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ORIGINAL RESEARCH

Voltammetric sensor based on Co_3O_4/SnO_2 nanopowders for determination of diltiazem in tablets and biological fluids

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Abstract In this work, an anodic stripping voltammetry for nanomolar determination of diltiazem with a chemically modified carbon paste electrode (CMCPE) containing Co_3O_4/SnO_2 nanopowders was studied. The accumulation potential and time were selected at, -0.2 V and 190 s, respectively. The electroanalytical performance of the CMCPE was evaluated regarding the carbon paste composition, the solution pH, the time and potential accumulation, and the potential interferences. The novel electrode showed linear response to diltiazem concentration range of 50–650 nM with a lowest detection limit value of 15 nM. The precisions for six consecutive determinations of 350 and 550 nM diltiazem were 3.2 and 2.5 %, respectively. It was demonstrated that the proposed method was free from most interference. Finally, the method was effectively applied to the determination of diltiazem in pharmaceutical tablets and biological samples.

Introduction

Diltiazem, (+5)-5-[2-(dimethylamino) ethyl]-*cis*,2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl-1,5-benzothiazepin-4(5H)-one acetate monohydrochloride (Fig. 1), is an important

coronary vasodilator drug of the calcium channel-blocker, used in the therapy of heart disease and hypertension [1]. The drug has a mean biological half-life of 3–6 h in plasma [2]. The absolute bioavailability of the tablets ranges between 30 and 42 % largely due to presystemic hepatic metabolism [3, 4]. After absorption, diltiazem undergoes extensive hepatic metabolism through three major metabolic pathways, N-demethylation, O-deacetylation, and O-demethylation [2–5]. Diltiazem undergoes hydrolysis to desacetyl diltiazem in acidic solutions and is most stable at pH 5. The extrapolated room temperate shelf-life was 42 or 15.8 days at pH 5 or 2, respectively [6], as well as a stock solution of the drug was prepared daily during the measurements and protect from the light. Its therapeutic and toxic effects require very sensitive methods for determination of trace levels. Various analytical methods have been employed for this purpose, e.g. high-performance liquid chromatography in human cardiac tissue [7], in blood [8] and in human plasma [9–13], high-performance thin-layer chromatographic [14], gas chromatography [15], spectrophotometry [16, 17], liquid–solid extraction [18] and voltammetry [19]. Since employed techniques for determination of diltiazem in the presence of other drugs are mostly spectroscopy and HPLC, and these methods often are complex and consuming cost solvents, must easy-handled and simple-operating methods need be applied.

Recently, we used modified CPEs for trace analysis of some drugs and heavy metals in various environments [20–24]. Newly we showed that the application of nanopowders of Fe_2TiO_5 in CPEs catalyses the oxidation of salbutamol and enhances the peak current values in the differential pulse anodic stripping voltammetric (DPASV) determination of it at sub-nanomolar levels [25]. The developed method has also been satisfactorily applied for the

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determination of diltiazem in human serum and pharmaceutical samples.

In this study, we present an electroanalytical method based on anodic stripping voltammetry on a carbon paste electrode modified by Co_3O_4/SnO_2 nanopowders for determination of trace amount of diltiazem in pharmaceutical and biological samples. The factors that affect on the performance of the DPASV were optimized and the proposed method was applied in the determination of diltiazem. In accordance with our resulting data, the Co_3O_4/SnO_2 nanopowders offered several distinct advantages, including an extraordinary stability, reproducibility, low background response and a satisfactory detection limit for diltiazem.

Tin and cobalt-based oxides and complexes are universally known as inorganic or organometallic materials with wide electrocatalytic applications in modified electrodes, gas sensors, solar cells, and high-performance catalysts [26–29]. One of these usages is electro-catalytic role that applied in chemically modified electrodes. Some studies showed the electrocatalytic of Co or Sn-based materials such as cobalt phthalocyanine, [30] iron-doped cobalt oxide [31] or tin-modified palladium electrodes [32].

