



Square wave voltammetric determination of nitrofurantoin in pharmaceutical formulations on highly boron-doped diamond electrodes at different boron-doping contents

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ABSTRACT

The influence of the boron-doping levels in boron-doped diamond film electrodes on the electrochemical response of nitrofurantoin (NFT) and the development of an electroanalytical procedure for NFT determination were investigated. The investigations were carried out using the techniques of cyclic voltammetry and square wave voltammetry on diamond film electrodes with different boron-doping levels (i.e., 5000, 10,000 and 20,000 mg L⁻¹). The level of boron-doping in the diamond film electrodes influenced the electrochemical reduction of NFT. The appropriate cyclic voltammetric response of NFT was obtained with Britton–Robinson buffer at pH 4 and for diamond films doped with 10,000 and 20,000 mg L⁻¹ of boron. These two films were selected for the development of the electroanalytical procedure. The use of square wave voltammetry with the optimized parameters demonstrated a good linear relationship between the peak current and the NFT concentration for a wide range of concentration. The lower limit of detection for the electrodes doped with 10,000 and 20,000 mg L⁻¹ of boron were 2.69×10^{-8} mol L⁻¹ (6.40 μg L⁻¹) and 8.15×10^{-9} mol L⁻¹ (1.94 μg L⁻¹), respectively, while the lower limits of quantification were 8.96×10^{-8} mol L⁻¹ (21.33 μg L⁻¹) and 2.72×10^{-8} mol L⁻¹ (6.47 μg L⁻¹), respectively. The applicability of the proposed procedure was tested using a commercial pharmaceutical formulation of NFT, and the results were compared with the procedure recommended by the British Pharmacopeia. The proposed procedure was sensitive, accurate and precise for analysis of NFT and did not require complex preparations or renovations of the electrode surface. This presents the advantage of eliminating mercury waste and minimizing the adsorption problems related to the use of other electrochemical solid surfaces.

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1. Introduction

The replacement of mercury electrodes with solid electrodes is difficult due to the poisoning of the electrode surface, which is caused by the adsorption of compounds, analytical solution constituents or redox reaction products. This results in a loss of sensitivity and reproducibility. The search for non-toxic solid materials to be used as electrodes for the electroanalytical determination of organic compounds has risen in the last two decades. This pursuit falls into the newly developed field of green electroanalytical chemistry.

Several materials have been tested toward this aim, including solid amalgam electrodes (SAE), carbon paste electrodes (CPE), nanotube carbon paste electrodes (NTCPE), glassy carbon electrodes (GCE), solid composite electrodes (SCE) and boron-doped diamond film electrodes (BDDFE). Several reviews illustrating the use of these materials in the electroanalytical field have been published in recent years [1–11].

Among these materials, BDDFE has attracted the attention of electroanalytical researchers as a candidate for the electrochemical determination of pharmaceutical compounds, since BDDFE presents a stable background current, wide potential window for aqueous and non-aqueous electrolytes, high thermal conductivity, high hardness, high electrochemical stability, low organic molecule adsorption and high sensitivity for analytical purposes [5,8,9,12–14]. However, little attention has been given in the literature concerning the influence of different boron-doping levels

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on the electrochemical response of the pharmaceutical compounds.

In addition, some reports have been published showing that nitrofurazone, which is in the group of nitrofuran antibacterial agents, has a good electrochemical response on the BDDFE [15,16]. This enables the application of this electrode for the electrochemical detection and quantification of compounds belonging to the nitrofuran group. Among them, nitrofurantoin [NFT; 1-((5-nitro-2-furfurylidene)-1-amino)hydantoin] is a drug synthesized from nitrofuran that is very useful in the treatment of urinary tract diseases. Depending on its concentration at the inflammation site, this drug may act as a bacteriostatic or bactericidal agent [17]. As pointed out by Hamman [17], this drug can act against various gram-negative bacteria, as well as some gram-positive bacteria, including *Citrobacter*, *Corynebacterium*, *Enterobacter*, *Escherichia coli*, *Klebsiella*, *Neisseria*, *Salmonella*, *Staphylococcus aureus* and *Enterococcus faecalis*. It is efficient against these bacteria in the concentration range of 1–32 $\mu\text{g mL}^{-1}$. However, this drug is partially metabolized, and 24 h after the application of a single oral dose, 30–50% of this drug is excreted in its original form and 1% is excreted as aminofurantoin in the urine [17]. Thus, this drug can become a water contaminant, which can be dangerous for human health.

Several non-electrochemical techniques have been reported in the literature for the detection of NFT. Colorimetric and spectrophotometric methods have been used since the 1960s [18–20], and the use of high performance liquid chromatography (HPLC) began in the 1970s [21,22]. However, according to Jain et al. [23], the colorimetric and spectrophotometric techniques do not offer a satisfactory quantification limit for the determination of this drug. In addition, the chromatographic methods require pre-treatment and extraction stages for the sample, which demand a great amount of time and increase the cost of the analysis. These stages also increase the exposure time of the drug to light, which can promote the partial photochemical degradation of the compound.

