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Boron-Doped Diamond Film Electrode as a Sensitive and Selective Electrochemical Sensor for the Determination of Paracetamol

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Abstract: A simple, sensitive and selective differential pulse voltammetry method for determination of paracetamol on a bare (unmodified) boron-doped diamond film electrode has been developed. It was found by cyclic voltammetry that paracetamol provided the quasi-reversible wave with oxidation peak on the forward scan about +0.90 V and smaller reduction peak on the reverse scan at +0.68 V *vs*. Ag/AgCl. The effect of supporting electrolyte, pH and scan rate on voltammetric response of paracetamol was studied to select the optimum experimental conditions. The optimal conditions for quantification of paracetamol were obtained in acetate buffer solution at pH 5.0. The oxidation peak of paracetamol was chosen for evaluation and showed a systematic increase in peak current with increase of its concentration. Linear response of peak current on the concentration in the range from 2×10^{-7} to 6×10^{-5} mol L^{-1}, good repeatability (RSD of 1.4% for ten successive measurements) and the detection limit of 1.1×10^{-7} mol L^{-1} were observed without any chemical modifications and electrochemical surface pretreatment of boron-doped diamond film electrode. The effect of possible interferents appeared to be negligible which evidently proved good selectivity. The practical analytical utility of proposed method was successfully demonstrated by determination of paracetamol in human urine samples and in pharmaceutical formulations (tablets) with results in a close statistical agreement to those declared by producer.

Keywords: Paracetamol; Boron-doped diamond film electrode; Differential pulse voltammetry; Pharmaceutical formulation; Human urine

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Introduction

Paracetamol (*N*-acetyl-*p*-aminophenol, PCM) is the most commonly used analgesic and antipyretic drug in recent times. It was firstly introduced into medicine as an antipyretic/analgesic at the end of 19th century and is accepted as a very effective treatment for the relief of pain including headache, rheumatic pains, pains from minor injuries and all the everyday aches of normal life [1]. It is very effective in bringing down high temperature in fevers including colds and flu. PCM is also used for the treatment of neuropathic pain, sciatica, dysmenorrhoea and osteoarthritis [2,3]. It is the most used medicine after acetylsalicylic acid in many countries as an alternative to aspirin [4]. Thus the analysis of PCM represents an important and relevant part of analytical chemistry, which plays a significant role in clinical and pharmaceutical chemistry.

A range of methods have been utilized for detection and quantification of PCM, alone and in mixtures, in formulations and biological samples, such as high performance liquid chromatography [5-7], spectrophotometry [8], spectrofluorimetry [9], capillary electrophoresis [10,11], micellar electrokinetic chromatography [12] and Raman spectrometry [13]. However, these methods suffer from some disadvantages such as high cost, long analysis time and requirement for sample pretreatment when some procedures as derivatization, extraction and purification are usually included. In some cases low sensitivity and selectivity can make these methods unsuitable for routine analysis. This fact opens the opportunities for the electrochemical methods employment which have many inherent advantages that eliminate these limitations such as simplicity, low cost and amenability to miniaturization [14]. Since, PCM can be electrochemically oxidized, its determination on various electrode surfaces using electrochemical methods has received considerable interest in the past few decades [15–20]. However, from our knowledge it is obvious that there are very few reports on using bare boron-doped diamond electrodes for individual (or simultaneous with other drugs) determination of PCM [21,22].

Boron-doped diamond film (BDDF) electrodes have attracted attention in last few years and many biologically and electrochemically active compounds have been determined at such electrodes. This material represents a modern electrode material which opens new possibilities of electrochemical investigations due to its excellent features, such as the wide potential window in aqueous solutions, low background current, long-term stability of response, low sensitivity to dissolved oxygen and a good resistance to surface fouling due to weak adsorption [23,24].

The properties of BDDF electrodes are commonly induced by morphologic factors, crystallographic orientation and presence of impurities (non-diamond sp^2 carbon). The electrochemistry of BDD and its advantages compared to conventional electrodes have been reported for electrochemical determination of several important drugs [25-27]. The versatility of this electrode material has also been utilized for the development of sensors and biosensors [28-30]. Reviews on utilization and benefits of BDDF electrode have also appeared in literature [31-33].

Based on the above mentioned facts this paper demonstrates the application of BDDF electrode as sensitive electrochemical sensor for individual determination of PCM without any chemical modifications and/or electrochemical pretreatment of electrode surface. This simple and practical analytical approach is illustrated on pharmaceutical formulations (tablets) and human urine samples.

