A SIMPLE SQUARE-WAVE VOLTAMMETRIC METHOD FOR THE DETERMINATION OF SCOPOLAMINE IN PHARMACEUTICALS USING A BORON-DOPED DIAMOND ELECTRODE

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A simple procedure is described for the determination of scopolamine by square-wave voltammetry using a cathodically pretreated boron-doped diamond electrode. Cyclic voltammetry studies indicate that the oxidation of scopolamine is irreversible at a peak potential of 1.59 V (vs. Ag/AgCl (3.0 mol L\(^{-1}\) KCl)) in a 0.50 mol L\(^{-1}\) sulfuric acid solution. Under optimized conditions, the analytical curve obtained was linear (r = 0.9996) for the scopolamine concentration range of 1.0 to 110 \(\mu\)mol L\(^{-1}\), with a detection limit of 0.84 \(\mu\)mol L\(^{-1}\). The method was successfully applied to the determination of scopolamine in pharmaceutical formulations with minimum sample preparation.

Keywords: scopolamine determination; hyoscine butylbromide determination; BDD electrode.

INTRODUCTION

Scopolamine, or hyoscine butylbromide, is a tropane alkaloid drug with analgesic, sedative and anticonvulsant properties.\(^1\) Thus simple and rapid analytical procedure for the determination of scopolamine in pharmaceutical formulations is highly desirable, especially for drug-quality control purposes.

Several methods for the determination of scopolamine in pharmaceutical formulations, plasma and urine samples have been reported in the literature, including gas chromatography mass spectrometry (GC-MS),\(^2\) liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI MS/MS),\(^3\) high performance liquid chromatography (HPLC) with UV\(^4,5\) and indirect conductometric\(^6\) detection, liquid chromatography and tandem mass spectrometry (LC-MS/MS),\(^7\) capillary electrophoresis,\(^8,9,10\) spectrophotometry,\(^11,12\) potentiometry.\(^13-18\) Many of these procedures are laborious and time-consuming, that are not appropriate for simple and rapid quality control to support pharmaceutical production processes.

Square-wave voltammetry (SWV) represents one of the most promising techniques for development of analytical procedures for several routine applications. This technique has several distinct advantages including a low nonfaradaic current, high sensitivity and rapidity of data acquisition. Furthermore, the analysis of the characteristic parameters of this technique enables the assessment of the electrochemical mechanistic process of the analyte.\(^19\)

There are one voltammetric method published for scopolamine determination, underscoring the importance of this work for publication. Farhadi and Karimpour\(^20\) develop a voltammetric method for determination of scopolamine in pharmaceutical and urine samples by the oxidation of this analyte on the platinum electrode in aqueous solution (0.10 mol L\(^{-1}\) HNO\(_3\)) and organic solution (acetoniitride containing 0.10 mol L\(^{-1}\) tetrabutylammonium perchlorate). This method presents a linear concentration range of 10 to 1000 \(\mu\)mol L\(^{-1}\) exploring differential-pulse voltammetry (DPV). The regeneration of the surface of platinum electrode was realized in a 0.10 mol L\(^{-1}\) hydroxide sodium solution after each scan, which it was the greatest drawback in the practical application of this electrode.

One of the carbon electrodes that have been used with successful in individual and simultaneous determination of organic compounds is a boron-doped diamond electrode (BDDE).\(^21-28\) It has low and stable background current, extreme electrochemical stability in alkaline and acidic media, excellent long-term response stability, high response sensitivity, and a very wide working potential window.\(^29-30\) Moreover, BDDE can be readily coupled with flow system analysis.\(^27,28\)

In the present study, a new voltammetric method for the determination of scopolamine in pharmaceutical formulations is proposed. This method is based on the electrochemical oxidation of scopolamine in 0.50 mol L\(^{-1}\) sulfuric acid solution. In the following sections we will show the advantages of the proposed procedure, with detach to the good sensibility, simplicity, and rapidity obtained using the BDDE. The obtained results were compared with those from the reference potentiometric method of Brazilian Pharmacopoeia.\(^16\)

EXPERIMENTAL

Reagents and solutions

All chemicals were of analytical grade: scopolamine and sulfuric acid were obtained from Sigma-Aldrich. All the solutions were prepared with ultra-purified water supplied by a Milli-Q system (Millipore\(^®\)) with resistivity greater than 18 M\(\Omega\) cm. Commercial pharmaceutical samples (tablets and liquid) were purchased from a local drugstore.

