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Nanostructured interfaces containing MWCNT and nitro aromatics: A new tool to determine Nimesulide

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ABSTRACT

A novel type of multiwalled carbon nanotube-modified glassy carbon electrode with an entrapped nimesulide drug was constructed. The new electrode surface was characterized by scanning electrochemical microscopy and scanning electron microscopy. Additionally, using cyclic voltammetry, the electrochemical behaviour of nimesulide on the modified electrode was studied in detail, and this material was used as a sensor for the drug. The analytical parameters of this sensor were adequate, with a recovery value of 98.4% and detection and quantification limits of 1.6 nM and 5.5 nM, respectively. Finally, the developed sensor was applied successfully to determine the drug in commercial tablets.

The method developed herein represents an unconventional way to perform voltammetry, where the electroactive species (nimesulide) is trapped in the electrode phase instead of dissolved in solution. This method is especially recommended for drugs that have low solubility in water.

1. Introduction

Nimesulide (NSD), N-(4-nitro-2-phenoxyphenyl)methanesulfonamide (Fig. 1), is a non-steroidal anti-inflammatory drug (NSAID) that possesses antipyretic and analgesic properties and is structurally characteristic because it contains a nitroaromatic group and is selective for cyclooxygenase-2 (COX-2) inhibitors, which provide analgesic and antipyretic effects [1]. Although the main indication of this drug in many countries is for the asymptomatic treatment of osteoarthritis, tendinitis, bursitis and pain after surgery [2], NSD is not approved as a clinical agent in some countries due to the incidence of hepatic toxicity with its use [3]. The reduced form of the nitro group of NSD is thought to be responsible for hepatoxicity. The redox form of NSD could include the formation of hydroxylamine derivatives or the generation of radical species such as the nitro radical anion [4]. NSD has been shown to be toxic to primary rat and human hepatocytes with an IC_{50} of 40 mM for rats and 213 mM for human hepatocytes [5].

The analytical determination of NSD has been performed by several authors with various techniques, including spectrometry [6], chromatography [7–10], electrochemical methods [11,12], capillary zone electrophoresis [13,14], HPLC with a monolithic column [15] and at a glassy carbon electrode [16] as a detector and with tandem mass spectrometry [17].

The quantification of NSD through electrochemical techniques has been significant over recent decades, from early studies describing its differential pulse polarographic determination in pharmaceuticals [18] until the most recent one that describes Amberlite XAD-4-modified electrodes for highly sensitive electrochemical determination of NSD in human urine [19]. There are a large number of electrochemical determinations described in the literature since the NSD molecule offers considerable versatility from an electrochemical perspective. In fact, NSD is susceptible to reduction [12,20,21], oxidation [19,22–25], adsorption [26] and even generation of catalytic waves of hydrogen [27].

Carbon nanomaterials have been important in recent years, mainly due to their unique properties as electrode materials in electroanalysis. This electrode material presents a singular structure and dimensions, high surface area and a wide potential window [28,29]. Additionally, carbon nanomaterials can facilitate electron transfer between electroactive species and the electrode. Multiwalled carbon nanotubes (MWCNTs) are among carbon nanomaterials that are routinely applied as electrode materials. In fact, MWCNTs have been used as the electrode phase for voltammetric determination of NSD either in combination with a carbon paste electrode (CPE) [25] or with a glassy carbon electrode (GCE) [12]. Both of these voltammetric methods detect the NSD molecule as the electroactive species dissolved in solution.

