Differential Pulse Voltammetric and Conductimetric Determination of Diphenylpyraline HCl in Raw Material and Pharmaceutical Preparation

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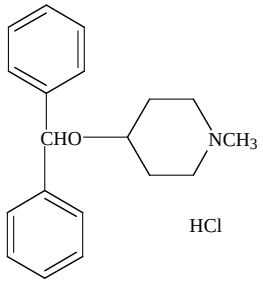
Abstract: Diphenylpyraline hydrochloride (Di-HCl) has been determined in raw material and its pharmaceutical preparation Eskornade capsule (5mg/capsule) using differential pulse voltammetry (DPV) and conductimetric determination. It was found that Di-HCl gives a characteristic cyclic voltammetric (CV) and differential pulse voltammetric (DPV) peak in acetonitrile using platinum and glassy carbon sensors as working electrodes. The peak current (I_p) of the DPV peak increases linearly within the concentration range 4.5 x 10^{-4}-1x10^{-2} mol/L of the investigated drug. The concentration of Di-HCl in raw drug material and in its pharmaceutical preparations was determined using standard addition method, Randles-Sevcik equation and indirectly *via* its complexation with sodium tetra phenylborate (NaTPB), the obtained average recoveries were 101.44 and 100.49 with standard deviation (SD) 0.45 and 0.38 (n = 4) for platinum and glassy carbon electrodes respectively. The effect of scan rate, sample concentration and supporting electrolyte on the peak current (I_p) and peak potential (E_p) was investigated.

In addition a simple and sensitive conductimetric method was used for determination of Di-HCl based on its ion association with sodium tetraphenylborate (NaTPB). The effect of solvent, reagent concentration, temperature and molar ratio was studied. The obtained average recovery was 101.44 with SD 0.45 (n = 4).

Keywords: Diphenylpyraline hydrochloride (Di-HCl), cyclic voltammetry, differential pulse voltammetry, acetonitrile, platinum, glassy carbon, sodium tetraphenylborate, conductimetry.

INTRODUCTION

Di-HCl is a very important antihistamine drug which present in combination with other active ingredient for common cold treatment. Few number of methods have been adopted for the determination of Di-HCl including its determination in human plasma with other ten antihistamine drugs using pipette tip solid-phase extraction, gas chromatography and mass spectrometry [1], in syrup using HPLC [2, 3], in raw material and pharmaceutical preparation using spectrophotometric method *via* the formation of mixed aggregates with surfactants [4]. No electroanalytical methods have been published for the determination of the investigated drug. The aim of the present work is to introduce new voltammetric and conductimetric methods for the determination of Di-HCl in raw material and its pharmaceutical preparation. The conductimetric determination has been carried out in water and acetonitrile and since Di-HCl doesn't show inherent voltammetric activity in aqueous media the voltammetric determination was carried out only in acetonitrile.



Diphenylpyraline Hydrochloride

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MATERIALS AND METHODOLOGY

Reagents and Solutions

The active ingredient pharmaceutical drug Di-HCl (mol.wt 317.9) and its pharmaceutical preparations Eskornade capsule (5mg/capsule) were provided from EPICO, Egypt. All other chemicals used such as acetonitrile, NaTPB and supporting electrolytes ($LiClO_4$, Bu_4NPF_6 and Bu_4NCl_4) were analytical grade reagent (Merk and Fluka). In voltammetric determination the solutions were dearated with purified Argon. Standard solution 5x 10^{-2} mol/L of Di-HCl was prepared by weighing the appropriate weight and dissolving it either in acetonitrile or in doubly distilled water then transferred in a 50 ml flask and completed to the mark with the appropriate solvent. For capsule solution ten capsules of Eskornade capsule were weighed, finely grounded and amount equivalent to the calculated weight of pharmaceutical preparations to produce a 1x10^{-2} mol/L solution was weighed and dissolved in the required solvent then filtered in 50 ml measuring flask and completed to the mark with the same solvent.

