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Imipramine sensing in pharmaceutical formulations using boron-doped diamond electrode

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ABSTRACT

This paper describes the development of an electroanalytical procedure proposal for the determination of tricyclic antidepressant imipramine (IMP) in commercial pharmaceutical formulations using boron-doped diamond electrode and square-wave voltammetry. The electrochemical oxidation of imipramine was studied in 0.04 mol L^{-1} Britton-Robinson buffer solution. The voltammetric results showed two well-defined oxidation peaks with potentials of 0.04 V and 0.82 V vs. Ag/AgCl/3 mol L^{-1} Cl^{-} for peaks 1 and 2, respectively. The effect of the experimental and voltammetric parameters was evaluated and the best performance was obtained in pH 7.4, pulses application frequency of potential of 100 Hz, amplitude of 50 mV and potential increment of 2 mV. Under these conditions, the analytical curves were obtained in the linear range of concentration from 1.73×10^{-7} mol L^{-1} to 2.53×10^{-6} mol L^{-1} ($r = 0.9984$), with detection and quantitation limits 4.35×10^{-8} mol L^{-1} and 1.45×10^{-7} mol L^{-1}, respectively. The proposed method was applied with success in the determination of IMP in commercial pharmaceutical formulations and validated by comparison with standard method for determination of imipramine. The obtained results were in close agreement, at a 95% confidence level, with those obtained using an official method of the British Pharmacopeia.

1. Introduction

Imipramine (3-(10,11-dihydro-5H-dibenzo[*b*,*f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine, IMP) is a tricyclic antidepressant, so named because of its chemical structure of three rings, of the dibenzazepine group. IMP is mainly used in the treatment of major depression and enuresis [1]. The chemical structure of this compound is illustrated in Fig. 1.

The precise molecular mechanism responsible for the antidepressant action of the IMP is unknown, although a number of hypotheses have been generated [2]. Many of these involve alterations in neurotransmission of norepinephrine or serotonin, or both. Safe and effective use of the IMP requires monitoring of serum levels and quality assurance in pharmaceutical preparation. The therapeutic doses of IMP vary considerably, but the maximum recommended dose is 100 to 300 ng mL^{-1} daily. It has been reported the amount of more than 500 ng mL^{-1} could cause overdose and amounts of more than 1 μg mL^{-1} could be lethal [3,4]. The importance of this monitoring is based on the relatively narrow range between therapeutic and toxic doses [5].

Several analytical methods have been reported for the determination of IMP in pharmaceutical formulations and biological fluids, including high-performance liquid chromatography with ultraviolet [6–8], electrochemical [9,10] and fluorescence [11] detectors, gas chromatography [12], capillary electrophoresis [13,14], spectrophotometry [15–17], spectrofluorimetric [18,19] and radioimmunoassay [20]. However, most of these techniques are time-consuming, involve the use of large volumes of organic solvents or require expensive and sophisticated instruments.

Within this context, electroanalytical techniques have proved to be excellent alternatives to determine this and other pharmaceutical compounds, since they are simple, cost effective, and require relatively short analysis times, without the need for derivatizations or time-consuming extraction steps, in most cases [21]. In addition, these techniques are less sensitive to matrix effects — presence of excipients, for example — compared with other analytical techniques. Furthermore, the knowledge of the electrochemical properties of a drug is an important pharmaceutical tool since it can be relevant to understand its metabolic fate or in vivo redox processes and pharmacological activity [22,23].

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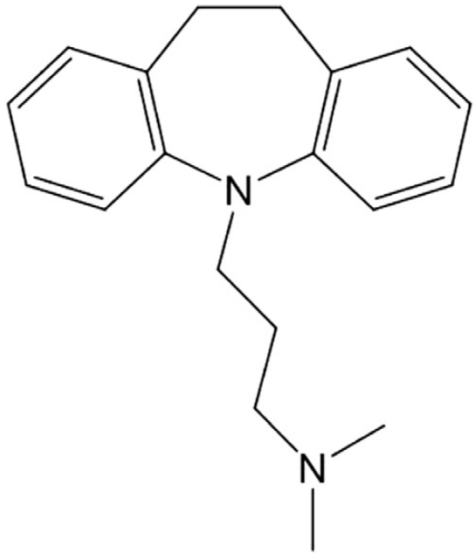


Fig. 1. Scheme: Molecular structure of imipramine.

Some studies are reported in literature concerning the electrochemical behavior of IMP [24–28]. In addition, some electroanalytical methods for quantitative determination of IMP in commercial formulations and biological fluids have been reported using different electrode surfaces including graphite polyurethane composite electrodes [25], functionalized carbon paste electrodes [29–31], carbon fiber ultramicroelectrodes [32] and functionalized molecularly imprinted polymers electrodes [33].

