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Original Article

CONDUCTOMETRIC DETERMINATION OF THE ANTIHISTAMINIC DIPHENHYDRAMINE HYDROCHLORIDE USING SILVER NITRATE AS A TITRANT

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ABSTRACT

Objectives: The present study developed and validated a conductometric method for determination of Diphenhydramine HCl (DPH) in its pure form and in a syrup formulation using silver nitrate ($AgNO_3$).

Methods: Conductometric titration method was achieved by using $AgNO_3$. The method is built on the reaction of chloride ions coming from the DPH with $AgNO_3$ yielding silver chloride precipitate. Conductance of the solution is measured as a function of the volume of titrant. The proposed method is linear over the range of 1-10mg.

Results: Statistical analysis of the experimental results indicates that the method is precise and accurate. The accuracy of the method is indicated by the excellent recovery and the precision is supported by the low relative standard deviation (< 0.935). The method was also applied successively to a pharmaceutical syrup formulation. The proposed method provides a high degree of accuracy and precision. Results showed that there is no significant difference between the proposed method and the reported one.

Conclusions: This proposed method is described as an alternative approach to the more complex and expensive previously reported methods for assay of DPH and is highly reproducible as compared to similar reported methods.

Keywords: Conductometry, Preciptimetry, $AgNO_3$, Diphenhydramine HCl (DPH).

INTRODUCTION

Conductometric titration is one of the simplest analytical techniques used in drug analysis. Several titrimetric assay methods can be found in different pharmacopoeias [1]. Conductometric titrations using silver nitrate ($AgNO_3$) as a titrant were used for determination of hydrochloric acid content of ciprofloxacin HCl [2], propafenone HCl and sotalolHCl [3], metformin HCl [4], verapamil HCl [5], propranolol HCl [6], mebeverine HCl [7] and diltiazem HCl [8] where AgCl was precipitated.

DPH (Fig. 1) is a first generation anti histaminic (H1-receptor antagonist) possessing anti allergic, antitussive, antiemetic and sedative properties that is mainly used to treat allergies. It is found in various pharmaceutical preparations [9]. DPH has been found to have a higher efficacy in the treatment of allergies than some second-generation antihistamines such as desloratadine [10]. Several analytical methods have been recorded for determination of DPH in pharmaceutical formulations. Most of these studies focused on titrimetry [11], fluorimetry [12], HPLC [13], HPTLC [14], capillary electrophoresis [15], gas chromatography [16], voltammetry [17] and spectrophotometry [18].

There is no previous study reported about conductometric analysis of DPH. Thus, the aim of this study was to report a new condutometric method that is simple, time-saving and accurate for the determination of DPH as a raw material and in pharmaceutical syrup formulation.

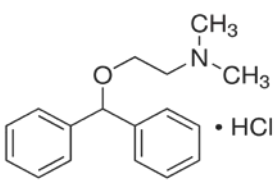

Fig. 1: Chemical structure of Diphenhydramine HCl (DPH)

MATERIALS AND METHODS

Instrumentation

Jenway 470 model portable conductivity/TDS meters was used for measurement of conductance.

Chemicals and reagents

DPH (99.90%) was obtained from Adwia Pharmaceuticals and Chemical Industries (Cairo, Egypt), 5 x 10^{-3} M $AgNO_3$ (Merck, Darmstadt, Germany). DPH 12.5 mg/5 mL in syrup formulation Amydramine-II® (product of Julphar Gulf Pharmaceutical Industries (U. A. E.) was purchased from the Saudi market.

Standard solution

Stock solution 1 mg/mL DPH was prepared by dissolving 100mg of DPH in 100 mL bi-distilled water.

General procedure

Aliquots of the standard solution (1-10mg) were transferred to 50 mL volumetric flasks and made up to the mark with bi-distilled water. The contents of the calibrated flask were transferred quantitatively to a conductometric titration cell.