Recently, we have developed a non-conventional voltammetric method that involves first trapping an electroactive species on the surface of a modified MWCNT electrode, then washing the electrode

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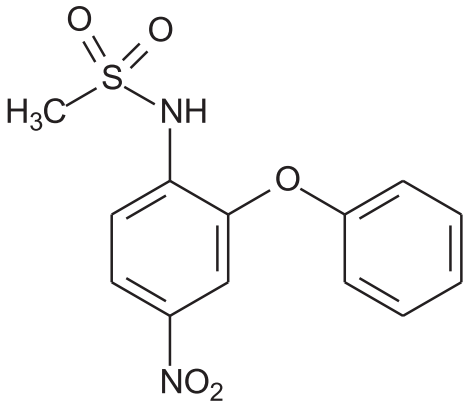

Fig. 1. Chemical structure of nimesulide.

and finally applying a potential scan in a fresh buffer solution. Using the above approach, it was possible to trap the electroactive species in the porous network of the MWCNTs on the electrode, prioritizing thin-layer-type mass transport and leading to larger peak currents and smaller concentration overpotentials [30]. We have tested this new method to develop voltammetry with several nitroaromatic compounds, including mono-, di- and tri-nitro [30,31]. One of the advantages of this new method of carrying out voltammetric experiments is that it is especially favourable for poorly soluble compounds, as exemplified for weakly soluble coumarins, but can be extrapolated to other weakly soluble compounds [32]. A similar principle is used in adsorptive stripping transfer voltammetry used earlier by Palecek et al., [33]. In fact, that work proposes a method based on the adsorption of biomacromolecules at a mercury electrode and the transfer of the layer to another medium, where the voltammetric measurements are carried out. In our case, the electroactive molecule is not a biomacromolecule and the electrode is not Hg, but rather a nanostructured platform of MWCNTs.

In this paper, a novel type of MWCNT-modified glassy carbon electrode (GCE/MWCNT) with NSD, a drug very sparingly soluble in water (≈ 0.01 mg/mL), was constructed [34]. The electrochemical behaviour of NSD on the modified electrode was studied in detail. The new modified electrode was successfully used as a sensor to determine NSD.

2. Experimental

2.1. Reagents and drugs

NSD was purchased from Sigma Aldrich. Commercial tablets of NSD (declared amount of 100 mg NSD per tablet, Laboratorio Chile®, Santiago, Chile) were purchased from a local market. Ferrocene methanol and 1,3-dioxolane were purchased from Sigma Aldrich.