Among the materials, boron-doped diamond electrode (BDDE) has attracted the attention of electroanalytical researchers as an option for the electrochemical determination of pharmaceutical compounds. The main reason for the interest in BDDE is because of their low capacitive current, leading to an enhanced signal to noise ratio. The large potential window also opens up several important applications which could not be accomplished with conventional electrode materials [34–40]. Low adsorption of contaminants leads to low fouling and this feature is very important for an extended use. Therefore, BDDE exhibits high stability, high sensitivity, and a low detection limit. The advantageous property of this material is this inherent stability with very low background currents [41]. Moreover, square-wave voltammetry (SWV) technique has been applied successfully with BDDE and other electrode surfaces, proving to be extremely sensitive for the detection of medicines [39,40,42–44].

The aim of this work is to develop an electroanalytical methodology for the determination of IMP using SWV and employing BDDE and its quantification in commercial formulations.

2. Experimental

2.1. Reagents and equipments

All the voltammetric measurements were taken with a potentiostat (Autolab PGSTAT 30, Metrohm-Eco Chemie) controlled by a personal computer, using GPES version 4.9 software (General Purpose Electrochemical System, Metrohm-Eco Chemie). A Micronal B474 pH meter equipped with a 3.0 mol L^{-1} Ag/AgCl/KCl-glass combined electrode was used to adjust the pH values. All the solutions were prepared with water purified by a Milli-Q system (Millipore Corp.). A double beam spectrophotometer model Cary 1E (Varian) with quartz cells with 1 cm optical path was used for recording the ultraviolet-visible (UV–Vis) measurements.

A conventional cell with a three-electrode system incorporating an Ag/AgCl/3.0 mol L^{-1} Cl^- electrode as the reference electrode, a platinum wire as the auxiliary electrode and a BDDE as a working electrode were used in all experiments. BDDE was manufactured by the "Centre Suisse d'Eletronique et d'Microtechnique" Neuchâtel, Switzerland, with boron content of 8000 ppm and estimated geometric area of 0.26 cm^2.

0.04 mol L^{-1} of Britton-Robinson (BR) buffer as used as the supporting electrolyte and the pH was adjusted to the desired value by adding appropriate amounts of 0.2 mol L^{-1} NaOH stock solution.

A stock solution of 1.0×10^{-4} mol L^{-1} of USP-grade IMP was prepared daily by dissolving an appropriate quantity of it in ultrapure water, which was then stored in a dark flask and kept in a refrigerator to prevent degradation.

2.2. Working procedure

In this work, all the electrochemical measurements were taken under ambient conditions and were carried out in triplicate. Prior to the experiments, the BDDE was polarized at 3.0 V for 15 s in a cell containing 0.50 mol L^{-1} H_2SO_4 solution. After this, the electrode was polarized at −3.0 V for 30 s.

The cyclic voltammetry performed in different scan rate, the second cycle obtained of each sweep speed was used, in order to verify only the influence of the speed. The electrolyte exchange with each scan rate.

The voltammetric parameters of maximum peak current and maximum selectivity (half-peak width) were optimized based on a systematic study of the experimental parameters that affect the responses, such as the potential pulse frequency (f), the amplitude of the pulse (a) and the height of the potential step (ΔE_s) or scan increment. All the parameters were optimized, since their values strongly affect the sensitivity of voltammetric analyses.

After the optimization of the voltammetric parameters, analytical curves were obtained in supporting electrolyte using the standard addition method. The standard deviation of the mean current measured for ten blank voltammograms in supporting electrolyte (S_b) and the slope of the straight line of the analytical curves (s) were employed for DL and QL determinations using DL = $3S_b/s$ and QL = $10S_b/s$ [45,46].

The proposed procedure was compared to the ultraviolet-visible spectrophotometry measurements, according to procedure recommended by British Pharmacopeia [47], where the spectrum and the characteristic absorbance of the IMP were evaluated at 270 nm. Analytical curves also constructed and the DL and QL values were calculated.

2.3. Analysis of the commercial formulation

The recovery experiments were carried out using the voltammetric and spectrophotometry procedures. For this, a known amount of pharmaceutical formulations were added to the supporting electrolytes, followed by standard additions of the IMP stock solutions, and plotting of the resulting analytical curves.

The recovery efficiencies were calculated by relationships between the IMP concentration value found, which refers to the concentration obtained by extrapolating the analytical curves of the corresponding spiked samples, and the IMP concentration added value, which corresponds to the nominal concentration of the samples, multiplied by 100.

The precision of the proposed procedure was evaluated based on reproducibility experiments realized with different standard solutions of IMP in different days (inter-day). The accuracy was evaluated from experiments of the repeatability obtained in ten replicated determinations in the same solution of IMP (intra-day).

