Voltammetric determination of paracetamol in pharmaceutical tablet samples using anthraquinone modified carbon paste electrode

Meareg Amare¹* and Welday Teklay¹

Abstract: After cyclic voltammetric investigation of the electrochemical behavior of paracetamol and dependence of peak current on scan rate and pH; square wave voltammetric method based on anthraquinone modified carbon paste electrode was developed for direct determination of paracetamol in pharmaceutical tablet samples. In contrast to the peak potential at the unmodified electrode, appearance of the oxidative peak at a lower potential at the modified electrode indicated a catalytic property of the modifier towards paracetamol oxidation. While the observed peak potential shift with scan rate confirmed the irreversibility of the reaction, comparable correlation coefficients for the dependence of peak current of scan rate and square root of scan rate indicated that the irreversible oxidation reaction was controlled by both diffusion and adsorption. The peak current response of the developed method showed a linear dependence on the paracetamol concentration in the range 5 to 150 ppm. Excellent recoveries (93.5%), wide dynamic range, low limit of detection (0.13 µM), and limit of quantification (0.43 µM)

ABOUT THE AUTHOR

Dr Meareg Amare, who has MSc in analytical chemistry and PhD in physical chemistry is now an Associate Professor at the Department of Chemistry, Bahir Dar University, Ethiopia. He has over 20 articles published in reputable journals most of which are on electrochemical method development for determination of electroactive pharmaceutical ingredients. He is also working on method development for assessment of the level of selected pollutants in industrial effluents including tanneries.

PUBLIC INTEREST STATEMENT

There are a lot of well established conventional reported methods for determination of paracetamol. Whereas most of these methods are so expensive and use organic solvents which are not environmentally friendly, Voltammetric methods use relatively cheaper instruments and usually aqueous medium. The active ingredient in “paracetamol tablet” used as a pain killer is an electroactive that can be detected using voltammetric techniques. Developing a voltammetric method for the determination of such electroactive species helps researchers interested in the field to monitor their levels before they cause health problems specifically on the users and the environment in general. Carbon paste is the simplest and hence the cheapest form of the carbon-based electrodes used in voltammetry. Modification of an electrode including carbon paste usually improves its response for the analyte may be due to increased surface area, adsorption, or electron exchange. The developed method using anthraquinone modified carbon paste electrode was used for determination of paracetamol in four brands of paracetamol tablets with an excellent accuracy.
validated the method for determination of paracetamol in real samples. The proposed method was applied for paracetamol determination in four brands of tablet samples (Julphare Aldol, Panadol Adva, Kelvin, and Para Denk) all of which labeled 500 mg/tablet. The paracetamol content of the analyzed four brands of tablet samples using the reported method was ranged between 83.04% (Panadol Adva, Kenya) and 95.08% (Para Denk, Germany) of the labeled amount. The discrepancy might be ascribed to the possible matrix difference among the companies and/or failure of the companies to comply the standard.

Subjects: Analytical Chemistry; Physical Chemistry; Material Science

Keywords: anthraquinone modified carbon paste electrode; cyclic voltammetry; paracetamol; tablet formation samples; square wave voltammetry

1. Introduction

Paracetamol or acetaminophen (N-acetyl-p-aminophenol) is an acetylated aromatic amide (Figure 1). It is commonly used as over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) (Goyal, Gupta, Oyama, & Bachheti, 2005; Kang et al., 2010). It is generally used for the relief of headaches and other minor aches and pains such as muscular aches, chronic pain, migraine headache, back ache, tooth ache, and other aches and pains (Kachoosangi, Wildgoose, & Compton, 2008).

When administered combined with opioid analgesics, paracetamol can also be used to alleviate more cruel pain such as post-surgical pain as well as offer palliative care in advanced cancer patients (Fernandez et al., 2015). However, overdose and the chronic use of paracetamol produce toxic metabolite accumulation that will cause nervousness, trembling, nausea, seizures, insomnia, headaches, kidney and liver damages (Fernandez et al., 2015; Solomon, Shimelis, Merid, & Theodros, 2011). Therefore, assessment of the level of paracetamol content in any matrix containing paracetamol including tablet formulation is crucial to evade the possible side effects of overdoses.

