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Conductometric determination of Betahistine dihydrochloride and Heptaminol hydrochloride using silver nitrate

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ABSTRACT

A simple, precise and cost effective conductometric method was developed for determination of betahistine dihydrochloride and heptaminol hydrochloride in pure form and pharmaceutical formulations. The method is based on the precipitation of chloride ions present in cited drugs with silver ions, yielding silver chloride, the conductance of the solution is measured as a function of the volume of titrant. Effect of solvent, reagent concentration, temperature were studied and evaluated. The suggested method was applied for determination of betahistine dihydrochloride and heptaminol hydrochloride in pure forms and pharmaceutical preparations. The described procedure allowed the determination of betahistine dihydrochloride and heptaminol hydrochloride in the range of 2-10mg/ml and 2-13mg /ml respectively.The molar ratio confirmed by the molar conductance, indicate that (2:1),(1:1) (drug:reagent) ion associates are formed between betahistine dihydrochloride and heptaminol hydrochloride with silver nitrate respectively. The suggested procedure was applied successfully to the analysis of these drugs in their pharmaceutical formulations, and the results obtained were in agreement with those given by the official methods.

Key words*: Betahistine dihydrochloride, heptaminol hydrochloride, silver nitrate,conductometric method*

Running title: *conductometric determination using silver nitrate*

1. INTRODUCTION

Betahistine2-[2-(methylamino)ethyl] pyridine Fig.(1.a), is an anti-vertigo drug which is commonly prescribed to patients with balance disorders or to alleviate vertigo symptoms associated with Meniere -'s disease.it is a strong antagonist for histamine H3 receptors and has a weak affinity as an agonist for histamine H1 receptors. Betahistine has two modes of action. Primarily, it has a direct stimulating (agonistic) effect on H1receptors, which are located on the blood vessels in the inner ear. This causes to local vasodilation and increase permeability, which helps to reverse the underlying problem of endolymphatic hydrops. Secondly, which is more important, is powerful antagonistic effects of Betahistine at H3 receptors (Martindale. 2010).

Betahistine dihydrochloride was determined using procedures with application of various physical and chemical methods such as HPLC (Khedr and Sheha, 2008; Battula et al., 2017; Soni et al., 2017; Mistry and Mishra, 2018), electrochemical methods (Ensafiet et al.,2010; Jain et al.,2010; Jain et al.,2014; Ganjali et al., 2015), spectrophotometry assay (Anis et al.,2011; Kashyap

and Makavana, 2013; Donchenko and Vasyuk, 2018), Pharmaco -poeial methods have been also reported for determination of HCT such as potentiometry and TLC (BP, 2017)

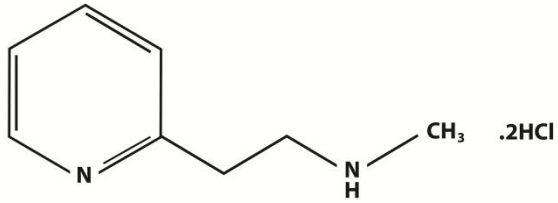


Fig.(1.a) Betahistine dihydrochloride

Heptaminol (HEP) (6-amino-2-methyl-2-heptanol hydrochloride) Fig.(1.b), is an amino alcohol drug that affects the cardiovascular system due to its positive inotropic action that causes an increase in the coronary blood flow accompanied by a slight peripheral vasoconstriction making it most commonly used for the treatment of orthostatic hypotension (Martindale., 2010).The British Pharmacopeia has recommended potentiometry and TLC methods for its determination(BP., 2017).