The relative standard deviations (RSD) were calculated for reproducibility and repeatability measures, using the relationships between the standard deviation and the mean of the peak current values obtained.

The commercial formulation chosen was Tofranil®, which contained 25 mg of IMP per tablet. Then, the tablets were crushed into a power and a carefully weighed portion of the powder, sufficient to produce a final

concentration of 1.0×10^{-4} mol L^{-1} of IMP, was transferred into volumetric flasks and diluted to volume with purified water. The mixture was sonicated for 15 min, after which the solution was filtered and an aliquot was transferred to an electrochemical cell containing the supporting electrolyte for evaluation of the analytical parameters. All solutions were used immediately after their preparation to prevent decomposition by light or heat.

3. Results and discussion

3.1. Study of the electrochemical behavior of IMP

The initial experiments of cyclic voltammetry were conducted using standard solutions of IMP in Britton-Robinson (BR) buffer solution (0.04 mol L^{-1}) pH 7.4 as electrolyte. Fig. 2 shows the voltammograms obtained for the first and tenth cycle, with the potential ranging from −0.4 V to 1.2 V at a scan rate of 0.10 V s^{-1}.

The experimental results showed in the first cycle between 0.60 V and 1.2 V, the presence of two anodic processes, a_2 and a_3, in 0.83 V and 1.05 V, respectively. When the potential sweep was inverted, there is a process of reduction (c_1) at −0.01 V, which presents the corresponding quasi-reversible process in a_1 in subsequent cycles, at around 0.09 V. It is observed that process a_1 exhibited an increase at current values with the number of cycles, while decay occured in the current values of a_2 process.

The a_2 process is assigned to irreversible oxidation of IMP [27] which occurs at the nitrogen atom in the cyclohexane ring resulting in the formation of a radical, while c_1 was associated with reduced dimer that is formed in a chemical step following the step of electrochemical oxidation of IMP [24,27], which is oxidized to the a_1 in the subsequent scans. Moreover, process a_3 could be related to a strong adsorption of the reagent [48] or, as quoted by Bishop et al. [24], attributed to the oxidation of IMP molecules that have been regenerated to its form and not oxidized due to the coupling of a chemical step involving the dimer molecules formed and IMP already electrochemically oxidized.

In addition to these processes, there is a broad peak next to the processes of oxidation and reduction of dimer at around −0.19 V and 0.57 V, which increases with the number of cycles. These processes may be less intense with the formation of an electroactive film based on the adsorption of dimer molecules near the electrode surface. The formation of such film on the electrode surface is reported in studies with exhaustive electrolysis experiments in aqueous solutions of IMP [24]. The reactions are as depicted in Scheme 1.

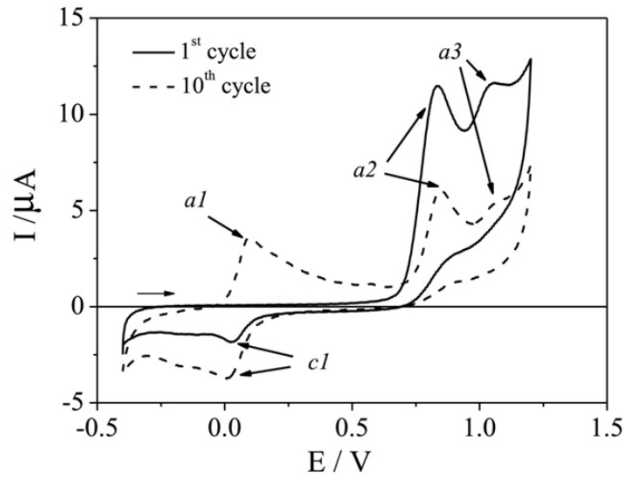


Fig. 2. Cyclic voltammograms for 1.43×10^{-5} mol L^{-1} of IMP at BDDE in BR buffer 0.04 mol L^{-1} (pH 7.4), with scan potential ranging from −0.40 V to 1.20 V at a scan rate of 0.10 V s^{-1}.

The influence of the scan rates on the IMP peak potential and peak current values was evaluated in the range of 0.02 to 0.1 V s^{-1} as show in Fig. 3A. A linear correlation between the square root of the scan rates and the peak current values indicates a diffusion-controlled redox process as show in Fig. 3B. This conclusion was confirmed for peak a_1 obtained for peaks a_1 ($I_p = -1.28 \times 10^{-6} + 3.14 \times 10^{-7}\, \nu^{1/2}$, $R^2 = 0.9878$) and a2 ($I_p = -1.28 \times 10^{-6} + 9.55 \times 10^{-7}\, \nu^{1/2}$, $R^2 = 0.9989$) considering only the anodic peaks. This deduction was confirmed by correlation between the logarithm of the peak currents and that of the scan rates, for peak a2 ($\log I_p = -6.33 + 0.63 \log \nu$). The similar correlation for peak a_1 ($\log I_p = -8.45 + 1.39 \log \nu$) could be showed, indicating that occur a mixed control in the redox process.

