

# Flow injection potentiometric determination of Chlorphenoxamine Hydrochloride

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**Abstract** New Chlorphenoxamine (Ch) ion selective plastic membrane electrodes for both conventional and coated wire types based on the ion associate of Ch-HCl with sodium tetraphenylborate (NaTPB) and phosphotungstic acid (PTA) were prepared. The conventional type electrode was fully characterized in terms of membrane composition, plasticizer, filling solution, life span, pH, ionic strength, temperature. The membranes of optimum compositions were used for the preparation of both graphite and copper coated wire electrodes. The prepared electrodes were used for the potentiometric determination of the investigated drug in raw material and pharmaceutical preparations under batch and flow injection analysis conditions. The selectivity of the electrodes towards a large number of excipients like inorganic cations, sugars, amino acids and other antihistaminic drugs was tested. Determination of Ch-HCl, the solubility product of the ion associate and the formation constant of the precipitation reaction leading to the ion associate formation of Ch-HCl with NaTPB and PTA were carried out using conductimetric measurements.

**Keywords** Chlorphenoxamine Hydrochloride (Ch-HCl) · Ion selective electrode · Flow injection analysis (FIA) · Potentiometry · Sodium tetraphenylborate · Phosphotungstic acid and conductimetry

## 1 Introduction

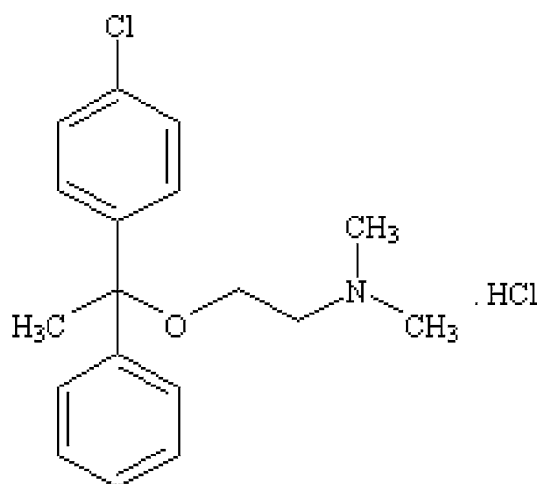
Chlorphenoxamine Hydrochloride is a fast acting anti-allergic agent with antipruritic properties and pleasantly cooling and sedative effect. Chemically, it is 2-[1-(4-chlorophenyl)-1-phenylethoxy]-*N,N*-dimethylethanamine hydrochloride. (Molecular formula  $C_{18}H_{22}ClNO \cdot HCl$  and molecular weight 340.29) [1].

Several methods have been reported in the literature for the determination of Ch-HCl including spectrophotometric methods [2–8], potentiometric method using NIO Metrohm electrode [9], thin layer chromatography [10, 11], plastic membrane ion selective electrode based on Tetraakis (4-chlorophenyl)borate [12], indirectly via its complexation with metal ions using Atomic Absorption Spectrometry [13], polarography [14] and differential pulse voltammetry [15].

In the present work, new selective plastic membranes electrodes for Chlorphenoxamine ion (Ch) of both conventional and coated wire type have been constructed; they are based on the incorporation of Ch-TPB or Ch-PTA ion exchangers in polyvinyl chloride (PVC) membrane plasticized with a proper plasticizer (dioctyl phthalate (DOP) or dibutyl phthalate (DBP)). The electrodes were fully characterized under batch conditions, and used for the determination of the drugs in pure solutions and in their pharmaceutical preparations by applying the standard additions and direct potentiometric titration methods in batch conditions and peak heights comparison in FIA conditions.

The conductimetric measurements were also applied to throw more light on the solubility and molar ratio of the used ion-exchangers and for the drugs determination in their pure state or pharmaceutical formulations.

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Chlorphenoxamine Hydrochloride

## 2 Experimental

### 2.1 Reagent and solutions

All reagents used were chemically pure grade. Bi-distilled water was used throughout all experiments. Pure grade Ch-HCl and its pharmaceutical preparations (Allergex and Allergex caffeine 20 mg/capsule) were provided by EPI-CO, Egypt. Poly (vinyl chloride) (PVC) of high molecular weight (Aldrich, England), dioctyl phthalate (DOP), dibutyl phthalate (DBP), nitrobenzene (NB), Paraffin oil (Fluka, Germany), tetrahydrofuran (THF) (Aldrich, England), sodium tetraphenylborate (NaTPB) and phosphotungstic acid (PTA) (Fluka, Germany) were used. During the FIA measurements the carrier and reagent solutions were degassed by mean of vacuum suction. Stock solutions  $5.0 \times 10^{-2} \text{ mol L}^{-1}$  of Ch-HCl, TPB and PTA were prepared by dissolving the accurately weighed amounts in water and completed to the mark in a 50 mL volumetric flask. For tablet solution, 10 tablets of the pharmaceutical preparation were weighed, finely grounded and amount equivalent to the calculated weight of pharmaceutical preparations to produce a  $1.0 \times 10^{-2} \text{ mol L}^{-1}$  solution was weighed and dissolved in bi-distilled water then filtered in 50 mL measuring flask and completed to the mark. Lower concentration solutions were prepared by appropriate dilutions.

### 2.2 Apparatuses

The potentiometric measurements in the batch mode were carried out with multimeter (Sanwa, Japan). A Techne circulator thermostat Model C-100 (UK) was used to control the temperature of the test solution. Saturated

calomel electrode (SCE) was used as external reference electrode.

The flow injection set-up was composed of four channel peristaltic pump (ISM 827) (Ismatec, Zurich, Switzerland) and an injection valve (model 5020) with exchangeable sample loop from Rheodyne (Cotati, CA, USA). The electrode was connected to a WTW pMX 2000 microprocessor pH/ion meter and interfaced to a Model BD111 strip chart recorder from Kipp and Zonn (Delft, The Netherlands). The flow injection measurements were carried out in a two line system [16, 17] where the sample was injected into a carrier stream, which then merged with another stream; the same tubing size was used in both lines to offer the same flow rate. A wall-jet cell, providing a low dead volume, fast response, good wash conditions and compatibility with electrodes of different shape and size, was used in flow measurements, where a Perspex cup with axially positioned inlet polypropylene tubing was mounted at the sensing surface of the electrode body. The optimized distance between the nozzle and the sensing surface of the electrode was 3 mm; this provides the minimum thickness of the diffusion layer and consequently a fast response [18]. The ion selective electrode (ISE) with flow cup, reference electrode (SCE) and the outlet tubes were placed in a beaker, where the level of solution was kept 1 cm above the electrode surface.

For conductimetric determination a Jenway conductivity meter model 4510 was used for conductance measurements, the bridge is connected with a temperature sensor for temperature measurements and the cell constant  $k_{\text{cell}} = 1.0$ .

### 2.3 Preparation of the ion exchanger

Chlorphenoxaminum tetraphenylborate (Ch-TPB) ion exchanger was prepared by mixing 100 mL ( $1.0 \times 10^{-2} \text{ mol L}^{-1}$ ) of NaTPB with 100 mL ( $1.0 \times 10^{-2} \text{ mol L}^{-1}$ ) of Ch-HCl while the chlorphenoxaminum phosphotungstate (Ch-PTA) ion exchanger was prepared by mixing 100 mL ( $1.0 \times 10^{-2} \text{ mol L}^{-1}$ ) of phosphotungstic acid with 300 mL ( $1.0 \times 10^{-2} \text{ mol L}^{-1}$ ) of Ch-HCl.

The resulting white precipitates of both Ch-TPB and Ch-PTA were left in contact with their mother liquors overnight to assure complete digestion. The precipitates were then filtered, washed by double distilled water until chloride ion free (as tested by acidic solution of  $\text{AgNO}_3$ ) and dried at room temperature for at least 48 h. The product was subjected to elemental analysis for C, H, and N in the Micro analytical Center of Cairo University-Egypt. The results showed a good agreement with the calculated values for a 1:1 and 1:3 ion exchangers for both Ch-TPB and Ch-PTA, respectively.

