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Fine Chemical Technologies

- Theoretical Bases of Chemical Technology
- Chemistry and Technology of Organic Substances
- Chemistry and Technology of Medicinal Compounds and Biologically Active Substances
- Biochemistry and Biotechnology
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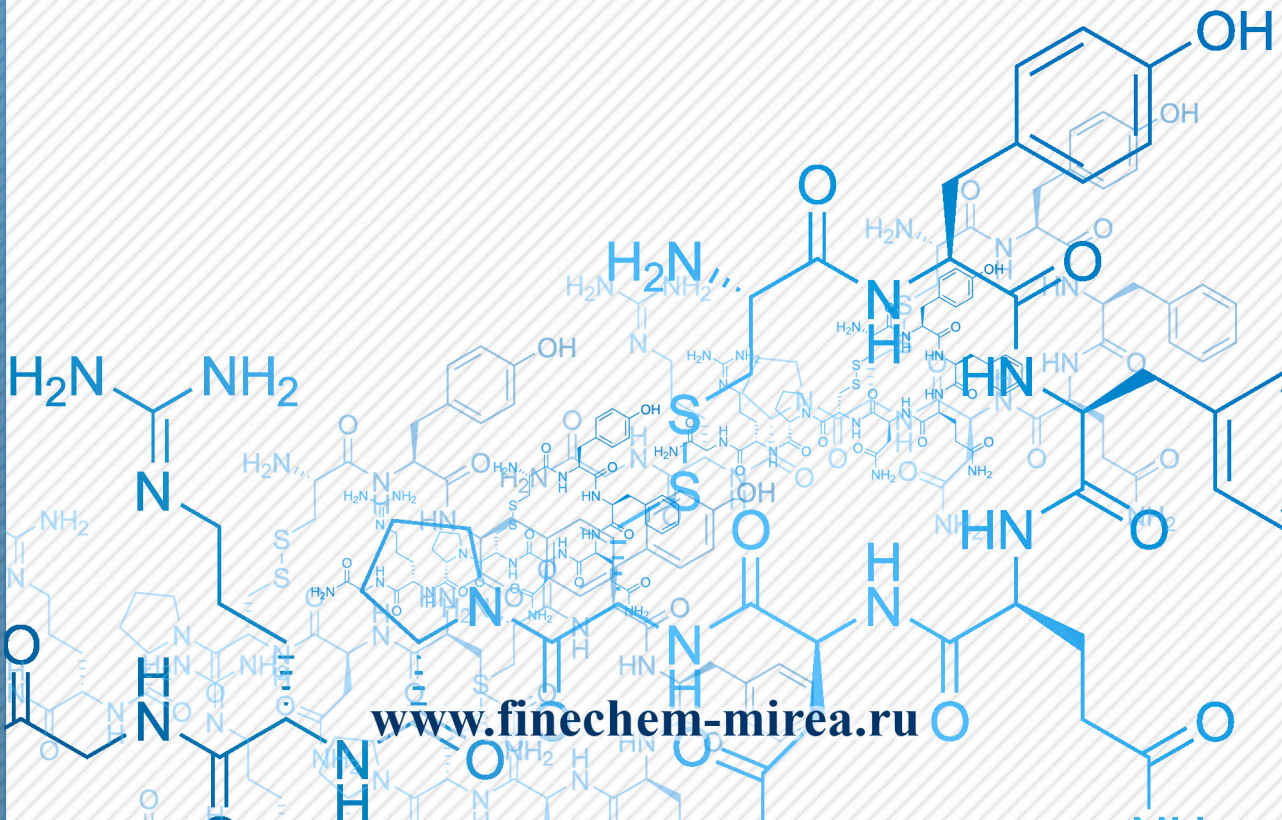

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Phone: +7 (499) 600-80-80 (#31288)
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119571, Москва, пр. Вернадского, 86, оф. Л-119.
Тел.: +7 (499) 600-80-80 (#31288)
E-mail: *seredina@mirea.ru*

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Ivan A. Novakov – Academician at the RAS, Dr. Sci. (Chem.), Professor, President of the Volgograd State Technical University, Volgograd, Russian Federation.
Scopus Author ID 7003436556, ResearcherID I-4668-2015, http://orcid.org/0000-0002-0980-6591, *president@vstu.ru.*

Alexander N. Ozerin – Corresponding Member of the RAS, Dr. Sci. (Chem.), Professor, Enikolopov Institute of Synthetic Polymeric Materials of the RAS, Moscow, Russian Federation.
Scopus Author ID 7006188944, ResearcherID J-1866-2018, https://orcid.org/0000-0001-7505-6090, *ozerin@ispm.ru.*

Tapani A. Pakkanen – PhD, Professor, Department of Chemistry, University of Eastern Finland, Joensuu, Finland.
Scopus Author ID 7102310323, *tapani.pakkanen@uef.fi.*

Armando J.L. Pombeiro – Academician at the Academy of Sciences of Lisbon, PhD, Professor, President of the Center for Structural Chemistry of the Higher Technical Institute of the University of Lisbon, Lisbon, Portugal.
Scopus Author ID 7006067269, ResearcherID I-5945-2012, https://orcid.org/0000-0001-8323-888X, *pombeiro@ist.utl.pt.*

Dmitrii V. Pyshnyi – Corresponding Member of the RAS, Dr. Sci. (Chem.), Professor, Institute of Chemical Biologyand Fundamental Medicine, Siberian Branch of the RAS, Novosibirsk, Russian Federation.
Scopus Author ID 7006677629, ResearcherID F-4729-2013, https://orcid.org/0000-0002-2587-3719, *pyshnyi@niboch.nsc.ru.*

Alexander S. Sigov – Academician at the RAS, Dr. Sci. (Phys. and Math.), Professor, President of MIREA – Russian Technological University, Moscow, Russian Federation.
Scopus Author ID 35557510600, ResearcherID L-4103-2017, *sigov@mirea.ru.*

Alexander M. Toikka – Dr. Sci. (Chem.), Professor, Institute of Chemistry, Saint Petersburg State University, St. Petersburg, Russian Federation.
Scopus Author ID 6603464176, ResearcherI D A-5698-2010, http://orcid.org/0000-0002-1863-5528, *a.toikka@spbu.ru.*

Andrzej W. Trochimczuk – Dr. Sci. (Chem.), Professor, Faculty of Chemistry, Wrocław University of Science and Technology, Wrocław, Poland.
Scopus Author ID 7003604847, *andrzej.trochimczuk@pwr.edu.pl.*

Aslan Yu. Tsivadze – Academician at the RAS, Dr. Sci. (Chem.), Professor, A.N. Frumkin Institute of Physical Chemistry and Electrochemistry of the RAS, Moscow, Russian Federation.
Scopus Author ID 7004245066, ResearcherID G-7422-2014, *tsiv@phyche.ac.ru.*

Новаков Иван Александрович – академик РАН, д.х.н., профессор, президент Волгоградского государственного технического университета, Волгоград, Российская Федерация.
Scopus Author ID 7003436556, ResearcherID I-4668-2015, http://orcid.org/0000-0002-0980-6591, *president@vstu.ru.*

Озерин Александр Никифорович – член-корр. РАН, д.х.н., профессор, Институт синтетических полимерных материалов им. Н.С. Ениколопова РАН, Москва, Российская Федерация.
Scopus Author ID 7006188944, ResearcherID J-1866-2018, https://orcid.org/0000-0001-7505-6090, *ozerin@ispm.ru.*

Пакканен Тапани – PhD, профессор, Департамент химии, Университет Восточной Финляндии, Йоенсуу, Финляндия.
Scopus Author ID 7102310323, *tapani.pakkanen@uef.fi.*

Помбейро Армандо – академик Академии наук Лиссабона, PhD, профессор, президент Центра структурной химии Высшего технического института Университета Лиссабона, Португалия.
Scopus Author ID 7006067269, ResearcherID I-5945-2012, https://orcid.org/0000-0001-8323-888X, *pombeiro@ist.utl.pt.*

Пышный Дмитрий Владимирович – член-корр.РАН, д.х.н., профессор, Институт химической биологии и фундаментальной медицины Сибирского отделения РАН, Новосибирск, Российская Федерация.
Scopus Author ID 7006677629, ResearcherID F-4729-2013, https://orcid.org/0000-0002-2587-3719, *pyshnyi@niboch.nsc.ru.*

Сигов Александр Сергеевич – академик РАН, д.ф.-м.н., профессор, президент МИРЭА – Российского технологического университета, Москва, Российская Федерация.
Scopus Author ID 35557510600, ResearcherID L-4103-2017, *sigov@mirea.ru.*

Тойкка Александр Матвеевич – д.х.н., профессор, Институт химии, Санкт-Петербургский государственный университет, Санкт-Петербург, Российская Федерация.
Scopus Author ID 6603464176, Researcher ID A-5698-2010, http://orcid.org/0000-0002-1863-5528, *a.toikka@spbu.ru.*

Трохимчук Анджей – д.х.н., профессор, Химический факультет Вроцлавского политехнического университета, Вроцлав, Польша.
Scopus Author ID 7003604847, *andrzej.trochimczuk@pwr.edu.pl.*

Цивадзе Аслан Юсупович – академик РАН, д.х.н., профессор, Институт физической химии и электрохимии им. А.Н. Фрумкина РАН, Москва, Российская Федерация.
Scopus Author ID 7004245066, ResearcherID G-7422-2014, *tsiv@phyche.ac.ru.*

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RESEARCH ARTICLE

Study of calcium-containing compounds as catalysts for the esterification of glycerol with higher carboxylic acids

Yuriy L. Zotov✉, Daria M. Zapravdina, Evgeniy V. Shishkin, Yuriy V. Popov

Volgograd State Technical University, Volgograd, 400005 Russia
✉Corresponding author, e-mail: ylzotov@mail.ru

Abstract

Objectives. *To investigate the catalytic activity of calcium-containing basic catalysts for the esterification of glycerol with higher carboxylic acids in order to develop a low-waste technology for the production of multifunctional additives, as well as to assess the possibility of using the reaction products for the processing of polyvinyl chloride.*

Methods. *The consumption of oleic acid during synthesis was monitored using a titrimetric method of analysis with visual indication. The structure of the synthesized calcium-containing catalysts was confirmed by infrared spectroscopy; elemental analysis was additionally performed for calcium glyceroxide. Quantitative and qualitative analyses of the resulting mixtures of oleic acid glycerides were carried out using chromato-mass spectrometry. A sample of a multifunctional additive was tested in a model formulation of a medical plastic compound based on polyvinyl chloride.*

Results. *It is shown that the catalytic activity of calcium derivatives in the reaction of esterification of glycerol with higher carboxylic acids increases in the series* $CaO < Ca(OH)_2 < Ca(C_{17}H_{33}COO)_2 < Ca(C_2H_5O)_2 < Ca(C_4H_9O)_2 < Ca(C_3H_7O_3)_2$*, while the use of calcium glyceroxide as a catalyst in an amount from 1 to 6 mol % increases the conversion of carboxylic acid from 58 to 86% in 10 h of synthesis. However, varying the amount of calcium glyceroxide from 1.5 to 6 mol % results in no observed changes in the conversion of carboxylic acid. The multifunctional additive obtained by selecting calcium glyceroxide*

as a catalyst has a thermally stabilizing and plasticizing effect on the polymer composition. The introduction of the developed additive into the formulation of a polyvinyl chloride composition for medical purposes reduces the processing torque and time to reach the dry point. By combining these factors, energy costs during production were reduced by more than 11% compared to the control composition.

Conclusions. *It is established that calcium alcoholates catalyze the reaction of esterification of glycerol with oleic (or higher) acid to increase the conversion of the initial substances and selectivity for the formation of monoglycerides as compared with calcium oxide, hydroxide, and oleate. By optimizing the ratio of glycerol : oleic acid : calcium glyceroxide at 1 : 1 : 0.015, the maximum conversion of oleic acid of up to 86% in 10 h was obtained via synthesis. The proposed method for esterification of glycerol with higher carboxylic acids in the presence of a calcium-containing catalyst avoids the stage of purification from the catalyst to obtain a composition with multifunctional additive properties for the processing of polyvinyl chloride.*

Keywords: *esterification, glycerol, oleic acid, calcium alcoholates, calcium glyceroxide*

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НАУЧНАЯ СТАТЬЯ

Исследование кальцийсодержащих соединений в качестве катализаторов этерификации глицерина высшими карбоновыми кислотами

Ю.Л. Зотов✉, Д.М. Заправдина, Е.В. Шишкин, Ю.В. Попов

Волгоградский государственный технический университет, Волгоград, 400005 Россия
✉Автор для переписки, e-mail: ylzotov@mail.ru

Аннотация

Цели. *Исследовать каталитическую активность кальцийсодержащих основных катализаторов для процесса этерификации глицерина высшими карбоновыми кислотами с целью разработки малоотходной технологии получения многофункциональных добавок. Провести оценку возможности применения продуктов реакции для переработки поливинилхлорида.*

Методы. *За расходованием олеиновой кислоты во время синтеза наблюдали с использованием титриметрического метода анализа с визуальной индикацией. Строение синтезированных кальцийсодержащих катализаторов было подтверждено методом инфракрасной спектроскопии. Для глицерата кальция дополнительно был проведен элементный анализ. Количественный и качественный анализ полученных смесей глицеридов олеиновой кислоты проводили с использованием хромато-масс-спектрометрии. Образец многофункциональной добавки прошел испытания в модельной рецептуре пластиката медицинского назначения на основе поливинилхлорида.*

Результаты. *Установлено, что каталитическая активность производных кальция в реакции этерификации глицерина высшими карбоновыми кислотами возрастает в ряду* $CaO < Ca(OH)_2 < Ca(C_{17}H_{33}COO)_2 < Ca(C_2H_5O)_2 < Ca(C_4H_9O)_2 < Ca(C_3H_7O_3)_2$*, при этом использование глицерата кальция в качестве катализатора в количестве от 1 до 6 мол. % повышает конверсию карбоновой кислоты с 58 до 86% за 10 ч проведения синтеза. Обнаружено, что при изменении количества глицерата кальция от 1.5 до 6 мол. % конверсия карбоновой кислоты практически не меняется. Выбранный в ходе исследований глицерат кальция в качестве катализатора позволяет получить многофункциональную добавку, обладающую термостабилизирующим и пластифицирующим действием на полимерную композицию. Введение разработанной добавки в рецептуру поливинилхлоридной композиции медицинского назначения снижает при переработке крутящий момент и сокращает время достижения «сухой» точки. Оба этих фактора позволили снизить затраты энергии при выпуске продукции более чем на 11% по сравнению с контрольной композицией.*

Выводы. *Установлено, что алкоголяты кальция катализируют реакцию этерификации глицерина олеиновой (или высшими) кислотой, повышают конверсию исходных веществ и селективность образования моноглицеридов по сравнению с оксидом, гидроксидом и олеатом кальция. Найдено, что оптимальное соотношение компонентов глицерин : олеиновая кислота : глицерат кальция составляет 1 : 1 : 0.015 и позволяет достичь максимальной конверсии олеиновой кислоты (до 86%) за 10 ч синтеза. Предложен способ этерификации глицерина высшими карбоновыми кислотами в присутствии кальцийсодержащего катализатора. Данный способ позволяет исключить стадию очистки от катализатора и получить композицию, обладающую свойствами многофункциональной добавки для переработки поливинилхлорида.*

Ключевые слова: *этерификация, глицерин, олеиновая кислота, алкоголяты кальция, глицерат кальция*

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INTRODUCTION

Global production of biodiesel, representing an alternative fuel derived from renewable natural resources, is currently about 40 mln tons/year [1]. As compared with traditional diesel, biodiesel offers a combination of valuable properties that significantly extend the life of engines running on it [2]. One of the by-products in the production of biodiesel is the formation of approximately 10 wt % glycerol. Thus, according to the latest report from *Global Industry Analysts* (USA)[1], the development of biodiesel fuel production technologies has led to an increase in the amount of glycerol on the world market. In this regard, the development of new approaches for using glycerol to obtain products with high added value represents an urgent task, which solution will expand medium- and long-term prospects for industrial uses of glycerol.

Glycerol can serve as a raw material for the production of acrolein, 1,3-propanediol, glyceric acid, and a number of other valuable products [3]. Representing surfactants having amphiphilic, non-ionic and excellent emulsifying properties, mono- and diglycerides of higher carboxylic acids are widely used in the food, cosmetic and pharmaceutical industries [4], as well as non-toxic plasticizers for the polymer industry [5].

[1] https://strategyr.blogspot.com/2016/10/the-global-market-for-private-tutoring.html. Accessed September 22, 2022.

In earlier works, we proposed to use the products of glycerol esterification with higher carboxylic acids in the presence of calcium compounds as a multifunctional additive for the processing of polyvinyl chloride (PVC) [6], including mono- and diglycerides of higher carboxylic acids [7]. In this case, the spent calcium-containing catalyst remaining in the reaction mass as part of the multifunctional additive acts as a heat stabilizer. Implementation of such approach to the use of the obtained products significantly simplifies the technological process, as well as reduces the stage of isolation and purification.

The synthesis of glycerol esters with carboxylic acids on an industrial scale is generally carried out by esterification of glycerol with a fatty acid, which is catalyzed by strong acids such as sulfuric (H_2SO_4), orthophosphoric (H_3PO_4) acids, etc. [8]. However, the classical methods of esterification have a number of disadvantages: the occurrence of side processes, such as the dehydration of alcohols to olefins and sulfonation of unsaturated compounds; the formation of a large amount of acidic waste water with a high chemical oxygen demand; corrosion of equipment; low selectivity for the formation of monoglycerides (40–50%).

Currently, research and development of new catalysts for the esterification of glycerol is underway. For example, mesoporous silicon dioxide, metal oxides, modified zeolites, catalysts based on heteropoly acids [9], ion exchange resins (Amberlyst 15, Amberlyst 16, Amberlyst 31) [10], complexes of double metal cyanides Fe–Zn [11], and layered double hydroxides of the $MgAlCO_3$ complex [12], as well as processes based on sulfated metal oxides [13] are being used. Such catalysts are used to increase the conversion of raw materials and reuse processed alcohols while obviating the laborious stage of neutralization of the reaction mass. However, their disadvantages include the higher cost compared to acid catalysts, the need to use high temperatures (180–200°C), and chemical contamination of the product by the catalyst.

In recent decades, studies have been carried out on the effectiveness of calcium oxide, calcium hydroxide, and calcium alcoholates when used in processes of transesterification of vegetable oils with alcohols. The results presented in [14] demonstrate that the most effective method for increasing the catalytic activity of CaO is its activation with glycerol to form calcium glyceroxide. The studied calcium alkoxide has several advantages compared to calcium oxide, including higher catalytic activity during the transesterification reaction [15, 16] and greater resistance to air [17].

While the literature describes the use of calcium-containing compounds (CaO, $CaFe_2O_4$, and $Ca(OOCR)_2$) as catalysts for the esterification, we did not find studies on the catalytic activity of calcium alcoholate derivatives in the esterification of glycerol with higher carboxylic acids.

The aim of the present work is to study the use of calcium-containing basic catalysts for the esterification of glycerol with higher carboxylic acids, to carry out the process selectively for the formation of monoglycerides and with a high conversion of the starting materials, and to evaluate the possibility of using the reaction products for the processing of polyvinyl chloride.

MATERIALS AND METHODS

This work includes the use of reagents manufactured by *CHIMMED*, Russia: glycerol (chemically pure, 98.5%, GOST 6259-75[2]), oleic acid grade B-115 (tech., 97.4%, TU 9145-172-4731297-94), calcium hydroxide (analytical grade, 97%, GOST 9262-77[3]), calcium oxide (pure, 97%, GOST 22688-77[4]) was used after calcination at 900°C for 2 h, metallic calcium (pure, 98.6%, TU 083.5.314-94), ethyl alcohol (pure, 96%, GOST R 55878-2013[5]) was used after dehydration with calcium oxide, butyl alcohol (analytical grade, 99.7%, GOST 6006-78[6]), toluene (analytical grade, 99%, GOST 14710-78[7]), 1% alcoholic solution of phenolphthalein (indicator), potassium hydroxide (analytical grade, 99%), as well as sodium hydroxide (analytical grade, 99%).

The consumption of carboxylic acid during the esterification process was determined by the titrimetric method with visual indication. For titration,

[2] GOST 6259-75. Interstate Standard. Reagents. Glycerin. Specifications. Moscow: IPK Izdatelstvo standartov; 2001 (in Russ.).

[3] GOST 9262-77. State Standard of the USSR. Reagents. Calcium hydroxide. Specifications. Moscow: IPK Izdatelstvo standartov; 1996 (in Russ.).

[4] GOST 22688-77. State Standard of the USSR. Lime for building purposes. Test methods. Moscow: IPK Izdatelstvo standartov; 1997 (in Russ.).

[5] GOST R 55878-2013. National Standard of the Russian Federation. Rectified hydrolytic technical ethyl alcohol. Specifications. Moscow: Standartinform; 2014 (in Russ.).

[6] GOST 6006-78. Interstate Standard. Reagents. 1-Butanol. Specifications. Moscow: IPK Izdatelstvo standartov; 2002 (in Russ.).

[7] GOST 14710-78. Interstate Standard.Petroleum toluene. Specifications. Moscow: IPK Izdatelstvo standartov; 2004 (in Russ.).

a 0.1 N alcoholic solution of potassium hydroxide and a 1% alcoholic solution of phenolphthalein (indicator) were used.

The esterification product of glycerol and carboxylic acids was identified using chromato-mass spectrometric analysis (GC–MS) on a Saturn 2100T GC/MS instrument (*Varian*, USA) equipped with a VF-1ms 30 M × 0.25 mm quartz capillary column × 0.25 μm (*Agilent Technologies*, USA). Carrier gas was helium grade 6.0 (with an impurity content not more than 0.00001%), carrier gas flow rate—1.2 cm^3/min; split injection 1:10; injector temperature—280°C. When programming the capillary column temperature, the initial temperature was 80°C, isotherm time—3 min, final temperature—300°C, isotherm time—2 min; temperature rise rate—10.0°C/min; total analysis time—30 min. An ion trap mass-spectrometric detector was used. Electron ionization (EI) mass spectra (70 eV) were recorded in the full mass spectrum scanning (SCAN) mode in the range from 40 to 650 *m*/*z* at a rate of 1 mass spectrum per second.

Elemental analysis was performed using an Elementar Vario EL cube universal elemental analyzer (*Abacus Analytical Systems GmbH*, Germany).

The infrared (IR) spectra of the obtained basic catalysts were recorded in air at room temperature (20°C) on a Nicolet-6700 IR-Fourier spectrometer (*Thermo Scientific*, USA) in the region of 400–4000 cm^{-1} with a scanning step of 0.5 cm^{-1}.

Synthesis of calcium oleate

Into a glass reactor equipped with a reflux condenser, a Dean-Stark trap, and an overhead stirrer, 0.177 mol (50 g) of oleic acid, 0.088 mol (4.96 g) of calcium oxide, and 50 mL of toluene were loaded. The reaction mixture was refluxed for 16 h at a stirring speed of 400 ± 10 rpm. Reaction water was removed by azeotropic distillation in a Dean–Stark trap. The obtained calcium oleate was purified by repeated reprecipitation with diethyl ether from toluene. Melting point 82–83°C (~80°C [18]). IR spectrum, $\tilde{\nu}$, cm^{-1}: 3404 w (OH), 2917 s (C–H), 2849 s (C–H), 1573 s (COO^-), 1536 s (COO^-), 3644 w (Ca–O).

Synthesis of calcium ethoxide

Calcium ethoxide [19] was synthesized in a 250 mL glass reactor equipped with an overhead stirrer and a reflux condenser protected from air moisture. Mixing speed was 300 ± 10 rpm. Calcium metal in an amount of 5 g was placed in a reactor with 100 mL of absolute ethanol and refluxed for 8–16 h air moisture. The resulting calcium ethoxide was stored in a desiccator under argon over solid sodium hydroxide (NaOH). IR spectrum, $\tilde{\nu}$, cm^{-1}: 3645 m (OH), 2951 w (C–H), 2802 w (C–H), 2701 w (C–H), 1059 s (C–O), 3645 w (Ca–O).

Synthesis of calcium butoxide

Calcium butyrate was similarly synthesized to calcium ethylate using 5 g of metallic calcium and 100 mL of butyl alcohol. The resulting calcium butoxide was stored in a desiccator under argon over solid NaOH. IR spectrum, $\tilde{\nu}$, cm^{-1}: 3645 m (OH), 2958 w (C–H), 2910 w (C–H), 2873 w (C–H), 1077 w (C–O), 3644 w (Ca–O).

Synthesis of calcium glyceroxide

The synthesis of calcium glyceroxide [20] was carried out by the interaction of glycerol with calcium hydroxide (Fig. 1). 1.36 mol (125 g) of glycerol, 0.22 mol (16.6 g) of calcium hydroxide, and 30 mL of toluene as azeotrope-forming agent were loaded into a reactor equipped with a Dean–Stark trap for removing reaction water by azeotropic distillation, as well as a reflux condenser and an overhead stirrer. The reaction mixture was stirred at 450 ± 10 rpm. After distilling off the calculated amount of reaction water (duration about 7 h), the reaction mass was cooled. The formed precipitate was filtered off under vacuum, washed with ethanol until completely removal of unreacted glycerol, and dried for 1 h at 105°C. The resulting calcium glyceroxide was stored in a desiccator under argon over solid NaOH. IR spectrum, $\tilde{\nu}$, cm^{-1}: 3229 w (OH), 2874 m (C–H), 2836 w (C–H), 1128 w (C–O), 1091 m (C–O), 3641 w (Ca–O), 1370 w [δ(C–O–H)], 1306 s [δ(C–O–H)]. Elemental analysis: obtained C (29.9 ± 3.0%), H (6.0 ± 0.6%) [$Ca(C_3H_7O_6)_2$]; calculated C (32.4%), H (6.3%).

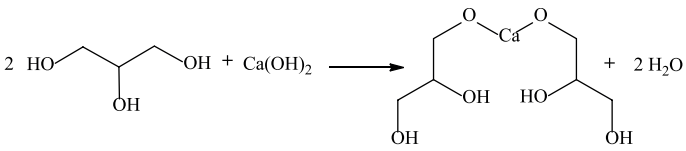

Fig. 1. Scheme of calcium glyceroxide synthesis.

Carrying out catalytic experiments

1) To study the effect of the main catalysts on the rate of esterification of glycerol with oleic acid, the following calcium-containing catalysts were chosen: calcium oxide, calcium hydroxide, calcium oleate, calcium ethoxide, calcium butoxide,

and calcium glyceroxide. 1 mol (92.09 g) of glycerol, 1 mol (282.46 g) of oleic acid, and 70 mL of toluene were used. After loading one of the catalysts from the above list (Table 1) with stirring in an amount of 1.5 mol %, the temperature of the reaction mass was raised to the boiling point of the azeotrope and kept at this temperature for 4 h. The reaction water was collected in a Dean–Stark trap.

2) To study the effect of the amount of calcium glyceroxide on the rate of esterification of glycerol with oleic acid, esterification was carried out under similar conditions. The only difference was in the amounts of catalyst used in each experiment—from 1 to 6 mol % (Table 2)—as well as the longer period of synthesis (10 h). Following the end of the synthesis, unreacted glycerol was separated in a separating funnel and the azeotrope-forming agent (toluene) was distilled off in a vacuum water jet pump.

Products were identified by chromato-mass spectrometry. Oleic acid monoglyceride: *m*/*z* (I_{rel}, %): 356 (3.2) $[M]^+$, 339 (23.7), 264 (99.9), 166 (15.7), 137 (24.9), 112 (23.3), 98 (45.9), 83 (31.8), 69 (32.4), 55 (60.3), 41 (55.7). Oleic acid diglyceride: *m*/*z* (I_{rel}, %): 339 (11.8), 265 (8.6), 185 (51.2), 129 (99.9), 97 (14.3), 83 (21.4), 69 (28.2), 55 (59.1), 41 (42.4). Oleic acid: m/z (I_{rel}, %): 282 (5.5) [M]+, 264 (41.9), 151 (18.9), 123 (24), 111 (30.3), 97 (65), 83 (67.8), 69 (66.4), 55 (99.9), 41 (80).

The material balance of laboratory syntheses of the esterification of glycerol with oleic acid was calculated to determine the technological parameters (conversion and selectivity) on the basis of the data obtained by gas chromatography-mass spectroscopy.

RESULTS AND DISCUSSION

Three groups of calcium compounds were tested as catalysts: the first group being calcium oxide and hydroxide, the second comprising a salt of calcium and oleic acid, while the third group is made up of calcium alcoholates: ethyl alcohol, butyl alcohol, and glycerol. The catalytic activity of the obtained basic catalysts based on calcium compounds was studied using the model of esterification of glycerol with oleic acid.

Esterification reactions are known to occur at several hydroxyl groups of glycerol with the formation of mixtures of products. The interaction of glycerol with oleic acid proceeds according to the scheme of successive reactions. Once sufficient amounts of oleic acid monoglyceride have been accumulated, it becomes available for consumption in the formation of diglyceride.

Calcium oxide and hydroxide were used to achieve a conversion for glycerol of 27.07% and 28.66%, respectively; for oleic acid, the equivalent conversion rates were 28.65% and 30.17% under the same conditions (Fig. 2). The use of calcium oleate turned out to be even more efficient: the conversion for glycerol was 35.54%, while, for oleic acid, the equivalent conversion was 37.36%. However, the highest value was achieved when using calcium alcoholates: for calcium glyceroxide, the conversion rate was 48.48% for glycerol and 49.56% for oleic acid. At the same time, no significant difference was found between ethoxide, butoxide and calcium glyceroxide. It is likely that calcium ethoxide and butoxide are converted during synthesis to calcium glyceroxide.

Table 1. Loads of calcium-containing catalysts

Catalyst	CaO	$Ca(OH)_2$	$Ca(C_{17}H_{33}COO)_2$	$Ca(C_2H_5O)_2$	$Ca(C_4H_9O)_2$	$Ca(C_3H_7O_3)_2$
Amount, mol %	1.5	1.5	1.5	1.5	1.5	1.5
Amount, g	0.84	1.11	9.04	1.95	2.79	3.33

Table 2. Loading amounts of calcium glyceroxide, catalyst $Ca(C_3H_7O_3)_2$

Amount, mol %	1	1.25	1.5	2	4	6
Amount, g	2.22	2.78	3.33	4.44	8.88	13.33

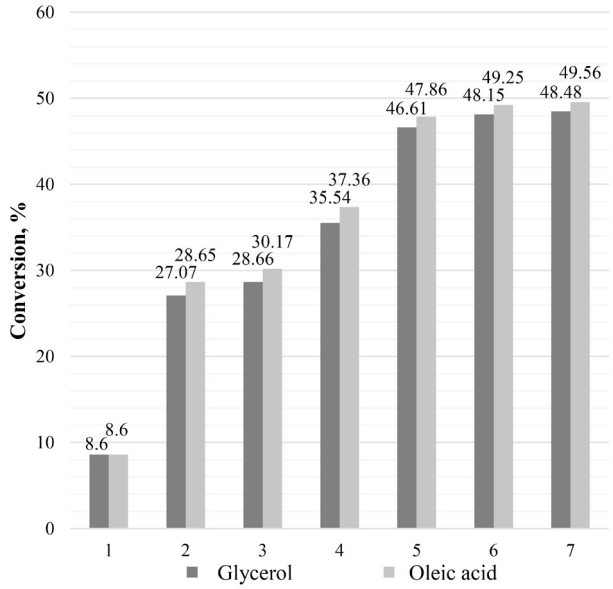

Fig. 2. Influence of a catalyst on the reagent conversion: 1 – no catalyst used, 2 – calcium oxide CaO, 3 – calcium hydroxide $Ca(OH)_2$, 4 – calcium oleate $Ca(C_{17}H_{33}COO)_2$, 5 – calcium ethoxide $Ca(C_2H_5O)_2$, 6 – calcium butoxide $Ca(C_4H_9O)_2$, 7 – calcium glyceroxide $Ca(C_3H_7O_3)_2$.

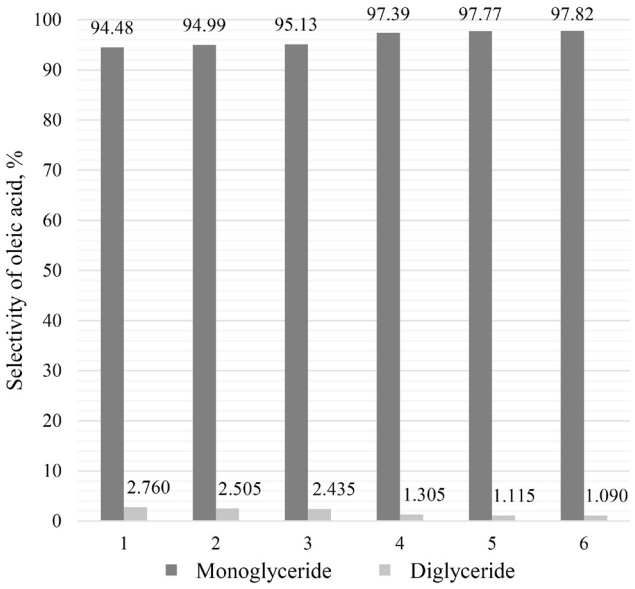

Fig. 3. Influence of the catalyst type on the selectivity for the oleic acid consumption: 1 – calcium oxide CaO, 2 – calcium hydroxide $Ca(OH)_2$, 3 – calcium oleate $Ca(C_{17}H_{33}COO)_2$, 4 – calcium ethoxide $Ca(C_2H_5O)_2$, 5 – calcium butoxide $Ca(C_4H_9O)_2$, 6 – calcium glyceroxide $Ca(C_3H_7O_3)_2$.

