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Development of a sensitive and selective kojic acid sensor based on molecularly imprinted polymer modified electrode in the lab-on-valve system

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ABSTRACT

In this work, a kojic acid electrochemical sensor, based on a non-covalent molecularly imprinted polymer (MIP) modified electrode, had been fabricated in the lab-on-valve system. The sensitive layer was synthesized by cyclic voltammetry using *o*-phenylenediamine as the functional monomer and kojic acid as the template. The template molecules were then removed from the modified electrode surface by washing with NaOH solution. Differential pulse voltammetry method using ferricyanide as probe was applied as the analytical technique, after extraction of kojic acid on the electrode. Chemical and flow parameters associated with the extraction process were investigated. The response recorded with the imprinted sensor exhibited a response in a range of 0.01–0.2 μmol L^{-1} with a detection limit of 3 nmol L^{-1}. The interference studies showed that the MIP modified electrode had excellent selectivity. Furthermore, the proposed MIP electrode exhibited good sensitivity and low sample/reagent consumption, and the sensor could be applied to the determination kojic acid in cosmetics samples.

1. Introduction

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4-pyrone) has many applications in cosmetics. Many consumers use products containing kojic acid and its derivatives to lighten freckles and other dark spots on the skin. In the area of food production, kojic acid is used to preserve food color and kill certain bacteria because it can inhibit the formation of dihydroxyphenylalanine from tyrosine in the process of melanin biosynthesis [1–3]. In addition, kojic acid plays an important role in monitoring fermentation process. However, because of the 4-pyrone in kojic acid molecules, it may have adverse effect on human health like benzene [4,5], so it is necessary to develop an assay method for the analysis of kojic acid.

Current methods used to determinate kojic acid are high performance liquid chromatography (HPLC) [6,7], ion pair liquid chromatography (IPLC) [8] and electrochemistry [9]. Among these methods, chromatography analysis is commonly adopted for specific determination of kojic acid, nevertheless this requires relatively expensive and complicated instruments. Electrochemistry shows attractive characteristics of high sensitivity, relatively inexpensive instrument and multi-element detection. Reports can be found for kojic acid electrochemical determinations with different modified electrode [10–12].

In recent years, the development of highly selective sensors for diverse applications has been the target of great research efforts. The demand of selectivity can be qualified by the specific interaction between analytes and chemical matrix of the sensor. Therefore, molecularly imprinted polymer (MIP) with excellent recognition ability appears as promising candidates to accomplish such requirements [13–15]. In particular, MIP offers important advantages such as the possibility of synthesizing polymers with a redetermined selectivity for a particular analyte. The imprinting process is obtained by polymerizing in the presence of a template molecule. After polymerization, the template is removed by washing, and then MIP demonstrates recognition properties towards the target analyte, due to the shape and chemical functionality considerations in the sites in the polymer matrix [16–18]. For the fabrication of the MIP based sensor, electrochemical methods are very often used both at the stages of preparing and using the MIP to detect the analytes. However, these methodologies are restricted to batch mode operations, which were laborious and large sample/reagent. From this respect, coupling of the on-line flow system using MIP as selective determination can be used as an excellent alternative for the development of electrochemical detection. Although some flow injection procedures based on amperometric detector using MIP as a selective solid phase extraction sorbent for sample preconcentration were described, due to

