INNOVARE JOURNAL OF MEDICAL SCIENCES

Vol 4, Issue 3, 2016

ISSN - 2321-4406

Research Article

CONDUCTOMETRIC TITRATION METHOD FOR DETERMINATION OF ETILEFRINE HYDROCHLORIDE, FENOTEROL HYDROBROMIDE, AND PIPAZETHATE HYDROCHLORIDE USING SILVER NITRATE

MAGDA AYAD, HISHAM ABDELLATEF, MERVAT HOSNY*, YASSMIN SHARAF

Department of Analytical Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt. Email: Mermaka89@yahoo.com

Received: 07 May 2016, Revised and Accepted: 07 May 2016

ABSTRACT

Objective: The objective of this work is to develop a simple, precise, rapid, and low-cost conductometric method for the determination of etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride in pure form and in pharmaceutical formulations using silver nitrate.

Methods: The method is based on the precipitation of chloride or bromide ions coming from the cited drugs with silver ions yielding silver chloride or silver bromide, and the conductance of the solution is measured as a function of the volume of titrant. The studied drugs were evaluated in double distilled water in the range of 1-10 mg; various experimental conditions were established.

Results: Results obtained showed good recoveries with relative standard deviation of 0.684, 0.817, and 0.864 for etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride, respectively. The proposed procedures were applied successfully to the analysis of these drugs in their pharmaceutical formulations; results were successfully comparable to the official or reference methods.

Conclusion: Simple and rapid procedure described in this work can be an alternative to the more complex and expensive methods for assay of the cited drugs.

Keywords: Conductometric titration, Etilefrine, Fenoterol, Pipazethate.

INTRODUCTION

Etilefrine hydrochloride [2-Ethylamino-1-(3-hydroxyphenyl) ethanol hydrochloride] [1] is a direct-acting sympathomimetic with beta1-agonist properties, and some alpha- and beta2-agonist actions. It is used for the treatment of hypotensive states [2]. Different techniques were reported for the determination of etilefrine hydrochloride including spectrophotometry [3,4], spectrofluorimetry [5], automated sequential injection spectrophotometry [6], Flow-injection spectrophotometry [7], flow-injection chemiluminometric assay [8], and high-performance liquid chromatography [9].

Fenoterol hydrobromide [(1RS)-1-(3,5-dihydoxyphenyl)-2-[[(1RS)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethanol hydrobromide] [1] is direct-acting sympathomimetic with beta-adrenoceptor stimulant activity largely selective for beta2 receptors (a beta2 agonist). It is used as a bronchodilator in the management of reversible airways obstruction, as occurs in asthma and in some patients with chronic obstructive pulmonary disease [2]. Various analytical methods have been applied for the determination of fenoterol hydrobromide in raw material, pharmaceuticals, and biological fluids. These methods include liquid chromatography [10-12], gas chromatography [13], voltammetry [14], electrophoresis [15,16], spectrophotometry [17,18], and spectrofluorimetry [19].

Pipazethate HCl (2-(2-piperidinoethoxy) ethyl 10H-pyrido [3,2-b] [1,4]benzothiadiazine-10-carboxylate hydrochloride is a centrally acting cough suppressant which also has some peripheral actions in a non-productive cough [2]. Different techniques were reported for the determination of pipazethate hydrochloride including spectrophotometry [20-24], electrochemical [25-26], and chromatographic [27] methods.

Silver nitrate has been used for conductometric determination of many drugs such as naftidrofuryl oxalate, propafenone HCl and sotalol HCl [28], ciprofloxacin HCl [29], metformin hydrochloride [30], and verapamil hydrochloride [31].

METHODS

Instrumentation

Conductometer model 470 portable conductivity/TDS meter, 25 DEG. C-C10 dip-type cell was used with a cell constant, K_{cell}, of 1.09.

Materials and reagents

All materials and reagent used were of analytical grade, solvents were of spectroscopic grade, and bidistilled water was used.

1. Etilefrine HCl (obtained from chemical industrial development, CID)
2. Fenoterol hydrobromide (obtained from Sigma Pharmaceutical Industries)
3. Pipazethate hydrochloride (obtained from Egyptian International Pharmaceutical Industries Company [EPICO])
4. (5×10^{-3} M) Silver nitrate.