In none of the experiments was the formation of triglycerides detected. The use of $Ca(C_{17}H_{33}COO)_2$, $Ca(OH)_2$, and CaO showed similar selectivities for the formation of mono- and diglycerides – at about 95% and 2.5%, respectively (Fig. 3). The highest selectivity (above 97%) for the formation of monoglycerides was achieved when calcium alcoholates were used as catalysts.

Studies of the influence of the amount of calcium glyceroxide on the process of esterification of glycerol with oleic acid have been carried out. The amount of catalyst was changed in the range from 1 to 6 mol %. The initial data on the loading of reagents and catalyst are presented in Table 2.

During the reaction, the change in the degree of conversion of oleic acid in the reaction system over time was monitored. Samples were taken during 10 h of synthesis. The results of changing the conversion of oleic acid for each catalyst concentration are shown in Fig. 4.

The study of the effect of the amount of calcium glyceroxide on the conversion of oleic acid showed that the conversion of oleic acid increases with a change in the amount of catalyst from 1 to 1.5 mol % from 58% to 86% for 10 h of synthesis. No further increase in catalyst concentration has a significant effect on the course of the synthesis. Thus, the optimal concentration of the catalyst—equal to 1.5 mol %—was used to achieve the maximum value of the conversion of oleic acid with a minimum catalyst content.

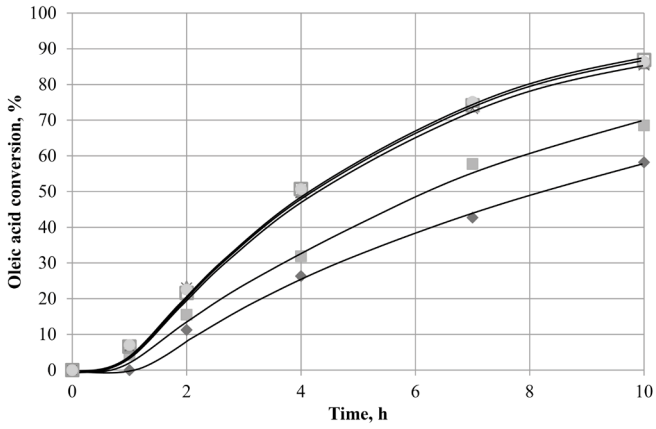

Fig. 4. Time dependence of oleic acid conversion. The amount of calcium glyceroxide, mol %: ♦ 1; ■ 1.25; × 1.5; ▲ 2; ● 4; □ 6.

A multifunctional additive for polymer processing was obtained using the proposed method for esterification of glycerol with oleic acid in the presence of calcium glyceroxide as a catalyst. This additive combines plasticizing agents in the form of mono- and diglycerides of oleic acid and calcium-containing compounds that have a thermally stabilizing effect on chlorine-containing polymers [7]. The main characteristics of the obtained multifunctional additive according to the developed method are presented in Table 3.

Table 3. Main characteristics of the obtained multifunctional additive

Analytically controlled components	Value
Content of oleic acid monoglycerides, %	82–86
Content of diglycerides of oleic acid, %	1.5–5
Mass fraction of calcium, %	<0.2
Acid number, mg KOH/g	20–25

The developed additive is assigned to hazard class 4 by the sanitary service of the Russian Federation, which permits the use of this additive without restrictions in any PVC products, including plastic compounds for medical purposes.

A sample of the multifunctional additive was tested in a model formulation of a medical plastic compound based on ultra-high molecular weight PVC-S8059U [21] produced by *Kaustik*, Volgograd, Russia. The introduction of the additive was carried out by partial replacement (5%) of dioctyl terephthalate in the formulation without changing the total mass of the composition. The production of the PVC composition in the P-600 mixer of the Brabender complex (*Brabender Technologie*, Germany) permits automatical control of changes in temperature and load on the mixing device during the process [22].

The parameters for obtaining PVC compositions in the mixer of the Brabender complex are presented in Table 4: temperature—93–94°C; mixing time—20 min; stirring device rotation speed—100 min^{-1}.

When using the studied additive in the production of PVC compositions, no technological difficulties were observed. Both the control and experimental compositions comprised free-flowing powders without agglomerates. Since the torque has a lower value (0.39 N·m) compared to the control composition (0.41 N·m) upon reaching the dry point of the experimental composition, the resistance exerted by the composition during operation of the mixer is lower. Moreover, by introducing the developed additive, it was possible to reduce the time taken to reach the dry point. Taken together, these factors confirm the effectiveness of the additive, which reduces energy costs for the production of a PVC composition by more than 11%.

Table 4. Production mode for polyvinyl chloride (PVC) compositions

Torque on the mixing device, N·m	Experimental composition	Control composition
Maximum	0.81	0.86
At the dry point	0.39	0.41
At the end of the test (12 min)	0.34	0.44
Time to reach the dry point, s	240	246
Specific energy consumption during the production of PVC composition, N·m/g	6.8	7.7

Table 5. Indicators of PVC composite materials

Indicator	Experimental composition	Control composition
Thermal stability at 190°C, (Congo red method), min	122	86
Melt flow rate at 190°C and a load of 10 kg through a capillary with a diameter of 2 mm, g/10 min	17.7	11.1

The resulting PVC compositions were poured out of the loading device into the working area of the extruder, where a strand was formed from the powder, from which granules were subsequently obtained for further testing.

Indicators of the material obtained from the control and experimental compositions are given in Table 5.

The obtained results showed a significant increase in the thermal stability of the PVC composition. The increase in the thermostabilizing effect is due to the presence of calcium-containing compounds in the composition of the additive, which provides its multifunctionality.

Thus, the developed method can be used to obtain an additive, which acts as a processing additive in the production of medical products and improves processing performance. As well as reducing internal friction and preventing sticking to metal parts of processing machines, the additive improves thermal stability and melt flow rate.

CONCLUSIONS

Calcium alcoholates are shown to catalyze the reaction of esterification of glycerol with oleic (or higher) acid, increasing the conversion of the initial substances and the selectivity of monoglyceride formation as compared to calcium oxide, hydroxide and oleate. The obtained optimal ratio of components—glycerol : oleic acid : calcium glyceroxide, 1:1:0.015, respectively—achieves the maximum conversion of oleic acid (up to 86%) over 10 h of synthesis. The proposed method for the esterification of glycerol with higher carboxylic acids in the presence of a calcium-containing catalyst also obviates the stage of purification from the catalyst when obtaining a composition having the properties of a multifunctional additive for the processing of polyvinyl chloride.

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Authors' contributions

Yu.L. Zotov – design of the research concept, development of the experiment, discussion and analysis of the results, and writing the text of the article;

D.M. Zapravdina – design of the research concept, planning and conducting experimental studies, processing the data obtained, and preparation of the data obtained for publication;

E.V. Shishkin – consultation on conducting individual stages of the study, scientific editing.

Yu.V. Popov – consultation on conducting individual stages of the study, scientific editing.

The authors declare no conflicts of interest.

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About the authors:

Yuriy L. Zotov, Dr. Sci. (Chem.), Professor, Department of Organic and Petrochemical Synthesis Technology, Volgograd State Technical University (28, pr. im. V.I. Lenina, Volgograd, 400005, Russia). E-mail: ylzotov@mail.ru. Scopus Author ID 7003371961, RSCI SPIN-code 7543-9740, http://orcid.org/0000-0001-6301-0570

Daria M. Zapravdina, Assistant, Department of Organic and Petrochemical Synthesis Technology, Volgograd State Technical University (28, pr. im. V.I. Lenina, Volgograd, 400005, Russia). E-mail: zapravdinadasha94@gmail.com. RSCI SPIN-code 2913-1891, https://orcid.org/0000-0002-8654-2382

Evgeniy V. Shishkin, Dr. Sci. (Chem.), Professor, Department of Organic and Petrochemical Synthesis Technology, Volgograd State Technical University (28, pr. im. V.I. Lenina, Volgograd, 400005, Russia). E-mail: shishkin@vstu.ru. Scopus Author ID 7004314557, RSCI SPIN-code 3280-1800, https://orcid.org/0000-0002-2994-422X

Yuriy V. Popov, Dr. Sci. (Chem.), Professor, Department of Organic and Petrochemical Synthesis Technology, Volgograd State Technical University (28, pr. im. V.I. Lenina, Volgograd, 400005, Russia). E-mail: iury.popov@yandex.ru. Scopus Author ID 26028090100, RSCI SPIN-code 4582-3342, http://orcid.org/0000-0001-5659-028X

Об авторах:

Зотов Юрий Львович, д.х.н., профессор кафедры технологии органического и нефтехимического синтеза ФГБОУ ВО «Волгоградский государственный технический университет» (400005, Россия, Волгоград, пр-т им. В.И. Ленина, д. 28). E-mail: ylzotov@mail.ru. Scopus Author ID 7003371961, SPIN-код РИНЦ 7543-9740, http://orcid.org/0000-0001-6301-0570

Заправдина Дарья Михайловна, ассистент кафедры технологии органического и нефтехимического синтеза ФГБОУ ВО «Волгоградский государственный технический университет» (400005, Россия, Волгоград, пр-т им. В.И. Ленина, д. 28). E-mail: zapravdinadasha94@gmail.com. SPIN-код РИНЦ 2913-1891, https://orcid.org/0000-0002-8654-2382

Шишкин Евгений Вениаминович, д.х.н., профессор кафедры технологии органического и нефтехимического синтеза ФГБОУ ВО «Волгоградский государственный технический университет» (400005, Россия, Волгоград, пр-т им. В.И. Ленина, д. 28). E-mail: shishkin@vstu.ru. Scopus Author ID 7004314557, SPIN-код РИНЦ 3280-1800, https://orcid.org/0000-0002-2994-422X

Попов Юрий Васильевич, д.х.н., профессор кафедры технологии органического и нефтехимического синтеза ФГБОУ ВО «Волгоградский государственный технический университет» (400005, Россия, Волгоград, пр-т им. В.И. Ленина, д. 28). E-mail: iury.popov@yandex.ru. Scopus Author ID 26028090100, SPIN-код РИНЦ 4582-3342, http://orcid.org/0000-0001-5659-028X

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RESEARCH ARTICLE

Assessment of resource-saving technologies in low-tonnage chemical industries for compliance with best available technologies principles

Natalia A. Kostikova✉, Elena N. Glukhan, Pavel V. Kazakov, Maria M. Antonova, Dmitry I. Klimov

GosNIIOKhT, State Scientific Center of the Russian Federation, Moscow, 111024 Russia
✉Corresponding author, e-mail: kutkin@gosniiokht.ru

Abstract

Objectives. *To develop a methodology for the quantitative assessment of new technologies in accordance with the principles of best available technologies (BAT). To evaluate the developed technologies of low-tonnage chemical production of tetramethylthiuram disulfide, N-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthohen disulfide, and N-phenyl-2-naphthylamine for compliance with BAT principles and compare with alternative (implemented, known) technologies in terms of environmental impact.*

Methods. A methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with BAT principles was used.

Results. The developed methodology for the quantitative assessment of new technologies in accordance with BAT principles based on the calculation of comprehensive comparison indicators with alternative technologies for technological and environmental indicators allowed us to determine the level of implemented technologies for the production of tetramethylthiuram disulfide, N-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthohen disulfide, and N-phenyl-2-naphthylamine to minimize the impact on the environmental, including through the development of special technological solutions for resource conservation and waste reduction, and to conduct a quantitative assessment of the achieved environmental outcome. It is established that the

considered new technologies of low-tonnage chemical production comply with BAT principles and are more environmentally advanced compared to alternative ones previously implemented in the USSR.
Conclusions. For the first time, a methodology for quantifying new technologies in accordance with BAT principles is proposed. The possibility of its use at the stage of making basic technological decisions on the implemented production method in order to ensure compliance with legislative requirements for technologies in the field of environmental safety to achieve environmental protection goals is shown on the example of low-tonnage technologies for the production of tetramethylthiuram disulfide, N-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthohen disulfide, and N-phenyl-2-naphthylamine created in GosNIIOKhT.

Keywords: *low-tonnage chemical production technologies, quantitative assessment methodology, best available technologies (BAT) principles, tetramethylthiuram disulfide, N-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthogen disulfide, N-phenyl-2-naphthylamine*

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НАУЧНАЯ СТАТЬЯ

Оценка ресурсосберегающих технологий малотоннажных химических производств на соответствие принципам наилучших доступных технологий

Н.А. Костикова✉, Е.Н. Глухан, П.В. Казаков, М.М. Антонова, Д.И. Климов

Государственный научно-исследовательский институт органической химии и технологии, Москва, 111024 Россия
✉*Автор для переписки, e-mail: kutkin@gosniiokht.ru*

Аннотация

Цели. *Разработать методику количественной оценки новых технологий в соответствии с принципами наилучших доступных технологий (НДТ). Провести оценку разработанных технологий малотоннажных химических производств тетраметилтиурамдисульфида, N-циклогексил-2-бензотиазолилсульфенамида, диизопропилксантогендисульфида и N-фенил-2-нафтиламина на соответствие принципам НДТ и сравнить с альтернативными (реализованными, известными) технологиями по уровню воздействия на окружающую среду (ОС).*
Методы. *Методика количественной оценки новых технологий производства органических веществ в соответствии с принципами НДТ.*
Результаты. *Разработанная методика количественной оценки новых технологий в соответствии с принципами НДТ на основании расчета комплексных индексов сравнения с альтернативными технологиями по технологическим и экологическим показателям позволила определить уровень внедряемых технологий получения тетраметилтиурамдисульфида, N-циклогексил-2-бензотиазолилсульфенамида, диизопропилксантогендисульфида и N-фенил-2-нафтиламина по минимизации воздействия на ОС, в том числе*

за счет разработки специальных технологических решений по ресурсосбережению и снижению отходности, и провести количественную оценку достигаемого экологического результата. Установлено, что рассмотренные новые технологии малотоннажных химических производств соответствуют принципам НДТ и являются более экологически совершенными по сравнению с альтернативными, ранее реализованными в СССР. ***Выводы.*** *Впервые предложена методика количественной оценки новых технологий в соответствии с принципами НДТ и показана возможность ее использования на этапе принятия основных технологических решений по внедряемому способу производства для обеспечения выполнения законодательных требований к технологиям в сфере э кологической безопасности по достижению целей охраны ОС на примере созданных во ФГУП «ГосНИИОХТ» малотоннажных технологий производства тетраметилтиурамдисульфида, N-циклогексил-2-бензотиазолилсульфенамида, диизопропилксантогендисульфида и N-фенил-2-нафтиламина.*

Ключевые слова: *стехнологии малотоннажных химических производств, методика количественной оценки, принципы наилучших доступных технологий, НДТ, тетраметилтиурамдисульфид, N-циклогексил-2-бензотиазолилсульфенамид, диизопропилксантогендисульфид, N-фенил-2-нафтиламин*

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INTRODUCTION

One of the tasks of state industrial policy in the field of production consists in the introduction of resource-saving and environmentally friendly technologies according to the provisions of the Federal Law of December 31, 2014 No. 488-FL "On Industrial Policy in the Russian Federation". The implementation of this policy is carried out by abandoning the use of outdated and inefficient technologies according to best available technologies (BAT) principles. BAT criteria are legally defined for evaluating technologies in terms of their environmental impact. Currently, the selection of BAT is carried out on the basis of expert assessments[1]. However, in order to substantiate BAT [1], present the BAT selection process [2], and identify technologies as BAT-compliant [3], various models are proposed based on a systematic approach and the use of mathematical tools, as well as on conducting environmental and economic BAT analysis. In the context of the state reform of the environmental regulation system and in accordance with the concept of introducing BAT as the primary mechanism for implementing state policy in the field of environmental safety at the stage of new technology development, special attention should be paid to addressing issues involved in determining the level of harmful effects on the environment and the minimization of such harmful effects to standard BAT values. This becomes all the more relevant due to the legal assignment of the production of basic organic

[1] Decree of the Government of the Russian Federation of December 23, 2014, No. 1458 "On the procedure for determining technology as the best available technology, as well as the development, updating and publication of information and technical reference books on the best available technologies" (as amended by Decrees of the Government of the Russian Federation of September 9, 2015, No. 954; dated December 28, 2016, No. 1508; dated March 09, 2019, No. 250). URL: http://www.consultant.ru/. Accessed February 13, 2022 (in Russ.).

chemicals to areas of BAT application[2] and objects of category I (significant) in terms of their negative impact on the environment[3].

These factors determine the relevance of conducting a preliminary assessment of new technologies to determine their compliance with modern environmental requirements. However, there is currently no methodological basis for such an assessment. The development and implementation of highly efficient resource-saving technologies for obtaining materials that are in demand by the industrial complex of the Russian Federation under conditions of low-tonnage industrial production is one of the main directions of scientific and practical activities of *GosNIIOKhT*. Ensuring the current level of implemented technologies to minimize the impact on the environment is achieved, among other things, by developing special technological solutions for resource saving and waste reduction. To assess the achieved environmental outcome, we have developed the "Methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with BAT principles" [4].

Compliance with the approach for evaluating new technologies is determined on the basis of BAT principles by calculating comprehensive indicators of comparison with alternative (already implemented or known) technologies in terms of technological (amount of waste, emissions, and discharges) and environmental indicators (degree of use of raw materials and waste and the effectiveness of measures for the treatment of gas emissions and discharges into water bodies).

The evaluation of new technologies for compliance with environmental protection goals is a necessary but insufficient development element, since one of the key targets is achieving a high level of efficiency. The "Methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with economic and environmental efficiency criteria" developed in our previous work [5] can be used to determine the most effective option for organizing production based on the calculation of comparative economic and environmental efficiency coefficients. The comparative economic efficiency coefficient includes an assessment of the cost of raw materials and instrumentation of a technological process. The comparative environmental efficiency ratio reflects the achieved level of minimization of the negative impact on the environment during the implementation of the technology, as well as the cost effectiveness of ensuring this environmental outcome. At the same time, the assessment of the economic efficiency of environmental costs makes it possible to exclude unreasonably costly options in comparison with the obtained environmental outcome and ensure that the developed technological solutions comply with the BAT criteria.

This article discusses new technologies for the production of tetramethylthiuram disulfide, *N*-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthogen disulfide, and *N*-phenyl-2-naphthylamine developed at *GosNIIOKhT*; technologies, as well as possible directions for their modernization.

METHODS

The calculation of the main and additional indicators [4] for comparing the developed technologies (Table 1) was carried out using data from technological production regulations.

The final assessment of the developed technology was carried out by comparing the relevant indicators with those of the alternative (implemented or known) technology, while the consumption coefficients for raw materials and auxiliary materials, production waste generation rates, as well as basic and additional technological indicators, were determined on the basis of the material balances of these technologies.

Further, comprehensive indicators of comparison of the developed and alternative production technologies were calculated along with the final indicator of the assessment of the developed technology for compliance with BAT principles (Table 2).

Indicator K_1 characterizes the degree of reduction of waste of the new technology in comparison with the existing alternative. Here, since the target

[2] Decree of the Government of the Russian Federation dated December 24, 2014 (as amended on May 24, 2018) No. 2674-r. "On Approval of the List of Areas of Application of the Best Available Technologies." URL: http://www.consultant.ru/. Accessed February 17, 2020 (in Russ.).

[3] Decree of the Government of the Russian Federation "On approval of the criteria for classifying objects that have a negative impact on the environment as objects of categories I, II, III and IV" dated September 28, 2015, No. 1029. URL: http://www.consultant.ru/. Accessed February 17, 2020 (in Russ.).

[4] Decree of the Government of the Russian Federation of December 23, 2014, No. 1458 "On approval of the rules for determining technology as the best available technology, as well as the development, updating and publication of information and technical reference books on the best available technologies." URL: http://www.consultant.ru/. Accessed September 09, 2022 (in Russ.).

Table 1. Main and additional technological indicators for comparing production technologies

Indicator	Indicator characteristics and calculation method
	Main technological indicators of production
A_T	Generation rate of solid and liquid waste, t/t, according to the regulations
B_T	Specific emissions into the atmosphere, t/t, according to the regulations
C_T	Wastewater generation rate, t/t, according to the regulations
	Additional technological indicators of production
J_K	The degree of complexity and completeness of the extraction of useful components from a feedstock is calculated as the sum of the recovery factors of the feedstock components, taking into account the yield and excluding technological losses of the product, t/t $$J_K = \sum_{i=1}^{K} J_i = \sum_{i=1}^{K} \frac{\sum_{Rec=1}^{N} P_i^{Rec}}{\sum_{Raw=1}^{M} P_i^{Raw}}$$ where K is the quantity of valuable components in the raw material; N is the number of product flows; M is the number of raw material flows; P_i^{Rec} is the amount of i useful substance, passed into finished products, t; P_i^{Raw} is the amount of i useful substance contained in raw materials, t
J_O	The degree of utilization of generated waste is calculated as the share of the regenerated component in the total mass of waste, t/t, and calculated according to the material balance of the regeneration operation per single operation. $$J_O = \frac{\sum Q^{Pr} + \sum Q^{P}}{\sum Q^{O}},$$ where $\sum Q^{Pr}$ is the amount of waste used in the production of other products, t/year, $\sum Q^{P}$ is the amount of waste sold, t/year; $\sum Q^{O}$ is the amount of generated waste, t/year.
J_A	The degree of purification of emissions of harmful substances into the atmosphere, which is calculated as the share of captured gases and vapors in the total mass of production off-gases, t/t, can be calculated from material balance data per operation. $$J_A = \frac{\sum_i V_i}{\sum_j V_j},$$ where $\sum_i V_i$ is the total mass of captured emission components, t/year; $\sum_k W_k$ is the total mass of substances contained in gas emissions formed during the production process, t/year
J_B	The degree of purification of discharges into water bodies is calculated by dividing the mass of discharges cleaned from harmful impurities to the total mass of their formation, t/t, using the material balance data per operation. $$J_B = \frac{\sum_l W_l}{\sum_k W_k},$$ where $\sum_l W_l$ is the total mass of discharges, t/year; $\sum_k W_k$ is the total mass of wastewater generated, t/year

is to minimize waste, the values related to the developed technology are given in the numerator to ensure the ratio $K_1 < 1$.

The K_2 indicator characterizes the increased complexity and completeness of the extraction of useful components using the new technology as compared to the existing alternative. Since the aim is to increase the level of raw material utilization, the values related to the developed technology are given in the denominator to ensure the ratio $K_2 < 1$.

The value of the final indicator for assessing the new (developed) technology $I < 2$ supports the conclusion that the developed technology conforms with BAT principles and is more environmentally friendly than the existing alternative [4].

RESULTS

Assessment of the compliance of the tetramethylthiuram disulfide production technology with the BAT principles

The technology for the production of tetramethylthiuram disulfide is based on the one-stage method for its preparation published in our previous work [6], which includes the condensation of dimethylamine with carbon disulfide followed by peroxidation of the formed dimethyldithiocarbamic acid without its isolation.

The formation reaction of tetramethylthiuram disulfide is described by Scheme (1).

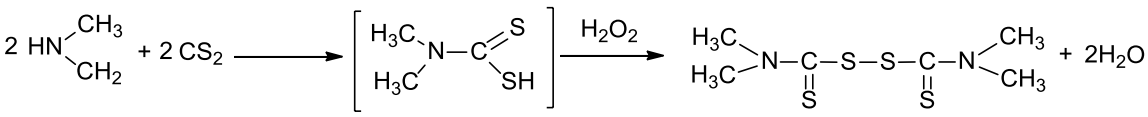
Condensation of dimethylamine with carbon disulfide is carried out at an equimolar ratio of components; peroxidation of the resulting dimethyldithiocarbamic acid is carried out at a molar ratio of dimethylamine : carbon disulfide : hydrogen peroxide equal to 1 : 1 : 0.55–0.57. The process is carried out in a methanol medium.

The calculation of the main and additional technological indicators of the production of tetramethylthiuram disulfide was carried out using the data of the "Temporary technological regulations for the pilot low-tonnage production of tetramethylthiuram disulfide based on domestic raw materials, No. TTR-3-350" on consumption coefficients for raw materials (Table 3) and waste generation rates (Table 4). The calculation data of the main and additional technological indicators of the production of tetramethylthiuram disulfide are presented in Table 5.

We carried out a final assessment of the developed technology for the production of tetramethylthiuram

Table 2. Comprehensive comparison indicators and the final indicator of the assessment of the developed technology for compliance with BAT principles

Indicator	Formula for calculating the indicator
Comprehensive indicator of comparison of the main technological indicators of the developed and alternative technologies K_1	$K_1 = \frac{1}{3}\left(\frac{A_{T,P}}{A_{T,A}} + \frac{B_{T,P}}{B_{T,A}} + \frac{C_{T,P}}{C_{T,A}}\right)$, where $A_{T,P}$, $B_{T,P}$, $C_{T,P}$ and $A_{T,A}$, $B_{T,A}$, $C_{T,A}$ are specific indicators of waste, atmospheric emissions and discharges into natural waters for the developed and alternative technologies, respectively
Comprehensive indicator of comparison of additional technological indicators of the developed and alternative technologies K_2	$K_2 = \frac{1}{4}\left(\frac{J_{K,A}}{J_{K,P}} + \frac{J_{O,A}}{J_{O,P}} + \frac{J_{A,A}}{J_{A,P}} + \frac{J_{B,A}}{J_{B,P}}\right)$, where $J_{K,P}$, $J_{O,P}$, $J_{A,P}$, $J_{B,P}$ and $J_{K,A}$, $J_{O,A}$, $J_{A,A}$, $J_{B,A}$ are additional technological indicators for the developed and alternative technologies, respectively
Final indicator for evaluating the developed technology I	$I = K_1 + K_2$



(1)

disulfide by comparing it with an existing method for obtaining the product by oxidation with hydrogen peroxide in the presence of sulfuric acid of the sodium salt of dimethyldithiocarbamic acid, which is synthesized by the reaction of dimethylamine with carbon disulfide in the presence of alkali at a molar ratio of carbon disulfide : dimethylamine : sodium hydroxide, equal to 1 : 1 : 1.03 [7]. The precipitate of tetramethylthiuram disulfide was filtered off, washed, granulated, and dried [8]. This process was already implemented in the USSR at the Khimprom Volgograd production association [9].

Based on the calculated material balances, the consumption coefficients for raw materials and auxiliary materials (Table 6) were determined along with the waste generation rates for the production of tetramethylthiuram disulfide using an alternative technology (Table 7).

Table 3. Consumption coefficients for raw materials and auxiliary materials in the tetramethylthiuram disulfide production

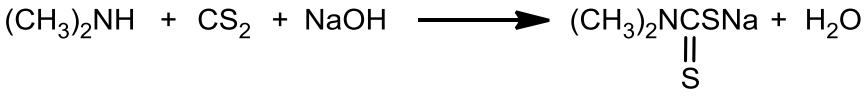
Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Dimethylamine (33%)	72.2	1.29	–
Carbon disulfide	40.2	0.73	–
Hydrogen peroxide (37%)	27.8	0.50	–
Methanol	4.5	0.08	With regeneration
	565.4	10.10	Without regeneration

Table 4. Waste generation standards, emissions, and discharges in the tetramethylthiuram disulfide production

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue of methanol regeneration	Liquid	VAT residue, including	100.00	83.9	1.50
		Water	91.18	76.5	1.37
		Organic impurity	4.17	3.5	0.06
		Tetramethylthiuram disulfide	4.65	3.9	0.07
Air emissions		None			
Wastewater discharge		None			

Table 5. Basic and additional technological indicators calculated for the developed and existing alternative technologies used in the tetramethylthiuram disulfide production

Indicator	Calculation method and indicator value	
	Developed technology	**Alternative technology**
Main technological indicators of production		
Generation rate of solid and liquid waste	$A_{T,P}$ = 1.5 t/t (Table 4)	$A_{T,A}$ = 4.58 t/t (Table 7)
Specific emissions into the atmosphere	Off-gases are locally cleaned in contact devices. Since the cleaning efficiency is 100%, there are no emissions into the atmosphere (Tables 4 and 7)	
	$B_{T,P}$ = 0 t/t	$B_{T,A}$ = 0 t/t
Wastewater generation rate	There is no wastewater discharge (Tables 4 and 7)	
	$C_{T,P}$ = 0 t/t	$C_{T,A}$ = 0 t/t
Additional technological indicators		
Degree of complexity and completeness of the extraction of useful components from the feedstock	It is calculated as the sum of the extraction coefficients of dimethylamine P_{DMA} and carbon disulfide P_{CS_2} taking into account the yield of tetramethylthiuram disulfide (56.1 kg per operation, 95%) without taking into account technological losses of the product in the filtrate and washing solution. P_{DMA} = 0.41/0.43 = 0.95 t/t P_{CS_2} = 0.69/0.73 = 0.95 t/t $J_{K,P}$ = 0.95 + 0.95 = 1.90 t/t $J_{K,P}$ = 1.90 t/t	$J_{K,A}$ = 1.90 t/t
Degree of generated waste utilization	It is calculated as the share of regenerated methanol in the total mass of waste according to the material balance of the methanol regeneration stage per one operation $J_{O,P}$ = 558.2/644.9 = 0.87 t/t	$J_{O,A}$ = 0.69 t/t
Degree of purification of emissions of harmful substances into the atmosphere	It is calculated as the share of captured methanol vapors in the trap and in the process of local purification in contact devices in the total mass of off-gases, taking into account 100% efficiency of their purification (Tables 4 and 7)	
	$J_{A,P}$ = 1.00 t/t	$J_{A,A}$ = 1.00 t/t
Degree of purification of discharges into water bodies	There is no wastewater discharge (Tables 4 and 7)	
	$J_{B,P}$ = 0 t/t	$J_{B,A}$ = 0 t/t



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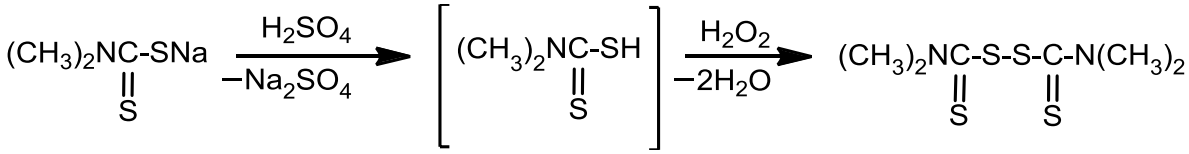

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Table 6. Consumption coefficients for raw materials and auxiliary materials in the tetramethylthiuram disulfide production using an alternative technology

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Dimethylamine (33%)	72.20	1.29	–
Carbon disulfide	40.20	0.73	–
Hydrogen peroxide (37%)	27.80	0.50	–
Sodium hydroxide (44%)	50.92	0.91	–
Sulfuric acid (60%)	45.75	0.82	–
Methanol (99.47%)	1.81	0.03	With regeneration
	240.00	4.28	Without regeneration
Water	76.97	1.37	With regeneration
	412.00	7.34	Without regeneration

Table 7. Waste generation standards, emissions, and discharges in the alternative tetramethylthiuram disulfide production technology (with methanol and water regeneration)

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue (methanol regeneration operation)	Liquid	VAT residue, including:	100.00	7.57	0.13
		Water	91.17	2.71	0.05
		Organic impurities	8.83	4.86	0.09

Table 7. Continued

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue (water regeneration operation)	Liquid	VAT residue, including:	100.00	249.46	4.45
		Sodium sulfate	15.95	39.78	0.71
		Water	83.06	207.19	3.69
		Organic impurities	1.00	2.49	0.04
Air emissions		None			
Wastewater discharge		None			

Further, we calculated comprehensive indicators for comparing the developed and alternative technologies used in the production of tetramethylthiuram disulfide along with the final indicator for evaluating the developed technology for compliance with BAT principles (Table 8).

The value of the final indicator I of the assessment of the new technology 1.04 < 2 supports the conclusion that the technology developed by us for the production of tetramethylthiuram disulfide meets BAT principles and is more environmentally friendly compared to the alternative one originally implemented in the USSR [4]. The technology developed by us was introduced in the branch of *GosNIIOKhT—Separate Plant No. 4* (Novocheboksarsk, Chuvash Republic), whose experimental low-tonnage tetramethylthiuram disulfide production capacity is 5000 kg/year.

The high efficiency (K_1 = 0.11) of the developed technology for the production of tetramethyl thiuram disulfide (Table 8) was determined by the low waste rate of the technological process. The achieved level of environmental friendliness of production (K_2 = 0.93) was ensured by the regeneration of raw materials (methanol).

Table 8. Comprehensive indicators and the final evaluation indicator of the developed tetramethylthiuram disulfide production technology

Indicator	Calculation method and indicator value
Comprehensive indicator of comparison of the main technological indicators of the developed and alternative technology K_1	Due to the absence of emissions of harmful substances into the atmosphere or discharges into water bodies for the developed and alternative technologies, no comparison of specific indicators of such emissions and discharges is carried out. $K_1 = (A_{T,P}/A_{T,A})/3$ $K_1 = (1.50/4.58)/3 = 0.11$
Comprehensive indicator of comparison of additional technological indicators of the developed and alternative technology K_2	Due to the absence of discharges of harmful substances into water bodies for the developed and alternative technologies, no calculation or comparison of the degree of purification of discharges into water bodies is carried out. $K_2 = (J_{K,A}/J_{K,P} + J_{O,A}/J_{O,P} + J_{A,A}/J_{A,P})/3$ $K_2 = (1.9/1.9 + 0.69/0.87 + 1.00/1.00)/3$ $K_2 = 0.93$
Technology assessment outcome I	$I = 0.11 + 0.93 = 1.04$

Assessment of the compliance of the *N*-cyclohexyl-2-benzothiazolylsulfenamide production technology with the BAT principles

The technology for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide is based on the one-stage method for its preparation published in [9], which includes the condensation of 2-mercaptobenzothiazole and cyclohexylamine, followed by peroxidation of the resulting intermediate compound, cyclohexylammonium 1,3-benzothiazole-2-thiolate, without its selection. The process is carried out in an aqueous medium at a molar ratio of 2-mercaptobenzothiazole : cyclohexylamine : hydrogen peroxide equal to 1 : 3 : 1.1 and is described by Scheme (4).

