Orbital: The Electronic Journal of Chemistry
journal homepage: www.orbital.ufms.br
ISSN 1984-6428

| Vol 8 | | No. 3 | | April-June 2016 |

Full Paper

Square-Wave Voltammetric Determination of Antihistaminic Drug Hydroxyzine in Pharmaceuticals Using a Boron-doped Diamond Electrode

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Article history: Received: 19 December 2015; revised: 29 March 2016; accepted: 02 April 2016. Available online: 30 June 2016. DOI: http://dx.doi.org/10.17807/orbital.v8i3.833

Abstract: The determination of antihistaminic hydroxyzine using square-wave voltammetry and a cathodically pretreated boron-doped diamond electrode is described. The obtained analytical curve was linear in the hydroxyzine concentration range 0.50 – 20.0 μmol L^{-1} in 0.1 mol L^{-1} HCl solution, with a detection limit of 0.43 μmol L^{-1}. Addition and recovery studies in commercial tables and liquid formulations showed excellent recovery values ranging from 94.3 % to 104 %. Furthermore, the proposed method was successfully applied in the determination of hydroxyzine in several pharmaceutical formulations and the results were in a close agreement at a 95 % confidence level with those obtained using an official potentiometric method.

Keywords: hydroxyzine determination; boron-doped diamond electrode; cathodic pretreatment; antihistaminic drug; pharmaceutical formulations

1. INTRODUCTION

Hydroxyzine dihydrochloride (HDZ) (2-[2-[4-[(4-chlorophenyl) phenylmethyl] piperazine-1-yl] ethoxy] ethanol dihydrochloride – Fig. 1) is used primarily as an antihistaminic to treat allergic reactions, an antiemetic for the reduction of nausea and as a rapid anxiolytic agent for the treatment of anxiety. Thus, the therapeutical and pharmacological relevance of this compound justifies the interest in developing accurate analytical procedure to assess the quality of pharmaceutical formulations that contain it. Controlling the amount of HDZ in a given commercial formulation is important and vital for health of patient during of treatment [1].

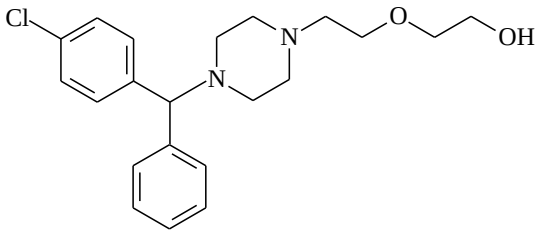

Figure 1. Chemical structure of hydroxyzine.

Some analytical procedures were developed for HDZ quantification in pharmaceutical formulations. These include chromatography [2-5], capillary electrophoresis [6], spectrophotometry [7, 8], and indirect titrimetry [7, 9]. Most of the reported procedures suffer from some disadvantages such as high costs, complicated procedure, long analysis times, low detection ability, and requirement for sample pretreatment that makes them unsuitable for routine analysis.

Electroanalytical methods, such as conductometric titration [10, 11], potentiometry [12, 13], and voltammetry [14, 15] were also developed for the analysis of HDZ in pharmaceutical formulations. Mikulski and Dembinski [10] developed a method for HDZ determination based on a conductometric titration using ammonium molybdate reagent. This technique was also used by Youssef and Farghali [11] for HDZ determination in pharmaceutical formulation, using phosphotungstic, phosphomolybdic and silicomolybdic acids. The endpoints were located by conventional and first derivative conductometric method. The British Pharmacopoeia method [12] is based on the

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potentiometric titration of HDZ in non-aqueous medium using perchloric acid. Bouklouze *et al.* [13] constructed a poly(vinyl chloride) (PVC) matrix membrane sensor for the potentiometric determination of HDZ in pharmaceutical formulations based on the use of ion association complex of HDZ with silicotungstate. This electrode exhibited a near-Nernstian response (57 mV/decade) in the HDZ concentration range from 6.0×10^{-7} mol L^{-1} to 1.0×10^{-2} mol L^{-1}, with a detection limit of 2.5×10^{-7} mol L^{-1}.