Apparatuses

The voltammetric experiments were performed using EG&G Princeton research potontiostate/Galvanostate model 263A which equipped with computer software (Echem M270). The used cell has a 3-electrodes system; a platinum wire auxiliary electrode and silver wire reference electrode which are 0.5 and 1 mm in diameter respectively, are used in conjunction with either platinum or glassy carbon as working electrode (2mm in diameter). An automatic pipette (0-250 µl), Brand GMBH Germany, has been used to take the required volumes. For conductimetric determination a Jenway conduc-

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tivity meter model 4510 was used for conductance measurements, the bridge is connected with a thermocouple for temperature measurements and the cell constant $k_{cell} = 1.0$.

Effect of Supporting Electrolyte

4 ml acetonitrile containing 10^{-1} mol/L $LiClO_4$ was subjected to the three electrode cell and deaerated with argon for 1 min. and the background voltammogram was recorded by scanning the potential toward the positive direction using the selected waveform [5] then 1 ml $5x10^{-2}$ mol/L of the investigated solution was introduced to the electrolysis cell and the produced voltammogram was recorded. The previous procedure has been repeated with both Bu_4NPF_6 and Bu_4NCl_4 as supporting electrolytes where the electrode should be polished before each measurement [6].

Effect of Scan Rate

Scan rate (v) is one of the most important factors that affect the measurements in cyclic voltammetry since it reflects the type of mass transfer takes place [7], the effect of scan rate was studied by recording the obtained voltammograms of $5x10^{-3}$ mol/L of the investigated drug solution at different scan rates ranging from 10 to 200 mVs^{-1}.

Voltammetric Determination of Di-HCl in Pure Form and Pharmaceutical Preparations

The concentration of Di-HCl was determined using the following methods:

1. Standard Addition Method [8]

The voltammogram of the supporting electrolyte was recorded then a known volume (V_u) of unknown concentration (C_u) of the investigated drug was added and the resulting DPV was recorded and I_{p1} was measured then a known volume (V_s) of known concentration (C_s) of Di-HCl was added and the DPV was recorded and I_{p2} was measured. The C_u can be calculated using the following equation:

$$C_u = \frac{I_{p1} C_s V_s}{(I_{p2}(V_u + V_s)) - I_{P1} V_u}$$

2. Randles-Sevcik Equation [9]

Randles-Sevcik equation is an equation that correlates peak current (I_p) with concentration (C), $I_p = k\,C$, where k is a constant that include different cell parameters such as transfer coefficient, number of electrons involved in the reaction, electrode area, diffusion coefficient and scan rate. The unknown concentration Di-HCl can be easily determined in two steps; firstly, determining k by introducing known concentration of Di-HCl to the three electrode cell and recording the DPV then measuring I_p and using Randles-Sevcik equation the constant k can be calculated secondly, under the same conditions the unknown concentration of the investigated drug was determined using the previously calculated value of k after measuring I_p.

3. Complexation with NaTPB

NaTPB is a well known complexing agent that commonly used in potentiometric [10] and conductimetric [11] determination of pharmaceutical raw materials and it was found that NaTPB is soluble in acetonitrile and reacts in it with Di-HCl to form soluble complex which has a characteristic DPV. It was found that the I_p of the formed complex increases and that of Di-HCl decrease with the addition of NaTPB. The concentration of Di-HCl can be determined by the addition of small volume increment of known concentration of NaTPB to the unknown concentration of the investigated drug and recording the produced voltammogram after each addition and the end point takes place by determining the volume where no further decrease on the peak of Di-HCl occurs.

Conductimetric Determination of Di-HCl in Pure Form and Pharmaceutical Preparations

Volumes containing 3-12 mg Di-HCl from stock solution of raw material or pharmaceutical preparations Eskornade capsule (5mg/capsule) were transferred to a 50 ml volumetric flask and made to the mark with bi-distilled water or to 25ml volumetric flask and made to the mark with acetonitrile. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed, then 10^{-2} mol/L NaTPB dissolved in bi-distilled water or in acetonitrile was added from micro burette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading taken after 1-2 min, after each addition was corrected for dilution [12] by mean of the following equation, assuming that conductivity is a linear function o f dilution:

$$\Omega_{corr} = \Omega_{obs}\,[(v_1+v_2)/v_1]$$

where Ω is the electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of the added reagent (corr., corrected; obs., observed). A graph of corrected conductivity versus the volume of titrant added was constructed and the end point was determined graphically at the intersection of two lines.

