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Assay of terfenadine in pharmaceutical formulation and human plasma by adsorptive stripping voltammetry

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Abstract

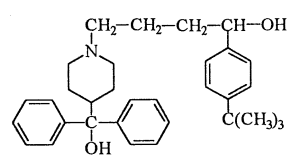
The controlled adsorptive accumulation of Zn(II)-terfenadine complex (1:1) onto a hanging mercury drop electrode (HMDE) provides the basis for determination of the antihistamine drug terfenadine by differential pulse cathodic adsorptive stripping voltammetry. The adsorbed Zn(II)-terfenadine complex (1:1) at the HMDE developed a stripping voltammetry peak at more negative potential than that of the free Zn(II) ions. The peak current was used for the determination of terfenadine in pharmaceutical formulation and human plasma in 0.1 mol l^{-1} sodium perchlorate solution under the optimized conditions (E_{acc}, -0.5 V; t_{acc} 360 s; scan rate, 5 mV s^{-1} and pulse height 100 mV). The developed peak current (i_p) showed a linear dependence with terfenadine concentration within the range of 6×10^{-8}–9×10^{-7} mol l^{-1}. The recoveries were found 98.97–99.35%, 99.72–99.02% and 100.58–101.08% with the R.S.D. 0.16–0.27%, 0.25–0.82% and 0.44–1.14% in authentic form, pharmaceutical formulations and human plasma, respectively. The detection limits were 0.4505 and 0.6115 ng ml^{-1} terfenadine in pharmaceutical formulations and human plasma, respectively.

Keywords: Differential Pulse Cathodic Adsorptive stripping voltammetry; HMDE; Pharmaceutical formulation; Human plasma; Terfenadine determination

1. Introduction

Terfenadine (I) (α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenyl methyl)-1-piperidinebutanol) is an antihistamine, which is chemically and pharmacologically distinct from other antihistamines.

Terfenadine binds preferentially to peripheral than central H1-histamine receptors, so it exerts its antihistaminic action without impairing the individual's performance. It has no effect on psychomotor skills or subjective feelings. Terfenadine is used to relieve the symptoms of many allergic disorders, such as allergic rhinitis (e.g. hay fever), allergic conjunctivitis, allergic asthma, and allergic dermatological disorders like urticaria, angioneurotic edema and atopic dermatitis or eczema [1].



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In one study [1] in healthy adults, the mean peak plasma terfenadine concentrations of 1.5 or 4.5 ng ml^{-1}, respectively, occurred at about 1 h following oral administration of a single 60- or 180 mg dose of the drug.

Various techniques have been utilized for the determination of terfenadine in its pharmaceutical formulations and biological fluids. These techniques include: ion-pair formation [2], ternary complex formation [3,4], HPLC [5–13], HPLC-MS [14–17], TLC [18], non aqueous titration and TLC [19], fluoroimmunoassay [20], spectrophotometry [21,22], and extraction colorimetry [23].

Surveying the literature revealed that no electroanalytical methods for determination of terfenadine was reported. The present work aimed to optimize a simple, fast, accurate and low cost electroanalytical method to be applied in trace analysis and clinical laboratories for the determination of terfenadine in pharmaceutical formulations and human plasma.

2. Experimental

2.1. Materials and solutions

Terfenadine was kindly donated by Squibb Company Cairo, Egypt.

A stock standard solution (1×10^{-3} mol l^{-1}) of authentic terfenadine was freshly prepared before measurements by dissolving an accurate weight of the solid compound in ethanol (Merck) and stored in a dark bottle. Aliquots of this solution were diluted with ethanol to produce 1×10^{-4}–1×10^{-6} mol l^{-1} terfenadine solutions. The prepared terfenadine solutions are stable and their concentrations do not change with time.

2.2. Pharmaceutical preparations

Histadin tablets (terfenadine of Amoun Pharmaceutical Industries Co.) and Triludan tablets (terfenadine of Marion Merrell Dow Ltd) were purchased from local market of Egypt.

