The proposed method has been used in toxicological experiments on animals to establish the maximum permissible concentrations of the substances in air, as well as in a hygienic investigation of the atmosphere of work rooms.

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USE OF ION-EXCHANGE CHROMATOGRAPHY FOR QUALITY CONTROL OF SULFOCAMPHOCAINE

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Sulfocamphocaine is a 10% aqueous solution of novocaine base and camphor sulfonate. It contains ions, namely cations of the protonated novocaine base and camphosulfonic acid anions. The following substances may also be present: camphor, camphoric acid, p-aminobenzoic acid (PABA), aniline, and diethylaminoethanol.

Camphor is an impurity and a possible product of the decomposition of camphosulfonic acid. We established the presence of camphor in camphosulfonic acid by means of gas–liquid chromatography. Camphoric acid is a product of the oxidation of camphor by atmospheric oxygen [1], which may be contained in ampuls. However, it is not likely for a similar process to occur in the presence of such unstable substances as PABA, aniline, and diethylaminoethanol, being the decomposition products of novocaine [2]. The decomposition of other benzoic acid and PABA esters, particularly Novocainamid, benzocaine, tetracaine hydrochloride, and bencaine, is similar to that of novocaine.

The decomposition of novocaine during storage was studied by means of thin-layer chromatography on Silufol UV-254 in a solvent system of heptane–dioxane (1 : 1). Here it was established that pharmaceutical-grade novocaine (powder) was nearly free of decomposition products even after 4-year storage. Sulfocamphocaine and a 0.5% aqueous solution of novocaine in ampuls show an increase in PABA content during storage. However, even after 2 years the content of aniline remains negligible. A substantial amount of aniline is formed, in addition to PABA, when the ampuls are stored longer at high temperatures (80°C). No other absorbents were observed in the UV region even after 24 days of storage. High temperature leads to a yellowing of the solutions, with the intensity of the coloration evidently approaching a definite limit related to the content of the oxygen in the ampul [3]. It is important to note that all of the decomposition products of novocaine are basic substances. Thus, with the passage of 10 ml of a 1% solution of novocaine, stored for 24 days at 80°, through a column with a cation exchanger (conditions for sulfocamphocaine are described below) and with recording of the spectrum, we obtained a reference line which begins to ascend only at 210 nm. Under the same conditions, 2 ml of a 10% aqueous solution of sulfocamphocaine yields the spectrum of camphosulfonic acid, despite the large coefficients of absorption of novocaine and its decomposition products. This permits the use of ion-exchange chromatography for the quantitative determination of camphosulfonic acid in sulfocamphocaine.

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TABLE 1. Optical Properties of Camphosulfonic Acid, PABA, Aniline, and Novocaine in Water

Compound	λ_{max}, nm	ε_{max}	$E_1^{1\%}$ cm
Camphosulfonic acid	286.5	35.7	1.44
Novocaine	221	8500	360*
	292	17560	743*
PABA	266	15000	1094
	284	14000	1021
Aniline	230	8600	925
	280	1430	153.8

*In terms of novocaine base.

In present VFS practice, camphosulfonic acid is determined by means of acid–base titration according to the biologically inactive sulfo group. Ever-present sulfate ions and novocaine base decomposition products render this method nonobjective. It is doubtful, for this reason, that camphosulfonic acid can be determined in the form of dinitrophenylhydrazones [4] and oximes [5] without preliminary separation of amines. Ion-exchange chromatography ensures reliable separation of interfering impurities and decomposition products. For quantitative determination of camphosulfonic acid separated in this manner, we propose to use in this case absorption spectrophotometry based on the fundamental absorption band (Table 1). Camphor, which is not retained by the cation exchanger, does not interfere with the determination since its optical properties and those of camphosulfonic acid are practically identical and since the biological activity of the latter is conditional upon the presence of a camphor skeleton in its molecule. Camphoric acid is also not retained by the cation exchanger, but absorbs in the far-UV region.

