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Comparison of the paracetamol electrochemical determination using boron-doped diamond electrode and boron-doped carbon nanowalls

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Abstract

Two different type of electrodes, boron-doped diamond electrode (BDD) and boron-doped carbon nanowalls (B:CNW) electrode, were used for the electrochemical determination of paracetamol using the cyclic voltammetry and the differential pulse voltammetry in phosphate buffered saline, pH = 7.0. The main advantage of these electrodes is their utilization without any additional modification of the electrode surface. The peak current was linearly related to the concentration of paracetamol in the range from 0.065 μM to 32 μM for BDD electrode and from 0.032 μM to 32 μM for B:CNW electrode. The limit of detection was 0.430 μM and 0.281 μM for BDD and B:CNW electrode, respectively. Additionally, we studied the effect of pH on the redox reaction of paracetamol at the both electrodes in Britton-Robinson buffer solution in the range of pH 3.0-12.0, indicating the pH 7.0 value as the most suitable for the current experiments. The studies also included the various scan rates in range of 50 to 500 mV/s. Finally, our team selected the B:CNW electrode for the determination of paracetamol in the artificial urine sample using differential pulse voltammetry method, obtaining the calculated limit of detection on the level of 0.08006 μM.

Keywords: boron-doped diamond electrode, boron-doped carbon nanowalls electrode, cyclic voltammetry, differential pulse voltammetry, paracetamol

1. Introduction

Paracetamol (acetaminophen, N-acetyl-*p*-aminophenol, 4-acetamidophenol) is an acylated aromatic amide used in the treatment of pain and fever. Chemically paracetamol is a weak acid (pK_a = 9.5) rapidly absorbed after ingestion (Parojčić et al., 2003). Human body excretes only 1% to 4% of this compound unchanged in the urine after oral dosing (Kulo et al., 2013). The occurrence of the environmental contamination in water is reported at concentrations of up to 10 $\mu g \cdot L^{-1}$ (Boxall, 2004; Heberer, 2002).

Numerous analytical methods and techniques were reported for the determination of paracetamol, such as: spectrophotometric (Fatibello-Filho and Vieira, 2008; Morelli, 1989; Sirajuddin et al., 2007), spectrofluorometric (de los A. Oliva et al., 2005; Madrakian et al., 2009; Martinez Calatayud and Gomez Benito, 1990), chromatographic (Belal et al., 2009; El-Obeid and Al-Badr, 1985; Gioia et al., 2008), electrophoretic (Heitmeier and Blaschke, 1999; Solangi et al., 2011; Zhao et al., 2006), titrimetric (Burgot et al., 1997; Kumar and Letha, 1997; Srivastava et al., 1985), FTIR spectrometric (Mallah et al., 2015, 2012; Zimmermann and Baranović, 2011), and voltammetric (Khaskheli et al., 2013; Radovan et al., 2008; Tefera et al., 2016).

Unfortunately, all these methods are usually time-consuming and require numerous sample pretreatment steps. To overcome these drawbacks, many electroanalytical methods have been developed (Sanghavi et al., 2015). These methods exhibit many advantages, such as high selectivity, high sensitivity, low cost requirements, and quick responsiveness.

The lowest detection limits of paracetamol using commonly available electrochemical techniques described in literature were 10 nM using multiwalled carbon nanotube modified basal plane pyrolytic graphite electrode (MWCNT-BPPGE), 7 nM using flow injection analysis combined with the electrochemical detection (Wangfuengkanagul and Chailapakul, 2002), and

6.7 nM using diglycolic acid (DA) polymer coated on the glassy carbon electrode (Xu et al., 2012).

Boron-doped diamond (BDD) is an electrode material with the excellent characteristics, including the wide potential window, the low background current, the stability of response, and the electrochemical durability in various media (Hupert et al., 2003). Due to their unique properties, BDD the electrodes are widely used for the electroanalytical applications concerning the determination of pharmaceutical compounds (Ardila et al., 2013; Batista et al., 2010; Sartori et al., 2009).

