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DETERMINATION OF NAPROXEN BY USING DIFFERENTIAL PULSE VOLTAMMETRY WITH POLY(ANILINE-2-SULFONIC ACID) MODIFIED BORON DOPED DIAMOND ELECTRODE

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In this study, an electrochemical sensor based on a boron doped diamond electrode (BDDE) was developed for the determination of naproxen (NAP) using a poly(aniline-2-sulfonic acid)/boron doped diamond electrode, *p*(A2SA/BDDE). Polymerization of A2SA was conducted in a water/acetonitrile (1:1) mixture containing 0.1 M sodium perchlorate ($NaClO_4$) on bare BDDE and the electrochemical properties studied by cyclic voltammetry in ferricyanide/KNO_3 solution. The prepared *p*(A2SA/BDDE) was used for detection of NAP. Effects of parameters such as monomer type and concentration, the number of cycles, and scan rate were investigated using differential pulse voltammetry (DPV) in phosphate buffer containing 0.75 mM NAP. The effect of electrolyte type and pH on DPV responses to NAP were also studied. The oxidative current peak stem from NAP concentration observed at 1.1 V potential. A linear calibration curve was obtained in the range of 0.05–1.00 mM NAP concentration. Correlation coefficient (R^2), detection limit, and quantification limit were calculated as 0.9944, 0.0328 mM, and 0.1093 mM, respectively. In conclusion, it may be claimed that the modified electrode constructed in this work can be used successfully as a naproxen-selective membrane due to its ease of preparation, high R^2 value, and good reproducibility.

Keywords: naproxen; aniline-2-sulfonic acid; boron doped diamond electrode

ОПРЕДЕЛУВАЊЕ НА НАПРОКСЕН СО ПРИМЕНА НА ДИФЕРЕНЦИЈАЛНА ПУЛСНА ВОЛТАМЕТРИЈА СО ДИЈАМАНТСКА ЕЛЕКТРОДА ШТО СОДРЖИ БОР, МОДИФИКУВАНА СО ПОЛИ(АНИЛИН-2-СУЛФОНСКА КИСЕЛИНА)

Во рамките на оваа студија е развиен електрохемиски сензор за определување напроксен со употреба на дијамантска електрода што содржи бор, модификувана со поли(анилин-2-сулфонска киселина). Полимеризацијата на поли(анилин-2-сулфонската киселина) беше спроведена врз дијамантската електрода што содржи бор во раствор од вода и ацетонитрил (1:1) што содржи и натриум перхлорат во концентрација од 0.1 mol/l, додека електрохемиските својства на модификуваната електрода беа испитувани со примена на калиум хексацијаноферат II во раствор на KNO_3. Вака модификуваната бор-дијамантска електрода беше употребена за определување на напроксен. Влијанието на параметрите како што се типот на мономерот и неговата концентрација, бројот на циклизации и брзината на промена на потенцијалот врз волтаметриските одговори на напроксен, беше испитувано со диференцијална пулсна волтаметрија во фосфатен пуфер со концентрација од 0,75 mm/l. Притоа волтаметриски пик добиен како резултат на оксидација на напроксен беше детектиран на потенцијали од околу +1,1 V. Линеарна зависност помеѓу интензитетот на струјата на волтаметриските пикови и концентрацијата на напроксен беше детектирана во концентрацискиот опсег помеѓу 0,05 mm/l и 1,00 mm/l. Коефицинетот на корелација (R^2), границата на детекција и границата на квантификација изнесуваа 0,9944 mm/l, 0,0328 mm/l и 0,1093 mm/l, соодветно. Од резултатите добиени во оваа студија може да се заклучи дека вака модификуваната дијамантска електрода што содржи бор може успешно да се употреби како селективна мембрана за напроксен поради едноставниот начин на подготовка, како и поради добрата репродуктивност на резултатите.

Клучни зборови: напроксен; анилин-2-сулфонска киселина; дијамантска електрода што содржи бор

1. INTRODUCTION

Naproxen (NAP; (*S*)-6-methoxy-a-methyl-2-naphthalene acetic acid) is an anti-inflammatory drug. It is a widely prescribed medicine to provide relief for rheumatoid arthritis, pain, acute gout, and other inflammatory rheumatic diseases.[1] Naproxen overdose causes changes to cognitive status, seizures, serious toxicity, and metabolic acidosis. Due to these possible side effects, determination of NAP concentration in drug formulations and body fluids is of critical importance for human health. Many methods, such as room temperature phosphorimometric,[2] UV-spectrophotometric,[3,4] spectrofluorimetric,[5,6] capillary isotachophoretic,[7] high-performance liquid chromatographic,[8–11] amperometric[12] and liquid chromatograpic-mass chromatographic / mass chromatographic[13] methods exist for the detection of NAP in drug formulations and body fluids. There are also electrochemical and optical NAP measurement methods.[14] Since the accurate and fast determination of low drug concentration in samples is always a challenge, research into new methods of NAP determination is needed. Some of these methods require large volumes of solvents, expensive instrumentation, and skilled operators. However, since the analysis with these methods takes a long time, electrochemical analysis methods that give results in a short time are more suitable.