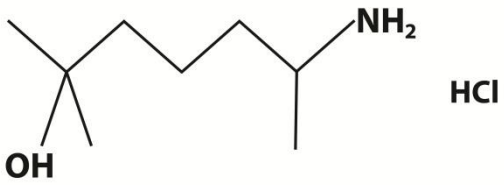


Fig.(1.b) Heptaminol HCl

Various methods have been reported for determination of HEP such as spectrophot -ometric (Belal et al., 2008;El-Gindy et al.,2004), spectrofluorimetric (EI-Adl.,20 --02;Omar et al.,2018), capillary electrophoretic (Casado-Terrones et al. 2006) and chromatographic (Badoud et al., 2010; Hsu et al., 2011; Domínguez-Romero et al., 2014; Jeong et al., 2015; Nováková et al., 2015).

Conductometric titrationis considered to be one of the convenient analytical techniques used in drug standardization. High accuracy and relatively low cost of conductivity instrumentation make it one of the most simplest techniques in the analytical assay. Conductometric analysis can be used in many titration procedures(Elazazy et al., 2012; Ayad et al., 2016). Conductometric titration through precipitation reaction was successfully applied for the determination of different pure drug materials and their pharmaceutical preparations.

2. EXPERIMENTAL

2.1 Instrumentation

Jenway 470 model portable conductivity -/TDS meter was used for the measurement of conductance.

2.2 Materials and Reagents

All chemicals used were of analytical reagent grade, solutions were made by bidistelled water.Betahistine dihyrochloride was kindly provided by Egyptian International Pharmaceutical Industrial Company, (EIPICO).10th of Ramadan City, Egypt

Betaserc® tablets :labeled to contain 24 mg betahistine dihydrochloride per tablet, Product of Abbott Pharmaceutical Company.

Heptaminol HCl: was kindly provided by Amoun Pharmaceutical. Co. (El-Obour city, City, Egypt)

Corasore® Tablets: labelled to contain heptaminol HCl 187.8 mg. equivalent. To heptaminol 150mg,Product of Amoun Pharmaceutical. Co. El-Obour city,Egypt Silver nitrate, Riedel-de-Haën (Germany)

Acetone, methanol, and ethanol: obtained from El NASR Pharmaceutical Chemical Company (Egypt).

2.3 Standard Drug Solutions:

Standard solution (1.0 mg/mL) of each of Betahistine dihydrochloride and heptaminol HCl were prepared by dissolving 100.0 mg of the pure drugs in 100 mL of bi-distilled water.

2.4 General Procedure:

Aliquots of standard solution containing 1.0-13.0 mg or 2.0-10.0 mg of either betahistine dihydrochloride or heptaminol HCl respectively were transferred into 50mL

volumetric flasks and made up to the mark with bi-distilled water. The contents of the calibrated flask were transferred quantitatively to beaker, the conductivity cell was immersed in the sample solution, the solution was then titrated conductometrically against 4.3x10-3M or 5.4x10-3M, silver nitrate and the conductance was measured subsequent to each addition of the reagent solution and after thorough stirring for two min. The conductance reading was corrected for dilution by means of equation (1), assuming that conductivity is a linear function of dilution.

Ω-1correct=Ω-1obs[V1+V2/V1] (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 reagent added.

A graph of corrected conductivity versus the volume of added titrant was constructed and the endpoint was determined conductometrically.

The amount of drugs under study was calculated according to equation (2),

Amount of drug = V. M. R/N (2)

Where V is volume (mL) of titrant, M is molecular weight of the drug, R is the molar concentration of titrant and N is number of moles of titrant consumed by one mole of the drug.

2.5 Assay of tablets:

Ten tablets were weighted and finely powdered and an amount equivalent to24mg or 187.8 mg betahistine dihydrochloride or heptaminol HCl respectively were shaken with 30 mL bi-distilled water, then filtered and diluted to 100 mL with bi-distilled water. Then proceed as described under "General Procedure"

3. RESULTS AND DISCUSSION:

Conductometric measurements can be used in quantitative precipitation titrations in which the conductance of the solution varies before and after the equivalence point. Conductometric titrations using silver nitrate are commonly used for quantitative determination of many pharmaceutical compounds. Silver nitrate has been used for conductometric determination of many drugs (Elen Roma˜o Sartori, Willian Toito Suarez 2009; Caetano et al. 2011; Sartori et al. 2011; Elazazy et al. 2012; Ayad et al.2013). On using silver nitrate as titrant for determination of betahistine dihydrochloride, heptaminol HCl, silver chloride is precipitated leading to straight line during the first segment of the titration curve corresponding to excess silver nitrate Fig. (2)

