

Carbon-Based Electrochemical Detection of Pharmaceuticals from Water

M. Ardelean, F. Manea, A. Pop, J. Schoonman

Abstract—The presence of pharmaceuticals in the environment and especially in water has gained increasing attention. They are included in emerging class of pollutants, and for most of them, legal limits have not been set-up due to their impact on human health and ecosystem was not determined and/or there is not the advanced analytical method for their quantification. In this context, the development of various advanced analytical methods for the quantification of pharmaceuticals in water is required. The electrochemical methods are known to exhibit the great potential for high-performance analytical methods but their performance is in direct relation to the electrode material and the operating techniques. In this study, two types of carbon-based electrodes materials, i.e., boron-doped diamond (BDD) and carbon nanofiber (CNF)-epoxy composite electrodes have been investigated through voltammetric techniques for the detection of naproxen in water. The comparative electrochemical behavior of naproxen (NPX) on both BDD and CNF electrodes was studied by cyclic voltammetry, and the well-defined peak corresponding to NPX oxidation was found for each electrode. NPX oxidation occurred on BDD electrode at the potential value of about +1.4 V/SCE (saturated calomel electrode) and at about +1.2 V/SCE for CNF electrode. The sensitivities for NPX detection were similar for both carbon-based electrode and thus, CNF electrode exhibited superiority in relation to the detection potential. Differential-pulsed voltammetry (DPV) and square-wave voltammetry (SWV) techniques were exploited to improve the electroanalytical performance for the NPX detection, and the best results related to the sensitivity of $9.959 \mu\text{A} \cdot \mu\text{M}^{-1}$ were achieved using DPV. In addition, the simultaneous detection of NPX and fluoxetine -a very common antidepressive drug, also present in water, was studied using CNF electrode and very good results were obtained. The detection potential values that allowed a good separation of the detection signals together with the good sensitivities were appropriate for the simultaneous detection of both tested pharmaceuticals. These results reclaim CNF electrode as a valuable tool for the individual/simultaneous detection of pharmaceuticals in water.

Keywords—Boron-doped diamond electrode, carbon nanofiber-epoxy composite electrode, emerging pollutants, pharmaceuticals.

I. INTRODUCTION

NPX, (2S)-2-(6-methylnaphthalen-2-yl)propanoic acid is a non-steroidal anti-inflammatory drug from the phenylpropanoic acid class, used in the treatment of osteoarthritis, rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis, acute gout and primary dysmenorrhea

M. Ardelean is with the National Institute for Aerospace Research "Elie Carafoli" INCAS - Bucharest, Romania (e-mail: Magdalena.ardelean@gmail.com).

F. Manea and A. Pop are with the Politehnica University of Timisoara, Romania (e-mail: florica.manea@upt.ro, anela.pop@upt.ro).

J. Schoonman is with Delft University of Technology, The Netherlands (e-mail: J. Schoonman@tudelft.nl).

[1]-[4]. Due to the annual consumption of NPX, its traces with the concentration ranging between 31 ng/L and 12.5 $\mu\text{g/L}$ were found in rivers, drinking waters, influent and effluent sewage treatment plants in several states, e.g., Canada, Sweden, Belgium, Germany, Slovenia, USA, China, Japan, South Korea [5]-[8]. Among other pharmaceuticals, NPX belongs to emerging pollutants class [9] that presents the characteristics of lack of the environmental long-term effects of continuous low-level exposure to NPX, as well as other drugs. This compound was detected in sewage, river and stream waters at concentration levels of the ng/L to $\mu\text{g/L}$. In general, the detection of the emerging pollutants is particularly challenging because of the low detection limits required [10]. Nevertheless, powerful and selective analytical methods, able to detect trace levels of pharmaceuticals, were developed based on chromatographic methods, e.g., gas chromatography (GC) [11], high performance liquid chromatography (HPLC) [7], [12], coupled with mass spectroscopy (MS) or tandem mass spectroscopy (MS/MS) [13], [14].

