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ORIGINAL ARTICLE

Sensing of chlorpheniramine in pharmaceutical applications by sequential injector coupled with potentiometer

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Abstract This paper reports on development of a system consisting of a portable sequential injector coupled with potentiometric unit for sensing of chlorpheniramine (CPA), based on the reaction of CPA with potassium permanganate in acidic media. Various experimental conditions affecting the potential intensity were studied and incorporated into the procedure. Under the optimum conditions, linear relationship between the CPA concentration and peak area was obtained for the concentration range of 0.1–50 ppm. The method reflects good recovery with relative standard deviation (RSD) < 3%. The detection limit was 0.05 ppm. The developed method was successfully applied for determination of CPA in pure form and in pharmaceutical dosage forms. The results, obtained using the method, are in accord with the results of the British pharmacopoeia method. In addition to its accuracy and precision, the method has the advantages of being simple, inexpensive and rapid.

1. Introduction

Chlorpheniramine, marketed in its salt chlorpheniramine maleate, is a first-generation alkyl amine antihistamine drug. It is commonly used in pharmaceutical preparations for symptomatic relief of common cold and allergic diseases. Chlorpheniramine is one of the most commonly used antihistamines in small-animal veterinary practice. Chlorpheniramine (Fig. 1) is one of a series of antihistamines including pheniramine (Naphcon) and its halogenated derivatives and others including fluorpheniramine, dexchlorpheniramine, dexbrompheniramine, brompheniramine, deschlorpheniramine and diphenhydramine.

Different methods for the assay of chlorpheniramine maleate in pharmaceutical formulas have been reported in the literature. An aqueous titration method was proposed involving the back-titration of excess HCl that is not taken up by the free base of the drug [1]. In addition, acid-base titrations were performed potentiometrically with 0.1 M solution of perchloric acid as titrant [2]. Spectroscopic method was proposed for the determination of chlorpheniramine maleate in injection, syrup and tablets [3]. Several other spectroscopic

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methods have been proposed. The procedure for the determination of chlorpheniramine maleate and phenylephrine hydrochloride in nasal drops has been described [4]. Gas liquid chromatography was used for separation of antihistamine [5]. Numerous high performance liquid chromatographic methods have been developed for the determination of chlorophenir-amine maleate in commercial pharmaceutical preparations [6–10]. A micellar electrokinetic chromatographic procedure has been reported for simultaneous determination of paracetamol and chlorpheniramine maleate [11]. Recently, a direct current polarographic method for the determination of chlorpheniramine maleate in pharmaceutical preparations has been reported [12]. The method was based on the reduction of chlorpheniramine maleate in an acidic medium (pH 1.2–4.0). Chlorpheniramine maleate was determined by an electrochemiluminescent method based on Ru $(bpy)^{32+}$ immobilized in a nano-Titania/Nafion membrane [13]. Flow injection chemiluminescence analysis was reported for chlorpheniramine maleate determination [14]. However, those previous methods generally either are involved in complicated procedures or demand many chemicals, which are main drawbacks leading to contamination problems.

This paper reports on the developing a system of sequential injector coupled with potentiometer, for sensing and fast determination of chlorpheniramine. The procedure was optimized and its analytical performance was thoroughly evaluated. The method was successfully applied to the determination of chlorpheniramine in pharmaceutical formulas. The method is cost-effective, sensitive and reproducible with a sampling rate of 18 samples per hour.

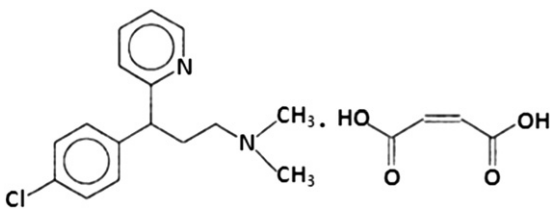

Figure 1 Chemical structure of chlorpheniramine maleate.

