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Iron Oxide Nanoparticle and Multiwalled Carbon Nanotube Modified Glassy Carbon Electrodes. Application to Levodopa Detection

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Abstract: The combination of iron (III) oxide nanoparticles ($\text{Fe}_2\text{O}_3\text{NP}$) with functionalized multi-walled carbon nanotubes (MWCNT) has been used to develop a new and easily prepared modified glassy carbon electrode (GCE). The $\text{Fe}_2\text{O}_3\text{NP}$ -MWCNT/GCE were electrochemically characterized by cyclic voltammetry with the model hexacyanoferrate(III)/(II) redox probe. Their application

as electrochemical sensors was demonstrated using levodopa oxidation, with excellent analytical performance. The analytical parameters compare favourably with other similar modified electrodes reported in the literature. Excellent selectivity was shown in interference studies and the determination of levodopa was carried out in pharmaceutical samples.

Keywords: electrochemical sensors · iron (III) oxide nanoparticles · multi-walled carbon nanotubes · levodopa.

1 Introduction

The search for novel electrochemical sensors and biosensors with enhanced analytical and electrochemical performances and associated lower costs has led to a growing interest in the development of new modified electrodes for the fast, sensitive and selective determination of important analytes. In this context, the use of nanomaterials with enhanced physical and chemical properties for the improvement of current sensor technologies has attracted much attention [1–4]. Among others, nanoparticles of various iron oxides (hematite, magnetite, amorphous Fe_2O_3 , $\beta\text{-Fe}_2\text{O}_3$, ferrihydrite) have proved to be interesting materials to be employed in the construction of (bio)sensing devices. They have unique magnetic and electrical properties, high stability, low toxicity, large surface-to-volume ratio, high surface reaction activity, good catalytic efficiency, strong adsorption ability, and are cost-effective [5–7], as well as showing good biocompatibility, important for biosensors [1,3,8,9]. Multiwalled carbon nanotubes (MWCNT) also possess outstanding characteristics, including good electrical conductivity, high mechanical strength and modulus, high chemical stability, large adsorption ability and catalytic properties [2,10]. Furthermore, they can be an ideal matrix to interact with various inorganic and organic molecules, an advantageous property in the design and development of modified electrode electrochemical sensors [2,11–19].

Iron oxide nanoparticles (IONP) have been used independently [7,20–23] or in combination with other materials (nanomaterials, polymers, proteins, etc.) [9,12–14,21,24–29] for the construction of (bio)sensors, presenting improved responses, excellent electrocatalytic activity, and high sensitivity in the detection of analytes in the health, environment and agriculture fields. In particular, the combination with MWCNT has been shown to bring

additional electrocatalytic advantages and enhanced performance, besides offering simplicity of construction and low cost [13,14,25]. Fe_2O_3 /MWCNT-based glassy carbon electrodes (GCE) have been used in the successful detection of hydrogen peroxide [13], and Fe_3O_4 /MWCNT-modified GCEs for dopamine [14], and epinephrine and norepinephrine [25].

A challenging issue associated with the preparation of IONP is the control of their stability and dispersibility in desired solvents. IONP have a large surface area-to-volume ratio and thus tend to aggregate to reduce their surface energy. In addition, bare IONP are easily oxidized in air due to their high chemical reactivity, resulting in a loss of magnetism and dispersibility [30,31]. Consequently, it is of the utmost importance to employ an effective protection strategy to stabilize bare IONP. Several approaches have been proposed to functionalize IONP, the most common being coating their surface with organic materials such as surfactants, polymers, and biomolecules [30–36]. One of the most common materials is chitosan and its derivatives. It has been shown [32–36] that chitosan, a hydrophilic, non-toxic and biocompatible natural polymer, stabilizes IONP by electrostatic repulsions leading to stable ferrofluids. The binding of the biopolymer does not change the main structure of the nanoparticles and the chitosan-bound IONP have strong magnetic responses, although aggregation is less probable

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due to the presence of functional groups in the polymeric shell.

