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Short Communication

A Direct Current Polarographic Method for the Determination of Chlorpheniramine Maleate in Pharmaceutical Preparations

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ABSTRACT

A direct polarographic method for the determination of chlorpheniramine maleate in pharmaceutical preparations had been developed. The method was based on the reduction of chlorpheniramine maleate in an acidic medium (pH 1.2-4.0). The effect of pH on the polarographic wave was investigated by recording d.c. polarograms in various supporting electrolytes. The calibration graphs were rectilinear for 5 to 20 g ml^{-1} of chlorpheniramine maleate in 0.1 mol L^{-1} hydrochloric acid pH 1.2, chloride buffer pH 2.0 and phthalate buffer pH 4.0 respectively. The method was simple and rapid, results being reproducible within ±2.53% (in 0.1 mol L^{-1} hydrochloric acid or chloride buffer pH 2.0), and ±1.06% (in phthalate buffer pH 4.0) for 10 determinations respectively. The method was applicable to the analysis of chlorpheniramine maleate in tablets, syrup and injection. There was no interference from acetaminophen, phenylpropanolamine hydrochloride and ascorbic acid.

Keywords: chlorpheniramine meleate, direct current polarography, pharmaceutical preparations.

1. INTRODUCTION

Chlorpheniramine maleate (CPM) is an antihistamine drug that is widely used in phamarceutical preparations for symptomatic relief of common cold and allergic diseases [1]. Numerous methods for the determination of chlorpheniramine maleate has been reported in the literature, including acid-base titrations were performed potentiometrically using non-aqueous solvents, with 0.1 mol L^{-1} perchloric acid as titrant [2]. An aqueous titration assay [3] has also been proposed that involves the back-titration of excess hydrochloric acid that is not taken up by the free base. Ultraviolet spectroscopy has been used for the determination of chlorpheniramine maleate in injection, syrup and tablets. The absorbance was measured at 264 nm [4]. One of the drawbacks of this procedure is that it involves extraction of the free base from the sample and subsequent comparison of the UV spectrum to that of maleate. According to Hamilton et al [5] this gives rise to a 2-3% negative bias, since the maleate salt gives a higher absorbance than

the free base alone. Several colorimetric procedures for the assay of chlorpheniramine maleate have been proposed. Among the earliest spectroscopic methods [6,7], it involved the formation of the Reinecke salt which was then dissolved in acetone and the absorbance was measured. The disadvantages of this method are that it lacks specificity and that the coloured complex can be decomposed by the presence of water. The reaction of cyanogen bromide with chlorpheniramine maleate in the presence of sulphanilic acid to give a yellow complex was reported by Hudanick [8]. Procedures for the complexation of chlorpheniramine maleate with sulfonephthalein dyes such as bromocresol green [9] bromocresol purple [10] or bromothymol blue [11] have been described. Fluorescence spectroscopy has been used for the determination of chlorpheniramine maleate. The complexation of rose bengal dye was described by Lange et al [12]. Jensen et al [13] described a comparison of two methods oxidation by hydrogen peroxide and attack by cyanogen bromide. Gas liquid chromatography has been used for separation of antihistamine [14,15]. At present, the above methods are still used for quality control of this drug. Most of the recent developed methods found in the literature for the assay of CPM are based on HPLC and derivative spectrophotometry [16-21]. Several high performance liquid chromatographic procedures have been developed for the determination of chloropheniramine maleate in commercial pharmaceutical preparations [16-19] and derivative spectrophotometry [19-21]. Recently, a micellar electrokinetic chromatographic method has been described for simultaneous determination of paracetamol and chlorpheniramine maleate [22].

This present study were to develop a simple, low-cost direct current polarographic method for chlopheniramine maleate. Because electrochemical methods including polarographic method provides the advantages over the previous methods in that rapidity, cost effectiveness, less consumption of sample and reagent, ease of operation, being non-destructive, simultaneous determination without separation. Investigation of the experimental conditions on the reduction of the chlorpheniramine maleate at the dropping mercury electrode was carried out. Application of the optimum conditions to the quantitation of chlorpheniramine maleate in pharmaceutical dosage forms was also included.

2. MATERIALS AND METHODS

2.1 Equipment

All polarograms were recorded on a polarograph (Polarecord E 506 with Polarography stand E 505, Metrohm, AG, CH-9100, Herisau, Switzerland) equipped with silver-silver chloride reference electrode and dropping mercury electrode as indicating electrode. A pH meter (Corning model 10X) fitted with a glass-calomel electrode system was used for all pH measurements. A micro pipette (model 5000, Nichiryo) was also used.

2.2 Reagents

All chemicals used were of analytical reagent grade and used without further purification.