Chromatography (Gilmartin & Hart, 1994; Wang & Dewald, 1984), and spectroscopy (Das, Sharma, Talwar, & Sethi, 1989) are among the common techniques reported for determination of paracetamol in real samples. However, most of these methods are time consuming, costly, need special trained operators and complicated sample pretreatment which usually involves...
preconcentration step such as extraction prior to the analysis. Electroanalytical techniques on the contrary are simple, do not need trained personnel, are usually environmentally friendly and relatively cheap (Farghaly, Abdel Hameed, & Abu Nawwas, 2014; Miner, Rice, Riggin, & Kissinger, 1981). Attempts have been made on the electrochemical determination of paracetamol in real samples including tablet formulations using different electrodes (Burns, Tungkananuruk, Kasemsumran, & Tungkananuruk, 2004; Li & Jing, 2007; Pournaghi-Azar & Saadatirada, 2010; Solomon et al., 2011; Su & Cheng, 2010).

To the best of our knowledge, no work has been reported on the application of anthraquinone modified carbon paste electrode (AQMCPE) for determination of paracetamol in tablet formulations. Thus, this work describes a cyclic voltammetric investigation of the electrochemical behavior of paracetamol, square wave voltammetric determination of paracetamol in four brands of tablet samples using the AQMCPE.

2. Experimental part

2.1. Chemicals

The chemicals used were paracetamol (Sigma, German), K$_2$HPO$_4$ (98–101%, BDH, England), KH$_2$PO$_4$ (Titar, India), NaOH (Blulux, India), H$_3$PO$_4$ (85%, India), Graphite powder (Abron chemical, India), paraffin oil light (BDH, England), anthraquinone (98.8%, India). Distilled water or deionized water was used for solution preparation.

2.2. Apparatus and instruments

CHI 760d Electrochemical Workstation (Austin, Texas, USA) connected to a personal computer with a three-electrode system (unmodified carbon paste or anthraquinone 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. pH meter (AD8000, Romania), and electronic balance (Nimbus, ADAM) were used to measure the pH and mass, respectively.

2.3. Procedures

2.3.1. Preparation of working electrodes

The unmodified carbon paste electrode (UCPE) was prepared by mixing 70% (w/w) graphite powder and 30% (w/w) paraffin oil homogenized by hand for 30 min using pestle and mortar. The homogenized paste was allowed to rest for 24 hr, and then the paste was packed into the tip of the plastic syringe at the back of which copper wire was introduced to provide electrical contact. The surface of the electrode was smoothed on weighing paper before use (Tadesse, Tadesse, Saini, & Pal, 2013).

Anthraquinone modified carbon paste electrode (AQMCPE) was also prepared with minor modification of a reported procedure (Tadesse et al., 2013). Briefly: A mixture of 2.015 g of graphite powder and 0.15 g of anthraquinone put on a small agate mortar was agitated for about 5 min. A 0.825 g of paraffin oil was added to the mixture followed by milling for additional 30 min to homogenous. The homogenized paste was then allowed to rest for 24 hr. An amount of the paste was then packed into the cavity of the syringe. The surface of the fabricated anthraquinone modified carbon paste electrode was then refined on a clean paper before being used.

2.3.2. Preparation of supporting electrolyte

Supporting electrolyte of phosphate buffer solutions (PBS) were prepared by mixing equi-molar (0.1 M) KH$_2$PO$_4$ and K$_2$HPO$_4$ in distilled water. The PBS of the required pH was prepared by mixing appropriate volumes of the solutions followed by adjusting the pH using drops of HCl (0.1 M) and NaOH (0.1 M).
2.3.3. Preparation of standard solution of paracetamol
1000 ppm stock solution of paracetamol was prepared by dissolving 0.1 g of paracetamol in 100 ml of pH 5 PBS. From the stock solution, while 100 ppm paracetamol solution was used for the cyclic voltammetric investigations, working solutions of different concentrations of paracetamol (5, 10, 20, 40, 60, 80, 100, 120, 150 ppm) in pH 5 PBS were prepared from 1000 ppm stock solution and 100 ppm intermediate solution through serial dilution.

