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Electrooxidation of cetirizine dihydrochloride with a glassy carbon electrode

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The electrochemical oxidation of cetirizine dihydrochloride (CTZH) at different pHs and concentrations using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) with a glassy carbon (GC) electrode was studied. This study indicated that CTZH was susceptible to oxidation. The statistical analysis proved that the CV and DPV methods were reproducible and selective for the determination of CTZH. The results showed that voltammetric determination of CTZH could be made in the concentration ranges of 2×10^{-5} M – 1×10^{-4} M by CV and 2×10^{-5} M – 1×10^{-4} M by DPV with a GC electrode. The oxidation process was found to be irreversible over the pH range studied (2–10) and was shown to be mainly diffusion controlled. The determination of CTZH was performed in phosphate buffers covering the pH range of 2–10. No satisfactory results were obtained in 0.5 M H_2SO_4 solution. With both of the methods used the best results were obtained in phosphate buffer of pH 8. Application of the suggested methods to pharmaceutical formulations is presented and compared with the first derivative spectrophotometric method. No interference was observed from common pharmaceutical adjuvants.

1. Introduction

Cetirizine dihydrochloride (Zitek or Zyrtec, [2–[4-[(4-chlorophenyl)phenylmethyl]-piperazin-1-yl] ethoxy acetic acid dihydrochloride, CTZH) is a potent and well tolerated non-sedating antihistamine drug for treatment of seasonal and prennial allergic rhinitis and chronic urticaria (Sweetman 2002). For this drug the literature reveals a variety of analytical methods such as HPTLC (Makhija and Vavia 2001), LC-MS (Rudaz et al. 2003; Eriksen et al. 2002), spectrophotometry (Basavaiah et al. 1999; Gowda et al. 2001; Gazy et al. 2002), RP-LC (Zaater et al. 2000), HPLC (Moncrieff 1992; El Walily et al. 1998; Macek et al. 1999), and spectrofluorimetry (Melwanki et al. 2001). Most of these methods are time-consuming, expensive and cumbersome. In the literature there are some publications related to the partition of the zwitterionic antihistamine cetirizine, e.g. (Bouchard et al. 2001), but as far as we know there is no voltammetric investigation of this drug aiming at its analytical determination.

In the present study the electrooxidation of CTZH was investigated using a glassy carbon (GC) electrode by cyclic voltammetry (CV), differential pulse voltammetry (DPV) and first derivative spectrophotometry.

2. Investigations, results and discussion

Voltammetric experiments were performed using a GC electrode. 0.5 M H_2SO_4 and phosphate buffers in the pH range 2–10 were used as solvents. CV and DPV techniques were applied and the results were evaluated from the viewpoint of quantitative analysis.

CV curves were recorded over a wide range of scan rates (10–400 mVs^{-1}). Cyclic voltammograms of 4×10^{-4} M CTZH obtained in pH 8 phosphate buffer (Fig. 1a, b) showed two anodic peaks at 830 mV and 1050 mV.

In Fig. 1b voltammograms showing the effect of the scan rate are given. As scan rate increased peak potentials shifted to more positive values and peak currents increased. The peak current of the first anodic peak is linearly dependent on CTZH concentration for all the scan rates given in Fig. 1b. For analytical purposes the best results were obtained with a scan rate of 400 mVs^{-1}.

The effect of pH was investigated in phosphate buffers at various scan rates (Fig. 2). At pH 7, 8, and 10 two anodic peaks were observed at about 700 mV and 1000 mV. When scan rate increased anodic peak shifted to more positive potentials.

Repeatibility of the curves obtained in the test solutions using the same stock solution revealed the stability of CTZH. The peak potential-pH relationship for peak I was found to be linear for a broad scan rate interval (Table 1). From the equations of these linear sections it can be concluded that at lower pH values ($pH < 7$), the reaction occurs with one proton transfer for one electron while at higher pH values one proton transfers for two electrons.

