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Short communication

Anodic polarographic determination of ciclopirox olamine in pure and certain pharmaceutical preparations

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Abstract

The anodic polarographic behavior of ciclopirox have been studied in Britton Robinson buffer (BRb) over the pH range 6–11. In BRb of pH 7 a well defined anodic wave was produced with diffusion current constant (Id) of 4.86 ± 0.048 (n = 6) using DC_t mode. Adopting both of direct current (DC_t) and differential pulse polarographic (DPP) modes, the current-concentration relationship was found to be rectilinear over the range 4 to 24 and 2 to 12 μg ml^{-1} respectively, with minimum detectability (S/N = 2) of 0.2 μg ml^{-1} (1×10^{-6} M) using the DPP mode. The average percent recovery was favourably compared to a reference method, with a satisfactory standard deviation, the proposed method was further applied to the determination of ciclopirox olamine in certain pharmaceutical preparations including lotion and cream. The average percentage recoveries for lotion were 100.06 ± 0.94 and 100.06 ± 1.08 using DC_t and DPP modes respectively, and for cream were 100.17 ± 0.64 and 100.34 ± 1.28 using DC_t and DPP modes, respectively. A pathway for the electrode reaction was postulated.

Keywords: Ciclopirox; Pharmaceutical preparations; Anodic polarography; Voltammetry

1. Introduction

Ciclopirox, 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone is a synthetic antifungal agent with in vitro activity against most pathogenic fungi, including dermatophytes, candida albicans and it has some antibacterial activety [1].

Few methods have been described for the quantitative determination of ciclopirox. A part from some reports on ciclopirox including HPLC [2,3], pharmacokinetics [4–7] solublization [8] and microbiological methods [9,10], no official methods for its assay has been reported.

All the reported methods are either not sufficiently sensitive or tedious and require highly sophisticated instrumentation [2,3]. The voltammetric techniques offered the possibility for the sensitive estimation of ciclopirox. Reviewing the literature revealed that, up to the present time, nothing has been published concerning the electrochemical oxidation of ciclopirox at the dropping mercury electrode (DME). There is, therefore, a need for a simple and sensitive method for the determination of ciclopirox. The molecular

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structure of ciclopirox is characterized by the presence of an electroactive N–OH group that initiated the present study. A polarographic method was developed for the determination of ciclopirox based on oxidation of N–OH group at the DME. The proposed method is more specific and less liable to interference encountered from other drugs. The results obtained are promising.

2. Experimental

2.1. Apparatus

The polarographic study and DPP measurements were carried out using the Polarecord E 506 Metrohm (Herisau, Switzerland). The drop time of 1 s was electronically controlled using a 663 VA Stand from the same company. The polarograms were recorded using a potential scan rate of 10 mV s^{-1}. A three-electrode system composed of a DME as the working electrode, Ag/AgCl reference electrode, and a graphite rod as the auxiliary electrode, was used. Polarograms were scanned between −0.4 and +0.16 V versus Ag/AgCl electrode. The solutions were purged with pure nitrogen for 5 min before being polarographed at room temperature.

2.2. Materials and reagents

Ciclopirox olamine was kindly provided by Egyptian Int. Pharmaceutical Industries Co. A.R.E. and was used as received. Batrafen Lotion, each 1 ml contains 10 mg of ciclopirox olamine (Batch # 17103). Batrafen Cream, each 1 g contains 10 mg of ciclopirox olamine (Batch # 191). Britton Robinson buffer (BRb) (0.08 M), covering the pH range 6–11 [11] were used.

A stock solution containing 200 μg ml^{-1} of ciclopirox olamine was prepared in distilled water and was further diluted with the same solvent to give the appropriate concentrations (Table 3). The stock solution is stable at least for 1 week when kept in the refrigerator.

2.2.1. Calibration graph

Transfer aliquot volumes of ciclopirox olamine covering the working range (cited in Table 1) into 25 ml volumetric flasks. Complete to the mark with BRb of pH 7.0. Pass pure nitrogen gas for 5 min. Record the anodic DC_t and DPP polarograms over the range −0.4 to +0.16 V versus Ag/AgCl, using a pulse amplitude of 70 mV in case of DPP mode. Plot the final concentration of the drug (μg ml^{-1}) versus the current (μA) to get the calibration curve. Alternatively, derive the corresponding regression equation.