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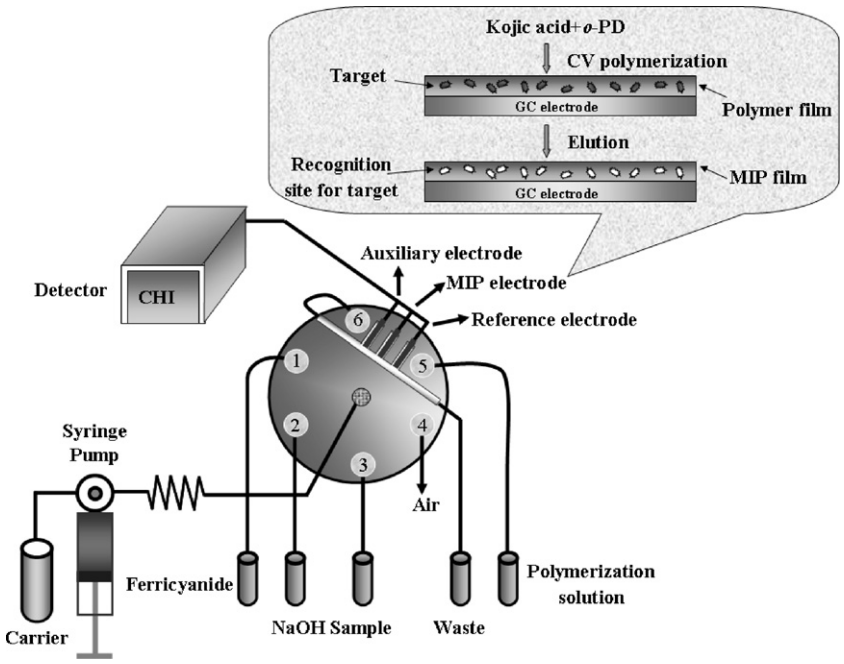

Fig. 1. Illustration of the SI-LOV manifold for the determination of kojic acid with MIP modified electrode.

their continuous flow character, still needed large amounts of reagent [19–21].

The sequential injection lab-on-valve (SI-LOV), as the third generation of flow injection, integrated all necessary laboratory facilities for fluidic handing, such as connecting ports, working channels and a multi-functioned flow cell [22–24]. It has been employed in a variety of applications of chemical and physical processes with detection by electrothermal atomic absorption spectrometry (ETAAS) [25], inductively coupled plasma mass spectrometry (ICPMS) [26], atomic fluorescence spectrometry (AFS) [27] and liquid chromatography (LC) [28]. In previous literatures, SI-LOV manifold coupled with electrochemical methods have been reported [29–31], which highlighted the advantages of electrochemical detection technique coupled with on-line operation systems. In this research we firstly developed a kojic acid sensor for sensitive and selective determination of kojic acid levels in cosmetics using a combination of molecular imprinting technology and electrochemical method in the SI-LOV system. The assay protocol comprised the following steps, including the electrode preparation, electrode washing, analyte extraction and electrochemical measurement. The characteristics of the MIP sensor were studied in details, and the proposed method was used successfully for kojic acid determination in cosmetics samples.

2. Experimental

2.1. Apparatus

Electrochemical studies were performed using a CHI660A electrochemical workstation (Chenhua Instrument, Shanghai, China). The SI-LOV system consisted of the following components: a FIAlab-3000 sequential injection system (FIAlab Instruments, Bellevue, WA, USA) and a home-made LOV unit. The sequential injection system equipped with a 2.5 mL syringe pump (Cavro, Sunnyvale, CA, USA) was employed for sample and reagent delivery. FIA software for Windows 5.0 was used to control the instrument. The LOV unit, incorporating an electrochemical flow cell (EFC) with a volume of 200 μL, was mounted on the multiport valve. A glassy carbon electrode modified with MIP was used as working electrode. A platinum wire and an Ag/AgCl electrode were used as the counter and reference electrodes, respectively. The scanning electron micrographs (SEM) images were obtained by scanning electron microscope (Hitachi S-4800, Japan). All externally used tubes were made of 0.8 mm i.d. PTFE tubing (Upchurch Scientific, OakHarbor, WA, USA).

