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Sensitive square-wave voltammetric determination of tadalafil (Cialis®) in pharmaceutical samples using a cathodically pretreated boron-doped diamond electrode

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ABSTRACT

This work presents the development of a novel voltammetric method for a sensitive, simple, fast and eco-friendly determination of tadalafil (TDL) using a cathodically pretreated boron-doped diamond electrode (CP-BDDE). Using cyclic voltammetry of TDL, this drug presented one irreversible and well resolved oxidation process at 0.905 V (vs Ag/AgCl (KCl 3.0 mol L^{-1})) in Britton-Robinson buffer solution (pH 4.0). A scan rate study demonstrated that TDL transport toward CP-BDDE is diffusion controlled and one proton and one electron are involved in its electrooxidation. Employing square-wave voltammetry under optimized parameters, there was a linear dependence of peak current and TDL concentration in the range of 0.15–1.28 μmol L^{-1} with a detection limit of 19.5 nmol L^{-1}. The proposed method was successfully applied in TDL determination in pharmaceutical formulations. The results obtained with the voltammetric method were not statistically different from the comparative spectrophotometric method, at a 95% confidence level.

1. Introduction

According to the U.S. National Institutes of Health [1], erectile dysfunction (ED) is defined by the inability of man on getting and/or maintaining an enough erection for a satisfactory sexual intercourse. There are some drugs used to treat erectile dysfunction such as sildenafil, vardenafil and tadalafil (TDL). Their mechanism of action is mainly the inhibition of phosphodiesterase-5, which allows dilate penis' vessels and corpus cavernosum by increasing the blood flow through the penis, and getting erection just when stimulated [2].

TDL (6R,12aR)–6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6] pyrido[3,4-*b*] indole-1,4-dione, Fig. 1) is also used for treating benign prostatic hyperplasia [2]. Considering that a lot of men are affected by erectile dysfunction, TDL has proved its efficacy on a daily usage with prescribed dosage. It is important that its content in tablets to be severe checked to guarantee an effective treatment. It is very interesting the development of a simple, rapid, less expensive, and sensitive analytical method for the quantification of TDL in pharmaceutical formulations as quality control.

Voltammetric methods attend these requirements. They constitute a highly convenient alternative approach for quantifying several compounds. There are few available studies on the voltammetric determination of TDL, which employs modified electrodes [3-5]. Demir et al. [3] developed an electroanalytical method for the determination of TDL using adsorptive stripping square-wave voltammetry (AdSSWV) at multiwalled carbon nanotube paste electrode (MWCNTPE) and modified TiO_2-multiwalled carbon nanotube paste electrode (TiO_2-MWCNTPE). Yang et al. [4] described the electrochemical detection of TDL using a glassy carbon electrode (GCE) modified with carboxymethyl-β-cyclodextrin and thiol-β-cyclodextrin functionalized Au@SiC. Zhao et al. [5] employed a GCE modified with p-sulfonated calix [6] arene functionalized reduced graphene oxide (SCX6@RGO/GCE) for trace levels TDL determination. In these last two works, acetonitrile was used to amplify the signal in the electrochemical measurements. Although these methods have good precision and sensitivity, they have some shortcomings such as the need of surface modification, pre-accumulation of the analyte and the necessity of the use of acetonitrile during the measurements, which it makes a lengthy procedure and not environmentally friendly. The best of our knowledge, no report has been published on the analysis of tadalafil in pharmaceutical samples using boron-doped diamond electrode (BDDE).

Since Pleskov started to study the electrochemical applications of

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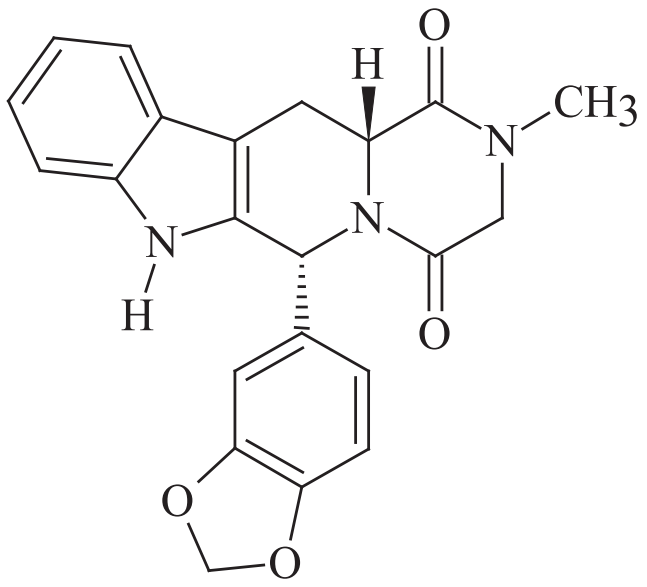

Fig. 1. Chemical structure of TDL.

