



Electrochemical behavior of atomoxetine and its voltammetric determination in capsules

M. Pérez-Ortiz, C. Muñoz, C. Zapata-Urzuía, A. Álvarez-Lueje*

Bioelectrochemistry Laboratory, Chemical and Pharmaceutical Sciences Faculty, University of Chile, P.O. Box 233, Santiago 1, Chile

ARTICLE INFO

Article history:

Received 26 March 2010

Received in revised form 27 April 2010

Accepted 28 April 2010

Available online 7 May 2010

Keywords:

Atomoxetine

Differential pulse voltammetry

Pharmaceutical

ABSTRACT

In this work, the electrochemical behavior and the analytical application of atomoxetine, a selective noradrenaline reuptake inhibitor, are studied. Atomoxetine, studied by differential pulse voltammetry and cyclic voltammetry on a glassy carbon electrode, exhibited an anodic response in aqueous media with pH between 1.5 and 7. In non-aqueous medium (acetonitrile), the drug exhibited two irreversible oxidation peaks that are diffusion controlled. From chronocoulometric studies in acetonitrile, it was determined that each oxidation signal involves two and four electrons, respectively. For analytical purposes, a differential pulse voltammetry technique in 0.1 mol L⁻¹ perchloric acid was selected, which exhibited adequate figures of merit. The percent recovery was 96.6 ± 1.2 and the detection and quantitation limits were 6.9 × 10⁻⁵ and 1.0 × 10⁻⁴ mol L⁻¹, respectively. Also, results indicate that excipients do not interfere with the oxidation signal of atomoxetine, which leads to the conclusion that the developed method is satisfactorily selective for atomoxetine quantification in pharmaceuticals with no prior separation or extraction necessary. Finally, the proposed voltammetric method was successfully applied to both the assay and the uniformity content of atomoxetine in capsules. For comparison, high-performance liquid chromatography analysis was also performed.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Atomoxetine, N-methyl-γ-(2-methylphenoxy)-benzenepropanamine (Fig. 1), is a highly selective noradrenaline reuptake inhibitor that is used as a non-stimulant pharmacotherapy for attention-deficit/hyperactivity disorder in the United States and Europe [1].

Atomoxetine is well-absorbed after administration of oral doses and peak plasma concentrations are achieved 1–2 h after administration. Atomoxetine is approximately 98% bound to plasma proteins. It undergoes oxidative metabolism in humans, which leads to the formation of a major phase I metabolite, 4-hydroxyatomoxetine, and a minor metabolite resulting from demethylation, N-desmethylatomoxetine. The primary enzyme responsible for the formation of 4-hydroxyatomoxetine is cytochrome P450 CYP2D6 [2,3].

Different chromatographic methods have been described for the determination of atomoxetine in human plasma, urine and various tissues. These methods include gas chromatography-electron capture [4], gas chromatography-mass spectroscopy [5], liquid chromatography-mass spectrometry [6,7], liquid chromatography-fluorescence detection using derivatization with

4-(4,5-diphenyl-1H-imidazol-2-yl) benzoyl chloride [8] and high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection [9–11]. HPLC-UV has been employed for the determination of atomoxetine in pharmaceutical dosage forms [12]. The determination of the enantiomer and positional isomer impurities in atomoxetine with liquid chromatography employing polysaccharide chiral stationary phases has also been described [13].

To the best of our knowledge, the electrochemistry of atomoxetine has not been described in the literature. Additionally, an official method for the assay of this drug in pharmaceutical forms has not been described in any pharmacopoeia. Due to this lack of knowledge, we investigated the electrochemistry of atomoxetine to develop a differential pulse voltammetric (DPV) method capable of quantifying this drug in commercial capsules. For comparative purposes, the applicability of the proposed DPV method to both the assay and the uniformity content of atomoxetine in capsules was confirmed using HPLC with UV detection [10].

2. Experimental

2.1. Apparatus

2.1.1. Voltammetric analyzer

Differential pulse voltammetric (DPV) and cyclic voltammetric (CV) experiments were performed using a fully automated workstation (BAS CV-50 W). A 25-mL thermostated measuring cell with

* Corresponding author. Fax: +56 7378920.

E-mail address: aalvarez@ciq.uchile.cl (A. Álvarez-Lueje).