The calculation of the main and additional technological indicators of the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide was carried out using the data of "Temporary technological regulations for pilot low-tonnage production of *N*-cyclohexyl-2-benzothiazolylsulfenamide, No. TTR-5-350" on consumption coefficients for raw materials (Table 9) and the generation rate of production waste (Table 10). The results of the calculation of the main and additional technological indicators are presented in Table 11.

The final assessment of the developed technology for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide was carried out by comparing this technology with an alternative one based on the method of its production by the interaction of the sodium salt of 2-mercaptobenzothiazole (captax) with cyclohexylamine in the presence of sodium hypochlorite. The sodium salt of Captax was mixed with cyclohexylamine, the reaction mass was acidified with 37% hydrochloric acid. This gave the cyclohexylamine salt of Captax, which was oxidized with sodium hypochlorite in the presence of alkali. Unreacted cyclohexylamine was isolated from wastewater by nitrogen purge at a temperature of 120–130°C. The described method for the preparation of *N*-cyclohexyl-2-benzothiazolylsulfenamide was implemented in the USSR at *Novokemerovo Chemical Plant* [11].

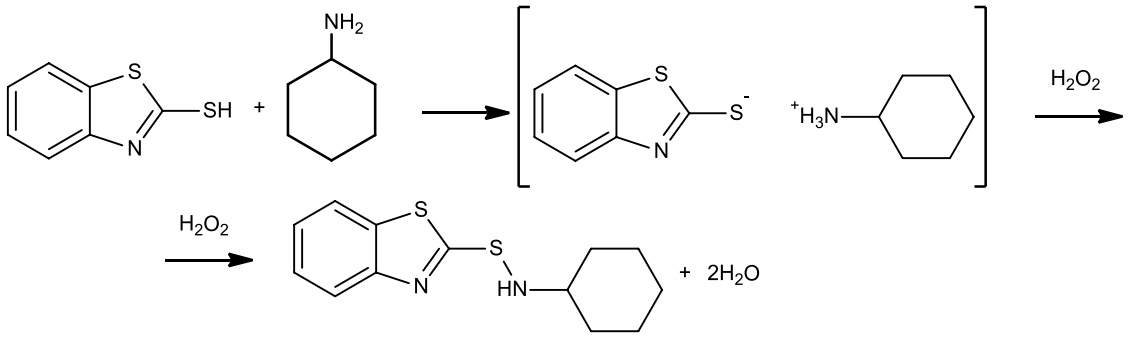

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Table 9. Consumption coefficients for raw materials and auxiliary materials in the *N*-cyclohexyl-2-benzothiazolylsulfenamide production

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
2-Mercaptobenzothiazole (97%)	68.80	0.872	–
Cyclohexylamine (99%)	33.31	0.422	With regeneration
	119.99	1.521	Without regeneration
Hydrogen peroxide (37%)	39.60	0.502	–
Water	0.00	0.000	With regeneration
	800.00	10.139	Without regeneration

Table 10. Waste generation standards, emissions, and discharges in the *N*-cyclohexyl-2-benzothiazolylsulfenamide production (with regeneration of water and cyclohexylamine)

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue (water regeneration operation)	Liquid	VAT residue, including:	100.00	64.76	0.821
		Water	62.25	40.31	0.511
		Organic impurities	37.75	24.45	0.310
Air emissions		None			
Wastewater discharge		None			

Table 11. Basic and additional technological indicators calculated for the developed and existing alternative technologies used in the *N*-cyclohexyl-2-benzothiazolylsulfenamide production

Indicator	Calculation method and indicator value	
	Developed technology	Alternative technology
Main technological indicators		
Generation rate of solid and liquid waste	$A_{T,P}$ = 0.821 t/t (Table 10)	$A_{T,A}$ = 4.45 t/t (Table 13)
Specific emissions into the atmosphere	Abgases are absent, emissions into the atmosphere are absent (Tables 10 and 13)	
	$B_{T,P} = 0$	$B_{T,A} = 0$
Wastewater generation rate	There is no wastewater discharge (Tables 10 and 13)	
	$C_{T,P} = 0$	$C_{T,P} = 0$
Additional technological indicators		
Degree of complexity and completeness of the extraction of useful components from the feedstock	It is calculated as the sum of the recovery factors of 2-mercaptobenzothiazole P_{MBT} and cyclohexylamine P_{CHA} taking into account the yield of *N*-cyclohexyl-2-benzothiazolylsulfenamide (78.9 kg per operation, 75%) and the regeneration of cyclohexylamine P_{MBT} = 0.632/0.846 = 0.75 t/t P_{CHA} = 1.447/1.506 = 0.96 t/t $J_{K,P}$ = 0.75 + 0.96 = 1.71 t/t	$J_{K,A}$ = 1.64 t/t

Table 11. Continued

Indicator	Calculation method and indicator value	
	Developed technology	Alternative technology
Degree of utilization of generated waste	It is calculated as the share of regenerated cyclohexylamine and water in the total mass of waste (mother liquor) per one operation: $J_{O,P}$ = (84.64 + 800)/949.40 = 0.93 t/t	$J_{O,A}$ = 0.55 t/t
Degree of purification of emissions of harmful substances into the atmosphere	Abgases are absent, emissions into the atmosphere are absent (Tables 10 and 13)	
	$J_{A,P}$ = 0 t/t	$J_{A,A}$ = 0 t/t
Degree of purification of discharges into water bodies	Wastewater is absent (Tables 10 and 13)	
	$J_{B,P}$ = 0 t/t	$J_{B,A}$ = 0 t/t

The reaction to obtain the sodium salt of 2-mercaptobenzothiazole is described by Scheme (5).

The formation of *N*-cyclohexyl-2-benzothiazolylsulfenamide can be described by Scheme (6).

Based on the material balances calculated by us, we determined the consumption coefficients for raw materials and auxiliary materials (Table 12) and the waste generation rates for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide using an alternative technology (Table 13).

Next, we calculated comprehensive indicators for comparing the developed and alternative technologies used in the production of this product along with the final indicator for evaluating the developed technology for compliance with BAT principles (Table 14).

(5)

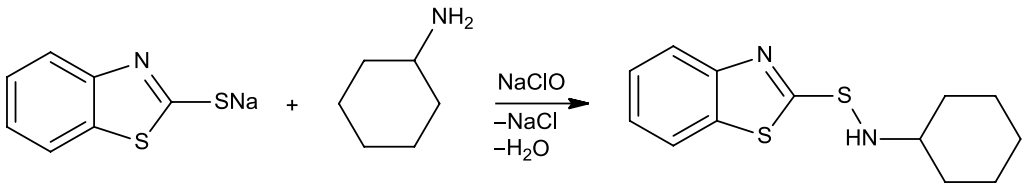

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Table 12. Consumption coefficients for raw materials and auxiliary materials in the *N*-cyclohexyl-2-benzothiazolylsulfenamide production using an alternative technology

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
2-Mercaptobenzothiazole, 97%	68.80	0.73	–
Sodium hydroxide, 44% solution	44.46	0.47	–
Water	581.04	6.16	Without regeneration
	52.24	0.55	With regeneration

Table 12. Continued

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Cyclohexylamine, 99%	47.98	0.51	Without regeneration
	40.12	0.42	With regeneration
Hydrochloric acid, 37% solution	51.30	0.54	–
Sodium hypochlorite, 15% solution	253.96	2.69	–
Sodium sulfite	14.69	0.16	–

Table 13. Waste generation standards, emissions, and discharges in the *N*-cyclohexyl-2-benzothiazolylsulfenamide production using an alternative technology (with water and cyclohexylamine regeneration)

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
Wastewater	Liquid	VAT residue, including:	100.00	420.38	4.45
		Total organic impurities	3.19	13.41	0.14
		Sodium chloride	14.47	60.84	0.64
		Sodium sulfate	3.94	16.56	0.18
		Water	78.40	329.57	3.49
Air emissions		None			
Wastewater discharge		None			

Table 14. Comprehensive indicators and the final evaluation of the developed technology for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide

Indicator	Calculation method and indicator value
Comprehensive indicator of comparison of the main technological indicators of the developed and alternative technologies K_1	Due to the absence of emissions of harmful substances into the atmosphere or discharges of effluents into water bodies for the developed and alternative technologies, no comparison of specific indicators of such emissions into the atmosphere and discharges into water bodies is carried out. $K_1 = (A_{T,P}/A_{T,A})/3$ $K_1 = (0.82/4.45)/3 = 0.06$
Comprehensive indicator of comparison of additional technological indicators of the developed and alternative technologies K_2	Due to the absence of discharges into water bodies and emissions of harmful substances into the atmosphere for the developed and alternative technologies, no calculation or comparison of the degree of purification of discharges into water bodies and emissions of harmful substances into the atmosphere is carried out. $K_2 = (J_{K,A}/J_{K,P} + J_{O,A}/J_{O,P})/4$ $K_2 = (1.64/1.71 + 0.55/0.93)/4 = 0.39$
Technology assessment outcome I	$I = 0.06 + 0.39 = 0.45$

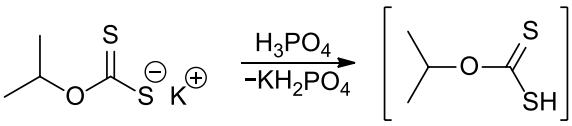
The value of the final indicator of technology assessment $I = 0.45 << 2$ supports the conclusion that the technology developed by us for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide meets BAT principles and is much more environmentally friendly compared to the alternative [11] implemented in the USSR. This process has been introduced in aforementioned *Separate Plant No. 4*; the capacity of the pilot low-tonnage production is 5000 kg/year.

A distinctive feature of the technology developed by us for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide compared to that implemented earlier in the USSR is a significant reduction in the level of waste generation and a high degree of raw material recovery, which makes it possible to characterize the new technology as much more efficient (K_1 = 0.06). The high level of environmental friendliness of the developed technology (K_2 = 0.39) is ensured by minimizing losses due to high rates of resource saving (raw material conversion) and recovery of the solvent (water) and excess raw material component (cyclohexylamine).

Assessment of the compliance of the diisopropyl xanthogen disulfide production technology with the BAT principles

The technology for the production of diisopropyl xanthogen disulfide is based on the method published in [12], which includes the oxidation of potassium isopropyl xanthate (PIX) [13] with hydrogen peroxide in the presence of phosphoric acid in water [14]. The interaction of PIX with phosphoric acid with the formation of the corresponding xanthogenic acid is described by Scheme (7).

The oxidation of the obtained xanthogenic acid with hydrogen peroxide to form diisopropyl xanthogen disulfide is represented by Scheme (8).



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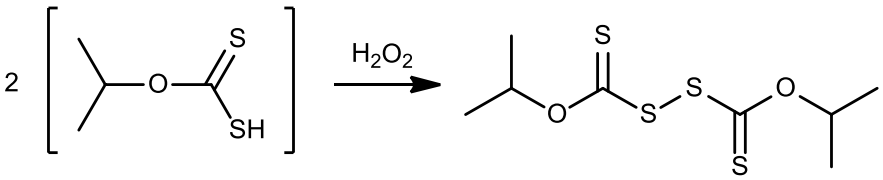

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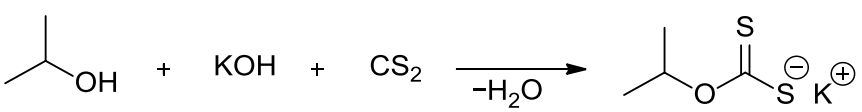

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The resulting suspension was filtered, washed with water and dried. Wash water was reused in the next synthesis as a solvent. PIX was obtained by the interaction of isopropanol, potassium hydroxide, and carbon disulfide according to Scheme (9).

The process was carried out in isopropanol at a molar ratio of isopropanol : carbon disulfide : potassium hydroxide equal to 7 : 1 : 1 and a temperature of 25–35°C. To restore the quality of alcohol, the method of two-stage distillation of the filtrate was used.

The calculation of the main and additional technological indicators of the production of diisopropyl xanthogen disulfide to assess the compliance of the technology with the principles of BAT was carried out using the data of the "Temporary process regulations for pilot low-tonnage production of potassium isopropyl xanthate, No. TTR-12-350" and "Temporary process regulations for pilot low-tonnage production of diisopropylxanthogendisulfide, No. TTR-13-350" on consumption coefficients for raw materials (Table 15) and the generation rate of production waste (Table 16). The results of calculating the main and additional technological indicators for the production of diisopropyl xanthogen disulfide using an alternative technology are presented in Table 17.

The final assessment of the developed technology for the production of diisopropyl xanthogen disulfide was carried out by comparing the developed technology with an alternative one based on the known method of its production by oxidation of alkali metal xanthate with sodium nitrite in the presence of mineral acids (HCl, H_2SO_4) [15]: one mole of acid is used to decompose sodium nitrite to nitrogen oxides, and the second mol—on the formation of xanthogenic acid from the corresponding salt. The liberated nitric oxide (IV) acts as an oxidizing agent in this process, which can be generally described by reaction Schemes (10)–(13):

Table 15. Consumption coefficients for raw materials and auxiliary materials in the production of diisopropyl xanthogen disulfide

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Obtaining PIX (98.88%)			
Isopropyl alcohol (99.59%)	416.16	2.593	–
	145.89	0.909	With regeneration
Carbon disulfide (100%)	72.68	0.453	–
Potassium hydroxide (86.11%)	61.70	0.384	–
Isopropanol recovery			
Toluene (99.5%)	98.63	0.616	–
Obtaining diisopropyl xanthogen disulfide			
PIX (98.88%)	150.00	1.42	–
Hydrogen peroxide (37%)	43.56	0.41	–
Orthophosphoric acid (85%)	99.39	0.94	–
Water	850.00	8.03	–
	440.00	4.16	Taking into account the return of wash water

Table 16. Waste generation standards, emissions, and discharges in the diisopropyl xanthogen disulfide production (with isopropanol regeneration and return of washing water)

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue after rectification of the filtrate (stage of obtaining PIX)	Liquid	VAT residue, including:	100.00	12.89	0.086
		Isopropanol	51.32	5.42	0.039
		Impurity	48.68	7.47	0.047

Table 16. Continued

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
Azeotrope isolated at the stage of rectified absolutization (stage of obtaining PIX)	Liquid	Azeotrope, including:	100.00	201.53	1.260
		Isopropanol	38.20	76.98	0.481
		Water	13.10	26.40	0.165
		Toluene	48.70	98.14	0.613
Distillation residue after absolute rectification (stage of obtaining PIX)	Liquid	VAT residue, including:	100.00	9.29	0.021
		Isopropanol	85.71	8.80	0.018
		Impurity	14.29	0.49	0.003
Wastewater (diisopropyl xanthogen disulfide production stage)	Liquid	Filtrate, including:	100.00	620.63	5.862
		Water	79.03	490.47	4.632
		Impurity	20.97	130.16	1.229
Air emissions	None				
Wastewater discharges	None				

Table 17. Basic and additional technological indicators calculated for the developed and alternative technologies used in the diisopropyl xanthogen disulfide production

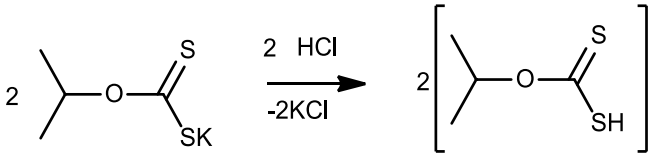
Indicator	Calculation method and indicator value	
	Developed technology	Alternative technology
Main technological indicators		
Generation rate of solid and liquid waste	$A_{T,P}$ = 7.228 t/t (Table 16)	$A_{T,A}$ = 7.337 t/t (Tables 20 and 21)
Specific emissions into the atmosphere	Process off-gases are water vapor. There are no emissions of harmful substances into the atmosphere (Table 16) $B_{T,P}$ = 0 t/t	Off-gases are a mixture of nitrogen and carbon dioxide. There are no emissions of harmful substances into the atmosphere (Tables 20 and 21) $B_{T,A}$ = 0 t/t

Table 17. Continued

Indicator	Calculation method and indicator value	
	Developed technology	**Alternative technology**
Wastewater generation rate	There is no wastewater discharge due to the high hazard class for fishery water bodies (hazard class 2*). $C_{T,P}$ = 0 t/t	There is no wastewater discharge due to the high hazard class of the leachate for water bodies of fishery significance (hazard class 1*). $C_{T,A}$ = 0 t/t
Additional technological indicators		
The degree of complexity and completeness of the extraction of useful components from the feedstock	It is calculated as the sum of the recovery factors for isopropanol P_{IP}, potassium hydroxide P_{KOH}, carbon disulfide P_{CS_2}, PIX P_{PIX}, hydrogen peroxide $P_{H_2O_2}$, and phosphoric acid $P_{H_3PO_4}$ taking into account the yield of diisopropylxanthogendisulfide (105.88 kg per operation, 90%). P_{IP} = 0.341/0,358 = 0.95 t/t P_{KOH} = 0.319/0.334 = 0.95 t/t P_{CS_2} = 0.433/0.453 = 0.95 t/t P_{PIX} = 1.261/1.401 = 0.90 t/t Taking into account the degree of extraction of the components of the PIX production process: P_{PIX} = 0.95 × 0.90 = 0.86 t/t $P_{H_2O_2}$ = 0.123/0.152 = 0.81 t/t $P_{H_3PO_4}$ = 0.713/0.798 = 0.89 t/t $J_{K,P}$ = 0.86 + 0.81 + 0.89 = 2.56 t/t	Recovery factors for carbon disulfide P_{CS_2}, isopropanol P_{IP}, potassium hydroxide P_{KOH} for the stage of obtaining PIX: P_{IP} = 0.341/0.358 = 0.95 t/t P_{KOH} = 0.319/0.334 = 0.95 t/t P_{CS_2} = 0.433/0.453 = 0.95 t/t Recovery factors of PIX, sodium nitrite P_{NaNO_2}, and phosphoric acid $P_{H_3PO_4}$ taking into account the yield of the product (108.25 kg per operation, 94.1%). P_{PIX} = 0.95 × 0.94 = 0.89 t/t P_{NaNO_2} = 0.44/0.47 = 0.94 t/t $P_{H_3PO_4}$ = 0.611/0.611 = 1.00 t/t $J_{K,A}$ = 0.89 + 0.94 + 1.00 = 2.83 t/t
Degree of utilization of generated waste	It is calculated as the share of regenerated isopropanol in the total mass of waste (filtrate and condensate). According to the material balance of isopropanol regeneration per 1 t of product: $J_{O,P}$ = (0.984 + 0.700)/3.049 = 0.55 t/t	It is calculated as the share of returned water in the total mass of waste (filtrate, wash water and waste absorbent). According to the material balance per 1 t of product: $J_{O,A}$ = 4.610/9.772 = 0.47 t/t
Degree of purification of emissions of harmful substances into the atmosphere	Process off-gases are water vapor. There are no emissions of harmful substances into the atmosphere. $J_{A,P}$ = 1.00 t/t	It is calculated as the share of captured nitrogen oxide in the total mass of off-gases: $J_{A,A}$ = 0.030/0.030 = 1.00 t/t
Degree of purification of discharges into water bodies	There is no wastewater discharge (Tables 16, 20, and 21)	
	$J_{B,P}$ = 0 t/t	$J_{B,A}$ = 0 t/t

* Order of the Ministry of Natural Resources of Russia dated December 4, 2014 No. 536 "On approval of the criteria for classifying wastes as hazard classes I–V according to the degree of negative impact on the environment" (Registered in the Ministry of Justice of Russia on December 29, 2015, No. 40330).

(10)



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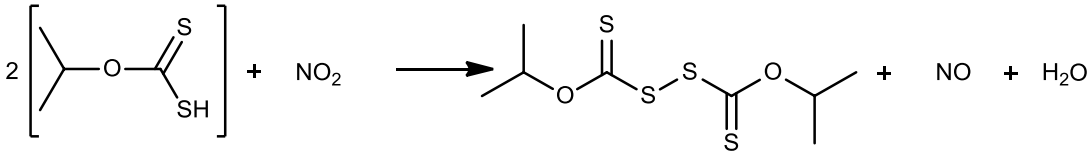

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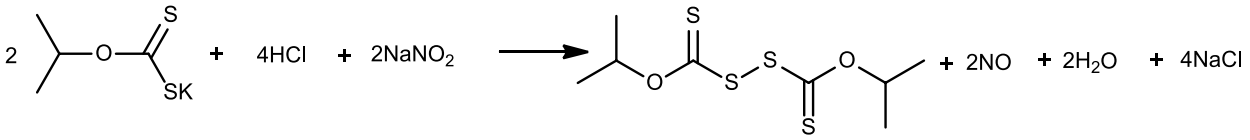
In total:



(13)

Purification of gas emissions is carried out by absorption of off-gases with an aqueous solution of urea. The process of absorption of nitrogen oxides can be described by Scheme (14):

$$NO + NO_2 + (NH_2)_2CO = 2H_2O + CO_2 + 2N_2 \quad (14)$$

Based on the calculated by us material balances, the consumption coefficients for raw materials and auxiliary materials (Tables 18 and 19) and the waste generation rate in the production of diisopropyl xanthogen disulfide using an alternative technology were determined (Tables 20 and 21).

Table 18. Consumption coefficients for raw materials and auxiliary materials in the potassium isopropyl xanthate production

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Obtaining PIX			
Isopropyl alcohol (99.6%)	416.16	2.593	–
	145.89	0.909	With regeneration
Carbon disulfide (100%)	72.68	0.453	–
Potassium hydroxide (86.8%)	61.70	0.384	–
Isopropanol recovery			
Toluene (99.5%)	98.63	0.616	–

Table 19. Consumption coefficients for raw materials and auxiliary materials in the diisopropyl xanthogen disulfide production using an alternative technology

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
PIX (98.88%)	150.00	1.355	–
Sodium nitrite (98.50%)	59.60	0.552	–
Orthophosphoric acid (85%)	127.10	1.196	–

Table 19. Continued

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Water	850.00	7.870	–
	433.86	4.017	With the return of wash water and condensate from the sludge drying process
Urea (100%)*	133.02*	0.172	With recycling
	121.63*	0.157	With the regeneration of the absorbent
Water for absorbent preparation*	399.06*	0.515	With recycling

* Based on 7 operations for obtaining diisopropyl xanthogen disulfide.

Table 20. Waste generation standards, emissions, and discharges in the potassium isopropyl xanthate production

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
VAT residue after distillation of the filtrate	Liquid	VAT residue, including:	100.00	12.89	0.086
		Isopropanol	51.32	5.42	0.039
		Impurities	48.68	7.47	0.047
Azeotrope isolated at the stage of absolute rectification	Liquid	Azeotrope, including:	100.00	201.53	1.260
		Isopropanol	38.20	76.98	0.481
		Water	13.10	26.40	0.165
		Toluene	48.70	98.14	0.613
Distillation residue after absolute rectification	Liquid	VAT residue, including:	100.00	9.29	0.021
		Isopropanol	85.71	8.80	0.018
		Impurities	14.29	0.49	0.003
Air emissions		None			
Wastewater discharges		None			

Table 21. Waste generation standards, emissions, and discharges in the diisopropyl xanthogen disulfide production using an alternative technology

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
Wastewater	Liquid	Filtrate, including:	100.00	629.60	5.830
		Water	74.13	466.72	4.321
		Impurities	1.25	7.87	0.073
		Sodium and potassium salts of phosphoric acid	24.62	155.01	1.435
Wastewater	Liquid	Waste absorbent, including:	100.00	15.45	0.140
		Urea	2.78	0.43	0.004
		Water	97.22	15.02	0.136
Abgases	Gas	Abgases, including	100.00	13.82	0.125
		Nitrogen	10.34	1.43	0.013
		Carbon dioxide	89.66	12.39	0.112
Air emissions		None			
Wastewater discharges		None			

Further, we calculated the comprehensive indicators for comparing the developed and alternative technologies used in the production of diisopropyl xanthogen disulfide along with the final indicator for evaluating the developed technology for compliance with BAT principles (Table 22).

The value of the final indicator of the technology assessment $I = 1.97 < 2$ supports the conclusion that the technology developed by us for the production of diisopropyl xanthogen disulfide meets BAT principles and is more environmentally friendly compared to the alternative one [4]. This technology was introduced in *Separate Plant No. 4*; the capacity of the pilot low-scale production is 2000 kg/year for diisopropyl xanthogen disulfide and 3000 kg/year for PIX.

Thus, the developed technology is more environmentally friendly than the alternative one due to the high level of environmental friendliness achieved through the regeneration of isopropanol at the stage of PIX production. However, the specific indicator of waste generation by this technology is quite high (7.23 t/t, Table 17), and the main production waste is the filtrate from the stage of obtaining diisopropyl xanthogen disulfide (5.862 t/t, Table 21), the water content of which is 79.03%. It should be noted that during the development process, we managed to reduce the hazard class of this waste from 1st to 2nd, which, in our opinion, is a significant result in achieving environmental protection goals and increases the level of environmental friendliness of the technology we developed for the production of diisopropyl

[6] Order of the Ministry of Agriculture of Russia dated December 13, 2016, No. 552 (as amended on March 10, 2020) "On approval of water quality standards for fishery water bodies, including standards for maximum permissible concentrations of harmful substances in the waters of fishery water bodies" (Registered with the Ministry of Justice of Russia on January 13, 2017, No. 45203) (in Russ.).

Table 22. Comprehensive indicators and the final evaluation indicator of the developed diisopropyl xanthogen disulfide production technology

Indicator	Calculation method and indicator value
Comprehensive indicator of comparison of the main technological indicators of the developed and alternative technologies K_1	Due to the absence of emissions of harmful substances into the atmosphere or discharges into water bodies for these technologies, no comparison of specific indicators of emissions into the atmosphere and discharges into water bodies is carried out. $K_1 = A_{T,P}/A_{T,A} = 7.23/7.34 = 0.98$
Comprehensive indicator of comparison of additional technological indicators of the developed and alternative technologies K_2	Due to the absence of discharges of harmful substances into water bodies using these technologies, no calculation or comparison of the degree of purification of discharges into water bodies is carried out. $K_2 = (2.83/2.56 + 0.47/0.55 + 1.00/1.00)/3 = (1.11 + 0.85 + 1.00)/3 = 0.99$
Technology assessment outcome I	$I = 0.98 + 0.99 = 1.97$

xanthogen disulfide. Regeneration of the solvent (water) from the waste (filtrate) can be considered as a possible direction for the modernization of the technology, which will lead to a decrease in the specific indicator of production waste and will increase the degree of use of raw materials and generated waste.

Assessment of the compliance of the developed technology for the *N*-phenyl-2-naphthylamine production with the BAT principles

The technology for the production of *N*-phenyl-2-naphthylamine was based on a one-stage method developed in [16], which includes the aramination of 2-naphthol with aniline in the presence of catalytic amounts of orthophosphoric acid at a molar ratio of 2-naphthol : aniline : orthophosphoric acid equal to 1 : 1.065 : 0.017, within 2.0–2.5 h [17, 18]. The return of the initial aniline to the reaction sphere is ensured by separating the azeotropic aniline/water mixture and separating *N*-phenyl-2-naphthylamine in the form of a powder by crystallization from the reaction mass in an isobutanol/xylene mixture [16, 17]. The process of obtaining *N*-phenyl-2-naphthylamine is described by Scheme (15).

The calculation of the main and additional technological indicators [4] of the production of *N*-phenyl-2-naphthylamine was carried out by us using data of "Temporary process regulations for pilot low-tonnage production of *N*-phenyl-2-naphthylamine, No. TTR-8-350" on consumption coefficients for raw materials (Table 23) and

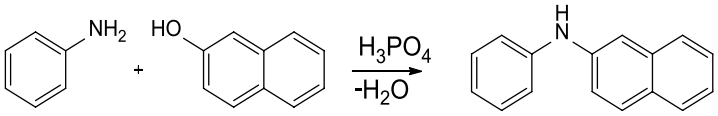


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Table 23. Consumption coefficients for raw materials and auxiliary materials in the *N*-phenyl-2-naphthylamine production

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Aniline (99.9%)	121.00	0.475	–
2-Naphthol (99.5%)	175.00	0.686	–
Phosphoric acid (85%)	2.40	0.009	–
Isobutanol (99.3%)	433.42	1.700	Without regeneration
	1.90	0.007	With regeneration
Petroleum xylene (99.6%)	82.91	0.325	Without regeneration
	32.27	0.127	With regeneration

production waste generation rates (Table 24). The results of the calculation of the main and additional technological indicators are presented in Table 25.

The final assessment of the developed technology for the *N*-phenyl-2-naphthylamine production was also carried out by comparing this technology with an alternative one, which was implemented in the 1960s at *Novomoskovsk Anilino-Paint Plant* (*Novomoskovsk Organic Synthesis Plant*) [19]. The technology was based on the condensation of 2-naphthol with aniline in the presence of a benzenesulfonic acid catalyst at a molar ratio of 2-naphthol to aniline equal to 1 : 1.5. The process of formation of *N*-phenyl-2-naphthylamine can be described by the Scheme (16).

Table 24. Waste generation standards, emissions, and discharges in the *N*-phenyl-2-naphthylamine production (with regeneration of isobutanol–*o*-xylene mixture)

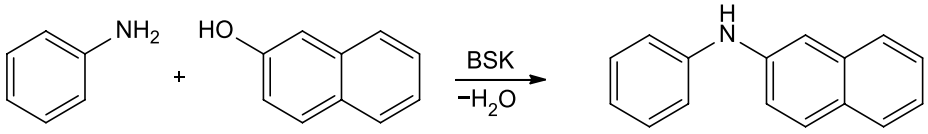
Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
Distillation residue after regeneration of isobutanol-xylene mixture	Liquid	VAT residue, including:	100.00	54.23	0.213
		N-phenyl-2-naphthylamine	8.32	10.03	0.039
		Aniline phosphate	3.30	3.98	0.016
		o-Xylene	81.07	31.90	0.125
		Aniline	5.09	6.14	0.024
		Impurities	1.14	2.18	0.009
Aqueous phase (azeotrope)	Liquid	Water	100.00	22.15	0.087
Organic phase (azeotrope)	Liquid	Organic phase, including:	100.00	2.61	0.010
		Aniline	13.08	0.34	0.001
		Isobutanol	70.11	1.90	0.007
		Xylene	16.81	0.37	0.001
Air emissions	None				
Wastewater discharges	None				

Table 25. Basic and additional technological indicators calculated for the developed and alternative technologies used in the *N*-phenyl-2-naphthylamine production

Indicator	Calculation method and indicator value	
	Developed technology	Alternative technology
Main technological indicators		
Generation rate of solid and liquid waste	$A_{T,P}$ = 0.310 t/t (Table 24)	$A_{T,P}$ = 1.85 t/t (Table 27)
Specific emissions into the atmosphere	There are no emissions into the atmosphere (Tables 24 and 27)	
	$B_{T,P}$ = 0 t/t	$B_{T,A}$ = 0 t/t

Table 25. Continued

Indicator	Calculation method and indicator value	
	Developed technology	Alternative technology
Wastewater generation rate	There is no wastewater discharge (Tables 24 and 27)	
	$C_{T,P}$ = 0 t/t	$C_{T,A}$ = 0 t/t
Additional technological indicators		
The degree of complexity and completeness of the extraction of useful components from the feedstock	It is calculated as the sum of the recovery factors of 2-naphthol and aniline, taking into account the yield of *N*-phenyl-2-naphthylamine (255.00 kg per operation, 96%) $P_{2\text{-Naphthol}}$ = 0.659/0.683 = 0.96 t/t $P_{Aniline}$ = 0.424/0.474 = 0.89 t/t $J_{K,P}$ = 0.96 + 0.89 = 1.85 t/t	$J_{K,A}$ = 1.59 t/t
Degree of utilization of generated waste	It is calculated as the share of regenerated isobutanol and xylene in the total mass of the waste (filtrate, washing solution, and condensate). It can be calculated from the material balance data for the regeneration of the isobutanol/xylene mixture per operation. $J_{O,P}$ = (431.47 + 50.60)/538.39 = = 0.90 t/t	$J_{O,A}$ = 0.31 t/t
Degree of purification of emissions of harmful substances into the atmosphere	There are no emissions into the atmosphere (Tables 24 and 27)	
	$J_{A,P}$ = 0 t/t	$J_{A,A}$ = 0 t/t
Degree of purification of discharges into water bodies	There is no wastewater discharge (Tables 24 and 27)	
	$J_{B,P}$ = 0 t/t	$J_{B,A}$ = 0 t/t



(16)

The condensation of 2-naphthol and aniline was carried out at a temperature of 240 ± 5°C until the content of 2-naphthol was 0.8%. Aniline vapor was partially returned to the reactor by reflux. The reaction mass was neutralized with solid caustic soda. Unreacted aniline was distilled off with live steam until it was completely absent in the reaction mass. The selection of the target *N*-phenyl-2-naphthylamine was carried out in the form of a melt, followed by distillation and flaking.

Regeneration of excess aniline that did not react with 2-naphthol was carried out using vacuum distillation and rectification methods. The extraction of aniline from aniline water was carried out in the process of rectification by azeotropic distillation, followed by separation of the heteroazeotrope by centrifugation.

