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Electrochemical determination of ascorbic acid and paracetamol in pharmaceutical formulations using a glassy carbon electrode modified with multi-wall carbon nanotubes dispersed in polyhistidine

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ABSTRACT

This work reports on the analytical performance of glassy carbon electrodes (GCE) modified with a dispersion of multi-wall carbon nanotubes (MWCNT) in polyhistidine (Polyhis) (GCE/MWCNT–Polyhis) for the simultaneous determination of ascorbic acid (AA) and paracetamol (PA). The modified electrode exhibited enhanced current responses and lower oxidation overvoltages, demonstrating excellent catalytic activities towards AA and PA oxidation compared to bare GCE. The linear dependence between the anodic peak currents and the square root of scan rates over the range of 0.005–0.300 V s^{-1} demonstrate that the electrooxidation of AA and PA occurs under diffusional control. The MWCNT–Polyhis modified GCE displayed a sensitivity of $(3.8 \pm 0.1) \times 10^4$ μA M^{-1} ($r = 0.998$) and a detection limit of 0.76 μM for the selective determination of AA in the presence of 1.00×10^{-4} M PA. Conversely, for the direct quantification of PA in the presence of 5.00×10^{-4} M AA, the sensitivity and the detection limit were $(6.3 \pm 0.2) \times 10^5$ μA M^{-1} ($r = 0.997$) and 32 nM, respectively. The proposed electrochemical sensor was successfully applied for quantifying AA and PA in commercial pharmaceutical formulations without any sample pretreatment.

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1. Introduction

Ascorbic acid (vitamin C, AA) plays an important role in several enzymatic reactions and in the defense against oxidative stress, acting as a radical scavenger in different metabolic processes that involve redox mechanisms. In addition, AA is extensively used for the prevention and treatment of the common cold, some mental illnesses, and cancer [1,2]. Due to these properties, AA is widely used as antioxidant agent in foods, drinks, and pharmaceutical products. Paracetamol (acetaminophen, PA) is a non-salicylate drug commonly used for fever, headaches, and minor pain relief [3]. Since AA and PA are active principles commonly found either solely or in combination in pharmaceutical formulations, it is very important for the pharmaceutical industry to have a simple and fast method for the routine determination of these compounds.

A wide variety of analytical techniques, such as titrimetry, spectrophotometry, and chromatography have been reported for the determination of AA [4–13] and PA [14–20]. However, these methods are generally time-consuming and require laborious sample pretreatment. Since AA and PA are electroactive compounds, electrochemical sensors represent an interesting alternative for their quantification.

Due to their unique properties, carbon nanotubes (CNTs) have increasingly been used for the construction of electrochemical sensors aiming to improve their analytical response [21–23]. Still, one of the problems for the preparation of CNT-based sensors is their poor solubility in polar solvents. In this sense, several strategies for dispersing CNTs and immobilizing them on the surface of electrochemical transducers have been attained and have demonstrated to be very important for sensing diverse analytes [21].

Recently, we have reported the efficient dispersion of multi-wall carbon nanotubes (MWCNTs) in the polycation polyhistidine (Polyhis), and the excellent performance of the electrochemical sensors based on the modification of glassy carbon electrodes (GCEs) with this dispersion [24]. The resulting electrodes have been successfully used for the sensitive and selective electrocatalytic detection of uric acid (UA) or dopamine (Do) in the presence of AA.

In this work, we propose the use of GCEs modified with MWCNT–Polyhis dispersion as a sensing layer for the highly selective quantification of AA and/or PA in 0.050 M phosphate buffer pH 7.40. Cyclic voltammetry was used to investigate the electrocatalytic activity of the modified electrode towards AA and PA, and differential pulse voltammetry was employed for the quantification of these analytes. The analytical performance of GCE/MWCNT–Polyhis was evaluated determining AA and PA in

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commercial pharmaceutical samples containing both or one of these analytes without pretreatment.

