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Sensitive Determination of Paracetamol Using Ferrocene Nanoparticles by Chitosan-Functionalized - Modified Carbon Past Electrode

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ELECTRO analytical methods are rapid, an accurate and cheap alternative which offer very low detection limits for electroactive molecules Ferrocene have been used in electroanalysis of paracetamol studies, due to its large surface area, high conductivity and electroanalysis characteristics. Chitosan have basket type physical shapes are useful in number of commercial and applied chemicals as electrochemical. Determination of paracetamol using differential pulse voltammetry is introducing new effective electrochemical sensor. The sensor is constructed on a carbon paste electrode modified with ferrocene and Chitosan in Britton-Robinson buffer of pH 7.0. The effect of various experimental parameters is including pH, number of cycles of ferrocene and Chitosan and scan rate was investigated. At the optimum conditions, a linear range from 1.0 x 10^{-9} to 6.2 x 10^{-8} at 0.9995 as correlation coefficient of and a detection limit of 4.14 x 10^{-9} mol was obtained. The modified electrode can be used for the determination of the used drug in human urine samples with excellent recovery results.

Keywords: Ferrocene, Paracetamol, Chitosan, Pulse Voltammetry, Urine analysis.

Introduction

In last years, the combination of electrochemical techniques presented good contribution in analytical chemistry. One application of this combination is a direct determination of drugs

Paracetamol (acetaminophen) is one of the most popular analgesics and antipyretic drugs [1]. Paracetamol is available in different dosage forms tablet, capsules, drops, suspensions and suppositories dosage forms.

Paracetamol, N-(4-hydroxy-phenyl ethanamide, there are two activating groups which are caused the paracetamol highly electro active. The chemical structure of PAR was shown in Fig. 1a.

Several methods for simultaneous determination of paracetamol have been recently reported such as thin layer chromatography, voltammetry, and chromatographic [2-6] and spectrophotometric techniques [7-10].

Electro analytical methods are rapid, an accurate and cheap alternative which offer very low detection limits for electroactive molecules. Applications of modified electrodes have great interest in various areas of research and development, such as electroanalysis, biosensors and electroanalysis [11-14].

Ferrocene is an organometallic compound with the formula $Fe(C_5H_5)_2$. It is the prototypical metallocene, a type of organometallic chemical compound consisting of two cyclopentadienyl rings bound on opposite sides of a central metal atom, Such organometallic compounds are also known as sandwich compounds[15,16]. Ferrocene have been used in electroanalysis of pharmaceutical compounds studies, due to its large surface area, high conductivity and electroanalysis characteristics. They can act as centers in tiny conduction and electrons transferring are facilitated [17-20]. The chemical structure of Ferrocene was shown in Fig. 1b.

Chitosan, M.F ($C_{56}H_{103}N_9\ O_{39}$) as chelating agent, which binds ions in solution. Chitosan

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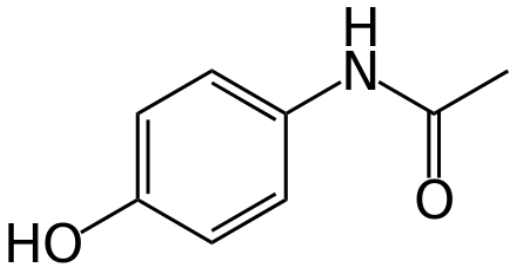
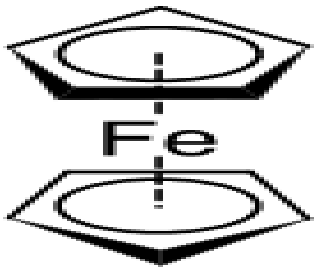


(a)



(b)

Fig. 1a. The chemical structure of PAR.