Only a few reports described the electrochemical analyses of paracetamol using a BDD bare electrode. Wangfuengkanagul and Chailapakul (2002) extensively studied the electrochemistry of paracetamol at a BDD thin film electrode The unmodified BDD electrodes were widely used for the simultaneous determination of paracetamol and other analytes. Radovan et al. (2008) used the BDD electrodes for the simultaneous determination of paracetamol and ascorbic acid using voltammetry and (DPV) method. Svorc et al. (2012) used the square wave voltammetry (SWV) method for the simultaneous determination of paracetamol and penicillin V with the bare BDD electrode. Moreover, Santos et al. (2015) applied (SWV) and (DPV) techniques for the simultaneous determination of codeine and paracetamol in both pharmaceutical formulations and human body fluids at the bare BDD electrode. Lourenção et al. (2009) utilized these two methods for the single or simultaneous determination of paracetamol and caffeine in aqueous media using the bare (BDD) electrode. Additionally, Pereira et al. (2013) used BDD electrode for the simultaneous determination of paracetamol and nimesulide.

Recently, a new type of diamond electrodes was discovered – Boron-doped carbon nanowalls B:CNW manufactured using the microwave plasma-assisted chemical vapor

deposition (CVD) process. These electrodes are characterized by improved charge transfer and enhanced electrochemical performance due to the boron doping and their properties are comparable to these of the glassy carbon electrodes (Siuzdak et al., 2017; Sobaszek et al., 2017).

The present study describes the electrochemical behavior of paracetamol analyzed using selected BDD and B:CNW electrodes and presents the comparison of the selective and sensitive paracetamol determination using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. Additionally, authors discuss the mechanism of paracetamol oxidation at various pH values. According to the best of our knowledge, the analyses in buffered media have not been yet described.

2. Experimental section

2.1. Materials and Methods

Paracetamol was purchased from Sigma-Aldrich and all other chemicals were of the analytical grade and used without further purification. The voltammetric determination of paracetamol was carried out in 0.01 M phosphate buffer solution (PBS), (pH = 7.0) using the cyclic voltammetry CV and the differential pulse voltammetry (DPV). All electrochemical measurements at various pH values were performed in Britton-Robinson buffer solutions (B-R). The pH of the buffer solutions was measured using the pH-meter electrode. The artificial urine sample – Negative Urine Control (SurineTM) – was obtained from Sigma-Aldrich. The Negative Urine Control was diluted with 0.1 M (PBS), (pH 7.0) (1:1) before use in the measurements. The electrochemical characterizations of BDD and B:CNW electrodes were carried out in 0.5 M Na_2SO_4 solution with the reference redox system: $[Fe(CN)_6]^{3-/4-}$ at 5 mM concentration (Supplemental Information). Electrochemical measurements were performed using the potentiostat AutoLab PGStat 128N (Metrohm) at room temperature in a standard three-electrode assembly, utilizing Ag/AgCl/0.1 M NaCl as the reference electrode, a platinum

wire as the counter electrode, and BDD electrode or B:CNW electrode (disk diameter: 8.0 mm; surface area: ca. 0.5 cm^2) as the working electrode. The experimental conditions: cyclic voltammetry CV, the potential ranging from -0.2 to 1.0 V, scan rate 100 mV/s and 50-500 mV/s. Differential pulse voltammetry (DPV), the potential ranging from 0 to 1.0 V, the amplitude modulation of 50 mV, the pulse width of 70 ms, and the scan rate of 5 mV/s.

2.2. Preparation of BDD electrode and B:CNW electrode

BDD and B:CNW were synthesized using the MWPECVD system (SEKI Technotron AX5400S, Japan). Both BDD and B:CNW thin films were grown on (100)-oriented silicon substrates. The detailed parameters of the thin film synthesis can be found elsewhere, for the BDD in Bogdanowicz et al. (2013b) and for the B:CNW in Siuzdak et al. (2017) and Sobaszek et al. (2017). For both films the time of deposition was 6 hours resulting in the film thickness of ca. 3 μm. All various deposition parameters for each sample are listed in the Table S1 (Supplemental Information).

2.3. Characterization of boron-doped diamond (BDD) and boron-doped carbon nanowalls (B:CNW)

The major difference in comparison of the BDD electrode with B:CNW is their surface morphology, structure, and chemical composition. The carbon electrodes doped with the boron atoms have different properties due to the synthesis parameters, what have a crucial impact on the final product. The BDD is a polycrystalline electrode and can be considered as a bulk electrode which is a well-known material described previously (Bogdanowicz et al., 2013b; Lee and Park, 2005; Sarada et al., 2000). The B:CNW electrode is a more complex material and can be considered as a 3D-structure material. B:CNW electrodes are usually called the “Graphene nanowalls” due to the multilayered graphene walls oriented vertically to the substrate. BDD is an sp^3-rich phase material (Bogdanowicz et al., 2013a) while B:CNW is an sp^2-rich phase

material (Siuzdak et al., 2017, 2017; Yu et al., 2011). The main advantage of the B:CNW electrode is the developed active surface which is about three times higher than the BDD electrode.

