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Polarographic behaviour of loratadine and its direct determination in pharmaceutical formulation and human plasma by cathodic adsorptive stripping voltammetry

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Abstract

The polarographic behaviour of the antihistaminic drug loratadine has been investigated in B.R. buffer solution of different pH values. Contradictory to that mentioned before in a previously published work, loratadine is electro-active at the mercury electrode. In B.R. buffer solution of pH values ≥ 6 it is reduced via a single 2-electrons irreversible wave corresponding to saturation of carbon–nitrogen double bond of the pyridine ring. The electrode reaction pathway was proposed and discussed. A sensitive differential pulse stripping voltammetric method based on controlled adsorptive accumulation of loratadine on a hanging mercury drop electrode has been developed for its direct determination at nanomolar concentrations without nitration of the drug. The optimized conditions for the direct cathodic adsorptive stripping voltammetric determination of the drug are: 0.1 M sodium hydroxide solution as a supporting electrolyte, accumulation potential, -1.2 V; accumulation time, 30 s; scan rate, 2–5 mV s^{-1} and pulse amplitude 100 mV. The proposed procedure was applied for the assay of loratadine in pharmaceutical formulation and human plasma. The average recoveries were 99.32–99.44 and 100.33–102.99% with the RSD 0.27–0.42 and 0.39–0.90% in pharmaceutical formulation and human plasma, respectively. The limits of detection of 1.60×10^{-7} and 1.25×10^{-7} M loratadine were found in pharmaceutical formulation and human plasma, respectively.

Keywords: DC-polarography; Cathodic adsorptive stripping voltammetry; Loratadine determination

1. Introduction

Loratadine (I): 4-(8-chloro-5,6-dihydro-11 H-benzo-[5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylic acid ethyl ester, is a potent long-active tricyclic antihistaminic with selective H_1-receptor antagonistic activity [1].

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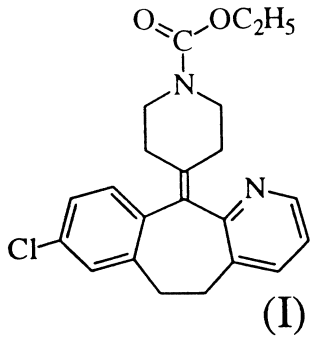

(I)

It has been stated in a previously published work [2] that loratadine is polarographically-inactive as evidenced by the absence of reduction waves in the available potential range, whereas the nitro-loratadine derivative exhibited a differential pulse polarographic peak due to the reduction of the nitro group. The peak current was proportional to nitrated loratadine concentration. loratadine have been determined using several techniques including the use of HPLC [3], gas–liquid–chromatography [4], GC-MS [5] and spectrophotometry [6–8].

In the present work, it is aimed to reconsider the polarographic behaviour of loratadine in B.R. buffer solution of various pH values. It is aimed also to optimize a differential pulse cathodic adsorptive stripping voltammetry procedure for direct determination of the drug in pharmaceutical formulation and human plasma without the need for its nitration. Adsorptive stripping voltammetry has been demonstrated as a sensitive analytical method for a wide range of pharmaceutical compounds adsorbing on the electrode surface [9,10], with the advantage of being less sensitive to matrix effects than other methods.

2. Experimental

2.1. Materials

Authentic loratadine was obtained from Squibb, Cairo, Egypt and Claritine tablets (MUP) was purchased from the Egyptian market. Human plasma sample was supplied by the city blood bank.

2.2. Reagents and solutions

(i) A stock standard solution of 1×10^{-3} M authentic loratadine was prepared in ethanol (Merck) and stored in the dark at 4°C. More dilute solutions (10^{-6}–10^{-4} M) were prepared daily by accurate dilution with ethanol just before use. A series of buffer solutions of pH values 2–11 was prepared according to Britton [11].

(ii) Ten tablets of the pharmaceutical preparation (Claritine) were weighed and finely grounded in an Agate Mortar. A quantity of the finely grounded tablets equivalent to 100 mg of loratadine was extracted with 20 ml successive portions of ethanol. The alcoholic extract was filtrated through 0.45 μm milli-pore filter (Gelman, Germany) into 100 ml volumetric flask and completed with ethanol. Aliquots of this solution were diluted with ethanol to produce 1×10^{-4}–1×10^{-6} M loratadine solutions, which were used as the assay solutions.

