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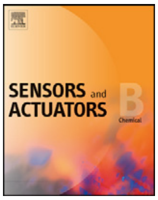

Novel amperometric sensor based on mesoporous silica chemically modified with *ensal* copper complexes for selective and sensitive dopamine determination

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ABSTRACT

Disordered mesoporous silica (DMS), prepared by the sol–gel method, was chemically modified with *ensal* functional groups. Copper complexes were formed on the surface of the resulting material. A homogeneous mixture of the DMS/(ensal)$_2$Cu with ultra pure graphite (99.99%) was pressed in disk format in order to fabricate a working electrode that displayed an excellent specific electrocatalytic response to dopamine (DA) oxidation. Under optimized conditions, at −20 mV vs. SCE in 0.04 mol L^{-1} Britton–Robinson buffer (BRB) solution (pH 7.0) containing 200 μmol L^{-1} of H_2O_2, a linear response range for dopamine from 5 up to 130 μmol L^{-1} was obtained with a sensitivity of 21.2 (±0.003) nA L μmol^{-1} cm^{-2} and the limit of detection LOD was 0.52 μmol L^{-1}. The sensors presented stable response during successive determinations. The repeatability, evaluated in terms of relative standard deviation of <3% for $n = 10$ and 10 μmol L^{-1} dopamine. The response time was 1 s and life time at least 6 months. Finally, the sensor was tested to determine dopamine in the sample, showing a good performance for its determination. The presence of ascorbic acid and NADH did not show any interference in the detection of dopamine on this electrode, even in the same concentration as the dopamine.

1. Introduction

Dopamine (DA) is an important neurotransmitter in the mammalian central nervous system and plays a vital role in the function of central nervous, renal, hormonal and cardiovascular system [1,2]. Low levels of DA in the brain may result in serious diseases such as Parkinson's disease [3,4], caused by the degeneration and loss of midbrain substantia nigra neurons that produce DA, resulting in tremors during rest, inability to initiate or complete movements, muscle rigidity, postural instability, and lack of facial expression [5]. For this reason, monitoring the concentration fluctuations of DA is of great importance, and consequently, the development of simple, rapid, sensitive, and selective detection methods for DA has received much interest over the past two decades.

Especially necessary is the development of simple and rapid methods for its determination in routine analysis. In this regards, different methods have been described in the literature for dopamine determination in biological samples and pharmaceutical formulations, such as spectrometry [6,7], chromatography [8,9] chemiluminescence [10] and electrochemical [11–14]. DA possesses high electrochemical activity and has been widely studied by electro analytical techniques [15–17].

Among the electrochemical methods, amperometric biosensors have shown great potential for developing versatile analytical techniques for catecholamines determination [18–20].

Electrochemical methods have proven to be rapid, simple, sensitive, selective and miniaturizing in the determination of DA. The significant problem encountered with the detection of DA arising from the coexistence of ascorbic acid (AA) with a concentration of 100–1000 times higher than that of DA greatly renders electrochemical strategy very challenging for DA determination. This is because AA can easily be oxidized at a potential close to that of DA and the oxidized DA mediates AA oxidation electrochemically as well as the electrode surface can be easily fouled by the oxidation product of AA. Thus, it is necessary to distinguish DA from AA or to eliminate the interference of AA. For this purpose, various modified electrodes have been constructed. For example, DA can be selectively detected in the presence of AA at electrodes modified with titanate-nanotube [21], boron-doped diamond [22], polyelectrolytelayer [23], monolayer [24], carbon-nanotube (CNT) [25] negatively charged polymer [26], and composite electrode involving the immobilization of methylene blue (MB) on a phosphorylated zirconia–silica matrix [27].