A 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) supporting electrolyte solution was chosen for the scopolamine determination. Stock solutions of 10 mmol L\(^{-1}\) scopolamine were prepared before use in this supporting electrolyte. Appropriate dilutions were made from this solution. Scopolamine working solutions were protected from light by using amber-glass material.

Instrumentation

Voltammetric measurements were carried out in a PalmSens potentiostat/galvanostat controlled with the PalmSens PC software. Surface pretreatment of BDDE was carried out using a MQPG-01 potentiostat (Microquímica). All the electrochemical experiments...
were conducted at room temperature in a three-electrode single-compartment glass cell, with a BDDE (doped with 8000 ppm; 0.33 cm² exposed area; obtained from Centre Suisse de Electronique et de Microtechnique SA (CSEM, Switzerland) employed as working electrode. Detailed information on the preparation of the diamond films was reported elsewhere. A platinum sheet and an Ag/AgCl (3.0 mol L⁻¹ KCl) were used as auxiliary electrode and reference electrode, respectively. The reference electrode was constructed by insert a silver wire coated with anodized AgClₙ₀ in a glass tube (3 mm of diameter) containing 3.0 mol L⁻¹ KCl, which one end contained a sintered glass disc. Since dissolved oxygen did not interfere in anodic potential window, no deaeration of solution was needed.

Prior to the experiments, the BDDE was electrochemically pretreated in a 0.50 mol L⁻¹ H₂SO₄ solution, either anodically by applying 0.5 A cm⁻², during 30 s, or cathodically by applying −0.5 A cm⁻², during 120 s. With the anodic or cathodic pretreatment, the BDDE is made predominantly oxygen- or hydrogen terminated, respectively, according to previously reported results including XPS analysis.

All experiments were carried out at room temperature. The pH was measured at 25.0 ± 0.5 °C using a pH-meter (Hanna Instruments), model HI-221, employing a combined glass electrode with an Ag/AgCl (3.0 mol L⁻¹ KCl) external reference electrode.

Measurement procedures

After optimization of experimental parameters for the proposed method, the analytical curves were obtained by adding different aliquots of 1.0 mmol L⁻¹ scopolamine solution into the electrochemical cell containing 10 mL of the 0.50 mol L⁻¹ H₂SO₄. All measurements were carried out in triplicate for each concentration.

The proposed method was carried out for determining scopolamine in different pharmaceutical formulations samples (tablets and liquid). Ten tablets of each sample were reduced to a homogeneous fine powder. These powders were weighed and transferred to 10 mL calibrated volumetric flask containing 0.50 mol L⁻¹ H₂SO₄ solution. Non-dissolved solids were filtered using a filter paper. Then, 200 μL of this solution was diluted to 2.0 mL using 0.50 mol L⁻¹ H₂SO₄ solution. For liquid sample, an adequate aliquot was diluted in a 10.0 mL calibrated flask containing 0.50 mol L⁻¹ H₂SO₄ solution. For each sample (tablet or liquid), an aliquot of each these solutions was directly transferred to the electrochemical cell containing 10 mL of 0.50 mol L⁻¹ H₂SO₄ solution, after which the square-wave voltammograms were obtained. Finally, the scopolamine concentration in each sample solution was determined directly by interpolation in the previously obtained analytical curve.

Recovery studies were done in triplicate, which aliquots of the standard solution of scopolamine were added to the solutions of the commercial pharmaceutical samples of scopolamine.