Chloride Buffer pH 2.0. This solution was prepared by dissolving 6.57 g of potassium chloride (BDH) in distilled water, then 119.0 ml of 0.1 mol L^{-1} hydrochloric acid (BDH) were added and diluted with distilled water to 1000 ml. The pH of this solution was checked by means of a pH meter.

Phthalate Buffer pH 4.0. This solution was prepared by dissolving 2.042 g of potassium hydrogen phthalate (BDH) in 50 ml of deionized distilled water, then 0.40 ml of 0.2 mol L^{-1} sodium hydroxide (BDH) were added and diluted with water to 200 ml. The pH was checked by using a pH meter.

This following reagents were also prepared:-

0.1 mol L^{-1} Tetrabutylammoniumbromide (Fluka) in water

0.1 mol L^{-1} Hydrochloric acid (BDH)
0.1 mol L^{-1} Sulphuric acid (BDH)

2.3 Preparation of Stock and Standard Solutions

The stock solution of chlorpheniramine maleate (1000 g ml^{-1}) was prepared by dissolving 100 mg of chlorpheniramine meleate (Fluka) in 0.1 mol L^{-1} sulphuric acid to make 100 ml of the solution. The standard chlorpheniramine maleate solution (100 g ml^{-1}) was prepared from this stock solution by appropriate dilution.

2.4 Investigation of Optimal Supporting Electrolyte

The following reagents wtih different pH values over the range of 1.0-4.5 were tested as supporting electrolyte for CPM determination, namely 0.1 mol L^{-1} tetrabutylammonium bromide, phthalate buffer, chloride buffer and 0.1 mol L^{-1} hydrochloric acid. It was found that the optimum pH value of each supporting electrolyte tested were as follows:

(1) 0.1 mol L^{-1} tetrabutylammonium bromide pH 4.0
(2) phthalate buffer pH 4.0
(3) chloride buffer pH 2.0
(4) 0.1 mol L^{-1} hydrochloric acid pH 1.2

Appropriate volumes of chlorpheniramine maleate solution (100 g ml^{-1}) were transferred into four separate 25 ml volumetric flasks, in order to prepare a series of chlorpheniramine maleate solutions containing 5, 10, 15 and 20 g ml^{-1} of chlorpheniramine maleate respectively. Each solution was diluted to volume with the above supporting electrolyte (1) (2) (3) or (4). Twenty millilitres of each standard solution was pipetted into the dry polarographic cell and the solution was deaerated for 15 minutes with nitrogen and then the polarogram was recorded from -0.6 to -1.2 V at sensitivity $4x10^{-7}$ A/mm.

2.5 Procedures

2.5.1 Calibration Graphs

Appropriate volumes of chlorpheniramine maleate solution (100 g ml^{-1}) were transferred into four separate 25 ml volumetric flasks, in order to prepare a series of chlorpheniramine maleate solutions containing 5, 10, 15 and 20 g ml^{-1} of chlorpheniramine maleate respectively. Each solution was diluted to volume with phthalate buffer pH 4.0. Twenty millilitres of each standard solution was pipetted into the dry polarographic cell and the solution was deaerated for 15 minutes with nitrogen and then the polarogram was recorded from -0.6 to -1.2 V at sensitivity 4x 10^{-7} A/mm.

Similarly, the polarograms of commercial sample solution were also recorded as described above.

2.5.2 Procedures for Dosage Forms

(1) Tablets

A suitable quantity of the powdered material was accuratedly weighed and transfered into a 100 ml volumetric flask, 60 ml of 0.1 mol L^{-1} sulphuric acid were added and the mixture was stirred for 10 minutes. Then the solution was filtered through Whatman No.42 filter paper. The clear filtrate was quantitatively transferred to a 100 ml volumetric flask and diluted to volume with 0.1 mol L^{-1} sulphuric acid (concentration of stock solution 100 g ml^{-1}).

A 2.5 ml aliquot of the stock solution was quantitatively transferred to a 25 ml volumetric flask and diluted to volume with phthalate buffer pH 4.0. A 20 ml aliquot of this solution was transferred into the polarographic cell. Deaeration was carried out, and the polarogram was obtained as previously described.

(2) Syrups

The liquid preparation was thoroughly mixed, and then a suitable quantity was pipetted into a 100 ml volumetric flask and diluted to volume with 0.1 mol L^{-1} sulphuric acid (concentration of stock solution 100 g ml^{-1}).

A 2.5 ml aliquot of the stock solution was taken and analyzed polarographically as described for tablets.

(3) Injections

Suitable quantity of the injections was tranferred into a 100 ml volumetric flask and diluted to volume with 0.1 mol L^{-1} sulphuric acid (concentration of stock solution 100 g ml^{-1}). Again the drug content in this stock solution was determined in the same manner as described for tablets.