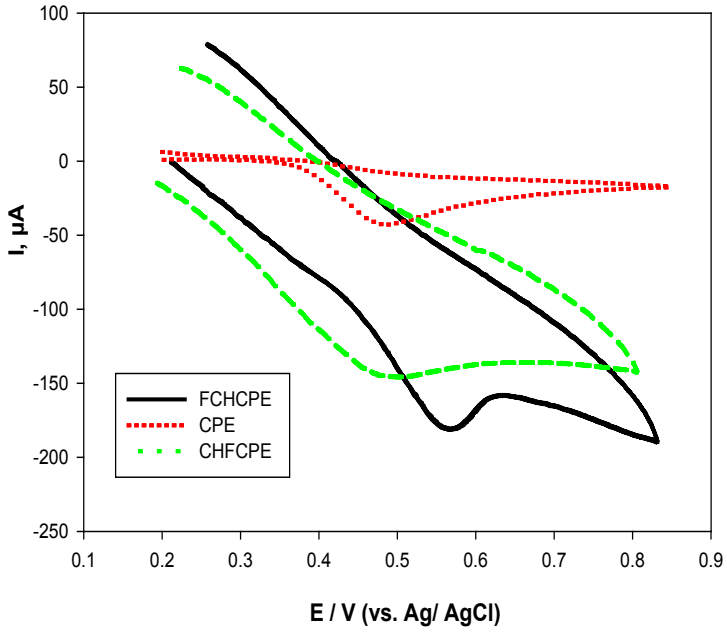


Fig. 1b. Chemical and stereo structure Ferrocene.

catchers that are capable of engaging differently sized target molecules respectively due to physically unique molecular structures. So Chitosan is hydrophobic inside and hydrophilic outside, it can form complexes with hydrophobic compounds. Its basket type physical shapes are useful in number of commercial and applied chemicals as electrochemical, also known as the host guest recognition [21].

Sensitive quantification of PAR using differential pulse voltammetry (DPV) is based on ferrocene nanoparticles carbon paste modified electrode was fabricated in the presence of Chitosan solution for the enhancement effect of ferrocene nanoparticles and formation of inclusion complex with Chitosan.

Experimental

Materials and methods

Materials

Standard PAR and its pharmaceutical dosage form, Paracetamol 500 mg tablets, were provided by Nasr Company for Pharmaceuticals and Chemical Industries, Egypt.

PAR stock solution was prepared by dissolving an appropriate amount of PAR powder in deionized water to obtain 1.0 x 10^{-2} mol L^{-1} solution. Standard working solutions were prepared by dilutions of the stock solution just before use. Chitosan was purchased from Fluka. Ferrocene, graphite powder and paraffin oil were supplied from Sigma-Aldrich.

Britton-Robinson (BR) buffer 4.0 x 10^{-2} mol L^{-1} was prepared by mixing phosphoric acid, acetic acid and boric acid [22]. An appropriate amount 0.2 mol L^{-1} of NaOH was added to BR buffer to obtain solutions of pH values varied from 2.0 to 11.0.

Methods

Preparation of ferrocene modified carbon paste electrode

Carbon paste electrode (CPE): the carbon paste was prepared by mixing of 0.5 g graphite powder (particle dimension 20 lm, Sigma–Aldrich, Egypt) with 0.3 mL of paraffin oil in mortar with a pestle [23]. The hole of the electrode body was packed by carbon paste and smoothed on a filter paper until its shiny appearance. CPE was immersed into a 6 mmol Ferrocene solution containing 0.1mol L^{-1} methanol. Around 500 mV as constant potential was applied for 200 sec versus calomel electrode. This reversible oxidation has itself been used as standard in electrochemistry as Fc+/ Fc=0.4 V versus the standard hydrogen electrode [24]. Ferrocene as salts are used as oxidizing agent, in part because the ferrocene is fairly inert and readily separated from ionic products [25]. The ferrocene particles modified carbon paste electrode (FCPE) was washed with distilled water and before usage must drying carefully [26].

Experimental and instrumental set up

Measurements were given by a pc-controlled AEW2 electrochemistry work station and electrochemical measurements were analyzed with ECprog3 electrochemistry software, manufactured by Sycopel Scientific Limited (Tyne & Wear, UK). The three electrodes were connected in glass cell to the electrochemical workstation through a C-3-stand from BAS (USA). Platinum wire as auxiliary electrode and Ag/AgCl (3.0 mol L^{-1} NaCl) as reference electrode each are from BAS (USA). Measurements of pH was performed using JENWAY 3510 pH meter (England) with glass combination electrode.