Preliminary experiments using SWV were performed to determine the electroanalytical responses of IMP on BDDE and to evaluate the presence of forward and backward components of current that can be applied to determine the reversibility of the electrochemical redox process. Thus, to obtain the signal related to oxidation of the dimer the second voltammetric cycle was recorded. Fig. 4 shows the square-wave voltammograms obtained with tests of IMP electroactivity in BR buffer 0.04 mol L^{-1} pH 7.4 on BDDE, showing the forward and backward components of current. SWV experiments were performed with $f = 100$ Hz, $a = 50$ mV and $\Delta E_s = 2$ mV.

The square-wave voltammograms showed two well-defined oxidation peaks at 0.04 V and 0.82 V for peak 1 (a_1) and peak 2 (a_2) in respect to oxidation of dimer and IMP, respectively. The absence of the backward component of current for IMP oxidation confirmed the irreversibility of this process, while for the dimer the presence of the forward and backward components of current indicate a possible quasi-reversible process as can be seen from the results of cyclic voltammetry.

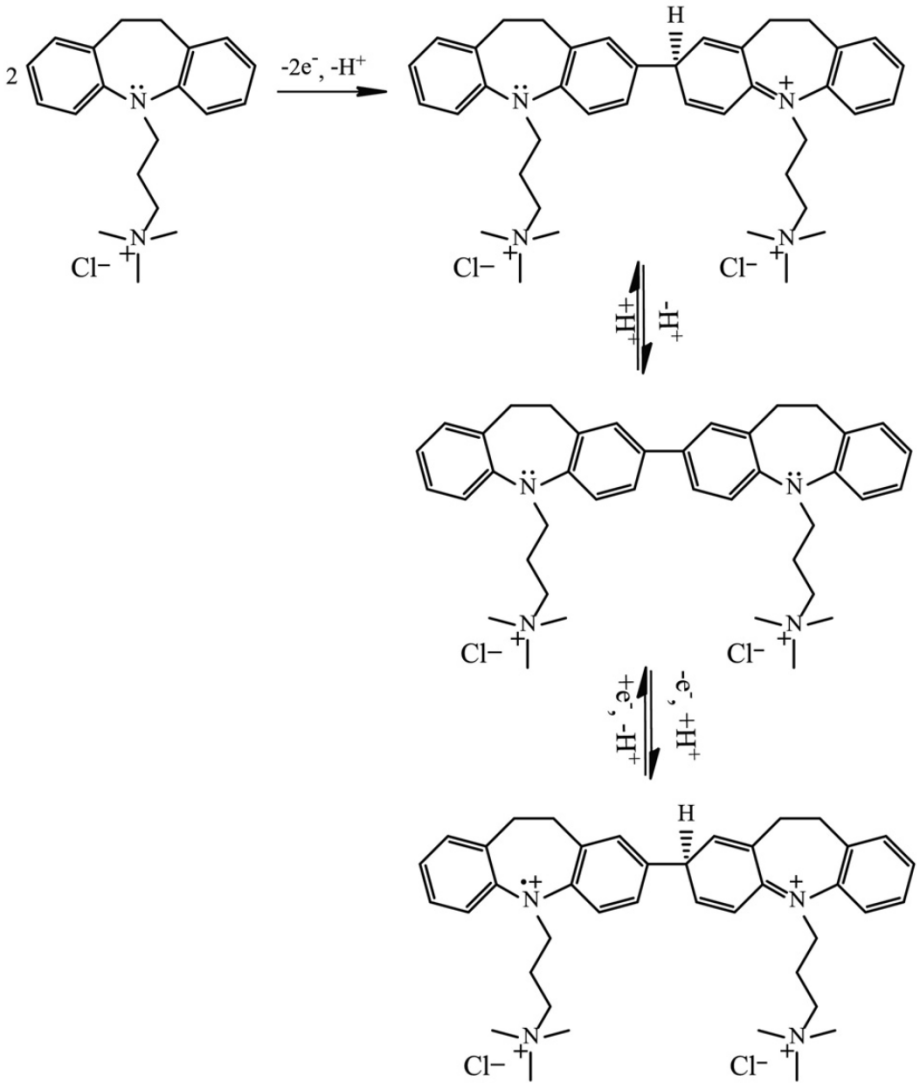
Based on the SWV profiles for the development of analytical methodology, the resultant current component was used as the analytic signal instead of the peak resulting from IMP oxidation by the following factors: the analytical signal of the dimer increases when the sum of the modules and direct current reversed after the application of potential pulses; greater analytical sensitivity is achieved by the signal of the dimer, since it is more pronounced and the analytical selectivity is higher at low potential where the reaction occurs as compared to IMP oxidation peak, prevents the occurrence of interferences from other electroactive compounds, possibly present in the matrix to be analyzed.