#### 2.4 Preparation of conventional and coated type electrodes

Membranes of different composition were prepared by dissolving the required amounts of PVC, plasticizer (DOP, DBP, Nitrobenzen or paraffin oil) and ion exchanger(s) of total weight 0.4 g in about 10 mL tetrahydrofuran, the solution mixture was poured into a 7.5 cm Petri-dish and left to dry in air (not less than 24 h), The conventional electrode was constructed as previously described [19]. A 12 mm diameter disk was cut out from the membrane and glued to the polished end of a PVC plastic cap attached to a glass tube. The electrode body was filled with a solution that is  $1.0 \times 10^{-1}$  mol L<sup>-1</sup> in NaCl and  $1.0 \times 10^{-3}$ ,  $1.0 \times 10^{-4}$  or  $5 \times 10^{-4}$  mol L<sup>-1</sup> in Ch-HCl. A Ag/AgCl wire was immersed in the internal solution of the electrode to act as internal reference.

The coated graphite or copper type electrodes were prepared using graphite or copper rods that are 5 cm length and 4 mm diameter. One of the two ends of the rod was used for connection while the other, about 1 cm length, was dipped in a solution of the same optimum membrane composition used for the conventional type and left to dry in air. The process was repeated several times till a layer of the proper thickness was formed covering the terminal of the rod. Soaking for half an hour in Ch-HCl solution of the same concentration of the filling solution was required to precondition the conventional type electrodes, while the coated graphite and copper types can be used without preconditioning.

#### 2.5 Construction of the calibration graphs

For batch measurements, suitable increments of standard drug solutions were added to 50 mL bi-distilled water to cover the concentration range  $1.0 \times 10^{-6}$ – $5.0 \times 10^{-2}$  mol L<sup>-1</sup>. The sensor and the reference electrodes were immersed in the solution and the e.m.f. value was recorded at  $25 \pm 1$  °C, after each addition. The mV readings were plotted versus the negative logarithmic values of the drug concentration (pC).

For FIA measurements, a series of freshly prepared solutions of the drug covering the same concentration range used in batch measurements was injected to the flow stream and the corresponding peak heights were recorded and used to draw the calibration graphs.

#### 2.6 Potentiometric determination of Ch-HCl

Ch-HCl was determined potentiometrically using the investigated electrodes under batch conditions by applying the standard addition [20] and potentiometric titration

[21] methods. In the standard addition method known volumes of standard drug solution were added to 50 mL water containing different amounts of pure compound or the pharmaceutical preparations (allergex and allergex caffeine tablets). The change in mV reading was recorded for each increment and used to calculate the concentration of the drug in sample solution using the following equation:

$$C_x = C_s(V_s/(V_x + V_s))[10^{n(\Delta E/S)} - (V_x/(V_x + V_s))]^{-1}$$

where  $C_x$  and  $V_x$  are the concentration and the volume of the unknown solution respectively,  $C_s$  and  $V_s$  are the concentration and the volume of the standard solution, respectively,  $S$  is the slope of the calibration graph and  $\Delta E$  is the change in millivolt due to the addition of the standard solution.

In potentiometric titration different weights of the investigated drug were transferred into 100 mL cell and diluted to 50 mL by distilled water. The resulting solutions were then titrated against  $1 \times 10^{-2}$  mol L<sup>-1</sup> NaTPB or  $5 \times 10^{-3}$  mol L<sup>-1</sup> PTA according to the corresponding ion-exchanger used in constructing the electrode. The relation between the volume added and the mV reading were graphically constructed and the end point was determined by the conventional S-shaped curves. The differential graph of the titration curves have also been constructed whenever it needed to obtain well defined and sharp end points using the computer program Origin lab.

Under FIA conditions, a series of solutions of different concentrations was prepared from allergex and allergex caffeine (20 mg/tablet) or unknown pure solution and the peak heights were measured using flow rate 9.7 mL min<sup>-1</sup> and then compared with those obtained by injecting the standard series solutions under the same conditions and the recovery could be calculated as the ratio between the peak height of a sample and that of its corresponding standard concentration [21].

#### 2.7 Conductimetric determination of the investigated drug and the solubility products of the ion-exchangers

Chlorphenoxamine Hydrochloride has been determined conductimetrically by taking different volumes of  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> stock solution of pure drug (Ch-HCl) or its pharmaceutical preparations, the taken volumes were transferred to a 50 mL volumetric flask and made to the mark with bi-distilled water. The contents of the volumetric flask were transferred to a beaker and the

conductivity cell was immersed, then  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> NaTPB or PTA solution was added from micro burette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading, taken after 1–2 min, after each addition was corrected for dilution [22] by mean of the following equation, assuming that conductivity is a linear function of dilution:

$$\Omega_{\text{corr}} = \Omega_{\text{obs}}[(V_1 + V_2)/V_1]$$

where  $\Omega$  is the electrolytic conductivity,  $V_1$  is the initial volume and  $V_2$  is the volume of the added reagent (corr., corrected; obs., observed). A graph of corrected conductivity versus the volume of titrant added was constructed and the end point was determined graphically at the intersection of two lines.

To determine the drug–titrant ratio, 2 or 6 mL of  $5 \times 10^{-3}$  mol L<sup>-1</sup> Ch-HCl completed to the required volume with bi-distilled water was titrated with  $5 \times 10^{-3}$  mol L<sup>-1</sup> of NaTPB and PTA, respectively and the conductance was measured after each addition with thorough stirring.

For determining the solubility product a series of solutions of different concentrations ( $C = 1.0 \times 10^{-5}$  to  $5.0 \times 10^{-3}$  mol L<sup>-1</sup>) was prepared for each of Ch-HCl, PTA and Na-TPB. The measured conductivities of these solutions at 25 °C were used to calculate the specific conductivities ( $K$ ), corrected for the effects of the solvent and dilution, then the equivalent conductivities ( $\lambda$ ) of the solutions, ( $\lambda = 1000 K/C$ ) were obtained. Straight-line plots of  $\lambda$  versus ( $C^{1/2}$ ) were constructed and the equivalent conductance at infinite dilution ( $\lambda_0$ ) values was determined for Ch-HCl ( $\lambda_{0 \text{ Ch-HCl}}$ ), PTA ( $\lambda_{0 \text{ PTA}}$ ) and Na-TPB ( $\lambda_{0 \text{ Na-TPB}}$ ) from the intercept of respective lines with the  $\lambda$ -axis. The activity coefficients of the ions employed were taken as unity because all solutions were sufficiently dilute and  $\lambda_{0 \text{ Ch-TPB}}$  and  $\lambda_{0 \text{ Ch-PTA}}$  were calculated from Kohlrausch's law of independent migration of ions [23]. The solubility ( $S$ ) and solubility product ( $K_{\text{sp}}$ ) of the ion pair were obtained applying the following equations:

$$S = K_s \times 1000 / (\lambda_{0 \text{ Ion-exchanger}})$$

and

$$K_{\text{sp}} = S^2 \quad \text{for } 1 : 1 \text{ Ch-TPB ion pair}$$

$$K_{\text{sp}} = 27S^4 \quad \text{for } 3 : 1 \text{ Ch-PTA ion associate}$$

where  $K_s$  is the specific conductivity of a saturated solution of the ion exchanger determined at 25 °C and corrected for the effect of the solvent. This was done by stirring suspensions of the solid precipitates in distilled water for 3 h and measuring the conductivities.

### 3 Results and discussions

#### 3.1 Optimization of the ISEs response in batch conditions

##### 3.1.1 Effect of membrane composition and plasticizer

Several membrane compositions were investigated in which the content of the ion exchanger ranged from 3 to 10% of Ch-PTA and Ch-TPB. For each composition, the electrodes were repeatedly prepared four times. The preparation process was highly reproducible, as revealed from the low standard deviation SD values of the obtained slope for calibration graphs of the prepared membranes (SD average 1.30). The best performances were obtained by using membrane compositions containing 3.0% Ch-TPB, 48.5% plasticizer and 48.5% PVC for Ch-TPB electrodes and 7.0% Ch-PTA, 46.5% plasticizer and 46.5% PVC for Ch-PTA electrodes. Plasticizer plays a vital role in the sensor performance, as it is responsible for the ion-pair solvation and distribution in the membrane, thus controlling the detection limit [24], affecting the selectivity and sensitivity [25, 26] and give the membrane the proper elasticity and strength. Therefore the effect of four different plasticizers (DOP, DBP, nitrobenzene and Paraffin oil) on the performance characteristics of the prepared electrodes has been investigated. It was found that the membranes prepared using paraffin oil were too rigid to be attached to the plastic cape of the electrodes and those prepared using nitrobenzene as plasticizer have weak response to the concentration change where the slope of their calibration graphs never exceed 38 mV/conc. decade. It seems that DOP or DBP, as a low polarity solvent mediator, provides more appropriate conditions for incorporation of the highly lipophilic Ch<sup>+</sup> ions into the membrane, therefore DOP or DBP has been used throughout the present investigation.

