Voltammetric behavior of naratriptan and its determination in tablets

C. Velasco-Aguirre, A. Álvarez-Lueje *

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

ABSTRACT

The electrochemical behavior and the analytical application of the selective serotonin agonist naratriptan (N-methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide) are presented herein. Naratriptan exhibits an anodic response in aqueous media over a broad pH range (pH 2–12), as determined by differential pulse voltammetry and cyclic voltammetry using glassy carbon electrodes. This response is irreversible in nature, diffusion-controlled and probably caused by the oxidation of the naratriptan indole moiety. The differential pulse voltammetry technique was performed in $0.1\,mol\,L^{-1}$ Britton–Robinson buffer (pH = 3), which elicited the most reproducible results. The percentage of naratriptan recovery was $102.1 \pm 1.8\%$, and the limits of detection and quantitation were 9.5×10^{-6} and $2.0 \times 10^{-5}\,mol\,L^{-1}$, respectively. Selectivity trials revealed that the oxidation signal of the drug was not disturbed by the presence of excipients or degradation products. Thus, we conclude that the method presented herein is useful for the quantification of naratriptan in pharmaceutical drugs and that this method requires no separations or extractions. Finally, this voltammetric method was successfully applied to determine the quantity and the content uniformity of naratriptan in drug tablets. A comparison of this technique to the standard high-performance liquid chromatography technique was conducted at the end of our study.

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1. Introduction

The indolic derivative naratriptan (N-methyl-4-piperidyl)indole-5-ethanesulfonamide, Fig. 1) is a selective serotonin agonist, which acts at 5-HT$_1$ receptors to cause the vasoconstriction of cranial arteries. Drugs such as naratriptan are commonly known as triptans and are believed to act mainly at 5-HT$_{1B}$ and 5-HT$_{1D}$ subtype receptors (referred to as 5-HT$_{1B/1D}$-receptor antagonists). Naratriptan is used for the acute treatment of the headache phase of migraine attacks. The drug undergoes hepatic metabolism by cytochrome P450 isoenzymes. It is mainly excreted in urine containing 50% unchanged drug and 30% inactive metabolites from the drug. The elimination half-life is 6 h and is significantly prolonged in patients with renal or hepatic impairment [1,2].

A select few methods for the quantification of naratriptan have been described in the literature, which include liquid chromatography–electrospray mass spectrometry for human serum [3,4] and high-pressure liquid chromatography with fluorescence detection for pharmacokinetic studies [5]. Micellar electrokinetic capillary chromatography has been used to examine naratriptan in pharmaceuticals [6], and reversed phase techniques have been developed to investigate impurities during the forma-

tion of naratriptan [7]. The official methods described in the United States Pharmacopoeia for the quantitation of this drug in both naratriptan raw materials and tablets employ high-performance liquid chromatography (HPLC) [8].

Recently, some electrochemical features of naratriptan have been reported in a review article focused on describing the analytical methods available for the identification and determination of triptans [9], but to the best of our knowledge no scientific literature regarding the electrochemical behavior of naratriptan has been published.

Thus, we have examined the electrochemical behavior of naratriptan by developing a differential pulse voltammetric assay to study its content uniformity in the tablet form.

2. Experimental

2.1. Reagents and drugs

Naratriptan hydrochloride (100.1% chromatographically pure) was supplied by Bagó Laboratories (Santiago, Chile). Commercial tablets of Bagomigral® (the declared amount of naratriptan is 2.5 mg per tablet in the hydrochloride form, Bagó Laboratories, Santiago, Chile) were purchased. Melatonin was obtained from Sigma–Aldrich.

Phosphoric acid, triethylamine and isopropyl alcohol (HPLC grade) were obtained from Merck. All other reagents were of analytical grade unless indicated otherwise. Solutions were prepared with

* Corresponding author. Fax: +56 7378920.
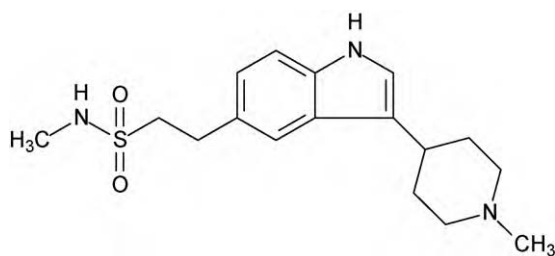*E-mail address:* aalvarez@ciq.uchile.cl (A. Álvarez-Lueje).

Fig. 1. Chemical structure of naratriptan.

ultrapure water (ρ = 18 MΩ cm) from the Milli-Q water purification system (Millipore).

2.2. Apparatus

2.2.1. Voltammetric analyzer

Differential pulse voltammetric (DPV) and cyclic voltammetric (CV) experiments were performed with a fully automatized workstation Bioanalytical Systems (BAS) CV-50W. A 25-mL thermostated BAS measuring cell with a glassy carbon electrode (GCE) (Ø = 3 mm, BAS) was used as the working electrode. A platinum wire and an Ag/AgCl were used as the counter electrode and reference electrode, respectively. The operating conditions were as follows: the sensitivity ranged from 10 to 100 μA V^{-1}, the potential range was 0–1700 mV and the sweep rate was 50–3000 mV s^{-1} for CV experiments. For dynamic experiments, a glassy carbon rotating disk electrode (3-mm diameter, BAS) was also employed via its connection to a rotating disk electrode (RDE-2, BAS). The working electrode surface was polished with 0.3-μm and 0.05-μm alumina slurries before each measurement [10].

