Original Article

Development of a microcomposite with single-walled carbon nanotubes and Nd$_2$O$_3$ for determination of paracetamol in pharmaceutical dosage by adsorptive voltammetry

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**A B S T R A C T**

This study presents for the first time a new composite of carbon paste (CP), single-walled carbon nanotubes (SWCNTs) and Nd$_2$O$_3$ ($\text{NdOX}$). This versatile composite ($\text{NdOX}$-SWCNT/CPE) was applied to the oxidation of paracetamol (PCM). The newly formed surface was characterized by scanning electron microscopy (SEM), electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV). The results showed greater conductivity and a higher surface area for the composite than those of the carbon paste alone. Moreover, the anodic peak currents for PCM increased from 1.6 to 3.6 $\mu$A with CPE and $\text{NdOX}$-SWCNT/CPE, indicating an increase of nearly 51.0% for the anodic peak current. On the other hand, the anodic peak potentials shifted from 0.67 to 0.57 V. The detection limits were 0.05 mol/L with $\text{NdOX}$-SWCNT/CPE and 0.50 mol/L with SWCNT/CPE. The relative standard deviations (RSDs) were 1.5% ($n = 7$). The accuracy and interference of the methods were evaluated with a urine chemistry control spiked with known quantities of PCM, uric acid, dopamine, ascorbic acid, caffeine, acetylsalicylic acid, tartrazine, sunset yellow, allure red, rutin, morin and metal ions. Finally, the novelty and usefulness of the composite were evaluated to quantify PCM in pharmaceutical dosage forms such as tablets, powders and syrups for children.

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**1. Introduction**

N-(4-Hydroxyphenyl) acetamide is called paracetamol (PCM) or acetaminophen; it is an analgesic for pain, known as a nonsteroidal anti-inflammatory drug (NSAID) [1]. The use of PCM is safe, but there are some reports that indicate that it may be slightly harmful to the liver and kidneys, especially regarding the biokinetics, pharmacodynamics, and structural modification of PCM [2,3]. Thus, being one of the most used drugs, it is necessary to develop new rapid, selective and sensitive methodologies that allow the detection of PCM due to the extensive quality controls in the pharmaceutical industry. The most commonly used techniques to detect PCM have been spectrophotometry [4,5], high-performance liquid chromatography (HPLC) with a UV–Vis detector [6–8], HPLC with GC-MS [9,10], HPLC NMR-MS [11] and HPLC with a fluorescence detector [12].

In the 1990s, Iijima reported for the first time carbon structures that are known as carbon nanotubes [13], which have shown great application potential for electrode modification due to their structural properties, such as high conductivity and biocompatibility [14,15]. Cernat et al. [16] have recently reported that the nanomaterials most commonly used to detect PCM are carbon nanotubes, which are even more commonly used than materials such as graphene. The advantage of using carbon nanotubes in the development of electrochemical sensors is due to a decrease in overpotentials, an increase in the active surface area, and improved charge transfer at the analyte-substrate electrode interface [17]. In addition, CNTs combined with other materials, such as pyrolytic graphite [18], graphene nanosheets [19–21], carbonceramics [22], polyaniline [23], ethynylferrocene [24], alumina [25], and thionine [26], have been applied in the detection of PCM with limits of detection in the range of 0.12–0.01 mol/L. These reports indicate that electroanalytical techniques are as sensitive as the conventional techniques mentioned above but with the advantage of being less expensive and easier to apply in...
real samples. On the other hand, nanoparticles of metals such as Zr [27], Ni [28,29], Au-In [30], Ti [31], Bi [32] and Ag-Pd [33] without CNTs have been used in the modification of electrodes to detect PCM and biological substances with detection limits in the range of 7.8–0.18 μmol/L. These reports show that electrodes that include CNTs in their preparation are more sensitive. There are few reports that use CNTs combined with metals for the detection of PCM. One of these reports used Ni(NO₃)₂ with ethynylferrocene and observed a detection limit of 0.50 μmol/L.

