Eclética Química
ISSN: 0100-4670
atadorno@iq.unesp.br
Universidade Estadual Paulista Júlio de Mesquita Filho
Brasil

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Eclética Química, vol. 36, núm. 1, 2011, pp. 110-121
Universidade Estadual Paulista Júlio de Mesquita Filho
Araraquara, Brasil

WWW.SCIELO.BR/EQ

VOLUME 36, NÚMERO 1, 2011

Conductometric determination of propranolol hydrochloride in pharmaceuticals

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Abstract:

In this paper the conductometric titration of propranolol hydrochloride in pharmaceutical formulations using silver nitrate as titrant is proposed. The method was based on the formation of an insoluble salt ($AgCl_{(s)}$) between the chloride of propranolol hydrochloride molecule and Ag(I) ions of the titrant $AgNO_3$. The effect of the PROP-$AgNO_3$ concentrations and the interval of time between the successive additions of the titrant on the shape of the titration curve were studied. The obtained recoveries for four samples ranged from 96.8 to 105%. The proposed method was successfully applied in the determination of propranolol hydrochloride in several pharmaceutical formulations, with results in close agreement at a 95 % confidence level with those obtained using official spectrophotometric method.

Keywords: Conductometric titration, propranolol hydrochloride, silver nitrate, pharmaceutical formulations.

Introduction

Propranolol hydrochloride (PROP) (Figure 1), is a cardioselective β-adrenergic receptor blocking agent, which is orally used in the form of chlorhydrates. It is generally prescribed for the treatment of various cardiovascular disorders, such as angina pectoris, hypertension, cardiac arrhythmias, and myocardial infarction [1].

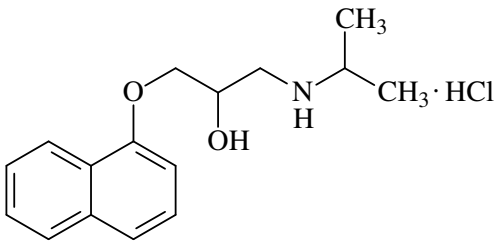

Figure 1. Chemical structure of propranolol hydrochloride.

The British [2] and Brazilian [3] Pharmacopoeias described a potentiometric and a spectrophotometric method of assay, respectively. Several other analytical methods involving colorimetry [4], spectrophotometry [5-9], atomic absorption spectrometry [9], spectrofluorometry [10-13], diffuse reflectance spectroscopy [14], chromatography [15, 16], titrimetry [17], chemiluminescence combined with flow injection analysis (FIA) [18, 19], potentiometry [20], and voltammetry [21-23] were reported. Most of the reported methods possess some disadvantages, such as long analysis time, sample pretreatment, and expensive instrumentation that make them unsuitable for routine analysis.

There is only one conductometric method described for the determination of PROP in pharmaceutical formulations [24]. In this method, Issa and Amin determined PROP by conductometric titration using ammonium reineckate and potassium tetracyanonickelate as titrant in an ethanol-water (50% v/v) mixture. The use of ammonium reineckate should be avoided because of its toxicity.

In this study, a simple, precise, rapid, and low-cost conductometric titration method for the determination of PROP in pharmaceuticals is proposed using silver nitrate as titrant. The same reagent has been employed with success in many analytical methods for pharmaceuticals' quality control [25-31]. The obtained results in this work were compared with those obtained from an official spectrophotometric method [3].

Experimental

Apparatus

Conductometric measurements were carried out in a thermostated glass cell employing an automatic microburet Methrom/Herisau, model E274, a conductivimeter Micronal, model B330 and a conductometric cell Digimed DMC-010. The solution was kept under constant agitation during all measures at a temperature of 25 $\pm$ 1 °C.

The PROP determinations by the spectrophotometric reference method [3] were carried out using a Hewlett Packard UV-visible spectrophotometer, model 8452A, coupled to a microcomputer.

Reagents and solutions

Propranolol and $AgNO_3$ were obtained from Sigma-Aldrich. All solutions were prepared using chemical reagents of analytical grade and ultra-purified water supplied by a Milli-Q system (Millipore®) with resistivity higher than 18 MΩ cm.