2.2. Reagents and materials

Kojic acid and *o*-phenylenediamine (*o*-PD) were purchased from Aladdin Reagent Company (Shanghai, China). Other chemicals were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). 1 mmol L^{-1} ferricyanide solution that serves as probe was prepared by dissolving ferricyanide in 0.1 mol L^{-1} KCl medium. 1.2 mol L^{-1} NaOH solution was used for template removal. 5 mmol L^{-1} *o*-PD containing 10 mmol L^{-1} kojic acid in 0.2 mol L^{-1} acetate buffer solution (pH 5.2) was used for electropolymerization. 0.2 mol L^{-1} acetate buffer solution (pH 5.2) was employed as carrier stream. The chemicals and reagents were at least of analytical reagent grade and used without further purification. Double de-ionized water (18 MΩ cm^{-1}) was used throughout the experiments. Nitrogen gas (99.999%) was used for purging oxygen.

2.3. Operating procedure

Before determination, the glassy carbon electrode surface was polished manually to obtain a fresh surface. The proposed flow system for the determination of kojic acid was depicted in Fig. 1. The central port was connected to the syringe pump and also to any of the six ports of the multiport valve, at the same time, allowing the aspiration of ferricyanide (port 1), NaOH (port 2), sample (port 3) and polymerization solution (port 5) into the holding coil. The procedure consisted of the following steps, as described below: 200 μL of polymerization solution was aspirated by syringe pump and stored in the holding coil. Then the solution was reversed, and dispensed into the EFC while a potential range between 0 and 0.8 V was applied to the glassy carbon electrode during nine cycles (scan rate: 50 mV/s). After the electropolymerization process, 200 μL of NaOH solution was drawn pass the EFC to remove the template inside the polymer. Thereafter, 200 μL of sample solution was aspirated

into the holding coil followed by incubating the MIP electrode by stopped-flow approach for 8 min. At last, 200 μL of 1 mmol L^{-1} ferrocyanide containing 0.1 mol L^{-1} KCl was drawn and remained in the EFC. The electrochemical properties of the MIP were performed by differential pulse voltammetric measurements in the potential range from 0 to 0.4 V with the following instrumental parameters: pulse amplitude 50 mV, pulse width 0.05 s and step potential 4 mV. The non-imprinted polymer (nMIP) was prepared using the same procedure except that kojic acid did not exist in the polymerization mixture.

3. Results and discussion

3.1. Molecularly imprinting electropolymerization

In general, functional monomers are chemical species responsible to form the binding sites imprinted in the polymer, which should have the advantages of ease preparation and the possibility of obtaining very thin films with good reproducibility on many conductive substrates. Moreover, the monomers correspond to the template functional groups and the bonds should be strong enough to form the binding sites, yet weak enough to be further removed from the template. *o*-PD can be mentioned as the most frequently used acidic and basic functional monomers [32,33]. In most cases, the electrosynthesis of *o*-PD was performed by cyclic voltammetry in acid media to produce a very compact and stable polymeric film. The typical cyclic voltammograms recorded during the electropolymerization of *o*-PD on glassy carbon electrode in the presence of kojic acid are shown in Fig. 2, and the oxidation wave appears completely irreversibly. When the number of cycles increases, the peak current drops dramatically. Finally, the current intensity diminished, indicating the formation of nonconducting film, which hinders the monomer access to electrode surface. In addition, no significant difference was observed between the cyclic voltammograms obtained in the presence of kojic acid and in its absence under the same conditions, which can be explained by the fact that kojic acid does not have any electroactivity on glassy carbon electrode in the potential window chosen for the polymerization in acetate buffer (pH 5.2). As a result, the structure of kojic acid is not electrochemically changed in the polymerization process, and the mass transfer occurred by diffusion controlled process. Hence, the development of the molecular imprints favored by the diffusion of the template generated a higher number of recognition sites. The SEM pictures of kojic acid imprinted polymer after electropolymerization and being washed with NaOH solution were shown in Fig. 3. From Fig. 3a, we can see that the surface of kojic acid imprinted polymer was relatively smooth. After being washed with NaOH solution, kojic acid was removed from the molecularly imprinted polymer. As illustrated in Fig. 3b, kojic acid imprinted pores were revealed on the surface, and the surface of molecularly imprinted polymer without kojic acid was irregular, all obviously due to the templating process of the polymer with kojic acid.