The drug-titrant ratio was determined by taking 2 ml of $5x\ 10^{-3}$ mol/L Di-HCl dissolved in bi-distilled water or in acetonitrile to a measuring flask and completed to the required volume by bi-distilled water or acetonitrile. The contents were transferred to a beaker and the conductivity cell was immersed, then $5x10^{-3}$ mol/L NaTPB dissolved in bi-distilled water or in acetonitrile was added from micro burette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring.

Validation of Method

The validation of the proposed procedure for the quantitative assay of examined drugs was done *via* evaluation of the LOD, LOQ, repeatability, recovery, selectivity and ruggedness. Linearity and concentration range of the proposed method was performed by constructing a calibration curve within the concentration range 10^{-5}-$5x10^{-2}$ mol/L and find out the regression equation, limit of detection (LOD) and limit of quantification (LOQ).

Precision and accuracy of the method was demonstrated by repeatability studies where the measurement of standard solutions was repeated four times and the mean recovery and percentage RSD was calculated.

The selectivity of the proposed procedure was examined in presence of some common excipients and the mean recovery was calculated.

The ruggedness of the method was carried out by changing the experimental conditions such as, changing the source of reagents and solvent (different manufactures), changing the supporting electrolytes, working and reference electrodes.

Stability of the analytes, standard, and sample solutions were subjected to long term (3 days) stability studies. The stability of these solutions was studied by performing the experiment and looking for the change in the voltammogram compared with freshly prepared solutions.

RESULT AND DISCUSSION

Diphenylpyraline hydrochloride doesn't show inherent voltammetric activity in aqueous buffer solutions but it shows an anodic response in acetonitrile at platinum and glassy carbon electrode and this may be attributed to the more basic character of acetonitrile [13] than that of water where the conjugate acid $CH_3C \equiv N^+H$ can add the hydrochloride moiety of the drug analogous to the addition of water at the first stage of hydration [14] The peaks were obtained around 1200mVand 1400mV for platinum and glassy carbon electrode respectively, the peak potential shifts to more positive value with increasing the concentration of Di-HCl.

The study of the effect of the nature of the supporting electrolyte ($LiClO_4$, Bu_4NPF_6 and Bu_4NCl_4) showed that $LiClO_4$ gives the heights I_p and at E_p far from the other peaks that appear as the result of presence of other excipient in the Eskornade capsule such as isoprobamid iodide.

Plotting I_p with the square root of the scan rate ($\nu^{1/2}$), Fig. (**1**), shows that the I_p increases linearly with $\nu^{1/2}$ which reveal that the mass transfer takes place *via* diffusion [15]. All subsequent experiments have been done using $LiClO_4$ as supporting electrolyte and at scan rates 100 mVs^{-1} for platinum and glassy carbon electrodes, because at this value the sensitivity is relatively high and voltammetric curves were well-shaped with a relatively narrow peak width.

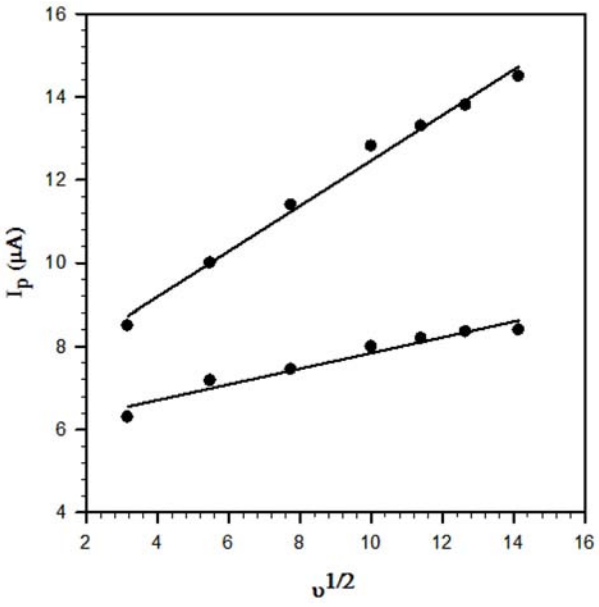


Fig. (1). Variation of the I_p 5 X 10^{-3} mol/L of Di-HCl with $\upsilon^{1/2}$ using (a) platinum (b) glassy carbon working electrodes.