Electrochemical detection methods have advantages over other NAP detection methods.[15,16] Electrochemical sensors prepared by modifying various electrodes to create selective regions specific to analytes are very useful for clinical, environmental, and biomechanical analysis.[17] Naproxen has been determined voltammetrically using various electrodes, including mercury,[18] platinum,[19,20] boron-doped diamond,[2,21] gold,[22] glassy carbon,[23] carbon nanofiber,[24] graphite,[25,26] multiwalled carbon nanotubes/glassy carbon[27,28] graphene oxide[29] and nanomaterial modified carbon paste[30–32] electrodes.

Poly(aniline-2-sulfonic acid) *p*(A2SA) is one of the most important conductive polymers due to its easy synthesis, high electrical conductivity, environmental stability and the ability to switch rapidly between insulating and conducting states thanks to reversible proton doping/dedoping.[33] Due to these advantages, fabrication and use of boron doped electrode surfaces modified with *p*(A2SA) for NAP determination was the aim of this work.

2. MATERIALS AND METHODS

2.1. *Apparatus and reagents*

All differential pulse voltammetry (DPV) and cyclic voltammetry (CV) analyses were performed with an Ivium Vertex One potentiostat. The potentiostat is controlled by Ivium Soft™ software, which is used for both data collection and data analysis and includes different electrochemical techniques. The bare and *p*(A2SA) modified BDDE were characterized by CV in ferricyanide/KNO_3 solution. Electroanalytical experiments were carried out in a BASi C3 Cell Stand electrochemical cell using a three-electrode system. For this purpose, a boron doped diamond electrode (BDDE; Biologic M-BDD-3-#977; Ø 3 mm) working electrode, Ag/AgCl (BASi®-MF 2052) reference electrode and platinum wire (BASi®-MW-1032) auxiliary electrode were used. Before each measurement in the voltammetric cell, nitrogen gas was passed through for about 5 min to remove oxygen from the solution inside the cell. Surface structure and morphology of the prepared *p*(A2SA)/BDDE were also determined by atomic force microscopy (AFM, XE-100E; Park Systems Corp.) in noncontact mode.

Aniline-2-sulfonic acid, 5-nitro-2-furaldehyde, 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, 3-aminophenylboronic acid monohydrate, and 4-vinylbenzeneboronic acid were obtained from Sigma-Aldrich Chemical Company, as were boric acid (H_3BO_3), citric acid ($C_6H_8O_7$), potassium chloride (KCl), potassium dihydrogen phosphate (KH_2PO_4), potassium ferricyanide ($K_3[Fe(CN)_6]$), sodium citrate ($Na_3C_6H_5O_7$), sodium monohydrogen phosphate dihydrate ($Na_2HPO_4{\cdot}2H_2O$), and phosphoric acid (H_3PO_4). Sodium acetate (CH_3COONa) and acetic acid (CH_3COOH) were supplied by Across Organics Company. Acetonitrile (AcN), sodium hydroxide, sodium perchlorate ($NaClO_4$), and nitric acid (HNO_3) were supplied by Merck (Darmstadt, Germany). Naproxen was obtained from Boston USA Chemistry.

2.2. *Construction of the modified sensor (p(A2SA)/BDDE)*

Firstly, monomer solutions were prepared of aniline-2-sulfonic acid (A2SA), 5-nitro-2-furaldehyde (5N2FA), 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (2A1BT3C), 3-aminophenylboronic acid monohydrate (3APBA) and 4-vinylbenzeneboronic acid (4VBBA) in water/AcN (1:1) containing 0.1 M $NaClO_4$. The

BDDE surface was modified with each of the above-mentioned monomers by electrochemical method and the NAP voltammetric responses of the electrodes obtained. The highest peak current for NAP was obtained with the *p*(A2SA) modified BDDE surface produced under conditions of 8 mM A2SA and a film thickness of four cycles at 100 mV/s scan rate.

2.3. *Electrochemical procedures*

Electrochemical analyses were carried out by using different voltammetric techniques, namely CV and DPV. CV was used to obtain information about the surface properties of the bare BDD electrode and *p*(A2SA)/BDDE. A potential range of –1.2 to 1.6 V, a scanning rate of 100 mV/s, and equilibrium time of 2 s were used for CV measurements. DPV analysis was performed after two seconds of equilibration time in the potential range –1.2 to 1.2 V, 10 mV pulse amplitude and 10 ms pulse time. The 0.75 mM NAP standard solution was prepared using phosphate buffer at pH 7.00. Then, NAP solutions were prepared from the standard solution and diluted with electrolyte solutions before electrochemical measurements.

