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ARTICLES

Selective Determination of 4-Aminobenzoic and 4-Aminosalicylic Acid Derivatives in Mixtures by Flow-Injection Analysis

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Abstract—The working conditions were found for the determination of medicinal substances anesthesin (benzocaine, **I**), novocaine (**II**), novocainamide (procainamide, **III**), and sodium 4-aminosalicylate (**IV**) as their 4,6-dinitrobenzofuroxan derivatives by flow-injection analysis with spectrophotometric detection (λ 510 nm). The best conditions were attained using a mixture of ethanol (methanol) and a buffer solution of pH 6.68 (30 : 70 vol %). The analytical range for the analytes was 0.08–5.0 μg/mL. The detection limits (3σ, $n = 4$) were 0.04 (I), 0.05 (II), 0.07 (III), and 0.03 (IV) μg/mL. Procedures for determining 4-aminobenzoic and 4-aminosalicylic acid derivatives in pharmaceuticals containing ephedrine, atropine, dimedrol, and inorganic salts and in biological fluids (protein hydrolyzate, blood plasma, and whole blood) were developed.

4-Aminobenzoic and 4-aminosalicylic acid derivatives are widely used in medicine as local anesthetics (anesthesin and novocaine), antiarrhythmic agents (novocainamide), and antitubercular drugs (4-aminosalicylate, sodium salt) [1]. However, possibilities of rapidly and efficiently determining these substances by flow-injection analysis in both technological mixtures and multicomponent drugs are essentially restricted, because of an insufficient selectivity of the spectrophotometric detection of their derivatives forming in the flow. The reaction of the formation of diazo derivatives of *o*-phthalic aldehyde is not selective to phenols and other compounds containing labile hydrogen atoms bound to carbon atoms [2, 3]. The spectrophotometric determination of primary arylamines as their derivatives with carbonyl compounds also does not solve the selectivity and sensitivity problems [4]. It was found previously [5–7] that reactions with chlorodinitro-substituted benzo-2,1,3-oxadiazoles provide the most selective determination of these compounds by flow-injection (FI) spectrophotometric analysis.

The aim of this work was to find the conditions for the selective determination of 4-aminobenzoic acid (PABA) and 4-aminosalicylic acid (PASA) as their 4,6-dinitrobenzofuroxan and 5,7-dinitrobenzofurazan derivatives in complex medicinal substances and biological fluids using flow-injection analysis.

EXPERIMENTAL

An SF-26 spectrophotometer was used for recording absorption spectra. An MV-87S potentiometer (Germany) with an ESL-43-07 glass electrode and a SE-20 silver–silver chloride reference electrode was used for pH measurements. The experiments were performed using a reverse-mode single-channel flow-injection system [5–7] equipped with a D1 plunger pump (Mikrotechna, Czech Republic) and a photometric flow cell (6 μL, $l = 0.5$ cm). A Spekol-210 spectrophotometer (Carl Zeiss, Germany) was used as a detector. A TZ-4100 recorder (Laboratorni Pristroje, Czech Republic) was used for recording flowgrams. A six-way injection valve (Mikrotechna, Czech Republic) with a calibrated loop (110 μL) was used throughout. Communication tubes (inside diameter 0.6 mm) were made of Teflon. The reaction coil (coil diameter 20 cm) was 2.0 m in length. The intensity of the analytical signal was calculated by subtraction of the blank signal.

Chromatographic analyses were performed on an HP-1100 chromatograph (Germany). Anesthesin (ethyl 4-aminobenzoate), novocaine (diethylamino 4-aminobenzoate hydrochloride), novocainamide (4-aminobenzoic acid β-diaminoehtylamide hydrochloride), and sodium 2-aminosalicylate as well as drugs containing these substances were of pharmaceutical grade. If required, organic solvents were purified using the procedure described in [8, 9]. 4-Chloro-5,7-dinitrobenzofurazan (BFZ) and 7-chloro-4,6-dinitrobenzofuroxan (BFO) were synthesized by the procedures described in [10, 11]. A protein hydrolyzate reference solution and serum albumin were obtained from Reanal (Hungary). Whole blood was sampled from patients in the course of clinical examinations. The deproteinization of biological fluids was performed using the procedure described in [5]. 5,7-Dinitrobenzofurazan derivatives of medicinal substances were synthesized by adding a methanol solution of BFZ (0.6 mmol) to a solution of the equivalent amount of anesthesin or PASA in methanol. Yellow or orange crystalline precipitates were washed with a methanol–water mixture and recrystallized from methanol.

