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Polarographic determination of clioquinol in pharmaceutical preparations*

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Introduction

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is an antibacterial and antifungal agent widely used in creams and ointments for the treatment of skin diseases and in tablets for the treatment of amoebiasis. The current USP method for its determination in creams and ointments is based on gas-chromatography [1]. Data on the polarographic behaviour of clioquinol [2] and related compounds [3] suggest that this technique may be used for the determination of small amounts of clioquinol.

In this paper a differential pulse (dp) polarographic method for the determination of clioquinol in creams and ointments is proposed, which makes use of the main cathodic wave exhibited at pH lower than 1.5. At pH values below 1.5 the corticosteroids and excipients normally found in preparations containing clioquinol do not interfere [4, 5].

Experimental

Materials

5-Chloro-7-iodo-8-hydroxyquinoline ("Supro" Troponwerke) was recrystallized from ethanol and its purity was determined by titration with perchloric acid in acetic acid medium [6].

Aqueous buffer solutions (ionic strength = 1 M) were in the pH range 1–13. The range was extended with hydrochloric acid. Solutions at pH lower than 2 were prepared with potassium chloride and hydrochloric acid [7]; buffers in the pH range 2–6 were prepared with disodium hydrogen phosphate, citric acid and potassium chloride [8]; buffers in the pH range between 7 and 8 were prepared with acetic acid, phosphoric acid, boric acid and sodium hydroxide solutions [9]; buffers at pH 9 and 10.5 were prepared with boric acid potassium chloride and sodium hydroxide solutions [10]; and buffers at

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pH higher than 11 were prepared with phosphoric acid, boric acid, acetic acid and sodium hydroxide solutions [10]. All chemicals were analytical grade, and the buffer solutions were tested polarographically before use. The supporting electrolyte was a solution containing <0.50 M potassium chloride in 0.50 M hydrochloric acid.

Apparatus

Polarograms were recorded on a Metrohm–Herisau E 506/505 polarograph with a Metrohm E 441/5 Ag/AgCl electrode as a reference, a Metrohm E1019/2 dropping mercury electrode (m = 0.696 mg.s^{-1}) and a platinum wire as a third electrode. A circulation thermostat and double-jacketed vessel were used to maintain the temperature of the solutions at 25 ± 0.1°C.

The pH values were measured with a Metrohm E350B pH meter equipped with a Metrohm CH9100 combined electrode.

Method

Stock solutions of clioquinol were prepared in isopropyl alcohol. As the solubility of clioquinol in water is low, and as previous assays have shown that the best polarographic response is obtained with test solutions containing 50% v/v isopropyl alcohol:water, stock solutions were diluted with appropriate amounts of aqueous buffer and isopropyl alcohol to give test solutions of the required concentration and pH. The apparent pH values were measured and the solutions were thermostatted at 25°C and deaerated with nitrogen just before recording the polarogram. Nitrogen was passed through three solutions containing vanadous cation to eliminate possible oxidants [11] and then through a 50% v/v isopropyl alcohol:water solution so that the composition of the test solution remained unaltered.

The techniques used were rapid direct current (DC rapid) and differential pulse (DP) polarography. Drop times varied between 0.4 and 3 s and pulse amplitudes between −60 and +60 mV.

Preparation of samples

Synthetic ointments and creams, similar to those used in pharmaceuticals, were prepared with 5-chloro-7-iodo-8-hydroxy-quinoline and suitable excipients. These products were homogeneous and contained between about 0.5 and 3% w/w of clioquinol.

Procedure

1.0–1.5 g of sample was placed in a beaker, isopropyl alcohol (50 ml) was added and the mixture was heated to 50–60°C and shaken to disperse the sample. It was then filtered through a Whatman No. 42 filter paper, allowed to cool in a refrigerator, filtered again if necessary and diluted to 250 ml with isopropyl alcohol. Ten millilitres of this solution were placed in 100-ml volumetric flasks, 50 ml of supporting electrolyte and the required amount of a standard solution of clioquinol in isopropyl alcohol were added and then diluted to the mark with isopropyl alcohol. The solutions were thermostatted to 25°C and deaerated, and then the polarograms were recorded. The technique of standard addition was selected, using DP polarography with 1 s drop time and −40 mV pulse amplitude.

Although three different standard additions were carried out for each sample, one is sufficient, provided that the amount of clioquinol added is similar to that contained in the sample.

Results and Discussion

Waves obtained by using DP polarography were more clearly defined than those obtained by using DC rapid polarography and consequently most measurements were made using DP polarography, usually with a drop time of 1 s and a pulse amplitude of −40 mV.

Solutions of clioquinol (approximately 10^{-4}M in 50% v/v isopropyl alcohol:water) in highly acidic medium gave only one cathodic wave. Between about pH 1.8 and 6.0 a second wave appeared at more negative potentials, but with lower intensity and decreased definition. Between pH 6.8 and 9.0 two well defined waves were observed. At pH higher than 9 there was only one wave and above pH 11 there was no cathodic activity.

The half-wave potential of the main cathodic wave shifted to more negative potentials as the pH increased between pH 1.8 and 9, with a slope of −61 mV per pH unit. Outside this range it was independent of pH.

The intensity of the main cathodic wave depended on pH throughout the acidic pH range, reaching a maximum at about pH 2. Between pH 6 and 9 the intensity was independent of pH, but this pH range is not suitable for the determination of clioquinol in pharmaceutical products because corticosteroids and excipients interfere. This interference is not found at pH lower than 1.5 [4, 5], and this has been experimentally confirmed in the present study. Consequently, all subsequent work was carried out at a pH lower than 1.5.

A plot of the logarithm of peak intensity (i) against the logarithm of drop time in the range 0.4–3 s (t) showed that the exponent x in equation $i = kt^x$ had a value of 0.61, approximately 2/3, ($\log i = 0.61\ t - 6.86$; $r = 0.9992$) for the main wave, which agreed with the data for a diffusion-controlled process.

The dependence of peak intensity on pulse amplitude and on pulse sign (Table 1) suggest a one-electron irreversible process.

Table 1
Variation of peak characteristics with pulse modulation amplitude (pH 1.05; 6.923×10^{-5}M)

E(mV)	Ip_a/Ip_c	Ep_a-Ep_c
60	0.425	128
40	0.452	92
20	0.598	36
10	0.718	18

Table 2
Assay results for synthetic and commercial preparations

Sample	Content of clioquinol (%)	Found* (%)
Synthetic	3.02	2.99 ± 0.15
Synthetic	1.49	1.45 ± 0.18
Synthetic	0.72	0.72 ± 0.19
Ointment	3.0†	3.19 ± 0.18
Cream	3.0†	3.12 ± 0.16

*Each value is the average of seven determinations.
†Label claim.

At pH lower than 1.5 a linear relationship between peak intensity and concentration (c) of clioquinol was obtained in the range 4×10^{-7}M–5×10^{-4}M ($i = 0.0134\ c + 1.72 \times 10^{-8}$; $r = 0.9991$).

Ten separate determinations of a standard solution of clioquinol containing 28.2 μg ml^{-1} gave a standard deviation of 0.1.

The results obtained for synthetic preparations and commercial samples are given in Table 2. They are in good agreement with expected or labelled amounts.

This polarographic method is fast and simple, has adequate accuracy and precision, and it also allows the determination of amounts of clioquinol much lower than those usually found in commercial preparations.

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