Experimental

Reagents and Apparatus

PCM (CAS No. 103-90-2, purity 99.5%), sugars (fructose, sucrose, lactose and starch), urea, uric acid, stearic acid and ascorbic acid were obtained from Zentiva (Hlohovec, Slovak Republic) and used as received without any further purification. Various supporting electrolytes such as Britton-Robinson buffer (BRS), acetate buffer (ABS), phosphate buffer (PBS), sulfuric acid (H_2SO_4, 93% w/w), acetic acid (CH_3COOH, 99% w/w) and sodium hydroxide (NaOH) were purchased from Lachema (Brno, Czech Republic). All reagents were of analytical grade. All aqueous solutions were made with double-distilled deionised water with resistivity above 18 MΩ cm. Stock solution of PCM (1.0×10^{-3} mol L^{-1}) was prepared by dissolving of its accurately weighted amount. Calibration standard solutions were prepared from the stock solution by appropriate dilution with supporting electrolyte. Commercial tablets of PARALEN® (125, 500 and 700 mg of PCM declared by producer) were obtained from local pharmacy and human urine samples collected from three voluntary patients treated by PARALEN® 500.

Apparatus

Voltammetric measurements were carried out using an AUTOLAB PGSTAT-302N (EcoChemie, The Netherlands) potentiostat/galvanostat controlled with the NOVA 1.7 software. All electrochemical experiments were performed in a three-electrode single compartment glass cell.

This cell consisted of Ag/AgCl (3 mol L^{-1} KCl) reference electrode, a platinum wire as counter electrode and bare BDDF (boron doping level of 1000 ppm, electrical resistivity of 0.075 Ωcm) electrode inserted in an inert polyether ether ketone (PEEK) body with inner diameter of 3 mm (Windsor Scientific Ltd, United Kingdom) used as the working electrode. All potentials reported in this paper were obtained *vs*. Ag/AgCl electrode at an ambient temperature of 25 ± 1 ºC. All pH values were measured with pH meter Model 215 (Denver Instrument, USA), which was calibrated with standard buffer solutions.

Measurement Procedures

20 mL of the supporting electrolyte containing an appropriate amount of PCM was added to the electrochemical cell. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were employed without deaeration, since dissolved oxygen did not interfere in high anodic potentials. Five CV voltammograms were obtained for each measurement, and the last scan was considered for evaluation and making the figures reported in this paper. DP voltammograms were recorded after optimization of instrumental parameters and the calibration curve was constructed from the average of six successive measurements for each calibration standard solution. The calibration curve was analyzed by linear least-square regression in OriginPro 7.5 (OriginLab Corporation, USA) and the relevant results (slope and intercept) were reported with 95% confidence level. The detection limit (LOD) was calculated as three times the standard deviation for the blank solution (supporting electrolyte) divided by the slope of the calibration curve. The calibration curve and standard addition method was used for analysis of pharmaceutical formulations and human urine samples.

Results and Discussion

Electrochemical behavior of COD on unmodified BDDF electrode

Effect of Supporting Electrolyte. Cyclic voltammetry (CV) was applied to study the electrochemical behaviour of PCM on bare BDD electrode. All necessary factors influencing the current response of PCM were carefully checked to reach the conditions at which the best analytical performance was achieved.

In order to find the appropriate medium for electrode reaction of PCM on bare BDDF electrode the various supporting electrolytes such as sulfuric acid, acetic acid, sodium hydroxide, phosphate buffer solution (PBS), Britton-Robinson buffer solution (BRS) and acetate buffer solution (ABS) were tested. The use of sulfuric acid, acetic acid and sodium

hydroxide were inconvenient due to the less sensitive, bad shaped and reproducible current responses (results not shown). The quasi-reversible wave appertaining to electrode reaction of PCM was very well-defined in PBS, BRS and ABS. The best results were obtained in ABS in which the magnitude of both oxidation and reduction peak current was found to be approximately two times higher than in PBS and BRS. Following these facts ABS was chosen in further experiments. Generally, the presence of buffer was necessary for stabilization of pH in the solution.

