Available online at www.sciencedirect.com
SCIENCE DIRECT®
Talanta 66 (2005) 1225–1233
Talanta
www.elsevier.com/locate/talanta

Fourier transform cyclic voltammetric technique for monitoring ultratrace amounts of salbutamol at gold ultra microelectrode in flowing solutions

Mohammad Reza Ganjali *, Parviz Norouzi, Maryam Ghorbani, Ali Sepehri

Department of Chemistry, Tehran University, Tehran, Iran

Received 3 December 2003; received in revised form 26 December 2004; accepted 13 January 2005
Available online 17 March 2005

Abstract

This work introduce an easy and fast continuous cyclic voltammetric technique for the propose monitoring of ultra trace amounts of salbutamol in a flow–injection system. The potential waveform, which consisted of the potential steps for cleaning, stripping and potential ramp, was continuously applied on an Au disk microelectrode (with a radius of 12.5 μm). The detection method we propose has some advantages, the greatest of which are: (1) removing oxygen from the analyte solution is no longer necessary, and (2) it is a very fast and appropriate technique for the determination of the drug compound in a wide variety of chromatographic analysis methods. The detection limit for salbutamol was 2.0×10^{-9} M. The relative standard deviation (R.S.D.) of the proposed technique at 10 ng/mL was 3.5% for 10 runs. The effects of pH of eluent, accumulation potential, sweep rate, and accumulation time on the sensitivity of the method for the determination of the salbutamol were investigated. The proposed method was applied to the determination of salbutamol in pharmaceutical preparation and biological samples.

Keywords: Salbutamol; Flow injection analysis; Cyclic voltammetry

1. Introduction

Salbutamol {2-(*tert*-butylamino)-1-(4-hydroxy-3-(hydroxymethyl)phenylethanol}, was also known as albuterol, is clinically the most widely used B_2-adrenoceptor agonist in the treatment of bronchial asthma (Fig. 1). Depending on their route of administration, B_2-agonists produce a certain amount of anabolic-like effect. The use of salbutamol is therefore restricted by the International Olympic Committee (IOC). It is only permitted by inhalation and, even then, must be declared in writing to the relevant medical authority prior to the competition [1]. Salbutamol is also applied as a tocolytic agent in humans as well as in veterinary medicine (this drug may display lipolytic effect in higher doses) and residues of these compounds, which are most abundant in liver and meat, can be toxic to humans [2,3].

Literature survey revealed that several techniques have been adopted for the determination of salbutamol. These include, high-performance liquid chromatography (HPLC), HPLC–mass spectrometry (MS), gas chromatography–MS, electrokinetic chromatography, MS, LC, immunoassay, capillary electrophoresis, spectrophotometry, polarography, potentiometry using ion-selective electrodes, and voltammetry [4–15].

Stripping voltammetric techniques have the advantages of being both rapid and economical in the determination of most organic and inorganic compounds in aqueous systems, with a sensitivity range of parts-per-billion [16]. In fact, because of the movement of analyte zone in an electrochemical flow cell, application of such techniques in the flowing solutions requires fast accumulation of the analyte and fast potential sweeping, which is not appropriate in the case of large electrodes [17,18]. Electrochemical measurements, which are kinetically controlled (or in other words, irreversible), are not generally well-suited to such processes, if performed at solid electrodes. This resulted from the fact that the surface of the

* Corresponding author. Tel.: +98 21 6112294; fax: +98 21 6495291.
E-mail address: ganjali@khayam.ut.ac.ir (M.R. Ganjali).

0039-9140/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.talanta.2005.01.045

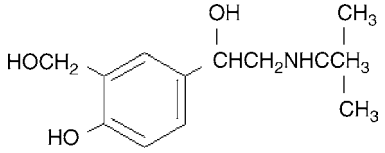

Fig. 1. Structure of salbutamol sulfate.

solid electrodes can be easily poisoned (or deactivated) by the products of the red/ox reactions of the desired species or impurities present in the test solution. However, application of ultra microelectrodes (UMEs) solves most of the problems of these detection methods. In fact, use of voltammetric techniques,, has been further stimulated by the advent of UMEs, due to their steady state currents, higher sensitivity, increased mass transport, and their ability to be used in electroanalysis in solutions with a very high resistance.

Another problem is caused by the changes in the properties of the electrode surface during the potential scan. If the surface of the solid electrode is repeatedly oxidized and reduced during voltammetric measurement, is associated with high levels of noise due to the structural changes of the electrode surface (the electrode signal will have a large background current) [19]. Since such currents, can interfere with the desired electrode processes, and may adversely affect the detection limits of the method [20]. Application of a potential sweeping technique, such as cyclic voltammetry or square wave voltammetry, associated with a potential waveform for electrode cleaning, can be of great help [21]. Electrochemical conditioning (EC) permits the maintenance of a clean and active electrode surface for long periods of time.

The background current in voltammetric measurements, as we will discuss, can provide useful information about the adsorption processes and changes occurring in the double layer at the electrode surface. In square wave voltammetric measurements, for instance, the change in the double layer capacitance occurs due to adsorption of species on gold UMEs was used for the determination of medicines [22]. In addition, a low adsorption of species existing in the solution and on the electrode surface can strongly affect the cathodic and anodic currents of red/ox reaction that occur at the electrode.

Recently, a number of electrochemical methods such as electrochemical impedance spectroscopy, mathematical modeling of the ac voltammetry, and modulated linear-ramp voltammetry have been combined with FFT methods for the increasing of sensitivity and simplicity of data analysis [23–26].