Table 1: Peak potential-pH relationship for peak I

Scan rate(mVs^{-1})	pH range	Equation of the linear relationship	r (%)
400	2–7	$y = 1.41 - 0.06.X$	99,9
400	7–10	$y = 1.16 - 0.03.X$	99,9

Table 2: Determination of CTZH by CV, DPV and first derivative spectrophotometry

	Parameters		
	CV	DPV	First der. Spectr.
Range (M)	$2 \times 10^{-5} - 1 \times 10^{-4}$	$2 \times 10^{-5} - 1 \times 10^{-4}$	$1 \times 10^{-5} - 1 \times 10^{-4}$
Regression equation(Y)[a]			
Slope (b)	3.75×10^{5}	5.45×10^{4}	0.194
Std.dev.on slope(s_b)	1.72×10^{-6}	1.19×10^{-7}	4.07×10^{-6}
Intercept (a)	7.62	1.95	0.038
Std.dev.on intercept (S_a)	0.18×10^{-7}	0.37×10^{-7}	3.72×10^{-6}
Std.error of estimation (S_e)	0.93×10^{-5}	0.048×10^{-6}	1.97×10^{-6}
Correlation coefficient (r)	0.99	0.99	0.99

[a] $Y = a + bC$ where C is concentration in M and Y in first derivative absorbance and current units for first derivative spectrophotometric and voltammetric methods, respectively

Phosphate buffer solutions were chosen as the supporting electrolyte and the best results were obtained in these solutions as regards repeatibility.

The effect of potential scan rate on the peak current and the peak potential of CTZH was evaluated. Fig. 3 shows the influence of the square root of the scan rate on peak current the logarithm of scan rate ($\log_{ip}$-$\log_v$) relationship was also linear.

This relationship revealed that the reaction mainly diffusion controlled. As pH increased the effect of surface reactions also increased. The slope values of the equations differed from 0.5.

The effect of pH was investigated in phosphate buffer. In Fig. 4a, and 4b peak potential vs pH plots are presented for CV and DPV. The potential of the anodic peak decreases lineary with pH. In the range pH 7–10, it was constant.

Fig. 5a gives differential pulse voltammograms obtained in phosphate buffers. A sharp peak at 1,1 V in pH 2 buffer shifted to lower values as pH increased. In Fig. 5b differential pulse voltammograms obtained in pH 8 phosphate buffer solutions having different concentration of CTZH are shown.

Evaluation of these curves revealed that quantitative determination of CTZH could be made by DPV and the optimum conditions were found to be 20 mVs^{-1} scan rate, 50 mV pulse amplitude, 17 ms sample width, 50 ms pulse width and 200 ms pulse period. Under these conditions the peak current of the DPV curve is linearly dependent on concentration.

Statistical treatment of this dependence is given in Table 2. Reproducibility of DPV peak current and peak potential was tested by repeating ten experiments at 4×10^{-4} M. The applicability of the CV and DPV methods for the assay of a simple dosage form was examined by analysis of a tablet form. The results confirm the suitability of the proposed method for the accurate and sensitive analysis of CTZH. The CV and DPV results were compared with those of first derivative spectrophotometric method by means of Student's t-test at a 95% confidence level and no significant difference was found between them (Table 3).

The validation of the procedures was carried out by evaluation of the limit of detection (LOD), limit of quantita-