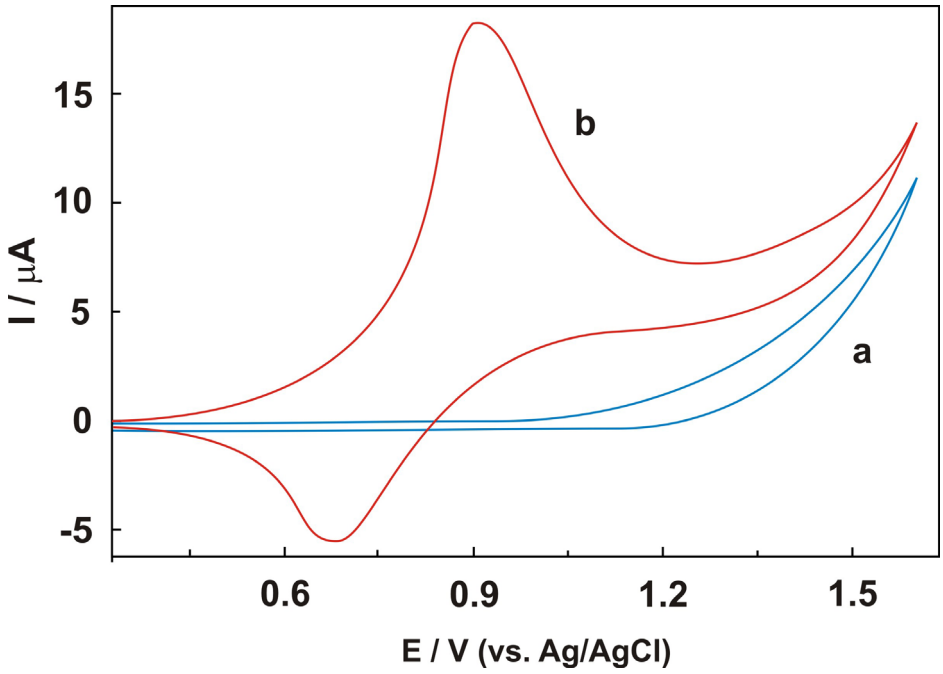


Fig. 1: *Cyclic voltammograms of (a) 0 μM PCM (blank), (b) 1 × 10^{-5} mol L^{-1} PCM in ABS at pH 5.0 on BDDF electrode with scan rate of 0.05 $V \cdot s^{-1}$*; CV: initial and final potential, E_{INIT} and E_{FIN} = +0.35 *vs*. Ag/AgCl, vertex potential, E_{VX} = +1.6 V vs. Ag/AgCl.

Fig. 1 illustrates CV voltammograms in the absence (curve a) and presence of 1 × 10^{-5} mol L^{-1} PCM (curve b) in ABS at pH 5.0. In the presence of PCM the quasi-reversible wave with oxidation peak on the forward scan at about +0.90 V and smaller reduction peak on the reverse scan at +0.68 V *vs*. Ag/AgCl was observed. These facts are in good agreement with data previously reported in the literature dealing with determination of PCM [29,38]. It is also apparent from Fig. 1 that in the absence of PCM (curve a) no oxidation and reduction peaks were observed and background current appeared to be sufficiently low at higher potentials on bare BDDF electrode. This evidently proves the benefits of this electrode material.

Effect of pH and Oxidation Mechanism. In general, the pH value of supporting electrolyte is a significant factor that usually affects electrochemical behavior of biologically active molecules. It was found that the pH value of ABS influences the peak potential of PCM suggesting the involvement of protons in the oxidation reaction. The effect of pH on the peak potential of oxidation process was investigated in the pH range of 3-6.

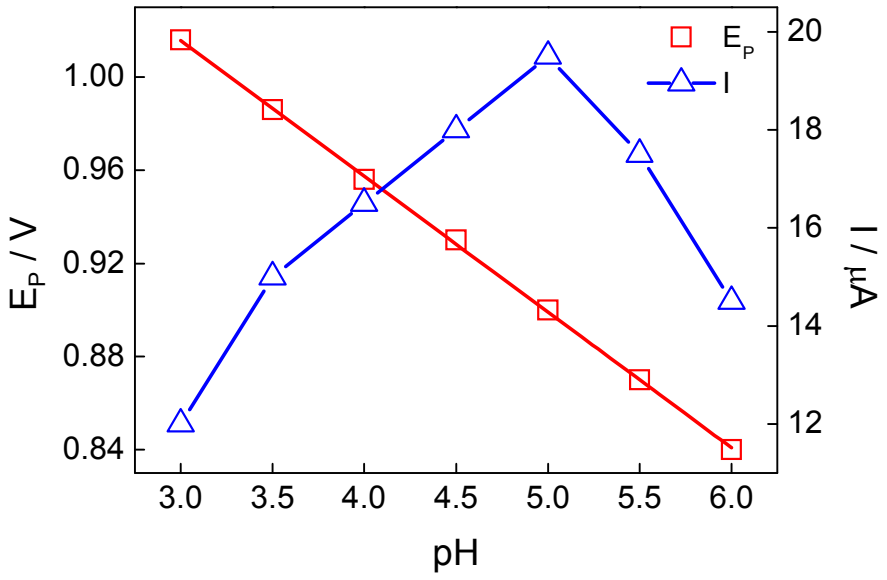
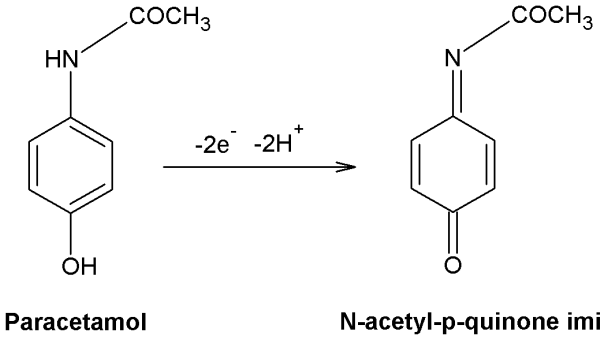


