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DETERMINATION OF SODIUM METABISULFITE IN PARENTERAL FORMULATIONS BY HPIC WITH SUPPRESSED CONDUCTIVITY DETECTION

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Abstract: Sulfurous compounds: sodium sulfite Na_2SO_3 (E 221), sodium bisulfite $NaHSO_3$ (E 222), and sodium metabisulfite $Na_2S_2O_5$ (E 223) are largely used as antioxidants in many pharmaceutical formulations. A method for determination of sodium metabisulfite in parenteral formulations containing tartrate ions was developed. High-performance ion chromatography (HPIC) method with suppressed conductivity detection was used. A satisfactory separation of SO_3^{2-} and SO_4^{2-} was achieved by the proposed HPIC method with 15 mM $NaHCO_3$/0.6 mM Na_2CO_3 mobile phase and columns with various packing materials: methacrylate polymer - Allsep A-2 Anion (100 × 4.6 mm, 7 µm) and styrene-divinylbenzene copolymer - IonPac AS14A (250 × 4.0 mm, 7 µm). Use of the Allsep A-2 Anion column provides separation of SO_3^{2-}, SO_4^{2-} and $C_4H_4O_4^{2-}$ present in the investigated products. The calibration plot was linear for 8-267.3 µg/mL sulfite (r = 0.99978, n = 6) and for 3-165.9 µg/mL sulfate (r = 0.9998, n = 6). The limit of detection for SO_3^{2-} and SO_4^{2-} were 3 µg/mL and 1 µg/mL, respectively.

Keywords: sodium metabisulfite, sodium sulfite, HPIC, suppressed conductivity detection

The antioxidants are substances with lower oxidation potential compared to that of active substances they protect. A choice of proper antioxidant and its quantity guarantees quality and safety of pharmaceutical formulations. The legislators all over the world specify the compounds that may be included as antioxidants in pharmaceutical formulations. Twenty three antioxidants are permitted in Poland, including sodium sulfite (E 221), sodium bisulfite $NaHSO_3$ (E 222), and sodium metabisulfite $Na_2S_2O_5$ (E 223).

These sulfur species are used in various formulations: oral, topical, and most commonly, parenteral, usually at concentrations of 0.01–0.1%. Sodium metabisulfite is used in the acidic preparations, where it undergoes an instantaneous hydrolysis to sodium bisulfite and further to a weak sulfurous acid.

Sulfur-containing antioxidants are used in injectable pharmaceuticals containing readily oxidable active substances, such as: adrenaline, norepinephrine, morphine, apomorphine, or *p*-aminosalicylic acid. Antioxidant activity is usually aided by the addition of synergetic agents, whose role is to form complexes of heavy metals – catalysts of the oxidation processes. The common synergetic agents are: EDTA, salicylic acid, citric acid, tartaric acid, and malic acid.

The Polish law imposes an obligation on drug manufacturers to justify the use of sulfites and metabisulfites. Control tests of finished products should include identification and assay of antioxidants (the ordinance of the Ministry of Health of 15 December 1993).

A necessity for a strict control of sulfites and metabisulfites usage results from their adverse effect on health – cytotoxicity and mutagenicity of those compounds is confirmed. They may also increase blood pressure, cause allergic and hypersensitivity-type reactions including bronchospasm and anaphylaxis (1-8).

Due to its antimicrobial activity, sulfites are commonly used as food preservatives.

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Most of the literature data concerns determination of sulfites in food and beverages. The methods for determination of sulfites in underground water, soil and industrial wastes are widely researched.

Many analytical techniques for determination of sulfites after derivatization were developed: spectroscopy (9-19), chemiluminescence (20-23), and phosphorimetry (24).

The electrochemical methods: potentiometric (25-26) , amperometric (27-29), voltamperometric (30) and polarographic (31) have often been used as well. The literature also contains chromatographic methods for determination of sulfites: electrophoresis (32-38), HPLC with various detection modes: indirect spectrophotometric (39-41), amperometric (42), fluorometric (43), conductometric (44-47), and conductometric detection, with various types of suppression (48-55).

