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Sub-second adsorption for the pico-molar monitoring of diltiazem in pharmaceutical preparations by fast Fourier transformation with the use of continuous cyclic voltammetry at an Au microelectrode in a flowing system

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Diltiazem was determined at the sub-nanomolar level for the first time by a new technique, involving fast Fourier continuous cyclic voltammetry in a flow-injection system. The best performance was achieved with the basic parameters being set at pH value of 2.0, scan rate value of 35 V/s, accumulation potential of 300 mV and accumulation time of 0.8 s. This paper additionally introduces a special computer based numerical method for the calculation of the analyte signal and the noise reduction. Concerning the electrode response calculations were carried out according to the partial and total charge exchanges on the electrode surface after subtraction of background current from that of noise. Furthermore, to obtain a sensitive determination, the currents integration range included all potential scan ranges, even oxidation and reduction of the Au surface electrode, during the measurements. In general, the potential waveform includes the potential steps for cleaning, accumulation and the step of the potential ramp of the analyte. This potential waveform was applied to an Au disk microelectrode in a continuous way. Finally, the method was found to be linear for the concentration range of 1–41450 pg/ml ($r = 0.9986$), while showing a limit of detection and quantitation of 0.29 and 1 pg/ml, respectively.

1. Introduction

Automated solid-phase extraction (Ascalone et al. 1994) high-performance liquid chromatography (Zarghi et al. 2000) and other chromatography methods (Gil-Agustí et al., 2000) have been reported for the analytical determination of the calium-channel blocker diltiazem and its main metabolites in pharmaceuticals and biological samples.

This research demonstrates the development of a fast, convenient and sensitive electrochemical method for the quantification of diltiazem in pharmaceutical samples. The method is based on fast Fourier continuous stripping cyclic voltammetry in a flow injection analysis. It should be stressed here that the technique developed is simple, precise, accurate, time saving and economical, compared with those previously reported. (Norouzi et al. 2005a, b; Ganjali et al. 2005a, b; Norouzi 2006a) Moreover, it presents certain advantages such as a sub-nanomolar detection limit, and no requirement for oxygen removal from the test solution, as well as a high determination speed for any such compound in several chromatographic methods.

2. Investigations and results

For the preparation of the gold UMEs (12.5 μm in diameter), metal micro-wires (Goodfellow Metals Ltd., UK) sealed into a soft glass capillary were used. The capillary was then cut perpendicular to its length to expose the wire. Silver modified epoxy (Johnson Matthey Ltd., UK) was used for the electrical contacts.

Next, the electrode surface was polished for 1 min with extra fine carborundum paper and, afterwards, for 10 min with 0.3 μm alumina. The electrode was washed with water before being placed in the cell. An Ag(s)|AgCl(s)|KCl (aq, 1 M) reference electrode was used for all measurements, while the auxiliary electrode consisted of a Pt wire (1 cm in length and 0.5 mm in diameter).

Figure 1 depicts the electrochemical cell for flow-injection analysis. In particular, a 10-roller peristaltic pump (UltrateckLabs Co., Iran) and a four-way injection valve (Supelco Rheodyne Model 5020) with a 50 μl sample injection loop were used for the flow injection analysis. Also, the solutions were introduced into the sample loop with the aid of a plastic syringe. During experiments, the flow rate of the eluent solution was set to 3 ml/min and the cell volume was 100 μl.

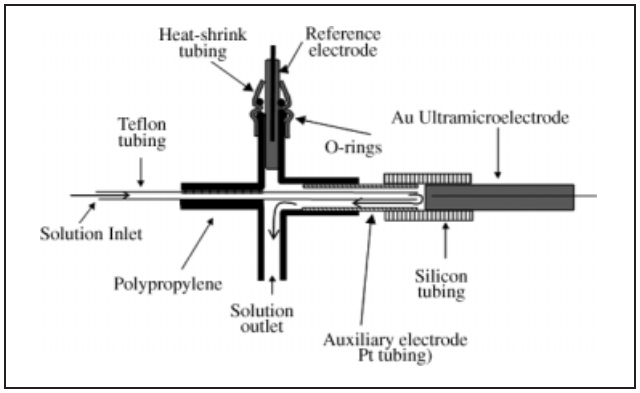

Fig. 1: Electrochemical cell

A PC PIV Pentium 900 MHz microcomputer, equipped with a data acquisition board (PCL-818HG, Advantech. Co.) and a custom made potentiostat were used for data acquisition and data processing. The relevant programs were developed in the Delphi® 6 program environment.

