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PVC Membrane Electrode for the Direct Determination of Chlorpheniramine Maleate in Pharmaceutical Preparations

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A PVC membrane electrode for chlorpheniramine maleate and phosphomolybdic acid association complex was constructed. The basic electrode's performance characteristics were evaluated. The prepared electrode exhibits a near Nernstian response (57.9 mV per decade) over the concentration range of chlorpheniramine maleate in solutions of pH 4-7. Common organic and inorganic cations showed negligible interference. Direct potentiometric determination of 1×10^{-2}-1×10^{-5} M aqueous chlorpheniramine maleate using this membrane electrode system showed an average recovery of 99.9 % with a mean standard deviation of ± 0.811. The electrode gave a good stability reproducibility and fast response. These characteristics of the electrode enable it to be used successfully for the determination of chlorpheniramine maleate in pure form and in pharmaceutical preparations.

Key Words: Ion-selective electrode, Chlorpheniramine maleate determination, Pharmaceutical preparations, Potentiometry.

INTRODUCTION

Chlorpheniramine maleate, (±)-3-(4-chlorophenyl)-N,N-dimethyl-3-(2-pyridyl) propylamine (Fig. 1), is an antihistamine (H_1-receptor antagonist) competitively inhibit histamine at H_1 receptor sites. It does not inactivate or prevent the release of histamine, but can prevent histamine's action on the cell. Besides its antihistaminic activity, this agent has varying degrees of anticholinergic and CNS activity (sedation)[1].

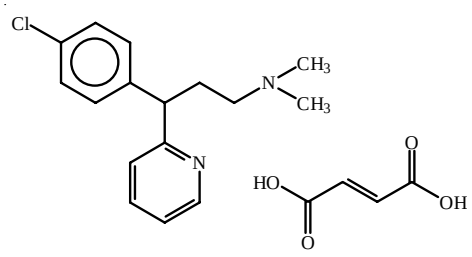

Fig. 1. Chemical structure of chlorpheniramine maleate

Several methods have been reported for the determination of chlorpheniramine maleate including spectrophotometry[2-5], high performance liquid chromatography[6-14], liquid chromatography[15,16], liquid chromatography-mass spectrometry[17-19], gas chromatography[20,21], capillary zone electrophoresis-mass spectrometry[22], polarographic method[23], mass-spectrophotometry[24,25] and ^{1}H NMR[26]. Although potentiometric methods of analysis using ion-selective electrodes are simple, economical and applicable for the samples, the present work describes a new selective membrane electrode of the plasticized poly(vinyl chloride) type, for the determination of chlorpheniramine maleate in pure solutions and in pharmaceutical preparations. The electrode is based on the incorporation of an ion-pair complex of the phosphomolybdate anion with chlorpheniramine cation in a poly (vinyl chloride) matrix.

EXPERIMENTAL

All chemicals used of analytical or pharmacopoeial grade. Doubly distilled water was used throughout the experiments. chlorpheniramine maleate was provided by Sigma Co. for chemicals and pharmaceuticals (Germany), poly (vinyl chloride) (PVC) was from Aldrich (Germany), di-butyl sebacate was from (Fluka, Switzerland), phosphomolybdic acid and tetrahydrofuran (THF) were from Memphis-Delagrange, (France), (Pirafene® ampoules, tablets, Allergyl® syrup, tablets and Anallerge-4® tablets, syrup) were purchased from local drug stores). Stock chlorpheniramine maleate solution (1×10^{-1} M) was prepared fresh everyday by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilution.

Jenway 3010 pH/mV meter (U.K.) with a chlorpheniramine maleate-PVC membrane electrode in conjunction with double Junction Ag/AgCl electrode (Orion 90-02) (Taiwan, R.O.C.) containing 10 % w/v potassium nitrate in outer compartment. An Orion 91-02 glass-calomel combination electrode, (Taiwan, R.O.C.) was used for pH adjustment. All potentiometric measurements were carried out at 25 ± 1ºC with constant magnetic stirring.

Recommended procedures

Preparation of chlorpheniramine maleate ion-pair: The ion-pair was prepared by mixing 50 mL aliquots of 1×10^{-2} M chlorpheniramine maleate and phosphomolybdic acid. The resulting yellowish precipitate was filtered through G_4 sintered glass crucible and washed thoroughly with deionized water then dried at room temperature for 24 h.

