Talanta 81 (2010) 1418–1424

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Square-wave voltammetric determination of propranolol and atenolol in pharmaceuticals using a boron-doped diamond electrode

Elen Romão Sartori, Roberta Antigo Medeiros, Romeu C. Rocha-Filho, Orlando Fatibello-Filho*

Departamento de Química, Universidade Federal de São Carlos, C.P. 676, 13.560-970 São Carlos, SP, Brazil

ARTICLE INFO

Article history:
Received 11 December 2009
Received in revised form 11 February 2010
Accepted 15 February 2010
Available online 24 February 2010

Keywords:
Propranolol determination
Atenolol determination
Boron-doped diamond electrode
Cathodic pretreatment
Pharmaceutical formulations

ABSTRACT

The independent determination of two β-blocker agents, namely propranolol (PROP) and atenolol (ATN), in pharmaceutical formulations using square-wave voltammetry and a cathodically pretreated boron-doped diamond electrode is described. These electroanalytical determinations of propranolol or atenolol were carried out in 0.1 mol L^{-1} H_2SO_4 or 0.5 mol L^{-1} $NaNO_3$ (pH 1.0, adjusted with concentrated HNO_3), respectively. Excellent linear calibration curves, ranging from 0.20 to 9.0 μmol L^{-1} for PROP and from 2.0 to 41 μmol L^{-1} for ATN, with detection limits of 0.18 and 0.93 μmol L^{-1}, respectively, were obtained. The obtained recoveries range from 93.9% to 105.0%, for PROP, and from 92.5% to 106.0%, for ATN. The proposed method was successfully applied in the determination of both β-blockers in several pharmaceutical formulations (tablets), with results in close agreement at a 95% confidence level with those obtained using official spectrophotometric methods.

1. Introduction

Propranolol (PROP) (1-isopropylamino-3-(1-naphthyloxy)-2-propranolol – Fig. 1A) and atenolol (ATN) (4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide – Fig. 1B) are cardioselective β-adrenergic receptor blocking agents. These β-blocker agents are most frequently prescribed for the management of various cardiovascular disorders, such as hypertension, angina pectoris, cardiac arrhythmias, and myocardial infarction [1]. Thus, the therapeutical and pharmacological relevance of these compounds justifies an interest in developing accurate analytical procedures to assess the quality of pharmaceutical formulations that contain them.

Several methods for the analytical determination of PROP in pharmaceutical formulations have been reported in the literature, by colorimetry [2], spectrophotometry [3–8], atomic absorption spectrometry [8], spectrofluorometry [9–12], diffuse reflectance spectroscopy [13], chromatography [14,15], titrimetry [16], and chemiluminescence combined with flow injection analysis (FIA) [17,18]. However, these methods suffer from some disadvantages, such as high cost, long analysis time and requirement for sample pretreatment; on the other hand, some methods present low sensitivity and selectivity, which make them unsuitable for routine analysis. Electroanalytical methods, using conductometric titration [19], potentiometry [20], and voltammetry [21,22], were also developed.

There are few studies available on the voltammetric behavior of PROP in pharmaceutical formulations. El-Ries et al. [21] determined PROP after its transformation into nitropropranolol, because PROP is not electroreducible at a mercury electrode. Nitropropranolol gave rise to a well-resolved differential pulse polarographic peak at −0.275 V versus Ag/AgCl (saturated KCl), in a pH 2.0 Britton–Robinson buffer. The corresponding analytical curve was linear in the PROP concentration range 0.50–10 μmol L^{-1}, with a detection limit of 0.10 μmol L^{-1}. Radi et al. [22] reported on the voltammetric behavior of PROP using anodic adsorptive stripping differential pulse voltammetry (DPASV) with a carbon paste electrode. The obtained analytical curve was linear in the PROP concentration range 0.60–50 μmol L^{-1}, with a detection limit of 0.20 μmol L^{-1} and an accumulation time of 5 min, in a pH 2.0 Britton–Robinson buffer.

Several analytical methods were also developed for the determination of ATN in pharmaceutical formulations, using colorimetry [23], spectrophotometry [6,24,25], chromatography [14,26], and electroanalytical techniques [20,27,28].

Nikolelis et al. [29] developed an amperometric minisensor based on stabilized bilayer lipid membranes made from egg phosphatidylcholine. This sensor showed a linear response to ATN in the concentration range 2.0×10^{-5}–2.0×10^{-4} mol L^{-1}, with a detection limit of 1.8 μmol L^{-1} and a lifetime exceeding 48 h.

Goyal et al. [30,31] reported that ATN was not electrooxidizable at a bare glassy-carbon electrode within its accessible potential window in aqueous media, but a well-defined oxidation wave was observed with a C_{60}-modified electrode using differential pulse voltammetry (DPV). Calibrations curves were obtained in the ATN concentration ranges

* Corresponding author. Tel.: +55 16 33518098; fax: +55 16 33518350.
E-mail address: bello@ufscar.br (O. Fatibello-Filho).

0039-9140/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.talanta.2010.02.046

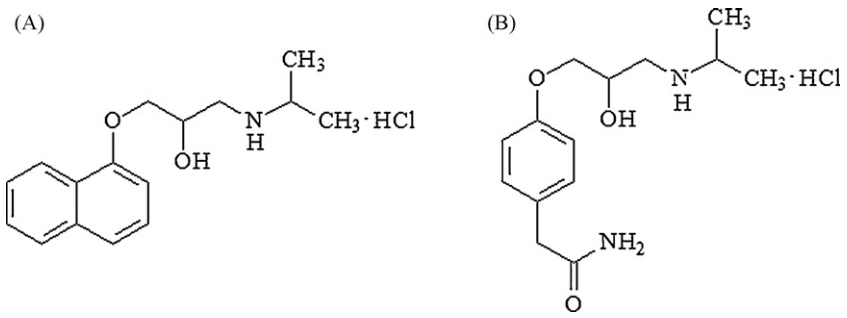

Fig. 1. Chemical structures of (A) propranolol and (B) atenolol hydrochloride.

