Voltammetric Determination of Paracetamol in Pharmaceutical Formulations at Iodine-Coated Polycrystalline Platinum Electrode

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Recieved: April 05, 2021; Accepted: May 31, 2021
DOI: 10.17721/moca.2021.103-111

In this work the modified iodine-coated polycrystalline platinum electrode was used to develope a voltammetric sensor for paracetamol determination in pharmaceutical formulations. The optimized experimental parameters for the determination of paracetamol were using 0.5 M H_2SO_4 as a supporting electrolyte with a scan rate of 50 mV/s. The anodic peak related to paracetamol oxidation was centered at about +0.60 V. The extended calibration graph was constructed between 1 ppm and 500 ppm. The anodic current showed excellent linearity with $R^2 = 0.9985$. The limit of detection (LOD) and limit of quantitation (LOQ) were 0.046 and 0.139 ppm, respectively, which attests to the sensitivity of the method. The investigation for the effect of potential interferences from the content of tablet matrices indicated a specific selectivity toward paracetamol and the absence of any electrochemical response toward these components. The developed method was successfully applied to analysis paracetamol in three brands of pharmaceutical formulations and the obtained results were in good agreement with the labeled values, besides that, the statistical tests indicated no significant difference at p = 0.05 with a 95% confidence level.

Keywords: paracetamol, pharmaceutical formulation, voltammetric analysis, iodine-coated platinum electrode, modified platinum electrode

Determination of paracetamol in pharmaceutical formulations is of great importance. Paracetamol (acetaminophen) is one of the most common drugs around the world used for relief fever, headaches, and minor pain [1]. Also, paracetamol is renowned as multimodal analgesia with excellent safety profile except in significant overdoes [2] .Since paracetamol found solely or in combination in pharmaceutical formulation, it is a paramount important to have a simple, fast, sensitive, and selective analytical method for routine analysis of this compound.

A numerous analytical methods have been reported for paracetamol determination in pharmaceutical formulations. These methods include, potentiometry [3-7], high performance liquid chromatography [8-13], and spectrophotometry [14] . These reported methods have some limitations such as instruments, skills, cost, and the environment. In contrast to these traditional methods, the electrochemical methods have attracted much attention due to the low sensitivity toward the matrix effects compared to other analytical techniques [15]. Also, the electroanalytical methods offer many advantages such as simple analysis procedures, environmentally–friendly chemical reagents. Many voltammetric methods based on modified electrodes have been reported for paracetamol determination in pharmaceutical tablets [16-24]. The Iodine-coated platinum electrode considers as a typical example for the modification of a highly reactive platinum electrode surface. Where the adsorbed iodine monolayer at platinum electrode surface transforms the highly reactive surface to an apparent passive electrode with a low current background [25].

Iodine is one the anions simply adsorbed to electrode surface. The chemisorptions process can be achieved by two ways; from solution or from vacuum to form stable chemisorbed mono layers even the iodine coated electrode would be rinsed or evacuated [26]. The iodine is adsorbed at potential 0.2 V (double layer potential) vs. Ag/AgCl or SCE reference electrodes [27]. At the surface of polycrystalline platinum electrode an oxidation reaction of iodine anions from solution leads to spontaneous chemisorption of iodine anion to form stable neutral iodine atoms at the electrode surface accompanied by hydrogen gas evolution. The adsorbed iodine is less reactive toward electrochemical oxidation compared with the free iodine anion in solution [28]. The chemisorbed iodine can be desorbed from platinum electrode surface if the potential scanned lower than -0.2 V which lead to reduction of hydrogen ions and generation hydrogen gas [28]. Also the rate of iodine desorption from electrode surface increase as the potential become more negative [29]. At the positive direction, the chemisorbed iodine begins to be desorbed at potential 1.0 [27]. Carbon monoxide is completely desorbed iodine from platinum electrode surface at potential lower than 0.35 V while at higher potential incomplete desorption is occurred [30].

