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Sensitive determination of anticancer drug imatinib in spiked human urine samples by differential pulse voltammetry on anodically pretreated boron-doped diamond electrode

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ABSTRACT

In the present work, the electrochemical oxidation of a new generation of anticancer drug, imatinib (*Ima*), using differential pulse voltammetry (DPV) on anodically pretreated boron doped diamond electrode (BDDE) has been reported. The results of a study showed that *Ima* provided well-shaped oxidation peak at positive potential of around +1.0 V (*vs.* Ag/AgCl/KCl) in the Britton–Robinson (B–R) buffer at pH 2.0. The experimental conditions, *i.e.* pH, a modulation amplitude, a modulation time, a step potential, and a scan rate, were optimized. A simple, rapid, selective and sensitive DPV procedure for the determination of *Ima* was performed in the concentration range of 3.0×10^{-8}–2.5×10^{-7} mol L^{-1} with the limit of detection (*LOD*) and the limit of quantification (*LOQ*) of 6.3×10^{-9} mol L^{-1} and 2.1×10^{-8} mol L^{-1}, respectively. The proposed methodology with using an anodic signal of imatinib at BDDE shown comparable detection limit as for hanging mercury drop electrode in the determination of this anticancer drug. A biological significance of the developed DPV procedure was demonstrated by a quantitative analysis of the spiked human urine samples with satisfactory recoveries (from 102.2% to 105.5%). Additionally, the influence of some interfering compounds and ions (*Int*) was also evaluated. The cyclic voltammetry (CV) was used for the investigation of the electrooxidation mechanism of *Ima*. The developed approach could be beneficial in analysis of imatinib in biological samples using BDDE as up-to-date electrochemical sensor and could represent non-toxic analytical alternative to HMDE.

1. Introduction

Cancer is considered to be one of the leading causes of morbidity and mortality worldwide [1]. It is a disease which involves uncontrolled cellular multiplication and spread of abnormal cells throughout the body. The most commonly used in anticancer drug therapy are cytostatic drugs [2], which act to inhibit the growth of cell lines or directly kill cells, but the effect is relatively unselective, *i.e.* they act on both healthy and cancerous cells [3]. Many of them have been classified as carcinogenic, teratogenic and mutagenic. The widespread use of cytostatic drugs invoke concerns about their occupational exposure, and moreover, toxicological risks to the environment [4].

One of the representative of cytostatics is a first-generation drug, imatinib (*Ima*, Fig.1.), which is the first protein kinase inhibitor approved for clinical applications, and it is a seminal drug used in targeted therapy [5]. *Ima* is applied in the treatment of chronic myelogenous leukemia (CML), and it is active against a number of related tyrosine kinases, such as ABL, BCR-ABL, KIT, PFGFR, and TEL [6]. In this way, *Ima* blocks the abnormal proteins, and simultaneously removes the proliferative advantage that it provides to cancer cells [7]. Under therapy with *Ima*, the bulk of patients achieve complete hematologic remission, and 75% of patients attain cytogenetic remission [7]. It is also worth noting that today, after 15 years of its launching to clinical practice, *Ima* is still the first-line treatment for CML, especially active against a BCR-ABL tyrosine kinases [8]. Its tremendous success is based on high efficacy and progression-free survival, relatively low toxicity, as well as a convenient dosing schedule [8]. However, although some patients treated with *Ima* may experience prolonged disease control, 20–25% of them will eventually develop *Ima* resistance [9].

Based on the available literature data, there are several studies on the analytical determinations of *Ima* in biological fluids or pharmaceuticals [10–21]. So far, the most commonly used technique for the *Ima* determination has been chromatography, *i.e.* liquid chromatography-electrospray-tandem mass spectrometry (LC–ESI–MS/MS) [10,11], liquid chromatography-tandem mass spectrometry (LC–MS/MS) [12], high-performance liquid chromatography with UV detection (HPLC–UV) [13,14], HPLC with mass detection (HPLC–MS) [15,16], and ultra high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS) [17]. Additionally, electrophoretic methods, *i.e.* capillary zone electrophoresis (CZE) [18], and nonaqueous capillary

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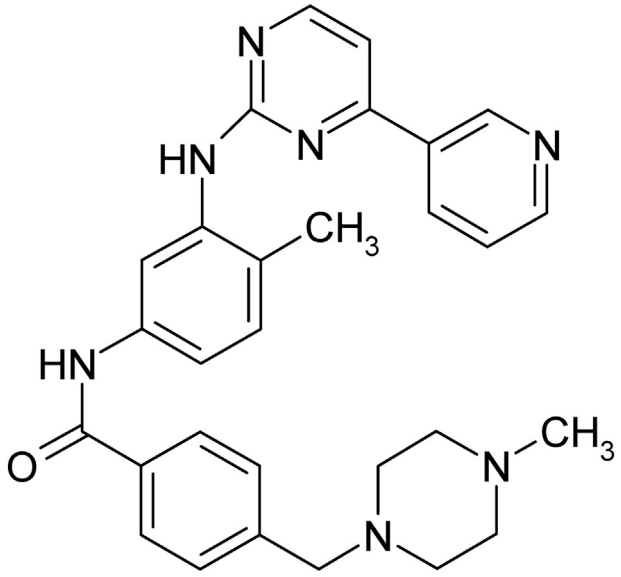