The available literature contains a few studies of determination of sulfites in pharmaceutical formulations. Capillary electrophoresis with intermediate detection is utilized as a method for determination of sulfites in the soluble tablets for treating hyperacidity, including magaldrate and simeticon (33), and in injection solutions containing lidocaine hydrochloride and adrenaline (35). Amperometric sensors (29) are used for the analysis of sulfites content during production process of injection solutions containing diclofenac sodium or diclofenac potassium.

Application of widely recognized chromatographic methods for determination of sulfites in pharmaceutical formulations may cause problems due to various compositions of drugs and interferences of excipients.

The aim of this study is to develop a method for determination of sodium metabisulfite in the injection solutions: Difadol, Stresnil, Adrenalina WZF. The selected products have different compositions of excipients. HPIC method with suppressed conductivity detection was used.

The versatile conductivity detector with suppression provides high sensitivity of the method and can be used for analysis of inorganic ions for industrial and environmental purposes, and provides determination of ions in μg/L (ppb) to mg/L (ppm) range.

EXPERIMENTAL

Chemicals, reagents and formulations

The following standard substances were used: sodium metabisulfite (USP), sodium sulfate (Merck); active substances: diclofenac sodium, azaprenone, adrenaline tartrate; excipients: sodium chloride, tartaric acid, mannitol, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, benzyl alcohol, propylene glycol; chemicals: EDTA, salicylic acid, malic acid, oxalic acid, sulfuric acid, sodium carbonate, sodium bicarbonate. All chemicals were of analytical grade. Mili-Q water (≥ 18 mΩ) was used for mobile phase preparation. The preparations are presented in Table 1.

Equipment

The ion chromatography system ICS-90 (Dionex Co, USA) controlled by a computer, with conductivity detector DS5, Anion MicroMembrane

Table 1. Preparations used in this study.

STRESNIL solution for injection; 40 mg/mL		**Declared content**	**Release specification**	**Shelf-life specification**
active substance	azaperone	40 mg/mL		
excipient	sodium metabisulfite [1]	2 mg/mL	1.2 – 2.2 mg/mL	0.6 – 2.2 mg/mL
DIFADOL solution for injection; 25 mg/mL				
active substance	diclofenac sodium	25 mg/mL		
excipient	sodium metabisulfite [2]	0.8 mg/mL	≥ 0.56 mg/mL	≥ 0.40 mg/mL
ADRENALINA WZF solution for injection; 300 μg/0.3 mL				
active substance	adrenaline tartrate	1.8 mg/mL		
excipient	sodium metabisulfite [3]	1.0 mg/mL	0.7 – 1.1 mg/mL	0.5 – 1.1 mg/mL

Other excipients: [1] tartaric acid, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sodium hydroxide; [2] benzyl alcohol, mannitol, propylene glycol, sodium hydroxide; [3] sodium chloride

Table 2. Retention times of SO_3^{2-}, SO_4^{2-}, and $C_4H_4O_4^{2-}$ on different columns.

Ion	Retention time (min)					
	Allsep Anion 7 µm 150 × 4.6 mm (MMA)	Allsep Anion 7 µm 50 × 4.6 mm (MMA)	Wescan Anion/R 10 µm 250 × 4.6 mm (PS/DVB)	**Allsep A-2 Anion 7 µm 100 × 4.6 mm** (MMA)	**IonPac AS14A 7 µm 250 × 4.0 mm** (PS/DVB)	IonPac AS4A 15 µm 250 × 4.0 mm (PS/DVB)
$C_4H_4O_4^{2-}$	11.1	7.7	51.2	**29.6**	**34.8**	12.5
SO_4^{2-}	12.1	8.5	51.4	**35.2**	**40.0**	12.7
SO_3^{2-}	12.1	8.5	51.0	**38.3**	**35.1**	11.8

Conditions: Mobile phase: 15 mM $NaHCO_3$/0.6 mM Na_2CO_3; Flow rate: 1.3 mL/min; Column temperature: 20°C; Precolumn: Ion Pac AG 14A (50 × 4.0 mm, 7 µm); Injected volume: 10 µL; Suppressor: AMMS III (4 mm), Regeneration: 37.5 mM H_2SO_4; Background conductivity: 41 µS

Table 3. Effect of stabilizing agents on calibration line parameters.