Experimental

Reagents and chemicals

All chemicals were of analytical grades and obtained from Merck (Germany). Diltiazem was purchased from Amin Pharmacy Corporation. Graphite powder (particle diameter 1–2 μm) and high-viscosity paraffin with high density was used as the pasting liquid for the carbon paste electrode purchased from Merck. Double distilled water was used throughout. Diltiazem stock solution (1.0 mM) was prepared by dissolving 0.0207 g of diltiazem separately in buffer phosphate solution in a 50 mL volumetric flask. Working solutions were prepared by appropriate dilution of the stock solution with buffer solution.

Apparatus

Electrochemical measurements were performed using a Metrohm 797 VA Potentiostat–Galvanostat. The experiments were carried out in a single-compartment three-electrode cell, at room temperature (25 °C). The counter electrode was a platinum wire, and an Ag/AgCl saturated KCl electrode was used as the reference electrode. Carbon paste electrodes modified with Co_3O_4/SnO_2 nanopowders (MCPEs) were used as the working electrode. The preconcentration step was conducted using a magnetic stirrer

at 200 rpm. The electrochemical experiments were performed in an electrolytic cell with 20 mL solutions. A digital pH meter (Metrohm 827) was used for the preparation of the buffer solutions in voltammetric experiments. A double water distiller with extremely pure distillation with conductivity of 1 μS/cm was used.

Procedures

Preparation of Co_3O_4/SnO_2 nanopowders

The Co_3O_4/SnO_2 nanopowders were prepared according to the similar procedure described previously [33]. For the synthesis of this compound, first 0.05 mol of cobalt acetate was mixed with 0.2 mol of melted stearic acid to produce cobalt stearate sol. In the next step 0.05 mol of tin tetrachloride was reacted to stoichiometric mol of n-butanol (in ice bath) to produce tin alkoxide solution. Then cobalt stearate sol was mixed with tin alkoxide solution for production of gel precursor. Afterwards the gel precursor was calcined to a temperature of 800 °C for 4 h. Finally during pulverization the Co_3O_4/SnO_2 nanocatalyst was obtained.

Fabrication of Co_3O_4/SnO_2 modified carbon paste electrode

Carbon paste electrodes (CPE) were prepared by mixing 68.9 % graphite powder with 8 % Co_3O_4/SnO_2 nanopowders and 23.1 % paraffin oil (ratio of C:Paraffin: Co_3O_4/SnO_2, 68.9:23.1:8, w/w) on mortar for at least 20 min to produce the modified carbon paste electrode (MCPE). The MCPE was finally obtained by packing the paste into an insulin syringe and arranged with a copper wire serving as an external electric contact. Appropriate packing was achieved by pressing the electrode surface against a weighing paper until a smooth surface was obtained.

General analytical procedure

Solutions (20 mL) containing appropriate amounts of diltiazem in 0.1 M phosphate buffer at pH 6.3 were transferred into the voltammetric cell. The differential pulse voltammograms were recorded by applying positive going potentials from 0.53 to 0.98 V. The voltammograms showed anodic peaks around 0.78 V corresponding to diltiazem of heights proportional to the concentrations in solution. The calibration curve was obtained by plotting anodic peak currents of diltiazem versus the corresponding concentrations. After each measurement, the MCPE was regenerated by pushing an excess of paste out of the tube, removing the excess, and mechanically polishing the electrode surface.

Real sample preparation for measurements

Twenty tablets were weighed accurately and finely powdered. A portion of the powder, equivalent to 0.232 g of diltiazem was transferred to a 100 mL volumetric flask and dissolved in approximately 90 mL of choloridric acid/water (1:10). The solution was then filtered and the first portion of the filtrate was discarded. An accurate measured volume of the filtrate was quantitatively diluted with buffer phosphate to yield a sample solution having a final concentration assumed to be 0.1 mM diltiazem. An aliquot was then transferred to a voltammetric cell containing 20 mL of buffer phosphate (pH 6.3) to yield a final concentration of 30 μM diltiazem.