Membrane composition: The membrane was prepared by dissolving 190 mg of powdered PVC, 0.35 mL of the plasticized (di-butyl sebacate)

and 10 mg of the ion-pair in 5 mL tetrahydrofuran (THF). The solution was poured into a petri dish (3 cm in diameter), covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature.

Electrode construction: A punched circular membrane was attached to a poly-ethylene tube (8 mm in diameter) in an electrode configuration by means of PVC-THF solution. A mixture containing equal volumes of 1×10^{-3} M chlorpheniramine maleate and potassium chloride was used as internal reference solution in which the Ag/AgCl reference electrode was dipped. The constructed electrode was pre-conditioned after preparation by soaking for at least 24 h in 1×10^{-3} M drug solution and stored in the same solution. The electrochemical system is represented as follow: Ag/AgCl/inner solution/membrane/test solution/KCl/salt bridge//SCE.

Electrode calibration: 10 mL aliquots of 1×10^{-1}-1×10^{-6} M standard chlorpheniramine maleate solution were transferred into 50 mL beaker and the sensor in conjunction with Ag/AgCl reference electrode were immersed in the solution. The measured potential was plotted against the logarithm of drug concentration. The electrode was washed with deionized water and dried with tissue paper between measurements.

Effect of pH: The effect of pH on the potential of the electrode was measured using two pH/mV meters. The combined glass calomel electrode was connected to one instrument and the PVC-chlorpheniramine maleate membrane with the double junction Ag/AgCl reference electrode was connected to the second instrument. 30 mL aliquots of 1×10^{-5} M, 1×10^{-4} M, 1×10^{-3} M and 1×10^{-2} M, drug solutions were transferred to a 100 mL beaker where the three electrodes were immersed, the potential readings corresponding to different pH values were recorded. The pH was gradually increased or decreased by the addition of small aliquots of dilute solutions of 0.1 N sodium hydroxide or 0.1 N hydrochloric acid respectively and the pH-mV was measured and plotted.

Selectivity of the electrode: Selectivity coefficients were determined by the separate solution method[27] in which the following equation was applied.

$$K^{Pot}_{CP,J^{z+}} = (E_2 - E_1)/S + \log[CP] - \log[J^{Z+}]^{1/z}$$

where E_1 is the electrode potential in 1×10^{-3} M chlorpheniramine maleate solution. E_2 is the potential of the electrode in 1×10^{-3} M solution of the interferent ion J^{z+} and S is the slope of the calibration plot. The selectivity of the electrode towards sugars, amino acids, certain cations and alkaloids was studied. The tested interferents are listed in Table-2.

Standard addition method: An electrode was immersed into a sample of 50 mL with unknown concentration (*ca.* 10^{-4} M) and the equilibrium potential of E_1 was recorded. Then 0.1 mL of 10^{-1} M of chlorpheniramine

maleate standard was added into the testing solution and the equilibrium potential of E_2 was obtained. From the change of $\Delta E(E_2\text{-}E_1)$ one can determine the concentration of the testing sample[28]. The standard addition technique was used for the analysis of chlorpheniramine maleate formulations, Pirafene® tablets, ampoules, Allergyl® tablets, syrup and Anallerge-4® tablets, syrup.

Analytical applications

Determination of chlorpheniramine maleate in dosage forms:

Tablets: The content of ten tablets were shaken with 100 mL distilled water and serial dilution performed to obtain different concentrations in the range of 1×10^{-2}-5×10^{-5} M. The prepared solutions were adjusted to pH 4 using 0.1 N dilute hydrochloric acid. The PVC chlorpheniramine maleate membrane electrode was immersed in the solution. The electrode system was allowed to equilibrate with stirring and the e.m.f. recorded and compared with the calibration graph. The standard addition (spiking technique) was also applied by recording the electrode potential after the addition of 0.1 mL of standard 1×10^{-1} M chlorpheniramine maleate solution to the above drug test solutions.

Syrups and ampoules: The prepared solution was diluted with deionized water to give serial dilutions ranging from 5×10^{-3}-1×10^{-5} M for ampoules and syrups. These solutions were transferred into 50 mL beaker, adjusted to pH 4 using 0.1 N hydrochloric acid and the procedure was completed as described under tablets.