Despite the research effort over the last few years and the promising potentialities, the incorporation of iron oxide nanoparticles in film coatings on electrodes, and particularly on glassy carbon electrodes, is still far from being fully exploited. Only a few attempts [13, 14, 25] have been made to develop GCEs modified with iron oxide/MWCNT nanocomposites, and the architectures proposed so far involve time-consuming and technically complex preparation procedures.

In this work, a new modified electrode based on a composite obtained by the incorporation of iron (III) oxide nanoparticles ($\text{Fe}_2\text{O}_3\text{NP}$) into MWCNT/chitosan dispersions has been developed, using a simple, cost-effective and efficient approach. Different $\text{Fe}_2\text{O}_3\text{NP}$ loadings were evaluated. The $\text{Fe}_2\text{O}_3\text{NP}/\text{MWCNT}$ -modified electrodes were electrochemically characterized by cyclic voltammetry (CV), using the oxidation of hexacyanoferrate (II), as model electroactive species. They were then applied as electrochemical sensors, illustrated by the electrocatalytic oxidation of levodopa (LD), a precursor for dopamine production in the human body, used as an important drug in the treatment of Parkinson's disease [37–40].

2 Experimental

2.1 Reagents and Solutions

Iron (III) oxide nanoparticles ($\text{Fe}_2\text{O}_3\text{NP}$), with 20–40 nm diameter, were obtained from NanoArc, Germany. Multi-walled carbon nanotubes (MWCNT) were from NanoLab, USA, with $\geq 95\%$ purity, 30 ± 10 nm diameter and 1–5 μm length. Potassium chloride, chitosan, 3,4-dihydroxy-L-phenyl-alanine, uric acid and carbidopa were acquired from Sigma-Aldrich, Germany. Potassium hexacyanoferrate (II) trihydrate and tyramine were purchased from Fluka, Switzerland. Nitric acid was from Chem-Lab, Belgium, acetic acid was from Carlo Erba Reagents, France, potassium nitrate and potassium dihydrogen phosphate were from Riedel-de Haën, Germany, and dipotassium hydrogen phosphate 3-hydrate was from Panreac, Spain. All chemicals were of high purity and analytical grade and were used without further purification.

Standard 1.0 mM potassium hexacyanoferrate (II) solutions were freshly prepared by dissolving the salt in 0.1 M KCl electrolyte solution.

Buffer solutions of 0.1 M phosphate buffer (PB), with various pH values, were prepared from potassium dihydrogen phosphate and di-potassium hydrogen phosphate trihydrate.

A stock solution of 1% (m/v) chitosan in 1% (v/v) acetic acid was prepared for modifying the electrode surface. This solution was kept in the refrigerator at 4 °C.

Stock solutions of 1 mM and 0.5 mM levodopa in 0.1 M PB were prepared for levodopa determination and for the interference study, respectively.

The commercial samples used for levodopa determination were Sinemet[®] (100 mg of levodopa + 25 mg of carbidopa per tablet), MSD, Portugal, and Madopar[®] (200 mg of levodopa + 50 mg of benserazide per tablet), Roche, Portugal purchased from a local pharmacy. They were dissolved in 0.1 M PB solution, pH 6, and diluted appropriately with buffer to make 0.1 mM stock solutions. The solutions were prepared immediately before analysis.

Millipore Milli-Q nanopure water (resistivity $\geq 18 \text{ M}\Omega \text{ cm}$) was used for the preparation of all solutions. All experiments were performed at room temperature (25 ± 1) °C.

2.2 Instrumentation

All electrochemical measurements were performed using a computer-controlled Ivium-n-Stat Multichannel Potentiostat/Galvanostat/ZRA with Ivium Software (Ivium Technologies, Netherlands). A three-electrode electrochemical cell of volume 15 cm^3 was used, containing the modified glassy carbon electrode (GCE) as working electrode, a platinum wire counter electrode and a Ag/AgCl (3 M KCl) electrode as reference. Two GCE were used, one with geometric area of 28.3 mm^2 and the other of 7.09 mm^2 .