For sample preparation of plasma, the plasma samples was diluted with 25 mM ammonium acetate (pH 5.0), then centrifuge 20 min at 8000 rpm to remove of proteins. Then 1 mL portion of plasma was added to 2 mL of acetonitril for remove excess of proteins. After mixing for 2 min and centrifugation for 10 min at 7000 rpm, the aqueous layer was discarded and the organic layer was evaporated to dryness under stream of nitrogen. The residues were reconstituted in phosphate buffer pH 6.3 so as the final concentration was in range (100–500 nM) and transferred to the voltammetric cell.

For preparation of urine sample, urine of a healthy person was filtered and was diluted with phosphate buffer (1:10). Other steps are similar to the plasma treatments.
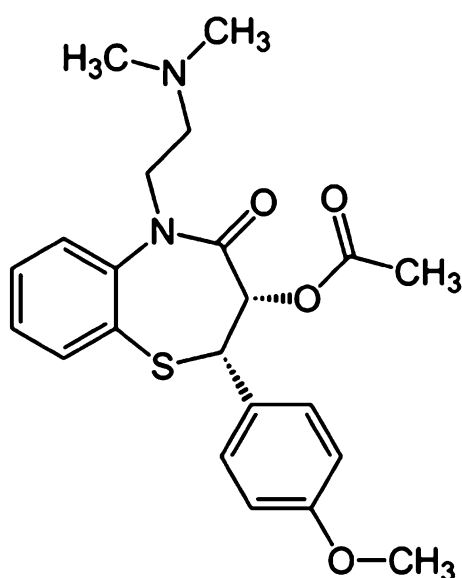
Fig. 1 Chemical structure of diltiazem

Results and discussion

Characterization of Co_3O_4/SnO_2 nanopowders

To analyse the crystal phases, XRD pattern was recorded. The obtained XRD pattern of Co_3O_4/SnO_2 nanopowders after heat treatment in 800 °C in air for 4 h is shown in Fig. 2. The pattern includes two main phases, cobalt oxide (JCPDS: 78-1969) and tin oxide (JCPDS: 77-0452) phase. The particle size of crystallites (L) has been estimated with Scherrer formula [34] [Eq. (1)]:

$$\left(L = \frac{K \times \lambda}{\Delta(2\theta) \times \cos(\theta)} \right) \tag{1}$$

where K is the form factor (equal to 0.9), $\lambda = 0.15418$ nM, 2θ is the peak position and $\Delta(2\theta)$ is the full width at half maximum of the diffraction peak in terms of radians.

In this way, we obtained the crystallite size of the nanopowders calcined at 800 °C about 42 nM.

Electrochemical behavior at CPE and MCPE

Cyclic voltammograms of diltiazem were recorded at the phosphate buffer (pH 6.3) at both bare CPE and CPE modified with 8 % (w/w) Co_3O_4/SnO_2 nanopowders. The voltammograms recorded in buffer solution at the bare CPE exhibited no any voltammetric peak over the entire pH range (Fig. 3, curve C) and in diltiazem solution (curve B). Whereas the voltammograms recorded in 100 nM diltiazem solution at the modified Co_3O_4/SnO_2 nanopowders electrodes exhibited a single irreversible anodic peak over the entire pH range. However, this peak was sharp and better developed in phosphate buffer of pH 6.3 when using CPE modified with 8 % (w/w) Co_3O_4/SnO_2 nanopowders (Fig. 3, curve A).

In addition, the electroactivity of the modified electrode is demonstrated in the differential pulse voltammograms (DPVs) observed for 100 nM diltiazem at the Co_3O_4/SnO_2 modified electrode and the bare CPE in 0.1 M phosphate buffer with pH 6.3 (Fig. 4). At the modified electrode, the oxidation peaks became well defined and appeared at 780 mV. This enhancement in current responses is a clear evidence of the electroactivity effect of the modified electrode towards the oxidation of diltiazem.