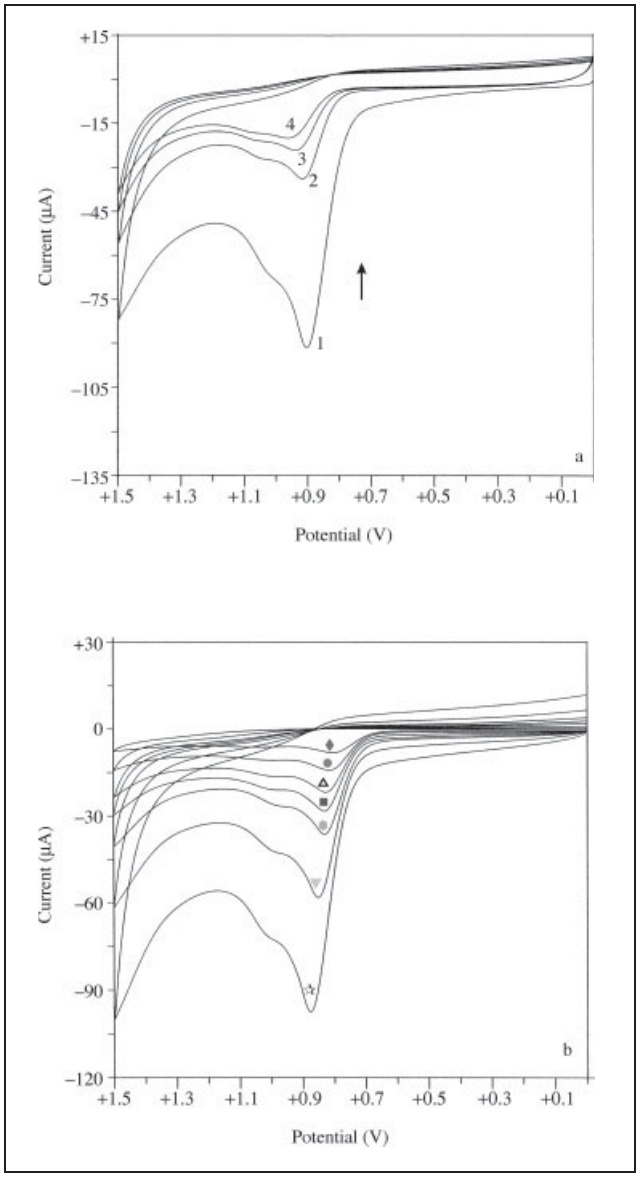


Fig. 1: (a) Multi scan voltammograms of 4×10^{-4} M CTZH taken in pH = 8 phosphate buffer, scan rate 400 mVs^{-} **(b)** Voltammograms of 4×10^{-4} M CTZH obtained in pH = 8 phosphate buffer at various scan rates. ♦) 10mVs^{-1} ●) 25 mVs^{-1} △) 50 mVs^{-1} ■) 75 mVs^{-1} ●) 100mVs^{-1} ▽) 200mVs^{-1} ☆) 400mVs^{-1}

Table 3: Comparative studies for CTZH formulations

Formulation[a] (Tablet)	Analysis techniques		
	CV	DPV	First derivative spectrophotometry
Mean (mg)[b]	9.84	9.91	9.93
R.S.D. (%)	0.37	0.21	0.17
Calculated t value			
T, theoretical (p = 0.05)	1.19[c]	0.96[c]	

[a] Tablet, 10 mg per tablet
[b] Each value is the mean of five experiments
[c] NS, not significant