It was found that DOP is the proper plasticizer for Ch-PTA membrane, where the slope of its calibration graph was 55.80 mV/conc. decade within the concentration range  $2.0 \times 10^{-6}$  to  $5.0 \times 10^{-2}$  mol L<sup>-1</sup> and DBP is the proper one for Ch-TPB membrane where the slope of its calibration graph was 55.65 mV/conc. decade within the concentration range  $4.0 \times 10^{-6}$  to  $1.0 \times 10^{-2}$  mol L<sup>-1</sup>. The optimum membrane compositions were also used for the preparation of coated wire electrodes where the slope of their calibration graphs was 53.00, 54.10 and 62.50 mV/conc. decade within the concentration ranges  $4.0 \times 10^{-6}$ – $5.0 \times 10^{-2}$ ,  $2.0 \times 10^{-6}$ – $1.0 \times 10^{-2}$  and  $1.2 \times 10^{-5}$ – $1.0 \times 10^{-2}$  mol L<sup>-1</sup> for Ch-TPB graphite, Ch-TPB copper and Ch-PTA graphite electrodes, respectively. Ch-PTA copper electrode could not be constructed since during its drying a green color is formed on the copper wire and

imparts the membrane a green color and the potential reading of the constructed electrode was fluctuated and did not show Nernstian behavior.

### 3.1.2 Effect of filling solution

Varying the composition of internal reference solution could considerably improve the linear range and limit of detection [27, 28], therefore the response of the electrode in relation to the variation of internal solution was investigated using the optimum membrane composition. Three different concentrations of Ch-HCl ( $1.0 \times 10^{-3}$ ,  $5.0 \times 10^{-4}$  and  $1.0 \times 10^{-4}$  mol L<sup>-1</sup>) with  $1 \times 10^{-1}$  mol L<sup>-1</sup> NaCl in filling solution were investigated. It was found that the Ch-TPB and Ch-PTA electrodes containing  $1.0 \times 10^{-4}$  mol L<sup>-1</sup> of Ch-HCl were nearly Nernstian with stable reading and smaller response time (15 s) within the concentration ranges  $4.0 \times 10^{-6}$ – $1.0 \times 10^{-2}$  and  $2.0 \times 10^{-6}$ – $5.0 \times 10^{-2}$  mol L<sup>-1</sup> for Ch-TPB and Ch-PTA electrodes, respectively.

### 3.1.3 Effect of soaking

For these study the constructed electrodes were soaked in a solution ( $1.0 \times 10^{-4}$  mol L<sup>-1</sup>) of the respective drug at different intervals and the effect of soaking on the slope of their calibration graph, usable concentration range were studied for each electrode independently. The soaking process firstly activates the surface of the freshly prepared electrode to form an infinitesimal thin gel layer at the inter-junction boundary separating the membrane from the test solution; however the continuous soaking affects negatively the response of the electrode due to the leaching of the active ingredients (ion-exchanger and plasticizer) to the bathing solution [29]. It was found that the Ch-TPB conventional type electrodes worked in nearly Nernstian behavior in the first 12 days then the slope decreased gradually to reach 50 mV/conc. decade after about 22 days. The Ch-PTA electrode showed longer life time where the electrode worked in nearly Nernstian behavior for about 22 then the slope decreased gradually to reach 51.7 mV/conc. decades after 37 days. It was noted that, the electrodes which had been kept dry in closed vessel and stored in a refrigerator showed nearly constant slope values and response properties for several months if they were preconditioned before using by soaking in  $1.0 \times 10^{-4}$  mol L<sup>-1</sup> Ch-HCl for 1 h. It was found that the life spans of the coated type electrodes are less than those of conventional type which may be attributed to the poor mechanical adhesion of the PVC-based sensitive layer to the conductive bed surface and insufficient electrochemical stability [30]. However, Some of the studied electrodes

showed reasonable life span which indicated by their near-Nernstian behavior and wide concentration linearity range for 5 days or more, Ch-TPB/graphite (6 days), Ch-PTA/graphite (40 days), Ch-TPB/copper (10 days), if they were kept in dry vessel at room temperature and presoaked for half hour before use.

## 3.2 Optimization of the ISEs response in FIA conditions

To evaluate the working characteristics of the constructed electrodes, and to make the developed FIA system suitable for the determination of the studied drugs in different samples, several parameters that controlling the system should be optimized, which include, dispersion coefficient, injection volume, flow rate and carrier composition.

### 3.2.1 Effect of injection volume

Different sample loops of different volumes range from 20.0 to 500.0  $\mu$ L were connected to the flow injection system to select the most appropriate one for the measurements. In general the higher the sample volume, the higher are the peak heights but with a longer time to reach the steady state, base line and greater consumption of sample. A sample volume of 150  $\mu$ L and 75  $\mu$ L was used through out this work for Ch-PTA and Ch-TPB electrodes, respectively, giving about 96% of the maximum peak height obtained by a 500  $\mu$ L loop but with a shorter time to reach the base line and less reagent consumption [31].

### 3.2.2 Effect of flow rate

The dependence of the peak height and time to reach the base line on the flow rate were studied. The response of the electrode to a solution that is  $5 \times 10^{-3}$  mol L<sup>-1</sup> was studied at different flow rates (4.15, 5.35, 7.50, 9.70, 12.50, 17.85, 23.25, 25.00, 27.00 and 30.00 mL min<sup>-1</sup>). It was found that with a constant injection volume, the residence time of the sample was inversely proportional to the flow rate and the recovery time increased linearly with residence time of the sample at the active membrane surface [32]. It was found also that as the flow rate increased, the peaks become sharper until a flow rate of 7.5 and 9.5 mL min<sup>-1</sup> was reached for Ch-TPB and Ch-PTA electrodes, respectively, above this values the peak heights were nearly the same over that a noise was observed in the base line at higher flow rates, for these reasons flow rates of 7.5 and 9.70 mL min<sup>-1</sup> were chosen for further investigations for



Ch-TPB and Ch-PTA electrodes, respectively, where about 99% of the maximum peak height is achieved with stable base line, short time to reach the base line and less consumption of the carrier.

### 3.2.3 Carrier composition

The base line attainment for the studied electrodes takes a very low short time by using bi-distilled water as a carrier stream. The use of other carrier solutions such as buffer or ionic strength adjuster such as potassium chloride in the second channel of the flow system did not affect the stabilization time, i.e. the time required to attain the base line, but only led to a decrease in the peak heights and higher consumption of reagents, therefore bi-distilled water was used as a carrier in both channels in the system through out the present work.

Under the aforementioned optimum conditions of injection volumes and flow rates the dispersion coefficients were calculated as the ratio between the peak height obtained at steady state conditions (where the sample act as carrier stream) and at the state of maximum peak height, maximum dispersion (where the sample is injected in the carrier stream) [33]. The dispersion coefficients were found to be 1.24 and 1.27 for Ch-TPB and Ch-PTA electrodes, respectively, these values reflect the limited dispersion of the sample that provide optimum sensitivity and fast response of the electrodes [34].

### 3.2.4 Electrode response under optimum FIA conditions

In potentiometric measurements using FIA, the electrode potential depends on the activity of the main ion sensed and this dependence is semi-logarithmic over a wide analyte activity range which is the main advantage of the device; however, the main unfavorable feature of this method is the slow response of electrode potential to concentration change and that is the reason for the super-Nernstian sensitivities obtained in FIA measurements using the investigated electrodes at different flow rates [35].

An increase in the slope of the calibration plots was observed compared with batch measurements, where potential is measured under conditions very close to the equilibrium at the membrane-solution interface [36]. It was found that the slope of the calibration graphs under FIA conditions ranged from 60.00 to 71.14 compared with 55.80 mV/conc. decade under batch condition for Ch-PTA electrode and from 56.0 to 67.10 under FIA conditions compared with 55.65 mV/conc. decade under batch condition for Ch-TPB electrode within the usable concentration range  $1.0 \times 10^{-5}$ – $5.0 \times 10^{-2}$  mol L<sup>-1</sup> for Ch-TPB and Ch-PTA electrodes. Figure 1a and b represent the

recordings obtained by the studied electrodes at optimum FIA conditions.

