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Polarographic determination of ciclopirox olamine in pure substance and in different pharmaceutical preparations

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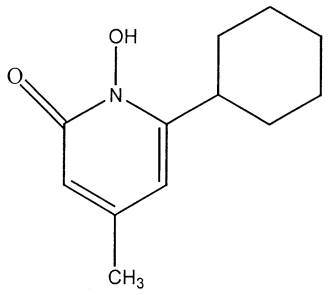
Abstract

Two simple and sensitive methods are described for the determination of ciclopirox olamine in its pure form and different dosage forms. The proposed method depends upon the polarographic activity of ciclopirox olamine at the dropping mercury electrode (DME) in Britton Robinson buffer, whereby, well-defined cathodic waves were produced over the pH range 7–9. The polarographic wave was characterized as being irreversible diffusion-controlled with limited adsorption properties. The current–concentration relationship was found to be rectilinear over the range 8–32 and 2–12 μg ml^{-1} using direct current (dc_t) and differential pulse polarographic (DPP) modes respectively, with minimum detectability of 0.53 μg ml^{-1} (2.65×10^{-6} M) and 0.1 μg ml^{-1} (5×10^{-7} M) using the dc_t and DPP modes, respectively. The average percent recovery was favorably compared to spectrophotometric method. The proposed method was further applied to dosage forms including ciclopirox lotion and cream.The average percentage recoveries for lotion were 100.34 ± 0.84 and 99.96 ± 1.06 using dc_t and DPP modes, respectively, and for cream were 100.53 ± 0.59 and 100.02 ± 0.89 using dc_t and DPP modes, respectively.

Keywords: Ciclopirox; Pharmaceutical preparations; Polarography; Voltammetry.

1. Introduction

Ciclopirox olamine, the 2-aminoethanol salt of 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 activity [1].



Few methods have been described for the quantitative determination of ciclopirox. A part from some reports on ciclopirox including spectrophotometric method (USP 25) [2] based on the use of ferrous sulphate with determination at 440 nm, and chromatographic (HPLC) [3,4] procedures have been proposed; pharmacokinetics [5–7] solublization [8] and microbiological [9,10] studies have also been reported.

The voltammetric techniques can offer another possibility for the sensitive estimation of ciclopirox.

Reviewing the literature revealed that, up to the present time, nothing has been published concerning the electrochemical behavior of ciclopirox. There is therefore a need for alternative simple and sensitive methods for the determination of ciclopirox. The molecular structure of ciclopirox is characterized by the presence of an electroactive carbonyl group that initiated the present study. A polarographic method was developed for the determination of ciclopirox based on the reduction of the carbonyl group at the DME. The results obtained are promising.

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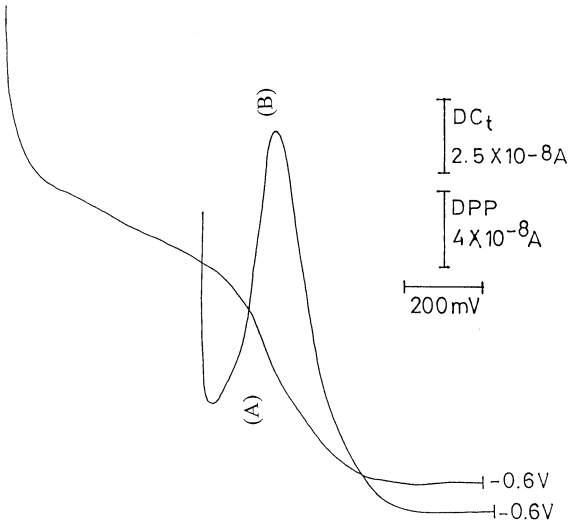


Fig. 1. Typical polarogram of ciclopirox olamine (40 μg ml^{-1}) in BRb of pH 7.0. (A) dc_t mode. (B) DPP mode.

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

pH	$E_{1/2}$ (V)	$\Delta E_{1/2}/\Delta pH$	Half peak width, $W_{1/2}$ (mV)	αn_a
7.0	−1.15		130	0.800
		−50		
8.0	−1.20		250	0.620
		−27.77		
8.36	−1.21		220	0.620
		−27.02		
9.1	−1.23		180	0.589
		−55.55		
10.0	−1.28		250	0.509
		−41.66		
11.2	−1.33		210	0.415

$W_{1/2}$ 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.