(iii) Plasma spiked with loratadine was obtained by diluting aliquots of the stock standard loratadine 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 tube. The precipitated protein was separated by centrifugation for 5 min at 5000 r.p.m. The clear supernatant layer was filtrated through 0.45 μm milli-pore filter to produce protein free-spiked human plasma.

(iv) A 0.2M sodium hydroxide solution was prepared by dissolving an accurate weight of the solid material (BDH) in a specific volume of deionized water, then standardized against standard HCl solution.

2.3. Instrumentation

Polarograph Model 4001 (Sargent-Welch) was used for studying the polarographic behaviour of authentic loratadine solution. The polarographic cell bottom contained a dropping mercury electrode as a working electrode ($m = 1.03$ mg s^{-1}, $t = 3.3$ s at mercury height = 60 cm) and a saturated calomel electrode (SCE) as a reference electrode. The voltammograms were recorded using a potentiostat Model 273A–PAR interfaced with

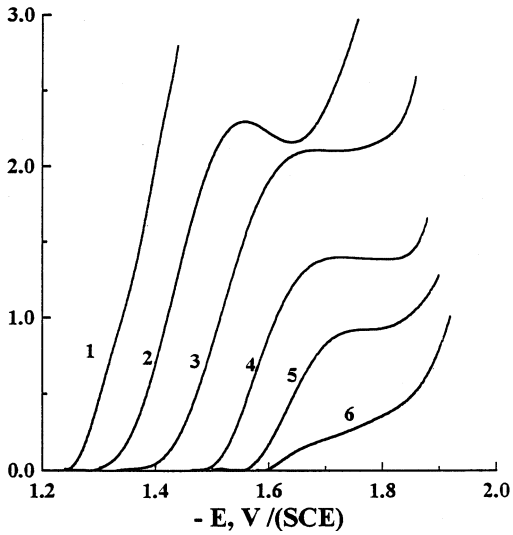

Fig. 1. DC-polarograms for 5.0×10^{-4} M loratadine in B.R. buffer solution of different pH values. (1) 5.1; (2) 6.3; (3) 7.2; (4) 8.2; (5) 9.2; (6) 10.1.

PC-computer loaded with the software package 270/250 (from EG&G). The electrode assembly 303A with a micro-electrolysis cell of stationary mercury drop electrode (SMDE) as a working electrode, Ag/AgCl as a reference electrode and a platinum wire as a counter electrode were used. Mettler balance (Toledo-AB104) was used for weighing the solid materials. Deionized water was obtained from AquaMatic bidistillation system attached with a Purite Still Plus HP deionizer system.

2.4. Procedure

A known volume of the analyte (loratadine containing solution) was pipetted into 5 ml of 0.2 M sodium hydroxide solution and made up to 10 ml with deionized water. The solution was transferred into the electrolysis cell and deoxygenated with pure nitrogen for 10 min. A suitable accumulation potential was applied to a new mercury drop for a selected time while the solution was stirred at 400 rpm. The stirring was then stopped and after 15 s the voltammogram was recorded by applying a negative going differential pulse scan. All data were obtained at room temperature.

3. Results and discussion

3.1. Polarographic behaviour

The electrochemical behaviour of lorataine was studied polarographically in Britton- Robinson buffer solution of different pH values. Contradictory to the work published before [2] the dc-polarogram for 5×10^{-4} M loratadine was found to exhibit a single 2-electrons irreversible reduction wave in solutions of pH ≥ 6 (Fig. 1). At lower pH values (< 6) the reduction wave overlapped with that due to the hydrogen evolution. A large polarographic maximum was observed on the rising part of the reduction wave and covered most of the limiting current region. Its suppression with Triton X-100 leads to a considerable decrease of the limiting current.