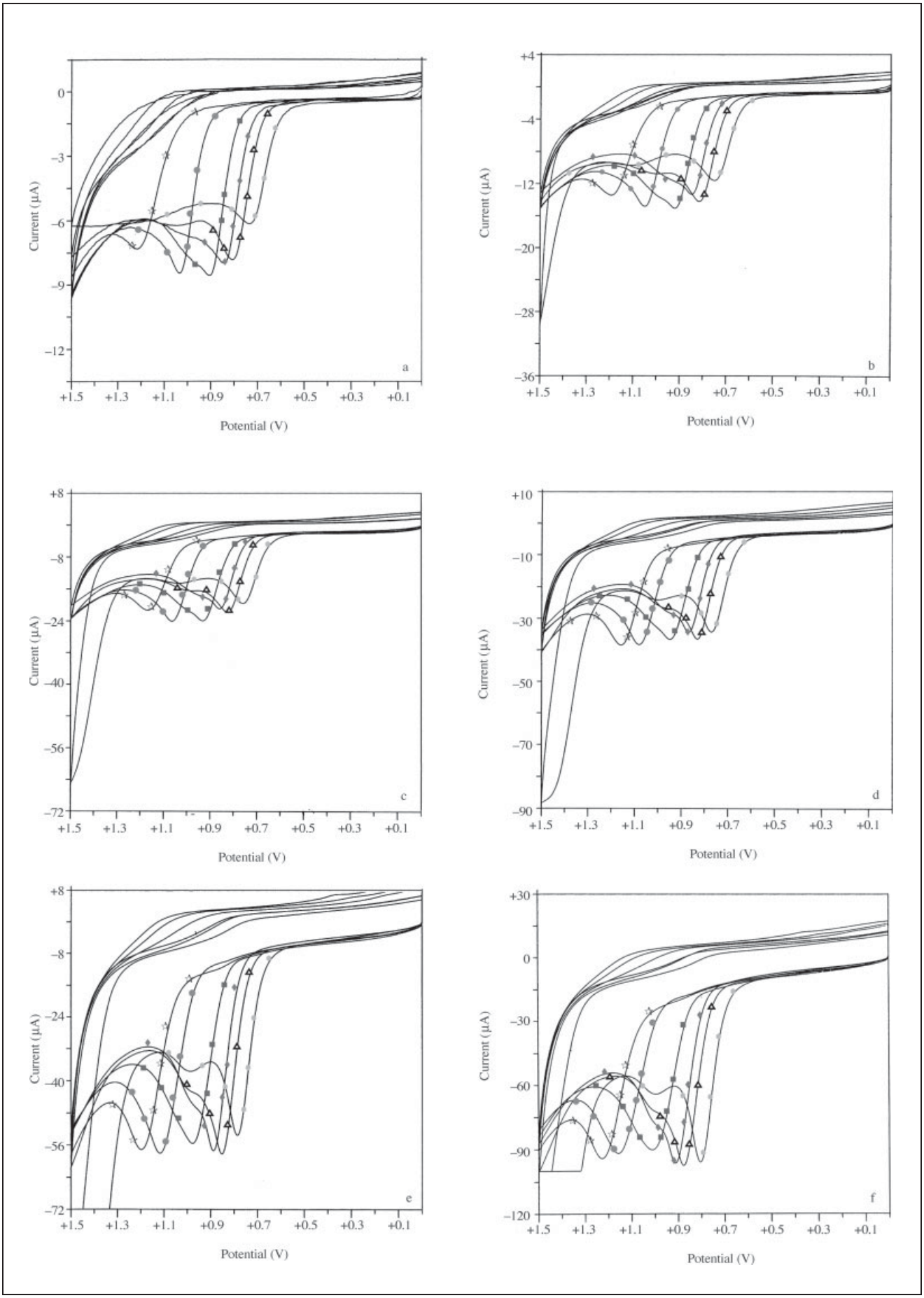


Fig. 2: Voltammograms taken in phosphate buffer solutions having different pH values for $4x10^{-4}$ M CTZH, scan rate (a) $10mVs^{-1}$; (b) $25\ mVs^{-1}$; (c) $50\ mVs^{-1}$; (d) $100\ mVs^{-1}$; (e) $200\ mVs^{-1}$; (f) $400\ mVs^{-1}$; pH, ☆ 2.00 ; ● 4.00 ; ■ 6.00 ; ♦ 7.00 ; △ 8.00 ; ● 10.00.

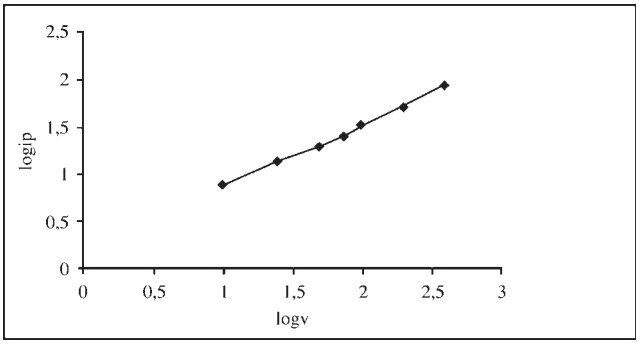
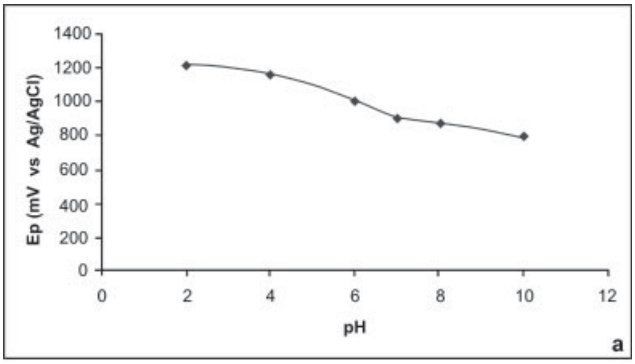


Fig. 3: The potential scan rate on the peak current- logarithm of scan rate ($\log i_p$ – logv) relationship.



