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DETERMINATION OF HYDROXYZINE BY DIFFERENTIAL PULSE ANODIC VOLTAMMETRY USING CARBON PASTE ELECTRODE

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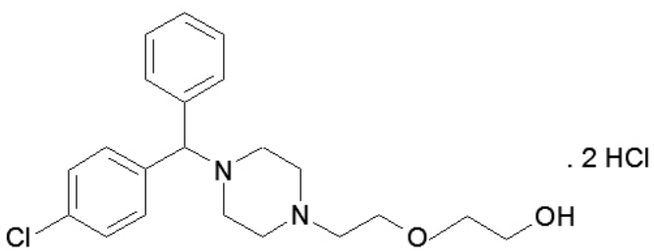
ABSTRACT

The electrochemical oxidation of hydroxyzine dihydrochloride at carbon paste electrode has been studied in 0.04 M Britton-Robinson buffer pH 6.2 using cyclic and differential pulse voltammetry. The oxidation process has been shown to irreversible and diffusion controlled with adsorption characterstics. Based on these studies, simple, rapid, and sensitive differential pulse anodic voltammetric method has been developed for the determination of the drug over the concentration range 0.45-5.36 µg/ml, with detection and quantification limits of 0.27 and 0.90 µg/ml hydroxyzine dihydrochloride, respectively. The proposed method was successfully used for quantification of hydroxyzine dihydrochloride in Atarax tablets and spiked human urine.

Keywords: Hydroxyzine dihydrochloride, differential pulse anoding voltammetry, carbon paste electrodes, pharmaceutical dosage form, human urine.

INTRODUCTION

Hydroxyzine dihydrochloride, (RS)-2-{2-[4-(p-Chloro-a-phenylbenzyl) piperazin-1-yl]ethoxy}ethanol dihydrochloride [2192-20-3] (Scheme 1). It is antihistaminic drug which has several pharmacological effects, sedation, relaxation of muscles, and hypnotic properties. It is mainly used to reduce anxiety and tension for skeletal muscular relaxation or as an antiemetic drug. Its antispasmodic effect is probably due to its interference with the mechanism that responds to spasmogenic agents such as serotonin, acetylcholine, and histamines.[1]



Scheme 1. Structural formula of hydroxyzine dihydrochloride.

Several analytical methods have been reported for the determination of hydroxyzine, including, high performance liquid chromatography (HPLC),[2-11] gas chromatography (GC),[12] thin-layer chromatography,[13] spectrophotometry,[14-17] capillary electrophoresis,[18] potentiometry,[19-21] and conductimetric titration.[22] Also two voltammetric methods have been reported for determination of the drug based on oxidation of the drug on glassy carbon or modified glassy carbon electrodes.[23,24] Carbon paste electrodes are widely used applicable in electrochemical studies due to their low background current compared to solid graphite or noble metals electrodes, low cost, easy preparation, and simple renewal of their surfaces. The present work aimed to study of the voltammetric behavior and assay of hydroxyzine dihydrochloride at carbon paste electrode using cyclic and differential pulse voltammetry.

EXPERIMENTAL

Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments,. Pure grade hydroxyzine dihydrochloride, and the pharmaceutical preparation, Atarax tablets (10 mg hydroxyzine dihydrochloride/ tablet) were kindly supplied by Chemical Industries Development CID, Giza, Egypt. graphite powder (1-2 micron) from Aldrich. and paraffin oil from BDH. As a supporting electrolyte, a series of 0.04 M Britton-Robinson (BR) buffer pH 2.0-11.5 (a mixture of each of acetic, orthophosphoric and boric acids), adjusted to the required pH with 0.2 M sodium hydroxide was prepared.

Apparatus

All voltammetric measurements were performed using Metrohm 797 VA Computrace (Herisau, Switzerland) equipped with a Metrohm VA 694 stand. The three electrodes assembly cell consisted of carbon paste electrode (CPE) as working electrode, an Ag/AgCl in 3 mol/L KCl as a reference electrode, and platinium wire as an auxiliary electrode. The pH measurements were carried out using Hanna pH 211 microprocessor pH meter.