2. Experimental

2.1. Reagents

Polyhis (catalog number P9386) was obtained from Sigma. Ascorbic acid (AA) was purchased from Baker, and paracetamol (PA) was from A.N.M.A.T. Argentina. MWCNTs of 15–45 nm diameter and 1–5 μm length were obtained from NanoLab, USA. The pharmaceutical formulations, were purchased from local pharmacies and used as received without any further purification. The brand name and composition of AA and PA formulations are the following: Factus (100 mg AA, 250 mg PA, and excipients), Bayaspirina C Effervescent (240 mg AA, 400 mg aspirin, and excipients), Redoxon Effervescent (1000 mg AA and excipients), Redoxon Drops (200 mg mL^{-1} AA and excipients), Raffo (1000 mg PA and excipients), and Tafirol (500 mg PA and excipients). Ultrapure water (ρ = 18 MΩ cm) from a Millipore-MilliQ system was used to prepare all the solutions. Polyhis solutions were prepared in 75:25 (v/v) ethanol/0.200 M acetate buffer solution pH 5.00. The stock solutions of PA and AA were prepared in 0.050 M phosphate buffer pH 7.40 before starting each set of experiments, covered with aluminum foil, and stored in ice bath.

2.2. Apparatus

The electrochemical measurements were performed with EPSILON (BAS) and TEQ_02 potentiostats. A conventional three-electrode system was inserted into the cell (BAS, Model MF-1084) through holes in its Teflon cover. GCEs (3 mm diameter, from CH Instruments) modified with MWCNT dispersed in Polyhis were used as working electrodes, a platinum wire and a Ag/AgCl, 3 M NaCl (BAS, Model RE-5B) were used as counter and reference electrodes, respectively. All potentials are referred to the latter. A magnetic stirrer provided the convective transport during the amperometric measurements.

2.3. Preparation of the MWCNT–Polyhis dispersion

The dispersion of MWCNT in Polyhis was obtained by mixing 1.00 mg of MWCNTs with 1.00 mL of 0.25 mg mL^{-1} Polyhis solution followed by sonication for 30 min.

2.4. Preparation of GCE modified with MWCNT–Polyhis dispersion (GCE/MWCNT–Polyhis)

GCEs were polished with alumina slurries of 1.0, 0.30, and 0.05 μm for 1 min each. After polishing, the electrodes were rinsed with water and cycled 10 times in supporting electrolyte between −0.200 V and 0.800 V at 0.100 V s^{-1}. They were modified with an aliquot of 10 μL of MWCNT–Polyhis dispersion dropped on the top of the polished GCE, allowing the solvent to evaporate at room temperature.

2.5. Procedure

The electrochemical experiments were carried out in a 0.050 M phosphate buffer solution pH 7.40. Differential pulse voltammetry (DPV) parameters were the following: a pulse height of 0.004 V, a pulse amplitude of 0.050 V, a period of 200 ms, and a potential range between −0.200 V and 0.500 V. Amperometric experiments were performed by applying the desired potential (0.000 V) and allowing the transient current to reach a steady-state value prior to the addition of the analyte and the subsequent current monitoring. All the experiments were conducted at room temperature.

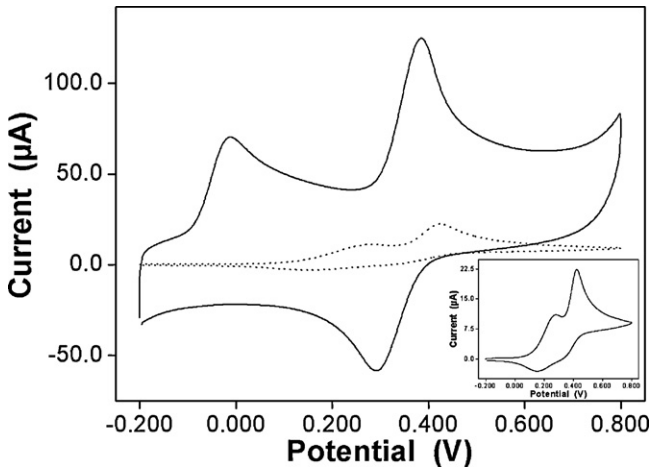

Fig. 1. Cyclic voltammograms obtained at bare GCE (dotted line) and GCE/MWCNT–Polyhis (solid line) for a mixture of 5.00×10^{-4} M AA and 5.00×10^{-4} M PA. The inset shows the cyclic voltammogram at GCE. Supporting electrolyte: 0.050 M phosphate buffer solution pH 7.40. Scan rate: 0.100 V s^{-1}.

2.6. Preparation of real samples

Different drugs containing either AA, PA or both of them (see Section 2.1) were used to evaluate the analytical performance of the proposed sensor. The solid samples (tablets) were dissolved in 0.050 M phosphate buffer solution pH 7.40 to prepare the stock solutions. The liquid sample was conveniently diluted with 0.050 M phosphate buffer solution pH 7.40 to obtain the stock solution. These stock solutions were further diluted with the same buffer solution to obtain the desired concentration.

