Selective detection of morphine in the presence of paracetamol with anodically pretreated dual layer Ti/tetrahedral amorphous carbon electrodes

Niklas Wester[a,*], Jarkko Etula[a], Tuomas Lilius[b,c,d], Sami Sainio[a], Tomi Laurila[e], Jari Koskinen[a]

[a] Department of Chemistry and Materials Science, School of Chemical Technology, Aalto University, Kemistintie 1, Espoo 02150, Finland
[b] Department of Pharmacology, Faculty of Medicine, University of Helsinki, Finland
[c] Department of Clinical Pharmacology, Faculty of Medicine, University of Helsinki, Finland
[d] HUSLAB, Helsinki University Hospital, Finland
[e] Department of Electrical Engineering and Automation, School of Electrical Engineering, Aalto University, PO Box 13500, 00076 Aalto, Finland

ARTICLE INFO

ABSTRACT

We investigated the effect of anodic treatment of titanium/tetrahedral amorphous carbon electrodes on the electrochemical detection of morphine and paracetamol. The anodic treatment caused both oxidation of the carbon and, more importantly, exposure and oxidation of the underlying Ti layer. This treatment anodically shifted the oxidation potential of paracetamol while that of morphine remained unaffected. The resulting electrode also showed better selectivity than a ta-C electrode without Ti. After anodic treatment at 2.5 V, selective detection of morphine with a physiologically meaningful detection limit of 9.8 nM and a linear range of 0.1–10 μM was obtained in the presence of 100 μM paracetamol.

1. Introduction

Morphine (MO, IUPAC name: (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol) is a strong opioid used for the treatment of moderate to severe pain. Its use is, however, associated with adverse effects including sedation, nausea, constipation, respiratory depression, and development of tolerance as well as dependence [1]. Morphine is also the active metabolite of the prodrug codeine, a weak opioid used to treat mild and moderate pain. Paracetamol or acetaminophen (IUPAC name: N-(4-hydroxyphenyl)acetamide) is one of the most widely used non-prescription medicines in the world [2]. It is a weak non-opioid analgesic and an antipyretic that is relatively safe when used at recommended doses [1]. Co-administration of paracetamol with morphine has been reported to decrease the need for morphine in patient-controlled analgesia (PCA) after major surgery [3]. Therefore, paracetamol (PA) is combined with codeine as a compound analgesic and co-administered with morphine in many countries. Consequently, a selective electrochemical sensor for direct determination of morphine without time-consuming separation is highly desirable.

Paracetamol and morphine are electroactive compounds that can be oxidized electrochemically [4,5]. However, they typically show overlapping oxidation peaks [4–7]. The peak plasma concentration following a therapeutic oral dose (1 g) of paracetamol ranges from 130 to 200 μM [2]. In contrast, plasma morphine concentrations usually range between only 7 and 100 nM [8–10]. However, higher concentrations of up to 1 μM have been reported for patients with advanced cancer [11]. The overlapping oxidation peaks and considerable differences in therapeutic concentrations make selective detection of morphine in the presence of paracetamol challenging. To our knowledge, only one report of the simultaneous voltammetric determination of morphine in the presence of paracetamol has been published [6]. That study, however, used a relatively complicated CdO nanoparticle ionic liquid modified carbon paste electrode.