2.5.3 Determination of Chlorpheniramine Maleate by Standard Method [23]

Chlorpheniramine maleate in the same sample solutions were also determined by official method [23] based on spectrophotometry.

3. RESULTS AND DISCUSSION

3.1 Optimization of Experimental Conditions

Various reagents were tested as supporting electrolytes namely 0.1 mol L^{-1} tetrabutylammoniumbromide pH 4.0, phthalate buffer pH 4.0, chloride buffer pH 2.0 and 0.1 mol L^{-1} hydrochloric acid pH 1.2. Most supporting electrolytes gave well defined polarographic waves except 0.1 mol L^{-1} tetrabutylammoniumbromide which exhibited no polarographic wave (see Figure 1).

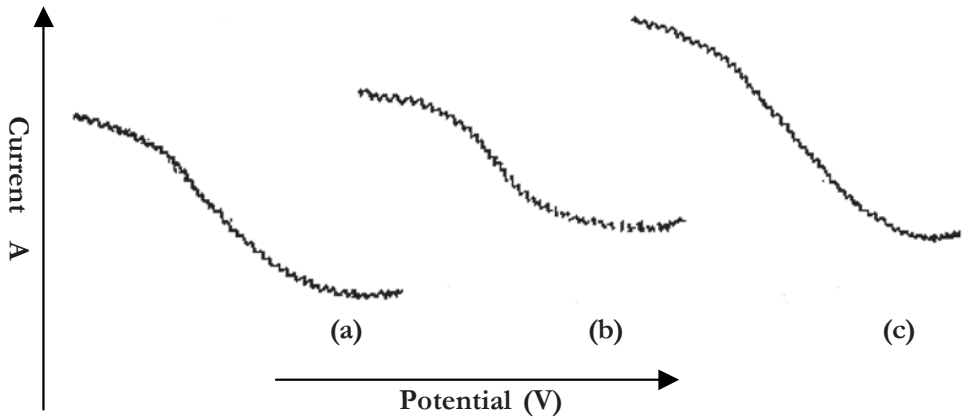

Figure 1. Current A and potential.

Different instrumental sensitivities over the range $1.0x10^{-8}$ - $6.0x10^{-7}$ A/mm were investigated using the above supporting electrolyte for the drug determination. It was found that in phthalate buffer pH 4.0, the suitable instrumental sensitivity was $4x10^{-7}$ A/mm and the half wave potential was -0.93 volts. In 0.1 mol L^{-1} hydrochloric acid or chloride buffer pH 2.0, the suitable instrumental sensitivity was $1.5x10^{-8}$ A/mm, and the half wave potential of which were slightly different. They were -0.60 volts and -0.66 volts respectively. Phthalate buffer pH 4.0 provided the highest sensitivity whereas the other two supporting electrolytes gave slightly differed in sensitivity judging from the half wave potential obtained.

3.2 Construction of Calibration Graphs

In order to examine the sensitivity (defined as slope of calibration graph) using the above three electrolytes, calibration graphs over the range 5-20 g mL^{-1} of chlorpheniramine maleate using phthalate buffer pH 4.0, chloride buffer pH 2.0 and 0.1 mol L^{-1} hydrochloric acid as supporting electrolytes were constructed. All of them were rectilinear with the regression equations as follows:

At pH 4.0 : $y = 0.029x + 0.36$ ($R^2 = 0.9938$).

At pH 1.2 and pH 2.0 : y = 0.025x + 0.18 (R^2 = 0.9988).
where y = diffusion current (i_d) and x = chlorpheniramine maleate concentration (g mL^{-1}).

The diffusion currents obtained in phthalate buffer pH 4.0 were higher than those obtained in the other two supporting electrolytes (see Fig.1). With respect to the sensitivity defined as the slopes of the calibration curves were found to be 0.029, 0.025 and 0.025 A/(g mL^{-1}) of chlorpheniramine in phthalate buffer pH 4.0, chloride buffer pH 2.0 and 0.1 mol L^{-1} hydrochloric acid respectively. Therefore, the greatest sensitivity was obtained when the phthalate buffer pH 4.0 was as supporting electrolyte which was chosen for subsequent experiments.

3.3 Interference Studies

Various concentrations of acetaminophen, ascorbic acid or phenylpropanolamine hydrochloride were added into 10 g mL^{-1} of chlorpheniramine maleate in phthalate buffer pH 4.0, chloride buffer or 0.1 mol L^{-1} hydrochloric acid. The polarograms were recorded. It was evident that the presence of about 20 folds of phenylpropanolamine hydrochloride, 25 folds of ascorbic acid and 250 folds of acetaminophen did not interfere. None of the common excipients employed in the chlorpheniramine maleate formulations was found to interfere with the assay for the chlorpheniramine meleate.