Based on the calculated by us material balances, the consumption coefficients for raw materials andauxiliary materials (Table 26) and the generation rate of *N*-phenyl-2-naphthylamine production waste using an alternative technology were determined (Table 27).

Next, we calculated comprehensive indicators for comparing the developed and alternative technologies and the final indicator for evaluating the new technology for compliance with BAT principles (Table 28)

Table 26. Consumption coefficients for raw materials and auxiliary materials in the *N*-phenyl-2-naphthylamine production using an alternative technology

Name of raw materials	Expense coefficients		Note
	kg/operation	t/t	
Technical aniline (99.8%)	1854.55	0.663	Without regeneration
	1185.99	0.424	With regeneration
2-Naphthol (98.5%)	1940.00	0.693	–
Benzenesulfonic acid (95%)	8.90	0.003	–
Technical sodium hydroxide (98.5%)	2.30	0.001	–
Water	3500.00	1.250	Without regeneration
	2659.57	0.950	With regeneration
Water vapor	2238.24	0.800	–

Table 27. Waste generation standards, emissions, and discharges in the *N*-phenyl-2-naphthylamine production using an alternative technology (with water and aniline regeneration)

Type of waste	Aggregate state of waste	Composition	Amount, %	Production waste generation rate	
				kg/operation	t/t
Wastewater	Liquid	Filtrate, including:	100.00	121.099	0.433
		2-Naphthol	0.09	0.114	0.0004
		Sodium salt of benzenesulfonic acid	0.60	0.722	0.0026
		Sodium salt of sulfuric acid	0.02	0.029	0.0001
		Water	95.06	115.117	0.4113
		Impurities	4.23	5.118	0.0183
Wastewater	Liquid	Wash water, including:	100.00	255.532	0.913
		2-Naphthol	0.09	0.222	0.0008
		Sodium salt of benzenesulfonic acid	0.09	0.241	0.0009
		Sodium salt of sulfuric acid	0.004	0.010	0.00004
		Water	99.31	253.779	0.9067
		Impurities	0.50	1.280	0.0046
VAT residue	Liquid	VAT residue, including:	100.00	0.400	0.001
		Resin	100.00	0.400	0.001
Wastewater	Liquid	Water, including:	100.00	141.110	0.504
		Aniline	0.15	0.210	0.0008
		Water	99.85	140.900	0.5034
Air emissions		None			
Wastewater discharges		None			

Table 28. Comprehensive indicators and the final evaluation indicator of the developed *N*-phenyl-2-naphthylamine production technology

Indicator	Calculation method and indicator value
Comprehensive indicator of comparison of the main technological indicators of the developed and alternative technologies K_1	Due to the absence of emissions of harmful substances into the atmosphere or discharges into water bodies for the technologies under consideration, the formula for calculating the indicator is transformed as follows: $K_1 = A_{T,P}/A_{T,A}$ $K_1 = 0.31/1.85 = 0.17$
Comprehensive indicator of comparison of additional technological indicators of the developed and alternative technologies K_2	Due to the absence of emissions of harmful substances into the atmosphere for the technologies under consideration, no calculation or comparison of the degree of purification of emissions of harmful substances into the atmosphere is carried out. $K_2 = (J_{K,A}/J_{K,P} + J_{O,A}/J_{O,P} + J_{B,A}/J_{B,P})/3$ $K_2 = (1.59/1.85 + 0.31/0.90 + 1.00/1.00)/3 = 0.73$
Technology assessment outcome I	$I = 0.17 + 0.73 = 0.90$

The value of the final technology assessment indicator $I = 0.90 << 2$ supports the conclusion that the *N*-phenyl-2-naphthylamine production technology developed by us meets BAT principles and is much more environmentally friendly [4] compared to the alternative one implemented in the USSR. The technology developed by us has been implemented in *Separate Plant No. 4*; the capacity of the experimental low-tonnage production is 5000 kg/year.

An analysis of the evaluation of the developed *N*-phenyl-2-naphthylamine production technology determines it as highly efficient ($K_1 = 0.17$) and having a high level of environmental friendliness ($K_2 = 0.73$). The new technology is distinguished by a significantly lower (almost 6 times) level of waste generation compared to the alternative technology implemented in the USSR, and is also characterized by a high degree of resource saving and recuperation of generated waste. The obtained result is ensured by the adopted technological solutions using the return of aniline to the reaction sphere after the separation of the condensed in florentine vapors of the azeotropic aniline–water mixture, as well as the regeneration of the mixture of solvents (isobutanol/xylene).

DISCUSSION

Based on the analysis of new low-tonnage chemical production technologies developed at *GosNIIOKhT* according to the criteria for achieving environmental protection objectives using the methodology [4], the adopted technological solutions for resource saving and environmental protection are concluded to be highly effective.

The quantitative assessment methodology [4] is based on determining achieved levels of manufacturability and environmental friendliness of new technologies along with the calculation of comprehensive indicator for comparison with alternative (BAT) technologies (Table 29). The calculated values of the main technological indicators characterize the achieved level of technology efficiency: the lower the value of the K_1 indicator, the higher the efficiency of the new technology compared to the existing alternative. In turn, the values of additional technological indicators of technologies reflect the achieved level of environmental friendliness of the technology, while the criterion for the effectiveness of the development (compared to the existing technology) also consists in the achievement of the minimum values of the K_2 indicator. The effectiveness of development as a whole characterizes the final indicator of comparison I: the lower its value, the higher the achieved degree of compliance of the new technology with BAT principles and the current level of development according to the criteria for achieving the environmental protection objectives.

The current absence of BAT for the production of tetramethylthiuram disulfide (thiuram D), *N*-cyclohexyl-2-benzothiazolylsulfenamide (sulfenamide C), diisopropyl xanthogen disulfide (diproxide and *N*-phenyl-2-naphthylamine (neozone D) is due to these materials having previously been produced in the USSR.

As a result of the calculations, it was found that all the new technologies developed by us in accordance with BAT principles are environmentally more advanced than those implemented earlier during the Soviet period (Table 30). The most

Table 29. Criteria for the development and evaluation indicators of new technologies in accordance with BAT principles

Criteria for development in accordance with BAT principles	Evaluation indicators for developed and alternative production technologies in accordance with BAT principles		
	K_1 (achieved level of technology efficiency)	K_2 (achieved level environmental friendliness of the technology)	I (overall development efficiency)
Development efficiency criterion	$K_1 < 1$ Reaching the minimum values of K_1	$K_2 < 1$ Reaching the minimum values of K_2	$I < 2$ Reaching the minimum values of I
Characteristics of development evaluation indicators	Comprehensive indicator of comparison of the main technological indicators of production technologies	Comprehensive indicator of comparison of additional technological indicators of the developed and alternative production technologies	Final indicator of the comparison of the developed and alternative production technologies
Semantic content of development evaluation indicators	Level of waste generation, air emissions and water discharges.	Degree of complexity and completeness of the extraction of useful components from the feedstock, the use of waste generated, the purification of emissions of harmful substances into the atmosphere and discharges into water bodies.	Degree of compliance of the new technology with BAT principles and the current level of development according to the criteria for achieving the objectives of environmental protection
Conclusion on the results of the development evaluation	$K_1 < 1$. The lower the K_1 indicator, the higher the achieved level of efficiency of the developed technology compared to the alternative.	$K_2 < 1$. The lower the K_2 indicator, the higher the achieved level of environmental friendliness of the developed technology compared to the alternative.	$I < 2$. The lower I, the more the developed technology complies with BAT principles and is more environmentally friendly compared to the alternative.

Table 30. Results of the quantitative assessment of the developed technologies for the production of materials in accordance with BAT principles

Development evaluation indicators in accordance with BAT principles	Subject of development—production technology			
	Tetramethylthiuram disulfide	*N*-cyclohexyl-2-benzothiazolylsulfenamide	Diisopropyl xanthogen disulfide	*N*-phenyl-2-naphthylamine
Development evaluation results				
K_1	0.11	0.06	0.98	0.17
K_2	0.93	0.39	0.99	0.73
I	1.04	0.45	1.97	0.90

Table 30. Continued

Development evaluation indicators in accordance with BAT principles	Subject of development—production technology			
	Tetramethylthiuram disulfide	***N*-cyclohexyl-2-benzothiazolylsulfenamide**	**Diisopropyl xanthogen disulfide**	***N*-phenyl-2-naphthylamine**
Conclusion on the results of the development evaluation:				
Achieved level of efficiency	Very high	Very high	Comparable	Very high
Achieved level of environmental friendliness	Comparable	Very high	Comparable	High
Overall development efficiency	Very high	Very high	Comparable	Very high
Compliance with BAT principles	Yes	Yes	Yes	Yes
Identification of possible directions for development modernization				
Possible modernization measures	Regeneration of water from waste (leachate)	–	Solvent (water) recovery from waste (filtrate)	–
Expected result of modernization measures	Reducing the specific indicator of production waste	–	Reducing the specific indicator of production waste	–
	Increasing the utilization of generated waste	–	Increasing the utilization of generated waste	–
	Further improvement of the environmental friendliness of the development	–	Further increase in efficiency and environmental friendliness	–

effective technological solutions have been developed for the production of tetramethylthiuram disulfide (K_1 = 0.11 << 1), *N*-cyclohexyl-2-benzothiazolylsulfenamide (K_1 = 0.06 << 1) and *N*-phenyl-2-naphthylamine (K_1 = 0.17 << 1). The maximally efficient use of raw materials and purification of emissions and discharges is achieved by implementing the technologies for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide (K_2 = 0.39 < 1) and *N*-phenyl-2-naphthylamine (K_1 = 0.73 < 1). The achieved levels of manufacturability (K_1) and environmental friendliness (K_2) provide a high level of efficiency and compliance with BAT principles for the production of tetramethylthiuram disulfide (I = 1.04 << 2), *N*-cyclohexyl-2-benzothiazolylsulfenamide (I = 0.45 << 2) and *N*-phenyl-2-naphthylamine (I = 0.9 << 2).

The developed new technology for the production of diisopropyl xanthogen disulfide is characterized by the levels of manufacturability (K_1 = 0.98 ≈ 1) and environmental friendliness (K_2 = 0.99 ≈ 1) comparable with the alternative option. The efficiency of the developed technological solutions is also comparable with the efficiency of the alternative (I = 1.97). Nevertheless, compliance with the development efficiency criterion (I = 1.97 < 2) supports the conclusion that the new technology offers some advantage in terms of achieved resource saving and environmental protection in accordance with BAT principles.

A possible direction for the modernization of this development consists in the search for new technological solutions for the recovery of a solvent (water) from waste (filtrate), which will increase its efficiency and environmental friendliness by reducing the specific indicator of waste production and enhancing the utility of generated wastes.

CONCLUSIONS

The introduction of modern low-tonnage chemical production technologies on an industrial scale is a complex system task, whose successful solution is ensured by the achievement of high levels of efficiency, safety and quality of development. Decisions on the prospects for industrial implementation of possible new technologies should be made based on the results of their analysis according to criteria for determining the result achieved during implementation, as well as compliance with regulatory and legislative requirements. An objective assessment must have a scientific methodological basis that takes technological, economic and environmental factors into account, as well as an algorithm for evaluating achieved indicators, comparing them with the target ones, and drawing a conclusion about the level of development.

To assess the compliance of new technologies with modern environmental requirements, we have developed a "Methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with BAT principles," which is used in the development process to make decisions on resource saving and waste reduction.

On the example of low-tonnage technologies for the production of tetramethylthiuram disulfide, *N*-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthogen disulfide and *N*-phenyl-2-naphthylamine created at *GosNIIOKhT*, the quantitative assessment of new technologies based on the calculation of comprehensive indicators of comparison with alternative technologies by technological (quantity waste, emissions and discharges) and environmental indicators (the degree of use of raw materials and waste and the effectiveness of measures to clean up gas emissions and discharges into water bodies) is shown to be useful for assessing the compliance of new technologies with BAT principles, as well as determining the directions for modernizing existing industries.

The developed "Methodology for a comprehensive assessment of possible technological solutions according to the criteria of economic and environmental efficiency," along with the "Methodology for the quantitative assessment of new technologies for the production of materials in accordance with BAT principles" allowed us to create a methodological basis for use at the stage of making basic technological decisions on the introduced production method to ensure a high level of economic and environmental efficiency, as well as fulfilling legal requirements for technologies used in the field of environmental safety for achieving environmental protection objectives.

Authors' contributions

N.A. Kostikova – development and industrial implementation of technologies for the production of tetramethylthiuram disulfide, *N*-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthohen disulfide, and *N*-phenyl-2-naphthylamine; development of the "Methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with BAT principles," approbation of this technique, and the comparative evaluation of developed and alternative (previously implemented in the USSR) technologies by the level of environmental impact.

E.N. Glukhan – formation of the scientific concept of quantitative assessment of new technologies in accordance with BAT principles, development of "Methodology for the quantitative assessment of new technologies for the production of organic substances in accordance with BAT principles."

P.V. Kazakov – development of technology for obtaining tetramethylthiuram disulfide, industrial introduction of technologies for obtaining tetramethylthiuram disulfide, *N*-cyclohexyl-2-benzothiazolylsulfenamide, diisopropyl xanthohen disulfide, and *N*-phenyl-2-naphthylamine.

M.M. Antonova – development and industrial implementation of technologies for the production of diisopropyl xanthohen disulfide and *N*-phenyl-2-naphthylamine.

D.I. Klimov – development and industrial implementation of technologies for the production of *N*-cyclohexyl-2-benzothiazolylsulfenamide and *N*-phenyl-2-naphthylamine.

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About the authors:

Natalya A. Kostikova, Cand. Sci. (Eng.), Associate Professor, Head of Department, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, sh. Entuziastov, Moscow, 111024, Russia). E-mail: kutkin@gosniiokht.ru. RSCI SPIN-code 1540-8520, https://orcid.org/0000-0001-8796-124X

Elena N. Glukhan, Dr. Sci. (Eng.), Assistant Professor, Adviser to the Director-General, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, sh. Entuziastov, Moscow, 111024, Russia). E-mail: dir@gosniiokht.ru. Scopus Author ID 8706397600, RSCI SPIN-code 6274-1908, https://orcid.org/0000-0002-2369-5648

Pavel V. Kazakov, Dr. Sci. (Chem.), Assistant Professor, Deputy General Director, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, sh. Entuziastov, Moscow, 111024, Russia). E-mail: kutkin@gosniiokht.ru. RSCI SPIN-code 1920-2930, https://orcid.org/0000-0001-8164-274X

Mariya M. Antonova, Cand. Sci. (Eng.), Head of the Research Department, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, sh. Entuziastov, Moscow, 111024, Russia). E-mail: kutkin@gosniiokht.ru. Scopus Author ID 56165662600, RSCI SPIN-code 4136-5290, https://orcid.org/0000-0001-6492-2483

Dmitry I. Klimov, Cand. Sci. (Eng.), Head of Sector, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, sh. Entuziastov, Moscow, 111024, Russia). E-mail: kutkin@gosniiokht.ru. RSCI SPIN-code 7113-2691, https://orcid.org/0000-0002-0649-1440

Об авторах:

Костикова Наталья Алексеевна, к.х.н., начальник отдела, ФГУП «Государственный научно-исследовательский институт органической химии и технологии» (ФГУП «ГосНИИОХТ»), Государственный научный центр Российской Федерации (111024, Россия, Москва, шоссе Энтузиастов, 23). E-mail: kutkin@gosniiokht.ru. SPIN-код РИНЦ 1540-8520, https://orcid.org/0000-0001-8796-124X

Глухан Елена Николаевна, д.т.н., доцент, советник генерального директора, ФГУП «Государственный научно-исследовательский институт органической химии и технологии» (ФГУП «ГосНИИОХТ»), Государственный научный центр Российской Федерации (111024, Россия, Москва, шоссе Энтузиастов, 23). E-mail: dir@gosniiokht.ru. Scopus Author ID 8706397600, SPIN-код РИНЦ 6274-1908, https://orcid.org/0000-0002-2369-5648

Казаков Павел Васильевич, д.х.н., доцент, заместитель генерального директора, ФГУП «Государственный научно-исследовательский институт органической химии и технологии» (ФГУП «ГосНИИОХТ»), Государственный научный центр Российской Федерации (111024, Россия, Москва, шоссе Энтузиастов, 23). E-mail: kutkin@gosniiokht.ru. SPIN-код РИНЦ 1920-2930, https://orcid.org/0000-0001-8164-274X

Антонова Мария Михайловна, к.х.н., начальник научно-исследовательского отделения, ФГУП «Государственный научно-исследовательский институт органической химии и технологии» (ФГУП «ГосНИИОХТ»), Государственный научный центр Российской Федерации (111024, Россия, Москва, шоссе Энтузиастов, 23). E-mail: kutkin@gosniiokht.ru. Scopus Author ID 56165662600, SPIN-код РИНЦ 4136-5290, https://orcid.org/0000-0001-6492-2483

Климов Дмитрий Игоревич, к.х.н., начальник сектора, ФГУП «Государственный научно-исследовательский институт органической химии и технологии» (ФГУП «ГосНИИОХТ»), Государственный научный центр Российской Федерации (111024, Россия, Москва, шоссе Энтузиастов, 23). E-mail: kutkin@gosniiokht.ru. SPIN-код РИНЦ 7113-2691, https://orcid.org/0000-0002-0649-1440

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CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Design and synthesis of 4-nitroimidazole derivatives with potential antitubercular activity

Tatiana S. Vedekhina[1,✉], Mikhail V. Chudinov[2], Alexey Yu. Lukin[2]

[1]Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow, 119435 Russia
[2]MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
✉Corresponding author, e-mail: taveda@gmail.com

Abstract

Objectives. *To develop the procedures for synthesis of hybrid molecules with potential antitubercular activity containing heterocyclic cores of 4-nitroimidazole and 1,3,4-thiadiazole within the framework of a double-drug strategy and predict bioactivity of target structures and drug-likeness physicochemical parameters.*

Methods. *Target compounds were prepared by classical organic synthesis methods. The structure of the obtained compounds was characterized by melting points, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry. The calculation of the physicochemical parameters of the target compounds and prediction of their biological activity were carried out using publicly available software for cheminformatics and molecular modeling.*

Results. *Acylation of propargylamine with (2-methyl-4-nitro-1H-imidazol-1-yl)acetic and (4-nitro-1H-imidazol-1-yl)acetic acids provided the corresponding amides, which were cyclized with seven different benzylamines in the presence of zinc triflate. In this way, seven new compounds were obtained at 20–30% yields. Ten arylamines were acylated with chloroacetyl chloride and the resulting chloroacetamides were converted into corresponding thio-oxahydrazides by the Willgerodt–Kindler reaction. Following acylation by (4-nitro-1H-imidazol-1-yl)acetic acid, these compounds were converted into the target hybrid imidazolyl-thiadiazoles at 29–54% yields.*

Conclusions. *Two series of new heterocyclic compounds with a hybrid structure including a privileged 4-nitroimidazole moiety linked to the second heterocycle, imidazole, or thiadiazole, were obtained. The synthesis and characterization of compounds by physicochemical methods was aimed at searching for anti-tuberculosis activity. The bioactivity potential of target compounds was demonstrated by preliminary calculations performed using public prognostic programs.*

Keywords: *nitroimidazoles, biimidazoles, 1,3,4-thiadiazoles, N-propargylamides, thiosemicarbazides, zinc triflate*

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НАУЧНАЯ СТАТЬЯ

Дизайн и синтез производных 4-нитроимидазола с потенциальной антитуберкулезной активностью

Т.С. Ведёхина[1,✉], М.В. Чудинов[2], А.Ю. Лукин[2]

[1]Федеральный научно-клинический центр физико-химической медицины имени академика Ю.М. Лопухина Федерального медико-биологического агентства, Москва, 119435 Россия
[2]МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
✉Автор для переписки, e-mail: taveda@gmail.com

Аннотация

Цели. *Разработка синтеза гибридных молекул с потенциальной противотуберкулезной активностью, содержащих гетероциклические системы 4-нитроимидазола и 1,3,4-тиадиазола, в рамках стратегии «double drug». Анализ соответствия их расчетных физико-химических параметров интервалам значений для лекарственно-подобных («drug-likeness») соединений.*
Методы. *Целевые соединения были получены классическими методами органического синтеза. Структура полученных соединений была охарактеризована температурами плавления, спектроскопией ядерного магнитного резонанса ^{1}H и ^{13}C, масс-спектрометрией высокого разрешения. Расчет физико-химических параметров целевых соединений и прогнозирование их биологической активности проводили с использованием общедоступного программного обеспечения для хемоинформатитки и молекулярного моделирования.*
Результаты. *Ацилированием пропаргиламина (2-метил-4-нитро-1Н-имидазол-1-ил)уксусной и (4-нитро-1Н-имидазол-1-ил)уксусной кислотами были получены пропаргиламиды, которые циклизовали с 7 различными бензиламинами в присутствии трифлата цинка. Таким способом с выходами 20–30% от теоретического была получена серия из 7 новых 2-[(4-нитро-1Н-имидазол-1-ил)метил]-1-бензил-5-метил-1Н-имидазолов. 10 ариламинов*

были ацилированы хлорацетилхлоридом. Полученные хлорацетамиды реакцией Вильгеродта–Киндлера превратили в соответствующие тиооксагидразиды. Эти соединения после ацилирования (4-нитро-1Н-имидазол-1-ил)уксусной кислотой были превращены циклодегидратацией в целевые гибридные имидазолил-тиадиазолы, с выходами 29–54%.
Выводы. *Получены две серии новых гетероциклических соединений с гибридной структурой, включающей привилегированный фрагмент 4-нитроимидазола, соединенный алкильным линкером со вторым гетероциклом – имидазолом или тиадиазолом. Соединения сконструированы с целью поиска противотуберкулезной активности, синтезированы и охарактеризованы физико-химическими методами. Предварительные расчеты, выполненные с помощью общедоступных прогностических программ, показали возможный потенциал биологической активности целевых структур.*

Ключевые слова: *нитроимидазолы, биимидазолы, 1,3,4-тиадиазолы, N-пропаргиламиды, тиосемикарбазиды, трифлат цинка*

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INTRODUCTION

One of the most studied structures in medicinal chemistry comprises the imidazole heterocyclic system. Many drugs that are currently on the market or in the process of being developed are based on an imidazole core [1]. Imidazole derivatives are present among antibiotic, antiviral and anticancer drugs, as well as antiprotozoal agents and many other medicinal compounds. These compounds play an important role in the fight against tuberculosis, a socially significant infection that has recently created increasingly serious problems for public health due to the spread of multidrug-resistant strains. Delamanid (**1**) was approved for the treatment of antibiotic-resistant forms of tuberculosis in 2014; another imidazole derivative, Pretomanid (PA-824) (**2**), is currently undergoing phase III clinical trials [2]. Both structures are based on the heterocyclic 4-nitroimidazole system (Fig. 1). 5-Nitroimidazoles have been used antibacterial and antiprotozoal agents [3] since the 1960s; in this connection, it is sufficient to mention the well-known metronidazole (**3**) and ornidazole (**4**) variants. Due to the less well-developed

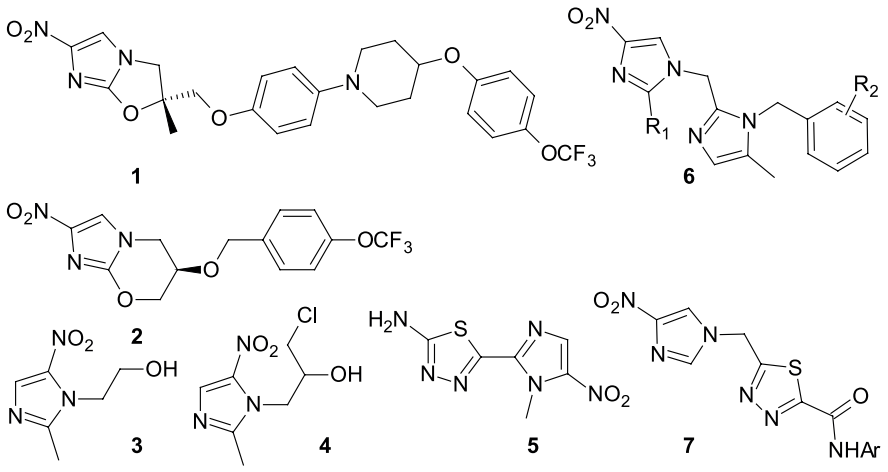


Fig. 1. Structures of nitroimidazole drugs **1**–**5** and synthesized compounds **6**, **7**.

approaches to the synthesis of these substances, the activity of 4-nitroimidazoles only became the subject of studies more recently. The mechanisms of action and biological targets of nitroimidazoles are very diverse. At the first stage of metabolism, cell enzyme systems reduce the nitro group to an amine, while aminoimidazoles inhibit the synthesis of DNA and proteins. Some drugs block mitochondrial oxidation processes to deplete the cell structure [4].

Another example of a privileged structure is the 1,3,4-thiadiazole system. The biological activity of 1,3,4-thiadiazole derivatives is very diverse [5]. Among these substances are antimicrobial, antiprotozoal and antituberculosis agents [6] with high pharmacological potential, as well as registered drugs, for example, megazole with antitrypanosomal activity (**5**). However, the mechanisms of action of these compounds have been much less studied. One of the recent publications suggests inhibition of one of the key enzymes of fatty acid synthesis, enoyl-ACP reductase (EC 1.3.1.9) as comprising such a mechanism [7]. Nevertheless, the very nature of the electron-deficient azole cycle suggests the possibility of effective binding to a wide variety of targets; therefore, other reasons for the antimicrobial action are also likely, for example, inhibition of inosine monophosphate dehydrogenase (EC 1.1.1.205), a key enzyme in the *de-novo* synthesis of purine nucleotides [2].

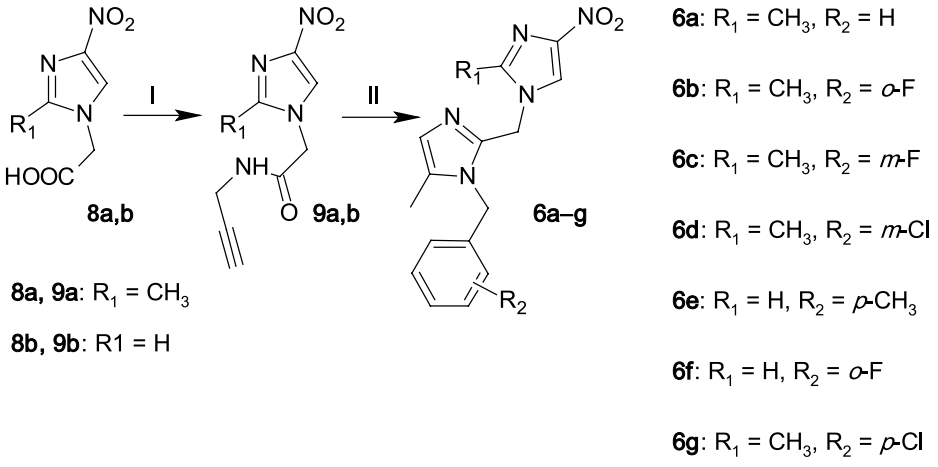
The aim of the present work is to develop the procedures for synthesis of hybrid molecules containing such heterocyclic systems within the framework of a "double-drug strategy". Such a strategy, which is widely used in the search for new active structures [8], was previously used by us to obtain active derivatives of the 5-nitrofuran pharmacophore [9]. The design of the target structures included an analysis of the correspondence of their calculated physicochemical parameters to the ranges of values for drug-likeness compounds. The structures of the synthesized compounds **6**, **7** are shown in Figs. 1.

RESULTS AND DISCUSSION

The first series of compounds **6a–g** was designed similarly to several previously described compounds offering high antituberculosis activity [10, 11]. The structures of the prototype compounds include 2 imidazole cycles attached via an alkyl linker. The advantages of such a structure from the point of view of biological activity are considered in review papers [2, 12]. The inclusion of a flexible linker between pharmacophore fragments presumably increases the likelihood of the molecule binding to different target sites.

Target compounds **6a–g** were synthesized by the zinc promoted reaction of propargylamides **9a** and **9b** with primary amines [13–15] (Scheme 1).

Propargylamides **9a** and **9b** were obtained by acylation of propargylamine with (2-methyl-4-nitro-1*H*-imidazol-1-yl)acetic (**8a**) and (4-nitro-1*H*-imidazol-1-yl)acetic (**8b**) acids in dimethylformamide (DMF) in the presence of 1,1'-carbonyldiimidazole (CDI). The yield of propargylamides was 64% and 53%, respectively. Next, propargylamides **9a** and **9b** were heated for 6 h in toluene with the corresponding benzylamines in the presence of zinc triflate; the reaction product was isolated by silica gel column chromatography. Following isolation



Scheme 1. Synthesis of compounds **6a–g**.
Reagents and conditions: (I) carbonyldiimidazole (CDI), propargyl amine, dimethylformamide (DMF), 16 h; (II) $Zn(CF_3SO_3)_2$, $R_2–PhCH_2NH_2$, toluene, reflux, 6 h.

and purification, the yields of compounds **6a–6g** varied in the range of 20–30% of the theoretical maximum. The structure of the obtained compounds was confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy.

Hybrid imidazolyl-thiadiazoles **7** include two heterocyclic nuclei linked by a methylene linker—4-nitroimidazole and thiadiazole—as well as a peripheral aryl group. The general structure of **7** is similar to the compounds of series **6** and the structure of megazole **5**; its isosteric compounds having an oxadiazole ring exhibit significant antibacterial activity [16]. Series **7a–j** was obtained using a 5-step scheme starting with the acylation of arylamines **10** with chloroacetyl chloride [17] (Scheme 2).

In the next step, chloroacetamides **11** were used without additional purification following treatment in the Willgerodt–Kindler reaction with elemental sulfur and morpholine, and then with hydrazine hydrate. Thus, without isolation of intermediate thiooxamides **12**, compounds **13a–13j** were obtained, which were purified by crystallization from ethanol and characterized by physicochemical methods. The thio-oxahydrazides **13** were acylated with commercially available (4-nitro-1*H*-imidazol-1-yl)-acetic acid and then subjected to cyclodehydration in glacial acetic acid. The yields of target arylamides **7a–7j** after column chromatography were 29–54%. Compounds **7a-j** were characterized by melting points, ^{1}H- and ^{13}C-NMR spectra.

The calculation of the physicochemical parameters of the target compounds using the publicly available Molinspiration[1] and SwissADME[2] software demonstrated a correspondence between their lipophilicity and molecular weight ratios with the Lipinski criteria [18] for drug-likeness compounds (Fig. 2).

The prediction of the biological activity of structures **6** and **7** using the Molinspiration Virtual Screening Toolkit shows additional significant similarity with known GPCR ligands, representing the bulk of drug-active compounds. On this basis, positive results of the proposed biological screening can be expected.

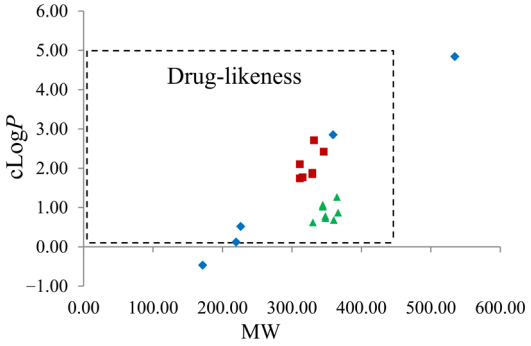
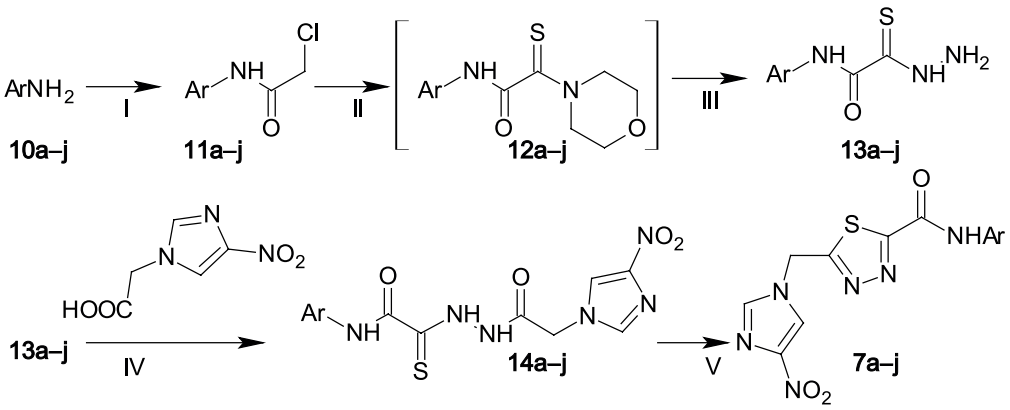


Fig. 2. Calculated physicochemical parameters of the target compounds:
♦ compounds 2–5; ■ compounds 6; ▲ compounds 7.
MW — molecular weight; cLogP — average lipophilicity value calculated from five predictions using the standard 1-octanol–water system.



Ar: Ph (**a**); 3,4-F-Ph (**b**); 4-MeOPh (**c**); 3-Cl-Ph (**d**); 4-Me-Ph (**e**);
2,4-F-Ph (**f**); 2-F-Ph (**g**); 2-Me-Ph (**h**); 4-F-Ph (**i**); 3-Me-Ph (**j**)

Scheme 2. Synthesis of 5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxyaryl amides(**7a–j**).
Reagents and conditions: (I) Et_3N, CH_2Cl_2; (II) S_8, morpholine, Et_3N, DMF, room temperature (r.t. is assumed to be equal to 25°C), 16 h; (III) $N_2H_4 \cdot H_2O$, DMF, r.t., 16 h; (IV) CDI, DMF, r.t., 16 h; (V) AcOH, reflux, 0.5 h.