2.3.4. Tablet sample preparation
Five tablets from each of the four brands of tablet samples (Julphar Aldol. Ethiopia; Panadol Adva, Kenya; Kelvin, India; and Para Denk, Germany; all labeled 500 mg paracetamol/tablet) were weighed and powdered using mortar and pestle. A 0.1 g of the homogenized powdered tablet from each brand was transferred to a 100 ml volumetric flask, dissolved with deionized water by sonication and the mixture solution was centrifuged for 20 min at 4000 rpm. 6 ml from the aliquot solution was transferred in to 100 ml volumetric flask and diluted up to the mark with pH 5 PBS. The same procedure was followed for all the four brands of tablet samples. Finally, the SWV oxidative current was measured in triplicate and the paracetamol content was calculated taking the average in to the calibration regression equation.

3. Results and discussion

3.1. Electrochemical behavior of paracetamol at AQMCPE
Figure 2. presents the cyclic voltammograms of unmodified and modified carbon paste electrodes in pH 5 PBS containing 100 ppm paracetamol. Appearance of the well resolved oxidative peak at the AQMCPE (curve b) at a potential 100 mV lower than at the unmodified electrode (curve a) indicated the electrocatalytic role of the modifier towards oxidation of paracetamol and hence suitability of the modified electrode for paracetamol analysis.

3.2. Effect of scan rate on peak current and peak potential
To investigate the reversibility and type of reaction kinetics the paracetamol followed at the anthraquinone modified carbon paste electrode, cyclic voltammograms of 100 ppm paracetamol in pH 5 PBS at various scan rates in the range 20–200 mVs\(^{-1}\) were recorded (Figure 3A). As can be seen from the figure, 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.

In order to investigate whether the oxidation process of paracetamol at AQMCPE is diffusion controlled, surface confined process, or combination of the two; the determination coefficients (R\(^2\)) for the dependence of peak current on the scan rate (Figure 3B) and square root of scan rate (Figure 3C) were compared. As can be seen from the figures, comparable determination coefficient value (R\(^2\) = 0.994) for the dependence of current on square root of scan rate and on the scan rate
Figure 3. (A) Cyclic voltammograms of anthraquinone modified carbon paste electrode in pH 5 PBS containing 100 ppm paracetamol at different scan rates (a-i: 20, 40, 60, 80, 100, 125, 150, 175, and 200 mV s\(^{-1}\), respectively), (B) plot of peak current vs scan rate, and (C) plot of peak current vs square root of scan rate.

Figure 4. (A) Cyclic voltammograms of AQMCPE in PBS of various pHs (a-g: 3, 4, 5, 6, 7, 8, 9, and 10, respectively) containing 100 ppm paracetamol; (B) plot of anodic peak potential vs pH. Inset: plot of peak current vs pH.

(R\(^2\) = 0.992) signified that the oxidation reaction of paracetamol at the modified electrode was controlled both by diffusion and adsorption.

3.3. Effect of solution pH on peak current and peak potential
Figure 4A presents the cyclic voltammograms of 100 ppm of paracetamol in PBS of pHs in the range 3 to 9. As can be seen from the inset of the figure, the oxidative peak increased with pH from 3 to 5 and then decreased at pHs beyond 5. From this trend, it was possible to conclude that pH 5 is the optimum pH value which was taken for further analyses. The oxidative peak potential was also observed to shift with increasing pH in the negative direction (Figure 4B) confirming the participation of protons during the oxidation reaction of paracetamol at the modified electrode.

3.4. Square wave voltammetric determination of paracetamol in tablet samples using AQMCPE
Once the candidacy of the AQMCPE was checked using cyclic voltammetry, due to its sensitivity and ability to discriminate Faradaic current from non-Faradaic current square wave voltammetry was selected for quantitative analysis of paracetamol.
3.4.1. Dependence of SWV peak current on concentration of paracetamol

Figure 5. shows the square wave voltammograms of AQMCPE in pH 5 PBS containing various concentrations (a-i: 5, 10, 20, 40, 60, 80, 100, 120, and 150 ppm, respectively) at AQMCPE (step potential 4 mV; amplitude 25 mV; and frequency 15 Hz). Inset: plot of oxidative peak current vs concentration of paracetamol.