2.5×10^{-4}–1.5×10^{-3} mol L^{-1}, for the C_{60}-modified glassy-carbon electrode, and 0.5×10^{-6}–1.0×10^{-3} mol L^{-1}, for a nanogold-modified indium tin oxide electrode, with respective detection limits of 0.16 mmol L^{-1} and 0.13 μmol L^{-1} in a pH 7.2 phosphate buffer. However, recently Hegde et al. [32] reported on the electrooxidation of ATN at a glassy-carbon electrode in tetramethylammonium chloride in methanolic media by cyclic voltammetry (CV). Additionally, Griese et al. [33] presented evidences that the electrochemical oxidation of ATN is achievable on a bare glassy-carbon electrode (pH 7.2 phosphate buffer solution), which is in direct contrast to what was previously reported by Goyal et al. [30,31].

Cervini et al. [34] used a bare graphite–polyurethane composite electrode in the determination of ATN in pharmaceutical formulations. The analytical curve was linear in the ATN concentration range 4.0×10^{-6}–1.0×10^{-4} mol L^{-1} in a pH 10.0 Britton–Robinson buffer, with a detection limit of 3.16 μmol L^{-1}. Later on, this electrode was evaluated as an amperometric detector in a FIA system [35], when a linear analytical curve in the ATN concentration range 2.0×10^{-4}–3.0×10^{-3} mol L^{-1} was obtained, with a detection limit of 18.1 μmol L^{-1} and an analytical frequency of 90 determinations/h.

Voltammetry is considered an important electrochemical technique for electroanalytical chemistry because it provides low cost, sensitivity, and precision, as well as accuracy, simplicity, and rapidity. On the other hand, boron-doped diamond (BDD) electrodes have been receiving increasing attention for application in the electroanalytical determination of pharmaceutical compounds [36–40], especially by our group [41–45]. BDD has very attractive properties when compared with other conventional electrodes (*e.g.* glassy-carbon or platinum electrodes): a very low and stable background current, an extreme electrochemical stability in both alkaline and acidic media, a high response sensitivity, and a very wide working potential window [46–48]. However, it is clear that the analytical performance of BDD electrodes greatly depends on their surface termination (*e.g.* hydrogen or oxygen terminated) [49,50].

In this paper, the determination of PROP and ATN in pharmaceutical formulations by square-wave voltammetry (SWV) using a cathodically pretreated BDD electrode was evaluated. The obtained results are compared with those from official spectrophotometric methods [3,24].

2. Experimental

2.1. Apparatus

The electrochemical experiments were conducted in a three-electrode single-compartment glass cell. A Pt wire was used as counter electrode. An Ag/AgCl (3.0 mol L^{-1} KCl) electrode was used as reference; all potentials hereinafter are referred to this reference electrode. The working electrode (0.33-cm^2 exposed area) was a BDD film (8000 ppm boron) on a silicon wafer from the Centre Suisse de Electronique et de Microtechnique SA (CSEM), Neuchatêl, Switzerland. Detailed information on this BDD electrode was reported elsewhere [50], while Gandini et al. [51] reported details on the preparation of these diamond films. Prior to the experiments for the analysis of PROP and ATN, the BDD electrode was cathodically pretreated in a 0.5 mol L^{-1} H_2SO_4 solution by applying −1.0 A cm^{-2} for 120 s; thus, the BDD surface was made predominantly hydrogen-terminated [49,50]. The voltammetric measurements were carried out using an EG&G-PARC potentiostat/galvanostat (model 273A, USA). The pH was measured at 25 ± 1 °C using an Orion pH-meter, Expandable Ion Analyser (model EA-940, USA), employing a combined glass electrode with an Ag/AgCl (3.0 mol L^{-1} KCl) external reference electrode. The OriginPro 6.0 software was used for data treatment.

The PROP and ATN determinations by the spectrophotometric reference methods were carried out using a Hewlett Packard UV-visible spectrophotometer (model 8452A, Germany), coupled to a microcomputer.

2.2. Reagents and solutions

All chemicals were of analytical grade and were used as received without any further purification: propranolol and atenolol (Sigma, Germany) and H_2SO_4 and $NaNO_3$ (Merck, Germany). The commercial pharmaceutical samples (tablets) were purchased from a local drugstore. All solutions were prepared using ultra-purified water supplied by a Milli-Q system (Millipore®, USA) with resistivity higher than 18 MΩ cm.

After due investigation, as reported further below, the following supporting electrolyte solutions were chosen for the PROP and ATN independent determinations: aqueous 0.1 mol L^{-1} H_2SO_4 and 0.5 mol L^{-1} $NaNO_3$ (pH 1.0, adjusted with concentrated HNO_3) solutions, respectively. Hereinafter these are used as the respective supporting electrolyte solutions if not mentioned otherwise. Standard solutions of 10 mmol L^{-1} PROP and 10 mmol L^{-1} ATN were prepared in the respective supporting electrolyte solutions.

2.3. Analytical procedures

After optimizing the experimental parameters for the proposed methods, the analytical curves were obtained by adding small volumes of the concentrated standard solutions of the two analytes. Square-wave (SW) and differential pulse (DP) voltammograms were obtained after each aliquot addition. Thus, the analytical parameters were compared and the best results were used to quantify PROP and ANT in the commercial samples. The limit of detection (*LOD*) was estimated as $3S_B/b$, where S_B is the standard deviation of the blank solution ($n = 10$) and b is the slope of the analytical curve.

