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Electrochemical Quantification of Paracetamol in Locally Available Pain-Killer Drug Formulaions, Using Cobalt Hexacyano Ferrate Based Carbon Paste Sensor, Voltammetrically

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A B S T R A C T

Paracetamol, because of its palliative characteristics has found its worldwide applications in the service of humankind to get divest-off headache, backache, and arthritis including post-operative pains. At present, the electrochemical oxidation studies of Acetaminophen (APAP) at 0.1M phosphate buffer solution of pH-7 using cobalt hexacyano ferrate modified carbon paste electrode at scan rate 50 mV/s employing cyclic voltammetry (CV) and Differential pulse voltammetry (DPV) techniques have been carried out. The different experimental and voltammetric parameters that have their profound effect on the electrochemical response of paracetamol, like buffer pH, scan rate, concentration and mass-ratio of modified sensor have been worked out to set the optimum working conditions for present studies. On using these working parameters, the nature of electrochemical oxidation process involved at the sensor/ analyte interface has been observed an irreversible involving transference of two electrons and two protons, along with the diffusion controlled interfacial operation of the process. The enormity of diffusion coefficient (D), electron transfer coefficient (α) and heterogeneous transfer rate constant (k) have been calculated and cited as 7.3×10^{-6} cm^2s^{-1}, 0.541 and 3.2×10^{-6} cm s^{-1}, respectively. The sensor has displayed outstanding electrochemical catalytic activity towards the oxidation of APAP. Under optimized parameters, DPV technique has given away the improved sensitivity for APAP in low analyte concentrations and responded a linear behavior over 1.0 to 10.0 μML^{-1} range, following the regression equation *"Ip (μA) = 1.6126 C (μM) + 34.5 with correlation coefficient, R = 0.999 for repititions, n = 5"*. The limit of detection (LOD) calculated from oxidation peak currents in the linear range using, LOD = 3s/m, found 4.6 x 10^{-7}mol/L.

Keywords: Cobalthexacyanoferate, cyclic voltammetery, differential pulse voltammetry, paracetamol

A R T I C L E I N F O

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1. Introduction

Acetaminophen (APAP) / N-acetyl-p-aminophenol/ paracetamol is an effective analgesic and antipyretic drug along with limited anti-inflammatory characteristics. It is commonly used as pain killer drug during headache, backache, arthritis and postoperative pain, besides, reducing fevers of bacterial or viral origin [1] an alternative to aspirin, particularly for patients who cannot tolerate aspirin [2]. Overdoses of (APAP) lead to hepatic toxicity and even death in some cases associated with liver and kidney damage. Therefore, it is very important to establish a simple, fast, economical, sensitive and accurate method for detection of (APAP) in drug industry. Different methods have been exploited for this purpose, like titrimetric method, using ferrocine as indicator [3]. Its electrochemical determination using square-wave voltammetry (SWV) at a poly-aniline-multi-walled carbon nanotubes composite modified glassy carbon (GC) electrode [4], with Poly-3-Aminophenol modified carbon paste electrode [5] and with Poly-3, 4-ethylenedioxythiophene modified glassy carbon electrode [6]. Electrochemical technique, using gold nanoparticles application in tablets and human fluids [7], using MWCNTs: Graphite/GC electrodes in various concentrations of acetaminophen have been reported [8]. The simultaneous determination of paracetamol and *para*-amonophenol in pharmaceutical formulations has also been presented [9]. In this work the electrochemical oxidation of paracetamol was described using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in 0.1 M phosphate buffer using cobalt hexacyanofferrate modified carbon paste electrode.

2. Experimental

Reagents and chemicals

The chemicals used in this study were graphite powder (England) , paraffin oil, pure paracetamol, di-sodium hydrogen orthophosphate anhydrous (from BDH -England), sodium dihydrogen orthophosphate, sodium hydroxide, hydrochloric acid, potassium chloride, cobalt (II) chloride and potassium hexacyano ferrate (III) (from Nice-India), paracetamol tablets with brand name -paracetamol and panadol- were purchased from the local market. All the chemicals used were analytical grade and double distilled water was used for the preparation of all solutions.

Apparatus: The electrochemical experiments were conducted in laboratory using BAS-CV50W voltammetric analyzer, connecting with personal computer used for electrochemistry work station and data analyzed. All the electrochemical experiment were carried out using three electrode cell containing Ag/AgCl as a reference electrode, a platinum wire as a counter electrode and bare carbon paste electrode (BCPE) or cobalt (II) hexacyanoferrate (III) modified carbon paste electrode (MCPE) as working electrode. The pH of the buffer solution was measured with a 353 ATC digital pH meter with combination glass electrode. Syringe with size of 1 ml and Whatman 41 filter paper were used for the preparation of the working electrode in the experiment.