The calibration curve was obtained by plotting the voltammetric oxidation peak current values of NAP on *p*(A2SA)/BDDE against increasing NAP concentrations. The detection limit (DL) and quantification limit (QL) were calculated according to "3 *s*/*m*" and "10 *s*/*m*" formulas, respectively,[34,35] where *s* is the standard deviation of the oxidation peak currents and *m* is the slope of the calibration curve. In order to test the applicability of the prepared *p*(A2SA)/BDDE, electroanalytical detection and recovery studies were carried out on synthetic urine samples.

3. RESULTS AND DISCUSSION

3.1. *The effect of monomer type, monomer concentration, film thickness, and scan rate on NAP response*

In order to examine the electrochemical behavior of NAP, it was first necessary to determine the monomer type to be used to produce the optimum film structure. This task was carried out by using different monomers. For this purpose, for the CV technique, A2SA, 5N2FA, 2A1BT3C, 3APBA, and 4VBBA were electropolymerized on BDDE. Each monomer solution required for electropolymerization was conducted in a water/AcN (1:1) mixture containing 0.1 M sodium perchlorate ($NaClO_4$) at a scan rate of 100 mV/s. The prepared electrodes carrying different monomers were used for determination of 0.75 mM NAP by DPV. According to the results, obtained *p*(A2SA)/BDDE was chosen as the optimum electrode for NAP detection (Fig. 1).

To determine the effect of monomer concentration on electrode response, the monomer solutions were prepared with different concentration of A2SA (2, 4, 6, 8, 10, and 12 mM). Electrochemical polymerizations were carried out by CV in the potential range –1.2 to 1.6 V on bare BDDE at a scan rate of 100 mV/s. The effect of different A2SA concentrations on NAP oxidation peak height was investigated. The optimum monomer concentration of A2SA was selected as 8 mM (Fig. 2).

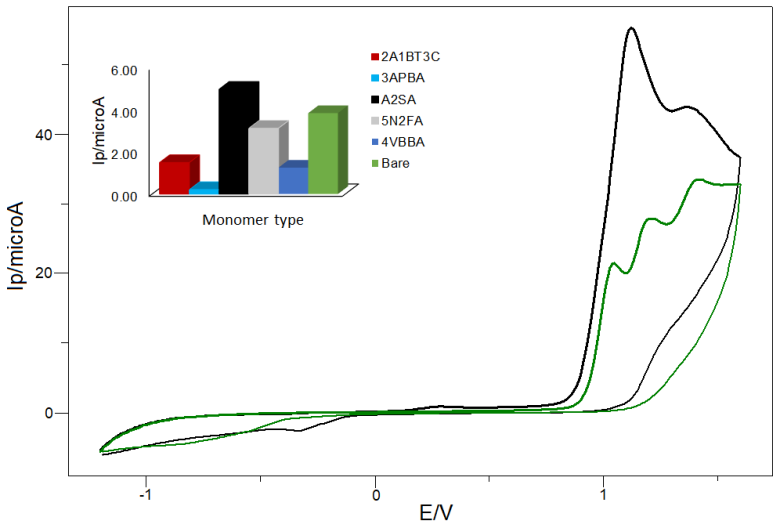

Fig. 1. The voltammograms obtained in the determination of 0.75 mM NAP by CV. The other monomers (inset): the effect on NAP response of bare electrode and electrodes coated with A2SA, 5N2FA, 2A1BT3C, 3APBA, 4VBBA