In this work we wish to introduce a simple and very fast voltammetric detection method in a flow–injection system for the monitoring ultra trace amounts of salbutamol. A special computer based numerical method is also introduced for calculating the analyte signal and noise reduction. The calculation of the signal was based on the net partial and total charge exchanges at electrode surface by integrating currents at whole potential range at the cyclic voltammogram (CV). Depending on applied conditions, the detector can be used in the determination of a variety of compounds in a choice of chromatographic analysis methods (e.g., capillary electrophoresis). Moreover, the sensitivity of the method was improved significantly depending on the mode of data processing used in the calculation of the detector response.

2. Experimental

2.1. Reagents

All solutions were prepared in double-distilled deionized water, using analytical grade reagents. The reagents used to prepare the stock eluent solution for flow injection analysis (0.05 M H_3PO_4 and 1.0 M NaOH used for adjusting the pH of the eluent) were obtained from Merck Chemicals. Salbutamol sulfate was a gift from center of quality control (Tehran, Iran). In all experiments, solutions were made up in the background electrolyte solution, and were used without removal of dissolved oxygen.

2.2. Procedure for the preparation of standard salbutamol solutions

Stock solution (1.0 mg mL^{-1}) of salbutamol sulfate prepared by dissolving 100 mg of the drug sample in 100 mL of distilled water. This solution was further diluted daily with water to give the appropriate concentration for the working solution.

2.3. Procedure for the determination of salbutamol in tablet

Weigh and thoroughly grind ten tablets. Extract an accurately weighed portion of the obtained powder equivalent to 5.0 mg of salbutamol with 25 mL of 0.05 M phosphoric acid. Shake for about 10 min, filter the mixture into 100 mL measuring flask and wash the residues several times and diluted to the mark with phosphoric acid. 10 μL of the final solution was diluted with 0.05 M phosphoric acid to a 100 mL flask and the method described for the determination of salbutamol sulfate was applied to the commercial prepared tablet.

2.4. Procedure for spiked urine and serum samples

An aliquot of a standard aqueous solution of salbutamol sulfate containing (1.0–5.0 μg) was added to 0.5 mL of urine or serum sample in a centrifuge tube and vortex for 20 s. Fifty microliter of 0.1 M NaOH solution was added, shaken for few seconds, followed by the addition of 2.5 mL dichloromethane. The mixture was vortex mixed at high speed for 2 min, and then centrifuged at 3000 rpm for 10 min. The resulting supernatant was transferred to a small conical flask. The extract was evaporated to dryness at 60 °C and the residue was dissolved in 0.5 mL water, diluted with 0.05 M

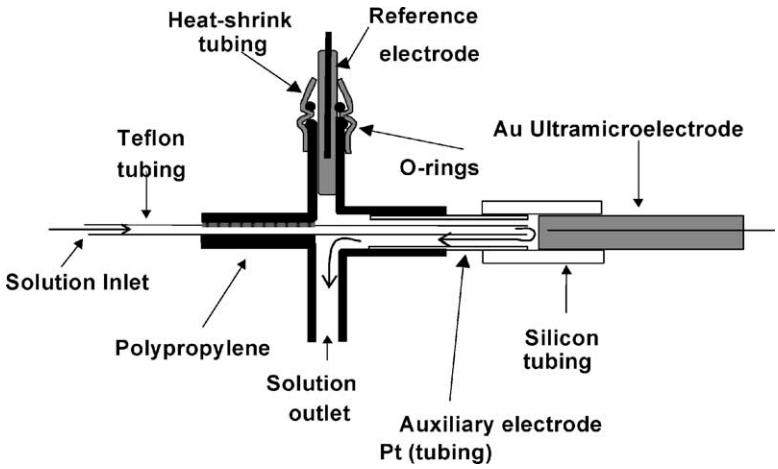

Fig. 2. Diagram of the electrochemical cell.

phosphoric acid to a 100 mL flask and then analyzed according to the recommended procedure.

2.5. Flow injection setup

The equipment for flow injection analysis included a 10 roller peristaltic pump (LKB Co. 2115 Miltiperpex) and a four-way injection valve (Supelco Rheodyne Model 5020) with a 50 μL sample injection loop. Solutions were introduced into the sample loop by means of a plastic syringe. The electrochemical cell used in flow–injection analysis is shown in Fig. 2. In all experiments described in this paper, the flow rate of eluent solution was 100 μL/min.

2.6. Electrode preparation

Gold UMEs (12.5 μm, in diameter) were prepared by sealing metal micro-wires (Good fellow Metals Ltd., UK) into a soft glass capillary. The capillary was then cut perpendicular to its length to expose the wire. Electrical contacts were made using silver epoxy (Johnson Matthey Ltd., UK). Before each experiment the electrode surface was polished for 1 min using extra fine carborundum paper and then for 10 min with 0.3 μm alumina. Prior to being placed in the cell the electrode was washed with water. In all measurements, an Ag (s) | AgCl (s) | KCl (aq, 1.0 M) reference electrode was used. The auxiliary electrode was made of a Pt wire, 1cm in length and 0.5 mm in diameter.

2.7. Data acquisition and processing

All electrochemical experiments were carried out using a setup comprised of a PC PIII Pentium 300 MHz microcomputer equipped with a data acquisition board (PCL-818HG, Advantech Co.) and a custom made potentiostate [27]. The diagram of applied potential waveform during cyclic voltammetric measurements is shown in Fig. 3. The potential waveform consists of two sections. In the first section, the electrode surface is electrochemically cleaned by applying two potential steps. The first step includes strong oxidation of the electrode surface by applying a very positive potential (E_{Ec1} = 1800 mV, for 100 ms). During this time, all the adsorbed analyte molecules are removed from the surface, and in the second step, the electrode surface is recovered(or renewed) by applying a negative potential (E_{Ec2} = −400 mV, for 100 ms). One reason for having a clean electrode surface is that after each injection the base line of the response curve returns to its original value (see Fig. 6). This part is followed by potential step *E*s, where stripping of the analyte takes place. Finally the current measurements take place during the potential ramp. All data acquisition and data processing programs were developed in Delphi 6® program environment.