Neodymium has rarely been used in electrode modification. The few available reports show that the element has been used for the simultaneous detection of dopamine and ascorbic acid on a glassy carbon electrode [34] and the detection of rutin with CNTs on glassy carbon [35]. These reports provide evidence of the ability of neodymium to improve the conductivity and increase the surface area of an electrode. The aim and novelty of this work is to take advantage of the conductivity and bioaffinity capabilities of CNTs and Nd to develop a sensor with similar properties of selectivity, sensitivity and stability as those in previous reports.

2. Materials and methods

2.1. Instruments and electrodes

Square-wave stripping voltamograms and cyclic voltamograms were obtained using a DropSens μStat400 potentiostat (Oviedo, Spain). Electrochemical impedance spectroscopy (EIS) was performed with a VersaSTAT 3 potentiostat/galvanostat from Princeton Applied Research (Oak Ridge, TN, USA). Scanning electron microscopy (SEM) was performed using a JEOL model JSM 6490-LV (Tokyo, Japan) with a secondary electron detector.

A system with three electrodes was used: a carbon paste working electrode (Sigma-Aldrich, Germany) supported inside a PVC cylinder with a copper wire as the electrical contact, a reference electrode of Ag/AgCl saturated with KCl (3 mol/L), a platinum wire as the auxiliary electrode and a magnetic stir bar formed the electrochemical cell. pH measurements were made with an Orion–430 digital pH/mV meter equipped with a combined pH glass electrode.

2.2. Chemicals

Type A water (ultrapure) was obtained from a Wasselab Purifier System (Spain). Ethanol, phosphoric acid, NaH₂PO₄ and Na₂HPO₄ were obtained from Merck (Germany). PCM, K₃Fe(CN)₆, SWCNTs (0.78 nm) and Nd₂O₃ were obtained from Sigma-Aldrich (Germany). Electrolyte solutions were prepared in a pH range from 2.0 to 7.0 with 0.010 mol/L phosphoric acid, sodium phosphate and disodium phosphate solutions.

2.3. Preparation of modified carbon paste electrodes

The CPE without Nd₂O₃ (NdOX) and SWCNT was prepared with 50.0 mg of graphite powder and 30 μL of paraffin oil. The SWCNT/CPE were prepared according to the following procedure: 2.0 mg of SWCNTs were mixed uniformly with 50.0 mg of graphite powder and 30 μL of paraffin oil. The NdOX-SWCNT/CPE was prepared with Nd₂O₃ between 2.0 and 5.0 mg and 2.0 mg of SWCNTs; this composite was mixed uniformly with 0.050 g of graphite powder and 30 μL of paraffin oil. Then, each mixture was pressed into a PVC cavity until contact was made with a copper wire as the electrical contact. The surfaces of the electrodes were polished with filter paper until the surfaces were smooth. It was possible to obtain three fresh surfaces with each electrode by removing the excess material from the surface and repolishing. The optimal amount of NdOX and SWCNT was 2.0 mg with 50.0 mg of CP. The electrodes were stored in dry state at room temperature.

2.4. Sample preparation

Pharmaceutical dosages of PCM in the form of tablets, powders and syrup were obtained from a pharmacy in Ibague City (Colombia). The tablets and powder samples were weighed and crushed in a mortar and then diluted with 100 mL of ultrapure water, and the syrup sample was diluted 10-fold. Before each analysis, no pretreatment as filtration to eliminate possible interference was necessary. For validation study, 5.0 mL of urine chemistry control from Bio-Rad was spiked with known amounts of PCM (9.20–27.5 μmol/L).

2.5. Measurement procedures

2.5.1. Stripping and cyclic voltammetry measurements

To the electrochemical cell, 9.5 mL of type A water (ultrapure), 0.5 mL of PBS (0.01 mol/L) and 50.0 μL of PCM (4.5 mmol/L) were added. Cyclic voltammograms were recorded from –0.4 to 1.2 V. Each voltammogram reading was repeated three times. Square-wave stripping voltammetry (SWV) was applied to the electrochemical cell containing 1.0–20.0 μL of 0.45 mmol/L PCM at 0.0 V for 30.0 s using a frequency of 10 Hz and a pulse amplitude of 50.0 mV. Each voltammogram reading was repeated three times.