3.4.2. Determination of paracetamol in tablet samples

The applicability of the method for determination of paracetamol in tablet formulation was evaluated. In this study, four brands of paracetamol tablets (Panadol adva, Julphar aldol, Para denk, Kelvin) available at a local pharmacy were analyzed for their labeled paracetamol contents. The two tests conducted with regard to tablet samples were; determination of the paracetamol content of each tablet brand and compare with the theoretical amount and the other is the validation of the method by recovery analysis.

As can be seen from the table, the method enabled to detect paracetamol in the range of 83.04% to 95.08% of what is expected. The deviation of the detected from the expected may be accounted for either low efficiency of the method used or inconsistency of the factories to maintain the paracetamol content per tablet during production.

3.4.3. Recovery study of the developed method

To evaluate the accuracy of the developed SWV method for its applicability for determination of paracetamol in real samples where matrix effect could be pronounced, recovery studies for spiked paracetamol in tablet sample solution was conducted. For this purpose, the Para Denk tablet sample solution which showed the highest paracetamol content of the tested brands was selected. Two Para Denk tablet solutions of 45.3 ppm paracetamol content were prepared to one of which,
40 ppm of standard paracetamol was spiked while the other unspiked. Figure 7 presents the corrected square wave voltamograms for the unspiked (curve a) and spiked (curve b) Para Denk brand of tablet sample solutions. Percent recovery of 93.5% for the spiked 40 ppm standard paracetamol (Table 2) confirmed the accuracy of the developed method and hence its applicability for determination of paracetamol in real samples including tablet formulation. From this, it could be concluded that the low paracetamol content detected in the paracetamol brands of tablets (Table 1) is not due to low performance of the method but due to lower paracetamol content than the labels.

### 3.5. Comparison with other methods

The performance of the square wave voltammetric method reported in this work was compared with methods in reported literature (Table 3). It can be seen from the table that the present method based on AQMCPE provides a reasonably low limit of detection with wider linear dynamic range than the others except the result reported using glassy carbon electrode (Su & Cheng, 2010) which of course is more expensive and less available.

### 4. Conclusion

The method presented in this study for determination of paracetamol is simpler, relatively cheaper, and more sensitive than most reported methods. The modified electrode used showed pronounced electrocatalytic property towards an irreversible oxidation of paracetamol. The oxidative peak current showed a linear dependence on a wide range of concentration (5 to 150 ppm) making...
the method suitable for paracetamol analyses. The applicability of the method for determination of paracetamol in tablet formulations was validated by its reasonable recovery result, 93.5%. Detected paracetamol content of the studied four brands of tablet samples were in the range between 83.04% and 95.08% of what is theoretically expected according to the label might be ascribed to possible matrix difference among the factories and/or failure of the companies in maintaining the 500 mg/tablet description.

Table 2. Summary of the paracetamol content in the Para Denk brand tablet solution before spiked, after spiked and hence percent recovery of the method

| Tablet sample | Paracetamol content (ppm) | Spiked paracetamol (ppm) | Detected paracetamol (ppm) | Recovery (%) |
|---------------|---------------------------|--------------------------|----------------------------|--------------|
| a             | 45.3                      | –                        | 45.3                       | –            |
| b             | 45.3                      | 40                       | 82.7                       | 93.5         |

Table 3. Comparison of the present method with literature reported methods

| Electrode                                      | Method   | Linear range (µM) | LOD (µM) | Reference                    |
|------------------------------------------------|----------|-------------------|----------|------------------------------|
| Poly (3,4-ethylenedioxy thiophene) modified glassy carbon electrode | DPV      | 2.5–150           | 1.13     | Solomon et al. (2011)        |
| Polyaniline-MWCNT modified electrode         | SWV      | 1–200             | 0.25     | Li and Jing (2007)           |
| Glassy carbon electrode                      | DPV      | 0–1983            | 0.09     | Burns et al. (2004)          |
| Poly (3,4-ethylenedioxy thiophene) modified screen printed electrode | DPV      | 4–400             | 1.39     | Su and Cheng (2010)          |
| Anthraquinone modified carbon paste electrode | SWV      | 33–992            | 0.13     | This method                  |
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Competing Interests
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Author details
Meareg Amare1
E-mail: amaremeareg@yahoo.com
Welday Teklay1
E-mail: welday2009@gmail.com
1 Department of Chemistry, Bahir Dar University, Bahir Dar, Ethiopia.

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