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Electrochemical sensor for dodecyl gallate determination based on electropolymerized molecularly imprinted polymer

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ABSTRACT

An electrochemical sensor based on molecularly imprinted polymer (MIP) film for dodecyl gallate detection at the surface of a glassy carbon electrode (GCE) was proposed in this paper. The GCE was modified with f-MWCNT and the MIP synthesis was performed in situ by means of electropolymerization using ortho-phenylenediamine as the monomer. The stepwise preparation of the MIP and NIP (non-imprinted polymer) was characterized electrochemically by means of cyclic and square wave voltammetry employing ferrocyanide/ferricyanide as a redox probe. The selective capacity performance of the MIP and its imprinted effect to the template molecule (analyte) was compared to the NIP. They were also characterized by scanning electron microscopy technique (SEM). The analytical performance of the MIP sensor performed using square wave voltammetry showed linear range from 0.50 to 8.0×10^{-9} mol L^{-1}, with a correlation coefficient of 0.9921. The sensor presented detection and quantification limit of 0.22×10^{-9} and 0.67×10^{-9} mol L^{-1}, respectively. The apparent dissociation constant (K_D) calculated was of 1.26×10^{-4} mol L^{-1} and 5.27×10^{-1} mol L^{-1} for the MIP and NIP respectively.

1. Introduction

Chagas' disease, caused by protozoan *Trypanosoma cruzi*, is one of the major health problems in Latin America [1]. Transmission occurs mostly by triatominae insect vectors, but also through blood transfusion, congenital routes and organ transplants [2].

Treatments for Chagas disease are extremely limited and often ineffective. No vaccines have been produced thus far to protect the population at risk from contracting the trypanosomiasis in the endemic regions, where the insect vector has not yet been controlled. The current chemotherapy treatment still relies on the use of nifurtimox and a benznidazole derivative, which is orally administered in the acute phase and short-term chronic phase [3,4]. These drugs frequently produce toxic side effects and have very limited efficacy in the treatment of chronic patients. The commercial production of nifurtimox has been discontinued in some countries like Brazil, Chile, Argentina and Uruguay [5].

Taking into account the problems mentioned above, investigation on new compounds, mainly based on natural products, for the treatment of Chagas disease have been done [6,7]. Research has indicated that extracts and pure compounds obtained from plants, such as gallic acid and catechin derivatives, have expressive activities against *T. cruzi* and demonstrate no side effects [6,8,9].

Güida and coworkers presented, for the first time, the *in vivo* trypanocidal activity of epigallocatechin gallate (EGCg) obtained from a murine model of experimental Chagas disease. The results shown suggested that this compound could actually induce a programmed cell's death (PCD)-like processed in *T. cruzi* epimastigotes [9].

The ester derivatives of gallic acid, such as octyl gallate (OG), propyl gallate (PG) and dodecyl gallate (DG) are used as antioxidants in cosmetics, as food additives, and also as antioxidants in the pharmaceutical industry [10]. Andreo and coworkers investigated the antitrypanosomal activity of gallic acid and its esters against epimastigote forms of *Trypanosoma cruzi*. The authors evaluated both the trypanocidal potential after esterifiation of gallates and the mechanisms of action of these compounds in *T. cruzi* organisms.

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The antitrypanosomal effects of nonyl, decyl, undecyl, and dodecyl gallates were compared to benznidazole and results showed that the esters presented more significant IC_{50} (1.46–2.90 μM for esters and 34.0 μM for benznidazole) [11].

Analytical methods have a significant role in drug quality control as well as in the evaluation and interpretation of bioavailability, bioequivalence and pharmacokinetic data, therefore the development of simple, sensitive, rapid and reliable methods for the determination of these parameters has great relevance. Current techniques commonly used for detecting synthetic phenolic compounds mainly include high performance liquid chromatography [12], gas chromatography [13] and capillary electrophoresis [14]. Although these techniques have the advantages of high sensitivity, they may present some drawbacks, such as complex pretreatment steps, long assay time, expensive experimental equipment, and large amounts of reagents consumption. Therefore, alternative methods for simple, rapid and cost-effective detection of the synthetic phenolic antioxidants (propyl gallate and dodecyl gallate, for example) are still being researched [15,16].