The stock solution of 5.0×10^{-2} mol L^{-1} $AgNO_3$ was prepared by dissolving an appropriate mass of this salt in Milli-Q water and the solutions in concentrations varying from 5.0×10^{-4} to 1.0×10^{-2} mol L^{-1} were obtained by adequate dilution of the stock solution.

Conductometric titration

In a thermostated glass cell, a 10-mL aliquot of pharmaceutical solution (reference or sample) was titrated with silver nitrate solution in the same concentration. For each addition of the titrant, in intervals of 15 s, the conductance was determined, and each L_{exp} obtained was corrected using $L_{corr} = L_{exp} \times ((V_i + V_a) / V_i)$, where L_{corr} is the corrected conductance, L_{exp} is the experimental conductance, V_i is the initial volume, and V_a is the titrant added volume. The equivalence volume was obtained in the inflexion point of conductance graph (L_{cor}) versus volume of $AgNO_3$ solution.

Determination of propranolol hydrochloride in commercial samples

Samples containing different amounts of propranolol hydrochloride were purchased from a local drugstore. To prepare the solutions of the PROP commercial samples, a representative number of tablets (10) of each different pharmaceutical dosage was reduced to a homogeneous fine powder in a mortar with a pistil. An adequate amount of the resulting powders was weighed and transferred to a 100-mL calibrated flask, which was dissolved in 100 mL of Milli-Q water. The solutions were filtered in filter paper to remove undissolved solids and then aliquots of 10 mL of filtered solution were titrated with $AgNO_3$ solution.

In order to compare the results obtained with the proposed conductometric method, the spectrophotometric method of the Brazilian Pharmacopoeia [3] for PROP was employed. An

accurate representative amount of powder from each PROP commercial sample in the different dosages was dissolved in methanol. Appropriate dilutions were made from this solution and then the absorbance was measured at 290 nm, in a quartz cell.

Results and discussion

Preliminary Studies

The method was based on the chemical reaction between the chloride of PROP molecule and Ag(I) ions of the titrant $AgNO_3$, yielding the precipitate $AgCl_{(s)}$ of low solubility (1.1×10^{-5} mol L^{-1}) [32].

The interval of time (10, 15, and 20 s) between the successive additions of the titrant using a 1.0×10^{-2} mol L^{-1} PROP and $AgNO_3$ solutions at the same concentration was investigated first. The smaller relative standard deviation and better resolution in the conductometric titration curve was obtained with the interval of time of 15 s between the measurements, which was consequently selected for further studies.

Secondly, the effect of the concentration of the PROP solution from 5.0×10^{-4} to 1.0×10^{-2} mol L^{-1} using the titrant $AgNO_3$ solution, at the same concentration of PROP solution on the shape of the titration curve was investigated. For the PROP concentrations lower than 5.0×10^{-4} mol L^{-1} the addition of the $AgNO_3$ caused small variations in the conductance, due to which the determination of the final point of the titration became unreliable. Hence, taking into account this result, the determination of the equivalence point can be determined until a minimum concentration of 5.0×10^{-4} mol L^{-1} of the PROP solution. It occurs due to the dilution of the solutions and the $AgCl_{(s)}$ solubility formed. As can be seen in Table 1, results obtained using the proposed conductometric method are in agreement with the theoretical values estimated for standard solutions of PROP.

Table 1. Comparison between reference solutions of propranolol hydrochloride and the results obtained by proposed method, at 25 °C

Standard PROP solutions (mol L^{-1})	Experimental (mol L^{-1})	Relative error (%)[a]
5.00×10^{-4}	$(5.03 \pm 0.01) \times 10^{-4}$	0.6
1.00×10^{-3}	$(1.02 \pm 0.01) \times 10^{-3}$	2.0
5.00×10^{-3}	$(4.99 \pm 0.05) \times 10^{-3}$	-0.2
1.00×10^{-2}	$(9.94 \pm 0.03) \times 10^{-3}$	-0.4

[a] Experimental versus theoretical values.