Tetrahedral amorphous carbon (ta-C) is resistant to wear, corrosion and biofouling [12]. It is also patternable and can be deposited at room temperature. Ultrathin ta-C films have been shown to support facile electron transfer with $Ru(NH_3)_6^{2+/3+}$ and $Fe(CN)_6^{4-/3-}$ [13,14]. It has also been used recently for electrochemical detection of dopamine [15] as well as other catechols [16]. Previous studies have shown that the amount and type of oxygen-containing functional groups as well as the C−C bonding on the surface of carbon electrodes affect both the electron transfer kinetics and their sensitivity toward biomolecules [14,17–19]. Various mechanical, chemical and physicochemical pretreatments have been used to functionalize the surface of carbon materials [20–22]. Electrochemical pretreatments have been widely used to improve the electrochemical properties of carbon electrodes and
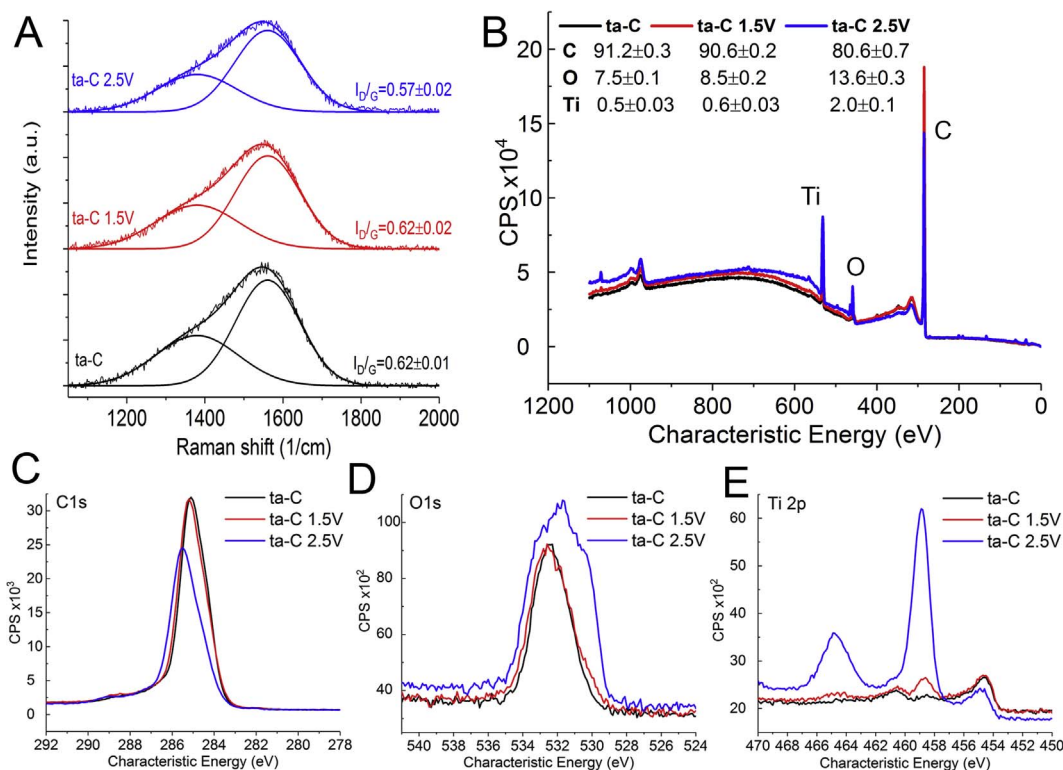
Fig. 1. (A) Raman and (B) XPS survey spectra of ta-C, ta-C 1.5 V and ta-C 2.5 V. High resolution XPS spectra of (C) C 1s, (D) O 1s and (E) Ti 2p for ta-C, ta-C 1.5 V and ta-C 2.5 V.

introduce oxygen-containing functional groups on the surface [20]. For example, anodic pretreatments of glassy carbon electrodes have been found to increase their sensitivity toward morphine [7] and decrease the sensitivity and oxidation kinetics of boron-doped diamond (BDD) electrodes toward paracetamol [23,24].

Little has been reported on the effect of electrochemical pretreatment of ta-C thin films and the implications for the electrochemical measurement of paracetamol and morphine. Here we report for the first time the effect of anodic pretreatment on the electrochemical performance of ultrathin Ti/ta-C electrodes. We studied the effect of the anodic treatment on the surface chemistry and electrochemistry of paracetamol and morphine. We also successfully demonstrate selective detection of morphine in the presence of paracetamol.

2. Experimental section

2.1. Reagents

Hexaammineruthenium(III) chloride and paracetamol were purchased from Sigma Aldrich. Morphine hydrochloride powder was obtained from the University Pharmacy, Helsinki, Finland. 1 and 5 mM solutions of hexaammineruthenium(III) chloride were prepared by dissolving in 1 M KCl (Merck Suprapur). 1 mM stock solutions of paracetamol and morphine in pH 7.4 phosphate-buffered saline (PBS) were prepared for injection into the cell. All aqueous solutions were prepared with water from a Millipore system ($> 18\ M\Omega\ cm$).