Solution preparation

Supporting electrolyte of phosphate buffers with pH 7 was prepared from 1M NaH_2PO_4 and 0.1M Na_2HPO_4 in distilled water. The pH of the solutions was adjusted by adding drops of 0.1M HCl and 0.1M NaOH as per requirement of buffer. Stock solution of paracetamol was prepared by dissolving 0.5 g of paracetamol in 100 mL of the supporting electrolyte. The required concentration of paracetamol solutions were prepared by diluting the stock solution with the supporting electrolyte.

Preparation of cobalt (II) hexacyanoferrate (III)

The precipitates of complex compound cobalt (II) hexacyanofferrate (III) was prepared by mixing a 0.25 M potassium hexacyanofferrate (III) solution and 0.5 M cobalt (II) chloride solution using Co/Fe atomic ratio 1:2. The obtained precipitate was filtered using whatman 41 filter paper, then washed with distilled water several times and dried at room temperature for 4 days.

Preparation of carbon paste electrode

The carbon paste electrode was prepared by mixing 3:1 weight ratio of graphite powder with paraffin oil. The mixture was homogenized with mortar and pestle for 30 minutes and allowed to rest for 24 hours. The homogenized paste was packed in to the tip of a plastic syringe equipped with copper wire inserted from the backside of the syringe to provide electrical contact. Then the surface of the electrode was smoothed against a filter paper until a shiny surface emerged.

Preparation of modified carbon paste electrode

The modified carbon paste electrode was prepared by carefully mixing the dispersed graphite powder with cobalt (II) hexacyanoferrate (III), (CHCF), at varying ratio and subsequently adding 0.250 g paraffin oil. Each mixture was homogenized with mortar and pestle for 30 minutes and allowed to rest for 24 hours. These were packed into an electrode body, consisting of plastic syringe equipped with copper wire to make electrical contact. MCPEs of different composition were obtained. Appropriate packing was achieved by pressing the electrode surface against a whatman 41 filter paper.

Preparation of real Sample

In order to determine the content of acetaminophen in two different commercial brands (paracetamol and Panadol) Tablets were collected. The tablet formulation of 500 mg each was crushed to powder and transferred to two different 100 ml volumetric flasks and this volume make up to mark with phosphate buffer of pH 7. Each solution was shacked till dissolved. The solutions were centrifuged followed by filtration using Whatman 41filter paper. An appropriate amount of these solutions were diluted with phosphate buffer solution for further experimental use. DPVs were recorded in the potential range -100 to +1000 mV versus Ag/AgCl at a scan rate 50 mV/s. The concentration of Paracetamol in these tablets was determined from the calibration curve.

3. Results and Discussion

Cyclic Voltammetric Investigation

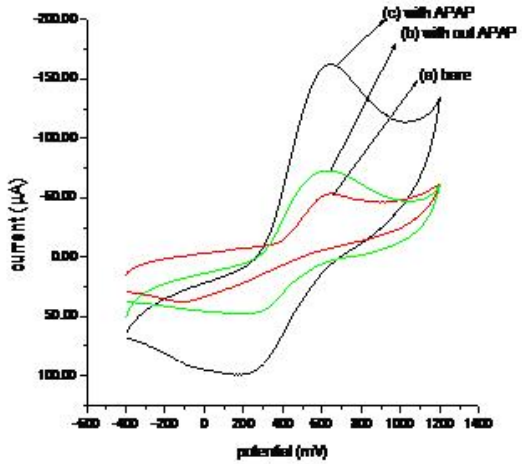


Figure 1: Cyclic voltammograms of 0.1M phosphate buffer pH 7 with 4 mM of APAP at scan rate 50 mVs^{-1} recorded at two different working electrodes BCPE (a) and CHCFE for the solution -without APAP (b) with APAP (c) .