Effect of Number of cycles of ferrocene and Chitosan

The cyclic voltammetry of 1.0 x 10^{-3} mol L^{-1} PAR (in BR buffer, pH 7.0) was performed on FCPE upon successive in presence of Chitosan solution (1.0 x 10^{-2} mol L^{-1}) at several cycles. The electrolytic cell and the voltammograms were recorded using cyclic voltammetry.

Applications to human urine

In centrifugation tubes, measured aliquots of PAR solutions were pipetted with containing 400 µL human urine in each tube for 10 min. Into each tube, 0.5 ml of methanol, 0.1 mL NaOH (0.1 mol L^{-1}) and 0.5 ml $ZnSO_4.7\ H_2O$ (5% w/v) [**27**] were added, then centrifuged for 10 min at 4000 rpm. The clear supernatant layer was filtered through 0.45 µm Milli-pore filter. By BR buffer (pH 7.0), supernatant liquor (0.1 mL) was completed to 5 mL into the voltammetric cell then. Then, PAR was quantified by means of the proposed DPV procedure.

Results

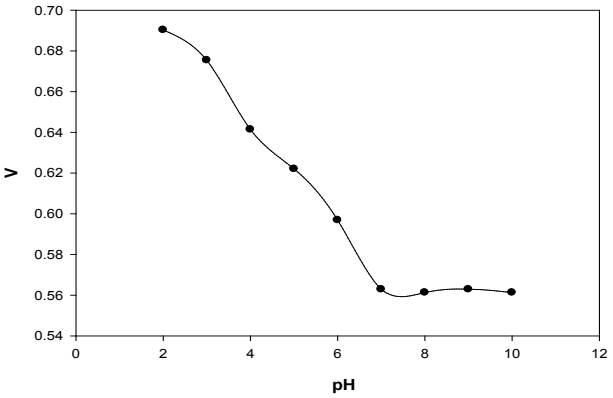
Type of modified electrode

Shows cyclic voltammograms of 1.0 x 10^{-3} mol L^{-1} PAR at CPE, FCHCPE, and CHFCPE, from the figure we note that the anodic peak currents of in case PAR of CPE, 45.78 µA (pH 2), CHFCPE ,145.92 µA (pH 2) and 173.22 µA (pH 2) in BR buffer background solutions, Thus

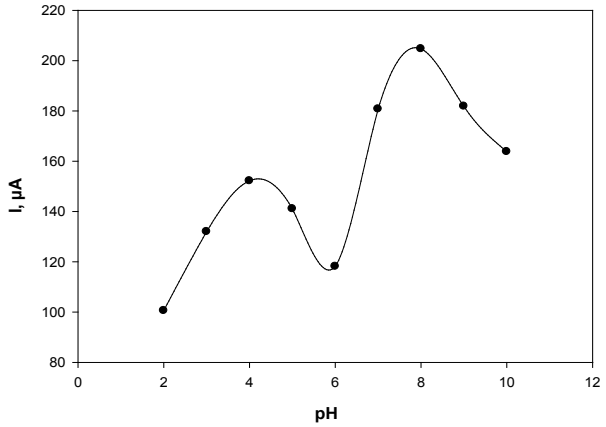
at pH is low, we chosen the optimum modified electrode for the determination of PAR at FCHCPE , since the presence of chitosan solution in acidic medium is suitable to form inclusion complex with PAR rather than neutral modified electrode. So Fig. 2 shows oxidation process of PAR due to the oxidation of hydroxyl group and Modified electrode FCHCPE is better than other electrodes.