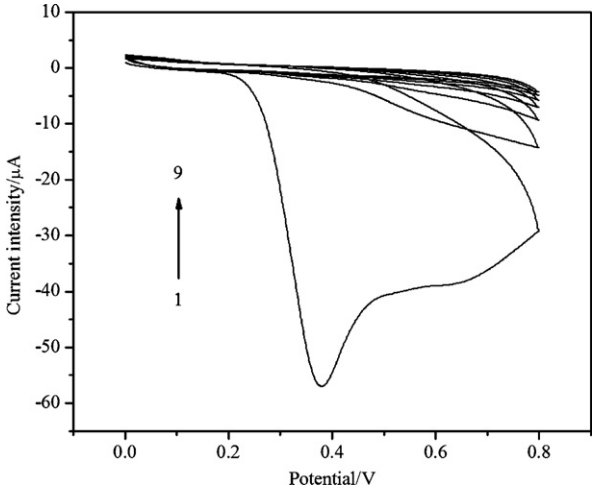

Fig. 2. Cyclic voltammograms for the electropolymerization of 5 mmol L^{-1} *o*-PD containing 10 mmol L^{-1} kojic acid at a GC electrode in acetate buffer solution (pH 5.2). Scan rate: 50 mV/s, sweep cycle: 9.

3.2. Electrochemical properties of MIP modified electrode

The oxidation of kojic acid at conventional carbon electrodes was kinetically sluggish and a relatively high overpotential was required. Hereby, ferrocyanide was chosen as the mediator between the imprinted electrode and substrate solution containing kojic acid. To further characterize the prepared electrodes, differential pulse voltammograms of different electrodes were performed in 1 mmol L^{-1} ferrocyanide solutions containing 0.1 mol L^{-1} KCl. Fig. 4 shows a comparison of differential pulse voltammograms among the four types of glassy carbon electrodes. The "*a*" curve shows the voltammogram on the bare glassy carbon electrode in the presence of ferricyanide. The "*b*" curve in Fig. 4 shows the voltammogram using the MIP glassy carbon electrode in the presence of ferricyanide, following removal of the imprinting kojic acid molecules. The "*c*" curve shows the same electrode after interaction with 0.1 μmol L^{-1} kojic acid. As expected, an obvious current decrease appears by using the MIP electrode comparing to the bare electrode. This behavior was attributed to the fact that the presences of cavities formed in film were partially occupied by kojic acid, which would lead to the decrease of current signal produced by ferrocyanide. Hence, the higher the concentration of kojic acid was, the lower the current would be. It is also noted that almost no electrochemistry properties could be observed with the nMIP

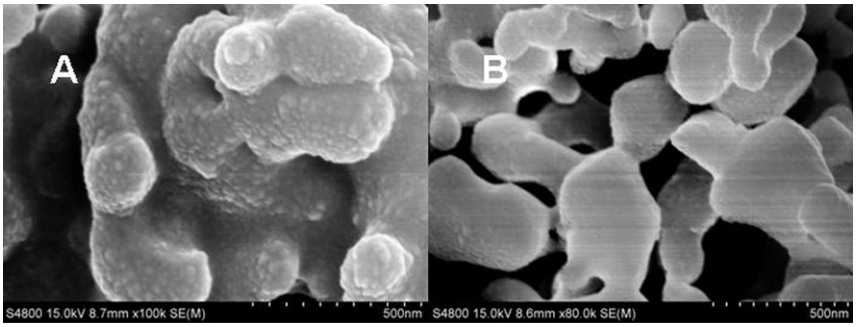

Fig. 3. SEM images of kojic acid imprinted polymer. (a) Was the high magnification image of kojic acid imprinted polymer; (b) was the high magnification of kojic acid imprinted polymer after being washed with NaOH solution.