Calibration Plots and Limits of Detections

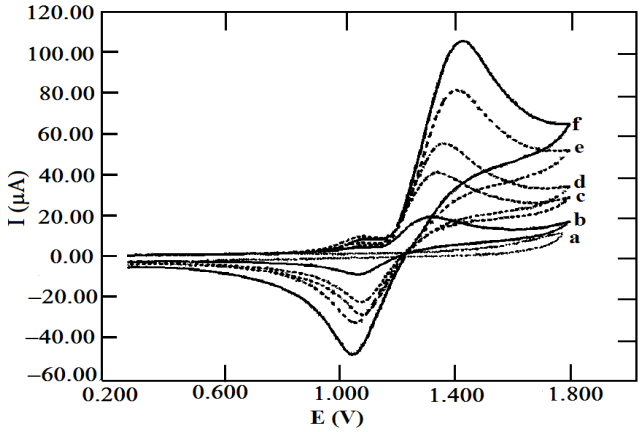
The CV and DPV voltammograms for different concentrations of Di-HCl were recorded at platinum and glassy carbon electrode as shown in Figs. (**2**, **3**) at scan rate 100 mVs^{-1}. The CV voltammograms exhibited smaller reverse peak, $I_{p,c}/I_{p,a} < 1$, which resemble to EC mechanism where the electrogenerated species are reacted chemically and this can be described by the following equations:

Electrode reaction: $O + ne \leftrightarrow R$

Chemical reaction C: $R \longrightarrow$ Product

In these equations the product of oxidation of the drug to form a radical cation is chemically removed from the surface [15], this reaction can be named as quasi-irreversible reaction where the rate of the chemical reaction is relatively slow.

(I)



(II)

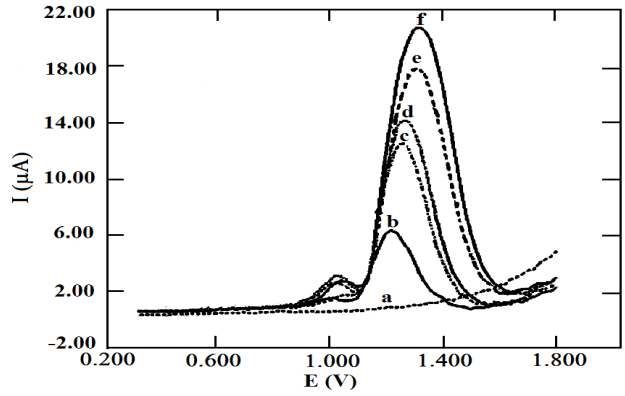


Fig. (2). CV (**I**) and its corresponding DPV (**II**) for different concentrations of Di-HCl at Pt electrode (a) Supporting electrolyte, (b) 3.7 x 10^{-4}, (c) 9.8 x 10^{-4}, (d) 5.4 x 10^{-3}, (e) 8.3 x 10^{-3}, (f) 10^{-2} mol/L.

The calibration graphs were constructed by plotting the drug concentration against the peak current (I_p) of the DPV. The dependence of the I_p on Di-HCl concentration show a linear relationship from 4.5 x 10^{-4} to 1x 10^{-2} mol/L for both platinum and glassy carbon electrode, the calibration graphs were constructed three times and the mean slope (m) and

standard deviation (SD) were calculated. The regression equations were:

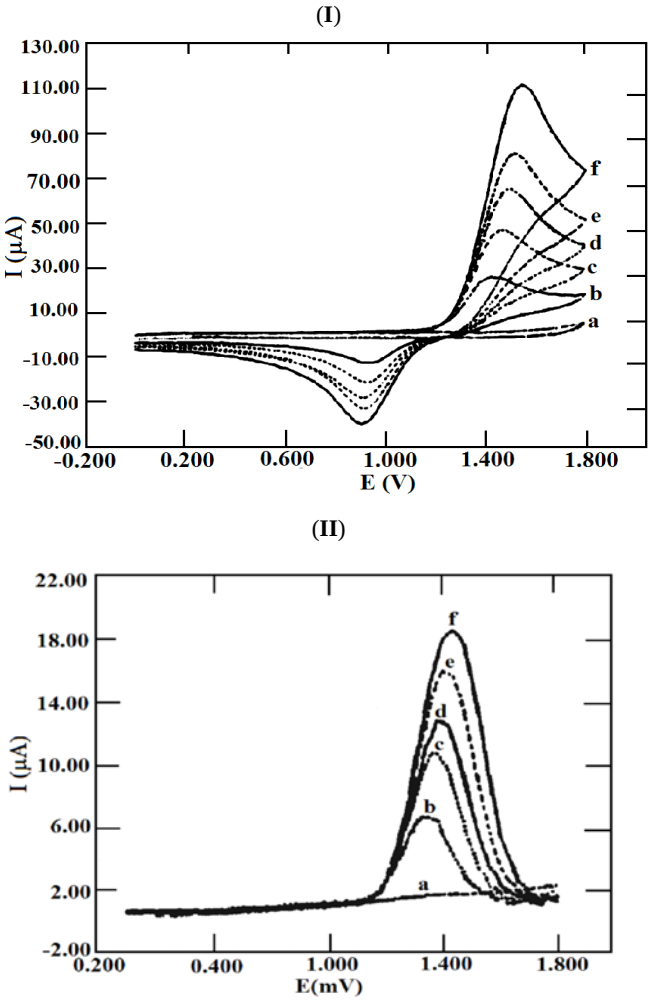


Fig. (3). CV (**I**) and its corresponding DPV (**II**) for different concentrations of Di-HCl at glassy carbon electrode (a) Supporting electrolyte, (b) 3.7 x 10^{-4}, (c) 9.8 x 10^{-4}, (d) 5.4 x 10^{-3}, (e) 8.3 x 10^{-3}, (f) 10^{-2} mol/L.

I (µA) = 2131.8 C (mol/L) + 1.35 (n = 10) and I (µA) = 1411 C (mol/L) + 1.04 (n = 12) for platinum and glassy carbon electrode respectively, the LOD and LOQ [16] were calculated using the equations LOD = 3SD/m and LOQ = 10SD/m. The LOD were 8.3 x 10^{-4} and 8.08 x 10^{-4} mol/L and the LOQ were 2.7 x 10^{-3} and 2.6 x 10^{-3} mol/L for platinum and glassy carbon electrodes respectively. Fig. (**4**) show the calibration plots for platinum and glassy carbon electrodes.

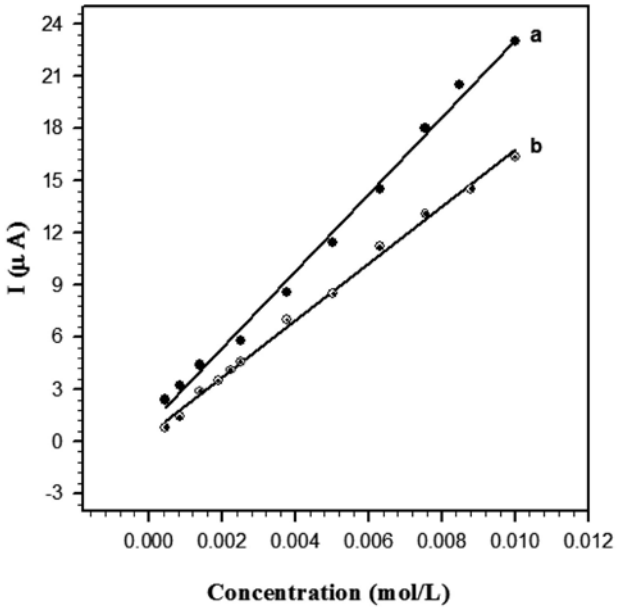


Fig. (4). Calibration curves obtained for Di-HCl using (a) platinum electrode (b) glassy carbon electrode.

Determination of Di-HCl in Raw Material and Pharmaceutical Formulations

Di-HCl was determined in raw material using the three proposed methods (Standard addition method, Randles-Sevcik equation and *via* complexation with NaTPB). Different weights were taken range from 3 to 12 mg and the determination has been repeated four times to calculate both average recovery (R) and Standard deviation (SD). The results shown in Table **1** support the validation of these methods for the determination of the investigated drug where the average recoveries ranges from 96.27 to 103.90 with standard deviation ranges from 0.23 to 0.78 by applying the three mentioned methods.