3. Results and discussion

3.1. Paracetamol determination

3.1.1. Cyclic voltammetry

Cyclic voltammetry was performed to investigate the electrochemical behavior of paracetamol using both studied electrodes at a scan rate of 100 mV/s. Figure 1a shows cyclic voltammograms with various concentrations of paracetamol using the BDD electrode (from 2 μM to 1 mM of paracetamol) and Figure 1b presents the B:CNW electrode (from 0.25 μM to 1 mM of paracetamol) in 0.01 M (PBS), (pH = 7.0). For both electrodes, an increase in paracetamol concentration results in the enhancement of the peak currents and a slight shift of the oxidation and reduction potentials. In comparison with the BDD electrode, the B:CNW electrode showed a distinct reversible peak.

In case of 1 mM of paracetamol concentration, the oxidation and reduction potentials at BDD electrode were found at +0.70 V and -0.36 V with a peak-to-peak separation of 1.06 V. At B:CNW electrode, oxidation potential was found at +0.44 V and reduction potential at +0.32 V. Additionally, the peak-to-peak separation value at B:CNW electrode is an order of magnitude smaller than for the BDD electrode and equals 0.12 V. The linear relationship between the peak current and paracetamol concentration can be expressed by the linear regression equation as $I_{pA}[\mu A] = 0.123C[\mu M] - 0.25$ ($R^2 = 0.999$) and $I_{pA}[\mu A] = 0.259C[\mu M] + 0.69$ ($R^2 = 0.996$) for BDD and B:CNW electrodes, respectively.