Electrochemical behavior of APAP was examined using cyclic voltammetry. Figure-1 represent typical cyclic voltammograms of 0.1M phosphate buffer pH 7 with 4 mM of APAP at scan rate 50 mVs^{-1} using BCPE (a) and CHCFE without APAP (b) and in the presence of APAP (c) . The results show that the modifier produced an anodic peak current $1.48x10^{-4}$ A in the presence of APAP (c) and anodic peak current -7.25×10^{-5} without APAP (b). It is apparent that the anodic current associated with the buffer solution is significantly less than that obtained in the solution containing APAP. It can be seen from the cyclic voltammograms of APAP in Fig.1 that an oxidation peak potential 661.8 mV and reduction peak potential -95.7 mV with low oxidation peak current of -5.36×10^{-5} A, at bare carbon paste electrode along with the peak to peak potential separation 757.5mV. In case of CHCFE the electrochemical response of paracetamol at the electrode shows both cathodic and anodic peak current $11.1x10^{-5}$ A and $1.48x10^{-4}$ A, respectively. The oxidation peak potential shifts negatively 627.8 mV and reduction peak potential at 201.9 mV (Vs.Ag/AgCl) when compared to BCPE. The peak to peak separation (ΔEp) was found to be 425.9 mV and the ratio of redox peak current (Ipa/Ipc) was 1.33. This is highly comparable to observed theoretical value 1.27 which indicates irreversible nature of electrode process as reported earlier [10]. The oxidation peak current of modified electrode was greater than that of bare electrode and the peak-to-peak potential separation of the modified electrode was less than that of the bare electrode. This indicates that the modified electrode has good electrocatalytic property for the redox reaction of paracetamol.

Effects of electrode composition on voltammogram

To study the effect of the amount of CHCF in carbon paste, the electrodes between 10 % to 25 % (w/w) modifiers were taken in present study and the cyclic voltammograms are presented in figure 2. The variation of anodic peak current with increasing mass of CHCF in modified electrode mixture using 4mM APAP in 0.1M phosphate buffer solution at pH-7 have been shown in figure 3. This figure indicates an increase up to 15 % composition (w/w) and results decrease, thereafter. The observation could be due to decrease in highly conducting graphite content in paste. So, the best electrodes composition (w/w) for present work is 15 % CoHCF, 60 % graphite and 25 % paraffin oil.

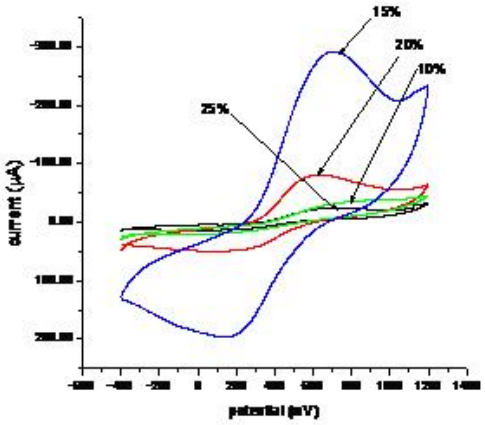


Figure 2: Cyclic voltammograms of different % of CHCF for 4 mM APAP in 0.1 M phosphate buffer solution at pH 7 with scan rate 50 mV/s.

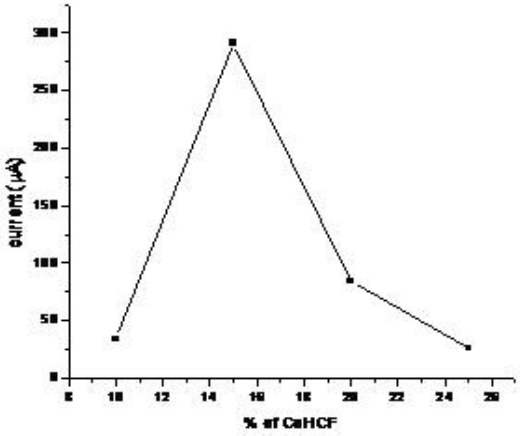


Figure 3: Variation of anodic peak current with composition of CoHCF, on for 4 mM paracetamol in phosphate buffer solution at pH 7 with scan rate 50 mV/s.

Effect of buffer pH

The effect of pH on the electrochemical oxidation of APAP at the CHCFE has been studied by varying pH of phosphate buffer between 5–9 using scan rate 50 mV/s, and depicted in figures 4 & 5. The best anodic oxidation signal of APAP was obtained at pH 7. The weak anodic peak signals at lower pH could be due to excess hydrogen ion which is one of the oxidation products of paracetamol. The high concentration of H^+ hinders the electrochemical oxidation of paracetamol due to common-ion effect. The poor oxidation signals at higher pH may be due to hydroxylation of the mediator. These observations find a good support from earlier studies [11]. Therefore, buffer solution of pH 7 was chosen for further study.