### 3.3 Effect of the temperature of the test solution on the electrodes response

It is very important to study the effect of temperature on the performance characteristics of the plastic membrane electrode because many potentiometric measurements concerning biological media and fluids are carried out at different temperatures. For this purpose the calibration graphs of optimum composition were constructed at different test solution temperatures covering the range 25–70 °C and the isothermal coefficient ( $dE^{\circ}/dt$ ) was calculated as the slope of the straight line obtained by plotting  $E_{\text{elec}}^{\circ}$  versus  $(t - 25)$ , according to Antropov's equation [37]:

$$E_{\text{elec}}^{\circ} = E_{(25)}^{\circ} + (dE^{\circ}/dt)(t - 25)$$

where  $E_{\text{elec}}^{\circ}$  is the standard electrode potential with respect to the normal hydrogen electrode at different temperatures which obtained from the calibration graphs as the intercepts at pCh = 0 (after subtracting the values of the standard electrode potential of the calomel electrode at this temperatures),  $t$  is the temperature of the test solution in °C and  $E_{(25)}^{\circ}$  is the standard electrode potential at 25 °C.

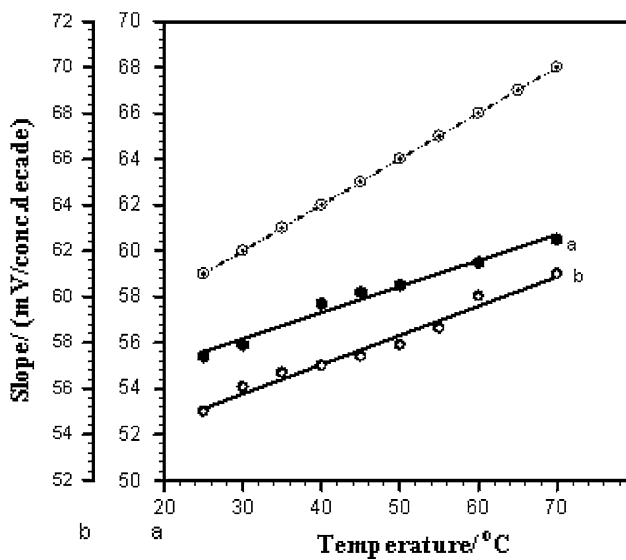
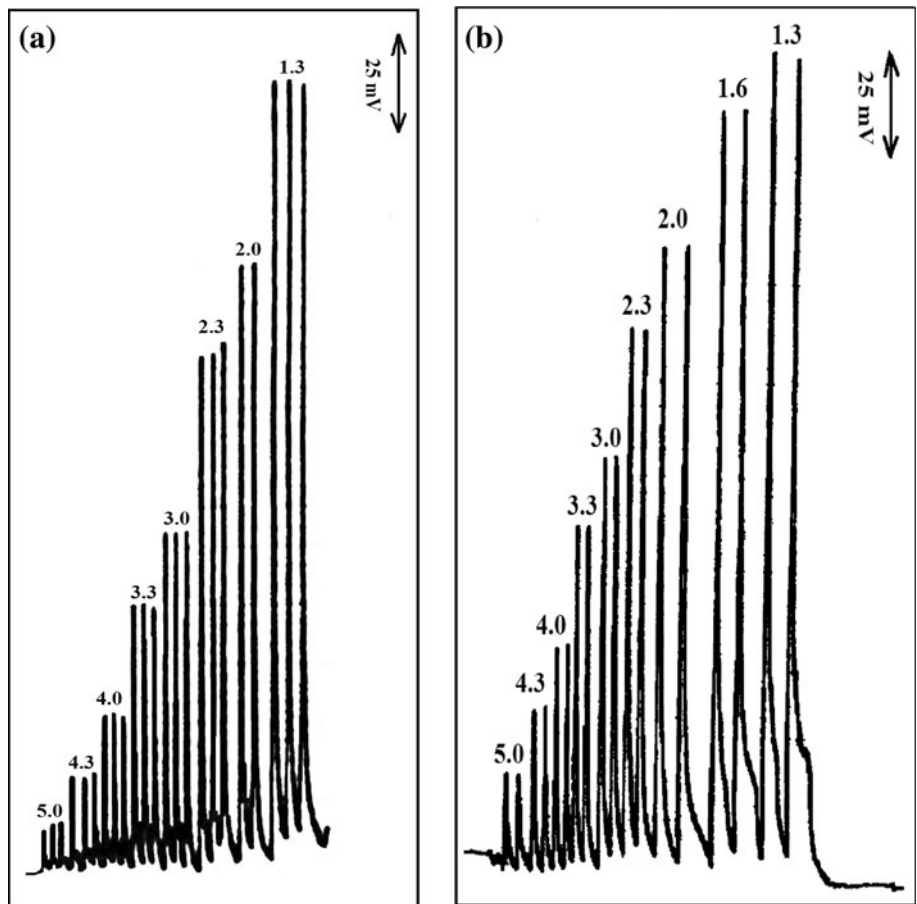
It was found that, the slope of the calibration graphs of the constructed electrodes is stable up to 70 °C with isothermal coefficient 1.80 and 1.48 mV/°C for Ch-TPB and Ch-PTA electrodes, respectively. These low isothermal temperature coefficients values reveal the successful applicability of the electrode over a wide temperature range. Figure 2 represents the variation of the slope of the calibration graph with the temperature of the test solution.

### 3.4 Effect of pH of the test solution on the electrodes response

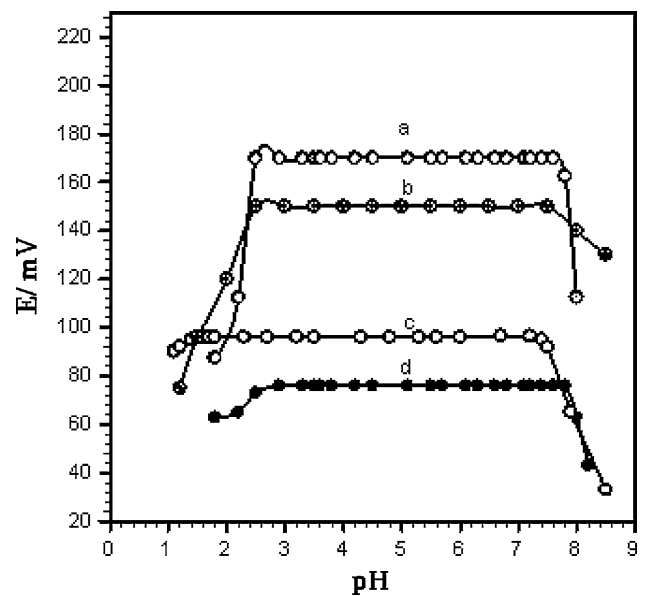
The variation of potential with changes of pH of the test solution ( $5 \times 10^{-2}$ ,  $1 \times 10^{-3}$  and  $5 \times 10^{-4}$  mol L<sup>-1</sup>) was recorded. The pH of the solution was varied over the range of 1–8.3. The mV readings were plotted against the pH values for the different drug concentration corresponding to each electrode, Fig. 3.

In FIA, a series of  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> Ch-HCl solutions of different pH values ranging from 1.0 to 8.3 was injected in the flow stream and the peak heights, representing variation of potential response with pH were measured, solutions of higher pH values can't be prepared due to the precipitation of chlorphenoxamine as base. It was found that Ch-TPB and Ch-PTA electrodes do not respond to pH changes in the range 2.5–7.8 for Ch-TPB and Ch-PTA electrodes under batch and FIA conditions.