2. Experimental

2.1. Apparatus

The polarographic study including dc_t 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 dropping mercury electrode (DME) as the working electrode, Ag°/AgCl reference electrode, and a graphite rod as the auxilliary electrode, was used. Polarograms were scanned between −0.6 and −1.6 V versus Ag°/AgCl electrode. The solutions were purged with pure nitrogen for 5 min before being polarographed at room temperature. The alternating current time controlled ac_t polarograms were recorded using the same instrument; the superimposed alternating voltage being 15 mV at a frequency of 75 Hz and a phase angle of 90°.

To test the accuracy of the method an amount of pure ciclopirox olamine (10 μg ml^{-1}) was added to Batrafen lotion (10 μg ml^{-1}) and analysed using both dc_t and DPP modes, respectively.

To test the reproducibility for the described polarographic methods the within-day precision was evaluated through replicate analysis of sample containing 12 μg ml^{-1} of ciclopirox olamine. The percentage recoveries based on the average of five separate determinations are determined.

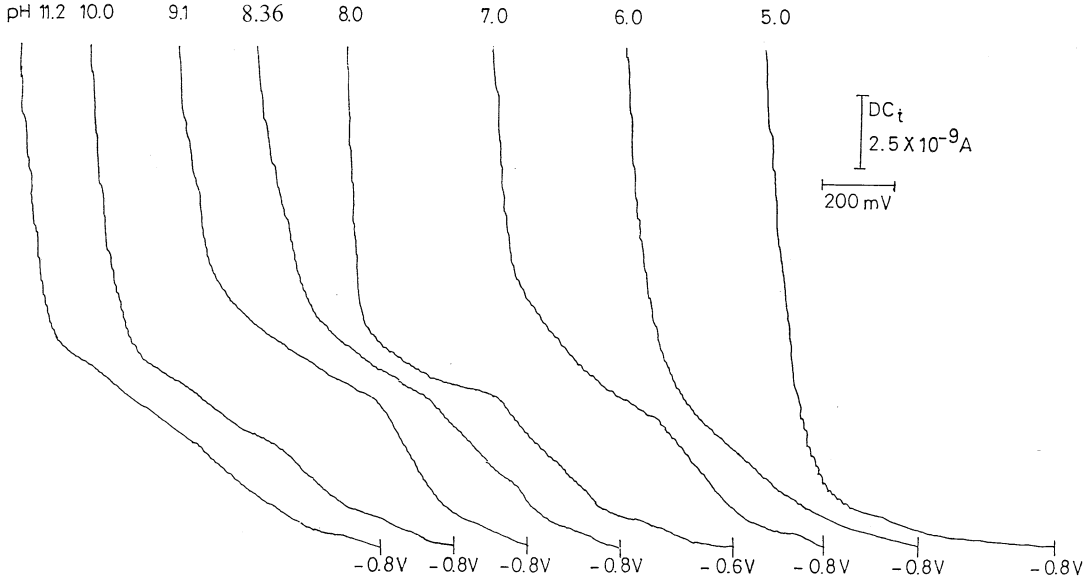


Fig. 2. Effect of pH on the development of the polarographic waves of ciclopirox olamine (40 μg ml^{-1}) in BRb.

The inter-day precision was evaluated through replicate analysis of sample containing 12 μg ml^{-1} of ciclopirox olamine on 4 successive days. The percentage recoveries based on the average of five separate determinations are recorded using the dc_t and DPP modes, respectively.

2.2. Materials

- Ciclopirox olamine was kindly provided by Egyptian
- Int. Pharmaceutical Industries Co. A.R.E. and was used as received.
- Batrafen Lotion, each 1ml contains 10 mg of ciclopirox olamine (batch no. 17103), product of Global Napi Pharmaceuticals, Egypt.
- Batrafen Cream, each 1 g contains 10 mg of ciclopirox olamine (batch no. 191), product of Hoechst Orient S.A.E. Cairo, R.C.C.106526.
- Britton Robinson buffer (BRb)(0.08M), covering the pH range 5–11.2 [11] were used.

2.2.1. Stock solution

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. The stock solution is stable for at least one week when kept in the refrigerator.