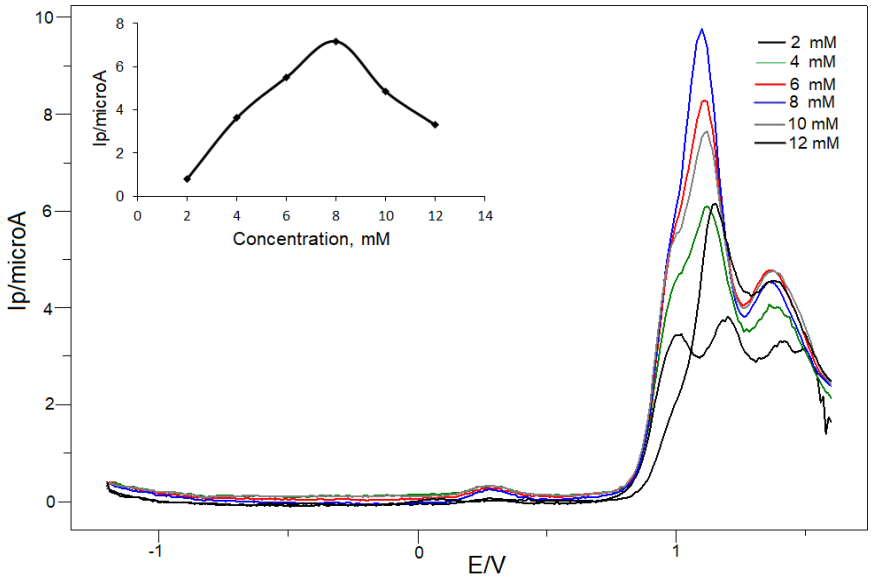

Fig. 2. The effect of monomer (A2SA) concentration on response to 0.75 mM NAP DPV.
Conditions: scan rate, 100 mV/s; solution medium, 0.1 M PB pH 7.00; potential step, 10 mV; pulse amplitude, 10 mV.

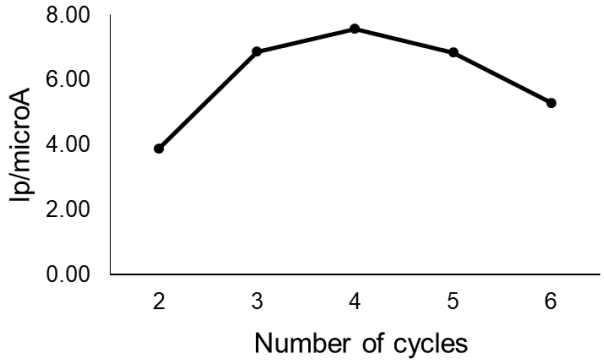

Fig. 3. Effect of the polymer film thickness on response of the modifed electrodes to 0.75 mM NAP DPV. Conditions: scan rate, 100 mV/s; solution medium, 0.1 M PB pH 7.00; potential step, 10 mV; pulse amplitude, 10 mV.

In this study, the optimum polymer film thickness was determined by studying cycle number by CV during electropolymerization. As shown in Figure 3, up to four cycles the response increased, after which thicker films form on the electrode surface, resulting in reduced 0.75 mM NAP responses. For this reason, the film thickness was chosen as four cycles.

The scan-rate effect during electropolymerization was investigated in the range of 50–150 mV/s. It is clearly seen from Figure 4 show that the highest 0.75 mM NAP oxidation peak current was obtained at a polymerization scan rate of 100 mV/s.

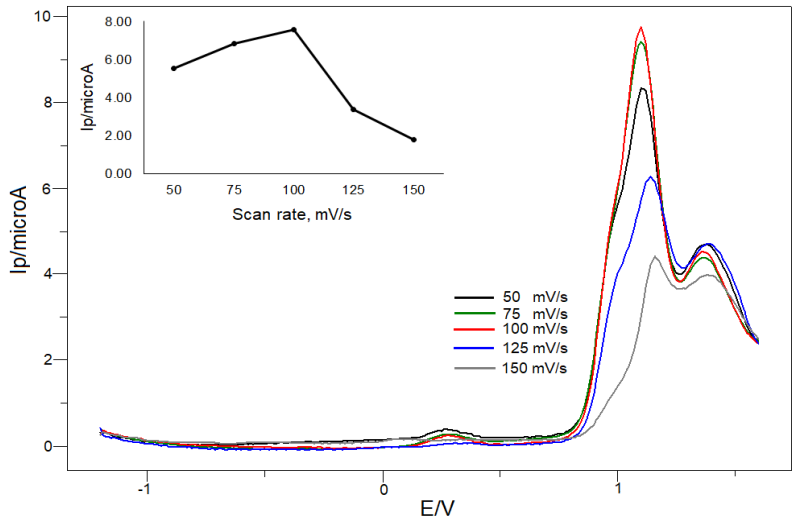

Fig. 4. The effect of scan rate on DPV peak current in the presence of 0.75 mM NAP.
Conditions: solution medium, 0.1 M PB pH 7.00; potential step, 10 mV; and pulse amplitude, 10 mV.

3.2. *Electrocatalytic activity*

CV was used to investigate the effect of the *p*(A2SA)/BDDE modification using Ivium software. The CV responses to 6 mM $K_3[Fe(CN)_6]$ of bare BDDE and *p*(A2SA)/BDDE in 0.1 M KNO_3 are shown in Figure 5.

CV results showed that the electron transfer ability of the modified electrode was slightly decreased, as indicated by the increased anodic–cathodic peak separation. This phenomenon is seen most times with modified electrodes. The degree of sluggishness of electron transfer depends on the type of modification agent, its concentration, and modification method used and hence on the resulting thickness and morphology of the films formed on the bare electrode surfaces. However, it can be said that the electrocatalytic activity of the prepared *p*(A2SA)BDDE was satisfactory for NAP determination.