[1] Molinspiration Cheminformatics. URL: https://www.molinspiration.com. Accessed December 13, 2022.
[2] SwissADME. URL: http://www.swissadme.ch. Accessed December 13, 2022.

EXPERIMENTAL

All reactions were carried out in glassware preliminarily dried at 140°C under a nitrogen atmosphere. Melting points as determined with a C-520 melter (*Büchi*, Switzerland) were not corrected. Analytical thin layer chromatography (TLC) was performed on Sorbfil plates (*IMID*, Russia) using the corresponding ethyl acetate/hexane and chloroform/methanol solvent systems. Compounds were visualized using shortwave ultraviolet light. ^{1}H and ^{13}C NMR spectra were recorded on a DPX-300 spectrometer (*Bruker*, Germany) in DMSO-d_6 and $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra of the final compounds were recorded on an Agilent 6210 TOF time-of-flight mass spectrometer (*Agilent*, USA) with electrospray ionization (ESI-MS). All reagents and solvents were obtained from commercial sources and used without further purification.

General procedure for the synthesis of compounds 9a–b

To 16.2 mmol of carboxylic acid **8** in 25 mL of dry DMF was added 17.8 mmol of CDI, and the mixture was left to stir at room temperature for 30 min. Then 17.8 mmol of propargylamine was added and left to stir at room temperature for 16 h. The reaction mixture was poured into water (150 mL) and extracted with ethyl acetate. The organic phase was washed with 5% K_2CO_3 aqueous solution (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated on a rotary evaporator under vacuum. The residue was suspended in diethyl ether; the precipitate was filtered off.

2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)-*N*-prop-2-yn-1-ylacetamide 9a

Yield of 2.3 g (64%), light yellow crystals, $T_{m.p.}$ = 150–151°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 8.80 (t, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 4.80 (s, 2H), 3.93 (dd, *J* = 5.3, 2.4 Hz, 2H), 3.19 (t, *J* = 2.4 Hz, 1H), 2.25 (s, 3H).

2-(4-nitro-1*H*-imidazol-1-yl)-*N*-prop-2-yn-1-ylacetamide 9b

Yield of 1.3 g (53.4%), orange crystals, $T_{m.p.}$ = 139–140°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 8.76 (t, *J* = 5.1 Hz, 1H), 8.33 (s, 1H), 7.80 (s, 1H), 4.86 (s, 2H), 3.93 (dd, *J* = 5.3, 2.4 Hz, 2H), 3.19 (t, *J* = 2.4 Hz, 1H).

General procedure for the synthesis of compounds 6a-g

To 0.90 mmol of propargylamide **9** in 20 mL of toluene, 1.08 mmol of the corresponding benzylamine and 0.2 mmol of $Zn(CF_3SO_3)_2$ were added, and the mixture was boiled for 8 h with distillation of water. The reaction mixture was evaporated, the residue was dissolved in ethyl acetate and washed with a 5% aqueous solution of K_2CO_3 (2 × 15 mL), dried over anhydrous Na_2SO_4, and evaporated on a rotary evaporator under vacuum. The residue was subjected to silica gel column chromatography, eluting with chloroform, increasing the polarity by adding methanol from 0% to 20%. Fractions containing the target product were combined and evaporated.

1-[(1-benzyl-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6a

Yield of 110 mg (26%), orange crystals, $T_{m.p.}$ = 119–120°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.37 (s, 1H), 7.30–7.27 (m, 1H), 7.26 (d, *J* = 2.0 Hz, 2H), 6.90 (s, 1H), 6.80–6.75 (m, 2H), 5.03 (s, 2H), 4.99 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.4, 144.8, 140.0, 135.0, 130.4, 129.4, 128.5, 126.7, 125.2, 119.9, 47.0, 43.7, 13.3, 9.7. ESI-MS: calculated for $[C_{16}H_{18}N_5O_2]^+$ 312.1461, found 312.1453.

1-[(1-(2-fluorobenzyl)-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6b

Yield of 80 mg (27%), orange crystals, $T_{m.p.}$ = 138–139°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.38 (s, 1H), 7.27–7.19 (m, 2H), 7.08–7.02 (m, 1H), 7.01–6.93 (m, 1H), 6.91 (s, 1H), 5.09 (s, 2H), 5.07 (s, 2H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 159.6 (d, *J* = 246.4 Hz), 146.3, 144.7, 139.9, 130.6 (d, *J* = 8.2 Hz), 130.4, 126.6, 126.5 (d, *J* = 3.3 Hz), 125.1 (d, *J* = 3.6 Hz), 122.0 (d, *J* = 14.0 Hz), 119.6, 115.9 (d, *J* = 20.5 Hz), 43.5, 41.4 (d, *J* = 5.4 Hz), 13.3, 9.8. ESI-MS: calculated for $[C_{16}H_{17}FN_5O_2]^+$ 330.1366, found 330.1371.

1-[(1-(3-fluorobenzyl)-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6c

Yield of 60 mg (20.2%), orange crystals, $T_{m.p.}$ = 156–157°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47 (s, 1H), 7.31–7.22 (m, 1H), 6.98 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.94 (s, 1H), 6.57 (broad.d, *J* = 7.7 Hz, 1H), 6.48 (broad.d, *J* = 9.2 Hz, 1H), 5.06 (s, 4H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 163.4 (d, *J* = 249.1 Hz), 146.4, 144.8, 139.9, 137.5 (d, *J* = 7.0 Hz), 131.2 (d, *J* = 8.4 Hz), 130.5, 126.7, 120.7 (d, *J* = 3.0 Hz), 119.8, 115.6 (d, *J* = 21.1 Hz), 112.3 (d, *J* = 22.7 Hz), 46.5 (d, *J* = 1.8 Hz), 43.6, 13.4, 9.7. ESI-MS: calculated for $[C_{16}H_{17}FN_5O_2]^+$ 330.1366, found 330.1362.

1-[(1-(3-chlorobenzyl)-5-methyl-1*H*-imidazol-2-yl)methyl]-2-methyl-4-nitro-1*H*-imidazole 6d

Yield of 80 mg (25.7%), orange crystals, $T_{m.p.}$ = 164–165°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47

(s, 1H), 7.24 (t, *J* = 6.1 Hz, 2H), 6.94 (s, 1H), 6.74 (broad.s, 1H), 6.68 (broad.d, *J* = 6.5 Hz, 1H), 5.04 (s, 4H), 2.32 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.4, 144.8, 139.9, 136.9, 135.7, 130.7, 130.5, 128.8, 126.7, 125.3, 123.3, 119.7, 46.4, 43.6, 13.4, 9.8. ESI-MS: calculated for $[C_{16}H_{17}ClN_5O_2]^+$ 346.1071, found 346.1066.

5-methyl-1-(4-methylbenzyl)-2-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1*H*-imidazole 6e

Yield of 90 mg (30.7%), orange crystals, $T_{m.p.}$ = 110–111°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.45 (s, 1H), 7.28 (s, 1H), 7.04 (broad.d, *J* = 7.6 Hz, 2H), 6.88 (s, 1H), 6.68 (broad.d, *J* = 7.7 Hz, 2H), 5.11 (s, 2H), 5.03 (s, 2H), 2.27 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 147.6, 140.1, 138.4, 137.4, 135.8, 132.2, 130.3, 129.9, 129.2, 126.6, 125.3, 119.6, 46.7, 44.2, 20.9, 9.7. ESI-MS: calculated for $[C_{16}H_{18}N_5O_2]^+$ 312.1461, found 312.1460.

1-(2-fluorobenzyl)-5-methyl-2-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1*H*-imidazole 6f

Yield of 80 mg (24.3%), orange crystals, $T_{m.p.}$ = 132–133°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.59 (s, 1H), 7.33 (s, 1H), 7.26–7.22 (m, 1H), 7.08–7.01 (m, 1H), 6.99–6.92 (m, 1H), 6.90 (s, 1H), 6.40 (t, *J* = 7.7 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 159.6 (d, *J* = 246.6 Hz), 147.9, 140.1, 135.7, 130.5, 130.3 (d, *J* = 8.1 Hz), 127.0, 126.8 (d, *J* = 3.3 Hz), 125.0 (d, *J* = 3.5 Hz), 122.3 (d, *J* = 14.1 Hz), 119.4, 115.9 (d, *J* = 20.7 Hz), 44.2, 41.3 (d, *J* = 5.1 Hz), 9.7. ESI-MS: calculated for $[C_{15}H_{15}FN_5O_2]^+$ 316.1210, found 316.1222.

1-[(1-(4-chlorobenzyl)-5-methyl-1*H*-imidazol-2-yl)methyl]-2-methyl-4-nitro-1*H*-imidazole 6g

Yield of 70 mg (22.5%), orange crystals, $T_{m.p.}$ = 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47 (s, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 6.92 (s, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 5.04 (s, 2H), 5.03 (s, 2H), 2.33 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.5, 144.9, 139.9, 134.6, 133.5, 130.4, 129.7, 126.8, 126.6, 119.8, 46.5, 43.7, 13.4, 9.7. ESI-MS: calculated for $[C_{16}H_{17}ClN_5O_2]^+$ 346.1071, found 346.1075.

General procedure for the synthesis of compounds 13a-j

5.0 mmol of the corresponding aniline **10** was dissolved in 25 mL of CH_2Cl_2. 5.5 mmol of triethylamine and 5.0 mmol of chloroacetyl chloride were added, and the reaction mixture was stirred at room temperature for 16 h. The triethylammonium chloride precipitate was filtered off and concentrated under vacuum to obtain 2-chloroacetamide **11**, which was further used without further purification.

Triethylamine (32.0 mmol) and morpholine (2.12 mmol) were successively added (dropwise) to a suspension of elemental sulfur (32.0 mmol) in dry DMF (40 mL), and the resulting mixture was stirred for 30 min. Then a solution of 1.0 mmol of 2-chloroacetamide **11** was added and the mixture was left to stir overnight. The mixture was poured into 100 mL of water, the resulting precipitate was filtered off and air dried. Then it was suspended in 100 mL of acetone and the insoluble residue of unreacted sulfur was filtered off and discarded. The filtrate was evaporated to dryness, and the dry residue of thiomorpholide **12** was dissolved in 30 mL of dry DMF, treated with 5 mL of hydrazine hydrate, and stirred for 12 h. The reaction mixture was poured into water, and the pH of the aqueous medium was adjusted to 5.0 with 2 M aqueous HCl. The resulting precipitate was filtered off, washed with water, air dried, and crystallized from ethanol to give analytically pure compounds **13** in the indicated yields.

2-hydrazino-*N*(1)-phenyl-2-thiooxacetamide 13a

Yield of 107 mg (55%), yellow crystals, $T_{m.p.}$ = 152–153°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.21 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 5H), 7.14 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.7, 158.4, 137.9, 129.3, 125.0, 120.5.

***N*(1)-(3,4-difluorophenyl)-2-hydrazino-2-thiooxacetamide 13b**

Yield of 175 mg (76%), yellow crystals, $T_{m.p.}$ = 164–165°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.41 (s, 1H), 7.91 (ddd, *J* = 13.0, 7.4, 2.4 Hz, 1H), 7.65–7.55 (m, 1H), 7.43 (dd, *J* = 19.5, 9.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.9, 149.5 (dd, *J* = 210.8, 12.9 Hz), 146.3 (dd, *J* = 210.4, 13.0 Hz), 135.1 (dd, *J* = 9.1, 3.0 Hz), 117.9 (d, *J* = 17.9 Hz), 117.43 (dd, *J* = 6.1, 3.4 Hz), 109.97 (d, *J* = 21.7 Hz).

2-hydrazino-*N*(1)-(4-methoxyphenyl)-2-thiooxacetamide 13c

Yield of 173 mg (77%), yellow crystals, $T_{m.p.}$ = 168–169°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.10 (s, 1H), 7.66 (t, *J* = 6.2 Hz, 2H), 6.92 (t, *J* = 6.1 Hz, 1H), 3.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.0, 156.6, 131.0, 122.2, 114.4, 55.7.

***N*(1)-(3-chlorophenyl)-2-hydrazino-2-thiooxacetamide 13d**

Yield of 146 mg (64%), yellow crystals, $T_{m.p.}$ = 162–163°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.38 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H),

7.73–7.68 (m, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.20 (dd, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.6, 159.0, 139.5, 133.5, 130.9, 124.7, 120.2, 119.2.

2-hydrazino-*N*(1)-(4-methylphenyl)-2-thiooxacetamide 13e

Yield of 115 mg (55%), yellow crystals, $T_{m.p.}$ = 155–156°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.13 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.7, 158.2, 135.4, 134.2, 129.7, 120.5, 21.0.

***N*(1)-(2,4-difluorophenyl)-2-hydrazino-2-thiooxacetamide 13f**

Yield of 164 mg (71%), yellow crystals, $T_{m.p.}$ = 174–175°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.19 (s, 1H), 7.91 (tt, J = 19.2, 9.6 Hz, 1H), 7.41 (ddd, J = 11.5, 9.0, 2.8 Hz, 1H), 7.28–7.04 (m, 1H), 7.19–7.08 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 165.81, 159.5 (dd, J = 244.7, 11.7 Hz), 157.9, 154.6 (dd, J = 248.4, 12.7 Hz), 125.0 (dd, J = 9.7, 2.3 Hz), 122.2 (dd, J = 11.5, 3.7 Hz), 111.9 (dd, J = 22.1, 3.7 Hz), 104.8 (dd, J = 27.1, 23.8 Hz).

***N*(1)-(2-fluorophenyl)-2-hydrazino-2-thiooxacetamide 13g**

Yield of 149 mg (70%), yellow crystals, $T_{m.p.}$ = 172–173°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.26 (s, 1H), 8.05 (ddd, J = 7.8, 5.6, 2.9 Hz, 1H), 7.40–7.29 (m, 1H), 7.28–7.19 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 165.7, 157.5, 154.0 (d, J = 244.9 Hz), 126.6 (d, J = 7.8 Hz), 125.5 (d, J = 10.9 Hz), 125.3 (d, J = 3.6 Hz), 122.8, 116.0 (d, J = 19.0 Hz).

2-hydrazino-*N*(1)-(2-methylphenyl)-2-thiooxacetamide 13h

Yield of 152 mg (73%), yellow crystals, $T_{m.p.}$ = 151–152°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.25 (dd, J = 13.5, 7.5 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 166.8, 157.4, 135.8, 130.9, 130.0, 126.9, 125.8, 122.1, 17.8.

***N*(1)-(4-fluorophenyl)-2-hydrazino-2-thiooxacetamide 13i**

Yield of 132 mg (62%), yellow crystals, $T_{m.p.}$ = 179–180°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.28 (s, 1H), 7.78 (ddd, J = 8.5, 5.2, 2.9 Hz, 1H), 7.23–7.16 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.9, 159.2 (d, J = 241.5 Hz), 158.5, 134.4 (d, J = 2.6 Hz), 122.7 (d, J = 8.0 Hz), 115.9 (d, J = 22.4 Hz).

2-hydrazino-*N*(1)-(3-methylphenyl)-2-thiooxacetamide 13j

Yield of 123 mg (59%), yellow crystals, $T_{m.p.}$ = 115–116°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.12 (s, 1H), 7.56 (s, 2H), 7.25 (dd, J = 11.4, 4.8 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.2, 138.6, 137.8, 129.2, 125.8, 120.9, 117.6, 21.6.

General procedure for the synthesis of compounds 7a–j

To 1.07 mmol of (4-nitro-1*H*-imidazol-1-yl) acetic acid **8b** and 25 mL of dry DMF was added 1.18 mmol of CDI and the mixture was left to stir at room temperature for 30 min. Then, 1.18 mmol of the corresponding compound **13** was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into 100 mL of water, the precipitation **14** that formed was filtered off and air dried. Without further purification, thiohydrazide **14** was boiled in 3 mL of glacial acetic acid with 12.8 mmol of succinic anhydride for 30 min, cooled, and poured into 25 mL of water. The resulting precipitation, predominantly consisting of compound **7**, was filtered off and air dried. The precipitation was purified by silica gel column chromatography (eluent, ethyl acetate). Fractions containing target product **7** were combined and exhausted.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-phenyl-1,3,4-thiadiazole-2-carboxamide 7a

Yield of 130 mg (36.7%), orange crystals, $T_{m.p.}$ = 182–183°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.16 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.8, 167.5, 155.9, 147.2, 137.9, 137.6, 128.8, 124.8, 121.9, 120.9, 45.4. ESI-MS: calculated for $[C_{13}H_{11}N_6O_3S]$+ 331.0613, found 331.0621.

***N*-(3,4-difluorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7b**

Yield of 180 mg (46%), orange crystals, $T_{m.p.}$ = 208–209°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.45 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 8.00–7.90 (m, 1H), 7.71–7.65 (m, 1H), 7.47 (q, J = 9.3 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.1, 167.0, 156.2, 148.8 (dd, J = 243.7, 13.2 Hz), 147.2, 146.2 (dd, J = 243.4, 12.6 Hz), 137.9, 134.6 (dd, J = 9.0, 3.1 Hz), 121.9, 117.6 (d, J = 18.0 Hz), 117.4 (dd, J = 6.3, 3.4 Hz), 110.0 (d, J = 21.7 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_9F_2N_6O_3S]^+$ 367.0425, found 367.0396.

***N*-(4-methoxyphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7c**:

Yield of 170 mg (44.1%), orange crystals, $T_{m.p.}$ = 204–205°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.09 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.96 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.7, 167.7, 156.3, 155.5, 147.2, 138.0, 130.6, 122.5, 122.0, 113.9, 55.3, 45.5. ESI-MS: calculated for $[C_{14}H_{13}N_6O_4S]^+$ 361.0719, found 361.0724.

***N*-(3-chlorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7d**

Yield of 110 mg (28.2%), orange crystals, $T_{m.p.}$ = 205–206°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.39 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 7.98 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.5, 167.5, 156.7, 147.6, 139.5, 138.4, 133.5, 131.0, 125.0, 122.4, 120.8, 119.7, 45.9. ESI-MS: calculated for $[C_{13}H_{10}ClN_6O_3S]^+$ 365.0224, found 365.0225.

***N*-(4-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7e**

Yield of 150 mg (40.7%), orange crystals, $T_{m.p.}$ = 215–216°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.07 (s, 1H), 8.55 (d, *J* = 1.2 Hz, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.96 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.6, 167.5, 155.7, 147.1, 137.8, 135.0, 133.9, 129.1, 121.8, 120.8, 45.4, 20.5. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0758.

***N*-(2,4-difluorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7f**

Yield of 190 mg (48.5%), orange crystals, $T_{m.p.}$ = 213–214°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.01 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.62–7.52 (m, 1H), 7.46–7.35 (m, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.1, 166.5, 160.5 (dd, *J* = 246.0, 11.7 Hz), 156.5, 156.4 (dd, *J* = 251.0, 13.0 Hz), 147.3, 138.1, 128.9 (dd, *J* = 9.9, 2.6 Hz), 122.1, 120.7 (dd, *J* = 12.7, 3.8 Hz), 111.7 (dd, *J* = 22.3, 3.6 Hz), 104.8 (dd, *J* = 26.8, 24.2 Hz), 45.5. ESI-MS: calculated for $[C_{13}H_9F_2N_6O_3S]^+$ 367.0425, found 367.0428.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-(2-fluorophenyl)-1,3,4-thiadiazole-2-carboxamide 7g

Yield of 170 mg (45.6%), orange crystals, $T_{m.p.}$ = 173–174°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.95 (s, 1H), 8.57 (d, *J* = 1.1 Hz, 1H), 8.08 (d, *J* = 1.1 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.36–7.31 (m, 2H), 7.27–7.21 (m, 1H), 5.98 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.0, 166.6, 156.2, 155.8 (d, *J* = 248.1 Hz), 147.2, 138.0, 128.1 (d, *J* = 7.8 Hz), 127.2, 124.5 (d, *J* = 3.5 Hz), 124.0 (d, *J* = 12.3 Hz), 122.0, 116.0 (d, *J* = 19.6 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_{10}FN_6O_3S]^+$ 349.0519, found 349.0520.

***N*-(2-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7h**

Yield of 200 mg (54.3%), orange crystals, $T_{m.p.}$ = 185–186°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.72 (s, 1H), 8.57 (d, *J* = 1.4 Hz, 1H), 8.08 (d, *J* = 1.4 Hz, 1H), 7.39–7.35 (m, 1H), 7.31–7.27 (m, 1H), 7.25–7.20 (m, 2H), 5.97 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.6, 167.1, 156.0, 147.2, 137.8, 134.7, 133.5, 130.4, 126.7, 126.3, 126.1, 121.8, 45.3, 17.6. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0764.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-(4-fluorophenyl)-1,3,4-thiadiazole-2-carboxamide 7i

Yield of 120 mg (32.2%), orange crystals, $T_{m.p.}$ = 228–229°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.24 (s, 1H), 8.55 (d, *J* = 1.1 Hz, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.88–7.82 (m, 2H), 7.22 (t, *J* = 8.9 Hz, 2H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.9, 167.393, 158.990 (d, *J* = 241.8 Hz), 155.9, 147.2, 137.9, 133.9 (d, *J* = 2.6 Hz), 122.8 (d, *J* = 8.0 Hz), 121.9, 115.4 (d, *J* = 22.4 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_{10}FN_6O_3S]^+$ 349.0519, found 349.0533.

***N*-(3-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7j**

Yield of 110 mg (29.8%), orange crystals, $T_{m.p.}$ = 200–201°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.05 (s, 1H), 8.55 (d, *J* = 1.0 Hz, 1H), 8.07 (d, *J* = 0.9 Hz, 1H), 7.67 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.96 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.8, 167.5, 155.9, 147.2, 138.1, 138.0, 137.5, 128.6, 125.5, 122.0, 121.4, 118.1, 45.4, 21.2. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0764.

CONCLUSIONS

In the course of the work, two novel series of heterocyclic compounds having a hybrid structure were obtained, including a preferred fragment of 4-nitroimidazole, which was connected by an alkyl linker with a second heterocycle, imidazole (**6**) or thiadiazole (**7**). The compounds designed as part of a search for anti-tuberculosis activity were synthesized and characterized by

physicochemical methods. Preliminary calculations using publicly available prognostic programs demonstrated the potential biological activity of target structures.

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Authors' contributions

T.S. Vedekhina – conducting experiments;

M.V. Chudinov – the research results analysis and presentation;

A.Yu. Lukin – creating a research concept.

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About the authors:

Tatiana S. Vedekhina, Cand. Sci. (Chem.), Senior Researcher, Laboratory of Structure and Functions of Biopolymers, Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency (1a, Malaya Pirogovskaya ul., Moscow, 119435, Russia). E-mail: taveda@gmail.com. ResearcherID AAZ-5822-2021, Scopus Author ID 57190025747, RSCI SPIN-code 9274-6340, https://orcid.org/0000-0001-7356-397X

Mikhail V. Chudinov, Cand. Sci. (Chem.), Associate Professor, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: chudinov@mirea.ru. ResearcherID L-5728-2016, Scopus Author ID 6602589900, RSCI SPIN-code 3920-8067, https://orcid.org/0000-0001-9735-9690

Alexey Yu. Lukin, Cand. Sci. (Chem.), Associate Professor, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: lukin@mirea.ru. ResearcherID P-1019-2016, Scopus Author ID 7102949868, RSCI SPIN-code 7264-1878

Об авторах:

Ведёхина Татьяна Сергеевна, к.х.н., старший научный сотрудник лаборатории структуры и функций биополимеров ФГБУ «Федеральный научно-клинический центр физико-химической медицины имени академика Ю.М. Лопухина Федерального медико-биологического агентства» (119435, Россия, Москва, ул. Малая Пироговская, д. 1а). E-mail: taveda@gmail.com. ResearcherID AAZ-5822-2021, Scopus Author ID 57190025747, SPIN-код РИНЦ 9274-6340, https://orcid.org/0000-0001-7356-397X

Чудинов Михаил Васильевич, к.х.н., доцент кафедры биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: chudinov@mirea.ru. ResearcherID L-5728-2016, Scopus Author ID 6602589900, SPIN-код РИНЦ 3920-8067, https://orcid.org/0000-0001-9735-9690

Лукин Алексей Юрьевич, к.х.н., доцент кафедры биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: lukin@mirea.ru. ResearcherID P-1019-2016, Scopus Author ID 7102949868, SPIN-код РИНЦ 7264-1878

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REVIEW ARTICLE

Technology and implementation of fermentative units for bioprotein production from natural gas

Vladimir M. Kochetkov✉, Ivan S. Gaganov, Vladimir V. Kochetkov, Pavel A. Nyunkov

GIPROBIOSINTEZ, Moscow, 123112 Russia
✉Corresponding author, e-mail: kwm@bk.ru

Abstract

Objectives. *To conduct a comparative analysis of the features of a fermentation unit design for obtaining bioprotein from natural gas and determine the main technical and structural solutions used in the development of fermentation apparatus, which vary according to the method of organizing hydraulic and mass transfer processes.*

Results. *An analysis of publications devoted to the problem of developing technological equipment for conducting the process of obtaining a bioprotein from natural gas is presented. Using the comparative analysis, the key features of bioreactors and their internal elements are indicated according to the method of organizing the hydrodynamic regime. The main approaches to the technological development of fermentation units for obtaining bioprotein from natural gas are described and technical solutions used in the implementation of these structures are identified.*

Conclusions. *Fermenter designs for the cultivation of methane-oxidizing microorganisms vary according to the main approaches for implementing the hydraulic regime inside the apparatus. While one class of fermentation systems is based on the principle of volumetric mixing in*

the working space of the apparatus, with the possibility of including external circulation circuits, additional tanks, and auxiliary bioreactors in the system, the other main class relies on the principle of flow (displacement) in the tube space with subsequent release of the gas phase from the circulating culture liquid.

Keywords: *bioreactor, fermenter, fermentation, biomass, protein, flowsheet, methanotrophs, Methylococcus capsulatus*

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ОБЗОРНАЯ СТАТЬЯ

Технологическое и аппаратурное оформление ферментационного узла процесса получения биопротеина из природного газа

В.М. Кочетков✉, И.С. Гаганов, В.В. Кочетков, П.А. Нюньков

ГИПРОБИОСИНТЕЗ, Москва, 119571 Россия
✉Автор для переписки, e-mail: kwm@bk.ru

Аннотация

Цели. *Провести сравнительный анализ особенностей аппаратурного оформления ферментационного узла процесса получения биопротеина из природного газа. Определить основные технические и конструкционные решения, применяемые при разработке ферментационных аппаратов, различающиеся по способу организации гидравлических и массообменных процессов.*

Результаты. *Проведен анализ литературы, посвященной проблеме разработки технологической аппаратуры для получения биопротеина из природного газа. С использованием метода сравнительного анализа были выявлены ключевые особенности конструкций биореакторов и их внутренних элементов, отличающихся способом организации гидродинамического режима в аппаратах. Описаны различные подходы к разработке оборудования для ферментационного узла процесса получения биопротеина, а также определены основные технические решения, используемые при создании данных конструкций.*

Выводы. *Установлено, что большинство конструкций ферментационных аппаратов, предназначенных для культивирования метанокисляющих микроорганизмов, базируется на реализации гидравлического режима внутри аппарата. Часть ферментационных систем построена на принципе объемного перемешивания в рабочем пространстве*

аппарата с возможным включением в систему внешних циркуляционных контуров, дополнительных емкостей и вспомогательных биореакторов, другая часть использует принцип движения потока (вытеснения) в трубном пространстве, с последующим выделением газовой фазы из рециркулирующей культуральной жидкости.

Ключевые слова: *биореактор, ферментер, ферментация, биомасса, белок, технологическая схема, метанокисляющие бактерии, Methylococcus capsulatus*

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INTRODUCTION

The rapid growth of the world's population poses the problem of providing humanity with the necessary food sources, in particular, protein, which contains essential amino acids. While the food market is currently dominated by proteins derived from plant and animal sources, a trend is developing towards the extraction of proteins from alternative sources. This group includes single cell proteins derived from unicellular bacteria or yeast organisms. For this purpose, bacterial cultures seem to be the most effective, since they grow faster and on a cheaper substrate [1]. As well as containing almost all essential amino acids, protein biomass derived from natural gas is richer in vitamins than that derived from vegetable sources (e.g., soy, oilcake, and meal) [2].

The use of meat and bone meal as animal-based sources of proteins involves certain restrictions linked to the source of its production. Periodic outbreaks of disease have led to bans on the use of animal meal in some countries around the world[1]. The use of fishmeal is complicated by the fact that the total volume of its production, currently at around 5 mln t/year, is significantly less than the demand, which is about 8–10 mln t/year. As a result, prices rise and the market is flooded with imitations and counterfeits [3].

Global trends in the use of feed ingredients are reflected in a significant increase in the demand for protein. According to 2019 data provided by *Global Market Insights*, annual global sales of protein supplements for livestock and aquaculture needs exceed USD 183 bn. A projected steady trend of sales growth implies that the figure will reach USD 220 bn by 2026. In Russia, the production of feed protein additives was projected to increase by 2.3 times, i.e., by 10.6 mln t for the period 2010–2019. The Russian market for protein is forecast to reach USD 4.7 bn by 2026[2].

The history of the development and evolution of microbial protein production processes in Russia demonstrates great successes in this field from the middle of the 20th century onwards. By 1980, there were 12 Soviet biochemical plants operating on the territory of the USSR, producing about 1 mln t of microbial protein. Some of the produce was supplied to the country's collective and state farms to meet the needs of the national economy, while the rest was exported[3].

The development of microbial protein production involved technologies for the production of paprin—feed yeast, whose production involves the use of paraffins as a raw material (substrate), and gaprin—a protein based on the cultivation of methane-oxidizing bacteria *Methylococcus capsulatus*.

[1] Food and Agriculture Organization of the United Nations. FAO/WHO Global Forum of Food Safety Regulators. BSE as a National and Trans-Boundary Food Safety Emergency. 28–30 January 2002. Marrakesh, Morocco. URL: https://www.fao.org/3/y2038r/y2038r.htm. Accessed October 11, 2022.

[2] Innopraktika. The animals will be fed with bacteria and bacteria will be fed with natural gas. Moscow, Russia. URL: https://innopraktika.ru/smi-o-nas/1583/ (in Russ.). Accessed September 22, 2022.

[3] Forum & Expo "ProteinTek". Food from Oil and Natural Gas. Moscow, Russia. URL: https://proteintek.org/novosti/1030/ (in Russ.). Accessed September 22, 2022

The main advantages of the gaprin production process are the non-pathogenicity of the main culture and the ability to grow cultures on methane-depleted gas, including associated gas. The use of the culture on an industrial scale using raw materials of a given quality was made possible by the selection of the initial strain found under natural conditions.

The question of the usefulness and applicability of microbial protein is currently under active consideration by specialized Russian research organizations, whose ultimate goal is to ensure the country's food security.

In accordance with the Priority 2030 program, an evaluation of the effect of gaprin on poultry productivity indicators is underway. The feasibility and economics of incorporating microbial proteins into industrial feed production technologies are also being evaluated. In terms of crude protein content, gaprin was shown to outperform fishmeal by 5% and equivalents grown from oil production wastes by 20–27.5% [4]. Compared to fishmeal, gaprin contains an order of magnitude more tryptophan (3.81 mg/kg vs. 0.6 mg/kg) and vitamin B_6 (35 mg/kg vs. 4.0 mg/kg), as well as containing vitamin B_{12} (up to 42 mg/kg).

The efficacy of gaprin as a feed additive has been reviewed in detail in [5]. The possibility of replacing fishmeal with gaprin in whitefish diets was investigated. Since gaprin does not reduce the growth rate of juveniles or cause deviations in physiological parameters, it can be used as an alternative to fishmeal.

When considering issues related to the use of bioproteins obtained from natural gas as feed additives, it is necessary to focus on the design of hardware and specific features associated with the technology used in their production process. The literature analysis presented below considers the main technical solutions used in the design of the reactor node involved in the process of obtaining bioprotein from natural gas along with the nodes of the technological chain connected to it.

MAIN TECHNICAL SOLUTIONS USED IN TECHNOLOGIES FOR OBTAINING MICROBIAL PROTEIN FROM NATURAL GAS

Technologies for obtaining microbial protein from natural gas can be generally represented by the group of technological blocks interconnected at various stages of production. Figure 1 shows the main stages of the process in the form of a flowchart.

The raw material preparation unit includes units for the preparation of working nutrient solutions, water treatment, and supply of oxygenated and methane-containing gases. The fermentation unit comprises a main reactor unit consisting of one or more fermenters designed for the cultivation of microbial proteins, which are supplemented by auxiliary capacitive and pumping equipment. The concentration unit may consist of several units for concentrating the biomass coming from the reactor unit, as well as the collection and transport of the spent culture fluid (SCF), comprising the light aqueous phase obtained following biomass concentration. The pre-condensed biomass is heat-treated in the inactivation unit. In addition to the drying and packaging unit of the finished products, an intermediate granulation stage may represent an additional block in the technological process.

In the context of the relationship of the reactor node with other nodes in the technological chain, the analysis of technologies for obtaining bioprotein from natural gas shows that one of the most often considered processes is the return of SCF from the separation unit directly into the bioreactor. This has a significant impact on the system of organizing the input of liquid flows into the fermenter, since the amount of fresh water injected into the bioreactor channel should be reduced by the amount of the incoming flow. In this case, it is important to determine the optimal entry points for the mineral nutrient components, which are supplied in the form of solutions that maintain the pH in the bioreactor and are returned directly to the reactor SCF.