Standard drug solutions

Aqueous solutions of 1 mg/ml were prepared by dissolving 100 mg of the pure drug of etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride in 100 ml bidistilled water.

Pharmaceutical preparations

1. Effortil® tablets containing 5 mg etilefrine HCl per tablet (obtained from CID under the licence of Boehringer Ingelheim Germany).
2. Effortil® Drops containing 7.5 mg etilefrine HCl per gm solution (obtained from CID under the licence of Boehringer Ingelheim, Germany).
3. Pronotrol® Syrup containing 2.5 mg fenoterol HBr per 5 ml (obtained from Sigma Pharmaceutical Industries).
4. Selgon® tablets containing 20 mg pipazethate hydrochloride per tablet (obtained from EPICO).
5. Selgon® Drops containing 40 mg pipazethate hydrochloride per ml solution (obtained from EPICO).

General procedure

Aliquots of drug solution (1-10 ml) containing 1-10 mg pure drug were transferred to a 50 ml calibrated flasks; volumes were made up to the mark using bidistilled water. The contents of the calibrated flask were transferred to a beaker; the conductivity cell was immersed and 5×10^{-3} M silver nitrate was used for titration. The conductance was measured subsequent to each addition of reagent solution and after thorough stirring for 2 minutes; the conductance was corrected for dilution [32] using the following equation, assuming that conductivity is a linear function of dilution.

$$\Omega^{-1}{}_{correct}=\Omega^{-1}{}_{obs}\,[v_1+v_2/v_1] \quad (1)$$

Where $\Omega_{correct}$ is the corrected electrolytic conductivity, Ω_{obs} is the observed electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of reagent added.

A graph of corrected conductivity versus the volume of added titrant was constructed, and end-point was determined conductometrically.

The amount of drugs under study was calculated according to the following equation:

Amount of drug=VMR/N

Where V is volume of titrant, M is molecular weight of drug, R is molar concentration of titrant and N is N^0 of moles of titrant consumed by one mole of drug.

Assay of the pharmaceutical formulations

Assay tablets

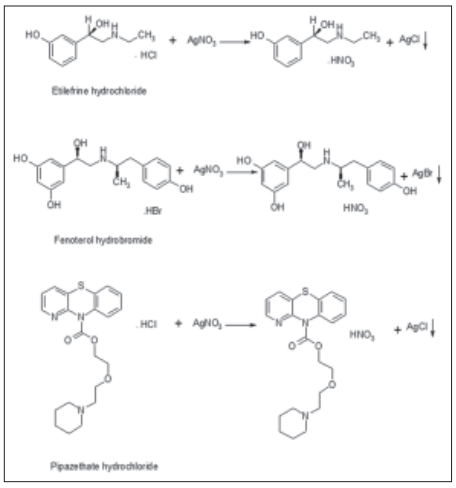
About 10 tablets were powdered and an amount equivalent to 100 mg etilefrine hydrochloride and pipazethate hydrochloride was shaken with 10 ml distilled water, then diluted to 100 ml with distilled water and filtered. The procedure was completed as in general procedure.

Assay of syrup and drops

Specific volumes of syrup and drops solutions equivalent to 100 mg pure drug were placed in 100 ml volumetric flask and diluted to 100 ml with distilled water for etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride. The procedure was completed as in general procedure.

RESULTS AND DISCUSSION

The conductometric methods of analysis are well suited for the determination of endpoints in precipitation titrations, where the shape of the titration curves can be predicted by summing the ionic conductance of the various species during the course of titration. On using silver nitrate as a titrant for the determination of etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride - silver chloride or silver bromide is precipitated leading to a straight line during the first segment of the titration curve. The second segment of this curve corresponds to the excess of $AgNO_3$ (Figs. 1-3).