It was observed that with increasing the pH ≥ 6 of the medium, the half-wave potential ($E_{1/2}$) shifted toward more negative values. As suggested by Zuman [12] this behaviour indicated the involvement of protons in the rate-determining step and the proton transfer precedes the electron transfer. The plot of $E_{1/2}$ versus pH [12] gave a linear correlation with slope value S_1 [$S_1 = (0.0591/\alpha n_a)\ Z_H^+$] given in Table 1. Furthermore, logarithmic analysis [13] of the polarographic wave in solutions of pH ≥ 6 was performed by

Table 1
Polarographic data obtained for 5×10^{-4} M loratadine in B.R. buffer solution of different pH values at 25°C

PH	$\delta E_{1/2}/\delta$pH (S_1), mV	$\delta E/\delta \log i/i_d - i$ (S_2), mV	αn_a	Z_H^+ (S_1/S_2)
6.3	79.17	81.90	0.73	0.97
7.2	79.17	83.10	0.73	0.95
8.2	79.17	78.70	0.75	1.01

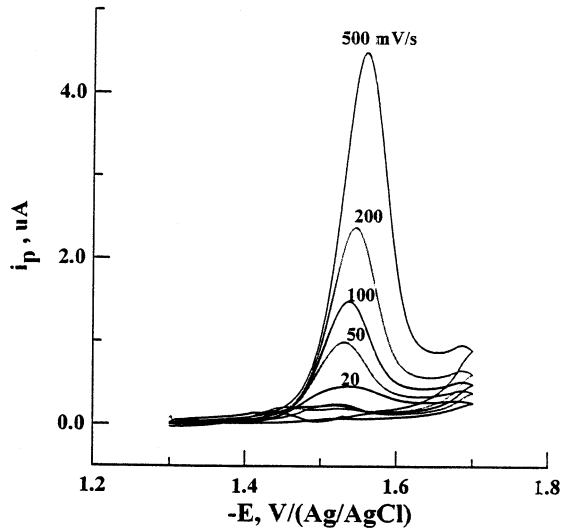

Fig. 2. Cyclic voltammograms for 1×10^{-4} M loratadine at different scan rates in B.R. buffer solution of pH 7.

plotting $E_{d.e}$ versus log $(i/i_d - i)$. The plots were straight lines with slope values S_2 [$S_2 = 0.0591/\alpha n_a$] from which αn_a values were evaluated (Table 1). The less than unity of αn_a values confirmed the irreversible nature of the electrode process.

The number of protons Z_H^+ participating in the rate-determining step was found to equal 1 (Table 1) as calculated from the relation $Z_H^+ = (S_1 \cdot \alpha n_a/0.0591) = S_1/S_2$ [14]. On the other hand, the overall reduction process was found to consume two electrons per drug molecule as confirmed by the complete electrolysis at controlled potential coulometry for loratadine in B.R. buffer solution of pH = 6. According to Zuman [12] when both $E_{1/2}$ and i_l of a polarographic wave are pH-dependent, it may indicate that both forms in which the depolarizer may exist in the solution are transported to the electrode surface, that one of them is electro-active, and that this electro-active form can be generated from the electro-inactive one at a rate that depends on pH. This pH-dependent electrode reaction can be either an acid–base reaction or a chemical reaction such as ring opening or dehydration [12]. In the present work, the polarographic wave of loratadine may be attributed to the saturation of the carbon–nitrogen double bond of the pyridine ring in the loratadine molecule [15].

Cyclic voltammograms of loratadine in B.R. buffer solution of pH ≥ 6 exhibit a single cathodic peak (Fig. 2). On increasing the scan rate v, the peak potential (E_p) shifted to more negative value, indicating the irreversible nature of the electrode process [16]. Plotting of peak current i_p versus scan rate v gives a linear correlation indicating the adsorption contribution [17]. The response for surface-adsorbed loratadine at saturation was used to determine the surface coverage. The surface coverage can be measured by cyclic voltammetry from the amount of charge consumed by the surface process as calculated by the integration of the area under the peak corrected to residual current [18]. According to the equation: $\Gamma = Q/nFA$, the surface coverage Γ (mol cm^{-2}) can be calculated, where n is the number of electrons consumed in the reduction process ($n = 2$), F is the Faraday's constant (96487 Coulombs) and A is the electrode surface area (0.026 cm^2)]. On dividing the number of coulombs transferred, 6.8113 μC, by conversion factor (nFA) yielded coverage of 1.3538×10^{-9} mole cm^{-2}. Each adsorbed loratadine molecule therefore occupies an area of 0.1223 nm^2, in a monolayer adsorption.