**Fig. 1** The FIA recordings obtained for different concentrations of Ch-HCl using **a** Ch-TPB and **b** Ch-PTA electrodes under optimum FIA conditions. The values above the peaks are for  $-\log [\text{Ch}]$



**Fig. 2** Variation of the slope of the calibration graphs with the test solution temperature (*a*) Ch-TPB and (*b*) Ch-PTA, the dotted line represents the theoretical values of the slope



**Fig. 3** Effect of pH of  $5.0 \times 10^{-3} \text{ mol L}^{-1}$  Ch-HCl on the potential response of (*a*) Ch-TPB and (*b*) Ch-PTA conventional electrodes under FIA conditions, (*c*) Ch-PTA and (*d*) Ch-TPB conventional electrodes under batch conditions

Ch-PTA electrode shows a relatively wider range under batch conditions where it does not respond to the pH change in the range 1.8–7.8, Fig. 3. At pH values lower than previously mentioned ranges the potential and peak height decreased gradually which, may be attributed to either the interference of the hydronium ion or the penetration of chloride ions into the membrane network at the test solution-membrane interface while the decrease in potential and peak height at pH higher than 8.0 may be attributed to deprotonation of the investigated drug, which lead to a consequent decrease in its concentration [38].

### 3.5 Effect of the ionic strength of the test solution on the electrode response

Using ionic strength adjustment solution helps not only in the adjustment of the ionic strength but also, the activity coefficient, and the activity of the electroactive species present in the test solution, this provide accurate determination of the concentration of a given ion potentiometrically, regardless of its original environment. For this purpose, the performance characteristics for Ch-TPB and Ch-PTA electrodes were studied as a function of variation of potassium chloride concentration as ionic strength adjustor. It was found that the slope of the calibration graph for Ch-PTA electrode decreases with the increase of the KCl concentration, while the slope of Ch-TPB electrodes slightly increases by increasing the concentration of KCl till reach its maximum value of 56.71 mV/conc. decade in  $1.0 \times 10^{-3}$  mol L<sup>-1</sup> of KCl then decreased in higher concentrations of KCl reaching 55.2 mV/concentration decade in  $1.0 \times 10^{-2}$  mol L<sup>-1</sup>. In all cases the decrease in the slope of the calibration graphs depends on the degree of interference of the K<sup>+</sup> with the investigated drugs.

### 3.6 Selectivity of the electrodes

Selectivity is the ability of the electrode to respond primarily to only one species in the presence of others. The selectivity coefficient  $K_{drug,j}^{pot}$  is the prime source of information concerning the effect of interferences on the electrode response. The response of the electrodes towards different substances and ionic species such as inorganic cations, amino acids, sugars and other antihistamine drugs (phenylpropranolamine hydrochloride and diphenylpyraline hydrochloride) that might be co-existing with the analyte as excipients, was checked under both of batch and FIA conditions using separate and mixed methods [39, 40] and the values of selectivity coefficients, shown in Table 1, were used to evaluate their degree of interference. The apparent selectivity coefficient  $K_{Ch,j}^{pot}$  measured under transient flow injection conditions might differ significantly from that measured under

batch conditions [41, 42]. This is interpreted by the difference in the time of interaction of interferent with the membrane surface in comparison with the main sensed ion, and also the interference process is highly dependent on the rate of diffusion and the exchange reaction of the interfering ion [42]. The determined selectivity coefficients of the Ch-TPB and Ch-PTA electrodes, Table 1, reflect a very high selectivity of the investigated electrodes for chlorphenoxamine cations under both FIA and batch conditions. Also the results obtained in case of amino acids and sugars under FIA are in a good agreement with those under batch conditions, where it was found that the Ch-PTA electrode could be used safely without interference in presence of glucose, maltose, sucrose, lactose, fructose, urea and glycine up to 950, 850, 3600, 1200, 1050, 330 and 2040 folds of chlorphenoxamine, respectively. On the other hand the Ch-PTA electrode could be used safely without interference in the presence of glucose, maltose, sucrose, lactose, fructose, urea and glycine up to 1120, 335, 1820, 1450, 1260, 185, 421 folds of

**Table 1** Selectivity coefficients for the Ch-PTA and Ch-TPB electrodes under Batch and FIA conditions

Interferent	$-\log K_{Ch,j}^{pot}$					
	Ch-TPB			Ch-PTA		
	Batch		FIA	Batch		FIA
	SSM <sup>a</sup>	MSM <sup>b</sup>		SSM <sup>a</sup>	MSM <sup>b</sup>	
Ag <sup>+</sup> <sup>c</sup>	2.76	–	4.25	3.53	–	3.69
Cu <sup>2+</sup>	4.41	4.52	3.52	4.13	4.30	2.90
NH <sub>4</sub> <sup>+</sup>	3.70	4.30	3.32	3.70	4.20	3.58
K <sup>+</sup>	4.45	4.87	2.70	3.40	3.20	2.40
Hg <sup>2+</sup>	4.70	4.66	3.60	4.70	4.45	3.43
Al <sup>3+</sup>	5.36	5.00	3.90	4.85	4.78	3.45
Na <sup>+</sup>	3.73	3.50	2.60	3.70	3.50	2.20
Fe <sup>3+</sup>	4.70	4.21	4.95	4.05	4.34	4.34
Ba <sup>2+</sup>	4.50	4.30	3.13	4.96	4.35	2.50
Ni <sup>2+</sup>	4.70	4.50	3.10	5.23	4.69	2.60
Co <sup>2+</sup>	4.20	4.50	3.55	4.60	4.62	3.30
Mn <sup>2+</sup>	4.61	4.35	3.55	5.12	4.90	3.04
Sr <sup>2+</sup>	4.20	4.39	3.20	4.71	4.40	3.77
Mg <sup>2+</sup>	4.90	4.52	3.53	5.11	4.55	3.00
Ca <sup>2+</sup>	4.45	4.67	3.16	5.23	4.60	2.80
Zn <sup>2+</sup>	4.30	4.56	3.51	5.33	4.90	3.23
Cd <sup>2+</sup>	4.67	4.32	3.13	5.00	4.65	3.23
Ph-HCl	3.40	3.40	2.30	2.90	2.70	2.00
Di-HCl	1.04	1.20	0.80	0.90	1.20	0.51

<sup>a</sup> Separate solution method

<sup>b</sup> Mixed solution method

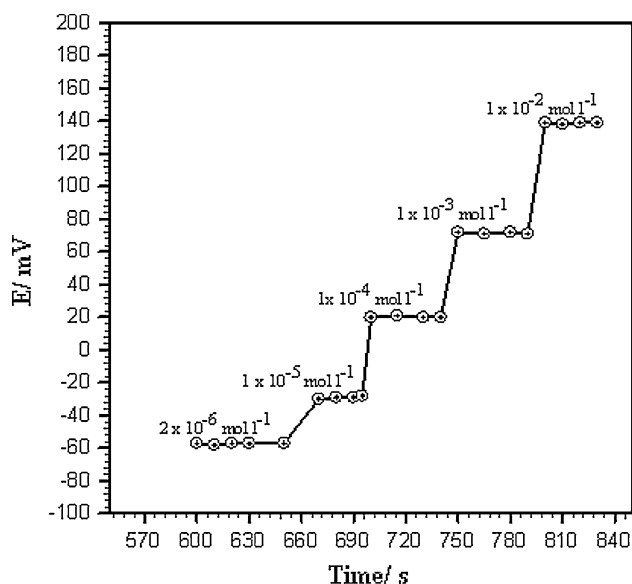
<sup>c</sup> The  $K_{Ch,Ag}^{pot}$  cannot be determined using MSM due to the precipitation of AgCl



chlorphenoxamine, respectively. Also, the electrodes can be used safely in the presence of two antihistaminic drugs, phenylpropranolamine hydrochloride and diphenylpyraline hydrochloride, as shown in Table 1.

### 3.7 Response time

The response time [43] of each electrode was tested by measuring the time required to achieve a steady state potential (within  $\pm 1$  mV) after successive immersion of the electrode in a series of its respective drug solution, each having a 10-fold increase in concentration from  $2.0 \times 10^{-6}$  to  $1.0 \times 10^{-2}$  mol L<sup>-1</sup>. The electrodes yielded steady potentials within 10–25 s. The potential reading stay constant, to within  $\pm 1$  mV, for at least 3 min. The



**Fig. 4** Potential-time plot for the response of Ch-PTA conventional electrode

typical potential plot for the response characteristics of Ch-PTA conventional electrode is shown in Fig. 4.