3. Results and discussion

3.1. Electrochemical behavior of AA and PA at MWCNT–Polyhis modified GCE

Fig. 1 shows cyclic voltammograms for a mixture of 5.00×10^{-4} M AA and 5.00×10^{-4} M PA at bare GCE (dotted line) and GCE/MWCNT–Polyhis (solid line). The inset displays more clearly the electrochemical behavior of the AA and PA mixture at bare GCE. As can be seen, the oxidation peaks for AA and PA are overlapped and present low currents at bare GCE, indicating slow electron transfer kinetics. On the contrary, two well-defined oxidation peaks are evident at the MWCNT–Polyhis modified GCE, one at −0.012 V and the other at 0.385 V for AA and PA, respectively. Therefore, the AA and PA peak potential separation is large enough to ensure the simultaneous determination of both compounds at the modified electrode. The currents and potentials for AA and PA oxidation at modified and unmodified GCEs are summarized in Table 1. The enhancement in the AA and PA oxidation peak current (almost 4 and 7 times for AA and PA, respectively) is mainly attributed to the significant increment in the electroactive area of the electrode due to the presence of MWCNTs. On the other hand, there is a decrease in the oxidation overvoltage for both compounds (292 mV for AA and 40 mV for PA) and an important improvement in the reversibility of PA electrooxidation (the peak separation decreases in 175 mV). These results indicate that MWCNTs catalyses AA and PA oxidation and that even after the dispersion within the Polyhis matrix, MWCNTs kept their electrocatalytic activity. The important improvement in the reversibility for PA electrooxidation could be

Table 1
Cyclic voltammetry parameters for 5.00×10^{-4} M AA and 5.00×10^{-4} M PA at bare GCE, and GCE modified with MWCNT–Polyhis dispersion. Other conditions as in Fig. 1.

Electrode	AA		PA				
	E_{pa}	I_{pa}	E_{pa}	E_{pc}	ΔE	I_{pa}	I_{pc}
Bare GCE	0.280 V	10.7 μA	0.425 V	0.155 V	0.270 V	12.0 μA	7.4 μA
GCE/MWCNT–Polyhis	−0.012 V	44.0 μA	0.385 V	0.290 V	0.095 V	85.0 μA	58.0 μA

explained through the interaction of its aromatic structure with the sp^2-like-planes at some exposed walls of MWCNTs [25].

Fig. 2A displays cyclic voltammograms for AA obtained at different scan rates (ν) in the range of 0.005–0.300 V s^{-1} at GCE/MWCNT–Polyhis. The results showed that increasing the scan rate, the AA oxidation peak current (I_{pa}) increases. The corresponding plot for the anodic peak current (I_{pa}) as a function of the square root of the scan rate ($\nu^{1/2}$) is shown as inset in Fig. 2A. The linear relationship between I_{pa} and $\nu^{1/2}$ (I_{pa} (μA) = $139.15\nu^{1/2} - 0.92$ (r = 0.998)) demonstrates that the electrochemical oxidation of AA at GCE/MWCNT–Polyhis is a diffusion-controlled process. The effect of the scan rate on the electrochemical response of PA at MWCNT–Polyhis modified GCE was also studied and the cyclic voltammograms are depicted in Fig. 2B. Similar to AA, the oxidation peak currents increase with the scan rate increment and the oxidation peak potentials shift towards more positive values. A linear relationship between I_{pa} and $\nu^{1/2}$ is found within the range from 0.005 to 0.300 V s^{-1} (I_{pa} (μA) = $312.23\nu^{1/2} - 3.04$), with a correlation coefficient of 0.998 (see inset in Fig. 2B), indicating that the electrooxidation process is controlled by the diffusion of PA to the GCE/MWCNT–Polyhis. Hence, the overall results suggest that a preconcentration step is not necessary, simplifying the procedure and reducing the analysis time for routine determinations of AA and PA.