Iodine-coated platinum electrodes have been applied for the electrochemical quantification of some species in aqueous solutions with and without further modification. A furtherly modified iodine-coated platinum electrode with quanternized poly(4-vinylpyridine), qPVP by Cox and Kulesa was used for analysis of nitrite [31]. Amayreh and co-workers have used the iodine-coated electrode for the analysis of iron(II) [32, 33] and copper(II) [34].

Iodine-coated platinum electrode is characterized by the simplicity in preparation, application, and the absence of the need for environmentally unfriendly chemical reagents. The simplicity of the instrumentations all stimulated the implementation of the present work. This work was undertaken with the main objective of method development for voltammetric analysis of paracetamol at iodine-coated platinum electrode in pharmaceutical formulations.

Experimental part

Chemicals and reagents. The following reagents along with their suppliers were used in the present work: Sulfuric acid (95-97 %, Merck), paracetamol (99.8 %, Merck), potassium iodide (Sigma-Aldrich). Milli-Q water (Millipore) was used for preparation of all solutions. The nitrogen gas was a five-G grade, 99.999 % minimum purity supplied from International Jordanian Gases Company (Amman, Jordan). All used chemicals and reagents were of analytical grade and used without further purification.

Apparatus. A potentiostat (PAR Model 362, EG&G) interfaced to a computer via GPIB interface (IEEE) equipped with a locally modified Labview® (IEEE) software was used for data acquisition and experimental control. A one-compartment electrochemical cell with an inlet/outlet system for deoxygenation and blanketing with highly pure nitrogen was used. A 0.5 mm polycrystalline platinum wire purchased from Aldrich (99.99 % minimum purity certified reagent) was used as a working electrode. The immersed end of the platinum electrode was curved at the end to make a mark for a consistent surface area of the immersed part of the electrode. A silver/silver chloride wire was used as a quasi-reference electrode (QRE). The used auxiliary electrode was a 0.5 mm polycrystalline platinum wire (Aldrich, certified 99.99 % minimum purity).

Preparation of iodine-coated platinum electrode. Preparation of iodine-coated platinum electrode was described in one of our earlier publications [32], These preparation steps include a cyclization of a platinum electrode placed in of 0.5 M H_2SO_4 between - 0.25V and 1.3 V until getting a reproducible cyclic voltammogram of polycrystalline platinum electrode with the well-known oxygen and hydrogen adsorption/desorption features, which is indicative of the cleanliness of the electrode surface and electrochemical cell contents (Fig.1).

Thereafter, the clean electrode was immersed in 0.5 M H_2SO_4 + 10^{-2} M KI solution for five minutes under closed-circuit potentiostatic conditions in the double layer region (~ 0.2 V) to accomplish dosing of the platinum electrode surface with iodine. After that the electrode was subjected to multiple rinses with water and 0.5 M H_2SO_4 solution, and then the electrode potential was cycled in supporting electrolyte solution between -0.2 V and +0.8 V at 50 mv/s to confirm the completeness of the coating process (Fig.1). The absence of oxygen and hydrogen adsorption/desorption peaks from the recorded cyclic voltammogram of an iodine-coated platinum electrode provides a conclusive evidence for the complete coverage of platinum electrode surface with a monolayer of iodine.

Standard solution preparation. A 1000 ppm of paracetamol stock solution was prepared by dissolving a 0.1g of paracetamol (151.163 g/mol) in 100mL of 0.5 M H_2SO_4. A working solution of different concentrations of paracetamol, 1, 10, 50, 100, 200, 300, 400, and 500 ppm in 0.5 M H_2SO_4 were prepared through a serial dilution procedure.