	Mannitol 0.02%		**Tartaric acid 0.02%**	
	SO_3^{2-}	**SO_4^{2-}**	**SO_3^{2-}**	**SO_4^{2-}**
Line equation (n = 6)	$y = 3.59 \cdot 10^{-2}x - 4.44 \cdot 10^{-2}$	$y = 8.16 \cdot 10^{-2}x - 1.33 \cdot 10^{-2}$	$y = 3.57 \cdot 10^{-2}x - 3.33 \cdot 10^{-2}$	$y = 8.17 \cdot 10^{-2}x - 3.36 \cdot 10$
Standard deviation (S)	$2.8 \cdot 10^{-2}$	$2.5 \cdot 10^{-2}$	$2.9 \cdot 10^{-2}$	$2.5 \cdot 10^{-2}$
Correlation coefficient (r)	0.9997	0.9998	0.9997	0.9998
Limit of detection (LOD)	2.6 µg/mL	1.0 µg/mL	2,9 µg/mL	1.0 µg/mL
Limit of quantitation (LOQ)	7.8 µg/mL	3.1 µg/mL	8,7 µg/mL	3.1 µg/mL

Table 4. Robustness of the developed HPIC method.

		Retention time (min)		**Symmetry factor $A_{10\%}$**		**Resolution R_S**
		SO_4^{2-}	**SO_3^{2-}**	**SO_4^{2}**	**SO_3^{2-}**	**SO_4^{2-} / SO_3^{2-}**
Flow rate	1.1 mL/min	37.2	39.4	1.00	1.22	1.34
	1.3 mL/min	**35.4**	**38.3**	**0.98**	**1.28**	1.33
	1.5 mL/min	33.3	35.9	1.06	1.26	1.29
Mobile phase	12 mM $NaHCO_3$ 0.4 mM Na_2CO_3	38.2	40.5	1.05	1.22	1.34
	15 mM $NaHCO_3$ 0.6 mM Na_2CO_3	**35.4**	**38.3**	**0.98**	**1.28**	1.33
	18 mM $NaHCO_3$ 0.8 mM Na_2CO_3	30.3	34.9	1.06	1.26	1.27

Table 5. Recovery of sodium metabisulfite from model solutions.

Preparations	**Stabilizing agent**	**Excipients**	**Theoretical concentration**	**recovery [%]**	**RSD [%]**
DIFADOL	0.02% mannitol	mannitol benzyl alcohol	80 µg/mL	99.3	1.23
ADRENALINA WZF	0.02% tartaric acid	sodium chloride	100 µg/mL	98.9	1.56
STRESNIL	0.02% tartaric acid	tartaric acid methyl *p*-hydroxybenzoate propyl *p*-hydroxybenzoate	80 µg/mL	99.9	1.09

Table 6. Results of sodium metabisulfite determination in preparations.

Preparations [expiry date]	Declared content of sodium metabisulfite (mg/mL)	Release specification (mg/mL)	Shelf-life specification (mg/mL)	Assay of sodium metabisulfite X ± ΔX (PU= 95%) (mg/mL)	RSD [%]
STRESNIL [07. 2010] analysis performed 09.2009	2.0	1.2 - 2.2	0.6 - 2.2	0.85 ± 0.01	1.48
DIFADOL [11. 2007] analysis performed 09.2009	0.8	≥ 0.56	≥ 0.40	0.34 ± 0.01	2.00
ADRENALINA WZF [10. 2009] analysis performed 09.2009	1.0	0.7 - 1.1	0.5 - 1.1	0.67 ± 0.01	1.69

Suppressor AMMS III (4 mm) and sample injection valve equipped with 10 µL loop. The software used for data processing and chromatography was Chromeleon 6.50. The following programs were used for statistical evaluation: EXCEL 98 and Chromeleon 6.50. Separation was achieved using the columns: Allsep Anion (150 × 4.6 mm, 7 µm, Alltech); Allsep Anion (50 × 4.6 mm, 7 µm, Alltech); Wescan Anion/R (250 × 4.6 mm, 10 µm, Alltech); Allsep A-2 Anion (100 × 4.6 mm, 7 µm, Alltech); IonPac AS14A (250 × 4.0 mm, 7 µm, Dionex); IonPac AS4A(250 × 4.0 mm, 15 µm, Dionex); precolumn: Ion Pac AG 14A (50 × 4.0 mm, 7 µm, Dionex).