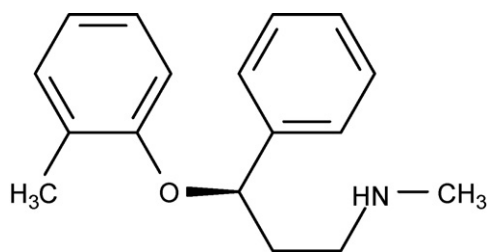


Fig. 1. Chemical structure of atomoxetine.

a glassy carbon working electrode (GCE) ($\varnothing = 3$ mm, BAS) was used. A platinum wire and an Ag/AgCl electrode were used as the counter and reference electrodes, respectively. For CV experiments, the operating conditions were as follows: sensitivity $10\text{--}100 \mu\text{A V}^{-1}$, potential range $0\text{--}3000$ mV and sweep rate $10\text{--}10000$ mV s $^{-1}$. The working electrode surface was polished with 0.3 and $0.05 \mu\text{m}$ alumina slurries before each measurement [14].

2.1.2. Controlled potential electrolysis

Assays were carried out using a fully automated assembly (BAS CV-50W) composed of a 100-mL electrolysis cell, a reticulated vitreous carbon as the working electrode and an Ag/AgCl and a platinum wire as the reference and counter electrodes, respectively. The electrolysis potential was set to either 1300 or 1800 mV in acetonitrile with 0.1 mol L^{-1} tetrabutylammonium perchlorate (PTBA) as the supporting electrolyte. The experiments were carried out in duplicate.

2.1.3. Spectroelectrochemical experiments

UV–vis spectra were recorded in the 200–400 nm range using an Agilent spectrophotometer 8453 with a diode array detector (quartz cell of 1 mm thickness of liquid layer as light path). A three-electrode circuit with an Ag/AgCl reference electrode and a platinum wire as the counter electrode were used. Platinum gauze electrodes were used as the working electrodes.

2.1.4. HPLC

HPLC analyses were performed using a Waters system equipped with a model 600 Controller pump and a model 996 Photodiode Array Detector. Data acquisition and analysis were performed using the Millennium version 2.1 software. A Bondapak/Porasil C18 chromatographic column ($3.9 \text{ mm} \times 150 \text{ mm}$) was used with a C18 Bondapak ($30 \text{ mm} \times 4.6 \text{ mm}$) guard column. The injector consisted of a $20\text{-}\mu\text{L}$ Rheodyne valve. UV detection at 210 nm was employed and the column was kept at a constant temperature using a Waters column heater cartridge, model 600. An isocratic elution using a mobile phase that consisted of a 40:60 (v/v) mixture of acetonitrile and phosphate buffer (0.023 mol L^{-1} , pH 6.6) was performed. The flow rate was 1.0 mL min^{-1} and the working temperature was kept constant at $30 \pm 1^\circ\text{C}$ [10]. Under these conditions, the retention time of atomoxetine was 5.79 ± 0.03 min.

2.2. Reagents and drugs

Atomoxetine hydrochloride (100.1% chromatographically pure) was supplied by Chile Laboratories (Santiago, Chile). Commercial tablets of Deaten[®] (declared amount per capsule: 25.0 mg atomoxetine as hydrochloride, Andromaco S.A. Laboratories, Santiago, Chile) were obtained commercially. HPLC grade di-sodium hydrogen phosphate, phosphoric acid and acetonitrile were obtained from Merck. All others reagents were of analytical grade unless indicated otherwise. Solutions were prepared in ultrapure water ($\rho = 18 \text{ M}\Omega \text{ cm}$) from a Millipore Milli-Q system.

2.3. Preparation of solutions

2.3.1. Buffer solutions

For voltammetric experiments, 0.1 mol L^{-1} Britton-Robinson buffer (BRB) (acetic/boric/phosphoric acid mixture) was used. The pH was adjusted appropriately using concentrated solutions of NaOH or HCl. For HPLC, 0.023 mol L^{-1} buffer phosphate solution (di-sodium hydrogen phosphate dodecahydrate salt) adjusted to pH 6.6 with phosphoric acid was used.

2.3.2. Stock drug solution

Stock standard solutions of atomoxetine hydrochloride were prepared daily at a concentration of $1 \times 10^{-2} \text{ mol L}^{-1}$ in ultrapure water. The solutions were stored in amber glass bottles to protect them from light.

2.3.3. Working solution

Appropriate volumes of the stock solution were diluted to 10 mL with 0.1 mol L^{-1} perchloric acid (HClO_4) for both electrochemical and HPLC experiments.