Electrochemical methods have also been used for polyphenol detection directly on the electrodes surface, as grafite electrode, in grape and olive extracts matrices containing anthocyanins and green tea extract with catechines [17]. However, the main disadvantage of the phenol electrochemical oxidation is the deactivation of the electrode surface ("electrode fouling") due to the formation of a passivating polymeric film [18]. This phenomenon is one of the main drawbacks of graphite based electrodes and can be to overcome by modification of electrode surface [19,20].

A molecularly imprinted polymer (MIP) as the recognition element, synthetized by electropolymerization process presents attractive advantages like simple preparation, reproducibility of the polymeric film, high mechanical and chemical stability and low costs [21–23]. The development of MIP based electrochemical sensors can be improved using nanomaterials or nanocomposites to enhance the sensitivity of these sensors [16].

Carbon nanotubes (CNTs) has attracted considerable attentions in many fields owing to its special properties, such as good electrical conductivity, high surface area, chemical stability, outstanding chargetransfer characteristics and low electrical resistance [24,25]. CNTs can significantly increase the active surface area and enhance the electron transfer efficiency, so as to improve the sensitivity of the electrochemical sensor [26,27].

The preparation of electropolymerized MIP consists of applying successive voltammetric cycles in a pre-established potential range. For this, a conventional electrochemical cell with three electrodes is used in an electrolytic solution at controlled pH, containing the functional monomer and template. After this step, a polymeric film is formed on the working electrode surface. The last stage is the removal of the template from the polymeric structure by successive washing using a solvente in which the analyte presents high solubility [28].

An eletrochemical sensor for propyl gallate was developed using ortho-phenylenediamine (o-PD) to form the MIP on a glassy carbon electrode surface modified with Pt and Au nanoparticles, graphene and carbon nanotubes. After optimizing several parameters, the authors reported a detection limit of 2.51×10^{-8} mol L^{-1}, linear range from 7×10^{-8} to 1×10^{-5} mol L^{-1} and good results for detection of PG in food samples [29].

This work describes the development of an electrochemical sensor using molecularly imprinted polymer technology as element recognizer for dodecyl gallate determination. The MIP was synthetized by electropolymerization of o-phenylenediamine around the analyte on the glassy carbon electrode, which was firstly modified with functionalized carbon nanotubes. The method proved to be useful for the detection and quantification of the galloyl group.

2. Material and methods

2.1. Reagents and solutions

Potassium ferricyanide ($K_3[Fe(CN)_6]$), potassium ferrocyanide ($K_4[Fe(CN)_6]$), dodecyl gallate (DG) ($C_{19}H_{30}O_5$), ortho-phenylenediamine (o-PD), epigallocatechin gallate (EGCG) ($C_{22}H_{18}O_{11}$) and N-benzyl-2-nitro-1H-imidazole-1-acetamide ($C_{12}H_{12}N_4O_3$) were obtained from Sigma-Aldrich (St.Louis, USA). Tetradecyl gallate (TG) ($C_{21}H_{34}O_5$) was synthesized following the procedure described by Ximenes et al. (2010) [30]. Multiwall carbon nanotubes (MWNTs) were purchased from DROPSENS. Ultrapure water obtained from a Millipore water purification system (resistence 18.2 MΩ cm) was utilized in all assays for dilution of the samples. All chemicals were of analytical grade.

2.2. Apparatus

All voltammetric experiments were performed using a potentiostat-galvanostat μAutoLab (Echo Chemie, B.V., Netherlands, NOVA software) connected to a personal computer and a conventional three-electrode configuration. The morphological characterization of the GCE surface was performed employing field emission scanning electron microscopy (FEG-SEM; Jeol JSM 6330F).

