Determination of Ophthalmic Drug Proparacaine Using Multi-walled Carbon Nanotube Paste Electrode by Square Wave Stripping Voltammetry

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Proparacaine, one of the most common local anesthetics to facilitate diagnosis and treatment of eye diseases, was assayed by square wave voltammetry using a paste electrode prepared with carbon nanotubes. In cyclic voltammetric studies, proparacaine has exhibited a single irreversible anodic peak at around +900 mV vs. Ag/AgCl in pH 6.0 Britton-Robinson buffer solution. It was suggested that the peak had appeared due to the oxidation of the NH₂ group on the proparacaine molecule. Prior to the determination of the proparacaine by square wave stripping voltammetry (SWSV) on the fabricated multi-walled carbon nanotube paste electrode (MWCNTPE), the accumulation potential (Eacc), accumulation time (tacc), pulse amplitude (ΔE), step potential (ΔEₜ) and frequency (f) parameters were optimized. The peak currents plotted in the range of 0.5 - 12.5 mg/L proparacaine exhibited two linear sections with a detection limit of 0.11 mg/L. The results for the determination of proparacaine on a pharmaceutical local anesthetic (Alcaine®) showed that relative standard deviation (RSD) and relative error (RE) were 4.1 and ~2.0%, respectively. Selectivity has also been investigated and results showed recoveries of 5.0 mg/L proparacaine in the presence of 5.0 mg/L dopamine, ascorbic acid and uric acid as 106.9 ± 0.8, 99.9 ± 1.2 and 94.1 ± 0.7, respectively.

Keywords Proparacaine, ophthalmic drug, voltammetry, carbon nanotube paste electrode, determination

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Introduction

Local ophthalmic anesthetic agents are highly beneficial medications that facilitate diagnosis and treatment of eye diseases. Proparacaine (PPC) is one of the most commonly used local anesthetics in ophthalmic examination and minor ophthalmological surgical interventions and cataract surgery due to its high efficiency and limited side effects.1–4 It is a short-acting local anesthetic of the ester type with an onset of running in 30 s, with full effect in 2 to 3 min. Such drugs block the spread of nerve stimulation by reversing (sodium channel antagonist) and offer the possibility to anesthetize the selected part of the body.5 Lidocaine, bupivacaine and oxybuprocaine are also used as local anesthetics for ophthalmic applications and have pharmacodynamic properties similar to proparacaine.

Proparacaine (3-amino-4-proxybenzoic acid 2-(diethylamino)ethyl ester) is one of the ester-type local anesthetic drugs and the structure of the molecule is given in Scheme 1.

Accurate and reliable analytical methods are needed in the determination of local anesthetic concentrations in body fluids, for both medical and judicial purposes in order to prevent an overdose and misuse of local anesthetics. Moreover, the active ingredients in commercial preparations must be prepared by sensitive and selective analytical methods in a quality controlled laboratory. Up to now, analytical determinations of local anesthetic drugs have generally been performed using high performance liquid chromatography,2,6,7 liquid phase micro extraction8 gas chromatography,9,10 solid phase extraction,11,12 chemiluminescence13 and capillary electrophoresis.5 However, these methods can often require long sample preparation and tedious pretreatment procedures, time consuming processes and usage of environmentally harmful and toxic solvents. Alternative to these analytical methods are potentiometric methods14 and various voltammetric methods including boron-doped diamond electrodes,15 graphite electrodes,16 carbon nanotube film coated electrodes17 and various modified carbon paste electrodes.18,19 Nanoparticle paste electrodes prepared with carbon nanotubes have recently been favored in the determination of molecules with biochemical precursors10,22 because of their fast response.

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Scheme 1 Proparacaine hydrochloride.
good selectivity, ease of preparation, low cost, easy electrode surface handling, high stability, low residual current and miniaturization.

Despite the existence of several voltammetric studies for procarbazine and lidocaine, according to our literature review, we could not find any voltammetric work on proparacaine determination. The present paper recommends a new sensitive and selective method for the determination of proparacaine hydrochloride by square wave stripping voltammetry with a prepared multi-walled carbon nanotube paste electrode. The method was also successfully applied to the ophthalmic local anesthetic drug Alcaine® as well as proparacaine in the presence of dopamine, ascorbic acid and uric acid.