2.4. Analytical procedure

2.4.1. Calibration curve preparation

Working solutions ranging between 1×10^{-4} and $1 \times 10^{-3} \text{ mol L}^{-1}$ were prepared by diluting the atomoxetine stock solution with $0.1 \text{ mol L}^{-1} \text{ HClO}_4$.

2.4.2. Synthetic samples

For recovery studies, excipients (dimethicone and pregelatinized starch) were added to the drug according to manufacturer's batch formulas for 25.0 mg atomoxetine (hydrochloride) per capsule.

2.4.3. Assay

The contents of 10 capsules were mixed and an amount containing the equivalent of 28.6 mg atomoxetine was dissolved in 10 mL of water. The solution was sonicated for 15 min and diluted to 25 mL with the same solvent. A $10\times$ dilution of this solution was performed using $0.1 \text{ mol L}^{-1} \text{ HClO}_4$ to obtain an atomoxetine concentration of $3.9 \times 10^{-4} \text{ mol L}^{-1}$. The final solution was transferred to a voltammetric cell and measurements were recorded at least twice from 0 to 2000 mV. The amount of atomoxetine, in milligrams, for the sample solution was calculated from the prepared standard calibration curve.

2.4.4. Uniformity of content

No less than 10 commercial capsules of atomoxetine (Deaten[®], amount declared: 25.0 mg atomoxetine as hydrochloride per capsule) were used. The contents of each individual capsule were suspended in 10 mL water using sonication to ensure complete dissolution of the drug. The solution was diluted to a final volume of 25 mL with the same solvent. A 1-mL aliquot of each solution was diluted to 10 mL with $0.1 \text{ mol L}^{-1} \text{ HClO}_4$ to obtain an atomoxetine concentration of $3.9 \times 10^{-4} \text{ mol L}^{-1}$. Each sample solution was transferred to a voltammetric cell and measurements were recorded at least twice from 0 to 2000 mV. The amount of atomoxetine, in milligrams, in the sample solution was calculated from the prepared standard calibration curve. The same procedure was carried out for HPLC analysis, but all the samples were filtered prior to injection.

2.4.5. Selectivity trials

2.4.5.1. Hydrolysis. For each trial, 28.6 mg atomoxetine were dissolved in a 50-mL distillation flask with either 25 mL $0.1 \text{ mol L}^{-1} \text{ HClO}_4$ or 25 mL of a water:ethanol: $0.1 \text{ mol L}^{-1} \text{ NaOH}$ (40:40:20)

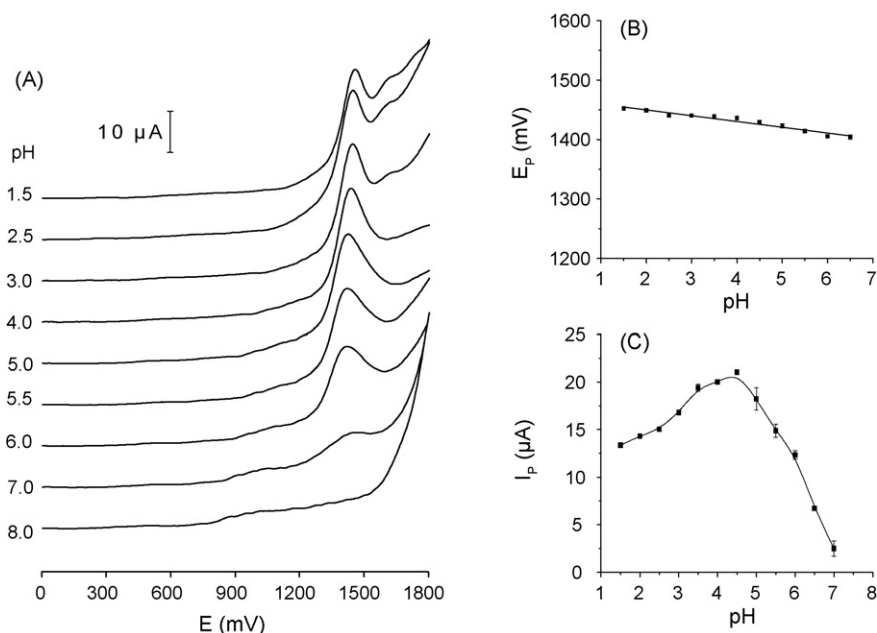


Fig. 2. (A) Typical DPV voltammograms of a $1 \times 10^{-3} \text{ mol L}^{-1}$ atomoxetine solution at different pHs, (B) E_p versus pH, and (C) I_p versus pH.

mixture for acid or alkaline hydrolysis, respectively. Each solution was boiled for 1 h at reflux.