The conductivity cell was immersed in the sample solution and then the solution was titrated conductometrically against 5 x 10^{-3} M $AgNO_3$. The conductance was measured subsequent to each addition of $AgNO_3$ after stirring for two min. The conductance was corrected for dilution [19] by means of the equation (1), assuming that conductivity is a linear function of dilution.

$$\Omega\text{-}1corrected = \Omega\text{-}1obs\ [v1 + v2/v1] \quad (1)$$

Where Ω-1correct is the corrected electrolytic conductivity, Ω-1obs is the observed electrolytic conductivity, $v1$ is the initial volume and $v2$ is the volume of titrant added ($AgNO_3$).

A graph of corrected conductivity versus the volume of added $AgNO_3$ was constructed and the end-point was determined conductometrically. The amount of the drug under study was calculated according to the equation (2),

$$\text{Amount of drug} = \text{V. M. R.}/N \quad (2)$$

Where V is volume of titrant ($AgNO_3$), M is molecular weight of the drug (291.816), R is the molar concentration of titrant (5 x 10^{-3}M) and N is number of moles of titrant consumed by one mole of drug.

Procedure for the pharmaceutical formulation

Aliquot of DPH syrup was taken into a 50 mL volumetric flasks and the volume was made up to the mark with bi-distilled water. The resulting solution for the analysis was carried out in accordance with the general procedure.

RESULTS AND DISCUSSION

Method development

Conductometric method of analysis was used for the determination of end-points in precipitation titrations. The shape of the titration curves can be easily predicted by summing the ionic conductance of the different species during the course of titration. On using $AgNO_3$ for the determination of DPH, silver chloride is precipitated leading to a straight line during the first segment of the titration curve (Scheme 1). The second segment of this curve corresponds to the excess of $AgNO_3$. Graphs of DPH raw form and DPH syrup formulation with two different concentrations are shown in fig. 2 to fig. 5.

The most favorable conditions for the reaction were chosen after numerous investigations. The effect of some variables on the reaction was studied as described below.

$$\text{DPH HCl} + AgNO_3 \rightarrow \text{DPH HNO}_3 + AgCl\downarrow$$

Scheme 1: The suggested mechanism of interaction between DPH and $AgNO_3$

Medium of titration

Preliminary experiments were tried for drug and titrant in H_2O, methanol, ethanol, acetone, H_2O/methanol, H_2O/ethanol and H_2O/acetone. An initial conductance was generated, and then the conductance increased after silver nitrate addition, however in water medium sharpest end point was detected. Hence water was the best and cheapest choice of medium for conductometric titration. The procedure using H_2O was found to be the most suitable for successful results.

Effect of temperature

The relation between the conductance values and temperature of the solutions of authentic DPH and DPH syrup formulation was examined in aqueous media in the range of 25-40 °C. The results showed that as the temperature increased there was no significant change of conductance so room temperature (25 °C) was chosen for further investigations.

Reagent's concentration

To achieve a constant and highly stable conductance reading after 2.0 min mixing, the optimum concentration of $AgNO_2$ was found to be 5 x 10^{-3} M. The results indicated that, concentrations of titrant solution lower than 10^{-2} M are not suitable for conductometric titrations as the conductance readings were unstable and the inflection at the end-point was very poor and more time was needed to obtain constant conductance values. So, the reagent concentration in each titration must be not less than ten times that of the drug solution in order to reduce, the dilution effect on the conductivity throughout the titration.

Validation of the studied method

The validity of the method for the analysis of DPH in pure state and a syrup formulation was examined by analyzing the samples using the proposed procedures.

$$\text{Recovery\%} = (\text{Found concentration}/\text{Taken concentration}) \times 100 \quad (3)$$

Results revealed in (Tables 1-5) showed that the proposed method is satisfactorily accurate, precise and reproducible. Analyzing six replicates of the drug tested the precision and accuracy of the method.

Fig. 2 to fig. 5 show clear evidence that there was a significant difference in shape of the curves between DPH raw substance and DPH in syrup. This difference can be attributed to the presence of high concentration of other ions in syrup, such as sodium citrate, citric acid and sodium benzoate, which lead to high conductance at the beginning of titration.

However, the presence of these ions has no impact on the end-point since they do not react with $AgNO_3$. Analysis of the DPH in the syrup formulation applying standard addition technique gave the recovery of 99.76±0.763.