In this work, we report a novel composite electrode involving the adsorption of copper complexes on the surface of mesoporous silica chemically modified with *ensal* organic groups, mixed with

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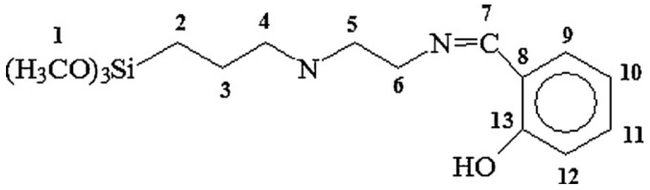

Fig. 1. Structure of the precursor functional group *ensal*.

graphite powder and pressed into a disk format. This electrode exhibits a strong catalytic activity toward dopamine oxidation and well-defined amperometric response was obtained by prior addition of H_2O_2. In addition, DA can be identified in the presence of a large excess of AA and NADH, which usually causes interference. One important advantage that arises from the chemical modification of the DMS with organic groups, such as *ensal*, followed by the adsorption of copper is its reusability. Since the *ensal* molecules are uniformly distributed, the surface of the electrode can be renewed through a simple polishing step.

2. Experimental procedure

2.1. Reagents

All the reagents used in this work were of analytical grade purity: tetraethyl orthosilicate, TEOS (Sigma–Aldrich, 98%), graphite (Aldrich, 99.99%), HNO_3 (Nuclear, 70%), tris(hydroxymethyl)aminomethane (Aldrich, 99.9%), dopamine (Sigma), H_3PO_4 (Nuclear, 85%), H_3BO_3 (Merck, 99.8%), acetic acid (Nuclear, 99.9%), KCl (Vetec, 99%), NADH (Sigma), ascorbic acid (Merck 99.7%). Other used reagents were: ethanol (99.9%); physiological solution (Arboeto) and HCl (37%, Synth).

2.2. Synthesis of the functionalized silica (DMS/ensal)

A disordered mesoporous silica (DMS) was prepared according to a procedure described previously [28]: 0.91 mL of HF (48%) was added to 76.0 mL of TEOS (tetraethylorthosilicate, Synth), 76.0 mL of ethanol and 25.0 mL of water. Stirring was carried out for 30 min. The resulting mixture was stored for 15 days at room temperature. The obtained xerogel was ground and the powder was washed with ethanol in a Soxhlet extractor for 12 h and subsequently submitted to a heat treatment at 333 K under vacuum to evaporate all residual solvent.

The synthesis of the functional group (*ensal*, Fig. 1) was carried out according to the following procedure: 4.0 mmol of *N*-[3-(trimethoxysilyl) propyl]ethylenediamine was dissolved in 30.0 mL of ethanol and reacted with 5 mmol of 2-hydroxybenzaldehyde, in a reflux system under nitrogen atmosphere for 4 h.

Into the resulting yellow solution (due to the *ensal* formation), 2.0 g of DMS was added and this mixture was stirred for 24 h. The yellow solid obtained was washed with ethanol in a Soxhlet system for 6 h and dried for 12 h under vacuum. The mesoporous silica functionalized with the *ensal* groups will be designated as DMS/ensal.

2.3. Characterization

The amount of organic groups immobilized onto the DMS surface was calculated based on the carbon and nitrogen contents, determined by means of elemental analyses on a Perkin-Elmer 2400 elemental analyzer apparatus.

Solid-state nuclear magnetic resonance spectroscopy for ^{13}C (CP/MAS NMR) and ^{29}Si (HPDEC) was performed on a Bruker AC300/P spectrometer operating at 100.6 MHz for ^{13}C with acquisition time of 2.20 ms and at 79.5 MHz for ^{29}Si with acquisition time of 0.16 ms. Adamantane was used as an external reference for the ^{13}C and kaolinite for the ^{29}Si chemical shifts.

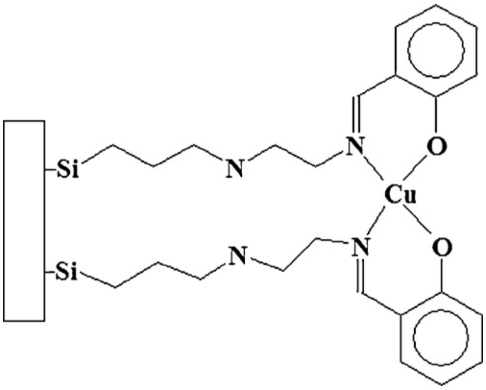

Fig. 2. Surface complex of DMS/$(ensal)_2Cu$.

N_2 adsorption–desorption isotherms were measured at 77 K on a Quantachrome Autosorb 1 instrument. The samples were previously outgassed at 353 K for 6 h. The Brunauer–Emmett–Teller (BET) method was employed to calculate the specific surface areas (S_{BET}).