2.2.2. Coulometric studies

Assays were carried out using a fully automatized assembly (BAS CV-50W), composed of a 100-mL electrolysis cell, reticulated vitreous carbon as a working electrode, an Ag/AgCl and a platinum wire as the reference electrode and counter electrode, respectively. The electrolysis potential was set at 1000 mV in 0.1 mol L^{-1} Britton–Robinson buffer. Experiments were performed in duplicate.

2.2.3. HPLC

HPLC measurements were performed using a Waters assembly equipped with a model 600 Controller pump and a model 996 Photodiode Array Detector (DAD). The data acquisition and analysis were made using Millenium version 2.1 software.

The chromatographic column consisted of a Waters XTerra phenyl column (150 mm × 4.6 mm, 3.5 μm). A 20-μL Rheodyne valve comprised the injector. Ultraviolet (UV) detection at 282 nm was employed, and the column was kept at a constant temperature by a Waters column heater cartridge, model 600.

An isocratic elution was applied using a mobile phase solution consisting of 0.01 mol L^{-1} triethylamine phosphate buffer (pH 2.5) and isopropyl alcohol (90:10, v/v). The flow was kept at 1.0 mL min^{-1}, and the working temperature remained at 35 ± 1 °C [8]. Under these conditions, naratriptan exhibited a retention time of 6.83 ± 0.07 min.

2.3. Preparation of solutions

2.3.1. Buffer solutions

For voltammetric experiments, 0.1 mol L^{-1} Britton–Robinson buffer (an acetic, boric and phosphoric acid mixture) was used. The desired pH was obtained through the addition of concentrated solu-

tions of NaOH or HCl. For use in the HPLC experiments, 0.01 mol L^{-1} triethylamine phosphate buffer (0.6 mL phosphoric acid in 900 mL water) was adjusted to pH 2.5 with triethylamine [8].

2.3.2. Stock drug solutions

Standard stock solutions of naratriptan hydrochloride were prepared daily at a constant concentration of 1×10^{-2} mol L^{-1} in 0.1 mol L^{-1} Britton–Robinson buffer. The solutions were protected from light using an amber glass material. A melatonin solution in methanol with a concentration of 1×10^{-2} mol L^{-1} was also prepared daily and protected from light.

2.3.3. Work solutions

Appropriate volumes of the stock solutions were diluted to 10 mL with 0.1 mol L^{-1} Britton–Robinson buffer prior to electrochemical and HPLC experiments.

2.4. Analytical procedure

2.4.1. Calibration curve preparation

By diluting the naratriptan stock solution with 0.1 mol L^{-1} Britton–Robinson buffer, working solutions ranging from 8×10^{-5} to 1×10^{-3} mol L^{-1} were prepared.

2.4.2. Synthetic samples

Excipients (carboxymethylcellulose sodium, croscarmellose sodium, anhydrous lactose, magnesium stearate, hypromellose, titanium dioxide, triacetin, iron oxide yellow monohydrate and indigo carmine) were added to the drug for recovery studies according to the manufacturer's batch formulas for 2.5-mg naratriptan (hydrochloride) tablets.

2.4.3. Assay

The mixed contents of 10 tablets containing the equivalent of 2.5 mg of naratriptan were dissolved as thoroughly as possible in 15 mL of 0.1 mol L^{-1} Britton–Robinson buffer. The mixture was then shaken on a vortexer for 5 min and filled to a 20-mL volume using the same solvent. The theoretical concentration of this solution was approximately 3.36×10^{-4} mol L^{-1}. This solution was transferred to a voltammetric cell, and recordings were taken at least twice from 0 to 1700 mV. The mass of naratriptan in the sample solution was calculated from the prepared standard calibration curve.

2.4.4. Uniformity of content

No less than 10 commercial tablets of naratriptan (Bagomigral®, 2.5 mg naratriptan in the hydrochloride form per tablet) were used. Each tablet was independently suspended in 15 mL 0.1 mol L^{-1} Britton–Robinson buffer and homogenized with a vortexer to assure the complete dissolution of the drug prior to its dilution to a final volume of 20 mL using the same solvent. Each sample solution was transferred to a voltammetric cell and recordings were taken at least twice from 0 to 1700 mV. The mass of naratriptan in the sample solution was calculated from the prepared standard calibration curve. The same procedure was followed for HPLC analysis with the added step of filtration prior to injection.

2.4.5. Selectivity trials

Hydrolysis. A total of 37.19 mg naratriptan was dissolved in 10 mL of either a 1 mol L^{-1} HCl or a 1 mol L^{-1} NaOH solution in a 50 mL-distillation flask for acid or alkaline hydrolysis, respectively. Each solution was boiled for 1 h at reflux.

