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MONITORING OF THERMAL AND OXIDATION STABILITY OF SODIUM PICOSULFATE BY MODIFIED RP-HPLC METHOD

A selective, precise and stability-indicating, modified high performance liquid chromatographic method for the analysis of sodium picosulfate both as a bulk drug and in formulations was developed and validated. As the method could effectively separate the drug from its degradation product, it can be employed as a stability-indicating one. The chromatographic separation was achieved on a ZORBAX Eclipse XDB C-18 analytical column. The mobile phase consisted of phosphate buffer (pH 7):acetonitrile (85:15 v/v). The absorbance was monitored with a DAD detector at 263 nm. The flow rate was 1.5 mL min^{-1}. Statistical analysis proved the method is repeatable, selective, and accurate for estimation of sodium picosulfate in the presence its degradation product. Forced degradation studies were performed on bulk sample of sodium picosulfate using heat (25, 40, 60 and 80 °C) and oxidation (0.1, 0.5 and 1% v/v hydrogen peroxide). The proposed method was successfully applied, with excellent recovery, to the analysis of a pharmaceutical formulation (Sodium picosulfate, Zdravlje-Actavis, Serbia).

Key words: sodium picosulfate; degradation; RP-HPLC; stability; kinetic.

Sodium picosulfate 4,4'-(2-pyridylmethylene)diphenyl bis(hydrogen sulfate) disodium is a medicine known as a stimulant laxative [1]. After being taken orally, it is activated by the bacteria naturally present in the large intestine. It then stimulates nerve endings in the intestinal wall. These nerves make the muscles in the intestine and rectum contract more often and with more force, a process known as peristalsis. This moves the contents of the intestine along so that the bowel can be emptied, and hence relieves constipation. Sodium picosulfate is also used to stimulate the emptying of the bowel before surgery, childbirth or medical investigation of the gut.

Early detection of laxative abuse may eliminate the costly tests these patients would undergo otherwise. Previous screens of laxative in urine have been described in the literature based on TLC [2-5], GLC/MS [6] and HPLC with diode array detection [7]. A modified procedure for the analytical control of a pharmaceutical formulation Evacoul® (Laboratorios Almiral, St. Andrey de la Barca, Spain) by capillary electrophoresis is proposed. It allows the simultaneous determination of the major compounds in the formulation: the active compound (sodium picosulfate) and preservative (methylparaben) and the degradation products of the preservative, which slowly degrades by hydrolysis or by transesterification with sorbitol (sweetener in excess in the formulation).

The HPLC is still not the official method in any pharmacopoeia for the analysis of sodium picosulfate [8,9]. The validated HPLC method for analysis sodium picosulfate in the presence of impurities was proposed in a new USP's Pending Standards monograph [10]. But that monograph is not a USP-NF monograph. Using that procedure we could not separate sodium picosulfate (Sodium picosulfate, Zdravlje-Actavis, Serbia) from degradation products obtained during forced degradation.

Therefore, the aim of this work was to develop and validate a modified RP-HPLC feasible and specific analytical procedure. The procedure should be suitable for the application in a drug quality control or regulatory laboratory analysis of sodium picosufate in the presence of its degradation product (Fig. 1). The analysis of the degradation product obtained during the thermal degradation at different temperatures and oxidation in H_2O_2 solutions with various concentrations, at room temperature was presented in this paper. The developed analytical method was validated as per International Conference on Harmonization

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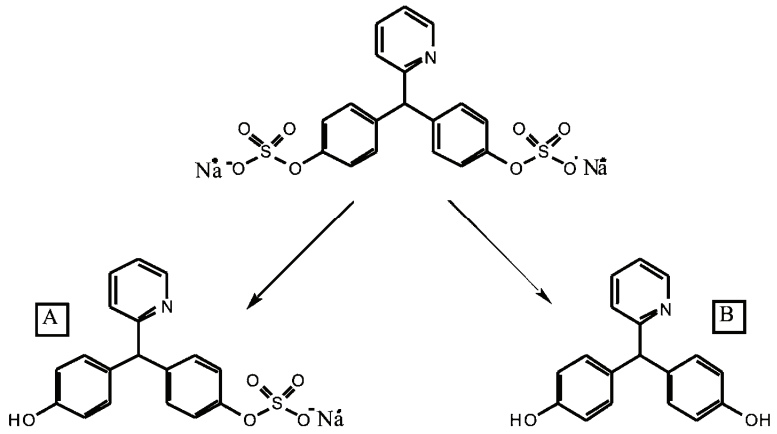