2.4. Synthesis of the copper complexes and fabrication of the working electrode

Copper chloride was adsorbed on the surface of the mesoporous silica functionalized with the *ensal* organic groups, with consequent formation of copper complexes. For the adsorption step, 0.05 g of the DMS/ensal was added to 50 mL of a $CuCl_2$ solution in ethanol (1.0 mmol L^{-1}). Since the adsorption parameters such as equilibrium constants and effective adsorption capacity were calculated (results not shown) [29,30], in such condition, 90% of the adsorbed copper species are DMS/$(ensal)_2Cu$, i.e. two neighbor functional groups on the DMS surface are chelated with one copper ion as illustrated in Fig. 2. The final material, designated as DMS/$(ensal)_2Cu$, washed with ethanol and the remaining solvent traces were eliminated under vacuum.

2.5. Electrochemical measurements

Electrochemical measurements were conducted using an autolab PGSTAT-20 potentiostat–galvanostat. The experiments were carried out at room temperature, i.e. 298 K, in a standard three-electrode configuration consisting of a platinum wire as an auxiliary electrode and a saturated calomel electrode (SCE) as reference were employed. The pressed disk of DMS/$(ensal)_2Cu$ was used as the working electrode. All the measurements were carried out in 0.04 mol L^{-1} Britton–Robinson buffer (BRB).

The working electrode, a disk with a 5 mm diameter and an approximately 2.5 mm thickness, was prepared by mixing 25 mg of DMS/$(ensal)_2Cu$ and 25 mg of pure graphite (Aldrich, 99.99%) and then pressed under 3 tonnes of pressure. The resultant disks (DMS/$(ensal)_2Cu$/C) were immersed in pure fused paraffin at 343 K under vacuum (10^{-3} Torr), until all adsorbed gas in the matrix pores was completely eliminated. The obtained disk was polished with emery paper to remove the paraffin from the disk surface, and then glued to the end of a glass tube (external area of 0.20 cm^2 and 15 cm length). The electrode was kept in a vertical position facing downward and allowed to air-dry at room temperature for 24 h. The electrical contact was made by a copper wire inserted inside the glass tube. In order to improve the connection between the wire

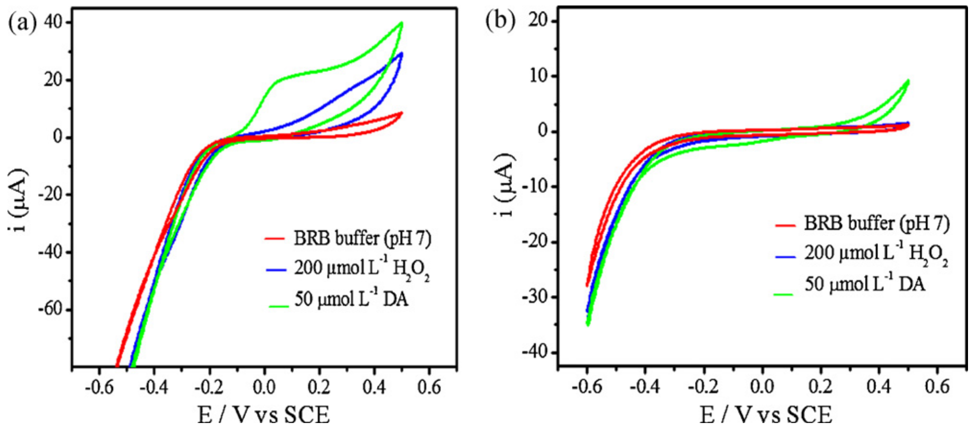

Fig. 3. Cyclic voltammograms obtained with (a) DMS/C electrode modified with $(ensal)_2Cu$, and (b) unmodified DMS/C electrode. Scan rate 10 mV s^{-1}, 0.04 mol L^{-1} BRB at pH 7.0 containing 1 mol L^{-1} KCl.

and the disk surface, pure graphite powder was added into the glass tube.