Sample preparation. The pharmaceutical formulation samples (Paracetamol commercial tablets), Revanin (Jordan), Panda (Jordan), and Myogesic (Jordan) were purchased from Jordanian local drug stores. The selected brands of pharmaceutical formulations were analyzed for their paracetamol content. The tablet of each brand was powdered using porcelain mortar and dissolved in warm 50.0 mL of 0.1 M H_2SO_4 supporting electrolyte to ensure complete dissolution of paracetamol. The solution of the samples was sonicated for 5 minutes and left to equilibrate for 10 minutes. Then, the solution was filtrated through a 0.45 μm Millipore filter and transferred to 100 mL volumetric flask and diluted to the mark. The stock solutions were kept in the refrigerator for succeeding analysis. An aliquot of this solution was diluted to 50.00 mL with 0.1 M H_2SO_4 to be within the constructed calibration curve concentrations' range. A 10.00 mL of the diluted solution was placed in the electrochemical cell. The solution was deaerated with nitrogen gas and kept under a nitrogen gas atmosphere during conducting the voltammetric measurements. Voltammetric analysis of the commercial tablets for their paracetamol content was conducted at the iodine-coated electrode within a potential window -0.2 V to 0.8 V where the adsorbed iodine is stable within this potential range.

Results and discussions

Electrochemical oxidation of paracetamol and method validation

Initially, as presented in Figure 1-a, a reproducible cyclic voltammogram for polycrystalline platinum electrode was obtained which confirms the cleanness of all components of the electrochemical system. On the other hand, the cyclic voltammogram of the iodine-coated electrode (Fig.1-b) indicates a complete and

successful as witnessed by absence of any surface activity in the scanned potential range (-0.2 – 0.80 V). The complete absence of hydrogen and oxygen reduction features is the main evidence for complete coverage of the platinum surface. The potential scan was limited to the above-mentioned range to avoid desorption of iodine from the platinum surface. The adsorbed iodine is stable toward rinsing with acidic or neutral supporting electrolytes. Also, the iodine-coated platinum electrode does not need to regenerate before each measurement where scanned potential window should between -0.2 and 1.0 V, which indicates to reliability of using the electrode for daily routine analysis.

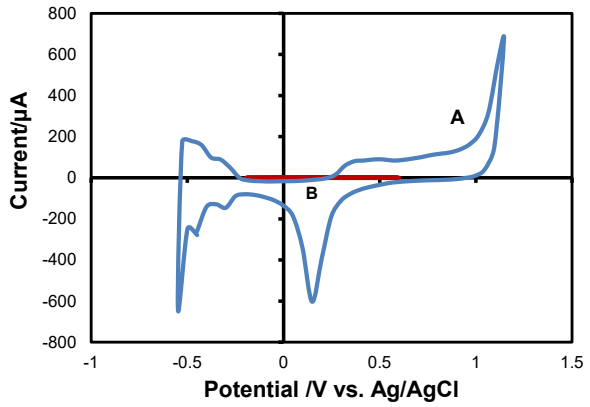
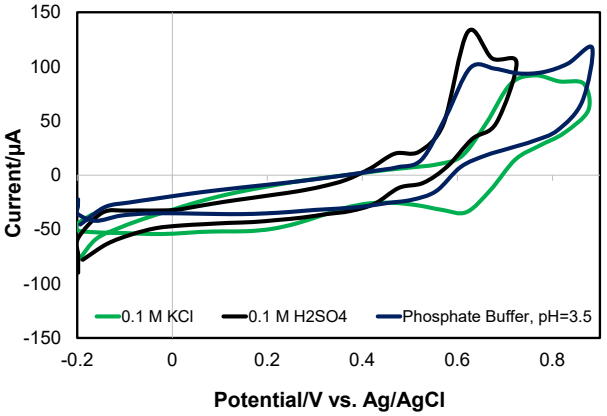


Fig. 1. Cyclic voltammogram curves of (a) poly-crystalline platinum electrode and(b) the same electrode after adsorption of iodine from 1x10^{-2} MKI in 0.5 M H_2SO_4 solution.