Five tablets of histadin or triludan were weighed and finely grounded in agate mortar. A quantity of the finely grounded tablets equivalent to 100 mg of terfenadine was extracted with 20 ml successive portions of ethanol (Merck). The alcoholic extracts were completed to 150 ml with ethanol then filtrated through 0.45 μm milli-pore filter (Gelman, Germany). Aliquots of this solution were diluted with ethanol to produce 1×10^{-5} mol l^{-1} terfenadine.

2.3. Additives solution

Commercially available terfenadine tablets also contain some additives e.g. starch, sodium bicarbonate, gelatin, lactose and magnesium stearate. For recovery study, a synthetic mixture containing terfenadine and these additives was prepared in ethanol in a preparation according to manufacture's batch formulas for 60 mg per tablet. The alcoholic terfenadine extract was completed to 100 ml with ethanol then filtrated through a fine milli-pore filter. Aliquot of this solution was diluted with ethanol to produce 1×10^{-5} mol l^{-1} terfenadine solution.

2.4. Spiked human plasma

Blood sample of healthy person was supplied by the Blood Bank of Tanta University Hospital, Tanta, Egypt.

Plasma spiked with terfenadine solution was obtained by diluting aliquots of the authentic stock standard terfenadine solution with the human plasma. A 100 μl aliquot of this spiked solution was diluted to 1.0 ml with ethanol in 10 ml centrifuge tubes. The precipitated protein was separated by centrifugation for 5 min at 5000 rpm. The clear supernated layer was filtrated through 0.45 μm filter to produce spiked protein free-human plasma of known terfenadine concentration.

2.4.1. Supporting electrolyte

The supporting electrolyte used in the present study was 0.1 mol l^{-1} sodium perchlorate. Its stock solution (0.2 mol l^{-1}) was prepared by dissolving an accurate weight of the salt (analytical grade) in specific volume of deionized water.

2.4.2. Metal salt solutions

Solutions of 10^{-3} mol l^{-1} of Zn(II) was prepared by dissolving an accurate weight of the metal nitrate (analytical grade) in deionized water. Deionized water was obtained from AquaMatic bidistillation system attached with a Pur1-TE Still Plus deionizer system (Hamilton, England).

2.5. Apparatus

The voltammograms were recorded using a potentiostat Model 273A- PAR interfaced with PC-computer loaded with a software Model 270/250 (supplied from EG&G). A 303 Å electrode assembly with a hanging mercury drop electrode (surface area $= 2.6 \times 10^{-2}$ cm^2) as a working electrode, a platinum wire as a counter electrode and Ag/AgCl as a reference electrode was used. Digital micropippetter (Volac 100 μl) was used for the solutions addition. Mettler balance (Toledo AB104) was used for weighing the solid materials.

The prepared solutions of authentic terfenadine, terfenadine tablets and spiked human plasma were analyzed by the following procedure. All the measurements were carried out at room temperature.

2.6. Procedure

A known volume of the analyte (terfenadine containing solution) was pipetted into 10 ml calibrated flask containing 5 ml of 0.2 mol l^{-1} sodium perchlorate and 0.2 ml of 1×10^{-3} mol l^{-1} $Zn(NO_3)_2$ solutions and made up to 10 ml with deionized water. The solution was transferred into a dark electrolysis cell and deoxygenated with pure nitrogen for 10 min. An accumulation potential of -0.5 V (vs. Ag/AgCl) was applied to a fresh drop of the working mercury electrode for a selected time, 360 s, while stirring the solution. After the accumulation time had elapsed, the stirrer was stopped and then after a quiescent period lasting 15 s the voltammogram was recorded, while polarizing the HMDE from the accumulation potential to more negative values. A calibration graph was obtained within the concentration range 6×10^{-8}–9×10^{-7} mol l^{-1} terfenadine.

3. Results and discussion

Terfenadine is an electro-inactive pharmaceutical compound. It selectively forms with Zn(II) ions a metal complex (1:1) in solution [24]. It would be of interest to optimize its determination by adsorptive stripping voltammetry via the adsorptive accumulation of the Zn(II)-terfenadine complex at the HMDE.