Fig. 2: *Effect of pH of supporting electrolyte (ABS) on the peak potential (□) and peak current (Δ) of 1 × 10^{-5} mol L^{-1} PCM on bare BDDF electrode with scan rate of 0.05 $V{\cdot}s^{-1}$*; CV: initial and final potential, E_{INIT} and E_{FIN} = +0.35 *vs*. Ag/AgCl, vertex potential, E_{VX} = +1.6 V vs. Ag/AgCl.

As depicted in Fig. 2 the peak potential (E_P) shifted towards less positive values as the pH of supporting electrolyte was gradually increased. The relationship between peak potential (E_P) and pH of ABS was linear and dependence can be presented as E_P (V) = 1.18 □ 0.0549 pH (R^2 = 0.998). The slope of equation is very close to the anticipated value of –0.059 V pH^{-1}. This result revealed that an equal number of participated protons and transferred electrons are involved in the oxidation process of PCM on bare BDDF electrode. On the basis of calculated slope (0.0549 V pH^{-1}), the number of protons *n* taking part in oxidation of PCM was found to be 1.86 for *z* = 2. From this value, it is obvious that approximately two protons are participated in the oxidation reaction of PCM. The calculated number of protons is biased from the expected value (2.00) due to quasi-reversibility of mass transfer during the oxidation process of PCM.

So, the overall oxidation process of PCM involves two protons and electrons to generate *N*-acetyl-*p*-quinoneimine as shown in Scheme 1. Our outcome is in agreement with mechanism reported by ShangGuan et al. [19] and Sanghavi et al. [22].

The effect of pH on the peak current was also studied in the range of 3-6. The obtained results showed that the peak current (I_P) of PCM increased slightly and reached the maximum approximately at pH 5.0 and then decreased as shown in Fig. 2. Based on these observations and in order to obtain high selectivity and sensitivity, ABS at pH 5.0 was chosen as optimum supporting electrolyte and used in further experiments.



Scheme 1: *The reaction of electrochemical oxidation of PCM.*

Effect of Scan Rate. The dependence of scan rate (v) on the peak current was investigated in order to characterize the mass transport in diffusion layer of BDDF electrode during electrode reaction of PCM. Fig. 3 demonstrates that the oxidation peak current of 1×10^{-5} mol L^{-1} PCM was increased with ascending scan rate.

Also, it was observed that the peak current is linearly proportional ($R^2 = 0.996$) to the square root of the scan rate within the range of 0.025-0.150 V s^{-1} indicating that the mass transport is controlled by diffusion thus proving that the rate-limiting adsorption and/or specific interactions on bare BDDF electrode surface are negligible. The slight shift of peak potential towards more negative potential was observed as the scan rate increased.

Analytical Performance

Optimization of DPV Parameters. DPV method has been applied to numerous biologically active compounds. In our case, this sensitive voltammetric method was chosen to investigate the dependence between oxidation peak currents and concentrations of PCM.

Before DPV measurement, an optimization of its instrumental parameters generally affecting the current response such as modulation amplitude, modulation time and scan rate was performed. During this procedure each parameter was changed while the others were kept constant. It was found that the peak current increased with the increasing of modulation amplitude in the range from 0.01 to 0.2 V accompanied by the widening peak width at the same time. When the modulation amplitude was higher than 0.1 V, the peak becomes much wider. For the modulation time, peak currents decreased with an increasing of modulation time in the range from 0.01 to 0.06 s and the most stable peak current was observed at 0.05 s. As the satisfactory value of scan rate, 0.05 V s^{-1} was chosen.