The effect of pH on the iodine coating on platinum electrode has been reported elsewhere [35] where it has been found that iodine coating is unstable upon cyclization in basic solution [36] . This fact limits usage of iodine-coated electrode to acidic solutions only. The effect of the pH in the acidic range was investigated by following the effect of pH change on the peak current for paracetamol oxidation. Three representative pH values; 7, 3.5 and 0.3 were selected to demonstrate the effect of solution acidity on the analytical signal (peak current). Paracetamol standard solution was analyzed in 0.5 M H_2SO_4 (pH = 0.3), phosphate buffer (pH = 3.5), and 0.1M KCl (pH = 7) media. Figure 2 shows the effect of pH on the paracetamol oxidation current peak. As displayed in Figure 2, the value of the oxidation peak current of paracetamol decreases with increasing pH. Thereafter, 0.5 M H_2SO_4 was considered as a supporting electrolyte for determination of paracetamol the following study. This might be attributed to the experimentally evidenced observation that the protonated form of the paracetamol is more easily oxidized than the deprotonated form [37]. The ease of oxidation of the protonated form of paracetamol is revealed by the shift in paracetamol peak potential with increasing pH of the medium.



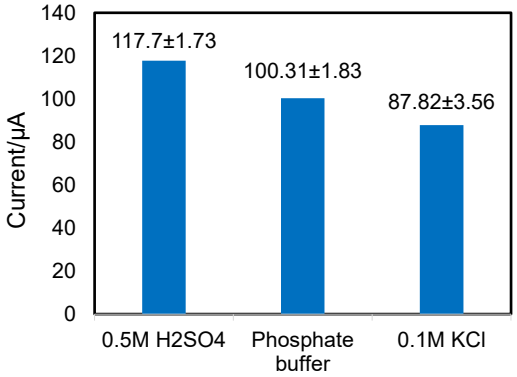


Fig. 2. Effect of type of supporting electrolyte on the electrochemical signal of paracetamol at iodine-coated platinum electrode, Paracetamol; 100 ppm, H_2SO_4; 0.5 M, phosphate buffer; pH=3.5; KCl, 0.1 M; n = 3; scan rate, 50 mV/sec.

The effect of scan rate from 10 mV/s to 100 mV/s on the paracetamol peak current was evaluated. As presented in Figure 3, there is a linear relationship between the square root of scan rate and the oxidation peak current of paracetamol: y = 14.798x - 10.932; (R^2 = 0.9976), which indicates that the oxidation process is a diffusion-controlled process.

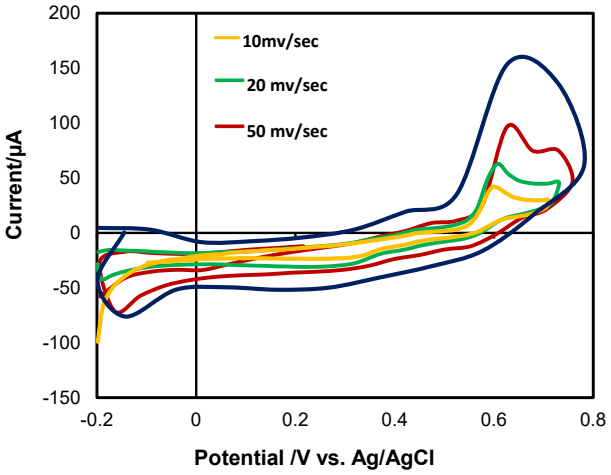


Fig. 3. Cyclic voltammograms of iodine-coated platinum electrode in 0.5M H_2SO_4 containing 50 ppm of paracetamol at various scan rates: 10, 20, 50, and 100 mv/s.

The obtained cyclic voltammograms for iodine-coated platinum electrode in a series of paracetamol standard solutions show that the oxidation current increases linearly with paracetamol concentration. Three voltammograms were recorded for each standard solution and the dimensions of each point were displayed in Figure 4. The anodic peak current was extracted for each cyclic voltammogram.