2. Experimental

2.1. Reagents and chemicals

Potassium permanganate and sulfuric acid were from Fisher Scientific Company, Chemical Division, Fair Lawn, New Jersey 07410, USA. Hydrochloric acid was from BDH Chemicals Ltd. Poole England. Chlorpheniramine maleate supplied from Sigma C3025 was used for preparing a standard solution of 200 ppm. This standard solution and the working standard solutions were immediately prepared before use. Chlorpheniramine maleate pharmaceutical forms were kindly donated by the pharmaceutical industry and used as received. Water used was deionized distilled water. Tablets samples were prepared by triturating 20 tablets. The required amount of the powder was dissolved in water, filtered and diluted to the required volume.

2.2. Preparation of solutions and real samples

Potassium permanganate 0.1 mol/L solution was prepared by dissolving 1.5804 g of potassium permanganate in 100 ml distilled water. After standardization, it was used to prepare working solutions at the appropriate concentrations.

Sulfuric acid 0.1 mol/L was prepared [15], followed by dilution process to get the appropriate concentrations.

CPA 1000 ppm was prepared by dissolving the required amount of chloropheniramine maleate in 100 ml of distilled water. This stock solution was used to prepare the standard solutions by appropriate dilution.

The method was applied to the determination of chlorpheniramine maleate in drug tablets (Chlorohistol Produced by

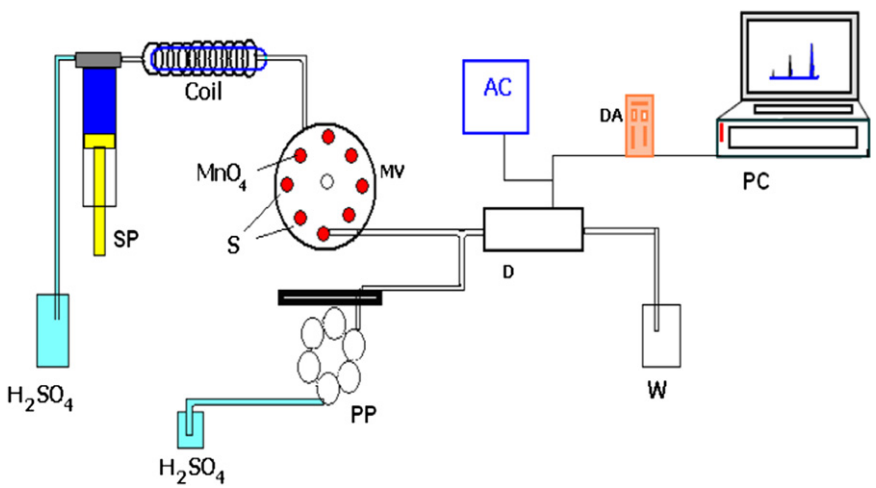

Figure 2 Schematic representation of the system used for sensing of chlorpheniramine with; H_2SO_4: carrier, SP: syringe pump, PP: peristaltic pump, MV: multiselection valves, S: sample; AC: current source, D: electrode detector, DA: digital-to-analog converter, PC: Readout desktop computer.

Gulf Pharmaceutical Industries, Patch 214, Ras AL Khaimah, U.A.E) and injections. Ten 4-mg-tablets of chlorpheniramine maleate were finely powdered. Then, an accurate weighed powder is taken and stirred at room temperature with enough amount of water. The resulted solution is filtered. The injection sample (Allerfin 10 mg, Batch No. 551218, The Arab Pharmaceutical Manufacturing Co. Ltd., Sult-Jordan) was also used for the analysis.