Preparation of carbon paste electrodes

The carbon paste was prepared by hand mixing of 5 g of graphite powder with 1.8 ml of paraffin oil in a mortar with pestle. The resulting carbon paste was tightly packed into the hole of the electrode body and smoothed on a clean paper until it had a shiny appearance. The electrode body was constructed by pressing a small rod of stainless steel (diameter 2 mm) inside a micropipette tip (1 ml volume capacity), leaving a depression at the tip surface of approximately 1 mm for housing the carbon paste, and a thin wire was inserted through the opposite end for electrical contact.[25] The prepared carbon paste electrode was immersed in the supporting electrolyte in the cell, and applying sweeps to obtain a low background current.

General procedure

A 10 ml 0.04 M BR buffer solution pH 6.2 was introduced into a clean and dry voltammetric cell, and the required amount of the drug was added to the cell, The differential pulse technique was applied by scanning from 0 to 1.4 V, with scan rate of 50 mVs^{-1}, and pulse amplitude of 50 mV.

Procedure for determination of hydroxyzine dihydrochloride in Atarax tablets

Twenty tablets were weighed, and the average mass per tablet was determined, then these tablets were powdered in a mortar. The required amount from the crushed tablet powder was dissolved in about 30 ml of bidistilled water and filtered in a 50 ml measuring flask. The residue was washed three times with bidistilled water; the volume was completed to the mark by the same solvent. After 10 ml volume of 0.04 M BR buffer solution pH 6.20 was introduced into the voltammetric cell, and a known amount of the tablet solution was added into the cell; the procedure is repeated as described above. The amount of hydroxyzine dihydrochloride is calculated using standard addition technique.

Determination of hydroxyzine dihydrochloride in spiked human urine

0.0448 g of hydroxyzine dihydrochloride was dissolved in bidistilled water and transferred to 100 ml measuring flask; 5 ml urine of a healthy person was added, and the mixture was completed to the mark by the same solvent to prepare 10^{-3} M hydroxyzine dihydrochloride in spiked urine sample. A 10 ml of 0.04 M BR buffer solution pH 6.20 was introduced into the voltammetric cell; different volumes of the above spiked urine sample were added into the cell; the procedure is repeated as described above. The amount of hydroxyzine dihydrochloride is calculated using standard addition technique.

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RESULTS AND DISCUSSION

Cyclic voltammetric studies

Cyclic voltammetric technique was applied as a diagnostic tool to get information about the electrochemical behavior of hydroxyzine dihydrochloride at carbon paste electrode. Fig. 1 shows the cyclic voltammograms for 1.96 x 10^{-5} M hydroxyzine dihydrochloride in 0.04 M BR buffer solution pH 6.2, at scan rate of 50 mVs^{-1}after accumulation time of 30 s.

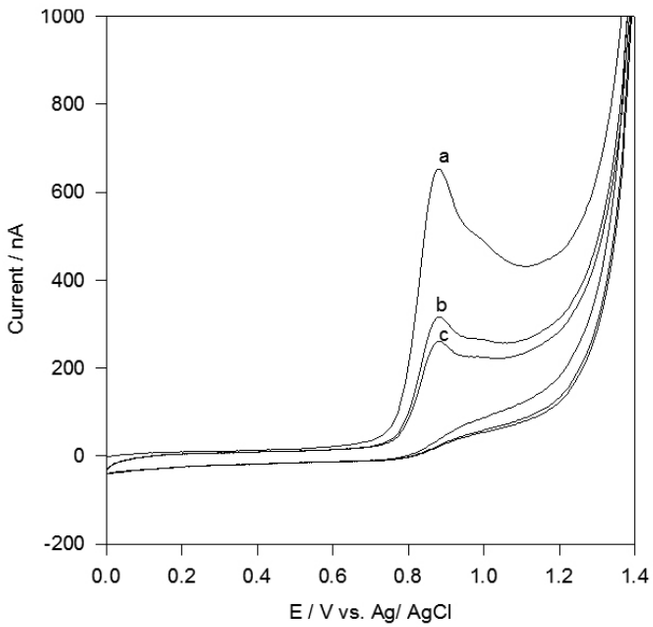

Figure 1. Successive cyclic voltammograms of 1.96 x10^{-5} M hydroxyzine dihydrochloride solution in 0.04 M Britton-Robinson pH 6.20 and scan rate of 50 mVs^{-1} after an accumulation of 30 s.