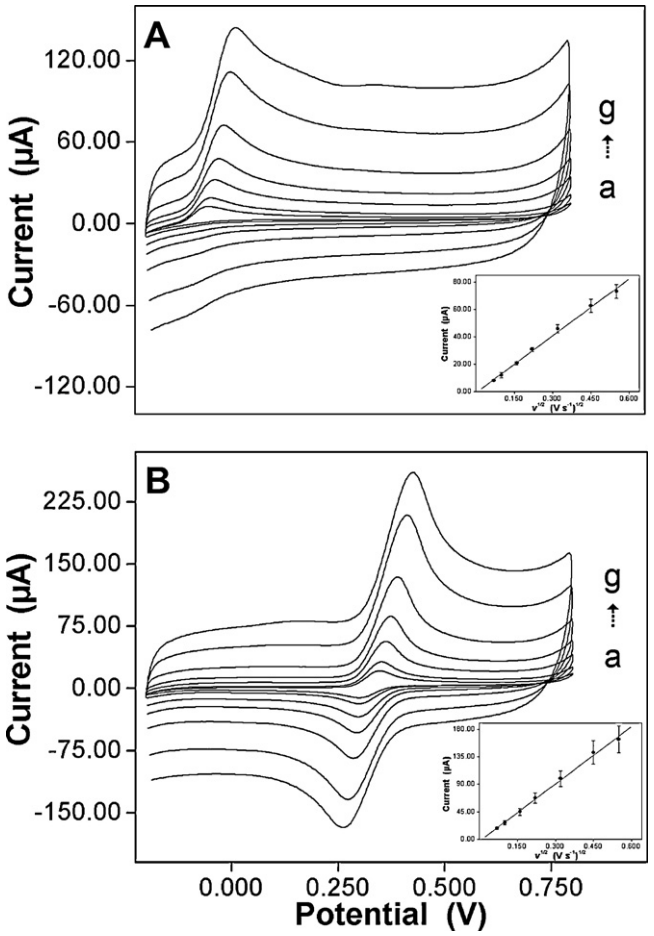

Fig. 2. Cyclic voltammograms for 5.00×10^{-4} M AA (A) and 5.00×10^{-4} M PA (B) in 0.050 M phosphate buffer solution pH 7.40 on MWCNT–Polyhis modified GCEs at scan rates of (a) 0.005, (b) 0.010, (c) 0.025, (d) 0.050, (e) 0.100, (f) 0.200, and (g) 0.300 V s^{-1}. Each inset plot shows the variation of the anodic peak current with the square root of scan rate.

3.2. Analytical application of GCE/MWCNT–Polyhis

DPV was used to obtain a sensitive and selective quantification of AA and PA. Fig. 3A displays the DPV response for increasing concentrations of AA from 2.50×10^{-5} to 2.50×10^{-3} M at MWCNT–Polyhis modified GCE in the presence of 1.00×10^{-4} M PA. Well-defined DPV peaks are obtained for the oxidation of AA and PA with peak potentials at 0.062 V and 0.330 V, respectively. The corresponding calibration plot (Fig. 3B) shows a linear relationship between current and AA concentration up to 1.25×10^{-3} M AA with an average sensitivity of $(3.8 \pm 0.1) \times 10^4$ μA M^{-1}, and a correlation coefficient of 0.995 (values obtained from 5 different sensors and three different dispersions). In the precedent conditions, the detection limit for AA was 0.76 μM (taken as $3.3\sigma/S$, where σ is the standard deviation of the blank signal and S, the sensitivity), and the quantification limit was 2.3 μM (taken as $10\sigma/S$). The sensitivity for AA obtained in the absence of PA was $(3.9 \pm 0.2) \times 10^4$ μA M^{-1} (r = 0.997). The small difference in sensitivity for AA in the absence and presence of PA (2.7%), clearly demonstrate the feasibility to determine AA and PA in mixtures of both compounds using the GCE/MWCNT–Polyhis without statistical interference.

DPV recordings and the corresponding calibration plot obtained at GCE/MWCNT–Polyhis for different concentrations of PA from 2.50×10^{-7} to 1.00×10^{-5} M in the presence of 5.00×10^{-4} M AA, are shown in Fig. 3C and D, respectively. The analytical characteristics for PA in the presence of AA are the following: linear range up to 5.00×10^{-6} M, average sensitivity of $(6.3 \pm 0.2) \times 10^5$ μA M^{-1}, correlation coefficient of 0.997 (values obtained from 6 different sensors and three different dispersions), detection and quantification limits of 32 nM and 97 nM, respectively (obtained as indicated previously). The difference in sensitivity for PA obtained in the presence and absence of AA at the proposed sensor was only 4.5% (the sensitivity of PA in the absence of AA was $(6.6 \pm 0.4) \times 10^5$ μA M^{-1}, r = 0.994). Moreover, compared to the analytical performance of some recently reported sensors for the simultaneous measurement of AA and PA [26–31], this one presents several advantages standing out the lower detection limit for both analytes, demonstrating the competitiveness and efficiency of our sensor.