Nowadays, the electroanalysis is a very promising method for the detection of various pharmaceuticals at low concentrations and the key for the good performance is given by the electrode materials and the electrochemical technique. Several carbon-based electrode materials have been reported for NPX detection using batch injection amperometry (BIA), pulsed amperometric detection (PAD), cyclic voltammetry (CV), DPV, SWV [3], [4], [15]-[17].

In this work, CNF-epoxy composite electrode was tested in comparison with BDD electrode for NPX detection. Even if there is the report about NPX detection on BDD electrode [17], BDD was tested also in our study for comparison using a different supporting electrolyte that is more suitable for the detection of the potential pollutants in water (0.1 M Na_2SO_4 solution). CNF electrode exhibited good detection performance for sulfide and pentachlorophenol [18], [19], constituting a premise for this study. Also, the potential of CNF electrode to detect simultaneously NPX and fluoxetine (FXT) was investigated. FXT, a very common antidepressant was detected individually by our group on BDD electrode [20].

II. MATERIAL AND METHODS

NPX with the structural formula presented in Fig. 1 was provided by AC Helcor SRL, Romania. A stock solution of 1 mM was prepared by using 0.1 M NaOH solution (Merck, Germany). FXT was provided by Lilly (Pantheon, France). The stock solution was prepared using ethanol (PAM Corporation, Romania) and 0.1 M NaOH solution in a volume

ratio of 1:1 to obtain 0.1 mM FXT solution [20]. The supporting electrolyte was 0.1 M Na_2SO_4 solution, prepared using Na_2SO_4 of analytical purity (Merck, Germany) with distilled water.

The electrochemical detection measurements were performed using an Autolab potentiostat-galvanostat PGSTAT 302 (Eco Chemie, The Netherlands) using the GPES 4.9 software and a three-electrode cell. The electrodes consisted of CNF-epoxy composite electrode as working electrode, a platinum foil as counter electrode and the SCE, reference electrode. For comparison, commercial BDD was used as working electrode. The BDD electrode supplied by Windsor Scientific Ltd. for electroanalytical use was a mirror polished doped polycrystalline industrial diamond (microcrystalline; doping degree about 0.1% boron). All measurements were performed in 0.1 M Na_2SO_4 supporting electrolyte at room temperature without further temperature control.

Details about the preparation of CNF electrode have been already published [18], [19]. Before the electrochemical applications, the working electrodes were cleaned mechanically by polishing on $0.2 \mu\text{m}$ Al_2O_3 powder, washed in water and then, in ethanol. CV, DPV and SWV were employed for the electrochemical detection.

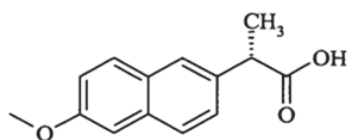


Fig. 1 Structural formula of NPX

III. RESULTS AND DISCUSSION

A. Individual Detection of NPX

CV was used for both electrochemical characterization of the electrode in the presence of NPX and also, for the detection applications. Figs. 2 (a) and 3 (a) show the CVs recorded at various concentrations of NPX in 0.1 M Na_2SO_4 supporting electrolyte at BDD and respective, at CNF electrode. On BDD electrode, a similar oxidation potential value was found as it was reported by Suryanarayanan et al. (1.425 V/SCE vs. 1.44 V/Ag/AgCl) [17]. In 0.1 M Na_2SO_4 supporting electrolyte, the oxidation process started at about +0.95 V/SCE, and a well-defined oxidation peak was noticed at about +1.425 V/SCE. The lack of cathodic peak suggests an irreversible process. A good linearity anodic current vs. NPX concentration was obtained with a sensitivity of $5.364 \mu\text{A}/\mu\text{M}$ (Fig. 2 (b)) that is higher in comparison with the reported one ($0.4049 \mu\text{A}/\mu\text{M}$) [17]. It should be mentioned that the supporting electrolyte is different vs. supporting electrolyte reported in the literature, taking into account the final application in water source.