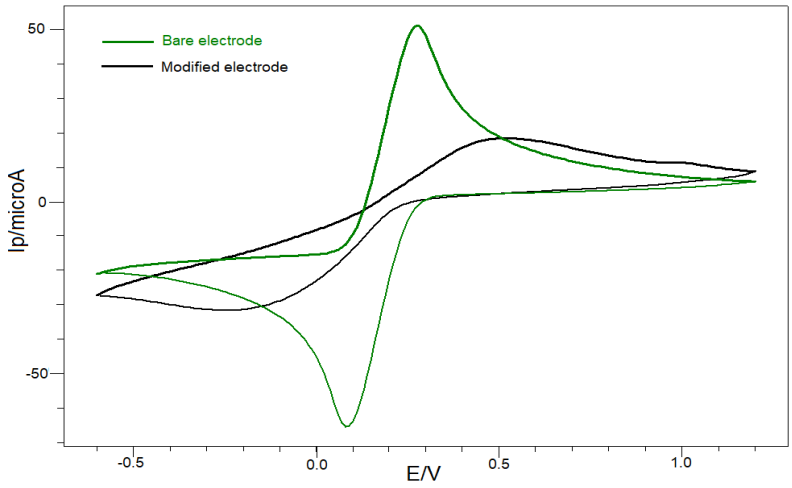

Fig. 5. Cyclic voltammograms of 6 mM $K_3[Fe(CN)_6]$ in 1 M KNO_3 of bare BDDE and A2SA modifed BDDE at a scan rate of 100 mV/s

3.3. *Effect of electrolyte type, pH, and scan rate on NAP peak current*

After selecting the monomer type, the best electrolyte solution for the analyte and its pH value were investigated. To determine the effect of electrolyte type on the NAP oxidation peak, acetate buffer (AcB), Britton–Robinson buffer (BRB), phosphate buffer (PB), citrate buffer (CB) and phosphate-citrate buffer (PCB) were examined. The effects of electrolyte on the oxidation peak current of NAP are shown in Figure 6, according to which the maximum and hence optimum peak current for NAP was obtained with 0.1 M PB.

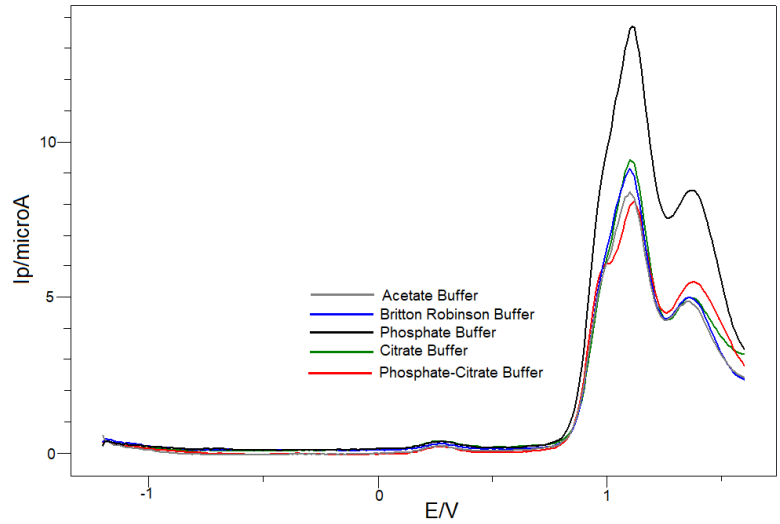

Fig. 6. The effect of electrolyte type on the 0.75 mM NAP DPV oxidation peak current for the *p*(A2SA)/BDDE

The effect of pH of the PB, which was determined as the best electrolyte, on the NAP response of the *p*(A2SA)/BDDE was investigated by DPV with PB solutions of pH 5.00, 6.00, 7.00, 8.00, and 9.00. The DPV results obtained for NAP for the modified electrode surface at different pH values are given in Figure 7. In accordance with which, the maximum and hence optimum peak currents for NAP were obtained in 0.1 M PB at pH 8.00.

