



A state-of-the-art approach for facile and reliable determination of benzocaine in pharmaceuticals and biological samples based on the use of miniaturized boron-doped diamond electrochemical sensor

Solomiya Pysarevska^a, Liliya Dubenska^b, Serhij Plotycya^c, Lubomír Švorc^{d,*}

^a Life Safety Department, Ivan Franko National University of Lviv, Doroshenko 41, Lviv, 79000, Ukraine

^b Department of Analytical Chemistry, Faculty of Chemistry, Ivan Franko National University of Lviv, Kyryla & Mefodiya 6, Lviv, 79005, Ukraine

^c State Scientific-Research Control Institute of Veterinary Medicinal Products and Feed Additives, Donetska 11, Lviv, 79019, Ukraine

^d Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, Bratislava, SK-812 37, Slovak Republic

ARTICLE INFO

Article history:

Received 1 February 2018

Received in revised form 14 April 2018

Accepted 3 May 2018

Available online 4 May 2018

Keywords:

Benzocaine

Electrochemical oxidation

Boron-doped diamond electrode

Limit of detection

Electrochemical sensor

ABSTRACT

For the first time, the miniaturized thick-film boron-doped diamond electrode was applied as progressive electrochemical sensor for simple, facile and reliable quantification of local anesthetic agent, benzocaine (BZC). Cyclic voltammetric measurements revealed that the electrode reaction of this analyte was manifested by one irreversible and diffusion-driven oxidation peak at +1.0V in Britton-Robinson buffer at pH 4.0. Pulse voltammetric techniques with the suitably chosen values of operating parameters were used for the construction of calibration curves for BZC determination with the essential analytical characteristics as follows: the linear concentration range of 0.1–400 μM and 0.4–200 μM , the limit of detection of 80 nM and 100 nM for differential pulse voltammetry (DPV) and square-wave voltammetry (SWV), respectively. The excellent repeatability with the relative standard deviation below 5% was reached for both pulse voltammetric techniques. The developed protocols were applied to analysis of the commercial pharmaceuticals with the recoveries ranging from 97.4 to 104.5% and from 97.0 to 102.7% for DPV and SWV procedures as well as model human urine samples with recoveries from 96.0 to 104.0% and from 98.5 to 100.8%. This platform based on biocompatible, portable and easy-to-operate electrochemical sensor could encourage the viability of the proposed state-of-the-art approach for field applications, such as quality control of pharmaceuticals and monitoring of BZC in biological samples.

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1. Introduction

Benzocaine (IUPAC name: ethyl 4-aminobenzoate, abbreviated as BZC) is a local anesthetic, an ester of *para*-aminobenzoic acid. It is used in many countries as a component of some free-sale formulations for topical use, for example in skin creams, as a dry powder for skin ulcers, as throat lozenges, and as teething formulations for young children. This drug is also contained in aerosol sprays for anesthetizing the oropharynx. In general, relatively high concentrations of local anesthetic are required to be effective topically, increasing tissue penetration and the risk of subsequent toxicity. BZC is typically available in formulations in contents of 1–20%

[1]. However, along with its needed effects, BZC may cause some unwanted side effects [1,2] such as dermatitis and urticaria, burning and stinging, angioedema and methemoglobinemia. Hence, development of facile, sensitive and reliable analytical methods and procedures for simple and fast detection and determination of BZC and other local anesthetic agents still remains a key challenge in quality control of pharmaceutical products and monitoring of drug concentration levels in clinical analysis.

As evidenced in literature, the British and European Pharmacopoeia propose nitritometric titration for BZC determination [3,4]. Otherwise, the most widely used analytical methods for its sensing are chromatographic ones [5–12]. They allow sensitive and selective determination of BZC traces with popular application in analysis of biological objects and foodstuffs. On the other hand, these methods are not always affordable in many laboratories and usually require usage of expensive equipment and reagents as well

* Corresponding author.

E-mail address: lubomir.svorc@stuba.sk (L. Švorc).

as trained laboratory staff. Nevertheless, other analytical methods and techniques such as spectrometric [13–16] and kinetic ones [17] have also been elaborated for BZC sensing, however, with necessary separation steps to be carried out prior to analysis.

A satisfactory (in many cases full-featured) alternative to chromatographic and spectrometric methods are electroanalytical methods. Especially in last decades, they have been widely used in scientific field, predominantly in the term of pharmaceutical analysis in quality control and clinical analysis. Nowadays, they have even attracted more attention for routine drug analysis, due to their comfortable facilities such as cheap instrumentation, fast response, portability, simple operation, time saving and high sensitivity, in most cases accompanied by satisfactory selectivity, precision and accuracy [18]. In consideration of BZC sensing, the amino group attached to the aromatic ring of this molecule considerably predetermines its electrochemical activity. Even so, the literature survey refers a small number of scientific papers for voltammetric quantification of BZC. In this respect, the oxidation of amino group has been the base for determination of BZC traces by differential pulse adsorptive stripping voltammetry (DPAdSV) on glassy carbon electrode (GCE) and Nafion modified GCE [19]. Furthermore, semiquantitative method using graphite working electrode coupled with square-wave voltammetry has been developed for determination of some local anesthetics including BZC [20]. The method of indirect determination of BZC on capsaicin-modified multiwalled carbon nanotube electrode has been described by Kachosangi et al. [21]. High-performance liquid chromatography (HPLC) [22], flow injection analysis (FIA) [23] and batch injection analysis (BIA) [24] with amperometric detection (AD) have also been introduced. Overall, in these works, different types of working electrodes, predominantly based on conventional carbonaceous electrode materials and chemically modified electrodes, have been used.