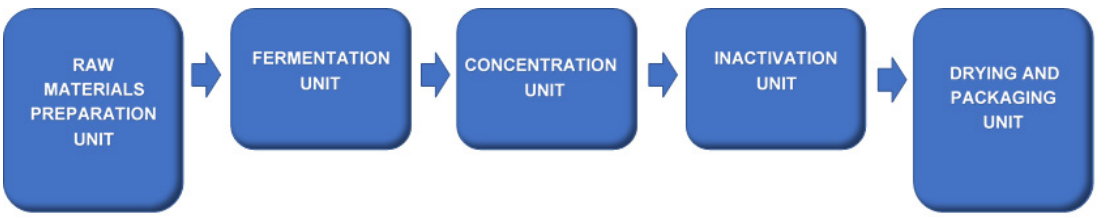

Fig. 1. Stages of the protein production process from natural gas.

Additional technological nodes may be introduced into the main production chain due to the specificity of the implementation of certain approaches to process optimization. The paper [6] describes the sequence of technological stages for obtaining microbial protein from natural gas. This comprises both the main technological units, such as fermentation, separation, inactivation, and drying, as well as auxiliary units—a system for extracting carbon dioxide from biomass entering the centrifuge (by reducing the pH), and an ultrafiltration system which can be used to obtain a more concentrated flow before its feeding to the drying unit. According to the data given in the source [7], fermenter biomass condensed in the centrifuges of the separation unit up to 80–90 g/L can be sequentially concentrated in an ultrafiltration unit up to a concentration of 220 g/L. Under ultrafiltration conditions, the amount of SCF returned to the bioreactor increases, having consequences for the system of organizing the input of flows into the fermenter.

The above-mentioned literature [6, 7] also mentions the need to ensure returns from the centrifugal separation system and, in particular, from the ultrafiltration system to the SCF digester. When considering the problem of reducing the water consumption of the fermentation system, the authors of [8] emphasize the possibility of returning the SCF after separation to the fermentation stage in a volume of up to 95% of the total amount of water supplied to the reactor.

The reciprocal relationship between the fermentation unit and the concentration unit involving the return of the SCF to the fermenter leads to the need for its purification, since the SCF sent to the apparatus comprises a certain quantity of organic compounds and accompanying microflora. The obvious solution to this problem is to introduce a culture liquid purification unit into the technological chain. One of the possible approaches discussed in [9] involves the following sequence: cooling the SCF obtained during separation to a predetermined temperature and feeding it to an additional aerobic fermentation, followed by returning the purified product to the main fermenter designed for the cultivation of biomass of methane-oxidizing bacteria.

The reactor unit, representing the key component in the technological chain of protein production from natural gas, involves hardware design and organization of the fermentation process. This determines the main parameters of the equipment for the further processing cycle of the synthesized bioprotein into a marketable product. In this context, specific features of the structural design of the bioreactors used in this technology will be further considered.

VARIATIONS IN THE STRUCTURAL DESIGN OF FERMENTATION EQUIPMENT FOR THE CULTIVATION OF METHANE-OXIDIZING BACTERIA

Despite the wide variety of bioreactor designs used in the microbiological industry, all the discussed fermentation devices are equipped with standard structural elements designed to provide optimal conditions for the biochemical process, as well as optimizing the underlying physical processes (hydrodynamic, thermal, and mass transfer) [10].

While the design of fermentation apparatus is based on standard structural solutions, it is necessary to take into account the specific characteristics of the cultivated organisms. When developing bioreactors for the cultivation of aerobic microorganisms, an important design criterion is the method of energy supply to the apparatus. Here, delivery options include gas-phase (barbotage and gas lifting devices), liquid-phase (ejection and jet devices), as well as combined energy delivery in both liquid- and gas phases (Fig. 2) [11].

The fermentation equipment used in the process of obtaining proteins from natural gas has a number of features that set it apart from other equipment used to grow aerobic microorganisms. The presence of an additional gas phase taking the form of natural gas injected into the digester leads to a significant increase in the total volume of gas distributed in the liquid phase. The input and distribution of natural gas by volume in the fermenter also affects the solubility of oxygen and carbon dioxide from the general gas phase of the apparatus.

In addition to the known standard design solutions, bioreactors are equipped with a large number of specific internal technical elements for the cultivation of methane-oxidizing bacteria. The structural elements of the fermenter perform local tasks related to the hydrodynamic component of the apparatus, such as eliminating water shocks during operation, reducing the amount of liquid carried away with the gas phase, as well as diverting and separating internal flows of the liquid phase or gas–liquid mixture.

Having identified the goal of developing a particular bioreactor design, it is important to consider the criteria that will be used to assess the effectiveness of its work. The most commonly used are the degree of oxygen conversion as a result of biochemical consumption and the volume coefficient of oxygen mass transfer. Methods for organizing the gas and liquid flows used in the various fermentation equipment designs have

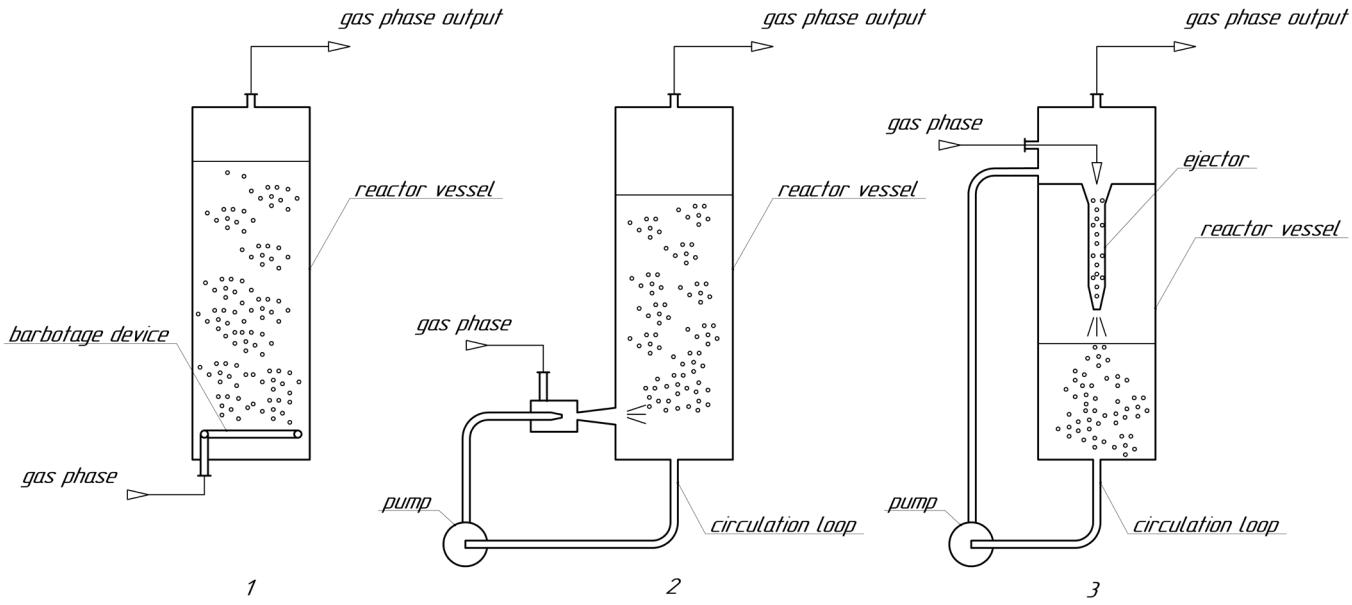

Fig. 2. Examples of bioreactors with different energy input methods:
(1) barbotage column apparatus (energy input with gas phase);
(2) ejection fermenter (energy input with liquid phase);
(3) jet fermenter (energy input with liquid phase).

a significant effect on the contact surface of the phases and, consequently, on the above parameters. The literature also describes effectiveness criteria based on the specific productivity of the process occurring in the apparatus, expressed as the amount of biomass produced per unit of reactor working volume, as well as the specific cost, expressed as the amount of energy expended per quantity of biomass produced.

The paper [12] presents the design of an apparatus based on the principle of separate supply of oxygen and natural gas to two separate fermenter sections connected by a circulating liquid phase. In the natural gas inlet section of the fermentation system, a gravitational ejector distributes the natural gas in the liquid phase towards the section where it is to be aerated. In the fermenter model presented, there are also basic technical solutions in the form of standard designs, such as barbotage and liquid phase circulation devices, which can be described in terms of a circulation pump. Additional sections in the apparatus are used to prevent gas saturation of the culture liquid by ensuring the removal of gaseous products of microorganisms from the reactor. While the authors failed to indicate criteria or parameters for evaluating the performance of this bioreactor, each described section comprises a separate local zone with different ways of organizing flows, implying separate mass exchange characteristics.

The main fermentation equipment presented in [13] is divided into sections to ensure a separate controlled process of dissolution of methane-containing and oxygen-containing gases. The combined technical solution uses mechanical mixing devices in auxiliary bioreactors, as well as a diffuser and a circulation pump, to create a predetermined distribution of flows in the volume of the main reaction zone of the column fermenter. For this design, which uses a mechanical mixing device for dissolving gas components, data on oxygen absorption reaching a value of 10 kg of $O_2/m^3 \cdot h$ with specific energy consumption of 0.3–0.4 kW·h/kg of O_2 are presented. Although the presented bioreactor design is claimed to provide a high mass transfer rate, it is important to note the technical complexity of this fermentation system, which has practical implications for its start-up and commissioning.

The principle of supplying of methane-containing and oxygen-containing gases to separate sections where they can be distributed in a liquid volume is presented in a bioreactor for growing methane-oxidizing microorganisms [14]. The sections in which the gases are dissolved are located on opposite sides of the body of the main part of the apparatus. Both sections, which are in the form of vessels that expand at the top, are equipped with turbine stirrers for dispersing a gas–liquid medium in each of them. After being fed into the central

circulation line of the bioreactor for mixing, a uniformly distributed gas–liquid mixture from each section is then discharged into the main volume of the apparatus. The circulation of the liquid phase in the apparatus and the relationship of the flows between the auxiliary sectors and the main volume of the fermenter are provided by pumping equipment installed on external circulation circuits. In terms of the method for organizing the process of dissolving methane-containing and oxygen-containing gases, the presented bioreactor model has similar features to the apparatus given in [13]. The developers of the fermenter state that the speed of the turbine agitators in the gas dissolving zones could reach 1400 rpm, which would certainly lead to technical difficulties in the operation of these zones, especially with increased bioreactor volumes as a result of scaling. While the authors indicate a productivity value of 4.4 kg of biomass/m^3·h with energy consumption for fermentation at 1.1 kW·h/kg of biomass, these data cannot be used to evaluate the mass transfer characteristics of the unit according to the above-mentioned criteria.

Considering the use of a gravitational ejector to ensure the mixing of gas and culture fluids in devices for cultivating methanotrophs, the fermentation devices presented in [15, 16] are worthy of note. The paper [15] presents a vertical apparatus equipped with an external circulation circuit, a gravitational ejector (jet aerator), a heat exchange device, and internal elements—a grate and a bump—for reorganizing the gas–liquid flow and separating the gas from the liquid. A special feature of the design is the presence of a liquid phase degasser installed on the inlet line to the flow inductor, which ensures the operation of the circulation circuit and the jet aerator. Rather than being removed from the system, the gas phase from the separator is sent to the overflow chamber of the aerator together with recirculated and fresh gases (oxygenated gas and methane). The operating principle of the vertical apparatus presented in [16] is based on the use of a jet aerator. The design features several circulation circuits operated by means of pumps and an internal jet aerator structure characterized by division into sections. The number of sections corresponds to the number of circulation circuits that provide sufficient energy to the gas–liquid jet leaving the jet aerator.

In bioreactors models involving various designs of jet aerators [10], average values of oxygen mass transfer coefficients in the range of 200–300 h^{-1} are achieved when ensuring the contact of the liquid and gas phases by means of jet aeration. However, the presence of a gas phase in the culture fluid entering the circulation circuits leads to additional pumping equipment requirements.

No additional capacitive sections are included in the fermentation apparatus model presented in [17]; instead, the main fermentation process takes place in a vertical volumetric apparatus. The gas phase is introduced into the fermenter in the lower part of the apparatus using ring bubblers. The liquid phase circulating through the pump is fed to a gas–liquid ejector. After entering the ejector from the upper part of the fermenter, the gas phase is mixed with the working liquid phase and introduced into the lower part of the apparatus. The use of a jet pressure liquid ejector on the external circulation circuit in the place of a gravity ejector entails significant adjustments to the requirements for the overall characteristics of the fermentation plant, in particular, the height of the bioreactor, which can be reduced in relation to its diameter. By introducing a gas–liquid mixture from the jet apparatus into the volume of culture liquid, the reaction volume of the bioreactor can be used as efficiently as in a design using a gravitational ejector. The authors of the publication indicate the concentration of absolute dry matter and reactor flow rate, from which it is possible to calculate the specific productivity of the process at 5 kg of biomass/m^3·h.

For further analysis of the group of fermenters based on jet pressure ejectors, we should also consider the designs given in [18, 19]. The described plants comprise fermentation systems consisting of three main units: a fermenter, a gas separator, and a storage tank. The units are equipped with liquid-phase recirculation circuits, which represent the working medium for the gas–liquid ejector, as well as remote heat exchangers. The gas separator device allows the circulation pump to run continuously without pressure loss due to the presence of bubble gas in the culture liquid produced in the fermenter. The basic differences between the systems described in [18] and [19] consist in the method for organizing the alignment of the flow rates of the gas–liquid mixture coming out of the main digester, as well as the degassed culture liquid entering the circulation pump from the gas separator and entering the ejector for mixing with the exhaust gas returned to the digester. In the prototype presented in [18], flow alignment is achieved by returning some of the culture fluid to the suction line of the recirculation pump. In the prototype presented in [19], the equilibrium in the fermenter–separator–pump–ejector–fermenter system is achieved by regulating the flow rates of the gas flows: fermenter–gas separator, gas separator–ejector, fermenter–ejector. The data presented in [18, 19] on the flow rate and concentration of absolute dry matter in the culture fluid can be

used to indicate the specific productivity of the process occurring in bioreactors of the proposed design in a range of 3.6–4.2 kg of biomass/m^3·h.

When considering structural solutions such as bioreactor zoning, pressure ejectors installed on remote recirculation circuits, and gravity ejectors built into the apparatus, a distinction should be made between fermentation equipment in which combined solutions are used. For example, in [20] the fermenter design comprises a vertical two-chamber apparatus in which communication between the chambers is achieved by several vertically oriented internal channels: a liquid phase flow line and a gas phase exchange system. The original technical solution of the design involves the use of two gravity ejectors together with pressure ejectors, each of which ensures the introduction of a gas–liquid mixture into its chamber. As mentioned above, jet irrigation cannot be used to achieve high mass transfer coefficients. However, the use of pressure ejectors makes a significant contribution to improving the mass transfer characteristics of the device. The authors claim that the presented bioreactor is capable of reaching 7 kg of biomass/m^3·h at an energy consumption of 1.3 kW·h/kg of biomass.

In addition to the widely used vertical fermenters for the cultivation of methane-oxidizing organisms, special designs are developed using original technical solutions. In [21], a horizontal apparatus is presented with a partition dividing it into two reaction zones: a zone for feeding oxygenated and methane-containing gases into the volume, followed by their dissolution, and a zone in which the liquid working phase circulates by means of specially shaped blades fixed to the rotor. By combining the types of blades installed on the structure, various technological tasks can be performed, for example, aeration of the circulating liquid and distribution of the gas phase in its volume. The proposed bioreactor differs significantly from other multi-section vertical devices designed for the cultivation of methane-oxidizing bacteria. The high specific energy consumption for fermentation here amounts to 2.1 kW·h/kg of biomass at a productivity of 4.2 kg of biomass/m^3·h.

A device for the cultivation of *Methylococcus capsulatus* methane-oxidizing microorganisms on the principle of energy supply with a gas phase is presented in [22]. The main body of the apparatus comprises a turbine agitator mounted on a shaft attached to a turbine driven by a jet of compressed air. The compressed air used to drive the turbine and ensure the operation of the mixer is then distributed throughout the volume of the fermenter to stimulate the cultivation process. The main advantage of this design is the use of compressed gas energy to drive the mechanical part of the bioreactor. However, due to the limited speed of the mixer, the oxygen uptake is below the typical range of 5–20 kg/m^3·h for mixers with a stirrer [10]. Accordingly, this design can be considered as an intermediate bioreactor for growing micro-organisms with an absolute dry matter concentration of no more than 4–5 g/L.

In some types of fermentation equipment for the cultivation of methane-oxidizing microorganisms, combined internal structural elements are used for ensuring multidirectional internal flows of a circulating gas–liquid mixture. An apparatus described in [23] comprises a vertical two-section fermenter with bubblers installed in each section for the introduction of natural and oxygenated gas, as well as nozzles located in the partitions at the entrance to each section. The nozzles are arranged in such a way that the gas–liquid mixture emerging from them in the upper part of the apparatus (from one section to another) enters internal tubular structural elements installed along the axis of the apparatus opposite each nozzle. By using special deflectors in each section of the fermenter, the gas–liquid mixture circulates in the space between the internal tubular structural elements and the wall of the apparatus to increase the useful working volume. In order to achieve uniform flow distribution in the working volume of this bioreactor design, it is necessary to ensure the exit velocity of the gas–liquid mixture from the nozzle in the range of 0.5–20 m/s. Here, a wide range of high-speed exit modes from the nozzle is assumed taking into account the cultivation process in different modes. The paper claims a specific productivity of 4.5 kg of biomass/m^3·h, but without providing information on energy consumption.

An additional group of devices for obtaining biomass from natural gas is represented by loop bioreactors or so-called U-shaped fermenters (Fig. 3).

A number of foreign publications have addressed the issue of optimizing mass transfer processes in this type of equipment to increase productivity. In particular, the paper [24] discusses development approaches related to the use of a multiphase model of a tubular bioreactor with forced mixing for assessing the degree of influence of mixing conditions and interphase mass transfer on the overall performance of closed-loop fermenters. Once a volumetric oxygen mass transfer coefficient of 360 h^{-1} is reached, the productivity of the process in a loop reactor is shown to be practically independent of the mass transfer characteristics of the apparatus. The paper [25] is devoted to an experimental study of the issues of energy consumption and increasing the efficiency of mixing

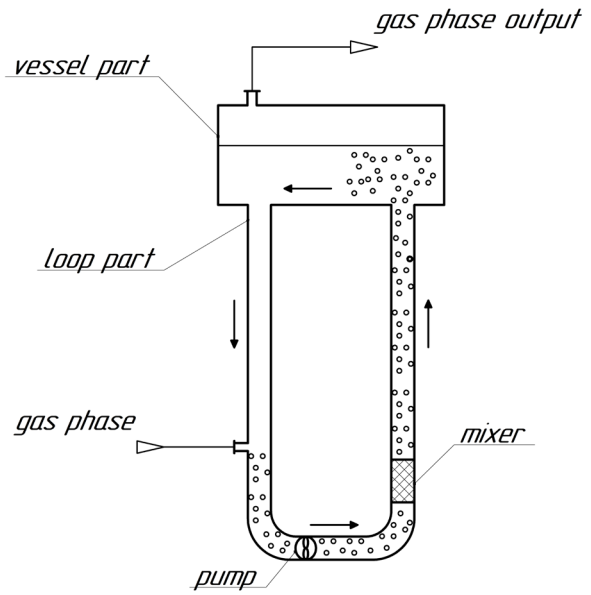

Fig. 3. Loop bioreactor.

in loop-type apparatuses. The increase in mixing efficiency is considered not only from the point of view of the static component of the bioreactor (mixer design), but also its dynamic component (pumping equipment). The cited literature sources illustrate the variety of approaches leading to the emergence of new and improved fermentation apparatus designs.

The design of the loop bioreactor in [26] is represented by two vertical piping sections for the ascending and descending flows of culture fluid, an axial circulation pump installed in one of the piping sections, and the upper cylindrical part of the apparatus where the gaseous phase is separated from the culture fluid. Gas flows into the unit are fed directly into the loop section of the system. Static mixers for ensuring uniform distribution of the gas in the culture liquid are located on the vertical sections of the loop part of the bioreactor.

The bioreactor design presented in [27] is considered according to the operating principle and design solutions used in loop fermenters. The apparatus is described in terms of an upper separation part, represented in the form of a horizontal cylindrical container, as well as two vertical pipelines for the circulation of a culture gas-saturated liquid and a horizontal pipeline section in the lower part of the bioreactor. The vertical sections of the pipeline are used to ensure the circulation of liquid and the supply of gases to the apparatus, as well as involving static mixers and additional means to control the pressure in the zones of the apparatus. By using special equipment, such as a pressure control valve, a nozzle or an axial pump placed in the loops of the bioreactor, pressure drops can be created in different parts of the apparatus to increase or decrease the solubility of gases circulating with the liquid.

Despite the variety of loop bioreactor technical designs involving the combined use of special internal structural elements located both in pipelines and in the gas separation zone, there are also descriptions of external geometric parameters [28]. In the presented design, this principle is articulated by the combined use of vertical and horizontal sections of the apparatus loop in which the gas–liquid mixture circulates, while the main part of the bioreactor loop occupies the horizontal plane.

The literature on loop design bioreactors includes a limited number of publications that address the issue of apparatus efficiency in terms of mass transfer. In [25], the presented values of the volumetric oxygen mass transfer coefficients of 400–3000 h^{-1} obtained in a loop reactor consider the optimal velocities of the gas phase and the correct choice of its entry points into the apparatus. In [26–28], the main problems associated with U-shaped (U-loop) fermenters include ensuring the specified pressure drops at various points of the bioreactor, as well as the timely supply of the transported culture liquid with a gas substrate and the removal of the gas phase containing carbon dioxide.

The loop bioreactor design presented in the patent [29] is characterized by a large number of static mixers located in the horizontal part of the loop and a vertical gas separator tank in which the hydraulic pressure of the liquid column is provided at the suction line of the circulation device. For this model, options for implementing pressure reduction zones at the inlet from the loop to the gas separator tank using equipment and special structural elements installed in the loop portion of the bioreactor are considered. Here, a given parametric control can be implemented for one or more consecutive steps.

One of the factors influencing the approach to the development of fermentation apparatus designs for the cultivation of methane-oxidizing bacteria is the problem of maintaining the concentration of dissolved carbon dioxide in the reaction volume of the fermenter. The fermenter design and technological installation described in [30] are aimed at maintaining the dissolved carbon dioxide content at a sufficient level to ensure high productivity. The bioreactor is made up of vertical sections for ensuring ascending and descending flows between two horizontal capacitive devices in which the culture fluid is to be degassed. Some of the technical solutions of the bioreactor are implemented using standard approaches to internal and external structural

elements: circulation in a closed circuit provided by a pump, gases entering the fermenter through bubblers, and uniform mixing of the culture liquid using static mixers. The most significant aspect of the design is the technical solution for transferring the gas from the degassing tanks to the carbon dioxide absorber. The purified waste gas is returned to the fermenter by means of a compression device for optimizing the cultivation process. As well as indicating the value of the achieved specific productivity of the process (5 kg of biomass/m^3·h), the authors give an example of a specific implementation of a laboratory fermentation system.

CONCLUSIONS

The presented literature analysis shows that all the considered designs of fermentation apparatuses intended for the cultivation of methane-oxidizing microorganisms are based on the basic approaches to the implementation of the hydraulic regime inside the apparatus. Here, one major class of fermentation systems is based on the principle of volumetric mixing in the working space of the apparatus, with the possibility of incorporating external circulation circuits, additional tanks, and auxiliary bioreactors into the system. The other class uses the principle of flow movement (displacement) in the tube space followed by release of the gas phase from the recirculating culture fluid. Internally, the most commonly used structural elements are static mixers placed in pipelines on the flow line of the culture liquid, bubblers that ensure the entry of oxygenated and methanated gases into the bioreactor, as well as nozzle devices and ejectors embedded in the main volume or placed in gravity and pressure circuits for ensuring the maximum degree of mixing of gas and liquid parts in the apparatus.

Authors' contributions

V.M. Kochetkov – concept of the research, writing and scientific editing the paper, drawing conclusions;

I.S. Gaganov – literature analysis on fermentation equipment designs, comparative analysis, and bibliography design;

V.V. Kochetkov – literature analysis on the technology for obtaining bioprotein from natural gas, technical editing the paper, and preparing illustrative materials;

P.A. Nyunkov – systematization of cited literature, critical analysis.

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About the authors:

Vladimir M. Kochetkov, Head of the Technological Department, GIPROBIOSINTEZ (10, Testovskaya ul., Moscow, 123112, Russia). E-mail: kwm@bk.ru. https://orcid.org/0000-0003-1194-9732

Ivan S. Gaganov, Leading Engineer-Technologist, GIPROBIOSINTEZ (10, Testovskaya ul., Moscow, 123112, Russia). E-mail: ivan.gaganov@yandex.ru. Scopus Author ID 57224575918, https://orcid.org/0000-0003-4837-2332

Vladimir V. Kochetkov, Technician-Technologist, GIPROBIOSINTEZ (10, Testovskaya ul., Moscow, 123112, Russia). E-mail: vvkochetkov@bk.ru. https://orcid.org/0000-0002-1570-5893

Pavel A. Nyunkov, General Manager, GIPROBIOSINTEZ (10, Testovskaya ul., Moscow, 123112, Russia). E-mail: nyunkov.p@gibios.ru. https://orcid.org/0000-0002-1232-7460

Об авторах:

Кочетков Владимир Михайлович, начальник технологического отдела, ООО «ГИПРОБИОСИНТЕЗ» (123112, Россия, Москва, ул. Тестовская, д. 10). E-mail: kwm@bk.ru. https://orcid.org/0000-0003-1194-9732

Гаганов Иван Сергеевич, ведущий инженер-технолог, ООО «ГИПРОБИОСИНТЕЗ» (123112, Россия, Москва, ул. Тестовская, д. 10). E-mail: ivan.gaganov@yandex.ru. Scopus Author ID 57224575918, https://orcid.org/0000-0003-4837-2332

Кочетков Владимир Владимирович, техник-технолог, ООО «ГИПРОБИОСИНТЕЗ» (123112, Россия, Москва, ул. Тестовская, д. 10). E-mail: vvkochetkov@bk.ru. https://orcid.org/0000-0002-1570-5893

Нюньков Павел Андреевич, генеральный директор ООО «ГИПРОБИОСИНТЕЗ» (123112, Россия, Москва, ул. Тестовская, д. 10). E-mail: nyunkov.p@gibios.ru. https://orcid.org/0000-0002-1232-7460

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SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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RESEARCH ARTICLE

Modification of accelerated thermal stabilization of polyacrylonitrile fibers by creating an oxygen concentration gradient in the production of carbon fiber

Evgeny A. Trofimenko✉, Tatyana V. Bukharkina, Svetlana V. Verzhichinskaya

Mendeleev University of Chemical Technology of Russia, Moscow, 125047 Russia
✉Corresponding author, e-mail: e.trofimencko2016@yandex.ru

Abstract

Objectives. *The work set out to modify the technology of accelerated thermal stabilization of polyacrylonitrile (PAN) fibers used in the production of high-strength carbon fibers by reducing the formation of a heterophase core–shell structure to create an oxygen concentration gradient in heat treatment furnaces while maintaining a total thermal stabilization time of 30 min. The optimized process conditions led to milder thermal stabilization conditions, reducing both the final heat treatment temperature and the temperature difference between the thermal stabilization zones while simultaneously maintaining the target volume density parameter with respect to the previously developed accelerated thermal stabilization technology.*

Methods. *The thermal stabilization study of an industrially produced 12S precursor under different conditions on an experimental carbon fiber production line included measurement of bulk density, analysis of the thermal effects of the oxidation reaction by differential scanning calorimetry (DSC), and a study of micrographs of the resulting samples.*

Results. *The optimum process of thermal stabilization of PAN fiber was determined in four stabilization zones using selected compositions. The formation of the core–shell structure is significantly reduced when the target volume density and DSC thermal oxidation reaction effect of the stabilized polymer fiber are achieved in a given time (30 min).*

Conclusions. *The resulting technology regime is promising for the production of high strength (4.5 GPa, 4.9 GPa) PAN fibers at a reduced cost. While maintaining the total thermal stabilization time of PAN at the level of 30 min, which is three times less than the industrial processes used, it was possible to reduce the formation of a heterophase structure, as well as lowering the final processing temperature and reducing the temperature difference between the stabilization zones. This is promising in terms of a positive effect on the stability and safety of the industrial process, as well as ensuring the quality of the obtained products.*

Keywords: *composites, polyacrylonitrile, carbon fibers, stabilization, carbonation*

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НАУЧНАЯ СТАТЬЯ

Модификация ускоренной термостабилизации полиакрилонитрильных волокон созданием градиента концентрации кислорода при получении углеродного волокна

Е.А. Трофименко✉, Т.В. Бухаркина, С.В. Вержичинская

Российский химико-технологический университет им. Д.И. Менделеева, Москва, 125047 Россия

✉*Автор для переписки, e-mail: e.trofimencko2016@yandex.ru*

Аннотация

Цели. *Модифицировать технологию ускоренной термостабилизации полиакрилонитрильного (ПАН) волокна при производстве высокопрочных углеродных волокон, при помощи которой удастся уменьшить образование гетерофазной структуры «ядро–оболочка» путем создания градиента концентрации кислорода в печах термообработки при сохранении общего времени термостабилизации ПАН (30 мин); оптимизировать процесс на основании предлагаемого режима с целью получения более мягких условий термостабилизации: снижения конечной температуры термообработки и разницы температур между зонами термостабилизации при сохранении целевого параметра объемной плотности (относительно ранее разработанной технологии ускоренной термостабилизации).*

Методы. *Термостабилизация промышленно выпускаемого прекурсора марки 12S в различных условиях на опытной линии получения углеродных волокон, последующее измерение объемной плотности, анализ тепловых эффектов реакции окисления методом дифференциальной сканирующей калориметрии (ДСК) и изучение микрофотографий шлифов получаемых образцов.*

Результаты. *Определен оптимальный процесс термостабилизации ПАН волокна в 4 зонах стабилизации с использованием подобранных составов, при котором существенно снижается образование структуры «ядро–оболочка» при достижении целевой обемной плотности и теплового эффекта реакции окисления ДСК стабилизируемого полимерного волокна за установленное время (30 мин).*
Выводы. *Полученный технологический режим является перспективным для получения высокопрочных (4.5 ГПа, 4.9 ГПа) ПАН волокон со сниженной себестоимостью. При сохранении общего времени термостабилизации ПАН на уровне 30 мин, что в 3 раза меньше используемых промышленных процессов, удалось снизить образование гетерофазной структуры, уменьшить конечную температуру обработки и снизить перепад температур между зонами стабилизации, что должно положительно сказаться на стабильности и безопасности ведения промышленного процесса и качестве получаемой продукции.*

Ключевые слова: *композиты, полиакрилонитрил, углеродные волокна, стабилизация, карбонизация*

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INTRODUCTION

The development of technologies for reducing the cost of carbon fiber (CF) production is one of the most significant directions in the industry today. Rather than aiming at the production of ultrahigh-strength products (4.5 GPa or more), such technologies are geared to the satisfaction of mass market demand. With a significant reduction in cost, fibers with a strength of 4.0–4.2 GPa will be in greater demand in the automotive, sports equipment, construction, shipbuilding, and wind energy industries, helping to stimulate the development of new design solutions in these industries and increasing the introduction of carbon composites into everyday life.

The total cost of producing a kilogram of CF is made up of many factors. These include the price of precursors (acrylonitrile, methyl acrylate, itaconic acid, etc.), the price of solvents for the commonly-used wet molding method (zinc chloride, dimethylacetamide, sodium thiocyanate, etc.), the price of auxiliary chemicals (oiling agents, antistatic agents, and dressing compositions), depreciation costs for expensive equipment, and electricity, large quantities of which are used in the main (synthesis, molding, and heat treatment) and auxiliary technological processes (solvent regeneration).

In connection with the above factors, work is underway to improve the efficiency of associated processes and thus reduce costs. The present work considers the heat treatment of polyacrylonitrile (PAN) to obtain desired hydrocarbon products. In our previously published works, proposals for modifying traditional CF production technology in order to reduce the time of thermal stabilization of the fiber prior to carbonization were presented and substantiated [1–3]. By pre-stabilizing the PAN fiber in nitrogen, followed by oxidation of the pre-stabilized fibers, the process time was reduced to 30 min without any loss of product quality. A comparison of the proposed system with classic industrial technology based on the oxidation process alone shows a three-fold reduction in thermal stabilization time. At the same time, the strength of the fibers obtained is in the order of 4.3 GPa, while the modulus of elasticity is around 240 GPa. Using the nominal value of 12K (12000 monofilaments), it was possible to maintain the standard linear

density of 785 tex (g/km) for this type of fiber, which is an extremely important indicator in industrial production [1,2,3,4].

An industrial line developed on the basis of the described technology offers a 2.5–3 times increase in the speed of fiber passage as compared to current industrial processes. A corresponding 40% reduction in the cost of CF production would represent a serious incentive for the development of the composites industry.

However, despite sufficient results in terms of mechanical tests and cost-benefit assessment, the technology proposed by the present authors in [1–3] involves a number of drawbacks:

– a high (up to 20°C) temperature difference between the furnace zones, representing a source of production concern, since such a temperature jump can lead to uncontrolled local overheating of the fiber due to exothermic reactions on its surface. This effect can lead to fiber breakage in an industrial furnace, increasing scrap yields and downtime on the refueling line;

– the formation of a heterophase core–shell structure, resulting in reduced physical and mechanical properties of the fiber at the heat treatment stage.

Thus, the present work continues the development of accelerated thermal stabilization processes in an attempt to eliminate these two serious shortcomings in the presented CF production technology.