2.2. Electrode preparation

Ti and ta-C films were deposited on p-type (100) Si wafers ($< 0.005\ \Omega\ cm$). A 20 nm Ti underlayer was deposited by direct current magnetron sputtering. A 7 nm ta-C surface layer was deposited using a pulsed filtered cathodic vacuum arc (p-FCVA). The deposition process is described in detail in [13]. Sample wafers were diced with an automated dicing saw into 5×5 mm electrodes. The electrodes were

placed on copper-clad FR4-PCB strips and covered with PTFE film (Saint-Gobain Performance Plastics, CHR 255-2) with pre-made 3 mm holes.

2.3. Instruments

Raman spectroscopy was carried out using LabRAM HR confocal Raman (Jobin Yvon Horiba) with an argon laser ($\lambda = 488$ nm, power 10 mW) and BX41 (Olympus) microscope with a $100 \times$ objective. X-ray photoelectron spectroscopy (XPS) was performed using an Axis Ultra electron spectrometer (Kratos Analytical, Manchester, UK) with monochromatic Al Kα irradiation at 100 W under neutralization. Before analysis, pre-evacuation was carried out overnight. High-resolution spectra of C 1s, O 1s, and Ti 2p were recorded in addition to survey spectra of 3–4 locations for each sample. The data were fitted with CasaXPS software, assuming Gaussian line shapes. 100% filter paper (Whatman) was used as an in-situ reference for charge correction [25].