2.8. Signal calculation

As mentioned above, the current passing through the electrode was sampled only during the potential ramp. In this detection method the integration of net current changes is applied all over the scanned potential range. It must be noted that in this case, the current changes at the voltammograms (as a result of the injected analyte) can be caused by vari-

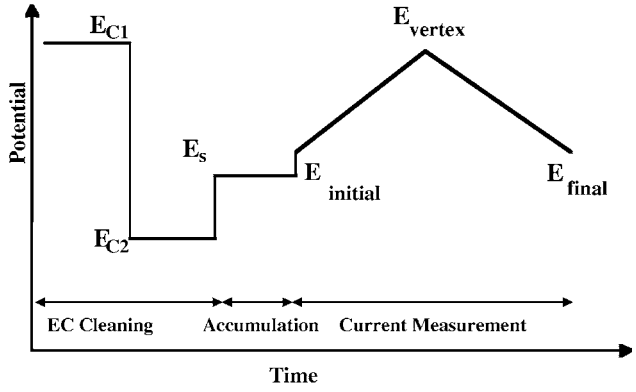

Fig. 3. Diagram of the applied potential waveform.

ous processes that can occur at the electrode surface. These processes include: (a) oxidation and reduction of adsorbed analyte and (b) inhibition of oxidation and reduction of the electrode surface by the adsorbed analyte molecules. Indeed, in order to see the influence of the adsorbed analyte on the oxidation and reduction peaks of the gold surface, the scan rate must be set very high (e.g., > 20 V/s). However, during the scan, some of the adsorbed analyte molecules are desorbed. Depending on the rate of these processes and the scan rate, the amount of the desorpted analyte molecules can change during the scan. The important point here is that part of the adsorbed analyte still remaining on the electrode surface can inhibit the redox process on the electrode surface.

In this method, which was used for nonselective measurement, ΔQ is calculated based on the all of the current changes at the CV. A total absolute difference function (ΔQ) can be calculated using the following equation:Where, s is the sweep number, τ is the time period between subsequent sweeps, Δt is the time difference between two subsequent sampling points on the CV curves, $i(s, E)$ represents the current of the CV curve recorded during the sth sweep and $i(s_r, E)$ is the reference current of the CV curve. E_i and E_v are the initial and vertex potential, respectively. The reference CV curve was obtained by averaging a few CV curves recorded at the beginning of the experiment (i.e. before injection of the analyte). Typically, the averaging of CVs included the 5–10 curves. These equations show that for the same flow injection experiment the analyte response can be obtained using different integration limits. However, the selectivity and sensitivity of the analyte response expressed in terms of ΔQ strongly depends on the selection of the integration limits.

It should be noted that in this method, all studied processes involve the adsorption of analyte; hence both charging and faradic currents may potentially carry useful analytical information. Also, in order to remove noise from the data a second order low pass filters with a 0.5–50 kHz cutoff frequency were placed between the current output of the potentiostate and the data acquisition board. If the main contribution to the baseline noise is from the "white" noise generated by the potentiostate, the integration procedure usually provides a 3–20-fold improvement in signal-to-noise(S/N) ratio compared to the simple monitoring of the current at a fixed potential. However, in the case of severe environmental noise (e.g. power line noise) the improvement may be much larger.

One of the important aspects of this method is the application of a special analog filtration, which is applied during the measurement. In this method, a CV of the electrode was recorded at first (see Fig. 4a) and then the existing high frequency noises were indicated (by applying FFT on the collected data) (see Fig. 4b). Finally, using this information, the cutoff frequencies of the analog and digital filters were set at a certain value (where the noises were removed from the CV). The resulted CV in Fig. 4c shows the successfulness of the filtering procedure. The FFT procedure for filtering noise is well established in electrochemistry.

