Research Article
Electrochemical Sensor Based on Nanodiamonds and Manioc Starch for Detection of Tetracycline

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The use of nanostructured materials is already well-known as a powerful tool in the development of electrochemical sensors. Among several immobilization strategies of nanomaterials in the development of electrochemical sensors, the use of low-cost and environmentally friendly polymeric materials is highlighted. In this context, a new nanostructured biocomposite electrode is proposed as an electrochemical sensor for the analysis and determination of tetracycline. The composite electrode consists of a modified glassy carbon electrode (GCE) with a nanodiamond-based (ND) and manioc starch biofilm (MS), called ND-MS/GCE. The proposed sensor showed better electrochemical performance in the presence of tetracycline in comparison to the unmodified electrode, which was attributed to the increase in the electroactive surface area due to the presence of nanodiamonds. A linear dynamic range from \(5 \times 10^{-6}\) to \(1 \times 10^{-4}\) mol L\(^{-1}\) and a limit of detection of \(2 \times 10^{-6}\) mol L\(^{-1}\) were obtained for the proposed sensor. ND-MS/GCE exhibited high repeatability and reproducibility for successive measurements with a relative standard deviation (RSD) of 6.3% and 1.5%, respectively. The proposed electrode was successfully applied for the detection of tetracycline in different kinds of water samples, presenting recoveries ranging from 86 to 112%.

1. Introduction

In recent years, there has been a great development of new materials for electrochemical applications such as carbon nanomaterials [1–6] and metal nanoparticles [7–11]. The attractiveness of nanomaterials is due, among other characteristics, to the greater surface area and surface energy compared to the same materials on a macroscopic scale [12–14], which significantly increase mass transport and the sensitivity of electrochemical measures [15]. Among the nanomaterials of carbon, the nanodiamonds (NDs) have optical transparency, chemical inertness, great surface specificity, and high hardness. Due to its surface \(\pi\) bonds and the ability to produce stable dispersions in aqueous media [16–19], NDs have become an excellent tool for the development of sensors [20–24]. This fact is due to the conductivity and the nanometric scale of the material. An example is the work presented by Ramos et al. [23], in which the presence of NDs increased the conductivity and surface area of the base electrode was observed, allowing a more sensitive determination of serotonin. Another characteristic of NDs is its low toxicity, being used in medicines and treatments for the most varied types of cancer [25–28]. The attractive characteristic of the material can allow its use in the development of modified electrodes for the determination of other substances with environmental concern.

The modification of bare electrodes with nanomaterials can be a challenge because often there are no anchoring sites.
Maybe, one of the most common strategies for immobilizing nanoparticles on base-electrodes is by the formation of a composite film based on a polymer and a nanoparticulate material, in general polymeric materials [15, 29, 30]. The use of films, usually polymeric films, allows a good distribution and incorporation of conductive material or other modifiers onto the base electrode. In the work developed by Huang et al. [30], the incorporation of carbon nanotubes and horseradish peroxidase enzyme was made on a carbon-based screen-printed electrode surface, which was only possible using an amphiphilic copolymer. However, there are some important conditions that these materials should present to be used as a modifier of electrodes, for example, low volatility, low solubility in water, and selective miscibility in organic compounds [31]. Also, nowadays, there is a great concern about the decrease in the use of sustainable and environmentally friendly organic compounds [32]. Therefore, researchers have used polymeric films, such as biological origin, for example, biofilm based on manioc starch [33]. Manioc is a tuberous plant widely used in Brazilian cuisine. The starch present in cassava (manioc starch (MS)) consists of a mixture of two polysaccharides, amylpectin and amylose, which are responsible for the gelatinization properties that control the formation of the film [34–37]. Some works with manioc starch film have shown promising results for anchoring carbon nanomaterials [38, 39]. The result is due to the easy dispersion of manioc starch in a suitable solvent obtaining a homogeneous mixing of the polymer and the conductive material, as observed in the work developed by Oliveira et al. [40]. In this work, a small amount of manioc starch (500:1—modifier:manioc starch) allowed the immobilization of nitrogen-doped titanium dioxide nanoparticles, which allowed the determination of toxic species in water, such as pesticide and hormone. This evidence allows increasing the possibility of these electrodes using biopolymers to determine other emerging pollutants in water, including antibiotics, for example, tetracyclines.