Electrochemical measurements were carried out with CH Instruments CHI630E and Gamry Reference 600 potentiostats. A three-electrode cell with an Ag/AgCl reference ($+ 0.199$ V vs RHE, Radiometer Analytical) and Pt counter was used for all measurements and anodic treatments. Before electrochemical measurements and anodic treatments, the cell was purged with N$_2$ for 15 min. During the measurements the cell was kept at N$_2$ overpressure. Prior to measurement and characterization, the electrodes were subjected to anodic treatment at 1.5 V (sample named ta-C 1.5 V) and 2.5 V (sample named ta-C 2.5 V) for 300 s in PBS of pH 7.4. For Raman and XPS analysis, separate electrodes were treated without Teflon film by partial immersion in PBS. These electrodes were rinsed in deionized water and cleaved for Raman and XPS spectroscopy. For EIS measurements, a 15 mV AC signal in the range 10 mHz to 100 kHz was used. The formal potential (around $- 0.165$ V vs Ag/AgCl) determined by cyclic voltammetry (CV) was used as the DC potential. The EIS data was fitted with a Randles circuit and the apparent heterogeneous rate constant (k^0) was calculated as in ref [13].
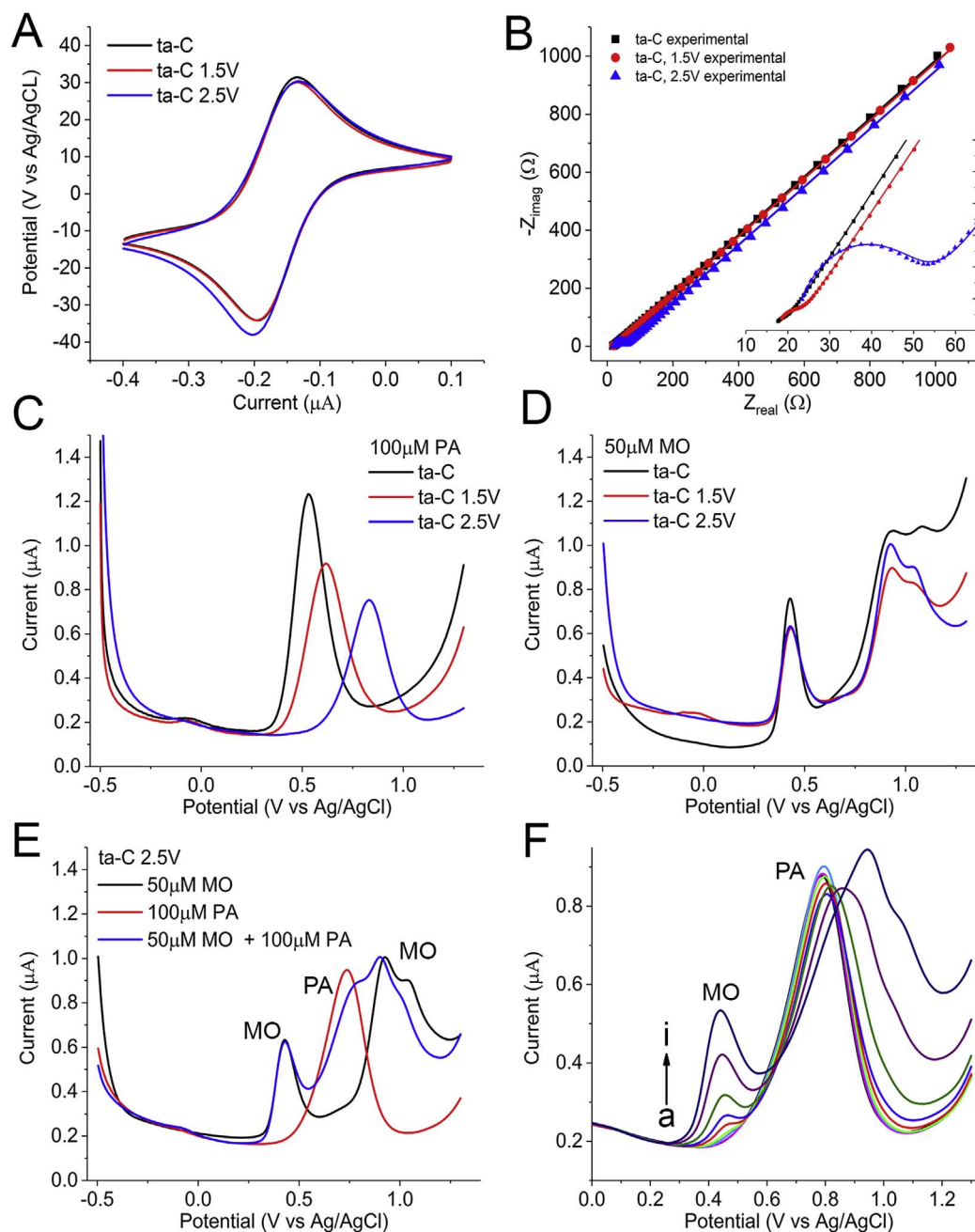
Fig. 2. (A) CV and (B) EIS of 1 mM and 5 mM Ru(NH$_3$)$_6$$^{2+/3+}$, respectively, in 1 M KCl. DPVs of (C) 100 μM paracetamol and (D) 50 μM morphine in PBS with ta-C, ta-C 1.5 V and ta-C 2.5 V. (E) DPV of 100 μM paracetamol and 50 μM morphine separately and in the same PBS solution. (F) Increasing concentrations of morphine (a) blank, (b) 100 nM, (c) 500 nM, (d) 1 μM, (e) 2.5 μM, (f) 5 μM, (g) 10 μM, (h) 25 μM, and (i) 50 μM in the presence of 100 μM paracetamol on ta-C 2.5 V.

3. Results and discussion

Raman spectroscopy and XPS were used to characterize the changes in carbon–carbon bonding and surface chemistry. Raman spectra (Fig. 1A) were fitted with Gaussians resulting in I_D/I_G ratios of 0.62 for ta-C and ta-C 1.5 V, and 0.57 for ta-C 2.5 V. These I_D/I_G ratios are typical of 7 nm thick ta-C films deposited with p-FCVA [13]. From the XPS survey spectra, all surfaces were found to contain mostly carbon and oxygen with traces of titanium. Residual traces of Na and Cl were detected on the treated samples. Such traces are expected from the PBS solution. The reference ta-C in Fig. 1B was found to have a relatively high O/C ratio of 0.08, consistent with previous studies [17]. The anodic treatment increased the O/C-ratio from the reference value to 0.09 and 0.17 for ta-C 1.5 V and ta-C 2.5 V, respectively. The anodic