RESULTS AND DISCUSSION

Method development

First, a HPIC system, which would provide separation of sulfites and the products of their oxidation – sulfates, as well as excipients present in aquous extracts of the analyzed drugs was searched. The excipients were: tartaric acid, sodium chloride and benzyl alcohol.

The ICS-90 ion chromatograph applied utilizes suppressed conductivity detection. Suppression of the eluent conductance enhances the sensitivity, while limiting a choice of mobile phases. The choice of eluents for this method is limited to solutions of alkali hydroxides, carbonates and borates. As a result of chemical suppression process, alkali hydroxides leave the membrane suppressor in form of neutral water molecules, whereas carbonates or borates as weak carbonic or boric acids.

Mobile phases with various $NaHCO_3/Na_2CO_3$ ratios were used, providing elution of most inorganic anions and allowing changes of phase pH, which can affect separation of compounds with low degree of dissociation – organic acids.

Several different stationary phases were tested: ionites with styrene-divinylbenzene copolymer (PS/DVB) and methacrylate polymer (MMA). Those types of polymer packings differ in polarity: styrene-divinylbenzene (PS/DVB) copolymers are non-polar, while methacrylate (MMA) polymers are polar. The differences affect secondary interactions in the separation systems. Mobile phase containing 15 mM $NaHCO_3$/0.6 mM Na_2CO_3 and columns with

Table 7. Retention times for most common anions in the developed HPIC system.

Anion	Retention time (min)
Fluoride	3.1
Acetate	3.6
Methanosulfonate	4.0
Formate	4.2
Sulfamate	4.2
Chloride	**6.4**
Nitrite	8.9
Bromide	12.1
Nitrate	15.1
Malate	24.9
Phosphate	25.2
Succinate	27.8
Phosphite	28.6
Tartrate	**29.6**
Malonate	31.9
Oxalate	34.9
Sulfate	**35.2**
Maleate	38.2
Sulfite	**38.2**
Benzenosulfonate	43.1
Fumarate	43.8
Iodide	46.4
EDTA	8.4, 25.1, 38.2

both packings were used in further analysis: Allsep Anion (150 × 4.6 mm, 7 μm), Allsep Anion (50 × 4.6 mm, 7 μm), Allsep A-2 Anion (100 × 4.6 mm, 7 μm) filled with methacrylate polymer (MMA) and Wescan Anion/R (250 ×4.6 mm, 10 μm), IonPac AS14A (250 × 4.0 mm, 7 μm), IonPac AS4A (250 × 4.0 mm, 15 μm) filled with styrene-divinylbenzene copolymers PS/DVB). The anions retention times in relation to chromatographic columns used are shown in Table 2.

The main analytical issue is related to achieving a satisfactory separation of SO_4^{2-} and SO_3^{2-} from $C_4H_4O_4^{2-}$ in Stresnil, where tartrates are present as excipients and in Adrenalina WZF, where tartrate is one of the active substances. Other substances, both active an excipients present in the analyzed formulations do not interfere with determination of the ions, since they do not generate analytical signals (azaperone, diclofenac sodium, adrenaline, mannitol, propylene glycol, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate) or their peaks are sufficiently separated (chloride, benzyl alcohol). Table 7 shows the corresponding anions' retention times.

Separation of sulfites, sulfates and tartrates in Stresnil and Adrenalina WZF (Table 2, Figure 2) was achieved with Allsep A-2 Anion (100 × 4.6 mm, 7 μm) MMA column. Good results were not achieved with other columns due to sulfites, sulfates and tartrates peaks coincidence.

A satisfactory separation of sulfites and sulfates was achieved with IonPac AS14A (250 × 4.0 mm, 7 μm) PS/DVB column, which can also be used for determination of those ions in formulations without tartrates, e.g., Difadol.