3.2. Experimental and voltammetric optimization

The influence of pH was investigated on the pH range of 2–12 employing the BR buffer in order to obtain the best voltammetric profile for analytical purposes. In pH 12 no well-defined voltammetric peak was observed. However, it was observed that as the pH of the medium was gradually increased, the potential shifted toward less positive values, suggesting the involvement of protons in the reaction, Fig. 5A.

From the plot of E_p vs. pH, the succeeding equation was reached for IMI and IMI-Dimer, E_p (V) = 0.9892 (V) −0.0204 pH (V/pH) ($R^2 = 0.6525$) and E_p (V) = 0.4876 (V) −0.053 pH (V/pH) ($R^2 = 0.9335$), respectively, for pH range of pH range of 2.0 to 10. The slope ($\partial E_p/\partial pH$) value for IMI-Dimer is close to the theoretical value predicted by the Nernst equation (0.059 V/pH) indicating that an equal number of proton and electrons are involved in the dimerization step [49]. For IMI, the slope value is indicative of an unequal number of electrons and protons being involved in the oxidation of IMP. This behavior is in accordance These results are in accordance with the literature [25,27,50]. This behavior is in agreement with the mechanism proposed (Scheme 1) by means of the processes observed in cyclic voltammetry as discussed in the Section 3.1.

The most intense response of the peak current was observed at pH 7.0, as shown in Fig. 5B. Furthermore, this pH also recorded considerable selectivity for the oxidation of the dimer, due to the fact the peak potential was close to zero.



Scheme 1. Proposed electrochemical mechanism for IMP at BDDE.

Aiming to develop electroanalytical methodology in conditions close to physiological fluids, pH 7.4 was investigated in order to verify its analytical sensitivity. For this purpose, voltammograms were obtained in this pH under the same conditions of pH 7.0. The results showed no significant variation in the values of current and potential peak, i.e., no loss of sensitivity and selectivity has been registered. Therefore, pH of 7.4 was chosen for the methodology.

With the optimized experimental conditions, SWV parameters (f, a, ΔE_s) were individually analyzed due to effects on the voltammetric responses, basically in relation to the maximum value of the peak current and the maximum selectivity (half-peak width), while also considering the improved reproducibility. The SWV parameters were optimized using the second voltammogram obtained for 1.10×10^{-5} mol L^{-1} of IMP in BR buffer pH 7.4 on BDDE with scan potential from −0.4 to 1.2 V. The f was evaluated within the range of 10 to 200 Hz, a within the range of 10 to 80 mV and ΔE_s within the range of 1 to 10 mV, Fig. 1S.

A linear dependence was observed between the peak current and the square root of frequency ($f^{1/2}$) for the oxidation of the dimer, Fig. 2S. This phenomenon has been previously analyzed by Mirceski et al. [51] and attributed to a reversible reaction with adsorption of reagents or products, corroborating the behavior obtained for the influence of scan rate obtained by cyclic voltammetry.

The variations in the f values, considering frequencies in the interval from 10 to 200 Hz, have shown that its increase promoted a displacement of the peak potential toward a more positive value with a considerable widening in the half-peak width ($\Delta E_{p/2}$). This widening in voltammetric responses represents a loss in analytical selectivity; thus, a frequency of 100 Hz was chosen.

The voltammetric responses for IMP determination as a function of variation in the pulse amplitude observed on BDDE, Fig. 3S, demonstrated that an increase in values of a promoted a linear increase in the peak current values. As expected from SWV theory [51], the values of peak current show a nearly linear variation with the pulse amplitude for values of a from 5 to 80 mV, while peak potential shows no variation as a function of a in practice, Fig. 4S. For analytical applications, a value of 50 mV was chosen for a.

To confirm the type of redox reaction, the ΔE_s was evaluated for the oxidation of IMP-Dimer on the BDDE, Fig. 5S. The results obtained showed that an increase in ΔE_s promotes a displacement in the peak potential to positive value. Moreover, with increasing ΔE_s the voltammetric profiles were losing definition. In subsequent experiments, a value of $\Delta E_s = 2$ mV was adopted.