3.1 Conditions for Conductometric Titrations:

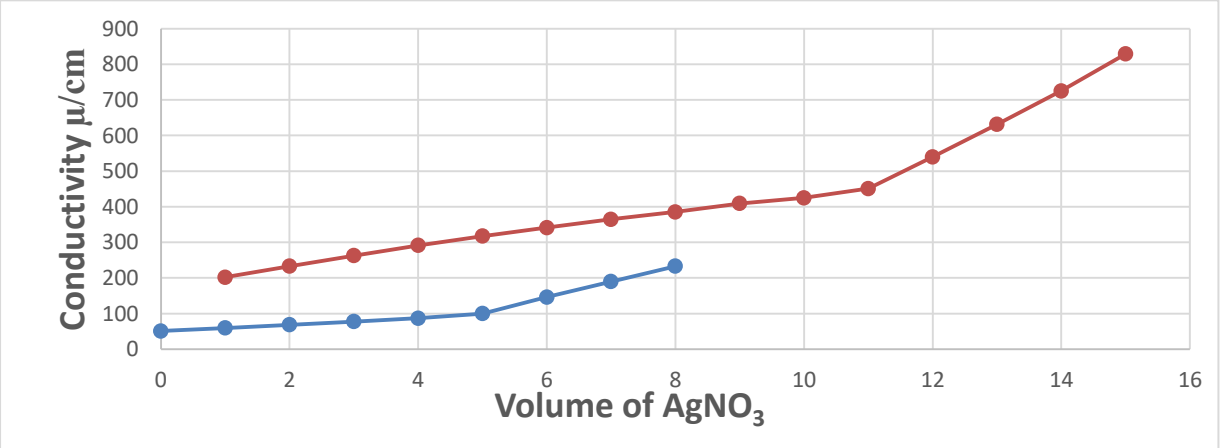


Fig.(2) Conductometric titration curve of 5.0 mg Betahistine dihydrochloride vs silver nitrate (4.2×10^{-3} M)and 5.0 mg Heptaminol HCl vs silver nitrate (5.4×10^{-3} M)

Investigations were carried out to establish the most suitable conditions for the precipitation formation of betahistine dihydrochloride, heptaminol HCl with silver

nitrate to attain sharp endpoint. The optimum conditions for performing the titration in a quantitative manner were elucidated.

3.1.1 Effect of solvent

Solvent used (i) water (ii) Ethanol (iii) ethanol-water (50%, V/V) mixture, (iv) methanol (v) methanol-water (50% V/V) mixture, (vi) Acetone and (vii) Drug and reagent solution in acetone-water (50% V/V) mixture, However in water, sharpest end point was detected. So water was the best and cheapest choice medium for conductometric titration for both drugs.

3.1.2 Reagent Concentration:

Concentrations of silver nitrate solutions were used ranging from to 5 × 10-4to 2 × 10-2M.optimum concentrations of silver nitrate were 4.2x10-3 and 5.4 x 10-3M for betahistine dihydrochloride and heptaminol HCl respectively.

3.1.3 Effect of Temperature:

Elevating the temperature to 40 ^{o}C, has no effect on the reaction. It was found that the same results were obtained. So room temperature (25^{o}C) was selected for the determination. Temperature cannot be increased more than 40 ^{o}C as conductivity cell could be affected by high temperature.

3.2 Methods Validation:

Validation of the proposed method was carried out via statistical analysis of the data obtained from its application on the drugs in their pure form and in their formulations. Under the optimum conditions described earlier, satisfactory results with good recovery values were obtained for both drugs.

