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Coulometric determination of some antiasthmatics*

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Abstract: A simple and rapid method for the assay of microquantities of fenoterol hydrobromide, orciprenaline sulphate and terbutaline sulphate in pure state and various pharmaceutical formulations, is presented. The method is based on the coulometric titration of the investigated compounds with electrogenerated chlorine in the presence of methyl orange as indicator. The method requires a simple apparatus and gives accurate and reproducible results.

Keywords: *Chlorocoulometric titration; drug analysis; antiasthmatics; fenoterol; orciprenaline; terbutaline.*

Introduction

Fenoterol, orciprenaline and terbutaline are antiasthmatic drugs which act mainly on beta$_2$-andrenergic receptors. They are direct-acting sympathomimetic agents with actions and uses similar to those of salbutamol.

Various analytical methods have been applied to these compounds. Orciprenaline sulphate in bulk has been determined by the titration in non-aqueous media [1], whereas in tablets [2] and injection solution [3] it was analysed spectrophotometrically and spectrofluorometrically [4]. Terbutaline in bulk has been determined by titration method in non-aqueous media [5] as well as spectrophotometrically [6]. Fenoterol hydrobromide has been analysed volumetrically in non-aqueous media [7], whereas small amounts of this compound were determined spectrofluorometrically [8]. Micro amounts of these substances have been determined by HPLC (fenoterol hydrobromide [9], orciprenaline sulphate in injection solutions and various dosage forms [10], terbutaline sulphate [11]).

Patriarche *et al.* [12–17] have published a great number of papers on coulometric determinations of pharmacologically active substances in various pharmaceutical preparations with electrogenerated oxidants such as cerium (IV), manganese (III), silver (II), gold (III) and titanium (III), along with electrogenerated halogens (chlorine, bromine and iodine) which gave rise to oxidation and halogenation reactions.

Chemical properties of the investigated substances make possible various oxidation and halogenation processes which can be applied to their quantitative analysis.

Experimental

Apparatus

The apparatus used consisted of an electrolytic cell connected to a current stabilizer (Mihailo Pupin, type STNS 50260) which produces a direct current of 1–100 (±0.03 mA) and a resistance of the electrolytic cell ranging up to 60,000 Ω. The current was measured with a "Chauvin Arnoux" milliammeter. The cathode and anode compartments of the electrolytic cell were separated by a sintered glass G-4 disk. The levels of liquids in both compartments were the same in order to avoid the mixing of electrolytes. Platinum electrodes of an area of 2 cm^2 were used.

Reagents and materials

Fenoterol hydrobromide and its aerosol preparation Berotec as well as orciprenaline sulphate and its pharamceutical dosage forms aerosol Alupent and ampoules of the latter preparation were produced by Zdravlje (Leskovac). Terbutalin tablets and Bricanil syrup were the product of Bosnalijek (Sarajevo).

Standard solution and sample preparation

All standard solutions used contained 0.1 mg ml^{-1} of the investigated substances

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dissolved in methanol. Standard solution for the quantitative analysis of aerosols, injection solutions and syrups were prepared by taking the corresponding amounts of the investigated pharmaceutical preparation.

For the determination of the content of terbutaline sulphate in tablets, 10 tablets were weighed, pulverized and a portion containing nominally 10 mg of terbutaline sulphate was weighed, treated with 90 ml of methanol with stirring, filtered off and filtrate was made up to 100 ml with methanol.

The indicator solution contained 10 mg of methyl orange dissolved in 100 ml of water. The supporting electrolyte comprised 0.5 M sulphuric acid and 0.2 M sodium chloride. All chemicals used were of analytical reagent grade.

Procedure

In the anode compartment were placed 50 ml of the supporting electrolyte, 0.5 ml of the indicator solution and an accurately measured volume of the solution containing the relevant amount of the investigated substance. A constant current of 1 mA was passed through the solution until the colour was bleached. The time of the titrant generation was measured with a chronometer, and a blank was run in parallel. The difference between the number of coulombs consumed for the titration of the investigated solution and the blank gives the number of coulombs, from which the amount of the investigated substance was calculated via Faraday's laws. One coulomb corresponds to 0.3982 mg of fenoterol hydrobromide, 0.3371 mg of orciprenaline sulphate and 0.35529 mg of terbutaline sulphate, respectively.

Results and Discussion

A common chemical feature of terbutaline, orciprenaline and fenoterol is the presence of phenolic groups and a secondary amino group whose nitrogen atom can be protonated. All the investigated substances can appear as an equilibrium mixture of four different forms depending on pH. These equilibria comprise cations, zwitterions, anions and neutral molecules. All the aforementioned ionic forms can take part in various concurrent reactions which can proceed at different rates on account of their different polar properties. All these ionic species can react with chlorine and bromine but, since the reaction may proceed at different rates and since concurrent processes can occur as well, we had to establish experimental conditions under which the undesired concurrent processes are avoided. In addition, we had to use an indicator whose chlorination rate is slower than the chlorination rates of the investigated substances.

On the basis of experimental experience we decided to carry out the chlorination of investigated substances at pH about 0.9, since under these conditions all the investigated substances are practically in the cationic form, avoiding the possibility of undesired concurrent reactions, and to use methyl orange as indicator.