treatment also increased the surface loading of Ti. In the case of ta-C 2.5 V, the Ti signal increased from the reference value of 0.5% to 2.0%. This is also reflected in the Ti 2p spectra (Fig. 1E), which indicated oxidized Ti [26]. The anodic treatment at 2.5 V also caused a shift in the C 1s high-resolution spectrum (Fig. 1C), indicating a decrease in C—C bonding and an increase in carbon-bonded oxygen moieties. The observed broadening of O 1s (Fig. 1D) can be attributed to the contribution of oxidized Ti and changes in carbon bonding.

It has been shown that multiwalled carbon nanotubes can be etched electrochemically at the relatively low potential of 1.7 V [27]. While the absence of any large changes in the I_D/I_G ratio indicates no significant changes for the bulk of the film, the subtle decrease could indicate oxidation or removal of sp^2-rich carbon surface. This could allow for exposure and oxidation of the underlying Ti layer, especially for the

ta-C 2.5 V electrode. AFM measurements (not shown) exhibited an increase in roughness (R_{rms}) to 3.06 nm in comparison to the reference 0.81 nm. Similar coarsening of sputtered Ti films as a result of anodic oxidation was also observed by Zia et al. [26].

Cyclic voltammetry and electrochemical impedance spectroscopy were used to study electron transfer with the outer sphere redox probe $Ru(NH_3)_6^{2+/3+}$. The anodic treatment caused a small increase in the peak potential separations (ΔE_p) (Fig. 2A). All electrodes showed reversible or close to reversible electron transfer with ΔE_p values of 59.4, 61.4 and 71.4 mV for ta-C, ta-C 1.5 V and ta-C 2.5 V, respectively (scan rate 500 mV/s). This trend was confirmed by EIS measurements (Fig. 2B), where R_{ct} values increased from 2.2 Ω for ta-C to 4.3 Ω for ta-C 1.5 V, and further to 30.0 Ω for ta-C 2.5 V. Based on the measured R_{ct} values, apparent heterogeneous rate constants (k^0) of 0.68 cm/s for ta-C, 0.35 cm/s for ta-C 1.5 V and 0.05 cm/s for ta-C 2.5 V were obtained.

$Ru(NH_3)_6^{2+/3+}$ is usually regarded as an outer sphere probe which is insensitive to changes in surface chemistry [20]. We have previously shown that Ti thin films quickly passivate in aqueous electrolytes, causing significant decreases in rates of electron transfer [13]. The decrease in k^0 of the ta-C 2.5 V electrode can probably be attributed to partial exposure and oxidation of the underlying Ti layer. The ta-C 2.5 V electrode also shows an increase in cathodic peak current, indicating adsorption of the reactant on the electrode [28]. Furthermore, the I_{pa}/I_{pc} ratio of this electrode decreased with increasing scan rate. Despite this, the peak currents were directly related to the square root of the scan rate and the overall reaction was still diffusion controlled.

The effect of the anodic treatment on the electrochemical oxidation of paracetamol and morphine was studied with differential pulse voltammetry (DPV). Comparison reveals an anodic shift in the paracetamol oxidation (Fig. 2C) from 532 mV for ta-C to 616 mV for ta-C 1.5 V, and further to 832 mV for ta-C 2.5 V. This shift is also associated with an apparent decrease in the oxidation current. As seen in Fig. 2D, no shift in the oxidation potential of morphine is observed, as was also reported in [7]. The anodic treatments caused a decrease in the oxidation currents of morphine and paracetamol. As no decrease in the redox currents was observed with $Ru(NH_3)_6^{2+/3+}$, the decrease in the oxidation current with both paracetamol and morphine is likely surface chemistry related.