Effect of pH and electrochemical behavior of PAR

Preliminary cyclic voltammetry (CV) experiments for 1.0 x 10^{-3} mol L^{-1} PAR were carried out at modified CPE in BR buffer background



(a)



(b)

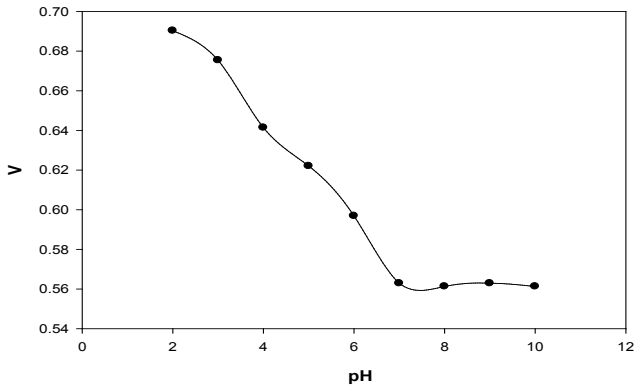
Fig. 2. voltammograms of the effect of solution pH on the oxidation of PAR (1.0 x 10^{-3} mol L^{-1}) at carried out at CPE, CHFCPE. and FCHCPE in BR buffer background solutions pH 2.0.

solutions over the pH range (2.0-10.0). Figure 3 shows reversible oxidation process of PAR within the acidic pH due to the oxidation of hydroxyl group.

Figure 3a shows that the anodic peak potential decreases by increasing the pH up to pH 7.0 reaching approximately steady state up to pH 7.0. Figure 3b shows that the anodic peak current (Ip) has two maximum values 150.23 µA and 209.05 µA at pH values 4.0, and 8.0, respectively. Therefore, we study the effect of modified electrode FCHCPE on the anodic peak current at pH 7.0

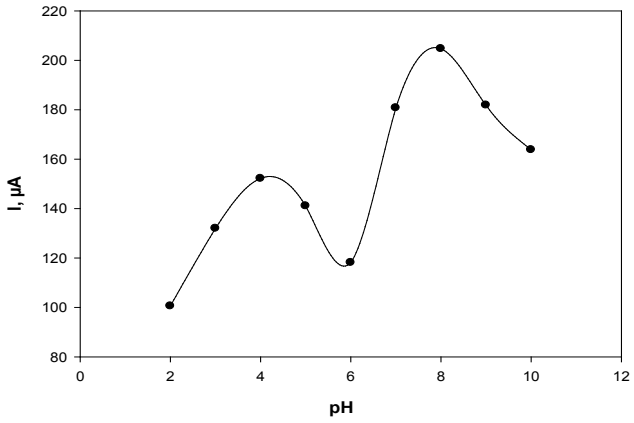
Effect of number of cycles of ferrocene and Chitosan

Figure 4 shows anodic peak current of 1.0 x 10^{-3} mol L^{-1} PAR at CPE (in BR buffer, pH 7.0) as a function of number of cycles in presence of Ferrocene



(a)

Fig.3a. The plot of anodic peak potential of MID (1.0 x 10^{-3}M) as a function of pH at FCHCPE.



(b)

Fig. 3b. The plot of anodic peak current of MID (1.0 x 10^{-3}M) as a function of pH at FCHCPE.

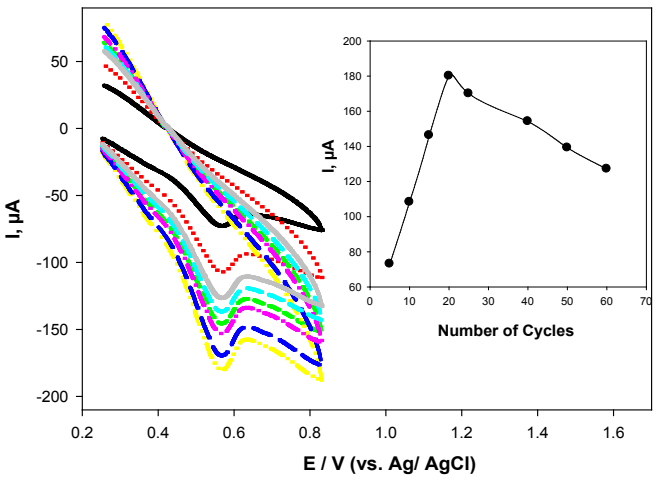
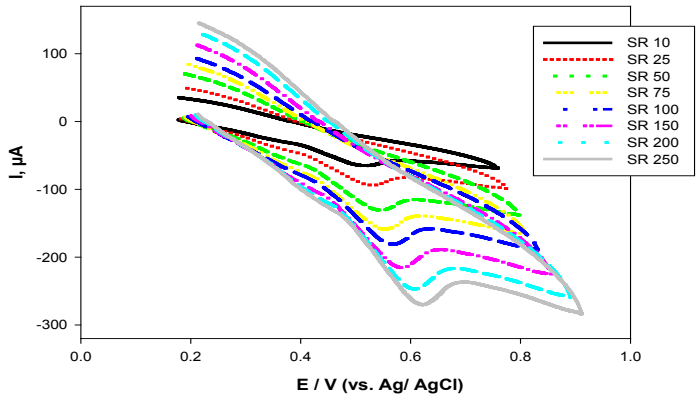