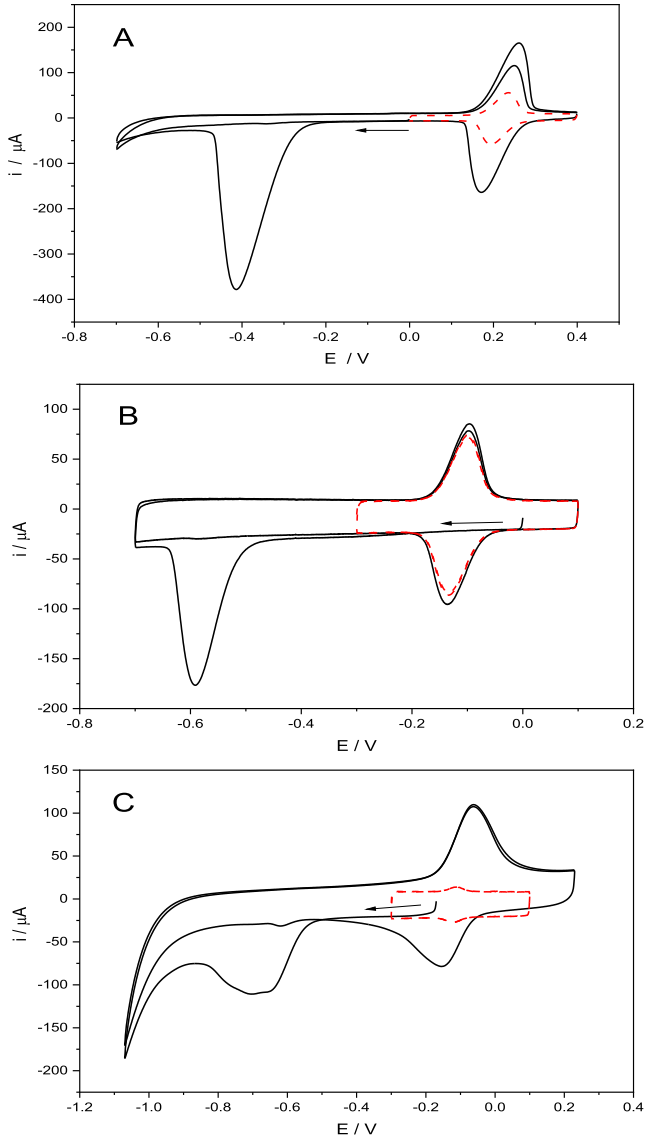

Fig. 3. Cyclic voltammograms at 0.1 V/s of 0.1 mM NSD in Britton-Robinson buffer. A. pH 2, B. pH 7, C. pH 10.

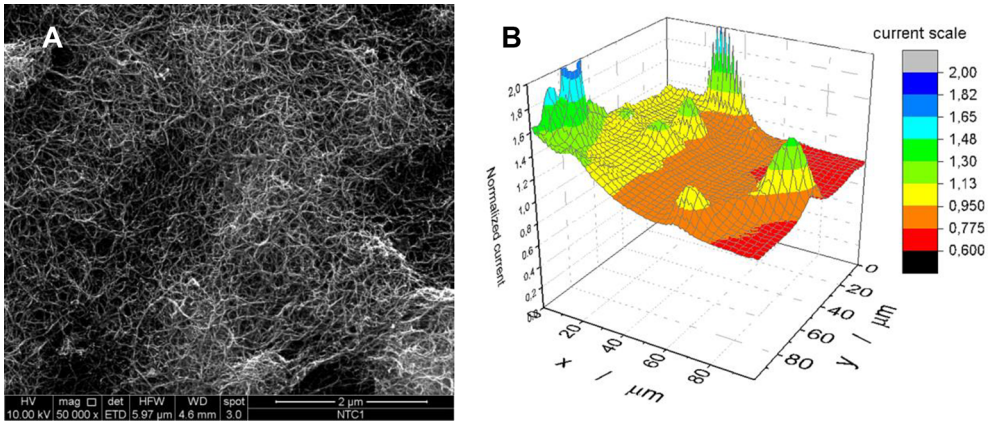

Fig. 2. A. SEM image obtained for a GC-MWCNT disc modified with nimesulide with 0.1 mM Britton-Robinson buffer, pH 7. (Magnification 50000X, acceleration of 10 kV, scale bar of 2 µm). B. 3D-SECM image of the GC/MWCNT NSD-modified electrode in 10 µM ferrocene methanol, pH 4.7.