Figure 2 presents a typical conductometric curve obtained for a10 mL of 1.0×10^{-3} mol L^{-1} PROP solution using $AgNO_3$ solution at the same concentration. The conductance measured before the addition of the titrant (volume of $AgNO_3$ solution equal zero) is related to the PROP solution. Until the equivalence point, the titration involves the precipitation of the ions Cl^- with Ag^+.

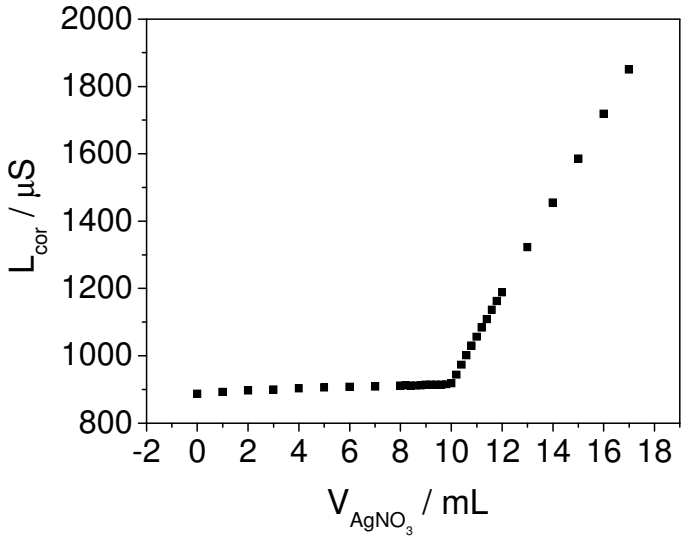

Figure 2. Conductometric titration of 1.0×10^{-3} mol L^{-1} PROP solution using a 1.0×10^{-3} mol L^{-1} $AgNO_3$ solution.

Because of high ionic conductivity of the ions H^+ (H_3O^+) it was expected that the first branch of the titration curve would have a slope higher than that observed experimentally (Figure 3). These results indicate that while chloride ions are being titrated, the ions H^+ (H_3O^+) were not released into the solution and the amino group of PROP molecule been protonated. Thus, the low slope of the conductometric curve is due to the increase of the nitrate concentration from titrant solution. After the equivalence point, as volumes of the titrant solution are added, a sharp rise occurs in the conductance because of the excessive volume of the $AgNO_{3(aq)}$ solution added. The increase of the concentrations of $Ag^+(aq)$ and $NO_3^-{}_{(aq)}$ in the remaining solution promotes the increase of the second branch slope of the titration curve. The end-point was determined by the intersection point of the two straight lines.

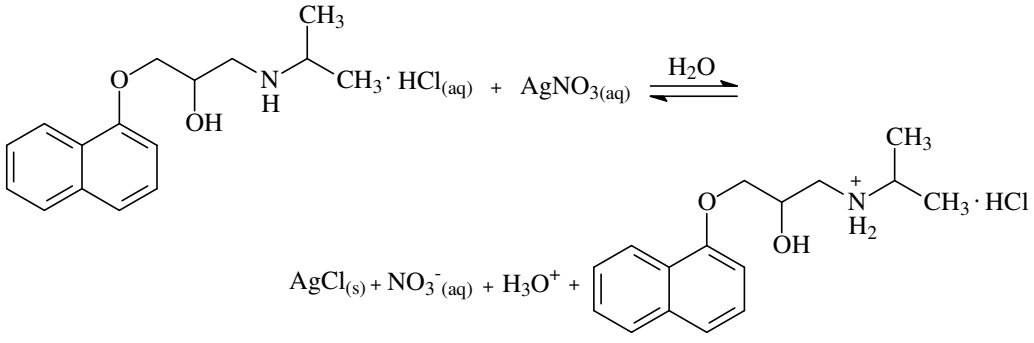

Figure 3. Reaction involved in conductometric titration of the PROP with $AgNO_3$ solution.