3. Results and discussion

3.1. Synthesis and characterization of DMS/ensal

The disordered mesoporous silica (DMS) was chemically modified with the *ensal* functional groups, previously prepared. The amount of organic groups immobilized on the surface of the silica was determined by elemental analyses. The amounts of each element, in wt%, are: C = 22.21, H = 2.89 and N = 3.81 and the degree of functionalization obtained for DMS/ensal is 1.36 mmol g^{-1}.

NMR peaks observed for the functional groups bonded to the matrix surface by solid state NMR are (in ppm): (A) HPDEC ^{29}Si NMR, [Q^3 = **Si**$(OSi)_3OH$] (−97) and [Q^4 = **Si**$(OSi)_4$] (−107); [T^2 = C**Si**(OR)$(OSi)_2$, R = H or CH_3] (−55) and [T^3 = C**Si**$(OSi)_2$(OSiOH)] (−63) [31–33]; (B) CP/MAS ^{13}C, C_1($-OCH_3$)(54), C_2(10), C_3(22), C_4(59), C_5(59), C_6(50), C_7(166), C_8,C_{10},C_{12}(118), C_9,C_{11}(131) and C_{13}(161), assigned according to the numbering shown in Fig. 1 above [34–37].

The specific surface area of bare DMS, determined by the BET method [38,39], showed an area of $S_{BET} = 277\ m^2\ g^{-1}$. Assuming an uniform distribution of the immobilized functional groups on the support surface, the surface density, δ, of *ensal* functional groups was determined $\delta = (N_f \times N)/S_{BET} = 1.5\ mol\ nm^{-2}$, where N is the Avogadro's number and N_f is the functionalization degree. The estimated intermolecular distance l_{ij} (where $l_{ij} = \delta^{-1/2}$) is in this case 0.82 nm [40].

3.2. Electrochemical study

The working electrode was prepared by the immersion of 0.05 g of DMS/ensal into 50 mL of a $CuCl_2$ solution in ethanol, with initial concentration of 1.0 mmol L^{-1}. According to the adsorption results, under these conditions, the copper specie formed predominantly (∼90%) on the surface of the material used to fabricate the working electrode is shown in Fig. 2.

3.2.1. Effect of the copper complex on the sensor response

In the first step, an experiment was conducted in order to test the response of the unmodified DMS/C electrode against the sensor response of the (DMS/C electrode modified with *ensal* copper complex), indicating clearly the role of the copper complex in sensor response (Fig. 3). From this figure it becomes evident that copper complexes act as a catalyst for dopamine oxidation.

3.2.2. Hydrogen peroxide influence

Fig. 4 shows the results obtained in the experiments conducted in the presence and the absence of hydrogen peroxide with the proposed sensor ($DMS/(ensal)_2Cu/C$). In the absence of H_2O_2 (curve a), no dopamine oxidation signal was observed, while in the presence of H_2O_2 (curve b), a good response for dopamine was observed, suggesting that the peroxide is very important in the sensor mechanism, which could be attributed to the inefficacy of the $DMS/(ensal)_2Cu/C$ to directly oxidize the dopamine. On the other hand, good cathodic current after adding peroxide and dopamine is observed (curve b in Fig. 4), demonstrating that peroxide plays an important role in the catalytic process. A good sensitivity was obtained for H_2O_2 concentration of 200 μmol L^{-1} (data not shown). Thus, 200 μmol L^{-1} hydrogen peroxide allows good sensitivity, without affecting the stability. This concentration was established for further experiments.

Based on these results, a possible mechanism for the sensor response was proposed as schematized in Fig. 5. In the proposed sensor, the prior addition of hydrogen peroxide, before adding dopamine, increased the sensitivity of the electrode. This fact can be explained based on the catalysis mechanism of the dopamine, very well explained in the literature [41–43].