**Experimental**

**Instrumentation**

Square wave and cyclic voltammograms were recorded using a Bioanalytical Systems-Epsilon potentiostat/galvanostat (BAS, West Lafayette, IN, USA) connected to a BAS-C3 voltammetric cell stand. The indicator electrode was a multi-walled carbon nanotube paste electrode (MWCNTPE) fabricated using the BAS MF-2010 with a diameter \( \phi = 3 \) mm. Ag/AgCl (3 mol/L NaCl) was used as a reference electrode and the auxiliary electrode was a platinum wire (BASMW1032). All experiments were carried out at room temperature. A glass electrode connected to a pH meter (Hanna HI 8521 Model, Singapore) was used to measure the pH of all the solutions.

**Reagents**

Stock proparacaine solution at a concentration of 5.0 g/L was prepared by dissolving 50 mg of standard proparacaine purchased from Sigma-Aldrich (proparacaine hydrochloride-analytical standard-P4554-1G; CAS 5875-06-9; MW: 330.85 g/mol) in 10 mL of distilled water. Britton-Robinson buffer (B-R buffer) solutions from pH 2.0 to 10.0 were prepared using 0.04 M H$_3$BO$_3$, 0.04 M H$_3$PO$_4$ and 0.04 M CH$_3$COOH. For the preparation of multi-walled carbon nanotube composite electrodes, graphite powder and mineral oil were used. Multiwall carbon nanotube powder (Mercorporation, mesh size <53 mm) and water-immiscible non-electrolytic mineral oil were mixed in 70 and 30% mass percentages, respectively. The paste was packed into a small inert holder (2.5 mm deep, 3 mm diameter and Teflon) with electrical contact at the back tip.

**Results and Discussion**

**Cyclic voltammetric behavior of proparacaine**

Cyclic voltammograms were recorded at different potential scanning rates to understand and interpret the electrochemical behavior of the proparacaine compound. Accordingly, cyclic voltammograms for 10 mg/L proparacaine were recorded at pH 6.0 B-R buffer solutions at selected scan rates ranging from 5 to 500 mV/s. In this voltammetric operation, a potential scan was performed in the positive direction from 0 to +1200 mV, followed by a negative scan of potential from +1200 to 0 mV. As shown in Fig. 1, proparacaine exhibited a single anodic peak at about +900 mV in the positive potential probe and no corresponding cathodic peak has been observed in the reverse scan. The influence of potential scan speed \( (\nu) \) on the peak potentials \( (E_p) \) showed that the peak potentials were shifted to the less positive regions with the following linear equation.

\[
E_p \text{ (V)} = 0.0289 \log \nu \text{ (V/s)} + 0.881 \quad (r^2 = 0.906) \quad (1)
\]

The fact that no cathodic peak can be observed despite the presence of an anodic peak clearly indicates that this reaction is irreversible. The shift of the peak potentials toward the less positive way also confirms irreversibility of the electrode response. On the other hand, the potential scan speed operation is one of the most important parameters that can be used to determine the number of electrons transferred in a voltammetric process. For irreversible processes the Laviron theory could be applied to calculate the number of transferred electrons in the electrode process.

\[
E_p = E^\prime + \left( \frac{2.303RT}{nF} \right) \log \left( \frac{RT \alpha nF}{\nu D^{1/2}} \right) \log \nu \quad (2)
\]

In this equation, \( F \) is the faraday constant (96485.3 C/mol), \( T \) is the room temperature in Kelvin, \( R \) is the gas constant (8.314 J/mol·K), \( \alpha \) is the electron transfer coefficient, and \( n \) is the number of electrons transferred in the electrode reaction. The slope of the \( \log \nu \text{ versus } E_p \) graph was found to be 0.0289 and the \( \alpha n \text{ term} \) could be calculated as 2.04 when written in place of the corresponding equation. Since the \( \alpha \) value for irreversible reactions could be accepted as 0.5, the number of electrons corresponding to the oxidation process was calculated as 4.08 (−4). Accordingly, the oxidation can be achieved by the oxidation of the NH$_2$ group to the nitroso.