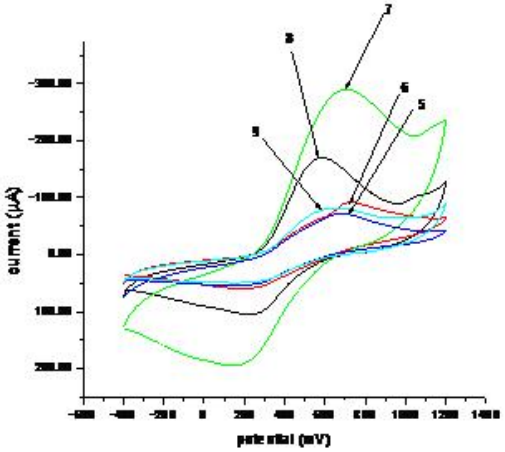


Figure 4: Cyclic voltammograms for electrochemical oxidation of 4 mM APAP at the CHCFE at different pH in range (5-9) using 0.1M phosphate buffer with scan rate 50 mV/s.

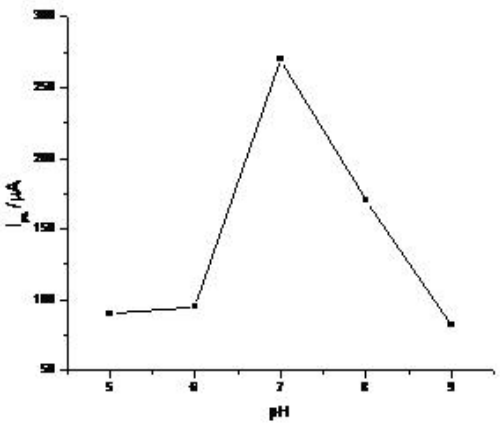
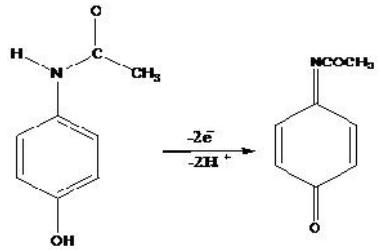


Figure 5: Effect of variation of pH of 0.1 M phosphate buffer solution on oxidation peak current of 4 mM APAP with scan rate 50 mV/s at CHCFE.

In figure-6 the anodic peak potential (Epa) plotted versus pH in the range of 5-9, which gave a linear response with a slope of -56.7 mV/pH and the correlation coefficient R=0.991. The magnitude of the slope is very close vicinity of the theoretically observed value i.e. -59 mV/pH. This is well-built evidence that suggests the flow of two electrons across the sensor/ analyte interface [12]. The signal for paracetamol was shifted to more cathodic potentials as pH is increased. This indicates that the number of protons and electrons involved in the oxidation of paracetamol are equal. Scheme.1 shows oxidation of APAP [13].



Scheme 1: The oxidation of paracetamol in 0.1 phosphate buffer (pH = 7)

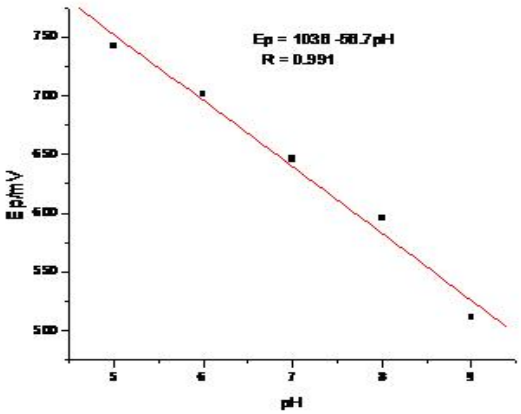


Figure 6: Effect of variation of pH of 0.1 M phosphate buffer solution at CHCFE on oxidation peak potential of 4 mM APAP using scan rate 50 mV/s.

2.4 Effect of scan rate

The effect of varying scan rate (*v*) on the cyclic voltammograms of 4 mM APAP in 0.1M phosphate buffer at pH 7 using CHCFE as working electrode has been studied between 10–100 mV/s and presented as in Figure-7. The oxidation peak current of paracetamol increase with rise in scan between -400 and 1200 mV. The peak broadening effect along with the slight peak diminishing result appears as the scan rate exceeds 60 mV/s. Therefore, a scan rate 50 mV/s was chosen for these experiments.

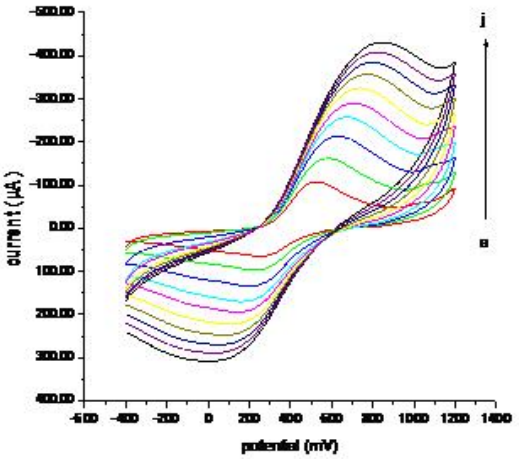


Figure 7: Cyclic voltammogram of 4mM paracetamol in 0.1M phosphate buffer of pH 7 using CHCFE at

scan rate of a) 10; b) 20; c) 30; d) 40; e) 50; f) 60; g)70; h 80; i) 90 and j) 100 mV/s.

