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Short Communication

Coulometric determination of nizatidine*

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Introduction

The H_2-receptor antagonists, metiamide and cimetidine are based structurally on the imidazole nucleus of histamine. Nizatidine is a competitive and selective antagonist of histamine at H_2-receptor sites and an effective inhibitor of gastric secretion. Nizatidine, which differs structurally from the earlier H_2-receptor antagonists in having a thiazole nucleus, in the inhibition of histamine-induced gastric acid secretion is more potent than cimetidine. Nizatidine is known to be effective in the treatment of gastric acid and duodenal ulcerous.

Liquid chromatography methods for the determination of nizatidine in human serum [1], urine [2, 3] and in pharmaceutical formulations [4] have been reported.

The chemical properties of nizatidine make possible various chemical reactions and, therefore, it was necessary to select the most suitable conditions for the determination of this compound. There is a great interest in determining small amounts of nizatidine, without the use of complicated chemical transformations. The present paper reports on the results obtained from a study of the reaction of nizatidine, with electrogenerated chlorine used as a titrant, in coulometric determination of this substance both in pure state and pharmaceutical formulations.

Experimental

Apparatus

The apparatus used is described in a previous paper [5].

Reagents and materials

Nizatidine was kindly supplied by Galenika (Belgrade). The identity and purity of the substance were verified by TLC and by UV, IR spectra. Galitidine capsules and ampoules were produced by Galenika.

The supporting electrolyte for chlorocoulometric titration contained 0.5 M sulphuric acid and 0.2 M sodium chloride. The indicator solution contained 10 mg of methyl orange in 100 ml of water. The stock solution for the analysis of nizatidine in capsules and in ampoules nominally contained 0.1 mg in 1 ml of water. All solutions were made immediately prior to use and all chemicals used were of analytical reagent grade.

Procedure

In the anode compartment of the apparatus for the coulometric titration were placed: 20 ml of the supporting electrolyte, 0.1 ml of the indicator solution and aliquots of the stock solution of nizatidine. A constant current of 1 mA was passed through the solution until the red colour of the indicator was bleached. The time of the titrant generation was measured

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with a chronometer and a blank was run in parallel. The difference between the number of coulombs used in the titration of the solution being analysed and the blank gave the number of coulombs for the titration of the investigated substance. The amount of nizatidine was calculated using Faraday's laws. One coulomb corresponded to 0.4294 mg of nizatidine.

Discussion and Results

Key chemical features of nizatidine are the presence of a thio group and a secondary amino group whose nitrogen atom can be protonated. The investigated substance can appear as equilibrium mixtures of two different forms depending on the pH. These equilibria comprise cations and neutral molecules. All these species can react with chlorine and bromine but, since the reaction may proceed at different rates and since concurrent processes can occur as well, were experimental conditions established to avoid the undesired concurrent processes.

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

Nizatidine possesses some structural similarity to ranitidine but differs in an essential point. Instead of the furane ring which makes the core of the raniditine molecule, nizatidine contains a thiazole ring.

Under the same experimental conditions these substances showed the difference in the reaction with chlorine and bromine. In supporting electrolyte for the chloro- and bromocoulometric titration ranitidine reacted with halogens in a 1:5 molar ratio [6], whereas in the case of nizatidine that ratio was 1:2. The difference in a number of halogens molecules consumed in the reaction with those substances was due to their different structures, i.e. the presence of a thiazole and furane ring in their molecules.

It was assumed that in the reaction with nizatidine two main processes took place: the oxidation of the nizatidine to the corresponding N-oxide (I) of nizatidine or to the corresponding S-oxide (II) of nizatidine (Fig. 1). These substances are known metabolites of nizatidine [1].

Before applying the method to the analysis of various pharmaceutical preparations, synthetic mixtures of nizatidine and a wide variety of excipients were investigated. It was established that the presence of excipients such as stearic acid, povidone, cellulose, starch, talc, mannitol, stearyl alcohol, polyethylene glycol and carbopol did not affect the accuracy of the determination. Hence, the determination of nizatidine in capsules and in injection solutions could be carried out directly.

Table I shows that the results are accurate

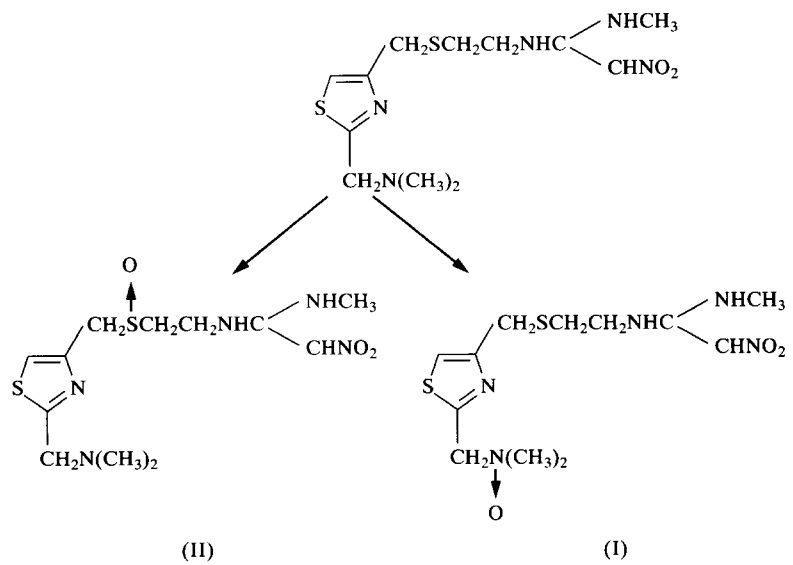

Figure 1
Reaction of nizatidine with electrogenerated halogens.

Table 1
Results of the coulometric determination

Taken (mg)	Found (mg) (±SD, $n = t$) Pure substance	Found (mg) (±SD, $n = 7$) Capsules	Found (mg) (±SD, $n = 7$) Ampoules
0.0100	0.0100 ± 0.0001	0.0101 ± 0.0001	0.0099 ± 0.0001
0.0200	0.0200 ± 0.0001	0.0201 ± 0.0001	0.0199 ± 0.0001
0.0300	0.0299 ± 0.0002	0.0300 ± 0.0002	0.0299 ± 0.0002
0.0400	0.0399 ± 0.0002	0.0399 ± 0.0002	0.0398 ± 0.0002
0.0500	0.0499 ± 0.0002	0.0499 ± 0.0002	0.0498 ± 0.0002
0.0600	0.0598 ± 0.0002	0.0598 ± 0.0002	0.0598 ± 0.0002

and reproducible, and that the proposed chlorocoulometric method can be applied to the determination of nizatidine. Due to a simple procedure which does not involve complex chemical transformations, this uniform electroanalytical method can be performed rapidly and is therefore recommended for routine determination of nizatidine in pure state and in pharmaceutical formulations.

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