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# A highly improved method for sensitive determination of amitriptyline in pharmaceutical formulations using an unmodified carbon nanotube electrode in the presence of sulfuric acid



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## ABSTRACT

The present paper describes a novel, simple and reliable differential pulse voltammetric method for determining amitriptyline (AMT) in pharmaceutical formulations. It has been described for many authors that this antidepressant is electrochemically inactive at carbon electrodes. However, the procedure proposed herein consisted in electrochemically oxidizing AMT at an unmodified carbon nanotube paste electrode in the presence of 0.1 mol L<sup>-1</sup> sulfuric acid used as electrolyte. At such concentration, the acid facilitated the AMT electrooxidation through one-electron transfer at 1.33 V vs. Ag/AgCl, as observed by the augmentation of peak current. Concerning optimized conditions (modulation time 5 ms, scan rate 90 mV s<sup>-1</sup>, and pulse amplitude 120 mV) a linear calibration curve was constructed in the range of 0.0–30.0 μmol L<sup>-1</sup>, with a correlation coefficient of 0.9991 and a limit of detection of 1.61 μmol L<sup>-1</sup>. The procedure was successfully validated for intra- and inter-day precision and accuracy. Moreover, its feasibility was assessed through analysis of commercial pharmaceutical formulations and it has been compared to the UV–vis spectrophotometric method used as standard analytical technique recommended by the Brazilian Pharmacopoeia.

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## 1. Introduction

Amitriptyline (AMT) (Fig. 1) is a tricyclic antidepressant that possesses antipsychotic, sedative and analgesic properties. This drug can be used in the treatment of depression, child bedwetting and psychomotor disorders such as aggression, hyperkinetic states and agitation [1–3]. On the other hand, even at therapeutic doses, it may provoke collateral effects related to drowsiness, sedation, confusion, dry mouth and blurred vision, whereas its overdoses may result in conditions that affect heart rhythms and changes in blood pressure. Therefore, quality control of pharmaceutical

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formulations is important nowadays [4]. The majority of methods reported for AMT quantification have been carried out by means of high-performance liquid chromatography [5], spectrofluorimetry [6] and UV–vis spectrophotometry [7], which are usually time-consuming and expensive. Besides, these methods present low sensitivity (especially for absorption in the UV–visible region) and require sample pretreatment via organic solvent extraction. Thus, it is highly desirable to search alternative procedures. In this respect, electroanalytical methods can be an excellent choice. However, even considering low electroactivity at conventional electrodes based on noble metal surfaces, such as platinum or gold, even using glassy carbon, only a few approaches based on electrode surface modification have been proposed for AMT determination. One of them was conducted by Turk et al. [8], who electrodeposited poly(thiophene) and poly(carbazole) on the reticulated surface of a glassy carbon electrode to quantify AMT. According to these authors, the presence of electron-donor

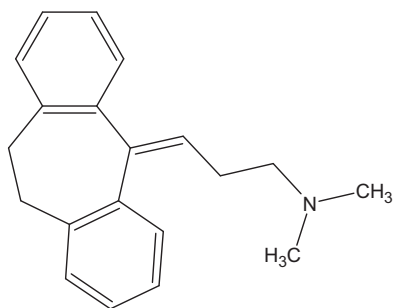


Fig. 1. Chemical structure of amitriptyline.

compounds that contain heteroatoms (e.g., sulfur (polythiophene) and nitrogen (polycarbazole)) enables the formation of radical cations which facilitate the electrooxidation of AMT and its voltammetric determination. In another study performed in a similar way, a carbon paste electrode modified with poly-(*N*-vinylimidazole) was developed [9]. Likewise, potentiometric measurements of AMT in a FIA system using an ion-selective electrode constructed with amitriptylinium phosphotungstate (Am-PTA) and amitriptylinium phosphomolybdate (Am-PMA) were carried out [10]. In another research, a carbon-polyurethane composite electrode (GPU) was employed to determine AMT by cyclic voltammetry [11]. However, in this study, the antidepressant was irreversibly oxidized and strongly adsorbed on the electrode surface with reagents and oxidation products. Another remark that should be pointed out relates on the fact that the majority of these electroanalytical methods have not been applied to real samples. Recently, our research group has developed a carbon paste electrode modified with DNA and inorganic matrix ( $\text{SiO}_2/\text{Al}_2\text{O}_3/\text{Nb}_2\text{O}_5$ ) for quantifying AMT in pharmaceutical formulations [12].

Considering the aforementioned, to the best of our knowledge, the development of electroanalytical methods for the AMT determination using unmodified (bare) carbon nanotubes paste electrodes in sulfuric acid solutions and their application to real samples have not been reported until now. Several reports have demonstrated the advantages of carbon nanotubes in the sensor preparation, such as electrocatalytic effect towards oxidation/reduction of many compounds, thus reducing the overpotential, insignificant surface fouling of CNT-based electrodes, high surface area and high sensitivity [13–16]. Despite these features the authors emphasize the improvements of carbon nanotubes performance in the presence of a suitable electrochemical mediator. A survey of literature shows that electrochemical sensors based on carbon nanotubes and carbon electrodes modified with electrochemical mediator for determining neurotransmitters, amino acids, vitamins and drugs in biological, environmental and pharmaceutical samples have been extensively developed [17–26]. Thus, in order to obtain an innovative, simple and facile method we have employed an unmodified carbon nanotube electrode for AMT determination in pharmaceutical formulation by using measures in sulfuric acid medium. It is worth emphasizing that depending upon the electrode nature, the AMT electrooxidation may take place through oxidation of alkylamine nitrogen atoms as a one-electron step leading to the formation of radical cations [27]. Moreover, taking into account that triethylamine radical cations may also be generated in sulfuric acid [28], it can be proven that the acid is able to improve the AMT electrooxidation. Furthermore, strong adsorption of sulfate ions on the electrode surface forming a negatively charged film may enhance the electrooxidation process of AMT positively charged in the acidic medium and decrease the over potential.