2.2.2. Calibration graph

Aliquot volumes of ciclopirox olamine covering the working range were transferred into 25 ml volumetric flasks and completed to the mark with BRb of pH 7.0. Pure nitrogen gas was passed for 5 min. The dc_t and DPP polarograms were recorded over the range -0.6 to -1.6 V versus $Ag^{\circ}/AgCl$, using a pulse amplitude of 70 mV in case of DPP mode. The final concentration of the drug (μg ml^{-1}) was plotted versus the current (μA) to get the calibration curve.

2.3. Procedure for lotion

A weighed quantity of lotion equivalent to 20 mg of the drug was transferred into 100 ml measuring flask and was diluted to the volume with distilled water, then mixed well. Aliquot volumes covering the working concentration range were transferred into 25 ml volumetric flasks. Complete to the mark with BRb of pH 7.0. The dc_t and DPP polarograms were recorded. The concentration of the drug was calculated using the regression equation.

2.4. Procedure for cream

A weighed quantity of the cream equivalent to 20 mg of the drug was transferred into a small beaker, extracted with 3×30 ml of distilled water into 100 ml measuring flask. The solution was completed to the volume with the same solvent. Centrifugation and filteration for 15 min was carried out. Aliquot volumes covering the working concentration range was transferred into 25 ml volumetric flasks. Complete to the mark with BRb of pH 7.0. The dc_t and DPP polaro-

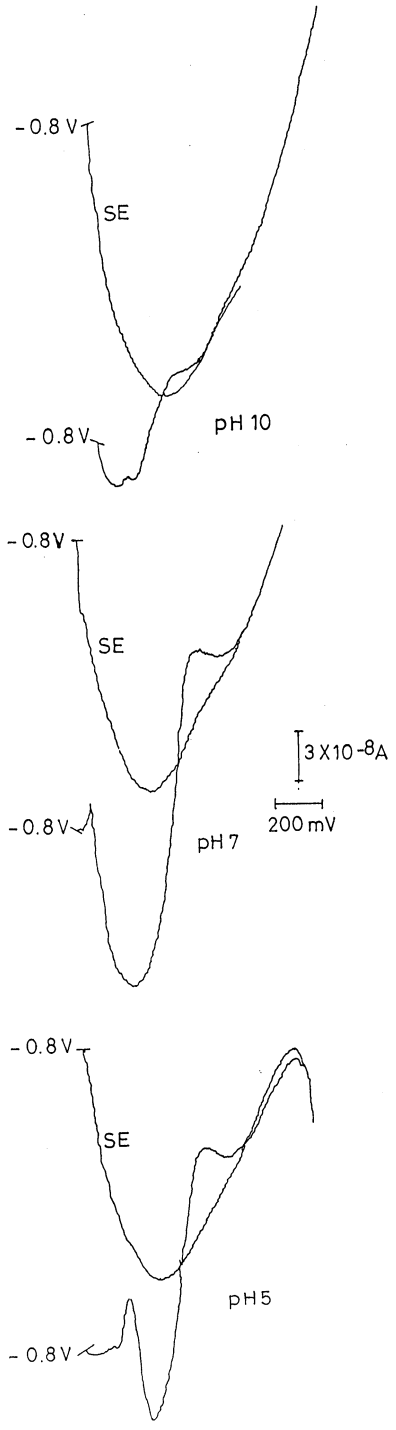


Fig. 3. Alternating current behaviour of ciclopirox olamine (30 μg ml^{-1}) in BRb of pH 5, 7 and 10. Superimposed alternating voltage: 15 mV; frequency 75 Hz; phase angle 90° (SE: supporting electrolyte).

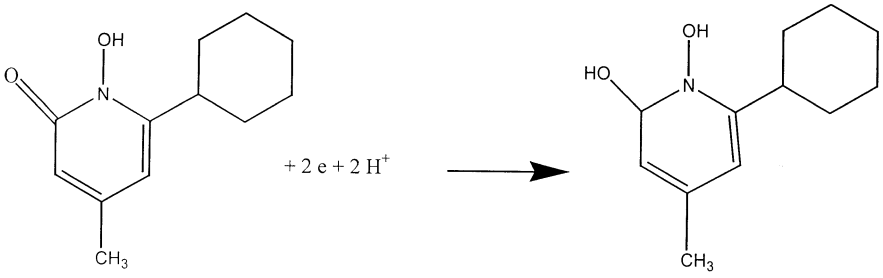
grams were recorded. The nominal concentration of the drug was calculated using the regression equation.