Figure 1. The potential impurities and degradation products of sodium picosulfate.

guidelines [11] and Serbian requirements [12]. Statistical tests were performed on validation data [13]. The validation consists of testing the method selectivity towards components and the assessment of the method precision, trueness and accuracy [14,17] at different concentration levels over the range investigated, as well as the confirmation of the limit of quantitation (LOQ) and the method linearity [14-16]. The adaptation of the proposed procedure for the analysis of the available dosage form, including the expired ones, is also an important task in order to solve problems encountered in the quality control.

EXPERIMENTAL

Samples. Standard substances of sodium picosulfate and 4-[(pyridin-2-yl)(4-hydroxyphenyl) methyl]-phenyl sodium sulfate, as well as sodium picosulfate tablets were kindly supplied by Zdravlje-Actavis, Leskovac. Each tablet is claimed to contain 5 mg of sodium picosulfate.

Reagents. All chemicals used were of analytical grade and deionized water was of HPLC grade. Disodium hydrogen phosphate, potassium dihydrogen phosphate and acetonitrile for HPLC were obtained from Merck, N.Y.C., U.S.A.

Apparatus. The method development was performed with an Agilent 1100-Series HPLC system (Agilent Technologies, USA) consisting of an Agilent 1100-Series variable wavelength UV detector and Agilent 1100-Series auto-sampler using a 50 µL sample loop (The Faculty of Technology, Leskovac). The system was controlled and data analyses were performed with the Agilent HPLC Data Analysis software. The reproducibility were performed with another LC system consisting of an Agilent 1100-Series binary pump and Agilent 1100-Series DAD detector (Zdravlje-Actavis, Leskovac). The detector was set at 263 nm and the peak areas were integrated automatically by the computer using the Agilent HPLC Data Analysis software program. The separation was carried out at 25 °C using a ZORBAX Eclipse XDB-C18 column (4.6 mm×250 mm, 5 µm), Agilent Technologies, USA. All the calculations concerning the quantitative analysis were performed with the external standardization by measuring the peak areas.

Chromatographic conditions. RP-HPLC analysis was performed by isocratic elution with a flow rate of 1.5 mL min^{-1}. A mobile phase consisting phosphate buffer in water:acetonitrile (85:15 v/v). Phosphate buffer: 0.5 g disodium hydrogen phosphate and 0.301 g potassium dihydrogen phosphate transfered to a 1 L flask and dissolved in water. All solvents were filtered through a 0.45 µm millipore filter. The volumes of 50 µL of the solutions and samples prepared were injected into the column. Quantification was effected by measurement at 263 nm as established from the 3-D chromatogram. Throughout the study, the suitability of the chromatographic system was monitored by calculating the capacity factor (k), the selectivity (α) and peak asymmetry (A_s).

Procedures

To prepare the solutions of different concentrations, aliquots of the stock solution were transferred into a series of 10 mL standard volumetric flasks and the volumes were made with the respective media. Ten different concentrations were prepared in the range of 10-100 g mL^{-1} of sodium picosulfate in a mobile phase for a standard curve. The final concentrations of sodium picosulfate in the samples were calculated by comparing the sample and standard peak area obtained with the average of three injections of standard solutions.

Stability study. In order to monitor the thermal stability, 5 mg of sodium picosulfate was dissolved in a 100 mL volumetric flask in the mobile phase. This solution was transferred into another clean dry conical

flask and refluxed in a thermostatically controlled water bath at 25, 40, 60 and 80 °C for 60 min. 1 mL of samples was taken. To monitor the oxidation stability, 5 mg of sodium picosulfate in 0.1, 0.5 and 1.0% H_2O_2 was dissolved in a 100 mL volumetric flask and completed to the mark with the same solvent. This solution was transferred into another clean dry conical flask and refluxed in a thermostatically controlled water bath at 25 °C for 30 min.