There are few studies available on the voltammetric behavior of HDZ in pharmaceutical formulations. Beltagi *et al.* [14] employed a glassy-carbon electrode and square-wave adsorptive anodic stripping voltammetry for HDZ determination in commercial tablets and human serum. The analytical curve was linear in the HDZ concentration range $5.0 \times 10^{-8} - 4.0 \times 10^{-6}$ mol L^{-1}, with a concentration time of 180 s, in a pH 4.0 Britton-Robinson buffer, and a detection limit of 1.5×10^{-8} mol L^{-1}. Nevertheless, this method requires methanol for extraction of HDZ from the samples and sonication for about 15 min. Huang *et al.* [15] developed a stripping voltammetric method to HDZ determination in drug tablets with a glassy carbon electrode modified with multiwalled carbon nanotubes (GCE-MWCNTs). The analytical curve was linear in the HDZ concentration range $5.0 \times 10^{-8} - 2.5 \times 10^{-5}$ mol L^{-1} in a pH 7.0 NaH_2PO_4-Na_2HPO_4 buffer, with a detection limit of 5.0×10^{-9} mol L^{-1}. Despite the very good results found by these authors, as shown above, they require a surface modification of electrode or a time-consuming step of pre-accumulation of the analyte into the working electrode before each determination.

The boron-doped diamond electrode (BDDE) is a useful alternative to carbon or platinum electrodes because of many important properties, such as very wide working potential window, which can be larger than 3.5 V, an extreme electrochemical stability in both alkaline and acidic media, a very low and stable background current, long term stability, slight adsorption of polar molecules, a high mechanical strength and a high response sensitivity [16-18]. Determination of several individual or simultaneous molecules in pharmaceuticals using BDDE has been satisfactorily determined [19-23], with good selectivity, repeatability and reproducibility in all cases.

In this paper, the determination of HDZ in pharmaceutical formulations by square-wave voltammetry (SWV), without accumulation step, using a cathodically pretreated BDDE was evaluated. The obtained results were compared with those from official potentiometric method [12].

2. MATERIALS AND METHODS

2.1 Reagents and solutions

All chemicals were of analytical grade and were used as received without any further purification. Hydroxyzine dihydrochloride was purchased from Sigma-Aldrich and hydrochloric acid from Merck. The commercial pharmaceutical samples (tablets and liquid sample) were purchased from a local drugstore. All solutions were prepared using ultra-purified water supplied by a Milli-Q system (Millipore®) with a resistivity not lower than 18 MΩ cm.

After due investigation, as reported further below, the 0.1 mol L^{-1} HCl solution was chosen as supporting solution. In this investigation, the standard solution of 10.0 mmol L^{-1} HDZ was prepared in the respective supporting electrolyte solution. Appropriate dilutions of these solutions were made in volumetric flasks of 10.0 mL using the same supporting solution.

2.2 Apparatus

The electrochemical experiments were conducted in a three-electrode single-compartment glass cell. A Pt wire was used as counter electrode. A 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 [24] (0.24-cm^2 exposed area) was a boron-doped (8000 ppm) diamond film on a silicon wafer from Centre Suisse de Electronique et de Microtechnique SA (CSEM), Neuchatêl, Switzerland. Prior to the experiments, the BDDE was anodically pretreated in a 0.5 mol L^{-1} H_2SO_4 solution by applying 0.5 A cm^{-2}, during 30 s, after the BDDE was cathodically pretreated in a 0.5 mol L^{-1} H_2SO_4 solution by applying –0.5 A cm^{-2}, during 120 s; thus, the BDDE surface was made predominantly hydrogen-terminated [25].

The voltammetric measurements were carried out using PalmSens potentiostat/galvanostat controlled with the PalmSens PC software. Surface pretreatment of BDDE was carried out using an MQPG-01 potentiostat (Microquímica). The measure

of pH (25 ± 1 °C) and the HDZ determination by the potentiometric reference method were carried out using a pH-meter (Hanna Instruments), model HI-221, employing a combined glass electrode with a Ag/AgCl (3.0 mol L^{-1} KCl) external reference electrode.

2.3 Analytical procedures

After optimizing the experimental parameters for the proposed methods, the analytical curves were constructed by addition of aliquots of the previously prepared standard solution of HDZ into the measurement cell containing 0.1 mol L^{-1} HCl solution. SW and differential pulse (DP) voltammograms were obtained after addition of each aliquot. Thus, the analytical parameters were compared and the best results were used to quantify HDZ in the commercial samples.