2.5.2. Electrochemical impedance spectroscopy (EIS)

EIS measurements were performed at the open-circuit potential (OCP) using a perturbation amplitude of 10 mV and a frequency range between 10.0 kHz and 0.10 Hz. The tested electrolyte was 10.0 mmol/L K₃Fe(CN)₆ in 10.0 mmol/L KCl.

2.5.3. Scanning electron microscopy (SEM)

SEM was performed using a JEOL model JSM 6490-LV with a secondary electron detector.

3. Results and discussion

3.1. Paracetamol activity on CPE, SWCNT/CPE and NdOX-SWCNT/CPE

The electrochemical redox behavior of PCM involves the deprotonation of the phenol group in the molecule in a quasi-reversible reaction [16]. Fig. 1A shows the cyclic voltammograms of 22.0 μmol/L PCM with the CPE (dashed line), SWCNT/CPE (dotted line) and NdOX-SWCNT/CPE (solid line) electrodes, and Fig. 1B shows the square-wave voltammograms of 1.0 μmol/L PCM with the SWCNT/CPE and NdOX-SWCNT/CPE electrodes in PBS at pH 3.2. The anodic peak currents for PCM increased from 1.6 to 3.6 μA with CPE and NdOX-SWCNT/CPE, indicating an increase of nearly 51.0% for the anodic peak current. On the other hand, the anodic peak potentials shifted from 0.67 to 0.57 V. The results showed that the anodic and cathodic peak currents were increased when the surface of the electrodes was modified and that the potential moved to less positive values. The NdOX-SWCNT/CPE presented the highest anodic and cathodic peak currents, indicating that the surface of this electrode showed the highest activity towards the oxidation of PCM. Moreover, AE decreased from 0.24 to 0.06 V. Therefore, the NdOX-SWCNT/CPE allowed a more reversible system than the unmodified CPE. It is possible that a considerable increase in the surface area and the high conductivity of the surface with Nd₂O₃ and SWCNTs contributed to the electrocatalytic performance of the electrode in the redox reaction with PCM as in previous reports with Nd₂O₃ with chitosan for detected dopamine and ascorbic acid [34]. By SWV (Fig. 1B), similar results were
observed using the dual composite, showing the highest activity for PCM oxidation, where the anodic peak current increased nearly 51.0% with the NdOX-SWCNT/CPE compared to that of the CPE. Similar results were reported in the detection of rutin, dopamine and ascorbic acid with Nd2O3 and SWCNTs on glassy carbon electrodes [34,35]. Based on the SWV results, the two composites that showed the greatest redox activity with PCM were the SWCNT/CPE and NdOX-SWCNT/CPE. Therefore, the morphologies and electrochemical properties of their surfaces were studied with SEM, EIS and CV. Regarding the potential (V) observed for the oxidation of PCM using the electrodes with nanomaterials and carbon nanotubes, the anodic peak potentials were observed at almost the same potential value as that of the carbon-ceramic electrodes [22,36].

3.3. Characterization of the microstructure of the SWCNT/CPE and NdOX-SWCNT/CPE with SEM and EDS

The morphologies of the SWCNT/CPE and NdOX-SWCNT/CPE surfaces were studied with SEM and EDS. The results are shown in Fig. 2. With the SWCNT/CPE, a smooth surface was observed, which is typical of carbon surfaces coated with mineral oil (Fig. 2A). For the NdOX-SWCNT/CPE, the SEM image clearly shows that Nd2O3 microparticles distributed homogeneously onto the SWCNT and carbon paste composite (Fig. 2B). The EDS image of the NdOX-SWCNT/CPE microstructure (Fig. 2C) shows the presence of C, Nd and O. Moreover, the percentage weight ratio of O/Nd given by the EDS analysis was 0.15. This value is close to 0.164, which is the percentage ratio of O/Nd in the Nd2O3. These results confirm that the microstructure is formed only by Nd2O3.