### 3.8 Solubility product of Ch-PTA and Ch-TPB ion exchangers

The determination of the solubility product of the ion-pair is important since its reciprocal is approximately equal to the formation constant of the ion-pair, which is tightly related to the degree of its hydrophobicity. So, as the hydrophobicity of the ion exchangers increases, the leaching process of them to the aqueous bathing solution decreases and this is the main determining factor in the lifetime of the electrodes membranes. The solubility product of the Ch-TPB and Ch-PTA was determined conductimetrically as described in the experimental part and was found to be  $1.53 \times 10^{-8}$  and  $2.10 \times 10^{-14}$  for Ch-TPB and Ch-PTA ion exchangers, respectively, indicating very low solubility of the ion exchangers ( $1.24 \times 10^{-4}$  and  $9.20 \times 10^{-6}$  mol L<sup>-1</sup> for Ch-TPB and Ch-PTA ion exchanger, respectively). Consequently, the formation constant of the following reactions,  $\text{Ch} + \text{TPB} \rightleftharpoons \text{Ch-TPB}$  and  $3\text{Ch} + \text{PTA} \rightleftharpoons (\text{Ch})_3\text{-PTA}$  are  $6.50 \times 10^7$  and  $4.75 \times 10^{13}$ , revealing that the degree of completeness of the reactions is more than 99.9%. In the above equilibria, the solubility of the undissociated ion exchangers in water (i.e., the intrinsic solubility) was omitted as it provides too small contribution to the total solubility [19].

### 3.9 Analytical application

#### 3.9.1 Determination of Ch-HCl using potentiometric titration

The potentiometric titration of Ch-HCl is based on the decrease of the drug cation concentration by precipitation with PTA and NaTPB, the feasibility of such titration

**Table 2** Result of potentiometric titration of Ch-HCl in pure solution, Allergex and Allergex caffeine tablet using Ch-TPB electrodes and TPB as titrant

Weight taken (mg)	Pure solution						Allergex tablet (20 mg/tablet)						Allergex caffeine tablet (20 mg/tablet)					
	Conventional		Graphite Coated wire		Copper coated wire		Conventional		Graphite Coated wire		Copper coated wire		Conventional		Graphite Coated wire		Copper coated wire	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
5.1	105.66	0.44	106.66	0.8	103.33	0.21	107.5	0.1	95.3	0.42	103.2	0.6	106.66	0.15	95.1	0.09	98.9	0.23
10.2	104.66	0.78	106.67	0.51	101.66	0.09	100	0.34	96.1	0.21	96.13	0.42	106.67	0.67	100.8	0.16	102.9	0.56
15.3	96.42	0.26	106.67	0.43	104.44	0.34	101.66	0.33	100.3	0.45	99.7	0.53	105.55	0.07	100.5	0.99	101.5	0.44
20.4	101.66	0.47	103.33	0.39	105	0.45	102	0.25	95.5	0.89	100.4	0.55	101.66	0.45	99.4	0.11	102	0.22

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

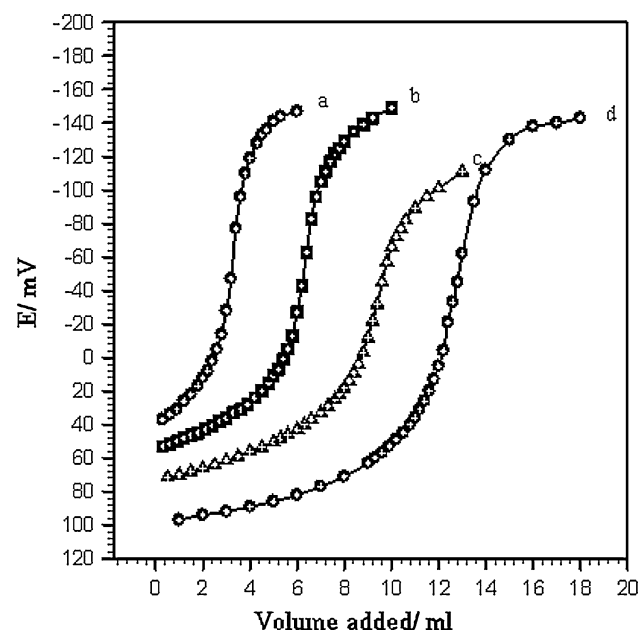
**Table 3** Result of potentiometric titration of Ch-HCl in pure solution, Allergex and Allergex caffeine tablet using Ch-PTA electrodes and PTA as titrant

Weight taken (mg)	Pure solution				Allergex tablet (20 mg/tablet)				Allergex caffeine tablet (20 mg/tablet)			
	Conventional		Graphite coated wire		Conventional		Graphite coated wire		Conventional		Graphite coated wire	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
10.20	105.00	0.26	100.29	0.24	106.47	0.23	100.41	0.56	105.19	0.55	100.49	0.67
15.30	104.26	0.31	104.96	0.44	95.74	0.56	100.78	0.78	97.00	0.12	100.98	0.45
30.60	99.84	0.89	105.33	0.21	101.66	0.50	99.69	0.34	97.51	0.45	100.32	0.27
40.80	101.25	0.14	99.26	0.56	101.25	0.11	101.00	0.23	98.33	0.23	100.36	0.34

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

depends on the degree of completeness of the reaction, since the equilibrium constant ( $K$ ) of precipitation titration is inversely proportional to the solubility product; it is natural that the smaller the solubility product of the formed ion associate the sharper is the end point. The potentiometric titration was used successfully in the determination of Ch-HCl in pure solution and its pharmaceutical preparations (allergex and allergex caffeine tablets).

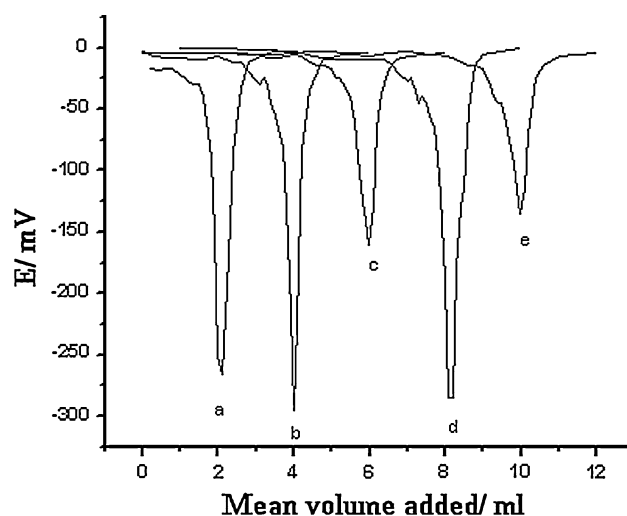
The mean recoveries obtained for pure solution based on Ch-TPB ion pair, Table 2, were 102.63, 105.83 and 103.60% with SD 0.48 and 0.53 and 0.47 for conventional, graphite and copper coated wire electrode, respectively, and those based on Ch-PTA, Table 3, ion associate were 102.02, 102.46% with SD 0.34 and 0.36 for conventional and graphite coated wire electrodes, respectively.



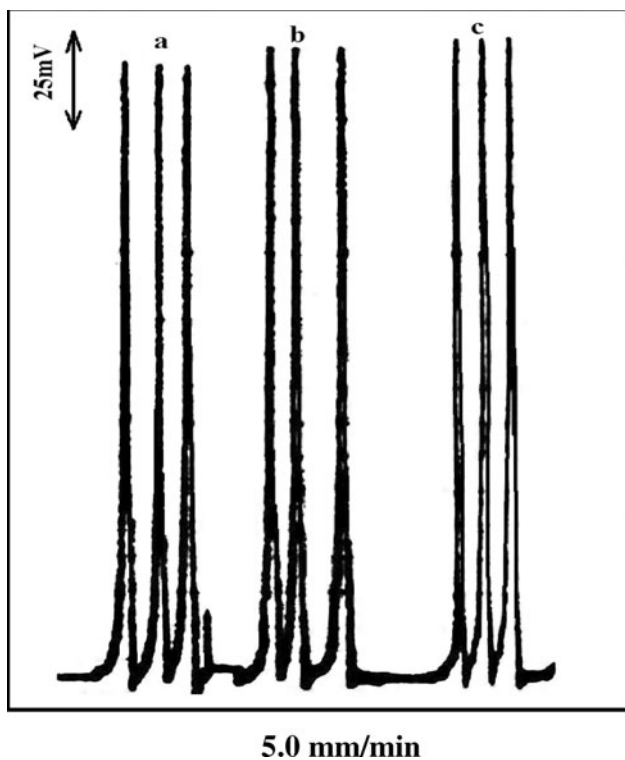
**Fig. 5** Potentiometric titration of (a) 3, (b) 6, (c) 9 and (d) 12 of  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> Ch-HCl using Ch-TPB conventional electrode and  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> NaTPB as titrant

The mean recoveries obtained for the determination of Ch-HCl in allergex tablets, Table 2, based on Ch-TPB ion pair were 102.79, 96.80 and 99.86% with SD 0.26, 0.49 and 0.53 for conventional, graphite and copper coated wire electrodes, respectively, and those based on Ch-PTA, Table 3, ion associate were 101.28 and 100.47% with SD 0.35 and 0.47 for conventional and graphite coated wire electrodes, respectively.