3. Results and discussion

3.1. Effect of pH on the development of the polarographic waves

Fig. 1A and B, shows the typical dc_t and DPP polarograms of ciclopirox respectively, in BRb of pH 7. Ciclopirox produces well-defined cathodic waves over the pH range of 7–9 in BRb (Fig. 2).

Logarithmic analysis of the reduction wave obtained in BRb of different pH values resulted in straight lines. The number of electrons transfer at the rate determining step (αn_a values) were calculated according to the treatment of Meites and Israel [12], at pH 7, it was found to be 0.8 (Table 1). Assuming that the rate-determining step involves the transfer of two electrons, the values of the slopes (the values of αn_a are less then 1) point out to the completely irreversible nature of the reduction process. It is noticed that the degree of reversibility decreased as the pH raised up to pH 11.2 [12].



3.2. Study of the wave characteristics

Changing the buffer concentration over the range 6×10^{-3} to 6×10^{-2} M was found to yield a negligible effect on the wave height of ciclopirox olamine. The alternating current behavior (ac_t) of ciclopirox was studied using a phase-selective angle of 90°. In BRb of pH 5, 7 and 10, the summit potentials (E_S) were shifted to more negative values by 150, 220 and 80 mV respectively, than the corresponding half electrode potential ($E_{1/2}$) values. Fig. 3 demonstrates that at these pH values, adsorption of the reactant only takes place while the reduction product is not adsorbed.

ciclopirox was found to be stable in BRb of pH 7 (the analytical pH) for about one and half hour at room temperature after which its stability began to decrease slowly.

The diffusion coefficient (D) was calculated at room temperature and was found to be $1.095 \times 10^{-6} \pm 0.022$ $cm^2\ s^{-1}$ [13]. This small value is attributed to the bulky nature of the compound.

3.3. Mechanism of electrode reaction

The number of electrons consumed during the reduction 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 praziquantel [14]. In BRb of pH 7.0 both compounds gave one wave while that of the drug is half that obtained from praziquantel, since praziquantel contains two carbonyl groups. Hence, it is concluded that two electrons are involved in the reduction process. Based on the presence of an activated carbonyl group and by analogy to the mechanism of reaction proposed for praziquantel, the following mechanism is postulated to proceed as:

3.4. 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 per se 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 8–32 and 2–12 μg ml^{-1} using dc_t and DPP modes respectively, with minimum detectability of 0.53 μg ml^{-1} ($2.65 \times$

Table 2
Analytical parameters for the polarographic determination of ciclopirox olamine in pure form

Parameters	dc_t mode	DPP mode
Concentration range (μg ml^{-1})	8–32	2–12
Minimum detectability (M)	(2.65×10^{-6} M)	(5×10^{-7} M)
Mean found (%).	99.97	99.87
Correlation coefficient (r)	0.9996	0.9999
Slope	9.27×10^{-3}	6.65×10^{-3}
Intercept	1.29×10^{-3}	1.22×10^{-4}
$S_{y/x}$	1.65×10^{-3}	x 10^{-4}
S_a	9.95×10^{-3}	1.93×10^{-4}
S_b	7.81×10^{-5}	2.08×10^{-8}
% Error	0.27	0.41

$S_{y/x}$ = standard deviation of residuals; S_a = standard deviation of intercept of regression line; S_b = standard deviation of slope of regression line. % Error = RSD%/$\sqrt{n}$.

10^{-6} M) and 0.10 μg ml^{-1} (5×10^{-7} M) using the dc_t and DPP modes respectively. Linear regression analysis of the data gave the following equations:

$$id = 1.29\times10^{-3} + 9.27\times10^{-3}C \ (r = 0.9996)$$

using dc_t mode... and

$$ip = 1.216\times10^{-4} + 6.65\times10^{-3}C \ (r = 0.9999)$$

using DPP mode, respectively, where C is the concentration in μg/ml, id is the diffusion current in μA in the dc_t mode and ip is the current in μA in the DPP mode.

Statistical evaluation of the regression lines regarding the standard deviation of the residuals ($S_{y/x}$); standard deviation of the intercept (S_a); standard deviation of the slope (S_b) is given in Table 2.

Statistical analysis [15] of the results obtained by the proposed and a reference 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 (Tables 3 and 4).