3.3. Analytical curves

Under the optimized conditions, analytical curves were obtained for IMP on BDDE. For this, aliquots from the stock solution were consecutively added to the electrochemical cell and the voltammetric responses

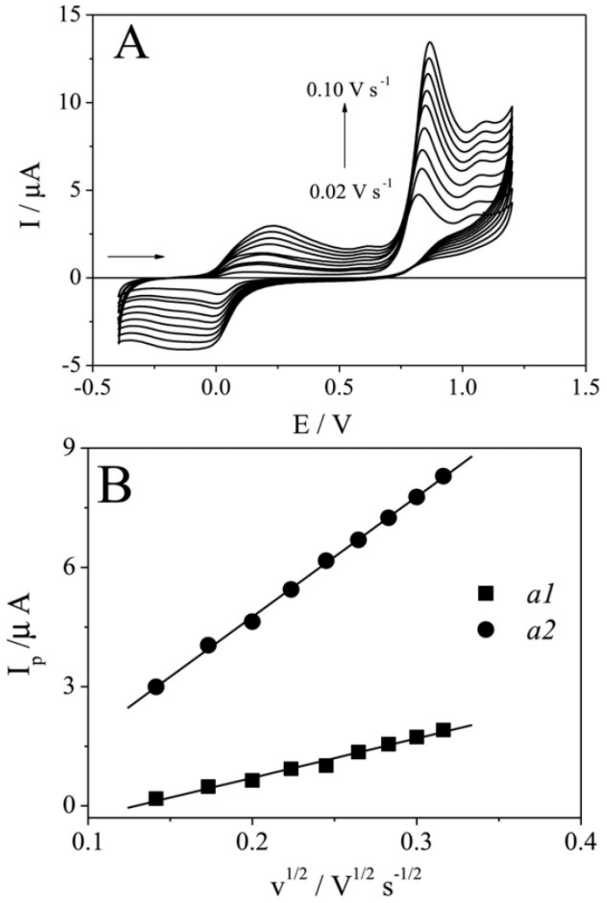


Fig. 3. (A) Second cyclic voltammogram for 1.43×10^{-5} mol L^{-1} of IMP at BDDE in BR buffer 0.04 mol L^{-1} (pH 7.4), with scan potential ranging from −0.40 V to 1.20 V at different scan rate 0.02 to 0.10 V s^{-1}, (B) Linear relationship of anodic peak current versus square root of scan rate for peaks a1 and a2 indicated in Fig. 2.

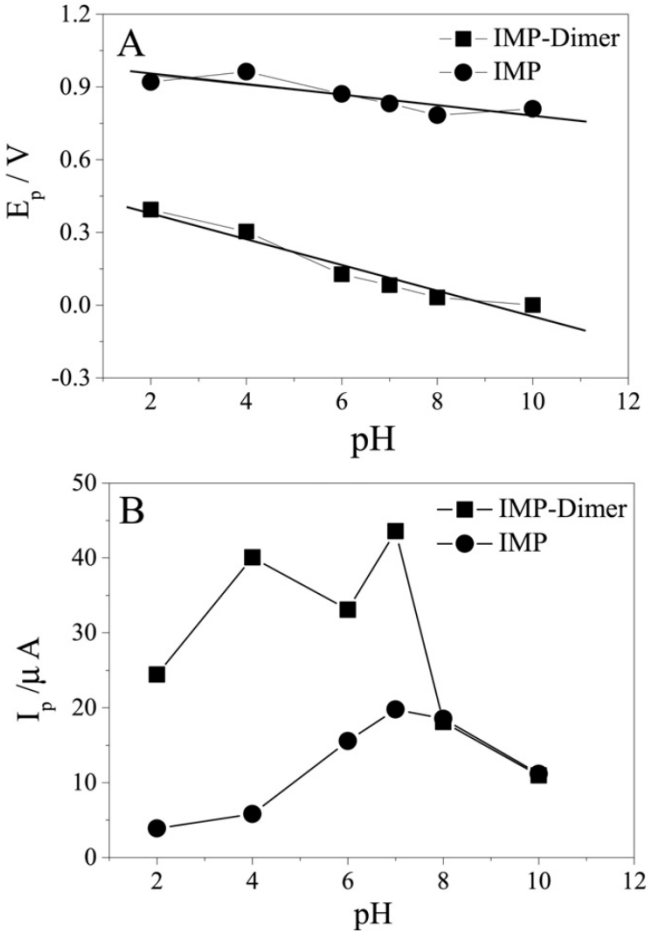


Fig. 5. Relationships between anodic peak potential (E_p) with pH (A) and anodic peak current (I_p) and pH (B) for the oxidation peak of IMP (●) and for the oxidation peak of the IMP-dimer (■), obtained from square-wave voltammograms with $f = 100$ Hz, $a = 50$ mV and $\Delta E_s = 2$ mV for 1.00×10^{-4} mol L^{-1} IMP in BR buffer 0.04 mol L^{-1} on EDDB.

were evaluated for each addition. The SWV responses showed that the dependence of peak currents on the IMP concentration was linear, in the range of concentration from 1.73×10^{-7} to 2.53×10^{-6} mol L^{-1}. The SWV responses were recorded with $f = 100$ Hz, $a = 50$ mV and $\Delta E_s = 2$ mV. The SWV responses together with the obtained linear relationship between peak currents and concentrations (as the inset) are presented in Fig. 6.

