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Size effects of multi-walled carbon nanotubes on the electrochemical oxidation of propionic acid derivative drugs: Ibuprofen and naproxen

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ABSTRACT

The superior electrochemical activity of multi-walled carbon nanotubes (MWCNTs) of shorter dimensions towards the oxidation of propionic acid derivative drugs, namely ibuprofen (IBF) and naproxen (NPX), is presented. A glassy-carbon electrode was modified with MWCNTs of different sizes (diameter × length: 100–170 nm × 5–9 μm and 6–9 nm × 5 μm, corresponding to LD- and SD-MWCNTs, respectively, larger and shorter diameter). Cyclic voltammetry of the SD-MWCNT-modified electrode showed a 200–300 mV decrease in the overpotential of oxidation reactions of both drugs and an increase in current (2 to 3.5-fold) in comparison with the LD-MWCNT-modified and unmodified electrodes. Similarly, the amperometric determination of both drugs using the SD-MWCNT-modified electrode presented an increase in sensitivity in comparison with LD-MWCNT-modified electrode (2 to 2.8-fold). Improved performance of the SD-MWCNT-modified electrode was in agreement with electrochemical impedance spectroscopy measurements. These results indicate the higher electrocatalytic activity of SD-MWCNTs, which can be explained by the increased defect density revealed by Raman spectroscopic measurements. Additionally, we report the first amperometric method for IBF determination using the SD-MWCNT-modified electrode, with a linear range from 10 to 1000 μmol L^{-1}, detection limit of 1.9 μmol L^{-1}, precision of 4%, and accuracy attested by capillary electrophoresis analyses.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely consumed by population worldwide due to their analgesic, antipyretic, and anti-inflammatory properties. Based on their chemical structure, NSAIDs are classified and the propionic acid derivatives (or arylpropionic acids known as profens), such as ibuprofen and naproxen, are massively used in the world [1]. On the other hand, these medicines are being classified as new emerging contaminants because NSAIDs have been detected in natural waters and effluents, probably due to their improper disposal (as a byproduct of manufacturing processes or from unused or expired products) [2].

Some methods have been reported for the determination of ibuprofen (IBF) and naproxen (NPX) in pharmaceutical and biological samples, including chromatographic methods (HPLC, GC, HPTLC, TLC) [2–7], electrophoretic methods [3,8–12], spectrophotometry [13,14], spectrofluorimetry [15–17], and titrimetric methods with visual and potentiometric end-point detection [18–20]. Typically, these analytical methods require time-consuming and laborious sample treatments such as solvent extraction, liquid-liquid extractions, excipient precipitation, and sample clean up steps, which can increase irreproducibility. On the other hand, electroanalysis can be an interesting alternative technique because it is simple, fast, sensitive, and does not require laborious sample treatment steps. Electroanalytical methods have been reported for the determination of IBF and NPX. The electrochemical oxidation of IBF was investigated at a boron-doped diamond electrode (BDDE) after anodic treatment and its oxidation occurred at around +1.7 V vs. Ag/AgCl (saturated KCl) using square-wave voltammetry [21] and amperometric detection in a flow-injection analysis (FIA) system [22]. NPX was detected on unmodified platinum [23], BDDE [24], glassy-carbon electrodes [25], and on modified electrodes with dysprosium nanowires [26], carbon nanotubes (CNTs) [27,28] and the composite ZnO attached to CNTs [29].

CNTs have been widely used to produce improved electrochemical sensors due to their exceptional features [30]. Decrease in the overpotential of electrochemical oxidation reactions, increase in the electrode active surface area, and anti-fouling properties of electrodes are the main advantages reached after electrode modification with CNTs [31]. These properties were obtained for NPX detection reported in previous studies using CNTs [27–29]. However, to the best of our knowledge, there are no reports on the use of CNTs for the electrochemical sensing of IBF.

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The influence of dimensions of CNTs on the electrochemistry of phenolic compounds (including hydroquinone, *tert*-butylhydroquinone, catechol, dopamine, and bisphenol A) and hydrogen peroxide was investigated and all these reports concluded that CNTs of lower dimensions presented higher electrocatalytic activity [32–34], which were correlated with higher density of defects on the CNT structure measured by Raman spectroscopy [33,34]. On the other hand, CNTs of larger dimensions presented higher analytical sensitivity for the voltammetric determination of nitroimidazole derivatives [35].

This work investigates the effect of CNTs dimension on the electrochemistry of two propionic acid derivative drugs widely consumed by population, namely IBF and NPX. Glassy-carbon electrode (GCE) modified with multi-walled carbon nanotubes (MWCNTs) of different sizes, larger diameter MWCNTs (diameter × length: 100–170 nm × 5–9 μm, corresponding to LD-MWCNTs) and shorter diameter MWCNTs (diameter × length: 6–9 nm × 5 μm, corresponding to SD-MWCNTs), were investigated using cyclic voltammetry (static condition) and amperometry (hydrodynamic condition). This work also presents the first electroanalytical method for IBF determination in pharmaceutical formulations using a MWCNT-modified electrode coupled to a FIA system.