Figure 2 shows the applied waveform potential diagram during the cyclic voltammetric measurements. The potential waveform consists of three parts; a) potential steps, E_{c1} and E_{c2} (which are used for the oxidation and reduction of the electrode surface, respectively), during which electrochemical cleaning of the electrode surface takes place, b) E_{acc}, where analyte accumulation takes place and c) the potential ramp, where the current measurements occur.

Special digital filtration, applied during measurement, is an important point of this technique. To start with, an electrode cyclic voltammogram (CV) was recorded and, then, the existing high frequency noises were found by applying FFT to the collected data. Based on this information, the cutoff frequency of the analog filter was set at a certain value (such that the noises were removed from the CV).

Given that the crystal structure of a polycrystalline gold electrode greatly depends on the condition of the applied potential waveform (Wightman and Wipf 1989), different potential waveforms were examined in order to obtain a reproducible electrode surface (or a stable background signal). As a matter of fact, the application of cyclic voltammetry to the determination of electroactive compounds is generally expected to show low stability of the background signal, owing to the changes taking place in the surface crystal structure during the oxidation and reduction of the electrode in each potential cycle. The waveform depicted in Fig. 2 was eventually found to be the optimum potential waveform, providing a stable background during the measurement, after the examination of many potential waveforms. During all experimental runs, the potential waveform was applied continuously while the collected data were filtered by the FFT method, before their use in the signal calculation.

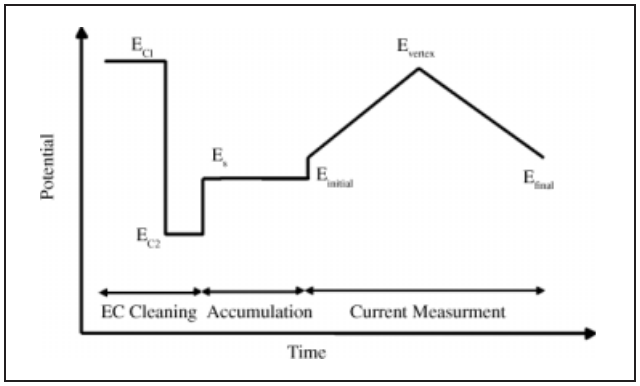

Fig. 2: Applied potential waveform

Hydroxyl ion electrosorption is the initiation point for the electrochemical oxidation process of the gold surface. At more positive potentials, it results in the formation of gold oxide, undergoing structural rearrangement (Lipkowski and Stolberg 1992). Moreover, the surface oxidation initiation can occur with the adsorption of water molecules where AuOH is formed at a more positive potential, leading to a two-dimensional phase formation of gold oxide;

$$2Au + 3H_2O \rightarrow Au_2O_3 + 6e + 6H^+ \qquad (1)$$

Figure 3 (a, b) presents an example of the recorded CVs. Firstly, Fig. 3a shows a CV sequence recorded during the flow analysis for drug determination. The injection volume was 50 µl of 5.0×10^{-6} M diltiazem (in 0.05 M H_3PO_4) into the eluent solution, containing 0.05 M H_3PO_4. In the graph, the time axis represents the time of the flow injection experiment. In the absence of diltiazem, the shape of the CV curves is typical of a polycrystalline gold electrode in acidic media (Bockris et al. 1980). Secondly, Fig. 3b illustrates the absolute current changes in the CVs curves, after the subtraction average background of the 4 CVs (in the absence of the analyte). In fact, it offers a better way to present the electrode response since it provides more details about the effect of the adsorbed ion effect on the CV currents. Actually, the curves show that the current changes mainly take place at the potential regions of the