A well defined anodic peak at 0.873 V, which may be attributed to the oxidation of the hydroxyl group of the aliphatic chain moiety of the analyte molecule.[23] On reverse scanning no cathodic peak was observed, confirming the irreversible nature of the process. The repetitive cyclic voltammograms show that the peak current decreases in the second and third cycles, and this behavior gives an indication of an adsorption character. A plot of logarithm of peak current versus logarithm of the scan rate within the range 10-100 mVs^{-1}, gave a straight line relation with a slope of 0.71 which is intermediate value between 0.5 and 1.0, suggested a mixed diffusion-adsorption oxidation process.

Differential pulse (DP) voltammetric studies

Various supporting electrolytes such as sodium perchlorate, phosphate buffer, citrate buffer, and Britton-Robinson buffer, were examined. The best results with respect to signal enhancement and peak shape was obtained with Britton-Robinson buffer, so this buffer was chosen for the subsequent experiments. The effect of pH on the peak current and oxidation potential were studied over the pH range 3.0-10.0 (figure 2).

The peak current gradually increases with increase of pH and reached a maximum value when the pH is 6.2, then further increase in the solution pH yield a decrease in current. A negative shift was observed in the oxidation peak potential with increase of pH suggesting involvement of protons in the electrode reaction process

The effect of accumulation potential E_a on the peak current was studied for 2x10^{-6} M hydroxyzine dihydrochloride at 30 s accumulation time, 50 mVs^{-1} scan rate, and 50 mV pulse amplitude, the peak current was nearly constant on changing the accumulation potential E_a from 0 to 700 mV.

The effect of accumulation time t_a on the peak current was studied for two concentration level 5x10^{-7} and 2x10^{-6} M hydroxyzine dihydrochloride (Figure 3).

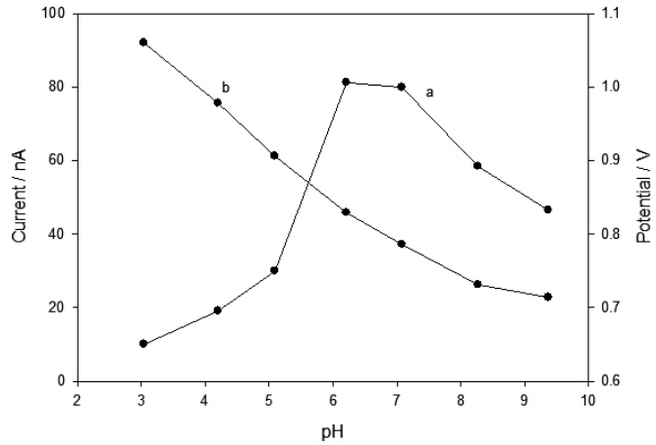

Figure 2. Effect of pH on the DP anodic peak current (a), and peak potential (b) of 2x10^{-6} M hydroxyzine dihydrochloride in 0.04 M BR buffer, scan rate 50 mVs^{-1}, and pulse amplitude of 50 mV.

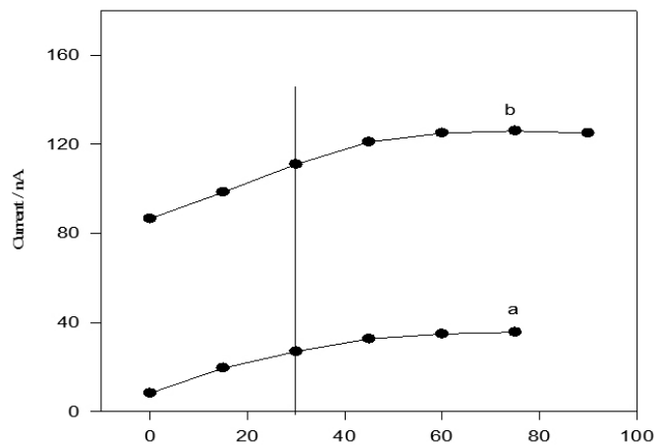

Figure 3. Effect of accumulation time (t_a) on the peak current for 5x10^{-7} and 2x10^{-6} M hydroxyzine dihydrochloride in 0.04 M BR buffer pH 6.20, accumulation potential (E_a = 0), scan rate = 50 mVs^{-1}, and pulse amplitude 50 mV.