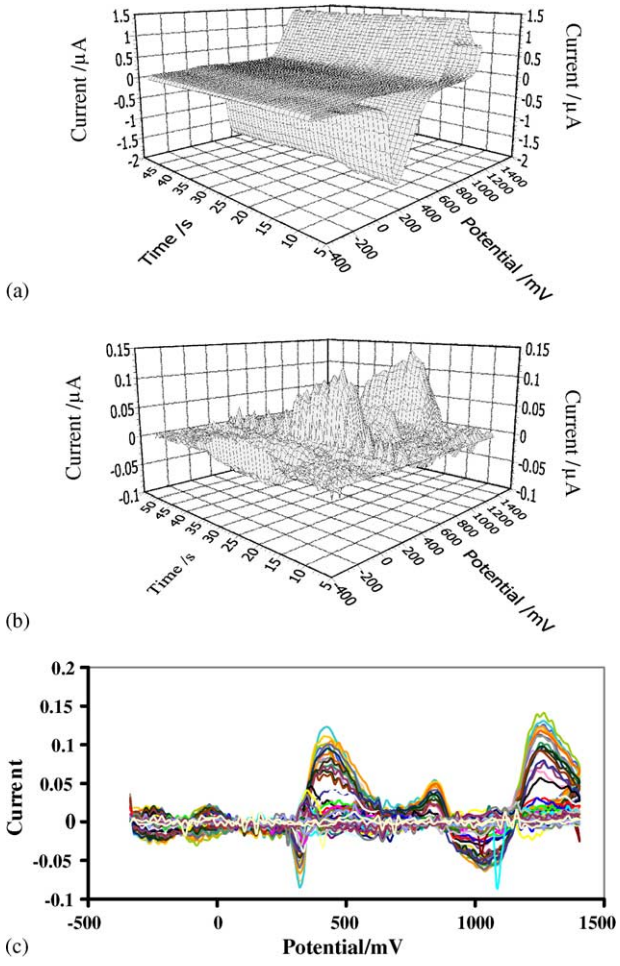

Fig. 4. Typical cyclic voltammogram of Au disk ultra-microelectrode in 0.05 M H_3PO_4 (eluent). The rate was 100 μL/min, and the sweep rate was 0.5 V/s. (a) without any filtration, (b) FFT diagram of the voltammogram, and (c) after applying filtration and removing (the cut off frequency was 40 Hz).

3. Results and discussion

The main problem was the stability of the background signal in this detection method. This was mainly due to the changes which occurred in the surface crystal structure during oxidation and reduction of the electrode in each potential cycle. Since the crystal structure of a polycrystalline gold electrode is strongly dependent on the condition of the applied potential waveform [28], therefore, various potential waveforms were examined in order to obtain a reproducible electrode surface (or a stable background signal). As a result, the best potential waveform that could produce a stable background and unchanged surface structure was the waveform shown in Fig. 3. An example of the application of that waveform is shown in Fig. 5. This figure shows a sequence of CVs recorded during the flow injection of 50 μL of 1.0×10^{-8} M salbutamol (in 0.05 M H_3PO_4) into the eluent solution containing 0.05 M H_3PO_4. The potential axis on this graph represents the potential applied to the working electrode during

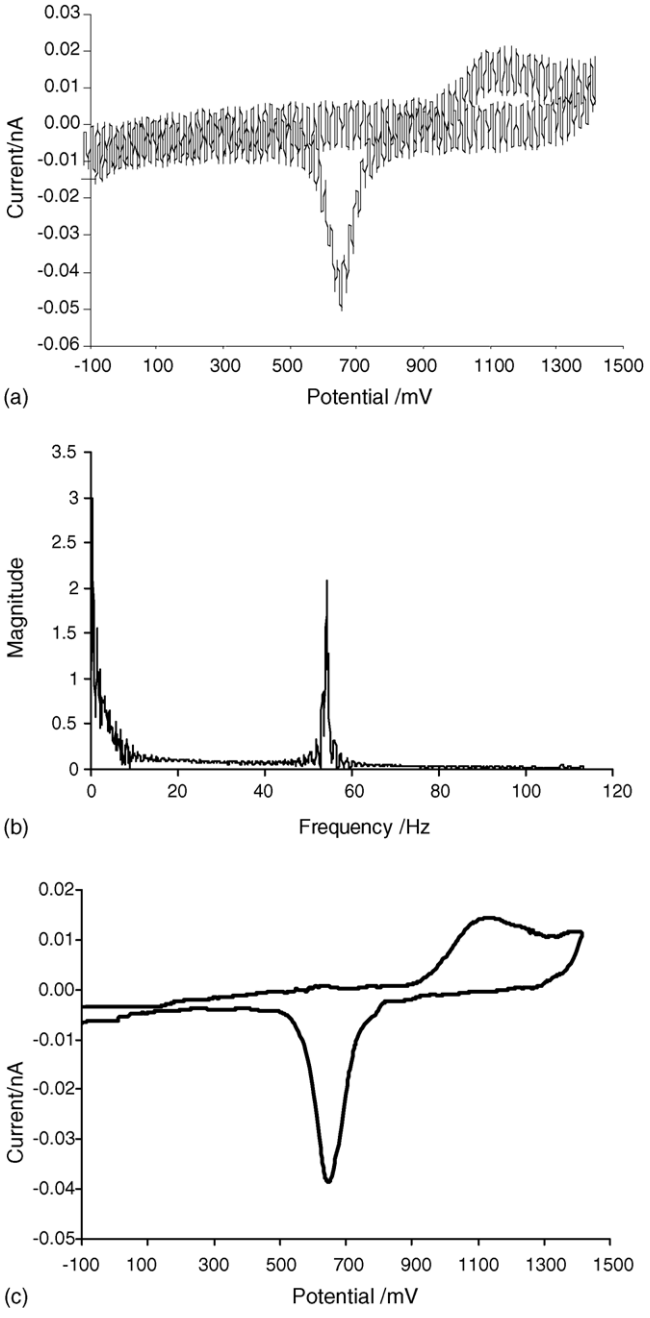

Fig. 5. (a) Cyclic voltammograms at a 12.5 μm Au ultra-microelectrode recorded during a flow–injection experiment. The eluent was 0.05 M H_3PO_4, the flow rate was100 μL/min, and the sweep rate was 125 V/s. Each scan was preceded by 100 ms (at 1600 mV) and 200 ms (at −400 mV) conditioning and accumulation period, respectively. The accumulation time was 700 ms at −300 mV. The injected solution (50 μL) contained 1.0×10^{-8} M salbutamol Sulfate in 0.05 M H_3PO_4. (b) Curves result of subtraction of an average CVs (in absent of the analyte) from test of the CVs in (a), (c) overlapping curves in (b).