3.4 Precision

The precision of the method was determined by assaying ten replicates of individually weighed and extracted sample of the same lot of chlorpheniramine maleate tablet containing 4 mg of the drug. In this procedure, phthalate buffer pH 4.0, chloride buffer pH 2.0 and 0.1 mol L^{-1} hydrochloric acid were used as supporting electrolytes. The relative standard deviations (%RSD) of the assay method were 1.06%, 2.53% and 2.53% for phthalate buffer pH 4.0, chloride buffer pH 2.0 and 0.1 mol L^{-1} hydrochloric acid respectively. It was indicated that the method was very reproducible and that the best reproducible results could be obtained when phthalate buffer pH 4.0 was used as supporting electrolyte because the %RSD (1.06%) was far more less than the acceptable %RSD (5.00%).

The precision of the method was evaluated by intra-day and inter-day (3 days) analysis of 10 replicate of 10 g mL^{-1} of chlorpheniramine maleate standard. The %RSD values were all less than 3.00 % indicating that the method is very precise.

Table 1. Recovery studies using phthalate buffer pH 4.0 as supporting electrolyte.

CPM* concentration (g ml^{-1}) added to 5 g ml^{-1} of CPM tablets solution	Total CPM concentration (g ml^{-1})	CPM concentration found (g ml^{-1})	Recovery** (%)
4	9	8.94	99.33
5	10	9.98	99.80
6	11	10.98	99.91
10	15	15.01	100.07
15	20	19.71	98.95
Average % recovery	-	-	99.61

*CPM = chlorpheniramine maleate
** Average from 5 determinations

3.5 Recovery Studies

In this experiment, known concentrations of standard chlorpheniramine maleate (4-15 g mL^{-1}) were spiked to chlorpheniramine maleate tablets solutions containing 5 g mL^{-1} of the drug and the recoveries were calculated, the chlorpheniramine maleate recovery data were given in Table 1. It was shown that the method was accurate. The average recovery was 99.61% with a coefficient of variation of ±1.06%.

3.6 Determination of Chlorpheniramine Maleate in Pharmaceutical Preparations

The proposed method was applied to the analysis of a number of pharmaceutical products using phthalate buffer pH 4.0 as supporting electrolyte. In general, satisfactory results were obtained with most dosage forms. Results were shown in Table 2. It was shown that the drug contents found in each sample compared favourable with the declared contents and the drug contents of all the tablets, syrups and injections in each batch showed good agreement with the official limit. Thus, the proposed polarographic method is inexpensive, simple, fast, accurate and precise. It would be of value in product formulation study. Comparative determination of chlorpheniramine maleate by official method [23] based on spectrophotometry was also carried out. Results obtained by both methods were in good agreement verified by student's t-test.

Table 2. Analysis of chlorpheniramine maleate in commercial formulations.

Sample No.	Drug	Decared contents	Drug contents found		% Labelled amount**
			Polarographic method	Spectrophotometry	
S1	Chlorpheniramine maleate	10 $mg.ml^{-1}$	10.00 $mg.ml^{-1}$	9.97 $mg.ml^{-1}$	100.00
S2	Chlorpheniramine maleate	2.5 $mg.tsp^{-1}$	2.48 $mg.tsp^{-1}$	2.46 $mg.tsp^{-1}$	99.20
S3	Chlorpheniramine maleate	4 $mg.tab^{-1}$	3.97 $mg.tab^{-1}$	3.98 $mg.tab^{-1}$	99.25
S4	Vit.C Chlorpheniramine	100 $mg.tab^{-1}$ 4 $mg.tab^{-1}$	4.00 $mg.tab^{-1}$*	3.96 $mg.tab^{-1}$*	100.00
S5	Paracetamol Chlorpheniramine maleate Phenylpropanolamine HCl	120 $mg.5ml^{-1}$ 1 $mg.5\ ml^{-1}$ 20 $mg.5\ ml^{-1}$	1.00 $mg.5ml^{-1}$*	0.98 $mg.5ml^{-1}$*	100.00
S6	Chlorpheniramine maleate	10 $mg.ml^{-1}$	10.00 $mg.ml^{-1}$	9.97 $mg.ml^{-1}$	100.00
S7	Paracetamol Chlorpheniramine maleate Ascorbic acid	125 mg 2 mg 50 mg t calculate	1.99 mg*	1.96 mg* 1.76	99.50

* Amount of Chlorpheniramine maleate found
** Average from 5 determinations
*** 95% confidence, t = 2.365 when n = 7

4. CONCLUSION

An inexpensive, simple, direct current polarographic methods has been proposed for chlorpheniramine maleate determination in commercial pharmaceutical formulations. Phthalate buffer pH 4.0 was found to be the most suitable supporting electrolyte due to its high sensitivity, reproducibility and accuracy. Results obtained by the method were in good agreement with those obtained by standard method. Interferences from common excipients were negligible.

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