2.4.5.2. *Photolysis*. Solutions consisting of 1 mg mL^{-1} atomoxetine in water were exposed to artificial daylight for 24 h.

2.4.5.3. *Thermolysis*. Approximately 100 mg atomoxetine raw material was heated at 105°C for 3 h.

Appropriate volumes of each solution obtained from the degradation trials or the corresponding mg amounts from the thermolysis trials for the raw material assays were diluted with $0.1 \text{ mol L}^{-1} \text{ HClO}_4$ to obtain a theoretical concentration of $3.9 \times 10^{-4} \text{ mol L}^{-1}$ atomoxetine. Samples were stored at -20°C and protected from light prior to voltammetric analysis. Each sample was analyzed in duplicate.

2.5. Statistical analysis

All statistical analyses were performed using the GraphPad Prism Software, version 5.00, for Windows.

3. Results and discussion

Atomoxetine exhibits an anodic response in aqueous media ($0.1 \text{ mol L}^{-1} \text{ HClO}_4$ and 0.1 mol L^{-1} Britton-Robinson buffer between pH 1.5 and 7) as studied by DPV on a glassy carbon electrode. In Fig. 2A, typical DPV voltammograms of atomoxetine at different pHs are shown. As can be seen, an oxidation peak appears at approximately 1500 mV and the oxidation appears to be virtually pH-independent ($E_p = -9.73 \text{ pH} + 1469$; Fig. 2B). At $\text{pH} < 3$ another signal begins to appear at more positive potentials. The main peak current increases until pH 4.5; however, above pH 4.5, the peak current decreases with increasing pH (Fig. 2C).

To study these signals, different solvents and media (i.e., acetonitrile, dimethylformamide, and various ratio mixtures of acetonitrile/Britton-Robinson buffer) were used for the assay. When acetonitrile was employed, atomoxetine exhibited two oxidation peaks around 1100 and 1700 mV. In Fig. 3, typical DPV and CV voltammograms for atomoxetine in acetonitrile are shown.

CV experiments revealed that the atomoxetine oxidation in both aqueous and non-aqueous media (i.e., acetonitrile) corresponds to a totally irreversible process (Fig. 3). We studied the irreversibility of the oxidation using a wide range ($10\text{--}10000 \text{ mV s}^{-1}$) of sweep rates. It was observed that the peak current increases with increases in the sweep rate. A linear relationship between the log of the peak current and the log of the sweep rate, with a slope of 0.4, was found for both media types. Consequently, it can be assumed that the oxidation process is diffusion controlled [15].

To determine the number of electrons transferred in the oxidation of atomoxetine, chronocoulometric studies were performed in acetonitrile. In Fig. 4, DPV voltammograms of electrolysis taken at different times are shown ($E_{\text{app}} = 1300 \text{ mV}$ in Fig. 4A and $E_{\text{app}} = 1800 \text{ mV}$ in Fig. 4B). Also, graphs of the charge versus electrolysis time at 1300 and 1800 mV for $5 \times 10^{-4} \text{ mol L}^{-1}$ atomoxetine solutions are inset in each figure. As shown in Fig. 4A, the oxidation peak of atomoxetine at 1020 mV vanished and the second peak at 1716 mV remains unchanged after 1 h of electrolysis using 1300 mV. At the same time, a new peak at 2264 mV appears in the voltammograms. When electrolysis was carried out at 1800 mV,

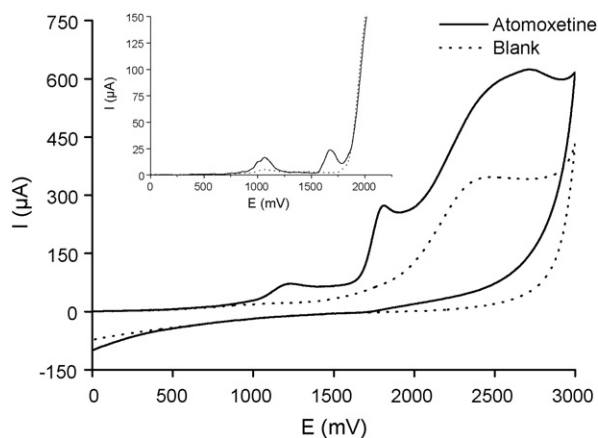


Fig. 3. Cyclic voltammogram of $1 \times 10^{-3} \text{ mol L}^{-1}$ atomoxetine in acetonitrile. Inset: DPV voltammogram of $1 \times 10^{-3} \text{ mol L}^{-1}$ atomoxetine in acetonitrile at 1000 mV s^{-1} (with PTBA as the supporting electrolyte).