Photolysis. A naratriptan solution with an approximate concentration of 1.2 mg L^{-1} in 0.1 mol L^{-1} Britton–Robinson buffer was exposed to artificial daylight for 48 h.
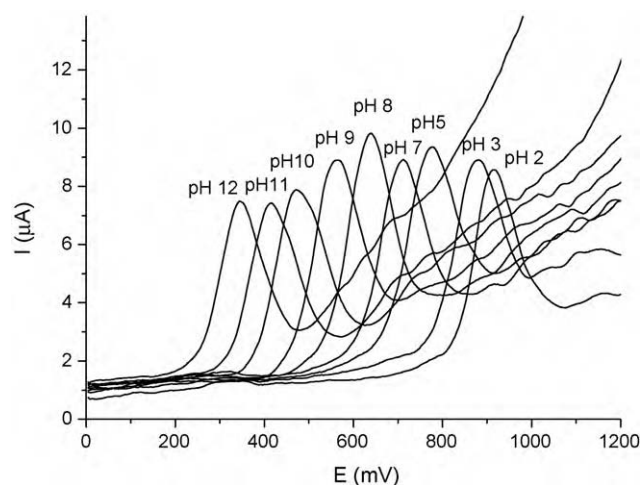
Fig. 2. Differential pulse voltammograms of a 3.38×10^{-4} mol L^{-1} naratriptan solution at different pHs in 0.1 mol L^{-1} Britton–Robinson buffer.

Chemical oxidation. To a 5×10^{-4} mol L^{-1} naratriptan solution in 0.1 mol L^{-1} Britton–Robinson buffer solution, 1 mL of 30% (v/v) H_2O_2 was added.

Appropriate volumes of each solution obtained from the degradation experiments were mixed with 0.1 mol L^{-1} Britton–Robinson buffer to generate theoretical concentrations of 5×10^{-4} mol L^{-1} naratriptan. Samples from these studies were stored at $-20\,^{\circ}C$ and protected from light prior to voltammetric analysis. Each sample was analyzed in duplicate.

2.5. Statistical analysis

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

3. Results and discussion

Naratriptan exhibits anodic responses in aqueous media (0.1 mol L^{-1} Britton–Robinson buffer solution) when it was studied by differential pulse voltammetry using glassy carbon electrodes. This response occurs over a broad range of pH values (2–12) and always displays a well-defined peak that shifts to lower potentials as pH increases. Fig. 2 shows the evolution of the DPV of naratriptan with pH.

Peak potentials varied linearly with pH over the entire tested pH range with two breaks at pH 4 and pH 9 that were probably due to a change in the protonation–deprotonation equilibrium of the electroactive components (Fig. 3A). The reported pK_a value of naratriptan is 9.7 for its piperidinyl nitrogen, which is in agreement with the break at pH 9 in the E_p vs. pH plot [11]. The break at pH 4 could be explained by the pK_a of the indolyl radical moiety, which can be 4.3 for the cation radical when tryptophan is the parent compound [12,14]. After pH 4, the peak potentials became slightly less positive as the pH increases. This seems pH-independent behavior and has a linear relationship (E_p vs. pH) with a slope of -24 mV per pH unit. Above pH 4, the increase in pH favors the oxidation, showing a decrease in potentials. The behaviors of the peak potentials are defined by the following linear regressions:

pH 2–4 : $E_p = -24\,pH + 981.3$ ($r = 0.991$);

pH 4–9 : $E_p = -63.4\,pH + 1146.3$ ($r = 0.997$);
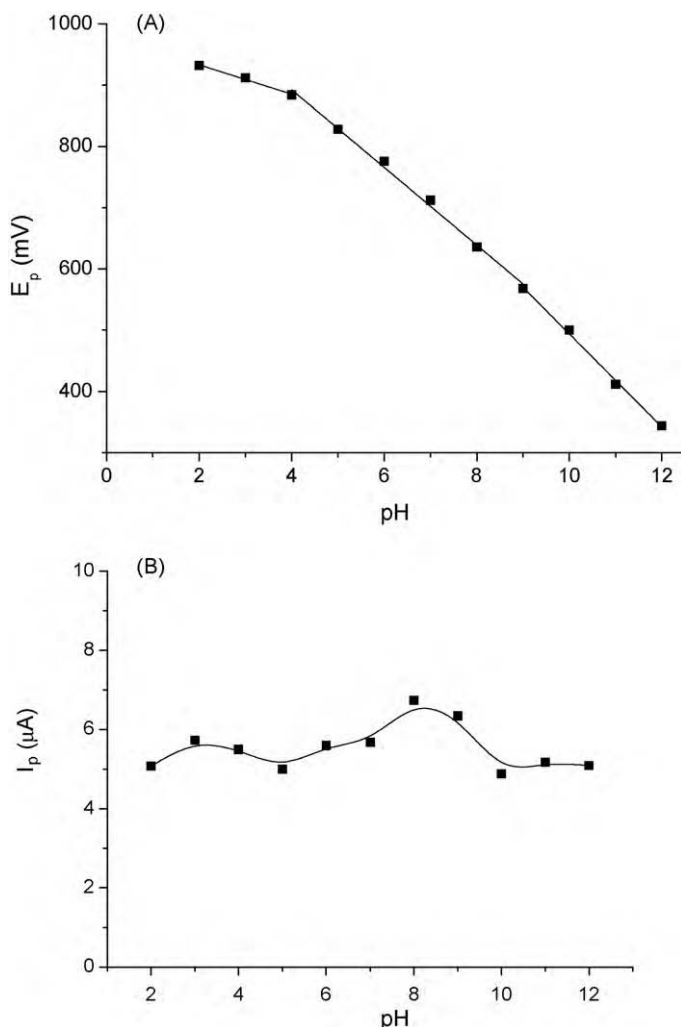
pH 9–12 : $E_p = -76\,pH + 1254$ ($r = 0.998$)