The accuracy of the method is the closeness of the measured value to the true value for the sample. To determine the accuracy of the proposed method, different levels of drug concentrations - lower concentration (LC, 80%), intermediate concentration (IC, 100%) and higher concentration (HC, 120%) were prepared from independent stock solutions and analyzed (n = 10). The accuracy was assessed as the percentage relative error and mean % recovery (Table 1). To provide an additional support to the accuracy of the developed assay method, a standard addition method was employed which involved the addition of different concentrations of the pure drug (10, 20 and 30 μg mL^{-1}) to a known preanalyzed formulation sample and the total concentration was determined using the proposed methods (n = 10). The % recovery of the added pure drug was calculated as %recovery = = $[(c_t-c_s)/c_a]\times100$, where c_t is the total drug concentration measured after the standard addition; c_s, drug concentration in the formulation sample; c_a, drug concentration added to formulation (Table 2).

The reproducibility was determined by using different levels of drug concentrations (the same concentration levels taken in the accuracy study), prepared from independent stock solutions and analyzed (n = 10) (Table 1). Inter-day, intra-day and inter-instrument variation were studied to determine the intermediate precision of the proposed analytical method. Different levels of drug concentrations in triplicates were prepared three different times in a day and studied for intra-day variation. The same procedure was followed for three different days in order to study the inter-day variation (n = 10). One set of different levels of the concentrations was reanalyzed using another HPLC Agilent 1100-Series system, by proposed methods to study inter-instrument variation (n = 10). The percent relative standard deviation (% *RSD*) of the predicted concentrations from the regression equation was taken as precision (Table 3). The precision studies were also carried out by using the real samples of sodium picosulfate in a similar way to a standard solution to prove the usefulness of the method.

Robustness. To determine the robustness of the developed method, experimental conditions were purposely altered. To study the effect of the flow rate on the resolution, it was changed by 0.5 units from 1 to 2 mL min^{-1}, while the other mobile phase components were held constant as per the method. The effect of the column temperature on resolution was studied at 20 and 30 °C instead of 25 °C while the other mobile phase components were held constant as per the method.

Table 1. Accuracy and the precision data for the developed method (n = 10)

Level	Predicted concentration (μg mL^{-1})		Mean recovery, %	Accuracy, %
	Mean (±*SD*)	% *RSD*		
LC (40 μg mL^{-1})	40.23 ± 0.33	0.81	100.57	0.57
IC (50 μg mL^{-1})	50.21 ± 0.34	0.67	100.42	0.42
HC (60 μg mL^{-1})	59.92 ± 0.32	0.53	99.87	-0.13

Table 2. Standard addition of sodium picosulfate (50 μg mL^{-1}) for accuracy (n = 10)

Pure drug added, μg mL^{-1}	Total drug found(±*SD*), μg mL^{-1}	%Recovery (±*RSD*)
0	50.21 ± 0.34	100.42 ± 0.67
10	59.92 ± 0.32	99.87 ± 0.53
20	70.35 ± 0.45	100.50 ± 0.64
30	79.87 ± 0.42	99.84 ± 0.53

Table 3. System precision study (n = 10)

Concentration, μg mL^{-1}	Estimated concentration, intra-day reproducibility ± *RSD*, n = 10			Intra-instrument reproducibility ± *RSD*, n = 10
	Day 1	Day 2	Day 3	
40	39.65 (0.81)	39.94 (0.67)	40.48 (0.51)	38.96 (0.89)
50	49.85 (0.05)	50.32 (0.21)	49.88 (0.08)	50.35 (1.41)
60	60.55 (0.18)	60.51 (0.84)	60.15 (0.08)	60.34 (1.55)

Procedure for tablets. A total of 20 tablets of studied pharmaceutical preparation (sodium picosulfate, Zdravlje-Actavis, Serbia) containing sodium picosulfate were weighed and finely powdered using a pestle and mortar. An accurately weighed quantity of the resulting powder, equivalent to 5 mg (weight of one tablet) of sodium picosulfate was dissolved in 10 mL of methanol. Then it was filtered directly into a 10 mL standard volumetric flask. For HPLC determination, aliquots (1 mL) of sodium picosulfate were taken and suitably diluted with the mobile phase in order to get a 50 g mL^{-1} concentration and the samples were injected into the chromatograph.