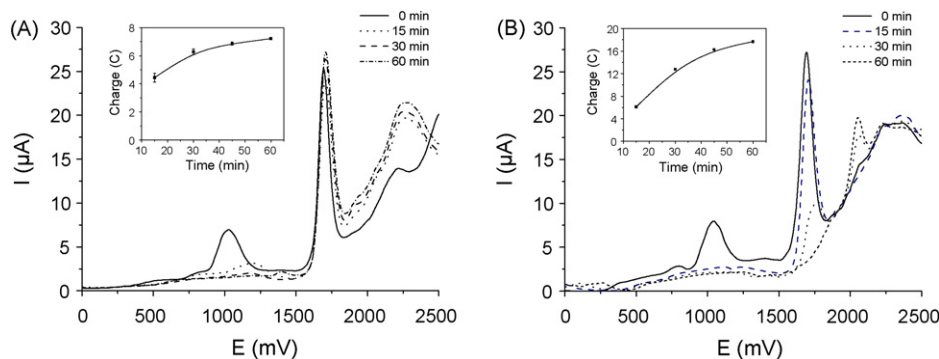


Fig. 4. DPV voltammograms of atomoxetine solutions (5×10^{-4} mol L $^{-1}$) at different time points: (A) $E_{app} = 1300$ mV and (B) $E_{app} = 1800$ mV. Insets: charge versus electrolysis time graphs.

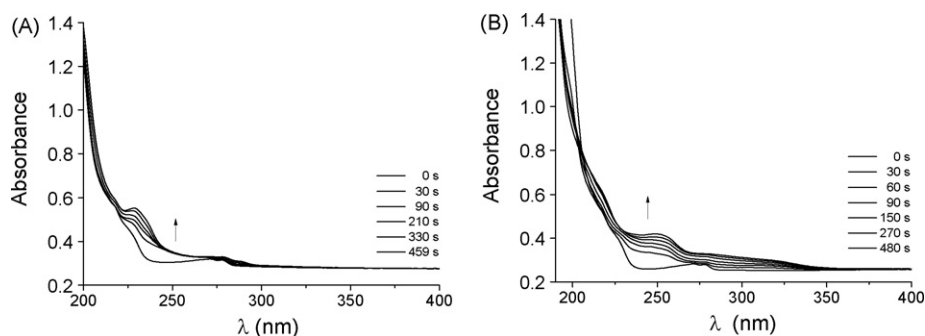


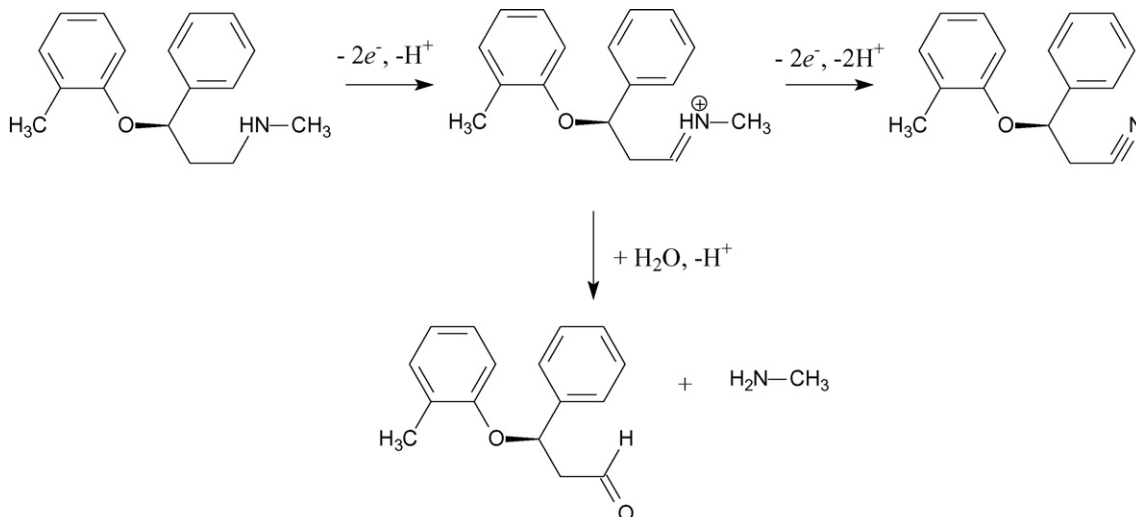
Fig. 5. Spectroelectrochemical experiments of 5×10^{-4} mol L $^{-1}$ atomoxetine solutions in acetonitrile: (A) $E_{app} = 1300$ mV and (B) $E_{app} = 1800$ mV.