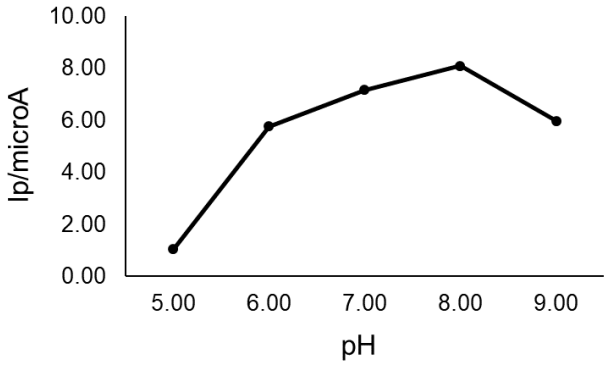

Fig. 7. The effect of the PB pH on the DPV response of *p*(A2SA)/BDDE in 0.75 mM NAP

The effect of scan rate on NAP oxidation peak current was investigated by DPV in the range of 50–175 mV/s. It can clearly be seen in Figure 8 that the peak current increased up to a scan rate of 125 mV/s and then decreased.

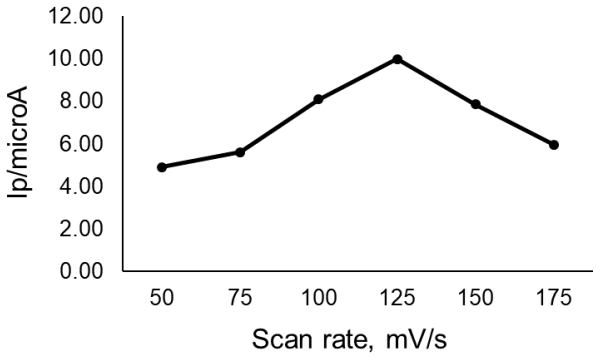

Fig. 8. The effect of scan rate on the peak current of 0.75 mM NAP in 0.1 M PB at pH 8.00. DPV responses of prepared modified electrodes with different scan rate of 50–175 mV/s. Film thickness, four cycles; potential step, 10 mV; pulse amplitude, 10 mV.

3.4. *Analytical parameters of p(A2SA)/BDDE*

Using the optimum polymerization and analysis parameters, the DPV response of *p*(A2SA)/BDDE to increasing NAP concentrations of 0.05–1.00 mM is shown in Figure 9. The peak currents increased linearly in parallel with the increase in NAP concentration. From the obtained DPV responses, the electrochemical performance of *p*(A2SA)/BDDE and its sensitivity to NAP were determined (Figs. 2–4). The calibration curve from the current readings is given in Figure 9 (inset). With the help of this calibration curve, DL and QL values of the modified electrode were calculated using the formulas "3 *s*/*m*" and "10 *s*/*m*", where *s* is the standard deviation and *m* is the slope of the calibration curve. The DL value was determined as 0.0328 mM and the QL value as 0.1093 mM.

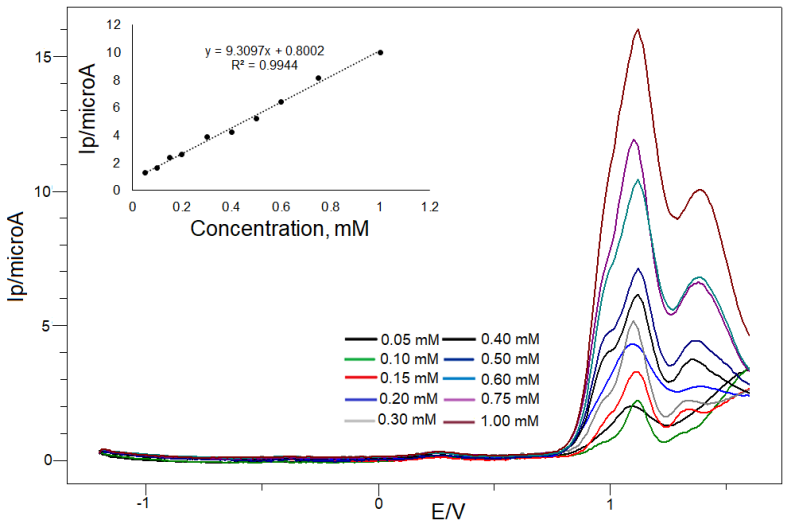

Fig. 9. DPV responses of *p*(A2SA)/BDDE to 0.05, 0.10, 0.15, 0.20, 0.30, 0.40, 0.50, 0.60, 0.75, and 1.00 mM NAP and calibration curve (inset). Solution medium, 0.1 M PB pH 8.00; potential step, 10 mV; pulse amplitude, 10 mV; scan rate, 125 mV/s; film thickness, four cycles.

3.5. *Reproducibility results of p(A2SA)/BDDE*

The reproducibility of the prepared *p*(A2SA)/BDDE was investigated by DPV measurements in 0.1 M PB at pH 8.00 containing 0.50 mM NAP. Voltammograms of the reproducibility of *p*(A2SA) modified BDDE are given in Figure 10. The reproducibility of the voltammetric responses of the prepared sensor was carried out by preparing 10 separate electrodes, and the developed method showed high stability. The oxidation peak currents and error bars of NAP from the voltammograms obtained by reading each electrode three times sequentially are given in Figure 10 (inset). Using this chart, the standard deviation for *p*(A2SA)/BDDE was calculated as 0.10 and the % relative standard deviation (%RSD) as 2.71; hence the precision of the sensor developed for NAP determination was proven.