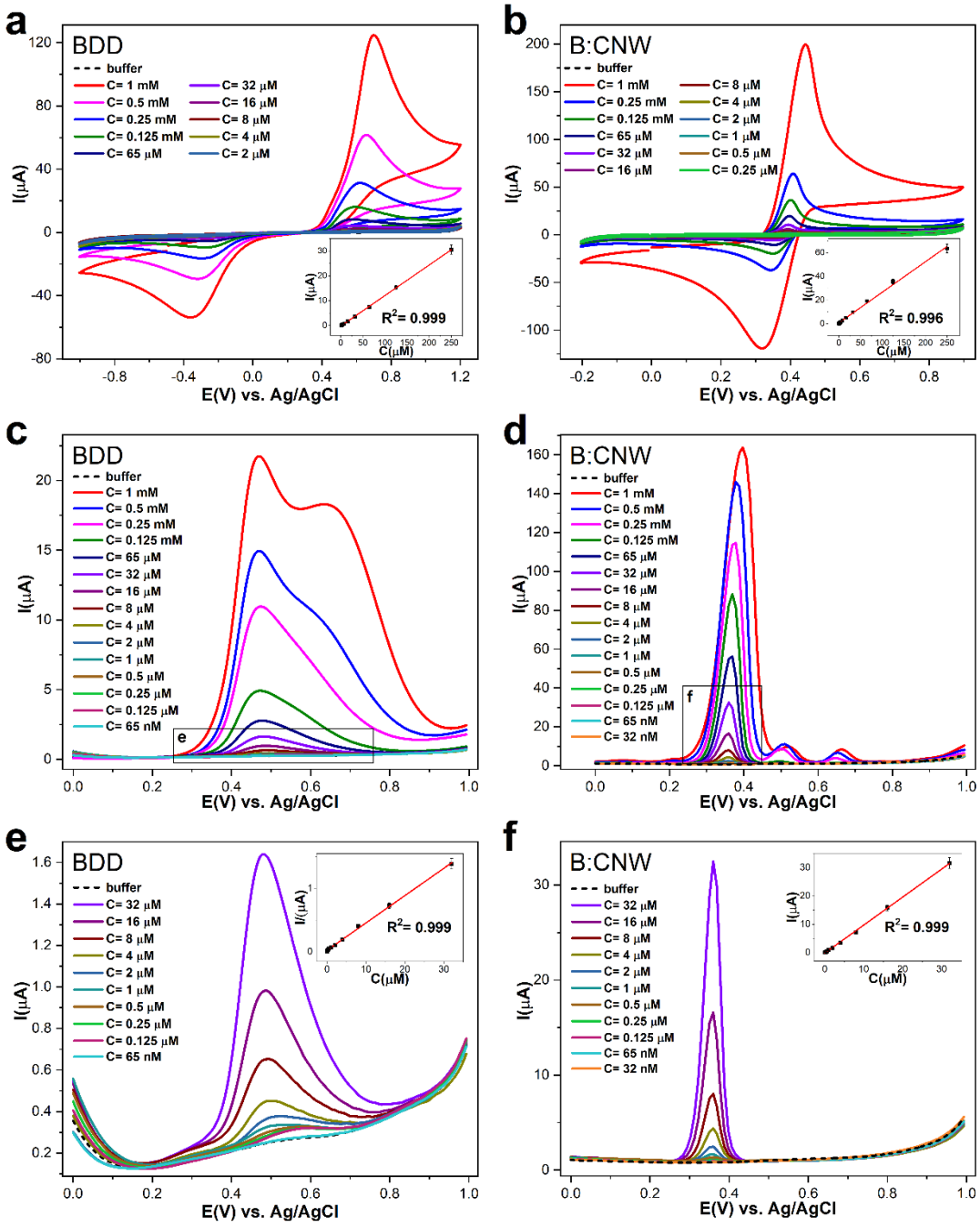

Fig. 1. Cyclic voltammograms of the various paracetamol concentrations (a) 1 mM to 2 µM at BDD electrode (b) 1 mM to 0.25 µM at B:CNW electrode, in 0.01 M (PBS), (pH = 7.0), scan rate: 100 mV/s. Insert: the plot of the peak current vs. concentration of paracetamol. Differential pulse voltammograms of the various paracetamol concentrations: (c) 1 mM to 65 nM, (e) 32 µM to 65 nM in 0.01 M (PBS), (pH = 7.0) at BDD electrode, scan rate: 100 mV/s. Insert: the

plot of the peak current vs. concentration of paracetamol. Differential pulse voltammograms of the various paracetamol concentrations of paracetamol: (d) 1 mM to 32 nM, (f) 32 μM to 65 nM in 0.01 M (PBS), (pH = 7.0) at B:CNW electrode, scan rate: 100 mV/s. Insert: the plot of the peak current vs. concentration of paracetamol.

3.1.2. Differential pulse voltammetry

The voltammetric determination of paracetamol was performed in 0.01 M (PBS), (pH = 7.0) using differential pulse voltammetry (DPV) at the boron-doped diamond and boron-doped carbon nanowall electrodes. Figures 1 c-f show the differential pulse voltammograms of paracetamol at the BDD and B:CNW electrodes in various concentrations. The oxidation peak current of paracetamol is observed at about +0.47 V on the boron-doped diamond electrode and about +0.38 V on the boron-doped carbon nanowall electrode. The anodic peak current of paracetamol is linear to its concentration and systematically increases with increasing concentration in the range 0.065 μM to 32 μM and 0.032 μM to 32 μM at BDD electrode and B:CNW