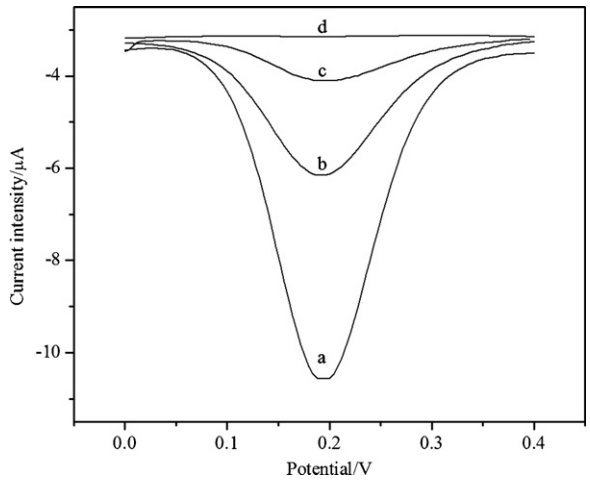

Fig. 4. Differential pulse voltammograms of three different electrodes in 1 mmol L^{-1} ferricyanide solution containing 0.1 mol L^{-1} KCl. (a) Bare GC electrode; (b) MIP modified glassy carbon electrode after removal of the template molecules; (c) MIP modified glassy carbon electrode after interaction with 0.1 μmol L^{-1} kojic acid; (d) nMIP modified electrode. Step potential 4 mV, pulse amplitude 50 mV; pulse width 0.05 s, scan range: 0–0.4 V.

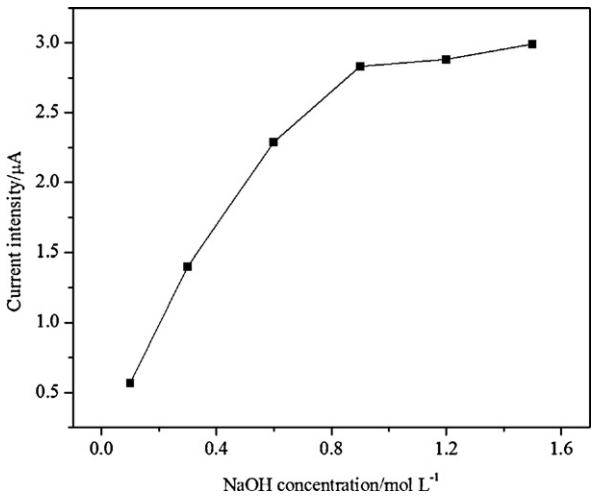

Fig. 5. Effect of NaOH concentration on the response current of the MIP electrode. Sample volume, 200 μL; soaking time 12 min; pH 5.2; incubation time 8 min.

electrode (Fig. 4d), which indicates that electro-inactive poly-*o*-phenylenediamine membranes completely covered on the surface of the glassy carbon electrode and hindered ferrocyanide access to electrode surface.

3.3. Effect of template concentration

The template concentration during polymerization has an important influence on the subsequent voltammetric behavior of the sensor. In order to find the best template concentration on the response of MIP electrode, the film was grown in solutions of 5 mmol L^{-1} of *o*-PD and varying kojic acid concentration in the range of 1–25 mmol L^{-1}. At first, the increasing of kojic acid concentration for MIP electropolymerization leads to an increase in the electrode response. This observation can be attributed to the fact that higher amounts of kojic acid concentration can increase the sensor response because of providing more recognition sites on the electrode surface. After a definite point of 10 mmol L^{-1}, further higher kojic acid concentration results in lowering the corresponding signal in the prepared electrode, probably because of electrode surface conductivity decreasing. Therefore, the template concentration of 10 mmol L^{-1} was selected as the best condition.