For the recovery studies, aliquots of the standard solutions of both analytes were added to real samples prepared from tablets

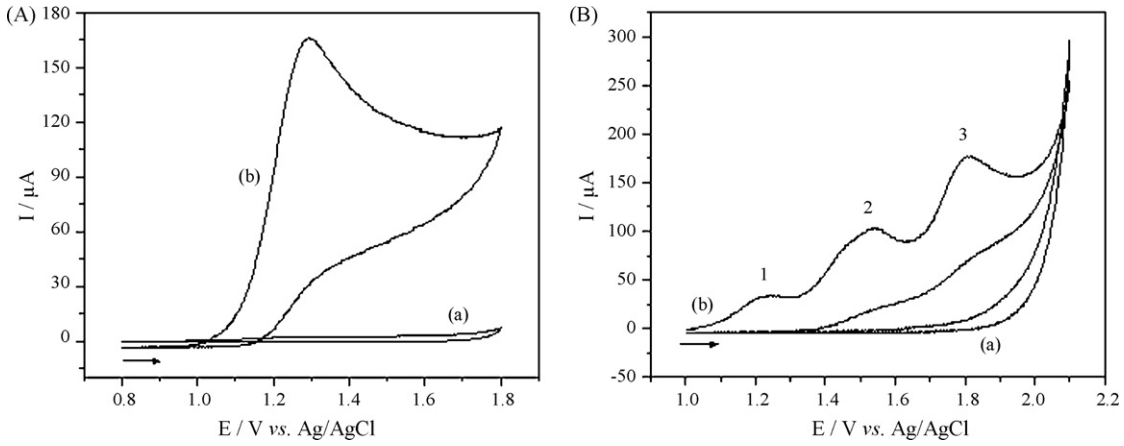

Fig. 2. Cyclic voltammograms obtained using a cathodically pretreated boron-doped diamond electrode as working electrode for: (A) (a) 0.1 mol L^{-1} H_2SO_4 and (b) 0.10 mmol L^{-1} PROP in 0.1 mol L^{-1} H_2SO_4, at 200 mV s^{-1} and (B) (a) 0.5 mol L^{-1} $NaNO_3$ and (b) 0.10 mmol L^{-1} ATN in 0.5 mol L^{-1} $NaNO_3$, at 50 mV s^{-1}.

of commercial pharmaceutical products. Sets of triplicate enrichments were carried out with increasing concentration of the β-blocker agents.

To prepare the solutions of the PROP and ATN commercial samples, a representative number of tablets (10) of each different pharmaceutical dosage was reduced to a homogeneous fine powder in a mortar with a pistil. An adequate amount of the resulting powders was weighed and transferred to a 25-mL calibrated flask, which was completed to volume with the respective supporting electrolyte solution. An aliquot of each sample solution was directly transferred to the electrochemical cell containing the respective supporting electrolyte, after which the SW voltammograms were obtained. The PROP and ATN concentration in each sample solution was determined directly by interpolation using the previously obtained analytical curves.

2.4. Reference methods

In order to compare the results obtained with the proposed SWV method, the spectrophotometric methods of the Brazilian and British Pharmacopoeias [3,24] for PROP and ATN, respectively, were employed. An accurate representative amount of powder from each PROP and/or ATN commercial sample in the different dosages was dissolved in methanol. Appropriate dilutions were made from this solution and then the absorbance was measured at 290 and 275 nm, respectively, in a quartz cell.

3. Results and discussion

3.1. Investigation of the electrochemical behavior

Initially, CV studies (not shown) of the electrochemical oxidation of 1.0 mmol L^{-1} PROP and 1.0 mmol L^{-1} ATN solutions at the cathodically pretreated BDD electrode were performed employing different supporting electrolytes, such as acetate, phosphate, and Britton–Robinson buffers, or sulfuric acid, potassium chloride, and sodium nitrate solutions. The voltammetric response for PROP in the sulfuric acid solution and that for ATN in the sodium nitrate solution were characterized by well-defined oxidation peaks and higher current values; thus, these solutions were selected as suitable supporting electrolytes for further experiments. The obtained voltammograms for PROP in 0.1 mol L^{-1} H_2SO_4 present one electrochemically irreversible anodic peak (Fig. 2A) at E_{ap} = 1.29 V. On the other hand, the obtained voltammograms for ATN in 0.5 mol L^{-1} $NaNO_3$ present three electrochemically irreversible anodic peaks (Fig. 2B); in this case, only peak 3, at E_{ap} = 1.80 V, will be used for further studies, because the intensity and resolution of its peak current were higher than those of peaks 1 and 2, which occur at less positive potentials.

The effect of the pH of the supporting electrolyte solution on the voltammetric response of PROP was firstly investigated (Fig. 3). Thus, H_2SO_4 concentrations from 0.10 mol L^{-1} to 0.50 mol L^{-1} were evaluated for 1.0 mmol L^{-1} PROP, at the 200-mV s^{-1} scan rate

