



Conductometric titration method for determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl using silver nitrate

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ABSTRACT

A simple, precise, rapid, and low-cost conductometric method for determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl in pure form and in pharmaceutical formulations using silver nitrate has been described. The method is based on the precipitation of oxalate or chloride ions coming from the cited drugs with silver ions, yielding silver oxalate or silver chloride 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 1-15 mg. Various experimental conditions were established and results obtained showed good recoveries with relative standard deviation of 0.909, 0.955 and 0.983 for naftidrofuryl, propafenone and sotalol, respectively. The proposed procedures were applied successfully to the analysis of these drugs in their pharmaceutical formulations. Results were favorably comparable to the official or reference methods.

1. Introduction

Naftidrofuryl oxalate is known as nafronyl oxalate, (2-(diethylaminoethyl)-2-[(naphthalene-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate hydrogen oxalate) [1]. It is used as a vasodilator in the treatment of peripheral and cerebral vascular disorders. It is claimed to enhance cellular oxidative capacity thereby protecting cells against the results of ischaemia [2].

Few analytical methods were reported for the determination of naftidrofuryl in biological fluids and/or pharmaceutical preparations. Most of these studies focused on kinetic spectrophotometry [3], derivative spectrophotometry, spectrofluorimetry, differential-pulse voltammetry [4], HPLC-fluorimetric [5,6], HPLC-UV detection methods [7, 8] and phosphorimetric analysis [9-12]. Others include a potentiometric method with nafronyl ion-selective electrodes [13] and flow injection analysis with fluorescence optosensor [14].

Propafenone hydrochloride is [2-(2-hydroxy-3-propylaminopropoxy)-3-phenylpropio phenone hydrochloride] [15]. It is used in the treatment of cardiac arrhythmias [2]. A spectrophotometric [16] and spectrofluorimetric methods were reported for its determination [17]. Several methods including capillary electrophoresis [18,19], HPLC methods [20-23] were reported for propafenone enantio selective determination and its metabolites in human plasma. Other reported methods of analysis include LC-MS [24].

Sotalol hydrochloride is *N*-[4-[(1*R*,*S*)-1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methanesulphonamide hydrochloride [1]. It is a non-cardio selective beta blocker with class II and III antiarrhythmic properties [2]. Several methods were used for sotalol HCl determination in pure and pharmaceutical dosage forms. These methods include

spectrophotometric [25-29], spectrofluorimetric [30,31], HPLC [29,32], LC [33], capillary zone electrophoresis [34] and NMR spectroscopic methods [35].

Silver nitrate has been used for conductometric determination of many drugs such as ciprofloxacin HCl [36], metformin hydrochloride [37] and verapamil hydrochloride [38]. In this study, a simple, precise, rapid, and low-cost conductometric titration method for the determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl in pharmaceuticals is proposed using silver nitrate as titrant.