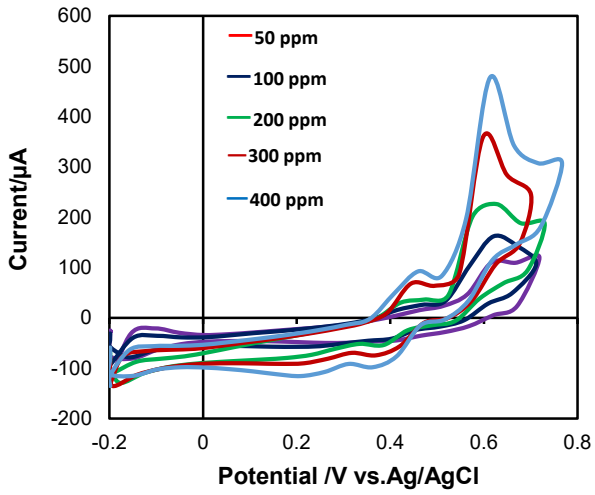


Fig. 4. Cyclic voltammograms of iodine-coated platinum electrode in 0.1 M H_2SO_4 solution containing 50, 100, 200, 300 and 400 ppm of paracetamol. All the scans were recorded at a scan rate of 50 mV/s.

Figure 5 shows a representative part of the cyclic voltammograms recorded for a standard solutions of paracetomol used for construction calibration curve. The established calibration curve between concentrations of 50, 100, 200, 300 and 400 ppm and the current values extracted from the recorded cyclic voltammograms shows a linear relationship with regression value of $R^2 = 0.986$.

Plotting the anodic peak current variation against paracetamol concentration give a straight and extended dynamic range with a concentration ranging from 1.0 ppm to 500.0 ppm. The calibration curve displayed in Figure 5 shows remarkable linearity; $R^2 = 0.9985$, and the calibration equation is given by

$$I = (\mu A) = 1.1517\ C_{paracetamol} + 1.0592$$

where I represents the anodic peak current, which attributed to the paracetamol oxidation.

The 95 % confidence intervals (α = 0.05, 6 degrees of freedom) for the slope and y-intercept are

$$\beta 1 = b_1 \pm ts_{b1} = 1.15 \pm 2.5 \times 0.0232 = 1.152 \pm 0.057$$

$$\beta 2 = b_0 \pm ts_{b0} = 1.059 \pm 2.5 \times 5.90 = 1.0 \pm 14$$

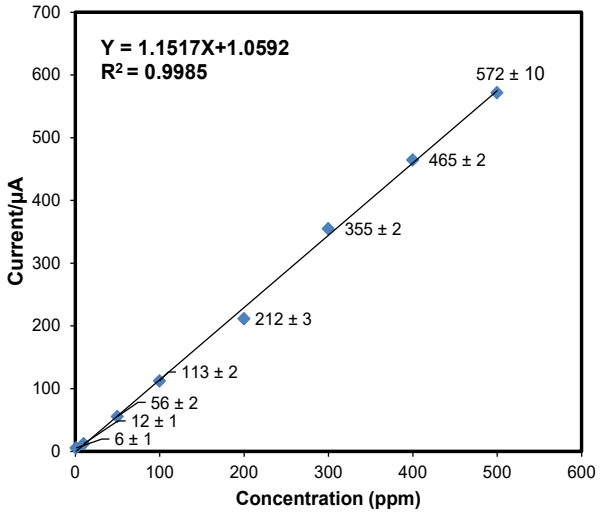
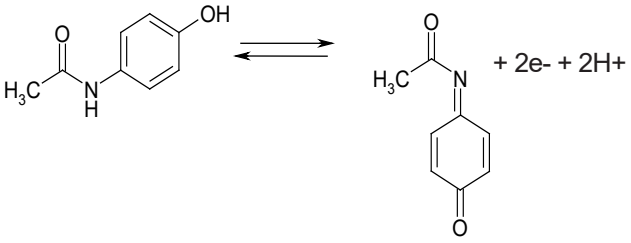


Fig. 5. An extended calibration curve shows the relationship between paracetamol concentration in ppm and the oxidation peak current measured from cyclic voltammograms for paracetamol in 0.5 M H_2SO_4 at iodine-coated platinum electrode. Scan rate = 50 mv.s^{-1}.