boron-doped diamond films [6], it has been used as working electrode in electroanalysis. These films provides a low background current in a considered range of potential [7-9] with the possibility of determining analytes at high anodic [10,11] and cathodic potentials [12-14]. BDDE presents interesting properties such as chemical inertness, low and stable background current and a wide working potential window in aqueous medium due to the high overpotential for both oxygen and hydrogen evolution [8,15]. Other important characteristic of BDDE is the fact that it can be used in two different surfaces (hydrogen or oxygen), and each analytes can react differently on each of those surfaces [8,16]. These surfaces can be reached by an appropriated electrochemical pretreatment, as cathodic or anodic pretreatment, respectively. When BDDE is anodically pretreated, its surface changes predominantly to oxygen, while under cathodic pretreatment its surface changes predominantly to hydrogen [16-18]. Both pretreatments can improve the performance of BDDE in sensing analytes by increasing its sensitivity. As presented by Oliveira-Brett [19], the different BDDE surface terminations were responsible for affecting the oxidation potentials and peak currents of some biomolecules. Besides, the hydrogen terminated BDDE presented better analytical parameters for the individual determination of linuron [20] and sildenafil citrate [21] or simultaneous determination of paracetamol/caffeine/orphenadrine [10] and hydrochlorothiazide/ramipril [13], while the oxygen terminated BDDE was the best surface for imatinib determination [22]. Due to this great diversity of results, one of the steps to be followed in the development of a procedure is to evaluate the both BDDE surfaces, because it allied to the voltammetric techniques results in very sensitive protocol for determination of several molecules [22-26]. In addition, analytical procedures employing voltammetric techniques using BDDE are low cost, rapid and eco-friendly, which has been employed in the analysis of several drugs [22,27-33].

In view of this, BDDE is used for the first time on the investigation of the electrochemical behavior of TDL and on the development of a sensitive procedure to quantify this drug in pharmaceutical samples using square-wave voltammetry (SWV). No modification of working electrode is required in this novel procedure and low detection limit was obtained with the use of the BDDE.

2. Experimental

2.1. Chemicals and solutions

All chemicals were analytical grade and all aqueous solutions were prepared using ultra-purified water (resistivity > 18.2 MΩ cm) supplied by a Milli-Q system (Millipore®). TDL was obtained from Sigma-Aldrich. Acetic, boric, ortophosphoric, lactic, formic, and citric acids as well as sodium hydroxide were obtained from Synth. Commercially available pharmaceutical samples used in these studies were TDL (declared amount of 5 and 20 mg). They were purchased from a local drugstore in the city of Londrina in Brazil.

BR buffer solution was chosen as supporting electrolyte for pH study and for TDL determination. This solution was prepared by mixing 0.04 mol L^{-1} in acetic, boric and orthophosphoric acids, with pH adjusted from 2.0 to 10.0 with a 2.0 mol L^{-1} NaOH solution.

Due to the low solubility of TDL in water, 10 mmol L^{-1} TDL stock solution was prepared in acetone. Prior to the use, working solutions were prepared by appropriated dilution of the stock solution with BR buffer solution (pH 4.0). These solutions were freshly prepared each day of experiment.

2.2. Apparatus

All the electrochemical experiments were conducted in a three-electrode single-compartment glass cell, including a BDDE as working electrode, a platinum plate as auxiliary electrode and an Ag/AgCl (3.0 mol L^{-1} KCl) as reference electrode to which all electrode potentials hereinafter are referred. The voltammetric measurements were carried out using a FRA2 μAutolab type III potentiostat/galvanostat (Metrohm Autolab B.V., The Netherlands) controlled with the GPES software.

BDDE (B/C ratio in gaseous phase of 8000 ppm; 0.25 cm^2 exposed area) was obtained from Adamant Technologies SA, Switzerland. Boron-doped diamond film was synthesized on a silicon substrate by Hot Filament Chemical Vapor Deposition (HFCVD) technique, where the gaseous phase consisted of methane with excess hydrogen gas and trimethylboron as doping [34].

The BDDE was subject to pretreatment steps at a beginning of every working day. It was cathodically pretreated in a 0.5 mol L^{-1} H_2SO_4 solution by applying − 0.5 A cm^{-2} during 120 s. This pretreatment was always preceded by an anodic pretreatment by applying 0.5 A cm^{-2} during 30 s in 0.5 mol L^{-1} H_2SO_4 [16]. The pretreatment of BDDE was carried out using a MQPG-01 potentiostat/galvanostat (Microquímica, Brazil).

pH was measured at 25.0 ± 0.5 °C using a pH-meter (Hanna Instruments, USA), model HI-221, employing a combined glass electrode with an Ag/AgCl (3.0 mol L^{-1} KCl) external reference electrode.

The spectrophotometric TDL determination was carried out using ThermoSpectronic spectrophotometer UV–visible (model Genesys), employing a 1 cm quartz cell, coupled to a computer [35].

2.3. Measurement procedures

Cyclic voltammetry (CV) and SWV were employed for preliminary studies on electrochemical behavior of TDL. SWV was used as a sensitive pulse technique for the development of a voltammetric methodology for the determination of TDL in pharmaceutical formulations.

Using optimized parameters, the particular calibration curves were obtained by successive addition of aliquots of TDL working solutions into electrochemical cell containing 10 mL of supporting electrolyte, BR buffer solution (pH 4.0). Square-wave voltammograms were recorded after each aliquot addition of the working solution. Detection limit (LOD) value was obtained by three times the signal to noise ratio (S/N) [36].

For recovery studies, carried out in triplicate, aliquots of the