On CNF electrode, the oxidation process started at +0.4 V/SCE and the current slightly increased until +0.9 V/SCE and after which, a more pronounced width peak was noticed. The current peak was recorded at the potential value of 1.2 V/SCE. Since the stock solution was prepared by using

sodium hydroxide, the influence of the hydroxide was studied and no relevant peaks were noticed. Also, the lack of the cathodic peak was noticed suggesting the irreversibility of the oxidation process. A good linearity anodic current vs. NPX concentration was observed, and for an oxidation potential of +1.20 V/SCE, a sensitivity of $4.028 \mu\text{A}/\mu\text{M}$ was achieved (Fig. 3 (b)).

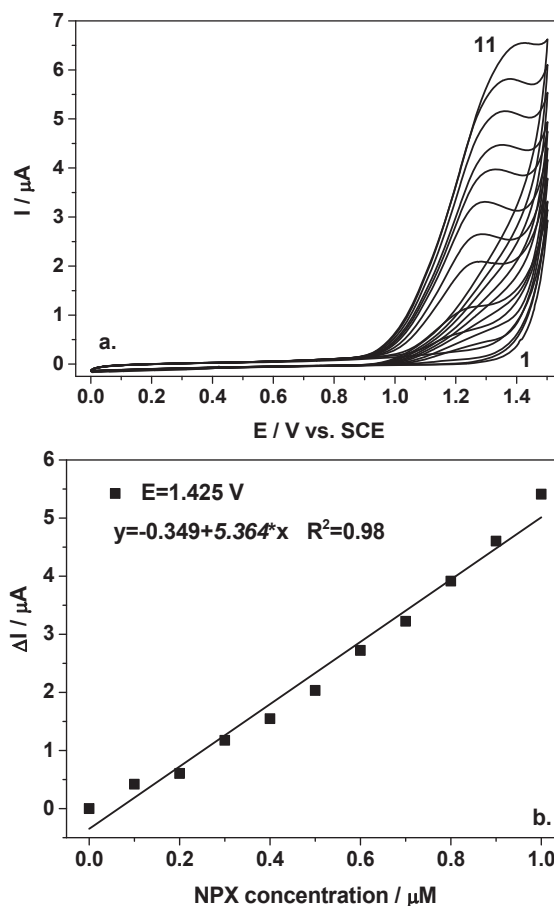


Fig. 2 (a) Cyclic voltammograms recorded on BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte (curve 1) in the presence of $50 \mu\text{L}$ 0.1 M NaOH (curve 2) and $0.1\text{-}1 \mu\text{M}$ NPX (curves 3-12), at a potential scan rate: 0.05 Vs^{-1} in a potential range: 0 to +1.5 V/SCE; (b) Calibration plot of the current vs. NPX concentration of the CVs recorded at $E_1 = +1.425 \text{ V/SCE}$

In comparison with BDD electrode, the sensitivity reached for CNF electrode is similar but the detection potential value is lower that is desired for the detection application. The lower potential value informs about an electrocatalytic effect of the CNF electrode towards NPX oxidation and as consequence, its detection.