Fig. 3. (A) Peak potential evolution of a 3.84×10^{-4} mol L^{-1} naratriptan solution at different pHs in 0.1 mol L^{-1} Britton–Robinson buffer and (B) a peak current (I_p) vs. pH graph.

Peak currents remain unaltered between pH 2 and 7 and slightly increase at pH 8. This is followed by a dip at pH 9, which levels off beginning at pH 10. The evolution of this peak current with pH is shown in Fig. 3B.

In the cyclic voltammetric experiments over all pH values (3, 7, 10) at many sweep rate values between 50 and 3000 mV s^{-1}, no peaks were observed in the reverse scans. This suggests that the oxidation of naratriptan has an irreversible character. Furthermore, a new anodic signal appears as the sweep rate increases at pH 7 and pH 10 (Fig. 4). This can be explained if oxidation at the glassy carbon is a multi-electron process that involves steps of the EC-type (electrochemical-chemical). If this were the case, then following each oxidation step there should be either a proton loss or an attack of a nucleophile (most likely an attack of water). The dependence of the peak currents (I_p) and peak potentials on the scan rates (v) were studied in the range of 50–3000 mV s^{-1} at pH 3, pH 7 and pH 10. These scan rate studies show whether the processes occurring on the glassy carbon electrode are under diffusion or adsorption control. A linear relationship was observed between the peak current and the square root of the scan rate for each studied pH. The corresponding relationships are given by:

pH 3 : $I_p\,(\mu A) = 0.475v^{1/2}\,(mV\,s^{-1}) + 5.2$ ($r = 0.986$)
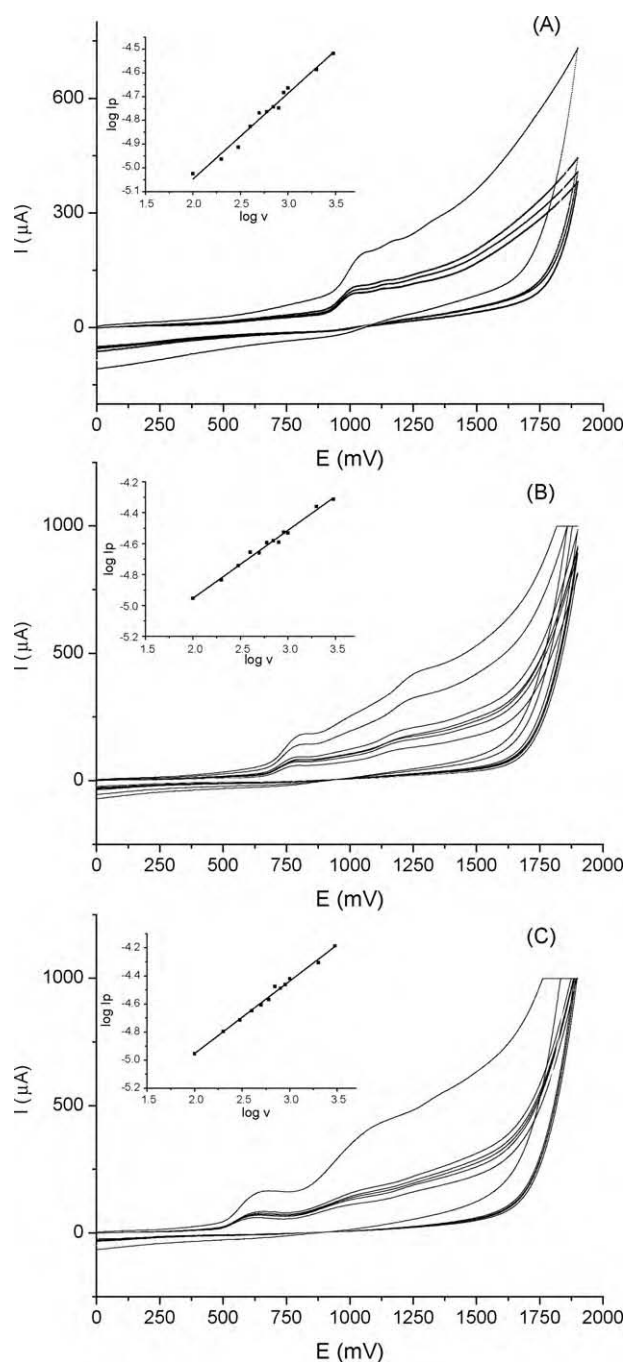
Fig. 4. Cyclic voltammograms of a $4 \times 10^{-4}\,\mathrm{mol\,L^{-1}}$ naratriptan solution in $0.1\,\mathrm{mol\,L^{-1}}$ Britton–Robinson buffer at different sweep rates between 50 and $3000\,\mathrm{mV\,s^{-1}}$. (A) pH 3, (B) pH 7 and (C) pH 10. Insets: log peak current and log sweep rate at each pH.

