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Fabrication and characterization of disposable sensors and biosensors for detection of formaldehyde

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ABSTRACT

Screen-printed carbon electrodes (SPCEs) electrochemically platinised (Pt-SPCEs) and screen-printed platinised carbon electrodes ($SPC_{Pt}Es$) have been chronoamperometrically characterized for the determination of formaldehyde (FA). The oxidation current registered at 600 mV in the FA concentration range from 0.99 to 9.09 mmol L^{-1}, led to higher precision values in terms of repeatability and reproducibility when using $SPC_{Pt}Es$. $SPC_{Pt}Es$ have been also used for alcohol oxidase (AOX) cross-linked immobilization in the development of enzymatic biosensors for FA. The enzymatic reaction produces hydrogen peroxide, which has been chronoamperometrically monitored and related to FA concentration in different kinds of samples. Experimental design methodology has been performed to optimize the pH and the applied potential. This method has shown a repeatability and reproducibility of 3% ($n=4$) and 6% ($n=4$) respectively, related to the slopes of the calibration curves performed in the range from 60 to 460 μmol L^{-1}. The use of this kind of biosensor, which has a detection capability of 60 μmol L^{-1} for a given probability of false positive and negative equal to 0.05, has been probed in the determination of FA in commercial samples for histology.

1. Introduction

FA is a human carcinogenic compound widely used in many industrial [1–11], pharmacology and medicine processes, as well as in household products [2–4,7,12]. Moreover, it can be found in fruits, vegetables, fish and biological fluids of human origin since it is a natural metabolite of living organisms [4,7,11,12]. Thus, simple, sensitive and selective methods for FA control analysis are then required in the different fields.

Many analytical methods for FA determination have been developed. They include spectrophotometry, fluorimetry, high-performance liquid chromatography, gas chromatography and electrochemistry. Electroanalytical methods enable direct, reliable and reproducible measurements, using inexpensive instrumentation. These characteristics may be improved by the use of screen-printed electrodes (SPEs), which allow the design of portable and disposable instrumentation [13].

SPEs have been used as sensors for the electrochemical detection of FA, bearing in mind the redox activity of this compound. Two different approaches have been mainly used. On one hand, metal catalysts have been used to enhance the FA redox activity [1,8,10,14]. On the other hand, it has been also described the use of electrochemical devices based on SPEs and selective molecules of biological origin [2,3,5,6,11,15]. Electrochemical biosensors have been considered a good alternative for FA detection due to its high sensitivity, selectivity and their potential for providing real-time measurements [15]. Publications concerning SPEs based biosensors for monitoring FA use either formaldehyde dehydrogenase (FDH) [2,3,5,15] or AOX [6,11] as the biological component (Table 1). FDH biosensors, which are NAD-dependent, are usually based on the oxidation of the reduced cofactor NADH. The main drawback of this systems is the high overpotentials required to follow this reaction [15], which lead to the use of mediators [3,5,6]. In the case of AOX biosensors, the enzymatic reaction generates formic acid and hydrogen peroxide. FA determination includes analysis of the oxygen consumption rate by the use of Clark electrodes [6], as well as potentiometric monitoring of the H^+ produced from formic acid dissociation [11]:

$$CH_2O + H_2O \xrightarrow{AOX} HCOO^- + H^+ + H_2O_2$$

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$$

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Table 1
Publications concerning SPEs based biosensors for monitoring FA.

Ref.	Screen-printed working electrode material	Enzyme	Immobilization type	Mode of operation	Mediator	Concentration range	Capability of detection
[2]	C	FDH	Entrapment within reverse micelles	Amperometry (E_{ap} = 800 mV)	–	1.3 ppb–1.2 ppm	–
[3]	C	FDH	Microencapsulation	Amperometry (E_{ap} = 350 mV; pH solution = 8)	Os polymer	0.3 ppb–1.5 ppm	0.3 ppb
[5]	Platinised carbon	FDH	Microencapsulation	Amperometry (E_{ap} = not said; pH solution = 7)	Tetrathiafulvalene	–	–
[6]	Pt	AOX + FDH	Entrapment in gel	Clark electrode (pH solution = 7)	–	1.5–90 ppm	22.8 ppm
[6]	Pt	AOX + FDH	Entrapment in gel	Amperometry (E_{ap} = 200 mV; pH solution = 7)	DCIP	30–210.2 ppm	22.22 ppm
[6]	Pt	AOX	Entrapment in gel	Clark electrode (pH solution = 7)	–	9.09–120.12 ppm	8.1 ppm
[15]	Carbon modified by carbon nanotubes	FDH	–	Amperometry (E_{ap} = 300 mV; pH solution = 7.5)	–	3 ppb–45 ppm	–
[11]	Ag/AgCl modified by acrylic microspheres	AOX	Adsorption	Potentiometry	–	9–9500 ppm	9 ppm
	This study	AOX	Cross-linking	Amperometry (E_{ap} = −100 mV; pH solution = 7.5)	–	1.8–15.4 ppm	1.8 ppm