The pH-measurements were done with a CRISON 2001 micro pH-meter (Crison Instruments S.A., Spain) at room temperature.

2.3 Sensor Preparation

Before use, the GCE surface was polished using diamond spray (Kemet, UK) and aluminium oxide (BDH Chemicals Ltd, England) on a polishing cloth down to 1 μm particle size and then rinsed with Milli-Q nanopure water.

MWCNT were first functionalized with carboxylic acid groups in 3 M nitric acid, following the procedure described in [10], and then dried in an oven at 80 °C for 24 h. The functionalized MWCNT and the commercial $\text{Fe}_2\text{O}_3\text{NP}$ were both dispersed in a 1% (m/v) chitosan in 1% (v/v) acetic acid solution, and sonicated for 30 min to ensure a homogeneous mixture. The two best dispersions prepared were (0.2% (m/v) $\text{Fe}_2\text{O}_3\text{NP}$ -1% (m/v) MWCNT) and (1% (m/v) $\text{Fe}_2\text{O}_3\text{NP}$ -1% (m/v) MWCNT). The polished GCE was coated with the (0.2% $\text{Fe}_2\text{O}_3\text{NP}$ -1% MWCNT) or (1% $\text{Fe}_2\text{O}_3\text{NP}$ -1% MWCNT) chitosan dispersions, 5 or 10 μL volume depending on the GCE, using a micropipette and allowing the assembly to dry at room temperature. This procedure was repeated because cyclic voltammograms of hexacyanoferrate (II) (results not presented) showed that drop-coating with two layers of dispersion leads to higher peak currents in comparison with one or three layers. The modified electrodes were left to dry overnight.

3 Results and Discussion

As mentioned above, there are only a few reports [13,14,25] on the development and application of (IONP-MWCNT)-based GCE, using different electrode modifications. Therefore, voltammetric evaluation of modified GCE architectures with different dispersion compositions was carried out.

3.1 Electrochemical Characterization of (Fe₂O₃NP-MWCNT)-Modified Electrodes

The (Fe₂O₃NP-MWCNT)-modified GCE, prepared by coating with different Fe₂O₃NP dispersion concentrations in chitosan/acetic acid solution, were characterized by cyclic voltammetry in a solution of 1.0 mM potassium hexacyanoferrate (II) in 0.1 M KCl supporting electrolyte using scan rates from 10 to 100 mVs⁻¹. Dispersion concentrations tested included 0.2, 0.5 and 1% of Fe₂O₃NP together with 1% MWCNT. Additional experiments, under the same conditions, using bare GCE, and GCE modified with a dispersion of only 1% (m/v) functionalized MWCNT in 1% (m/v) chitosan in 1% (v/v) acetic acid solution, were performed for comparison. Background-subtracted cyclic voltammograms obtained are presented in Figure 1.

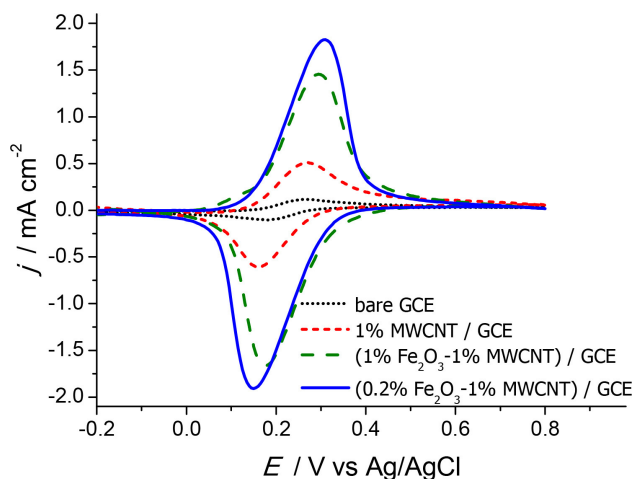


Fig. 1. Background-subtracted cyclic voltammograms at 50 mVs⁻¹ at bare GCE, and at 1%MWCNT- and (Fe₂O₃-MWCNT)-modified GCEs in 1 mM K₄Fe(CN)₆/0.1 M KCl solution.