both oxidation peaks disappear completely after 1 h and, over time, a new peak at 2060 mV appears in the voltammograms (Fig. 4B).

Using both the total charge transferred after application of a constant 1300 mV potential and the Faraday equation [16] resulted in a calculated value of 1.494 ± 0.002 electrons, which leads to the conclusion that two electrons are involved in the electrochemical process of atomoxetine oxidation. Furthermore, when the electrolysis potential was set at 1800 mV, it was calculated that 3.662 ± 0.004 electrons are transferred during atomoxetine oxidation, which leads to the conclusion that four electrons are involved. It was observed that at this potential ($E_{app} = 1800$ mV), the solutions turned yellow in color indicating that the products obtained are most likely dependent on the applied potential.

When the electrolysis measurements were followed by UV–vis analysis or when spectroelectrochemical experiments were performed, the main changes noted in the atomoxetine spectra were the following: (a) the shoulder at 225 nm undergoes a bathochromic effect and the band at 275 nm undergoes a hyperchromic effect when $E_{app} = 1300$ mV and (b) a new band appears at 250 nm and a hyperchromic effect is observed around 300 nm when $E_{app} = 1800$ mV. This is consistent with the appearance of the yellow color in the electrolyzed solutions (Fig. 5).

Based on the above results and literature reports [17], it is known that secondary and tertiary amines can be oxidized in acetonitrile to give the corresponding aldehyde and amine derivatives. The following mechanism is proposed for the oxidation of atomoxetine:



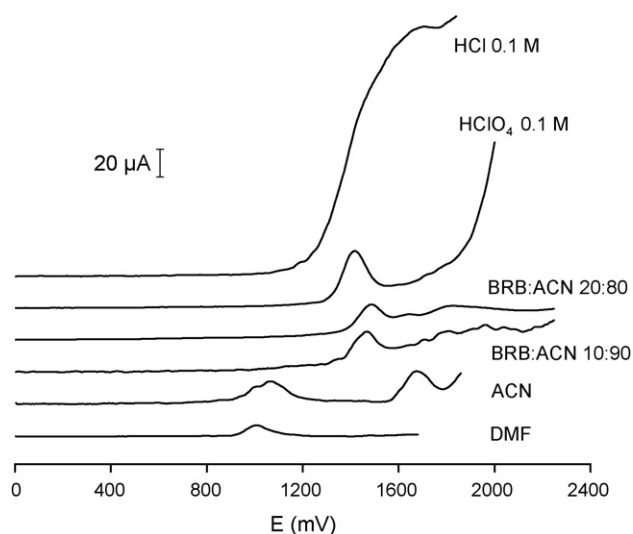


Fig. 6. DPV of $1 \times 10^{-3} \text{ mol L}^{-1}$ atomoxetine solutions in different media.

For analysis, we used the DPV technique with $0.1 \text{ mol L}^{-1} \text{ HClO}_4$ because it was found to provide the best experimental conditions in comparison to the other media tested (Fig. 6). In this medium, the I_p for the oxidation peak varied linearly with atomoxetine concentration between 1×10^{-4} and $1 \times 10^{-3} \text{ mol L}^{-1}$. The within-day and inter-day reproducibility was adequate with R.S.D. values lower than 3%. The analytical parameters are summarized in Table 1.

In order to confirm the selectivity of the method, we tested the excipients found in the oral formulation (dimethicone and pregelatinized starch) and used classical degradation methods such as hydrolysis (acidic and alkaline), artificial daylight exposure and thermolysis [18].

