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Titrimetric semi-micro Determination of Sodium Metamizole with Potassium hydrogenperoxymonosulphate

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ABSTRACT

A simple, rapid and accurate titrimetric procedure using potassium hydrogenperoxymonosulphate have been developed for the semi-micro determination of sodium metamizole in pure form and in tablets. The proposed method is based on the oxidation of bisulfite ions formed as a result of acid hydrolysis of sodium metamizole by known excess of the potassium hydrogenperoxomonosulphate with the following determination of the residual oxidant by iodometric titration. The optimum reactions conditions and other analytical parameters are evaluated. The influence of the substrates commonly employed as excipients with sodium metamizole has been studied. Statistical comparison of the results with those of an official method shows excellent agreement and indicates no significant difference in precision. RSD ≤1.49%; (δ =0.49 - 0.84%). LOQ=0.01 mg.

1. Introduction

Sodium metamizole is a derivative of pyrazole (sodium [1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-N-methylamino]methanesulfonate). It belongs to the pharmacotherapeutic group of drugs "Analgesics and antipyretics" (ATS Code N02B B02), has an analgesic, antipyretic and anti-inflammatory effect as a result of inhibiting the synthesis of prostaglandins, etc.[1, 2]. Its use as such has lately significantly decreased in the majority of European countries because of a series of side effects. However, sodium metamizole is widely used as part of combined drugs. As for today the domestic pharmaceutical market is represented by more than ten drugs containing sodium metamizole. It is produced as a powder substance, tablets of 0.5 g, which include refined sugar, potato starch, calcium stearate and talc

as excipients in addition to the active component, fat-based rectal suppositories for children of 0.1 and 0.25 g, solution for injections 25% and 50% in ampoules of 2 mL and also as combined drugs, for example, with quinine hydrochloride (Analgin-chinin®), pitofenone hydrochloride and fenpiverine bromide (Spasmalgon®) of 0.5 g to 1 tablet, or 1 mL of solution for injections, tempidone (Tempalgin®) and diphenhydramine (Analdim) in the form of tablets, etc.[2, 3].

"Analgin-Quinine" is a combined drug, which includes metamizole and quinine as APIs. Alkaloid quinine has an antipyretic effect, suppresses the thermoregulatory center. It has an anti-inflammatory and antibacterial effect, reduces the excitability of the myocardium and detects an antiarrhythmic effect. Quinine has a stimulating effect with a paralyzing effect on sensitive nerves.

Most of the titrimetric methods for the quantitative determination of sodium metamizole, including the official method of iodimetric titration[4], are based on its easy oxidizing ability by various oxidants such as free iodine (triiodide), iodine monochloride, potassium iodate, potassium permanganate, cerium (IV) sulfate[5, 6]. The disadvantages of these methods are low selectivity and comparatively low precision as a result of a series of side reactions and relatively low stability of titrant solutions. Because of this the achievement of titration endpoints is delayed and the reproducibility of the analysis results is insufficient. In addition, there is a loss of sulfur (IV) oxide in the process of titration in an acidic medium, which leads to underestimated results. Oxidation by iodine occurs too slowly, and on the contrary, the volatility of free iodine leads to overestimated determination results. Iodine monochloride has the same disadvantages. The State Pharmacopoeia of Ukraine (SPhU) recommends titration with a 0.05 mol/L triiodide solution at a temperature of +10ºC to obtain correct results, but it is very inconvenient[4]. Some number of sensitive and selective methods of extraction-photometric determination of sodium metamizole in a solution for injections and various combined drugs using the main dyes of the triphenylmethane line are described[7-10]. Their disadvantage is usage of toxic solvents such as dichloroethane, toluene, etc. to remove associates. Methods of quantitative determination of sodium metamizole by fluorimetry[11], flow-injection method with spectrophotometric registration[12], and chemiluminescence[13] are also described in the scientific literature. All these methods require the availability of expensive equipment and standard samples of the drug and highly qualified specialists, moreover, most of the methods are long-term in preparation and implementation.

Deserving of attention are methods based on the oxidative decomposition of sodium metamizole by hydrogen peroxide in an alkaline or acidic medium with the formation of sulfate ions, which are determined by the precipitation titration method with a 0.05 mol/L barium chloride solution in the presence of acetone or acidimetric titration (visually with nitrochromazo or pH-potentiometrically) respectively[14].

In the present work we have proposed sufficiently simple, rapid and accurate titrimetric procedure using potassium hydrogenperoxymonosulphate as reagent for the semi-micro determination of sodium metamizole in pure form and in tablets. This method is based on the oxidation of bisulfite ions formed as a result of acid hydrolysis of sodium metamizole by peroxomonosulfuric acid with the following determination of the residual oxidant by the iodometric titration.