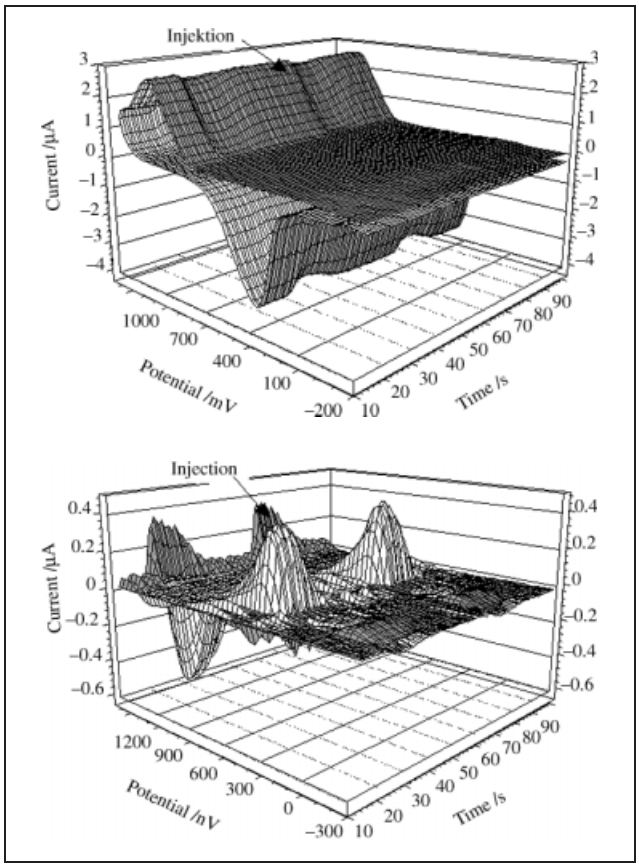

Fig. 3: (a) Cyclic voltammograms at the Au ultra-microelectrode recorded during the flow injection of 50 µL of 5.0×10^{-6} M of diltiazem under the optimum conditions. The eluent was 0.05 M H_3PO_4 and the flow rate was 3 ml/min. (b) Curves resulting from subtraction of average CV (in the absence of analyte) from the test CVs in (a)

oxidation and reduction of gold. When the electrode-solution interface is exposed to diltiazem, which can be adsorbed on the electrode, the oxide formation process becomes severely inhibited. In detail, the surface process inhibition causes significant change in the currents at the potential region and, as a consequence, profound changes in the shape of the CVs occure. In chromatographic analysis, the universality of the detector is beneficial where a mixture of compounds is present in the sample.

In general, the thermodynamic and kinetic parameters of adsorption, the mass transport rate and the electrochemical behavior of the adsorbed species influence the analyte response. Moreover, the free energy and the adsorption rate depend on the electrode potential, the electrode material and, to some extent, on the choice of the concentration and the type of the supporting electrolyte. Therefore, the effect of the experimental parameters (such as the pH of the supporting electrolyte, the potential, the accumulation time and the potential scan rate) must be examined and optimized to achieve of maximum detector performance (Norouzi 2004, 2005c, 2006b–f, 2007a–h; Nabi Bidhendi et al. 2007).

3. Discussion

The effect of eluent pH on detector performance was examined additionally. The results showed that the best S/N ratio was obtained in the pH range of 2–3. Moreover, it is seen that at pH values higher than 9, the noise level in the baseline (ΔQ vs. Time), is up to 12 % higher, compared with that of the acidic solution.

To investigate the influence of the scan rates and the eluent flow rate on the sensitivity of the detector response, solutions with a diltiazem concentration of 5.0×10^{-9} M were injected. Afterwards, the detector responses to the injected sample were recorded at different scan rates (from 20 to 60 V/s) and eluent flow-rates. These results show that the maximum sensitivity is at a scan rate of 35 V/s and flow rate of 3 ml/min.

It should be mentioned that the effect of sweep rate on detection performance is three-fold. The first influence is the speed of data acquisition. The second is the kinetics of diltiazem adsorption and the third one is the eluent flow rate, which controls the time window of the solution zone in the detector. In addition, the main reason for using high scan rates is preventing desorption of the adsorbed diltiazem during potential scanning (because under this condition, the inhibitory action of the adsorbed diltiazem on the oxidation process can take place). Indeed, the use of high scan rates is required to this detection method in conjunction with fast separation techniques such as capillary electrophoresis. It is also necessary to check how the sensitivity of the method is affected by the sweep rate. The employment of high sweep rates leads to the detection of the amount of analyte adsorbed on the electrode surface, since the potential scanning step is short in comparison with the accumulation period. Another significant factor is the time when diltiazem accumulation occurs at a potential that is greater or smaller than E_i. Mostly due to the adsorption kinetics as well as instrumental limitations, the potential sweep rate comprises the determining factor, defining the sensitivity of the detection system.