2.3. Electrochemical measurements

The 50 mL electrochemical cell consisted of a 3 mm diameter glassy-carbon working electrode (GCE), a Pt wire counter electrode and an $Ag|AgCl|KCl_{sat}$ reference electrode inserted through a Teflon cover. The stepwise of the MIP and NIP (non-imprinted polymer) construction was obtained by the cyclic voltammetry (CV) and square wave voltammetry (SWV) analysis performed using ferrocyanide/ferricyanide as a probe. This solution was prepared in KCl (0.1 mol L^{-1}) and $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (0.01 mol L^{-1}). CV for electropolymerization was scanned from −0.4 to +1.0 V at 50 mV s^{-1}. SWV was obtained under a frequency of 100 Hz, amplitude of 50 mV and step potential of 8 mV and was employed to monitor the analytical performance of the MIP and NIP sensor in different dodecyl gallate concentrations prepared in an etanol:water (60:40) solution. The CV was also carried out in order to characterize MIP modification on the electrode's surface using a potential range from −0.10 to +0.6 V at 50 mV s^{-1}. All electrochemical experiments were carried out at 25 ± 1 °C.

2.4. Fabrication of the imprinted electrode

The carboxylic group of MWCNTs was functionalized using H_2SO_4 and HNO_3 (3:1). The 100 mg solution of crude MWCNTs was added to 250 mL of the acid mixture and stirred for 12 h. Subsequently, the nanotubes were washed with ultrapure water, filtered by vacuum and dried at 70 °C [31]. After this step, the functionalized nanotube was called f-MWCNTs. Then, the GCE surface was manually polished with sandpaper (4000 grit) for 2 min and washed with ultra-pure water. Then, f-MWCNTs (5 mg) was added into 2.5 mL of dimethylformamide and the suspension was submitted to ultrasonic treatment for 30 min in order to obtain a homogeneous suspension. Finally, 5 μL of this suspension was added on the GCE surface and dried at room temperature to obtain a multiwall carbon nanotube/glassy carbon electrode (f-MWNTs/GCE). Before the electrosynthesis of MIP on the f-MWNT/GCE, the mixture of o-PD (0.005 mol L^{-1}, acetic acid/acetate buffer solution (ABS, pH 5.4)) and dodecyl gallate (0.05 mol L^{-1}, ethanol/water; 9:1) was incubated for 3 h. After this, the electropolymerization was performed using cyclic voltammetry from −0.40 to 1.00 V at 50 mV s^{-1} for 20 cycles

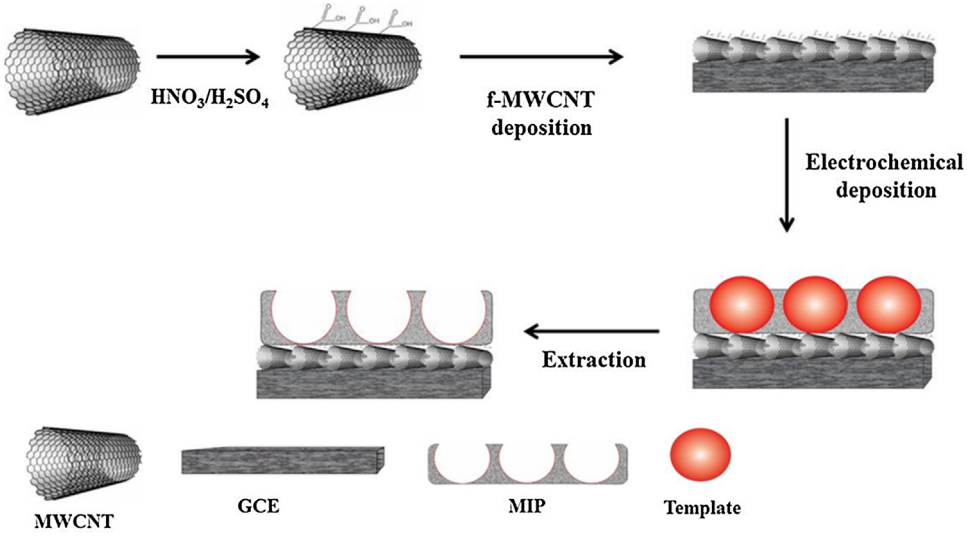

Fig. 1. Scheme of the preparation of the MIP/f-MWCNT/GCE electrode.

[32]. In order to remove the template from the imprinted film, the electrode was immersed in methanol for 25 min under mild stirring (MIP/f-MWCNT/GCE). The non-imprinted polymers (NIPs), called NIP/f-MWCNT/GCE, were polymerized using the same procedure, but without the addition of dodecyl gallate. The scheme of the MIP's electrode construction is shown in Fig. 1.