3.4. pH study of PCM with NdOX-SWCNT/CPE

To optimize the methods for the detection of PCM using the NdOX-SWCNT/CPE, the effect of pH on the PCM anodic peak currents was evaluated. The pH was evaluated between the values of 2.0 and 6.0 using PBS (0.01 mol/L) and PCM (20.0 μmol/L) by CV and the cyclic voltammograms and effect of pH on the anodic peak potential are shown in Fig. 4. The highest anodic peak currents were observed between the pH values of 3.2 and 4.8. Moreover, the anodic peak currents shifted to less positive values with increasing pH (Fig. 4A). This result indicates that protons are involved in the oxidation of PCM on the NdOX-SWCNT/CPE surface.
Moreover, the anodic peak potential values shifted to less positive values with increasing pH. The regression equation of the anodic peak potential as a function of pH (Fig. 4B) was $E_p (V) = 0.7842 / C_0^{0.0632}$ pH. These slope values are almost near the theoretical value of 0.059 for a reversible reaction. Therefore, the ratio of protons ($H^+$) and electrons (e-) is equal to 2:2 for PCM on the NdOX-SWCNT/CPE. This result is similar to previous reports in which the reversible reaction was due to the rapid electron transfer rate that catalytic nanomaterials provide [16]. A pH value of 3.2 was chosen for the supporting electrolyte for further studies.

3.5. Influence of the scan rates for PCM detection with the NdOX-SWCNT/CPE

With the aim of determining the transfer mass process of this new microcomposite, the influence of the scan rate ($\nu$) on the anodic peak current for PCM from 0.02 to 0.09 V/s at pH 3.2 was studied. The results are shown in Fig. 5. The anodic peak current increased proportionally as the scan rate was increased. The regression equations were $i_{pa} = 0.7340 + 0.1547\nu$ (correlation coefficient $R^2 = 0.991$) and $i_{pc} = -0.145 - 12.40\nu$ (correlation coefficient $R^2 = -0.994$). The slope values indicated that the redox reaction was reversible and that the process was controlled by adsorption. Moreover, the signals were observed after less than one minute of the immersion of the electrode in the solution of PCM. These results can indicate thin-layer effects. Similar results were reported for PCM using a glassy carbon electrode modified with multiwalled carbon nanotubes [38].

3.6. Detection limits for the new method

To obtain the detection limit sensitivity, a calibration curve was developed with the microcomposite SWCNT/CPE and NdOX-SWCNT/CPE by SWV at 0.0 V for 30 s with the following optimized conditions: pH 3.2 (PBS), frequency 10 Hz and pulse amplitude 0.05 V. Fig. 6A shows the voltammograms for 1.0–4.0 mmol/L PCM (insert: calibration curve) with the SWCNT/CPE, and Fig. 6B shows voltammograms for 0.10–9.5 mmol/L PCM (insert: calibration curve) with the Ndox-SWCNT/CPE. The detection limit ($3s/s$) values obtained from the calibration curves were 0.50 and 0.05 mmol/L PCM for the SWCNT/CPE and NdOX-SWCNT/CPE, respectively. The results showed that the NdOX-SWCNT/CPE microcomposite was more sensitive and that the lineal range was high compared with that of the SWCNT/CPE. The obtained detection limits were more sensitive than those from reports using glassy carbon with multi-walled carbon nanotubes [39] and carbon-ceramic electrodes with single-walled carbon nanotubes [22]. Moreover, similar detection limits were observed with carbon combined with other metal oxides, such as Ni [24,28]. In [30],

Fig. 3. (A) Cyclic voltammograms and (B) Nyquist plot of 10.0 mmol/L Fe(III)/Fe(II) in 10.0 mol/L KCl using the SWCNT/CPE (black lines) and NdOX-SWCNT/CPE (red lines) (Randles equivalent circuits inset). Conditions: scan rate 0.1 V/s.