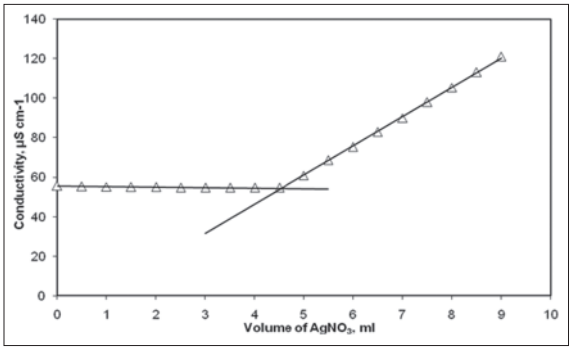


Fig. 1: Conductometric titration curve of 5 mg etilefrine hydrochloride versus (5×10^{-3}) M silver nitrate

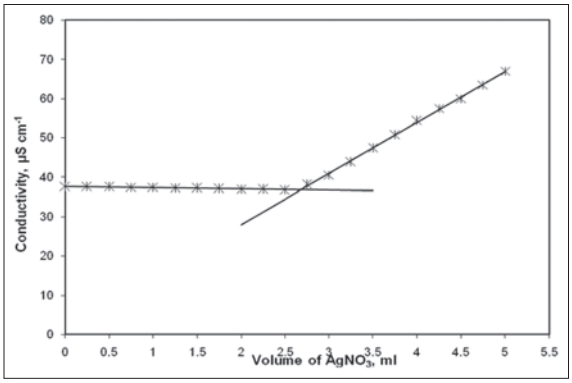


Fig. 2: Conductometric titration curve of 5 mg fenoterol hydrobromide versus (5×10^{-3}) M silver nitrate

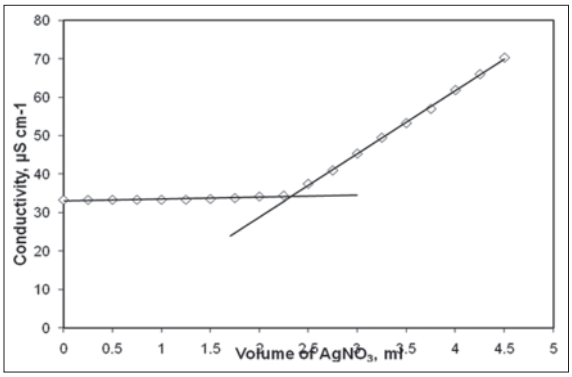


Fig. 3: Conductometric titration curve of 5 mg sotalol HCl versus (5×10^{-3}) M silver nitrate

Investigations were carried out to establish the most favorable conditions for the reaction attain end point. The influence of some variables on the reaction has been tested as follow:

The optimum conditions for performing the titration in a quantitative manner were elucidated as described as follows:

1. Titrations in different media were attempted to obtain the best results - Preliminary experiments in:
   i. Aqueous solutions of both drug and reagent,
   ii. Ethanolic solutions of both drug and reagent,
   iii. Drug and reagent solutions in ethanol–water (50%, v/v) mixture,
   iv. Methanolic solutions of both drug and reagent,
   v. Drug and reagent solutions in methanol-water (50% v/v) mixture,
   vi. Acetone solutions of both drug and reagent, and
   vii. Drug and reagent solution in acetone–water (50% v/v) mixture.

Preliminary experiments showed that procedure in aqueous media was the most suitable for successful results (higher conductance and most sharp end point.).

2. Reagent's concentration

   The optimum concentrations of silver nitrate were 5×10^{-3} M to achieve a constant and highly stable conductance reading after 2.0 minutes mixing. Concentrations less than these lead to unstable readings and more time was needed to obtain constant conductance values.
3. Effect of temperature

   On raising the temperature to 40°C, no change in the conductance reading was observed, so the experiment was done at room temperature.

Validation of the studied method

To address the validity of the proposed method, a statistical analysis of the data obtained from its application on drugs in the pure form and in pharmaceutical formulations was performed. Results revealed in Tables 1-3 showed that the proposed method is satisfactorily accurate, precise, and reproducible over a concentration range of 1-10 mg for all of the studied drugs.