2. Experimental

2.1. Instrumentation

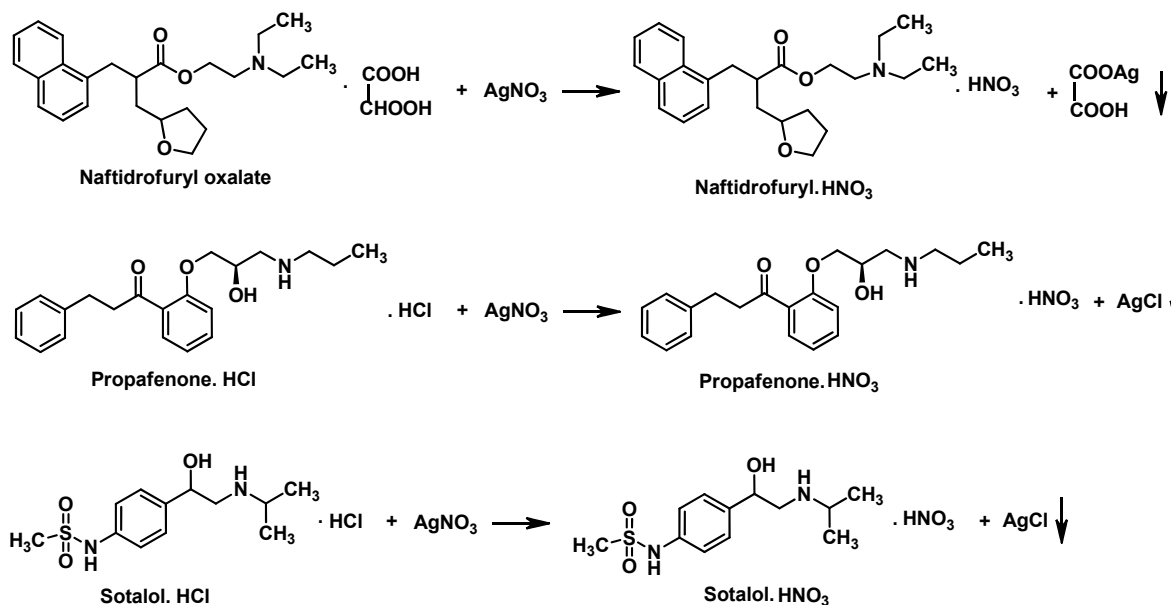
The Jenway 470 model portable conductivity/TDS meter was used for the measurement of conductance.

2.2. Materials and reagents

Naftidrofuryl oxalate was obtained from Mina Pharm, Cairo, Egypt under license of Merck Santé France, Propafenone HCl was purchased from Kahira Pharm. and Chem. Ind. Co., under license of Abott Laboratories. Sotalol HCl was obtained from Amoun Pharm, Egypt. 5×10^{-3} M silver nitrate was used.

2.3. Standard drug solutions

Aqueous solution of 1 mg/mL naftidrofuryl oxalate, propafenone HCl and sotalol HCl were prepared by dissolving 100 mg of the pure drug in 100 mL bi-distilled water.



2.4. Pharmaceutical preparations

1. Praxilene® tablets (Mina Pharm, under licence of Merck Santé France, Egypt) labeled to contain 200 mg naftidrofuryl oxalate per tablet.
2. Rytmonorm® tablets (Kahira Pharm. and Chem. Ind. Co., under the licence from Abott Laboratories, Egypt) labeled to contain 150 mg Propafenone HCl per tablet.
3. Betacor tablets (Amoun Pharm, Egypt) labeled to contain 80 mg sotalol per tablet.

2.5. General procedure

Aliquots of drug solution (1-15 mg) were transferred to a 50 mL calibrated flasks, volumes were made up to the mark using bi-distilled 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 two min., the conductance was corrected for dilution [39] by means of the equation (1), assuming that conductivity is a linear function of dilution.

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

where $\Omega-1_{\text{correct}}$ is the corrected electrolytic conductivity, $\Omega-1_{\text{obs}}$ 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 equation (2),

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

where V is volume of titrant, M is molecular weight of drug, R is molar concentration of titrant and N is no of moles of titrant consumed by one mole of drug.

2.6. Assay of the pharmaceutical formulations

Ten tablets were powdered and an amount equivalent to 100 mg naftidrofuryl oxalate, propafenone HCl and sotalol HCl was shaken with 10 mL distilled water, then filtered and diluted to 100 mL with distilled water.

3. Results and discussion

3.1. Method development

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 naftidrofuryl oxalate, propafenone HCl and sotalol HCl, silver oxalate or silver chloride is precipitated (Scheme 1) 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 , Figures 1-3.