Di-HCl was also determined in Eskornade capsule (5mg/capsule), Table **2** shows the results obtained where the recoveries range from 96.18 to 105.00 with SD ranges from 0.20 to 0.86. Fig. (**5**) shows the DPV developed during the complexation of 5 ml (5x10^{-3} mol/L) of the investigated drug

Table 1. DPV Determination of Di-HCl in Raw Material Using the Three Proposed Methods

Weight Taken (mg)	Standard Addition Method						Randles-Sevcik Equation						Complexation with NaTPB					
	Pt Electrode			Glassy Carbon Electrode			Pt Electrode			Glassy Carbon Electrode			Pt Electrode			Glassy Carbon Electrode		
	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD
3	2.98	99.27	0.70	3.00	100.00	0.76	3.03	101.00	0.73	3.03	101.00	0.59	2.98	99.30	0.65	2.90	96.73	0.77
6	6.19	103.25	0.53	5.93	98.80	0.58	6.18	103.06	0.62	5.90	98.35	0.75	5.96	99.30	0.57	5.94	99.10	0.82
9	9.12	101.20	0.65	8.80	97.85	0.67	9.02	100.20	0.72	9.10	101.13	0.62	9.21	102.33	0.80	8.66	96.27	0.78
12	12.27	102.25	0.50	12.47	103.90	0.95	12.15	101.26	0.81	12.43	103.75	0.63	12.43	103.57	0.90	11.75	97.92	0.64

[a] found; [b] Average recovery (n = 4).

Table 2. DPV Determination of Di-HCl in Eskornade Capsule (5 mg/Capsule) Using the Three Proposed Methods

Weight Taken (mg)	Standard Addition Method						Randles-Sevcik Equation						Complexation with NaTPB					
	Pt Electrode			Glassy Carbon Electrode			Pt Electrode			Glassy Carbon Electrode			Pt Electrode			Glassy Carbon Electrode		
	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD
3	3.07	102.27	0.70	2.98	99.51	0.86	3.04	101.40	0.56	3.00	100.00	0.20	2.95	98.36	0.24	2.89	96.18	0.32
6	6.16	102.27	0.43	5.97	99.55	0.48	6.05	100.74	0.78	6.18	103.13	0.32	5.87	97.92	0.37	6.02	100.36	0.30
9	9.22	102.5	0.75	9.45	105.00	0.77	9.32	103.57	0.47	9.37	104.1	0.23	8.80	97.78	0.35	8.87	98.62	0.46
12	12.05	100.45	0.40	11.90	99.18	0.85	12.28	102.34	0.91	12.12	100.97	0.30	11.93	99.40	0.66	11.72	97.63	0.23

[a] found; [b] Average recovery (n = 4).

in Eskornade capsule with 2.5 x 10^{-2} mol/L NaTPB using glassy carbon electrode as working electrode. Also, the conductance measurements are used successfully in quantitative titration of systems (Table **3**), in which the conductance of the solution varies before and after the equivalence point (Figs. **6**, **7**), the sudden change in the slope after the end point is may be related to the formation of RNH_x^+ and OH^- by hydrolysis. On adding NaTPB, the ion pair formed replaces $RNHx^+$ ions by mobile Na^+ and the conductivity increases [11]. After the end point, more reagent is added and the conductivity increase more rapidly.

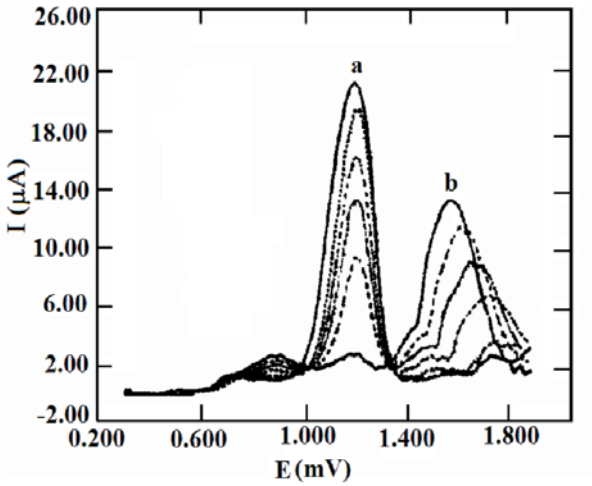


Fig. (5). DPV developed during the complexation of 5 ml ($5x10^{-3}$) Eskornade capsule (**a**) represent the increase of I_p of thecomplex formed and (**b**) represent the decrease of the I_p of the investigated drug with addition of different volumes of 2.5 x 10^{-2} mol/L NaTPB.