Comparative method. The employed procedures for the comparative method (potentiometric titration) is described in the European Pharmacopoeia [8].

RESULTS AND DISCUSSION

HPLC Analysis

The main target of the chromatographic method was to achieve the separation of sodium picosulfate and its degradation product (Imp-A) by using different stationary phases like C18, C8 and cyano, different mobile phases containing buffers like phosphate, sulfate and acetate with different pH (7-10) and using organic modifiers like methanol in the mobile phase. The chromatographic separation was achieved on a ZORBAX Eclipse XDB-C18 column (4.6 mm×250 mm), with a particle size of 5 μm. Satisfactory separation of used standards was obtained with a mobile phase consisting of 0.05% disodium hydrogen phosphate and 0.0301% potassium dihydrogen phosphate in water:acetonitrile (85:15 v/v). The optimum pH was 7 because at pH values higher than 7, a somewhat larger peak tailing and inferior resolution resulted. If methanol was used instead of acetonitrile, the separation of sodium picosulfate and the impurity was also with an unsatisfactory resolution. The maximum absorption of sodium picosulfate was detected at 263 nm and this wavelength was chosen for the analysis. The developed RP-HPLC method was found to be specific for sodium picosulfate and its degradation product. A corresponding HPLC chromatogram of mixture standards sodium picosulfate and its impurity A is shown in Fig. 2. The HPLC chromatogram of its products after thermal degradation at 40 °C and oxidation (0.5 % H_2O_2), recorded at 263 nm, is shown in Fig. 3. The obtained compounds during thermal degradation and oxidation were identified by using adequate standards. At retention time of 1.811 min sodium picosulfate was identified and at 1.274 min its thermal and oxido degradation product 4-[(pyridin-2--yl)(4-hydroxyphenyl) methyl]phenyl sodium sulfate (Fig. 3) was noticeable.

Chromatographic parameters, such as the efficiency column and peak asymmetry were reconsidered for the sodium picosilfate standard (Fig. 2). According to the obtained value of the number of theoretical plate (N = 1144), the conclusion is that the efficiency column is satisfactory (HETP = 0.2184). The asymmetry peak value of 0.368 indicates that the peak is not ideally symmetric, that is, it is not Gauss's peak. Having in mind that $W_{ab} < W_{bc}$, this means that