The discovery of the first member of the tetracycline family was carried out in 1945, by Benjamin Duggar. This drug is part of a class of antibiotics that acts against a wide variety of microorganisms, from gram-positive to gram-negative bacteria, being used both in veterinary medicine and in the treatment of human diseases as well as disease prophylaxis [41]. Chlortetracycline or tetracycline (Tc), as shown in Figure 1, is a product of the natural fermentation of a soil bacterium, Streptomyces aureofaciens, which caused a rush in research, and it is used as new tetracyclines with great success. Tc has low toxicity and low cost, which facilitates its indiscriminate use [41, 42].

The constant use of this drug promotes the increase of this substance in the sewerage network since there is no control over its discard. In spite of its low toxicity, the bioaccumulation effect can lead to an excess of toxic substances in the environment [43]. Some studies associate this drug, or its degradation products, to the liver and pancreatic dysfunctions [44, 45]. Thus, its determination and monitoring are crucial.

Several works in the literature have reported the determination of Tc by UV visible spectrophotometry [46–49], high-performance liquid chromatography [50–52], and high-performance liquid chromatography-mass spectrometry [53–55]. Many of these methods are accurate; however, they have some disadvantages, including complex pretreatment processes and high detection costs, while the electroanalytical determinations have simple equipment configuration and operation, high sensitivity, fast analysis, and low cost [56, 57]. These characteristics can be observed in the work developed by Baccarin et al. [56], which demonstrated the simple construction of a composite electrode based on low-cost nanomaterials and chitosan in the simultaneous determination of dopamine and paracetamol in urine samples. Other works in the literature also have highlighted the electrochemical techniques as a powerful tool for the development or proposals of analytical methodologies for monitoring and quality control of drugs [58–60]. In these works, the authors highlight the advantages of these techniques, such as operational simplicity, low cost, good sensitivity, and repeatability between measurements.

The use of environmentally friendly materials as manioc starch and low-toxic nanomaterials, such as NDs in the development of sensors together with electrochemical techniques, can be a powerful tool as an alternative to the conventional methods in the quality control and monitoring of antibiotics. Therefore, this work is aimed at proposing an alternative methodology for the determination of Tc in natural water, tap water, and pharmaceutical samples by using a thin biofilm based on NDs and MS on glassy carbon electrode (GCE).

2. Materials and Methods

2.1. Reagents and Solutions. The ND powder (<10 nm particle size) and Tc standard were purchased from Sigma-Aldrich (Merck group, Saint Louis, Missouri, EUA). The 1.0 × 10−2 mol L−1 Tc stock solution was prepared in absolute ethanol. The manioc starch (MS) was purchased at a local supermarket from Yoki® (São Bernardo do Campo, Brazil). All other chemical reagents were obtained from Sigma-Aldrich and/or Honeywell Fluka™ (Charlotte, North Carolina, US), in analytical grade. The solutions were prepared in Millipore Milli-Q pure water (resistivity ≥ 18.0 MΩ cm) (Merck group, Burlington, Massachusetts, EUA).
2.2. Equipment. The structural analyses of the samples were performed using scanning electron microscope JEOL LV-JSM 6360 with acceleration voltages between 3 and 10 keV. For electrochemical analyzes, potentiostat/galvanostat Metrohm AutoLab PGSTAT 101 was used managed by Nova 2.0 software. A conventional system of three electrodes and an electrochemical cell of 10 mL were used. Glass carbon electrode was used as a working electrode (GCE ∅ 3 mm), modified with a film from the dispersion of NDs in MS acid solution, called ND-MS/GCE; Ag|AgCl (3.0 mol L\(^{-1}\)) electrode was used as a working electrode (GCE ∅ 3 mm), modified with a film from the dispersion of NDs in MS acid solution, called ND-MS/GCE; Ag|AgCl (3.0 mol L\(^{-1}\)) as a reference electrode; and wire of platinum as a counter-electrode (Pt).