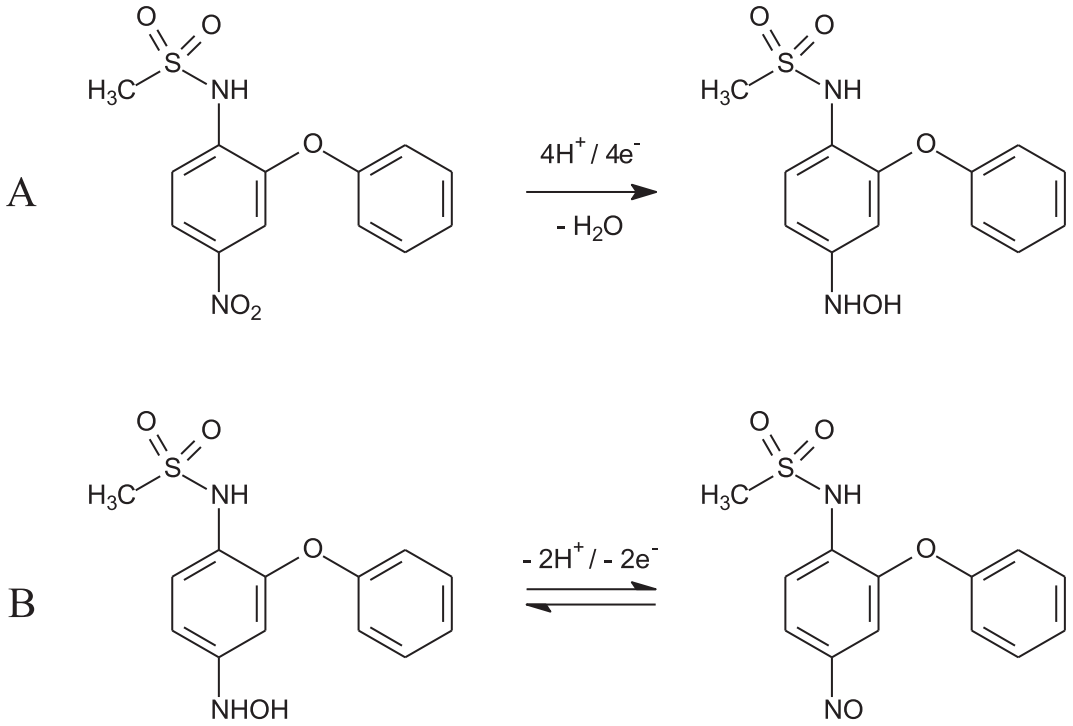

Fig. 4. A. Electrochemical reduction of NSD. B. Reversible mechanism of coupled nitroso/hydroxylamine derivatives.

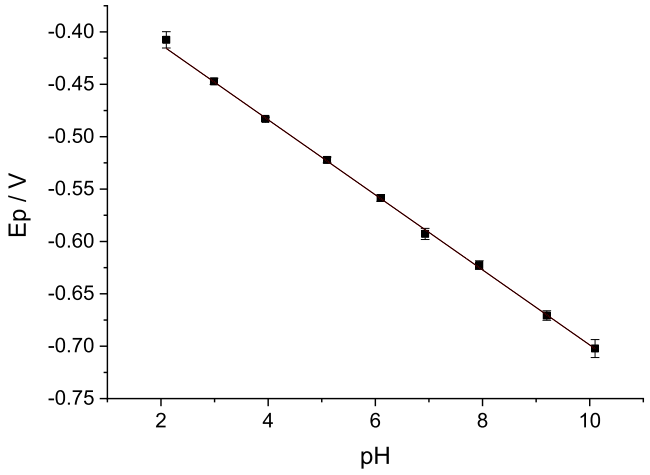

Fig. 5. Peak potential *vs* pH plot for NSD (NSD entrapped on GCE/MWCNT and measured in Britton-Robinson buffer solution).

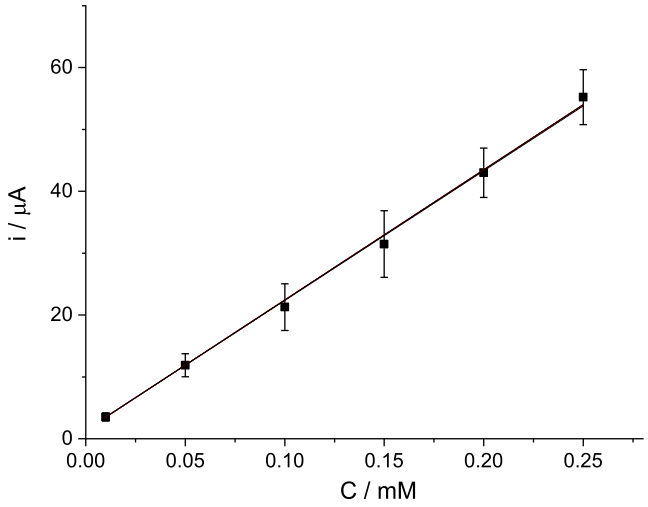

Fig. 6. Calibration curve for NSD (NSD entrapped on GCE/MWCNT from different NSD ethanol-solutions concentrations and measured in Britton-Robinson buffer, pH 7 by Cyclic voltammetry at 0.1 V/s).

MWCNTs (diameter ~ 10 nm, length ~ 1.5 µm) were purchased from DropSens® and were used without further purification. All other reagents were analytical grade.