3.3 Accuracy and Precision:

3.3.1 Accuracy:

The accuracy of the proposed method was evaluated by analyzing pure samples of the studied drugs with reported methods. Statistical analysis of the results obtained by both the proposed and comparison methods is shown in Table (1).

3.3.2 Precision:

Intra-day and inter-day precisions and accuracy results were summarized in Table (2) indicating the validity and applicability of the proposed methods and the reproducibility of the result.

Table (1) Application of the proposed and official methods to the determination of betahistine dihydrochloride and heptaminol HCl in pure form

Parameters	Betahistine dihydrochloride	Official Method (BP.2017)	Heptaminol HCl	Official method (BP.2017)
No.of experiments	6	6	7	6
Mean found %	99.92%	99.81%	100.74%	101.23%
± SD	1.33	1.45	1.08	1.24
RSD	1.33	1.45	1.07	1.22
t-value	0.14(2.23)*		0.75(2.20)*	
Variance ratio F-test	1.18(5.05)*		1.31(4.39)*	

The values of the tabulated t and F at p=0.05*
Note: Each result is the average of three separate determinations

3.4 Analytical Applications:

The proposed method was successfully applied to the assay of the studied drugs in their tablets using the standard addition technique. Results obtained for the % recoveries of the drugs were in good agreement with the label claim . The percentage recoveries of the drugs using the proposed method are shown in Table (3). These results are in good agreement with those obtained with the comparison methods.

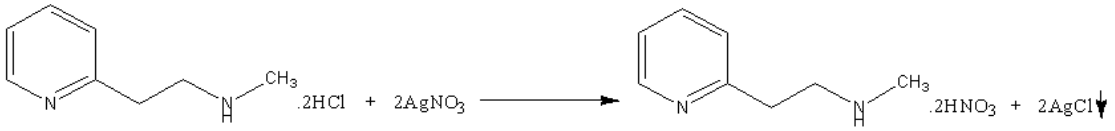
Table (2). Precision data for the determination of Betahistine dihydrochloride and Heptaminol HCl

	Conc (µg/ml)	Inter-day		Intra-day	
		Mean ± SD	RSD%	Mean ± SD	RSD%
Betahistine dihydrochloride	4.0	100.11±0.91	0.91	99.12±1.10	1.11
	8.0	99.95±0.51	0.51	100.11±0.25	0.25
	10.0	100.83±1.67	1.66	99.36±1.29	1.29
Heptaminol Hydrochloride	4.0	100.10±1.43	1.43	101.32±0.47	0.47
	8.0	100.74±1.27	1.26	100.96±0.84	0.83
	12.0	99.96±0.86	0.86	100.24±0.83	0.83

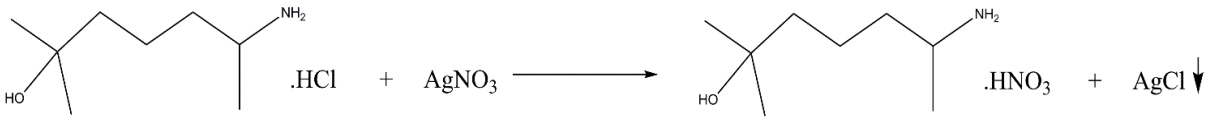
Note: Each result is the average of three separate determinations

3.5 Stoichiometry of the reaction:

The molar reactivity of the reaction was studied using the same molar concentrations of each drug and silver nitrate 4.9x10-3, 5.4x10-3M. The results of titration of these solutions indicated that the reaction proceeds in a 2:1 and 1:1 molar ratio (drug: reagent) for betahistine dihydrochloride and heptaminol HCl, respectively, as shown in Fig. (3 and 4).A Schematic proposal of the pathways for the reaction between each of betahistine dihydrochloride or heptaminol HCl and silver nitrate is shown in schemes (1 and 2).