In this work, AOX-based biosensors have been developed using $SPC_{Pt}Es$ for the determination of FA. Hydrogen peroxide production from the enzymatic reaction has been chronoamperometrically monitored and related to FA concentration for the first time. This modification avoids the formation of the typical adsorbed CO-layer due to the electrooxidation of small organic molecules, which decreases platinum activity [16,17].

The experimental conditions that can influence the chronoamperometric response have been optimized with respect to FA using the experimental design methodology [18–20]. Under these optimum conditions, reproducibility, repeatability and capability of detection of the biosensor towards FA have been analyzed. Finally, the developed biosensors have been applied to the determination of FA in commercial samples for histology.

2. Experimental

2.1. Reagents

Several inks were used in the fabrication of SPEs, namely C10903P14 (carbon ink) and C2050804D9 (platinised carbon ink) (Gwent Electronic Materials, Torfaen, UK), Electrodag 418 (Ag ink) and Electrodag 6037 SS (Ag/AgCl ink) (Acheson Colloiden, Scheemda, The Netherlands) and 242-SB (dielectric ink) (ESL Europe, Agmet Limited, Reading, UK).

All solutions were prepared with water purified with a Milli-Q device, which provided a resistivity of 18.2 MΩ cm.

1 mmol L^{-1} potassium hexachloroplatinate (IV) solutions were prepared in 100 mmol L^{-1} KCl (Merck, Darmstadt, Germany) for the electrochemical platinisation of SPCEs (Pt-SPCEs).

AOX solution from *Pichia pastoris* (EC 1.1.3.13; activity, 30 units/mg; Sigma, Steinheim, Germany), glutaraldehyde (GA) (Sigma, Steinheim, Germany) and bovine serum albumine (BSA) (Sigma, Steinheim, Germany) were used as received.

Stock standard solutions of FA were prepared by diluting the adequate amount of a FA solution (Sigma, Steinheim, Germany).

50 mmol L^{+-1} phosphate buffer containing 100 mmol L^{-1} KCl solutions were used as supporting electrolyte. 1 mol L^{-1} NaOH (J.T. Baker, Deventer, The Netherlands) was used to adjust the pH value.

2.2. Apparatus and software

SPCEs were produced on a DEK 248 printing machine (DEK, Weymouth, UK) using screen polyester mesh and polyurethane squeegees.

Electrochemical measurements were made by a μAutolab type II electrochemical system with GPES software (Eco Chemie, Utrecht, The Netherlands).

The pH of the solutions was measured with a Crison Model 2002 (Barcelona, Spain) pHmeter.

Data analysis was processed with PROGRESS for the robust regression [21] and DETARCHI [22] for the capability of detection.

2.3. Sensors manufacturing

SPCEs (working area, 4 mm^2) and $SPC_{Pt}Es$ (working area, 9 mm^2), were fabricated according to the procedure described anywhere else [23].

SPCEs were electrochemically platinised (Pt-SPCEs) in a 1 mmol L^{-1} solution of potassium hexachloroplatinate (IV) in 100 mmol L^{-1} KCl by cyclic voltammetry (−600 V to 400 V vs screen-printed Ag/AgCl reference electrode, at a scan rate of 50 mV s^{-1}, 4 potential cycles) [12].

$SPC_{Pt}Es$ were functionalised by AOX immobilized by cross-linking with GA and BSA (AOX-$SPC_{Pt}Es$). The optimum immobilization process was reached by mixing 3 μL of a 6% (w/v) BSA solution in 10 mmol L^{-1} phosphate buffer pH 6, 3 μL of a 2.5% GA solution in water and 6 μL of an AOX solution (1.32 units mL^{-1}). Then, 5 μL of this mixture was dropped onto the platinised carbon working electrode surface. Finally, it was left to dry 90 min at 4 °C.