2.2.2. Procedure for lotion

Transfer a weighed quantity of lotion equivalent to 20 mg of the drug into 100 ml measuring flask. Dilute to volume with distilled water and mix well. Transfer aliquot volumes covering the working concentration range into 25 ml volumetric flasks. Complete as described under 'Calibration Graph'. Determine the nominal concentration of the drug from the calibration curve or using the corresponding regression equation.

Table 1
Effect of pH on the development of the polarographic waves of ciclopirox olamine

pH	$E_{1/2}$ (mV)	$\Delta E_{1/2}/\Delta$pH	Half peak width $W_{1/2}$ (mV)	αn_a
6.0	+40	48	150	0.43
6.5	+16	48	140	0.93
7.0	−40	48	140	1.40
7.5	−64	96	160	1.27
8.0	−16		160	0.88

N.B. $W_{1/2}$ is the half-peak width in DPP mode. α is the transfer coefficient. n_a is the number of electrons transferred at the rate determining step.

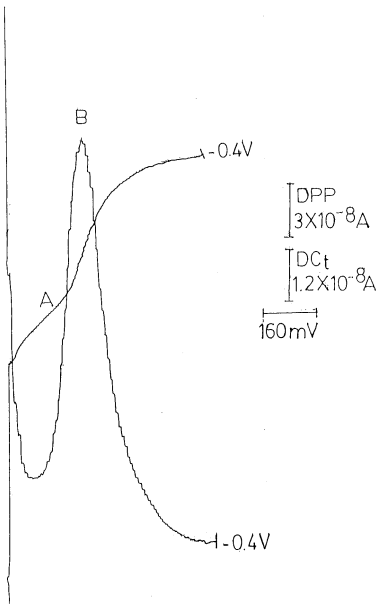

Fig. 1. Typical polarogram of ciclopirox olamine (24 μg ml^{-1}) in BRb of pH 7.0. A, DC_t mode; B, DPP mode.

2.2.3. Procedure for cream

Transfer a weighed quantity of the cream equivalent to 20 mg of the drug into a small beaker extract with 3×30 ml of distilled water into 100 ml measuring flask. Complete to the volume with the same solvent. Centrifuge for 15 min and filter. Transfer aliquot volumes covering the working concentration range into 25 ml volumetric flasks. Complete as described under 'Calibration Graph'. Determine the nominal concentration of the drug from the calibration curve or using the corresponding regression equation.

3. Results and discussion

Fig. 1 shows the typical polarograms of ciclopirox in BRb of pH 7. The anodic wave in the DC_t is well defined and the peak in the DPP mode is very steep. The polarographic behavior of ciclopirox at DME was found markedly pH dependent over the range of 6–11 in BRb (Fig. 2). The $E_{1/2}$