On the other hand, electroanalytical techniques are increasingly used to detect organic compounds. These techniques have several advantages, including that they are quick and reproducible, present low limits of detection and quantification and have relatively low cost compared with the more traditional techniques [8]. The two initial reports about the use of electroanalytical techniques to determine NFT came from the sixties and seventies years, when Jones et al. [24] and Mason and Sandmann [25] reported the use of the polarographic method and the reductive voltammetric method using a rotating platinum electrode, respectively. Recently, three reports have been published that demonstrate the use of square wave cathodic adsorptive stripping voltammetry for the detection on mercury electrodes [17,23] and on activated carbon fiber microelectrodes [26]. In these works, this technique was shown to be a very sensitive and selective methodology for NFT analysis [17,23,26].

A literature survey revealed that no electrochemical studies have been published concerning the electrochemical behavior of NFT on BDDFE. Thus, the aim of this work was to investigate the electrochemical behavior of NFT and develop an electroanalytical procedure to quantify this compound in commercial formulations. This was performed using BDDFE with different boron-doping levels combined with the square wave voltammetry technique.

2. Experimental

2.1. Reagents and equipment

All voltammetric measurements were taken with a potentiostat (Autolab PGSTAT 30, Metrohm-Eco Chemie), which was controlled by a computer using the General Purpose Electrochemical System

software, Version 4.9 (GPES; Metrohm–Eco Chemie). A Beckman Coulter model DU 640 spectrophotometer with 1.00 cm quartz cells was used for the ultraviolet–visible (UV–vis) measurements. 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 solutions were prepared with water purified by a Milli-Q system (Millipore Corporation). A conventional cell with a three-electrode system was used in all electrochemical experiments. The cell consisted of a saturated KCl Ag/AgCl/ Cl^- electrode as the reference electrode, platinum wire as the auxiliary electrode and BDDFE with different boron-doping levels as the working electrode. Prior to the electrochemical measurements, N_2 gas was bubbled through the solution to eliminate any dissolved oxygen. The BDDFE employed as the working electrode was produced by LAS-INPE (São Paulo, SP, Brazil). The BDDFE were grown on planar silicon substrates by chemical vapor deposition, using previously described conditions [14]. Three boron-doping contents were used in this work: 1.9×10^{19} , 7.6×10^{20} and 1.5×10^{21} atoms cm^{-3} , corresponding to about 5000, 10,000 and 20,000 mg L^{-1} , respectively, for the ratio of boron to carbon dissolved in methanol. The working electrodes were built following the procedure described by Julião et al. [15,16]. In this procedure, the silicon substrate with the boron-doped diamond film was attached to a brass plate with silver paste for electrical contact, and it was further insulated with Teflon to protect areas other than the planar surface from contact with solutions. A stock solution of $1.0 \times 10^{-3} \text{ mol L}^{-1}$ USP-grade NFT dissolved in methanol (P.A.) was prepared daily. This was stored in a dark flask and kept in a refrigerator to prevent degradation. The stock solution was used as the supporting electrolyte in 0.1 mol L^{-1} Britton–Robinson (BR) buffer, which was prepared as described in the literature [27]. Solution pH was adjusted to the desired value by adding appropriate amounts of 2.0 mol L^{-1} NaOH stock solution. Prior to the voltammetric NFT experiments, the active electrode surfaces were determined by cyclic voltammetry of the $\text{Fe}(\text{CN})_6^{4-}/\text{Fe}(\text{CN})_6^{3-}$ in 0.1 mol L^{-1} KCl.

2.2. Working procedure

In this work, all electrochemical measurements were taken under ambient conditions. Prior to the experiments, the BDDFE was submitted to an anodic pre-treatment, which was carried out in 0.5 mol L^{-1} H_2SO_4 by applying a current of 500 mA cm^{-2} for 3 min, followed by a cathodic treatment, which was performed by applying -500 mA cm^{-2} for 10 min. Afterwards, the cyclic voltammetry (CV) experiments were conducted at 100 mV s^{-1} using the potential interval of +1.3 to -0.8 V in a cell containing 0.5 mol L^{-1} H_2SO_4 to provide the stabilized electrochemical profile of the working electrode. After each measurement with NFT, the solution was stirred thoroughly for 1 min to remove any possible residues adsorbed on the electrodic surface, thus ensuring experimental reproducibility. The cyclic voltammograms were recorded between -0.75 V and 0.0 V to evaluate the influence of different boron-doping levels on the electrochemical response of NFT on the BDDFE and also to determine the best electrolyte pH for electroanalytical purposes. Square wave voltammetry (SWV) was used for the electroanalytical determination of NFT. The following parameters were investigated to obtain the best analytical signal: peak current (I_p), peak potential (E_p), frequency of pulse potential (f), pulse amplitude (E_{sw}) and scan increment (ΔE_s). All parameters were duly optimized, as their values strongly affect the sensitivity of the voltammetry. After the optimization of the voltammetric parameters, analytical curves were obtained in pure electrolyte using the standard addition method. The standard deviation of the mean current, measured at the oxidation potential of NFT for 10 blank voltammograms in pure electrolyte (S_b), and the slope of the straight line from the analytical curves (s) were employed for the determinations of the detection