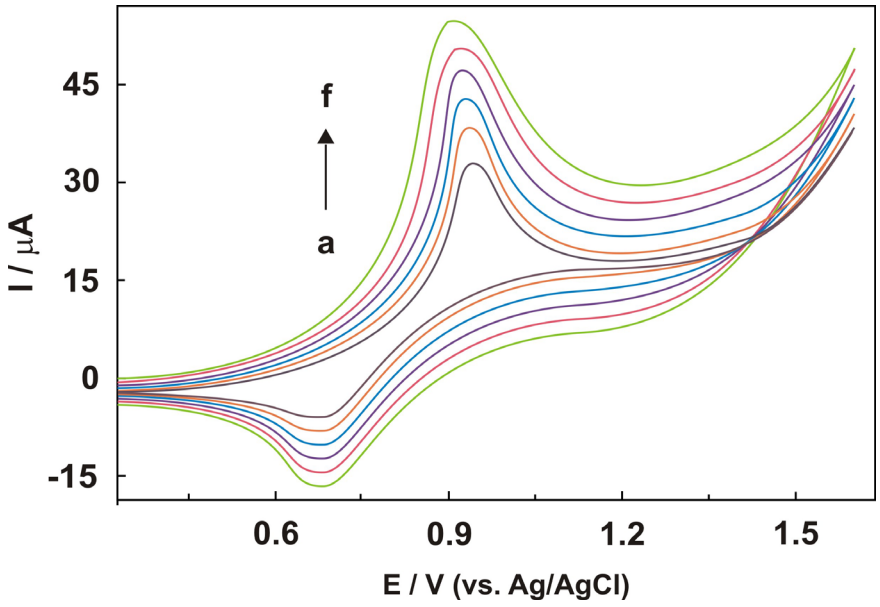


Fig. 3: *Cyclic voltammograms of 1 × 10^{-5} mol L^{-1} PCM in ABS at pH 5.0 on bare BDD electrode for series of scan rates* (v) of: (a) 0.025, (b) 0.05, (c) 0.075, (d) 0.1, (e) 0.125 and (f) 0.15 V s^{-1}; CV: initial and final potential, E_{INIT} and E_{FIN} = –1.0 V *vs*. Ag/AgCl, vertex potential, E_{VX} = 1.6 V vs. ref.

Determination of PCM. The calibration curve was constructed by measuring of peak current with optimized DPV parameters. An average of six successive measurements was used for calibration curve construction. Fig. 4 displays DP voltammograms at various concentrations of PCM in ABS at pH 5.0.

The dependence of peak current on concentration of PCM shows a good linearity (R^2 = 0.999) in the concentration range from 2 × 10^{-7} to 6 × 10^{-5} mol L^{-1} as depicted in the inset of Fig. 5 (see overleaf).

The linear regression equation was expressed as I_p (μA) = 0.7 + 0.79 C with R^2 = 0.999. The detection limit was found to be 1.1 × 10^{-7} mol L^{-1}. In order to examine the repeatability, repeated DPV experiments were run in 1 × 10^{-5} mol L^{-1} PCM in ABS at pH 5.0 on the bare BDDE. The DP voltammograms were evaluated by ten successive measurements under the same operating conditions over the short time interval. The relative standard deviation (RSD) of the peak current was about ±1.4%, revealing the good repeatability of the proposed method.

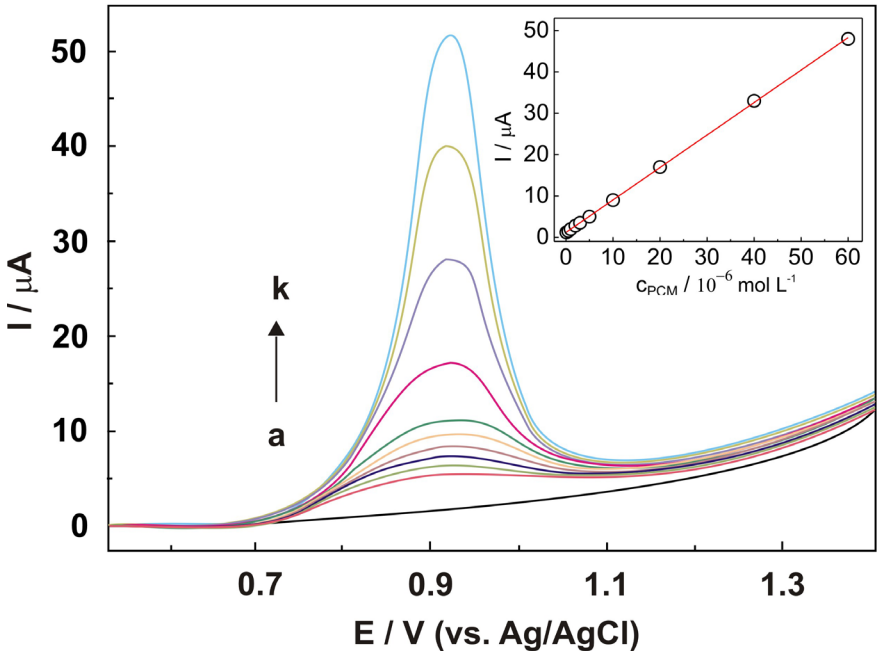


Fig. 4: *Differential pulse voltammograms of various concentrations of PCM:* (a) 0 (b) 2 × 10^{-7}, (c) 5 × 10^{-7}, (d) 1 × 10^{-6}, (e) 2 × 10^{-6}, (f) 3 × 10^{-6}, (g) 5 × 10^{-6}, (h) 1 × 10^{-5}, (i) 2 × 10^{-5}, (j) 4 × 10^{-5} and (k) 6 × 10^{-5} mol L^{-1} in ABS at pH 5.0 on bare BDDF electrode at optimized DPV parameters: modulation amplitude of 0.1 V, modulation time 0.05 s and scan rate 0.05 V s^{-1}. The dependence between peak current (μA) and concentrations of PCM (mol L^{-1}) is illustrated in the inset.