3.4. Effect of polymerization cycles

Kojic acid molecules diffuse towards the surface of the MIP electrode during the electropolymerization process and are trapped into the polymer matrix, hence, an excessively thick layer would not be beneficial for fast response kinetics. The thickness of the polymer can be easily controlled by the number of cyclic voltammetry cycles during electropolymerization. The optimum number of cycles to form the sensitive layer on the electrode is varied from 7 to 11 in this research in order to determine the optimal film thickness. If less than 9 cycles was applied, the electrode surface will not be covered completely and resulted in poor sensing reproducibility and isolating properties. However, in the case of higher numbers of cycles, kojic acid molecules are likely buried deeply within the polymer film, and no further improvements were observed with increasing number of scans. Hence, the optimum polymerization cycles was found to be 9 throughout the experiments.

3.5. Template removing treatment

In order to achieve a satisfactory sensitivity and reproducibility of the MIP electrode, the template removing treatment needs to be improved because more imprint sites can ensure a better analytical performance. Different solvent such as ethanol, methanol, ultra pure water and NaOH solution [33,34] were tested as eluent to remove template. The results indicated that alcohol, methanol and ultra pure water can only partially remove the template, while NaOH solution can remove it more quickly and completely because kojic acid can easily dissolve in NaOH solution. A more detailed study of the effect of NaOH concentration on the response was carried out within the range of 0.1–1.5 mol L^{-1}. The current responses of the ferrocyanide are presented in Fig. 5. The peak current increased with increasing concentration of NaOH, and a saturation value was achieved at NaOH concentration of 0.9 mol L^{-1}, which represented the template was washed completely. At last, using 1.2 mol L^{-1} NaOH solution was found to be suitable for template removal.

Moreover, the soaking time for template removal in a range from 4 to 16 min was carefully investigated. As can be seen in Fig. 6, the peak current considerably increased with the soaking time augmented from 4 to 10 min. With further increasing

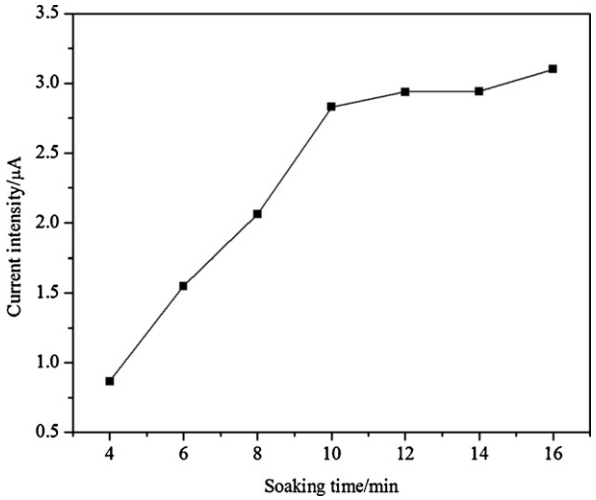

Fig. 6. Effect of soaking time on the response current of the MIP electrode. Sample volume, 200 μL; NaOH concentration 1.2 mol L^{-1}; pH 5.2; incubation time 8 min.

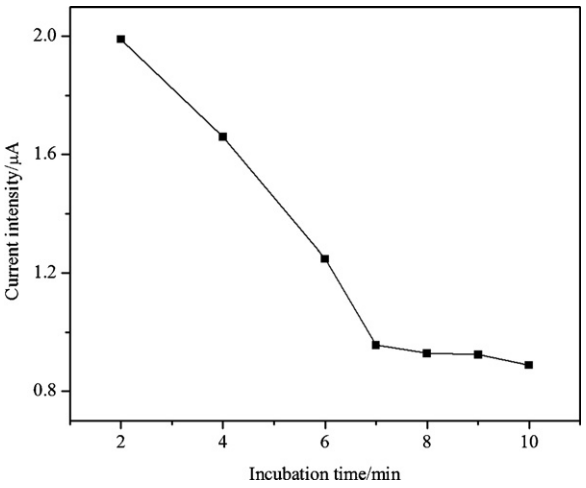

Fig. 7. Effect of incubation time on the response current of the MIP electrode. Sample volume, 200 μL; NaOH concentration 1.2 mol L^{-1}; soaking time 12 min; pH 5.2.

the soaking time higher than 10 min, the peak current gradually approached stable. Thus 12 min was selected as the best condition.