limit (DL) and of the quantification limit (QL), using $DL = 3S_b/s$ and $QL = 10S_b/s$ [28,29]. The proposed procedure was compared to the UV–vis spectrophotometric measurements, according to the procedure recommended by the British Pharmacopeia [30]. Thus, the spectrum and characteristic absorbance of NFT were evaluated at 368 nm. Analytical curves were also constructed, and the DL and QL values were calculated using the same relations employed for the voltammetric measurements. On the other hand, the S_b values were determined by the standard deviation of the y-intercept of the analytical curves. Recovery experiments were carried out using the voltammetry and spectrophotometry procedures. For this purpose, a known amount of a pharmaceutical formulation was added to the supporting electrolytes, followed by standard additions of the NFT stock solutions. The resulting analytical curves were plotted, and all measurements were taken in triplicate. The recovery efficiencies were calculated using the relationship between the determined NFT concentration, which was obtained by extrapolating the analytical curves of the corresponding spiked samples, and the NFT concentration added value, which corresponded to the nominal concentration of the samples, multiplied by 100. The precision of the proposed procedure was evaluated based on the reproducibility experiments, which were realized with different standard NFT solutions on different days (intra-day). The experimental accuracy was evaluated using the repeatability obtained in 10 replicated determinations with the same NFT solution (inter-day). The relative standard deviations (RSD) were calculated for the reproducibility and repeatability measurements, using the relationships between the standard deviation and the mean of the peak current values obtained.

2.3. Analysis of the commercial formulation

After calculating the DL and QL for the NFT determination in the supporting electrolyte, the accuracy, reproducibility, procedure precision and interference from excipients present in a commercial NFT formulation were studied. This was done by means of recovery experiments with a commercial product purchased locally. The commercial formulation chosen was Macrofantina (capsule form), which contained 100 mg of NFT. The content of 10 capsules was weighed, and the average mass of each capsule was calculated. The content was homogenized and the amount of NFT, required for the preparation of a solution with a final concentration of $1.0 \times 10^{-3} \text{ mol L}^{-1}$ NFT, was calculated based on the pharmaceutical product. This amount was then weighed and dissolved in methanol using an ultrasonic bath for 20 min. From this stock solution, a solution of $1.0 \times 10^{-4} \text{ mol dm}^{-3}$ was prepared in BR buffer. All solutions were used immediately after their preparation to prevent decomposition by light or heat.

3. Results and discussion

3.1. Cyclic voltammetry experiments

Fig. 1 shows the cyclic voltammograms of NFT in BR buffer at various pHs and the cyclic voltammograms obtained on the BDDFE containing different boron-doping levels. In these cyclic voltammograms, an irreversible reduction peak (C_1) can be observed in the cathodic scan. This cyclic voltammetric behavior was similar to that in previous reports in the literature that used other electrocatalytic surfaces and other antibacterial nitro compounds [15–17,23,26]. The peak C_1 was shifted to more negative potential values with increasing pH, indicating the involvement of hydrogen ions in the electrode reaction. This dependence of the cathodic potential on pH is in agreement with other reports in the literature [15–17,23,26]. Experimental evidences indicate that the electrochemical reduction mechanism of the nitro group in the NFT molecule to the