2. Materials and Methods

The triple potassium salt of Caro acid $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ ("*Oxone*®") (Sigma-Aldrich, USA) of "extra pure" qualification with potassium hydrogenperoxymonosulphate ($KHSO_5$) as the active substance was used as an analytical reagent. The content of active oxygen according to iodometric titration was 4.5%. A weight of about 0.615 g of oxone was dissolved in 100 mL of double-distilled water in a 100 mL flask to make a working solution of potassium hydrogenperoxymonosulphate 0.02 mol/L.

The pH value of the solutions was controlled using a glass electrode ЭСЛ-43-07 on an ionmeter "Laboratory ionmeter I-160M" (Belarus) paired with an argentumchloride electrode saturated with potassium chloride ЭВЛ-1М3.1.

The used bulk of sodium metamizole met the re-

quirements of the SPhU. The pure form of sodium metamizole contains main substance not less than 99.0% and not more than 101.0% in terms of dry substance; loss in weight on drying: not less than 6.0 and not more than 10.0%. Manufacturer: Hebei Jiheng (Group) Pharmaceutical Co., Ltd. (China).

We analyzed "Analgin-Darnytsia" tablets 500 mg of sodium metamizole No. 10 with excipients: potato starch, talc, calcium stearate; with the content of sodium metamizole 505 mg/tab (475-525 mg/tab). PrJSC "Pharmaceutical firm "Darnytsia". (Ukraine), series number: BE 550521. Certificate 035/2019/GMP.

To prepare model solutions, excipients potato starch, talc, calcium stearate of pharmacopeial purity were used.

Solutions of sodium thiosulfate c($Na_2S_2O_3 \cdot 5H_2O$, f=1)=0.1 mol/L and sulfuric acid c(H_2SO_4)=1 mol/L were prepared from fixanals of the titer standard. A 0.02 mol/L sodium thiosulfate solution was used as a titrant, which was prepared by the appropriate dilution of the starting solution with distilled water. A class 2 10 mL microburette was used to measure titrant volume with a precision of ±0.01 mL. A 5% solution of potassium iodide was produced by the volume-weight method.

General determination procedure.

The method of quantitative determination of sodium metamizole in pure form.

50 mL of distilled water and 10 mL of a 1 mol/L sulfuric acid solution were added to a 100 mL flask. About 0.20 – 0.42 g (exact weight) of sodium metamizole substance was dissolved in 50 mL of distilled water and the volume was diluted to 100 mL. 10.0 mL of the sodium metamizole solution was transferred to a 100 mL flask with a sulfuric acid solution, 10.0 mL of a 0.02 mol/L potassium hydrogenperoxymonosulphate solution was added and then the volume of was diluted to 100 mL with distilled water and mixed thoroughly. After 10 min, 10.0 mL of the solution was transferred to a conical flask for titration and 2 mL of 5% potassium iodide solution was added. The released iodine was titrated with a 0.02 mol/L sodium thiosulfate solution. A control experiment was conducted in parallel. The content of the main substance of sodium metamizole in the bulk X, in %, was calculated by the formula (1).

$$X = \frac{(V_0 - V) \cdot K \cdot T \cdot 10 \cdot 10 \cdot 100}{G \cdot (100 - w)} \cdot 100\% \quad (1)$$

where, V_0 is volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the control experiment, mL; V is volume of the standard 0.02 mol/L sodium thiosulfate solution used for titration in the working experiment, mL; K is concentration correction coefficient of the standard solution of sodium thiosulfate to 0.0200 mol/L; T is quantity of sodium metamizole corresponding to 1 mL of standard 0.0200 mol/L sodium thiosulfate solution, g/mL; 10, 10 is dilution coefficients; G is weight of the substance, g; 1 mL of a standard 0.0200 mol/L solution of sodium thiosulfate corresponds to 0,0035136 g of sodium metamizole, which should be 99.0-101.0% in the substance in terms of dry substance, w is loss in weight during drying,%.

The method of quantitative determination of sodium metamizole in tablets.

About 0.39 g (exact weight) of the powder of crushed tablets was dissolved in a 100 mL flask in 50 mL of distilled water and the volume was diluted to 100 mL with distilled water, filtered through a paper filter. Next, the determination was carried out in the same way as when determining the content of the main substance in the bulk of sodium metamizole. The content of sodium metamizole in tablets X, in g, was calculated by the formula (2).

$$X = \frac{(V_0 - V) \cdot K \cdot T \cdot 10 \cdot 10 \cdot \overline{m}}{G} \quad (2)$$

where, is average weight of the tablet; G is weight of the powder of crushed tablets, g; everything else is as in the previous method. 1.00 mL of a standard 0.0200 mol/L solution of sodium thiosulfate corresponds to 0.0035136 g of sodium metamizole, which should be 0.475-0.525 g in a tablet based on the average weight of one tablet.