Clearly, measurement sensitivity is greatly influenced by changes in the parameters which are related to the adsorption process and which affect the applied potential, and the accumulation time and potential. For that reason, the influence of accumulation potential and time on the response of the method to the injection of a 5.0×10^{-9} M solution of diltiazem in 0.05 M H_3PO_4 was studied. The detector response is studied over the accumulation potential ranges from −300 to 600 mV and the accumulation time range from 0.09 to 1.0 s. The optimum conditions were accumulation potential of 300 mV and accumulation time of 800 ms, on the grounds that the electrode surface becomes diltiazem saturated within an 800 ms time window.

As mentioned above, the surface of the gold ultra microelectrode is small and the electrode surface can be saturated in a short time. Assuming that an appropriate potential is selected, the diltiazem accumulation takes place on the electrode during the accumulation step. As a matter of fact, the differences which exist in the kinetics of electron transfer and mass transport result in different values for the saturation time of the various compounds.

The validation of the technique was estimated in relation to the selectivity, the precision, the accuracy, the ruggedness/robustness, the limit of quantitation (LOQ), the limit of detection (LOD), the recovery and the linearity (Mohammadi et al. 2006a, Mohammadi et al. 2005b, Mohammadi et al. 2007c)

To evaluate of the linearity, linear regression analysis was applied using the the least squares regression method (Miller and Miller 1984; Al-Kurdi et al. 1999). Over the concentration range of 1–41451 pg/ml, the calibration curves were linear. The peak areas of diltiazem were plotted versus its concentration and linear regression analysis was then carried out on the resultant curve. The results of this analysis provide a correlation coefficient with a value of $R = 0.9986$ with %RSD values, ranging from 0.24–3.85% across the concentration range studied. Typically, the regression equation for the calibration curve was found to be $Y = 0.1626\ X + 2.7384$. Fig. 4 presents the calibration graph obtained from the monitoring of diltiazem in 0.05 M H_3PO_4.

The LOQ was measured as the lowest amount of analyte that can be reproducibly quantified above baseline noise, for which triplicate injections resulted in an RSD ≤ 1.8%. A practical LOQ, giving a good precision and acceptable accuracy, equal led 1 pg/ml.

The LOD was measured as the lowest amount of analyte that may be detected to produce a response which is significantly different from that of a blank. The detection limit was verified by calculations, based on the standard deviation of the response (δ) and the slope (S) of the calibration curve at the levels approaching the limits according to equation LOD = 3.3 (δ/S) (ICH 1996). The LOD for diltiazem was found to be 0.29 pg/ml.

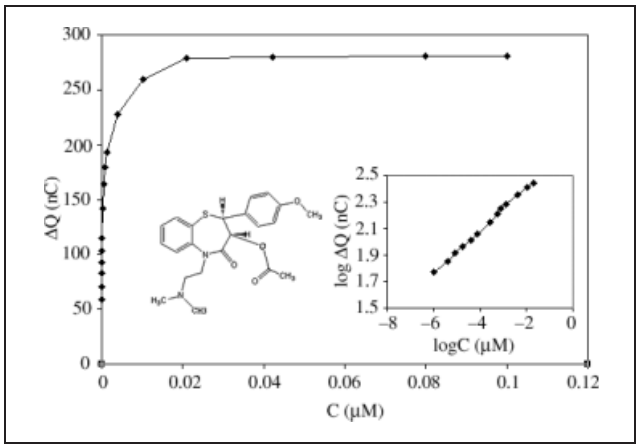

Fig. 4: Calibration curve obtained for the detection of diltiazem on the Au electrode in 0.05 M H_3PO_4

Table 1: Influence of the changes in the experimental conditions on the FIA system performance

Parameter	Modification	Diltiazem (% recovery)
Eluent pH	1.8	101.5
	2	100.1
	2.3	101.0
	3.0	100.2
Flow rate ml/min	2.8	101.6
	3.0	101.3
	3.2	99.9
Buffer composition (M)	0.04	99.9
	0.05	100.6
	0.06	101.4
Temperature (°C)	20	100.8
	25	99.8
	30	100.3

Repeatability and reproducibility were the basic factors that were examined in order to assess the precision of the method. The repeatability was investigated by injecting nine replicate samples of each of the 1, 100 and 41450 pg/ml standards, when the mean concentrations were found to be 1.027, 100.9 and 41375 with associated %RSD of 0.35, 1.0 and 3.7, respectively. The inter-day precision was assessed by injecting the same three concentrations over 3 consecutive days, resulting in mean diltiazem concentrations of 1.03, 101.2 and 41453 pg/ml and associated %RSD of 3.5, 2.4 and 1.15%, respectively.