Content uniformity assay of chlorpheniramine maleate tablets: 10 Individual tablets of 4.0 mg chlorpheniramine maleate were placed in separate 100 mL beaker and dissolved in 90-100 mL of distilled water. The electrode was directly immersed into 10 mL of each sample for 5 times and should be washed with deionized water to reach steady potential between the individual measurements. The mean potential was used to evaluate the content uniformity from the calibration graph. Fig. 4, showed the histogram of chlorpheniramine maleate content of tablets.

Dissolution test: Place 900 mL of water into the dissolution vessel and equilibrate to 37 ± 0.5ºC, place 1 tablet in the dissolution vessel and immediately operate the apparatus at 2:50 rpm after the stated time, withdrawn 20 mL of the dissolution medium. For the potentiometric determination, after an appropriate time interval (0.5-3 min), the potential values were recorded and the amount of the chlorpheniramine maleate was calculated from the calibration graph. In order to investigate all the important physical processes during the dissolution period, the release profiles were numerically simulated by a typical equation[29]. Fig. 5 showed the dissolution profile of chlorpheniramine maleate 4.0 mg tablets.

RESULTS AND DISCUSSION

Nature and response characteristics of the electrode: Chlorpheniramine maleate reacts with phosphomolybdic acid to form a stable chlorpheniramine maleate-phosphomolybdate ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran. The complex was prepared and tested as active material with di-butyl sebacate as a solvent mediator in a poly(vinyl chloride) membrane response for chlorphenir-amine maleate. The critical response characteristics of chlorpheniramine maleate-PVC membrane electrode were determined and results are summarized in Table-1. The electrode exhibits a Nernstain response over the concentration range from 1×10^{-2}-1×10^{-5} M chlorpheniramine maleate with a cationic slope of 57.9 ± 0.2 mV/decade change in concentration Fig. 2. The choice of membrane solvent to achieve the required selectivity is based on its electric permittivity and its immiscibility with aqueous phase, high viscosity, low solubility of the matrix in the membrane and ability to dissolve ion-pair complex. The response time of the electrode was tested for 1×10^{-2}-1×10^{-5} M chlorpheniramine maleate solutions. The sequence of measurements was from low to high concentrations. This electrode exhibits a fast dynamic response of about 10-20 s. The electrode used for a period of 40 d without significant change in the electrode parameters.

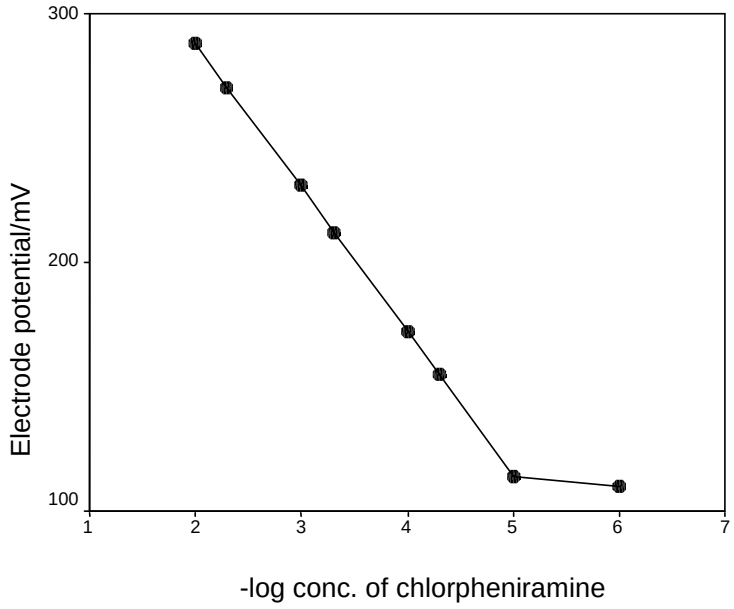

Fig. 2. Typical calibration graph of chlorpheniramine-phosphomolybdate-PVC membrane electrode.