Fig. 1. The structure of *Ima*.

electrophoresis (NACE) [19] were developed. Nevertheless, the above-mentioned methods are time consuming and relatively expensive, therefore, as a possible alternative to aforementioned analytical methods employed to determine *Ima*, voltammetric techniques can also be applied [20,21]. Electrochemical techniques seem to be one of the most promising methods, which are suitable especially for the monitoring of a wide range of electrochemically active organic compounds of biological importance. It is due to their numerous advantages, such as their satisfactory sensitivity, wide linear concentration range, low cost of equipment, miniaturization possibility, relatively short time of analysis, simple sample pretreatment procedures, and suitability for real-time detection [22]. According to the literature, voltammetric studies of *Ima* based on its reduction signal were performed, and hanging mercury drop electrode (HMDE) has been applied till now for the determination of *Ima* [20,21]. In the other published voltammetric assay, *Ima* was investigated by square-wave adsorptive stripping voltammetric (SWAdSV) technique using HMDE [20,21]. The applicability of the SWAdSV procedures was demonstrated by analysis of *Ima* in spiked urine samples [20], as well as in bulk form, pharmaceutical formulation, and human serum [21]. These studies were compared with our study in terms of linear calibration range and detection limit (LOD) and they are presented in Table 1. Although the detection limits of the above-mentioned voltammetric works are very low, however, their routine use might be limited because of the mercury as working electrode.

Due to the fear of the mercury toxicity, nowadays, there is a tendency to replace the mercury with other less- or non-toxic electrode materials. Therefore, the development of innovative electrode materials is one of the current trends in electrochemistry. Mainly, carbon materials have attracted great deal of interest as sensors for their application in the analytical electrochemistry. Some of them, exploited as working electrodes in voltammetry, are carbon paste [23,24], glassy carbon [24,25], screen-printed carbon [24,26], pyrolytic graphite [27,28] electrodes, *etc.*

Boron-doped diamond (BDD) as a relatively new, environmentally friendly, and perspective carbon-based electrode material opens new possibilities of electrochemical investigations [29–31]. To date, BDDE has been extensively utilized for the analysis of various biologically electroactive compounds [32–41]. BDDE have intriguing electrochemical properties, *i.e.* the widest usable electrochemical potential window in aqueous solutions (*ca* 3.5 V) among all electrode materials, very low and stable background current, long-term stability of response in different media. Furthermore, boron-doped diamond electrode point out good mechanical robustness, corrosion stability, a high resistance to deactivation by surface fouling, and a relative insensitivity to dissolved oxygen [37,42]. Consequently, BDDE can be applied at very high positive and negative potential values without causing the decomposition of the electrolyte [37,42]. It is also important to point out that the chemical and physical properties of BDDE are affected by the termination of their surface (*O*- and *H*-terminated surfaces are produced). An anodic or a cathodic pretreatment of the BDDE can be applied to re-activation of the electrode surface, enhancement of the voltammetric signals, and to ensure of repeatable and reproducible response of analytes [43,44,45]. It was found that the most successful strategy to prevent fouling of BDDE is an anodic activation with using very high positive potentials in the region of the water decomposition reactions in acid medium [46]. Due to the fact that OH radicals as products of the reaction of decomposition of water are powerful oxidants, they are capable of the electrochemical oxidation reaction by products passivating the surface of BDDE [37–41].

This work shows the capabilities of anodically pretreated BDDE for direct voltammetric determination of a new generation of anticancer drug, imatinib. Although *Ima* has already been determined by HMDE with accumulation step with satisfactory results [20,21], this approach reports a simple, rapid, selective and highly sensitive differential pulse voltammetric determination of *Ima* on anodically pretreated BDDE without a stripping step. Therefore, for the first time, the procedure for the DPV determination of *Ima*, based on its oxidation signal at environmentally friendly electrode in the spiked human urine samples, is reported. Considerable attention is given to the electrode reaction mechanism by CV and the influence of some co-existing interfering compounds and ions, as well as the robustness of the DPV method on the quantitative determination of *Ima*.

2. Materials and methods

2.1. Instrumentation

The voltammetric studies were carried out using an EmStat USB potentiostat controlled by PSTrace 4.22 software (Palm Instruments BV, The Netherlands) with an electrode stand type M164 (MTM Anko Instruments, Cracow, Poland). The electrochemical experiments were executed with use of a standard three–electrode single compartment glass electrochemical cell. A platinum wire (Pt, 99.99%, Mennica Państwowa S.A., Warsaw, Poland), and a silver/silver chloride electrode/potassium chloride (Ag/AgCl/3.0 mol L^{-1} KCl, Mineral, Poland) were applied as counter and reference electrodes, respectively. BDDE

Table 1
Comparison of different electrodes for the determination of *Ima*.

Electrode	HMDE	HMDE	BDDE
LDR [mol L^{-1}]	1.0×10^{-8}–4.8×10^{-7}	9.0×10^{-9}–3.0×10^{-8}	3.0×10^{-8}–2.5×10^{-7}
LOD [mol L^{-1}]	5.2×10^{-9}	2.6×10^{-10}	6.3×10^{-9}
LOQ [mol L^{-1}]	1.7×10^{-8}	8.7×10^{-10}	2.1×10^{-8}
Voltammetric method	SWAdSV	SWAdSV	DPV
Reference	[20]	[21]	This work