The differential pulse cathodic adsorptive stripping voltammograms of different terfenadine concentrations in presence of Zn(II) nitrate in 0.1 mol l^{-1} $NaClO_4$ solution were studied. On addition of terfenadine to Zn(II) nitrate solution, a new DP-CAdS voltammetry peak was developed at a more negative potential (-1.52 V) than that of the free Zn(II) (-1.0 V) (Fig. 1). This new peak was attributed to reduction of the adsorbed Zn(II)-ter-

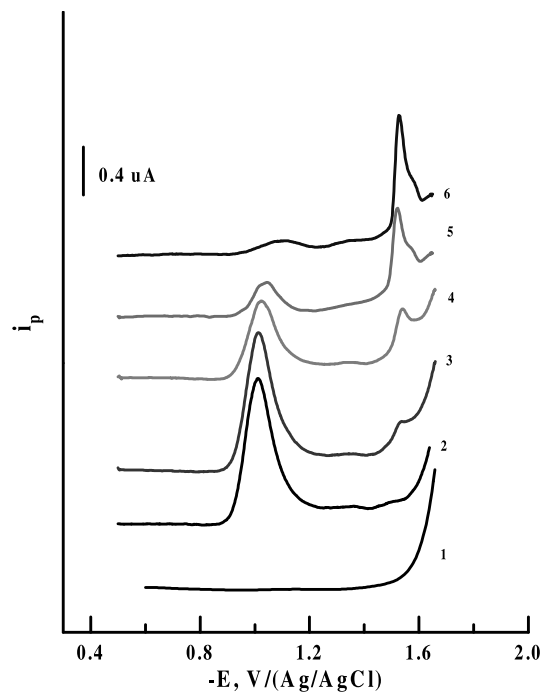

Fig. 1. Effect of terfenadine concentration on the DPCAdS voltamogram of $Zn(NO_3)_2$ in 0.1 mol l^{-1} $NaClO_4$ solution, $t_{acc} = 360$ s, $E_{acc} = -0.5$ V, scan rate $= 5$ mV s^{-1} and pulse height $= 100$ mV. (1) 4×10^{-7} mol l^{-1} terfenadine (alone); (2) 2×10^{-5} mol l^{-1} $Zn(NO_3)_2$ (alone); (3) 6×10^{-8}; (4) 2×10^{-7}; (5) 6×10^{-7}; and (6) 9×10^{-7} mol l^{-1} terfenadine in presence of 2×10^{-5} mol l^{-1} $Zn(NO_3)_2$.

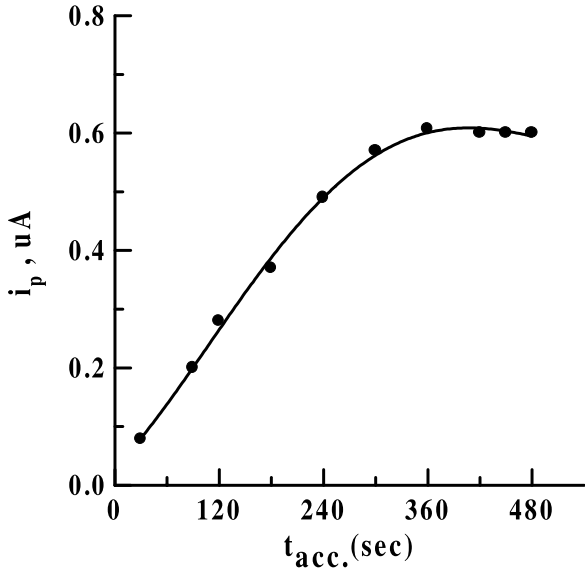

Fig. 2. Effect of accumulation time (t_{acc}) on the developed DPCAdS voltammetry peak of 2×10^{-7} mol l^{-1} terfenadine + 2×10^{-5} mol l^{-1} $Zn(NO_3)_2$ in 0.1 mol l^{-1} $NaClO_4$ solution at $E_{acc} = -0.5$ V, scan rate = 5 mV s^{-1} and pulse height = 100 mV.

fenadine complex (1:1) at the Hg surface [24]. The developed peak current (i_p) increased with increasing the terfenadine concentration while that of free Zn(II) decreased in the same direction. These results indicate that an effective interfacial accumulation of the Zn(II)-terfenadine complex film on the electrode surface took place. This provides the basis for determination of terfenadine by differential pulse cathodic adsorptive stripping (DPCAdS) voltammetry technique.