The statistical comparison between the results of the proposed method and those of reference method [11] using student's t-test and F-test shows that there is no significant difference between both methods (table 5).

Table 1: Conductometric titration of 5mg authentic DPH Vs $AgNO_3$ (5x10^{-3}M)

mL of $AgNO_3$	Corrected conductance
0.0	12.30
0.5	12.30
1.0	12.24
1.5	12.18
2.0	12.06
2.5	12.11
3.0	12.20
3.5	12.89
4.0	15.08
4.5	16.84
5.0	19.15
5.5	21.30
6.0	23.52
6.5	25.76
7.0	27.93

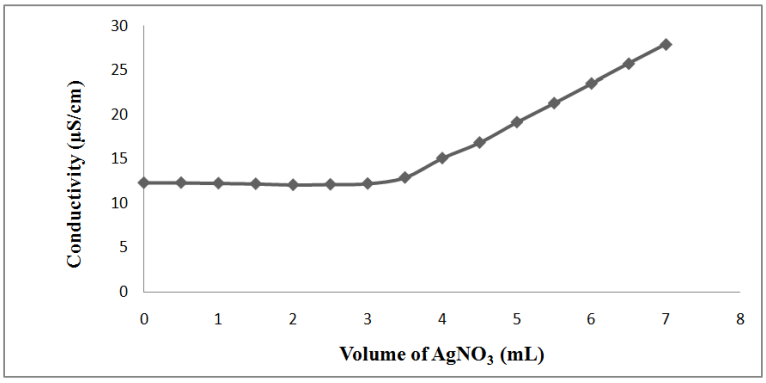

Fig. 2: Conductometric titration curve of 5mg authentic DPH Vs $AgNO_3$ (5x10^{-3}M).

Table 2: Conductometric titration of 10mg authentic DPH Vs $AgNO_3$ ($5x10^{-3}M$).

ml of $AgNO_3$	Corrected conductance	ml of $AgNO_3$	Corrected conductance
0.0	24.60	7.0	24.74
0.5	24.95	7.5	25.76
1.0	24.99	8.0	27.26
1.5	24.93	8.5	29.84
2.0	25.06	9.0	32.21
2.5	25.10	9.5	34.51
3.0	25.02	10.0	36.84
3.5	24.93	10.5	39.08
4.0	24.84	11.0	41.11
4.5	24.74	11.5	43.54
5.0	24.64	12.0	45.63
5.5	24.64	12.5	47.75
6.0	24.75	13.0	50.15
6.5	24.63	13.5	52.20

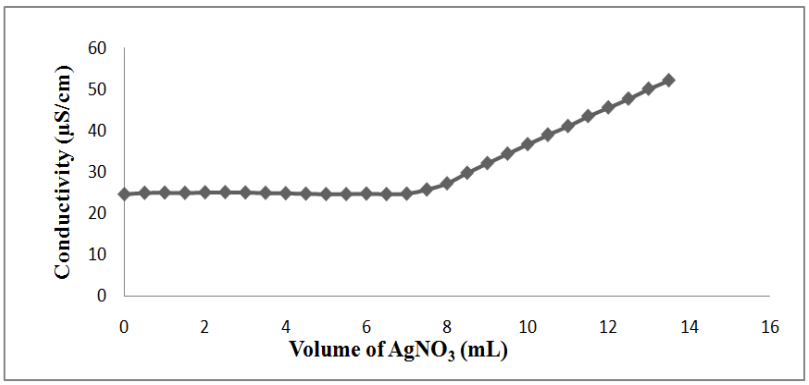

Fig. 3: Conductometric titration curve of 10mg authentic DPH Vs $AgNO_3$ ($5x10^{-3}M$)

Table 3: Conductometric titration of 5mg DPH (in syrup) Vs $AgNO_3$ ($5x10^{-3}M$)

mL of $AgNO_3$	Corrected conductance	mL of $AgNO_3$	Corrected conductance
0.0	59.10	3.6	59.60
0.3	59.25	3.9	60.15
0.6	59.00	4.2	60.60
0.9	58.84	4.5	61.80
1.2	58.88	4.8	63.13
1.5	58.92	5.1	64.14
1.8	58.85	5.4	65.26
2.1	58.67	5.7	66.62
2.4	58.90	6.0	67.87
2.7	58.92	6.6	70.30
3.0	59.25	7.0	71.93
3.3	59.60		