pH 7 : $I_p\,(\mu A) = 0.86 \nu^{1/2}\,(\mathrm{mV\,s^{-1}}) + 3.3$ $(r = 0.992)$

pH 10 : $I_p\,(\mu A) = 1.18 \nu^{1/2}\,(\mathrm{mV\,s^{-1}}) - 0.71$ $(r = 0.995)$

The peak potentials were shifted to less positive values at increasing scan rates, which confirms the irreversible nature of the oxidation process.

A plot of the logarithm of the peak current ($\log I_p$) vs. the logarithm of the scan rate ($\log \nu$) yielded straight lines within the same scan rate ranges as above. The linear relationships between the current and sweep rates are described by the following expressions:

pH 3 : $\log I_p = 0.40 \log \nu - 5.8$ $(r = 0.989)$;

pH 7 : $\log I_p = 0.44 \log \nu - 5.8$ $(r = 0.994)$;

pH 10 : $\log I_p = 0.51 \log \nu - 5.9$ $(r = 0.996)$.

The measured slopes were very close to the theoretically expected value of 0.5 for an ideal reaction of the solution species under a purely diffusion-controlled current [15]. Both the correlation coefficient of I_p vs. $\nu^{1/2}$ and the slope of $\log I_p$ vs. $\log \nu$ confirm the diffusion-controlled nature of the process. The values of the peak current function ($I_p/\nu^{1/2}$) vs. $\log \nu$ were constant with increasing scan rates in the range of 50–3000 mV s^{-1}. This behavior suggests that naratriptan electrooxidation is free from adsorption complications at the electrode surface and that the electrode reaction is controlled purely by diffusion [16,17].

Coulometric experiments to determine the number of electrons transferred during the oxidation of naratriptan were unsuccessful. This was probably due to the presence of side reactions that often occurred during the electrolysis of drugs. Additionally, the electrolysis was followed by HPLC-DAD, and two situations were observed: (a) the peak corresponding to naratriptan diminishes by 30% after 2 h of electrolysis and (b) a new signal appeared at low retention times (6.83 min for naratriptan vs. 6.12 min, respectively). Furthermore, the UV spectra of the electrolysis products retained their 231 nm peaks, which correspond to naratriptan. The signal corresponding to naratriptan at 285 nm vanished, and a new signal at 320 nm appeared. These spectral characteristics gave the solution a yellowish hue. The increase in the absorbance in the region above 300 nm is attributable to the formation of dimers with extensive π conjugation [18,19]. When we consider the electrochemical behavior previously reported for a related compound, sumatriptan [20] and the literature data regarding the anodic oxidation of nitrogen-containing compounds [21], the electrooxidation of naratriptan is likely caused by the oxidation of its indole moiety.