The linear uptake of the square root graph of the scan rate \( (\log \nu^{1/2}) \text{ versus } \log \nu \) peak current \( (I_p) \) showed that the mass transfer of the proparacaine to the electrode surface is diffusion controlled. The resulting equation is expressed below.

\[
I_p \text{ (\muA)} = 0.1161 \log \nu^{1/2} \text{ (V/s)} – 0.3324 \quad (r^2 = 0.9537) \quad (3)
\]

When the slope of \( \log I_p \text{ versus } \log \nu \) is around 0.5, the mass transfer to the electrode surface is theoretically diffusion controlled. However, if this slope is around 1.0, mass transfer is controlled by adsorption. The slope was found to be 0.4303 in our cyclic voltammetric studies as indicated in the following linear correlation, which is acceptable for an ideal diffusion controlled electrode reaction. The deviation from the linearity at high scan rates suggest that the relatively low regression
coefficient could be attributed to an irreversible electrode process.

\[
\log I_p (\mu A) = 0.4303 \log \nu (\text{mV/s}) - 0.3324 \quad (r^2 = 0.968)
\]  

Optimization of instrumental parameters for determination of proparacaine

Before proceeding to the determination of the proparacaine by SWSV technique on the MWCNTPE electrode, the accumulation potential \(E_{\text{acc}}\), accumulation time \(t_{\text{acc}}\), pulse amplitude \(\Delta E\), step potential \(\Delta E_s\) and frequency \(f\) parameters were optimized. Examination of these parameters, which significantly affect peak currents and peak potentials in stripping techniques, was performed in the presence of 5.0 mg/L proparacaine in pH 6 B–R buffer. Foremost, the accumulation potential \(E_{\text{acc}}\) was examined from 0 to +900 mV and the peak current increased linearly up to +600 mV then sharply decreased. Accordingly, the optimum accumulation potential of +600 mV was selected (Fig. 2a). Since the effect of accumulation time on peak sensitivity is well known, SWS voltammograms for proparacaine were then recorded at different accumulation times at +600 mV. The peak current showed a slight increase in accumulation between 10 and 20 s and showed a rapid increase until 30 s, and then gradually increased to 60 s until it reached saturation at equilibrium (Fig. 2b). There is no statistical significance for a slight decrease in deposits after 90 s. Accordingly, the optimum accumulation time of 60 s was selected. Later on, optimization of the pulse amplitude \(\Delta E\) and step potential \(\Delta E_s\) were carried out. Towards this goal, SWS voltammograms were recorded within the pulse amplitudes of 10 to 90 mV and step potentials of 1 to 14 mV. When the pulse amplitude was increased gradually to 60 mV, the peak current increased and then remained constant. The step potential showed a rapid increase up to 10 - 12 mV, and then reached equilibrium. Therefore, 60 and 10 mV were selected as optimum pulse amplitude and step potential, respectively (Figs. 2c and 2d). The effect of the frequency was also investigated (Fig. 2e). For this purpose SWS voltammograms were taken at frequencies ranging from 10 to 500 Hz. The peak current of proparacaine also increased linearly with increasing frequency up to 250 Hz, and then decreased with subsequent applications. Since the most sensitive and sharpest peaks were obtained at 250 Hz, it was selected as the optimum. All optimum instrumental parameters for proparacaine assay are summarized in Table 1.

Square wave voltammetric behavior of proparacaine

The square wave voltammograms of 5 mg/L proparacaine were recorded on the MWCNTPE electrode at a wide range of pHs. For this, 0.1 and 0.01 M H₂SO₄ were used for pH 1.0 and 2.0 and Britton-Robinson buffer solutions were used for pHs extending from 2.0 to 10.0. The square wave voltammetric behavior was examined at different pH’s and a single oxidation peak appeared from pH 1.0 to 10.0 (Fig. 3). The peak current from pH 1.0 to 6.0 increased sharply and reached a maximum value at pH 6, then remained somewhat steady and slowly decreased as it approached pH 10.0 (Fig. 4). Based on this graph, pH 6 B-R buffer solution was selected for proparacaine determination in subsequent studies.