2.4. Measuring chronoamperometric procedures

Chronoamperometric measurements were carried out in a batch system. All measurements were made at room temperature in a cell containing 5 mL of a 50 mmol L^{-1} phosphate buffer containing 100 mmol L^{-1} KCl solution, of the desired pH, with constant stirring.

The working electrode operated at 600 mV vs screen-printed Ag/AgCl reference electrode in the case of Pt-SPCEs and $SPC_{Pt}Es$. For AOX-$SPC_{Pt}Es$, a potential of −100 mV vs screen-printed Ag/AgCl reference electrode was applied, except for the experimental variables optimization process. The corresponding sample was added after reaching a stable baseline.

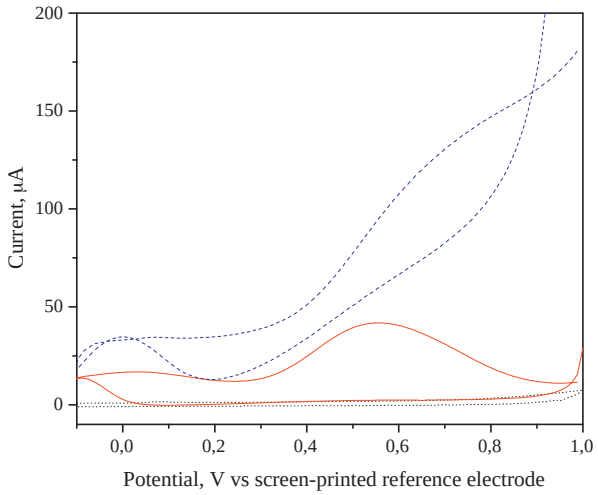

Fig. 1. Cyclic voltammograms of a 0.35 mol L^{-1} FA solution at SPCE (dot line), Pt-SPCE (solid line) and $SPC_{Pt}E$ (dash line) in 50 mmol L^{-1} phosphate buffer containing 100 mmol L^{-1} KCl solution pH 7.5. Scan rate, 100 mV s^{-1}.

3. Results and discussion

3.1. Electrochemistry at platinum based SPEs

SPEs based on conventional inks, such as carbon, have been reported not to be useful for the sensing of FA [1]. Taking into account the oxidation scheme of FA described at Pt electrodes [9], SPCEs have been modified with this metal following two different approaches. Firstly, SPCEs were electrochemically platinised using a hexachloroplatinate solution according to the produce described in Section 2.3 (Pt-SPCEs). In a second step, platinised carbon was used instead of the conventional carbon for the working electrode fabrication ($SPC_{Pt}Es$). Fig. 1 shows the cyclic voltammograms of a 0.35 mol L^{-1} FA solution at SPCE (dot line), Pt-SPCE (solid line) and $SPC_{Pt}E$ (dash line). An increase of peak current was observed at both modified electrodes compared with bare SPCE, which confirm the electrocatalysis towards the HCHO redox behaviour promoted by Pt particles [9].

Then, chronoamperograms were registered for consecutives additions of FA in 5 mL of a 50 mmol L^{-1} phosphate buffer containing 100 mmol L^{-1} KCl solution pH 7.5 at the operational potential of 600 mV, using Pt-SPCEs and $SPC_{Pt}Es$. It can be observed in Fig. 2 the higher sensitivity obtained for FA in the concentration range from 0.99 to 9.09 mmol L^{-1} when using $SPC_{Pt}Es$.

Repeatability, reproducibility and capability of detection were investigated by chronoamperometric measurements. Different calibration curves were recorded under the above-mentioned conditions. In order to detect anomalous points in these regressions, which would alter intercept and slope values leading to wrong conclusions, least median of squares (LMS) regressions were applied [21]. Those points were first detected and eliminated, and then, ordinary least squares (OLS) regressions were built. These last regression parameters were used to evaluate the precision of both sensors.