In order to evaluate the practical application of the proposed electrochemical sensor, the MWCNT–Polyhis modified GCE was employed to determine the content of AA and PA in different commercial pharmaceutical samples by DPV.

The results obtained for the quantification of AA and PA in different pharmaceutical samples are listed in Table 2 and Table 3, respectively. It is important to remark that the sensor was challenged with a medicine (Factus) that contains, in addition to the excipients, both AA and PA, and that it was possible to simultaneously quantify both of them in very good accordance compared to the values reported by the pharmaceutical laboratory. The values found for AA and PA in the rest of the samples (n = 3) were also in good agreement with the values declared in the labels, demonstrating that the sensor proposed here is reliable, selective, and

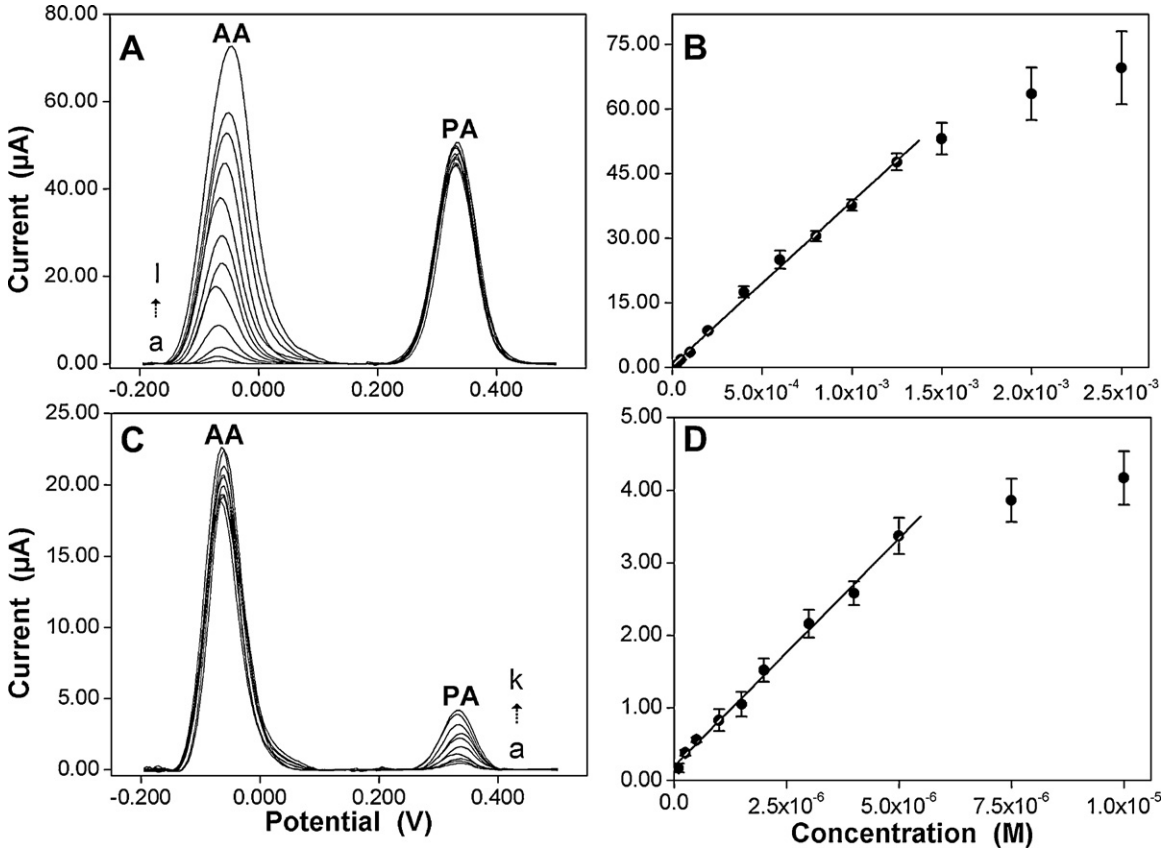

Fig. 3. (A) Differential pulse voltammetry response at GCE/MWCNT–Polyhis for mixtures containing 1.00×10^{-4} M PA and increasing concentrations of AA between 2.50×10^{-5} and 2.50×10^{-3} M. (B) Calibration plot obtained from the DPV recordings shown in (A). (C) Differential pulse voltammograms at GCE/MWCNT–Polyhis for different concentrations of PA between 2.50×10^{-7} and 1.00×10^{-5} M in the presence of 5.00×10^{-4} M AA. (D) Calibration plot obtained from the DPV recordings shown in (C). Other conditions as in Fig. 1. Pulse height: 0.004 V; pulse amplitude: 0.050 V; period: 200 ms.