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Chemical analysis data. For the anesthesin derivative anal. calcd. (wt %): H, 3.08; C, 50.42; N, 19.61; found (wt %): H, 3.16; C, 50.31; N 19.55. For the PASA derivative, calcd. (wt %): H, 2.03; C, 45.22; N, 32.46; found (wt %): H, 1.92; C, 45.01; N, 32.23.

Determination Procedures

Pharmaceuticals. Liquid pharmaceuticals (injection solutions and drops) were diluted with water to the analyte concentrations from 0.5 to 3.0 μg/mL. An aliquot portion of the solution was then placed in a 25-mL volumetric flask, to which a mixture of ethanol and a phosphate buffer solution (pH 6.86–7.1, 0.06 M, obtained from Radelkis, Hungary) 30 : 70 (vol %) was added. The resulting solution was used as a carrier stream (flow rate 1.3 mL/min). After injecting a 110-μL portion of a solution of BFO in acetonitrile (0.01 M), flowgrams were recorded at λ = 510 nm. The concentrations of medicinal substances were determined using calibration plots or by a standard addition method.

In the analysis of suppositories, a 0.5-g weighed portion of the test substance was mixed with ethanol (10 mL), and the mixture was heated on a water bath until the matrix melted. Next, the solution was stirred up and filtered. Treatment with 10-mL ethanol portions was repeated three times. The extracts were collected into a 50-mL volumetric flask. The subsequent procedure was similar to the procedure described above.

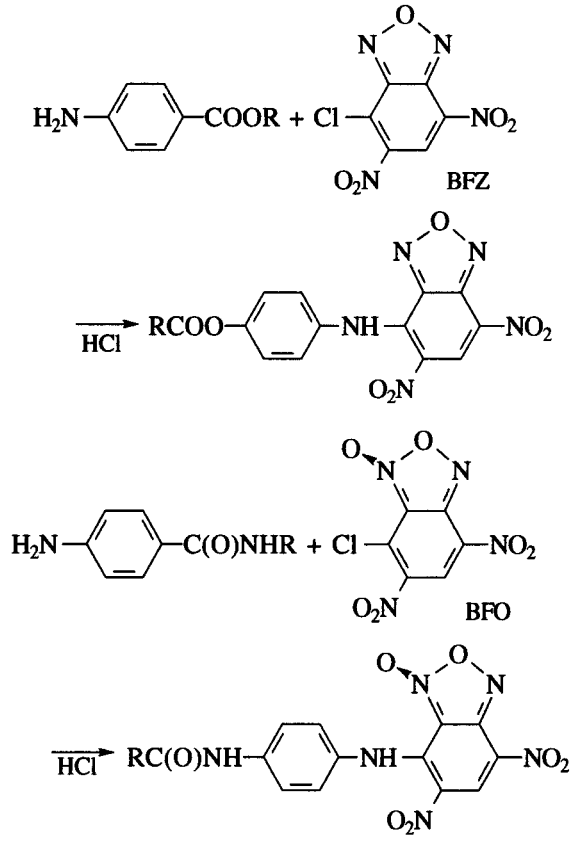
Tablets to be analyzed were crushed to powder. Next, 0.5-g portions were mixed with ethanol (20 mL), and the mixtures were shaken for 10 min. Extraction was repeated. The solution was placed in a 50-mL volumetric flask, diluted with ethanol to the mark, and analyzed by the procedure described above.