3. Results and discussion

3.1. MIP sensor construction

Direct oxidation of phenolic compounds on graphite electrodes produces a polymeric film by the coupling of electrogenerated phenoxy radical [18]. The result is a decrease in the oxidation current and an increase of the oxidation potential when consecutive cycles are performed on the same electrode. A negative effect of this behavior is the low reproducibility of the measurement. The modification of electrode surface with a recognition element to evaluate the polyphenol compounds can represent an alternative device for the detection of these compounds. After polishing the GCE electrode and adding f-MWCNTs to its surface, the electropolymerization of o-PD both in isolation and in the presence of DG (Fig. S1a) (Fig. S1b) were carried out for the construction of MIP and NIP.

o-PD is atractive due to the good homogeneity and high physical, thermal and mechanic stability of the formed polymer [33]. The monitoring of the analyte, when o-PD-MIP is used, is performed indirectly. In other words, the cavities are filled by the analytes, leading to the suppression of the redox probe's electrochemical signal (e.g. ferricyanide). Therefore, a decrease in the probe's signals is observed with the increase of analyte concentration [22]. The current intensity of the anodic peaks decreased dramatically in each cycle, until these peak currents were approximately zero; indicating that a nonconducting polymer film was formed on the f-MWNTs/GCE electrode surface.

3.2. Characterization of modified electrodes

The morphologies of different modification steps on the GCE surface in Fig. 2 were characterized using FEG-SEM. The image of bare GCE (Fig. 2a) shows the electrode's flat surface. However, after the addition of f-MWCNT, it becomes apparent that a large amount of these nanotubes get entangled and overlapped into a network structure on the electrode surface (Fig. 2b). The f-MWCNT has high surface area and good mechanical roughness and these network structures could serve as fast electricity conducting channels for further polymerization. Fig. 2c show the morphology of the sensor after MIP formation. Along with the coating of the MIP film, the electrode also presented a relatively dense network containing a few cavities, suggesting the occurrence of polymerization in presence of DG. The NIP images (Fig. 2d) show the presence of several aggregates distributed randomly on the f-MWCNT/GCE, which can be attributed to the polymerization of o-PD, forming a roughened surface. These results indicate the successful formation of a sensor based on MIP.

3.3. Template removal time

To obtain a MIP electrode with satisfactory sensitivity, selectivity and reproducibility, the template molecule should be removed thoroughly. In this work the template molecules were removed by methanol due to the high solubility of analytes in this solvent. The electrode was immersed in methanol and the immersion time to removal the analyte was optimized. The effect of washing time in 10 mL of methanol was investigated using SWV measurements. The peak current values of each of the periods analysed is shown in Fig. S2. Immersion of the sensor in methanol for 10 min resulted in a small increase in the current intensity value, indicating the beginning of template removal from the polymeric structure. After 20 min, the current intensity had risen, however, there was a more significant increase in current intensity at 25 min, and kept constant until 30 min. These results showed that the immersion of the sensor in methanol for 25 min was enough for complete removal of the DG from the MIP structure.

3.4. Electrochemical behavior of the MIP-sensor

The evaluations of the different steps that take place in the confection of the f-MWNT/GCE electrode were carried out using CV in 0.1 mol L^{-1} KCl containing 0.01 mol L^{-1} $K_3[Fe(CN)_6]$/ $K_4[Fe(CN)_6]$ as the electrochemical probe.

There was a pair of redox peak on the GCE, as shown in Fig. 2a (i). The f-MWCNTs were employed to promote a higher electron transfer rate with the increase of the available electroactive surface area and improve mechanical stabilyt of the MIP sensor. After f-MWCNTs coated onto CGE electrode, Fig. 3a (ii), the current response remarkably increased. The deposite of f-MWCNTs