On the bases of plot between oxidation peak current (I_{pa}) and square root of scan rate ($v^{1/2}$) as evidenced in figure 8, the electrochemical behavior observed linearity within the studied range 10–100 mVs^{-1} along with correlation coefficient R = 0.9968. This indication leads to the fact that the electrode process occurring at interface is a diffusion controlled process. Another support to the above said fact has been emerged out from the magnitude of sensitivity/slope obtained from the plot between log I_{pa} and. log v which has been presented with the linear regression equation as: log I_{pa}, logv+1.56 and correlation coefficient R=0.9996.

A slope of 0.53 which is quite comparable with theoretical slope of 0.5 for the reaction of diffusion controlled process as given in literature [14]. Now there will be no hesitation to report that approximately two protons transference involved in the reaction. Paracetamol oxidation is a two-electron two-proton process. This result is consistent with that reported in the literature [6]. These results conclude that the reaction was diffusion controlled process.

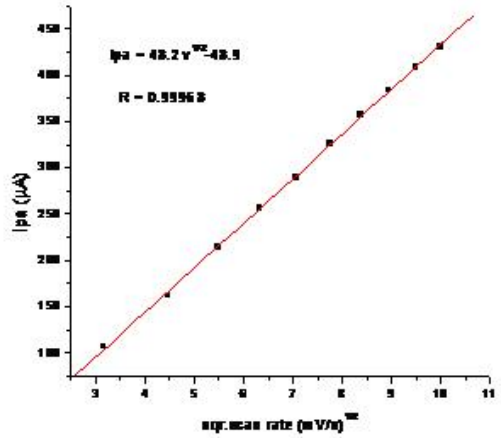


Figure 8: Effect of variation of square root of scan rate on oxidation peak current of 4 mM APAP in 0.1M phosphate buffer at pH 7 using CHCFE**.**

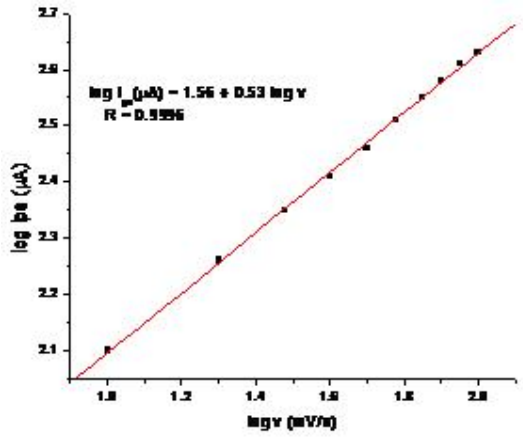


Figure 9: graph of log I/μA versus log scan rate (mV/s).

Studies of kinetic parameters

The magnitude of electron transfer coefficient (α) can be calculated from the slope of the curve resulted from the Tafel plot between observed anodic peak potential 'Ep' and logarithm of scan rate 'log v' as presented in Figure 9, by using equation (1) as reported in literature [15].

$$E_{pa} = K + \frac{2.303RT}{2(1-\alpha)n_\alpha F} log\ v \text{---------} (1)$$

$$Slope = \frac{2.303RT}{2(1-\alpha)n_\alpha F} \text{----------} (2)$$

$$E_p = E^0 - \left(RT/\propto n_a F\right)\left[0.78 - \ln\left(k^0/D^{1/2}\right) + \ln\left(\propto n_a Fn/RT\right)^{1/2}\right] \text{----------} (3)$$

Where *α* is transfer coefficient, n_α is the number of electrons involved in the rate-controlling step across the interface, *v* is applied scan rate, R is gas constant, Epa is peak potential, F Faraday constant, K is equilibrium constant and T absolute temperature. Using the magnitude of slope from figure 10, whose correlation coefficient is R=0.991, into the equation (2), the value of transfer coefficient (*α)* was calculated as 0.541.