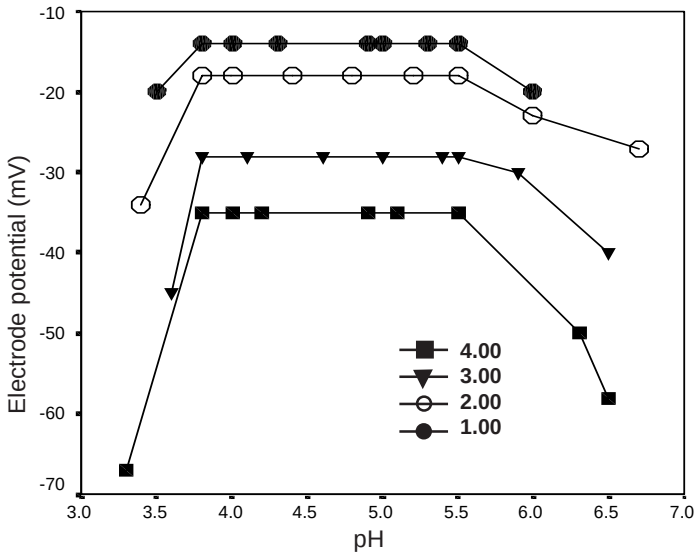

Fig. 3. Effect of pH on potential/mV of chlorpheniramine- phosphomolybdate-PVC membrane electrode.1.0×10^{-2}(1), 1.0×10^{-3} (2), 1.0×10^{-4} (3), 1.0×10^{-5} M (4)

TABLE-1
CRITICAL RESPONSE CHARACTERISTICS OF CHLORPHENIRAMINE- PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE

Parameter	Value
Slope (mV decade)	57.9 ± 0.2
Intercept (mV)	403.70
Correlation coefficient (r)	0.9998
Linear range (M)	1×10^{-2}-1×10^{-5}
Working pH range	4-7
Response time (10^{-3} M)	
Chlorpheniramine maleate (s)	10-20
Life time (day)	40

Quantification, accuracy and precision: Direct potentiometric determination of chlorpheniramine maleate using the chlorpheniramine maleate-phosphomolybdate-PVC membrane electrode was performed and calculated from the calibration curve. The statistical data of the analytical results obtained by the proposed method (direct and standard addition techniques) for the drug in pure form are listed in Table-3. Furthermore, the results obtained were encouraging so the proposed method was applied for the determination of chlorpheniramine maleate in some of its pharma-

ceutical preparations. In both cases, the results obtained were compared with the reference method (the non aqueous titration method was applied by dissolving 0.15 g chlorpheniramine maleate in 25 mL of anhydrous acetic acid). Titrate with 0.1 M perchloric acid determining the end-point potentiometrically[29] (Tables 4 and 5).

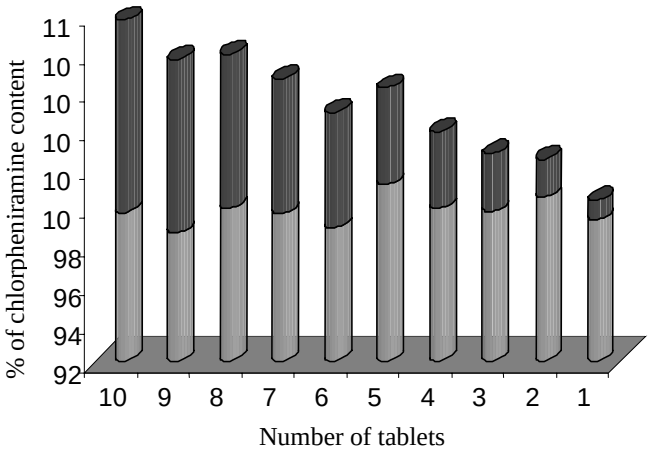

Fig. 4. Histogram of content uniformity of chlorpheniramine maleate 4 mg tablets

TABLE-2
SELECTIVITY COEFFICIENTS FOR SOME COMMON CATIONS WITH THE CHLORPHENIRAMINE MALEATE-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE

Interferent	$K^{pot}_{Chlor.ph.^+ maleate^-}$
* Glucose	5.1×10^{-3}
* Lactose	9.9×10^{-4}
* Sucrose	3.1×10^{-3}
* Calcium chloride	6.9×10^{-3}
* Potassium chloride	6.5×10^{-4}
* Sodium chloride	5.2×10^{-4}
* Barium chloride	5.5×10^{-3}
* Nickel chloride	1.4×10^{-2}
* Sodium citrate	8.3×10^{-4}
* Magnesium sulphate	6.2×10^{-3}
* Tryptophan	6.4×10^{-3}
* Atropine sulphate	3.9×10^{-3}
* Quinidine	5.3×10^{-3}
* Urea	7.5×10^{-4}
* Aminophylline	1.8×10^{-2}
* Sulfathiazole	8.4×10^{-4}
* Pseudo ephedrine	1.5×10^{-3}
* Anhydrous Caffeine	4.2×10^{-3}
* Ephedrine	7.5×10^{-3}