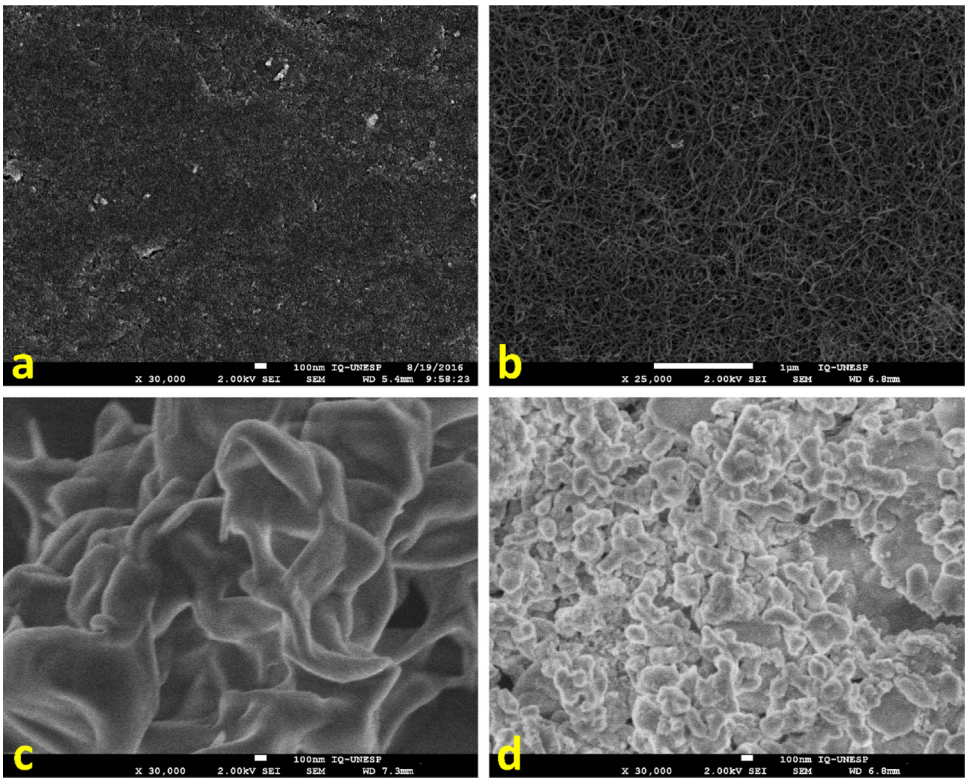

Fig. 2. Scanning electron microscopy images showing (a) bare GCE, (b) f-MWCNT/GCE, (c) MIP/f-MWCNT/GCE and (d) NIP/f-MWCNT/GCE.

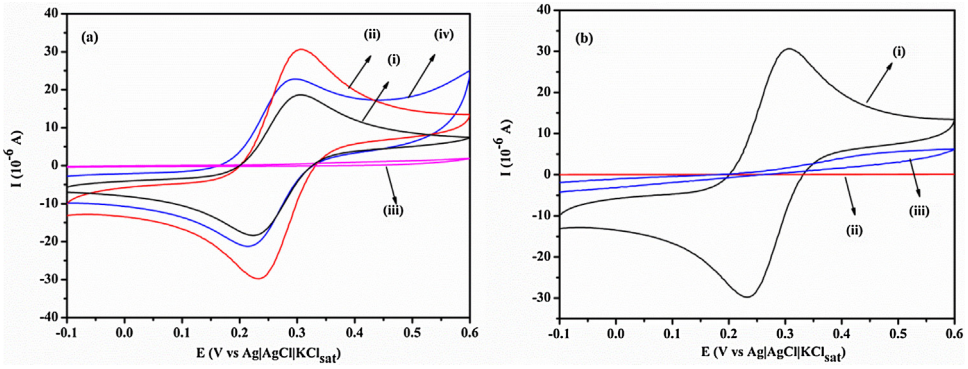

Fig. 3. Cyclic voltammograms of 0.01 mol L^{-1} $K_3[Fe(CN)_6]$/ $K_4[Fe(CN)_6]$ solution prepared in KCl 0.1 mol L^{-1} at: (a) (i) bare GCE; (ii) f–MWCNT/GCE; (iii) MIP/f–MWCNT/GCE after polymeric film formation; (iv) MIP/f–MWCNT/GCE after extraction of template. (b): (i) f–MWCNT/GCE; (ii)/MIP/f–MWCNT/GCE after from polymeric film; (iii) MIP/f–MWCNT/GCE after extraction of template. Conditions: Potential scan range, −0.20 V to +0.60 V; Scan rate, 50 mV s^{-1} in phosphate buffer solution (pH 7.4).

onto the GCE surface was considered successful, since the current intensity of the oxidation/reduction peaks increased 64% in comparison to the GCE electrode. This increase can be attributed to the improved conduction of the electrode and its increased surface area.