2.3. Apparatus

The sensing device used in this portable system consists of SIA combined with a potentiometric cell as a detection unit (Fig. 2). The system is the FIALab 3500 (Medina, WA USA). It is composed of a syringe pump, a multi-position valve, a Z-flow cell with SMA fiber optic connectors as well as pump tubing and PC. The syringe pump is 24,000 steps with an optical encoder feedback and 1.5 s–20 min per stroke of 2.5 mL size. It is of more than 99% accuracy at full stroke. The volume capacity of syringe is 2500 μL. The multi-position valve has eight ports with a standard pressure of 250 psi (gas)/ 600 psi (liquid); zero dead volume; chemically inert; port selection is usually done using the software program [16–18]. The Z-flow cell is 10 mm path length plexiglass compatible with standard SMA terminated fiber optics used. Pump tubing of 0.30 in. ID Teflon type supplied by Upchurch Scientific, Inc. (Oak Harbor, WA, USA) was used for connecting the different units and making both the holding coil (190 cm long) and the reaction coil (190 cm long).

The potentiometric cell consists of two platinum wires connected into small holes in the glass cylindrical cell. The ends of the electrodes are exposed to the solutions that pass through the cell hole. The other ends of the two electrodes are connected into the electrical circuit and to the LabJack. The circuit is used to supply current, and thus the difference in potential can be recorded. The LabJack can convert the signals into digital and therefore it can be drawn simply into the SIA software.

3. Results and discussion

3.1. Peaks location

The program for CPA determination was established and well optimized. The device sequence for one cycle for CPA determination was performed. Once started, it was noticed that the response was not stabile because of the difference in the response of electrodes during passing the solutions. To achieve a good response, peristaltic pump was used to continuously carry sulfuric acid solution, used as a carrier through the syringe pump. This allows for peak base stability.

3.2. Variables optimization

The variables that were optimized included concentrations and volumes of potassium permanganate, sulfuric acid and CPA solutions, flow rate, delay time, applied current and coil length representing the distance between mixing point and the electrodes.

3.2.1. Concentrations and volumes

The optimum concentration of potassium permanganate was found to be 0.001 mol/L, and the volume was 100 μL. The optimum concentration of sulfuric acid was 0.0001 mol/L, and its volume was 80 μL. The volume of the CPA was 110 μL. The optimum amounts of the reagents were selected based on the highest potential.

3.2.2. Flow rates

As shown in Fig. 3, the flow rate was studied in the range between 30 and 200 μL/s. It was found that the flow rate of 40 μL/s gave the highest and symmetric peak. At this flow rate, the electrodes gave high response to the difference in potential. At faster flow rates, there is no enough time of the electrodes to give proper response to the change in potential. On the other hand, at lower flow rate, the peak became broad and asymmetric.

3.2.3. Delay time

The time for the mixing of the reagents is essential in order for the reaction to take place. The delay time was investigated in the range between 0 and 50 s. The highest and symmetric peak

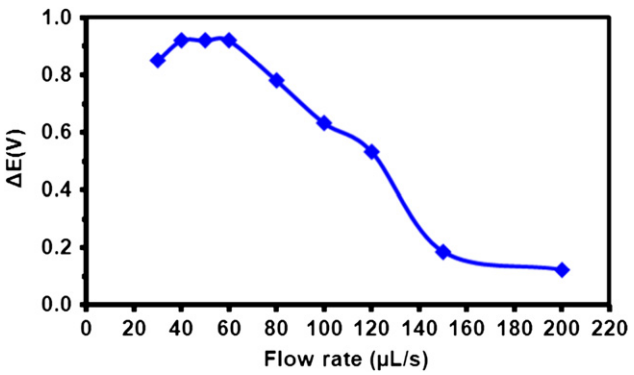

Figure 3 The influence of flow rate on the peak intensity. Conditions: CPA concentration 1 ppm; CPA volume 110 μL; potassium permanganate 0.001 mol/L, 100 μL; current density 10 μA/cm^2 ; delay time 20 s; coil length 20 cm.