electrode, respectively. The obtained equations of the linear regression plots can be expressed as: $I_{pA}[\mu A] = 0.043C[\mu M] + 0.02$ for BDD electrode and $I_{pA}[\mu A] = 0.988C[\mu M] - 0.14$ for B:CNW electrode, both with the correlation coefficient of $R^2 = 0.999$. The calculated limit of detection (LOD) was found to be 0.430 μM and 0.281 μM for the BDD electrode and B:CNW electrode, respectively (S/N = 3).

As can be seen, during electrochemical oxidation of paracetamol using differential pulse voltammetry additional peaks were observed for the high concentrations of paracetamol at 1 mM to 65 μM range. The by-products of the paracetamol electropolymerization occurring during these measurements cause the surface modifications of the investigated electrodes. The analysis using BDD electrode gives an additional peak at about +0.63 V which overlaps with the oxidation peak of paracetamol. In the case of B:CNW electrode, two sharp and well-defined

additional peaks were registered, first at about +0.5 V and the second one at +0.66 V. Additionally, these peaks do not interfere with each other. The obtained data indicate that paracetamol in the intermediate pH was oxidized to the N-acetyl-*p*-benzoquinone-imine (NAPQI) form which subsequently undergoes dimerization (Li and Chen, 2012). Table 1 shows the comparison between the results for the paracetamol determination using various electrodes at pH = 7.0. The obtained data reveals that both BDD and B:CNW electrodes show competitive analytical performance with very low detection limit comparing with other electrodes.