Table 1 Optimal parameters for proparacaine determination by SWS voltammetry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accumulation potential/mV</td>
<td>600</td>
</tr>
<tr>
<td>Accumulation time/s</td>
<td>60</td>
</tr>
<tr>
<td>Frequency/Hz</td>
<td>250</td>
</tr>
<tr>
<td>Pulse amplitude/mV</td>
<td>60</td>
</tr>
<tr>
<td>Step potential/mV</td>
<td>10</td>
</tr>
<tr>
<td>Supporting electrolyte</td>
<td>pH 6 B-R buffer solution</td>
</tr>
<tr>
<td>Peak potential/mV</td>
<td>880</td>
</tr>
</tbody>
</table>

Fig. 2 Optimization graphs for 5.0 mg/L proparacaine detection in pH 6.0 B-R buffer solution.

Fig. 3 SWS voltammograms at different pHs for 5.0 mg/L proparacaine.  
\(E_{\text{acc}} = 600 \text{ mV}, \quad t_{\text{acc}} = 60 \text{ s}, \quad f = 250 \text{ Hz}, \Delta E_s = 10 \text{ mV}, \Delta E = 60 \text{ mV}\).
53.3 mV/pH for pH 1.0 to 4.0 and 27.4 mV/pH for pH 5.0 to 10.0, respectively.

For pH between 1.0 and 4.0

\[ E_p (mV) = -53.3pH + 1073.3 \quad (r^2 = 0.9839) \quad (5) \]

For pH between 5.0 and 10.0

\[ E_p (mV) = -27.4pH + 874.2 \quad (r^2 = 0.9947) \quad (6) \]

Since the potential shift of 53.3 mV per unit pH is very close to the theoretical value of 59 mV, it can be considered that the electron and proton transferred in the electrode reaction are equal (4H+/4e−). The possible mechanism of electrode response could be suggested by combining the transferred electron and the irreversibility data from the cyclic voltammetry together with the H⁺ contribution from the pH effect and the electron transfer coefficient data from the square wave stripping voltammetry. The number of electrons corresponding to the electro-oxidation process was previously calculated as ~4 by utilizing the cyclic voltammetric technique. Accordingly, electro-oxidation can be performed according to the following mechanism by oxidizing the NH₂ group on the proparacaine molecule to the nitroso group (Fig. 5). The mechanism based on the oxidation of –NH₂ for the anodic peak of procaine on the

![Graph](image1)

**Fig. 4** The effect of pHs on peak current (x) and potential (▲) for 5.0 mg/L proparacaine.

![Graph](image2)

**Fig. 5** Proposed electro-oxidation mechanism of proparacaine.

![Graph](image3)

**Fig. 6** SWS voltammograms of proparacaine for construction of calibration graph (pH 6.0 B-R buffer solution, \( E_{acc} = 600 \text{ mV}, t_{acc} = 60 \text{ s}, f = 250 \text{ Hz}, \Delta E_s = 10 \text{ mV}, \Delta E = 60 \text{ mV} \)).
multi-walled carbon nanotube film coated glassy carbon electrode\(^1\) and the work suggesting that the peak obtained at +0.94 V from cyclic voltamograms of procaine originates from the electro-oxidation of procaine\(^19\). Supports the mechanism recorded at concentrations ranging from 0.5 to 12.5 mg/L in calibration graph. For this purpose, SWS voltammograms were recommended in this work.

**Calibration graph**

After setting the optimum experimental conditions for the determination of proparacaine, we proceeded to establish its calibration graph. For this purpose, SWS voltammograms were recorded at concentrations ranging from 0.5 to 12.5 mg/L in 10.0 mL of pH 6.0 B-R buffer solutions (Fig. 6).

The peak currents plotted against the concentrations in the range of 0.5 - 12.5 mg/L, and the peak current have a linear relationship to the low concentration of proparacaine. However, the slope of the relationship gradually decreases at higher concentration. The regression analysis data for the calibration graph and the validation parameters are summarized in Table 2.

\[
I_p = \frac{0.4595C}{mg \cdot L} + 0.045 \\
(r^2 = 0.9988 and linearity range = 0.5 - 2.5 mg/L) \quad (7)
\]

\[
I_p = \frac{0.1595C}{mg \cdot L} + 0.675 \\
(r^2 = 0.9971 and linearity range = 2.5 - 12.5 mg/L) \quad (8)
\]