each sweep. The time axis represents the time passing between the beginning of the flow injection experiment and the beginning of a particular sweep (i.e. it represents a quantity proportional to the sweep number). As can be seen, in the absence of salbutamol the shape of the CV curves is typical for a polycrystalline Au electrode in acidic media. The characteristic element of the CVs at the gold electrode is a set of peaks associated with the formation and dissolution of a surface oxide layer at about 1600 and 400 mV (when potential sweep rate is 125 V/s), respectively. The process is also initiated by the electro-sorption of the hydroxyl ion, which at more positive potentials undergoes deprotonation and structural rearrangement [29]. The surface oxidation can be initiated by adsorption of water molecule and then at more positive potential AuOH forms leading to the formation of a two-dimensional phase of gold oxide;

$$Au(H_2O) \rightarrow AuOH + e + H^+ \quad (1)$$

At more positive potentials AuO is made according to the following reaction:

$$AuOH \rightarrow AuO + e + H^+ \quad (2)$$

Fig. 4b and c show the absolute current changes in the CVs curves after subtracting the average background five CVs (in the absence of the analyte). As can be seen, this way of presenting the electrode response gives more details about the effect of the adsorbed the ions on currents of the CV. The curves show that current changes mainly take place at the potential regions of the oxidation and reduction of gold. When the electrode-solution interface is exposed to salbutamol, which can be adsorbed on the electrode, the oxide formation process is strongly inhibited [30]. In fact, the inhibition of the surface process causes significant change in the currents at the potential region, and as a consequence the profound changes in the shape of CVs take place. Universality of the detector in this mode is very advantageous for chromatographic analysis, where a mixture of compounds, are present in sample.

Fig. 6 illustrates the flow injection response-time of the detector due to the injection of 50 μL of solutions of 1.0×10^{-8} M salbutamol in H_3PO_4 0.05 M. Each curve is given using Eq. (1).

A few points must be taken into consideration in this detection method. Theoretically, the analyte response can be

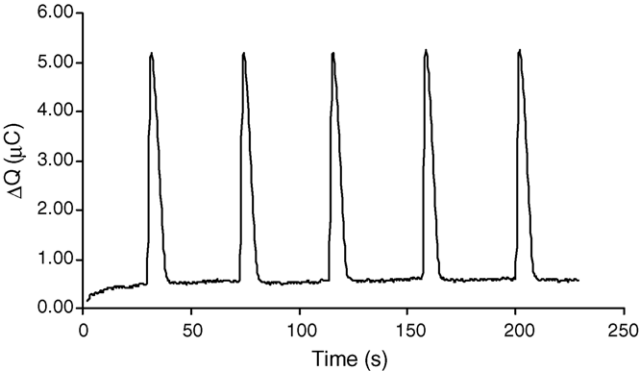

Fig. 6. Response of Au ultra-microelectrode to 5 consecutive injections of 1.0×10^{-8} M salbutamol sulfate. All experimental conditions as in Fig. 3. Curve represent [Q function calculated according to Eq. (1).

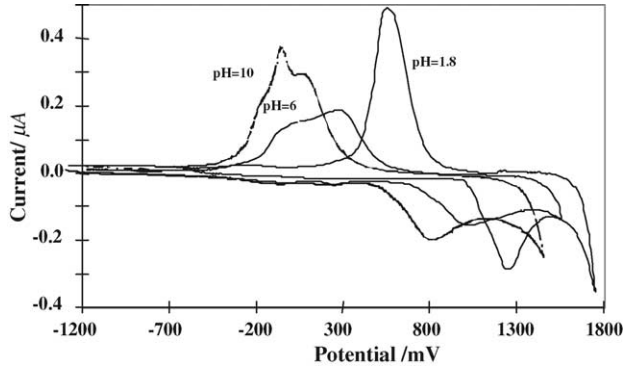

Fig. 7. Cyclic voltammograms of Au electrode in various pHs at the sweep rate 125 V/s.

affected by the thermodynamic and kinetic parameters of adsorption, the rate of mass transport, and the electrochemical behavior of the adsorbed species. The free energy and the rate of adsorption depend on the electrode potential, the electrode material, and to some extent, on the choice of concentration and the type of supporting electrolyte. In order to achieve maximum performance of the detector, the effect of experimental parameters were tested and optimized. These parameters were the pH of the supporting electrolyte, the potential and the time of the cleaning steps, the potential and the time of the accumulation and the potential sweep rate.

3.1. Effect of the pH of the eluent

The cyclic voltammograms of Au electrode in various pH of the eluent (H_3PO_4) were tested and the results are depicted in Fig. 7. As can be seen from Fig. 7, the pH of the eluent changes the potentials of oxidation and reduction of the gold electrode. The best S/N ratio was obtained between pH 2–3. In addition, the results show that at pH higher than 9, the noise level in the baseline (ΔQ versus Time) is higher up to 11.5% compared to acidic solution (pH 2).

3.2. Effect of sweep rate

A concentration of 2.0×10^{-8} M salbutamol was studied and the responses of the detector to the potential sweep rate were recorded at different sweep rates ranging from 50 to 400 V/s, and the results showed that the detector exhibits the maximum sensitivity at 125 V/s of scan rate. The effects of the sweep rate on the detection performance can be considered from two aspects: first, speed in data acquisition, and second, kinetic factors of adsorption of the salbutamol. Also, the use of this detection method in conjunction with fast separation techniques such as capillary electrophoresis requires the employment of high sweep rates. From this point of view, it is important to check how the sensitivity of the method is affected by the sweep rate. In fact to detect the adsorbed analyte on the electrode surface, high sweep rates must be employed so that the sweeping step is short in comparison with the stripping period. This is very significant in this detection method, especially, when the stripping of salbutamol occurs at a potential, which is very larger or smaller than E_i. The main reason for the application of a high sweep rate is the prevention of desorption of the adsorbed salbutamol during the potential scanning. In addition, under this condition, the inhibition effect of the adsorbed salbutamol on the oxidation process can take place. However, sensitivity of the detection system mostly depends on the potential sweep rate mainly due to kinetic factors in adsorption, and instrumental limitations. The results obtained for the examined salbutamol on the Au electrode show that the height of the electrode response is constant within experimental error for sweep rates between 40 and 180 V/s. This is not surprising since in this case the main contribution to the signal arises from the electrical charge needed to remove adsorbed salbutamol from the electrode surface. This charge depends on the accumulation conditions but should be independent of the sweep rate.