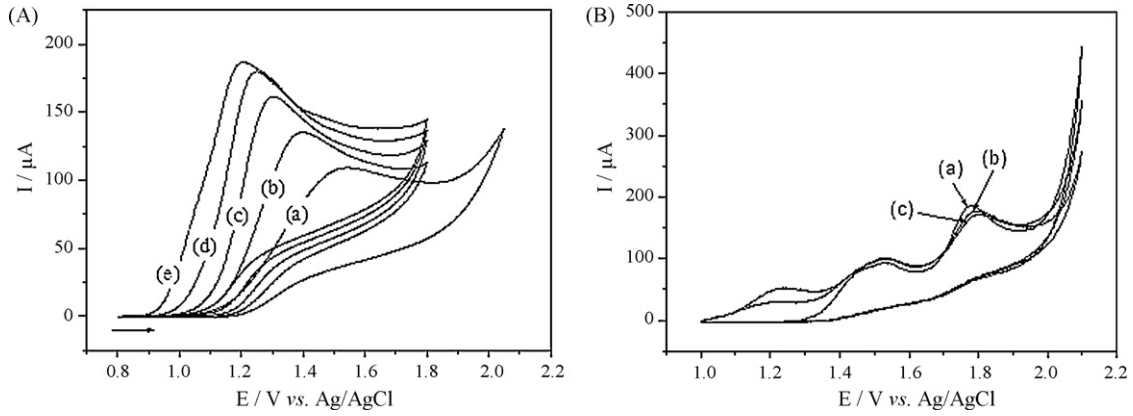

Fig. 3. Cyclic voltammograms obtained using a cathodically pretreated boron-doped diamond electrode as working electrode for: (A) for 1.0 mmol L^{-1} PROP in different concentrations of H_2SO_4: (a) 1.0×10^{-4} mol L^{-1}, (b) 1.0×10^{-3} mol L^{-1}, (c) 1.0×10^{-2} mol L^{-1}, (d) 1.0×10^{-1} mol L^{-1}, and (e) 5×10^{-1} mol L^{-1}, at 200 mV s^{-1} and (B) 1.0 mmol L^{-1} ATN in 0.5 mol L^{-1} $NaNO_3$ at different pHs: (a) 1.0, (b) 4.9, and (c) 10.0, at 50 mV s^{-1}.

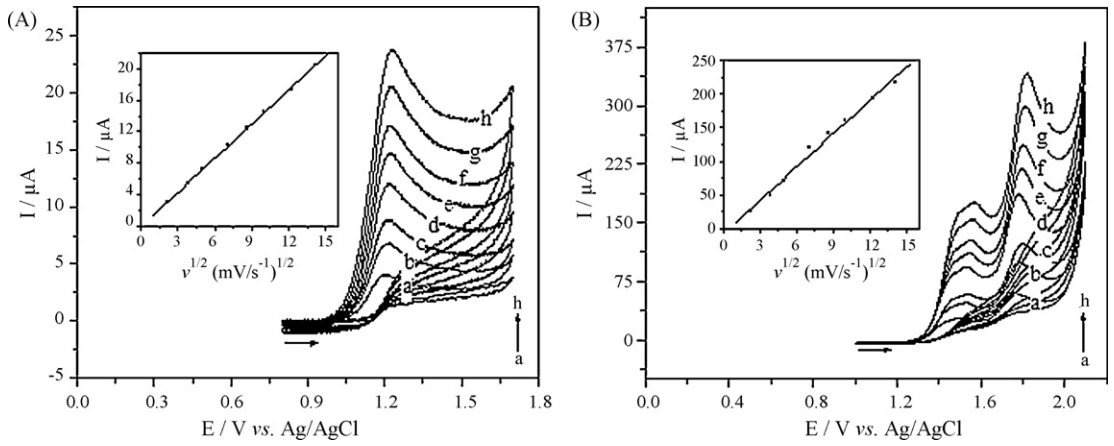

Fig. 4. Cyclic voltammograms obtained at different scan rates (ν) using a cathodically pretreated boron-doped diamond electrode as working electrode for: (A) 0.10 mmol L^{-1} PROP in a 0.1 mol L^{-1} H_2SO_4 solution and (B) 0.10 mmol L^{-1} ATN in a 0.5 mol L^{-1} $NaNO_3$ (pH 1.0) solution. ν = (a) 5 mV s^{-1}, (b) 15 mV s^{-1}, (c) 25 mV s^{-1}, (d) 50 mV s^{-1}, (e) 75 mV s^{-1}, (f) 100 mV s^{-1}, (g) 150 mV s^{-1}, and (h) 200 mV s^{-1}. Insert: linear dependence of the peak current with $\nu^{1/2}$.

(Fig. 3A). The peak potential shifted to less positive potentials as the H_2SO_4 concentration was increased; higher analytical signals were obtained for the 0.10 and 0.50 mol L^{-1} H_2SO_4 solutions (Fig. 3A(d) and (e), respectively). Hence, taking into account the reproducibility of the obtained results and the stability of the PROP solutions, 0.1 mol L^{-1} H_2SO_4 was selected as the supporting electrolyte for the PROP determinations.

Secondly, the effect of the concentration of the $NaNO_3$ solution (from 0.010 to 0.70 mol L^{-1}) on the voltammetric response of 1.0 mmol L^{-1} ATN was investigated (not shown). The highest value of the peak current was obtained for 0.50 mol L^{-1} $NaNO_3$, which was consequently selected for further studies. Then, the effect of pH (from 1 to 10, adjusted with concentrated HNO_3 or 2.0 mol L^{-1} NaOH) on the voltammetric response of ATN in this solution was also investigated. Fig. 3B shows the voltammograms obtained for pHs 1.0, 4.9, and 10. The oxidation potential associated to peak 3 for the 1.0 mmol L^{-1} ATN solution remained almost constant in this pH interval, but the best defined anodic peak was obtained in the pH 1.0 solution. Therefore, the 0.50 mol L^{-1} $NaNO_3$ solution (pH 1.0, adjusted with concentrated HNO_3) was selected as the supporting electrolyte for the ATN determinations.

As far as we know, there are no studies that reported an electrochemical mechanism for PROP oxidation. Possibly, the anodic peak here observed corresponds to the oxidation of the secondary alcoholic group in the PROP molecule, similarly to what was suggested by Goyal et al. [30,31] for the electrooxidation of ATN, based on results reported by Hiremath and co-workers [52,53] on the oxidation of ATN by permanganate in alkaline medium.

It should be called to attention that the cathodic pretreatment of the BDD electrode was most important for the herein reported independent determinations of PROP and ATN, as it has happened previously for some other analytes [42,43,45,54–56]. The voltammograms obtained for PROP and ATN with the cathodically pretreated BDD electrode presented a better peak definition and a higher current magnitude, indicating that the cathodic pretreatment of the electrode led to an enhanced electrochemical activity for the oxidation of both β-blocker agents.

The stability of the 0.10 mmol L^{-1} standard solutions of PROP and ATN was studied during an 8-h period at 25 °C by monitoring the PROP and ATN concentration by CV. The obtained results presented no significant differences in the peak currents and potentials among the measurements, with relative standard deviations of 1.0% and 1.2%, respectively, indicating that the degradation of PROP and ATN was negligible.

