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Electrochemical behaviour of Venlafaxine and its determination in pharmaceutical products using square wave voltammetry

José L.F.C. Lima, Debbie V. Loo [1], Cristina Delerue-Matos[1] *, Aida S. Roque da Silva

CEQUP/Departamento de Química-Física, Faculdade de Farmácia da Universidade do Porto, 4050 Porto, Portugal

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Abstract

An electrochemical method for the determination of Venlafaxine in pharmaceutical formulations recently available on the European market is described. The electrochemical oxidation of Venlafaxine was studied at a HMDE electrode over a wide pH range (1.9–10.0) of buffered aqueous solutions using different potential sweep techniques. The results obtained showed that the best definition of the analytical signals was found in boric acid/potassium tetrahydroxoborate buffer at pH 8.7 using anodic stripping square wave voltammetry. Recovery trials were performed to assess the accuracy of results and these were compared to those provided by a HPLC technique according to the method described in literature and to the features of the pharmaceutical formulations. A relative deviation of $< 0.2\%$ was obtained. With the developed methodology, the limit of detection was 0.124 mg/l.

Keywords: Venlafaxine; Voltammetry; Pharmaceutical formulations

1. Introduction

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride, is a nontricyclic antidepressant and is as effective as the tricyclic antidepressants, due to the fact that it imparts antidepressant effects by inhibiting the neuronal uptake of norepinephrine and serotonin, and has no affinity for muscarinic cholinergic receptors. Moreover, the effectiveness of Venlafaxine is much faster and it has less side effects, which are very common with tricyclic antidepressants [1–3].

This work reports the electrochemical behaviour of Venlafaxine in a hanging mercury drop electrode (HMDE) in buffer solutions with different pH values using different potential sweep techniques such as cyclic, differential pulse and square wave voltammetry. The electrochemical properties of Venlafaxine were used to develop a method of determining this compound in two pharmaceutical formulations recently available on the European market. Recoveries were performed to assess the accuracy of the results and these were compared to those provided by high-performance liquid chromatography (HPLC), according to the method referred in literature [4] and adjusted to our matrix.

2. Experimental

2.1. Apparatus

All experiments were performed using a 663VA Metrohm Stand containing a hanging mercury drop working electrode (Metrohm multimode 6.1226.030), an AgCl/Ag/KCl(sat.) reference electrode (Metrohm 6.0728.000) and a glassy carbon auxiliary electrode (Metrohm 6.1247.000) attached to a potentiostat PSTAT10 Ecochimie/Autolab running with a GPES version 3 software model.

A Metrohm E520 pH-meter and a combined glass electrode (Metrohm 6.0202.000) were used for the pH measurements.

A Sykan A1210 HPLC system equipped with a 3200 UV wavelength detector, set at 229 nm and connected with a computing integrator model chromatography

* Corresponding author.

[1] Present address: Instituto Superior de Engenharia do Porto, Rua S. Tomé, 4200 Porto, Portugal.

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data station PRIME version 2.2.6, was used for the results comparison method. For chromatographic separation a Supelcosil LC-8DB (150 × 4.6 mm, 5 μm particle size, Supelco, Bellefonte, PA, USA) was employed.

2.2. Reagents and solutions

Analytical grade reagents and bideionised water (conductivity < 0.1 μS/cm) were used throughout.

Experiments were carried out in buffer solutions over a wide pH range (1.0–12.0) obtained from Britton–Robinson [5] or a narrow pH interval (8.0–9.0) from boric acid/potassium tetrahydroxoborate and were used as the background electrolyte.

For the HPLC comparative method [4], the separation was carried out using acetonitrile (HPLC grade) as the mobile phase: 0.1 M ammonium phosphate (pH 4.4) was prepared by mixing 255 ml of acetonitrile with 745 ml of 0.1 M $(NH_4)H_2PO_4$ (Riedel), which was afterwards filtered through a 0.45 μm filter and degassed with a helium sparge.

2.3. Standards and samples preparation

Standard solutions were prepared with Wyeth–Ayerst Venlafaxine hydrochloride. An exact weight of the active principle was dissolved in water, two drops of concentrated hydrochloric acid were added and diluted up to 100.0 ml. Accurate volumes of the solution obtained were added in the cell to the support electrolyte in order to obtain Venlafaxine concentrations between 0.25 and 1.9 mg/l required for the calibrations.