3.3. The effect of the accumulation potential

The effect of the accumulation potential on the gold electrode response to the injection of a solution of 2.0×10^{-8} M salbutamol, in 0.05 M H_3PO_4 was also evaluated over the potential range −600 to +400 mV and the results showed that the adsorption process exhibits a strong dependence upon the applied potential. Thus, a −300 mV accumulation potential was chosen. The relation observed for salbutamol can be easily explained: at positive potentials, the efficiency of accumulation drops, because adsorption of cations on the positively charged electrode becomes thermodynamically unfavorable. The observed drop of response at negative potentials is most probably due to the competitive adsorption of hydronium ions.

3.4. Influence of the accumulation time

The sensitivity of the measurement strongly depends on time and potential of stripping. Mainly, accumulation of salbutamol on the electrode takes place during the stripping step (assuming that an appropriate potential is selected). As mentioned above, the surface of UMEs is very small and the electrode surface can be saturated in a very short time. Fig. 8 shows the plot of peak charge versus pre-concentration time for 2.0×10^{-8} M salbutamol in the presence of 0.05 M phosphoric acid. As it is seen, the electrode surface becomes saturated with the salbutamol within a 700 ms time window. In fact, the difference in the time of saturation of various compounds can be related to the existing differences in their kinetics of the electron transfer and mass transport.

3.5. Response stability of the detector signal

The stability of the response of the gold ultra microelectrode was evaluated for several hours and the results showed that the electrode exhibits a stable response without any chemical or mechanical treatment. The longest test

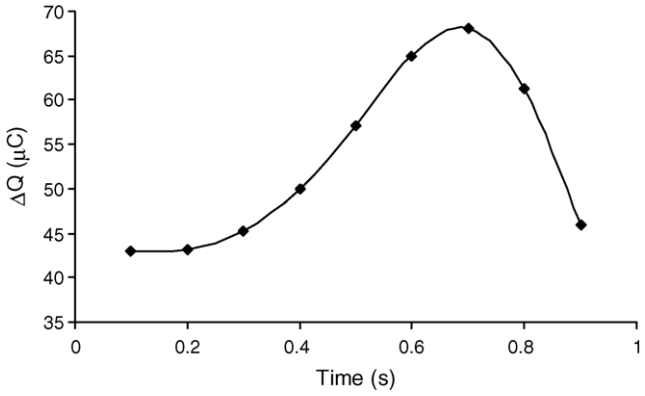

Fig. 8. Effect of the accumulation time on the electrode response to injections of 2.0×10^{-8} M salbutamol sulfate in 0.05 M H_3PO_4.

(24 h) involved replicate measurements of the response for 1.0×10^{-6} M salbutamol on a gold electrode in a continuously flowing 0.05 M of phosphoric acid. The scan rate of 125 V/s, the accumulation potential of −0.3 V, and accumulationtime of 0.7 s were applied for all experiments. The relative standard deviation of the results was 3.6%.

3.6. Calibration curve and detection limit

The experimental conditions were set at the optimum values in order to obtain the best detection limit and wide linear range for the detection of salbutamol in 0.05 M H_3PO_4. It should be noted that like classical stripping voltammetric method, in the calculation method, the analyte response is proportional to the electrode coverage. This assumption, however, may be less obvious when the inhibition of oxide formation by adsorbates is considered, but it is not unlikely. For example, it has been shown that a decrease of charge in the oxide formation region on gold caused by adsorption of species is proportional to the surface coverage [31]. Therefore, if the electrode coverage is controlled by the rate of mass transport, a linear calibration curve is expected up to the point when full electrode coverage is reached during the stripping time. But when thermodynamics of adsorption or kinetics of the interfacial step controls the electrode coverage, then a linear calibration curve can be expected for only very small coverage. Under typical experimental conditions used in this work and for strongly adsorbing salbutamol, the linear portion of the calibration curve extends from about 10×10^{-9} to about 1.0×10^{-7} M. Measurements carried out for small analyte concentrations allow the estimation of the detection limit C_{DL}:

$$C_{DL} = \frac{3s_b}{m} \quad (3)$$

Where s_b is the standard deviation (or noise) of the baseline around the flow injection peak and m is the sensitivity of the method (a change in the peak height divided by the change in concentration) near the detection limit. To insure the best S/N ratio, the measurements were carried out at high sweep rates. In all case the stripping time was 700 ms. The detection limit that obtained for salbutamol was 2.0×10^{-9} M (∼700 pg/mL).

3.7. Analytical applications

3.7.1. Determination of salbutamol in tablets

The proposed system was applied for the determination of salbutamol sulfate in the commercially available tablets of salbutamol (declared content is 2 mg of salbutamol in one tablet). It was found that each tablet contained 2.04 ± 0.02 mg of salbutamol (average value of three independent analyses), whereas the reported average value for this particular batch, and also the results of the standard HPLC determination method were 2.00 mg and 2.05 ± 0.04, respectively.