The cyclic voltammograms of hexacyanoferrate (II) (Figure 1) showed well-defined redox peaks for the modified GCEs, with mid-point potential at ca. +0.300 V vs Ag/AgCl (slightly higher than for the bare GCE at ca. +0.265 V). The shapes of the CVs were almost unaffected by the scan rate, and both cathodic and anodic peak currents depend linearly on the square root of the scan rate over the entire range of scan rates considered, indicating a diffusion-controlled electrochemical process, with no adsorption on either the IONP or MWCNT.

Larger differences between oxidation and reduction peaks were observed when Fe₂O₃NP are combined with the MWCNT, and increased slightly with increasing scan rate, as is common on carbon electrode surfaces [41]. The largest peak separation (~140 mV) corresponding to slower electrode kinetics occurred for the lowest Fe₂O₃NP concentration tested. A difference of ~85 mV, larger than the value of 57 mV for a reversible system, was observed at the bare GCE.

The cyclic voltammetry current response was significantly lower for electrode assemblies containing 0.5% of Fe₂O₃NP than with the dispersions of 0.2 and 1% of Fe₂O₃ (the peak current was ~40% of that obtained for 0.2% of Fe₂O₃NP). An explanation for this rather surprising observation, which was found for different electrodes prepared in the same way, must be related to the way in which chitosan interacts with the IONP. It has been shown that chitosan can coat and stabilize IONP, preventing aggregation whilst not impeding access [36]. As the amount of IONP is increased this prevention occurs to a lesser extent leading to a decreased available surface area. If the amount of IONP is further increased then the available surface increases owing to the higher loading, but even 1% Fe₂O₃ gives a lower signal than 0.2%, see Figure 1.

The electroactive surface area was calculated using the Randles-Sevcik equation

$$I_p = 2.69 \times 10^5 AD^{1/2} n^{3/2} \nu^{1/2} C \quad (1)$$

where I_p is the oxidation peak current (A), A is the electroactive area (cm²), D is the diffusion coefficient of the electroactive species (cm²s⁻¹), n is the number of electrons transferred, ν is the potential scan rate (Vs⁻¹) and C is the concentration of the redox species in bulk solution (molcm⁻³) [42]. The value of the diffusion coefficient of hexacyanoferrate (II) in 0.1 M KCl solution at the bare GCE (6.20×10^{-6} cm²s⁻¹) was taken from chronoamperometric measurements in [42]. The apparent standard electron transfer rate constants were also calculated, as described in [42].

The calculated values of electroactive areas (A_{ele}), of the ratio of electroactive to geometric areas (A_{ele}/A_{geo}), and of the standard electron transfer rate constants (k_0), are given in Table 1. As can be seen, the incorporation of Fe₂O₃NP leads to a significant increase of the electroactive area, more pronounced for the (0.2% Fe₂O₃-1% MWCNT) composition. The values of k_0 increase more at MWCNT-modified electrodes without Fe₂O₃NP than with Fe₂O₃NP, corresponding to a greater electrocatalytic effect, also reflected in the peak shifts. Since this effect was only of the order of a few tens of mV, the larger current response was deemed to be the more important criterion, and thus (0.2% Fe₂O₃-1% MWCNT)-GCE was chosen for evaluation as a sensor for the determination of levodopa.

Table 1. Characteristics of bare and modified GCEs (geometric area $A_{\text{geo}}=0.283 \text{ cm}^2$) from CVs in the scan range 10–100 mV s^{-1} , in 1 mM $\text{K}_4\text{Fe}(\text{CN})_6/0.1 \text{ M KCl}$ electrolyte solution. Electroactive area, A_{ele} , $A_{\text{ele}}/A_{\text{geo}}$, and standard electron transfer rate constant, k_0 .

