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Evaluation of electrochemical, UV/VIS and Raman spectroelectrochemical detection of Naratriptan with screen-printed electrodes

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ABSTRACT

Naratriptan, active pharmaceutical ingredient with antimigraine activity was electrochemically detected in untreated screen-printed carbon electrodes (SPCEs). Cyclic voltammetry and differential pulse voltammetry were used to carry out quantitative analysis of this molecule (in a Britton-Robinson buffer solution at pH 3.0) through its irreversible oxidation (diffusion controlled) at a potential of +0.75 V (*vs.* Ag pseudoreference electrode). Naratriptan oxidation product is an indole based dimer with a yellowish colour (maximum absorption at 320 nm) so UV–VIS spectroelectrochemistry technique was used for the very first time as an *in situ* characterization and quantification technique for this molecule. A reflection configuration approach allowed its measurement over the untreated carbon based electrode. Finally, time resolved Raman Spectroelectrochemistry is used as a powerful technique to carry out qualitative and quantitative analysis of Naratriptan. Electrochemically treated silver screen-printed electrodes are shown as easy to use and cost-effective SERS substrates for the analysis of Naratriptan.

1. Introduction

Active pharmaceutical ingredient Naratriptan (N-methyl-3-(1-methyl-4piperidyl)indole-5-ethanesulfonamide) is a selective agonist of serotonin, commonly used for the treatment of migraine headaches causing vasoconstriction [1,2]. Its analytical determination was always related to chromatographic [3,4], mass spectrometry [5,6] or colorimetric [7] techniques, and only a previous work dealing with its electrochemical detection has been already published [8]. A one electron oxidation process has been suggested for this molecule generating a cation radical that later dimerizes through the position number 3 in the indolic ring (Fig. 1). This oxidation product is stable enough to be detected optically after the electrochemical reaction and has a yellowish colour in aqueous solution, however to the best of our knowledge the *in situ* UV–VIS spectroscopic study of the electrochemical oxidation of Naratriptan has not been yet performed. Therefore, UV–VIS spectroelectrochemistry has been selected here as an *in situ* and real-time characterization and quantification technique because a more complete and specific information can be obtained. The miniaturized three electrode cell of screen printed carbon electrodes that only needs a drop of solution inside a reflection cell makes the experimental setup easy and reproducible in comparison with conventional electrodes [9–11]. UV–VIS spectroelectrochemistry is an autovalidated analytical technique and has been already used in combination with screen printed electrodes to follow the electrochemical reduction of graphene oxide [12], for the detection of biological active molecules like dopamine [13], herbicides like glyphosate [14] or hydrogen peroxide [15].

Raman spectroelectrochemistry is usually performed as a characterization technique to identify specific electrochemical oxidation or reduction products due to their characteristic fingerprint spectrum. It has also been well reported the use of electrochemical pretreatments as roughening steps to get SERS effect in the surface of metallic or nanostructured electrode materials [16,17]. However only a couple of works have already been published dealing with screen-printed electrodes and Raman Spectroelectrochemistry for the quantitative analysis of uric acid and melamine [18,19]. Therefore, to the best of our knowledge in this work screen-printed silver electrodes are shown for the very first time as cost-effective SERS substrates for the sensitive and quantitative detection of Naratriptan.

2. Experimental

2.1. Instrumentation

Voltammetric measurements were performed with a portable bipotentiostat/galvanostat μSTAT400 (DropSens, Spain) controlled by

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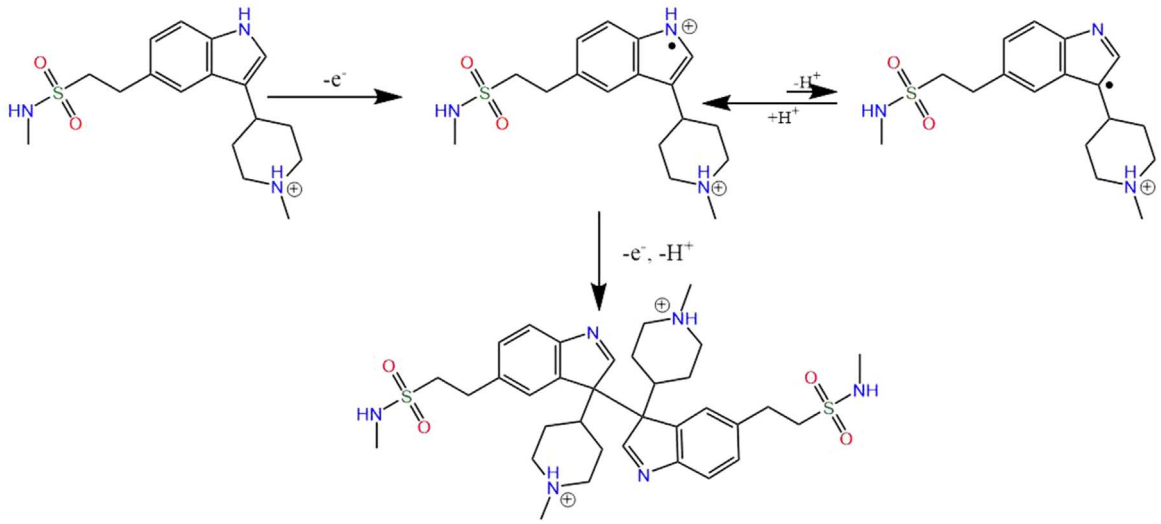

Fig. 1. Naratriptan chemical structure and its oxidation procedure to arise the yellowish colour diindole based product.