2.2. Solution/dispersion preparation

A stock solution of NSD was prepared at a concentration of 0.1 M in ethanol. For NSD working solutions, appropriate volumes of the stock solution were diluted to 10 mL with ethanol prior to electrochemical experiments.

A 3 mg/mL MWCNT dispersion was prepared in 1,3-dioxolane by adding the dispersing agent directly to the nanotubes in a capped microtube to avoid evaporation of the dispersing agent. To guarantee homogeneity, the dispersion was subjected to a sonic bath for three 5-minute periods, as previously reported [35].

2.3. Electrochemical measurements and apparatus

All voltammetric curves were recorded with a CHI 650 potentiostat (CH Instruments Inc., USA), and the experiments were carried out with a standard three electrode cell. A glassy carbon electrode (GCE) (3 mm diameter CHI104) or a modified GCE was used as working electrode, a Ag/AgCl reference electrode, and 1 M KCl (CHI 111) were purchased from CH Instruments®, Inc. A platinum gauze was used as the counter electrode. A 0.1 M Britton-Robinson buffer solution as the aqueous medium was used in all experiments. The pH of the supporting electrolyte was adjusted as required. Most of the experiments were performed at pH 7. Nitrogen was bubbled through the electrochemical cell for 10 min before the electrochemical experiments, and the nitrogen flow was maintained during the experiments to keep the cell's atmosphere free of air.

Table 1
Comparison of different techniques for the detection of NSD.

Methodology	LOD	LOQ	Ref.
Electrochemistry: DPV (Cysteic acid/CNT)	50 nM	–	[11]
Electrochemistry: LSV (GCE/MWCNT)	1.6 nM	–	[12]
Electrochemistry: DPP	2.5 μM	–	[18]
Electrochemistry: SWV (Amberlite XAD-4 electrode)	1.28 nM	42.8 nM	[19]
Electrochemistry: DPV (SiC-NPs/GCE)	30 nM	–	[20]
Electrochemistry: DPV (Fe_3O_4/GCE)	130 nM	–	[21]
Electrochemistry: DPV (gold electrode)	1.1 nM	–	[22]
Electrochemistry: SWV (GO and rGO/CPE)	1.08 nM	3.69 nM	[23]
Electrochemistry: SWV (Nanoclay/CPE)	1.01 nM	3.37 nM	[24]
Electrochemistry: DPV (MWCNT/CPE)	1.07 nM	3.24 nM	[25]
Electrochemistry: ALSV (GCE)	32 nM	106 nM	[26]
Electrochemistry: SWV (CB–DHP/GC)	16 nM	–	[39]
Electrochemistry: SWV (rGO and PEDOT)	2.4 nM	–	[40]
Electrochemistry: A (rGO nanoribbons)	3.50 nM	–	[41]
Electrochemistry: DPV (TiO_2/GCE)	3.3 nM	11.2 nM	[42]
Electrochemistry: DPV (5% BDZONP/GCE)	1.794 nM	5.9 nM	[43]
Electrochemistry: BIA-MPA (BDE)	0.963 μM	–	[44]
Electrochemistry: DPV (CPE)	8.57 nM	2.86 nM	[45]
Liquid chromatography (in rabbit aqueous humour)	–	0.162 μM	[8]
HPLC - electrochemical detection (in tablets)	2.2 μM	5.8 μM	[16]
HPLC (in human plasma)	97.3 nM	–	[46]
Derivative UV spectrophotometry	1.62 μM	6.5 μM	[47]
Liquid chromatography (HPTLC)	60 ng	100 ng	[48]
Electrochemistry: CV (GCE/MWCNT/NSD)	1.6 nM	5.5 nM	This work