Fig. 4. Shows anodic peak current of 1.0 x 10^{-3} mol L^{-1} PAR at FCHCPE (in BR buffer, pH 7.0) as a function of number of cycles at FCHCPE.

and Chitosan. From the figure we note that as number of cycle's increases, the peak current increases up 20 cycles and then decrease of peak current by increase number of cycles. Therefore, 20 cycles are chosen as the optimum one.

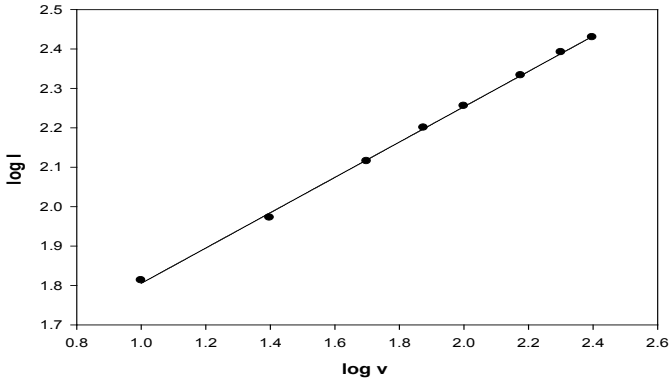
Effect of scan rate

Figure 5 shows the effect of scan rate (υ) on the anodic peak current of PAR at FCHCPE in BR buffer (pH 7.0), at 20 cycles in the range from 10 to 250 mV s^{-1}. It is found that the logarithm of oxidation peak current (log Ip) is linear to the logarithm of scan rate (log υ) as shown in Fig.



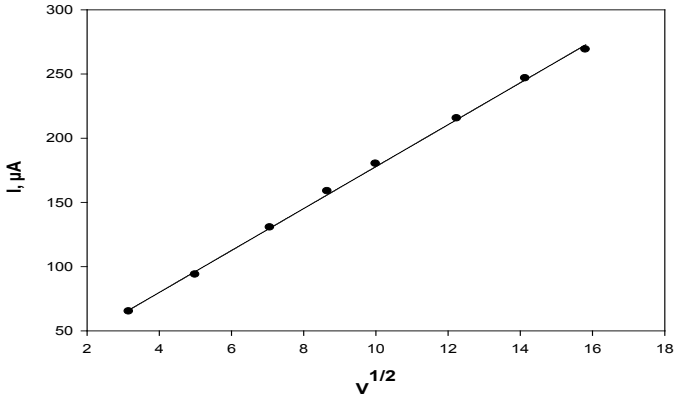
(a)

Fig. 5a. shows the effect of scan rate (υ) on the anodic peak current of PAR at FCHCPE in BR buffer (pH 7.0), at 20 cycles in the range from 10 to 250 mV s^{-1}.



(b)

Fig. 5b. logarithm of oxidation peak current (log Ip) with the logarithm of scan rate (log υ).



(c)

Fig. 5c. The anodic peak current of PAR vs. the square root of scan rate $v^{1/2}$.

5A, with the linear regression equations: log Ip = 0.4483 log υ + 1.3571, r (correlation coefficient) = 0.9996. From the slope values, it can be interpreted that the oxidation process of PAR is a diffusion controlled process at FCHCPE electrode [28].