Composition and stability of the MCPE

The effect of the carbon paste composition on the voltammetric response of the electrode modified with Co_3O_4/SnO_2 nanopowders was evaluated by differential pulse voltammetry. Electrodes with different percent of modifier were prepared and examined for their voltammetric signals under identical conditions (Table 1). The

Fig. 2 XRD pattern of Co$_3$O$_4$/SnO$_2$ nanopowders
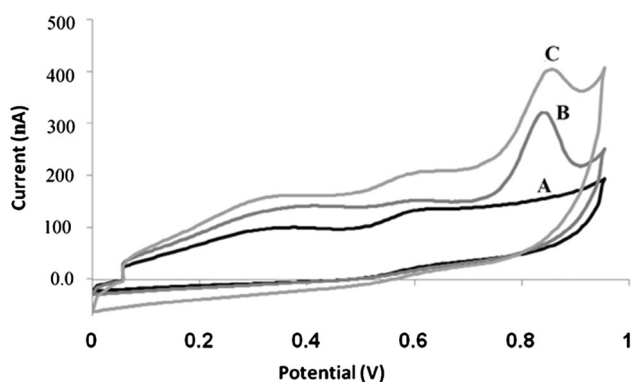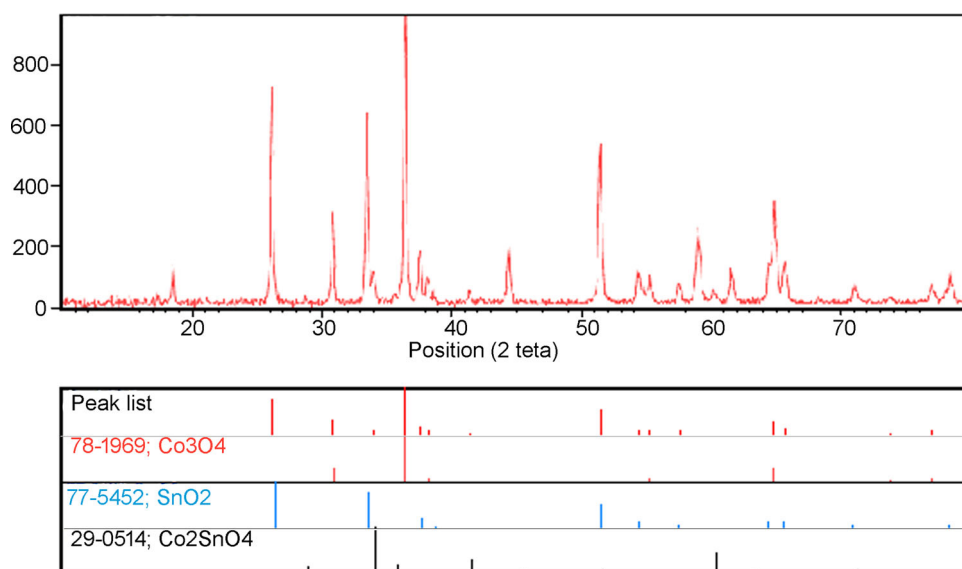
Fig. 3 Cyclic voltammograms of 0.1 M phosphate buffer solution (pH 6.3) recorded at the (A) modified CPE in the absence of diltiazem, (B) unmodified CPE with 1 µM diltiazem and (C) at the developed Co$_3$O$_4$/SnO$_2$ nanopowders modified CPE with 100 nM diltiazem
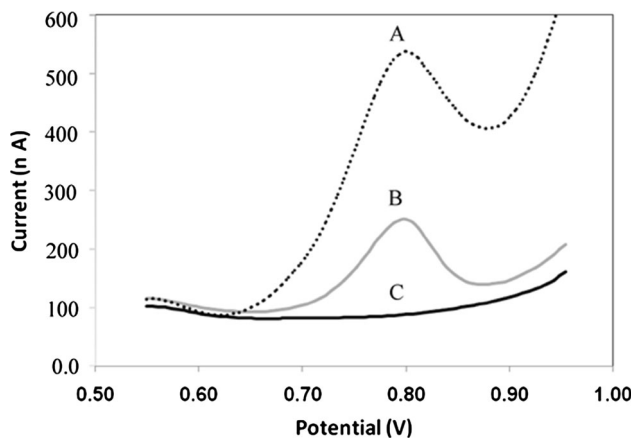
Fig. 4 Differential pulse voltammograms of buffer solution (pH 6.3) recorded (A) at the developed Co$_3$O$_4$/SnO$_2$ nanopowders modified CPE with 100 nM diltiazem in, (B) unmodified CPE with 1.0 µM diltiazem and (C) at the modified CPE in the absence of diltiazem