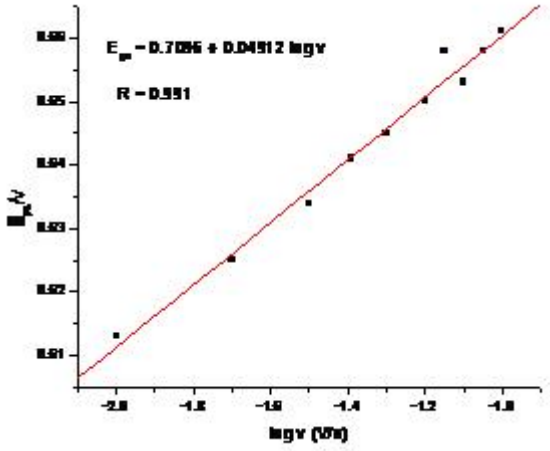


Figure 10: Graph of oxidation peak potential i.e. Ep (V) vs. log v (mV/s).

Using equation (4), derived from equation (3) and calculating *α* from the slope of Ep vs. log v curve, *k* value was calculated as follow.

$$K = E^0 + \frac{RT}{(1-\propto)n_\propto F} \times [0.78 + \frac{2.303}{2}\log\left(\frac{(1-\propto)n_\propto FD}{k^2 RT}\right)] \ldots (4)$$

here *α* is transfer coefficient, $n_\propto$ is the number of electrons involved in the rate-determining step, E° is formal electrode potential E°= (Epa + E_{pc})/2 = 414.85 mV, k is heterogeneous electron transfer rate constant, D *is* diffusion coefficient. Based on equation (2), the value of *α* was calculated as 0.541; and the value of diffusion coefficient at a scan rate of 50 mV/s was found to be D = 7.3 × 10^{-6} cm^2 s^{-1}, A = 7.02 × 10^{-2} cm^2, and *n* = 2. The experimental intercept of equation (1) from figure 9, K was obtained

0.7096. On substituting the above values in equation (4), the heterogeneous electron transfer rate constant was calculated and found to be, k =3.2 × 10^{-6} cm s^{-1}.

Investigation for differential pulse voltammetry

As shown in figure 11, 0.1M phosphate buffer solution with 4 mM APAP using modified carbon paste electrode (curve c) gave large differential voltammetric peak current as compared to bare carbon paste electrode (curve a) and 0.1M phosphate buffer solution without 4 mM APAP (curve b). It is evident that the oxidation peak potential shifts towards less positive value that the CHCFE accelerates the electron transfer process at the electrode surface. Hence, CHCFE was further systematically studied by differential pulse voltammetry for the determination of APAP in the potential range from -100 to 1000 mV.

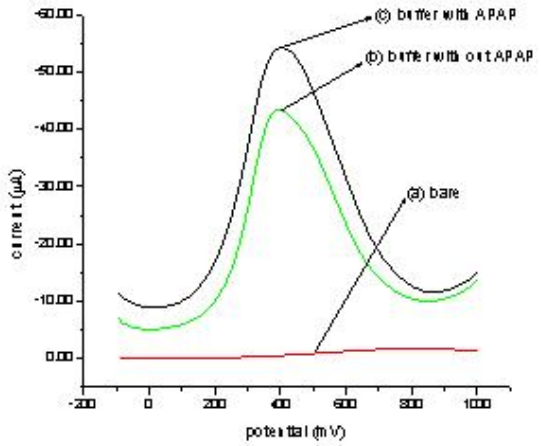


Figure 11: Differential pulse voltammograms of (a) 4 mM APAP using bare carbon paste electrode b) 0.1 M Phosphate buffer solution without and (c) with 4 mM APAP using CHCFE at a scan rate of 50 mV/s and pulse amplitude of 40 mV.

Effect of scan rate

Figure.12. shows the differential pulse voltammograms of 4 mM APAP in 0.1 M phosphate buffer solution of pH 7 at different scan rates, between 10 to 80 mV/s using CHCFE. The peak current increased with increasing scan rate, upto 50 mV/s there after it observe decrease. Therefore, the scan rate 50 mV/s was chosen for DPV experiments.

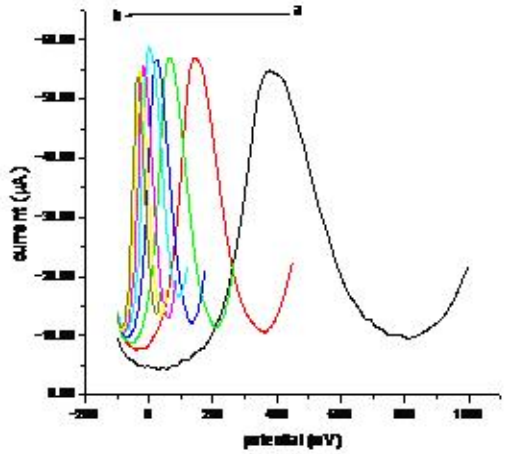


Figure 12: Differential pulse voltammograms of 4 mM APAP using CHCF in 0.1 M PBS of pH 7 at a scan rates of: (a) 10;(b) 20;(c) 30; (d) 40; (e) 50; (f) 60; (g) 70 and (h) 80 mV/s using pulse amplitude 40 mV.