Stability study

The aqueous solutions of sodium metabisulfite require additional stabilization because the compound undergoes hydrolysis to sodium hydrogen sulfite and further oxidation to sulfate. Oxidation process is mediated by free radicals and catalyzed by redox-sensitive metal ions, such as iron and

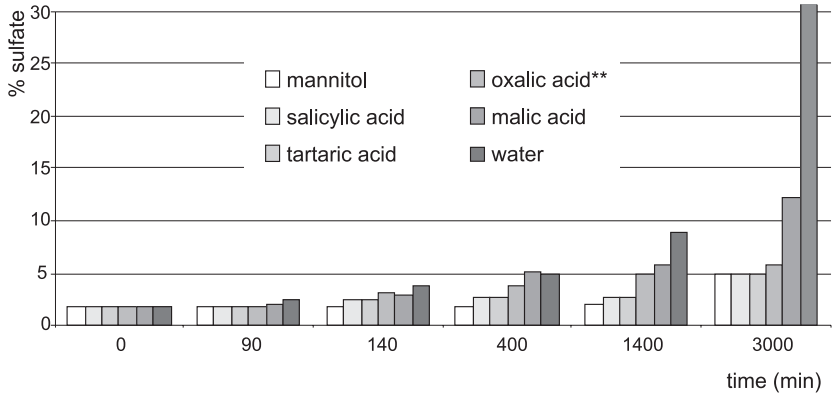

Figure 1. Influence of the added synergetic agents on stability of aqueous solutions of sodium metabisulfite

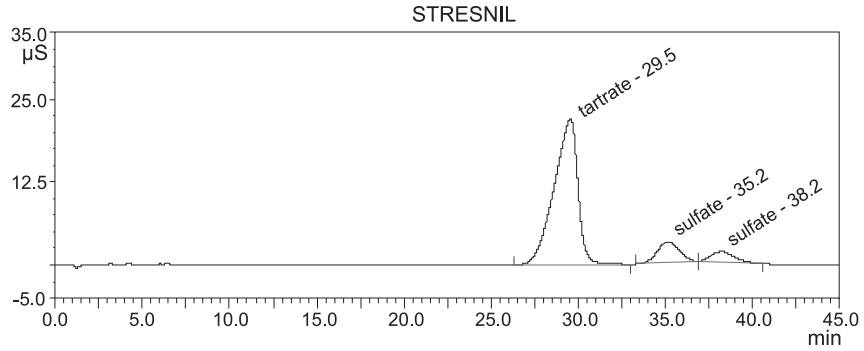

Figure 2. Chromatogram for STRESNIL – injection solution

cooper and occurs most rapidly in acidic solutions (56, 57). The available literature describes methods for inhibition of sulfite oxidation by an addition of stabilizing substances, such as: formaldehyde (58-60), acetone (57, 61), isopropanol (51, 58, 61), methanol (57) ethanol (57), glycerol (57, 58, 61), fructose (58, 61), glucose (61), and mannose (61).

Impact of several synergetic agents, which form complexes with heavy metals – catalysts of the oxidation process – were also verified in the course of study. Aqueous solutions of each compound at a concentration of 0.02% were used. Based on the analysis results, EDTA is not suitable for stabilization, because the EDTA and tartrate peaks coincide (Table 7). Influence of the agents on stability of sodium metabisulfite solutions is shown in Figure 1. It appeared that mannitol is the best stabilizer of sulfites' solutions. Other good stabilizers are salicylic acid, oxalic acid and tartaric acid. Difadol standard and test solutions can be stabilized with mannitol only, since a reduction of pH caused by the addition of an acid, causes the active substance to precipitate (pH of Difadol injection solution is 8.5). Stresnil and Adrenalina WZF solutions can be stabilized with tartaric acid, since it is part of the formulation.

Validation of the method

Determination of sodium metabisulfite in analyzed injection solutions: Stresnil, Adrenalina WZF and Difadol was carried out under the following conditions**:**

Detection: conductivity with an anion membrane suppressor
Column: Allsep A-2 Anion (100 × 4.6 mm, 7 µm)
Precolumn: Ion Pac AG 14A (50 × 4.0 mm, 7 µm)
Flow rate: 1.3 mL/min
Column temperature: 20°C
Mobile phase: 15 mM $NaHCO_3$/0.6 mM Na_2CO_3
Injected volume: 10 µL
Suppressor: AMMS III (4 mm)
Regeneration: 37.5 mM H_2SO_4
Background conductivity: 41 µS

Selectivity of the developed HPIC system was verified. Active substances: azaperone, diclofenac, and adrenaline as well as some excipients: propylene glycol, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, salicylic acid, and mannitol as a stabilizing agent do not generate analytical signals. Retention times of analyzed sulfite, sulfate and excipients: tartrate, chloride are shown in Table 7.