In the analysis of anesthesin- and novocaine- containing pharmaceuticals, a 0.5 mL-portion of the drug was mixed with water (5 mL). Anesthesin was extracted with 5-mL portions of ether under shaking for 1 min (four times). The ether layers were separated, and the solvent was removed by distillation. The residue was dissolved in ethanol. Anesthesin and novocaine in the residue after their dissolution in ethanol and in the aqueous phase were determined by the procedure described above.

Determination of novocainamide and PASA in the biological fluids. Blood serum samples were prepared after removing the blood clot from blood samples. Next, proteins were precipitated by adding trichloroacetic acid (1 mL of a 30% solution) followed by doubly repeated centrifugation (5000 rpm). The final centrifugate was analyzed.

RESULTS AND DISCUSSION

Conditions for the spectrophotometric detection of the derivatives of medicinal substances The reactions of BFO and BFZ with the derivatives of PABA and PASA in polar nonaqueous or mixed solvents give rise to intensely colored compounds. Absorption spectra of these compounds are shown in Fig. 1. The composition of the reaction products according to the data of chemical analysis and results of potentiometric titration of NH-acids with lithium methylate in methanol suggest the following reaction mechanism:



As a whole, the benzofuroxan derivatives of the compounds under study are characterized by stronger long-wave shifts of absorption maxima than the benzofurazan derivatives. Flow-injection determinations of primary arylamines using BFZ as a reagent are hampered by the partial overlapping of the absorption bands of the derivatives (the products of the analytical reaction) and of the hydrolyzed reagent. For the dinitrobenzofuroxan derivatives of arylamines, the overlapping of the bands of the products of concurrent reactions is negligible. Therefore, we used BFO for the FI determination of PABA and PASA derivatives. Moreover, compared to BFZ, this reagent possesses higher reactivity to primary amines [7]. The analytical wavelengths were selected taking into account the spectral properties of the derivatives (Fig. 1).

Selection of the composition of the carrier stream. The rate and degree of completion of the analytical reaction between amino compounds and BFZ or BFO in nonequilibrium conditions are affected by the solvent and the composition of the reaction solution [12, 13]. Thus, to optimize the conditions for the flow-injection determinations of PABA and PASA deriva-

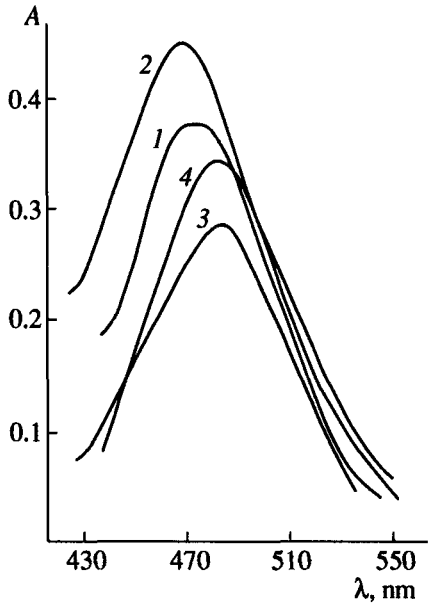


Fig. 1. Absorption spectra of the 4,6-dinitrobenzofuroxan derivatives (10^{-5} M) of (*1*) anesthesin, (*2*) novocaine, (*3*) novocainamide, and (*4*) sodium 4-aminosalicylate; solvents: (*1–3*) methanol–water (30 : 70 vol %) and (*4*) phosphate buffer solution (pH 6.68).

tives, we examined the effect of the carrier stream composition on the analytical signal.

The use of low-polarity solvents as carriers in the FIA of PABA and PASA derivatives is limited because of the existence of spectral equilibria between different forms of dinitrobenzoxadiazole derivatives of the substances under study. Thus, the addition of a nonpolar solvent (chloroform or tetrachloromethane) to a solution of derivatives in a polar nonaqueous solvent (dimethylsulfoxide or alcohols) resulted in the appearance of a new absorption band (λ_{max} = 430 nm) in the electronic spectra. The intensity of this band increased with an increase in the concentration of the nonpolar component (Fig. 2). The equilibrium is reversible and can be shifted to the initial substances as the concentration of the nonpolar component in the mixed solution containing the polar solvent decreases.