3.2. Effect of scan rate

Cyclic voltammograms were obtained at different scan rates from 5 to 200 mV s^{-1}, as shown in Fig. 4. The oxidation peak for both PROP in 0.1 mol L^{-1} H_2SO_4 and ATN in 0.5 mol L^{-1} $NaNO_3$ (pH 1.0 adjusted with concentrated HNO_3) shifted slightly toward more positive potentials as the scan rate increased, a behavior typical of irreversible electrochemical reactions [57]. Plots of the logarithm of the peak current versus the logarithm of the scan rate for PROP and ATN (peak 3) are linear, with slopes of 0.52 and 0.60, respectively, which are close to the theoretical value of 0.50 expected for an ideal reaction of species in solution. In addition, plots of the peak current versus the square root of the scan rate (inserts in Fig. 4A and B) are also linear, indicating that both electrooxidations are diffusion-controlled processes [57].

3.3. Optimization of SWV and DPV parameters

The optimization of the SWV and DPV parameters was carried out in a 0.10 mmol L^{-1} solution of PROP or ATN.

Table 1
Analytical parameters for the voltammetric determination of propranolol (PROP) and atenolol (ATN) by square-wave voltammetry (SWV) and differential pulse voltammetry (DPV) in respective supporting electrolytes, using a cathodically pretreated BDD electrode.

	PROP (in 0.1 mol L^{-1} H_2SO_4)		ATN (0.5 mol L^{-1} $NaNO_3$, pH 1.0)	
	SWV	DPV	SWV	DPV
Peak potential (V)	1.20	1.15	1.67	1.60
Linear range (μmol L^{-1})	0.20–9.0	0.20–11	2.0–41	2.0–41
Correlation coefficient	0.9994	0.9980	0.9997	0.9993
Slope (μA mol^{-1} L)	7.1×10^5	2.5×10^5	8.0×10^5	4.9×10^5
Intercept (μA)	0.25	0.19	1.3	0.73
Detection limit (μmol L^{-1})	0.18	0.19	0.93	1.3

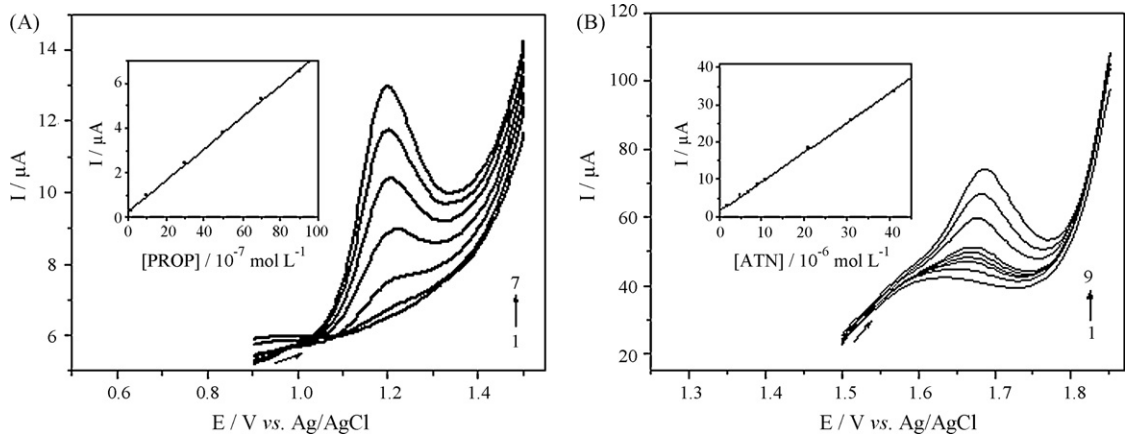

Fig. 5. Square-wave voltammetric response (direct current) obtained using a cathodically pretreated boron-doped diamond electrode as working electrode for: (A) (1) 0; (2) 0.20 μmol L^{-1}; (3) 1.0 μmol L^{-1}; (4) 3.0 μmol L^{-1}; (5) 5.0 μmol L^{-1}; (6) 7.0 μmol L^{-1}; and (7) 9.0 μmol L^{-1} PROP in 0.1 mol L^{-1} H_2SO_4 and (B) (1) 0; (2) 2.0 μmol L^{-1}; (3) 5.0 μmol L^{-1}; (4) 7.0 μmol L^{-1}; (5) 9.0 μmol L^{-1}; (6) 11 μmol L^{-1}; (7) 21 μmol L^{-1}; (8) 31 μmol L^{-1}; and (9) 41 μmol L^{-1} ATN in 0.5 mol L^{-1} $NaNO_3$ (pH 1.0). Inserts: Analytical curves for the PROP (A) and ATN (B) oxidation process.

The experimental parameters that affect the SWV response and their corresponding investigated ranges are: square-wave frequency (10 Hz ≤ f ≤ 200 Hz), pulse amplitude (10 mV ≤ a ≤ 100 mV), and scan increment (1 mV ≤ ΔE_S ≤ 7 mV). The obtained optimum values for these parameters were: f = 130 Hz, a = 50 mV, and ΔE_S = 6 mV, for PROP; f = 100 Hz, a = 40 mV, and ΔE_S = 4 mV, for ATN.

The influence of the experimental DPV parameters on the value of the peak oxidation current was also investigated: pulse amplitude (25 mV ≤ α ≤ 150 mV), scan rate (5 mV s^{-1} ≤ ν ≤ 20 mV s^{-1}), and modulation time (5 ms ≤ t ≤ 20 ms). The obtained optimum values for these parameters were α = 75 mV, ν = 10 mV s^{-1}, and t = 7 ms, for both PROP and ATN.