2.3. Preparation of ND-MS Dispersion and Sensor Fabrication. MS dispersion was prepared in a proportion of 1.0 g of powdered manioc starch to 100 mL of 5% acetic acid solution. The mixture was left under stirring at a temperature of 85°C for 2 hours until complete homogenization and a whitish transparent liquid was obtained. The resulting dispersion was stored under refrigeration. Then, 1.0 mg of NDs was added in 1.0 mL of MS, in which it remained in constant magnetic stirring for 2 hours, until complete dispersion homogenization.

GCE was carefully polished with activated alumina, 1:1 proportion (v/v), for 5 min on a piece of clean cotton fabric, and rinsed thoroughly with ultrapure water. Then, 5.0 μL of that dispersion was dropped on the GCE surface, and the solvent was evaporated at 25°C for 2 h. The ND-MS/GCE was used to detect Tc in natural water, tap water samples, and pharmaceutical products. The steps are shown in Figure 2.

2.4. Electroanalytical Procedure. The ND-MS/GCE was electrochemically characterized using an equimolar mixture of 1.0 × 10\(^{-3}\) mol L\(^{-1}\) potassium ferricyanide (K\(_3\)[Fe(CN)\(_6\)]\(_{3-}\)) and potassium ferrocyanide (K\(_3\)[Fe(CN)\(_6\)]\(_{4-}\)) in 0.1 mol L\(^{-1}\) KCl by cyclic voltammetry (CV). The pH effect of the supporting electrolyte was evaluated using phosphate buffer (0.2 mol L\(^{-1}\)) in different pH (5.6 until 8.0) by differential pulse voltammetry (DPV). Then, each parameter of the DPV technique, scan rate, modulation amplitude, and modulation time were evaluated (5 mV s\(^{-1}\)-25 mV s\(^{-1}\), 10 mV-100 mV, and 10 ms–70 ms, respectively).

Analytical curves were constructed by the addition of different concentrations of the Tc standard solutions. The detection of limit (LOD) was calculated as three times the standard deviation of the analytical curve by the sensitivity of the analytical curve [61]. The Tc concentration of each sample was analyzed in triplicate using the standard addition method.

2.5. Tetracycline Determination. The proposed electrode was evaluated to determine tetracycline in water samples: water from artesian wells of Federal University of São Carlos campus Araras (UFSCar-CCA) and natural water samples as collected from the Monjolinho River, in São Carlos at the Federal University of São Carlos (GPS, with coordinates: 21859°08.88”S 47852’43.21”W) being used without previous treatment. Samples were prepared by diluting in 20% absolute ethyl alcohol and enriched with Tc.

The pharmaceutical sample used was 500 mg tetracycline hydrochloride per capsule (Medquímica Pharmaceutical Industry, Juiz de Fora, Brazil). The preparation of the solution was carried out by diluting it in milli-Q water in 100 mL. After preparing this solution, filtration was carried out to remove insoluble substances.

The determination was performed by DPV measurements (n = 3) in different levels of Tc and extrapolation of the current intensity values in the analytical curve equation. It must be emphasized that all electrochemical measurements the error bars were obtained by the relative standard deviation (RSD), in which the RSD was calculated from the faradaic peak intensities (n = 3).

3. Results and Discussion

3.1. Morphological Characterization of the Film ND-MS. The morphological and structural characterizations of the film were made using the scanning electron microscopy (SEM) technique. Through SEM, the presence, stability, and distribution of MS in the film were investigated. Figure 3(a) shows a good homogeneity throughout the length of the MS film, presenting itself as a partially smooth surface, showing good solubilization and gelatization of the MS in the presence of the acid. In Figure 3(b), a good dispersion with NDs is observed with a greater roughness providing more electroactive surface areas and possibly better electrochemical performance.

Also, Figure 3(b) shows the presence of granules of the nanomaterial distributed throughout its extension of manioc starch film, indicating a good interaction between the dispersions of the NDs with the MS. It is possible to observe a morphological difference between MS film and ND-MS film...
images and the distribution of the NDs throughout the surface, which helps to increase the electroactive area surface and the analytical signal.