TABLE-3
DETERMINATION OF CHLORPHENIRAMINE MALEATE IN PURE FORM USING CHLORPHENIRAMINE-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE IN COMPARISON WITH REFERENCE METHOD [REF. 29]

Statistical parameters	Reference method[29]	Direct potentiometry	
		Calibration graphs	Standard addition method
Mean (%) recovery	99.52	99.96	99.25
N	7	7	6
Variance	0.845	0.651	0.449
S.D.	0.919	0.807	0.670
S.E.	0.347	0.305	0.274
R.S.D.	0.923	0.807	0.675
"t"		(0.952) (2.179)*	(0.611) (2.201)*
F		(1.30) (4.28)*	(1.88) (4.39)*

* Theoretical values of "t" and F at p = 0.05

Effect of pH: The effect of pH of the chlorpheniramine maleate solutions (10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, M chlorpheniramine maleate) on the electrode potential was investigated. The solutions were acidified by the addition of very small volumes of HCl then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential was recorded and thus the potential-pH curves for four chlorpheniramine maleate concentrations were constructed (Fig. 3). As is obvious, within the pH range 4-7, the electrode potential is practically independent of pH and in this range the electrode can be safely used for chlorpheniramine maleate determination. The potential increases gradually and this can be related to the interference of the hydronium ion. The decrease occurring at higher pH values is most probably attributed to the formation of the free chlorpheniramine base in the solution or the ionization of the hydroxyl group, leading to a decrease in the concentration of the chlorpheniramine cation.

Selectivity of the electrode: The selectivity of the ion-pair associates based membrane electrodes depends on the selectivity of the ion-exchange process at the membrane-test solution interface and the mobilities of the respective ions within the membrane. The selectivity coefficients obtained by the separate solution method (Table-2), showed that the proposed chlorpheniramine maleate-phosphomolybdate-PVC membrane is highly selective toward chlorpheniramine maleate ion. The inorganic cations did not interfere due to the differences in their mobilities and permeabilities as compared with chlorpheniramine maleate cation. In case of sugars and amino acids, the high selectivity is mainly attributed to the difference in polarity

and lipophilic character of their molecules relative to chlorpheniramine maleate.

TABLE-4
COMPARATIVE ANALYTICAL RESULTS OF THE PROPOSED AND OFFICIAL METHOD FOR THE TESTED DRUG IN SOME PHARMACEUTICAL PREPARATIONS

Sample	Statistical parameters	Direct potentiometry		Official method[29]
		Calibration graph	Standard addition	
Pirafene® tablets (Memphis-Delagrange) 4 mg/tablet	Mean (%) Recovery	98.97	99.10	99.72
	N	6	6	6
	Variance	0.615	0.667	0.440
	S.D.	0.784	0.817	0.663
	S.E.	0.320	0.334	0.271
	R.S.D.	0.792	0.824	0.665
	t	(1.789)(2.228)*	(1.441)(2.228)*	
	F	(1.40)(5.05)*	(1.52)(5.05)*	
Allyergyl® tablets (Adco) 4 mg/tablet	Mean (%) Recovery	98.77	98.91	99.45
	N	6	6	6
	Variance	0.326	0.814	0.317
	S.D.	0.571	0.902	0.563
	S.E.	0.233	0.368	0.230
	R.S.D.	0.578	0.912	0.566
	t	(2.077)(2.228)*	(1.244)(2.228)*	
	F	(1.03)(5.05)*	(2.57)(5.05)*	
Anallerge-4® tablets (Kahira) 4 mg/tablet	Mean (%) Recovery	99.91	99.62	99.38
	N	6	6	6
	Variance	0.473	0.376	0.841
	S.D.	0.688	0.613	0.917
	S.E.	0.281	0.250	0.374
	R.S.D.	0.689	0.615	0.923
	t	(1.133)(2.228)*	(0.533)(2.228)*	
	F	(1.78)(5.05)*	(2.24)(5.05)*	

*Theoretical values of "t" and F at p = 0.05.