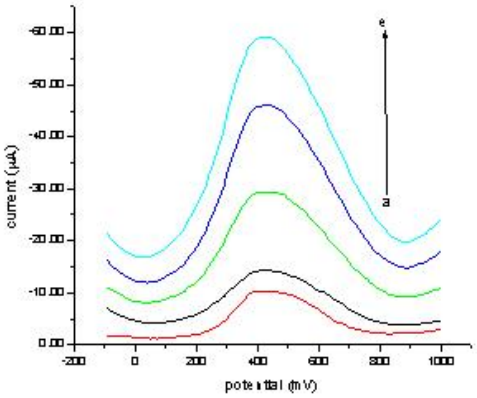


Figure 13: Differential pulse voltammogram of 4 mM APAP in 0.1 M Phosphate buffer solution of pH 7 using CHCFE at a scan rate of 50 mV/s and different pulse amplitudes of (a) 10; (b) 20; (c) 30; (d) 40 and (e) 50 mV.

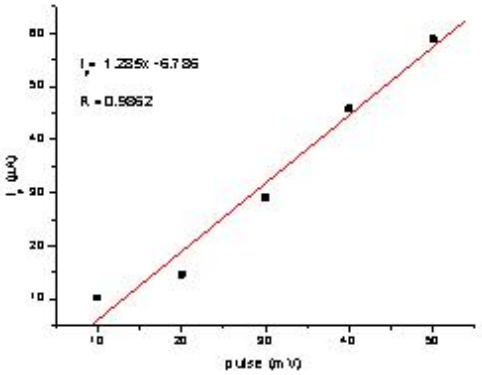


Figure 14: Effect of variation of pulse amplitudes on an oxidation peak current of 4 mM APAP in 0.1M phosphate buffer at pH 7 using CHCFE at scan rate of 50 mV/s.

Effect of analyte concentration and limit of detection

The differential pulse voltammograms in solutions of different concentration of APAP in 0.1M phosphate buffer solution of pH 7 at scan rate 50 mV/s and pulse amplitude 40 mV using CHCFE are demonstrated in figure 15. The oxidative peak current behavior has observed linearly with the rise in concentration of APAP in the range 1×10^{-6} to 1×10^{-5} mol $L^{-1,}$ as is observable in figure 16.

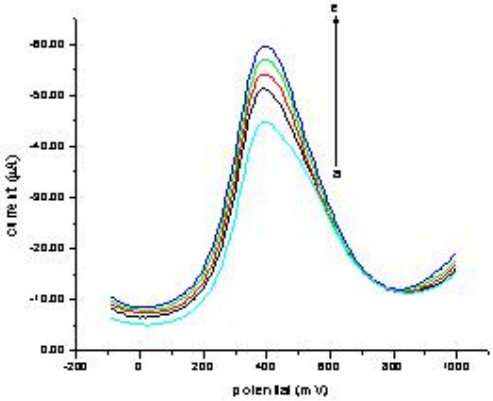


Figure 15: Differential pulse voltammograms of different concentrations of APAP (a) 1; (b) 2.5; (c) 5; (d) 7.5 and (e)

10 µM in 0.1 M Phosphate Buffer Solution of pH 7 at scan rate of 50 mV/s and pulse amplitude of 40 mV.

Analytical calibration curve

The magnitude of oxidation peak current and the paracetamol concentration follow a strong linear behavior in 1.0×10^{-6} to 1.0×10^{-5}mol L^{-1} concentration and expressed in the form of the regression equation:

Ip (µA) = 1.61261 C (µM) + 34.5

With correlation coefficient,

R = 0.999 for n = 5, and the standard deviation 0.2496.

The limit of detection (LOD) was calculated from the oxidation peak currents of the linear range by using the equation, 'LoD= 3s/m' from where it comes out 4.6 x 10^{-7} mol/L. Here's' is standard deviation of the blank solution and m is slope of the calibration curve.