Fig. 4. (A) Cyclic voltammograms (current vs pH) and (B) effect of pH on the anodic peak potential for PCM (20.0 μmol/L) using the NdOX-SWCNT/CPE. Conditions: scan rate 0.10 V/s.
3. Validation, interference and stability study for the detection of PCM using the NdOX-SWCNT/CPE

The validation of the proposed new methodology was evaluated with urine chemistry control from Bio-Rad spiked with known amounts of PCM (μmol/L). The results are summarized in Table 2. The relative error (% ER) was less than 10.0%, indicating acceptable accuracy, considering that the concentration of PCM was less than 10.0 μmol/L. Moreover, the slope values of the calibration equation for PCM were 0.120 ± 0.02 and 0.31 ± 0.03 for 9.20 and 27.5 μmol/L PCM, respectively. This small difference in slope values indicates that the matrix of the urine chemistry control did not affect the activity of the sensor. The voltammograms and calibration curves (insert) for samples 1 in Table 2 are shown in Fig. 7A.

The interference of some substances which have an important physiological function and which may be present in serum, urine and pharmaceutical dosage samples with PCM, such as caffeine (CA), glucose (GO) acetyl salicylic acid (AS), metal ions, synthetic dyes such as tartrazine (TZ), sunset yellow (SY) and allure red, biological substances such as dopamine (DP), uric acid (UA) and ascorbic acid (AA) and flavonoids such as rutin (RT), morin (MO) and quercetin (QC) [43] were evaluated in the presence of PCM (at concentrations 100-fold greater than that of PCM) by amperometry at 0.60 V. Metal ions were obtained from ICP multi-element standard solution IX (Merck) containing As, Be, Cd, Cr(VI), Hg, Ni,

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**Table 1**  Detection of PCM using modified electrodes.

| Working electrode     | Application              | Detection limit (μmol/L) | Ref. |
|-----------------------|--------------------------|--------------------------|------|
| MWCNT-BPPGE          | Tablets                  | 0.045                    | [18] |
| SWCNT–GNS            | Human serum              | 0.038                    | [19] |
| SWNT-EPPGE           | Pharmaceutical formulations | 0.0029                  | [21] |
| SWCNT/CCE            | Pharmaceutical formulations | 0.12                    | [22] |
| PANI–MWCNTs          | Tables                   | 0.25                     | [23] |
| EF-NiO/MWCN          | Tablets and urine samples | 0.50                     | [24] |
| MWCNT-ACS            | Commercial drugs         | 0.05                     | [25] |
| CPE-TN-MWCNT         | Commercial drugs         | 0.05                     | [26] |
| CPE-GdO-IL           |                          | 0.07                     | [42] |

MWCNT-BPPGE: multiwalled carbon nanotube modified basal plane pyrolytic graphite electrode; SWCNT–GNS: single-walled carbon nanotube graphene nanosheet; SWNT-EPPGE: single-walled carbon nanotubes edge plane pyrolytic graphite electrode; SWCNT/CCE: single-walled carbon nanotube-modified carbon-ceramic electrode; PANI–MWCNTs: polyaniline-multiwalled carbon nanotubes; EF-NiO/MWCN: multiwalled carbon nanotubes modified ethynylferrocene NiO carbon paste electrode; MWCNT-ACS: multiwalled carbon nanotube-alumina-coated silica; CPE-TN-MWCNT: carbon paste electrode modified with thionine immobilized on multi-walled carbon nanotube; CPE-GdO-IL: carbon paste electrode modified with GdO nanoparticles and ionic liquids.
Pb, and Se. Fig. 7B shows the amperograms where these substances did not interfere with the signal of PCM. Therefore, this microcomposite can be used in samples that contain these substances. The stability of the microcomposite NdOX-SWCNT/CPE as a working electrode for the analysis of PCM in pharmaceutical dosage samples was evaluated by performing 30 cycles from −0.30 to 1.0 V at 0.10 V/s by CV with PCM (30.0 μmol/L) (Fig. 8). The signal for PCM was increased from 6.14 μA to 6.8 μA. The increase was 0.32% per cycle. These results confirm the process of adsorption of PCM on the NdOX-SWCNT/CPE. Durability was evaluated with the same modified NdOX-SWCNT/CPE for six days with