2. Experimental

2.1. Reagents and samples

Pure deionized water ($R \geq 18$ MΩ cm) obtained from a Millipore Direct-Q3 water purification system (Bedford, MA, USA) was used to prepare all aqueous solutions. Analytical grade phosphoric acid (85% m/v) was purchased from Reagen (Rio de Janeiro, Brazil), sodium hydroxide from Dinâmica (Diadema, Brazil), boric acid from QM (Cotia, Brazil), glacial acetic acid from Carlo Erba (Milan, Italy), 2-(cyclohexylamino) ethanesulfonic acid (CHES), triethanolamine (TEA), ibuprofen (IBF) and naproxen (NPX) from Sigma Aldrich (St. Louis, United States), and dimethylformamide from Vetec (Rio de Janeiro, Brazil). All reagents were used without further purification. Stock solutions of IBF and NPX were freshly prepared just before the experiments in electrolyte for electrochemical measurements and in water for capillary electrophoresis (CE) measurements (comparative method for IBF). The Britton-Robinson (BR) buffer solution was composed by a mixture of 0.1 mol L^{-1} acetic acid, boric acid, and phosphoric acid and its different pH values were adjusted with sodium hydroxide. A buffer solution (pH 9.1) containing 10 mmol L^{-1} CHES and 3.5 mmol L^{-1} TEA was used as the background electrolyte (BGE) in CE analyses. Pharmaceutical formulations (tablets and liquid sample) were obtained from local drug stores. Five tablets were powdered in a mortar and a weight correspondent to one tablet was dissolved in electrolyte (amperometric analysis) or in water (CE analysis).

Two raw multi-walled carbon nanotubes (MWCNTs) with different diameters were used in this work and were purchased from Sigma-Aldrich (Milwaukee, WI, USA). MWCNTs of smaller diameter (SD-MWCNT) present a relative purity >95% (wt.) and dimensions of 6–9 nm in outer diameter and 5 μm in length, and MWCNTs of larger diameter (LD-MWCNT) presented relative purity >90% (wt.) and dimensions of 110–170 nm in outer diameter and 5–9 μm in length. An amount of 1.0 g of raw MWCNTs was first treated with a 3:1 (*v*/*v*) mixture of concentrated H_2SO_4 and HNO_3 acids (1000 mL). This mixture was then sonicated for 3 h at 40 °C in an ultrasonic bath to introduce carboxylic acid groups on the MWCNT surface. After cooling to room temperature, the carboxylated MWCNTs were added dropwise to 3000 mL of cold deionized water and then vacuum-filtered through a 0.05 mm pore size filter paper. The filter medium material was then washed with deionized water until pH was neutral. The sample was then dried in a vacuum oven at 80 °C for 8 h [36].

2.2. Apparatus

All electrochemical measurements including cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and amperometry were performed using a μ-Autolab Type III (Eco Chemie, Utrecht, Netherlands). The working electrode was a multi-walled carbon nanotube (MWCNT) modified glassy-carbon disk (Ø = 1.6 mm, ALS, Japan), while counter and reference electrodes were a platinum wire and a miniaturized Ag/AgCl/saturated KCl electrode [37], respectively.

EIS measurements were performed using a 5/5 mmol L^{-1} $K_3Fe(CN)_6/K_4Fe(CN)_6$ solution containing 0.1 mol L^{-1} KCl and the frequency range was from 0.1 Hz to 30 kHz with a signal amplitude of 10 mV with 10 data points per frequency decade. The electron transfer resistance was obtained through the non-linear regression analysis of the semicircle portion of the Nyquist plot (Z_{im} vs. Z_{re}). Three replicate measurements were carried out for each experiment.

Scanning electron microscopy (SEM) measurements were carried out using a Mira field emission gun FEG-SEM (TESCAN, Brno Kohoutovice, Czech Republic) operated at 10 kV. The samples were dispersed in ethanol and drop-casted on silicon substrates.

A Renishaw Raman spectroscopy microscope (Gloucestershire, United Kingdom) with 1 mm resolution and using a 632.8 nm He—Ne laser with an incidence power of 2 mW was used to characterize the MWCNTs.

2.3. Working electrode preparation

The cleaning of the GCE was initially carried out mechanically on a felt-polishing pad using an alumina powder (0.3 μm) suspension. Further the GCE was copiously rinsed with deionized water and sonicated in ethanol for 5 min. The electrode was placed immediately in the electrochemical cell after polishing, if no modification with MWCNTs was performed.

Suspension of functionalized MWCNTs was prepared by adding 5 mg of MWCNTs to 5 mL of dimethylformamide and agitating the mixture using an ultrasonic bath for 30 min and an ultrasonic processor (130 W, Cole Palmer) for 5 min. In order to fabricate MWCNT-modified electrodes, this suspension was dropped (10 μL) on inverted GCE. The solvent was evaporated by exposure at 50 °C for 30 min. The resulting films of the modified GCE were clearly visible to naked eye. The modified GCE was rinsed with deionized water and placed in the cell. Cyclic voltammetric experiments in background electrolyte (0.0 to 1.0 V at 50 mV s^{-1}) were performed until reproducible scans. Typically, after five cycles the modified GCE produced reproducible measurements.

2.4. Electrochemical measurements

Cyclic voltammograms were recorded at 50 mV s^{-1} (except to the experiments in which scan rate was varied from 10 to 1000 mV s^{-1}). All electrochemical measurements were performed at room temperature and in the presence of dissolved oxygen.

Constant-potential amperometric measurements coupled to FIA was performed to obtain analytical characteristics for the determination of IBF and NPX under hydrodynamic conditions. A lab-made electrochemical wall-jet cell with three electrodes was used for FIA measurements [38]. A single-line flow system was employed using 1.0-mm (i.d.) polyethylene tubing. The injection of standard or sample solutions was carried out by filling a loop (polyethylene tubing) of variable volumes (from 100 to 300 μL) of a manual injector valve [38], which was connected to the single-line flow system. A syringe was used to fill the injection loop with sample or standard solutions by producing a negative pressure. The solutions were propelled by a peristaltic pump (Gilson). FIA parameters, including loop volume and flow rate, were optimized for IBF determinations in the pharmaceutical samples.