Titrations in different media were attempted to obtain the best results, where it was found that aqueous medium is the more suitable for obtaining a stable conductimetric reading for the determination of Di-HCl in raw material, however the presence of phenylpropanolamine hydrochloride as active ingredient (50 mg/capsule) with Di-HCl in Eskornade capsule and since phenylpropanolamine hydrochloride react with NaTPB in aqueous media in the same way that Di-HCl do that makes acetonitrile the suitable medium for the determination where phenylpropanolamine Hydrochloride is insoluble in acetonitrile. A curve break is observed at a drug-reagent ratio of 1:1 when Di-HCl reacts with NaTPB in water, while the ratio changed to 1: 2 in acetonitrile which has

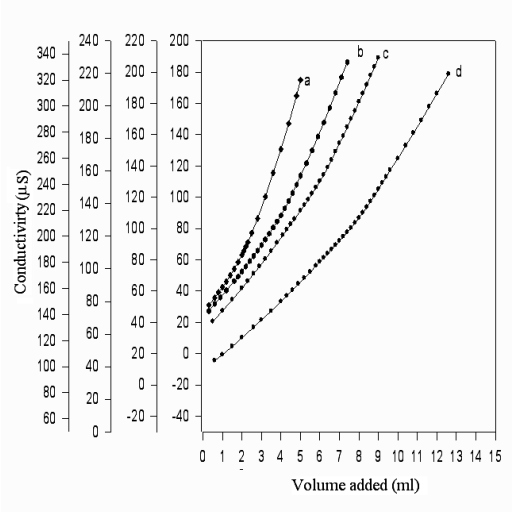


Fig. (6). Conductometric determination of Di-HCl in raw material using bi –distilled water and 5x 10^{-3} M NaTPB titrant (**a**) 2, (**b**) 4, (**c**) 6 and (**d**) 8 ml 5X 10^{-3} mol/L Di-HCl.

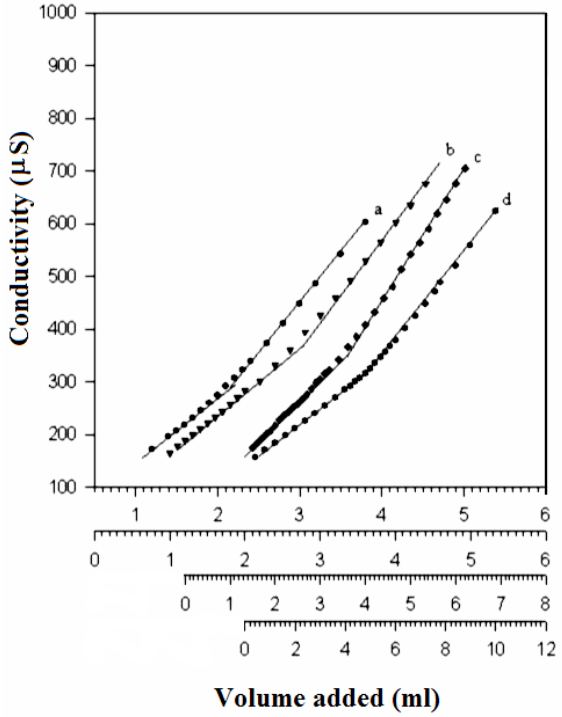


Fig. (7). Conductometric determination of Di-HCl in Eskornade capsule (5mg/capsule) using acetonitrile and 10^{-2} mol/L NaTPB titrant (**a**) 2, (**b**) 3, (**c**) 4 and (**d**) 5 ml 5X 10^{-3} mol/L Eskornade.