The electroactive area was estimated for GCE and ND-MS/GCE, from Figure 4, using different scan rate (50 to 500 mV s−1), in 0.1 mol L−1 KCl and 1.0 × 10−3 mol L−1 of an equimolar mixture of [Fe(CN)6]3− and [Fe(CN)6]4−, respectively, using the Randles–Sevčík equation:

\[ I_p = 2.69 \times 10^5 A D^{1/2} n^{1/2} v^{1/2} C, \]

where \( I_p \) is the anodic or cathodic peak current, \( n \) is the number of electrons transferred (\( n = 1 \)), \( A \) is the electroactive surface area, \( D \) is the diffusion coefficient (\( D = 7.6 \times 10^{-6} \text{cm}^2\text{s}^{-1} \) for \( K_3[Fe(CN)_6] \) in 0.1 mol L−1 KCl solution, and \( C \) is the redox concentration [Fe(CN)6]3− (1.0 × 10−6 mol cm−3). The area obtained for the ND-MS/GC was 0.075 cm2, and for the GCE, 0.061 cm2, showing an increase of 23% in the electroactive area with the use of the ND-MS. Also, the production batch can influence the characteristics of the nanodiamonds, which can be more or less conductive.

Figure 4(c) shows a comparison of cyclic voltammograms between the GCE and ND-MS/GCE electrodes in the presence of 1.0 × 10−3 mol L−1 [Fe(CN)6]3−/4− and 0.1 mol L−1 KCl solution, at a scan rate of 50 mV s−1. The difference of peak potentials (ΔEp) for the ND-MS/GCE electrode was 203 mV while for the GCE it was 403 mV, showing an improvement in reversibility for the redox pair for the ND-MS. These results indicate that the GCE–NDs exhibit remarkably better electrochemical performance than the GCE.

3.2. Electrochemical Response of Tetracycline. The cyclic voltammetry technique was tested using GCE and ND-MS/GCE in the presence of 5.0 µmol L−1 Tc with a scan rate of 5 mV s−1. Figure 5 presents the cyclic voltammograms for the GCE and ND-MS/GCE electrodes for comparison purposes, and an anodic peak at 0.75 V vs. Ag/AgCl (3.0 mol L−1 KCl) is observed for both. This suggests that the insertion of the nanomaterial improves the electronic transfer of the system and the electrochemical response of the analyte, and these results are in good agreement with the literature [62, 63]. Note that the current responses on the GCE and ND-MS/GCE were 0.37 µA and 1.96 µA, respectively. The current for Tc oxidation using ND-MS/GCE increases five times in comparison to GCE. These results indicate that the ND-MS/GCE shows better performance than the GCE in the electrochemical detection of Tc. On the other hand, this redox process is not so clear as the same measurement performed by differential pulse voltammetry (Figure 5(b)). Therefore, the development of an analytical methodology for Tc determination was performed by DPV.

3.3. Effect of pH of Support Electrolyte. Figure 6 shows the differential pulse voltammograms in the presence of 5.0 × 10−3 mol L−1 Tc at different pH values in 0.2 mol L−1 phosphate buffer.

In Figure 6, it can be observed that an increase in the anodic current when pH is changed from 5.6 to 6.3. Above 6.3, there is a decrease in the peak current value; hence, the pH 6.3 was selected for analytical evaluation of Tc determination. Regarding the effect of pH with Ep, there is a linear relationship between these quantities; this dependence on Ep with pH indicates the number of protons involved in the Tc oxidation reaction. A species distribution diagram (Figure S1A) was constructed from tetracycline pKa values (3.30, 7.68, and 9.69) [64] with four ionization equilibria and five different species (\( H_2Tc^{+}, H_3Tc\), \( H_4Tc\), \( HTc^{2−}\), and \( Tc^{3−}\)). The diagram has shown the predominance of the \( H_3Tc \) species in the pH range evaluated, as shown in Figure S1B. This pH range was chosen based on other works that realized the electrochemical determination of tetracycline [65–67].

In Figure 6(b), the dependence of Ep as a function of the pH value is observed. The relationship between the number of protons and electrons is possible to determine by the Nernst equation:

\[ Ep = E^0 - 0.0592 \left( \frac{N_m}{n} \right) pH, \]
Figure 4: Cyclic voltammograms recorded at different scan rates (50–400 mV s⁻¹) for 1.0 × 10⁻³ mol L⁻¹ [Fe(CN)₆]⁢⁢₃⁻/⁴⁻ in 0.1 mol L⁻¹ KCl solution (n = 3) using (a) GCE and (b) ND-MS/GCE. Inset: correlation curve between \( I_{pa} \) and \( \nu^{1/2} \). (c) Comparison between ND-MS/GCE (black) and GCE (red) at a scan rate of 50 mV s⁻¹.