Also, Ch-HCl was determined successfully in Allergex caffeine tablets using potentiometric titration, where the mean recoveries obtained based on Ch-TPB ion pair, Table 2, were 105.13, 98.95 and 101.33% with SD 0.34, 0.33 and 0.36 for conventional, graphite and copper coated wire electrodes, respectively, and those based on Ch-PTA ion associate, Table 3, were 98.86, 100.54% with SD 0.34 and 0.43 for conventional, graphite coated wire electrodes, respectively. Representative Potentiometric curves are shown in Figs. 5 and 6.



**Fig. 6** Differential curves for potentiometric determination of (a) 6, (b) 12, (c) 18, (d) 24 and (e) 30 mL  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> Ch-HCl using Ch-PTA conventional electrode and  $5.0 \times 10^{-3}$  mol L<sup>-1</sup> PTA as titrant



**Fig. 7** Peaks obtained for 15 mg of Ch-HCl in Allergex and allergex caffeine solutions in comparison with standard solution containing the same weight (*a*) Standard solution, (*b*) Allergex tablet and (*c*) Allergex caffeine tablet

### 3.9.2 Determination of Ch-HCl using standard addition method

The standard addition method described in the experimental part, was proved to be successful for the determination of the investigated drugs in their pure solution and in pharmaceutical preparations in batch conditions, using the respective electrodes as sensors.

Different weights of Ch-HCl in pure solution (5.00–20.00 mg) were determined by applying standard

addition method using Ch-TPB and Ch-PTA constructed electrodes and the mean recoveries obtained were 101.21, 100.16 and 100.24% with SD 0.47, 0.25 and 0.20 using Ch-TPB conventional, graphite and copper coated wire electrodes, respectively and those obtained using Ch-PTA electrodes were 99.08 and 102.43% with SD 0.35 and 0.27 using conventional and graphite coated wire electrodes, respectively, Tables 4 and 5.

Solutions of allergex and allergex caffeine contain the same weight range (5.00–20.00 mg) were also prepared and determined using the constructed electrodes by applying the standard addition method, where the mean recoveries obtained using Ch-TPB electrodes for the determination of Ch-HCl in allergex tablets were 99.28, 99.56 and 99.17% with SD 0.59, 0.20 and 0.42 for conventional, graphite and copper coated wire electrodes, respectively, and those obtained using Ch-PTA electrode were 99.40 and 103.33% with SD 0.33 and 0.24 for conventional and graphite coated wire electrodes, respectively, Tables 4 and 5.

The mean recoveries obtained using Ch-TPB electrodes for the determination of Ch-HCl in allergex caffeine tablets were 100.63, 100.20 and 100.57% with SD 0.30, 0.21 and 0.28 for conventional, graphite and copper coated wire electrodes, respectively and those obtained using Ch-PTA were 99.61 and 101.30% with SD 0.42 and 0.35 for conventional and graphite coated wire electrodes, respectively, Tables 4 and 5.

### 3.9.3 Determination of Ch-HCl using peak height comparison in FIA conditions

In FIA measurements the peak height comparison was used for the determination of the studied drugs in their pharmaceutical tablets where the peak heights corresponding to their solutions were measured and compared by those obtained by series of standard drug solutions under the same conditions as shown in Fig. 7. The percentage recovery is

**Table 4** Result of determination of Ch-HCl in pure solution, Allergex and Allergex caffeine tablet by applying the standard addition method using Ch-TPB electrodes

Weight taken (mg)	Pure solution						Allergex tablet (20 mg/tablet)						Allergex caffeine tablet (20 mg/tablet)					
	Conventional		Graphite coated wire		Copper coated wire		Conventional		Graphite coated wire		Copper coated wire		Conventional		Graphite coated wire		Copper coated wire	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
5	101.7	0.2	99.55	0.1	103.15	0.042	103.8	0.34	101.25	0.2	100.1	0.49	102.15	0.54	99.6	0.1	101.4	0.14
10	100.6	0.43	98.58	0.08	99.9	0.11	98.45	0.56	99.35	0.16	97.9	0.53	97.9	0.11	100.7	0.16	98.1	0.22
15	102.15	0.67	101.03	0.47	97.53	0.49	95.6	0.68	99.98	0.3	99.33	0.32	99.13	0.47	100	0.29	100.6	0.23
20	100.4	0.56	102.5	0.33	100.2	0.32	99.25	0.77	97.65	0.12	99.34	0.34	103.34	0.12	100.5	0.26	102.2	0.54

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

**Table 5** Result of determination of Ch-HCl in pure solution, Allergex and Allergex caffeine tablet by applying the standard addition method using Ch-PTA electrodes

Weight taken (mg)	Pure solution				Allergex tablet (20 mg/tablet)				Allergex caffeine tablet (20 mg/tablet)			
	Conventional		Graphite coated wire		Conventional		Graphite coated wire		Conventional		Graphite coated wire	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
5.00	96.60	0.48	103.12	0.14	103.6	0.11	107.20	0.08	98.60	0.50	103.36	0.20
10.00	98.60	0.48	105.70	0.22	97.20	0.08	106.30	0.09	100.40	0.30	104.50	0.30
15.00	101.20	0.20	100.19	0.12	98.40	0.40	99.62	0.44	101.2	0.32	97.70	0.44
20.00	99.90	0.24	100.73	0.61	98.40	0.73	100.2	0.33	98.25	0.56	99.65	0.45

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

**Table 6** Result of determination of Ch-HCl in Allergex and allergex caffeine tablet using Ch-PTA and Ch-TPB conventional electrodes under FIA conditions using bi-distilled water as carrier at flow rate 9.7 mL min<sup>-1</sup>

Weight taken (mg)	Ch-TPB electrode				Ch-PTA electrode			
	Allergex tablet (20 mg/tablet)		Allergex caffeine tablet (20 mg/tablet)		Allergex tablet (20 mg/tablet)		Allergex caffeine tablet (20 mg/tablet)	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
5.00	102.07	0.18	97.58	0.45	102.50	0.38	98.40	0.31
10.00	104.20	0.19	95.53	0.34	104.70	0.45	96.70	0.49
15.00	95.12	0.15	100.00	0.19	95.33	0.21	97.47	0.44
20.00	104.50	0.36	100.00	0.24	101.10	0.32	96.00	0.52
25.00	101.25	0.42	97.08	0.32	101.20	0.22	99.48	0.32
170.00	100.70	0.18	96.00	0.40	102.28	0.36	99.54	0.38

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

obtained as the ratio of the peak heights and thus the concentration could be calculated. The mean recoveries obtained using Ch-TPB electrode were 101.32 and 97.70% with SD 0.25 and 0.32 for Allergex and Allergex caffeine tablet, respectively, and those obtained using Ch-PTA electrode were 101.19 and 97.93% with SD 0.41 and 0.34 for Allergex and Allergex caffeine tablet, respectively, Table 6.

### 3.9.4 Conductimetric determination of Ch-HCl

The conductance measurements are used successfully in quantitative titration systems in which the conductance of

the solution varies before and after the equivalence point. The sudden change in the slope after the end point may be related to the formation of RNHx<sup>+</sup> and OH<sup>-</sup> by hydrolysis. On adding NaTPB and PTA the ion pair formed replaces RNH<sub>x</sub><sup>+</sup> ions by mobile Na<sup>+</sup> and H<sup>+</sup> and the conductivity increases [43]. After the end point, more reagent is added and the conductivity increase more rapidly.