A: amperometry, ALSV: adsorptive linear sweep voltammetry, BDE: boron-doped diamond electrode, 5% BDZONP/GCE: 5% barium-doped zinc oxide nanoparticle modified glassy carbon electrode, BIA-MPA: batch injection analysis system with multiple pulse amperometric detection, CB–DHP/GC: glassy carbon modified with carbon black within a dihexadecylphosphate film as a sensor, CPE: carbon paste electrode, CV: cyclic voltammetry, DPP: differential pulse polarography, DPV: differential pulse voltammetry, GO: graphene oxide, LSV: linear sweep voltammetry, PEDOT: poly(3,4-ethylenedioxythiophene), rGO: reduced graphene oxide, SiC-NPs/GC modified electrode: glassy carbon electrode modified with silicon carbide nanoparticles,SWV: square wave voltammetry, TiO_2/GCE: glassy carbon electrode modified with TiO_2 nanoparticles.

2.4. Electrode preparation

Before any modification, the GCEs were polished with 0.3 and 0.05 μm alumina and washed with plenty of nanopure water. The GCEs were modified with a 5 μL aliquot of the MWCNT dispersion; then, they were allowed to dry for 5 min at room temperature, and a modified GC/MWCNT electrode was obtained.

2.5. Electrode modification with NSD

To incorporate NSD into the electrodes, a nanomaterial-modified electrode (GCE/MWCNT) was immersed in a 0.1 mM NSD ethanol solution at open circuit potential (OCP) for 10 sec. then it was removed from the ethanol solution and washed with excess nanopure water. After washing, the electrode was introduced into the electrochemical cell containing only buffer to perform the voltammetric measurements. All electrochemical measurements were performed in electrochemical cells containing only buffer, ensuring that the electrochemical response is only from the NSD entrapped on the active sites of the GC/MWCNT-modified electrode.

2.6. Analytical procedure

2.6.1. Calibration curve construction

By diluting the NSD stock solution with ethanol, working solutions ranging from 0.01 mM to 0.25 mM were prepared. Each one of these ethanol solutions were employed to generate the modified electrode with NSD entrapped into MWCNT. For this purpose, a GCE/MWCNT was immersed into each NSD ethanol solution for 10 sec, and it was washed with nanopure water and then immersed in a cell containing Britton-Robinson buffer solution, pH 7. In these conditions, cyclic voltammograms corresponding to the NSD entrapped in the electrode were obtaining, scanning between −0.7 and 0.1 V at 0.1 V/s

2.6.2. Synthetic samples

Synthetic samples for recovery studies were prepared by weighing 100 mg NSD plus suitable excipients according to the manufacturer's batch formulas for 100-mg NSD tablets. The excipients tested were: microcrystalline cellulose, polyvidone, sodium lauryl sulfate, sodium starch glycolate, magnesium stearate, hypromellose, ethyl cellulose, diethyl phthalate, talc and titanium dioxide. All the components were suspended in ethanol, sonicated by 5 min to ensure the dissolution of the drug and completed to final volume of 50 mL with the same solvent. Then 1 mL aliquot was taken and diluted with ethanol up to 50 mL to obtain a theoretical NSD concentration of 0.13 mM. This solution was employed to entrap NSD in the electrode, according to procedure described above.

2.6.3. NSD determination in commercial tablets

The carbon nanotube-modified electrodes were tested with commercial tablets of NSD. For this purpose, ten tablets were weighed and ground into a powder in a mortar, and a solution equivalent to 0.1 mM NSD was prepared in ethanol. The modified electrodes were immersed in the drug ethanol solution according to the procedure described above, and a NSD-modified electrode was obtained. This time, the electrodes were modified with an ethanol NSD solution, prepared directly from the commercial tablets. Each electrode was taken to a cell containing only Britton-Robinson buffer. The amount of NSD in the sample solution was calculated using the calibration curve.