The slopes of the obtained current vs concentration regressions were used to evaluate repeatability (the same electrode) and reproducibility (different electrodes) in terms of relative standard deviation (RSD). The sensors showed acceptable RSD values of 8% ($n = 4$) and 9% ($n = 6$) in the case of repeatability of Pt-SPCE and $SPC_{Pt}E$, respectively, and 12% ($n = 5$) and 4% ($n = 6$) for reproducibility of Pt-SPCEs and $SPC_{Pt}Es$, correspondingly.

The capability of detection was calculated for a probability of false positive (α) and negative (β) equal to 0.05 [24,25], using the DETARCHI program [22]. The average capability of detection found was $[2.09 \pm 0.15]$ mmol L^{-1} and $[1.07 \pm 0.06]$ mmol L^{-1} in the case of Pt-SPCE and $SPC_{Pt}E$, respectively.

Taking into account the simplicity of the $SPC_{Pt}Es$ fabrication procedure, they were selected for the development of a selective FA biosensor.

3.2. AOX modified $SPC_{Pt}Es$

Different procedures were attempted for AOX immobilization onto the working electrode of the transducers, such as the establishment of covalent bonds enzyme/transducer surface [23,26–28], the direct screen-printing of a carbon ink containing the enzyme [29] or the cross-linking with GA and BSA [30]. In this case, the best analytical quality results, which are following shown, were obtained by connecting the enzyme to $SPC_{Pt}Es$ using the cross-linking procedure.

As it has been previously stated, the enzymatic reaction of FA and AOX produces hydrogen peroxide, which can be chronoamperometrically monitored and related to the FA concentration. In this way, experimental variables, such as pH of the buffer solution and operational potential (E_{ap}), determine the oxidation current registered. Thus, the effect of pH and E_{ap} and their interactions in the chornoamperometric response was evaluated by a 2^2 central composite design, taking as high (+), low (−) levels and central point (0) the following values [18–20],

pH (−) = 5.5	E_{ap} (−) = −400 mV
pH (0) = 7.5	E_{ap} (0) = −100 mV
pH (+) = 9.5	E_{ap} (+) = 200 mV

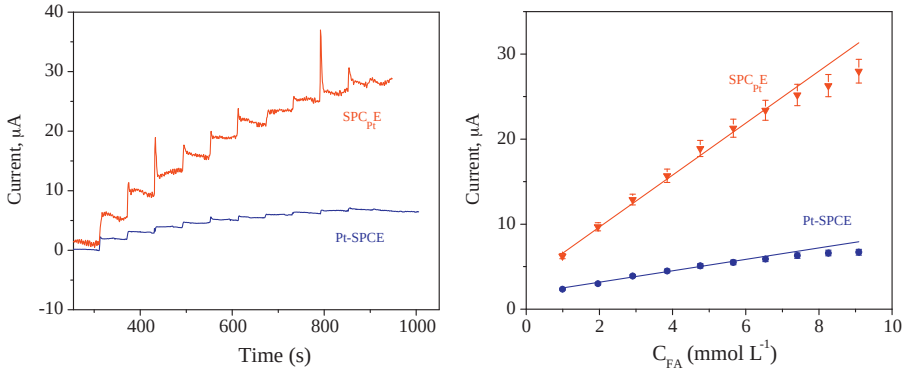

Fig. 2. (Left) chronoamperograms recorded for successive additions of 50 μL of a 100 mmol L^{-1} FA solution using a Pt-SPCE and a $SPC_{Pt}E$ at an operational potential of 600 mV in 5 mL of 50 mmol L^{-1} phosphate buffer containing 100 mmol L^{-1} KCl solution pH, 7.5. (Right) linear relationships between the oxidation current outputs and FA concentrations at both electrodes.

Table 2
Capability of detection obtained for probabilities of both false positive and negative errors equal to 0.05 in the determination of FA by chronoamperometry using an AOX-biosensor.