The relation between the anodic peak current of PAR and the square root of scan rate (Fig. 5B) can be used to determine diffusion coefficient of PAR using Randles-Sevcik equation: $Ip = (2{\cdot}99 \times 10^5)\, n^{3/2}\, A\, C_o^*\, D_o^{1/2}\, \upsilon^{1/2}$ [32] where Ip is the anodic peak current (A), D_o is the diffusion coefficient of the electroactive species ($cm^2\ s^{-1}$), υ is the scan rate ($V\ s^{-1}$), n is the number of electrons exchanged during oxidation, A is the electrode area of (0.0706 cm^2) and C_o^* is the concentration of the analyte. Value of diffusion coefficient for PAR at FCHCPE is 1.313×10^{-6} $cm^2\ s^{-1}$, which referring to molecules of analyte transfers quick towards surface of FCHCPE from bulk.

Analytical application

Quantitative measurements were performed using DPV at FCHCPE, In order to develop an analytical method for the determination of PAR. Calibration curve was constructed through consecutive additions of PAR solution (1.0×10^{-3} mol L^{-1}) to the electrolytic cell containing 5 mL BR buffer of pH 7.0 at 20 cycles by plotting the peak currents against PAR concentrations. Anodic peak current is increasing linearly with increasing concentration of PAR from 1.0×10^{-9} to 6.2×10^{-8} mol L^{-1} with correlation coefficient of 0.998 (Fig. **6**). The limits of quantification (LOQ) and detection (LOD) were found to be 1.71×10^{-8} mol L^{-1} and 4.14×10^{-9} mol L^{-1}, respectively. To check the validity [29-30] of the method, the relative standard deviations and the percentage recoveries were calculated for different concentrations in the linear range (4.0×10^{-9}, 1.1×10^{-8}, 3.6×10^{-8}, 5.2×10^{-8}, 5.0×10^{-8}, 1.6×10^{-8}, 2.2×10^{-8} and 2.8×10^{-8} mol L^{-1}). The relative standard deviation (RSD) and the percentage recovery values were found in the following ranges: 0.475-1.215% and 99.6-101.13%, respectively.

Applications to human urine

To check the applicability of the proposed method to determine PAR in biological fluids, spiked human urine samples were analyzed. Urine samples were collected from healthy volunteer and the samples were prepared as described in experimental section. The calibration curve (Fig. 7) shows a straight line in the range of 1.0×10^{-9} - 3.0×10^{-8}mol L^{-1} with correlation coefficient of 0.9982, the LOQ and LOD were found to be 2.57×10^{-8}mol L^{-1} and 7.70×10^{-9} mol L^{-1}, respectively[31-32]. The relative standard

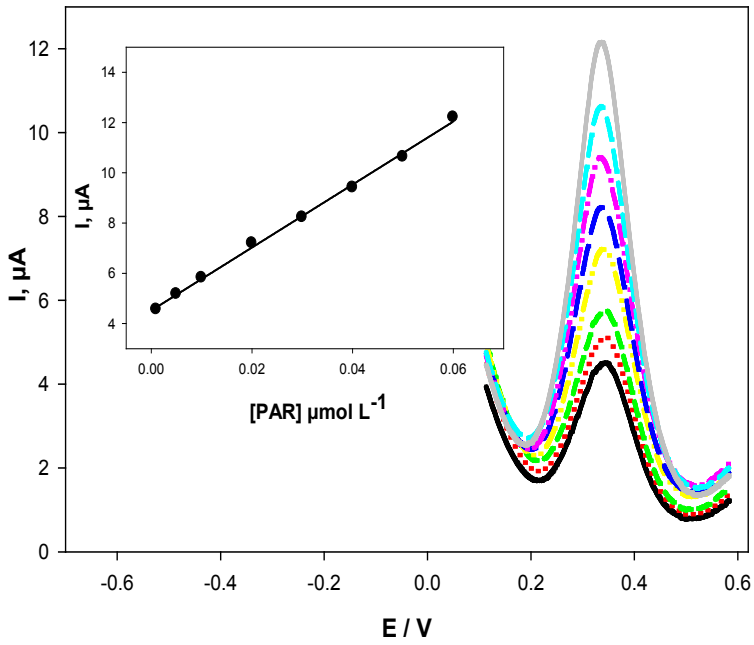


Fig. 6. Calibration voltammograms curve of PAR, using DPV mode at FCHCPE in BR buffer pH 7.0 and scan rate of 10 mV s^{-1}. The inset (B): The calibration plot of the oxidation peak current versus the concentration range of PAR.