After electropolimerization, MIP (Fig. 3a) and NIP (Fig. 3b) did not present the redox peaks of the probe. As the polymeric film is nonconductive, there were almost no channels permitting access through the film, which prevented the electrons from accessing the electrode's surface. However, after using methanol to remove the template from the polymeric structure, redox peaks were clearly observed in the curve of the MIP electrode, but with lower current intensity than the f-MWCNT/GCE.

This result indicates that ferricyanide had access to the electrode surface modified with the imprinted film after removal of the template. As for the NIP electrode, no current response was observed, even after washing in methanol under the same conditions as for the MIP. The results mean that no cavity was formed on the polymer structure, therefore the probe had no access the electode's surface.

3.5. Analytical performance of MIP-sensor

The analytical performance of the sensor was evaluated by analytical curve for MIP/f-MWCNT/GCE. The response of the MIP sensor was obtained using SWV measurements in $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (0.01 mol L^{-1}) after incubation of sensor in DG solution with several concentrations. The analytical performance of MIP sensor was evaluated using five differents electrodes for each DG concentration ($0.50–8.0 \times 10^{-9}$ mol L^{-1}). The sensor was prepared by construction of MIP film in each electrode. The DG antioxidant can be detected using the indirect MIP sensor method i.e., the current intensity of the anodic peak at 0.26 V (relates to redox couple $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$) decreased when the cavities in the imprinted film were occupied by analytes.

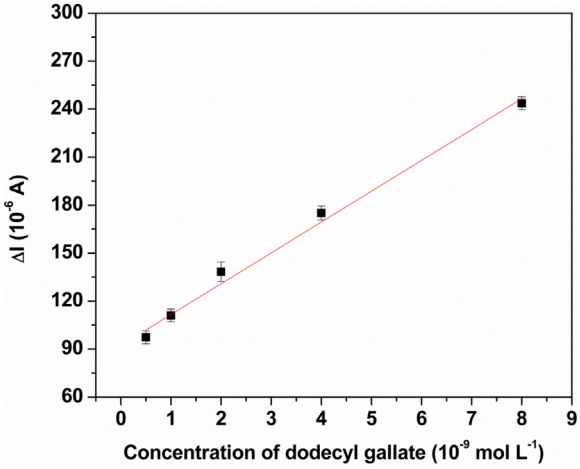

Fig. 4. Analytical curve for dodecyl gallate quantification. Linear relationship between the peak currents and the concentration of dodecyl gallate. Square wave voltammograms of MIP/f–MWCNT/GCE sensor at 0.01 mol L^{-1} $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution prepared in KCl 0.1 mol L^{-1} after immersion in different dodecyl gallate concentration: 0.5, 1.0, 2.0, 4.0 and 8.0×10^{-9} mol L^{-1}. Conditions: Potential scan range from 0.10 to +0.40 V; step potential 14 mV; frequency 100 Hz; amplitude 50 mV.

A linear relationship between the ΔI and DG concentrations was obtained in the range from 0.50 to 8.0×10^{-9} mol L^{-1}, which exhibited the following linear regression equation: $\Delta I = 1.976 \times 10^{10}$ [dodecyl gallate] + 92.31, with a correlation coefficient of 0.9921 (Fig. 4). The limit of detection (LOD) of the MIP sensor was determined as 3.3 SD/B, where SD is the standard deviation of the analytical curve and B is the slope calculated from the analytical curve [34,35]. The sensor presented LOD and LOQ of 0.22×10^{-9} and 0.67×10^{-9} mol L^{-1}, respectively.