Calibration	Intercept (nA)	Sensitivity (nA mmol^{-1} L)	S_{yx}	Coeff. of determination (R^2)	Capability of detection (mmol L^{-1})
I	0.05	6.96	0.09	0.994	0.06
II	0.14	6.76	0.09	0.994	0.06
III	0.04	6.58	0.08	0.995	0.05
IV	0.00	6.48	0.08	0.994	0.06

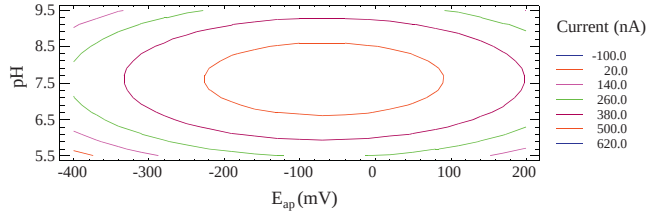

Fig. 3. Contours of estimated response surface for the 2^2 central composite design performed for the optimization of the experimental variables for the analysis of FA using AOX-SPC$_{Pt}$Es.

The 11 possible combinations with these factors, according to the chosen central composite design, were experimented. The analysis of the results presented in Fig. 3 pointed out the values of the experimental variables corresponding to the central point as the optimum ones for the analysis of FA. That is to say, chronoamperometric measurements applying −100 mV in buffer solutions pH 7.5 would allow registering the maximum oxidation current response, which results in a selective and sensitive AOX-based biosensor for FA determination. Fig. 4 shows a chronoamperogram registered under the optimum conditions for successive additions of FA in the concentration range from 60 to 460 μmol L^{-1}. The negative deviation from linearity at higher FA concentrations registered when using platinised electrodes (Fig. 2), due to the adsorption of CO formed as intermediate [16,17], is not observed. In this case, the indirect FA detection using AOX-SPC$_{Pt}$Es at 100 mV, avoids direct FA oxidation at Pt surface, avoiding electrode passivation and improving the repeatability of the method.

The performance of the developed biosensor was checked in terms of repeatability, reproducibility and capability of detection. Thus, several chronoamperograms were registered under the optimum conditions of the experimental variables to build the corresponding oxidation current vs FA concentration regressions in the concentration range from 60 to 460 μmol L^{-1}. First, the parameters of these linear regressions were optimally evaluated as it has been described. Then, repeatability and reproducibility were calculated in terms of RSD of the slopes of the calibration curves (Fig. 5), achieving values of 3% and 6% (n = 4), in that order. The capability of

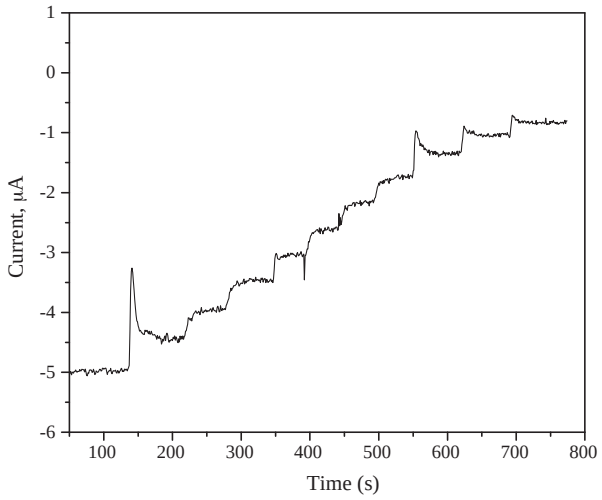

Fig. 4. Chronoamperogram recorded under the optimum conditions (pH 7.5 and E_{ap} = −100 mV) for successive addition of FA in the concentration range from 60 to 460 μmol L^{-1}.

detection was calculated for a probability of false positive (α) and negative (β) as well [24,25], using the DETARCHI program [22]. It can be seen in Table 2 that the average capability of detection found corresponds to the first value of the standards, 60 μmol L^{-1}, which is in good agreement with European regulations about the permissible level of FA in industrial areas, domestic products and ambient air (0.5–2.0 ppm) [31]. Therefore, the minimum detectable FA concentration has been improved in respect to the previously reported SPEs-based procedures, avoiding the complexity associated with the use of cofactors [15].

3.3. Application of AOX-SPC$_{Pt}$Es in commercial samples for histology

FA is widely used in hospitals as a disinfectant, as well as a fixative by pathologists, medical technicians, and researchers [3].