2.7. Scanning electrochemical microscopy (SECM)

SECM was performed with a 10 μm platinum electrode (CH Instrument, CH116 tip SECM electrode). All characterization with SECM was performed with a Model 900 scanning electrochemical microscope. Before each experiment, the tip was polished with 0.3 and 0.05 μm alumina and then rinsed with water. The substrate GC/MWCNT/NSD-modified electrode was characterized by scanning electrochemical microscopy. Ten micromolar ferrocene methanol in Britton Robinson buffer, pH 4.7, was used as the electrochemical mediator. The electrochemical sweep was performed on a sample of the electrode substrate of 100 μm × 100 μm (the sweep scan was 50 mV/s). The tip used was 10 μm platinum.

2.8. Scanning electron microscopy (SEM)

SEM measurements were carried out on glassy carbon discs (TED Pella brand, Inc. (N16524)) measuring 12.7 mm in diameter. The discs were polished with an alumina suspension of 0.05 and 0.3 μm diameter and subsequently modified with MWCNTs and NSD in the same way as the GCEs. The morphology of the modified electrode was investigated by SEM using an Inspect Scanning Electron Microscope F-50 operated at 10 kV.

3. Results and discussion

NSD is chemically characterized by the presence of a nitroaromatic group in its structure, giving this compound an extraordinary ability to be reduced. Recently, we developed a non-conventional method to carry out voltammetric experiments, especially those involving nitro aromatic compounds [30]. Consequently, in this paper, we apply this non-conventional method to NSD. The most similar paper describing the state of the art for the voltammetric determination of NSD is the

paper published by J. Zhang et al. [12] that describes NSD and its determination using MWCNT-modified glassy carbon electrodes (GCE/MWCNT). In that paper, the analyte NSD was included in the solution, and the electrode phase was GCE/MWCNT. In this work, we change those conditions by trapping the analyte NSD in the MWCNT instead of dissolving it in the solution. As expected, the electrochemical behaviour of NSD is somewhat different depending on the way the experiment is performed.

3.1. Microscopic characterization of GCE/MWCNT/NSD

According to the above-explained procedure, we modified electrodes formed by glassy carbon and MWCNTs with NSD to obtain a new modified electrode wherein NSD was trapped in the porous network of the MWCNTs on the electrode. The SEM image (Fig. 2A) shows a GC surface completely covered by randomly distributed nanotubes. No NSD cluster is observed above the MWCNT distribution, indicating that the NSD molecules are evenly distributed entrapped between the interstices formed between the nanotubes. The entrapped nitro compound between nanotube interstices was also confirmed in previous works by using X-ray diffraction analysis [36] and X-ray photoelectron spectroscopy [31]. The GC/MWCNT NSD-modified electrode was also characterized by scanning electrochemical microscopy (SECM). Fig. 2B shows that the scanned area has several irregularly shaped high-conductivity peaks because the nanotubes are randomly distributed over the electrode. There are even areas where the current is off the scale.

3.2. Electrochemical characterization of GCE/MWCNT/NSD

Cyclic voltammetry was used to evaluate the electrochemical behaviour of the GC/MWCNT NSD-modified electrode in a solution that contains only the buffer.