To identify the group responsible for the oxidation, naratriptan was compared to a drug with similar structure (melatonin) by DPV and rotating disk electrode (RDE). Both compounds exhibit anodic signals at similar potentials. This provides evidence that the indole moiety is involved in the electrooxidation of naratriptan. Further, a similar behavior was observed when the samples were evaluated and compared by the RDE voltammetry technique, which showed that two electrons are transferred in the electrochemical oxidation of naratriptan. These results allow us to assume that the oxidation steps occur on the nitrogen atom of the indole ring, which is electroactive in both acidic and basic media. These results strongly indicate that the naratriptan oxidation step is related to the nitrogen atom on its indole ring. It is expected that this mechanism will further undergo 1e$^-$, 1H$^+$ oxidation, as suggested by the slope value obtained from the E_p–pH equation at pH values greater than 4. In this process, the first step involves a one-electron process that yields a radical cation, which is further oxidized by the loss of a second electron and proton. This can generate a quinoneimine that is susceptible to nucleophilic attack. Thus, dimerization following the one-electron obstruction by radical–radical or radical–substrate coupling might be possible [22,23]. According to this hypothesis, we propose a tentative mechanism for the electrooxidation of naratriptan in the following scheme:
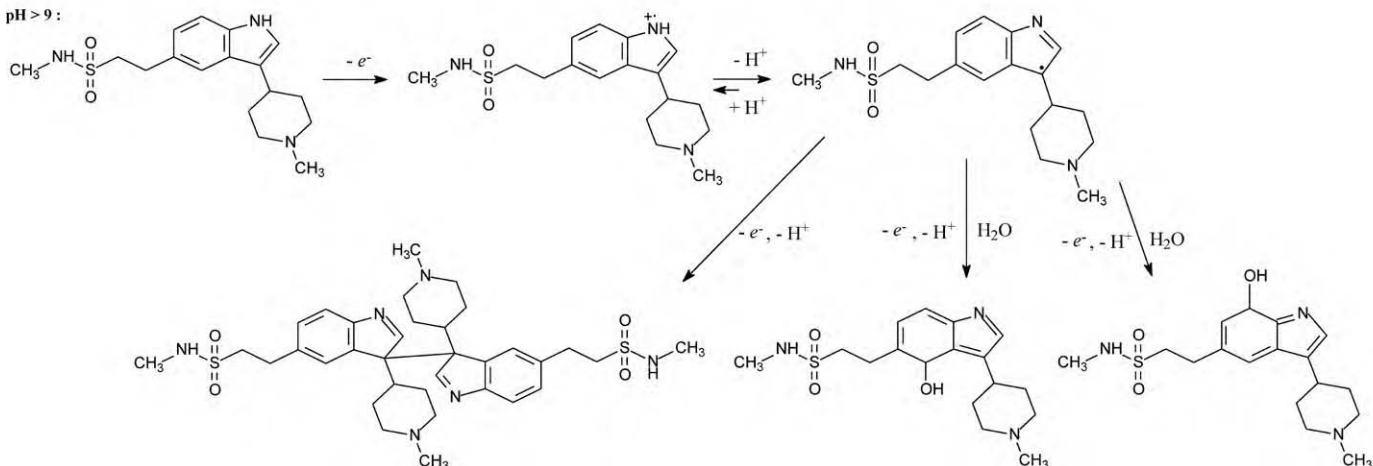
pH 2 - 4 :
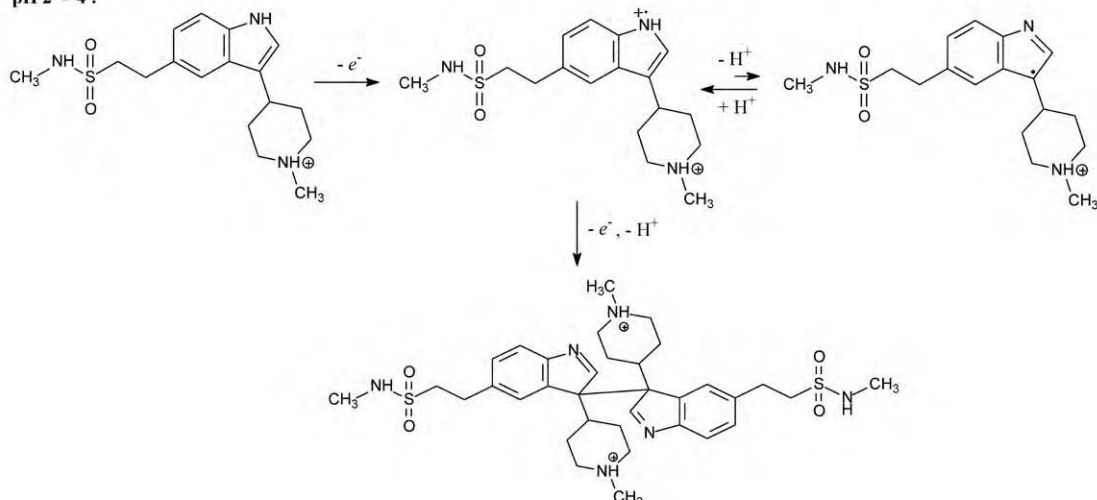
pH 4 - 9 :
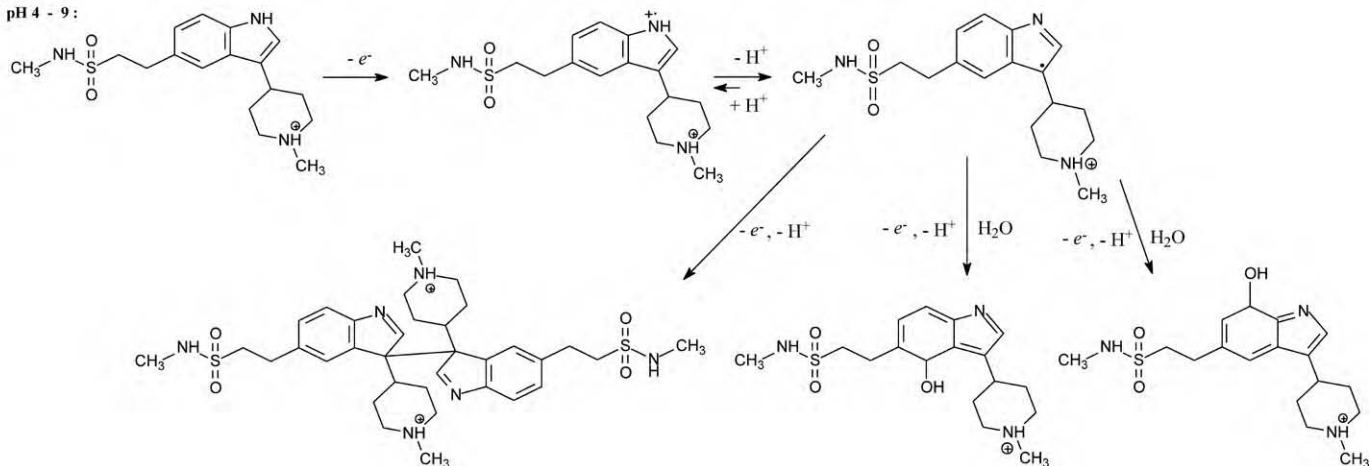
pH > 9 :