3.7.2. Determination of salbutamol in urine and serum

The proposed sensitive method was also applied for the detection of salbutamol in spiked human urine and serum samples. The recommended procedure was used for the detection of salbutamol and the results of the recoveries of salbutamol from spiked human urine and plasma samples are given in Table 1. As can be seen from Table 1, the recoveries are in the range of 95.0–105.0%.

3.8. The effect of interferences

Interferences by some alkali metal ions, common anions and some molecules were examined for 1.0×10^{-7}

Table 1
Determination of salbutamol in spiked human urine and plasma

Sample	Added (μg L^{-1}) ± S.D.%[a]	Found (μg L^{-1}) ± S.D.%[a]	Recovery (%)	R.S.D ± % (n = 3)
Urine	2.0 ± 1.4	1.9 ± 1.1	95.0	1.4
	3.0 ± 1.2	3.1 ± 1.4	103.3	2.4
	5.0 ± 1.0	4.9 ± 1.5	98.0	1.9
	10.0 ± 1.0	10.2 ± 0.8	102.0	1.8
Plasma	2.0 ± 1.3	2.1 ± 1.4	105.0	1.5
	3.0 ± 1.4	2.9 ± 1.1	96.6	1.1
	5.0 ± 1.0	5.1 ± 1.0	98.0	1.6
	10.0 ± 0.8	10.1 ± 0.6	101.0	2.2

[a] Mean of five measurements.

Table 2
Interferences examined for 1.0×10^{-4} and 1.0×10^{-5} M salbutamol in the presence of 0.05 Ms H_3PO_4, on addition of 1.0×10^{-3} and 1.0×10^{-4} M of any interference, under optimized conditions for salbutamol

	Interference concentration (M)	Salbutamol concentration (M)	Salbutamol recovery (%)	Error percentage
Acetate	1.0×10^{-3}	1.0×10^{-4}	101.2	1.2
	1.0×10^{-4}	1.0×10^{-5}	100.0	0.0
Ascorbic acid	1.0×10^{-3}	1.0×10^{-4}	98.5	−1.5
	1.0×10^{-4}	1.0×10^{-5}	98.8	−1.2
Glucose	1.0×10^{-3}	1.0×10^{-4}	100.7	0.7
	1.0×10^{-4}	1.0×10^{-5}	101.8	1.8
Tartarate	1.0×10^{-3}	1.0×10^{-4}	101.3	1.3
	1.0×10^{-4}	1.0×10^{-5}	100.1	0.1
Iodide	1.0×10^{-3}	1.0×10^{-4}	101.3	1.3
	1.0×10^{-4}	1.0×10^{-5}	102.6	2.6
Chloride	1.0×10^{-3}	1.0×10^{-4}	101.2	1.2
	1.0×10^{-4}	1.0×10^{-5}	102.6	2.6
Potassium ion	1.0×10^{-3}	1.0×10^{-4}	98.6	−1.4
	1.0×10^{-4}	1.0×10^{-5}	98.2	−1.8
Sodium ion	1.0×10^{-3}	1.0×10^{-4}	98.8	−1.2
	1.0×10^{-4}	1.0×10^{-5}	97.7	−2.3

and 1.0×10^{-8} M salbutamol in the presence of 0.05 M H_3PO_4. On addition of 1.0×10^{-6} and 1.0×10^{-7} M of these interferences, the responses of the detector were recorded. The results are given in Table 2. As it is seen, no significant error in the determination of salbutamol was observed.

3.9. *Comparison of the sensitivity of the method and other previously reported methods*

Table 2 compares the detection limit of the proposed method with the other reported methods [32–39]. As it is immediately obvious, the sensitivity of the method is superior to all previously reported methods. The data in Table 3 revealed that except for one method [32] the detection limit of which is three time higher than the present work, in the case of the other method the detection limit of this method is at least 160 times less [33–39].

Table 3
Comparison between the detection limits of the proposed method with the other previously reported methods

Reference	Detection limit (ng/mL)
[32]	2
[33]	200
[34]	10000
[35]	1000
[36]	1000
[37]	23000
[38]	100
[39]	5000
This work	0.67

4. Conclusion

The presented results in this paper indicate that adsorption voltammetry associated with the selective or nonselective detection of various compounds at UME can serve as a fast and reliable technique for the trace analysis of chemicals in flowing solution. Indeed, the electrochemical preconditioning of the electrode, which takes place before the potential sweeping has an important influence on the stability of the electrode and the sensitivity of the method. The detection limit can be further improved by increasing the stripping time, in cases where the adsorption process is limited by mass transport or a surface kinetics; however, this may lead to a deterioration of the zone resolution in same applications (e.g. CE or HPLC detection). An improvement in the detection limit can also be achieved by lowering the baseline noise. The noise level in such measurements depends, to a large extent, on the quality of the electronic equipment used. The gold UME provides a stable response for several hours without any mechanical or chemical treatment. For example, a 24 h test involved replicate measurements of the response for 1.0×10^{-6} M salbutamol on a gold electrode in a continuously flowing 0.05 M H_3PO_4, the relative standard deviation of the results was 3.6% and there was not any definite drift in the electrode sensitivity. The detector response, however, can be reliably expressed in terms of the total absolute difference only if the baseline drift is small (say, less than 1% during the entire experiment) such a situation is commonly encountered in flow–injection experiments. It should be stressed that both the baseline drift, and the choice of the reference CV curve have practically no effect on the detector response peaks expressed in terms of ΔQ

based on Eq. (1). Studies of the functional relation between the electrode response and the stripping time may provide some information about the kinetics of the adsorption process; here, however, only a brief discussion of this topic was provided.