The most important stage for dopamine quantification is the chemical oxidation of dopamine species by the activated $DMS/(ensal)_2Cu–OOH$ on the electrode surface, the oxidized dopamine is electrochemically reduced on the electrode surface recycling the substrate, and consequently resulting in signal amplification. The hydrogen peroxide is necessary to activate the

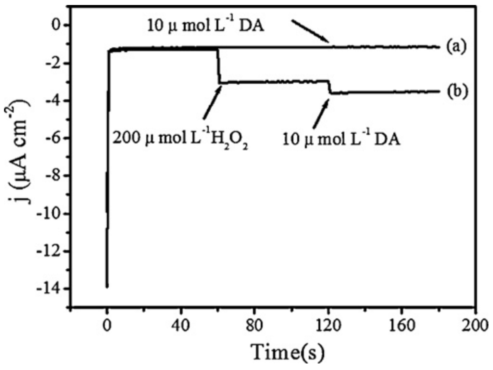

Fig. 4. Signals obtained with the proposed sensor using $DMS/(ensal)_2Cu/C$: (a) in the absence and (b) the presence of 200 μmol L^{-1} H_2O_2. Each step corresponds to the increment of 10 μmol L^{-1}dopamine. Applied potential −20 mV vs. SCE in 0.04 mol L^{-1}BRB at pH 7.0 containing 1 mol L^{-1} KCl.

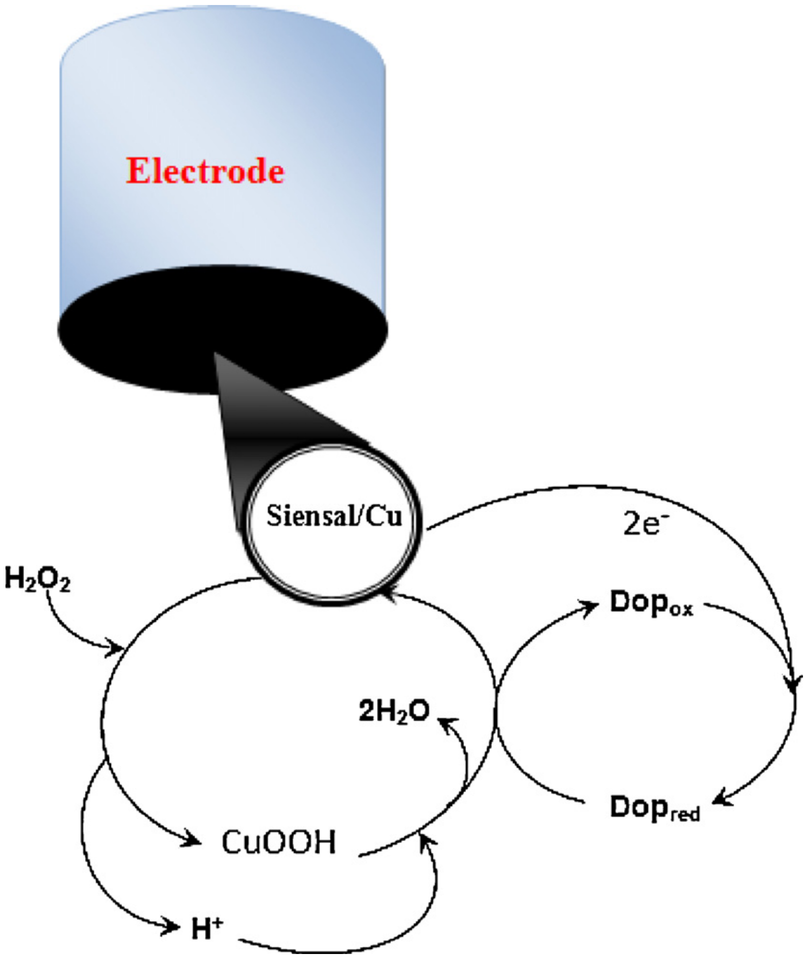

Fig. 5. Proposed mechanism for dopamine oxidation for the DMS/(ensal)$_2$Cu/C electrode.

DMS/(ensal)$_2$Cu/C forming an active form DMS/(ensal)$_2$Cu–OOH to oxidize dopamine, which is electrochemically reduced on the electrode surface. One point that should be emphasized is the role of the mesoporous silica DMS in this material. Copper is mostly adsorbed on SiO_2, which is insulator and thus, the electron transfer between DMS/(ensal)$_2$Cu/C and electrode is not favored, corroborating that the electrons transfer occur predominately between quinone species and carbon domain of the electrode.

Fig. 6 shows the prior addition of H_2O_2 to the solution before adding dopamine and shows a very good sensitivity of the electrode. It corroborates the proposed mechanism as depicted in Fig. 5.