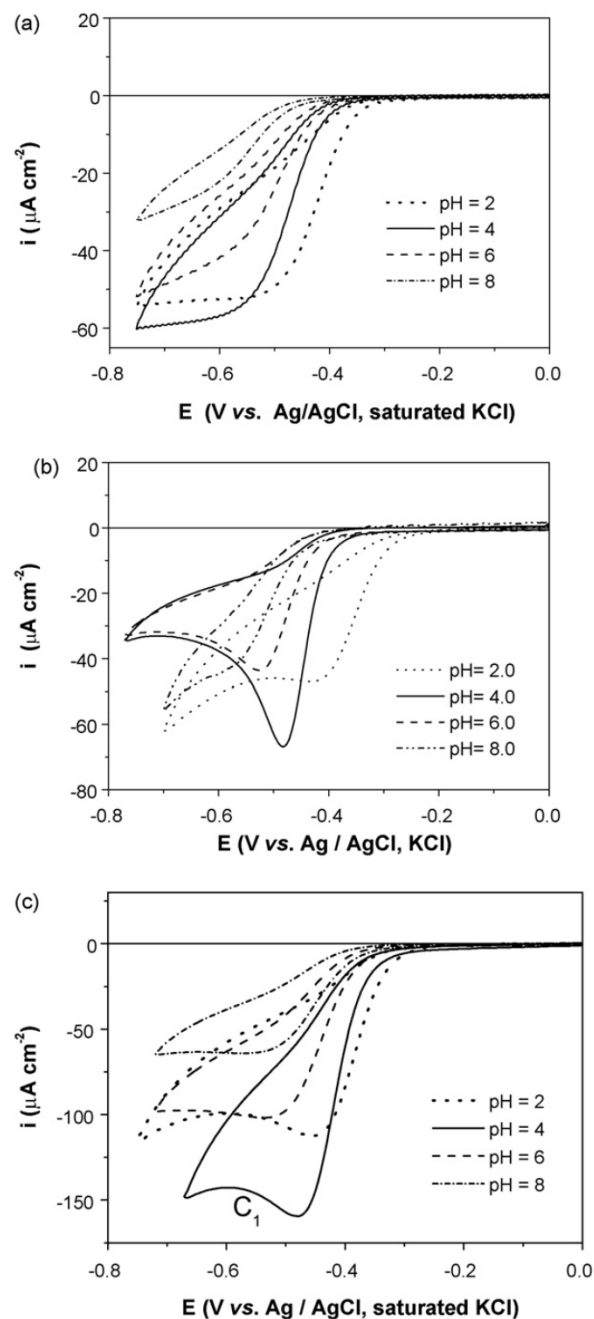


Fig. 1. Cyclic voltammograms for $1 \times 10^{-4} \text{ mol L}^{-1}$ NFT in BR buffer, at different pHs and at 100 mV s^{-1} , on the BDDFE with different levels of boron-doping: (a) 5000 mg L^{-1} ; (b) $10,000 \text{ mg L}^{-1}$; (c) $20,000 \text{ mg L}^{-1}$.

corresponding hydroxylamine involves four electrons and four protons [31].

Fig. 1 also shows that the boron-doping level affects the shape and the I_p of the peak C_1 . For the electrode doped with 5000 mg L^{-1} , the peak was not well defined due to the competition between the NFT reduction and the hydrogen evolution reaction (HER). This suggests that this is not a suitable electrocatalytic surface for the electroanalytical determination of NFT. For the electrodes with higher boron-doping contents, the peak C_1 was better defined in acidic pH because the hydrogen evolution reaction shifts to a more negative value, indicating that the increase in the boron-doping content in the diamond film decreased the electrocatalytic properties of this electrocatalytic material for the HER. On the other hand, the peak C_1 was not well defined at pH 8.

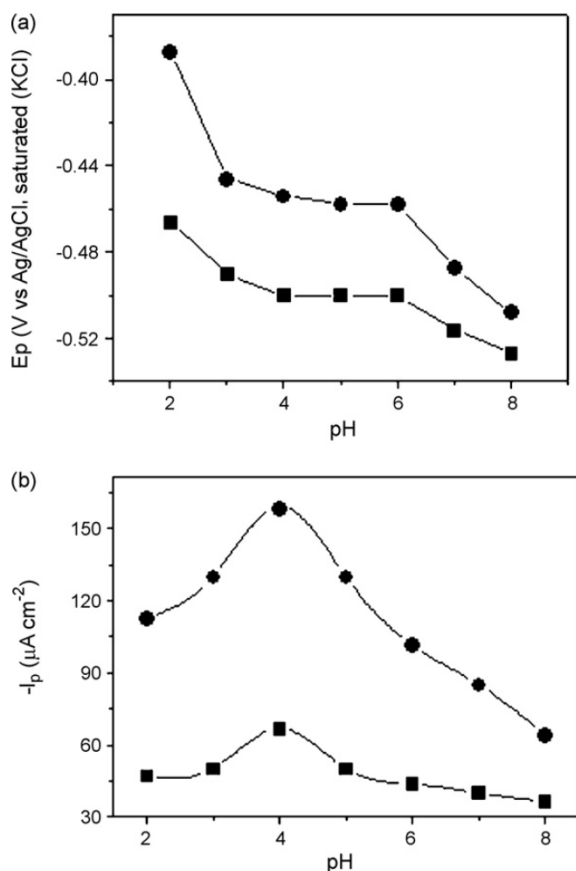


Fig. 2. Variation of E_p (a) and I_p (b) with pH for the electrochemical reduction of nitrofurantoin on the BDDFE doped with 10,000 mg L⁻¹ (■) and 20,000 mg L⁻¹ (●) of boron.