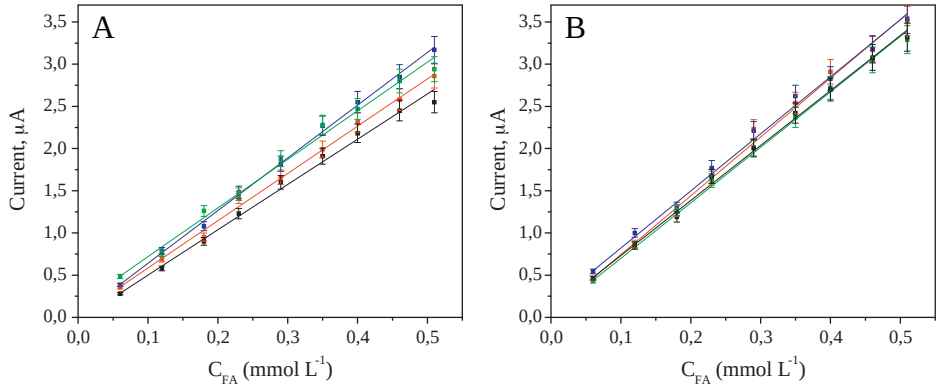

Fig. 5. Experimental points and OLS regressions for the different calibration curves carried out to evaluate the reproducibility (A) and repeatability (B) of AOX-SPC$_{Pt}$Es in the determination of FA.

Spanish law regulates FA used in the samples taken for histology, as well as the exposure to this compound (National Institute of Safety and Hygienic at Work, Regulation NTP248).

Therefore, the viability of the developed AOX-biosensor was tested in commercial samples for histology, HISTOGEN. The FA content of these samples, 10% according to the manufacturer, has been analyzed using AOX-biosensors by the standard addition method.

Thus, chronoamperograms were recorded under the optimum conditions. A volume of 30 μL of a diluted HISTOGEN solution was placed into the electrochemical cell, containing 5 mL of buffer solution, followed by successive additions of 30 μL of a 10 mmol L^{-1} FA solution. Current vs concentration regression parameters were optimally evaluated using the PROGRESS program [21]. The concentration of FA found was [10.05 ± 0.69]% ($n = 6$, $\alpha = 0.05$), with a RSD of 6%.

To test the viability of this procedure in the determination of FA in such complex matrices, recovery studies were also performed. A volume of HISTOGEN sample was spiked with a known concentration of FA. The total amount of FA in this spiked sample, 9.39 mmol L^{-1}, was determined by the standard addition method as well. The concentration of FA found was [9.15 ± 0.15] mmol L^{-1} ($n = 6$, $\alpha = 0.05$, RSD = 2%), with an average recovery of 97.46 ± 1.60%.

On the basis of these data, the method can be considered appropriate to be applied to FA determination in this kind of samples.

4. Conclusions

The chronoamperometrical determination of FA has been achieved using electrochemically platinised SPCEs, Pt-SPCEs, and screen-printing platinised carbon electrodes, $SPC_{Pt}Es$. The oxidation current registered at 600 mV in the FA concentration range from 0.99 to 9.09 mmol L^{-1}, has led to higher precision values in terms of repeatability, 9% ($n = 6$), and reproducibility, 4% ($n = 6$), when using $SPC_{Pt}Es$.

It has been demonstrated that the modification of $SPC_{Pt}Es$ by AOX improves the sensitivity and selectivity in determination of this compound. The enzyme catalyzes the chemical oxidation of FA to formic acid with hydrogen peroxide production, which has been chronoamperometrically monitored and related to the concentration of FA for the first time. The central composite design carried out to optimize the experimental variables has pointed out values of 7.5 for the pH and an applied potential of −100 mV as the best conditions in order to get the maximum oxidation current and, therefore, detect lower concentrations of FA. This method has shown a repeatability and reproducibility of 3% ($n = 4$) and 6% ($n = 4$) respectively, related to the slopes of the calibration curves performed in the range from 60 to 460 μmol L^{-1}. The analytical performance provided by the biosensor has been highlighted by the higher current values obtained at AOX-$SPC_{Pt}Es$ in relation to those obtained at $SPC_{Pt}Es$. The capability of detection of FA by the developed procedure has been 60 μmol L^{-1} for a given probability of false positive and negative equal to 0.05. This value is in good agreement with the permissible level of FA in industrial areas, domestic products and ambient air according to European regulations. It also improves the previously reported ones for SPEs-based procedures, avoiding the complexity associated with the use of cofactors in the case of FDH-based biosensors. The developed enzymatic biosensor has shown its viability in the determination of FA commercial samples for histology.

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