Table 1 presents peak heights for anesthesin and novocainamide obtained for organic and water–organic solutions. The data of Table 1 demonstrate that the signal intensity increases with an increase in the concentration of water in the binary mixture. However, the signal intensities for aqueous solutions are lower than for organoaqueous mixtures. Studying the effect of solvents on the recorded signal reveals an important role of the basic properties of the solution. This effect becomes evident if we compare signals obtained for water–alcohol mixtures. For these mixtures, the peak heights differ for ethanol, propanol, and methanol, provided that the water concentration is equal. The experimental data testify that the solvent acts as a basic catalyst in the reaction of the substances under study with BFO. This effect was noticed in the previous studies on the flow-injection determination of hydrazine and a number of aromatic and heteroaromatic amines [5–7]. It should be pointed out that the PABA and PASA

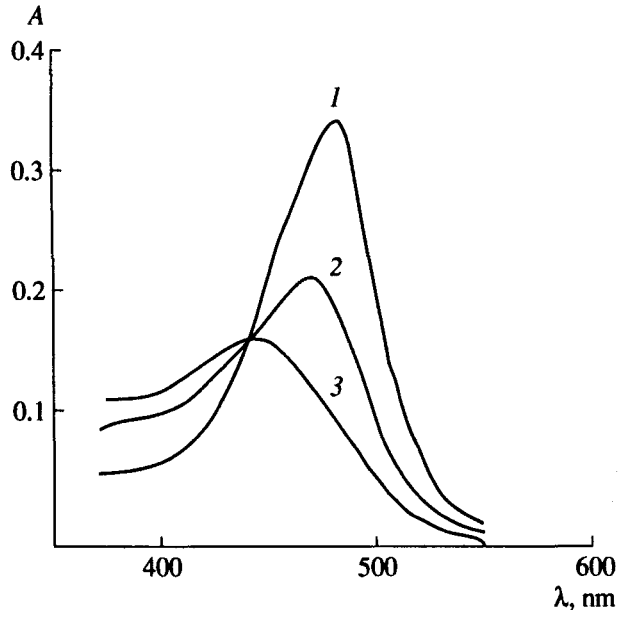


Fig. 2. Absorption spectra of the 5,7-dinitrobenzofurazan derivative of anesthesin (10^{-5} M) in dimethylsulfoxide recorded at various concentrations of chloroform (vol %): (*1*) 0, (*2*) 30, and (*3*) 60.

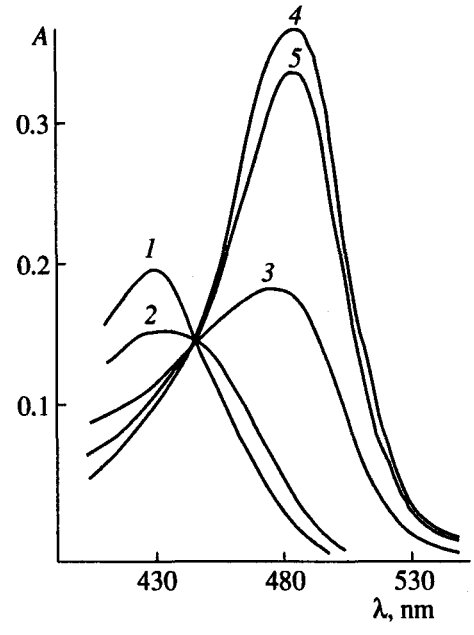


Fig. 3. Effect of pH on the absorption spectra of the 5,7-dinitrobenzofurazan derivative of anesthesin (10^{-5} M) in a dimethylsulfoxide–water solution (2 : 98, vol %): (*1*) 1.1, (*2*) 3.3, (*3*) 5.1, (*4*) 6.7, and (*5*) 9.18.

derivatives under study and their dinitrobenzofuroxan derivatives are poorly soluble in water and water–propanol solutions. Sedimentation processes that occur in aqueous solutions in a flow-injection system make the analysis difficult (almost impossible for anesthesin). At the same time, the solutions in ethanol (methanol)–water mixtures remain homogeneous. Therefore, the optimum ratio between the acidic and basic properties of the solvent and a sufficient solubility of both the source substances and the reaction products are achieved in ethanol (methanol)–water mixtures.