The BDDE modified for NAP measurement described in this study was sensitive, repeatable, and gave results with much higher sensitivity than bare BDDE. The reason for the sensitivity of these measurements is due to the *p*(A2SA) surface produced by electropolymerization of the modified electrode surface. For this reason, AFM measurements were made to examine the morphology and surface structure of *p*(A2SA) on the electrode surface, the results of which are given in Figure 11. According to the AFM images, it can be seen that the electrode surface was quite fractal and the surface roughness increased with modification. According to the surface roughness measurement results given in Figure 11, the roughness on the surface is around 30 nm and appears to be variable. This variability allows the surface area of the electrode to increase and the measurement sensitivity to increase.

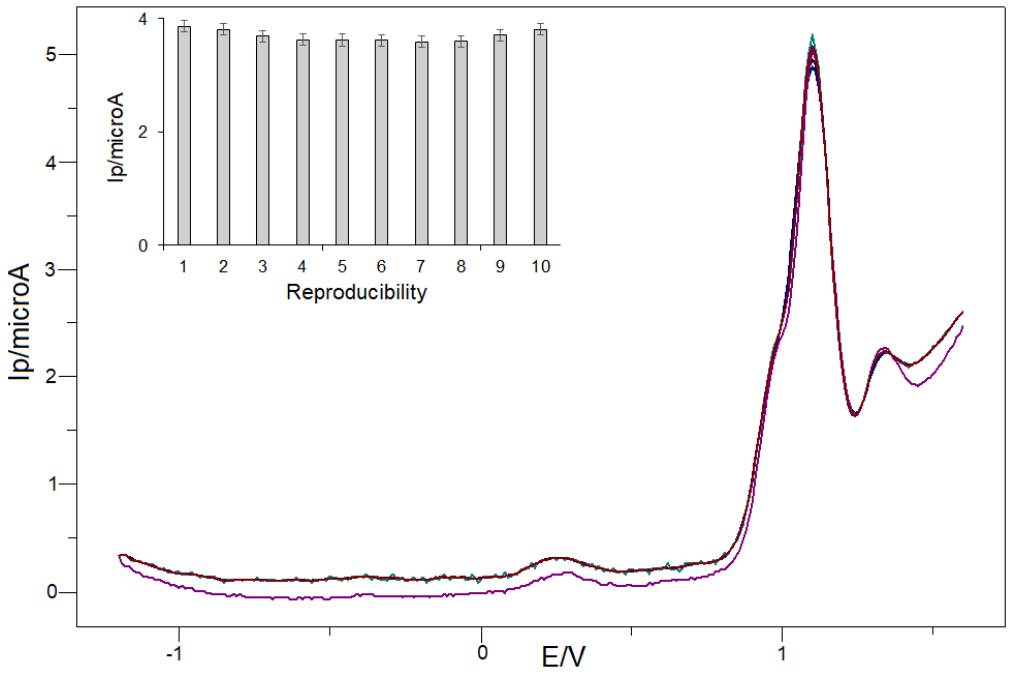

Fig. 10. The reproducibility in pH 8.00 PB for 0.50 mM NAP. Inset: bar graph of *p*(A2SA)/BDDE (n = 10). Potential step, 10 mV; pulse amplitude, 10 mV; scan rate, 125 mV/s; film thickness, four cycles.

3.6. *Synthetic urine sample analysis*

In order to test the applicability of the produced *p*(A2SA)/BDDE on real samples, synthetic urine was used. Three consecutive concentrations of NAP were added to the synthetic urine to determine the NAP with the *p*(A2SA)modified BDDE. The recovery results obtained are given in Table 1. As can be seen, detection of NAP content, in the range 99.15 to 100.18 % of the added value, indicated good agreement, confirming the suitability of the proposed method for the determination of NAP.