Venlafaxine determination was performed in commercial tablets available in Portugal and the Netherlands. Five tablets of the pharmaceutical formulations were thoroughly ground until a fine powder was obtained. The samples to be analysed were prepared by dissolving the exact weight of the compound (about 1/5 of the powder) in water and two drops of concentrated hydrochloric acid were added. The solution was stirred in an ultrasonic bath and then made up to 250.0 ml with water. A sample was taken from this solution in order to obtain a Venlafaxine concentration in the cell within the calibration curve range.

The stock solutions used for HPLC determinations were prepared by dissolving 0.1000 g of Venlafaxine hydrochloride in HPLC water to yield a primary solution with a 1.00 mg/ml concentration. Calibration standards were prepared by accurately diluting the stock solution to obtain a concentration range from 0.200 to 0.800 mg/l. The pharmaceutical formulation samples were prepared similarly to those used in voltammetric determinations and their concentrations adjusted to the calibration interval.

3. Results and discussion

The electrochemical behaviour of Venlafaxine hydrochloride was studied over a wide pH range (1.0–12.0) at a HMDE in buffered aqueous media using cyclic voltammetry, differential pulse and square wave voltammetry.

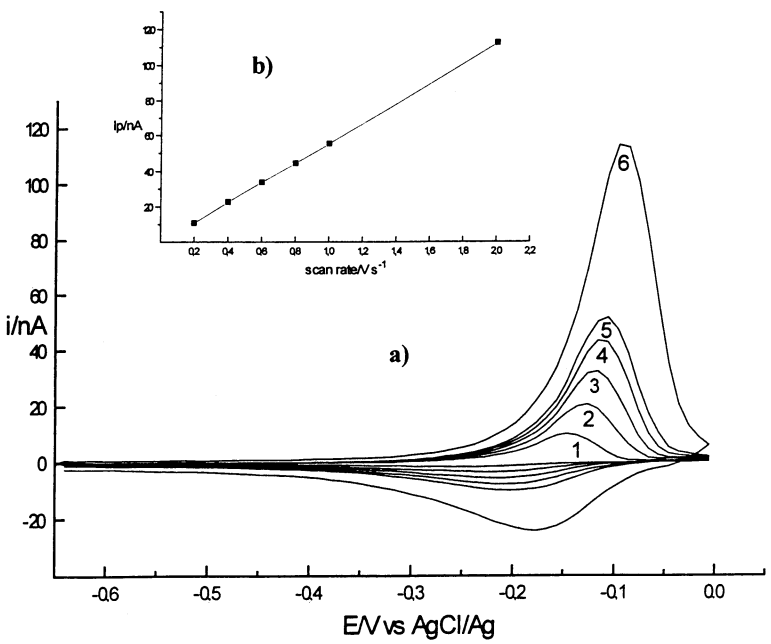

Fig. 1. (a) Cyclic voltammograms of Venlafaxine solution (1.11 mg/l) in boric acid/potassium tetrahydroxoborate buffer (pH 8.7) at different scan rates: 200, 400, 600, 800, 1000 and 2000 mV/s. (b) Variation of current intensity with scan rate.

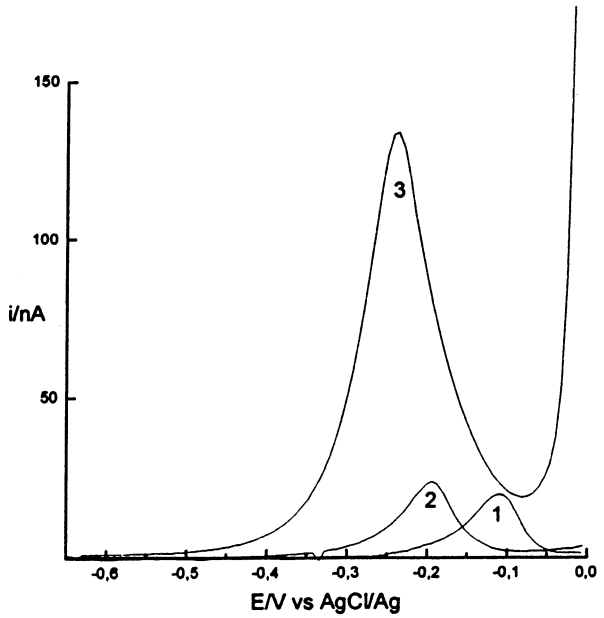

Fig. 2. Voltammograms of a Venlafaxine solution (1.11 mg/l) in boric acid/potassium tetrahydroxoborate buffer (pH 8.7). (1) Linear sweep; (2) differential pulse; (3) square wave voltammetry.