Optimization of pH. Because dinitrobenzoxazole derivatives exhibit acid properties (NH-acidity), the spectral properties (the positions of the absorption band and their intensities) are affected by the acidity of the solution. The intensity of the long-wave absorption bands decreases with an increase in the acidity of the solution (Fig. 3). Moreover, the rate of the formation of dinitrobenzofuroxan derivatives of the analytes in the flow system and, consequently, the magnitude of the analytical signals depends on the pH of the solution. For this reason, we examined the optimum conditions for the FIA determination of medicinal substances. Figure 4 shows a typical pH dependence of the peak height in determining novocainamide. As illustrated, the maximum intensities of the signals and, thus, the maximum sensitivity of determination are attained using a neutral solution. In an acid solution, the analytical reaction is suppressed. However, the high reactivity of BFO provides the detection of the reaction products even in acid solutions, although signal intensities in these solutions decrease significantly.

A decrease in the signal intensities in basic solutions is apparently due to the effect of the competing reaction of BFO with hydroxyl ions, which results in the formation of the hydroxyl derivative and in a decrease in the effective reagent concentration in the flow. Thus, we selected a phosphate buffer (pH 6.86) for the subsequent experiments.

Effect of the hydrodynamic parameters and the reagent concentration on the signal intensity. To select the working conditions for the determination of PABA and PASA derivatives in a flow-injection system, we studied the effect of the reagent concentration, flow rate of the carrier stream, and the length of the reaction coil on the intensity of the analytical signal. The height and shape of the peaks depended on the flow rate, the coil length (volume), and the injected sample volume. Moreover, the coil length and the flow rate affected the residence time of reaction zones in the system and, hence, the completeness of the chemical reaction. As an example, the data in Table 2 illustrate a typical dependence for anesthesin. As a whole, the dependence of the signal intensity for the substances under study on the flow rate of the carrier stream are flattened in the range 1–1.6 mL/min. We performed our experiments within this range. At low flow rates, a decrease in the signal intensity is due to diffusion processes. An increase in the coil length over 90 cm (inside diameter 0.6 mm) did not affect the signal intensity. In this case, the optimum injected volume was 110 μL.

Table 1. Effect of components on the signal intensity of dinitrobenzofuroxan derivatives. Concentration of the reagent 10^{-3} M; novocainamide (I), 4.5×10^{-6} M; and anesthesin (II), 7×10^{-6} M; flow rate 1.15 mL/min, λ 510 nm ($n = 4$)

Carrier-stream composition (vol %)	Analyte	Peak height (mean), mm
Methanol (100)	II	58
Methanol–water (85 : 15)	II	84
Methanol–water (70 : 30)	II	93
Methanol–water (50 : 50)	II	96
Methanol–water (30 : 70)	II	98
Methanol–water (15 : 85)	II	82
Methanol (100)	I	39
Methanol–water (30 : 70)	I	44
Ethanol (100)	I	45
Ethanol–water (70 : 30)	I	50
Ethanol–water (50 : 50)	I	53
Ethanol–water (30 : 70)	I	62
Ethanol–water (10 : 90)	I	51
Acetonitrile (100)	I	25
Acetonitrile–water (30 : 70)	I	43
DMSO (100)	I	20
DMSO–water (30 : 70)	I	36
Propanol-2 (100)	I	43
Propanol-2–water (30 : 70)	I	63
Water (100)	I	32