Each of dc_t and DPP modes were successfully applied to the assay of ciclopirox in pure form, lotion and cream and the results obtained are shown in Tables 3 and 4. The percentage found of declared in lotion and cream were; 100.34 ± 0.84, 100.53 ± 0.59 and 99.96 ± 1.06, 100.02 ± 0.89 using dc_t and DPP modes, respectively.

3.5. Accuracy and precision

The proposed method were evaluated by studying the accuracy as the percent standard error (% Er) and precision as percent relative standard deviation.

To test the accuracy of the method an amount of pure ciclopirox olamine (10 μg ml^{-1}) was added to Batrafen lotion (10 μg ml^{-1}) and analysed using both dc_t and DPP modes respectively. The mean percentage recovery of the added quantity based on four separate determinations was found to be 99.87 ± 0.62 and 100.85 ± 0.70 using the dc_t and DPP modes, respectively. This indicates that the proposed methods give accurate results. To test the reproducibility for the described polarographic methods the within-day precision was evaluated through replicate analysis of sample containing 12 μg ml^{-1} of ciclopirox olamine. The amount found of declared based on the average of five separate determinations were 100.40 ± 0.69 and 100.41 ± 0.43 using the dc_t and DPP modes respectively, thus indicating the high precision of the method.

The inter-day precision was evaluated through replicate analysis of sample containing 12 μg ml^{-1} of ciclopirox olamine on four successive days. The amount found of declared based on the average of five separate determinations are 100.46 ± 1.02 and 99.86 ± 0.41 using the dc_t and DPP modes respectively using the dc_t and DPP modes, respectively.

Table 3
Polarographic analysis of ciclopirox olamine in pure form using dc_t and DPP modes

Dc_t mode		DPP mode		Comparison method [16] % found of declared
μg taken	% found of declared	μg taken	% found of declared	
8.0	99.380	2.0	98.500	102.61
12	99.690	4.0	101.00	99.780
16	100.79	6.0	99.670	101.19
20	100.78	8.0	100.25	
24	99.530	12	99.920	
28	99.080			
32	100.55			
X^-	99.97		99.87	101.19
SD	0.66		0.82	1.42
Variance	0.52		0.83	2.0
Student's t-value	1.99 (2.31)		1.64 (2.45)	
Variance ratio F-test	3.85 (5.14)		2.41 (6.94)	

Each result is the average of three separate determinations. Figures between parentheses are the tabulated t and F values, respectively, at $p = 0.05$.

Table 4
Polarographic analysis of ciclopirox olamine in pharmaceutical preparations using dc_t and DPP modes

Pharmaceutical preparations	Dc_t mode		DPP mode		Comparison method [16] % found of declared [c]
	μg taken	% found of declared [c]	μg taken	% found of declared [c]	
1-Batrafen [a] lotion	12.0	100.25	4.0	99.75	
(10 mg of ciclopirox olamine/ml)	16.0	101.13	6.0	99.170	
	20.0	99.200	8.0	101.50	
	24.0	100.79	10	99.400	
X^-		100.34		99.960	99.44
SD		0.840		1.06	1.13
t-Value		1.22		0.630	
F-Value		1.79		1.13	
2-Batrafen [b] cream	12	100.64	4.0	99.150	
(10 mg of ciclopirox olamine/1 g)	16.0	99.940	6.0	100.32	
	20.0	101.30	8.0	101.14	
	24.0	100.25	10.0	99.480	
X^-		100.53		100.02	99.77
SD		0.590		0.890	1.19
t-Value		1.13		0.320	
F-Value		4.06		1.80	

Each result is the average of three separate determinations. The tabulated t and F values are (2.57) and (9.55), respectively at $p = 0.05$.
[a] Is the product of Global Napi Pharmaceuticals, Egypt.
[b] Is the product of Hoechst Orient S.A.E. Cairo, R.C.C.106526.
[c] Is the % found of declared.

4. Conclusion

Two simple and sensitive methods have been developed for the determination of ciclopirox olamine in formulations. However, the DPP mode proved to be advantageous over the dc_t mode regarding its sensitivity because 2 μg ml^{-1} could be determined with a well definite peak. The dc_t mode could be applied over the concentration range 8–32 μg ml^{-1} which is more suitable for dosage forms, since pharmaceutical preparations contain high concentration of ciclopirox olamine. The proposed methods can be considered a useful and convenient alternative to the existing methods regarding sensitivity and minimum feasibility. In fact it can be applied to the determination of ciclopirox in different pharmaceutical dosage forms.

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