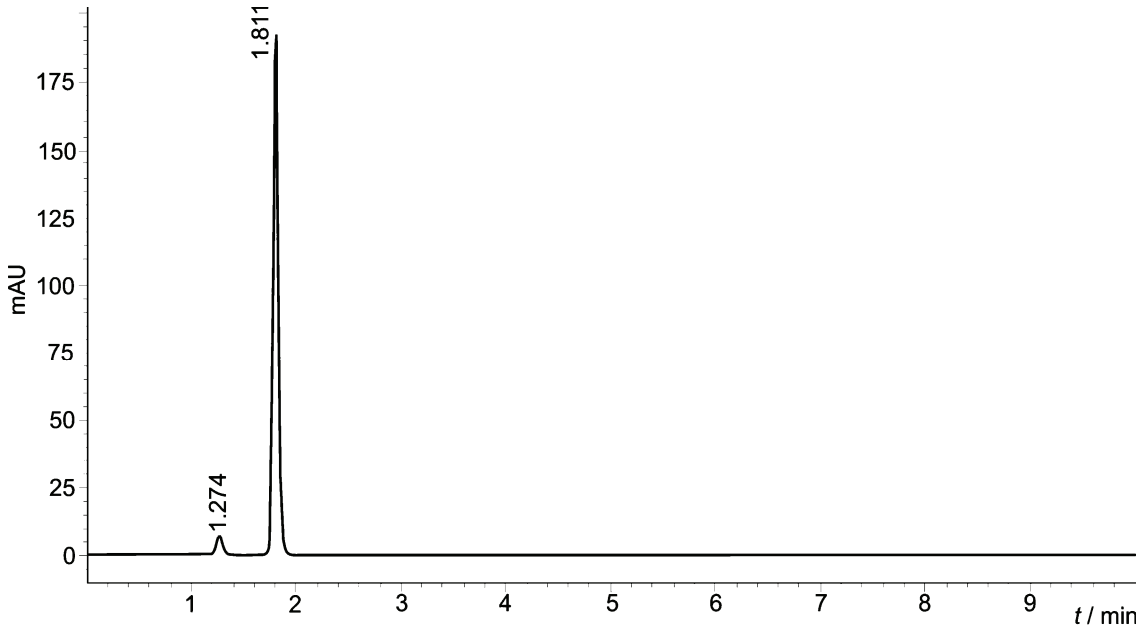

Figure 2. The HPLC chromatogram at 263 nm of mixture standards sodium picosulfate (t_r = 1.811 min) and 4-[(pyridin-2-yl)(4-hydroxyphenyl) methyl]phenyl sodium sulfate (t_r = 1.274 min).