Figure 5: (a) Cyclic voltammograms of GCE (black) and ND-MS/GCE (red) in the presence of 0.2 mol L⁻¹ phosphate buffer (pH 7.0) and 5.0 μmol L⁻¹ Tc at a scan rate 50 mV s⁻¹; (b) differential pulse voltammogram baseline-corrected for ND-MS/GCE in the presence of 5.0 μmol L⁻¹ Tc and 0.2 mol L⁻¹ phosphate buffer at pH 7.0. Conditions: \( \nu = 5 \) mV s⁻¹; \( a = 90 \) mV, and \( t = 30 \) ms.
where $E^0$ is the potential standard, $n_{H^+}$ is the number of protons, and $n$ is the number of electrons transferred in Tc oxidation. The slope value obtained of the linear adjustment of the oxidation potential and pH was 0.057 V per pH, which is close to the theoretical value (0.059 V per pH). This value is experimental indicating that the number of protons is equal to the number of electrons transferred. In similar works of Masawat and Slater [68] and Kazemifard and Moore [69] reported that electrochemical oxidation occurs involving one electron and one proton (Figure 7) in the phenol group in position C-10. It can be seen, in Figure 6(a), that at pH values greater than 7.0 the appearance of a second oxidation peak refers to the dimethylamine group at position C-4.

3.4. DPV Determination of Tetracycline. Tc determination using ND-MS/GCE was performed using the DPV technique. The main parameters were selected and studied to obtain the best voltammetric response for Tc determination. DPV parameters were evaluated in the following ranges: $5 \text{ mV s}^{-1} \leq \nu \leq 25 \text{ mV s}^{-1}$, $10 \text{ mV} \leq a \leq 100 \text{ mV}$, and $10 \text{ ms} \leq t \leq 70 \text{ ms}$. From this, the optimal values were $\nu = 5 \text{ mV s}^{-1}$, $a = 90 \text{ mV}$, and $t = 30 \text{ ms}$, using 0.2 mol L$^{-1}$ phosphate buffer pH 6.3.

The analytical curve for Tc was constructed using the best voltammetric conditions. The differential pulse voltammograms were recorded in the presence of different Tc concentrations (Figure 8), and the analytical curve (insert in Figure 8) was linear ($R^2 = 0.995$) in linear detection range (LDR) from $5.0 \times 10^{-6} \text{ mol L}^{-1}$ to $1.8 \times 10^{-4} \text{ mol L}^{-1}$ and equation of the line formed by $I_p (\mu A) = 0.0076 + 0.0084 \times 10^{-6} C_{\text{Tc}} ($mol L$^{-1}$), and the LOD obtained was $2.0 \times 10^{-6} \text{ mol L}^{-1}$ (LOD = 3 times the standard deviation of the analytical curve/sensitivity of the analytical curve) [70].
3.5. Determination of Tetracycline in Different Samples. The ND-MS/GCE sensor was applied for the determination of Tc in natural waters, water, and pharmaceutical samples. Thus, for this analysis, the addition and recovery method was used. Aliquots of the samples of natural water fortified (added) with Tc were added to the supporting electrolyte solution (phosphate buffer 0.2 mol L\(^{-1}\), pH = 6.3). These measurements were performed and calculated, and the results achieved are reported in Tables 2 and 3.

It has been observed that the recoveries varied between 86% and 112%, which indicates there was no significant interference from the matrix of the natural water, distribution waters, and pharmaceutical samples in the determination of Tc, evidencing the selectivity of the electroanalytical method. For the determination of the pharmaceutical sample, the ND-MS/GCE sensor recovered 108% of 500 mg tetracycline hydrochloride per capsule, indicating 540 mg of the active compound.