Using the RDE, the diffusion coefficient for naratriptan was obtained. For irreversible reactions, the relationship between the limiting current and the rotating speed is given by the Levich equation [13]:

$$I_{lim} = 0.62 nFAD^{2/3} \nu^{-1/6} \omega^{1/2} C,$$

where n, F, A, D, ν, ω and C are the number of electrons, Faraday constant, the electrode area (cm^2), diffusion coefficient ($cm^2 s^{-1}$), kinematics viscosity ($cm^2 s^{-1}$), rotation speed ($rad s^{-1}$) and substrate concentration ($mol cm^{-3}$), respectively. The diffusion coefficient of naratriptan was obtained from the slope of the Levich plot (I_{lim} vs. $\omega^{1/2}$). The mean value of D was found to be $1.26 \times 10^{-6} cm^2 s^{-1}$ for $n = 2$ electrons.

Table 1
Analytical parameters for the developed DPV method.

Parameter	DPV (E = 912 mV ± 8 mV)
Within-day reproducibility, CV (%)	2.7[a]–1.2[b]
Inter-day reproducibility, CV (%)	2.9[a]–1.4[b]
Recovery (%) ± S.D.	102.1 ± 1.8[c]
Concentration range (mol L^{-1})	7.5×10^{-5}–7.5×10^{-4}
Calibration curve (I_p, μA; C, mol L^{-1})	$I_p = 28234C + 1.91976$ ($r = 0.9997$; $n = 12$)
Detection limit (mol L^{-1})	9.5×10^{-6}
Quantitation limit (mol L^{-1})	2.0×10^{-5}

[a] Concentration level of 2.5×10^{-4} mol L^{-1}.
[b] Concentration level of 4.8×10^{-4} mol L^{-1}.
[c] Average of 10 determinations of the concentration level at 4.8×10^{-4} mol L^{-1}.

Based on the electrochemical response of naratriptan, a novel method for its determination is proposed. For analytical purposes, the DPV technique in 0.1 mol L^{-1} Britton–Robinson buffer at pH 3 was selected. Under these conditions, the peak current remains stable with pH (Fig. 3B), the signal is well-resolved (Fig. 2) and the signal has higher repeatability than signals at others pH values. Further, the signals vary linearly with naratriptan concentration between 7.5×10^{-5} and 7.5×10^{-4} mol L^{-1}. The detection (LOD) and quantitation limits (LOQ) of the method were calculated by using the average (Yb) and standard deviation (Sb) of the blank estimated response, the calibration curve slopes (m) and the signal/noise ratios of 3 and 10 according to the following expressions [24]:

$$\text{LOD} = \left[\frac{Yb + 3\,Sb}{m} \right], \qquad \text{LOQ} = \left[\frac{Yb + 10\,Sb}{m} \right]$$

Within-day and inter-day reproducibilities were deemed adequate with root square deviation values lower than 3%. In Table 1, the analytical parameters are summarized.

To prove that this method was selective, the excipients used in the oral formulation (carboxymethylcellulose sodium, croscarmellose sodium, anhydrous lactose, magnesium stearate, hypromellose, titanium dioxide, triacetin, iron oxide yellow monohydrate and indigo carmine) and classical degradation trials (hydrolysis, artificial daylight exposure, oxidation) were tested [24].

In the degradation trials, no effect on the voltammetric peak of naratriptan was observed during the chemical oxidation under either acid or alkaline hydrolysis. However, when the drug solution was exposed to artificial daylight, a 15%-decrease in the oxidation peak of naratriptan was observed, while no new signals appeared in the voltammogram (data not shown).

The signal belonging to the drug is not disturbed by the presence of any excipient. Consequently, we conclude that the developed DPV method has adequate selectivity for use as a naratriptan quantification tool in pharmaceuticals without requiring any previous separations or extractions.

As a final point, the developed DPV method was applied to both assay the quantity and the uniformity of naratriptan tablets. For comparison, an official Pharmacopoeia HPLC analysis was also performed. In Table 2, the results obtained for the assay are summarized. They show good agreement with no statistically significant differences (as assessed with the F-test for variance proportion

Table 2
Assay results of naratriptan in commercial tablets[a,b].

	Naratriptan (%)	S.D. (%)	R.S.D. (%)
DPV	105.3	0.990	0.94
HPLC	102.7	0.874	0.85

[a] Bagomigral© (amount declared per coated tablet was 2.5 mg naratriptan as hydrochloride).
[b] Each value represents the average of two samples tested in triplicate.

Table 3
Content uniformity results for naratriptan tablets using the proposed method and the HPLC[a] method.