	Bare GCE	+ 1% MWCNT	+ (0.2% Fe_2O_3 -1% MWCNT)	+ (1% Fe_2O_3 -1% MWCNT)
$A_{\text{ele}}/\text{cm}^2$	0.20 ± 0.006	0.77 ± 0.06	2.97 ± 0.07	2.42 ± 0.05
$(A_{\text{ele}}/A_{\text{geo}})$	0.71	2.72	10.51	8.56
$k_0 \times 10^3/\text{cm s}^{-1}$	2.6	13.7	3.6	4.4

3.2 Levodopa Detection

3.2.1 Determination of Levodopa at (0.2% Fe_2O_3 -1% MWCNT)-Modified GCE

In order to illustrate the benefits of the sensor platform developed in this work, it was applied to the measurement of levodopa, an important drug for treatment of Parkinson's disease. Levodopa is oxidized in several steps, the first of these occurring at potentials less than 0.4 V vs Ag/AgCl at physiological pH which makes it amenable to measurement electrochemically with good selectivity.

Cyclic voltammograms of levodopa oxidation in 0.1 M PB pH 6.0 are depicted in Figure 2 at various scan rates. Analysis of the voltammograms shows that the oxidation process is diffusion-controlled, as depicted in the inset of Figure 2. This is important as it shows there are no problems from product adsorption, which would affect repeatability and compromise the use of this modified electrode for successive analyses.

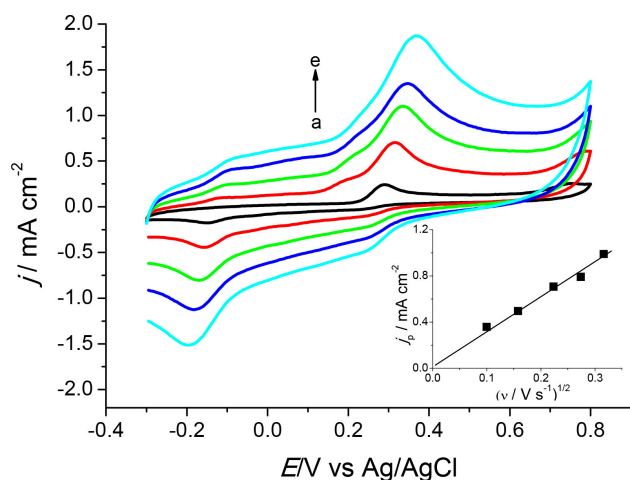


Fig. 2. Cyclic voltammograms for the oxidation of 1 mM levodopa in 0.1 M PB at (0.2% Fe_2O_3 -1% MWCNT) modified GCE at scan rates (a) 10; (b) 25; (c) 50; (d) 75; (e) 100 mV s^{-1} . The inset shows a plot of anodic peak current density, $j_{p,a}$, vs. square root of scan rate, $v^{1/2}$.

The effect of the pH of the supporting electrolyte on levodopa oxidation was evaluated in 0.1 M PB, in the pH range from 5.0 to 8.0. DP voltammograms obtained are depicted in Figure 3. The anodic peak of levodopa shifts to less positive potentials on increasing the pH, Figure 3b

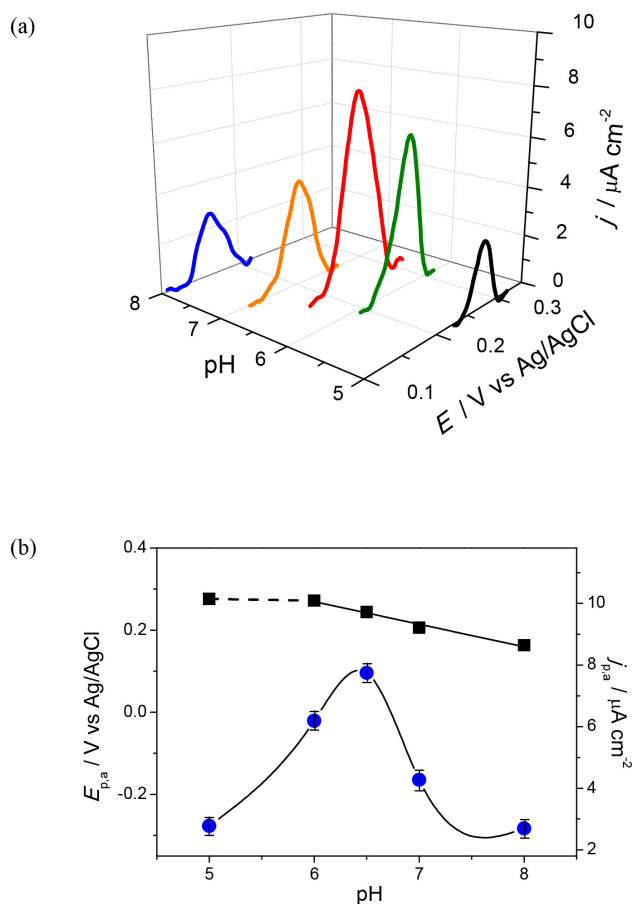
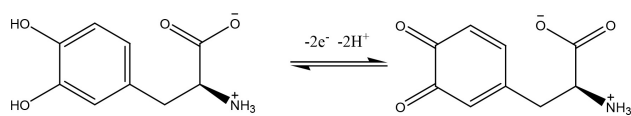