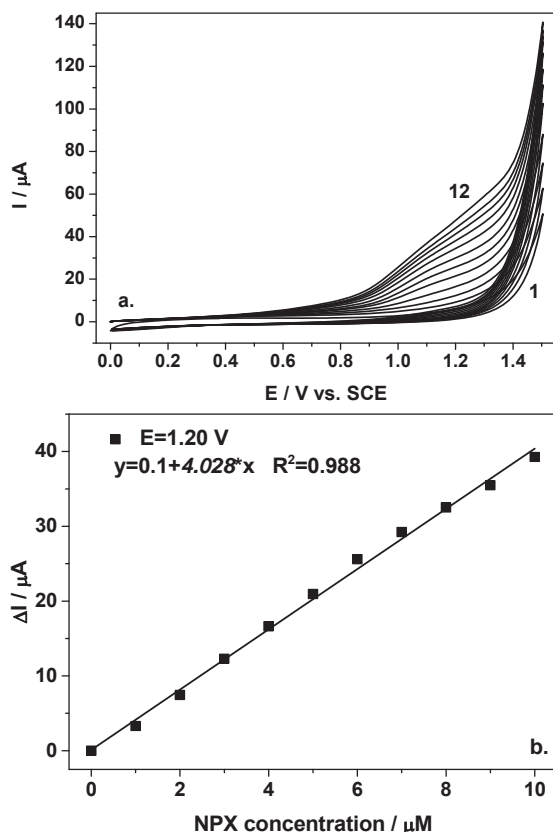


Fig. 3 (a) Cyclic voltammograms recorded on CNF electrode in 0.1 M Na₂SO₄ supporting electrolyte (curve 1) in the presence of 50 μ L 0.1 M NaOH (curve 2) and 1-10 μ M NPX (curves 3-12), at a potential scan rate: 0.05 V/s in a potential range: 0 to +1.5 V/SCE; (b) Calibration plot of the current vs. NPX concentration of the CVs recorded at E= +1.21V/SCE

For an improvement in relation with the sensitivity and oxidation potential, differential pulse voltammetry technique was employed. It is well-known that the pulsed voltammetry techniques are able to improve the electroanalytical parameters through the diminution of the background current and increasing the Faradaic response. The optimal parameters for this DPV were determined from the study of variation of voltammogram peculiarities regarding the shape, the detection potential and the accuracy with the modulation amplitude, the step potential and the scan rate. Under the optimized conditions of modulation amplitude of 0.2 V, step potential of 0.05 V and scan rate of 0.025 V/s, a good linearity and a better sensitivity were obtained. In Fig. 4 (a) are presented the voltammograms obtained under these conditions for NPX detection on BDD electrode. In this case, the oxidation process started at about +0.45 V/SCE and a well-defined peak was noticed at +0.95 V/SCE. In comparison with CV, the oxidation potential shifted to more negative values for DPV (+0.95 V/SCE vs. +1.21 V/SCE) and an improved sensitivity was reached (9.959 μ A/ μ M vs. 4.028 μ A/ μ M) (Fig. 4 (b)).

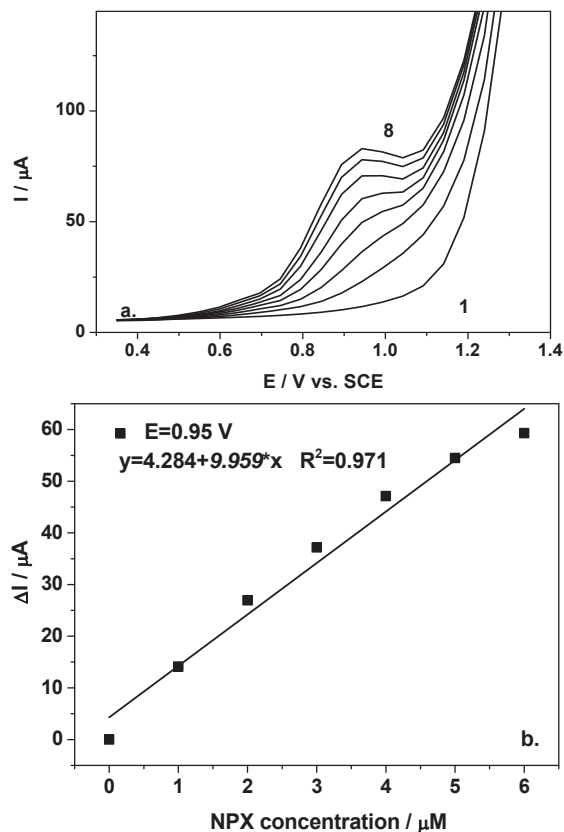


Fig. 4 (a) Differential-pulsed voltammograms recorded on CNF electrode under optimized conditions: Modulation amplitude of 0.2 V, step potential of 0.05 V and potential scan rate of 0.025 V/s⁻¹ between 0.35 and +1.35 V/ SCE in 0.1 M Na₂SO₄ supporting electrolyte (curve 1) in the presence of 50 μ L 0.1 M NaOH (curve 2) and 1-6 μ M NPX (curves 3-8); (b) Calibration plot of the current vs. NPX concentration recorded at E= +0.95 V/SCE