Table 1 Composition of the modified carbon paste electrodes and their DPV responses for 300 nM diltiazem in phosphate buffer 0.1 M

No.	Electrode composition			Peak current (nA)
	Modifier	Graphite powder	Paraffin oil	
CPE1	0	74.8	25.2	202
CPE2	2	73.3	24.7	250
CPE3	4	71.8	24.2	338
CPE1	6	70.3	23.7	406
CPE5	8	68.8	23.2	440
CPE6	10	67.3	22.7	436

maximum peak current was obtained for 8 % modified Co$_3$O$_4$/SnO$_2$ nanopowders in the paste. Higher concentrations (>10 %) showed a decrease in the peak current. This is presumably due to the reduction of conductive area at the electrode surface. According to these results, a carbon paste composition of 8 % modified Co$_3$O$_4$/SnO$_2$ nanopowders, 68.9 % graphite and 23.1 % paraffin oil was used in further studies.

Influence of accumulation time and accumulation potential

The influence of accumulation time is examined from 40 to 240 s. The DPV peak current of diltiazem increased with accumulation time increasing from 40 to 190 s, as shown in Fig. 5 for a 300 nM diltiazem solution. But when it exceeds 190 s, the peak current remains constant due to the surface saturation.

The influence of accumulation potential is examined from −0.1 to −0.5 V. However, with the potential increase
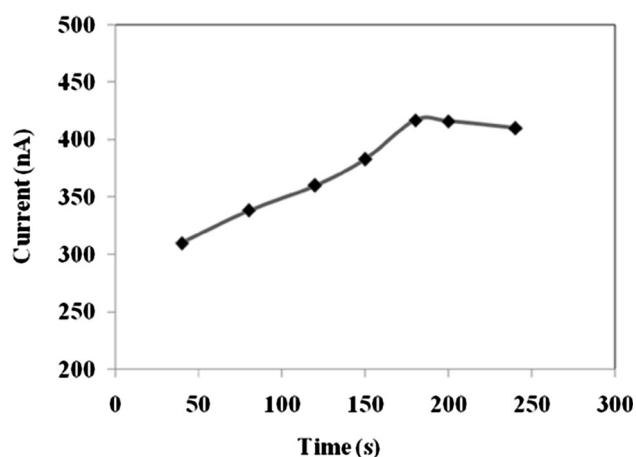
Fig. 5 The effect of accumulation time on the peak current of 300 nM diltiazem; with Co_3O_4/SnO_2 (8 %) modified CPE: accumulation potential, -200 mV (vs. Ag/AgCl); scan rate: 0.015 V s^{-1}; supporting electrolyte, 0.1 M phosphate buffer (pH 6.3)

Fig. 6 Response profile for the Co_3O_4/SnO_2 nanopowders-MCPE for preconcentration solutions at different pH values, containing 300 nM diltiazem; other conditions as Fig. 4
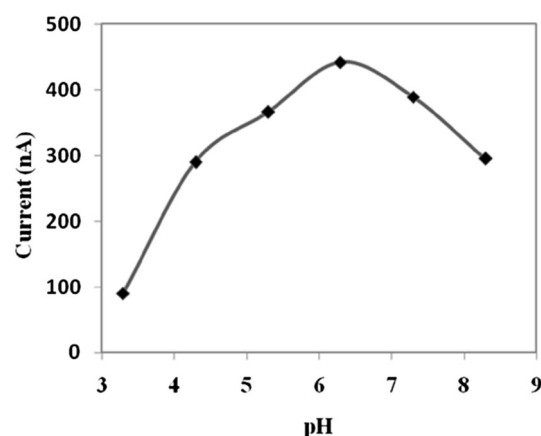
to -700 mV more current to come, but since the peak current also increased in electrolyte, potential -200 mV as the optimal deposition potential due to the lower background and absence of any peaks in the electrolyte is selected.