The limit of detection (LOD), limit of quantification (LOQ) and reproducibility values were calculated to determine the sensitivity and reproducibility of the proposed voltammetric method. LOD and LOQ values were found to be 0.11 and 0.37 mg/L, respectively. The equations of LOD = 3\(S_b/m\) and LOQ = 10\(S_b/m\) were used to calculate the LOD and LOQ values, respectively. In these equations, \(S_b\) is the standard deviation (n = 8) of the peak current of the blank, and m is the slope of the calibration graph. The intra-day reproducibility of peak potential and peak currents were found to be 0.44 and 3.30%, respectively.

**Application of the method**

Since life exists in water and medicinal drugs interact with water in some way, the developed method has been applied to drugs used in local anesthesia as well as tap water containing many matrices to verify the applicability, validity, accuracy and precision of the method.

**Proparacaine determination in pharmaceuticals**

First, 1.0 mL of the proparacaine ophthalmic local anesthetic (Alcaine\(^\circ\) 5.0 mg proparacaine in 1.0 mL ophthalmic solution) was introduced to a 10-mL volumetric flask and the final volume was completed with distilled water. After this solution was mixed in the ultrasonic bath for 5 min, 0.1 mL of pharmaceutical sample was added to 10 mL of the supporting electrolyte in the voltammetric cell and SW voltammograms were recorded under optimized conditions. Standard proparacaine additions were then carried out to the commercial drug in the voltammetric cell for its analytical assay. After each 0.1 mL of 5 mg/mL standard proparacaine addition to the voltammetric cell, square wave voltammograms were once recorded and the amount of proparacaine in the pharmaceutical sample was calculated from the peak increments. The results for the determination of proparacaine on pharmaceutical local anesthetic proparacaine HCl 0.5% ophthalmic drops (Alcaine\(^\circ\)) are summarized in Table 3 as %recovery. The proparacaine labeled as 5.0 g/L on the commercial formulation was calculated as 4.9 ± 0.2 and relative standard deviation and relative error were 4.1 and -2.0%, respectively. The result showed the relative standard deviation (RSD) and relative error mean that the reproducibility and accuracy of the method is quite good. The recommended method could be used in quality control laboratories for the determination of proparacaine drugs.

**Proparacaine determination in tap water**

Since aquatic life is a natural and indispensable solvent, to further test the validity of the method, it was applied to the spiked tap water sample prepared by adding 1.0 mL of 5 g/L proparacaine stock solution to 9.0 mL of tap water obtained from Ankara, Turkey. This solution was then stirred in the ultrasonic bath for 5 min. Square wave voltammograms were recorded after each 0.1 mL addition of 5 mg/mL proparacaine solution to the spiked proparacaine in the pH 6.0 B-R buffer solution prepared with tap water. The recovery values of

### Table 2 Regression analysis data and validation parameters of the calibration curve for proparacaine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SWSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak potential/mV</td>
<td>880</td>
</tr>
<tr>
<td>Range of concentration/mg L(^-1)</td>
<td>0.5 - 2.5 and 2.5 - 12.5</td>
</tr>
<tr>
<td>Slope/(\mu A) L mg(^-1)</td>
<td>0.4595 (\pm 0.0112)</td>
</tr>
<tr>
<td>Intersection/(\mu A)</td>
<td>(-0.045 \pm 0.0015)</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.9988</td>
</tr>
<tr>
<td>Limit of detection (LOD)/mg L(^-1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Limit of quantification (LOQ)/mg L(^-1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Intra-day reproducibility of peak potential, %</td>
<td>RSD(^a) 0.44</td>
</tr>
<tr>
<td>Intra-day reproducibility of peak current, %</td>
<td>RSD(^a) 3.30</td>
</tr>
</tbody>
</table>

\(a.\) n = 8.