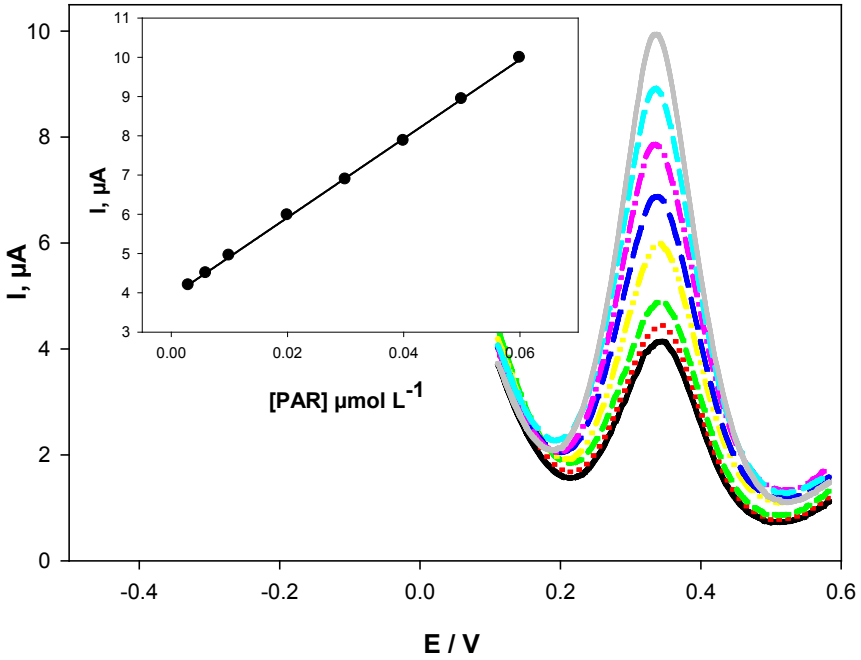


Fig. 7. Voltammograms of Quantitative assay of MID in urine using BR buffer pH 7.0, scan rate 10 mV s^{-1}. The inset (B): Linear relation between PAR concentration in urine and the current response.

TABLE 1. The robustness results of DPV method indicating that DPV method was not affected by deliberate changes in the optimum parameters for the determination of PAR.

Parameters		%RSD*	%Recovery*
pH	7.0 ± 0.2	0.932	99.22
Accumulation time (sec)	10.0 ± 1.0	1.037	99.54
Concentration of Chitosan (µmol L^{-1})	40.0 ± 2.0	1.090	100.81

deviations and the percentage recoveries were found in the following ranges: 0.621 - 1.420% and 99.53-101.93%, respectively. Therefore, the proposed procedure can be successfully and easily used to determine PAR in human urine.

The results obtained were compared statistically with those from reported Spectrofluorimetric method [11] by using Student's t-test and the variance ratio F-test. The results in Table 5 show that the t and F values were smaller than the critical values, indicating that there is no significant difference between the proposed voltammetric method and the published method with respect to accuracy and precision.

Reproducibility and stability

The reproducibility is important for electrode as sensor so under similar was examined in 0.04 M BR buffer (pH 7) for a set of five different DPV measurements for the same electrode. RSD was found to be 1.26 % which can be calculated of average values from five experiments referring to reproducibility of FCHCEP is good. Fabrication of modified FCHCPE required storing the FCHCPE at refrigerator condition for two weeks for Stability study, test of stability of the sensor was explored by using DPV at optimum conditions of experimental and every 5th day was checked periodically. The electrode retained 97% of the current activity towards drug on the 5th day,

TABLE 2. Determination of MID in tablets compared with the reported method.

	Reported method [11]	DPV method
Claimed (mg/tab)	Recovery (%) ± SDa	Recovery (%) ± SDa
2.5	99. 47 ± 1.023	99.88 ± 0.857
	F-testb	2.38
	t-testb	0.78

[a]Averaged from five determinations. [b] Tabulated F and t values at 95% confidence level = 6.39 and 2.776.