The results obtained using the proposed SWV method were compared with the reference potentiometric method recommended by Brazilian Pharmacopoeia. For such, accurate representative powdered amounts of the commercial pharmaceutical samples of scopolamine were dissolved in deionized water and potentiometrically titrated with AgNO₃ 0.10 mol L⁻¹ using a silver indicator electrode.

RESULTS AND DISCUSSION

Electrochemical behavior of scopolamine

Preliminary electrochemical measurements were carried out in order to identify the general behavior of scopolamine on the BDDE surface. Figure 1 shows cyclic voltammograms obtained at a cathodically pretreated BDDE in a 0.010 mol L⁻¹ H₂SO₄ solution in the presence and absence of 0.20 mmol L⁻¹ scopolamine. As can be seen, an anodic current due to the oxidation of scopolamine is observed with a peak potential at 1.59 V and no reduction peak is observed, which indicate that this is an irreversible charge-transfer process.

Next, the BDDE was anodically or cathodically pretreated and both responses were compared (Figure 2). The voltammograms obtained for scopolamine with the anodically pretreated BDDE presents a higher current intensity, but poor repeatability of analytical signals. On the other hand, the cathodically pretreated BDDE presented a less positive oxidation peak potential and a better repeatability of analytical signals, without adsorption effect, which allowed the use of the electrode for a long time with the same response. The adsorption effects were observed by Farhadi and Karimpour using a platinum electrode, which it should be cleaned in a 0.10 mol L⁻¹ hydroxide sodium solution after each scan. The cathodic surface of BDDE (hydrophobic characteristic) facilitated the oxidation of scopolamine and a lower potential than anodic surface was obtained. With this pretreatment is not observed adsorption effects of the scopolamine in the surface of BDDE and a better repeatability of signals were observed.

![Figure 1: Cyclic voltammograms (40 mV s⁻¹) in 0.010 mol L⁻¹ H₂SO₄ solution obtained using a cathodically pretreated BDDE: (dotted line) absence and (solid line) presence of 0.20 mmol L⁻¹ scopolamine](image1)

![Figure 2: Cyclic voltammograms (40 mV s⁻¹) in 0.010 mol L⁻¹ H₂SO₄ solution obtained using BDDE: comparison between (dotted line) anodic and (solid line) cathodic pretreatment](image2)
Thus, this pretreatment was selected for further experiments, as was previously observed for several other analytes.\textsuperscript{23-26} The subsequent scopolamine analytical determinations were all carried out using a BDDE that was cathodically pretreated during 120 s. This pretreatment, which was repeated daily before starting the voltammetric measurements, was always preceded by a 30 s anodic pretreatment, to cleanse the electrode surface by oxidizing any contaminant on its surface. This procedure guarantees reproducibility of the electrode response.

The electrochemical responses to scopolamine were studied in different supporting electrolytes, as sulfuric acid, Britton-Robinson buffer, phosphate buffer and acetate buffer. However, the best voltammetric response (repeatability of the obtained analytical signals) was obtained in sulfuric acid solution. Thus, H\textsubscript{2}SO\textsubscript{4} concentrations from 0.010 mol L\textsuperscript{-1} to 0.75 mol L\textsuperscript{-1} were evaluated. Higher current values were obtained for the 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solution. Hence, taking into account the repeatability of the obtained analytical signals of the scopolamine solutions, the concentration of 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} was selected as the supporting electrolyte for the scopolamine determination. This repeatability was obtained by six measurements of current signals with a relative standard deviation (RSD) of 0.5%. In addition, despite the high potential value for detection of the drug, this would not be a problem for analysis in pharmaceutical formulations.