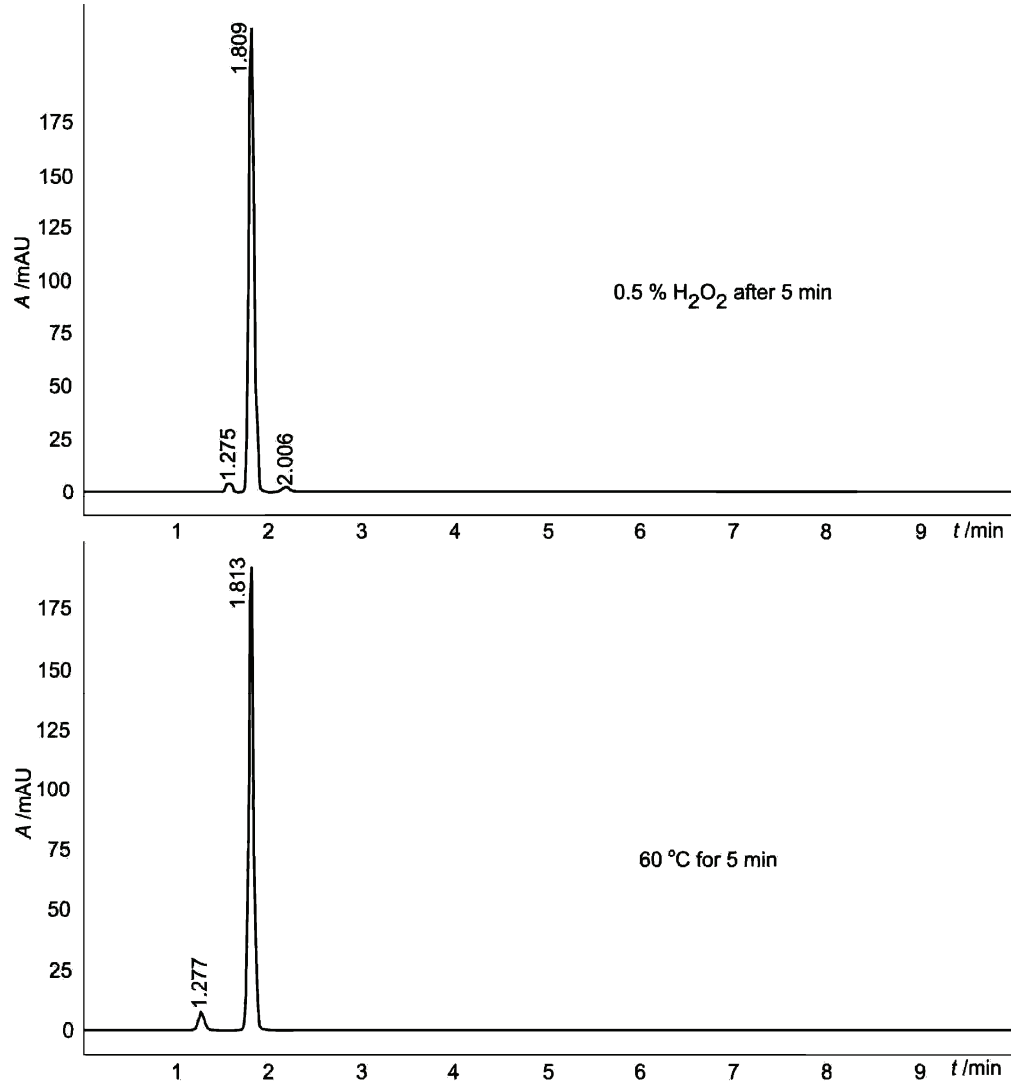

Figure 3. Typical HPLC chromatograms recorded during heat and oxidation.

there is a certain interaction between the stationary phase and the investigated component. The value of selectivity (α) was 1.77. In the optimized conditions, sodium picosulfate and its impurity A were well separated with a resolution greater than 2.5.

The good linearity was obtained between the peak areas and the concentrations. The linear regression equation (Eq. (1)), obtained with a regression coefficient (r) of 0.9933, was:

$$A_{263} = 21395.35 \times c(\mu g\, mL^{-1}) + 294.005 \quad (1)$$

The linearity range was obeyed in the range of decade 10-100 μg mL^{-1}. The chromatogram of sodium picosulfate was not changed in the presence of common excipients used in the pharmaceutical preparations. The chromatogram of the pure drug sample was matched with the formulation samples in a mobile phase. The calculated t-value of 1.468 was found to be less than that of the tabulated t-value (t = 2.225). Therefore, the proposed analytical method is specific and selective for the drug. The linearity range for sodium picosulfate estimation was found to be 10-100 μg mL^{-1} (r = 0.9933). Goodness of the fit of the regression equations was supported by high regression coefficient values.

The accuracy of the method was checked by determining recovery values. Series of solution were made containing 80, 100 and 120% of sodium picosufate regarding the declared content. The accuracy ranged from 40 to 60 μg mL^{-1} (Table 1). The excellent mean % recovery values, close to 100%, and their low standard deviation values (SD < 1.0) represent high accuracy of the analytical methods.

The validity and reliability of the proposed methods were further assessed by recovery studies *via* the standard addition method. The mean %recoveries (±RSD) for the concentration of 50 μg mL^{-1} are showed in Table 2. These results revealed that any small

change in the drug concentration in the solutions could be accurately determined by the proposed analytical methods.

The precision was determined by studying the repeatability and the intermediate precision. Repeatability (±*RSD*) ranged from 40 to 60 μg mL^{-1} (Table 3). The repeatability results indicated the precision under the same operating conditions over a short interval of time and the inter-assay precision. The intermediate precision expresses within-laboratory variations in different days and in different instruments. In the intermediate precision study, ±*RSD* values were not more than 2.0% in all the cases. *RSD* values found for the proposed analytical method were well within the acceptable range indicating that the method has the excellent repeatability and intermediate precision.

The limits of detection (LOD) and quantification (LOQ) were evaluated using the following equations [18-21]:

$$LOD = 3.3\frac{S_0}{b}$$

$$LOQ = 10\frac{S_0}{b}$$

were S_0 is the standard deviation of the calibration line and b is the slope. They were found to be 0.086 and 0.258 μg mL^{-1}, respectively.

Robustness. In all the deliberate varied chromatographic conditions (flow rate and column temperature) no significant change in the assay value was observed. The system suitability parameters like tailing and the *RSD* values are well within the limits. Tailing was 0.412 and 0.332 and *RSD* was 0.8 and 0.6% for flow rate and column temperature variations which confirms the robustness of the developed method.

Applicability of the proposed method. The proposed method was applied for the determination of sodium picosulfate in pharmaceutical formulations using a direct calibration curve. As it can be seen in Table 4, the results obtained for this method are in accordance with the official potentiometric titration. The results of the proposed method were statistically compared with this of the official method using a point hypothesis test [22,23]. Table 4 shows that the calculated F and t values at the 95% confidence level are less than the theoretical ones, confirming no significant differences between the performance of the proposed and the official method.