The adsorption of paracetamol on carbon is known to be surface-chemistry dependent, affected by hydrogen bonding, π-stacking and hydrophobic interactions [29,30]. Interestingly, Terzyk et al. [29] found that acidic functional groups, specifically carbonyls, lower the adsorbability of paracetamol on activated carbon. We have previously shown that the surface of our ta-C films contains polar carbonyl groups [17]. While the XPS results show an increase in O/C ratio after anodic treatment, more specific surface characterization is required to fully understand the effect of anodic treatment on the distribution of oxygen-containing functional groups. It has been shown that anodic treatments of BDD electrodes result in an anodic shift and lower oxidation current for paracetamol [23,24]. The observed anodic shifts were, however, significantly smaller than that of the ta-C 2.5 V electrode in this work. To further determine the role of the underlying Ti layer, an electrode with 30 nm ta-C and no Ti was measured before and after anodic treatment at 2.5 V (not shown). While a comparable decrease in oxidation current was observed, the anodic shift of paracetamol was only 138 mV. As for a bare Ti electrode, complete passivation and absence of signal was confirmed. These results suggest that interactions with locally exposed Ti_xO_y alters the voltammetry of paracetamol.

To demonstrate the applicability of the Ti/ta-C electrode for the determination of morphine, measurements in the presence and absence of paracetamol were carried out with electrodes treated anodically at 2.5 V. Fig. 2E reveals that the ta-C 2.5 V electrode can be used for detection of morphine in the presence of 100 μM paracetamol. Fig. 2F shows the measurement of increasing concentrations of morphine in the presence of paracetamol. The current was found to scale linearly with concentration in the range 100 nM to 10 μM, with a slope of $I_{morphine}$

(μA) = 0.0125 $C_{morphine}$ (μA) + 0.2064 and a correlation coefficient of 0.9983. At concentrations higher than 10 μM, the current deviated from the linear fit, likely due to passivation of the electrode. Passivation of the electrode is further supported by the measurements shown in Fig. 2E, where similar currents were obtained for 50 μM morphine both separately and in the presence of 100 μM paracetamol. To determinate the detection limit (S/N = 3), three consecutive DPVs were recorded in blank PBS solution. The standard deviation of the blank signals was used to calculate a detection limit of 9.8 nM.

4. Conclusions

We show that a simple 5 min anodic treatment of Ti/ta-C electrodes in PBS enables selective determination of morphine in the presence of paracetamol at clinically relevant concentrations. The anodic treatment results in exposed Ti that oxidizes to form Ti_xO_y. The combined effect of exposed Ti_xO_y and oxidized carbon surface is found to retard the electron transfer of paracetamol while that of morphine remains unaffected. Moreover, these results suggest that it is possible to control the oxidation potential of paracetamol with the applied anodization potential.

References

[1] S.A. Schug, D.A. Sidebotham, M. McGuinnety, J. Thomas, L. Fox, Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain, Anesth. Analg. 87 (1998) 368–372, http://dx.doi.org/10.1213/00000539-199808000-00024.

[2] G.G. Graham, M.J. Davies, R.O. Day, A. Mohamudally, K.F. Scott, The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings, Inflammopharmacology 21 (2013) 201–232, http://dx.doi.org/10.1007/s10787-013-0172-x.

[3] C. Remy, E. Marret, F. Bonnet, Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials, Br. J. Anaesth. 94 (2005) 505–513, http://dx.doi.org/10.1093/bja/aei085.

[4] I. Baranowska, M. Koper, The preliminary studies of electrochemical behavior of paracetamol and its metabolites on glassy carbon electrode by voltammetric methods, Electroanalysis 21 (2009) 1194–1199, http://dx.doi.org/10.1002/elan.200804536.

[5] J.M.P.J. Garrido, C. Delerue-Matos, F. Borges, T.R.A. Macedo, A.M. Oliveira-Brett, Voltammetric oxidation of drugs of abuse I. Morphine and metabolites, Electroanalysis 16 (2004) 1419–1426, http://dx.doi.org/10.1002/elan.200302966.

[6] S. Cheraghi, M.A. Taher, H. Karimi-Maleh, A novel strategy for determination of paracetamol in the presence of morphine using a carbon paste electrode modified with CdO nanoparticles and ionic liquids, Electroanalysis 28 (2016) 366–371, http://dx.doi.org/10.1002/elan.201500357.