3.6. Effect of pH

Since the extraction process was carried out by differential pulse voltammetry in EFC, an acetate buffer media was chosen to perform this procedure in order to facilitate the extraction of the template molecules. The sample solutions with various pH values were tested. As can be deduced from the results, the signal intensity of ferrocyanide increased with the pH increasing from 4.4 to 5.2, thereafter, a decline of signal intensity was observed by further increasing the pH up to 6.0. For further studies a pH of 5.2 was chosen.

3.7. Effect of incubation time

The incubation time of template molecules became more important when on-line MIP was exploited as a compromise between template rebinding kinetics and sampling frequency. In this paper, the influence of incubation time on the analytical signal was evaluated by stopped-flow approach. The protocol for a stopped-flow assay consisted of aspiration of defined sample into the holding coil, followed by a flow reversal that dispensed the solutions to the EFC for signal measurement. Compared with the traditional flow technique, stopped-flow assay could reduce sample and reagent consumption and waste generation. For this aim the sample solution with a volume of 200 μL remained in the EFC with various time for interaction with the MIP electrode. Afterwards the sample solution was removed from the EFC, and the electrochemical properties of the films were measured by differential pulse voltammetric measurements in ferrocyanide solution. Fig. 7 displayed the influence of incubation time on the analytical signal. According to this figure the increasing of incubation time leaded to an intensive decrease in the kojic acid extraction amount in the electrode until about 7 min. With further increasing the incubation time higher than 7 min, the number of the binding sites in the MIP would be completely occupied by kojic acid molecules, which caused the peak current to remain unchanged. Taking into accounts that a lower incubation time did not allow an efficient interaction whereas a higher one would impair the analytical frequency, the optimum incubation time of 8 min was used for the determination kojic acid.

3.8. Selectivity of the MIP electrode

After the optimization and establishment of the determination method, the selectivity of the MIP electrode in this work was evaluated in the determination of kojic acid. The tolerance limit was established as the maximum concentration of foreign species that caused a relative error of ±5% in the analytical response. For 0.1 μmol L^{-1} of kojic acid, some possible interfering ions and molecules with respect to their interference are tested. These substances are present in cosmetics samples and may interfere with the determination of kojic acid. It is found different species have almost no influence in the determination procedure of kojic acid, with a change of less than ±5%, such as 500-fold concentration of HCO_3^-, NO_3^- and SO_4^{2-}, 200-fold concentration of dopamine, glucose, cysteine, uric acid, thiamine, Ni^{2+}, Bi^{3+}, Pb^{2+}, Mg^{2+} and Ca^{2+}, 100-fold concentration of pyridoxine and ascorbic acid. However, 50-fold concentration of Cu^{2+} and Zn^{2+} and 5-fold concentration of Fe^{3+} and Al^{3+} had a significant influence on the signal of kojic acid due to the fact that these metallic ions could form complexes with kojic acid and affect the extraction of kojic acid at electrode surface. However, these interferences were easily alleviated by addition EDTA that formed stable complexes with Fe^{3+} and Al^{3+}. In our experiments, 0.02 mol L^{-1} of EDTA was sufficient to alleviate the interference by 40-fold of Fe^{3+} and 40-fold of Al^{3+} on 0.1 μmol L^{-1} kojic acid with no effect on the analytical signals. From the estimation results it can be seen that the method possessed good selectivity of recognition to kojic acid compared with the reported literatures [9,10,12] and can be used to analysis practical samples without any masking reagent by means of shape selection and the size of functional groups.