Table 1: Comparison of ND-MS/GCE with other modified electrodes for the determination of Tc.

| Electrode                | Method     | LDR (µmol L\(^{-1}\)) | LOD (µmol L\(^{-1}\)) | Ref.   |
|--------------------------|------------|------------------------|------------------------|--------|
| GR-L-Cys/GCE             | DPV        | 8–140                  | 0.12                   | [71]   |
| MWCNT-COOH-GO/CPE        | AdSDPV     | 20–310                 | 0.36                   | [72]   |
| ERGO-SPE                 | AdTDPV     | 20–80                  | 12                     | [73]   |
| GPE                      | DPV        | 4–22                   | 2.6                    | [74]   |
| Electrodeposited MWCNT on gold-coated GCE | DPV        | 11–320                 | 0.094                  | [75]   |
| ND-MS/GCE                | DPV        | 5–180                  | 2.0                    | *      |

*Present work. GR-L-Cys/GCE: Graphene-L-cysteine/glassy carbon; MWCNT-COOH-GO/CPE: multiwall carbon nanotube-graphene oxide/carbon paste electrode; ERGO-SPE: electrochemically reduced graphene oxide/screen-printed electrodes; GPE: graphite polyurethane composite electrode; AdSDPV: adsorptive stripping differential pulse voltammetry; AdTDPV: adsorptive transfer stripping differential pulse voltammetry.

Table 2: Results using the proposed method for the determination of Tc in three concentration levels (A, B, and C) for artesian wells water (UFSCar-CCA).

| Sample | Tetracycline (mol L\(^{-1}\)) | Recovery (%) |
|--------|-----------------------------|--------------|
|        | Added | Found     |              |
| A      | 5.9 × 10\(^{-2}\) | 5.6 × 10\(^{-2}\) | 95           |
| B      | 1.2 × 10\(^{-4}\) | 1.3 × 10\(^{-4}\) | 112          |
| C      | 1.8 × 10\(^{-4}\) | 1.4 × 10\(^{-4}\) | 94           |

Table 3: Results using the proposed method for the determination of Tc in natural waters of the Monjolinho River, in São Carlos at the Federal University of São Carlos.

| Sample | Tetracycline (mol L\(^{-1}\)) | Recovery (%) |
|--------|-----------------------------|--------------|
|        | Added | Found     |              |
| A      | 8.9 × 10\(^{-3}\) | 1.0 × 10\(^{-4}\) | 112          |
| B      | 1.2 × 10\(^{-4}\) | 1.2 × 10\(^{-4}\) | 100          |
| C      | 1.8 × 10\(^{-4}\) | 1.6 × 10\(^{-4}\) | 86           |

Repeatability (intraday) and reproducibility (n = 4) tests were performed by using the proposed sensor, in the presence of 5.0 µmol L\(^{-1}\) Tc. For the repeatability study, 10 consecutive measurements were performed with the ND-MS/GCE in the presence of Tc. For reproducibility, four GCE electrodes were modified with ND-MS and each was measured in the presence of the analyte. ND-MS/GCE exhibited relative standard deviation (RSD), for repeatability and reproducibility of 6.3% and 1.5%, respectively.

To evaluate the performance of the results obtained by the proposed method, the proposed sensor was compared with those already reported in the literature (Table 1). The ND-MS/GCE showed LDR similar or broader than most electrodes shown in Table 1. The ND-MS/GCE sensor provided a wide LDR and a low LOD at a relatively low cost.

4. Conclusion

The manioc starch allowed the incorporation of diamond nanoparticles on the glassy carbon electrode with high homogeneity and stability of the composite biofilm. The proposed electrode was simple to prepare with low cost and presented a better performance in comparison with the unmodified electrode. This better performance was due to the greater surface area and greater sensitivity of the electrode proposed by the presence of the nanoparticulate biofilm. Therefore, the electrode modified with NDs and MS has shown very promising results in the electrochemical sensing of Tc. Given this perspective, the ND-MS/GCE sensor was proved to be sensitive and suitable for analysis in the determination of Tc in the natural waters, distribution waters, and pharmaceutical applications in electrochemical applications.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

There are no conflicts of interest to declare.

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Supplementary Materials

Figure S1: (A) species distribution diagrams for the Tc for different pH values; (B) molecular structure of H\textsubscript{2}Tc.

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