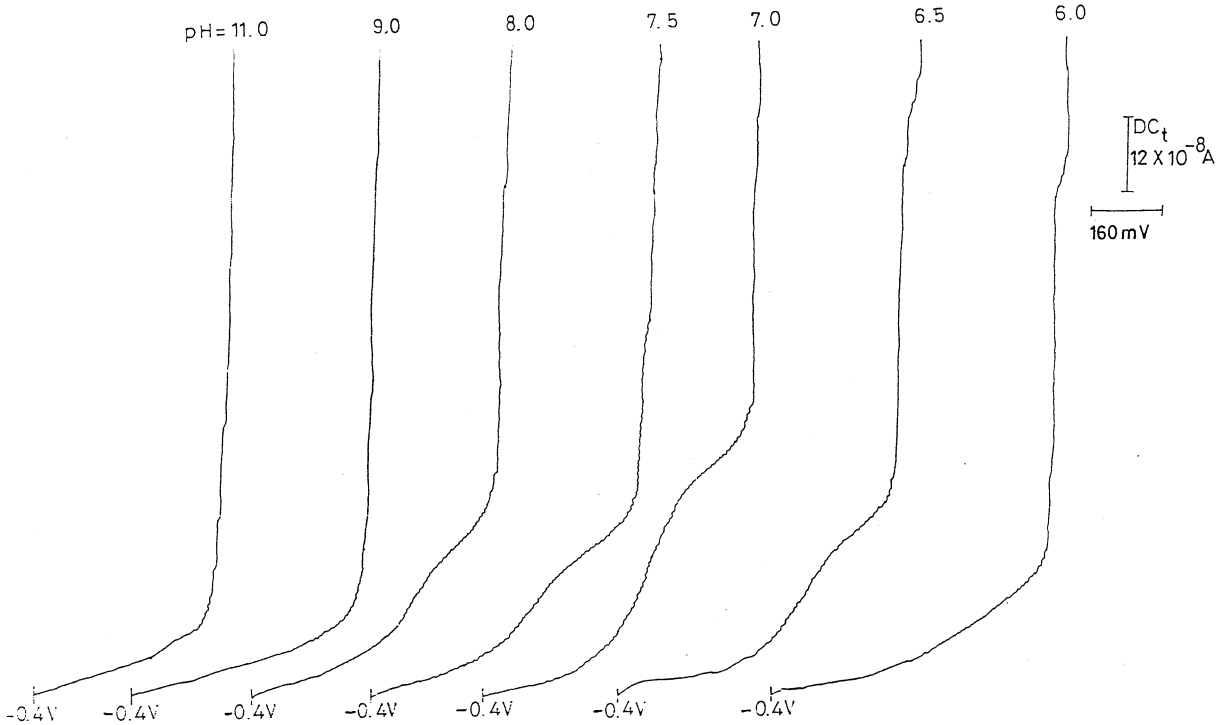

Fig. 2. Effect of pH on the development of the polarographic waves of ciclopirox olamine (24 μg ml^{-1}) in BRb.

values were shifted to more negative values upon increasing the pH value.

Logarithmic analysis of the resulted waves obtained in BRb of different pH values resulted in straight lines. The αn_a values were calculated according to the treatment of Meites and Israel [12], at pH 7, it was found to be 1.4 (Table 1). Assuming that the rate-determining step involves the transfer of two electrons, the values of the slopes point out to the completely irreversible nature of the electrode reaction.

3.1. Study of the wave characteristics

Changing the buffer concentration over the range 0.006–0.06 M was found to yield a negligible effect on the wave height of ciclopirox olamine. Ciclopirox was found to be stable in BRb of pH 7 (the analytical pH) for about 1.5 h at room temperature after which its stability began to decrease slowly. The alternating current behavior (AC_t) of ciclopirox was studied using a phase-selective angle of 90°. In BRb of pH 7, the summit potentials (E_S) were shifted to more negative values of 136 mV, than the corresponding $E_{1/2}$ values. Fig. 3 demonstrates that at this pH values, adsorption of both of the reactant and reduction product takes place.

The diffusion current constant (Id) was calculated at room temperature according to Ilkovic equation [13] for varying concentrations and was found to be 4.86 ± 0.048 ($n = 6$). The diffusion coefficient (D) was calculated at room temperature and was found to be $1.61 \times 10^{-5} \pm 0.029$ cm^2 s^{-1}.This small value is attributed to the bulky nature of the compound, the results are abridged in Table 2.

3.2. Mechanism of electrode reaction

The number of electrons released through the anodic process was determined through comparison of the wave height of ciclopirox with that obtained from an equimolar solution of a previously studied structurally related compound namely ascorbic acid [14]. In BRb of pH 7.0 both compounds gave one wave while, that of the drug is half that obtained from ascorbic acid, since ascorbic acid contains two hydroxyl group that are liable for the oxidation, and thus pointing out to a two-electron are released through this reaction (Table 3).