The precision and accuracy of this procedure were also tested using 8.59×10^{-7} mol L^{-1} of IMP. The precision was evaluated based on reproducibility experiments involving five different measurements. The relative standard deviations (RSD) were determined and the value was 2.07%. The accuracy of the measurements was also evaluated from ten replicate determinations (repeatability) with RSD equals to 2.27%.

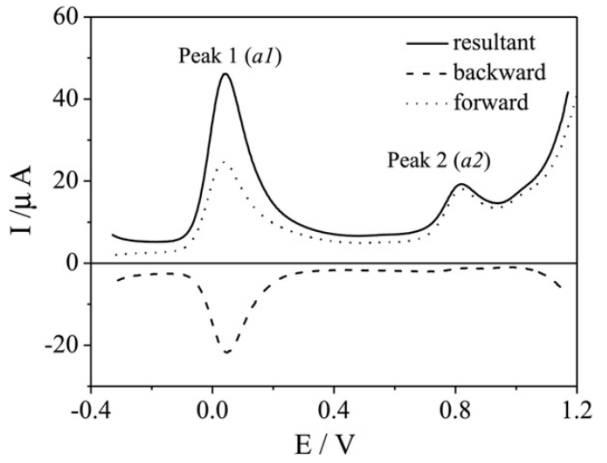


Fig. 4. Square-wave voltammograms (second cycle) for IMP oxidation, with forward, backward and resultant component of current, for 8.26×10^{-6} mol L^{-1} of IMP in BR buffer 0.04 mol L^{-1} (pH 7.4) on BDDE with $f = 100$ Hz, $a = 50$ mV and $\Delta E_s = 2$ mV.

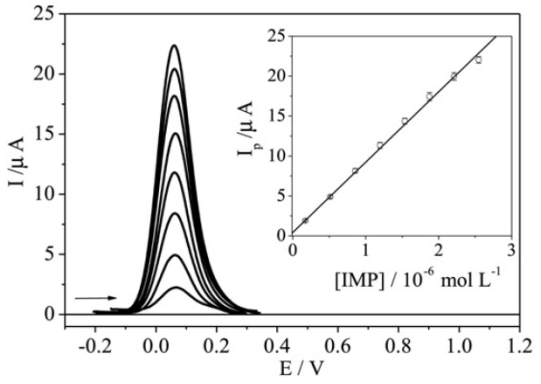


Fig. 6. Square-wave voltammograms obtained at different concentrations imipramine in BR buffer 0.04 mol L^{-1} (pH 7.4) on BDDE, with $f = 100$ Hz, $a = 50$ mV, $\Delta E_s = 2$ mV. The insert shows the average current obtained from three analytical curves.

With the SWV parameters optimized, a suitable electrochemical methodology was developed for the quantitative determination of IMP in pharmaceutical formulations. Stability, recovery, specificity and precision data of the pharmaceutical formulations were determined to evaluate the applicability of the proposed methodology to complex samples. To this end, we used a sample of IMP commercially available in Brazil: medicine tablets containing 25 mg of IMP per tablet.

In order to validate the proposed method, comparative studies were carried out by UV–Vis spectrophotometric procedure, standard methodology recommended by the British Pharmacopeia [47] for determination of IMP. Table 1 summarizes the results for electroanalytical methodology developed and the standard methodology recommended: range linearity, the analytical curve equation, the value of the correlation coefficient of analytical curve (r), the standard deviation of the arithmetic mean of ten whites (S_b), the calculated limit of detection (DL) and of quantification (QL) as well as the values relative standard deviation (RSD%) obtained for repeatability and reproducibility.

The detection and quantification limits obtained by the UV–Vis method were higher by 100 and 10 times, respectively, than those obtained by the electroanalytical methodology, showing that the electroanalytical methodology developed here can be perfectly used for determinations of IMP at lower concentrations than those obtained by the recommended procedure. In comparison with other methodologies for IMP detection, with different types of modified electrodes, the sensor proposed in this paper obtained similar results than the a rigid graphite polyurethane composite [25], carbon paste electrode modified with polymer [29], carbon paste electrode modified with β-cyclodextrin [30], ultramicroelectrodes [32], ITO electrodes modified by Au nanoparticles [33] and montmorillonite nanoclay into a carbon ionic liquid electrode [52] as demonstrated in Table 1S. These results indicate BDDE is outstanding electrode material for the IMP determination.