Stability study

The purpose of the stability testing was to investigate how the quality of a drug product changes with time under the influence of environmental factors. Since the temperature and oxidation-induced degradation of the drug may have a negative impact on the quality, safety and effectiveness of pharmacotherapy, the research focused on this point is definitely reasonnable.

Sodium picosulfate was exposed to temperature and oxidation. The percentage of the degradation product was observed every 5 min for 30 and for 60 min. The results are given in Tables 5 and 6. The obtained results showed that sodium picosulfate is a relatively thermal and oxide stable compound.

CONCLUSION

On the bases of the experimental results, the proposed method is suitable for the simultaneous qualitative and quantitative determination of sodium picosulfate and a related substance in pharmaceutical formulations. The method provides great sensitivity, adequate linearity and repeatability. It is also quicker and simpler for the sample preparation than already offered procedures. It was shown that sodium pico-

Table 4. Determination of sodium picosulfate by the HPLC and the official methods (potentiometric titration)

Compound	Taken, μg mL^{-1}	Sodium picosulfate found by HPLC[a] x±SD, μg mL^{-1}	± *RSD*[a]	Recovery[a], %	*F* Value[b]	*t* Value[b]	Potentiometric titration x±SD, μg mL^{-1}
Sodium picosulfate	50	51.20±0.02	2.16	102.41	1.36	0.609	51.30±0.01

[a]Data are based on the average obtained from five determinations; [b]theoretical F value (ν_1 = 4, ν_2 = 4) and t value (ν = 8) at the 95% confidence level are 6.39 and 2.306, respectively

Table 5. Thermal degradation product (%)

Temperature, °C	Time of exposure, min						
	0	5	10	15	20	30	60
25	-	0.010	0.023	0.039	0.057	0.078	0.084
40	-	0.014	0.027	0.045	0.068	0.094	0.110
60	-	0.015	0.031	0.057	0.076	0.107	0.130
80	-	0.018	0.038	0.064	0.084	0.118	0.160

Table 6. Oxide degradation product (% area)

Concentration (% area)	Time of exposure, min					
	0	5	10	15	20	30
0.1	-	0.33	0.54	0.88	1.23	1.73
0.5	-	0.50	1.00	1.38	1.82	2.10
1	-	0.83	1.21	1.86	2.21	2.84

sulfate is a relatively thermal stable and oxide stable compound. As the main decomposition product, impurity A was found by RP-HPLC. The chromatogram obtained after oxide degradation of sodium picosulfate shows that some other impurity is formed. A further study is necessary for the identification of this decomposition product.

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NAUČNI RAD

PRAĆENJE TERMO I OKSIDO-STABILNOSTI NATRIJUM-PIKOSULFATA MODIFIKOVANOM RP-HPLC METODOM

Razvijena je i validovana selektivna, precizna i stabilna modifikovana HPLC metoda za analizu natrijum-pikosulfata, kao čiste supstance i u obliku formulacija. Za efikasno odvajanje aktivne supstance od njenog degradacionog produkta mora se razviti stabilna metoda. Hromatografsko odvajanje postignuto je na ZORBAX Eclipse XDB C-18 koloni. Mobilna faza sadržala je fosfatni pufer (pH 7):acetonitril (85:15 v/v). Apsorbanca je praćena DAD detektorom na 263 nm. Brzina protoka bila je 1,5 mL min^{-1}. Statistička analiza pokazuje da je metoda ponovljiva, selektivna i tačna za određivanje natrijum-pikosulfata u prisustvu njegovog degradacionog produkta. Ispitivanja forsirane degradacije praćena su na čistim uzorcima natrijum-pikosulfata korišćenjem toplote (25, 40, 60 i 80 °C) i oksidacijom (0,1, 0,5 i 1% v/v vodonik-peroksid). Predložena metoda uspešno je primenjena, sa odličnim obnavljanjem, za analizu farmaceutske formulacije (natrijum-pikosulfat, Zdravlje-Actavis, Srbija).

Ključne reči: natrijum pikosulfat; degradacija; RP-HPLC; stabilnost.