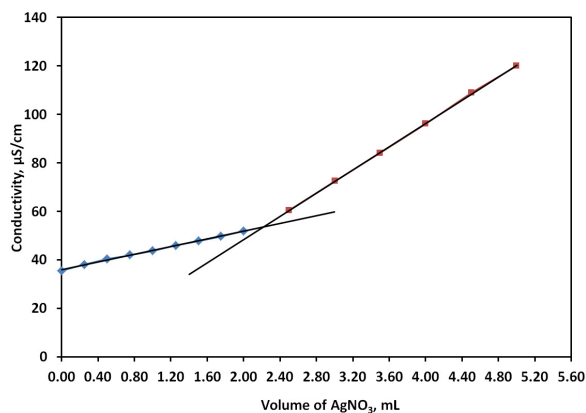
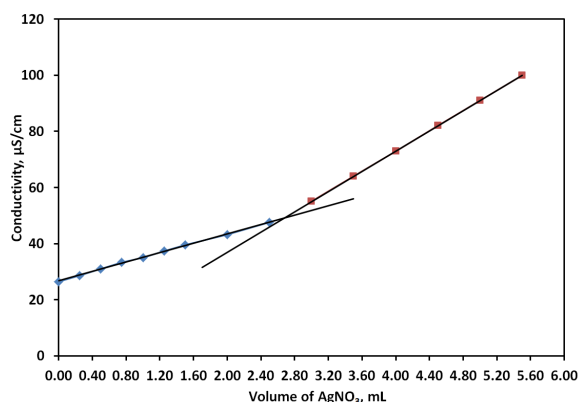
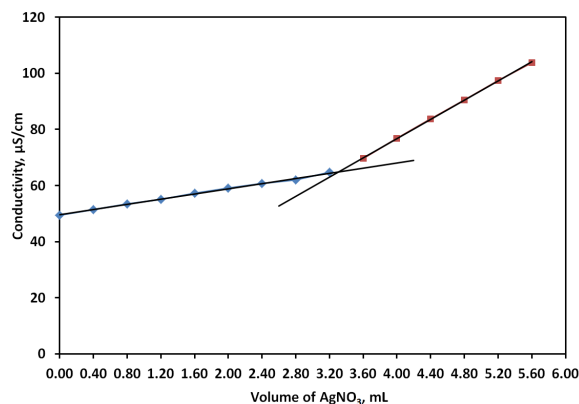


Figure 1. Conductometric titration curve of 5 mg naftidrofuryl oxalate vs silver nitrate (5×10^{-3} M).

Table 1. Conductometric determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl using silver nitrate*.

Compound	Naftidrofuryl oxalate			Propafenone HCl			Sotalol HCl		
	Taken (mg)	Found (mg)	Recovery (%)	Taken (mg)	Found (mg)	Recovery (%)	Taken (mg)	Found (mg)	Recovery (%)
Parameters	1.000	0.995	99.46	1.000	0.997	99.68	1.000	1.002	100.19
	3.000	3.055	101.82	3.000	3.041	101.37	3.000	2.975	99.18
	5.000	5.044	100.88	5.000	4.984	99.68	5.000	4.964	99.28
	7.000	6.962	99.46	7.000	7.096	101.37	7.000	6.983	99.75
	10.000	10.064	100.64	10.000	10.053	100.26	10.000	10.171	101.71
	15.000	15.037	100.25	15.000	14.868	99.12	15.000	14.876	99.18
Mean±S.D.	99.85±0.907			99.40±0.949			99.68±0.980		
N	6			6			6		
V	0.823			0.901			0.960		
S.D.	0.907			0.949			0.980		
R.S.D.	0.909			0.955			0.983		
S.E.	0.371			0.388			0.400		

* S.D.: Standard deviation; N: number of experiments; V: Variance; R.S.D.: Relative standard deviation; S.E.: Standard error; Mean: Mean of three different experiments.

**Figure 2.** Conductometric titration curve of 5 mg propafenone HCl vs silver nitrate (5×10^{-3} M).**Figure 3.** Conductometric titration curve of 5 mg sotalol HCl vs silver nitrate (5×10^{-3} M).

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. The optimum conditions for performing the titration in a quantitative manner were elucidated as described below.

3.1.1. Titrations in different media were attempted to obtain the best results

Preliminary experiments were tried for each drug 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.

It was found that procedure in aqueous media was the most suitable for successful results, as in case of (vi), (vii), (ii), (iii), the initial conductance was very low, the increase in conductance after silver nitrate addition, also was very low or absent and there was no end point inflection, and so end point detection is very difficult.

In case of (i), (iv), (v), the same initial conductance was obtained, then the conductance increased after silver nitrate addition, however in water medium sharpest end point was detected So water was the best and cheapest choice medium for conductometric titration.