To assess the accuracy of the method, replicate ($n = 6$) peak areas of three accuracy standards (1, 100 and 41450 pg/ml) were interpolated from a calibration curve, which was prepared as previously reported. The relevant error percentage and accuracy were calculated in each case. The resultant concentrations were 1.03 ± 0.032 pg/ml, 100.97 ± 1.03 pg/ml and 41352 ± 153 pg/ml with corresponding error percentages of 3.2, 1.0 and 0.25%, respectively.

The ruggedness of the method was also assessed. For this purpose the intra- and inter-day assay results for diltiazem, undertaken by two analysts were compared. The %RSD values did not exceed 3.7%; hence indicating the ruggedness of the method.

In addition, the robustness was examined under a variety of conditions such as small changes in the eluent pH, the flow rate, the buffer composition and the laboratory temperature (Heyden et al. 2001) Table 1 demonstrates that the percentage recoveries of diltiazem were good under most conditions, not showing any significant change when the critical parameters were modified.

To evaluate recovery of the suggested technique, a known amount of diltiazem hydrochloride standard powder was added to the injection samples. Afterwards, this amount was diluted and analyzed as previously described. The nominal diltiazem concentration was found to be 79.85 pg/ml. The assay was repeated ($n = 9$) over 3 consecutive days to obtain intermediate precision data. For this study, the resultant %RSD was 1.48% with a corresponding recovery percentage value of 99.81%.

The selectivity of the method was checked by monitoring diltiazem standard solutions in the presence of the formulation components. The responses were not different from those obtained in the calibration curve. Consequently, it was concluded that the determination of diltiazem in this formulation could be considered free from interference by formulation components.

Table 2: Detection limit (DL) comparison of the methods

DL	Methods	Ref. No.
2 ng/ml	Solid-phase extraction	2
10 ng/ml	HPLC	3
40 μg/ml	Chromatography	4
0.3 pg/ml	FFTCV	This work

In the present research, the technique developed was applied to the determination of diltiazem in injections from on the Iranian market. The results displayed a percentage recovery of 100.2% and a RSD of 1.65%.

The sensitivity (detection limit) of the proposed method was compared with those of previously reported methods in Table 2. Clearly, the sensitivity of this method is superior to the sensitivities illustrated by all the formerly reported ones. In particular, the detection limit of this method is 1000 times lower than that of the most sensitive of other methods.

4. Experimental

The Drug Quality Control Center (Tehran, Iran) kindly donated diltiazem chloride. Additionally, diltiazem tablets with a stated content of 60 mg diltiazem hydrochloride were purchased from a local pharmacy.

All solutions were prepared in double-distilled deionized water, using analytical grade reagents, made up with the background electrolyte solution and used without the removal of dissolved oxygen.

4.1. Background electrolyte (BGE)

For the preparation of the running buffer or BGE, 8.7 ml of phosphoric acid (85% w/v) were added into a 1000 ml volumetric flask. The resulting solution was then diluted to a constant volume with distilled water. The pH was adjusted to a value of 2 with sodium hydroxide. All solutions were freshly prepared and filtered, using a Millipore filter (0.45 μm), each day.

4.2. Standards and sample solutions

A standard stock solution of diltiazem hydrochloride (1 mg/ml) was prepared in the running buffer. This solution was protected from light using foil. It was stored at 4 °C for 24 hours and was found to be stable during this period.

Aliquots of the diltiazem standard stock solution were dispensed into 10 ml volumetric flasks, which were filled up with the running buffer to cover a final concentration range of 1–41450 pg/ml.

4.3. Sample preparation assay

Twenty tablets were weighed and finely powdered, and portions equivalent to 60 mg diltiazem were transferred into a 1000 ml volumetric flask; 500 ml of distilled water were added, shaken thoroughly to dissolve, filled up and mixed well. Suitable aliquots of solution were filtered through a Millipore filter (0.45 μm). 1 ml of the filtered solution was diluted with distilled water in a 1000 ml volumetric flask. Then, 100 μl of the resulting solution were added to a 100 ml volumetric flask and filled up to the mark with 0.05 M phosphoric acid to provide a starting concentration of 60 pg/ml.

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