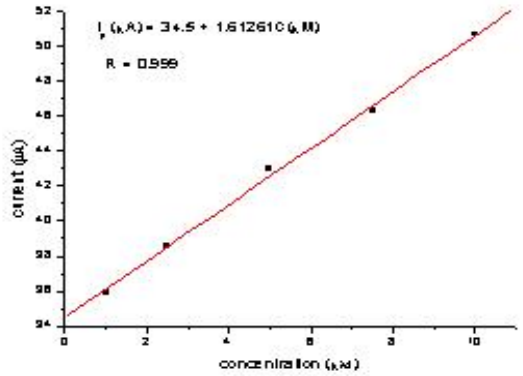


Figure 16: Calibration curve for determination of APAP in 0.1 M Phosphate Buffer Solution (pH 7) at CHCFE of a scan rate of 50 mV/s and pulse amplitude of 40 mV with different paracetamol concentrations: (a) 1; (b) 2.5; (c) 5; (d) 7.5 and (e) 10 µM

Table1: A comparative view of performance during present work to that recently reported results of quantification of paracetamol in pharmaceutical formulations.

Electrode	Conc. range mol/L	Detection limit mol/L	Method
Bi_2O_3 nanoparticle [14]	$5x10^{-7}$-$1.5x10^{-3}$	$2.0x10^{-7}$	CV
Polyanaline-MWCNT/GC [8]	$1x10^{-6}$-$2x10^{-3}$	$2.5x10^{-7}$	SWV
PEDOT/GCE [16]	$2.5x10^{-6}$-$1.5x10^{-4}$	$1.1x10^{-6}$	CV
GNP/GC [17]	$5x10^{-8}$-$2.7x10^{-4}$	$1.46x10^{-8}$	CV
Polyanaline – MCPE [5]	10^{-5}-10^{-4}	$1.1x10^{-6}$	SWV
CHCFE (present work)	1 x 10^{-6}-1 x 10^{-5}	4.6 x 10^{-7}	DPV

The above said table is presenting the comparison of different modified electrodes for determination of paracetamol pharmaceutical formulations using different electro-analytical techniques and electrochemical sensors. The magnitude of limit of detection, as reported from present work, is very low as compared to previous works. Therefore, it may be suggested that the sensor CHCFE has good sensitivity for determination of paracetamol using DPV technique.

Recovery test

The recovery test was performed by adopting standard addition method reported earlier from this laboratory [18]. A definite amount of standard solution of APAP added into the real sample solutions of pharmaceutical formulations under investigations, in order to assess the accuracy of the employed method. Table-2 revealed that the average recovery of APAP from three independent experiments, using the tablet -1 (Panadol) was calculated and obtained as 99.13 %, whereas in tablet -2 (Paracetamol) average recovery of APAP was calculated to be 101 %. These results indicate that the method was better for analysis of APAP in paracetamol (Ethiopian drug) and Panadol (Kenyan drug) tablets.

Table-2: Determination of APAP in commercial tablets (paracetamol and Panadol) using CoHCF/CPE by adding known concentration of standard solution.

Sample	Paracetamol added, µM	Paracetamol found, µM	Recovery %
Panadol	_	10.48±0.219	_
	1.0	11.52 ± 0.117	104.5
	2.5	12.92 ± 0.201	97.8
	5.0	15.23± 0.236	95.1
Paracetamol	_	9.63 ± 0.05	_
	1.0	10.59± 0.196	96
	2.5	12.23 ± 0.141	104
	5.0	14.78 ± 0.194	103

Mean value ± standard deviation (n = 4)

4. Conclusion

In this work, CHCFE was used for electrochemical determination of paracetamol in pharmaceutical tablets using CV and DPV techniques. The effects of composition of modified electrode, pH, analyte concentration and scan rate were studied voltammetrically. The recorded voltammograms have responded an irreversible nature of the electrode process at the interface of sensor with transference of two electrons and two protons per molecule of the analyte. Linearity of analyte's behavior with scan rate from CV and DPV studies inveterate that the system has followed diffusion controlled mechanism to electrode process. The parameters like electron transfer coefficient, diffusion coefficient and heterogeneous transfer coefficient have determined and cited in the paper. The advantage of the CHCFE is to enhance the sensitivity of the CP-electrode, significantly. The APAP recovery studies from the real samples of drug formulations have been found admirable. The results indicated that the method is simple and sensitive enough for the determination of paracetamol in pharmaceutical tablets. A linear rejoinder in the investigated range with the regression equation "Ip (µA) = 1.61261 C (µM) + 34.5 and R= 0.999 (n=5) with LoD 0.46 micro-molar/L".

5. Conflict of Interest

Authors declare that there is no conflict of potential interest among us.

6. Acknowledgements

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