Table 2
Determination of ascorbic acid in pharmaceutical formulations ($n = 3$) using MWCNT–Polyhis modified GCEs by differential pulse voltammetry (DPV) and amperometry (AMP) performed at 0.000 V.

Tablet/drops name	Labeled content	Electrochemical technique	Determined content	R.S.D. (%)	Error (%)
Factus	100 mg	DPV	94 mg	7.7	−6.0
		AMP	101 mg	3.6	1.0
Bayaspirina C Effervescent	240 mg	DPV	235 mg	4.7	−2.1
		AMP	236 mg	2.1	−1.7
Redoxon Effervescent	1000 mg	DPV	978 mg	3.8	−2.2
		AMP	994 mg	5.0	−0.6
Redoxon Drops	200 mg mL^{-1}	DPV	194 mg mL^{-1}	3.5	−3.0
		AMP	205 mg mL^{-1}	2.5	2.5

sensitive enough to be applied for the determination of AA and PA in real pharmaceutical formulations.

In addition to DPV determinations, the proposed sensor offers the possibility to perform the electrochemical analysis of commercial AA formulations from amperometric recordings at a potential as low as 0.000 V without interference of PA (see Table 2). The values determined by this methodology also presented a very good agreement with the ones informed by the suppliers.

Table 3
Determination of paracetamol in pharmaceutical formulations ($n = 3$) using MWCNT–Polyhis modified GCEs by differential pulse voltammetry.

Tablet name	Labeled content	Determined content	R.S.D. (%)	Error (%)
Raffo	1000 mg	963 mg	5.2	−3.7
Tafirol	500 mg	504 mg	5.6	0.8
Factus	250 mg	258 mg	1.2	3.2

4. Conclusions

The combination of the unique and outstanding catalytic properties of CNTs with the efficiency of Polyhis to disperse CNTs, the stability and reproducibility of the GCE modified with the dispersion, and the huge increase in the electroactive area of the resulting electrode, was successfully used for the simultaneous detection of AA and PA by differential pulse voltammetry. The new strategy was used for the quantification of AA and PA in pharmaceutical formulations without sample pretreatment. We are proposing here a simple, fast, sensitive and selective electrochemical sensor for the simultaneous quantification of AA and PA, offering interesting

possibilities for further applications such as quality control of medicines in pharmaceutical and related industries.

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María L. Pedano obtained her PhD in chemistry (2006) from the National University of Córdoba (Córdoba, Argentina). She was awarded the Prize Enrique Herrero Ducloux, from the Argentinean Chemical Association to the best doctoral thesis in Physical Chemistry in the period 2004–2006. She performed postdoctoral research at Joseph Fourier University (Grenoble, France) during 2007 and at Northwestern University between 2008 and 2009. At present, she is assistant professor at the Department of Physical Chemistry, Faculty of Chemical Sciences, National University of Córdoba, and Associate Researcher at the National Council for Scientific and Technological Research (CONICET). Dr. Pedano is an active member of the Biosensor's Group at the Physical Chemistry Department, and her research now is focusing in the development of plasmonic nanostructures and its application to optical and electrochemical biosensors.

Gustavo A. Rivas obtained his PhD in chemistry (1991) from the National University of Córdoba (Córdoba, Argentina). He did the postdoctoral training at the University of Valence, Valence (Spain) in 1994 and 1995 and at New Mexico State University, Las Cruces (USA) between 1995 and 1996. At present, he is full professor at the National University of Córdoba and Principal Researcher at the National Council for Scientific and Technological Research (CONICET). Professor Rivas is the recipient of the Ranwell Caputto Award from National Academy of Sciences of Argentina (2001) and Rafael Labriola Award from Argentinean Society of Chemistry (2004). Prof. Rivas is the Editor of Sensors and Actuators B and belongs to the Editorial Board of Analytical Letters, Electroanalysis, and *Journal of Biomedical Sciences*. His research interests focused on the study of DNA damage and the development and characterization of electrochemical (bio)sensors based on nanomaterials, polymers and biomolecules.