The reaction between electrogenerated chlorine and the compounds investigated is a complex process which involves a relatively great number of chlorine molecules. It has been found that under the conditions applied orciprenaline and terbutaline react with chlorine in a 1:4 molar ratio, whereas in the case of fenoterol that ratio is 1:5. The difference in the number of chlorine molecules consumed in the reaction with fenoterol with respect to those consumed with other two investigated substances is due to their different structures, namely, orciprenaline and terbutaline differ only in one methyl group in the side chain, whereas fenoterol contains a 4-hydroxyphenyl group in the side chain. We assume that in the reaction of electrogenerated chlorine with the investigated substance two main processes take place: electrophilic substitution of the resorcinol moiety which involves the consumption of three chlorine molecules, and the oxidation of the secondary benzylic alcoholic group to the corresponding keto group in which an additional chlorine molecule is consumed. Thus, orciprenaline and terbutaline consuming four chlorine molecule give rise to compounds **1a** and **1b** in Fig. 1. In the reaction with fenoterol five chlorine molecules are consumed since the *p*-hydroxyphenyl group in the side chain is also oxidized with chlorine to the corresponding *p*-quinone grouping giving rise to compound **1c**.

Since the rate of chlorination with electrogenerated chlorine is very important for the progress of the quantitative reaction, we have established experimentally that by using a constant current of 1 mA, accurate and reproducible results, are obtained (Table 1).

All the investigated substances are present in various pharmaceutical preparation which in

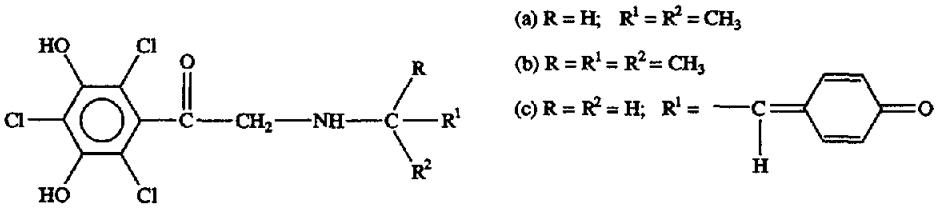

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Figure 1
Reaction of investigated compounds with electrogenerated chlorine.

Table 1
Results of the coulometric determination

Taken (mg)	Found (mg) (±SD, n = 7)	Found (mg) (±SD, n = 7)	Found (mg) (±SD, n = 7)
	Orciprenaline sulphate		
	Pure substance	Alupent spray	Alupent injections
0.0100	0.0101 ± 0.0001	0.0101 ± 0.0001	0.0100 ± 0.0001
0.0200	0.0201 ± 0.0001	0.0201 ± 0.0001	0.0201 ± 0.0001
0.0300	0.0299 ± 0.0002	0.0300 ± 0.0002	0.0301 ± 0.0002
0.0400	0.0400 ± 0.0002	0.0399 ± 0.0002	0.0400 ± 0.0002
0.0500	0.0500 ± 0.0002	0.0499 ± 0.0002	0.0499 ± 0.0002
	Terbutaline sulphate		
	Pure substance	Tablets	Bricanil syrup
0.0100	0.0102 ± 0.0001	0.0099 ± 0.0001	
0.0200	0.0202 ± 0.0001	0.0197 ± 0.0001	
0.0300	0.0301 ± 0.0002	0.0297 ± 0.0002	0.0306 ± 0.0002
0.0400	0.0401 ± 0.0002	0.0396 ± 0.0002	0.0406 ± 0.0002
0.0500	0.0499 ± 0.0002	0.0495 ± 0.0002	0.0508 ± 0.0002
	Fenoterol hydrobromide		
	Pure substance		Berotec spray
0.0100	0.0101 ± 0.0001		0.0101 ± 0.0001
0.0200	0.0200 ± 0.0001		0.0196 ± 0.0001
0.0300	0.0300 ± 0.0002		0.0302 ± 0.0002
0.0400	0.0396 ± 0.0002		0.0396 ± 0.0002
0.0500	0.0498 ± 0.0002		0.0499 ± 0.0002

addition to the active substance, contain various excipients and ingredients. Although the oxidation potential of the chlorine–chloride couple is such that many substances can be oxidized, we have established that the presence ingredients such as sucrose and lactose, and excipients such as talc and starch do not affect the accuracy of the determination. Similarly, the presence of various ingredients in the investigated pharmaceutical preparation listed in Table 1 was found not to interfere with the electrochemical and chemical processes which proceeded quantitatively, hence these pharmaceutical preparations could be directly assayed. This is a great advantage of this method.

The presence of phenone which can appear as impurity arising from the oxidation of investigated compounds does not affect the accuracy of the analytical procedure proposed.

In comparison with other methods prescribed by different pharmacopoeias, the procedures of which require 5 mg amounts of substances, the chlorocoulometric method is advantageous in that it can be carried out with microgram amounts of investigated compounds. Due to the use of a simple apparatus and direct analytical procedure, this method

can be recommended for the routine analysis of investigated substances.

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