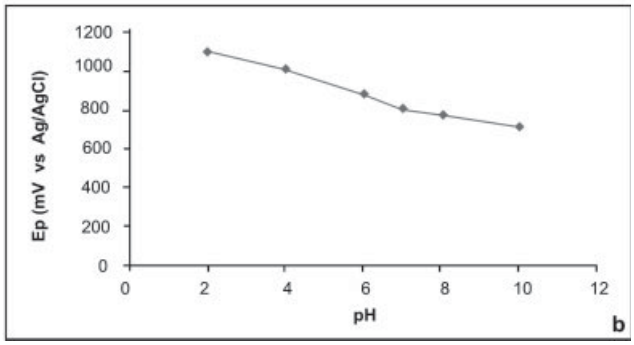


Fig. 4: **(a)** The peak potential vs pH plot at CV **(b)** The peak potential vs pH plot at DPV

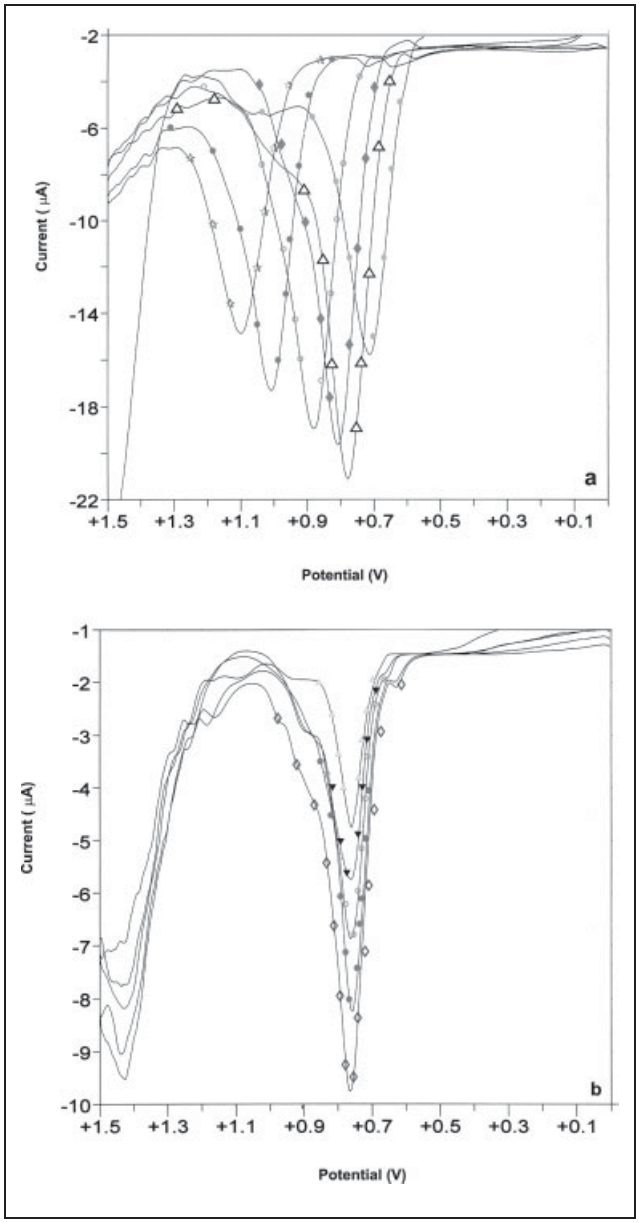


Fig. 5: (a) DPV curves obtained for 4×10^{-4} M CTZH in phosphate buffer solutions having different pH values. pH, ☆ 2.00; ● 4.00; ○ 6.00; ♦ 7.00; △ 8.00; ● 10.00. **(b)** DPV curves obtained in pH = 8 phosphate buffer solution having various CTZH concentration. △ 2×10^{-5} M; ▼ 4×10^{-5} M; ○ 6×10^{-5} M; ● 8×10^{-5} M; ◇ 10^{-4} M.