Electrode response in pharmaceuticals: The uses of chlorpheniramine maleate drug in various fields, from clinical to abuse in sports has necessitated an accurate and rapid, quantitative analysis in various matrices (dosage forms). This work proposed a fast, simple, easy, sensitive and

straightforward potentiometric method to determine chlorpheniramine maleate in dosage forms without the need for prior separation and preconcentration or derivatization procedures. The potential of the chlorpheniramine maleate-phosphomolybdate-PVC membrane electrode showed no significant difference of response time between aqueous solution of pure drug and its solutions from pharmaceutical preparations.

TABLE-5
COMPARATIVE ANALYTICAL RESULTS OF THE PROPOSED AND OFFICIAL METHOD FOR THE TESTED DRUG IN SOME PHARMACEUTICAL PREPARATIONS

Sample and Source	Statistical parameters	Direct potentiometry		Official method[29]
		Calibration graph	Standard addition	
Pirafene® ampoules (Memphis-Delagrange) 5 mg/1 mL	Mean (%) Recovery	99.34	99.38	99.69
	N	5	7	5
	Variance	0.071	0.067	
	S.D.	0.267	0.259	0.304
	S.E.	0.119	0.098	0.552
	R.S.D.	0.269	0.261	0.246
	t	(1.281)(2.262)*	(1.171)(2.228)*	0.553
	F	(4.28) (5.19)*	(4.54) (4.53)*	
Allyergyl® syrup (Adco) 2 mg/5mL	Mean (%) Recovery	99.70	99.90	99.54
	N	5	7	5
	Variance	0.445	0.461	0.940
	S.D.	0.667	0.679	0.970
	S.E.	0.298	0.257	0.433
	R.S.D.	0.669	0.680	0.974
	t	(0.304)(2.306)*	(0.715)(2.228)*	
	F	(2.11)(6.39)*	(2.04)(4.53)*	
Anallerge-4® syrup (Kahira) 2 mg/5 mL	Mean (%) Recovery	99.51	99.35	99.85
	N	6	7	5
	Variance	0.935	0.638	0.332
	S.D.	0.967	0.799	0.577
	S.E.	0.395	0.302	0.258
	R.S.D.	0.972	0.804	0.578
	t	(0.721)(2.306)*	(1.259)(2.228)*	
	F	(2.82)(6.39)*	(1.92)(4.53)*	

*Theoretical values of "t" and F at p = 0.05.

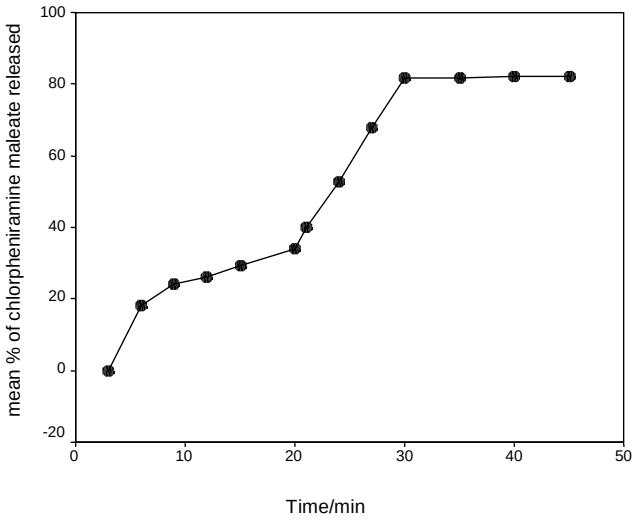

Fig. 5. Dissolution profile of chlorpheniramine maleate 4 mg tablets. All values are the average of six experiments

Conclusion

The potentiometric method developed for the determination of chlorpheniramine maleate has proved to be a good and advantageous over the reported analytical methods due to its sensitivity, rapidity and accuracy. The good recoveries and low relative standard deviation reflect the high accuracy and precision of the proposed method. Moreover, the method is simple, easy to operate and inexpensive making it an excellent tool for the routine determination of chlorpheniramine maleate in quality control laboratories, also a fast assay of chlorpheniramine maleate in its pharmaceutical preparations.

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