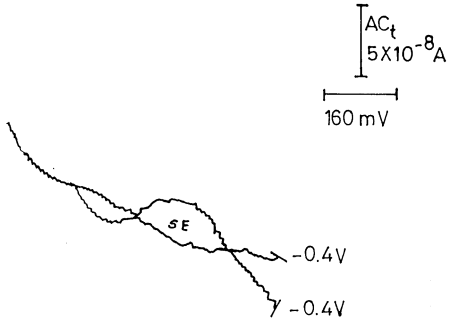

Fig. 3. Alternating current behavior of ciclopirox olamine (24 μg ml^{-1}) in BRb of pH 7. Superimposed alternating voltage: 15 mV; frequency 75 Hz; phase angle 90° (SE: supporting electrolyte).

Table 2
Correlation between the concentration of ciclopirox olamine and the diffusion current in the DC_t mode

Number	Concentration (mM)	Current (μA)	id/C (μA/mM)	Id = id/C $m^{2/3}$ $t^{1/6}$
1	0.02	0.1200	6.000	4.950
2	0.04	0.2340	5.850	4.827
3	0.06	0.3519	5.865	4.839
4	0.08	0.4742	5.928	4.891
5	0.10	0.5883	5.883	4.854
6	0.12	0.7020	5.850	4.827
Mean ± S.D.				4.86 ± 0.048

Table 3
Analytical parameters for the polarographic determination of ciclopirox olamine

Parameters	DC_t mode	DPP mode
Concentration range ($\mu g\ ml^{-1}$)	4–24	2–12
Minimum detectability (M)	–	$(1 \times 10^{-6}$ M)
Mean found (%)	99.83	99.53
Variance	0.48	2.72
Student's t-value	2.26 (2.37)	1.52 (2.45)
Variance ratio F-test	2.77 (5.79)	2.05 (6.94)
Correlation coefficient (r)	0.9999	0.9997
Slope	0.029	7.157×10^{-3}
Intercept	2.216×10^{-3}	5.270×10^{-4}
$S_{y/x}$		7.262×10^{-4}
S_a		6.064×10^{-4}
S_b		2.056×10^{-7}
% Error		0.63
Applications	Lotion and cream	Lotion and cream

N.B: Figures between parentheses are the tabulated t and F values, respectively, at $P = 0.05$ [15]; $S_{y/x}$ = S.D. of residuals. S_a = S.D. of intercept of regression line; S_b = S.D. of slope of regression line; % Error = R.S.D.%/$\sqrt{n}$.

3.3. Analytical applications

Polarograms of ciclopirox exhibit well-defined cathodic waves. The current is diffusion-controlled and is proportional to the concentration of the depolarizer over a convenient range. Both the DC_t and DPP modes were successfully applied to the assay of ciclopirox both in pure form and in different pharmaceutical dosage forms. Plots representing the relationship between the concentration of ciclopirox and the diffusion current gives straight lines over the concentration range of 4–24 and 2–12 $\mu g\ ml^{-1}$ using DC_t and DPP modes, respectively, with minimum detectability (S/N = 2) of 0.2 $\mu g\ ml^{-1}$ (1×10^{-6} M) using DPP mode (Table 4).

Linear regression analysis of the data gave the following equations:

$$id = 2.216 \times 10^{-3} + 0.029\ C \quad (r = 0.9999)$$

using DC_t mode ... and

$$ip = 5.270 \times 10^{-4} + 7.157 \times 10^{-3}\ C \quad (r = 0.9997)$$

using DPP mode, respectively, where C is the concentration in $\mu g\ ml^{-1}$, id is the diffusion current in μA in the DC_t mode and ip is the peak current in μA in the DPP mode.

Statistical analysis [15] of the results obtained by the proposed and a comparison spectrophotometric method [16], using the student's t-test and variance ratio F test, shows no significant difference between the performance of the two methods regarding the accuracy and precision, respectively, (Table 3).

Each of DC_t and DPP modes were successfully applied to the assay of ciclopirox in lotion and cream and the results obtained are abridged in Table 5. The percentage recoveries for the drug in lotion and cream were; 100.34 ± 0.73, 100.53 ± 0.51 and 99.96 ± 0.92, 100.02 ± 0.77 using DC_t and DPP modes, respectively.