tion (LOQ), repeatibility, recovery, specificity and robustness. The LOD and LOQ were calculated from the calibration curves as k SD/b where k = 3 for LOD and 10 for LOQ, SD is the standard deviation of the intercept and b is the slope of the calibration curve. The values of LOD and LOQ were 4.3×10^{-6} M (for CV), 4.5×10^{-6} M (for DPV), and 1×10^{-5} M (first derivative spec.) and 1.43×10^{-5} M (for CV), 1.49×10^{-5} M (for DPV), and 1.92×10^{-5} M (first derivative spec.) respectively. Repeatibility and recovery were examined by performing five replicate measurements of the concentration of 6×10^{-5} M CTZH (for CV), 6×10^{-5} M (for DPV), and 5×10^{-5} M (first derivative spec.) respectively. Mean recoveries of 98.4% for CV, 99.1% for DPV and 99.3% for first derivative spectrophotometry were achieved.

The applicability of the proposed voltammetric methods to the assay of simple dosage forms was examined by analysing tablets. The voltammetric results were compared with the first derivative spectrophotometry results by means of Student's t-test at a 95% confidence level. No significant difference was found (Table 2). Based on the above results, all the methods developed may be recommended for routine and quality control analysis of the drug investigated in pharmaceutical dosage forms.

3. Experimental

3.1. Apparatus

Voltammetric measurements were made using a BAS 100 W/B electrochemical analyser and a HP 1100 laserjet printer. The three-electrode system comprised a BAS MF 2012 glassy carbon disc electrode, a BAS MF 1063 type silver/silver chloride/saturated KCl reference electrode and a BAS MV 1032 platinum wire auxiliary electrode. The potentials in the text were given versus a silver/silver chloride electrode.

A double beam, Shimadzu model 1601 spectrophotometer with a fixed slit width (2 nm) connected to an IBM-PC computer was used. The derivative UV spectra of standard and test solutions were recorded in 1 cm quartz cells.

3.2. Reagents

CTZH was obtained from Hoechst Marion Roussel without prior purification. Zyrtec^R tablets containing a 10 mg dose were obtained from local drugstores. Analytical grade phosphoric acid, and Merck grade methanol were purchased from Merck & Co. All other chemicals were of analytical-reagent grade and were used as received.

3.3. Solution preparation

Three stock solutions of 10^{-3} M CTZH were prepared in phosphate buffer, 0,5 M H_2SO_4 and methanol : 0.1 N HCl (1 : 1 v/v). Diluted working standard solutions were then prepared daily from fresh stock solution and contained phosphate buffer and 0,5 M H_2SO_4. Tests were performed in 0,5 M H_2SO_4 and phosphate buffers. Phosphate buffers were prepared according to the USP pharmacopeial procedure.

3.4. Pretreatment of the working electrode

The glassy carbon (GC) electrode was polished with 0,5 μm alumina powder on a polishing cloth prior to each measurement. Then, it was throughly rinsed with methanol and double distilled water, and gently dried with a paper tissue.

3.5. Procedure

Stock solutions of concentrations $2 \times 10^{-5} - 1 \times 10^{-4}$ M and $1 \times 10^{-5} - 1 \times 10^{-4}$ M CTZH were prepared in phosphate buffer and methanol : 0.1 N HCl (1 : 1 v/v) and stored in dark bottles at $+4$ °C. The working solutions for voltammetric and first derivative spectrophotometric investigations were prepared by dilution of the stock solution. The CTZH concentration does not change with time. Phosphate buffer in the pH range 2.0–10.0 was used as supporting electrolyte when studying the influence of pH. All working solutions were prepared freshly every day.

3.6. First derivative spectrophotometry

Absorption spectra of CTZH in methanol : 0.1 N HCl were determined by first derivative spectrophotometry of this drug in tablet forms. For determination of CTZH measurement of the peak-zero amplitude in the first derivative spectra at 240.5 nm was used.

3.7. Analysis of tablets

A commercial pharmaceutical preparation was assayed. Ten tablets of CTZH (containing 10 mg CTZH) were accurately weighed and finely powdered. The correct amount of powder was dissolved in the supporting electrolyte and methanol : 0.1 N HCl (1 : 1 v/v) and by stirring this solution for about 15 min, a stock solution of 10^{-3} M was prepared, respectively. All the test solutions were obtained by diluting this stock solution with the selected supporting electrolyte and methanol : 0.1 N HCl (1 : 1). Voltammograms and first derivative spectrums were recorded.

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