The repeatability of the conductometric method was determined by successive titrations (n = 5) of 1.0×10^{-3} mol L^{-1} PROP solution with a 1.0×10^{-3} mol L^{-1} $AgNO_3$ solution, when relative standard deviations smaller than 0.5% were obtained.

Interferences and recovery study

The effect of some potential interferent compounds was investigated by addition of the different concentrations of these compounds to standard solutions containing 1.0×10^{-3} mol L^{-1} of PROP solution. The excipients, hydrochlorothiazide (associated with PROP), manithol, lactose, starch, povidone, magnesium stearate, and magnesium carbonate, present in the analyzed pharmaceutical samples were tested. The obtained responses showed that these compounds do not interfere in the determination of PROP at the used working conditions.

To evaluate the recovery of the PROP from pharmaceutical products, four commercial samples were used. Recoveries of the analytes were examined by adding standard solution of PROP at three concentrations (1.0×10^{-3} mol L^{-1}, 3.0×10^{-3} mol L^{-1} and 5.0×10^{-3} mol L^{-1}) to pharmaceutical products and the results obtained were compared with the added concentrations. The results showed good recoveries for the commercial tablets, ranging from 96.8 to 105%, indicating that there is not any important matrix interference for the samples analyzed by the proposed conductometric method.

Analytical Application

Table 2 presents the PROP concentrations determined in commercial tablets of different dosages employing the proposed conductometric titration and a comparative spectrophotometric method of the Brazilian Pharmacopoeia [3]. Three determinations were carried out for each sample, and the standard deviations were calculated. As it can be seen in this table, no significant differences were observed between the values found for the amounts of PROP in the tablets

using the conductometric titration proposed method and the spectrophotometric reference method [3].

Table 2. Determination of propranolol hydrochloride (PROP) in pharmaceutical formulations by spectrophotometric reference method and by the proposed conductometric method

	PROP (mg/tablets)			
Sample	Label value	Reference method[a]	Conductometric method[a]	Relative error (%)[b]
A	10	9.93 ± 0.08	9.98 ± 0.02	0.50
B	40	40.3 ± 0.7	40.6 ± 0.5	0.74
C[c]	40	40.1 ± 0.6	39.6 ± 0.4	-1.2
D	80	78.8 ± 0.9	77.0 ± 0.8	-2.3

[a] Average of 3 measurements.

[b] [100 × (conductometric value – reference method)] / reference method.

[c] Containing 25 mg hydrochlorothiazide.

Beside, the paired *t*-test [33] was applied to the results obtained for PROP using both methods; since the calculated *t* value (0.9015) is smaller than the critical value (3.182, $\alpha = 0.05$), it may conclude that the results obtained with the proposed procedure are not statistically different from those from the comparative method, at a 95 % confidence level.

Conclusions

The proposed conductometric procedure for PROP determination in pharmaceutical products is simple, precise, of low cost, faster than the conductometric method reported in the literature [24] and, could be implemented in laboratories for routine analysis.

Acknowledgements

The authors gratefully acknowledge the financial support from the Brazilian foundations (FAPESP (Proc. 2009/14454-8; 2009/04048-2), CAPES and CNPq).

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Determinação condutométrica de cloridrato de propranolol em farmacêuticos

Resumo: Neste trabalho descreve-se a titulação condutométrica do cloridrato de propranolol em formulações farmacêuticas usando nitrato de prata como titulante. O método é baseado na formação de um sal insolúvel ($AgCl_{(s)}$) entre o cloreto da molécula do cloridrato de propranolol e os íons Ag(I) do titulante $AgNO_3$. O efeito das concentrações PROP-$AgNO_3$ e o intervalo de tempo entre adições sucessivas de titulante no formato da curva de titulação foram estudados. Recuperações para quatro amostras variaram de 96,8 a 105%. O método proposto foi aplicado na determinação do cloridrato de propranolol em diversas formulações farmacêuticas, com resultados concordantes com àqueles obtidos empregando-se o método oficial espectrofotométrico, a um nível de confiança de 95 %.

Palavras-chave: Titulação condutométrica, cloridrato de propranolol, nitrato de prata, formulações farmacêuticas.