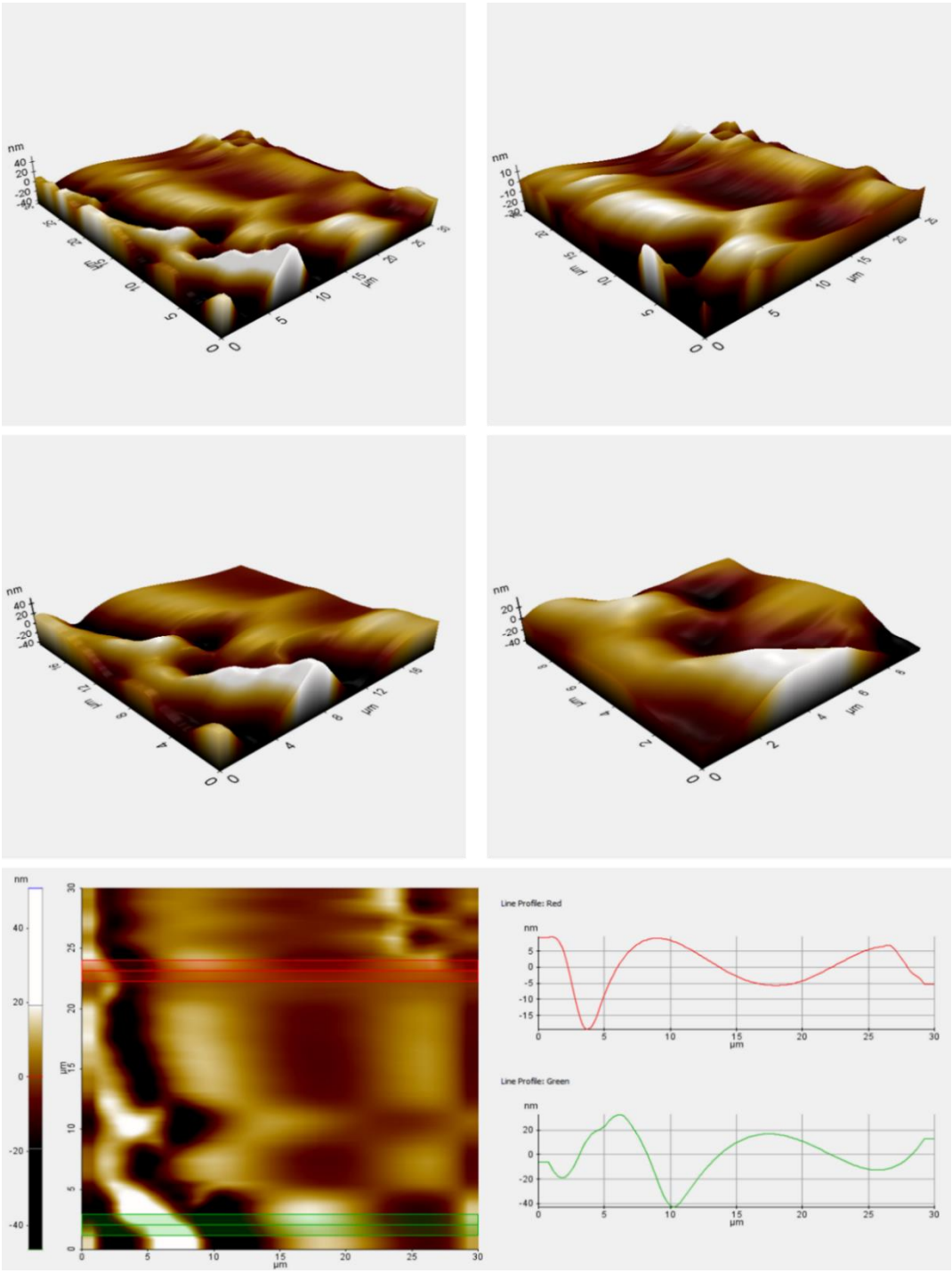

Fig. 11. AFM images of prepared *p*(A2SA)/BDDE at different magnifications and the surface roughness measurements of this electrode

T a b l e 1

Analysis by DPV of synthetic urine with standard NAP solution added

Sample	Standard added (mmol/l)	Total found (mmol/l)	RSD (%)	R (%)
Synthetic urine	0.050	0.0495 ± 0.011	0.874	99.15
Synthetic urine	0.100	0.1001 ± 0.010	0.615	100.18
Synthetic urine	0.150	0.1497 ± 0.013	0.556	99.83

4. CONCLUSIONS

For the preparation of a NAP-selective electrode, the modification of BDDE with *p*(A2SA) was successfully made by electropolymerization. Electroanalytical responses of prepared *p*(A2SA)/BDDE to NAP were investigated in 0.1 M PB (pH 8.00) solution by CV and DPV. The NAP detection performance of the *p*(A2SA)/BDDE was also confirmed by CV and DPV. Low DL and QL values were obtained for the prepared modified electrode in the determination of NAP. The developed method was applied with 99.15–100.18 % recovery of NAP. The application of *p*(A2SA)/BDDE has proven to show excellent reproducibility and stability. Further, the study with synthetic urine confirmed the successful application of the method. Thus, it has been proved that NAP in real samples can easily be detected with the novel *p*(A2SA)/BDDE developed, and prepared *p*(A2SA)/BDDE has the potential for use in biomedical and clinical applications.

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