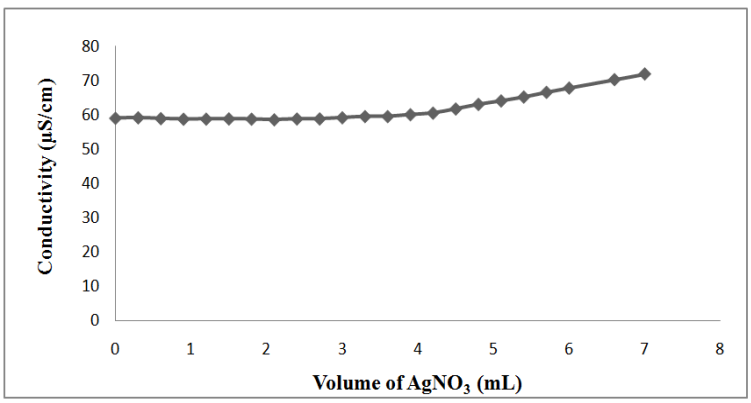

Fig. 4: Conductometric titration curve of 5mg DPH (in syrup) Vs $AgNO_3$ ($5x10^{-3}M$)

Table 4: Conductometric titration of 10mg DPH (in syrup) Vs $AgNO_3$ ($5x10^{-3}M$)

ml of $AgNO_3$	Corrected conductance	ml of $AgNO_3$	Corrected conductance
0.0	110.90	6.5	108.82
0.5	110.90	7.0	108.87
1.0	109.96	7.5	109.02
1.5	109.28	8.0	110.08
2.0	108.68	8.5	112.55
2.5	109.41	9.0	113.99
3.0	109.39	9.5	116.14
3.5	108.18	10.0	117.48
4.0	108.54	11.0	120.05
4.5	108.89	11.5	122.26
5.0	109.23	12.0	124.37
5.5	109.22	13.0	127.13
6.0	108.64	14.0	130.05
6.5	108.82		

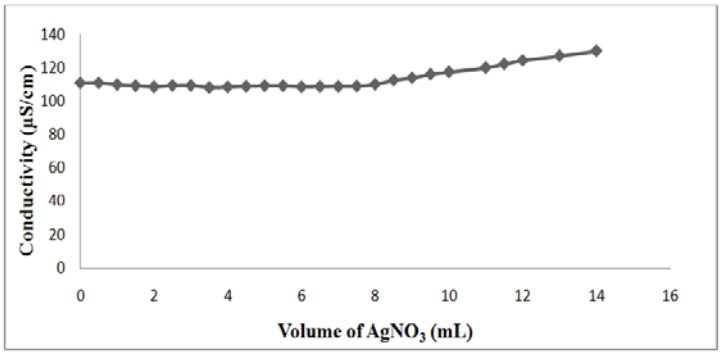

Fig. 5: Conductometric titration curve of 10mg DPH (in syrup) Vs $AgNO_3$ ($5x10^{-3}M$)

Table 5: Statistical comparison between the proposed method and the reference method for determination of DPH

Parameters	Proposed method	Reference method [11]
Mean±SD	99.76±0.763	100.17±0.954
N	6	3
Variance	0.582	0.910
Student's t-test	0.706(2.365)*	-
F-test	0.640(5.790)*	-

* Theoretical values of 't' and 'F' at p=0.05.

CONCLUSION

The proposed conductometric titration for determination of DPH can be an alternative to the more expensive and more complicated published methods. The proposed procedure is very simple, accurate and can be readily adopted for routine analysis in quality control laboratories. Additionally, the proposed method can be easily applied for determination of DPH in pharmaceutical syrup formulation.

Also, it has been proved that there is no interference of the common excipients present in the dosage form and there is no significant difference between the proposed method and the reference one.

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CONFLICT OF INTEREST

The authors confirm that they have no conflicts of interest in relation to the contents of this article.

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