DropView 8400 2.2 software. UV–VIS Spectroelectrochemistry was carried out with UV–VIS SPELEC instrument (DropSens, Spain) used in combination with a bifurcated reflection probe, working in a near normal reflection configuration in a reflection cell (DRP-REFLECELL, DropSens, Spain). Raman Spectroelectrochemistry was performed using RAMAN SPELEC instrument (laser 785 nm), a Raman probe and a specific Raman Cell for screen printed electrodes (DropSens, Spain). Both spectroelectrochemical instruments were controlled by DropView SPELEC 2.0 software.

2.2. Reagents and solutions

Naratriptan was purchased from Sigma and stock solutions were prepared in Britton–Robinson solution for voltammetric and UV–VIS spectroelectrochemical assays and in 0.1 M KCl solution for Raman spectroelectrochemistry measurements. Potassium chloride, sodium hydroxide and boric acid were also purchased from Sigma (Spain). Ortho-phosphoric acid (85%), acetic glacial (100%), were provided by Merck. All other chemicals employed were of analytical reagent grade. Ultrapure water obtained with a Millipore Direct-Q™ purification system from Millipore Ibérica S.A. (Spain) was used throughout this work.

2.3. Screen-printed electrodes (SPEs)

The DropSens´ electrodes incorporate a three-electrode cell configuration printed on ceramic substrates (dimensions: 3.4 × 1.0 × 0.05 cm; length x width x height) and were previously described [20]. Carbon working (disk-shaped 4 mm diameter, DRP-110) and silver working electrodes (disk-shaped 1.6 mm diameter, DRP-C013) were used in combination with counter-electrodes made of carbon ink, whereas pseudoreference electrode and electric contacts are made of silver. Voltammetric measurements were performed by placing a 50 µL drop of the corresponding solution to the working area, whereas UV/VIS and Raman spectroelectrochemical measurements were performed using drops of 100 µL and 60 µL, respectively.

2.4. Density functional theory calculations

Nwchem quantum chemistry software [21] was used to estimate the theoretical vibrational frequencies of naratriptan. The calculations were performed using density functional theory (DFT) at the B3LYP theoretical level and the SVP basis set. The effect of the solvent was accounted for using the COSMO solvation model [22]. No imaginary frequencies were found. The predicted frequencies were multiplied by a scaling factor of 0.987.

3. Results and discussion

Naratriptan (NRT) shows an irreversible anodic peak at +0.75 V (vs Ag pseudoreference electrode) when it is oxidized by cyclic voltammetry in aqueous solution (0.1 M Britton-Robinson buffer solution, pH = 3.0) in the surface of untreated screen-printed carbon electrodes (Fig. 2A, blue colour line). Velasco-Aguirre et al. have studied the different voltammetric behaviour at different pH values and concluded that pH 3 leads to a well-resolved and stable analytical signal [8]. By performing the cyclic voltammetry experiments at different scan rates (50–500 mV/s), it was found that the oxidation is a diffusion controlled process with equation: i_p (µA) = 1.01 $v^{1/2}$ (µA·$s^{1/2}$/$mV^{-1/2}$) + 0.44. The peak current was proportional to the NRT concentration with a linear equation: i_p (µA) = 25.95·[NRT](mM) + 0.93; r^2 = 0.998 in the range $5{\cdot}10^{-5}$ M to $1{\cdot}10^{-3}$ M, with a detection limit of $5{\cdot}10^{-6}$ M, calculated as the NRT concentration that gives a signal corresponding to three times the standard deviation of estimate. The precision (inter-electrode) measured in terms of RSD was 0.8% for a concentration of $2.5{\cdot}10^{-4}$ M of NRT, when different electrodes are used.

Differential pulse voltammetry was also used as quantitation technique and a linear calibration curve i_p (µA) = 32.64·[NRT](mM) + 1.06; r^2 = 0.993 was obtained between $1{\cdot}10^{-5}$ M and $1{\cdot}10^{-3}$ M, so it is shown as a more sensitive technique than cyclic voltammetry as expected. The limit of detection in this case was 0.9 µM, calculated as the NRT concentration that gives a signal corresponding to three times the standard deviation of estimate. A precision (inter-electrode) of 0.6% (RSD) was obtained when using 5 different SPEs to measure a 0.25 mM concentration of NRT.

The monitoring of spectral changes occurred during the voltammetric oxidation of NRT can be easily carried out by UV–VIS Spectroelectrochemistry and it was *in situ* evaluated for the very first time in this work according to our knowledge. Naratriptan (colourless solution) is transformed to a diindole based dimer after electrochemical oxidation (yellowish colour solution) leading to an increase of a broad absorbance band between 300 and 430 nm with a maximum intensity at around 320–360 nm (Fig. 3). The corresponding voltabsorptogram obtained at 320 nm is shown in Fig. 2B. Absorbance does not change the initial zero value up to the overpotential is positive enough to oxidise NRT at around +0.65 V. From this potential upwards, absorbance increases until the oxidation is completed and it does not decrease in the backward scan, indicating that an irreversible oxidation of