Fig. 3. (a) Differential pulse voltammograms for the oxidation of 10 μM levodopa at glassy carbon electrodes modified with (0.2% Fe_2O_3 -1% MWCNT) in 0.1 M PB at pH 5.0, 6.0, 6.5, 7.0, 8.0 (b) The effect of pH on the oxidation peak current, $j_{p,a}$ (●, blue), and peak potential, $E_{p,a}$ (■) ($n=3$).

with slope according to $E_{p,a}=0.599-0.055 \text{ pH}$, close to 59 mV per pH unit, suggesting the involvement of an equal number of electrons and protons. From the DP voltammograms in Figure 3a, the peak-width at half height ($W_{1/2}$) for the acetaminophen oxidation peak in the DP voltammograms is $\sim 50 \text{ mV}$, suggesting a mechanism involving two electrons and two protons, which is in agreement with the literature, e.g. [37,43] as shown in Scheme 1. The maximum value of the peak current is observed at pH 6.0, which was therefore chosen for all the quantification studies reported here.



Scheme 1. Proposed electrochemical oxidation mechanism for levodopa in neutral pH.

Typical DP voltammograms for the determination of levodopa at the (0.2% Fe₂O₃-1% MWCNT)-modified GCE in 0.1 M PB solution pH 6.0, are depicted in Figure 4A, in the concentration range from 0.10 to 8.0 μM, and the corresponding calibration plot is shown in Figure 4B. Analysis of the calibration plot leads to a sensitivity of $0.484 \pm 0.005 \mu\text{A cm}^{-2} \mu\text{M}^{-1}$ (intercept zero,