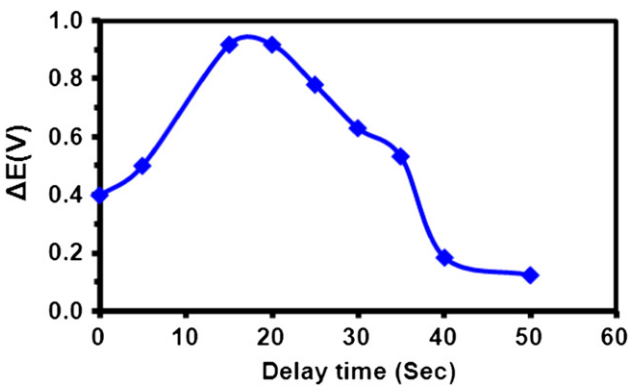

Figure 4 The influence of delay time on the peak intensity. Conditions: CPA concentration 1 ppm; CPA volume 110 μL; potassium permanganate 0.001 mol/L, 100 μL; current density 10 μA/cm^2; flow rate 40 μL/s; coil length 20 cm.

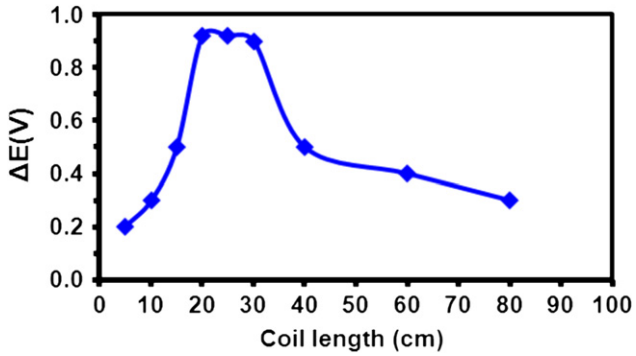

Figure 5 The influence of coil length on the peak intensity. Conditions: CPA concentration 1 ppm; CPA volume 110 μL; potassium permanganate 0.001 mol/L, 100 μL; current density 10 μA/cm^2; flow rate 40 μL/s; delay time 15 s.

was obtained at delay time of 15 s, as depicted in Fig. 4. Consequently, the delay time of 15 s was chosen for subsequent experiments in this work.

3.2.4. *Coil length*

The distance between reagents' mixing point and the electrodes was investigated by using tubes of different lengths, 80, 60, 40, 30, 25, 20, 15 and 10 cm. As depicted in Fig. 5, the highest peak was obtained when 20 cm tube was used. This can be attributed to the response of the electrodes once the mixture reaches the electrodes while the reaction takes place at its optimum. At longer distance, the mixture reaches the electrodes at the end of its life. At shorter distance, the mixture reaches the electrodes at the beginning of its life.

3.2.5. *Current*

The applied current was investigated in the range of 1–30 μA/cm^2. The current density of 10 μA/cm^2 was found to give the best symmetric and highest response. The very small amount of current is found to be essential for electrode polarization and for electrodes' regeneration due to its reversibility.

3.3. *Method evaluation and application*

3.3.1. *Precision and recovery*

The precision was tested with seven injections [19,20]. The intraday (within day) precision was below 1.2% (Fig. 6). From these results, it can be concluded that the method has a good repeatability. The very good interday (between days) precision from the 1st to the 10th day was 1.6%. From these results, it can be concluded that the adopted method has a good sense of reproducibility. Recovery of the procedure was also evaluated at three concentration levels. The recovery ranged from 97% to 99%.

3.3.2. *Sample frequency*

On applying the optimum conditions, the proposed method was used for the determination of CPA. Sampling rate of about 18 samples per hour was achieved.

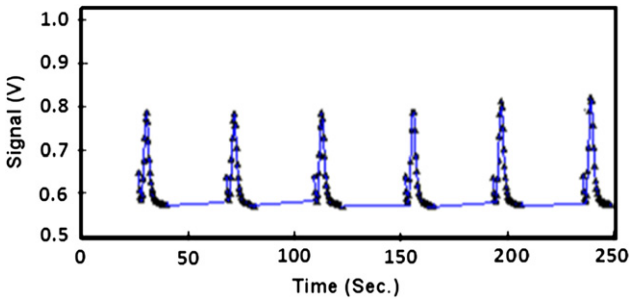

Figure 6 Represents repeated measurements of CPA by the proposed method. Conditions: CPA concentration 1 ppm; CPA volume 110 μL; potassium permanganate 0.001 mol/L, 100 μL; current density 10 μA/cm^2; flow rate 40 μL/s; delay time 15 s; coil length 20 cm.