Scheme (1): The proposal pathway for the reaction between betahistine dihydrochloride and silver nitrate



Scheme (2): The proposal pathway for the reaction between heptaminol HCl and silver nitrate

4. CONCLUSION

The proposed method is easy and very useful to be used in the routine analysis of betahistine dihydrochloride, heptaminol HCl determination in pharmaceutical tests with low price. It does not require any treatment of the sample and can be used to selectively determine betahistine dihydrochloride, heptaminol HCl in pharmaceuticals after suitable dilution of the sample without interference from the common excipients of tablets, such as talc powder, lactose, magnesium stearate, starch, avisil, microcrystalline cellulose

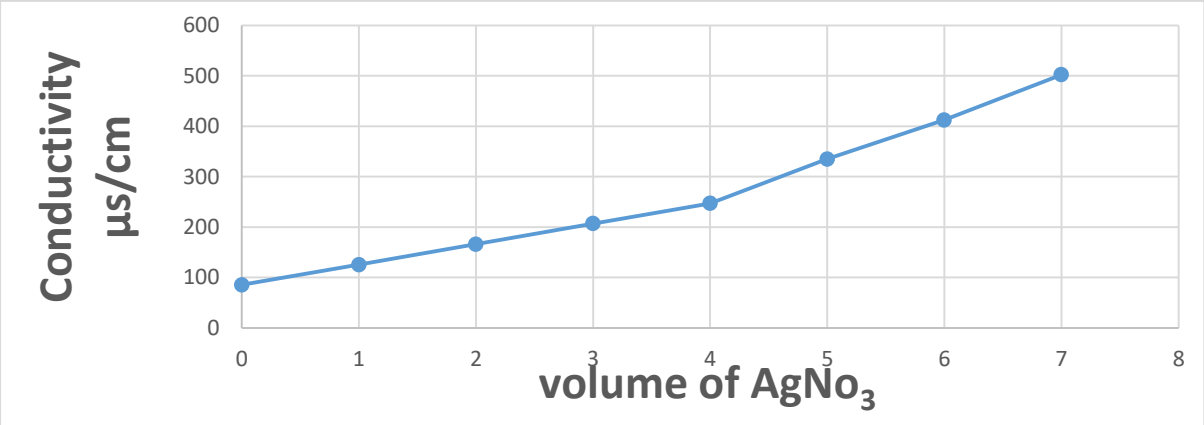
Conflict of Interest:

All the authors declare no conflict of interest.

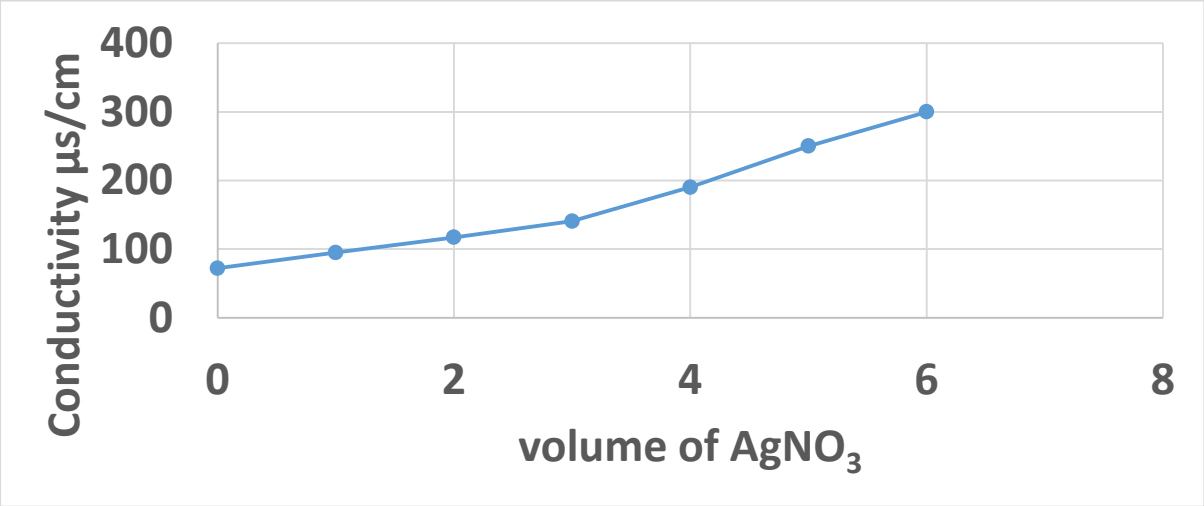
Table (3). Conductometric determination of betahistine dihydrochloride and heptaminol HCl in their pharmaceutical preparations using silver nitrate.