The present work introduces the state-of-the-art approach for simple and sensitive voltammetric quantification of BZC based on the use of innovative electrochemical sensor, namely boron-doped diamond (BDD) electrode. This electrode material has been found as progressive one providing significant benefits unlike conventional gold and carbonaceous (graphite, glassy carbon, carbon paste) materials. As is largely referred in the scientific literature over the past years, BDD yields distinguished chemical stability (due to sp^3 hybridized carbon atoms in diamond structure), low background current, excellent biocompatibility, the widest potential range in both aqueous and non-aqueous media and usually weak adsorption for most organic molecules [25–28]. In the meantime, BDD electrochemical sensors do not totally replace sensors based on conventional electrode materials in particular practice analysis, but on the other hand, they enable many electrochemical processes that were before impossible, especially owing to of high overpotential for hydrogen and oxygen evolution [29,30]. Some comprehensive reviews on performance of BDD in analytical chemistry have demonstrated that plenty of organic substances can be precisely and accurately determined with the use of BDD electrodes [31,32]. Among these examples, the applications for successful determination of some local anesthetics and other related amines have also been described [25,31].

In view of the lack of electrochemical methods for the determination of local anesthetics in various areas, the objective of the proposed paper is to introduce the state-of-the-art approach for facile and reliable BZC sensing in commercial pharmaceutical dosages and model human urine samples based on the use of miniaturized and easy-to-operate BDD electrochemical sensor coupled with pulse techniques. This work also fits into the objectives in medicinal chemistry which are recently focused on the broad

development of the progressive miniaturized tools and devices to be used for health impact assessment.

2. Experimental

2.1. Chemicals

BZC (CAS. No 94-09-7, purity $\geq 98\%$) was purchased from Sigma Aldrich, China. 1 mM BZC stock solution was prepared by dissolution of its appropriate amount in deionized water with addition of 1 mL 10 mM hydrochloric acid (p.a., Lachema, Czech Republic). This solution was stored in a glass volumetric flask in fridge for few weeks without observation of any changes in consistency. The Britton-Robinson (BR), phosphate, acetate buffers, hydrochloric acid and sodium hydroxide (p.a., Lachema, Czech Republic) solutions were used as supporting electrolytes in the preliminary experiments. BR buffer solutions (pH 2.0–12.0) were prepared by mixing of 40 mM H_3BO_3 , H_3PO_4 , CH_3COOH adjusted with 0.2 M NaOH (p.a., Lachema, Czech Republic). The acetate buffer (pH 4.0) was prepared by mixing 0.2 M CH_3COOH with 0.2 M NaOH. The phosphate buffer (pH 9.0) was made from 0.1 M Na_2HPO_4 and adjusted with 0.2 M NaOH. The BZC working and calibration solutions of different concentrations were set up from the stock solution by dilution of appropriate volume with supporting electrolyte. All solutions were prepared in deionized water with the resistivity above 18 M Ω cm.

2.2. Equipments

All voltammetric measurements were performed using potentiostat PSTAT 910 mini (Metrohm Ltd., Switzerland) driven by software PSTAT 1.0. The three-electrode system (purchased from DropSens, Asturias, Spain) situated on ceramic substrate, consisted of the miniaturized thick-film BDD working electrode (commercially marked as CBDD110, with the diameter of 3.6 mm and boron content of 2500 ppm), screen-printed carbon auxiliary electrode and silver pseudoreference electrode. pH values were measured using *pHenomenal*[®] pH1100L meter (VWR, Slovakia) with a combined glass-reference electrode.

2.3. Working electrode surface pretreatment

Before each measurement, the active surface of three-electrode system was simply rinsed with deionized water. Subsequently, the cathodic and anodic pretreatment of the working electrode was carried out in the presence of 1 M HNO_3 applying either -2.0 or $+2.0$ V (both for period of 40 s) to get hydrogen- and oxygen-terminated BDD electrode surface. The current response of BZC was then examined and compared from the perspective of intensity and stability.

2.4. Measurement procedure

Cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square-wave voltammetry (SWV) were applied for the investigation of electrochemical behaviour of BZC and assessment of the analytical performance and the method applicability. CV was used for exploration of the effect of electrochemical pretreatment, supporting electrolyte (pH) and scan rate. The calibration curves were examined from the DPV and SWV records with the operating parameters such as modulation amplitude, modulation time and frequency to be suitably selected in term of selectivity and sensitivity. The peak current (I_p) of BZC was estimated from the straight lines connecting the minima before and after the voltammetric peak maximum, without applying any background correction. All voltammograms were recorded after addition of particular volumes

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