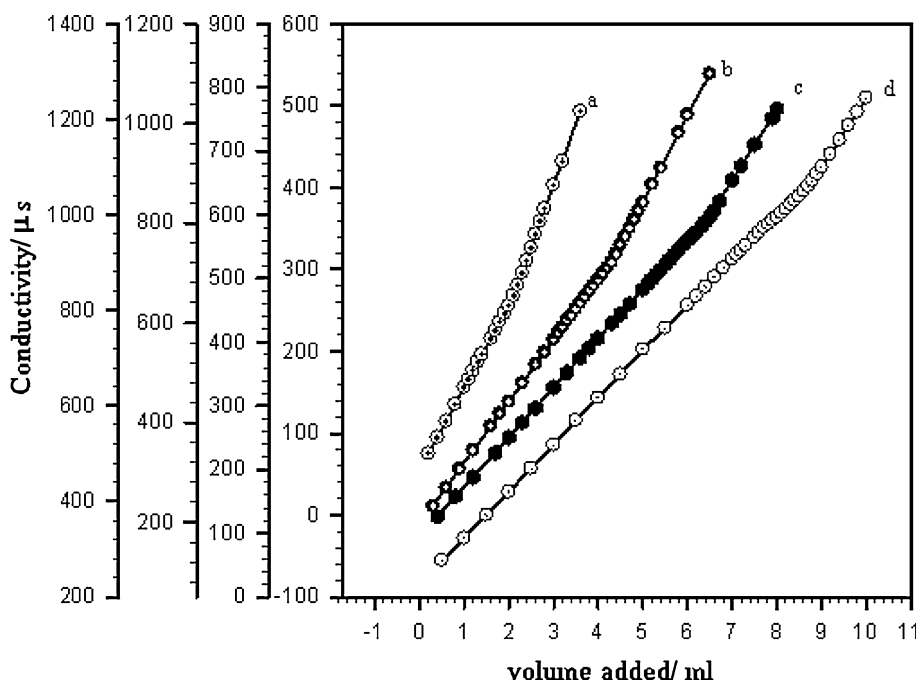
Titration in different media were attempted to obtain the best results, where it was found that aqueous medium is more suitable for obtaining a stable conductimetric reading with less consumption of reagents for the determination of Ch-HCl in raw material and pharmaceutical preparations,

**Table 7** Result of determination of Ch-HCl in raw material, Allergex and Allergex caffeine tablet using conductimetric titration

Weight taken (mg)	PTA titrant						Weight taken (mg)	TPB titrant					
	Raw material		Allergex tablet		Allergex caffeine tablet			Raw material		Allergex tablet		Allergex caffeine tablet	
	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>		R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>	R <sup>a</sup> (%)	SD <sup>b</sup>
10.20	103.75	0.34	96.25	0.67	100.00	0.19	5.10	105.00	0.39	96.20	0.67	95.80	0.39
20.40	103.75	0.87	101.25	0.31	95.00	0.56	10.20	100.83	0.54	97.00	0.09	103.50	0.44
30.60	105.83	0.45	100.00	0.51	98.33	0.24	15.30	102.22	0.81	95.11	0.27	98.00	0.75
40.80	103.75	0.23	97.50	0.12	98.75	0.29	20.40	100.83	0.35	101.20	0.80	104.78	0.87

<sup>a</sup> Recovery, <sup>b</sup> Standard deviation

**Fig. 8** Conductimetric determination of (a) 6, (b) 12, (c) 18 and (d) 24 mL  $5.0 \times 10^{-3} \text{ mol L}^{-1}$  Ch-HCl in raw material using  $5.0 \times 10^{-3} \text{ mol L}^{-1}$  PTA as titrant



**Table 8** Statistical data obtained for Ch-HCl using ISE and conductimetric determination in comparison with spectrophotometric method [4]

Method used in the determination	Linear range (mol L <sup>-1</sup> )	Average recovery ± SD <sup>b</sup>	Average recovery ± SD <sup>b</sup>	Slope of the regression line <sup>a</sup>	Intercept of the regression line	Variance	F-value (3, 4) (6.59) P = 0.05	t-value (DF = 5) (2.60)
Spectrophotometric method:	$5.8 \times 10^{-3}$ – $1.9 \times 10^{-2}$	99.98 ± 0.85	99.98 ± 0.85	–	–	0.72	–	–
Conductimetric determination								
PTA titrant	–	100.34 ± 0.39	100.34 ± 0.39	1.040	–0.005	0.16	4.50	0.08
NaTPB titrant	–	100.04 ± 0.53	100.04 ± 0.53	1.002	0.210	0.28	2.56	0.43
Potentiometric determination								
Ch-PTA conventional electrode	$2.0 \times 10^{-6}$ – $5.0 \times 10^{-2}$	100.03 ± 0.36	100.03 ± 0.36	1.015	–0.230	0.13	5.50	0.07
Ch-PTA Graphite C.W.	$4.0 \times 10^{-6}$ – $5.0 \times 10^{-2}$	101.40 ± 0.40	101.40 ± 0.40	0.988	0.360	0.16	4.46	1.65
Ch-TPB conventional electrode	$4.0 \times 10^{-6}$ – $1.0 \times 10^{-2}$	101.40 ± 0.41	101.40 ± 0.41	1.005	0.075	0.17	4.23	1.60
Ch-TPB Graphite C.W.	$2.0 \times 10^{-6}$ – $1.0 \times 10^{-2}$	100.31 ± 0.45	100.31 ± 0.45	1.037	–0.34	0.21	3.58	0.39
Ch-TPB Cu-C.W.	$1.2 \times 10^{-5}$ – $1.0 \times 10^{-2}$	100.79 ± 0.35	100.79 ± 0.35	0.987	0.130	0.12	5.88	1.02
Flow injection analysis								
Ch-PTA conventional electrode	$1.0 \times 10^{-5}$ – $5.0 \times 10^{-2}$	99.57 ± 0.38	99.57 ± 0.38	1.020	–0.27	0.14	5.1	0.39
Ch-TPB conventional electrode	$1.0 \times 10^{-5}$ – $5.0 \times 10^{-2}$	99.51 ± 0.41	99.51 ± 0.41	1.006	0.098	0.17	4.2	0.80

<sup>a</sup> Regression analysis (found values *versus* taken) ideal values are 1.00 and zero for slope and intercept, respectively

<sup>b</sup> (*n* = 4) for the proposed methods and (*n* = 3) for spectrophotometric method

C.W. Coated wire

where the mean recoveries obtained using NaTPB were 102.22, 97.38 and 100.52 with SD 0.52, 0.46 and 0.61 for raw material, allergex and allergex caffeine, respectively

and those obtained using PTA were 104.27, 98.75 and 98.02 with SD 0.47, 0.40 and 0.32 for raw material, Allergex and Allergex caffeine respectively, Table 7.



Figure 8 shows the corrected conductimetric titration curves of the drug versus PTA from which the end points were determined

Finally, the results were subjected to linear regression analysis (*found values versus taken*), using the computer program sigma plot-2 in order to establish whether the investigated electrodes exhibit any fixed or proportional bias. The slopes and intercepts of the regression lines did not differ significantly from the ideal values, revealing the absence of a systematic error during the measurements within the investigated concentration range.

The *F*- and *t*-tests [45] were performed to compare the average and SD of the results of the proposed methods with those obtained using spectrophotometric method [4]. The results shown in Table 8 indicate that the calculated *F* and *t* values were lower than those tabulated which indicate there is no significant difference or constant error between the two methods at the indicated significant level.

#### 4 Conclusion

In the present work five electrodes of both conventional and coated wire types have been constructed for the determination of chlorphenoxamine hydrochloride in raw material and pharmaceutical preparations with high degree of precision, selectivity and accuracy in comparison with the reference method, within wide concentration, temperature and pH ranges that have been confirmed by recoveries, standard deviations, *F*- and *t*-values. Over that, the coated wire types are simple in construction and easy in store where no filling or soaking solutions are needed. In addition, applying flow injection technique shortened the time needed for the determination when compared with batch technique or previously published methods. Also, the conductimetric titration was used successfully for the determination of the investigated drug which is considered a simple way of application and of low expense. In general the proposed methods are valid for the determination of the investigated drug and can be used as a shelf stability test in drug stores and in quality control and quality assurance during the manufacturing of pharmaceutical preparations.

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