The repeatability of the sensor response was performed by replicated measurements of a single electrode using 4.00×10^{-9} mol L^{-1} of DG for 4 successive determinations. The MIP electrode was immersed in DG solution and the peak current of analyte was evaluated. The MIP electrode was washed with water between each experiment. After three consecutive incubation of DG the peak current decreased substantially. The results showed that MIP sensor can be used only thrice. After that, the decrease in current response was greater than 10%. The current values obtained for stability of MIP sensor after consecutives measurements to dodecyl gallate are presented in Supplementary material (Fig. S3).

3.6. MIP-sensor reproducibility and stability

The reproducibility of the MIP sensor was investigated by single electrode. After the polymerization and the template removal, the MIP/f-MWCNT/GCE was analysed employing SWV in 0.010 mol L^{-1} $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$. The standard deviation found for 4 successive measurements was 2.0%, which means that the MIP sensor has good stability after its preparation.

The stability of the MIP sensor was evaluated by measuring its response current of three electrodes, which, after template removal from MIP structure, were stored dry at 25 °C for two months. The current results revealed that the analytical response was preserved during the first 20 days and 7 measurements, with standard deviation of 2.5%, indicating its good stability. After this period, the loss of the analytical response was greater than 10%.

3.7. Binding isotherm studies

The binding properties of the analyte to the MIP and NIP sensors were monitored by SWV measurements and evaluated using

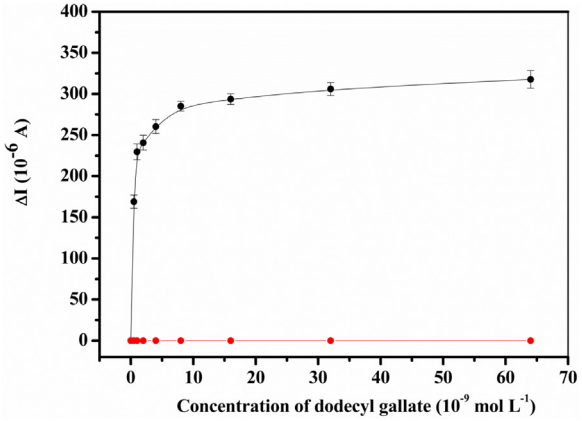

Fig. 5. Isotherm curve of the MIP (black line) and NIP (red line) for different dodecyl gallate concentrations. Measurements performed in 0.01 mol L^{-1} $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution prepared in KCl 0.1 mol L^{-1} (n = 3). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the isotherm curve in a range from 0.50 to 64.0×10^{-9} mol L^{-1} of DG and Fig. 5 shows the isotherm curves of NIP and MIP. The result was satisfactory, since there is a great difference between the curves' current intensities. The MIP curve (black line) presented a hyperbolic response with a proportional increase of ΔI in relation to the concentration of DG. On the other hand, the NIP curve (red line) presented insignificant ΔI value when compared to MIP. Therefore, it is clear that selective cavities for DG were formed successfully on the MIP struture. Moreover, the percentage of nonspecific binding in the polymeric structure is almost inexistent. This can be stated because there was no retention of DG to the NIP.

The apparent dissociation constant (K_D) of the MIP was calculate to evaluate the affinity of analytes to the polymer. The correlation between the binding capacity to the seletieve cavities of polymer film and the DG concentrations in solution was performed using the Langmuir isotherm model described in Eq. (1). For comparisson, the NIP constants were also calculated. The K_D can be determined from the curve fittings using the Langmuir isotherm model, and the results are shown in Fig. 5.

$$I_S = \frac{I_{max}}{1 + (K_D / [S])} \quad (1)$$

This constant is a combination of the amount of DG that interacts/binds to the film and its affinity. A low K_D value indicates large binding affinity between the polymer and analyte, consequently the reaction will approach the maximum velocity ($V_{máx}$) more rapidly. On the other hand, a high constant value shows that the interaction is not as efficient and the maximum binding capacity (B_{max}) will only be reached if the DG concentration is high enough to saturate the binding sites in the film [36].

The K_D was determined based on the slope of the linear region of the kinetic curves for $1/I_{max}$ vs. 1/C. The affinity constants of the MIP and NIP were calculated and the MIP film showed better features in terms of K_D when compared to NIP film. The K_D value for MIP films was 1.26×10^{-4} mol L^{-1} and 5.27×10^{-1} mol L^{-1} for NIP.