The type of supporting electrolyte

The effect of different salt solutions (as supporting electrolyte) on DPV voltammogram of diltiazem was investigated. Sample solutions containing salts such as KCl, KNO_3, $NaNO_3$ and phosphate buffer in the concentration range of 0.01–0.2 mol L^{-1} were tested. The results revealed that the peak current and sensitivity of the method do not change significantly with type and salt concentration and the phosphate buffer was chosen as the best electrolyte.

The effect of pH on the peak current of diltiazem

The effects of the pH values of both the preconcentration and stripping solutions on the response of the Co_3O_4/SnO_2 nanopowders to diltiazem were investigated. The response of the MCPE is strongly affected by these conditions (the pH or the ionic strength) in the ion exchange reactions. The effect of pH on the electrode response was tested in solutions of 300 nM diltiazem prepared at different pHs. Figure 6 shows the effect of the pH of the preconcentration solution on the anodic stripping peak current of diltiazem, and shows that the pH has a strong influence on the preconcentration process. The anodic stripping peak current of diltiazem increased with increasing pH over the range of 3.3–6.3, and reached a maximum level at pH 6.3. During this process, diltiazem selectively enters paste due to simple electrostatic attractive forces, since it exists as

cation at pH 6.3. The anodic stripping peak current of diltiazem decreased with increasing pH at basic pH, which can be attributed to the deprotonation of diltiazem. The results indicated that the effect of the stripping solution pH on the response of Co_3O_4/SnO_2 nanopowders-MCPE to diltiazem is similar behavior to that seen for the preconcentration solution.

Linearity, limit of detection and limit of quantitation

Relationship between oxidation peak current magnitude and concentration of diltiazem was examined in phosphate buffer of pH 6.3 by the developed DP-ASV method utilizing the developed 8 % (w/w) Co_3O_4/SnO_2 nanopowdes modified CPE. A linear dynamic range of 50–650 nM diltiazem was obtained following its preconcentration onto the developed 8 % (w/w) MCPE electrode by adsorption/accumulation for 190 s at -0.2 V (Fig. 7). Its corresponding regression equation was: i_p (nA) $= 1.136$ C $+ 53.25$, $R^2 = 0.997$. Limits of detection (LOD) and quantitation (LOQ) of bulk diltiazem were estimated 15 nM and 50.1 nM diltiazem based on 3 S/N and 10 S/N, respectively. The results indicated the reliability of the developed DP-ASV method for the trace assay of bulk diltiazem. This method shows a LOD of lower or compatible with other works such as high-performance liquid chromatography (0.9 μM), [13] and voltammetric sensor (0.5 nM) [35].

Trueness and precision

Trueness and precision of the optimized DP-ASV method were evaluated by performing five replicate measurements for various concentrations of diltiazem (250, 350 and 550 nM) through intraday and inter-day assays following
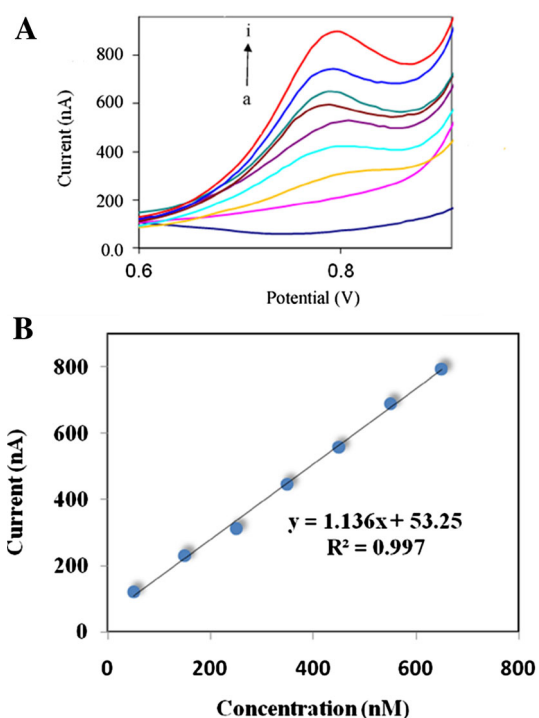
Fig. 7 Differential pulse voltammetric responses for successive additions of diltiazem from 50 (*a*) to 650 nM (*i*) concentration (**a**) and the calibration curve (**b**) at the Co_3O_4/SnO_2 (8 %) nanopowders modified CPE; other conditions: preconcentration time: 190 s; preconcentration potential: −200 mV; scan rate: 15 mV/s