### Table 3 Determination of proparacaine by SWS voltammetry on pharmaceutical local anesthetic proparacaine HCl 0.5% ophthalmic drops (Alcaine\(^\circ\))

<table>
<thead>
<tr>
<th></th>
<th>SWSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeled quantity/mg mL(^-1)</td>
<td>5.0</td>
</tr>
<tr>
<td>Amount found/mg mL(^-1)</td>
<td>4.9 (\pm 0.2)</td>
</tr>
<tr>
<td>Recovery, %</td>
<td>98.0</td>
</tr>
<tr>
<td>RSD, %</td>
<td>4.1</td>
</tr>
<tr>
<td>Relative error, %</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

\(a. n = 3.\)

### Table 4 Determination of proparacaine in spiked tap water sample by SWS voltammetry

<table>
<thead>
<tr>
<th></th>
<th>Tap water(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added/(\mu g) L(^-1)</td>
<td>500.0</td>
</tr>
<tr>
<td>Found/(\mu g) L(^-1)</td>
<td>500.2 (\pm 2.5)</td>
</tr>
<tr>
<td>Recovery, %</td>
<td>100.04</td>
</tr>
<tr>
<td>Relative standard deviation, %</td>
<td>0.50</td>
</tr>
<tr>
<td>Relative error, %</td>
<td>+0.04</td>
</tr>
<tr>
<td>Added/(\mu g) L(^-1)</td>
<td>1000.0</td>
</tr>
<tr>
<td>Found/(\mu g) L(^-1)</td>
<td>994.2 (\pm 2.8)</td>
</tr>
<tr>
<td>Recovery, %</td>
<td>99.4</td>
</tr>
<tr>
<td>Relative standard deviation, %</td>
<td>0.28</td>
</tr>
<tr>
<td>Relative error, %</td>
<td>-0.58</td>
</tr>
</tbody>
</table>

\(a.\) Provided from Ankara, Turkey; \(n = 3; 95\%\) confidence level.
proparacaine in spiked tap water are given in Table 2 together with relative standard deviations and relative errors. Proparacaine in tap water containing 500.0 μg/L was determined by the recovery of 500.2 ± 2.5 and the resulting 0.50% relative standard deviation and +0.04% relative error reflect the high precision and accuracy. Likewise, proparacaine in tap water containing 1000.0 μg/L proparacaine was determined by 99.4% recovery with a 0.28 and −0.58% relative standard deviation and relative error, respectively.

**Interference effect on the proparacaine determination**

The selectivity of the voltammetric methods has been investigated in the presence of certain metal ions and some compounds that are electroactive in terms of oxidation. The recoveries were calculated by taking the ratio of the peak currents of 5.0 mg/L proparacaine to the peak currents in the presence of 5.0, 10.0 and 15.0 mg/L dopamine, ascorbic acid and uric acid. The recoveries of 5.0 mg/L proparacaine in the presence of 5.0 mg/L dopamine, ascorbic acid and uric acid were calculated as 106.9 ± 0.8, 99.9 ± 1.2 and 94.1 ± 0.7, respectively. According to these results, when the proparacaine was of the same ratio to that of dopamine, ascorbic acid and uric acid, the proparacaine content could be determined within the 7% tolerance limit. When dopamine and uric acid were more than twice the amount of proparacaine, the relative error in the proparacaine assay exceeded 10%. However, when the same situation was assessed for ascorbic acid, the relative error was below the 10% tolerance limit.

On the other hand, the relative error for the determination of 5 mg/L proparacaine in the presence of 5, 10 and 15 mg/L lead(II), nickel(II), magnesium(II), potassium(I), copper(II) and cobalt(II) were assessed below 3, 5 and 8%, respectively. It can be concluded that the proposed SWS voltammetric method can be used to determine proparacaine in the presence of dopamine, ascorbic acid and uric acid as well as some metal ions with an acceptable and reasonable margin of error.

**Conclusions**

Nanoparticle paste electrodes prepared with carbon nanotubes have recently been favored in the determination of pharmaceuticals because of their fast response, good selectivity, ease of preparation, low cost, easy electrode surface handling, high stability, low residual current, and miniaturization. Despite the presence of several analytical methods for proparacaine determination, no detection by square wave stripping voltammetry technique was found. The developed method has been applied to drugs used in local anesthesia as well as in the presence of dopamine, ascorbic acid and uric acid to verify the applicability, validity, accuracy and precision. The resulting low relative standard deviation, low relative error and high recoveries prove that the reproducibility, accuracy and selectivity of the method are quite good.

**References**