In 1 h of acid hydrolysis, the oxidation signal of atomoxetine decreased and a new signal appeared in the voltammogram at 908 mV that did not interfere with the main atomoxetine signal (Fig. 7). In the voltammograms from alkaline hydrolysis, artificial daylight exposure and thermolysis trials, no changes were observed. Additionally, degradation trials were assayed using HPLC and, in both acid and alkaline hydrolysis, degradation of 80% and 50%, respectively, was observed leading to the conclusion that the proposed voltammetric method is not sufficiently selective for these experimental conditions.

Also, the results show that the presence of excipients do not interfere with the atomoxetine signal. Thus, it can be concluded that the developed DPV method is satisfactorily selective for atomoxetine quantification in pharmaceuticals and that no prior separations or extractions are necessary.

Finally, the developed DPV method was applied to both the assay and the uniformity content of atomoxetine capsules. For compar-

Table 1
Analytical parameters for the developed DPV method.

Parameter	DPV ($E = 1416 \pm 10 \text{ mV}$)
Within-day reproducibility, CV (%)	$2.78^a - 2.69^b$
Inter-day reproducibility, CV (%)	$3.13^a - 2.65^b$
Recovery (%) \pm S.D.	96.6 ± 1.2^c
Concentration range (mol L^{-1})	1×10^{-4} to 1×10^{-3}
Intercept (μA) \pm S.D.	1.6858 ± 0.1783
Slope (L mol^{-1}) \pm S.D.	28739 ± 543
Regression coefficient	0.9968 ($n=9$)
Detection limit (mol L^{-1})	6.9×10^{-5}
Quantitation limit (mol L^{-1})	1.0×10^{-4}

^a Concentration level of $5 \times 10^{-4} \text{ mol L}^{-1}$.

^b Concentration level of $1 \times 10^{-3} \text{ mol L}^{-1}$.

^c Average of 10 determination on a concentration level of $3.9 \times 10^{-4} \text{ mol L}^{-1}$.

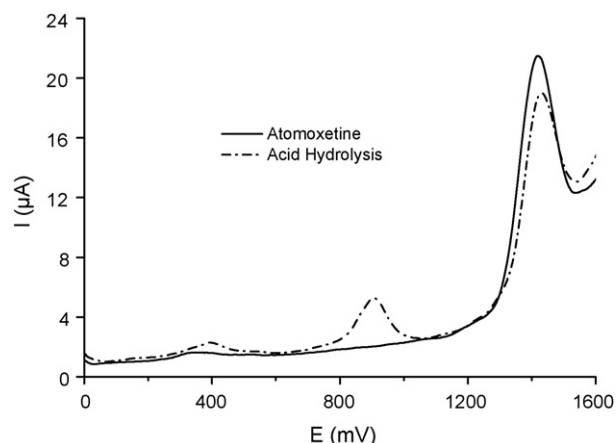


Fig. 7. DPV voltammograms from 1 h acid hydrolysis of $3.9 \times 10^{-4} \text{ mol L}^{-1}$ atomoxetine solutions.

Table 2

Assay results of atomoxetine in commercial capsules^{a,b}.

	Atomoxetine (%)	S.D. (%)	R.S.D. (%)
DPV	92.6	1.9	1.18
HPLC	93.3	0.6	0.60

$F_{\text{calc}} = 3.794$, $F_{\text{table}} = 9.197$; $t_{\text{calc}} = 1.031$, $t_{\text{table}} = 2.31$ ($p < 0.05$).

^a Deaten[®] (declared amount per capsule 25.0 mg atomoxetine as hydrochloride).

^b Each value represents the average of three samples analyzed in quadruplicate.

Table 3

Uniformity of content results of atomoxetine capsules for the proposed method and HPLC^a.

Capsule	Percentage found	
	DPV	HPLC
1	98.4	100.6
2	96.1	97.5
3	100.8	100.9
4	101.8	102.6
5	101.0	102.1
6	102.9	104.7
7	105.6	105.4
8	95.9	98.8
9	97.3	98.9
10	96.9	99.2
Average	99.7	101.1
S.D.	3.2	2.6
R.S.D., %	3.2	2.6

^a Deaten[®] (declared amount per capsule 25.0 mg atomoxetine as hydrochloride).

ison, HPLC analysis was also carried out. In Table 2, the results obtained for the assay are summarized and show good agreement using the F -test for variance proportion and the Student's t -test ($p < 0.05$). In Table 3, the results for the uniformity content of atomoxetine capsules are listed. As shown in this table, all the tested capsules fulfill the general Pharmacopoeia requirement that the average uniformity content of capsules must be within 85.0–115.0% of the label claim and that no individual value is out of the range of 75.0–125.0% of the label claim.