preconcentration by adsorptive accumulation onto MCPE at −0.2 V for 190 s. To characterize the precision of the modified electrode, repetitive determinations of diltiazem were carried out at 350 and 550 nM concentrations at 0.1 M phosphate buffer. The results of five replicate measurements showed a relative standard deviation of 3.2 and 2.5 % (relative standard deviation), respectively, indicating that the results are reproducible. Also for determination of trueness as percentage relative error (Er %) was performed five replicate measurement for 250 nM diltiazem that was 0.16 %.

Interferences

The influence of various foreign species and co-formulated drugs on the determination of 100 nM diltiazem was investigated. The tolerance limit was taken as the maximum concentration of the foreign substances, which caused an approximately ±5 % relative error in the determination. The results showed that no interference occurred for the co-formulated drugs such as atenolol, phenobarbital and phenytoin and common substances and ions such as Na^+, Ca^{2+}, K^+, Ni^{2+}, Fe^{3+}, glucose, acid citric, urea, glycine, and ascorbic acid. The fact that Na^+, K^+, Ca^{2+}, acid citric, glucose, urea, glycine, atenolol and phenobarbital (a 1000-fold excess) and ascorbic acid (a 100-fold excess) and phenytoin (a tenfold excess) were not interference is of particular significance.

Analytical application

Assay of tablet

The validity of the proposed voltammetric method was investigated by assaying diltiazem in tablets (each is labeled to contain 60 mg diltiazem per tablet). The recoveries were calculated by the calibration graph. The statistical calculations for the assay results show a good precision of the proposed method (Table 2).

Assay of diltiazem in spiked human urine

The proposed method was also successfully applied to the determination of diltiazem in spiked urine samples from healthy volunteers using calibration curve. This determination carried out at three different levels of concentrations (250, 300 and 420 nM) and six determinations were carried at each concentration level (Table 3). The mean apparent recoveries for the three concentrations were 101.4, 99.64 and 97.33 % with relative standard deviations of 4.9, 4.5 and 4.1 %, respectively.

Table 3 Apparent recovery of diltiazem from human urine

Sample	Added (nM)	Found (nM)	Apparent recovery (%)	RSD	E_r (%)
1	0	0	–	–	–
2	250	253.6	101.4	4.9	1.4
3	300	292.0	97.3	4.1	2.7
4	420	420	99.6	4.5	0.4

Average of four determinations

Table 2 Analysis of diltiazem in tablet

Company	Labeled (mg/tablet)	Found (mg/tablet)	Apparent recovery (%)	RSD	E_r (%)
Arya pharmaceutical co.	60	60.8	101.4	4.9	1.4
Sobhan Darou co.	60	58.4	97.3	4.1	−2.7

Average of three determinations

Table 4 Apparent recovery of diltiazem from human plasma

Sample	Added (nM)	Found (nM)	Apparent recovery (%)	RSD	E_r (%)
1	0	0	–	–	–
2	350	340.0	97.1	5.3	2.8
3	410	417.0	101.7	3.4	1.7
4	480	465.5	97.0	5.5	3.0

Average of four determinations

Assay of diltiazem in spiked human plasma

The proposed method was applied to the determination of diltiazem in spiked human serum using the calibration curve. The direct determination of diltiazem in human serum was found to be possible after dilution of the sample with the supporting electrolyte. The percentage recovery of the drug in serum, based on the average of six replicate measurements, is listed in Table 4. The values obtained for recovery are acceptable for biological fluids.

Conclusion

The Anodic stripping voltammetry method (ASV) for the quantitative determination of diltiazem with carbon paste electrode modified with Co_3O_4/SnO_2 nano-powder was found to be simple and highly sensitive over the reported data for the determination of diltiazem. It can be used successfully to stability-indicating assay the drug in dosage form as well as in urine and plasma at trace levels.

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