3.8. Selectivity study

The selectivity of the MIP sensor for DG was evaluated using three compounds: tetradecyl gallate, epigallocatechin gallate and N-benzyl-2-nitro-1H-imidazole-1-acetamide, whose structures are showed in Fig. 6. The first two compounds were chosen due to their similarity of functional groups, while N-benzyl-2-nitro-1H-imidazole-1-acetamide was used because it's the comercial drug used to treat Chagas disease. The analysis

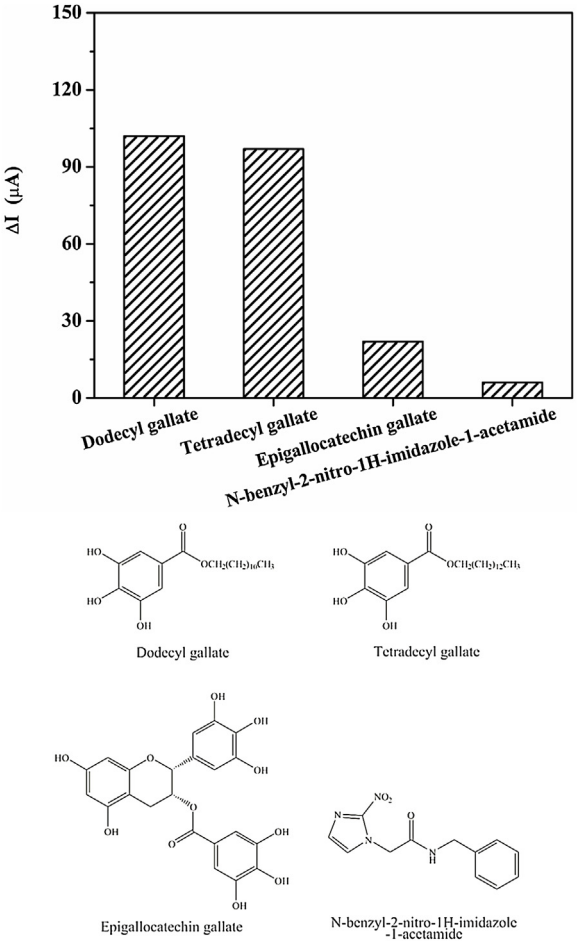

Fig. 6. Interaction of MIP with dodecyl gallate tetradecyl gallate, epigallocatechin gallate and N-benzyl-2-nitro-1H-imidazole-1-acetamide (4.0×10^{-9} mol L^{-1}) in 0.01 mol L^{-1} $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution prepared in KCl 0.1 mol L^{-1}, and chemical structures of such compounds.

were carried out interacting the MIP/f-MWCNT/GCE sensor and 4.0×10^{-9} mol L^{-1} of each compound during 2 min and then the current intensities obtained by SWV mesauremnts were compared (Fig. 6).

MIP for DG is quite selective compared to epigallocatechin gallate and N-benzyl-2-nitro-1H-imidazole-1-acetamide, since the last two compounds showed very low current intensity, indicating that there was practically no binding of these molecules to MIP cavities. However, tetradecyl gallate presented a current value very close to the DG value. As these two compounds have similar structures, differentiating only the linear methylene chain length bound to the galloyl moiety, probably the polymer mimicked cavieties for the galloyl group, demonstrating that the MIP/f-MWCNT/GCE sensor has the specific ability to recognize this moiety in dodecyl gallate.

4. Conclusions

Using o-phenylenediamine to prepare the polymeric film on the f-MWCNT/GCE, the MIP for dodecyl gallate was successfully synthesized. The MIP/f-MWCNT/GCE sensor proposed in this study presented good rebinding of the analyte to the selective cavities of MIP and high selectivity to the galloyl group. Therefore, the use of this MIP as a recognition element for electrochemical sensors represents a promising alternative for the determination of DG in aqueous solutions. Furthermore, it has other advantages, such as easy preparation at low cost and excellent selectivity, sensitivity and repeatability.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at **http://dx.doi.org/10.1016/j.snb.2017.06.127**.

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