The effect of scan rate (5–200 mV s\textsuperscript{-1}) for 100 µmol L\textsuperscript{-1} scopolamine was also evaluated using cyclic voltammetry (CV) (Figure 3) in 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solution. Increasing the scan rate, the peak current increased and the peak potentials shifted to more positive values. A linear behavior was found when peak currents were plotted versus the square root of the scan rate, indicating that rate determining step of the reaction is characterized by electroactive species reaching the cathodically pretreated BDDE by diffusion,\textsuperscript{28} according to the linear relation \(I = -8.12 \times 10^{13} + 1.16 \times 10^{4} v^{1/2} (r = 0.9934)\). In addition, plot of the logarithm of the peak current versus the logarithm of the scan rate was linear (inserted in Figure 3), according to: \(\log I_{\text{p}} = -0.039 + 0.53 \log v (r = 0.9960)\), which the value of slope is close to the theoretical value of 0.50 expected for an ideal reaction of species in solution.\textsuperscript{28}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Cyclic voltammograms for 0.10 mmol L\textsuperscript{-1} scopolamine in 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solution obtained using a cathodically pretreated BDDE at different scan rates (v): 5 – 200 mV s\textsuperscript{-1}. Insert: linear dependence of \(\log I_{\text{p}}\) with \(\log v\).}
\end{figure}

In order to develop an analytical method for determination of scopolamine, both DPV and SWV at cathodically pretreated BDDE were studied. The effects of experimental parameters of the DPV and SWV on the peak potential and peak current were optimized for a 50 µmol L\textsuperscript{-1} scopolamine in 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solution.

For DPV, the parameter ranges studied were: 10–175 mV, for the pulse amplitude (\(\alpha\)); 5–20 mV s\textsuperscript{-1}, for the scan rate (\(v\)); and 3–7 ms, for the modulation time (\(t\)). The optimized values were \(\alpha = 150\) mV, \(v = 10\) mV s\textsuperscript{-1}, and \(t = 5\) ms.

For SWV, the corresponding investigated ranges were: 10–40 s\textsuperscript{-1}, for the square-wave frequency (\(f\)); 10–60 mV, for the pulse amplitude (\(\alpha\)); 1–6 mV, for the scan increment (\(\Delta E_{s}\)). The optimized values were \(f = 30\) s\textsuperscript{-1}, \(\alpha = 50\) mV, and \(\Delta E_{s} = 5\) mV. The slope of 0.0576 V obtained from the \(\Delta E_{s} / \Delta \log f\) plot (not shown) was used to estimate the number of electrons transferred (\(n\)) in the redox process by the following equation \(\Delta E_{s} / \Delta \log f = 2.3RT/(nF)\),\textsuperscript{19} where \(\alpha\) is the charge transfer coefficient and other symbols have their usual meanings. The \(\alpha\) value was estimated to be 0.972 and thus, assuming \(\alpha = 0.5\), which is commonly done for totally irreversible system,\textsuperscript{39} \(n\) is estimated as 2; thus also indicating that two electrons per molecule are involved in the oxidation of scopolamine in the sulfuric acid 0.50 mol L\textsuperscript{-1}. The functional group involved in this oxidation is probably the OH of the scopolamine molecule (Figure 4). Farhadi and Karimpour\textsuperscript{39} describes that this oxidation can be stated that two moles of Br ions in aqueous solution are reversibly oxidized to Br\textsubscript{2} with the loss of two electrons.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Proposed mechanism of oxidation of scopolamine}
\end{figure}

Analytical curves

Using the optimal DPV and SWV instrumental parameters, corresponding analytical curves for scopolamine were constructed in 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solutions using a cathodically pretreated BDDE. The analytical parameters thus obtained for both the DPV and SWV proposed methods are summarized in Table 1, where the detection limit (LOD) is equal to three times the standard deviation of the blank solution divided by the slope of the analytical curve. As can be observed, higher sensitivity and lowest detection limit was obtained using SWV. Other advantage of the use of SWV is that this technique is faster than DPV to routine analysis of pharmaceutical formulations. Hence, this method was selected for determination of scopolamine in pharmaceuticals. The intra-day repeatability of magnitude of the peak current was determined by successive measurements (\(n = 10\)) of 15 µmol L\textsuperscript{-1} scopolamine solution using SWV and DPV techniques. The inter-day repeatability of magnitude of the peak current was evaluated by measuring the peak current for similar fresh solutions over a period of 5 days. As can be seen in Table 1, a good RSD values were obtained. No significant differences were observed between the values found for the repeatability of scopolamine obtained by both techniques.