3.2. Cathodic adsorptive stripping voltammetry of loratadine

The cathodic adsorptive stripping (CAdS) voltammograms for 8×10^{-5} M loratadine was recorded in different types of supporting electrolyte solutions (e.g. 0.1 M sodium sulphate, 0.1 M sodium nitrate, 0.1 M sodium perchlorate, 0.1 M sodium hydroxide, borate buffer of pH 9.2, and B.R. buffer solutions of pH 7 & 8). A more sensitive and sharper cathodic peak was obtained in 0.1 M sodium hydroxide solution due to the saturation (reduction) of carbon–nitrogen double bond of the pyridine ring of the adsorbed loratadine molecules at the mercury electrode surface.

At higher or higher scan rate than 2–5 mV s^{-1} the peak current decreased (Fig. 3(a)). At preconcentration time $t_d = 30$ s, an equilibrium surface concentration is reached (Fig. 3(b)). The effect of the accumulation potential on the CAdS peak

current of loratadine is studied between −1.0 and −1.4 V. The peak current decreased markedly on shifting the potential either to lower or to higher values than −1.2 V (Fig. 3(c)). This behaviour indicates a weak interaction between loratadine and the mercury surface at potential values higher or lower than −1.2 V. The peak current for the adsorbed loratadine was directly proportional to the pulse height. In the present study, a 100 mV pulse height was used. Accordingly, the optimal conditions for recording the CAdS voltammograms are: preconcentration time 30 s, accumulation potential −1.2 V, scan rate 2–5 mV s^{-1} and pulse height 100 mV in 0.1 M sodium hydroxide solution as a supporting electrolyte.

The applicability of the optimized cathodic adsorptive stripping voltammetry procedure for the determination of authentic loratadine concentration was tested (Fig. 4). The calibration curve was constructed over the concentration range 1×10^{-6}–3×10^{-5} M of authentic loratadine. The variation of peak current (i_p) with loratadine concentration C (M) was represented by a straight line equation i_p (μA) $= 3.098 \times 10^4$ $C + 0.0705$, $r = 0.998$ ($n = 12$), where r is the correlation coefficient and n is the number of points. The percentage recovery (%R) was found to equal 99.22–99.61% with relative standard deviation (RSD) 0.24–0.39%. The detection limit (1.6×10^{-7} M) of loratadine was calculated using the equation [19] $dl = 3SD/a$, where SD is the standard deviation of the blank, and a is the slope of the calibration curve.

In order to establish the reliability of the proposed method, authentic loratadine was determined in presence of the excepients containing the drug in tablets (e.g. starch, talc, gelatin, lactose and magnesium stearate). It was found that the excepients had no effect on the accuracy of determination of loratadine.

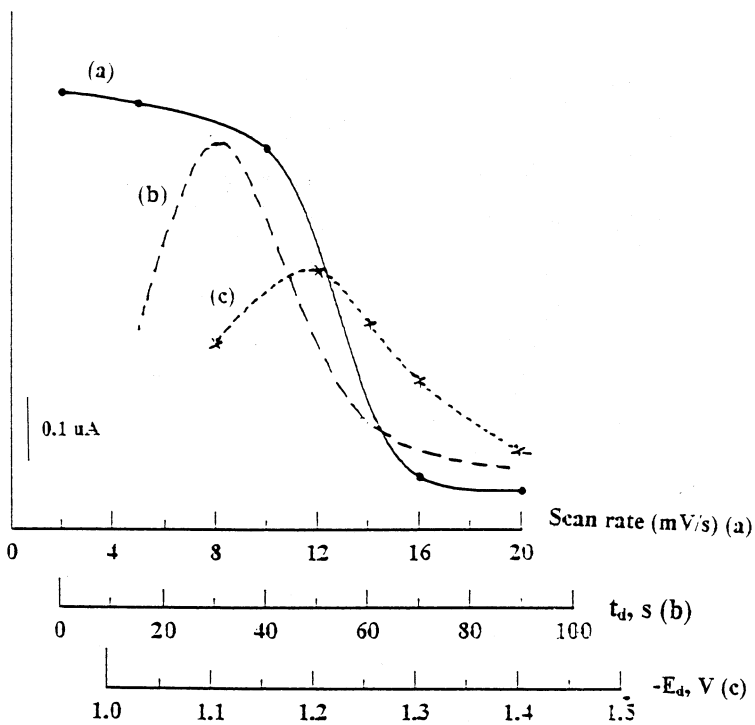

Fig. 3. (a) Effect of scan rate on the CAdS peak current for 8×10^{-5} M loratadine in 0.1 M NaOH solution. (b) Effect of accumulation time (t_d) on the CAdS peak current for 8×10^{-5} M loratadine in 0.1 M NaOH solution. (c) Effect of accumulation potential (E_d) on the CAdS peak current for 8×10^{-5} M loratadine in 0.1 M NaOH solution.