In order to better understand the influence of the pH in the electrochemical response of the nitrofurantoin, the variations of E_p and I_p with pH for the electrodes doped with 10,000 and 20,000 mg L⁻¹ of boron are shown in Fig. 2. The E_p versus pH plot (Fig. 2a) shows three regions for both electrodes. Initially, a shift to more negative potentials was observed in the pH range from 2 to 4. For the pH range between 4 and 6, the E_p values remained approximately constant, followed by a shift to more negative potentials for higher pH values. Fig. 2a also shows that the E_p values obtained for the electrode doped with 10,000 mg L⁻¹ of boron were slightly more negative than those obtained for the electrode doped with 20,000 mg L⁻¹ of boron, suggesting that the increase in the amount of boron-doping favors the electrochemical reduction of the nitrofurantoin. Furthermore, the I_p versus pH plot (Fig. 2b) showed a maximum at pH 4, which indicates this pH as the optimum for electroanalytical purposes. In addition, comparing the electrodes doped with 10,000 and 20,000 mg L⁻¹, it can be observed that I_p increases about 2.4 times with twice the boron-doping level in the BDDFE. Zhang et al. [32] showed that the resistivity of the boron-doped diamond films decrease linearly with the increase in the amount of boron in the diamond film. Accordingly, the observed increase in I_p can be associated with the increase in the conductivity of the diamond film when the amount of boron is doubled. Unfortunately, a similar comparison cannot be done with the 5000 mg L⁻¹ BDDFE because the current shown in the cathodic branch of Fig. 1a also has the contribution of the current related the hydrogen evolution reaction and well defined peaks were not observed. Morales et al. [33] used the polarographic technique to study the electrochemical reduction of nitrofurantoin on the Hg electrode; they observed three linear portions in the $E_{1/2}$ versus pH plot, and they found

that the diffusion-limited current was also pH dependent. From the present authors [33], the decreases in the I_p for pH below 4 can be associated with an acid–base equilibrium. For pH higher than 4, the decrease in the I_p can be explained as due to the fact that the hydroxylamine intermediate in the reduction of the nitro group is no longer protonated and it is not easily reduced. Finally, the cyclic voltammetry studies at pH 4 showed a linear dependence between the peak current and the square root of the scan rate, indicating that the electrochemical reduction of NFT was controlled by diffusion. This is also in close agreement with the reports previously published in the literature for other nitro compounds [15–17,23,26].

Thus, to develop an electroanalytical procedure for the NFT determination on a BDDFE, a BR buffer solution with pH adjusted to 4.0 and electrodes doped with 10,000 and 20,000 mg L⁻¹ boron were selected.

3.2. Square wave voltammetry experiments

Typical square wave voltammograms (SWV) for 1×10^{-4} mol L⁻¹ NFT in BR buffer (pH 4) on the BDDFE are shown in Fig. 3. This figure shows a well-defined cathodic square wave voltammetric peak, which was observed for the two selected electrodes. The SWV parameters (f , E_{sw} and ΔE_s) were evaluated to determine the optimal values for obtaining the best analytical signal. The correlations between the peak current and the frequency of the pulse potential, the pulse amplitude and the scan increment are shown in Fig. 4.

The frequency was optimized in the range of 10–100 Hz, using an increment of 2 mV and a pulse amplitude of 50 mV. The variation of I_p with frequency for both selected electrodes is shown in Fig. 4a. A linear relationship was observed between the peak current and the frequency (f) for both selected electrodes, which yielded similar slopes. The increase in I_p with f suggests that the NFT was weakly adsorbed on the electrode surfaces [34–36]. This was corroborated by the experimental evidence, as the voltammetric profile of NFT on the BDDFE surface was obtained again following agitation of the solution. For the BDDFE doped with 10,000 mg L⁻¹ of boron, linearity was maintained up to 80 Hz. However, for the electrode doped with 20,000 mg L⁻¹ boron, linearity was observed over the entire analyzed frequency range. In addition, the electrode doped with 20,000 mg L⁻¹ boron presented higher I_p values, while the E_p values were approximately independent of frequency.

The influence of E_{sw} on the I_p intensities was evaluated for values of E_{sw} from 10 to 80 mV, and the results are shown in Fig. 4b.

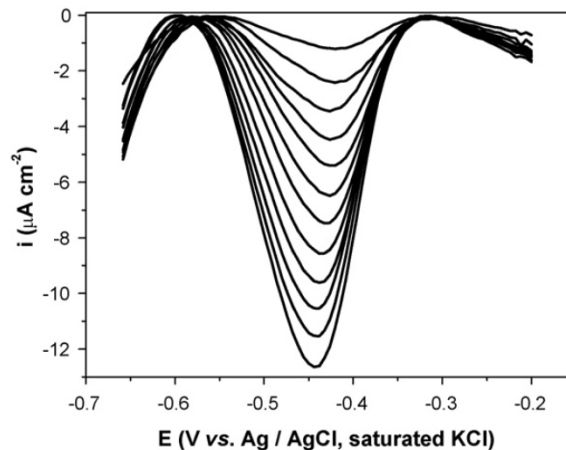


Fig. 3. Typical square wave voltammograms obtained for the NFT in BR buffer at pH 4 in the concentration range of $4.97\text{--}56.6 \times 10^{-7}$ mol L⁻¹ NFT on the BDDFE. In this case, the BDDFE electrode was doped with 10,000 mg L⁻¹ boron.