3.2.3. Influence of the applied potential

In Fig. 7, it can be clearly seen that the best sensor response was obtained at −20 mV (vs. SCE). This result is a concession between the optimum potential for electrochemical reduction of quinone species to dopamine, and the peroxide consumption at more negative potentials, through its electrochemical reduction. Thus, in more negative potentials the amount of H_2O_2 available to form copper-oxy species diminishes, due to the electrochemical reduction of H_2O_2, consequently the sensitivity observed is lower.

3.2.4. Influence of the pH, buffer and buffer concentration

The investigation to evaluate the pH effect on the sensor response showed an optimum pH at 7.0 (figure not shown) in 0.04 mol L^{-1} Britton–Robinson buffer solution. In the investigations to evaluate the buffer influence on the sensor response, experiments in three different buffer solutions (Tris, KOH/HCl and BRB) were carried out using the buffer concentrations of 0.1 mol L^{-1}. The results obtained indicated that Britton–Robinson buffer gives the best response. Finally, the influence of the Britton–Robinson buffer concentration on the sensor response showed that the best result was obtained in a concentration of 0.04 mol L^{-1} (Fig. 8).

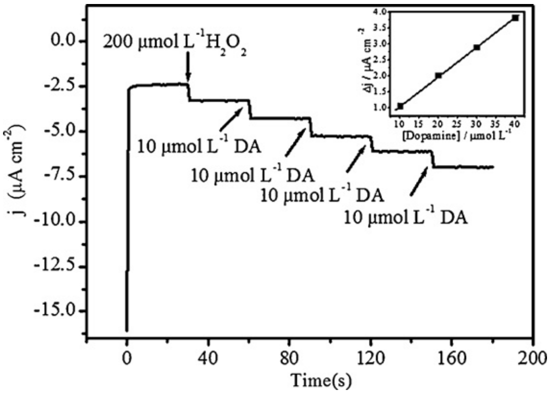

Fig. 6. Amperometric response for dopamine. Each step corresponds to the increment of 10 µmol L^{-1} dopamine and containing 200 µmol L^{-1} of H_2O_2. The inset figure shows the analytical curve. Applied potential −20 mV vs. SCE in 0.04 mol L^{-1} BRB at pH 7.0 containing 1 mol L^{-1} KCl.

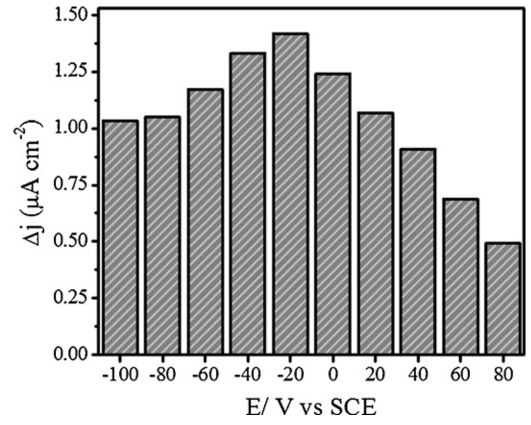

Fig. 7. Influence of the applied potential on the sensor response. Measurements carried out in 0.04 mol L^{-1} BRB (pH 7.0), containing 10 μmol L^{-1} of dopamine and 200 μmol L^{-1} of H_2O_2 and 1 mol L^{-1} KCl.

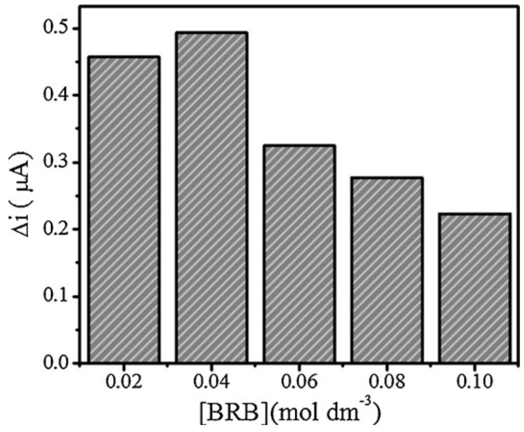

Fig. 8. Profile of response for the sensor in different concentration of BRB solution at pH 7. Applied potential of −20 mV (vs. SCE), containing 10 μmol L^{-1} of dopamine and 200 μmol L^{-1} of H_2O_2, and 1 mol L^{-1} KCl.