Table 3. Conductimetric Determination of Di-HCl in Raw Material and Eskornade Capsule (5 mg/Capsule) Using Acetonitrile and Bi-Distilled Water Solvents

Weight Taken (mg)	In Raw Material						Weight Taken (mg)	In Eskornade Capsule		
	In Bi-Distilled Water			In Acetonitrile				In Acetonitrile		
	F.[a] (mg)	R[b]. (%)	SD	F.[a] (mg)	R[b]. (%)	SD		F.[a] (mg)	R[b]. (%)	SD
3.00	3.10	103.33	0.83	3.15	105.18	0.36	**3.00**	3.10	103.33	0.23
6.00	6.11	101.87	0.45	6.22	103.60	0.49	**4.77**	4.69	98.33	0.15
9.00	8.90	98.95	0.75	9.34	103.80	0.90	**6.00**	5.93	98.83	0.69
12.00	11.74	97.81	0.55	12.24	102.00	0.70	**8.00**	7.92	99.00	0.30

[a] found; [b] Average recovery (n = 4).

Table 4. Statistical Treatment of Data Obtained for Di-HCl using DPV and Conductimetric Determination in Comparison with HPLC Method [3]

	HPLC Method	Conductometric Determination		DPV Method	
		In Water	In Acetonitrile	Pt Electrode	Glassy Carbon Electrode
Linear Range	4.7×10^{-6}-1.4×10^{-5}	----------	----------	4.5×10^{-4}-1×10^{-2} M	4.5×10^{-4}-1×10^{-2} M
Regression Equation	----------	----------	----------	I (μA) = 2131.8 C (M) + 1.35	I (μA) = 1411 C (M) +1.04
Average Recovery ± SD	101.2 ± 1.42	100.5±0.32	103.6±0.80	101.44 ± 0.30	100.49 ±0.25
r*	0.999	0.999	0.999	0.994	0.988
SD**	1.42	0.65	0.8	0.72	0.71
Variance	2.1	0.42	0.64	0.52	0.51
n	6	4	4	4	4
Probability		0.05	0.05	0.05	0.05
F-value$^{(4,6)}$ (6.16)		5.0	3.28	4.04	4.12
t-value$^{(D.F. = 8)}$ (2.31)		0.30	1.02	0.07	0.31

*r: regression coefficient, ** SD = standard deviation for indicated n value.

been confirmed by determining drug-titrant ratio as mentioned in the experimental part and this may be attributed to the fact that electroanalytical measurements reflect the activity of species in the liquid phase which in turn is related not only to the concentration of the species present, but also to the total concentration of electrolytes in the solution. A change in the dielectric constant of the solvent causes the response to vary where the solute can dissociate or polymerize on solution and the degree of variation changes with the concentration of material present and with the nature of the solvent being used [13].

The F-and t-testes [17] were performed to compare the average and the SD of the proposed methods with those obtained using HPLC [3], the results shown in Table **4** indicate that the calculated F and t values were lower than that tabulated which indicate that there is no significant difference or constant error between the two methods at the indicated significant level.

SELECTIVITY STUDIES

Di-HCl was determined successfully in Eskornade capsule in the presence of others excipient where the peaks appeared due to the presence of these excipient such as isobropamide iodide are far from that of Di-HCl and has no effect on the recoveries obtained, on the other hand the other active ingredient phenylpropanolamine hydrochloride present in Eskornade (50 mg/capsule) is insoluble in acetonitrile and can be easily removed by filtration. So Di-HCl can be easily determined in Eskornade without further extraction or treatment. Which, reflect the high selectivity of the proposed method.

CONCLUSION

From the previous results we can conclude that DPV is simple rapid and sensitive electrochemical method for the determination of Di-HCl. The method has been successfully proven to be suitable for the determination of the studied drug in raw material and in pharmaceutical preparations using either platinum or glassy carbon electrode without significant difference in recovery or in the linear range. It can be considered as a comparable or promising methods substitute for HPLC technique. Also, the proposed method shows clear advantages such as short period of real time of drug analysis and no pretreatment, dervatizing agents or time consuming extraction steps are required. Moreover, because of its low limits of detection and quantification, the proposed method can be applied in clinical laboratories and shelf life drug store check.

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Received: November 16, 2008 Revised: December 9, 2008 Accepted: December 11, 2008