Table 1. Comparison of the electrodes performance in respect of the electrochemical paracetamol detection

Electrode	**Medium**	**Linear range (µM)**	**LOD (µM)**	**Potential (V)**	**Reference**
Nano-TiO_2/ poly(acid yellow 9)	pH = 7.0 (PBS)	12 - 120	2	0.39	(Kumar et al., 2008)
C-Ni/GCE	pH = 3.0 (B-R)	7.8 - 110	2.3	0.52	(Wang et al., 2007)
PEDOT/GCE	pH = 7.0 (PBS)	2.5 - 150	1.13	0.37	(Mehretie et al., 2011)
NiONPs-CB-DHP/GCE	pH = 3.0 (B-R)	3.0 - 47.8	0.48	1.13	(Batista Deroco et al., 2015)
MWNT/GCE	pH = 7.38 (PBS)	5 - 100	2.4	0.36	(Wan et al., 2009)

BDD	pH = 7.0 (PBS)	0.065 - 32	0.430	0.47	present study
B:CNW	pH = 7.0 (PBS)	0.032 - 32	0.281	0.38	present study

(MWNT) – multi-walled carbon nanotube, (PBS) – phosphate buffered saline, (B-R) – Britton-Robinson buffer solutions.

The comparison of the BDD and B:CNW electrodes electrochemical properties is described in the Supplemental Information.

3.2. Effect of pH

The oxidation mechanism of paracetamol was extensively investigated in the literature and two possible paths were described: two- or one-proton mechanism. (Kang et al., 2010), (Nematollahi et al., 2009;) (Rochefort and Wuest, 2009), (Tyszczuk-Rotko et al., 2014), (Ghadimi et al., 2013; Miner et al., 1981; ShangGuan et al., 2008), (Kachoosangi et al., 2008; Karikalan et al., 2016; Nematollahi et al., 2009). The detailed mechanism is discussed in the Supplemental Information.

In present study the effect of pH on the voltammetric response of paracetamol was studied in various pH solutions in the range of pH 3.0 – 12.0 with 1 mM paracetamol to select the optimum value for the detection.

The peak potential is shifted toward the negative value in both cases with an increase in the solution pH from 3.0 to 12.0, what indicates the involvement of protons in the paracetamol redox process (Fig. 2a, Fig. 2b) (Puttaiah and Yanjerappa, 2017).

Fig. 2a shows the effect of pH on the cyclic voltammograms of paracetamol on a boron-doped diamond electrode – the potential of peaks drops with increasing pH values of the

solution. The pH dependence of the electrochemical process shows the involvement of protons in the oxidation mechanism (Ullah et al., 2015).

The formal potential (E_0) varied linearly in correlation with the pH in 4.5 to 10.5 range. (Fig. 2c). The regression equation is E_0= -0.0341pH + 0.3508 (R^2 = 0.99037). Based on the equation $dE_0/dpH = 2.303mRT/nF$, where dE_0/dpH is the slope of E_0 vs pH curve, R is the gas constant (R = 8.3145 $Jmol^{-1}K^{-1}$), T is the temperature (298 K), F is the Faraday constant (F = 96.485 $Cmol^{-1}$), *m* is the number of protons, *n* is the number of electrons (Laviron, 1974), calculated *m/n* is 0.5. Thus, the electrochemical reaction of paracetamol using BDD in pH range 4.5-10.5 is demonstrated to be an one-proton and two-electron process, what is consistent with the proposed oxidation mechanism (Scheme S1) and in agreement with the literature (Fan et al., 2011; Kang et al., 2010; Khan Anish et al., 2015; Puttaiah and Yanjerappa, 2017).

Figure 2b shows the cyclic voltammograms of paracetamol for various pH values with B:CNW electrode, indicating that the anodic peak potential shifted to the negative side with increasing pH ranges. This phenomenon is caused by the participation of proton(s) in the oxidation reaction to N-acetyl-*p*-benzoquinone-imine (NAPQI).

Figure 2e shows a relationship between the formal potential (E_0) and solution pH in range 3-9 with the linear regression equation as: E_0= -0.06371 pH + 0.7504 (R^2 = 0.99933). Based on the equation $dE_0/dpH = 2.303mRT/nF$, where dE_0/dpH is the slope of E_0 vs pH curve, R is the gas constant (R = 8.3145 $Jmol^{-1}K^{-1}$), T is the temperature (298 K), F is the Faraday constant (F = 96.485 $Cmol^{-1}$), *m* is the number of protons, *n* is the number of electrons (Laviron, 1974), calculated *m/n* is 1.077. This result shows that the number of protons and electrons involved in the redox process is equal. We suppose that the oxidation of paracetamol involves $2e^-/2H^+$ transfer processes, as shown on the schemes appended in the Supplemental Information. Thus, the electrochemical reaction of paracetamol on B:CNW in pH range 3 – 9

is a two-proton and two-electron process, which is comparable with the proposed oxidation mechanisms (Schemes S2-4) and likely to be in agreement with the literature (Chitravathi and Munichandraiah, 2016; Filik et al., 2014; Jia et al., 2007; Kachoosangi et al., 2008; Mahmoud et al., 2017; N. Goyal and Singh, 2006; Nematollahi et al., 2009; Săndulescu et al., 2000; ShangGuan et al., 2008; Van Benschoten et al., 1983).