Comparison with Other Electrochemical Methods. A comparison between the analytical performance of the proposed method and some reported electrochemical methods from recent years for determination of PCM are given in Table I. Carbon nanotubes modified carbon electrodes have been used for the determination of PCM with higher or comparable detection limits with this obtained in our work [16,17,20]. The electroanalytical method using carbon nanotubes modified basal plane pyrolytic graphite electrode the most sensitive method for determination of PCM with lowest limit of detection to date [18].

Moreover, the preparation of modified electrodes is sometimes time consuming process that involves various steps in incorporation of the different modifier to the electrode surface leading to the not always reproducible results [29]. Further, it is sometimes useless to modify the electrode surface for selectivity and sensitivity improvement in a practical process of analysis. This fact may seem to be less important, however this observation decreases number of operations in analytical process (lower risk of measurement errors), reduces expenses and operational skills of analyst related to chemical modification. Accordingly, the good linear concentration range and low detection limit was reached with no electrochemical pretreatment or chemical modification of BDDF electrode in our experiments.

Table I: *Comparison of the proposed method with reported electrochemical methods from recent years for determination of PCM*.

Electrode	Method	LCR (μmol L^{-1})	LOD (μmol L^{-1})	Sample analyzed	Ref.
Graphene/GCE	SWV	0.1-20	0.05	pharmaceuticals	15
MWCNT/GCE	DPV	3-300	0.6	human serum	16
SWCNT/CCE	DPV	0.2-100	0.12	pharmaceuticals	17
MWCNT/BPPGE	SWAdSV	0.01-20	0.01	pharmaceuticals	18
CILE	DPV	1-2000	0.3	human urine	19
CNT/SPCE	FIA	0.25-100	0.1	pharmaceuticals	20
BDDF electrode	DPV	0.5-83	0.49	pharmaceuticals	21
BDDF electrode	DPV	0.2-60	0.11	pharmaceuticals human urine	This work

Abbreviations: SWCNT: single-walled carbon nanotube, MWCNT: multi-walled carbon nanotubes, CCE: carbon ceramic electrode, GCE: glassy carbon electrode, BPPGE: basal plane pyrolytic graphite electrode, SWAdSV: square-wave adsorptive stripping voltammetry, CILE: carbon ionic liquid electrode, SPCE: screen-printed carbon electrode, FIA: flow injection analysis, LCR: linear concentration range, LOD: detection limit

Interference Study. The influence of interfering compounds commonly existing in pharmaceutical formulations and human urine was also examined by DPV under the same experimental conditions. This procedure was realized by addition of each substance with varying concentration to the solution containing fixed amount of 1×10^{-5} mol L^{-1} PCM in ABS (pH 5.0). It was found that a 100-fold excess of common ions such as Na^{+}, K^{+}, Mg^{2+}, Zn^{2+}, Fe^{3+}, Cu^{2+}, Al^{3+}, Ti^{4+}, Cl^{-}, NO_3^{-}, PO_4^{3-} and SO_4^{2-} showed no effect on oxidation peak of PCM.

Glucose did not influence the peak current of PCM even up to 10-fold excess. Stearic acid, sugars (fructose, sucrose, lactose and starch), urea, uric acid and ascorbic acid did not significantly interfere in 50-fold excess with oxidation of PCM (RSD < 5%). The ascorbic acid as an illustrated example is depicted in Fig. 5. These results suggested that determination of PCM was not affected by the most common interfering compounds present in pharmaceutical formulations and human urine samples and the proposed method is sufficiently selective.