In connection with the fact that the principal product of the decomposition of novocaine is PABA, for the quantitative determination of novocaine base in sulfocamphocaine we propose ion-exchange chromatography on anion exchangers with subsequent absorption spectrophotometry based on the fundamental absorption band.

It is not possible to differentiate novocaine and its decomposition products by means of VFS nitritometry. The proposed extraction spectrophotometric method eliminates this difficulty, but does require measurement of optical density in highly volatile organic solvents [7]. Ion-exchange chromatography separates any quantity of PABA. With regard to aniline, calculations show that even with a 10% conversion of novocaine into aniline, the error introduced by aniline in the determination of novocaine does not exceed 0.5%.

EXPERIMENTAL

The cation exchanger is KU-2–8 (H form) prepared according to Section 2.1 of GOST 10896-72 on "Ion Exchangers." The anion exchanger is AV-17–8 (Cl form) soaked for 1 h in hydrochloric acid and washed with water, and alcohol and water (until disappearance of alcohol odor).

The height of the ion-exchanger layer is 37 cm. The rate of passage through the anion exchanger is 4 ml/min, and through the cation exchanger 2 ml/min.

Method of Quantitative Determination of Camphosulfonic Acid in Sulfocamphocaine. We passed through a column with cation exchanger 1.5 ml of ampul injection solution of sulfocamphocaine washed in water in a 25-ml graduated flask. The optical density of the resultant solution was measured at 287 nm. Water passed through the cation exchanger served as the control. To construct a calibration curve, 1.6 g (exact weighted portion) of camphosulfonic acid crystallized from chloroform was dissolved in water and brought up to the 25-ml mark of a 25-ml graduated flask. Samples of 0.4, 0.8, 1.2, 1.6, and 2.0 ml of the resultant solution were taken and treated as described for the compound. The results obtained were analyzed by the least-squares method.

Method of Quantitative Determination of Novocaine Base in Sulfocamphocaine. A 10% ampul solution of sulfocamphocaine was diluted with 100 parts water. We passed 1.5 ml of the resultant solution through a column with anion exchanger, washed it with 25 ml water in a 100-ml graduated flask, and filled the flask to capacity with water. The optical density of the resultant solution was measured at 292 nm. The control was 25 ml of water passed through the anion exchanger and placed in a 100-ml graduated flask which was then

TABLE 2. Results of Analysis of a Production Series of Sulfocamphocaine, %

No. of series	Camphosulfonic acid		Novocaine base	
	by VFS	by the proposed method	absorption spectrometry	by the proposed method
10 773	5,00	4,87	4,84	4,78
20 773	5,13	4,86	4,86	4,79
30 773	5,11	4,92	4,97	4,90
20 974	5,19	5,18	5,08	5,06
30 974	5,12	5,03	4,97	4,95

filled to capacity with additional water. To construct a calibration curve, 0.1 g (exact weighted portion) of novocaine crystallized from alcohol was placed in a 25-ml graduated flask which was then filled to capacity with water. Samples of 1, 2, 3, 4, and 5 ml of the resulting solution were transferred to separate 25-ml measuring flasks and made up to the marks with water. From each of the solutions so obtained a 1.5-ml sample was treated as described for the compound. The concentration of novocaine is expressed in terms of novocaine base (the concentration of novocaine multiplied by the coefficient 0.8665), and the data obtained are analyzed by the least-squares method.

To determine the service life of the cation-exchange column, 1.5 ml of a 5.5% solution of novocaine was passed through it under conditions described for analysis of camphosulfonic acid in camphosulfocaine. Measurement of the optical densities of the resultant solutions showed zero absorption after 33 tests. This is its service life. The service life of the anion-exchange column was not determined since calculations show that it exceeds 1000 tests.

Analysis of the artificial series of sulfocamphocaine by the proposed method gave a 2.5% reproducibility for camphosulfonic acid and 1.9% reproducibility (three tests, P = 0.95) for novocaine (in a 1:1 mixture with PABA).

Analysis of a production series of sulfocamphocaine is shown in Table 2.

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