3.4. Analytical curves and validation parameters of the methods proposed for PROP and ATN determination

The previously optimized SWV and DPV experimental parameters were employed to record the analytical curves for PROP and ATN using the cathodically pretreated BDD electrode. The analytical parameters thus obtained for both the SWV and DPV proposed methods are summarized in Table 1 for PROP and ATN. Clearly, the best values for analytical parameters such as sensitivity and precision were obtained by SWV, which was thus the chosen method for the determination of both PROP and ATN.

SW voltammograms obtained after successive additions of the respective standard solution of each β-blocker using the cathodically pretreated BDD electrode are shown in Fig. 5 for the following concentration ranges: 0.20–9.0 μmol L^{-1}, for PROP (Fig. 5A), and 2.0–41 μmol L^{-1}, for ATN (Fig. 5B). The inserts in these figures depict the respective analytical curves obtained for PROP (r = 0.9994) and ATN (r = 0.9997), whose corresponding regression equations are I_{ap} (μA) = 0.25 + 0.71[c (μmol L^{-1})] and I_{ap} (μA) = 1.3 + 0.80[c (μmol L^{-1})], respectively, where I_{ap} is the anodic peak current and c the analyte concentration. The calculated *LOD* values are 0.18 μmol L^{-1}, for PROP, and 0.93 μmol L^{-1}, for ATN.

The intra-day repeatabilities of the peak current were determined by successive measurements (n = 10) of 5.0 μmol L^{-1} PROP and 11 μmol L^{-1} ATN solutions, when relative standard deviations of 0.33% and 0.78%, respectively, were obtained. The inter-day repeatabilities of the peak current were evaluated by measuring the peak current for similar fresh solutions over a period of 5 days. When these values were compared with the original peak current values, RSDs of 3.5% and 4.5% were obtained for PROP and ATN, respectively.

3.5. Interference studies

The effect of some possible interferents was investigated by addition of these compounds to standard solutions containing 3.0 μmol L^{-1} PROP or 11 μmol L^{-1} ATN. Hydrochlorothiazide (associated with PROP), chlortalidone, and nifedipine (associated with ATN), manithol, lactose, starch, povidone, magnesium stearate, and magnesium carbonate, present in the analyzed pharmaceutical samples, were tested at the concentration ratios (standard solution:interferent) 1:1, 1:10, and 10:1. The corresponding current

Table 2
Determination of propranolol (PROP) in pharmaceutical formulations by the proposed square-wave voltammetric (SWV) method, using a cathodically pretreated BDD electrode, and by the spectrophotometric reference method [3].

Samples	PROP (mg/tablet)			Relative error[a] (%)
	Label value	Reference method[b]	SWV method[b]	
A	10	9.93 ± 0.04	9.97 ± 0.02	0.4
B	40	37.0 ± 0.8	37.6 ± 0.6	1.6
C	40	39.8 ± 0.6	40.8 ± 0.5	2.5
D	40	40.3 ± 0.7	38.6 ± 0.6	−4.2
E[c]	40	43.7 ± 0.6	41.7 ± 0.4	−4.6
F	80	77.0 ± 0.9	78.8 ± 0.9	2.3

[a] [100 × (SWV value − reference method)]/reference method.
[b] Average of three measurements.
[c] Containing 25 mg of hydrochlorothiazide.

Table 3
Determination of atenolol (ATN) in pharmaceutical formulations by the proposed square-wave voltammetric (SWV) method, using a cathodically pretreated BDD electrode, and by the spectrophotometric reference method [24].

Samples	ATN (mg/tablet)			Relative error[a] (%)
	Label value	Reference method[b]	SWV method[b]	
A	25	24.2 ± 0.9	23.6 ± 0.6	−2.5
B	25	25.1 ± 0.5	25.8 ± 0.8	2.8
C[c]	25	25.7 ± 0.8	26.3 ± 0.7	2.3
D[d]	25	25.8 ± 0.9	26.3 ± 0.5	1.9
E	50	49.4 ± 0.8	47.7 ± 0.5	−3.4
F	100	98.7 ± 0.9	99.9 ± 0.7	1.2

[a] 100 × (SWV value−reference method)/reference method.
[b] Average of three measurements.
[c] Containing 12.5 mg of chlortalidone.
[d] Containing 10 mg of nifedipine.

Table 4
Comparison of the analytical parameters obtained using different electrodes and/or techniques for the determination of propranolol (PROP) and atenolol (ATN).

Analyte	Technique	Electrode	Concentration range (mol L^{-1})	*LOD* (mol L^{-1})	Reference
PROP	DPV	Static mercury drop	5.0×10^{-7}–1.0×10^{-5}	1.0×10^{-7}	[21]
	DPASV	Carbon paste	6.0×10^{-7}–5.0×10^{-5}	2.0×10^{-7}	[22]
	SWV	Boron-doped diamond (BDD)	2.0×10^{-7}–9.0×10^{-6}	1.8×10^{-7}	This work
ATN	DSC	Surface stabilized bilayer lipid membranes	2.0×10^{-5}–2.0×10^{-4}	1.8×10^{-6}	[29]
	DPV	C_{60}-modified glassy carbon	2.5×10^{-4}–1.5×10^{-3}	1.6×10^{-4}	[30]
	DPV	Nanogold-modified indium tin oxide	5.0×10^{-7}–1.0×10^{-3}	1.3×10^{-7}	[31]
	DPV	Graphite–polyurethane composite	4.0×10^{-6}–1.0×10^{-4}	3.16×10^{-6}	[32]
	Amperometry/FIA system	Graphite–polyurethane composite	2.0×10^{-4}–3.0×10^{-3}	1.81×10^{-5}	[33]
	SWV	Boron-doped diamond (BDD)	2.0×10^{-6}–4.1×10^{-5}	9.3×10^{-7}	This work

signals were compared with those obtained in the absence of each interferent. In the case of povidone, the concentration ratio 1:10 led to an error of −7.4% for PROP. On the other hand, in the case of lactose and magnesium carbonate, the concentration ratio 1:10 led to errors of 11.9% and 11.2%, respectively, for ATN. However, in the analyzed samples the contents of these interferents are much lower than those here investigated, thus not significantly interfering with the proposed method; consequently, PROP and ATN in the concomitant presence of those compounds can be accurately determined using the proposed method.

