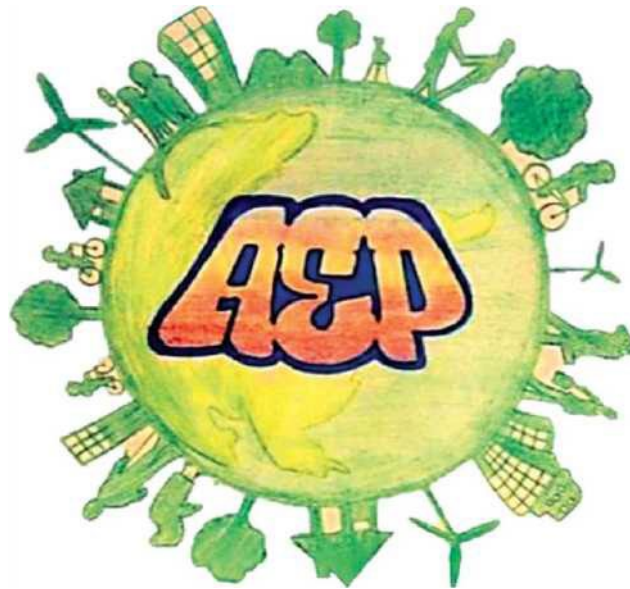


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«International Sakharov Environmental Institute»



ACTUAL ENVIRONMENTAL PROBLEMS

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DETERMINATION OF AMBROXOL HYDROCHLORIDE CONCENTRATION IN THE AIR OF PHARMACEUTICAL PRODUCTION BY SPECTROPHOTOMETRIC METHOD

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The results of development of the author's spectrophotometric technique for determination of the mass concentration of ambroxol hydrochloride in the air of pharmaceutical enterprises are proposed. It is based on concentration of ambroxol hydrochloride from air on paper filters AFA-VP, its extraction from filters with methanol under the action of ultrasound, concentration of the extract by complete removal of methanol, dissolution of the dry residue in distilled water, derivatisation reactions with 3-methyl-2-benzothiazolinone hydrazone hydrochloride in the presence of ammonium cerium (IV) sulphate and subsequent determination of the reaction product by spectrophotometric method. Quantitative determination is performed by absolute calibration method.

Keywords: ambroxol hydrochloride, spectrophotometry, determination methodology, working zone

Lack of methodology to determine ambroxol hydrochloride concentration in the working zone air of pharmaceutical enterprises of the Republic of Belarus is relevant both for the manufacturer and for controlling organisations.

The aim of the work is to develop a method for the determination (measurement) of ambroxol hydrochloride concentration in the working zone air of pharmaceutical production by spectrophotometric method, to establish its characteristics and metrological evaluation (certification).

Ambroxol hydrochloride (trans-4-[(2-amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride) is a drug that belongs to the group of mucolytics and has expectorant effect, being a metabolite of bromhexine, has local anaesthetic properties [Lebedinskaya K. S., Krymskaya T. P., Lamotkin S. A., 2023]. Ambroxol hydrochloride is produced in various dosage forms (tablets, solutions, syrups) by the enterprises of Belarus: JSC "Borisov Medical Preparations Plant", LLC "Lekpharm", LLC "Pharmtechnology", LLC "Lamira-Pharmakar".

According to the requirements of GOST 12.1.007-76, ambroxol hydrochloride belongs to the 3rd class of hazard (moderately hazardous substance). The maximum permissible concentration of harmful substances in the working area air for ambroxol hydrochloride is 4.0 mg/m³. In the pharmaceutical industry in the production of finished dosage forms, this compound can enter the air of the working zone in the form of fine aerosol (dust), and have an adverse effect on the health of workers [Vasilkevich V. M., Kolesneva E. M., Kolesneva E. V., 2021; Vasilkevich V. M., Bogdanov R. M., Bogdanov R. V., Drozdova E. B., 2020].

The spectrophotometric method for the determination of ambroxol hydrochloride by interaction with 0.2 % solution of 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) in the presence of 0.1 % solution of cerium (IV) sulphate ammonium [Narayana Reddy M., Kanna Rao K., Swapna M., 1998] was chosen in the development of the method.

The stage of selection and sample preparation is based on concentration of ambroxol hydrochloride from air onto analytical aerosol filters AFA-VP-20 with its subsequent extraction from the filters with methanol under the action of ultrasound, concentration of the extract by complete removal of methanol, dissolution of the dry residue in distilled water.

Extraction using ultrasonic bath increased the extraction rate from 80 to 85 %. After extraction, the filtrate was evaporated at a rotary evaporator and the resulting dry residue was dissolved in 1 cm³ of water, respectively.

After derivatisation reactions with 0.2 % 3-methyl-2-benzothiazolinone hydrazone hydrochloride in the presence of 0.1 % cerium (IV) sulphate ammonium solution, the optical density of the obtained reaction product (crimson-coloured

solution) was measured at a wavelength of 570 nm with an absorbing layer length of 1 cm. Experimental measurements of optical density were carried out on a spectrophotometer "Cary 60", Agilent Technologies, USA.

Quantitative determination was performed by absolute calibration method. graph has a linear dependence of optical density on mass concentration in the range from 100 to 500 $\mu\text{g}/\text{cm}^3$.

The mass concentration of ambroxol hydrochloride in the air of the working zone was calculated taking into account the extraction coefficient, taking into account losses during sample preparation, in relative units), mass concentrations found from the calibration graph, the volume of the sample solution, the sampled volume of air reduced to standard conditions. The range of measured concentrations of ambroxol hydrochloride in the working area air is from 2.0 to 50.0 mg/m^3 .

The following metrological characteristics of the method for determination of ambroxol hydrochloride in the working zone air were established: repeatability limit $r = 11\%$, intermediate precision limit $\text{RI}(\text{TO}) = 29\%$, expanded uncertainty $U = 23\%$ at confidence probability $P = 0.95$ and coverage factor $k = 2$.

Thus, the developed method AMI.GM 0088-2022 "Mass concentration of ambroxol hydrochloride in the air of the working zone. Measurement procedure by spectrophotometric method" with established metrological characteristics allows controlling ambroxol hydrochloride concentration level in the air of the working zone at the level of $\frac{1}{2}$ MAC.