Student's t-test and F-test (at 95% confidence level) were applied to the results obtained compared with that obtained when applying the official

Table 1: Conductometric determination etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride using silver nitrate

Etilefrine hydrochloride			Fenoterol hydrobromide			Pipazethate hydrochloride		
Taken (mg)	**Found (mg)**	**Recovery (%)**	**Taken (mg)**	**Found (mg)**	**Recovery (%)**	**Taken (mg)**	**Found (mg)**	**Recovery (%)**
1	1.012	101.23	1	0.999	99.91	1	1.007	100.73
3	2.993	99.78	3	3.017	100.55	2	2.956	98.54
5	5.007	100.14	5	5.072	101.45	5	5.037	100.73
7	7.021	100.29	7	7.013	100.19	7	7.007	100.11
9	8.925	99.17	9	9.030	100.34	9	8.978	99.76
10	10.041	100.41	10	9.895	99.95	10	10.073	100.73
Mean±SD	100.17±0.685		100.23±0.817			100.10±0.865		
N	6		6			6		
V	0.469		0.668			0.748		
SD	0.685		0.817			0.865		
RSD	0.684		0.815			0.784		
SE	0.242		0.289			0.306		

SD: Standard deviation, RSD: Relative standard deviation, SE: Standard error

Table 2: Conductometric determination of etilefrine hydrochloride and fenoterol hydrobromide in their pharmaceutical preparations using silver nitrate

Etilefrine hydrochloride (Effortil tablets)				Etilefrine hydrochloride (Effortil drops)				Fenoterol hydrobromide (Bronotrol syrup)			
Taken (mg/ml)	**Added (mg/ml)**	**Found (mg/ml)**	**Recovery (%)**	**Taken (mg/ml)**	**Added (mg/ml)**	**Found (mg/ml)**	**Recovery (%)**	**Taken (mg/ml)**	**Added (mg/ml)**	**Found (mg/ml)**	**Recovery (%)**
1	-	1.001	100.14	1	-	0.990	101.37	1	-	0.999	99.91
	1	0.990	99.05		1	1.001	100.14		1	0.999	99.91
	3	3.026	100.86		3	3.037	101.23		3	3.036	101.19
	5	4.985	99.70		5	4.996	99.92		5	4.957	99.14
	7	7.053	100.76		7	6.955	99.36		7	7.071	101.01
	9	9.012	100.14		9	9.023	100.26		9	8.992	99.91
Mean±SD	100.10±0.755			100.18±0.679				100.32±0.854			
N	5			5				5			
V	0.570			0.461				0.730			
SD	0.755			0.679				0.854			
SE	0.267			0.240				0.302			

SD: Standard deviation, SE: Standard error

Table 3: Conductometric determination of pipazethate hydrochloride in its pharmaceutical preparations using silver nitrate

Selgon tablets				Selgon drops			
Taken (mg/ml)	**Added (mg/ml)**	**Found (mg/ml)**	**Recovery (%)**	**Taken (mg/ml)**	**Added (mg/ml)**	**Found (mg/ml)**	**Recovery (%)**
1	-	1.029	102.92	1	-	1.007	100.73
	1	1.007	100.73		1	1.007	100.73
	3	2.978	99.27		3	3.066	102.19
	5	5.102	102.05		5	5.015	100.29
	7	7.073	101.05		7	6.986	99.79
	9	9.044	100.49		9	9.066	100.73
Mean±SD	100.72±1.002			100.75±0.895			
N	5			5			
V	1.003			0.801			
SD	1.002			0.895			
SE	0.354			0.316			

SD: Standard deviation, SE: Standard error

Table 4: Statistical data for the conductometric determination of naftidrofuryl etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride using silver nitrate

Drug	Silver nitrate method	Reference or reported method
Etilefrine hydrochloride		
Mean±SD	100.17±0.685	100.06±0.655 [1]
N	6	6
Variance	0.469	0.429
Student's t-test	0.284 (2.228)*	
F-test	1.093 (5.050)*	
Fenoterol hydrobromide		
Mean±SD	100.23±0.817	99.08±1.209 [1]
N	6	4
Variance	0.668	1.460
Student's t-test	1.814 (2.306)*	
F-test	2.186 (5.410)*	
Pipazethate hydrochloride		
Mean±SD	100.10±0.865	100.05±0.604 [29]
N	6	8
Variance	0.748	0.360
Student's t-test	0.128 (2.179)*	
F-test	2.078 (3.970)*	

*Theoretical values of t and F at p=0.05. SD: Standard deviation

methods [1] for etilefrine hydrochloride and fenoterol hydrobromide or reported method [20] for pipazethate hydrochloride. The results showed that there is no significant difference between the proposed and official or reported methods. Results of different statistical data are shown in Table 4.