Table 2. Effect of the flow rate on the signal intensity. Concentration of BFO and anesthesin are 10^{-2} and 5.36×10^{-6} M, respectively; methanol–water (30 : 70 vol %); λ 510 nm ($n = 4$)

Flow rate, mL/min	Peak height (mean), mm
0.66	23
0.80	49
1.00	75
1.34	75
1.43	75
1.53	76
1.75	60
2.07	47
2.50	38

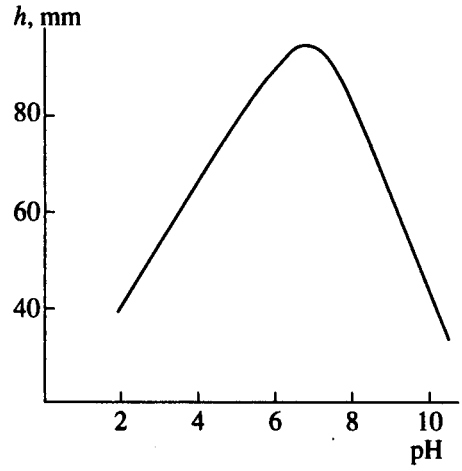


Fig. 4. pH dependence of the peak height of novocainamide (7.2×10^{-5} M); ethanol–phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); flow rate 1.3 mL/min.

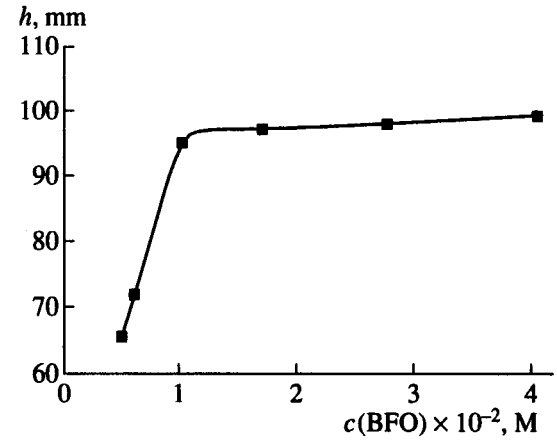


Fig. 5. Effect of the reagent concentration on the signal intensity in determining novocaine (5.6×10^{-6} M); methanol–water mixture (30 : 70, vol %); pH 7.12; flow rate 1.2 mL/min.

The selection of a solvent for the FIA determination of drugs is governed by the possible effect of the hydrolytic transformations of the reagents with the formation of inactive hydroxy derivatives [14]. We selected acetonitrile as a solvent, because it provided high hydrolytic stability of the reagent solutions [7]. The reagent concentrations in the injected solution in determining the drugs were $(1–2) \times 10^{-2}$ M. A decrease in the signal intensity was observed for the reagent concentrations lower than 8×10^{-3} M. Meanwhile, an increase in the BFO concentration to 4×10^{-2} M and higher made the flow inhomogeneous, which led to a baseline drift and hampered the analysis (Fig. 5).

Selectivity of the determination of PABA and PASA derivatives. The characteristics of the determinations of PABA and PASA derivatives under the optimized conditions are listed in Table 3. The data of Table 3 demonstrate that the calibration graphs for the analytes are linear within the range from 0.08 to 5.0 μg/mL. The detection limits (3σ, $n = 4$) are 0.04, 0.05, 0.07, and 0.03 μg/mL for anesthesin, novocaine, novocainamide, and sodium 4-aminosalicylate, respectively.