The DPCAdS developed peak current increased with increase of the accumulation time, t_{acc}, up to 360 s indicating the enhancement of the concentration of Zn(II)-terfenadine complex at Hg electrode surface. After 360 s, the peak current tends to level off, showing that the adsorption equilibrium is reached (Fig. 2). The effect of accumulation potential, E_{acc}, on the developed peak current was examined over the potential range -0.4 to -0.8 V. When the potential was shifted to more negative value than -0.5 V, the peak current decreased (Fig. 3). The dependence of the DPCAdS developed peak current on the scan rate showed that a 5 mV s^{-1} scan rate gave a maximum response (Fig. 4). A more sharp and sensitive peak was obtained at pulse height of 100 mV. Accordingly, the optimum conditions for recording a maximum developed and sharper DPCAdS voltammetry peak of Zn(II)–terfenadine complex are: $t_{acc} = 360$ s, $E_{acc} = -0.5$ V, scan rate = 5 mV s^{-1} and pulse height = 100 mV in 0.1 mol l^{-1} $NaClO_4$ solution as supporting electrolyte. Under these conditions, the terfenadine is preconcentrated by accumulation onto the Hg electrode surface as a film of Zn(II)–terfenadine complex, prior to the voltammetric measurements.

The applicability of DPCAdS voltammetry technique as an analytical method for the determination of terfenadine was tested as a function of its concentration in presence of $Zn(NO_3)_2$ solution (2×10^{-5} mol l^{-1}) under the optimized conditions. The variation of the developed peak current (i_p) with terfenadine concentration (C) was represented by a straight line equation i_p (μA) = 4.711×10^6 $C + 0.0354$, $r = 0.998$ ($n =$

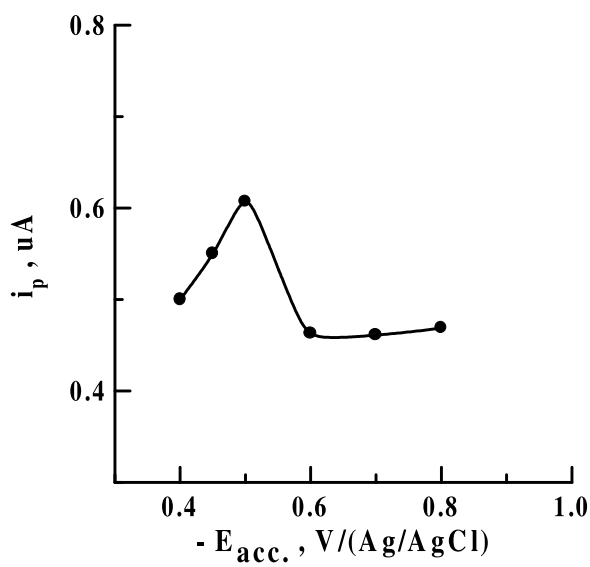

Fig. 3. Effect of accumulation potential (E_{acc}) on the developed DPCAdS voltammetry peak of 2×10^{-7}mol l^{-1} terfenadine + 2×10^{-5} mol l^{-1} $Zn(NO_3)_2$ in 0.1 mol l^{-1} $NaClO_4$ solution at $t_{acc} = 360$ s, scan rate = 5 mV s^{-1} and pulse height = 100 mV.