4. Conclusions

Atomoxetine exhibits an anodic response on a glassy carbon electrode with one or two peaks depending on the solvent tested. Transfer of two and four electrons was calculated for each peak and an overall oxidation reaction was proposed to show the generation of aldehyde and amine derivatives as well as the nitrile derivative.

On the basis of the anodic response of atomoxetine, a DPV method for its detection was developed and compared to a HPLC method. The proposed DPV method was successfully applied to both the assay and uniformity content of the drug in capsules without interference from excipients. Finally, sample preparation was simple and the method was not time consuming or expensive compared to the HPLC method.

References

- [1] G. Dell'Agnello, D. Maschietto, C. Bravaccio, F. Calamoneri, G. Masi, P. Curatolo, D. Besana, F. Mancini, A. Rossi, L. Poole, R. Escobar, A. Zuddas, *Eur. Neuropsychopharmacol.* 19 (2009) 822.
- [2] J.M. Sauer, B.J. Ring, J.W. Witcher, *Clin. Pharmacokinet.* 44 (2005) 571.
- [3] V.L. Pulito, X. Li, S.S. Varga, L.S. Mulcahy, K.S. Clark, S.A. Halbert, A.B. Reitz, W.V. Murray, L.K. Jolliffe, *J. Pharmacol. Exp. Ther.* 294 (2000) 224.
- [4] N.A. Farid, R.F. Bergstrom, E.A. Ziege, C.J. Parli, L. Lemberger, *J. Clin. Pharmacol.* 25 (1985) 296.
- [5] D. Garside, J.D. Roper-Miller, E.C. Riemer, *J. Forensic Sci.* 51 (2006) 179.
- [6] E. Choong, S. Rudaz, A. Kottelat, D. Guillardme, J.L. Veuthey, C.B. Eap, *J. Pharm. Biomed. Anal.* 50 (2009) 1000.
- [7] J.H. Mullen, R.L. Shugert, G.D. Ponsler, Q. Li, B. Sundaram, H.L. Coales, J.E. Yakupkovic, R.M. Lelacheur, W.J. Wheeler, F.J. Belas, J.M. Sauer, *J. Pharm. Biomed. Anal.* 38 (2005) 720.
- [8] H.J. Zhu, J.S. Wang, J.L. Donovan, C.L. Devane, B.B. Gibson, J.S. Markowitz, *J. Chromatogr. B* 846 (2007) 351.
- [9] C. Patel, M. Patel, S. Rani, M. Nivsarkar, H. Padh, *J. Chromatogr. B* 850 (2007) 356.
- [10] W. Guo, W. Li, G. Guo, J. Zhang, B. Zhou, Y. Zhai, C. Wang, *J. Chromatogr. B* 854 (2007) 128.
- [11] P.F. Gavin, B.A. Olsen, *J. Pharm. Biomed. Anal.* 46 (2008) 431.
- [12] S.S. Kamat, V.B. Choudhari, V.T. Vele, S.S. Prabhune, *Chromatographia* 67 (2008) 143.
- [13] J.A. Sellers, B.A. Olsen, P.K. Owens, P.F. Gavin, *J. Pharm. Biomed. Anal.* 41 (2006) 1088.
- [14] I.F. Hu, D.H. Karweik, T. Kuwana, *J. Electroanal. Chem.* 188 (1985) 59.
- [15] D.K. Gosser Jr., *Cyclic Voltammetry. Simulation and Analysis of Reaction Mechanisms*, VCH Publishers, Inc., New York, 1993, p. 43.
- [16] P. Kissinger, W. Heineman, *Laboratory Techniques in Electroanalytical Chemistry*, 10th ed., Marcel Dekker, New York, 1984.
- [17] H. Lund, in: H. Lund, O. Hammerich (Eds.), *Organic Electrochemistry*, 4th ed., Marcel Dekker, New York, 2001, p. 547.
- [18] O.A. Quattrochi, S.A. De Andrizzi, R.F. Laba, *Introducción a la HPLC, Aplicación y Práctica*, Artes Gráficas Farro S.A., Argentina, 1992.