3.3. Sensor characteristics

Under optimized conditions, the proposed sensor showed a linear response range for dopamine concentration, varying from 5 up to 130 μmol L^{-1} with a sensitivity of 21.2 nA L μmol^{-1} cm^{-2} (Fig. 9), and expressed by the equation:

$$\Delta j\ \ (\mathrm{nA\ \ cm^{-2}}) = 88.40(\pm 0.02) + 21.20(\pm 0.01)\ \ [\mathrm{DA}]\ \ (\mu\mathrm{mol\ \ L^{-1}}) \qquad (1)$$

with a correlation coefficient of 0.999 for $n = 15$. The sensitivity of this sensor was better than those described in the literature for dopamine determination using Cu^{2+} ions trapped in a various substrate with potentiometric detection [14,44,45]. The limit of detection (3 times standard deviation of the blank divided by the slope of calibration curve), LOD = 0.52 μmol L^{-1} was found.

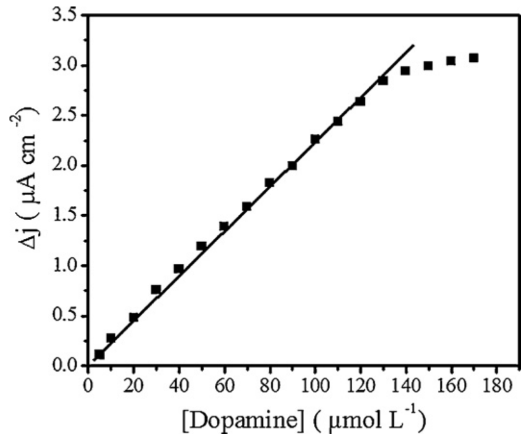

Fig. 9. A typical profile of the sensor response using the optimized conditions. Applied potential of −20 mV vs. SCE, in 0.04 mol L^{-1} BRB at pH 7.0 containing 1 mol L^{-1} KCl, and 200 μmol L^{-1} of H_2O_2.

The response time, considering the time to reach 100% of the signal, was approximately 1 s, which is better than the other sensors presented in the literature for phenolic compounds [44,46,47]. In the case of the sensor based on potentiometric detection [44], the main problem is due to copper (II) regeneration on the electrode surface by the H_2O_2. This short response time indicates that the proposed enzymeless biosensor can be coupled to flow systems or used in real time monitoring.

The repeatability in the measurements was evaluated through six successive experiments carried out with 10 μmol L^{-1} dopamine solution. The repeatability was evaluated as the relative standard deviation (RSD) resulting in a value lower than 3%.

Repeatability, in the construction of sensors was evaluated constructing five sensors and determined the sensitivity obtained for each one. The repeatability expressed as RSD was 5%. This result indicates an optimum repeatability in the sensor construction and it was possible due to the facility in the membrane preparation, containing the copper (II) complex.

This sensor can be kept at room temperature and used without loss of sensitivity, after several months. On the other hand, under operational conditions the proposed sensor presents good stability during 10 successive determinations (figure not shown). However, the sensor presents good sensitivity until approximately one hundred successive determinations, and the stability of the sensor was limited by the strongly bonding of the copper within the complex.

A comparison of the analytical parameters for dopamine with those previously reported for other sensors [14,45,48–51], under

Table 1
Analytical parameters for dopamine detection with electrochemical sensors under optimized amperometric conditions.