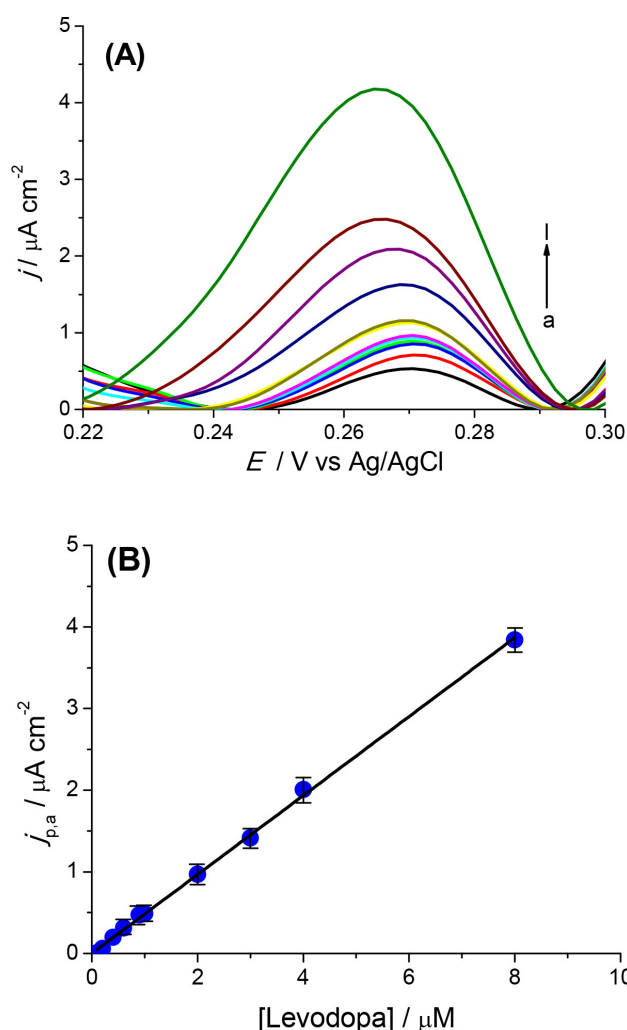


Fig. 4. Differential pulse voltammograms (A) and calibration curve (B) (from 3 independent measurements at each concentration) for levodopa at GCE modified with (0.2% Fe₂O₃-1% MWCNT), in 0.1 M PB solution, pH 6.0. Scan rate 4 mV s^{-1} ; step potential 2 mV . Concentration of levodopa: (a) 0.1; (b) 0.2; (c) 0.4; (d) 0.6; (e) 0.8; (f) 0.9; (g) 1.0; (h); 2.0; (i) 3.0; (j) 4.0; (l) 8.0 μM.

with correlation coefficient 0.9990), an LoD of $0.20 \mu\text{M}$ and a linear dynamic range from $0.10\text{--}8.0 \mu\text{M}$.

As can be seen in Table 2, the incorporation of Fe₂O₃NP into MWCNT/chitosan dispersions for the modification of GCE leads to robust and easy-to-prepare sensing devices with lower limits of detection and excellent analytical characteristics, compared to other levodopa sensors described in the literature. The electrochemical sensors with incorporated MWCNT, [37,38], although with a larger linear range, have higher limits of detection than the electrochemical sensor developed in this work. Other sensors in Table 2, [39,40], were constructed with different architectures. The sensor in [39] which does not have nanoparticles incorporated presents a limit of detection that is larger by a factor of 2. In the case of [40], the carbon nanotube paste with deposited ferrocene showed an even higher limit of detection by a factor of 5, evidencing the superior performance of the electrochemical sensor developed.

3.2.2 Selectivity

The presence of other electroactive species in real samples, is an important issue in the practical application of electrochemical (bio)sensors. Thus, the interference effect of ascorbic acid, uric acid, fructose, lactose, folic acid, K⁺, Na⁺, Zn²⁺, H₂PO₄⁻, NO₃⁻, SO₄²⁻ were investigated, using DP voltammetry. The concentration of levodopa used ($2 \mu\text{M}$ in 0.1 M PB solution) was three times lower than that of the interferent species. As shown in Table 3, none of these compounds causes a significant change in the peak current, and the sensor recovery was close to 100%.

3.2.3 Determination of Levodopa in Real Samples

The potential practical application of the 0.2% Fe₂O₃-1% MWCNT/GCE electrochemical sensor was evaluated. For this purpose, the modified electrode was used for the quantification of levodopa in pharmaceutical tablets, using the standard addition method, and DP voltammetry (scan rate 4 mV s^{-1} ; step potential 2 mV). Stock solutions of 0.1 mM concentration (according to the labelled values) were prepared by dissolving one tablet in 0.1 M PB, pH 6.0, as described in Section 2.1. Further dilution with 0.1 M PB gave a final concentration of $\sim 1 \mu\text{M}$ in a 5 mL volume of analyte solution. Three successive additions of $50 \mu\text{L}$ of a standard solution of 0.10 mM levodopa corresponded to concentration increments of $\sim 1 \mu\text{M}$, which was calculated accurately. These experiments were repeated 3 times.

The values obtained for the amount of levodopa in the tablets, see Table 4, are in good agreement with those declared by the producers and show no interference from the presence of benserazide (Madopar[®]) and carbidopa (Sinemet[®]).