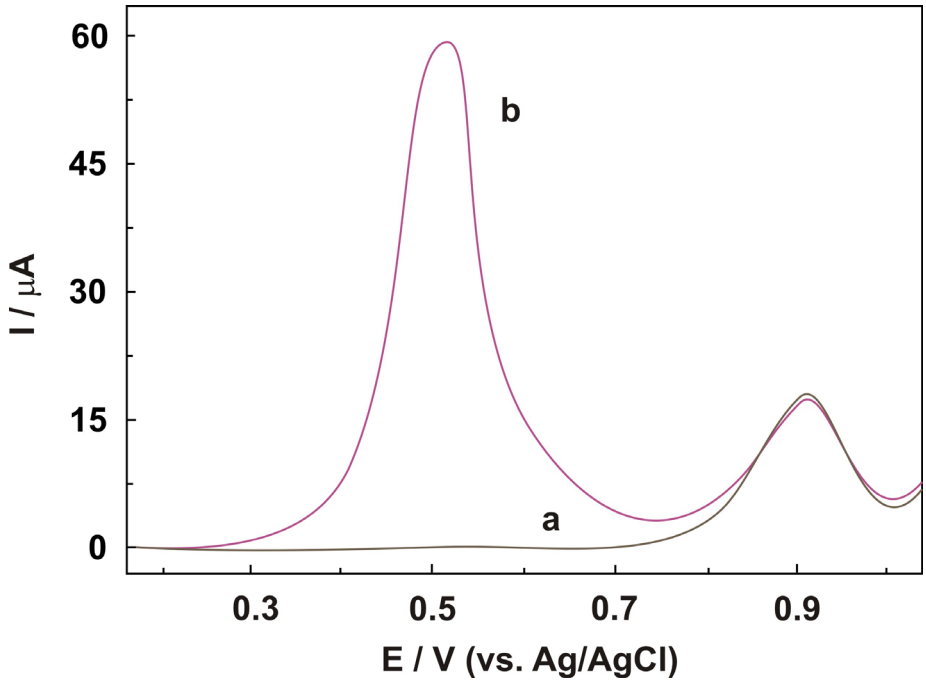


Fig. 5: *Differential pulse voltammograms of 1 × 10^{-5} mol L^{-1} PCM*: (a) in the absence, (b) in the presence of 5 × 10^{-4} mol $L^{-1}$of ascorbic acid in ABS at pH 5.0 on bare BDDF electrode at optimized DPV parameters: modulation amplitude of 0.1 V, modulation time 0.05 s and scan rate 0.05 V s^{-1}.

Real Sample Analysis. At first, the developed method was applied to the pharmaceutical formulations. Commercial tablets of PARALEN® were obtained from local pharmacy. The tablets were weighted, ground into powder and then dissolved in deionized water with intensive stirring of magnetic stirrer for 30 min. The mixture was filtered and transferred into 25 mL volumetric flask. To obtain the final concentrations in the range of calibration curve, the sample solutions were suitably diluted with ABS at pH 5.0 and then added in amount of 20 mL to the electrochemical cell for determination of PCM using DPV.

In order to estimate the accuracy of the proposed analytical technique, the standard additions method was performed by spiking of aliquots amount of standard of PCM prepared from its stock solution. The diluting process can actually help to reduce the matrix effects of real samples. The determined results for six successive measurements expressed as confidence interval for 95% probability and recoveries are summarized in Table II. The average recovery values (from 98 to 102%) revealed the good accuracy of presented method. This fact indicated that no important matrix effects were present in the samples analyzed by the DPV method. The method is rapid and simple and thus it can be recommended for the analysis of PCM in pharmaceutical formulations. As it can be seen in Table II, no significant differences were observed between the values found by the DPV method and those declared by the producer.

Table II: *Determination results of PCM in pharmaceutical formulations (mg per tablet) by DPV method (n = 6).*

PCM content (mg/tablet)	Determined (mg)*	Spiked (mg)	Found after spiking (mg)**	Recovery (%)
125	121 ± 5	50	172 ± 6	98
500	507 ± 7	100	613 ± 10	102
750	755 ± 12	150	906 ± 9	101

Legend: The confidence interval for 95% probability: $\bar{x} \pm t_{n-1,\alpha}\, SD/n^{1/2}$ ($t_{5;0.05} = 2.0150$) for results determined by: *calibration curve and **standard addition method

The analysis of human urine samples of three voluntary patients of different age and sex (patient 1: male, 33 years, 85 kg, 182 cm, patient 2: male, 55 years, 92 kg, 179 cm and patient 3: female, 38 years, 63 kg, 165 cm) was performed in order to evaluate the validity and practical applicability of herein proposed method. Generally, after drug intake some unmetabolized amounts usually secrete in patient urine. The individual urine samples were collected 2 h after patient´s intake of PARALEN® 500. Each 1.0 mL of fresh urine sample was taken and diluted to 20 mL with ABS at pH 5.0 and then directly analyzed. It was observed that oxidation peak at about 0.90 V was recorded in the urine samples of patients as illustrated in the case of patient 1 in Fig. 6.