Also, the SWV was employed for a better improvement of the detection characteristics. Under the optimum conditions of modulation amplitude of 0.05 V, a step potential of 0.005 V and a frequency of 10 Hz, the sensitivity of 4.366 μ A/ μ M was reached (Figs. 5 (a), (b)). These optimum conditions were found in relation with a stable response. No stable responses were found under other operating working conditions.

It is obvious that no improvement was reached for SWV technique in relation to DPV that was the best of the tested techniques.

TABLE I
ELECTROANALYTICAL PARAMETERS OBTAINED ON CNF ELECTRODE FOR NPX DETECTION

Tech.	E _{ox} / V	Sens. (μ A/ μ M)	R ²	RSD* (%)	LOD** (μ M)	LOQ*** (μ M)
CV	1.21	4.028	0.988	5.2	0.133	0.444
DPV	0.95	9.959	0.971	4.24	0.146	0.450
SWV	1.1	4.366	0.997	19.01	0.124	0.415

*-for three replicates

**-the lowest limit of detection determined in according with the literature [17]

***-the lowest limit of quantification determined in according with the literature [17]

In Table I are gathered all the electroanalytical parameters obtained for NPX detection in aqueous media on CNF

electrode using CV, DPV and SWV.

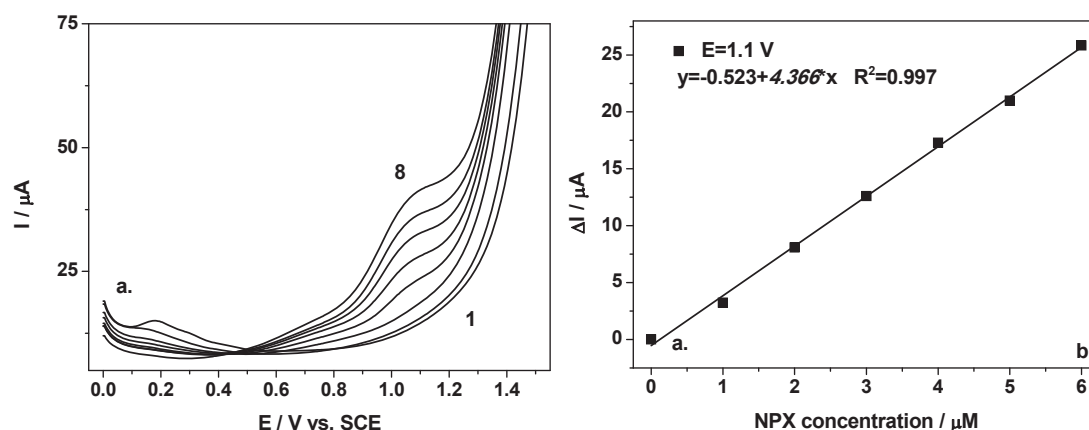


Fig. 5 (a) Square-wave voltammograms recorded on CNF electrode under optimized conditions: Modulation amplitude of 0.05 V, step potential of 0.005 V and a frequency of 10 Hz between 0 and +1.45 V/SCE in 0.1 M Na₂SO₄ supporting electrolyte (curve 1) in the presence of 50 μ L 0.1 M NaOH (curve 2) and 1-6 μ M NPX (curves 3-8); (b) Calibration plot of the current vs. NPX concentration recorded at E = +1.1 V/SCE