Sensor	Dynamic range (μmol L^{-1})	LOD (μmol L^{-1})	Sensitivity (nA L^{-1} μmol^{-1} cm^{-2})	Ref.
SiO_2/C/CuPc	10–140	0.60	0.630	[14]
[Cu(bipy)$_2$]Cl_2·6H_2O[a]	35–240	8.00	2.020	[45]
Fe^{III}T4MpyP-His[b]	0.6–6.0	0.35	0.061	[48]
Th^{IV}-HCF[c]	8–2000	4.70	–	[49]
Ag/CCE[d]	6.6–120	1.40	26.30	[50]
RuO_2/MWNT[e]	0.6–360	0.06	0.084	[51]
SMD/(ensal)$_2$Cu	5–130	0.52	21.20	This work

[a] [Cu(bipy)$_2$]Cl_2: bis(2,2′-bipyridil) copper chloride.
[b] Fe^{III}T4MpyP-His: iron tetra-(*N*-methyl-4-pyridyl)porphyrin-histidine.
[c] (Th^{IV}-HCF): thorium (IV)-hexacyanoferrate.
[d] Ag/CCE: silver ceramic composite electrode.
[e] MWNT: multiwalled carbon nanotubes.

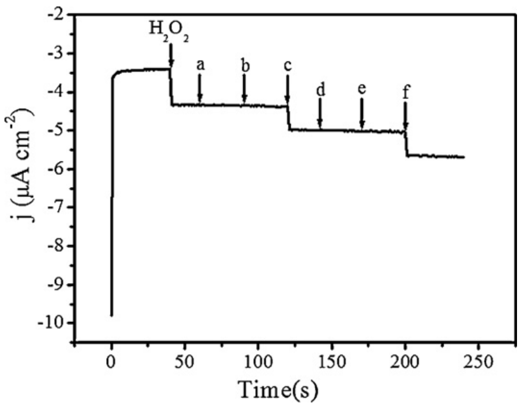

Fig. 10. Current density *j* vs. time for the addition of NADH, ascorbic acid (AA) and DA into the electrochemical cell in sequence at 60 s, 90 s, 120 s, 140 s, 170 s and 200 s. Concentrations (in μmol L^{-1}) of the analytes in the reaction cell: (a) [NADH] = 10, (b) [AA] = 10, (c) [DA] = 10, (d) [NADH] = 20, (e) [AA] = 20 and (f) [DA] = 20. Applied potential of −20 mV vs. SCE, in 0.04 mol L^{-1} BRB at pH 7.0 containing 200 μmol L^{-1} H_2O_2 and 1 mol L^{-1} KCl.

similar experimental conditions, is presented in Table 1. A low detection limit and a higher sensitivity are observed, even when compared to biosensors based on peroxidase or tyrosinase enzymes [52,47] for phenol determinations. Such good analytical responses can be attributed to the efficiency of the reaction between the peroxide and DMS/(ensal)$_2$Cu/C and also DMS/(ensal)$_2$Cu–OOH with dopamine as well as the electrons transfer from quinone to electrode surface.

3.3.1. Sensor application: interference and determination of dopamine in physiological solution

The sensor response was tested in the presence of 10 μmol L^{-1} dopamine and compounds such as NADH and ascorbic acid, at two different concentration ratios. Fig. 10 shows the results obtained, practically no interference was observed from NADH and ascorbic acid. In order to evaluate the sensors applicability, dopamine was determined in a sample. A known concentration of dopamine solution was made in the physiological solution (0.9%, m/v) and also physiological solution was used as supporting electrolyte. The sensor gives a very good response for dopamine determination in this solution. The recovery data about 101 (±2)% was obtained using standard addition method (data not shown).

4. Conclusions

The proposed enzymeless biosensor, as a DMS/(ensal)$_2$Cu/C, showed a wide response range (10–130 μmol L^{-1}), high sensitivity of 21.2 nA L μmol^{-1} cm^{-2} and with a detection limit of 0.52 μmol L^{-1} of dopamine. This sensor showed a long lifetime of 6 months, great stability and repeatability and a short response time of (1 s) for determination of dopamine. The proposed sensor was better than the most of conventional biosensors (based on enzyme) and other enzymeless biosensors described in the literature. These characteristics can be assigned to the conductivity of the material and the environment of the copper complex in the porous material keeping the great reactivity after activating it with hydrogen peroxide. The proposed sensor is highly selective for dopamine determination; it does not show any interference with other ascorbic acid, NADH. Indeed, this sensor was successful employed for determination of dopamine in sample. In this sense, this work depicts that the development of enzymeless biosensors is a promising subject, since simple stable molecules can be used to catalyze redox reaction of extremely important analytes like dopamine.

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