3.1.2. Reagent's concentration

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

3.1.3. Effect of temperature

Different temperatures were tested (25, 30, 35 and 40 °C) and it was found that the same results were obtained so room temperature (25 °C) was selected for determination. Temperature couldn't be increased more than 40 °C as conductivity electrode (conductivity cell) could be affected by elevated temperature.

3.2. Validation of the studied method

In order to address the validity of the proposed methods, statistical analysis of the data obtained from their application on the drugs in the pure form and in pharmaceutical formulations was performed.

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

For application (standard addition technique),

$$\text{End point of authentic} = \text{End point of (authentic + End point of tablets)} - \text{End point of tablets} \quad (4)$$

Results revealed in (Tables 1, 2) showed that the proposed methods are satisfactorily accurate, precise and reproducible over a concentration range of 1-15 mg for all the studied drugs

Table 2. Conductometric determination of naftidrofuryl oxalate propafenone HCl and sotalol HCl in their pharmaceutical preparations using silver nitrate*.

Compound	Naftidrofuryl oxalate (Praxilene tablets)				Propafenone HCl (Rytmonorm tablets)				Sotalol HCl (Betacor tablets)			
	Taken (mg/mL)	Added	Found	Recovery (%)	Taken (mg/mL)	Added	Found	Recovery (%)	Taken (mg/mL)	Added	Found	Recovery (%)
	1.000	0.000	1.006	100.64	1.000	0.000	1.014	101.37	1.000	0.000	0.987	98.67
	1.000	2.000	1.977	98.86	1.000	2.000	1.977	98.84	1.000	2.000	2.019	100.95
	1.000	4.000	3.966	99.16	1.000	4.000	4.055	101.37	1.000	4.000	4.023	100.57
	1.000	6.000	5.956	99.26	1.000	6.000	5.964	99.40	1.000	6.000	6.057	100.95
	1.000	9.000	8.939	99.32	1.000	9.000	9.039	100.43	1.000	9.000	9.032	100.36
	1.000	14.000	14.150	101.06	1.000	14.000	14.020	100.16	1.000	14.000	13.890	99.12
Mean±S.D.	99.53 ± 0.873				100.04 ± 0.974				100.41 ± 0.714			
N	5				5				5			
V	0.761				0.950				0.510			
S.D.	0.873				0.974				0.8714			
S.E.	0.390				0.436				0.319			

* S.D.: Standard deviation; N: number of experiments; V: Variance; R.S.D.: Relative standard deviation; S.E.: Standard error; Mean: Mean of three different experiments.

Table 3. Statistical data for the conductometric determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl using silver nitrate.

Drug	Parameters	Silver nitrate method	Reference or reported method
Naftidrofuryl oxalate	Mean±S.D	99.85±0.907	100.05±0.420 [1]
	N	6	3
	Variance	0.823	0.175
	Student-t-test	0.352 (2.365)*	-
	F-test	4.703 (5.790)*	-
Propafenone HCl	Mean±S.D	99.40±0.949	100.29±0.630 [16]
	N	6	3
	Variance	0.901	0.395
	Student-t-test	1.447 (2.365)*	-
	F-test	2.281 (5.790)*	-
Sotalol HCl	Mean±S.D	99.69±0.980	100.11±0.930 [31]
	N	6	8
	Variance	0.960	0.865
	Student-t-test	0.818 (2.179)*	-
	F-test	1.110 (3.970)*	-

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

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 [1, 15] or reported [27] methods for naftidrofuryl oxalate, propafenone HCl or sotalol HCl, respectively. The results showed that there is no significant difference between the proposed and official or reported methods. The results of different statistical data are shown in Table 3.

4. Conclusions

The simple and rapid procedure described in this paper can be an alternative to the more complex and expensive methods for assay of naftidrofuryl oxalate, propafenone HCl and sotalol HCl. There is no interference from the common excipients. The proposed method is easy, cheap, accurate and very useful for the determination of the studied drugs in their pharmaceutical formulations and can be applied in laboratories for routine analysis.

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