Cyclic voltammetry (Fig. 1(a)) showed that the oxidation of Venlafaxine was an irreversible process and a strong adsorption of the products of the electrochemical reaction on the electrode surface was observed as a second cycle showed a decrease in the peak height and the plot of the peak current intensity versus scan rate present a linear correlation (Fig. 1(b)).

Differential pulse, linear sweep and square wave voltammetry were used for a Venlafaxine solution at a concentration of 1.11 mg/l in boric acid/potassium tetrahydroxoborate buffer and the analytical signals provided showed that the oxidation peak is much more intense using the latter technique (Fig. 2). Hence, this technique was selected for the determinations of Venlafaxine, because it allows lower concentrations and consequently reduces adsorption effects on the electrode surface.

Venlafaxine behaviour was studied over a large pH range in a Britton–Robinson electrolyte and it was found that the anodic potential peak, E_p, is independent of pH below pH 8, and reached positive levels up to pH 9.5. The current intensity peak, I_p, upper limit was obtained at pH 9, whereas higher pH levels led to a sudden decrease in peak intensity. No peak was observed for pH values higher than 10. Because the best definition peak was found at a pH range 8.0–9.0, the effect of the support electrolyte was studied in this range and boric acid/potassium tetrahydroxoborate buffer was selected for subsequent experiments. The effect on the square wave frequency (f), pulse amplitude (E_s), deposition potential and time deposition, support electrolyte pH and ionic strength (I), was assessed with the aim of optimising the experimental conditions. The optimal parameters found were $f = 50$ Hz, $E_s = 40$ mV, pH 8.7 and $I = 0.1$ M. A -1.0 V potential and a deposition time of 10 s were selected due to the fact that lower potentials led to worse reproducibility and longer deposition times did not improve the results.

Different voltammograms were recorded for Venlafaxine concentrations ranging from 0.25 to 1.23 mg/l and the corresponding calibration curves outlined, which provided the Venlafaxine concentrations in the tablets. Table 1 lists the mean results and the corresponding relative standard deviation (RSD) obtained with ten replicate determinations of each sample. Recoveries were determined to assess the accuracy of results and the values obtained were close to 100%. Results were also compared to those provided by a HPLC method [4]. The quantity of active ingredient is determined by comparing the mean response factor (RF) of the samples to the mean RF of the standards.

The results obtained with the electrochemical method and the comparative HPLC technique are in good agreement (R.D. $< 0.19\%$). Using anodic stripping square wave voltammetry under the experimental conditions described, a determination limit of 0.124 mg/l was estimated according to IUPAC recommendations [6].

4. Conclusions

Anodic stripping square wave voltammetry using a HMDE is a good alternative for the determination of Venlafaxine in pharmaceutical formulations in relation to other conventional methods, such as chromatography, because it provides fast, sensitive and selective

Table 1
Determination of Venlafaxine content in two pharmaceutical products, using square wave voltammetry (SWV) and HPLC[a]

Samples	SWV (mg/tablet)	HPLC (mg/tablet)	R.D. (%)	Recovery[b] (%)
Portuguese	37.55 ± 1.05	37.48 ± 1.75	0.19	100.0
Dutch	37.50 ± 0.69	37.46 ± 1.73	0.11	99.5

[a] Mean and standard deviation of ten determinations. All formulations refer to 37.5 mg of Venlafaxine per tablet.
[b] Obtained with SWV for ten determinations.

determinations. The sample preparation procedure is very simple and accuracy and precision of the results is accomplished.

The very low detection limit obtained with this technique ensures that Venlafaxine will be able to be determined in biologic fluids, thus allowing electrochemical therapeutic drug monitoring.

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