3. Results.

The results of determining sodium metamizole in pure form and tablets are presented in Table 1 and Table 2.

Table 1. Results of determination of sodium metamizole content in pure form
(n = 5; P = 0.95)

Amount taken* mg	Amount found	Recovery ± RSD %	** %
2.06	2.07±0.035	100.49±1.37	0.49
3.58	3.61±0.039	100.84±0.87	0.84
4.22	4.25±0.04	100.71±0.75	0.71

** The content of sodiūm metamizole was determined according to data of the standard pharmacopoeial method, μ[4]. ** δ = (x - μ) 100%/ μ*

This good level of precision was suitable for analysis of sodium metamizole in its pharmaceutical dosage forms.

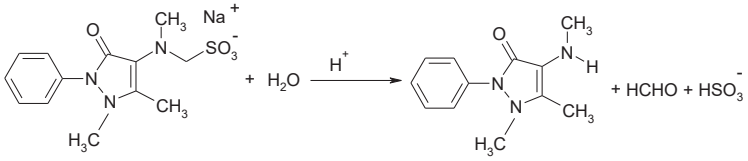
Table 2. Results of determination of sodium metamizole content in tablets
"Analgin-Darnytsia", PrJSC "Pharmaceutical firm "Darnytsia", Ukraine; (n = 5; P = 0.95)

Amount taken* mg	Amount found	Recovery ± RSD %	** %
4.04	4.07±0.075	100.74±1.49	0.74
5.05	5.09±0.078	100.79±1.23	0.79
6.06	6.10±0.083	100.66±1.09	0.66

** The content of sodium metamizole was determined according to data of the Certificate of Analysis. ** δ = (x - μ) 100%/ μ*

4. Discussion.

Sodium metamizole is quantitatively hydrolyzed in an acidic medium under the conditions of the analysis with the formation of monomethylaminoantipyrine, formaldehyde and bisulfite ions, which are immediately quantitatively oxidized by potassium hydrogen peroxomonosulfate:



$$HSO_3^- + HSO_5^- \rightarrow 2HSO_4^- \leftrightarrow 2H^+ + SO_4^{2-}.$$

The results of studying the stoichiometry of the reaction show that monomethylaminoantipyrine and formaldehyde under the conditions of analysis (pH 1.2-1.7) show complete inertness to hydrogenperoxymonosulphate and triiodide ions. 0.1 or 1.0 mmol of hydrogenperoxymonosulphate is consumed when interacting with 0.1 or 1.0 mmol of sodium metamizole respectively; that is, the quantity of oxidant consumed in the reaction, which is found by the back iodometric titration method, is equivalent to the content of sodium metamizole in the solution.

$$HSO_5^- + H^+ + 2KI = I_2 + H_2O + SO_4^{2-} + 2K^+$$

$$I_2 + 2Na_2S_2O_3 = Na_2S_4O_6 + 2\,NaI$$

The time of acid-oxidative decomposition of sodium metamizole under the action of potassium hydrogenperoxymonosulphate does not exceed 10 min at 20ºC. It was established in separate experiments that the excipients included in the tablets do not affect the stoichiometry of the analytical reaction.

The accuracy and precision of the developed method was determined at three levels of sodium metamizole concentration. Five replicates of each sample were analyzed. The obtained relative

standard deviations, RSD did not exceed 1.49%, and assessment of the significance of the systematic error showed that the calculated values of the relative systematic error, $\delta = (\bar{x} - \mu) \cdot 100\ \%/\mu$, did not exceed the half-width of the relative confidence interval $t_\alpha \times RSD / \sqrt{n}$, which indicates a fairly high reproducibility and correctness of the results obtained. LOQ=0.01 mg.

A number of substances that may be present in preparations with sodium metamizole as excipients were studied under analytical conditions, comparing the difference in titart volumes (V_0 - V) (see analysis method) in the absence and presence of their regulated quantities. The following substances in the indicated quantities had virtually no effect on the difference (V_0 - V) and therefore do not interfere with the analysis: potato starch - 2 mg, talc - 13 mg, calcium stearate - 5.5 mg and sodium lauryl sulfate - 5.5. mg (excipients).

5. Conclusions

New methods were developed and the possibility of quantitative determination of sodium metamizole in pure form and in "Analgin" tablets of 0.5 g was shown. The methods are carried out according to the reaction of peroxoacidic oxidation which are based on the oxidation of bisulfite ions formed as a result of the acid hydrolysis of sodium metamizole with peroxomonosulfuric acid with following determination of the residual oxidant by the method of iodometric titration. They are characterized by sufficiently high selectivity, rapid and simplicity of execution and satisfactory precision and do not require the use of toxic reagents or special conditions of execution, which corresponds to the principle of "Green Chemistry". This method can be suitable for determining of other sulfur-containing compounds. □

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