The voltammetric behaviour of the GCE/MWCNT/NSD-modified electrode in an aqueous buffer solution was rather different from that previously reported for the NSD solution in GCE/MWCNT-modified glassy carbon electrodes [12]. The cyclic voltammograms of NSD entrapped in GCE/MWCNT show in the first cathodic scan, starting at 0 V, one sharp peak with a peak potential of Ep = − 0.415 V at pH 2 (Fig. 3A). This peak corresponds to the reduction of the nitro group present in NSD to form a hydroxylamine derivative according to equation A in Fig. 4. The nitro group is reduced to the hydroxylamine derivative, which is subsequently oxidized to the nitroso derivative in the reverse anodic scan, producing an anodic peak at a potential of Ep = 0.26 V. In the second cathodic scan, one peak corresponding to the reduction of the nitroso group to the hydroxylamine derivative appears at 0.17 V. Furthermore, in the second cathodic scan, the nitro reduction peaks disappear entirely, showing that all the trapped nitro compounds were reduced during the first scan. In subsequent cycles, only the redox couples of the nitroso/hydroxylamine derivatives were detected. This behaviour was similar in all pH ranges, as shown in Fig. 3 for pH values of 2, 7 and 10. In Fig. 3, the response obtained at each pH is compared. The voltammograms obtained show a more intense and defined signal at pH 2, which shifts to more negative potentials but decreases with increasing pH value. The voltammogram of the isolated NO/NHOH redox pair was recorded 5 min after reduction of the NSD nitro group using the same modified electrode (GCE/MWCNT/NSD). The decrease in current intensity between the first and second redox pairs is an index of how much NSD derivative is retained on the electrode. At pH 10, the NSD derivative has the lowest retention on the electrode, followed by pH 2 and finally pH 7. In Fig. 3, the voltammogram represented by the dotted line corresponds to the isolated nitroso/hydroxylamine redox pair, measured immediately after the first scan without removing the electrode from the cell. This indicates how much NSD is retained on the electrode in its NO or NHOH form. At pH 7, little loss of the NSD derivative of the electrode is observed. For this reason, the analytical signal measurements for the quantification of NSD were carried out at pH 7. Fig. 5 shows the plot of Ep *vs* pH for the reduction signal of the nitro group of NSD entrapped on GCE/MWCNT and measured in Britton-Robinson buffer solution. A linear dependence on pH was observed between pH 2 and pH 10 and was defined by the following equation: Ep (V) = −0.036 pH − 0.334 (r^2 = 0.99927).

3.3. Electrochemical determination of NSD.

Based on the results described above, an analytical method was proposed for the determination of NSD. Using the redox signal of the nitro group, a calibration plot was obtained between concentrations of 0.01 mM and 0.25 mM NSD (Fig. 6). Each point on the graph was measured in triplicate, and the linear plot was described by the following equation: Ip (μA) = 210.5C (mM) + 1.38 (r^2 = 0.99867).

The within-day and inter-day reproducibilities of the seven independent electrodes were considered adequate for a modified electrode, with coefficients of variation of 4.9% and 5.7%, respectively. Furthermore, the percentage recovery was 98.4% ± 5%.

The limit of detection (LOD) and the limit of quantification (LOQ) were calculated as LOD = 1.6 nM (S/N = 3) and LOQ = 5.5 nM (S/N = 10). An important parameter that affects the limit of detection (LOD) and the quantification limit (LOQ) is the immersion time in the test sample. In this work, a standard time of 10 sec was used for all measurements, but at longer immersion times, the electrode can encapsulate a greater amount of compound, thus improving the analytical parameters of the method.

The carbon nanotube-modified electrodes were tested with commercial tablets of NSD. The modified electrodes were immersed in the solution according to the procedure described above and transferred to a cell containing only Britton-Robinson buffer. The results for the NSD assay were found to be 97.5% ± 5.0% of the declared amount, and no interference of excipients was detected. Furthermore, the percentage found is in accordance with typical Pharmacopeia requirements for tablet assays (90.0–110.0% of the labelled amount) [37,38]. Table 1 compares the analytical parameters of this methodology with those obtained by other NSD analysis techniques. The values obtained in this research are in accordance with the detection and quantification limits reported by other authors, especially when carbon nanotubes have been used as electrode materials [12]. In comparison, our methodology stands out due to the encapsulation of the nitro compound in the nanotube network of the electrode. Each electrode was ready in 3 min, and the modification process with the nitro compounds was very fast. The modification time with NSD was 10 s.

4. Conclusions

It is concluded that the use of CNT prepared under the nitro compound encapsulation methodology is a useful, fast and sensitive tool for the determination of NSD. The methodology developed is simple and may compete with other more complex techniques that are generally used for the determination of NSD. The capacity of the electrodes to adsorb the analyte can be extended to other types of molecules with and without nitro groups that are of interest to analyse. Accordingly, the methodology described here can be extended to analyse the redox behaviour of the molecules encapsulated in the electrode and is highly recommended for compounds of low aqueous solubility, such as many drugs, including NSD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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