Experience with accelerated oxidation has shown that PAN fibers become extremely reactive after being pre-stabilized in nitrogen, leading to very rapid reactions with atmospheric oxygen when entering the oxidation furnace. On the one hand, such high reactivity can be useful when intensifying the process, including a reduction in total stabilization time and the number of required furnaces to four (the standard scheme of heat treatment in air includes 6–8 oxidation furnaces [4–6]). On the other hand, such rapid reactions—even those occurring at relatively low temperatures—lead to the formation of a shell of more stabilized PAN on the surface of the monofilament, which is poorly permeable to the gases (particularly oxygen) used for the thermal stabilization reactions in the formed core. Due to the appearance of such a shell, it becomes necessary to significantly increase the temperature in the subsequent zones in order to bring the final volume density of the stabilized fiber to 1.36 g/cm^3 (the minimum density value sufficient for safe carbonization of the fiber) [7, 8]. As a result, two distinct phases are distinguished depending on the radius of the monofilament: core and sheath. A less dense core lacks stability and may partially degrade during carbonization, leading to a reduction in the physical and mechanical properties of the final CF.

Despite previous work aimed at identifying heat treatment modes for minimizing this negative effect, it was not possible to eliminate it completely [2]: a significant increase in the temperature difference between the zones continues to be necessary for maintaining the core–shell effect.

To reduce this effect along with the temperature difference between the zones to at least 10°C, a series of experiments with a gradient of oxygen concentration between the zones was proposed (hereafter referred to as the "Gradient experiment"). The essence of these experiments was to reduce the formation of a gas-tight shell on the surface of the filament in the early stages of oxidation by reducing its rate without increasing the temperature gradient. Taking into account studies [9–11], the use of stabilization in nitrogen (or in a rarefied atmosphere) increases the yield of carbon fibers, which also improves the productivity of CF production lines and associated economic factors. Therefore, the first stage of oxidation following prestabilization in nitrogen was carried out in an oxygen-depleted environment. Here, it was assumed that the reduced oxygen concentration would intensify the formation of a heterophase structure, which would slightly increase its diffusion towards the center of the monofilament to improve the volume density set.

In the first stages of the study, the thermal stabilization parameters—in particular, the temperature and oxygen concentration in the specified heat treatment zone—were determined. The oxidation conditions in the subsequent zones were selected on the basis of the fiber properties.

MATERIALS AND METHODS

The methods used to develop and study the samples are described in the article [2]. All work and experiments were carried out at the *YUMATEKS* research center, which is part of the

[1] https://www.torayca.com/en/download/. Accessed August 10, 2022.

[2] https://umatex.com/production/fiber/. Accessed August 10, 2022.

[3] https://www.dowaksa.com/aksaca/. Accessed August 10, 2022.

[4] https://www.teijincarbon.com/ru/produkcija/uglerodnye-volokna-tenaxr/zhguty-tenaxr/. Accessed August 10, 2022.

New Materials and Technologies division of the *Rosatom* company group (Russia). The research center is equipped with an experimental line for the CF production, comprising a set of 6 three-pass oxidation furnaces, a low temperature carbonization (LTC) furnace, a high temperature carbonization (HTC) furnace, a surface treatment module, as well as receiving equipment. In addition, the line is equipped with the necessary ancillary equipment, starting with a nitrogen station for operations involving high purity nitrogen (>99.9999%). The exothermic effect of the oxidation reaction of PAN samples stabilized to different densities was determined using a DSC214 differential scanning calorimeter (*Netzsch*, Germany). An RR/DGA gradient column (*Ray-Ran Test Equipment*, United Kingdom) was used to determine the changes in bulk density of the material as a function of heat treatment conditions. A Tegramin-20 grinding system (*Struers*, France) and Olympus BX-51 microscope with U-TV0.63XC camera (*Olympus*, Japan) were used for the comparative evaluation of the formation of heterophase core–shell structures in samples developed by classical accelerated oxidation for the development of the stages of the experimental gradient mode.

As in previous experiments, the industrially produced PAN precursor Jilin 12k was used as the base precursor. Until recently, this was the fiber used at *ALABUGA-Volokno*, the largest enterprise in Russia for CF production. Based on the characteristics and parameters of this PAN, it is possible to obtain industrial quantities of hydrocarbons having a strength of 4.5 GPa, a modulus of elasticity of 250 GPa, and a linear density of 800 ± 20 tex, representing a considerable CF market niche.

The PAN harness was pre-stabilized in a high purity nitrogen medium using an LTC furnace. The experimental line for the CF production transport system was used to create continuous fiber movement through a nitrogen-blown carbonation furnace. At the same time, the operation of the transport system was organized in such a way as to ensure that the fiber remained in the working chamber of the furnace for 10 min at a temperature of 255°C. This unchanged parameter was accepted as optimal according to the results of previous studies [1, 2]. After winding the pre-stabilized fiber onto the spool using an automatic take-up device, it was mounted onto the feed spool for unwinding the fiber and passing it through the heat stabilization zones.

To function as a reduced oxygen thermal stabilization chamber, one of the oxidation furnaces was selected. Since there was no requirement for connecting gases other than atmospheric air during the design and construction of these furnaces, a new connection was made via a fitting inserted into the atmospheric air inlet pipe below the level of the adjustable valve. Pipes were then laid from the nitrogen station to the oxidation furnaces to supply the system with inert gas. At the nitrogen station itself, the gas supply system was split between the LTC and HTC furnaces, as well as, separately, to the oxidation furnace. A regulator installed between the nitrogen station's gasifier and the pipes leading to the oxidation furnaces was used to maintain the nitrogen supply pressure at 3 atm. In order to ensure the required level of purity, a 150 L/min capacity rotameter was used to regulate the flow of supplied nitrogen; this was installed at the end of the system before the nitrogen is supplied to the oxidation furnace No. 1 (OF1). Immediately prior to commencing the process, the ambient air inlet valve was closed and the nitrogen consumption was increased at the rotameter. The nitrogen concentration in OF1 was monitored using an external oxygen analyzer SGM7T (*Zirox*, Germany), whose inlet tube was placed in the working area of the furnace. By changing the nitrogen consumption at the rotameter, the composition of the medium can be controlled by the gas analyzer to achieve the required oxygen content in the working atmosphere.

Similar changes only affected OF1. The remaining zones of thermal stabilization (oxidation furnaces OF2 and OF3) operated in normal mode without additional supply of inert gas.

The transport system provided the same fiber dwell time (6.6 min) in each of the three OF1–OF3 zones. The total residence time of the fiber in the heat treatment zone, taking into account the time of pre-stabilization in nitrogen and subsequent treatment in oxidation furnaces, was ~30 min.

The samples were produced at different temperatures in OF1–OF3 and different (5.5 and 11%) oxygen concentrations in OF1.

The samples obtained from the Gradient experiment were analyzed on the DSC214 and compared with differential scanning calorimetry (DSC) data obtained in accelerated oxidation mode. The bulk density of the samples and the appearance of the monofilament were analyzed under a microscope at different processing stages.

RESULTS AND DISCUSSION

Since the density of the nitrogen pre-stabilized fiber was 1.225 g/cm^3, in order to achieve a bulk density ≥1.36 g/cm^3, it becomes necessary to

increase the fiber density in each of the three following zones by at least 0.045 g/cm^3.

The installed OF1 nitrogen supply system created a working atmosphere with an oxygen content of 5.37–5.49%, which is close enough to the target. The temperature in the furnace was raised to 240°C. Based on the results of the density measurement following heat treatment in OF1, it was decided to change the temperature. The results of the selection of the working conditions of OF1 are presented in Table 1 along with the data on the measurement of the bulk density of the obtained samples and the thermal effects of the DSC reaction in air (ΔH_{ox}).

The characteristics of Samples 3 and 4, which were developed at temperatures of 250 and 260°C, respectively, are close to those of reference Sample 6 (Table 1).

Figure 1 shows the sections of the micrographs of the samples developed according to the modes shown in Table 1 modes (also included is the micrograph of the reference sample with standard accelerated oxidation).

From Figure 1, it can be seen that an oxygen concentration gradient in the OF1 and OF2 furnaces results in a significantly less pronounced core–shell structure along with comparable values of volume density and thermal oxidation effects as measured by DSC. While the presence of such a structure is not in itself a limiting factor in obtaining high quality fibers, it is associated with high filament surface reactivity, which prevents the diffusion of oxygen into the central part of the elementary fiber [12].

In the second stage of the experiment, the change in fiber parameters was analyzed at different processing temperatures in a working environment with an oxygen concentration of 11%. The results of the selection of conditions in OF1 are shown in Table 2.

It is worth noting that, at a concentration of 11% and increasing temperature, the change in ΔH_{ox} passes through the minimum point (Sample 2), after which it begins to increase. As confirmed by the developed heterophase structure of the samples shown in Fig. 2, this may be explained in terms of the extremely rapid formation of the core–shell structure at high temperatures and an increased oxygen content in the process atmosphere as compared to the previous series of experiments.

From the presented comparative data, it can be concluded that the use of an 11% oxygen regime in OF1 is less promising since it does not prevent the formation of a heterophase structure. A further selection of modes was made at an oxygen concentration of 5.5%. The volume density of stabilized PAN closest to the target was obtained at a temperature of 260°C. This temperature in OF1 was used for future process development.

The process conditions in OF2 and OF3 were selected sequentially. The results of the calculation of OF2 working conditions are presented in Table 3.

The closest properties to the required bulk density were found at a temperature of 260°C. The ensuing fiber was highly manufacturable, without damaged filaments or damaged harness areas. To test the heat treatment conditions

Table 1. Results of the heat treatment mode selection in OF1 at an oxygen concentration of ~5.5%

Number of sample	Temperature T_{OF1}, °C	Density ρ, g/cm^3	ΔH_{ox}, J/g
1	240	1.2445	1282
2	245	1.2456	1266
3	250	1.2581	1110
4	260	1.2676	1096
5	270	1.2786	1069
6*	240	1.2580	1016

*This sample is a sample for comparison. Its properties are typical of the fiber after the first oxidation zone according to the accelerated oxidation mode presented in [2]—standard accelerated oxidation.

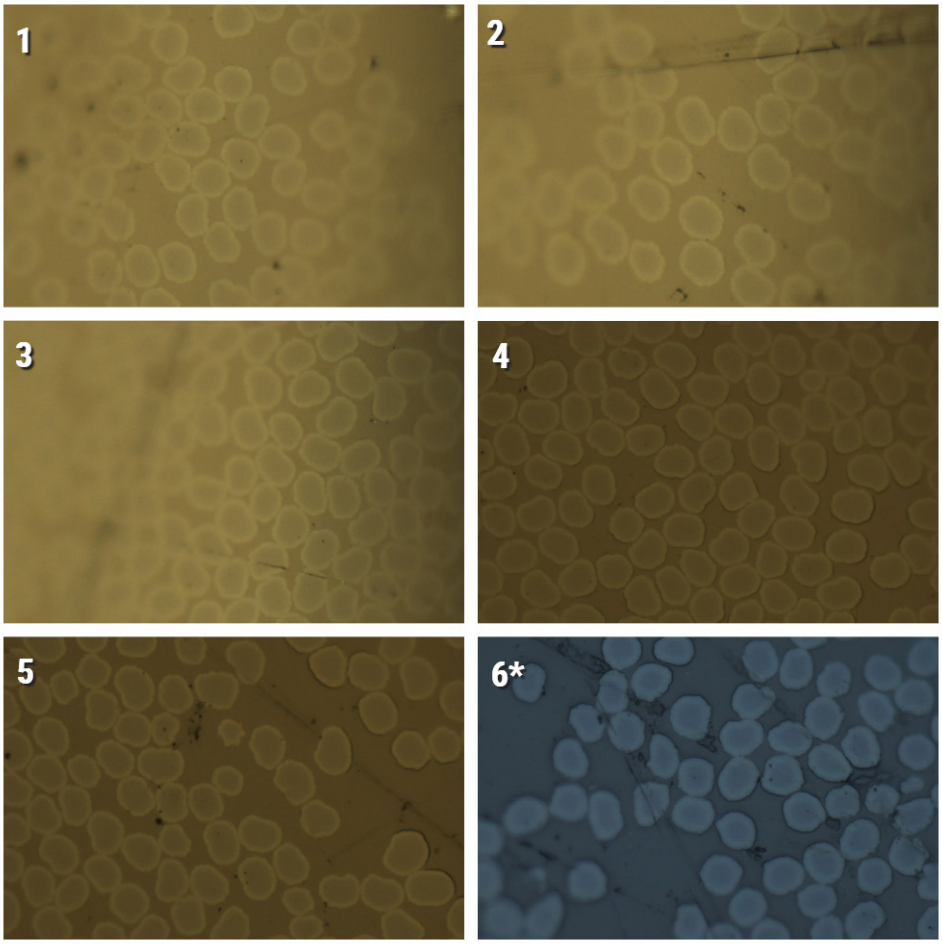

Fig. 1. Photomicrographs of fiber samples stabilized at different temperatures in an oxygen concentration of 5.5% in OF1: 1 – 240°C, 2 – 245°C, 3 – 250°C, 4 – 260°C, 5 – 270°C, and 6* – comparison sample.

Table 2. Results of the heat treatment mode selection in OF1 at an oxygen concentration of ~11%

Number of sample	Temperature T_{OF1}, °C	Density ρ, g/cm^3	ΔH_{ox}, J/g
1	240	1.249	1081
2	245	1.260	929
3	250	1.267	950
4	255	1.273	1060
5	260	1.283	1141
6	270	1.301	1297
7*	240	1.258	1016

*This sample is a sample for comparison.

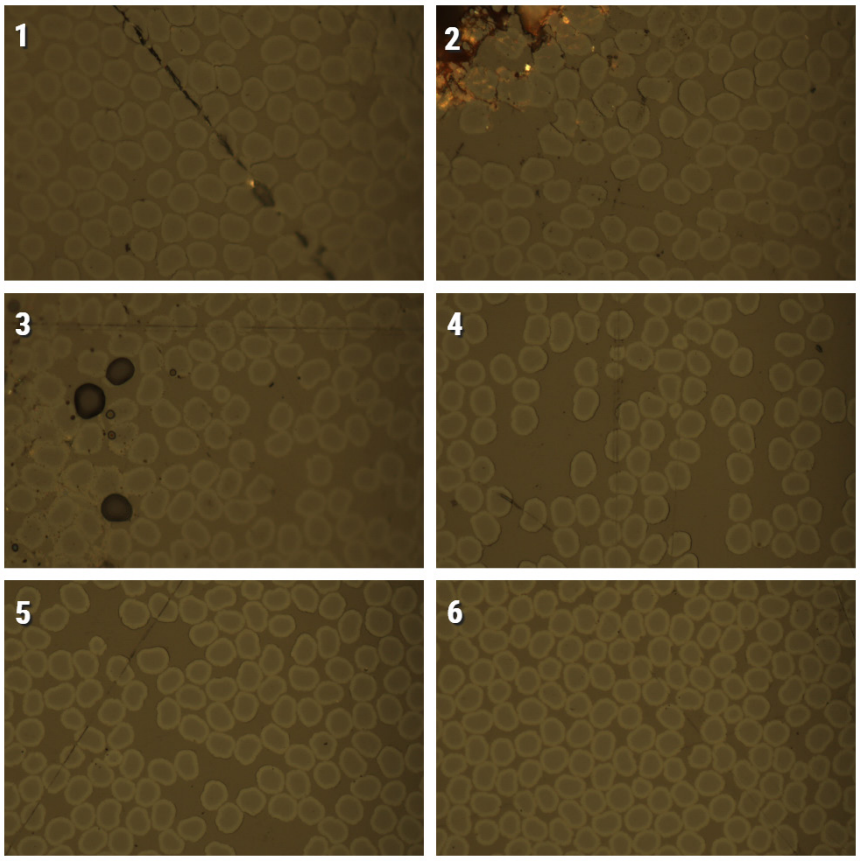

Fig. 2. Photomicrographs of samples of fibers stabilized at different temperatures in an oxygen concentration of 11% in OF1: 1 – 240°C, 2 – 245°C, 3 – 250°C, 4 – 255°C, 5 – 260°C, and 6 – 270°C.

in the OF3 zone, the OF2 temperature was fixed at 260°C. The results of the selection of conditions for OF3 are shown in Table 4.

A bulk density above the required value of 1.36 g/cm^3 was achieved at a process temperature of 270°C in the final thermal stabilization zone. The high manufacturability of the harness at the exit of the oxidation zones was also noted. Moreover, the smaller size of the shell in the heterophase structure, having comparable values of linear density and thermal effect of the oxidation reaction according to DSC, may indicate higher core stability (Fig. 3).

Table 3. Results of the heat treatment mode selection in OF2

Number of sample	Temperature T_{OF2}, °C	Density ρ, g/cm^3
1	210	1.2855
2	220	1.2848
3	230	1.2910
4	240	1.3002
5	250	1.3192
6	260	1.3309

Table 4. Results of the heat treatment mode selection in OF3

Number of sample	Temperature T_{OF3}, °C	Density ρ, g/cm^3	ΔH_{ox}, J/g
1	250	1.3380	874
2	255	1.3405	856
3	260	1.3498	848
4	265	1.3547	861
5	270	1.3616	754
6*	280	1.3672	715

*This sample is a sample for comparison.

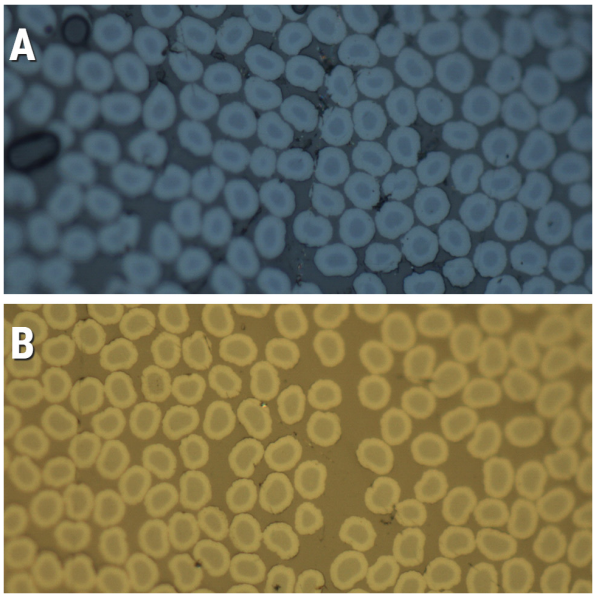

Fig. 3. Comparison of stabilized fiber pulps using standard accelerated thermal stabilization technology (A) [2] and the results of the Gradient experiment (B).

While the main disadvantage of the proposed solution is its increased nitrogen consumption, this problem can be partially solved on an industrial line by recovering part of the nitrogen from the pre-stabilization zone and returning it to the OF1 zone.

CONCLUSIONS

The experiments demonstrated that an atmosphere with a depleted oxygen content in OF1 can be used to reduce the formation of a heterophase structure and obtain a more stable fiber core while maintaining a pre-stabilization zone in nitrogen. The temperature profile of the thermal stabilization process proposed in the described Gradient experiment has advantages over the classical accelerated stabilization process considered by the authors in previous works. The 10°C lower final temperature of the heat treatment and reduced temperature difference (<10°C) between two adjacent stages of thermal stabilization helps to prevent damage and fiber breakage on the processing line by significantly reducing the risk of local overheating. This is particularly important when factory CF production lines are operated in canvas mode in order to increase productivity; here, the individual bundles are packed as closely together as possible, effectively forming a wide ribbon of processed material. By reducing the final processing temperature by as little as 10°C, the risk of uncontrolled exothermic overheating and spontaneous ignition of the material can be significantly reduced.

At the same time, the Gradient mode retains the main advantage of classical accelerated stabilization in terms of the short process time of 30 min. A threefold reduction in thermal stabilization time as compared to the generally accepted oxidation PAN technology provides significant savings in capital costs required to build larger workshops by reducing the number of required furnaces and overall energy consumption. In addition to the greater economic potential as compared to the generally accepted technology of oxidative stabilization, its increased safetymakes the Gradient mode promising for introduction into industrial production.

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Authors' contributions

E.A. Trofimenko – study concept, conducting experiments, analyzing the results, and writing the text of the article.

T.V. Bukharkina – refining the structure of experiments, analyzing the results, and developing the concept of further study.

T.V. Verzhichinskaya – analyzing the results, correcting the program of further study, and editing the article.

The authors declare no conflicts of interest.

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About the authors:

Evgeny A. Trofimenko, Postgraduate Student, Department of Chemical Technology of Natural Energy Sources and Carbon Materials, Mendeleev University of Chemical Technology of Russia (9, Miusskaya pl., Moscow, 125047, Russia). E-mail: e.trofimencko2016@yandex.ru. RSCI SPIN-code 9855-0716, https://orcid.org/0000-0003-0084-9103

Tatyana V. Bukharkina, Dr. Sci. (Chem.), Professor, Department of Chemical Technology of Natural Energy Sources and Carbon Materials, Mendeleev University of Chemical Technology of Russia (9, Miusskaya pl., Moscow, 125047, Russia). E-mail: tvb_53@mail.ru. Scopus Author ID 55925186900, RSCI SPIN-code 1138-2040

Svetlana V. Verzhichinskaya, Cand. Sci. (Chem.), Associate Professor, Department of Chemical Technology of Natural Energy Sources and Carbon Materials, Mendeleev University of Chemical Technology of Russia (9, Miusskaya pl., Moscow, 125047, Russia). E-mail: verlanasv@muctr.ru. Scopus Author ID 6504274958, RSCI SPIN-code 8957-0316

Об авторах:

Трофименко Евгений Александрович, аспирант кафедры химической технологии природных энергоносителей и углеродных материалов ФГБОУ ВО «Российский химико-технологический университет имени Д.И. Менделеева» (125047, Россия, Москва, Миусская пл., д. 9). E-mail: e.trofimencko2016@yandex.ru. SPIN-код РИНЦ 9855-0716, https://orcid.org/0000-0003-0084-9103

Бухаркина Татьяна Владимировна, д.х.н., профессор кафедры химической технологии природных энергоносителей и углеродных материалов ФГБОУ ВО «Российский химико-технологический университет имени Д.И. Менделеева» (125047, Россия, Москва, Миусская пл., д. 9). E-mail: tvb_53@mail.ru. Scopus Author ID 55925186900, SPIN-код РИНЦ 1138-2040

Вержичинская Светлана Владимировна, к.х.н., доцент кафедры химической технологии природных энергоносителей и углеродных материалов ФГБОУ ВО «Российский химико-технологический университет имени Д.И. Менделеева» (125047, Россия, Москва, Миусская пл., д. 9). E-mail: verlanasv@muctr.ru. Scopus Author ID 6504274958, SPIN-код РИНЦ 8957-0316

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ANALYTICAL METHODS IN CHEMISTRY AND CHEMICAL TECHNOLOGY

АНАЛИТИЧЕСКИЕ МЕТОДЫ В ХИМИИ И ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Determination of chlorine-containing compounds in disinfectants using ion-exchange chromatography

Eugenia A. Lapina[1], Sergey A. Zverev[1,✉], Sergey V. Andreev[1], Konstantin A. Sakharov[2]

[1]F.F. Erisman Federal Scientific Center of Hygiene, Research Institute of Disinfectology, Rospotrebnadzor, Moscow, 117246 Russia

[2]School of Materials Science and Engineering, Nanyang Technological University, Singapore, 639798 Republic of Singapore

✉Corresponding author, e-mail: niid.chemlab@gmail.com

Abstract

Objectives. *To develop a method for the determination of hypochlorite, chloride, chlorite, chlorate, and perchlorate ions in solution; to determine the limits of detection and quantitation for ClO^-, Cl^-, ClO_2^-, ClO_3^-, and ClO_4^- ions; to evaluate the applicability of the developed method and its suitability for disinfectant analysis.*

Methods. *Ionic chromatography using a conductometric detection system in isocratic elution mode.*

Results. *The method developed for chromatographic determination of chlorine-containing ions can be used to quantify the content of hypochlorite, chloride, chlorite, chlorate, and perchlorate ions. In isocratic elution mode at 7.5 mM NaOH and a flow rate of 0.4 mL/min, the content of chlorine-containing ions can be determined with high sensitivity. The presented method does not require the use of expensive equipment for the ultrasensitive analysis of the studied compounds.*

Conclusions. *A novel method for the simultaneous determination of hypochlorite, chloride, chlorite, chlorate, and perchlorate ions in case of their combined presence is proposed. The technique can be used to carry out routine control of the content of these disinfectant components during use, increasing their effectiveness at the same time as managing associated toxicological risks.*

Keywords: *hypochlorite ion, chloride ion, chlorite ion, chlorate ion, perchlorate ion, ionic chromatography, disinfectants*

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НАУЧНАЯ СТАТЬЯ

Определение хлорсодержащих соединений в дезинфицирующих средствах с использованием ионообменной хроматографии

Е.А. Лапина[1], С.А. Зверев[1,✉], С.В. Андреев[1], К.А. Сахаров[2]

[1]Институт дезинфектологии ФБУН ФНЦГ им. Ф.Ф. Эрисмана Роспотребнадзора, Москва, 117246 Россия
[2]Школа материаловедения и инженерии, Наньянский технологический университет, Сингапур, 639798 Сингапур
[✉]Автор для переписки, e-mail: niid.chemlab@gmail.com

Аннотация

Цели. *Разработать методику определения гипохлорит-, хлорид-, хлорит-, хлорат- и перхлорат-ионов при их совместном присутствии в дезинфицирующих средствах. Определить пределы обнаружения и пределы количественного определения ионов ClO^-, Cl^-, ClO_2^-, ClO_3^-, ClO_4^-. Провести расчеты валидационных параметров разработанной методики, а также оценить ее пригодность для анализа дезинфицирующих средств.*
Методы. *Ионообменная хроматография с системой кондуктометрического детектирования в изократическом режиме элюирования.*
Результаты. *Новая методика хроматографического определения хлорсодержащих ионов позволяет количественно оценить содержание гипохлорит-, хлорид-, хлорит-, хлорат- и перхлорат-ионов при их одновременном нахождении в модельном растворе и в дезинфицирующих средствах. Изократический режим элюирования 7.5 мМ NaOH при скорости движения потока 0.4 мл/мин позволяет с высокой чувствительностью определять ионы, содержащие атом хлора. Разработанная методика не требует использования дорогостоящего оборудования, необходимого для сверхчувствительного анализа исследуемых соединений.*

Выводы. *Впервые предложена методика определения гипохлорит-, хлорид-, хлорит-, хлорат- и перхлорат-ионов при совместном присутствии. Ожидается, что разработанная методика позволит проводить рутинный контроль содержания этих компонентов в дезинфицирующих средствах при их практическом использовании, что приведет к повышению эффективности применения дезинфектантов на их основе и снижению возможных токсикологических рисков.*

Ключевые слова: *гипохлорит-ионы, хлорид-ионы, хлорит-ионы, хлорат-ионы, перхлорат-ионы, ионообменная хроматография, дезинфицирующие средства*

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INTRODUCTION

One of the key roles in public health consists in preventing the transmission of infectious diseases. The main basis of non-specific prophylaxis consists in implementing disinfection measures using appropriate means. Nowadays, many food products undergo thorough disinfection treatment during the preparation of goods for sale [1–3], typically involving the use of chlorine-containing disinfectants. Since, due to its high toxicity, pure chlorine is not suitable for these purposes, various chlorine-containing compounds—e.g., sodium hypochlorite—are used [2, 4–7]. The industrial production of sodium hypochlorite involves the electrolytic dissociation of an aqueous solution of sodium chloride. In the process, byproducts containing chlorite, chlorate, and perchlorate ions can also be formed [3, 8]. In an aqueous medium, due to being in chemical equilibrium, such ions can transform into different forms [9].

Chlorine-containing anions pose a particular risk to human health [3, 10]. For example, perchlorate ions have a negative effect on the production of thyroid hormone, which affects the functioning of the brain. The US Environmental Protection Agency has set the maximum allowable concentration of such substances at 15 μg/L, while the maximum pollution limit is set at 2 μg/L [11]. The World Health Organization, which is responsible for controlling the content of chlorate ions in drinking water, sets its maximum permissible concentration at 0.7 mg/L [12]. Since disinfectants based on chlorine compounds are typically used in food production processes, their residual amounts are found in dairy products, vegetables, and drinking water [1, 2, 10, 13–16].

Classical methods for the determination of chlorine-containing compounds in various objects are iodometric and potentiometric titration, colorimetric and fluorometric methods, capillary electrophoresis, etc. [4, 6, 12, 17–19]. Contemporary approaches are based on the use of ultrasensitive sensors to chloride-containing ions, which use elements of the platinum and palladium series in tandem with spectrophotometry, as well as on high-performance liquid chromatography methods using a mass-selective detection system [5, 7, 11, 20, 21]. Although such methods offer high sensitivity and a low detection limit of the studied compounds, they remain expensive.

Ion-exchange chromatography has been used in the analysis of chlorine-containing compounds since the end of the 20th century [22]. The first studies with chromatographic separation of chlorate and chlorite ions were carried out under conditions of low pH values. However, this solution led to the degradation of other compounds in the analyzed solution. Subsequent methods for analyzing the content of chlorine-containing ions in drinking water and other inorganic objects are based on the use of weakly alkaline or weakly acidic eluents to achieve a better separation of the compounds under study [16, 23].

Contemporary analysis techniques are based on a similar class of eluents [24, 25]. For example, depending on the type of analytical column for the analysis of chlorine-containing ions, eluents can be based on orthophthalic acid and acetonitrile. Eluents based on sodium carbonate and bicarbonate (also separately) and alkaline eluents based on sodium or potassium hydroxide in various concentrations are also used. In order to improve existing ion exchange chromatography methods, high resolution mass-selective detection systems are used in place of classical conductometric detection. This makes it possible to increase the analysis sensitivity and suppress the effect of high concentrations of side ions [26–28].

An analysis of the literature data shows that works based on the quantitative assessment of chlorine-containing ions fail to present a general picture of the analysis of all such ions simultaneously. Most studies in this area are aimed at studying ions having dangerous effects on human health: chlorite, chlorate, and perchlorate ions [24, 28]. At the same time, the complexity of chromatographic analysis involves a large number of "interfering" ions, for example, Cl^-, whose chromatographic peaks, due to high concentrations, overlap the signals of other compounds [13].

Thus, the present study sets out to develop a method for determining hypochlorite, chloride, chlorite, chlorate, and perchlorate ions in their combined presence in solution using ion exchange chromatography with a conductometric detection system. The improved approach can be used to carry out quality control of manufactured disinfectants and other possible objects without the use of expensive equipment. The technique can additionally be used to determine the studied compounds even in trace amounts, thus reducing possible toxicological risks.

MATERIALS AND METHODS

Reagents

The study used sodium chlorite (80%), potassium chlorate (99%), potassium perchlorate (99.9%), and sodium hypochlorite solution having a base substance content of 10%, manufactured by *Sigma-Aldrich* (USA). Sodium hydroxide (99.3%) was produced by *VWR* (USA). Potassium permanganate, hydrochloric acid, iodine, sodium thiosulfate, potassium bromide, sodium carbonate, sodium bicarbonate, and potassium biphthalate used in the work were of analytical grade or higher and used without further purification.

Samples of disinfectants

In order to assess the suitability of the developed method, three commercially available samples of disinfectants—anolytes were studied. In order to maintain experimental independence, the samples were submitted for testing after removing information about the manufacturer and component composition of the studied products from the packaging.

Equipment

The following equipment was used in the work: Elmasonic S 70 H ultrasonic bath (*Elm*a, Germany); EBA 280 centrifuge (*Hettich*, Germany); Millipore Direct Q3 water purification system (*Millipore*, USA); Adventure AR-2140 balance with a resolution of 0.0001 g (*Ohaus*, Switzerland); variable volume dispensers (*Sartorius*, Germany).

Preparation of solutions

For the preparation of eluents and solutions of the studied compounds, degassed deionized water was used. Degassing was carried out for 15–20 min at a temperature of 50°C using an ultrasonic bath with an ultrasound frequency of 37 kHz. The preparation of eluent solutions was carried out by weighing the required amount of the substance to an accuracy of four decimal places and diluting it in prepared water. The preparation of solutions of chlorine-containing compounds used to develop calibration curves was carried out by diluting the stock solution of compounds. The stock solution was prepared by weighing the required amount of the substance to an accuracy of four decimal places and diluting it in prepared water.

Synthesis of sodium hypochlorite

Sodium hypochlorite was synthesized by gradual addition of crystalline potassium permanganate (0.025 mol) to concentrated hydrochloric acid (0.20 mol; 4 M) with heating. Gaseous chlorine (0.063 mol) released as a result of the reaction was introduced into a sodium hydroxide solution (0.13 mol; 45 wt %) until the end of gas evolution. The resulting solution was filtered, cooled to 15°C, and centrifuged at 5000 rpm. The formed precipitate was separated by decantation and dried under vacuum for 24 h in a dark place. The content of sodium hypochlorite in the product confirmed by iodometric titration was 39.8 wt %.

Infrared (IR) spectroscopy

The IR spectra of sodium hypochlorite hydrate, potassium chlorate, and sodium chloride were recorded on an InfraLYUM FT-08 IR-Fourier spectrometer (*Lumex*, Russia) using a KBr beam splitter in the spectral range of 500–2000 cm^{-1}.

Chromatograph parameters

Chromatographic analysis was performed on a Stayer-M instrument (*Akvilon*, Russia) using an analytical column *Shodex IC SI-90 4E* 4.0 × 250 mm, PEEK particle size 9 μm (*Shodex*, USA) with a conductometric detection system. The volume of the injected sample was 20 μL, while the temperature of the column thermostat was 35°C and the conductivity scale of the detector was 40 mA.