3.9. Analytical features of the method

Using the optimized conditions for the proposed method, the calibration graph of the prepared sensor showed a linear relationship over kojic acid concentration in the range of 0.01–0.2 μmol L^{-1}. Linear regression was $i_p = -7.6481\, C_{\text{kojic acid}}(\mu\text{mol L}^{-1}) + 1.6804$ and the linearity correlation coefficient was 0.9964. The limit of detection (LOD) was evaluated using the expression $3\sigma/s$, where σ indicated the standard deviation of the response, s was the sensitivity obtained from the slope of the analytical calibration curve. The LOD of 3 nmol L^{-1} was obtained. When higher concentrations of kojic acid were employed, saturation of rebinding sites occurred and linear response became curved. Reproducibility of the sensor was evaluated under eleven continuous voltammetric measurements of the 0.1 μmol L^{-1} kojic acid solution and the relative standard deviation (RSD) for the same sensor was 4%. The developed kojic acid selective electrode was able to be used at least 20 times, with subsequent washing and measuring operations, obtaining a repetitive signal. Thus, it can be affirmed that the covering has a good stability.

3.10. Comparison of the other methods

The proposed method is compared with several other methods such as HPLC and electrochemistry that have been used for kojic acid determination. The results are shown in Table 1. As illustrated, the linear range and detection limit of this work are better than those of the other reported methods. In addition, the main advantages of the established methodogy are simplicity, automatic, and low cost and these advantages of the method make it very convenient for the determination of trace amount of kojic acid in real samples.

3.11. Detection of kojic acid content in commercial samples

The practical applicability of the developed MIP sensor was applied to the determination of kojic acid in commercially available

Table 1
A comparison of analytical performance by the present procedure versus HPLC and some modified electrodes for the determination of kojic acid.

Methods	System	Linear range (μmol L^{-1})	Limit of detection (μmol L^{-1})	Ref.
HPLC	Batch	0.5–2	0.07	6
HPLC	Batch	–	21	7
PVP (polyvinylpyrrolidone) modified acetylene black paste electrode	Batch	1.0–100	0.5	9
Hollow CuO/Fe_2O_3 hybrid microspheres and Chi modified glassy carbon electrode	Batch	0.2–674	0.08	10
Preanodized screen-printed carbon electrode	Batch	up to 260	0.17	11
Carbon nanotube/alizarin red S modified electrode	Batch	0.4–60	0.1	12
MIP modified electrode	Automatic	0.01–0.2	3×10^{-3}	This work

Table 2
Analytical results obtained from analysis of some real samples.

Sample	Found by the proposed method[a] (μmol L^{-1})	Spiked (μmol L^{-1})	Found (μmol L^{-1})	Recovery (%)
1	0.0314	0.0200	0.0508	97.0
		0.0400	0.0730	104.0
2	0.1047	0.0200	0.1243	98.0
		0.0400	0.1449	100.5

[a] Represents the average of three determination.

cosmetic products. Two kinds of kojic acid cosmetics samples were purchased from a local super market. Before determination, 0.4 mL of sample solution was transferred to 100 mL volumetric flask, followed by the dilution with 0.2 mol L^{-1} acetate buffer solution (pH = 5.2). The concentration of kojic acid was determined directly or further appropriately diluted to draw the kojic acid concentration within the linear range. Differential pulse voltammograms were then recorded under optimized conditions and the analytical results for spiked samples were listed in Table 2. The spiked recoveries, in a range from 97 to 104%, are acceptable under all conditions, indicating that the proposed method is feasible with high accuracy for the determination of kojic acid.

4. Conclusions

A new MIP-based electrochemical sensor was implemented in a lab-on-valve system for separation/preconcentration of kojic acid. A comparison of the performance characteristics of the developed procedure with those of the previously reported ones revealed that the assembled sensor has shown promising results in the kojic acid detection at μM concentration and a significant selectivity being able to exclude the coexisting interferences in samples. Moreover, coupling of MIP in the LOV could be developed as an advantageous alternative to the traditional electrochemical analytical systems working in batch mode in terms of low cost, improved system ruggedness and flexibility. The prospects of future development of this method would be used to estimate the parameters in the MIP recognition process as well as eliminate the potential interference of some heavy metals.

Acknowledgements

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