CONCLUSION

The simple and rapid procedure described in this paper can be an alternative to the more complex and expensive methods for assay of etilefrine hydrochloride, fenoterol hydrobromide, and pipazethate hydrochloride. The proposed method is easy and a very useful for the determination of the studied drug in pharmaceutical formulations and can be applied in laboratories for routine analysis.

REFERENCES

1. Her Majesty's Stationery Office. The British Pharmacopoeia. Vol. III. London, UK: Her Majesty's Stationery Office; 2013.
2. Sweetman SC. Martindale-The Complete Drug Reference. 35th ed. London: The Pharmaceutical Press; 2007.
3. Ragab GH, Elmasry MS, Kheir AA. Spectrophotometric determination of some phenolic drugs in pure form and in their pharmaceutical preparations. Jordan J Pharm Sci 2009;2(1):66-75.
4. Bakry RS, El Walily AF, Belal SF. Spectrophotometric determination of some phenolic sympathomimetic drugs through reaction with 2,6-dihaloquinone chlorimides. Mikrochim Acta 1997;127(1-2):89-93.
5. Osso BQ, Rodriguez FM, Domingo JJ, Gonzalez MC, Gomez JT. Flourecence quenching of etilefrine by acetate anion. Spectrochim Acta A Mol Biomol Spectrosc 1999;55(2):279-88.
6. Beyene NW, van Staden JF, Stefan RI. Sequential injection spectrophotometric determination of etilefrine hydrochloride. Farmaco 2004;59(12):1005-10.
7. El-Gendy AE. Flow injection analysis of some phenolic sympathomimetic drugs. Anal Lett 2000;33(14):2927-38.
8. Aly FA, Al-Tamimi SA, Alwarthan AA. Determination of phenolic sympathomimetic drugs in pharmaceutical samples and biological fluids by flow-injection chemiluminescence. J AOAC Int 2000;83(6):1299-305.
9. Kojima K, Yamanaka M, Nakanishi Y, Arakawa S. High-performance liquid chromatographic determination of etilefrine in human plasma using combined solid-phase and organic solvent extraction and electrochemical detection. J Chromatogr 1990;525(1):210-7.
10. Sanghvi M, Ramamoorthy A, Strait J, Wainer IW, Moaddel R. Development and validation of a sensitive LC-MS/MS method for the determination of fenoterol in human plasma and urine samples. J Chromatogr B Analyt Technol Biomed Life Sci 2013;933:37-43.
11. Siluk D, Kim HS, Cole T, Wainer IW. HPLC-electrospray mass spectrometric assay for the determination of (R,R)-fenoterol in rat plasma. J Pharm Biomed Anal 2008;48(3):960-4.
12. Shen S, Ouyang J, Baeyens WR, Delanghe JR, Yang Y. Determination of beta2-agonists by ion chromatography with direct conductivity detection. J Pharm Biomed Anal 2005;38(1):166-72.
13. Jacobson GA, Peterson GM. High-performance liquid chromatographic assay for the simultaneous determination of ipratropium bromide, fenoterol, salbutamol and terbutaline in nebulizer solution. J Pharm Biomed Anal 1994;12(6):825-32.
14. Henze MK, Opfermann G, Spahn-Langguth H, Schänzer W. Screening of beta-2 agonists and confirmation of fenoterol, orciprenaline, reproterol and terbutaline with gas chromatography-mass spectrometry as tetrahydroisoquinoline derivatives. J Chromatogr B Biomed Sci Appl 2001;751(1):93-105.
15. Belal F, Al-Malaq HA, Al-Majed AA. Voltammetric determination of isoxsuprine and fenoterol in dosage forms and biological fluids through nitrosation. J Pharm Biomed Anal 2000;23(6):1005-15.