For the recovery studies, aliquots of the standard solution of HDZ were added to real samples prepared from tablets and liquid sample of the commercial pharmaceutical products. Sets of triplicate enrichments were added with increasing concentration of the HDZ.

To prepare solutions of the commercial samples of HDZ, a representative number of tablets (10) of each different pharmaceutical dosage were reduced to a homogeneous fine powder in a mortar. An adequate amount of the powders was weighed and transferred to a 25.0 mL calibrated flask, which was completed to volume with the respective supporting electrolyte solution. Non-dissolved solids were filtered through a filter paper. For the liquid sample, an adequate aliquot was diluted in a 10.0 mL calibrated flask of supporting electrolyte solution. An aliquot of each sample solution was directly transferred to the electrochemical cell containing the supporting electrolyte, after which the SW voltammogram was obtained. The HDZ concentration in each sample solution was determined directly by interpolation in the previously obtained analytical curve.

In order to compare the results obtained with the proposed SWV method, the potentiometric method of the British Pharmacopoeia was employed, which the samples (tablets or liquid sample) in different dosages of HDZ were titrated with a standardized 0.10 mol L^{-1} perchloric acid solution. The end-point was determined potentiometrically.

3. RESULTS AND DISCUSSION

3.1 Electrochemical behavior of HDZ

The electrochemical behavior of HDZ at the BDDE was studied by cyclic voltammetry (CV) employing different supporting electrolytes such as, Britton–Robinson buffer, H_2SO_4, and HCl solutions. The voltammetric response for HDZ in the HCl solution was characterized by a well-defined oxidation peak with a good repeatability of the obtained analytical signal; thus, HCl solution was selected as suitable supporting electrolyte for further experiments. The electron transfer process of HDZ may be attributed to the oxidation of the hydroxyl group of the aliphatic chain moiety of the molecule, as previously reported by Beltagi *et al.* [14].

The obtained voltammograms for 1.0 mmol L^{-1} HDZ in 0.1 mol L^{-1} HCl solution present one electrochemically irreversible anodic peak (Fig. 2) (E_{ap}) at a potential of 1.57 V. Next, the effect of pH on the voltammetric response for HDZ was also studied in acidic medium (pH 1.0), moderately acidic (pH 5.0) and alkaline medium (pH 9.0) (adjusted with concentrated HCl or 2.0 mol L^{-1} KOH solution). Fig. 3 shows the voltammograms obtained for pH values. As observed, the oxidation potential for the 1.0 mmol L^{-1} HDZ solution remained almost constant in this pH interval, but the most well defined anodic peak was obtained at pH 1.0 solution. Therefore, 0.1 mol L^{-1} HCl solution was selected as the supporting electrolyte for the HDZ determinations.

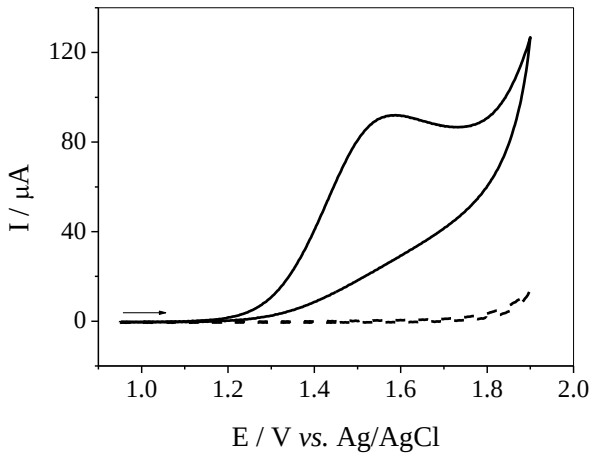

Figure 2. Cyclic voltammograms obtained using the BDDE for: (dashed line) 0.1 mol L^{-1} HCl solution and (solid line) 1.0 mmol L^{-1} HDZ in 0.1 mol L^{-1} HCl solution, at 50 mV s^{-1}.

Next, the BDDE was anodically (0.5 A cm^{-2} for 40 s) or cathodically (–0.5 A cm^{-2} for 180 s) pretreated and its response was assessed in 0.1 mol

L^{-1} HCl solution, as presented in Fig. 4. This study was carried out to obtain an improvement of the electrochemical response of the BDDE for the determination of the HDZ. The cathodically pretreated BDDE presented a less positive anodic peak potential, a better peak definition, and a higher current magnitude, indicating that this pretreatment of the electrode led to a larger electrochemical activity for HDZ oxidation, as it was observed previously for other analytes [20-23]. In addition, a better repeatability of the obtained analytical signal was obtained when compared with anodic pretreatment.