The peak current ratio (I_{pC}/I_{pA}) can be considered as a criterion for the hydrolysis reaction rate (Nematollahi et al., 2009). The redox peak current ratio (I_{pC}/I_{pA}) of the paracetamol was plotted as a function of electrolyte pH and shown in Fig. 2d. The (I_{pC}/I_{pA}) of the paracetamol was examined as an assessment of NAPQI instability and tautomeric intermediates (Scheme S1) in various pH values. It confirms the assumption that these compounds are most stable in the pH range 4 – 8. Intrinsic instability (pH = 9) may be caused by the dimerization transient reagents (Fischer et al., 1985).

These studies confirm that pH value 7.0 is the most suitable condition for the optimal paracetamol electrochemical behavior. The optimal voltammetric response was observed at pH 7.0, corresponding to physiological pH (Karikalan et al., 2016), and therefore this pH value was used throughout the analytical protocol in our study.

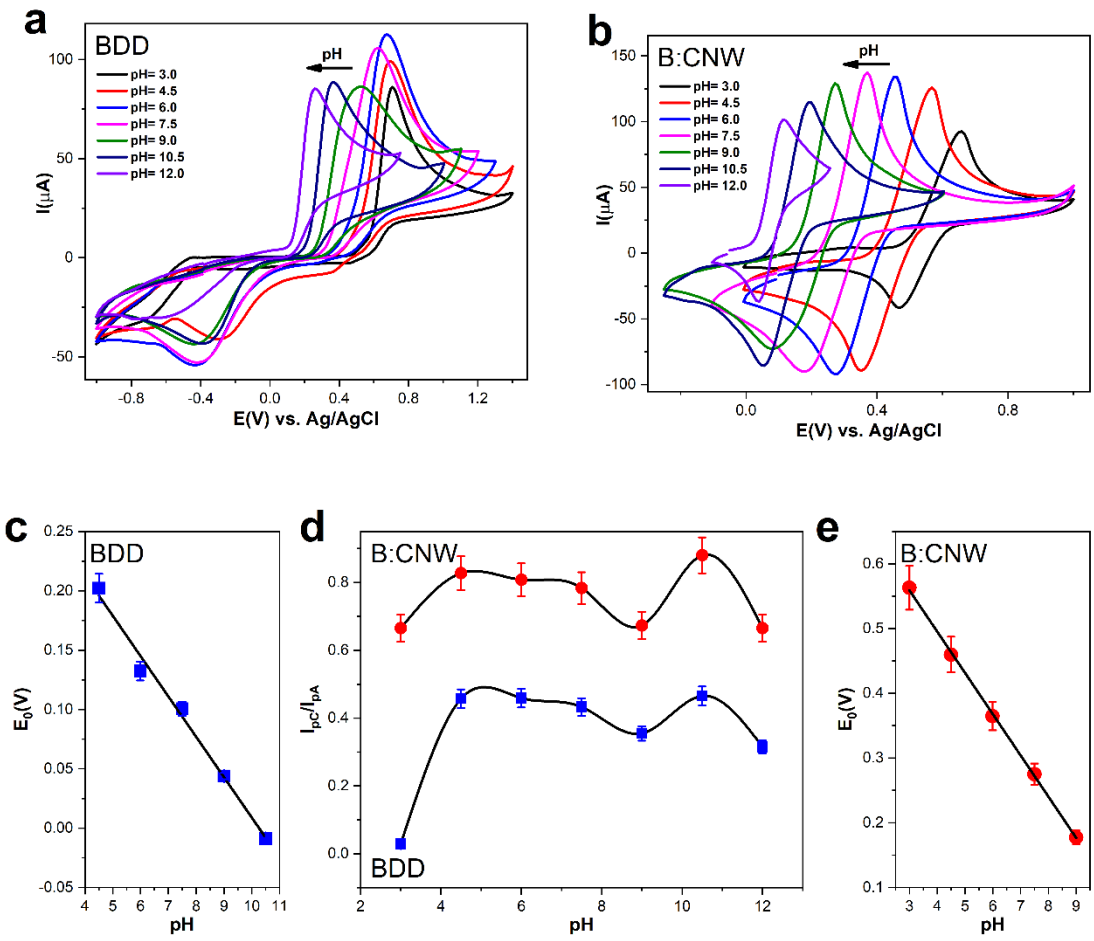

Fig. 2. Cyclic voltammograms of paracetamol (C = 1 mM) using (a) BDD, (b) B:CNW electrode in B-R buffer solution at various pH values (3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0), scan rate: 100 mV/s. (c, e) The plots of formal potential versus pH value. (d) Variation of peak current ratio (I_{pC}/I_{pA}) as a function of pH.

3.3. Effect of scan rate

The present study investigated the effect of scan rate on the electrochemical behavior of paracetamol using both tested electrodes. Figure 3 shows cyclic voltammograms recorded in a solution containing 2 mM of paracetamol in 0.01 M (PBS), (pH=7.0) in various scan rates from 50 to 500 mV/s. In the case of B:CNW, (Figure 3b) increase in the scan rate causes the linear increase of the anodic and cathodic peak currents with $\nu^{1/2}$. The anodic and cathodic peak

currents revealed a linear behavior with the square root of the scan rate depicted in Fig. 3b. Following linear regression equations were adopted for the anodic and cathodic peak currents: $I_{pA}[\mu A] = 0.589\ \nu^{1/2}(Vs^{-1}) + 0.08$ and $I_{pC}[\mu A] = -0.402\ \nu^{1/2}(Vs^{-1}) - 0.04$ giving the following correlation coefficient values: $R^2 = 0.9992$ and $R^2 = 0.9901$, respectively. This result indicates the diffusion-controlled mechanism of the process at the B:CNW electrode.

Another process occurs in the case of BDD electrode. The redox peak currents increase nonlinearly with $\nu^{1/2}$. Figure 3a shows that the anodic peak currents are higher than the cathodic. This phenomenon suggests that the oxidation of paracetamol on the surface of the BBD electrode occurs more efficient than its reduction or possibly by-products of the oxidation are adsorbed on the electrode. Following linear regression equations were adopted for the anodic and cathodic peak currents obtained at BDD electrode: $I_{pA}[mA] = 0.115\nu^{1/2}(Vs^{-1}) + 0.04$ and $I_{pC}[mA] = -0.049\nu^{1/2}(Vs^{-1}) - 0.01$ with the correlation coefficient value of $R^2 = 0.9933$ and $R^2 = 0.9812$, respectively.