Figure 5 shows the square-wave voltammograms obtained for solution containing scopolamine (1.0 to 110 µmol L\textsuperscript{-1}) in 0.50 mol L\textsuperscript{-1} H\textsubscript{2}SO\textsubscript{4} solution. The insert in this figure depicts the respective analytical curve for scopolamine, whose corresponding equation is \(I_{\text{p}} (\mu A) = -0.018 + 0.066 [c \text{ (µmol L}^{-1})] (r = 0.9996)\), where \(I_{\text{p}}\) is the anodic peak current and \(c\) the scopolamine concentration. The calculated LOD value was 0.84 µmol L\textsuperscript{-1}. The LOD value obtained by scopolamine using the herein proposed method is ten times lower than that obtained by Farhadi.
Table 1. Analytical parameters for the voltammetric determination of scopolamine in 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution by SWV and DPV using a cathodically pretreated BDDE

<table>
<thead>
<tr>
<th></th>
<th>DPV</th>
<th>SWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak potential (V)</td>
<td>1.54</td>
<td>1.54</td>
</tr>
<tr>
<td>Linear range (µmol L(^{-1}))</td>
<td>1.0 to 110</td>
<td>1.0 to 110</td>
</tr>
<tr>
<td>Correlation coefficient, (r)</td>
<td>0.9919</td>
<td>0.9996</td>
</tr>
<tr>
<td>Slope (µA µmol(^{-1}) L)</td>
<td>0.044</td>
<td>0.066</td>
</tr>
<tr>
<td>Intercept (µA)</td>
<td>-0.43</td>
<td>-0.018</td>
</tr>
<tr>
<td>Detection limit (µmol L(^{-1}))</td>
<td>0.90</td>
<td>0.84</td>
</tr>
<tr>
<td>Repeatability Intra-day (RSD%)</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Repeatability Inter-day (RSD%)</td>
<td>3.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

and Karimpour\(^{20}\) using a platinum electrode. In addition, platinum electrode should be clean in sodium hydroxide solution after each measurement, which it makes a lengthy procedure. The use of the BDDE did not lead to any passivation effect, which allowed using the electrode for a long time with the same response. It should be emphasized that the pretreatment of BDDE surface is done once, at the beginning of a day’s work, which led to excellent reproducibility in the determination of scopolamine, because adsorption effects were not observed on its surface. The proposed voltammetric method is simple and does not involve the use of AgNO\(_3\), as is the case in the reference method of the Brazilian Pharmacopoeia.

The selectivity of the proposed method was evaluated by the addition of possible interferent compounds present in commercial samples containing 10 mg scopolamine labeled. Some possible interferent compounds (commonly present in analyzed pharmaceutical formulations), such as povidone, ethyl alcohol, saccharose, magnesium stearate, calcium phosphate, paracetamol, and dipyrone were investigated for 15 µmol L\(^{-1}\) scopolamine solutions at the concentration ratios (standard solution: interferent compound) of 1:1, 1:10, and 10:1 (m/m). The corresponding current signals were compared with those obtained in the absence of each interferent compound. The responses obtained showed that these compounds do not interfere (except dipyrone) with the determination of scopolamine at the used working conditions. The analyzed samples do not contained paracetamol or dipyrone.