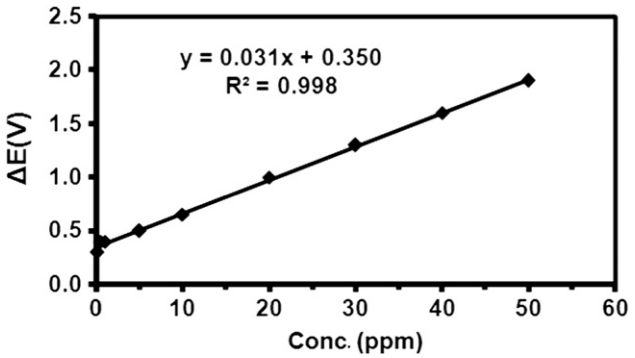

Figure 7 The signal response to different chlorphenireamine concentartions; 0.1, 0.5, 1, 5, 10, 20, 30, 40 and 50 ppm. Other conditions are: CPA volume 110 μL; potassium permanganate 100 μL; current density 10 μA/cm^2; delay time 15 s; coil length 20 cm; flow rate 40 μL/s.

3.3.3. *Calibration curve*

The linearity of the method for CPA determination was studied under the optimum conditions. Fig. 7 presents the signal response to different CPA concentartions; 0.1, 0.5, 1, 5, 10, 20, 30, 40 and 50 ppm. The applied optimium conditions were 110 μL of CPA; 100 μL of potassium permanganate; 10 μA/cm^2 current density; 15 s delay time; 20 cm coil length and 40 μL/s flow rate. Linearity of the calibration curve was obtained in the range of 0.1–50 ppm. When samples with concentration less than 0.1 ppm were applied, the response was irreproducible. While at concentrations more than 50 ppm, the signal was nonlinear. The detection limit was 0.05 ppm with less than 2% relative error. The correlation coefficient (R^2) was 0.998.

3.3.4. *Recovery and application*

The developed method was applied for the sensing of chlorpheniramine maleate in pharmaceutical preparations collected from drug stores. It is worth mentioning that the excipient (starch) showed negligible interference with the process. The mean recovery and the RSD% (relative standard deviation) are presented in Table 1. The same samples were analyzed in parallel using the pharmacopoeia standard method (BP, 2000). Each sample was analyzed in septuplicate using the both proposed system and BP method. The results obtained are summarized in Table 1.

Table 1 Results obtained by the proposed system and BP method for the analysis of chlorpheniramine maleate; synthetic sample, injections and tablets.

Chlorpheniramine sample	Recovery by proposed method (%)	Recovery by BP (%)	Official range[a] (%)	RSD[b] (%)
Synthetic sample (1 mg was added)	99	98	98–101	±1.1
Allerfin 10 mg (injection)	97	96	90–110	±1.5
Anallerg 4 mg (tablets)	98	98	92.5–107.5	±2.1

[a]Official range of the content of a drug specified by the British Pharmacopoeia (BP).
[b]Relative standard deviation of seven measurements.

The results obtained showed acceptable accuracy and repeatability. The proposed method is cost-effective and has the advantages of being simple and automated with rapid analysis. It may be suitable for point of care applications and quality control laboratories.

4. Conclusions

A sensitive portable sequential injection setup for the quantitative sensing of CPA was successfully developed, based on measuring the difference in potential generated when CPA reacts with potassium permanganate in acidic media. Under the optimium conditions, the method is characterized by a low detection limit, excellent reproducibility and a wide dynamic range along with sampling frequencies of 18/h. The method was applied to the analysis of commercially available dosage forms with no interference. This method is cost-effective, and therefore suitable for routine pharmaceutical analysis application. The method is of sufficient accuracy and precision and permitted a portable, simple, and time saving assay.

Acknowledgments

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