Table 2
Assay of loratadine in its pharmaceutical formulation using the proposed method compared to the reported HPLC method [3] based on the average of four separated experiments

Brand name (producer)	Labelled conc. (Drug)	% Recovery ± RSD	
		Proposed method	Reported method
Claritine (MUP)	10 mg/tablet	99.39 ± 0.329	101.12 ± 0.672

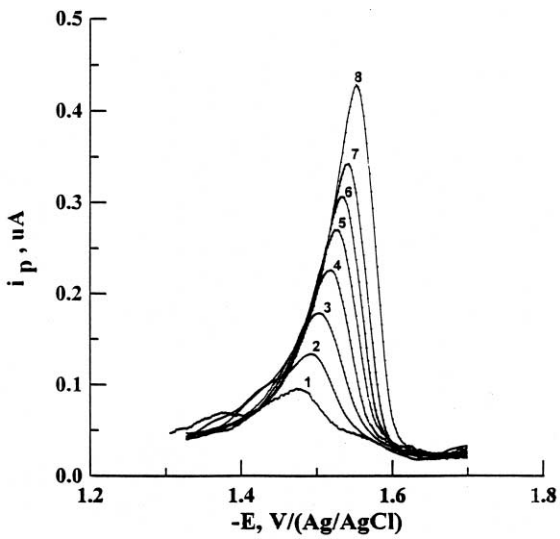

Fig. 4. CAdS voltammograms in 0.1 M NaOH solution at different concentration of loratadine. (1) 2.0×10^{-6}; (2) 5.0×10^{-6}; (3) 7.0×10^{-6}; (4) 9.0×10^{-6}; (5) 1.1×10^{-5}; (6) 1.3×10^{-5}; (7) 1.5×10^{-5}; (8) 2.0×10^{-5} M at $t_d = 30$ s, $E_d = -1.2$ V, scan rate = 2 mV s^{-1} and pulse height = 100 mV.

3.3. Application

3.3.1. Assay of loratadine in pharmaceutical formulation

The proposed analysis procedure was successfully applied for the assay of loratadine in pharmaceutical formulation. The percentage recovery (%R) of loratadine in Claritine tablets, based on the average of four separate experiments was found to equal 99.32–99.44% with RSD: 0.27–0.42%. The result was favorably compared with that obtained by assay of the same tablets solution 101 ± 0.672 with HPLC method [3] (Table 2).

3.3.2. Assay of loratadine in human plasma

The optimized cathodic adsorptive stripping voltammetry procedure was also successfully applied for the determination of loratadine in protein-free spiked human plasma.

The variation of (i_p) versus the loratadine concentration C (M) was represented by a straight line equation i_p (μA) = $4.02297 \times 10^4 C + 0.083$, $r = 0.997$ ($n = 12$). The calibration graph was rectilinear within the concentration range 1×10^{-6}–2×10^{-5} M. The reliability of the method for the determination of loratadine in human plasma was checked using different spiked human plasma samples. The percentage recovery (%R) of loratadine based on the average of four separate experiments was found to be 100.33–102.99% with RSD 0.39–0.91%. The detection limit of loratadine in human plasma was found to be within the concentration level of 1.25×10^{-7} M.

4. Conclusion

Contradictory to the previously published work [2] loratadine is found to be an electro-active compound since it was reduced in B.R. buffer solution of pH ≥ 6 via a single 2-electrons irreversible wave. It could be determined directly in pharmaceutical formulation and human plasma with a great success using a CAdS voltammetry procedure without nitration of the drug. The proposed procedure is accurate enough, simple and fast for the assay of the drug with a detection limit of 1.25×10^{-7}–1.6×10^{-7} M loratadine. The method could be extended for the direct determination of loratadine in other biological fluids.

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