Figure 6 shows the voltammetric behavior of scopolamine in comparison with paracetamol and dipyrone in 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution using a cathodically pretreated BDDE. Paracetamol is oxidized in a small potential compared to scopolamine, thus it does not interfere in determination of scopolamine in the sample of pharmaceuticals. However, dipyrone shows the oxidation peak in same potential of oxidation of scopolamine. Therefore, the proposed method is limited to samples of pharmaceutical formulations that not contain dipyrone labeled.

![Figure 5. Square-wave voltammograms in 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution obtained using a cathodically pretreated BDDE for the following of scopolamine: (1) 0, (2) 1.0, (3) 2.0, (4) 3.5, (5) 5.0, (6) 6.5, (7) 7.9, (8) 9.9, (9) 15, (10) 20, (11) 29, (12) 38, (13) 48, (14) 57, (15) 65, (16) 74, (17) 83, (18) 91, (19) 110 µmol L\(^{-1}\). Insert: Corresponding analytical curve](image1)

![Figure 6. Square-wave voltammograms obtained using the cathodically pretreated BDDE for (solid line) 75 µmol L\(^{-1}\) scopolamine, (dotted line) 25 µmol L\(^{-1}\) paracetamol, and (dashed line) 25 µmol L\(^{-1}\) dipyrone in 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution. SWV parameters: f = 20 s\(^{-1}\), a = 40 mV, and ΔE\(_a\) = 2 mV](image2)

Analytical application

To evaluate the accuracy of the application of the proposed method, scopolamine was determined in three different commercial pharmaceutical samples (tablets and liquid) using a cathodically pretreated BDDE in 0.50 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution. Addition and recovery studies were evaluated for investigated commercial tablets. Recoveries from 95.2% to 103% of scopolamine were obtained, indicating the proposed method does not suffer from any significant effects of matrix interference.

Furthermore, the results obtained employing the proposed method were compared with those obtained employing the reference potentiometric method presented at the Brazilian Pharmacopoeia\(^{16}\) (Table 2). As it can be seen in this Table 2, no significant differences were observed between the values found for the amounts of scopolamine in samples using the SWV proposed method and the reference potentiometric method. Besides, considering that the paired \(t\)-test was applied to these results and the calculated \(t\) value (1.084) is smaller than the critical value (4.303, \(α = 0.05\)), one may conclude that the results obtained with either method are not statistically different, at a 95% confidence level.

CONCLUSIONS

A cathodically pretreated BDDE was successfully used for square-wave voltammetric determination of scopolamine in real pharmaceutical samples using 0.5 mol L\(^{-1}\) H\(_2\)SO\(_4\) solution. Under this condition, a linear analytical curve was obtained for the scopolamine concentration range 1.0 to 110 µmol L\(^{-1}\), with a detection limit
of 0.84 µmol L⁻¹. The obtained detection limit was lower than that reported by Farhadi and Karimpour²⁰ using DPV with a platinum electrode. No absorption effects were observed on the BDDE, without the necessity of renovation of surface of this electrode. Furthermore, recoveries of scopolamine from commercial samples range from 95.2% to 103%. In addition, the reported results demonstrate that the proposed method is simple, rapid, sensitive, precise and accurate, being applicable directly to the analysis of the commercial pharmaceutical simply after dissolution of their samples, dispensing any use of organic reagents or expensive apparatus.

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Table 2. Scopolamine content in pharmaceutical formulations determined by the proposed SWV method, using a cathodically pretreated BDDE, and a reference potentiometric method ¹⁶

<table>
<thead>
<tr>
<th>Samples</th>
<th>Label value</th>
<th>Reference method</th>
<th>SWV method</th>
<th>Relative error (％)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>9.58 ± 0.03</td>
<td>9.37 ± 0.02</td>
<td>−4.4</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>9.73 ± 0.02</td>
<td>9.82 ± 0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>10.1 ± 0.4</td>
<td>9.90 ± 0.02</td>
<td>−2.0</td>
</tr>
</tbody>
</table>

¹Average of 3 measurements. ²¹⁰₀ × ([SWV method – reference method] / reference method). mg/tablet. mg/mL.