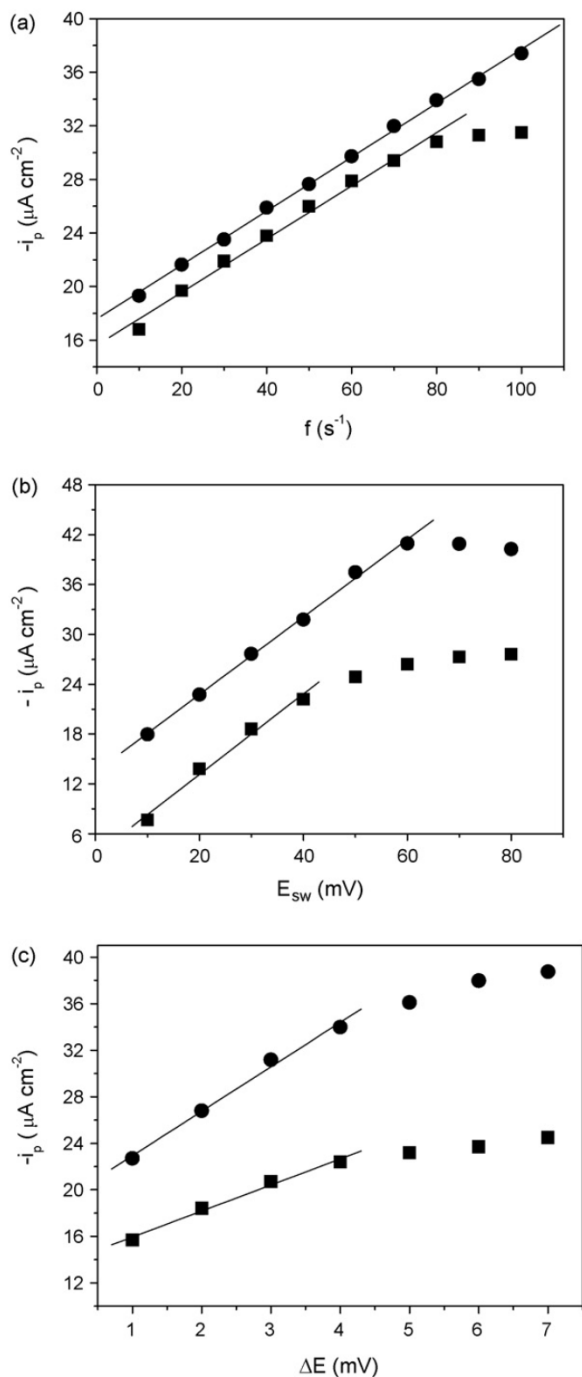


Fig. 4. Variation of the peak current with the frequency of the pulse potential (a), pulse amplitude (b) and scan increment (c) obtained from the square wave voltammograms of $1 \times 10^{-4} \text{ mol L}^{-1}$ NFT in BR buffer at pH 4 on the BDDFE doped with $10,000 \text{ mg L}^{-1}$ (■) and $20,000 \text{ mg L}^{-1}$ (●) of boron.

For both electrodes, the increase of E_{sw} led to an increase in I_p . For the $10,000 \text{ mg L}^{-1}$ boron electrode, a linear relationship was observed up to 40 mV, while for higher E_{sw} , the I_p tended to reach a plateau. For the $20,000 \text{ mg L}^{-1}$ boron electrode, a linear relationship between E_{sw} and I_p was observed up to 60 mV, and for E_{sw} higher than 60 mV, the I_p remained approximately constant. For the higher boron-doping contents, the I_p values were higher than those obtained for $10,000 \text{ mg L}^{-1}$ of boron. Additionally, the E_p value showed no variation with E_{sw} .

The response of I_p with ΔE_s is shown in Fig. 4c. These results show that I_p increased with increasing ΔE_s . Additionally, a linear

relationship between I_p and ΔE_s was observed from 1 mV to 4 mV, and the slopes were similar. For ΔE_s higher than 4 mV, the increase in the I_p values with ΔE_s was not linear.

Therefore, for investigations concerning the influence of the boron-doping content of the BDDFE on the electroanalytical NFT determination, the discussion presented in the previous paragraphs indicates that the optimized experimental conditions are as follows: $f=80 \text{ Hz}$, $E_{sw}=40 \text{ mV}$ and $\Delta E_s=4 \text{ mV}$ for the electrode doped with $10,000 \text{ mg L}^{-1}$ boron, and $f=100 \text{ Hz}$, $E_{sw}=60 \text{ mV}$ and $\Delta E_s=4 \text{ mV}$ for the electrode doped with $20,000 \text{ mg L}^{-1}$ boron.