The capabilities of the FIA spectrophotometric procedure in determining PABA and PASA derivatives in the matrices under study were tested using anesthesin, novocaine, and novocainamide in various model mixtures; pharmaceuticals; and biological liquids as examples (Tables 4, 5). It was preliminary found that tablet excipients did not affect the results of analysis. The results of analyses indicate that various components of biological fluids bearing functional amino groups (amino acids and biogenic amines) do not influence the results of FIA determination of the PABA and PASA derivatives. The experimental data also demonstrate that, in the analyses of protein hydrolyzate, serum albumin, blood plasma, and whole blood, the recorded signals insignificantly differ from the background signals. This fact allows the determination of PABA and PASA derivatives in these biological matrices. An insignificant decrease in the PASA concentration in blood samples (Table 4) is, probably, due to secondary reactions between the medicinal substance and the components of biological matrices of individual patients. Moreover, these substances can be selectively determined even in

Table 3. Analytical characteristics of flow-injection determinations of 4-aminobenzoic and 4-aminosalicylic acid derivatives

Analyte	Stream components (30 : 70, vol %)	Calibration function	r	Concentration range (μg/mL)	Throughput (samples/hour)
Anesthesin	Methanol–water	h(mm) = 83.84c_X (μg/mL) – 0.4	0.9998	0.1–2.5	25
Novocaine	Methanol–phosphate buffer (pH 6.68)	h(mm) = 63.73c_X (μg/mL) + 0.2	0.9998	0.12–3.5	24
Novocainamide	Ethanol–phosphate buffer (pH 6.68)	h(mm) = 48.2c_X (μg/mL) – 0.8	0.9999	0.16–5.0	26
Sodium 4-aminosalicylate	Ethanol–phosphate buffer (pH 6.68)	h(mm) = 95.1c_X (μg/mL) + 0.5	0.9999	0.08–2.5	28

Table 4. Determination of novocainamide and sodium 4-aminosalicylate in biological fluids using the standard addition method; ethanol–phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); carrier flow rate 1.3 mL/min

Biological fluid	Analyte	Added, μg/mL	Found ($\bar{c} \pm \delta$), μg/mL	RSD, % ($n = 4$, $P = 0.95$)
Protein hydrolyzate	PASA	0.55	0.60 ± 0.06	6
	Novocainamide	1.3	1.4 ± 0.1	6
Serum albumin	Novocainamide	0.85	0.90 ± 0.08	6
	PASA	1.8	1.8 ± 0.1	5
Blood plasma	Novocainamide	5.12	4.8 ± 0.4	5
	PASA	16.5	16 ± 1	5
Blood	PASA	4.30	3.9 ± 0.3	5
	Novocainamide	2.8	2.9 ± 0.2	5
	Novocainamide	10.25	10 ± 1	5
	PASA	28.1	28 ± 2	4

Table 5. Determination of 4-aminobenzoic and 4-aminosalicylic acid derivatives in pharmaceutical preparations; methanol–phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); carrier flow rate 1.3 mL/min ($n = 4$, $P = 0.95$)

Mixture composition	Analyte	Found according to the RF Pharmacopoeia, g	Found, g
Novocaine hydrochloride, 0.25 g HCl 0.1 M, 0.3 mL NaCl, 0.85 g Water to 100 mL	Novocaine	0.24 ± 0.01	0.25 ± 0.01
$CaCl_2$ (6.0 g) solution, 200.0 mL NaBr, 4.0 g Novocaine hydrochloride, 1.0 g	Novocaine	0.98 ± 0.03	1.01 ± 0.03
Ephedrine hydrochloride, 6.0 g Novocaine hydrochloride 1%, 200 mL Dimedrol, 2.0 g	Novocaine	1.98 ± 0.06	1.99 ± 0.06
Atropine sulfate, 0.02 g Ephedrine hydrochloride, 0.05 g Novocaine hydrochloride, 0.04 g Water to 10.0 mL	Novocaine	0.043 ± 0.002	0.042 ± 0.002
Dimedrol, 0.025 g Ephedrine, 0.025 g Novocaine hydrochloride, 0.2 g NaCl, 0.06 g	Novocaine	0.18 ± 0.01	0.19 ± 0.01
Novocaine suppositories Novocaine, 0.1 g	Novocaine	0.11 ± 0.01	0.10 ± 0.01
Anesthesol suppositories Anesthesin, 0.1 g Dermatol, 0.04 g Zinc oxide, 0.02 g Menthol, 0.004 g Polyethylene-oxide matrix, to 2.73 mg	Anesthesin	0.095 ± 0.03	0.096 ± 0.02
Novocaine, 0.5 g Anesthesin, 0.5 g Menthol, 1.25 g Ethanol 70%, 50.0 g	Novocaine Anesthesin	0.49 ± 0.02 0.48 ± 0.02	0.50 ± 0.02 0.49 ± 0.01
Novocainamide tablets, 0.25 g	Novocainamide	0.23 ± 0.01	0.22 ± 0.01
Sodium 4-aminosalicylate, 3% solution for injections	Sodium 4-aminosalicylate	0.028 ± 0.002 g/mL	0.029 ± 0.003 g/mL