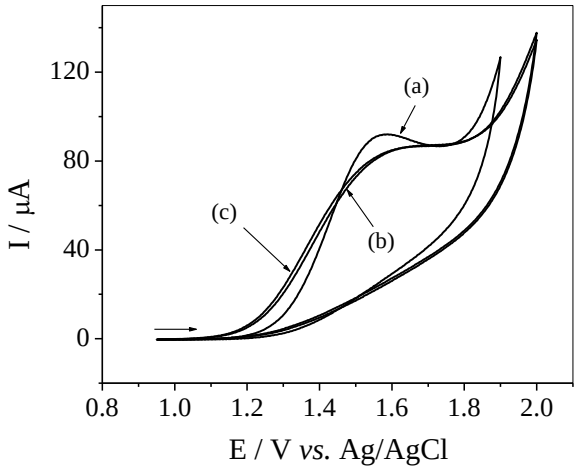

Figure 3. Cyclic voltammograms (50 mV s^{-1}) obtained using the BDDE for: 1.0 mmol L^{-1} HDZ in different pH values: (a) 1.0, (b) 5.0, and (c) 9.0.

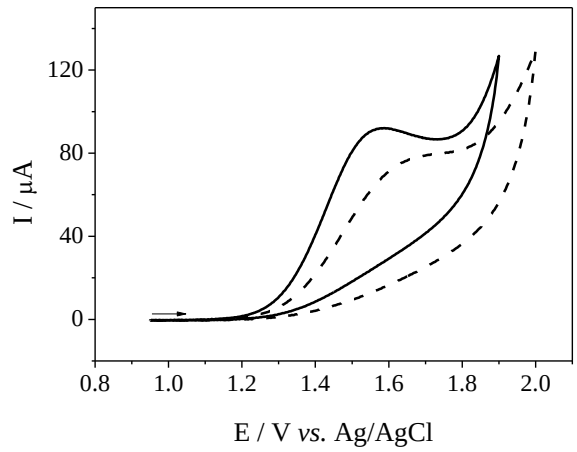

Figure 4. Cyclic voltammograms (50 mV s^{-1}) on BDDE for 1.0 mmol L^{-1} HDZ in 0.1 mol L^{-1} HCl soution: (dotted line) anodic and (solid line) cathodic pretreatment.

The stability of the 1.0 mmol L^{-1} HDZ stock solution in 0.1 mol L^{-1} HCl was studied during an 8-h period at 25 °C by monitoring the HDZ concentration by cyclic voltammetry. The obtained results presented no significant differences in the peak currents and potentials among the measurements and a relative standard deviation of 2.4 % was obtained, indicating that the degradation of HDZ was negligible in this time period.

Cyclic voltamograms were obtained at different scan rates from 15 to 200 mV s^{-1}. The oxidation pea for HDZ in 0.1 mol L^{-1} HCl solution shifted slightly toward more positive potentials as the scan rate increased, a typical characteristic of an irreversible electrochemical reaction [26]. Plots of the logarithm of the peak current versus the logarithm of the scan rate for HDZ is linear, with a slope of 0.53, which are close to the theoretical value of 0.50 expected for an ideal reaction of solution species. In addition, a plot of the peak current versus the square root of the scan rate is also linear, indicating that the electro-oxidation is a diffusion-controlled process [26].

3.2 Analytical curves for HDZ

The influence of the instrumental SWV and DPV parameters on the magnitude of the oxidation peak current was investigated. The parameters of both were optimized using solutions of 0.10 mmol L^{-1} in 0.1 mol L^{-1} HCl solution.