Table 4
Polarographic analysis of ciclopirox olamine in pure form using DC_t and DPP modes

DC_t mode			DPP mode			Comparison method [16] % recovery
Taken (μg)	Found (μg)	Percentage recovery	Taken (μg)	Found (μg)	Percent recovery	
4	4.02	100.50	2	1.94	97.00	
8	7.91	98.88	4	4.03	100.75	
12	11.93	99.42	6	5.96	99.33	
16	16.11	100.69	8	8.10	101.25	
20	20.00	100.00	12	11.92	99.33	
24	23.88	99.50				
X^-		99.83			99.53	101.19
S.D.		0.69			1.65	1.15

Each result is the average of three separate determinations.

Table 5
Polarographic analysis of ciclopirox olamine in pharmaceutical preparations using DC_t and DPP modes

Pharmaceutical preparations	DC_t mode			DPP mode			Comparison method [16] % recovery
	Taken (μg)	Found (μg)	Percentage recovery	Taken (μg)	Found (μg)	Percent recovery	
1-Batrafen[a] lotion (10 mg of ciclopirox olamine per ml)	12.0	12.12	101.00	4.0	3.95	98.75	
	16.0	15.80	98.77	6.0	6.06	101.00	
	20.0	20.07	100.35	8.0	8.07	100.88	
	24.0	24.03	100.13	10.0	9.96	99.60	
X^-			100.06			100.06	99.44
S.D.			0.94			1.08	0.92
t-value			0.87			0.80	
F-value			1.04			1.36	
2-Batrafen[b] cream (10 mg of ciclopirox olamine per 1 gm)	12	11.94	99.50	4.0	3.959	98.98	
	16.0	16.09	100.56	6.0	6.096	101.43	
	20.0	20.17	100.85	8.0	7.959	99.50	
	24.0	23.94	99.75	10.0	10.144	101.44	
X^-			100.17			100.34	99.77
S.D.			0.64			1.28	1.19
t-value			0.58			0.6	
F-value			3.49			1.15	

Each result is the average of three separate determination. The tabulated *t* and *F* values are (2.57) and (9.55), respectively, at $P = 0.05$ [15].
[a] It is a product of Global Napi Pharmaceuticals, Egypt.
[b] Ir is a product of Hoechst Orient S.A.E. Cairo, R.C.C. 106526.

3.4. Validation of the proposed method

The method was tested for linearity, specificity, precision and reproducibility. By using the above polarographic modes, linear regression equations were obtained.

Statistical evaluation of the regression lines regarding the standard deviation (S.D.) of the residuals ($S_{y/x}$); S.D. of the intercept (S_a) and S.D. of the slope (S_b) is given in Table 3. The small figures point out to the low scattering and good linearity of the calibration graph.

4. Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variation in method parameters. To optimize the assay parameters, the effect of pH and buffer concentration were studied.

5. Ruggedness

To examine the ruggedness of the procedure the within- and between-day precision were evaluated. The within-day precision was evaluated through replicate analysis of different sample concentrations (8, 12, 16 and 20 μg ml^{-1}). The percentage recoveries based on the average of four separate determinations were 99.75 ± 0.78, using the DC_t mode, the precision of the proposed method is fairly high, as indicated by the low value of S.D.

The inter-day precision was evaluated through replicate analysis of sample on 4 successive days. The percentage recoveries based on the average of four separate determinations are 99.92 ± 1.14, using the DPP mode, thus indicating the high accuracy of the method.

6. Conclusion

A simple and sensitive methods have been developed for the determination of ciclopirox olamine in formulations. However, the DPP mode proves a specificity over the DC_t mode regarding its sensitivity, where 2 μg ml^{-1} could be determined with a reasonable reproducibility. The DC_t mode could be applied over the concentration range 4–24 μg ml^{-1} which is more applicable for dosage forms. The proposed method has distinct advantages over other existing methods regarding sensitivity, time saving and minimum detectability, moreover, it can be applied to the determination of different pharmaceutical dosage forms. In addition no sophisticated instrumentation is required.

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