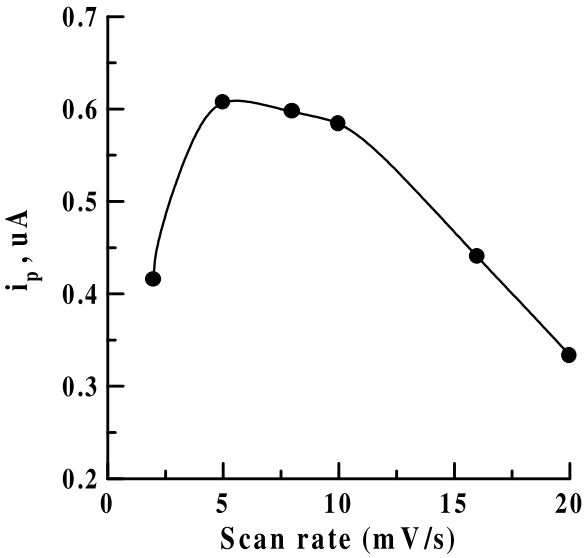

Fig. 4. Effect of scan rate on the developed DPCAdS voltammetry peak of 2×10^{-7}mol l^{-1} terfenadine + 2×10^{-5} mol l^{-1} $Zn(NO_3)_2$ in 0.1 mol l^{-1} $NaClO_4$ solution at $t_{acc} = 360$ s, $E_{acc} = -0.5$ V and pulse height = 100 mV.

12), where r is the correlation coefficient and n is the number of points. The calibration graph was rectilinear within the concentration range of 6×10^{-8}–9×10^{-7} mol l^{-1}. The percentage recovery (%R) was found 98.66–99.35% with a relative standard deviation (%R.S.D.) 0.16–0.27%. The detection limit of authentic terfenadine was calculated using the equation [25] $dl = 3sd/a$, where sd is the standard deviation of the blank, and a is the slope of the calibration curve. So, the detection limit under the optimal experimental conditions was found 0.4505 ng ml^{-1}.

3.1. Additives interference

The effect of the additives (starch, sodium bicarbonate, gelatin, lactose and magnesium stearate) solution on the assay of standard terfenadine solution was studied by our proposed analysis method. In comparing the assay results in absence and presence of these additives, it was found that these additives had no effect on the accuracy of terfenadine determination.

3.2. Applications

3.2.1. Determination of terfenadine in its pharmaceutical formulations

The proposed analysis procedure was successfully applied for the assay of terfenadine in its pharmaceutical formulations (histadin and triludan). The percentage recovery (%R) with %R.S.D. of terfenadine in histadin and triludan tablets, based on the average of four replicate measurements was found: $99.72\% \pm 0.25$ and $99.02\% \pm 0.82$, respectively. The results were favorably compared with those obtained by assay of the same tablets solution with a reported HPLC method [5] (Table 1). The results indicated that no significant difference between the performance of the two methods regards the accuracy and precision, so, the present method is more simple, fast and low cost tool for terfenadine analysis in pharmaceutical formulation.

3.3. Determination of terfenadine in human plasma

Our proposed stripping voltammetry procedure was also successfully applied for the determination of terfenadine in spiked human plasma under the present optimized conditions. The variation of (i_p) of the developed voltammetry peak versus the terfenadine concentration (C) was represented by a straight line equation i_p (μA) = 3.4708×10^6 $C + 0.001$, $r = 0.995$ ($n = 12$). The calibration

Table 1
Assay of terfenadine in pharmaceutical formulation solution using the proposed DPCAdS voltammetry procedure and HPLC reported methods based on the average of four replicate measurements

Brand name	Labeled conc.	% Recovery ± S.D.	
		Proposed method	Reported method [5]
Histadin	60 mg per tablet	99.72 ± 0.25	99.58 ± 0.82
Triludan	60 mg per tablet	99.02 ± 0.82	99.79 ± 0.76

graph was rectilinear within the concentration range 8×10^{-8}–9×10^{-7} mol l^{-1}. The percentage recovery (%R) of terfenadine based on the average of four replicate measurements was found 100.58–101.08% with R.S.D.: 0.44–1.14%. The detection limit of terfenadine in human plasma was found 0.6115 ng ml^{-1}.

4. Conclusion

The described differential pulse cathodic adsorptive stripping voltammetry procedure allows simple, highly sensitive, highly accurate, fast response and low cost quantitative method for determination of terfenadine in the pharmaceutical formulations and human plasma. The accuracy and sensitivity of the described procedure are much better than those reported in literature [2–23]. The method can offer an attractive and easy quantitative analysis tool of terfenadine for the trace analysis and clinical laboratories.

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