[7] F. Li, J. Song, D. Gao, Q. Zhang, D. Han, L. Niu, Simple and rapid voltammetric determination of morphine at electrochemically pretreated glassy carbon electrodes, Talanta 79 (2009) 845–850, http://dx.doi.org/10.1016/j.talanta.2009.05.011.

[8] T. Heiskanen, K. Langel, T. Gunnar, P. Lillsunde, E.A. Kalso, Opioid concentrations in oral fluid and plasma in cancer patients with pain, J. Pain Symptom Manag. 50 (2015) 524–532, http://dx.doi.org/10.1016/j.jpainsymman.2014.09.004.

[9] R. Osborne, S. Joel, D. Trew, M. Slevin, Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide, Clin. Pharmacol. Ther. 47 (1990) 12–19, http://dx.doi.org/10.1038/clpt.1990.2.

[10] J. Kirchheiner, H. Schmidt, M. Tzvetkov, J. Keulen, J. Lötsch, I. Roots, J. Brockmöller, Pharmacokinetics of codeine and its metabolite morphine in ultrarapid metabolizers due to CYP2D6 duplication, Pharm. J. 7 (2007) 257–265, http://dx.doi.org/10.1038/sj.tpj.6500406.

[11] R.C. Goucke, P.L. Hackett, K.F. Ilett, Concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide in serum and cerebrospinal fluid following morphine administration to patients with morphine-resistant pain, Pain 56 (1994) 145–149, http://dx.doi.org/10.1016/0304-3959(94)90088-4.

[12] J. Robertson, Diamond-like amorphous carbon, Mater. Sci. Eng. R. Rep. 37 (2002) 129–281, http://dx.doi.org/10.1016/S0927-796X(02)00005-0.

[13] T. Palomäki, N. Wester, M.A. Caro, S. Sainio, V. Protopopova, J. Koskinen, T. Laurila, Electron transport determines the electrochemical properties of tetrahedral amorphous carbon (ta-C) thin films, Electrochim. Acta 225 (2017) 1–10,

http://dx.doi.org/10.1016/j.electacta.2016.12.099.

[14] N. Wester, S. Sainio, T. Palomäki, D. Nordlund, V.K. Singh, L.-S. Johansson, J. Koskinen, T. Laurila, Partially reduced graphene oxide (PRGO) modified tetrahedral amorphous carbon (ta-C) thin film electrodes as a platform for nanomolar detection of dopamine, J. Phys. Chem. C 121 (2017) 8153–8164, http://dx.doi.org/10.1021/acs.jpcc.6b13019.

[15] T. Laurila, V. Protopopova, S. Rhode, S. Sainio, T. Palomäki, M. Moram, J.M. Feliu, J. Koskinen, New electrochemically improved tetrahedral amorphous carbon films for biological applications, Diam. Relat. Mater. 49 (2014) 62–71, http://dx.doi.org/10.1016/j.diamond.2014.08.007.

[16] T. Palomäki, S. Chumillas, S. Sainio, V. Protopopova, M. Kauppila, J. Koskinen, V. Climent, J.M. Feliu, T. Laurila, Electrochemical reactions of catechol, methylcatechol and dopamine at tetrahedral amorphous carbon (ta-C) thin film electrodes, Diam. Relat. Mater. 59 (2015) 30–39, http://dx.doi.org/10.1016/j.diamond.2015.09.003.

[17] S. Sainio, D. Nordlund, M.A. Caro, R. Gandhiraman, J. Koehne, N. Wester, J. Koskinen, M. Meyyappan, T. Laurila, Correlation between sp^3-to-sp^2 ratio and surface oxygen functionalities in tetrahedral amorphous carbon (ta-C) thin film electrodes and implications of their electrochemical properties, J. Phys. Chem. C 120 (2016) 8298–8304, http://dx.doi.org/10.1021/acs.jpcc.6b02342.