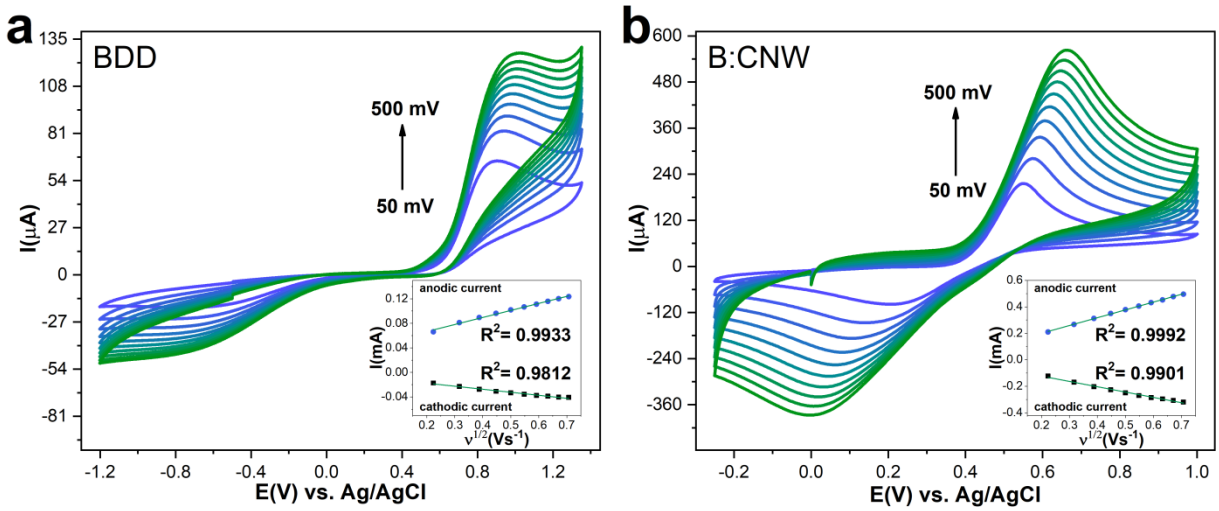

Fig. 3. Cyclic voltammograms of paracetamol (C = 2 mM) in 0.01 M (PBS), (pH = 7.0) on (a) BDD and (b) B:CNW electrodes at various scan rates: 50, 100, 150, 200, 250, 300, 350, 400, 450, 500 mV/s. Insert: the plot of the peak currents versus square root of scan rates.

3.6. Electrochemical determination of paracetamol in urine

According to the results obtained in the measurements of paracetamol at BDD and B:CNW electrodes, the B:CNW electrode was used for the practical application of the paracetamol measurement in the human urine sample using DPV technique (Fig. 4). The main advantage of the B:CNW electrode is its high sensitivity toward paracetamol and the elimination of tedious and expensive modification process. Urine model samples were based on the artificial urine (used without any pretreatment) spiked with the stock solution of paracetamol to obtain the appropriate concentration. 5.0 mL of this model urine sample solution were diluted in 0.01 M (PBS), (pH = 7.0) to 10.0 mL and used for the voltammetric measurement. The concentration of paracetamol in measured solution was increasing in the 65 nM to 1 μM range. The linear regression equation for the obtained peak currents was: I_{pA} [μA] = 0.527C[μM] + 0.06, with R^2 = 0.9908 correlation coefficient. The calculated limit of detection (LOD) was 0.075 μM, what is a highly satisfactory result compared with other electrodes (see, Table 1).

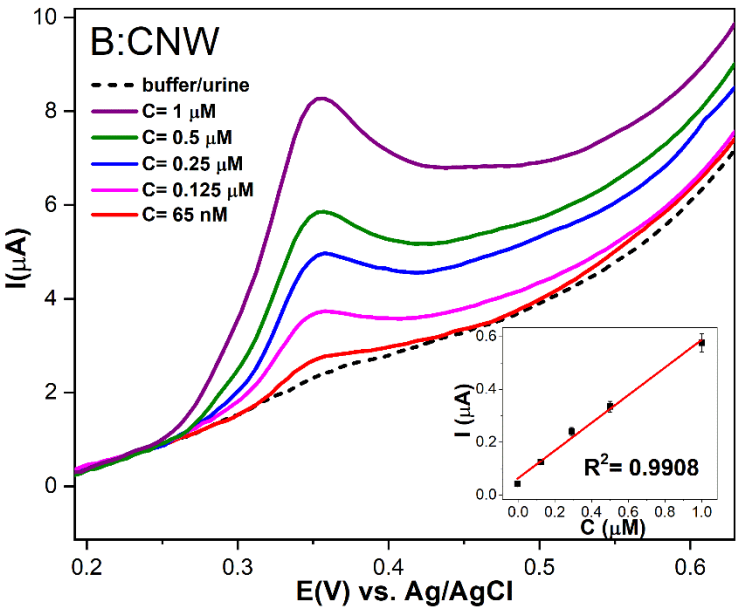

Fig. 4. Differential pulse voltammograms of various paracetamol concentration in urine in 1 μM to 65 nM range (0.01 M (PBS), pH = 7.0) using B:CNW electrode, scan rate: 100 mV/s. Insert: the plot of the peak current vs. concentration of paracetamol.

3. Conclusions

In summary, present study describes the electrochemical behavior of paracetamol using two different types of carbon electrodes: boron-doped diamond (BDD) and boron-doped carbon nanowalls (B:CNW). The electrochemical studies involving cyclic voltammetry and differential pulse voltammetry resulted with the following detection limits: 0.430 μM and 0.281 μM (S/N = 3) for DPV using the BDD electrode and the B:CNW electrode, respectively. Additionally, the study of paracetamol oxidation under various pH conditions and the analysis of the paracetamol electrochemical behavior were conducted for both electrodes using various scan rates. Moreover, the present analysis demonstrated the application of the B:CNW electrode for the paracetamol determination in urine samples with 0.075 μM limit of detection providing a proof-of-concept of its usefulness for the qualitative and quantitative characterization, even at physiologically relevant conditions. Our further scientific efforts will focus on the capabilities of the B:CNW electrode towards the detection of other analytes in samples of high biological significance.

Acknowledgments

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