16. Ullrich T, Wesenberg D, Bleuel C, Krauss GJ, Schmid MG, Weiss M, *et al.* Chiral separation of the ß2-sympathomimetic fenoterol by HPLC and capillary zone electrophoresis for pharmacokinetic studies. Biomed Chromatogr 2010;24(10):1125-9.
17. El-Shabrawy Y, Belal F, Sharaf El-Din M, Shalan Sh. Spectrophotometric determination of fenoterol hydrobromide in pure form and dosage forms. Farmaco 2003;58(10):1033-8.
18. Shalaby A, Salem H, Kheir AA. Spectrophotometric derermination of some sympathomimetic drugs by coupling with diazotized o-nitroaniline or p- aminobenzoic acid. Sci Pharm 1997;65:143-54.
19. Eid M. Spectrofluorimetric determination of fenoterol in pharmaceuticals. J Chin Chem Soc 2007;54(3):613-7.
20. Hosny MM. Extractive colourimetric determination of pipazethate HCl by ion-pair complex formation in pure form, dosage form, urine and in presence of its degradation products. Int J Instrum Sci 2013;2:8-14.
21. Hassan MA, El-Asmy AF, Abd El-Raheem YB. Novel methods for the visible spectrophotometric determination of pipazethate HCl and chlorphenoxamine HCl in pure and tablet dosage forms. Int J Pharm Sci Res 2011;2:2589-601.
22. Gouda AA, El-Sheikh R, El Shafey Z, Hossny N, El-Azzazy R. Spectrophotometric determination of pipazethate HCl and dextromethorphan HBr using potassium permanganate. Int J Biomed Sci 2008;4(4):294-302.
23. Amin AS, El-Sheikh R, Zahran F, Gouda AA. Spectrophotometric determination of pipazethate HCl, dextromethorphan HBr and drotaverine HCl in their pharmaceutical preparations. Spectrochim Acta A Mol Biomol Spectrosc 2007;67(3-4):1088-93.
24. El-Shiekh R, Zahran F, El-Fetouh Gouda AA. Spectrophotometric determination of some anti-tussive and anti-spasmodic drugs through ion-pair complex formation with thiocyanate and cobalt(II) or molybdenum(V). Spectrochim Acta A Mol Biomol Spectrosc 2007;66(4-5):1279-87.
25. Issa YM, Shoukry AF, El-Nashar RM. Conductimetric determination of reproterol HCl and pipazethate HCl and salbutamol sulphate in their pharmaceutical formulations. J Pharm Biomed Anal 2001;26(3):379-86.
26. Abdel-Ghani NT, Shoukry AF, el Nashar RM. Flow injection potentiometric determination of pipazethate hydrochloride. Analyst 2001;126(1):79-85.
27. Ismaiel O, Hosny M, Ragab G. A validated stability indicating RP-HPLC with photodiode array detector method for the determination of pipazethate hydrochloride in bulk drug and pharmaceutical formulations. Asian J Pharm Clin Res 2012;5(3):215-9.
28. Ayad MM, Abdellatef HE, Hosny MM, Sharaf YA. Conductometric titration method for determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl using silver nitrate. Eur J Chem 2012;3(3):332-6.
29. Belal F, Rizk FA, El-Enany NM. Conductimetric determination of some farmaceutically important 4-quinoline derivatives in dosage forms. Chem Anal 1999;44(4):763-72.
30. Sartori ER, Suarez WT, Fatibello-Filho O. Conductometric determination of metformin hydrochloride in pharmaceutical formulations using silver nitrate as titrant. Quim Nova 2009;32(7):1947-50.
31. Fabio RC, Ava G, Marcio FB, Luiz HM. A fast and simple conductometric method for verapamil hydrochloride determination in pharmaceutical formulations. Curr Pharm Anal 2011;7:275-9.
32. Lingane JJ. Electroanalytical Chemistry. 2nd ed. New York: Interscience; 1958.