The corresponding investigated ranges for SWV parameters were: 10–150 s^{-1}, for square wave frequency f; 10–100 mV, for pulse amplitude a; 1–7 mV, for the scan increment ΔE_S. The obtained optimized values were f = 70 s^{-1}, a = 50 mV, and ΔE_S = 5 mV. Additionally, the number of transferred electrons in the redox process was calculated using Eq. (1) [27]:

$$\Delta E_{ap}/\Delta \log f = 2.3RT/\alpha nF \qquad \text{(Eq. 1)}$$

where α is the charge transfer coefficient and n the number of electrons transferred. Other symbols have their usual meanings. From the slope of 0.054, obtained from the linear plot of ΔE_{ap} *vs.* $\Delta \log f$, αn value was calculated to be 1.2 and n was calculated to be 2, indicating that the two electrons per molecule are involved in the oxidation of HDZ in 0.1 mol L^{-1} HCl solution, as shown in Fig. 5. This result corroborates the results obtained by Beltagi *et al.* [14], in which the electron transfer takes place by the oxidation of the hydroxyl group of the aliphatic chain moiety of the HDZ.

The ranges studied for DPV parameters were 25–150 mV for pulse amplitude (α), 5–20 mV s^{-1} for

scan rate (ν) and 5–20 ms for modulation time (t). The optimized values were α = 50 mV, ν = 15 mV s^{-1}, and t = 10 ms.

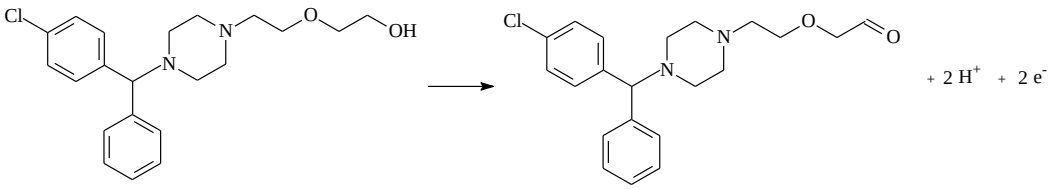

Figure 5. Proposed oxidation mechanism of hydroxyzine.

The previously optimized SWV and DPV experimental parameters were employed to record the analytical curves for HDZ in 0.1 mol L^{-1} HCl solution using the cathodically pretreated BDDE. The analytical parameters thus obtained for both the SWV and DPV of the proposed methods are summarized in Table 1 for HDZ. As can be observed, the best values for analytical parameters such as sensitivity and precision were obtained for SWV technique.

Table 1. Analytical parameters for the voltammetric determination of HDZ by SWV and DPV in 0.1 mol L^{-1} HCl solution, using a cathodically pretreated BDDE.

	SWV	**DPV**
Peak potential (V)	1.25	1.17
Linear range (µM)	0.50 to 20.0	1.0 to 20.0
Correlation coefficient (r)	0.9989	0.9954
Slope (µA mol^{-1} L)	2.9×10^5	1.6×10^5
Intercept (µA)	0.040	0.023
Detection limit (µmol L^{-1})	0.43	0.84

Furthermore, this analytical method for the determination of the HDZ was selected.

In Fig. 6 the SW voltammograms obtained for HDZ reference solutions at different concentrations (0.50 to 20.0 µmol L^{-1}) in 0.1 mol L^{-1} HCl solution were shown. The inset in this figure depicts the respective analytical curve obtained for HDZ (r = 0.9989), whose corresponding regression equation is I_{ap}/µA = 0.040 + 2.9×10^5 [c/(M)], where I_{ap} is the anodic peak current and c is the HDZ concentration. The calculated detection limit (LOD) value (three times the standard deviation of the blank solution/slope of the analytical curve) was 0.43 µmol L^{-1}. From these data, it can be seen that the LOD value for HDZ obtained in this work is higher than those obtained by voltammetric methods reported in the literature for the determination of this analyte in pharmaceutical formulations. On the other hand, the BDDE can be applied in the determination of HDZ without a modification of surface, regeneration of surface electrode (polishing) or a pre-accumulation of the analyte when the glassy carbon electrode is employed.