the presence of other drug constituents, such as inorganic salts, ephedrine, dimedrol, and others. Because of the selectivity of the analytical signal, 7-chloro-4,6-dinitrobenzofuroxan is superior to other reagents for derivatization in FIA.

Thus, spectral properties of 4,6-dinitrobenzofuroxan derivatives of medicinal substances provide their flow-injection determination in pharmaceuticals and biological fluids. Simple and rapid analytical procedures can be used in therapeutic monitoring in clinics.

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REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Medicinal Preparations), Moscow: Meditsyna, 1993, vol. 2.
2. Romero, J.S.E., Ramos, G.R., Coll, R.F., and Martin, V.S., *Anal. Chim. Acta*, 1991, vol. 242, p. 143.
3. Whiteside, I.R.C., Worsfold, P.J., and McKerrell, E.H., *Anal. Chim. Acta*, 1988, vol. 204, p. 343.
4. Korenman, I.M., *Fotometricheskii analiz: Metody opredeleniya organicheskikh soedinenii* (Analysis by Photometry: Methods for the Determination of Organic Compounds), Moscow: Khimiya, 1970, p. 149.
5. Evgen'yev, M.I., Garmonov, S.Yu., Evgen'yeva, I.I., and Budnikov, H.C., *Talanta*, 1995, vol. 42, no. 10, p. 1465.
6. Evgen'ev, M.I., Garmonov, S.Yu., Evgen'eva, I.I., and Ugrichich-Trebinskii, V.V., *Zh. Anal. Khim.*, 1998, vol. 53, no. 3, p. 272.
7. Evgen'ev, M.I., Evgen'eva, I.I., Goryunova, S.M., and Vasyakina, A.Kh., *Zh. Anal. Khim.*, 1998, vol. 53, no. 4, p. 432.
8. Weissberger, A.V., Proskauer, E.S., Riddick, J.A., and Toops, E.E., *Organic Solvents: Physical Properties and Methods of Application*, vol. 7 of *Technique of Organic Chemistry*, Weissberger, A., Ed., New York: Interscience, 1955. Translated under the title *Organicheskie rastvoriteli*, Moscow: Inostrannaya Literatura, 1958.
9. Gordon, A.J. and Ford, R.A., *The Chemist's Companion: A Handbook of Practical Data, Techniques and References*, New York: Wiley, 1972. Translated under the title *Sputnik khimika*, Moscow: Mir, 1976, p. 439, 440.
10. Sharnin, G.P., Levinson, F.S., Akimova, S.A., *et al.*, USSR Inventor's Certificate no. 657 025, *Byull. Izobret.*, 1979, no. 14.
11. Bailey, A.S. and Case, J.R., *Tetrahedron*, 1958, vol. 3, p. 113.
12. Connors, K.A., *Reaction Mechanisms in Organic Analytical Chemistry*, New York: Wiley, 1973, p. 178.
13. Reichardt, Ch., Solvents and Solvent Effects in Organic Chemistry, Weinheim: Verlagsgesellschaft, 1988. Translated under the title *Rastvoriteli i effekty sredy v organicheskoi khimii*, Moscow: Mir, 1991, pp. 21, 182, 403.
14. Terrier, F., Xiao Lan, Hlaibi Miloude, and Halle, I.C., *J. Chem. Soc., Perkin Trans. 2*, 1993, no. 3, p. 337.