The current increases linearly with increasing the accumulation time t_a indicating that the longer the accumulation time, the increase the drug concentration in the electrode surface, and the larger the peak current, then as the accumulation time increases the peak current tends to level off. 30 s accumulation time was used for subsequent studies.

The optimum instrumental parameters were chosen through the study of the variation of peak current of 2.0x10^{-6} M hydroxyzine dihydrochloride with change of pulse amplitude and scan rate, the results indicate that the current increases with increase of pulse amplitude over the range 10-50 mV, then remains nearly constant. The peak current also increased with increase of scan rate over the range 10-50 mVs^{-1}, so 50 mV pulse amplitude, and 50 mVs^{-1} scan rate were selected for further work.

Calibration graph, limit of detection and limit of quantification

Under the optimized conditions of accumulation potential of 0 volt, accumulation time 30 s, scan rate 50 mVs^{-1}, and 50 mV pulse amplitude, the peak current of differential pulse voltammograms was found to be linearly related to the hydroxyzine dihydrochloride concentration in the linear range 0.45-5.36 µg/ml (Figure 4). The linear regression equation was I (nA) = -16.69 + 159.36 C (µg/ml), with correlation coefficient of 0.9981. Limit of detection (LOD), and limit of quantification (LOQ), were calculated using the relation (k(SD_a)/b),[26] where k = 3 for LOD, and 10 for LOQ, SD_a is the standard deviation of the intercept, and b is the slope of the calibration curve, were found to be 0.27 and 0.90 µg/ml for LOD and LOQ, respectively. The analytical parameters of the calibration curve are summarized in Table 1.

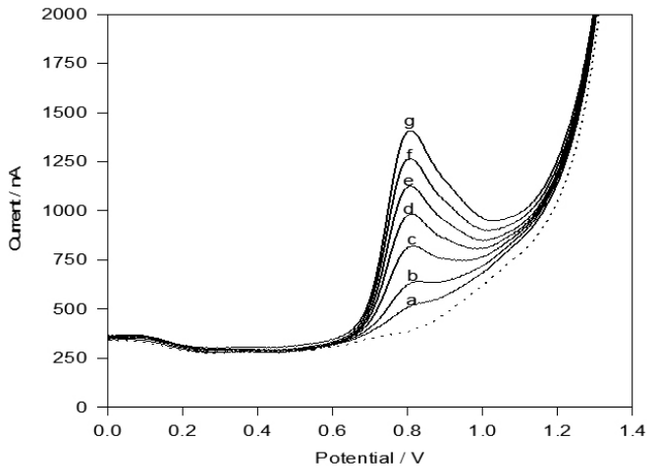

Figure 4. Differential pulse voltammograms for different concentration of hydroxyzine dihydrochloride in 0.04 M Britton-Robinson buffer pH 6.2, scan rate of 50 mVs^{-1} and pulse amplitude of 50 mV: a, 0.45; b, 0.89; c, 1.79; d, 2.68; e, 3.58; f, 4.47; and g, 5.36 µg/ml hydroxyzine dihydrochloride.
The dotted line represents the blank solution.

Table 1. The analytical parameters of the calibration graph for the determination of hydroxyzine dihydrochloride by differential pulse anodic voltammetric method.