3.6. Application of the proposed methods in the determination of PROP and ATN in pharmaceutical products

Commercial pharmaceutical samples (tablets) containing PROP and/or ATN were analyzed to determine these substances in order to evaluate the validity of the herein proposed methods. Addition and recovery studies were carried out by addition of known volumes of PROP and ATN standard solutions to a given sample followed by analysis using the SWV technique. Good recoveries were obtained for the investigated commercial tablets, ranging from 93.9% to 105.0%, for PROP, and from 92.5% to 106.0%, for ATN, indicating that the matrix effect does not present any significant interference.

The results obtained employing the proposed methods as well as the standard spectrophotometric methods of the Brazilian Pharmacopoeia [3], for PROP, and the British Pharmacopoeia [24], for ATN, in several commercial tablets are presented in Tables 2 and 3, respectively. Three determinations were carried out for each sample, and the standard deviations were calculated. The amount of PROP and ATN in each sample solution was determined by interpolation in the respective analytical curve previously obtained. As it can be seen in these tables, no significant differences were observed between the values found for the amounts of PROP and ATN in the tablets using the SWV proposed methods and the spectrophotometric reference methods [3,24]. Besides, the paired *t*-test [58] was applied to the results obtained for PROP and ATN using both methods; since the calculated *t* value (1.170 for PROP and 0.2700 for ATN) is smaller than the critical value (2.571, $\alpha = 0.05$), one may conclude that the results obtained with the proposed procedures are not statistically different from those from the comparative methods, at a 95% confidence level.

Finally, it should be mentioned once again that there are not many articles reporting on electroanalytical methods for the determination of PROP and ATN. Thus, the analytical characteristics resulting from the studies herein reported and those obtained with other electrodes and/or techniques are summarized in Table 4. From these data, it can be seen that the *LOD* value for PROP obtained in this work is quite similar to that obtained by El-Ries et al. [21] using a static mercury drop electrode and by Radi et al. [22] using a carbon paste electrode. On the other hand, the *LOD* value obtained for ATN using the herein proposed method is lower than those obtained by voltammetric methods [29,30,32,33], but higher than those obtained by Goyal et al. [31] using a nanogold-modified indium tin oxide electrode.

4. Conclusions

A cathodically pretreated BDD electrode was successfully used for the independent SW voltammetric determination of PROP and ATN in real pharmaceutical samples of different dosages using adequate supporting electrolyte solutions: 0.1 mol L^{-1} H_2SO_4, for PROP determination, and 0.5 mol L^{-1} $NaNO_3$ (pH 1.0, adjusted with concentrated HNO_3). Under these conditions, detection limits of 0.18 μmol L^{-1} for PROP and 0.93 μmol L^{-1} for ATN are attained. Furthermore, the obtained recoveries range from 93.9% to 105.0%, for PROP, and from 92.5% to 106.0%, for ATN. The proposed methods are simple, rapid, sensitive, precise, and accurate, being applicable directly to the analysis of the commercial pharmaceuticals simply after dissolution of their samples, dispensing any use of organic reagents or expensive apparatus.

Acknowledgements

The authors gratefully acknowledge financial support and scholarships from the Brazilian funding agencies CAPES, CNPq, and FAPESP.

References

[1] J.G. Hardman, L.E. Limbird, A.G. Gilman, Goodman & Gilman's—The Pharmacological Basis of Therapeutics, 9th ed., McGraw-Hill, New York, 1996.
[2] O.S. Idowu, O.A. Adegoke, A.A. Olaniyi, J. AOAC Int. 87 (2004) 573.
[3] Farmacopéia Brasileira—Part II, 4th ed., Atheneu Editora, São Paulo, 2002.
[4] C.S.P. Sastry, K.R. Srinivas, K.M.M.K. Prasad, Microchim. Acta 122 (1996) 77.
[5] B.G. Gowda, J. Seetharamappa, M.B. Melwanki, Anal. Sci. 18 (2002) 671.
[6] A.J. Gölcü, Anal. Chem. 63 (2008) 538.
[7] H. Salem, J. Pharm. Biomed. Anal. 29 (2002) 527.
[8] M.A. El-Ries, F.M. Abou Attia, S.A. Ibrahim, J. Pharm. Biomed. Anal. 24 (2000) 179.
[9] A.M. Delapena, F. Salinas, M.S. Duran, Anal. Chim. Acta 255 (1991) 317.
[10] T. Pérez Ruiz, C. Martínez-Lozano, V. Tomás, J. Carpena, Talanta 45 (1998) 969.
[11] K.C. Ramesh, B.G. Gowda, J. Seetharamappa, J. Keshavayya, J. Anal. Chem. 58 (2003) 933.
[12] A.B.J. Tabrizi, Food Drug Anal. 15 (2007) 242.
[13] M.A. Gotardo, J.O. Tognolli, H.R. Pezza, L. Pezza, Spectrosc. Acta A 69 (2008) 1103.
[14] I.R. Rapado-Martínez, M.C.G.A. Coque, R.M.V. Camañas, J. Chromatogr. A 765 (1997) 221.
[15] Y.S. El-Saharty, J. Pharm. Biomed. Anal. 33 (2003) 699.
[16] V.N. Pathak, M.S.R. Shukla, I.C. Shuklahukla, Analyst 107 (1982) 1086.
[17] A. Townshend, J.A. Murillo Pulgarín, M.T. Alañón Pardo, Anal. Chim. Acta 488 (2003) 81.
[18] G.Z. Tsogas, D.V. Stergiou, A.G. Vlessidis, N.P. Evmiridis, Anal. Chim. Acta 541 (2005) 151.
[19] Y.M. Issa, A.S. Amin, Microchim. Acta 118 (1995) 85.
[20] S.S.M. Hassan, M.M. Abou-Sekkina, M.A. El-Ries, A.A. Wassel, J. Pharm. Biomed. Anal. 32 (2003) 175.
[21] M.A. El-Ries, M.M. Abou-Sekkina, A.A. Wassel, J. Pharm. Biomed. Anal. 30 (2002) 837.
[22] A. Radi, A.A. Wassel, M.A. El-Ries, Chem. Anal. 49 (2004) 51.
[23] A.S. Amin, G.H. Ragab, H. Saleh, J. Pharm. Biomed. Anal. 30 (2002) 1347.
[24] British Pharmacopoeia, HMSO, London, 1998.
[25] S.M. Al-Ghannam, J. Pharm. Biomed. Anal. 40 (2006) 151.