Parameters	Proposed method			Official for betahistine dihydrochloride or reported method for heptaminol HCl (BP 2017;Omar et al. 2018)		
	Taken(mg/ml)	Added	Rec%	Taken(mg/ml)	Added	Rec%
Betahistine dihydrochloride (Betaserc®)	2	0	100.50%	0.25	0.5	100.93%
		2.0	100.88%		1.0	99.07%
		3.0	99.69%		2.0	99.07%
		4.0	100.19%		3.0	100.47%
		5.0	99.39%		5.0	100.62%
		6.0	102.02%		6.0	99.07%
		7.0	101.92%			
		8.0	100.38%			
Mean±SD	100.62±0.95	99.95±0.84				
t-value	1.44(2.16)*					
Variance ratio F-test	1.27(3.87)*					
Heptaminol HCl (Corasore®)	1	0	101.86%	2	0	99.95%
		7.0	99.05%		1.0	99.57%
		8.0	99.90%		2.0	100.81%
		9.0	99.74%		3.0	99.08%
		10.0	98.69%			
		11.0	100.99%			
		12.0	100.96%			
Mean±SD	100.17±1.14	99.85±0.73				
t-value	0.57(2.26)*					
Variance ratio F-test	2.44(4.76)*					

*The value of the tabulated t and F at p=0.05
Note: Each result is the average of three separate determinations



Fig(3): Titration plot of 4 ml of bethistine dihydrochloride with silver nitrate(4.2x10-3 M each)



Fig(4): Titration plot for 3 ml of heptaminol HCl with silver nitrate(5.4x10-3 M each)

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لتقدير الموصلي لهيدروكلوريد بيتاهستين وهيدروكلوريد الهيبامينول باستخدام نترات الفضة

ماجدة محمد عياد ، مرفت حسني ، عمر محمد العباسي وفتح الله بلال

تم تطوير طريقة موصلية بسيطة ودقيقة وفعالة من حيث التكلفة لتقدير ثنائي هيدروكلوريد بيتاهستين وهيدروكلوريد الهيبامينول في شكل نقي ومستحضرات دوائية. تعتمد الطريقة على ترسيب أيونات الكلوريد الموجودة في العقاقير المذكورة مع أيونات الفضة ، والتي تسفر عن كلوريد الفضة ، ويتم قياس سلوك المحلول كدالة لحجم المعايرة. تم دراسة تأثير المذيب ، تركيز الكواشف ، درجة الحرارة وتقييمها. تم تطبيق الطريقة المقترحة لتحديد ثنائي هيدروكلوريد بيتاهستين وهيدروكلوريد الهيبامينول في أشكال نقية والمستحضرات الصيدلانية. سمح الإجراء الموصوف بتحديد ثنائي هيدروكلوريد بيتاهستين وهيدروكلوريد الهيبامينول في حدود 2-10 ملغ / مل و 2-13 ملغ / مل على التوالي. وكانت النسبة المولية (2: 1) ، (1: 1) (الدواء: الكاشف) بين بيتاهستين ثنائي هيدروكلوريد وهيدروكلوريد الهيبامينول مع نترات الفضة على التوالي. تم تطبيق الإجراء المقترح بنجاح على تحليل هذه الأدوية في المستحضرات الصيدلانية ، وكانت النتائج التي تم الحصول عليها تتفق مع تلك التي قدمتها الطرق الرسمية