The actual concentration of PCM in urine samples of patients was evaluated by using calibration curve and the results expressed as confidence interval for 95% probability are listed in Table III. The standard addition method was used to verify the presence of studied drug under identical conditions when each diluted patient's urine sample was spiked with

3×10^{-5} mol L^{-1} of PCM standard followed by increasing of peak current as evidenced in Fig. 6. The recovery values in determination of PCM were satisfactory and ranged from 97 to 103%. It can be concluded that the proposed method is also suitable for determination of PCM in urine samples.

Table III: Determination results of PCM in patient's urine samples by DPV method (n = 6)

Patient	Analyzed (µmol L^{-1})*	Spiked (µmol L^{-1})	Expected (µmol L^{-1})	Found (µmol L^{-1})**	Recovery (%)
1	27 ± 2	20	47	48 ± 2	102
2	45 ± 3	20	65	63 ± 4	97
3	17 ± 2	20	37	38 ± 3	103

Legend: The confidence interval for 95% probability: $\bar{x} \pm t_{n-1,\alpha}\, SD/n^{1/2}$ ($t_{5;0.05}$ = 2.0150) for results determined by: *calibration curve and **standard addition method

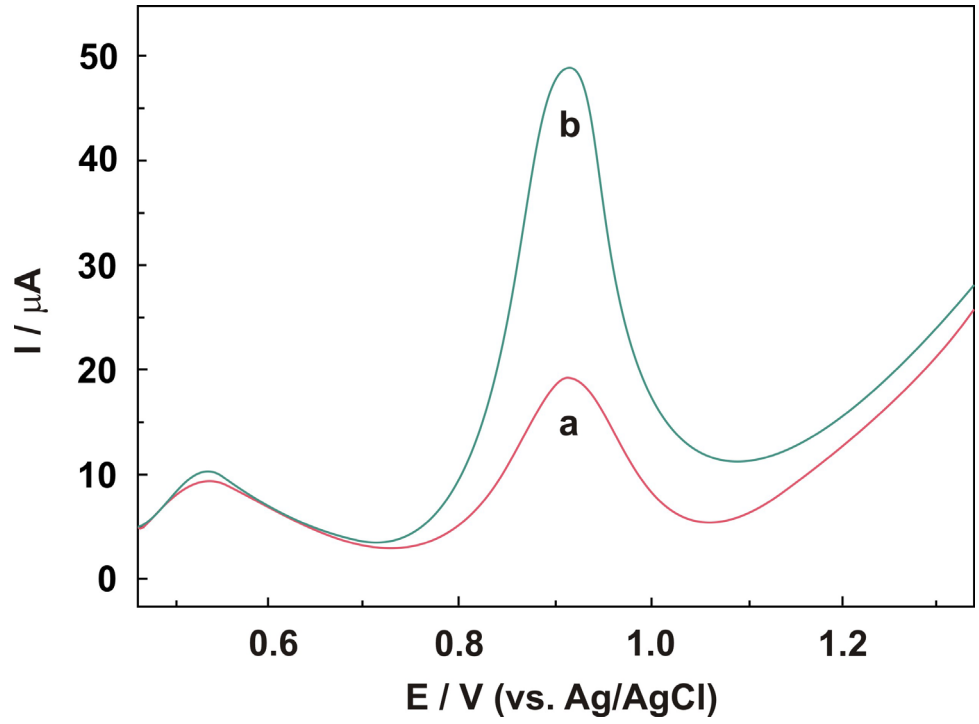


Fig. 6: *Differential pulse voltammograms of urine sample of patient 1 treated with PARALEN® 500*: (a) in the absence, (b) after spiking with 3×10^{-5} mol L^{-1} of PCM standard in ABS at pH 5.0 on bare BDDF electrode at optimized DPV parameters: modulation amplitude of 0.1 V, modulation time 0.05 s and scan rate 0.05 V s^{-1}.

Conclusions

In this study the BDDF electrode was applied as electrochemical sensor for the direct determination of PCM. Cyclic voltammetry and differential pulse voltammetry were used for the characterization of anodic charge transfer during oxidation of PCM, optimization of experimental and instrumental parameters as well as for the quantification in real samples is clearly presented.

Proposed analytical technique is simple and rapid in comparison with other analytical methods used for the determination of PCM. The detection limit (1.1×10^{-7} mol L^{-1}) is lower than previously reported electrochemical method and was obtained as a consequence of very high S/N ratio without any chemical modification and electrochemical pretreatment of BDDF surface. The practical analytical utility of method was successfully demonstrated in the analysis of pharmaceutical formulations and urine samples of patients undergoing treatment with PARALEN® 500 to determine its unmetabolized amount. Method is also highly selective because species usually present in pharmaceutical formulations and human urine do not interfere. Based on these facts, the presented method offers green, selective and sensitive possibility for drug quality control and analysis of biological samples containing PCM with no special pretreatment of samples except simple dilution.

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