Tablet	Percentage found	
	DPV	HPLC
1	100.8	102.8
2	97.2	97.9
3	97.1	100.2
4	99.0	100.7
5	101.1	101.9
6	104.1	104.6
7	101.8	102.8
8	99.9	101.5
9	99.6	101.3
10	98.7	99.5
Average	99.9	101.3
S.D.	2.13	1.89
R.S.D., %	2.13	1.87

[a] Bagomigral® (the amount declared per coated tablet was 2.5 mg naratriptan in the hydrochloride form).

and the t-Student test with $p = 0.1106$). In addition, in Table 3, the results pertaining to the content uniformity within the naratriptan tablets are shown. As can be seen from this table, the contents for all assayed tablets are within ±4.6% of the claimed amounts. This fulfills the Pharmacopoeia requirement for a uniform content of tablets, which permits a ±15% of tolerance in dosage [8]. Through a comparison of the results obtained in the content uniformity test by applying a Snedecor F-test (variance proportion) and then the t-Student test, we conclude that there is no significant difference between them and that they are statistically equivalent.

4. Conclusions

Naratriptan exhibits an irreversible anodic peak that is diffusion-controlled at a glassy carbon electrode and probably caused by the oxidation of the naratriptan indole moiety. Based on the anodic response of the drug, a DPV method for its determination was developed and compared with the officially described method for its measurement. The proposed DPV method was successfully applied to determine both the quantity and uniformity of naratriptan in coated tablets without excipients interferences. Preparation of the sample was easy and did not require any previous treatments. The method is not time consuming and is inexpensive when compared with the Pharmacopoeial HPLC method.

References

[1] S. Sweetman (Ed.), Martindale: The Complete Drug Reference, Pharmaceutical Press, London, 2005 (Electronic version, Edition 2005).
[2] P.J. Goadsby, A.R. Charbit, A.P. Andreou, S. Akerman, P.R. Holland, Neuroscience 161 (2009) 327.
[3] B.D. Duléry, M.A. Petty, J. Schoun, M. David, N.D. Huebert, J. Pharm. Biomed. Anal. 15 (1997) 1009.
[4] K. Vishwanathan, M.G. Bartlett, J.T. Stewart, Rapid Commun. Mass Spectrom. 14 (2000) 168.
[5] M.L. Christensen, S.K. Eades, E. Fuseau, R.D. Kempsford, S.J. Phelps, L.J. Hak, J. Clin. Pharmacol. 41 (2001) 170.
[6] K.D. Altria, R. McLean, J. Pharm. Biomed. Anal. 18 (1998) 807.
[7] U. Sampath Kumar, V. Ravi Sankar, S. Bharani Kumar, M. Pandi Prabhu, S. Mahender Rao, Org. Process Res. Dev. 13 (2009) 468.
[8] USP 30-NF 25, United States Pharmacopoeial Convention, Inc., Rockville, MD, USA, 2007.
[9] C. Saka, Crit. Rev. Anal. Chem. 39 (2009) 32.
[10] I.F. Hu, D.H. Karweik, T. Kuwana, J. Electroanal. Chem. 188 (1985) 59.
[11] J.L. Castro, I. Collins, M.G.N. Russell, A.P. Watt, B. Sohal, D. Rathbone, M.S. Beer, J.A. Stanton, J. Med. Chem. 41 (1998) 2667.
[12] X. Shen, J. Lind, G. Merényi, J. Phys. Chem. 91 (1987) 4403.
[13] S. Solar, N. Gtoff, P.S. Surdhar, D.A. Armstrong, A. Singh, J. Phys. Chem. 95 (1991) 3639.
[14] A. Harriman, J. Phys. Chem. 91 (1987) 6102.
[15] D.K. Gosser (Ed.), Cyclic Voltammetry, VCH, New York, 1994.

[16] E.R. Brown, R.F. Large, A. Weissberger, B.W. Rossiter (Eds.), Physical Methods of Chemistry, Wiley Interscience, Rochester, New York, 1964, p. 423.
[17] R.N. Goyal, V.K. Gupta, M. Oyama, N. Bachheti, Electrochem. Commun. 8 (2006) 65.
[18] R.N. Goyal, A. Sangal, Electrochim. Acta 50 (2005) 2135.
[19] Y.A. Udum, M. Düdükcü, F. KöHeli, React. Funct. Polym. 68 (2008) 861.
[20] K. Sagar, Z.M.F. Alvarez, C. Hua, R.M. Smyth, R. Munden, J. Pharm. Biomed. Anal. 2 (1992) 17.

[21] H. Lund, in: H. Lund, O. Hammerich (Eds.), Organic Electrochemistry, 4th ed., Marcel Dekker, New York, 2001, p. 454.
[22] A. Anne, J. Moiroux, J. Org. Chem. 53 (1988) 2816.
[23] K.Q. Ling, T. Ren, J.D. Protasiewicza, L.M. Sayrea, Tetrahedron Lett. 43 (2002) 6903.
[24] O.A. Quattrochi, S.A. De Andrizzi, R.F. Laba, Introducción a la HPLC, Aplicación y Práctica, Artes Gráficas Farro, SA, Argentina, 1992.