96% on 10th day and could retain 94% of its initial value after 15 days.

Discussion

Oxidation process of PAR due to the oxidation of hydroxyl group and Modified electrode FCHCPE is better than other electrodes. We study the effect of modified electrode FCHCPE on the anodic peak current at pH 7.0 and 20 cycles number of cycles of ferrocene and Chitosan of are chosen as the optimum condition. From scan rate study, value of diffusion coefficient for PAR at FCHCPE is 1.313 x 10^{-6} cm^2 s^{-1}, which referring to molecules of analyte transfers quick towards surface of FCHCPE from bulk. Quantitative measurements were performed using DPV at FCHCPE give the relative standard deviation (RSD) and the percentage recovery values were found in the following ranges: 0.475-1.215% and 99.6-101.13%, respectively. Determination of PAR in biological fluids, spiked human urine samples were analyzed, The relative standard deviations and the percentage recoveries were found in the following ranges: 0.621 - 1.420% and 99.53-101.93%. The modified electrode can be used for the determination of the used drug in human urine samples with excellent recovery results.

Conclusion

In the present work, a new, cheap, accuracy, simple and precise differential pulse voltammetric method was optimized for the quantitative determination of PAR concentrations in bulk, pharmaceutical formulations and urine at ferrocene modified carbon paste electrode (FCPE) in the presence of Chitosan solution based the enhancement effect of ferrocene and formation of inclusion complex with Chitosan. Under optimum conditions such as pH, number of cycles, scan rate and were applied for the determination of PAR with accuracy, good precision, and low detection limit (LDL). The developed method can be used in routine analysis of PAR in quality control laboratories in the pharmaceutical industry.

Declarations

- **Ethics approval and consent to participate** ” Not applicable ”
- Consent for publication “Not applicable”
- **Availability of data and material** that data will be shared in my manuscript and can be shared in additional supporting files at any time in necessary for any one
- **Competing interests** “Not applicable”
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Authors' contributions

Waheed M. Salem is participated in the design of the study and performed the statistical analysis, and conceived of the study.

Ali K. Attia is drafted the manuscript, and participated in its design.

All authors read and approved the final manuscript.

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تعين دقيق للباراسيتمول باستخدام جزيئات النانو من فيروسين بقطب كربونى معالج بالشيتوزان الموظف

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اهم مميزات طرق التحليل الكهربائي انها سريعه، ودقيقة و رخيصة وكما انها تستطيع تطبيقها فى الكشف عن القيم المنخفضة جدا للجزيئات النشطة كهربيا. وقد استخدمت مادة الفيروسين في دراسة التحليل الكهربائي للباراسيتامول، وذلك بسبب مساحة سطحها الكبيرة، ودرجة توصيلها العالية ولذلك فهى لها خصائص مميزة فى التحليل الكهربائي. كذلك الشيتوزان له أشكال فيزيائية كسلة يستفاد منها في عدد المواد الكيميائية ذات النواحى التجارية والتطبيقية فى مجال التحليل الكهروكيميائي. الدراسة تقوم على تقدير الباراسيتامول باستخدام فولتاميتر ذات النبض التفاضلي عن طريق حساس كهروكيميائي فعال وجديد. تم تحضير الحساس بواسطة قطب عجينة الكربون تم معالجة ب الفيروسين و الشيتوزان في محلول منظم من بريتون-روبيسون عند pH ٧,٠. تأثير العوامل التجريبية المختلفة بما في ذلك الرقم الهيدروجيني، وعدد دورات تحميل الفيروسين و الشيتوزان، معدل المسح قد تم دراستها؛ خلال الظروف المثلى، تم الحصول على نطاق خطي من ١,٠ × ١٠$^{-٩}$ إلى ٦,٢ × ١٠$^{-٨}$ بمعامل ارتباط ٠,٩٩٩٥ حيث تم الحصول على حد الكشف ٤,١٤ x ١٠$^{-٩}$مول. يمكن استخدام القطب المعالج كحساس لتقدير الادوية المستخدمة في عينات البول البشري مع نتائج استراجع ممتازة