[26] A.A. Elshanawane, S.M. Mostafa, M.S. Elgawish, J. AOAC Int. 92 (2009) 404.
[27] M. Arvand, M. Vedjani, M. Moghimi, Desalination 225 (2008) 176.
[28] N.K. Ramadan, H.E. Zaazaa, J. AOAC Int. 90 (2007) 987.
[29] D.P. Nikolelis, S.S.E. Petropoulos, M.V. Mitrokotsa, Bioelectrochemistry 58 (2002) 107.
[30] R.N. Goyal, V.K. Gupta, M. Oyama, N. Bacheeti, Electrochem. Commun. 8 (2006) 65.
[31] R.N. Goyal, S.P. Singh, Talanta 69 (2006) 932.
[32] R.N. Hegde, B.E. Kumara Swamy, B.S. Sherigara, S.T. Nandibewoor, Int. J. Electrochem. Sci. 3 (2008) 302.
[33] S. Griese, D.K. Kampouris, R.O. Kadara, C.E. Banks, Electrochem. Commun. 10 (2008) 1633.
[34] P. Cervini, L.A. Ramos, E.T.G. Cavalheiro, Talanta 72 (2007) 206.
[35] P. Cervini, E.T.G. Cavalheiro, Anal. Lett. 41 (2008) 1867.
[36] R.T.S. Oliveira, G.R. Salazar-Banda, V.S. Ferreira, S.C. Oliveira, L.A. Avaca, Electroanalysis 19 (2007) 1189.
[37] T. Spătaru, N. Spătaru, A. Fujishima, Talanta 73 (2007) 404.
[38] U. Bengi, B.D. Topal, S.A. Ozkan, Talanta 74 (2008) 1191.
[39] C.D. Souza, O.C. Braga, I.C. Vieira, A. Spinelli, Sens. Actuators B 135 (2008) 66.
[40] Y. Altun, B. Dogan-Topal, B. Uslu, S.A. Ozkan, Electrochim. Acta 54 (2009) 1893.
[41] E.R. Sartori, R.A. Medeiros, R.C. Rocha-Filho, O. Fatibello-Filho, J. Braz. Chem. Soc. 20 (2009) 360.
[42] B.C. Lourenção, R.A. Medeiros, R.C. Rocha-Filho, L.H. Mazo, O. Fatibello-Filho, Talanta 78 (2009) 748.
[43] L.S. Andrade, R.C. Rocha-Filho, Q.B. Cass, O. Fatibello-Filho, Electroanalysis 12 (2009) 1475.
[44] L.S. Andrade, M.C. de Moraes, R.C. Rocha-Filho, Q.B. Cass, O. Fatibello-Filho, Anal. Chim. Acta 654 (2009) 127.
[45] E.F. Batista, E.R. Sartori, R.A. Medeiros, R.C. Rocha-Filho, O. Fatibello-Filho, Anal. Lett. 43 (2010), doi:10.1080/00032710903491153.
[46] Y.V. Pleskov, Russ. J. Electrochem. 38 (2002) 1275.
[47] R.G. Compton, J.S. Foord, F. Marken, Electroanalysis 15 (2003) 1349.
[48] M. Hupert, A. Muck, R. Wang, J. Stotter, Z. Cvackova, S. Haymond, Y. Show, G.M. Swain, Diam. Relat. Mater. 12 (2003) 1940.
[49] H.B. Suffredini, V.A. Pedrosa, L. Codognoto, S.A.S. Machado, R.C. Rocha-Filho, L.A. Avaca, Electrochim. Acta 49 (2004) 4021.
[50] G.R. Salazar-Banda, L.S. Andrade, P.A.P. Nascente, P.S. Pizani, R.C. Rocha-Filho, L.A. Avaca, Electrochim. Acta 51 (2006) 4612.
[51] D. Gandini, P. Michaud, I. Duo, E. Mache, W. Haenni, A. Perret, C. Conminellis, New Diam. Front. Carbon Technol. 9 (1999) 303.
[52] G.C. Hiremath, R.M. Kulbarni, S.T. Nandibewoor, Ind. J. Chem. 44A (2005) 245.
[53] R.M. Mulla, G.C. Hiremath, S.T. Nandibe, J. Chem. Sci. 117 (2005) 33.
[54] R.A. Medeiros, A.E. de Carvalho, R.C. Rocha-Filho, O. Fatibello-Filho, Talanta 76 (2008) 685.
[55] R.A. Medeiros, A.E. de Carvalho, R.C. Rocha-Filho, O. Fatibello-Filho, Anal. Lett. 40 (2007) 3195.
[56] R.A. Medeiros, A.E. de Carvalho, R.C. Rocha-Filho, O. Fatibello-Filho, Quim. Nova 31 (2008) 1405.
[57] D.K. Gosser, Cyclic Voltammetry, VCH Publishers, New York, 1994.
[58] R.L. Anderson, Practical Statistics for Analytical Chemists, Van Nostrand Reinhold, New York, 1987.