[18] K. Sudhakara Prasad, G. Muthuraman, J. Zen, The role of oxygen functionalities and edge plane sites on screen-printed carbon electrodes for simultaneous determination of dopamine, uric acid and ascorbic acid, Electrochem. Commun. 10 (2008) 559–563, http://dx.doi.org/10.1016/j.elecom.2008.01.033.

[19] T. Palomäki, N. Wester, L. Johansson, M. Laitinen, H. Jiang, K. Arstila, T. Sajavaara, J.G. Han, J. Koskinen, T. Laurila, Characterization and electrochemical properties of oxygenated amorphous carbon (a-C) films, Electrochim. Acta 220 (2016) 137–145, http://dx.doi.org/10.1016/j.electacta.2016.10.063.

[20] R.L. McCreery, Advanced carbon electrode materials for molecular electrochemistry, Chem. Rev. 108 (2008) 2646–2687, http://dx.doi.org/10.1021/cr068076m.

[21] K. Štulík, Activation of solid electrodes, Electroanalysis 4 (1992) 829–834, http://dx.doi.org/10.1002/elan.1140040902.

[22] D. Tasis, N. Tagmatarchis, A. Bianco, M. Prato, Chemistry of carbon nanotubes, Chem. Rev. 106 (2006) 1105–1136, http://dx.doi.org/10.1021/cr050569o.

[23] A.M. Santos, F.C. Vicentini, L.C.S. Figueiredo-Filho, P.B. Deroco, O. Fatibello-Filho, Flow injection simultaneous determination of acetaminophen and tramadol in pharmaceutical and biological samples using multiple pulse amperometric detection with a boron-doped diamond electrode, Diam. Relat. Mater. 60 (2015) 1–8, http://dx.doi.org/10.1016/j.diamond.2015.10.005.

[24] A.P.P. Eisele, D.N. Clausen, C.R.T. Tarley, L.H. Dall'Antonia, E.R. Sartori, Simultaneous square-wave voltammetric determination of paracetamol, caffeine and orphenadrine in pharmaceutical formulations using a cathodically pretreated boron-doped diamond electrode, Electroanalysis 25 (2013) 1734–1741, http://dx.doi.org/10.1002/elan.201300137.

[25] L.-S. Johansson, J.M. Campbell, P. Fardim, A.H. Hultén, J.-P. Boisvert, M. Ernstsson, An XPS round robin investigation on analysis of wood pulp fibres and filter paper, Surf. Sci. 584 (2005) 126–132, http://dx.doi.org/10.1016/j.susc.2005.01.062.

[26] Z. Xia, H. Nanjo, T. Aizawa, M. Kanakubo, M. Fujimura, J. Onagawa, Growth process of atomically flat anodic films on titanium under potentiostatical electrochemical treatment in H_2SO_4 solution, Surf. Sci. 601 (2007) 5133–5141, http://dx.doi.org/10.1016/j.susc.2007.04.211.

[27] T. Ito, L. Sun, R.M. Crooks, Electrochemical etching of individual multiwall carbon nanotubes, Electrochem. Solid-State Lett. 6 (2003) C4–C7, http://dx.doi.org/10.1149/1.1526779.

[28] A.J. Bard, L.R. Faulkner, Electrochemical Methods: Fundamentals and Applications, 2nd edition, (2001) http://eu.wiley.com/WileyCDA/WileyTitle/productCd-0471043729.html (New York (N.Y.)).

[29] A.P. Terzyk, The influence of activated carbon surface chemical composition on the adsorption of acetaminophen (paracetamol) in vitro: part II. TG, FTIR, and XPS analysis of carbons and the temperature dependence of adsorption kinetics at the neutral pH, Colloids Surf. A Physicochem. Eng. Asp. 177 (2001) 23–45, http://dx.doi.org/10.1016/S0927-7757(00)00594-X.

[30] I. Villaescusa, N. Fiol, J. Poch, A. Bianchi, C. Bazzicalupi, Mechanism of paracetamol removal by vegetable wastes: the contribution of π–π interactions, hydrogen bonding and hydrophobic effect, Desalination 270 (2011) 135–142, http://dx.doi.org/10.1016/j.desal.2010.11.037.