TABLE II
ELECTROANALYTICAL PERFORMANCE OF THE ELECTRODE MATERIALS IN NPX DETECTION

Electrode	Electrochemical method	Supporting electrolyte	E _{ox} (V)	Sensitivity (μ A/ μ M)	LOD	Linear range	Ref.
GCE	BIA, PAD	0.05M PBS, pH=7	0.95	0.036	0.3 μ M	10-100 μ M	[11]
DyNW/CPE	CV, SWV	0.05M PBS, pH=7	0.88	0.387	0.5 μ M	1-500nM	[3]
ZnO/MWCNT/CPE	CV, SWV	0.1M PBS, pH=7	0.9	0.356	0.23 μ M	1-200 μ M	[12]
BDD	CV, DPV	0.1M LiClO ₄ +acetonitrile	1.41	0.4049	0.03 μ M	0.5- 50mM	[13]
Pt	LSV, DPV	0.1M LiClO ₄ +acetonitrile	1.44	0.114	1 μ M	1-25 μ M	[4]
CNF	DPV	0.1M Na ₂ SO ₄	0.95	9.959	0.146	1-10 μ M	This work

A comparison with the performance of the other electrodes for NPX detection is given in Table II. It can be noticed that CNF exhibited the best sensitivity and also, the lowest limit of detection is good, which gives a great potential for practical applications for NPX detection. In order to validate this method using CNF electrode, the recovery studies were carried out by spiking the water with known amount of NPX (10 μ g·L⁻¹). The analysis of NPX in water exhibited a mean recovery of 99.5% and relative standard deviation of 2.8% indicating adequate precision and accuracy of this electrode. The reproducibility was tested by analyzing the five independent concentrations of NPX containing 1 μ M in five different days, the peak variation was only about 1.5% after the last day, which informed about a good reproducibility.

B. Simultaneous Detection of NPX and FXT

The simultaneous detection of NPX and FXT was studied under similar conditions as the individual detection having the operational detection parameters of each pharmaceutical compound as reference points. The cyclic voltammograms recorded on CNF electrode in the potential ranged from 0 to +1.5 V/SCE are presented in Figs. 6 (a) and (b). The working procedure for detection consisted in two steps: First, the NPX was added into the solution until a concentration of 15 μ M NPX, and then FXT was added until a concentration of 15 μ M FXT was reached. As it can be noticed from Fig. 6 (a), well-

defined and good separated peaks were obtained for both analytes. The results regarding the sensitivities are shown in Table III.

TABLE III
ELECTROANALYTICAL PARAMETERS OF INDIVIDUAL/SIMULTANEOUS DETECTION OF NPX AND FXT ON CNF ELECTRODE

Type	Analyte	E / V vs. SCE	Sens. (μ A/ μ M)	Conc. Range (μ M)
Indiv.	FXT	0.98	3.686	0-10
	NPX	1.21	4.028	0-10
Sim.	FXT	0.785	1.439	0-15
	NPX	1.36	4.732	0-15

The differences between the values of FXT sensitivities could be explained by a possible fouling effect due to its previous applications for NPX detection without any cleaning step between the measurements. A detailed investigation will be further proposed for the simultaneous detection of NPX and FXT to avoid the interference of each other.