3.4. Application of methodology

In order to evaluate the selectivity in complex matrix, precision and accuracy of the method as well as its applicability, studies of recovery in the commercial formulation were performed using the proposed electroanalytical methodology and UV–Vis measurements. For this purpose, a form of IMP commercially available in Brazil (tablets) was used as described in Section 2. The experiments were carried out in triplicate with both the SWV and UV–Vis procedures. The recovery curves were built by the standard addition method, and the recovery percentage was identified graphically, with the abscissa referring to the IMP concentration in the electrochemistry cell. Extrapoling the curve along this axis yielded the sample concentration, allowing for the calculation of the recovery values. In addition, calculation of the level of bias, which provides an index of inaccuracy due to systematic errors in measurements was performed. The results obtained in this study of recovery are summarized in Table 2, showing a high percentage of recovery that is proof that the developed method has good precision. Despite the absence of sample treatment for the removal of interfering possible, there was no significant variation in values, which is demonstrates the robustness of the proposed methodology.

Aiming to compare the precision and accuracy of the two methodologies developed, mono-tailed *F*-test and paired Student's *t*-test [53] were carried out with confidence limit of 95%, respectively. For the mono-tailed *F*-test it was considered as a null hypothesis that the variances of the methods are equal and therefore have the same precision. While in the paired *t*-test was adopted as the null hypothesis so that no there is considerable difference in the accuracy of both methods.

The calculated value of *F* (81.84) exceeded the critical value tabulated (19.00) implying that the null hypothesis is false. Therefore, the variance of the standard is significantly higher than that of the developed method, so that the methodology developed electroanalytical presented itself as more precise. While the calculated value of t (1.80) was less than the tabulated value (4.30) implying that the null hypothesis is true. Thus, the accuracy of the method was statistically similar to the standard methodology adopted by the pharmacopeia. It means the method proposed could be reliably used for routine analysis.

Table 1
Parameters of the analytical curves obtained in IMP detection using BDDE combined with SWV (LR: linearity range; r: correlation coefficient; S_b: standard deviation from the arithmetic mean of ten blank solutions; DL: detection limits; QL: quantification limits; and RSD: relative standard deviation for repeatability and reproducibility experiments). All data were evaluated using medium values from three analytical curves.

Parameters	SWV	UV–Vis spectrophotometry
LR (mol L^{-1})	1.73×10^{-7} to 2.53×10^{-6}	5.00×10^{-5} to 2.50×10^{-4}
Equation curve	$I_p = 6.76 \times 10^{-7}$ ($\pm 5.98 \times 10^{-7}$) + 8.68 ($\pm$0.64) C_{IMP}	Abs = −0.0016 ($\pm$0.0035) + 2789.75 ($\pm$ 11.76) C_{IMP}
r	0.9984	0.9991
S_b	1.28×10^{-7} A	0.00136 au
DL (mol L^{-1})	4.35×10^{-8} (13.8 μg L^{-1})	1.46×10^{-6} (462.7 μg L^{-1})
QL (mol L^{-1})	1.45×10^{-7} (46.1 μg L^{-1})	4.81×10^{-6} (1543.3 μg L^{-1})
RSD (Repeatability)	2.27% (n = 10)	0.54% (n = 10)
RSD (Reproducibility)	2.07% (n = 5)	0.33% (n = 5)

Table 2
IMP concentrations recovered using SWV on BDDE and UV–Vis procedures in pharmaceutical formulation.

Parameters	SWV	UV–Vis spectrophotometry
$[IMP]_{added}$/mol L^{-1}	7.86×10^{-7}	9.11×10^{-5}
$[IMP]_{found}$/mol L^{-1}	7.51×10^{-7}	1.02×10^{-4}
Recovery%	95.5	111.9
RSD%	2.94	3.27
BIAS%	−4.4	12.0

4. Conclusions

The electrochemical oxidation of IMP involves the formation of a dimer product that produces a new peak with lower potential values. The appropriate square wave voltammetry response of IMP was obtained with a BR buffer at pH 7.4 on BDDE. The use of square wave voltammetry with the optimized parameters ($f = 100$ Hz, $a = 50$ mV and $\Delta E_s = 2$ mV) and showed a good linear relationship between the peak current and the IMP concentration over a wide concentration range. The proposed procedure proved to be sensitive, accurate and precise for the analysis of IMP and did not require complex preparations. The proposed method was applied with accomplishment in the determination of IMP in commercial pharmaceutical formulations and the results showed values of detection and quantification limits which were smaller than those found by the recommended procedure. Furthermore, electroanalytical techniques have characteristics of low cost and short analysis time. In addition, the proposed methods are simple, rapid, sensitive, precise, and accurate, being applicable directly to the analysis of the commercial pharmaceuticals simply after dissolution of their samples, dispensing any use of organic reagents or expensive apparatus.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jelechem.2017.01.067.

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