Where paracetomol is a phenolic compound that undergoes electrochemical oxidation by electrolytic etching on the aromatic ring with irreversible removal of two electrons and two protons, producing N-acetyl-p-quinoneimine according to the mechanism shown in equation [37]:



The inter-and intra-day precision was estimated by extracting the current values for four different paracetamol standard solutions sample between 10 and 200 ppm. The standard deviation was found to be within 0.49 and 2.79 for five successive determinations for each concentration. The measured values of standard deviation attest to the high repeatability for both of inter-and intra-day measurements.

The limit of detection based on the formula LOD = 3.3б/S, and limit of quantitation based on the formula LOQ = 10б/S, where б represents the blank signal (background current) and S represents the sensitivity of the calibration curve was calculated [38]. The estimated limits were 0.046 ppm and 0.139 ppm respectively. Acceptable sensitivity of the applied method with high precision was obtained. A higher sensitivity can be achieved by application of a more sensitive technique like differential pulse voltammetry. Differential pulse voltammetry, however, was not

attempted because cyclic voltammetry provides satisfactory sensitivity for paracetamol determination in pharmaceutical formulations.

Potential interference

In order to verify the existence of matrix effects of paracetamol tablets on paracetamol. The prepared stock solutions of pharmaceutical formulations were diluted 50-folds without further filtration pretreatment before each analysis. The samples were spiked with different concentrations of paracetamol standard solution to investigate any possible interference. The recorded cyclic voltammograms (Fig. 6) after each addition proved the absence of any possible interference with paracetamol in the studied samples where Panda tablets contain caffeine beside to paracetamol, Miogesic tablets contains orphenadrine citrate beside to paracetamol, and Revanin tablets contain only paracetamol formula . The investigation for the selectivity of iodine-coated platinum electrode toward paracetamol shows absence of the voltammetric response toward orphenadrine citrate and caffeine, which indicates to the selectivity of the developed method for paracetamol determination in the pharmaceutical formulations.

Recovery of the developed method

The feasibility of the developed voltammetric method for paracetamol determination was tested for three pharmaceutical formulation samples. Paracetamol standard of known concentration, 50 ppm, were spiked into a samples of tablet solutions in order to evaluate the percental recovery for each brand of paracetamol. As listed in Table 1, the recovery values were found between 101.42±0.64 and 104.05±4.19 for all samples of paracetamol brands which showing the appropriateness of the iodine-coated platinum electrode for the quantitative analysis of paracetamol in pharmaceutical formulations.