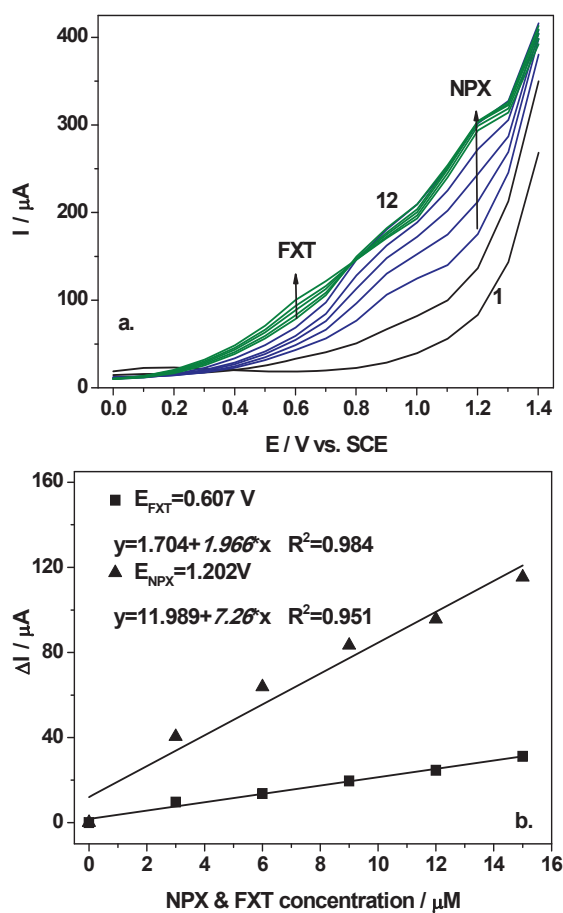


Fig. 6 (a) Cyclic voltammograms recorded on CNF electrode in 0.1 M Na₂SO₄ supporting electrolyte (curve 1) in the presence of 50 μL 0.1 M NaOH (curve 2) and 3-15 μM NPX (curves 3-7), and 3-15 μM FXT (curves 8-12) at a potential scan rate of 0.05 Vs⁻¹ in a potential range: 0 to +1.5 V/SCE; (b) Calibration plot of the current vs. NPX, respectively FXT concentration recorded at $E_{NPX} = +1.36$ V/SCE and $E_{FXT} = +0.785$ V/SCE

IV. CONCLUSION

NPX, a potential emerging pollutant in water can be detected on CNF-epoxy composite electrode. In comparison with BDD electrode, CNF exhibited better performance in relation with detection potential due to a higher electrocatalytic activity towards NPX oxidation. The best performance in relation with the sensitivity was obtained by employing DPV under optimized conditions: modulation amplitude of 0.2 V, step potential of 0.05 V and a scan rate of 0.025 V. No better results regarding the detection performance were reached by SWV because a few operating conditions allowed reaching stable response. The accuracy, the validation results and the reproducibility determined for NPX detection on CNF electrode gave a great potential for this electrode to be useful for low traces of NPX in water to monitor the water quality. Also, a great potential of CNF electrode for simultaneous detection of NPX and FXT was found, which makes it a valuable tool for practical application in detection

of pharmaceuticals from water.

ACKNOWLEDGMENT

Funding for this study was provided by the Romanian National Research Programs PN-II-TE-123/2015 and WATUSER PN-II-PCCA-60/2012.