References

[1] C. Lin, Y. Li, J. McGlotten, J.B. Morton, S. Symchowics, Drug Metab. Dispos. 232 (1982) 327.
[2] J. Vela, E.G. Yanes, A.M. Stalcup, Fresenius J. Anal. Chem. 369 (2001) 212.
[3] A. Koole, J. Bosman, J.P. Franke, R.A. de Zeeun, J. Chromatogr. B 726 (1999) 149.
[4] D. Satinsky, R. Karlicek, A. Svoboda, Anal. Chim. Acta 455 (2002) 103.
[5] Y.M. Issa, A.F. Shoukry, R.M. El-Nashar, J. Pharm. Biomed. Anal. 26 (2001) 379.
[6] G.G. Mohamed, M.S. Khalil, M.A. Zayed, M.A.E. El-Shall, J. Pharm. Biomed. Anal. 28 (2002) 1127.
[7] I.E. Valko, H.A.H. Billiet, A.L. Corstjens, J. Frank, LC–GC Int. 6 (1993) 420.
[8] M.I. Saleh, Y.M. Koh, S.C. Tan, A.L. Aishah, Analyst 125 (2000) 1569.
[9] A. Esquisabel, R.M. Hernandez, A.R. Gascon, M. Igartua, B. Calvo, J.L. Pedraz, J. Pharm. Biomed. Anal. 16 (1997) 357.
[10] M.C. Bonferoni, C. Caramella, M.E. Sangalli, U. Conte, R.M. Hernandes, J.L. Pedras, J. Controlled Release 18 (1992) 205.
[11] N.A. Peppas, Pharm. Acta Helvet. 60 (1985) 110.
[12] D.N. Wade, P.T. Mearrick, J.L. Morris, Nature 242 (1973) 463.
[13] J.J. Lima, H. Boudoulas, B. Shields, Drug Metab. Dispos. 13 (1985) 572.
[14] M. Eichelbaum, G. Mikus, B. Vogelgesang, Br. J. Clin. Pharmacol. 17 (1984) 453.
[15] R.T. Foster, F. Jamali, A.S. Ruselli, S.R. Alballa, J. Pharm. Sci. 77 (1988) 70.
[16] J. Wang, Stripping Analysis, VCH Publishers, Deerfield Beach Florida, 1985.
[17] P.T. Kissinger, in: P.T. Kissinger, W.R. Heineman (Eds.), Laboratory Techniques in Electroanalytical Chemistry, Marcel Dekker, New York, 1984.
[18] S.F.Y. Li, Capillary Electrophoresis: Principles, Practice and Applications, Elsevier, Amsterdam, 1992.
[19] B.E. Conway, H. Angerstein-Kozlowska, F.C. Ho, J. Klinger, B. MacDugall, S. Gottesfeld, Faraday Disc. Chem. Soc. 56 (1973) 199.
[20] L.D. Burke, K.J. O'Dwyer, Electrochim. Acta 34 (1989) 1659.
[21] G.T.A. Kovacs, C.W. Storment, S.P. Kounaves, Sens. Actuators B 23 (1995) 41.
[22] A.S. Baranski, P. Norouzi, L.J. Nelsson, Proc. Electrochem. Soc. 9 (1996) 41.
[23] M. Rosvall, M. Sharp, Electrochem. Commun. 2 (2000) 338.
[24] D.J. Gavaghan, A.M. Bond, J. Electroanal. Chem. 480 (2000) 133.
[25] J.C. Myland, K.B. Oldham, J. Electroanal. Chem. 535 (2002) 27.
[26] M. Rosvall, Electrochem. Commun. 2 (2000) 791.
[27] A.S. Baranski, T. Krogulec, L.J. Nelsson, P. Norouzi, Proc. Electrochem. Soc. 9 (1996) 41.
[28] R.M. Wightman, D.O. Wipf, in: A.J. Bard (Ed.), Electroanalytical Chemistry, Marcel Dekker, New York, 1988.
[29] J. Lipkowski, L. Stolberg, in: J. Lipkowski, P.N. Ross (Eds.), Adsorption of Molecules at Metal Electrodes, VCH, New York, 1992.
[30] S. Gilman, in: A.J. Bard (Ed.), Electroanalytical Chemistry, Dekker, New York, 1967.
[31] H. Angerstein-Kozlowska, B.E. Conway, B. Barnett, J. Mozota, J. Electroanal. Chem. 45 (1977) 75.
[32] M.I. Saleh, Y.M. Koh, S.C. Tan, A.L. Aishah, Analyst 125 (2000) 1569.
[33] J. Huclova, D. Satinsky, H. Sklenarova, R. Karlicek, Anal. Bioanal. Chem. 376 (2003) 448.
[34] G.G. Mohamed, S.M. Khalil, M.A. Zayed, M.A.E. El-Shall, J. Pharm. Biomed. Anal. 28 (2002) 1127.
[35] K. Basavaiah, H.C. Prameela, Chem. Anal. 48 (2003) 327.
[36] J. Vela, E.G. Yanes, A.M. Stalcup, Fresenius J. Anal. Chem. 369 (2001) 212.
[37] Y.M. Issa, A.F. Shoukry, R.M. El-Nashar, J. Pharma. Biomed. Anal. 26 (2001) 379.
[38] D. Satinsky, R. Karlicek, A. Svoboda, Anal. Chim. Acta 455 (2002) 103.
[39] X.X. Sun, L.Z. Sun, H.Y. Aboul-Enein, Electroanalysis 12 (2000) 853.