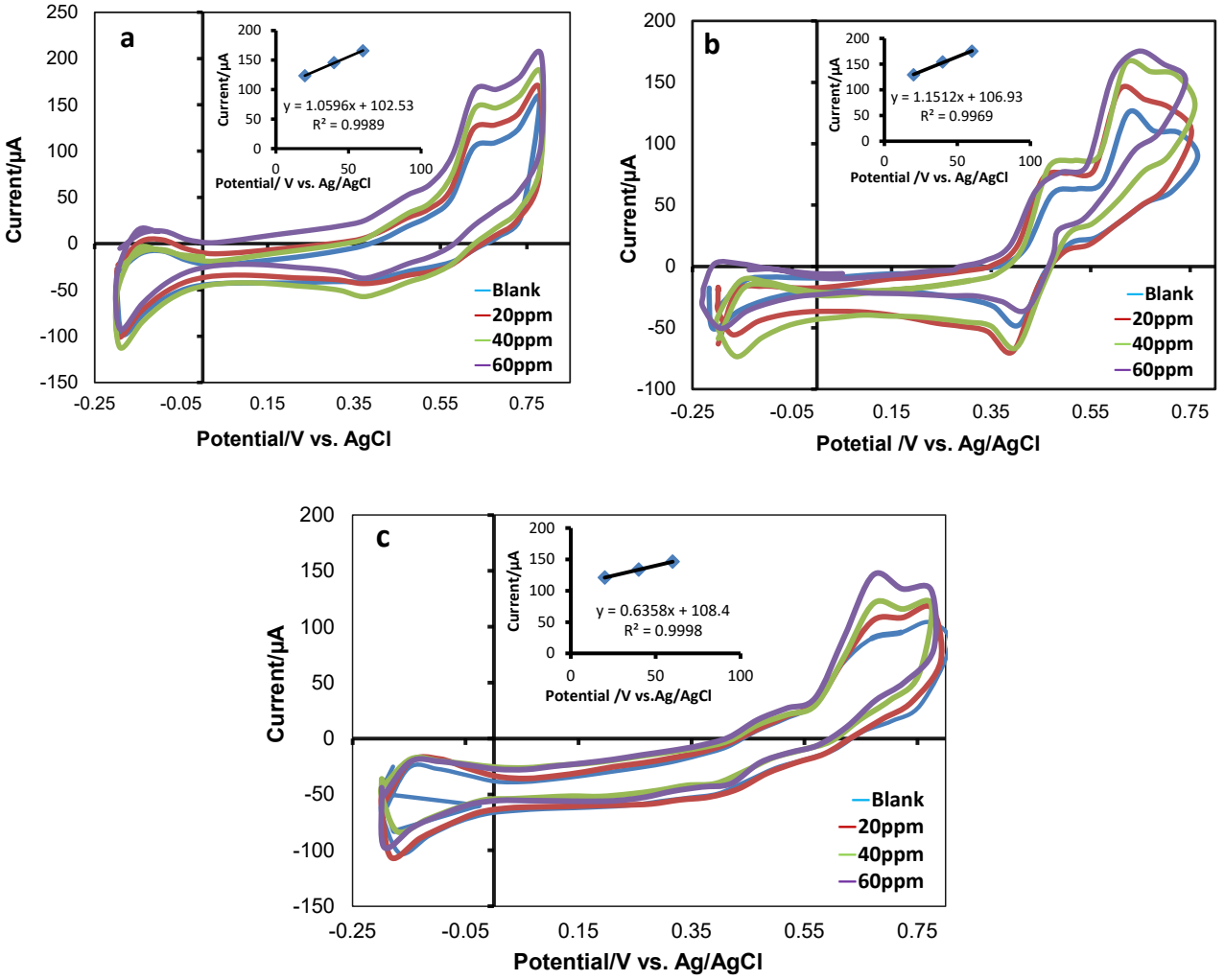


Fig. 6. Cyclic voltammograms of iodine-coated platinum electrode in 0.5 M H_2SO_4 containing (a) Revanin tablet solution (only paracetamol) with addition of 20, 40, and 60 ppm of paracetamol standard solution, (b) Panda tablet solution (Paracetamol and Caffeine) with the addition of 20, 40, and 60 ppm of paracetamol standard solution, (c) Myogesic tablet solution (Paracetamol and orphenadrine citrate) with the addition of 20, 40, and 60 ppm of paracetamol standard solution.

Table 1. Recoveries of paracetamol from spiked pharmaceutical formulations obtained by the developed method.

Samples	Content of paracetamol (ppm)	Spiked paracetamol (ppm)	Detected paracetamol after addition (ppm)	% Recovery*
Panda®	100	50.0	151	102 ± 5
Revanin®	50.0	50.0	102	104 ± 4
Miogesic®	45.0	50.0	95.7	101 ± 1

* Average of three determinations.