## 2. Experimental

### 2.1. Samples, solvents and reagents

Amitriptyline hydrochloride (99%; Sigma-Aldrich, St. Louis, MO, USA), sulfuric acid (95–97%; Merck, Darmstadt, Germany), orthophosphoric acid (85%; Merck), acetic acid ( $\geq 99.8\%$ ; Sigma-Aldrich, Steinheim, Germany), boric acid ( $\geq 99.5\%$ ; Sigma-Aldrich), sodium hydroxide (99%; Merck), hydrochloric acid (37%; Sigma-Aldrich), sodium sulfate ( $\geq 99\%$ ; Sigma-Aldrich), perchloric acid ( $\geq 69\%$ ; Sigma-Aldrich) and phosphate salt (99–102%; Merck) were dissolved in deionized water (resistivity  $18.2 \text{ M}\Omega \text{ cm}^{-1}$ ) from a Milli-Q purification system (Millipore, Billerica, MA, USA) to get their respective solutions and used without further purification. Multi-walled carbon nanotubes (MWCNTs) (93%, diameter 10–40 nm, and length 5–20  $\mu\text{m}$ ) were acquired from CNTsCo. Ltd. (Yeonsu-Gu, Incheon, South Korea), and mineral oil was supplied by Sigma-Aldrich. Graphite powder (purity 99.9%) was also purchased from Sigma-Aldrich, and black carbon (purity 99.5%) was obtained from Cabot Brasil Ind. Com. Ltda. (Paraiso, São Paulo, SP, Brazil). Pharmaceutical samples containing 25 mg AMT per tablet (Medley<sup>®</sup>, EMS<sup>®</sup>, Teuto<sup>®</sup>, Germed<sup>®</sup>, Eurofarma<sup>®</sup>) and 75 mg AMT per tablet (Amytril<sup>®</sup>) were bought at local drugstores. The inactive excipients used as possible interfering compounds magnesium stearate, talc, calcium phosphate, titanium dioxide, cellulose, lactose and silicon dioxide were supplied by local drugstores. A  $0.1 \text{ mol L}^{-1}$  phosphate solution was prepared by dissolving monobasic salt in  $1.0 \text{ mol L}^{-1} \text{HCl}$ , with further pH adjustment to the desired value. A  $0.1 \text{ mol L}^{-1}$  Britton–Robinson (BR) buffer solution was prepared from a mixture of acetic, orthophosphoric and boric acids dissolved in  $1.0 \text{ mol L}^{-1} \text{NaOH}$ , once more with further pH adjustment to the desired value. A  $0.1 \text{ mol L}^{-1}$  AMT stock solution was prepared from  $0.1 \text{ mol L}^{-1}$  sulfuric acid. All the solutions were stored at  $< 5^\circ \text{C}$  and in absence of light.

### 2.2. Apparatus

Electrochemical measurements were performed with an Autolab PGSTAT-101 potentiostat/galvanostat (Eco Chemie B.V., Utrecht, The Netherlands) controlled by means of a GPES 4.9 (General Purpose Electrochemical System) software package (Eco Chemie B.V.). A conventional three-electrode electrochemical cell containing a reference electrode ( $\text{Ag}/\text{AgCl}$ ,  $3.0 \text{ mol L}^{-1}$ ), an auxiliary electrode (spiral platinum wire) and a working electrode (carbon nanotube paste) was used. The accuracy of the proposed method was checked by an analysis of pharmaceutical formulations using a Lambda-25 A UV-vis spectrophotometer (Perkin Elmer Inc., Waltham, MA, USA) at 239 nm, with a quartz cell (optical path 1 cm). For in-situ FTIR experiments, a single-compartment glass cell fitted with a  $60^\circ$  prismatic  $\text{CaF}_2$  window in a thin electrolyte layer pattern was employed. FTIR spectra were recorded on a Nicolet Nexus 670 spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) equipped with an MCT detector.

A glassy carbon electrode (diameter 2.0 mm; Metrohm, Herisau, Switzerland) was also used as working electrode. It was carefully polished with a  $0.5\text{-}\mu\text{m}$  alumina slurry on a flat surface, rinsed thoroughly with deionized water, and then sonicated immediately before using in deionized water for 2 min. pH values of the samples were measured with an 826 pH mobile digital pH meter (Metrohm).

### 2.3. Preparation of carbon nanotube paste electrode

The composition of carbon nanotube paste electrode was based on our previous publication [29,30] using a MWCNTs/mineral oil ratio equal to 22:78% (w/w). This composition was found to be

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