Table 2. Analytical parameters obtained from levodopa calibration curves recorded at different modified electrodes in 0.1 M PB solution.

Modified electrode	Linear range/ μM	LoD/ μM	pH	Ref.
MWCNT/PNB/GCE [a]	1–100	0.37	6.0	[37]
Q/fMWCNT/GCE [b]	0.9–85	0.38	7.0	[38]
Poly(2,5-diaminobenzenesulfonic acid)- β -cyclodextrin/GCE	1–200	0.42	7.2	[39]
Ferrocene/Carbon nanotube paste	2–500	1.2	7.0	[40]
(0.2% Fe ₂ O ₃ -1% MWCNT)/GCE	0.3–8	0.24	6.0	This work

[a] Glassy carbon electrode modified with Poly(Nile blue-A) (PNB) and multiwalled carbon nanotube. [b] Electrodeposition of quercetin (Q) on a functionalised multiwalled carbon nanotube (fMWCNT) immobilised on the surface of a glassy carbon electrode.

Table 3. Determination of levodopa in the presence of interferent species at (0.2% Fe₂O₃+1% MWCNT)/GCE, in 0.1 M PB solution.

Interferent	Recovery (%)
Ascorbic acid	97.6
Uric acid	101.3
Fructose	97.9
Lactose	98.0
Folic acid	103.6
K ⁺	99.0
Na ⁺	99.0
Zn ²⁺	97.7
H ₂ PO ₄ ⁻	99.0
NO ₃ ⁻	99.0
SO ₄ ²⁻	97.7

Table 4. Determination of levodopa (LD) in pharmaceutical tablets ($n=3$) at (0.2% Fe₂O₃+1% MWCNT)/GCE, in 0.1 M PB solution.

Sample	LD labelled/mg	LD found/mg	Recovery (%)
Sinemet®	100	95.71 ± 0.03	96
Madopar®	200	198.30 ± 0.03	99

4 Conclusions

A novel electrochemical sensor has been developed using iron(III) oxide nanoparticles together with multi-walled carbon nanotubes to modify the surface of glassy carbon electrodes, using a simple and cost-effective approach.

The (0.2% Fe₂O₃-1% MWCNT)/GCE and (1% Fe₂O₃-1% MWCNT)/GCE showed well-defined voltammetric responses to the probe species hexacyanoferrate (II), with a pronounced increase in the electroactive area, compared to GCE modified only by MWCNT.

The (0.2% Fe₂O₃/1% MWCNT)-based electrode showed better analytical parameters for levodopa determination than MWCNT/GCE, as well as than other previously reported modified GCE. The quantification of levodopa in pharmaceutical samples gave results in agreement with the labelled values.

This work suggests that the combination of IONP with MWCNT can be used to construct cost-effective electrochemical sensors with enhanced performance, using a

simpler approach than other previously proposed architectures and with good limits of detection.

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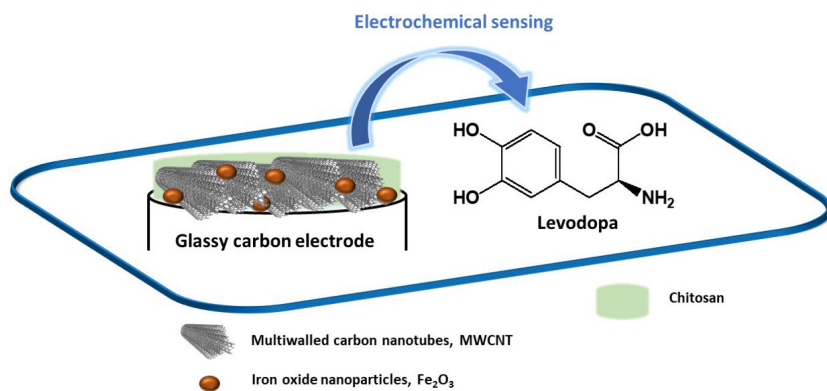
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1 – 8

Iron Oxide Nanoparticle and Multiwalled Carbon Nanotube Modified Glassy Carbon Electrodes. Application to Levodopa Detection