Pharmaceutical formulations analysis

The developed and validated voltammetric method was evaluated in the detection of paracetamol in three real samples with matrices of low complexity of pharmaceutical formulation as tablets. The standard addition method was applied to a diluted real samples analysis to avoid the matrix effect. The evaluation paracetamol concentration was found to be more suitable with the aid of the calibration graph. The results for the analysis of these pharmaceutical formulations with the developed voltammetric method were mentioned in Table 2.

The obtained results by applying of cyclic voltammetry technique at an iodine-coated platinum electrode were compared with the labeled values claimed by manufacturers. The data displayed in Table 2 shows that all nominal values are within the 95% confidence interval which indicates the clear absence of errors in the results. The relative errors of the analysis of the three types of pharmaceutical formulations were less than 0.7%, which attests to the accuracy of the developed method. The measured coefficient of variation values (0.69-1.1%), are considered as obvious evidence to the precision of the developed method. The paired t-test was used to examine the significant difference at 95 % confidence level between the labeled values and the obtained results determined by the developed voltammetric method. The comparison of the calculated t value which is 0.127 with the critical t value which is 4.30 at p = 0.05 [39] shows that this result supported the null hypothesis and indicates there is no significant difference between the values determined by the voltammetric method and the nominal value obtained by manufacturers.

A comparison between the developed voltammetric method and some of the common analytical and voltammetric methods for paracetamol in terms of limit of detection and linear range was presented in Table 3. As shown, the iodine-coated platinum electrode exhibited lower detection limit than that of differential pulse voltammetry methods which are based on modified carbon electrodes [41, 42]. Wheras, the obtained linear range was wider and more extended than that obtained for other systems [10, 12, 40, 43] .

Table 2. Paracetamol content in a pharmaceutical formulations collected from the Jordanian local pharmacies as determined by cyclic voltammetry at iodine-coated platinum electrode.

Pharma-ceutical formulation	Actual mass(mg) of paracetamol/ tablet	Average of determined mass (mg) of paracetamol / tablet (n=3)	Standard deviation	95% confidence limits	95% confidence interval	Relative error	Coeffi-cient of variation
Revanin®	500	503	4.04	503 ± 10	493 - 513	+0.5	0.80%
Panda®	500	503	3.49	503 ± 9	495 - 512	+0.6	0.69%
Myogesic®	450	453	5.32	453 ± 13	440 - 466	+0.7	1.17%

Table 3. A comparison of analytical performance of developed voltammetric method using iodine-coated platinum electrode with other analytical methods that reported in literature.

Method	Linear range	Detection Limit	Reference
HPLC	5-60mg/L	0.1mg/L	10
Spectrophotometry	0.1-6 mg/L	0.1mg/L	12
Potentiometry	0.60-6.04mg/L	0.604 mg/L	40
Differential pulse voltammetry (DPV); glassy carbon electrode modified with poly(3,4-Ethylenedioxythiophene)	0.38-22.67mg/L	0.17mg/L	41
Differential pulse voltammetry (DPV); screen printed electrode modified with poly(3,4- ethylenedioxythiophene)	0.604-60.04mg/L	0.21mg/L	42
Square wave voltammetry (SWV); carbon paste electrode modified with anthraquinone	4.99 -149.95mg/L	0.0196mg/L	43
Cyclic voltammetry(CV)	1-500mg/L	0.046mg/L	This work

Conclusion

In this work, a successive using of iodine-coated platinum electrode for determination of paracetamol was achieved. The developed method does not include any sophisticated procedures. On the contrary, it is considered a green method for the simplicity of analysis procedures. The reported extended dynamic range (1-500) ppm of paracetamol supports the applicability of the voltammetric method for paracetamol analysis in pharmaceutical products. The absence of any interference from the other ingredients of pharmaceutical formulations considered as an evident indicator for selectivity of the developed method. The statistical analysis of the results showed no significant difference between the values obtained by the voltammetric method and the labeled values claimed by the manufacturers.

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