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### Table 2

Results of PCM analysis in urine chemistry control (n = 3).

| Urine chemistry control | PCM (μmol/L) | % Relative error |
|-------------------------|--------------|------------------|
| Added                   | Found        |                  |
| 1'                      | 9.20         | 10.1 ± 0.05      | 9.70            |
| 2                       | 27.5         | 25.4 ± 0.09      | 7.63            |

* Voltammograms and calibration curve (insert) are shown in Fig. 7A.

### Table 3

Results of PCM analysis in real samples (n = 3).

| Samples   | PCM (mg/L) | % Recovery |
|-----------|------------|------------|
| Real date | 500.0      | 463 ± 0.5  | 92.6        |
| Powder    | 500.0      | 456 ± 0.3  | 91.2        |
| Syrup     | 100.0      | 105 ± 0.1  | 105.0       |

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Fig. 7. (A) Voltammograms and calibration curve (insert) of urine chemistry control standard (sample 1 in Table 2) and (B) amperometry for PCM with DP, AU, AA (ascorbic acid), CA, AS, TZ, AR, SY, RT, MR, and QC at 0.60 V using the NdOX-SWCNT/CPE. For SWV, the same conditions were used as in Fig. 5.

Fig. 8. Cyclic voltammetry curves (30 cycles) on NdOX-SWCNT/CPE in PBS solution containing 12.0 μmol/L, pH = 3.0. Scan rate was 0.10 V/s.

Fig. 9. Voltammograms and calibration curves (insert) of the pharmaceutical dosage samples tablets (A), syrup (B) and powder (C) using the NdOX-SWCNT/CPE electrode. The same conditions were used as in Fig. 5.
PCM (4.0 μmol/L). The anodic peak currents for PCM were measured over six days with an average anodic peak current of 0.42 μA ± 0.05 and coefficient of variation of 1.5%. These results indicate that the performance of the sensor is relatively reliable and can be used for a long time without considerable loss of activity.

3.8. Analytical application

The detection and quantitation of PCM in pharmaceutical dosage samples in different matrices, such as tablets, syrups and powders, were performed to confirm the utility and versatility of the new method by the standard addition method. The results are summarized in Table 3. Dyes, such as sunset yellow, allura red and tartrazine, which are present in powder and syrup samples, do not interfere with the analysis of PCM. Fig. 9 shows the voltammograms and the calibration curve for sample 1. Moreover, the observed average values of the slopes of each curve were 0.201 ± 0.02, 0.185 ± 0.01 and 0.193 ± 0.02. These results indicated that the matrix of the samples did not affect the stability of NdOX-SWCNT/CPE. Moreover, recovery percentage was greater than 100% for the syrup sample, probably due to the matrix. This was more viscous than the other two samples and there was possibly a competitive effect on the adsorption on the surface of the electrode increasing the signal by 5.0%.

4. Conclusions

The new composite NdOX-SWCNT/CPE was well characterized by SEM, CV and EIS. The combination of SWCNTs and Nd2O3 allowed the new method by the standard addition method. The results are summarized in Table 3. Dyes, such as sunset yellow, allura red and tartrazine, which are present in powder and syrup samples, do not interfere with the analysis of PCM. Fig. 9 shows the voltammograms and the calibration curve for sample 1. Moreover, the observed average values of the slopes of each curve were 0.201 ± 0.02, 0.185 ± 0.01 and 0.193 ± 0.02. These results indicated that the matrix of the samples did not affect the stability of NdOX-SWCNT/CPE. Moreover, recovery percentage was greater than 100% for the syrup sample, probably due to the matrix. This was more viscous than the other two samples and there was possibly a competitive effect on the adsorption on the surface of the electrode increasing the signal by 5.0%.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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