Parameter	
Linear range, µg/ml	0.45-5.36
Slope	159.36
Intercept	-16.69
Correlation coefficient (r)	0.9981
LOD, µg/ml	0.27
LOQ, µg/ml	0.90

Reproducibility and robustness

The intra-day and inter-day (day-to-day) precision, were examined by analysis of $2x10^{-6}$ M hydroxyzine dihydrochloride wih 8 replicates in the same day or three consecutive days. The RSD value for intra-day and the inter-day precision were 0.93% and 4.98%, respectively. The robustness[26] of the proposed method was tested by evaluating the effect of small change in some of the most important procedure parameters, including pH (6.0-6.4), accumulation time (28-32 s), and pulse amplitude (48-52 mV). The results showed that none of the changes significantly affect the recovery of the drug (Table 2), and consequently the optimized procedure was reliable for the assay of the drug, and it could be considered robust.

Interferences

In order to prove the selectivity of the proposed voltammetric method, interference from excipients usually present in pharmaceutical formulations was tested. The results indicate that no interference (< 4.2% change in the oxidation current), was observed in the presence of 100 fold excess of lactose, talc, maize starch or magnesium stearate. The results indicate that the proposed voltammetric method is sufficiently selective and no previous separations or extractions were needed.

Analytical application

The proposed differential pulse anodic voltammetric method was successfully applied for the assay of hydroxyzine dihydrochloride in the pharmaceutical formulation Atarax tablets (10 mg hydroxyzine dihydrochloride /tablet). The percentage mean recovery based on the average of four replicate determinations and the relative standard deviation values are summarized in Table 3. The results indicate that there is no interference from the excipients used in the formulations of the tablets. The results of the proposed method were compared with the results obtained by analysis of the tablets by using the HPLC official method of United States USP pharmacopeia.[27] The results are in good agreement with the nominal value and with the average recovery obtained from the official method. Statistical comparison of the accuracy and precision of the proposed voltammetric method with the official method was performed using Student's t-test and the Fisher-Snedecor (F-test) at a 95% confidence level.[28] The t- and F- values did not exceed the theoretical values; there is no significant difference in accuracy or precision between the proposed voltammetric and the official methods.

Table 2. Robustness results of the proposed method at the optimum parameters.

Variable	Recovery, %	SD, %
pH = 6.0	98.99	1.667
6.2	97.56	1.543
6.4	102.55	1.969
Pulse ampltude		
= 48	99.56	0.937
50	97.56	1.543
52	98.93	1.158
Accumulation time		
= 28	100.00	0.606
30	97.56	1.543
32	100.60	1.081

Average of four determinations

Table 3. Statistical comparison between the results of Atarax tablets using the proposed DP voltammetric method and the official HPLC method.

Parameters	Proposed DP voltammetric	Official HPLC Method[27]
Mean recovery, %	99.55	99.87
SD	1.46	0.50
RSD, %	1.47	0.50
F-ratio (9.12)	8.526	
t-test (2.365)	0.232	

Hydroxyzine may given orally as the hydrochloride or embonate, Absorption of hydroxyzine from the GI tract is rapid and complete, less 2% of the administered dose is recovered unchanged in feces and urine.[29] The high selectivity of the proposed method allowed the determination of the drug in spiked human urine samples at two different levels of concentrations: $7.49x10^{-7}$ and $1x10^{-6}$ M hydroxyzine dihydrochloride. Four determinations were carried at each concentration level (Table 4). The mean recoveries for the two concentration levels were 99.87 and 99.40%, with relative standard deviations of 2.21% and 0.92%, respectively.

Table 4 Determination of hydroxyzine dihydrochloride in spiked human urine samples using the proposed differential pulse anodic voltammetric method

Taken (M)	Found (M)	Recovery, %	RSD
$7.49x10^{-7}$	$7.48x10^{-7}$	99.87	2.21
$1.00x10^{-6}$	$9.94x10^{-7}$	99.40	0.92

Average of four determinations.

CONCLUSION

In this work electrochemical oxidation of hydroxyzine dihydrochloride at carbon paste electrodes has been investigated using cyclic and differential pulse voltammetry. Differential pulse voltammetric procedure have been developed for the determination of this drug in its pharmaceutical formulation and spiked human urine. The developed method was a good alternative for the analytical determination of the drug, because it was, simple, rapid, low cost, and had sufficient precision, accuracy and sensitivity.

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