3.3. Analytical curves

The optimized parameters were employed to draw the analytical curves for NFT reduction on the BDDFE in BR buffer solution. These parameters were also used to evaluate the influence of the boron-doping content on the sensitivity of the proposed procedure and for the applications of the commercial pharmaceutical formulation.

The NFT analytical curves were obtained, as described in Section 2, for the concentration range of $4.97\text{--}56.6 \times 10^{-7} \text{ mol L}^{-1}$. Aliquots from the NFT stock solution were added consecutively to the electrochemical cell, and the voltammetric responses were recorded and are presented in Fig. 5. A linear relationship can be observed between the peak current and the added concentration of NFT for both BDDFE. The linear behavior was maintained for the electrode doped with $20,000 \text{ mg L}^{-1}$ of boron for all studied NFT concentrations. However, for the electrode doped with $10,000 \text{ mg L}^{-1}$, the I_p values slightly deviated from colinearity for the higher concentrations of NFT.

Table 1 presents the analytical parameters obtained for the NFT determination using the SWV and UV-vis spectrophotometry procedures. These include the linearity range (LR), analytical curve equations, correlation coefficients (r ; determined by the degree of linearity for the correlation between NFT concentration and peak currents), standard error of the intercept (SE_a), standard error of the slope (SE_b), standard deviation of the arithmetic mean of 10 blank solutions (S_b), detection limits (DL), quantification limits (QL), repeatability and reproducibility. All data shown in this table were obtained in triplicate, and the results reported here represent the average of the values obtained.

The results for the regression equation associated with the analytical curves exhibited good linearity, as shown in Table 1, indicating the validation of the proposed procedure. In addition, the electrode doped with $20,000 \text{ mg L}^{-1}$ presented a higher slope

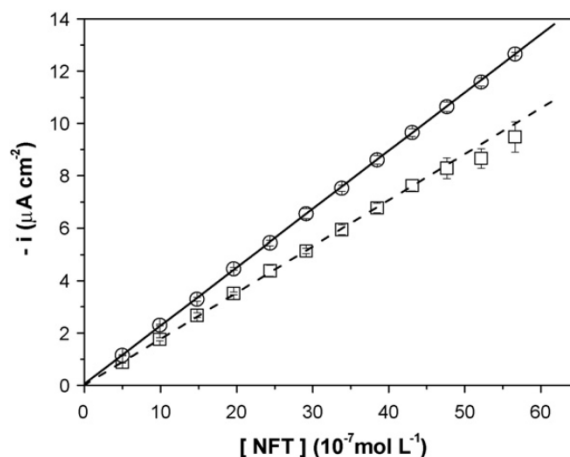


Fig. 5. Analytical curves obtained for the BDDFE with boron-doping levels of $10,000 \text{ mg L}^{-1}$ (□) and $20,000 \text{ mg L}^{-1}$ (○).

Table 1

Analytical parameters obtained for the NFT determination using SWV and UV–vis spectrophotometry procedures. LR: linearity range; r: correlation coefficient; SE_a: standard error of the intercept; SE_b: standard error of the slope; S_b: standard deviation of the arithmetic mean of 10 blank solutions; DL: detection limit; QL: quantification limit; RSD: relative standard deviation.

Parameters	BDDFE-SWV		UV–vis spectrophotometry
	10,000 mg L ⁻¹	20,000 mg L ⁻¹	
LR	4.97–47.62 × 10 ⁻⁷	4.97–56.6 × 10 ⁻⁷	4.90–51.9 × 10 ⁻⁷
Equation curve	$I_{pc} = 7.35 \times 10^{-7} + 1.74$ [NFT]	$I_{pc} = 5.74 \times 10^{-7} + 2.22$ [NFT]	$ABS = 5.23 \times 10^{-3} + 1.78 \times 10^4$ [NFT]
R	0.9997	0.9998	0.9957
SE _a	3.5 × 10 ⁻⁷ A	1.1 × 10 ⁻⁷ A	2.59 × 10 ⁻³
S _b	1.56 × 10 ⁻⁸	6.03 × 10 ⁻⁹	3.29 × 10 ⁻³
SE _b	0.357 A mol ⁻¹ L	0.147 A mol ⁻¹ L	51.4 mol ⁻¹ L
DL (mol L ⁻¹)	2.69 × 10 ⁻⁸ (6.40 μg L ⁻¹)	8.15 × 10 ⁻⁹ (1.94 μg L ⁻¹)	5.56 × 10 ⁻⁷ (132 μg L ⁻¹)
QL (mol L ⁻¹)	8.96 × 10 ⁻⁸ (21.33 μg L ⁻¹)	2.72 × 10 ⁻⁸ (6.47 μg L ⁻¹)	1.85 × 10 ⁻⁶ (440 μg L ⁻¹)
Repeatability (%)	1.20% (n = 10)	0.95% (n = 10)	4.37% (n = 13)
Reproducibility	3.40% (n = 5)	1.19% (n = 5)	7.22% (n = 9)

Table 2

Results obtained from the recovery curve of NFT for the commercial formulation and using the two analytical procedures employed here.