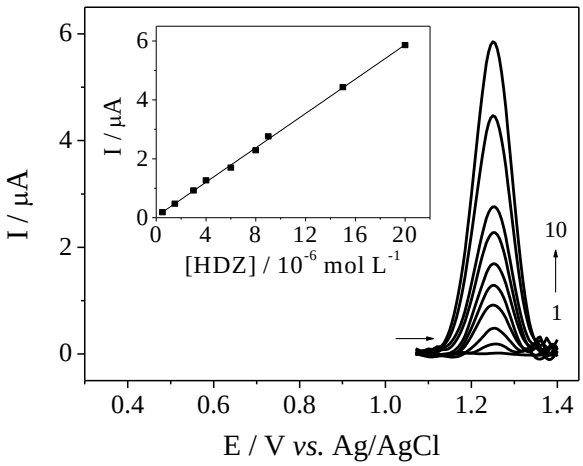

Figure 6. Square-wave voltammetric response obtained using the cathodically pretreated BDDE for: (1) 0; (2) 0.50; (3) 1.5; (4) 3.0; (5) 4.0; (6) 6.0; (7) 8.0; (8) 9.0 (9) 15.0 (10) 20.0 µmol L^{-1} HDZ in 0.1 mol L^{-1} HCl solution. Inset: Analytical curve for the HDZ oxidation

The intra-day repeatability of the peak current was determined by successive measurements (n = 10) of 6.0 µmol L^{-1} HDZ solution and a relative standard deviation of 0.94 % was obtained. The inter-day repeatability of the peak current was evaluated by measuring the peak current for similar fresh solutions over a period of 5 days a RSD of 3.1 % was obtained, showing thus the importance of the proposed method.

3.3. Application of the proposed method in the determination of HDZ in pharmaceuticals

The effect of some possible interferent compounds was investigated by addition of these compounds to standard solutions containing 6.0 µmol L^{-1} HDZ. Lactose, magnesium stearate, and poly(vinylpyrrolidone), present in the analyzed pharmaceutical samples were tested at the concentration ratios (standard solution:interferent compound) of 1:1, 1:10, and 10:1. The corresponding current signals were compared with those obtained in the absence of each interferent compound. The obtained responses showed that these compounds do not significantly interfere with the determination of HDZ at the used working conditions.

Commercial pharmaceutical samples (liquid and tablets) containing HDZ were analyzed to determine this substance in order to evaluate the validity of the herein proposed method. Addition and recovery studies were carried out by addition of known volumes of HDZ standard solution to a given sample followed by analysis using the SWV technique. Good recoveries were obtained for the investigated commercial tablets and liquid, ranging from 94.3 % to 104.0 %, indicating a free-interference determination of HDZ in these samples.

The results obtained employing the proposed method as well as the standard potentiometric method of the British Pharmacopoeia [12], in commercial tablets and liquids are presented in Table 2. Three determinations were carried out for each sample, and the standard deviations were calculated. The amount of HDZ 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 contents found for the amounts of HDZ in the tablets and liquid samples using the SWV proposed methods and the potentiometric reference method [12]. Besides, the paired *t*-test [28] was applied to the results obtained for HDZ using both methods; since the calculated t value (0.7901) is smaller than the critical value (4.303, α = 0.05), one may conclude that the results obtained with the proposed procedures are not statistically different from those from the comparative method, at a 95 % confidence level.

4. CONCLUSION

A cathodically pretreated BDDE was successfully used for the voltammetric determination of HDZ in pharmaceutical sample of different dosages using 0.1 mol L^{-1} HCl solution. Under these conditions, a detection limit of 0.43 µmol L^{-1} for HDZ was attained. Moreover, addition and recovery tests were satisfactory, with values similar to those obtained using a potentiometric reference method. The proposed method was also rapid, sensitive, precise, and accurate, being applicable directly to the analysis of the commercial pharmaceuticals without the tedious sample preparation, dispensing any use of organic reagents or expensive apparatus and does not require preparation or renovation of electrode surface [14,15].

Table 2. Determination of HDZ in pharmaceutical formulations by the proposed square-wave voltammetric (SWV) method, using a cathodically pre-treated BDDE, and the potentiometric reference method [12].

Sample	Label value	Potentiometric[a]	SWV[a]	E[b] (%)
A[c]	2	1.95 ± 0.02	1.90 ± 0.03	–2.6
B[d]	10	9.92 ± 0.02	9.98 ± 0.04	+0.60
C[d]	25	24.8 ± 0.3	25.1 ± 0.2	+1.2

[a] Average of 3 measurements.
[b] Relative error = [100 × (SWV value – Potentiometric value / Potentiometric value)].
[c] mg mL^{-1}.
[d] mg $tablet^{-1}$.

5. ACKNOWLEDGMENTS

Financial support and scholarships from the Brazilian funding agencies Fundação Araucária, CNPq, and CAPES are gratefully acknowledged.

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