Linearity was successfully tested within a concentration range 8-267.3 µg/mL for $SO_3^{2-}$and 3-165.9 µg/mL for SO_4^{2-} in 0.02% mannitol and tartaric acid solutions. Addition of the stabilizing agents does not influence slopes of the calibration lines, neither the limit of detection (LOD) and limit of quantification (LOQ). LOD and LOQ were established based on calibration line parameters, as per the formula: LOD = 3.3 S_y/a and LOD = 10 S_y/a, where S_y is the standard error of estimate of the regression line. The results are shown in Table 3.

Robustness of the HPIC method was verified (column effect was not verified due to the lack of another column). The results are shown in Table 4.

Accuracy was verified with model solutions containing sodium metabisulfite (in a quantity as given in the specifications of the drugs) added to excipients and stabilizers solutions (0.02 % mannitol or tartaric acid). The results are shown in Table 5.

Content determination

Stresnil – injection solution (declared content of sodium metabisulfite: 2.0 mg/mL).

Adrenalina WZF – injection solution (declared content of sodium metabisulfite: 1.0 mg/mL).

The solutions were prepared in brown volumetric flasks and stored in refrigerator. Sodium metabisulfite standards: six sodium metabisulfite solutions at a concentration of 20 μg/mL to 150 μg/mL in 0.02% aqueous solution of tartaric acid were prepared.

Sample solutions: 1.0 mL Stresnil was transferred to a 25 mL volumetric flask or 1.0 mL Adrenalina WZF was transferred to a 10 mL volumetric flask. The flasks were made up to volume with 0.02% aqueous solution of tartaric acid. Ten μL samples of prepared solution were injected into the column.

The analysis was carried out using the HPIC system and readouts from the calibration graph. A chromatogram for Stresnil is presented in Figure 2. The results are shown in Table 6.

Difadol – injection solution (declared content sodium metabisulfite: 0.8 mg/mL)

The solutions were prepared in brown volumetric flasks and stored in refrigerator. Sodium metabisulfite standards: six sodium metabisulfite solutions at concentrations of 20 μg/mL to 150 μg/mL in 0.02% aqueous solution of mannitol were prepared. Sample solutions: 1.0 mL Difadol was transferred to a 10 mL volumetric flask and made up to volume with 0.02% aqueous solution of mannitol. Ten μL samples of prepared solution were injected into the column. The analysis was carried out using a HPIC system and readouts from the calibration graph. The results are shown in Table 6.

Possible applications of the developed HPIC method

The developed HPIC method with suppressed conductivity detection can be used for quantification of sodium metabisulfite in pharmaceutical formulations, especially in parenteral ones. This method has also been successfully applied to analysis of many organic and inorganic anions, which may be practical in determination of the anions in other preparations (Table 7).

CONCLUSIONS

A satisfactory separation of SO_3^{2-} and SO_4^{2-} was achieved with a developed HPIC system.

Allsep A-2 Anion is the only column that allows separation of SO_3^{2-} and SO_4^{2-} from $C_4H_4O_4^{2-}$ in Stresnil (tartrates present as excipients) and Adrenalina WZF (active substance in the form of tartrate.

On account of the required stabilization of sulfites in aqueous solutions, an effect of several stabilizing agents was verified, and it was observed that the best of them is 0.02% mannitol solution, followed by salicylic acid, oxalic acid, and tartaric acid at the same concentration (Fig. 1).

The following parenteral products were selected for analysis: Adrenalina WZF, Stresnil (valid) and Difadol (expired). The developed HPIC method with suppressed conductivity detection allows determination of sodium metabisulfite in the products with sufficient precision and accuracy (RSD below 2%). Due to chemical suppression it is possible to achieve high method sensitivity; limit of detection for SO_3^{2-} is approx. 3 μg/mL (3 ppm), for SO_4^{2-} approx. 1 μg/mL (1 ppm).

The method can also be applied to analyze many organic and inorganic anions in parenteral products and to evaluate sodium metabisulfite initial content based on the determined SO_4^{2-} concentration. The developed HPIC method with suppressed conductivity detection may also be used in routine analysis of many pharmaceutical formulations containing anions, instead of iodimetric titration recommended by the manufacturers.

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