Parameters	BDDFE-SWV		UV–vis
	10,000 mg L ⁻¹	20,000 mg L ⁻¹	
[NFT] _{added} (mol L ⁻¹)	9.9 × 10 ⁻⁷	9.9 × 10 ⁻⁷	10.15 × 10 ⁻⁷
[NFT] _{found} (mol L ⁻¹)	(10.36 ± 0.2) × 10 ⁻⁷	(10.23 ± 0.2) × 10 ⁻⁷	(10.87 ± 0.7) × 10 ⁻⁷
Recovery (%)	105 ± 3	103 ± 2	107 ± 4

for the calibration curve, indicating that the increase in the boron-doping content led to an increase in the sensibility of the proposed procedure.

The validation of the procedure was also examined by evaluating the DL and QL, as described in Section 2 and as recommended by the IUPAC [28]. These values were compared to similar results obtained using UV–vis spectrophotometry, as recommended in the British Pharmacopeia [30]. As shown in Table 1, the more highly boron-doped electrodes presented lower DL and QL calculated values. The DL and QL values for both selected electrodes, as calculated by the proposed procedure, were very close to the values reported in the literature for NFT determination using SWV, with previous cathodic adsorptive stripping that utilized a mercury electrode [17,23] and a carbon fiber microelectrode [26]. The DL and QL of the proposed procedure were lower than those presented by the recommended procedure, indicating that the BDDFE combined with SWV is a suitable tool for the NFT determination. Furthermore, the BDDFE proved to be suitable electroodic surfaces for the NFT determination, as it was possible to perform the NFT determination without modification of the electrode surface or complex electrochemical pre-treatments. This enables the simplification of the analytical procedure, thus lowering the cost and providing reliable sensitivity for analytical purposes.

The precision and accuracy were also evaluated using the proposed SWV procedures, considering the two selected electrodes and using the recommended UV–vis spectrophotometry procedure. The precision was evaluated from reproducibility experiments in which five different measurements, performed on different days, were carried out employing a standard solution containing 9.9 × 10⁻⁷ mol L⁻¹ NFT and using the procedure described earlier. The measurement accuracy was also evaluated from 10 repetitive determinations (repeatability) of the same standard solution.

From the obtained results (Table 1), it is apparent that the BDDFE with 20,000 mg L⁻¹ boron as the doping level presented better reproducibility and repeatability compared to the BDDFE with 10,000 mg L⁻¹ boron. However, the reproducibility and repeatability of the NFT electrochemical reduction process on both selected BDDFE were very good.

These results indicate that both electrodes are excellent electroodic materials for the NFT determination. They can replace other

electroodic surfaces, such as mercury electrodes. Also, the proposed procedure using BDDFE with the SWV technique can be a substitute for the UV–vis spectrophotometry procedure.

3.4. Application of the proposed procedure to a commercial formulation

The determination of NFT in its pharmaceutical formulation was carried out to evaluate the applicability of the proposed procedure toward complex samples. There was no need for an extraction step prior to the drug assay. 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 axis referring to the NFT concentration in the electrochemical cell. Extrapolating the curve along this axis yielded the sample concentration, allowing for the calculation of the recovery values. Table 2 shows the results obtained from the NFT recovery curve for the commercial formulation and using the two analytical procedures employed here. The calculated values are shown to be in a suitable range for analytical purposes (i.e., from 70% to 130%) [37,38], indicating that the proposed procedure is appropriate for NFT quantification in complex samples, such as pharmaceutical formulations. In addition, the recovery values for both selected electrodes were similar to those reported in the literature for the NFT determination on mercury electrodes using square wave cathodic adsorptive stripping voltammetry. These recovery values were 101.49 [18] and 99.87 [23]. Finally, the boron-doping content did not influence the recovery value.

4. Conclusions

The electrochemical reduction of NFT is influenced by the level of boron-doping in diamond film electrodes. The appropriate cyclic voltammetric response of NFT was obtained with a BR buffer at pH 4 on diamond films doped with 10,000 and 20,000 mg L⁻¹ boron. The use of square wave voltammetry with the optimized parameters showed a good linear relationship between the peak current and the NFT concentration over a wide concentration range. The proposed procedure proved to be sensitive, accurate and precise for the

analysis of NFT and did not require complex preparations or renovation of the electrode surface. Finally, boron-doped diamond film electrodes can be considered as environmentally friendly alternatives for the electroanalytical determination of NFT. This presents the advantage of eliminating mercury waste and minimizing the adsorptive problems related to the use of other electrodic solid surfaces.

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