REFERENCES

- [1] National Center for Biotechnology Information. PubChem Compound Database; CID=156391, (accessed Sept. 9, 2016) <https://pubchem.ncbi.nlm.nih.gov/compound/156391>
- [2] DrugBank: Showing Naproxen (DB00788)." *DrugBank: Home*. N.p., n.d. Web. 9 Sept. 2016 DrugBank website, <http://www.drugbank.ca/drugs/DB00788>
- [3] P. Norouzi, F. Dousty, M. R. Ganjali, R. Daneshgar, "Dysprosium nanowire modified carbon paste electrode for the simultaneous detection of naproxen and paracetamol: applications in pharmaceutical formulations and biological fluids", *Int. J. Electrochem. Sci.*, vol. 4, pp. 1371-1386, Nov. 2009.
- [4] N. Adhoum, L. Monser, M. Toumi, K. Boujlel, "Determination of naproxen in pharmaceuticals by differential pulse voltammetry at a platinum electrode", *Anal. Chim. Acta*, vol. 495, pp. 69-75, Oct. 2003.
- [5] S. Zorita, L. Martensson, L. Mathiasson, "Occurrence and removal of pharmaceuticals in a municipal sewage treatment system in the south of Sweden", *Sci. Total. Environ.*, vol. 407, pp. 2760-2770, Apr. 2009.
- [6] L. H. Santos, A. N. Araujo, A. Fachini, A. Pena, C. Deleure-Matos, M.C.B.S.M. Montenegro, "Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment", *J. Hazard. Materials*, vol.175, pp. 45-95, Mar. 2010.
- [7] C. D. Metcalfe, X. S. Miao, B. G. Koenig, J. Struger, "Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada", *Environ. Toxicol. Chem.*, vol. 22, no. 12, pp. 2881-2889, Dec. 2003.
- [8] K. Fent, A. A. Weston, D. Caminada, "Ecotoxicology of human pharmaceuticals", *Aquat. Toxicol.*, vol. 76, pp. 122-129, Feb. 2006.
- [9] B. Petrie, R. Barden, B. Kasprzyk-Hordern, "A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring", *Water Res.*, vol. 72, pp. 3-27, Apr. 2015.
- [10] D. D. Snow, S.L., Bartelt-Hunt, D. L. Brawn, J. Sangster, D. A. Cassada, "Detection, occurrence and fate of pharmaceuticals and steroid hormones in agricultural environments", *Water Environ. Res.*, vol. 82, no. 10, pp. 869-882, Jan. 2010.
- [11] G.R. Boyd, H. Reemtsma, D.A. Grimm, S. Mitra, "Pharmaceuticals and personal care products (PPCPs) in the surface and treated waters of Louisiana, USA and Ontario, Canada", *Sci. Total Environ.*, vol. 311, pp.135-149, Jul. 2003.
- [12] K.P. Singh, P. Rai, A.K. Singh, P. Verma, S. Gupta, "Occurrence of pharmaceuticals in urban wastewater of north Indian cities and risk assessment", *Environ. Monit. Assess.* vol. 186, pp. 6663-6682, Oct. 2014.
- [13] R.H. Lindberd, M. Ostman, U. Olofsson, R. Grabic, J. Fick, "Occurrence and behaviour of 105 pharmaceutical ingredients in sewage waters of municipal sewer collection data", *Water Res.*, vol. 58, pp. 221-229, Jul. 2014
- [14] Y. Vystavna, F. Huneau, V. Grynenko, Y. Vergels, H. Celle-Jeanot, "Pharmaceuticals in rivers of two regions with contrasted socio-economic conditions: occurrence, accumulation and comparison for Ukraine and France", *Wat. Air Soil Poll.*, vol. 223, pp. 2111-2124, Jun. 2012.
- [15] J. S. Stefano, A. P de Lima, R. H. O. Montes, E. M. Richter, R. A. A. Muñoz, "Fast determination of naproxen in pharmaceutical formulations by batch injection analysis with pulsed amperometric detection", *J. Braz. Chem. Soc.*, vol. 23, no. 10, pp. 1834-1838, Oct. 2012.
- [16] J. Tashkhourian, B. Hemmateenejad, H. Beigizadeh, M. Hoseini-Sarvari, Z. Razmi, "ZnO nanoparticles and multiwalled carbon nanotubes modified carbon paste electrode for determination of naproxen using electrochemical techniques", *J. Electroanal. Chem.*, vol. 714-715, pp. 103-108, Feb. 2014.
- [17] V. Suryanarayanan, Y. Zhang, S. Yolshihara, T. Shirakashi, "Voltammetric assay of naproxen in pharmaceutical formulations using

- boron doped diamond electrode”, *Electroanal.*, vol. 17, no. 11, pp. 925-932, Jun. 2005.
- [18] M. Ardelean, F. Manea, N. Vaszilcsin, R. Pode, “Electrochemical determination of sulphide in water/seawater using nanostructured carbon-epoxy composite electrode”, *Anal. Methods*, vol.6, pp. 4775-4782, Jul. 2014.
- [19] A. Baciú, F. Manea, A. remes, S. Motoc, G. Burtica, R. Pode, “Anodic determination of pentachlorophenol from water using carbon nanofiber-based composite electrode”, *EEMJ*, vol. 9, pp. 1555-1562, Nov. 2010.
- [20] M. Ardelean, F. Manea, R. Pode, “Electrochemical detection of fluoxetine on a boron-doped diamond electrode”, *Int. J. Pharm. Pharm. Sci.*, vol. 5, pp.318-322, 2013.