solutions.

#### *Preparation of calibration curve*

0.1 M PBS (pH 7.0) was used to prepare the stock and working solutions of paracetamol and ascorbic acid. Keeping the optimum experimental parameters constant, a calibration curve using SWV was

obtained for PA in the concentration range from 10 $\mu$ M to 180  $\mu$ M at constant concentration of AA and for AA in the concentration range from 0.1 mM to 0.95 mM at constant PA concentration.

#### *Sample preparation*

An adequate amount of paracetamol + vitamin C (500 mg PA / 300 mg AA), which is equivalent to the standard powder was accurately weighed and added in to 100 mL volumetric flask and was shaken till it was dissolved. The solution was centrifuged to ensure complete dissolution then filtered by Whatman filter paper. The prepared solution was filled with 0.1 M PBS (pH 7.0) and further diluted to volume with the same solvent. The diluted solution was containing specified amount of PA and AA. From calibration curve concentrations of PA and AA were extrapolated and recovery was calculated by dividing the obtained concentration to the spiked.

#### **Conclusions**

aGCE has been used successfully for the electrocatalytic oxidation and determination of PA and AA at a physiological pH PBS. It was found that the oxidation and reduction peak current of both PA and AA were improved significantly and the oxidation peak shifted towards less positive potentials at the surface of the aGCE compared to the untreated GCE which indicating that aGCE displays excellent electro-catalytic property. In addition, the aGCE facilitates the determination of PA and AA with good sensitivity, selectivity and enhancement of peak currents compared to the bare GCE. The practical analytical utility of the method was successfully demonstrated in the analysis of pharmaceutical formulations and the interfering study showed that uric acid interfere paracetamol. The most

simple, selective, cost effective, fast and sensitive electrochemical method for the simultaneous determination of PA and AA, interesting for the further application such as quality control of medicines in pharmaceutical and related industries.

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