Data processing

A Stayer-M liquid chromatograph was controlled and chromatographic data were processed on a PC using the MultiChrom program (*Ampersend*, Russia). The chromatograms of the analyzed compounds were designed using the OriginPro 2016 program (*OriginLab*, USA). The IR spectra of the compounds were designed using the Omnic 9.2 program (*Thermo Fisher Scientific*, USA). The calculation and processing of validation calculation data was carried out in Microsoft Excel 2016 program (*Microsoft*, USA).

RESULTS AND DISCUSSION

The chromatographic separation of chlorine-containing ions in isocratic mode using various types of eluents has been already described in the literature. At the initial stage, when selecting the conditions for the separation of chloride, chlorite, chlorate, and perchlorate ions, eluents based on Na_2CO_3–$NaHCO_3$ were used with concentrations in the ratios of 1.7–1.8 mM, 0.8–0.9 mM, and 2.5–0.4 mM, respectively[1]. In the first case, only the presence of Cl^-, ClO_2^-, and ClO_3^- ions was detected by varying the flow rate from 0.3 to 1.0 mL/min. When the concentration of eluents used was halved and their proportional ratios changed, chromatographic signals of chloride, chlorite, and chlorate ions were also observed. No chromatographic signals of perchlorate ions were detected upon increasing the concentrations of sodium carbonate and bicarbonate to 2.5 and 0.4 mM, respectively.

Further attempts at chromatographic determination of the studied ions using an eluent based on potassium biphthalate ($C_8H_5O_4K$) were carried out. When carrying out the analysis at an eluent rate ranging from 0.3 to 1.0 mL/min using 0.5 mM potassium biphthalate, it was not possible to detect chloride ions. However, an increase in the substance concentration in the eluent to 7.0 mM resulted in the identification of only chloride and chlorite ions in the studied solutions.

When determining chromatographically chloride-containing ions in isocratic mode, the use of a sodium hydroxide eluent is often described. When analyzing the same solutions of chlorine-containing ions using 20.0 mM NaOH as an eluent at a flow rate of 0.7 mL/min, it was possible to detect signals of chloride, chlorate, and perchlorate ions. In this case, varying the eluent flow rate did not lead to the detection of the chlorite ion: apparently, its chromatographic peak was overlapped by the signal of the chloride ion. A twofold decrease in the concentration of the alkaline eluent to 10.0 mM of sodium hydroxide at a flow rate of 0.3 mL/min led to the detection of only chloride and chlorate ions in the solution. However, in the case of such a substance being present in the eluent, an increase in the flow rate also resulted in the detected presence of perchlorate ions. An alkaline eluent based on 7.5 mM NaOH at a flow rate of 1.0 mL/min facilitates the detection of chloride, chlorate, and perchlorate ions. However, when the flow rate of this eluent was reduced to 0.7 mL/min, it was possible to detect all chloride, chlorite, chlorate, and perchlorate ions studied at this stage in the studied solutions (Fig. 1). At the same time, it should be noted that a greater decrease in the flow rate increases the time of a single chromatographic experiment.

Thus, to determine the quantitative assessment of Cl^-, ClO_2^-, ClO_3^-, and ClO_4^- ions, it is optimal to use 7.5 mM NaOH as an eluent at a flow rate of 0.7 mL/min.

As discussed earlier, the use of commercial samples of sodium hypochlorite to evaluate the content of hypochlorite ions is difficult due to the high chloride ion content. To solve this problem, we synthesized a sample of sodium hypochlorite with a higher content of the main substance according to the previously proposed method [29]. The method is based on the absorption of gaseous chlorine released as a result of the interaction of crystalline potassium permanganate with concentrated hydrochloric acid when heated with a solution of sodium hydroxide. Following complete gas evolution, the resulting solution was

[1] The analysis was carried out using an electrodialysis suppressor of carbonate and bicarbonate ions.

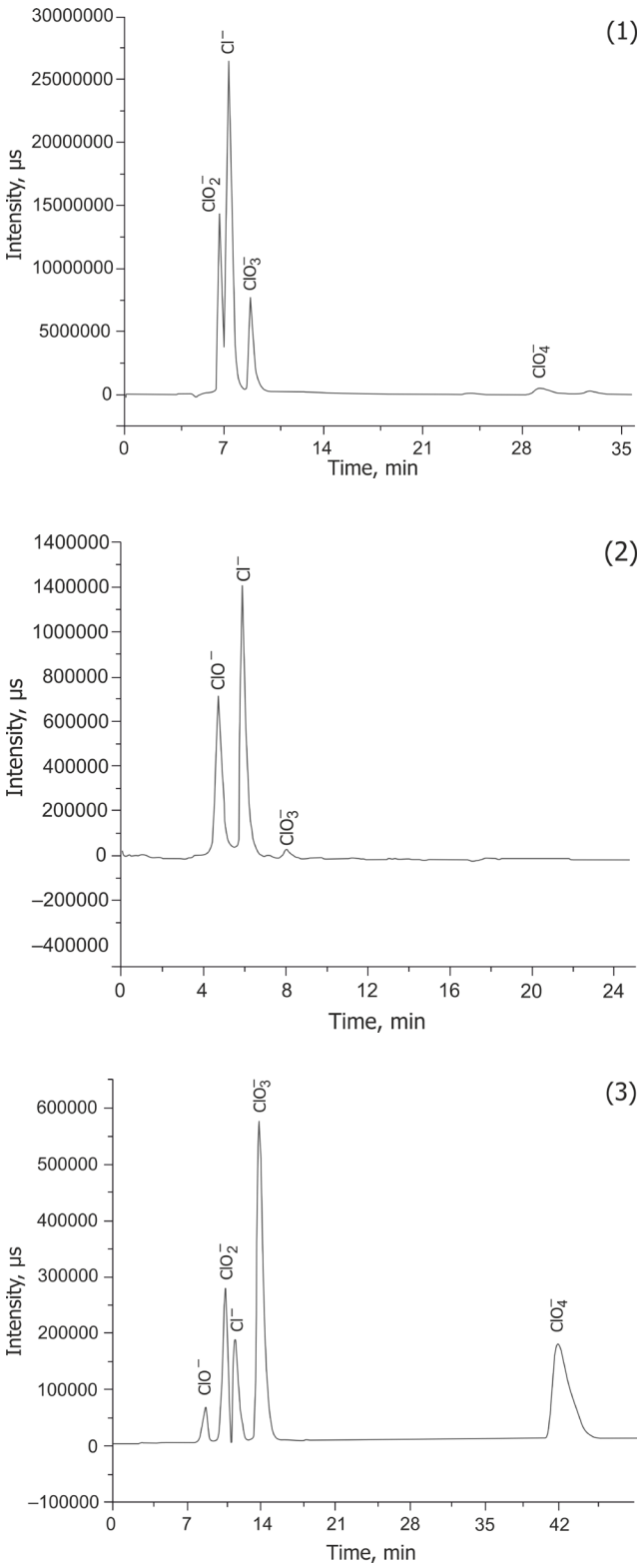

Fig. 1. Chromatograms of chlorine-containing compounds obtained by ion-exchange chromatography with conductometric detection under various conditions:
(1) eluent 7.5 mM NaOH, flow rate 1.0 mL/min;
(2) eluent 7.5 mM NaOH, flow rate 0.7 mL/min (synthesized NaClO sample);
(3) eluent 7.5 mM NaOH, flow rate 0.4 mL/min.

filtered to remove possible precipitated impurities, then cooled and centrifuged. The precipitate formed after centrifugation was separated from the main solution by decantation and dried under vacuum in a dark place. The analysis of the obtained substance was carried out using ion-exchange chromatography under previously developed conditions for the chromatographic determination of chlorine-containing ions (Fig. 1). In addition to the new signal assigned to the hypochlorite ion, the resulting substance as revealed by the chromatogram contains the chloride ion as a byproduct, as well as impurity amounts of the chlorate ion. According to ion-exchange chromatography, the content of sodium chloride was 1.21% ± 0.07%, while that of sodium chlorate was 0.015% ± 0.001%. According to the IR spectroscopy data, no other chlorine-containing ions were present in the samples of the obtained sodium hypochlorite crystalline hydrate (Fig. 2). Therefore, the content of hypochlorite ions was determined by iodometric titration. The average content of sodium hypochlorite in the crystalline hydrate was 39.8% ± 0.3%.

Analysis of the chromatographic determination of the resulting hypochlorite ions in combination with chloride, chlorite, chlorate, and perchlorate ions was carried out under previously selected conditions using 7.5 mM NaOH as an eluent. By varying the flow rate, it was possible to achieve the optimal separation of all ions already at an eluent flow rate of 0.4 mL/min (Fig. 1). In this case, the analysis time was 50 min. A decrease in the eluent flow rate led to an increase in the analysis time without affecting the resolution of chloride-containing ion determination.

To assess the applicability of the developed method, the validation parameters were also calculated in accordance with the recommendations for analytical methods [30]. The measurement accuracy was evaluated using the addition method for each compound. The obtained values of the extraction degree of all ions in the range of 99–101% testify to the lack of systematic measurement errors. Calibration curves for the studied chlorine-containing ions (hypochlorite ion 0.50–3.00 mg/L; chloride ion 0.249–2.50 mg/L; chlorite ion 0.373–2.61 mg/L; chlorate ion 0.498–2.52 mg/L; perchlorate ion 0.498–2.49 mg/L) are linear in all cases with a correlation coefficient above 0.9990 (Fig. 3 and Table). The calculation of the limit of detection (LOD) and limit of quantification (LOQ) values was based on the signal-to-noise ratio. Due to the high intensity of the chromatographic chloride ion signal, the detection and quantitation limits are 0.87 μg/L and 2.63 μg/L, respectively; this figure is much lower as compared to other ions. For example, according to the LOD and LOQ values for the

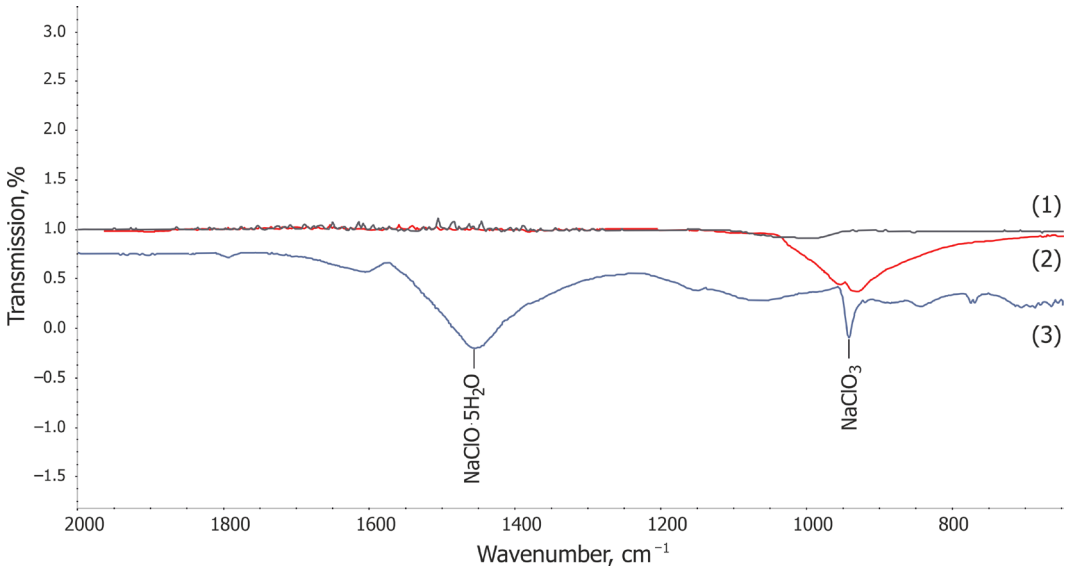

Fig. 2. IR spectra of sodium chloride (1), potassium chlorate (2), and sodium hypochlorite (3).

hypochlorite ions are at the level of 47.8 μg/L and 145 μg/L, respectively, the developed method can be additionally characterized as selective and sensitive. More detailed results of calculations of validation parameters for the studied chlorine-containing ions are given in the table.

The suitability of the developed method was assessed using three commercially available samples of disinfectants comprising anolytes produced by different manufacturers. In order to ensure a "blind" independent experiment, the studied samples of anolytes were encrypted under the codes Anolyte-1, Anolyte-2, and Anolyte-3. According to the results of the tests, samples Anolyte-1 and Anolyte-3 were found to contain only chloride ions 0.571 ± 0.027 and 0.730 ± 0.035 wt %, respectively. The Anolyte-2 sample, on the other hand, contained hypochlorite, chloride, and chlorite ions at concentrations of 0.0382 ± 0.0019, 0.0738 ± 0.0035, and 0.0181 ± 0.0008 wt %, respectively (Fig. 4). When comparing the obtained results with the data indicated by the manufacturers, the total concentrations of chlorine-containing ions in all the studied samples were found to exceed the values indicated in the instructions for use by the manufacturer. This finding additionally indicates the need for careful quality control and procedural accuracy when using anolytes.

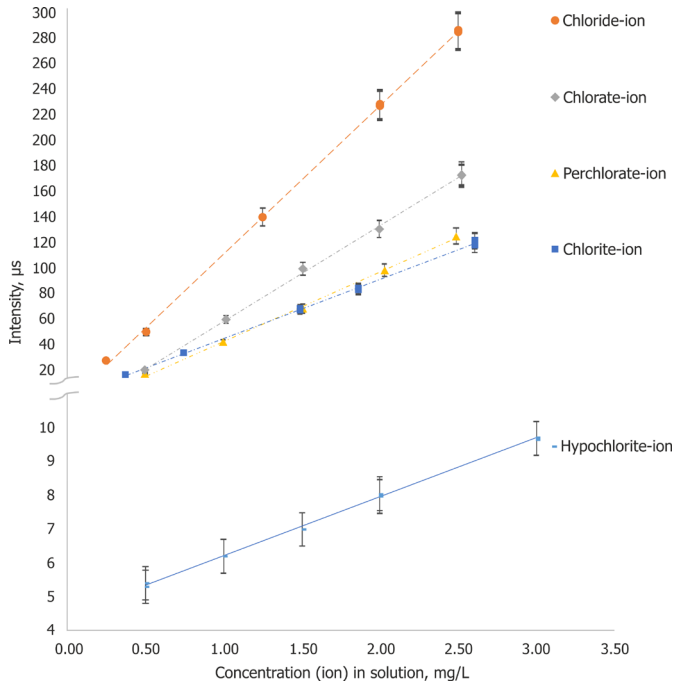

Fig. 3. Graphical representation of the calibration curves of hypochlorite, chloride, chlorite, chlorate, and perchlorate ions.

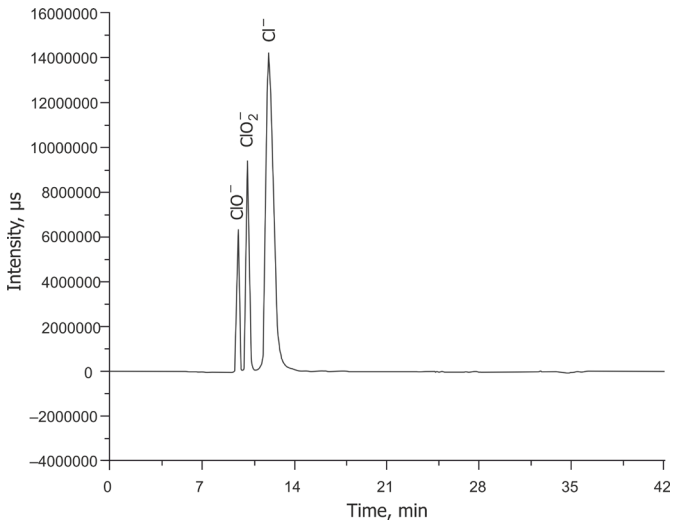

Fig. 4. Chromatogram of the Anolit-2 disinfectant.

Table. Results of calculation validation parameters (n = 5; P = 0.95)

Parameter		Ions				
		ClO^-	Cl^-	ClO_2^-	ClO_3^-	ClO_4^-
Retention time repeatability	RSD, %	0.66	0.28	0.23	0.15	0.029
Area repeatability	RSD, %	0.58	0.55	0.77	1.28	0.86
Theoretical plates		3123	3850	3695	2290	3296
Resolution		1.52	1.58	1.78	2.19	2.26
Peak asymmetry		1.50	1.04	1.23	1.21	1.47
Linearity	Correlation coefficient	0.9991	0.9994	0.9992	0.9992	0.9990
	Sensitivity factor	1.7450	116.15	46.282	74.780	54.421
	Axial displacement	4.4765	−4.7886	−1.1377	−16.154	−11.805
Accuracy	Recovery, %	99.4	100.3	99.8	100.1	99.1
	RSD, %	2.48	1.24	0.62	0.97	0.87
Limit of detection (LOD), μg·L^{-1}		47.8	0.867	7.11	18.0	52.9
Limit of quantitation (LOQ), μg·L^{-1}		145	2.63	21.5	54.9	160

Note: RSD – relative standard deviation, *S/N* – signal-to-noise ratio.

CONCLUSIONS

As part of the development of a procedure for the determination of hypochlorite, chloride, chlorite, chlorate, and perchlorate ions simultaneously present in solution, optimal conditions for their chromatographic separation were obtained using ion-exchange chromatography with conductometric detection. The best separation of the mixture components was obtained using a 7.5 mM NaOH solution as an eluent at a flow rate of 0.4 mL/min with a Shodex IC SI-90 4E anionic column. According to the validation parameter calculations, the developed method can be used to quantify all the listed chlorine-containing ions in the studied concentration ranges. The performed calculations also confirm the high sensitivity and extraction degree of each chlorine-containing compound under study.

The results of the study suggest the suitability of the developed method not only for the analysis of disinfectants, but also in the preparation centralized and non-centralized water supplies, as well as for determining residual quantities of chlorine-containing ions in wastewater.

Authors' contributions

E.A. Lapina – conducting the experiments, performance of chromatography research, analysis of the experimental data, and preparing illustrations;

S.A. Zverev – analysis of literary sources, developing the scientific concept, and writing the text of the article;

S.V. Andreev – offering consultations on research, editing the text of the article;

K.A. Sakharov – IR spectrum analysis, editing the text of the article.

The authors declare no conflicts of interest.

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About the authors:

Eugenia A. Lapina, Engineer, Chemical Department, F.F. Erisman Federal Scientific Center of Hygiene, Research Institute of Disinfectology, Rospotrebnadzor (18, Nauchnyi pr., Moscow, 117246, Russia). E-mail: zhenya_lapina@mail.ru. ResearcherID AEE-8223-2022, https://orcid.org/0000-0002-7430-4694

Sergei A. Zverev, Junior Researcher, Chemical Department, F.F. Erisman Federal Scientific Center of Hygiene, Research Institute of Disinfectology, Rospotrebnadzor (18, Nauchnyi pr., Moscow, 117246, Russia). E-mail: zverev.94@yandex.ru. ResearcherID C-1526-2019, https://orcid.org/0000-0002-3232-9332

Sergei V. Andreev, Cand. Sci. (Chem.), Deputy Director, F.F. Erisman Federal Scientific Center of Hygiene, Research Institute of Disinfectology, Rospotrebnadzor (18, Nauchnyi pr., Moscow, 117246, Russia). E-mail: svandreev.niid@gmail.com. Scopus Author ID 57192710116, ResearcherID R-9798-2016, RSCI SPIN-code 2039-3703, https://orcid.org/0000-0003-2405-9931

Konstantin A. Sakharov, Cand. Sci. (Chem.), Researcher, School of Materials Science and Engineering, Nanyang Technological University (NTU) (50, Nanyang Avenue, Singapore, 639798, Republic of Singapore). E-mail: konstantin.a.sakharov@gmail.com. Scopus Author ID 6602616498, ResearcherID A-7428-2016, RSCI SPIN-code 5531-3619, https://orcid.org/0000-0002-3247-5743

Об авторах:

Лапина Евгения Андреевна, инженер отдела химических исследований, Институт дезинфектологии ФБУН «ФНЦГ им. Ф.Ф. Эрисмана» Роспотребнадзора (117246, Россия, Москва, Научный проезд, д. 18). E-mail: zhenya_lapina@mail.ru. ResearcherID AEE-8223-2022, https://orcid.org/0000-0002-7430-4694

Зверев Сергей Александрович, младший научный сотрудник отдела химических исследований, Институт дезинфектологии ФБУН «ФНЦГ им. Ф.Ф. Эрисмана» Роспотребнадзора (117246, Россия, Москва, Научный проезд, д. 18). E-mail: zverev.94@yandex.ru. ResearcherID C-1526-2019, https://orcid.org/0000-0002-3232-9332

Андреев Сергей Викторович, к.х.н., и.о. заместителя директора Института дезинфектологии ФБУН «ФНЦГ им. Ф.Ф. Эрисмана» Роспотребнадзора (117246, Россия, Москва, Научный проезд, д. 18). E-mail: svandreev.niid@gmail.com. Scopus Author ID 57192710116, ResearcherID R-9798-2016, SPIN-код РИНЦ 2039-3703, https://orcid.org/0000-0003-2405-9931

Сахаров Константин Андреевич, к.х.н., научный сотрудник, Наньянский Технологический Университет (639798, Сингапур, Nanyang Avenue, 50). E-mail: konstantin.a.sakharov@gmail.com. Scopus Author ID 6602616498, ResearcherID A-7428-2016, SPIN-код РИНЦ 5531-3619, https://orcid.org/0000-0002-3247-5743

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MATHEMATICS METHODS AND INFORMATION SYSTEMS IN CHEMICAL TECHNOLOGY

МАТЕМАТИЧЕСКИЕ МЕТОДЫ И ИНФОРМАЦИОННЫЕ СИСТЕМЫ В ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Implementation of pharmaceutical development using multivariate analysis of multi-criteria optimization on the example of the stage of purification of oligohexamethyleneguanidine hydrosuccinate

Denis O. Shatalov[1,✉], Kirill N. Trachuk[1], Anna V. Aydakova[2], Diana A. Akhmedova[1], Ivan S. Ivanov[2], Dmitry S. Minenkov[3], Igor Yu. Blazhevich[4], Stanislav A. Kedik[1,2]

[1]MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
[2]Institute of Pharmaceutical Technologies, Moscow, 121353 Russia
[3]Ishlinsky Institute for Problems of Mechanics, Russian Academy of Sciences, Moscow, 119526 Russia
[4]M.V. Lomonosov Moscow State University, Moscow, 119234 Russia
✉Corresponding author, e-mail: shat-05@mail.ru

Abstract

Objectives. *The study set out to use mathematical modeling, in particular the method of multifactorial analysis of multicriteria optimization (MAMO), in the development of a pharmaceutical product.*
Methods. *After carrying out experimental tests based on the proposed algorithmic sequence, the obtained data were interpreted using MAMO.*
Results. *The possibility of using MAMO to solve the applied problem of purifying oligohexamethyleneguanidine hydrosuccinate (OHMG-HS), considered as a pharmaceutical precursor for the creation of medicines, was demonstrated.*
Conclusions. *The expediency of using the proposed algorithm as a tool for pharmaceutical development is substantiated by identifying dependencies of the influence of purification conditions on the final content of admixtures in the target product.*

Keywords: *pharmaceutical development, mathematical modeling, antibiotic resistance, oligohexamethyleneguanidines*

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НАУЧНАЯ СТАТЬЯ

Реализация фармацевтической разработки с применением многофакторного анализа многокритериальной оптимизации на примере этапа очистки гидросукцината олигогексаметиленгуанидина

Д.О. Шаталов[1,✉], К.Н. Трачук[1], А.В. Айдакова[2], Д.А. Ахмедова[1], И.С. Иванов[2], Д.С. Миненков[3], И.Ю. Блажевич[4], С.А. Кедик[1,2]

[1]МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
[2]Институт фармацевтических технологий, Москва, 121353 Россия
[3]Институт проблем механики им. А.Ю. Ишлинского Российской академии наук, Москва, 119526 Россия
[4]Московский государственный университет им. М.В. Ломоносова, Москва, 119234 Россия
[✉]Автор для переписки, e-mail: shat-05@mail.ru

Аннотация

Цели. *Данное исследование посвящено использованию математического моделирования, в частности метода многофакторного анализа многокритериальной оптимизации (МАМО), в фармацевтической разработке.*
Методы. *В ходе исследования была предложена алгоритмическая последовательность эксперимента и проведены необходимые испытания. Полученные данные были интерпретированы при помощи МАМО.*
Результаты. *Изучена возможность применения МАМО для решения прикладной проблемы очистки гидросукцината олигогексаметиленгуанидина (ОГМГ-ГС), рассматриваемого в качестве фармацевтической субстанции для создания лекарственных средств.*
Выводы. *Были выявлены зависимости влияния условий очистки на конечное содержание примесей в целевом продукте и доказана целесообразность использования предложенного алгоритма в качестве инструмента фармацевтической разработки.*

Ключевые слова: *фармацевтическая разработка, математическое моделирование, антибиотикорезистентность, олигогексаметиленгуанидины*

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INTRODUCTION

With the number of deaths worldwide caused by drug-resistant microorganisms exceeding 50000 per year, antimicrobial resistance is widely perceived as a major problem. However, the complex and multifactorial nature of antimicrobial resistance remains poorly understood, especially in the context of human-, animal- and environmental interactions. The situation is exacerbated by a lack of reliable information, the slow development of new antimicrobial drugs, and high infection incidence rates. Thus, the emergence and spread of antimicrobial resistance requires immediate attention from both medical professionals and developers of new compounds that may exhibit antimicrobial activity [1].

As a consequence of the reduced effectiveness of current means of prevention and treatment of human infectious diseases due to the resistance of microorganisms to drugs and disinfectants, the World Health Organization expects antibiotic resistance to become the biggest threat to human health by 2050 [2]. In 2017, in order to implement the National Security Strategy of the Russian Federation and the State Policy for ensuring the chemical and biological safety of the Russia for the period up to 2025 and beyond, the Government of the Russian Federation approved the Strategy to Prevent the Spread of Antimicrobial Resistance to 2030 [3]. A direction implemented within the framework of this Strategy is related to the search for new ways of synthesizing substances with antimicrobial activity that are capable of overcoming identified resistance mechanisms.

Previously proposed methods for the synthesis of oligohexamethyleneguanidine (OHMG) salts [4, 5] showed sufficient efficiency against various pathogenic and opportunistic microorganisms, including fungi and viruses [6, 7]. In this regard, OHMG derivatives are currently actively used to create drugs based on them [8, 9].

The process for obtaining derivatives of poly- and oligohexamethylene guanides consists in the polycondensation of hexamethylenediamine (HMDA) and guanidine salts followed by conversion into the required OHMG salt. However, the main problem inherent in this process is the content of a sufficiently large quantity of residual impurities in the target compound. Although a recent study [10] showed that the use of microfluidic synthesis makes it possible to achieve a low content of monomer impurities compared to bulk synthesis, the obtained results do not meet the requirements of the State Pharmacopeia of the Russian Federation[1]. Therefore, the aim of the present study is to identify the optimal conditions for the purification of the target compound from impurities using mathematical modeling.

MATERIALS AND METHODS

The following reagents were used in the experiments: HMDA (99.5%, *Acros Organics*, Belgium), guanidine hydrocarbonate (GHC) (99.5%, *Sigma-Aldrich*, USA), chloroform (99.5%, *EKOS-1*, Russia), acetone (99.75%, *EKOS-1*, Russia), carbon tetrachloride (99.6%, *EKOS-1*, Russia), methylene chloride (99.5%, *EKOS-1*, Russia).

The main methods of polymer purification consist of several dissolution cycles followed by precipitation and washing with various solvents [11]. For washing poly- and oligoguanidines [12], chloroform, carbon tetrachloride, and similar solvents are used. However, in order to establish the optimal time for the purification process, as well as the ratio of components and dependencies between the initial parameters and the values of residual impurities, it becomes necessary to conduct many experiments involving different variations and combinations of the initial values. In this case, significant increases in reagent consumption and time preclude the rapid achievement of satisfactory results. In this regard, mathematical modeling techniques such as multifactorial analysis of multicriteria optimization (MAMO) can become useful tools for improving process parameters and saving resources [13]. Taking into account the application of MAMO methods, we propose the following algorithmic sequence:

1) search for information in foreign and local literary sources;
2) conducting preliminary experiments in the absence of reliable literature data;
3) formulating a hypothesis of criteria dependence on various factors and determining parameters for verifying hypothesis validity;
4) obtaining an approximating function in accordance with paragraph 3 according to the experimental data;
5) search for optimal values;
6) conducting verification experiments for compliance with the verification parameters defined in clause 3;
7) selection of the most appropriate time-solvent ratio from those calculated.

The application of mathematical modeling can be described according to the algorithmic sequence

[1] State Pharmacopeia of the Russian Federation, 14th ed. OFS.1.1.0006.15 Pharmaceutical substances. URL: https://minzdrav.gov.ru/poleznye-resursy/xiv-izdanie-gosudarstvennoy-farmakopei-rossiyskoy-federatsii. Accessed February 15, 2023 (in Russ.).

proposed above on the example of purification of oligohexamethyleneguanidine hydrosuccinate (OHMG-HS) (Fig. 1).

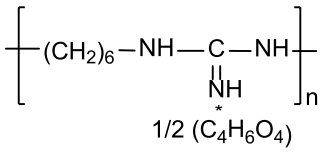

Fig. 1. Formula of oligohexamethyleneguanidine hydrosuccinate (OHMG-HS).

Based on the literature data [5], the following solvents were chosen for the purification process: chloroform, carbon tetrachloride, methylene chloride, and acetone. The most important and controllable factors were the amount of solvent added and the residence time of the sample in the chosen solvent.

The content of related impurities—HMDA and GHC, sulfate ash, heavy metals, as well as residual solvents (acetone, chloroform, methylene chloride, carbon tetrachloride)—were chosen as acceptance criteria for the target product. The corresponding data, which are taken from the State Pharmacopeia of the Russian Federation, 14th edition, are given in Table 1 (see Footnote 1).

Since no information about the mutual influence of factors was obtained, we assumed that there is mutual influence—that is, a nonlinear dependence on the factors expressed in quadratic terms taking the form *xy*. Therefore, to expand the range, we built experiments according to a full factorial design (containing all possible combinations of all factors at a certain number of levels, an equal number of times) (Table 2). To check hypothesis validity, the extraction coefficient (*R*) was used, which should lie within 10% for the test experimental points [14]. Having chosen the optimal purification method, the relative standard deviation for the quality indicators of OHMG-HS (Table 1) obtained during the measurements of 5 samples should not exceed 5%.

During the experiment, 20% aqueous solutions of the OHMG-HS salt were prepared, followed by the addition of the required amount of one of the solvents in accordance with Table 2 at room temperature (25°C). The solutions were thoroughly mixed and left to settle. After that, the target solutions were decanted and evaporated on a Laborota 4000 rotary evaporator (*Heidolph*, Germany) at 100°C

Table 1. Quality criteria for the OHMG-HS target product

Indicator	Requirement for the content of residual admixtures, no more %
Hexamethylenediamine (HMDA) admixture	0.0500
Guanidine hydrocarbonate (GHC) admixture	0.0500
Sulfate ash	0.1000
Heavy metals	0.0010
Chloroform	0.0060
Acetone	0.5000
Carbon tetrachloride	0.0004
Methylene chloride	0.0600

Table 2. Conditions of the salt purification process of OHMG-HS

No.	Solvent	Added, mL	Settling time, h
1	Chloroform	30	8
2		35	12
3		40	18
4		45	24
5	Carbon tetrachloride	30	8
6		35	16
7		40	24
8		45	28
9	Methylene chloride	30	16
10		35	24
11		40	28
12		45	36
13	Acetone	40	1.5
14		45	1
15		50	2
16		55	2.5

RESULTS AND DISCUSSION

During the preliminary experiments, the following data were obtained on the content of impurities in samples of OHMG-HS (Table 3).

To carry out mathematical calculations, it is necessary to normalize the obtained data. Data on the quantity of solvents (x) and the settling time of the mixture (y) are normalized according to the formula (1):

$$x_{norm} = \frac{x - x_{min}}{x_{max} - x_{min}}, y_{norm} = \frac{y - y_{min}}{y_{max} - y_{min}}. \quad (1)$$

Data on residual impurities (z) are normalized in such a way (2) that the value of 0 coincides with the actual value of 0 and that the value of 1 corresponds to the maximum permissible concentration (in the graphs, everything below the line $y = 1$ is acceptable):

$$z_{norm} = \frac{z}{z_{maximum\ allowed}}. \quad (2)$$

Normalized data are presented in Table 4.

Next, the response surface was constructed (approximation). In accordance with the full factorial design, the dependence of criteria on factors has the form (3):

$$F(x,y) = A + Bx + Cy + Dxy, \quad (3)$$

where x is the amount of solvent; y is settling time A, B, C, and D are regression coefficients. The term Dxy corresponds to the mutual influence of factors.

According to the experimental data, the value of the coefficients A, B, C, and D can be accurately determined. For the $F(x,y)$ dependence, the standard deviation was considered, after which it was differentiated by each of the coefficients. The

Table 3. Quantitative values of quality indicators after cleaning

No.	Solvent	Amount after cleaning, %	HMDA, %	GHC, %	Sulfate ash, %	Heavy metals, %
1	Chloroform	0.016	0.212	0.150	0.02	0.0017
2		0.007	0.138	0.076	0.04	0.0011
3		0.008	0.094	0.048	0.03	0.0008
4		0.006	0.066	0.091	0.03	0.0009
5	Carbon tetrachloride	0.076	0.212	0.149	0.03	0.0013
6		0.059	0.178	0.110	0.04	0.0012
7		0.043	0.121	0.076	0.04	0.0009
8		0.032	0.177	0.092	0.14	0.0010
9	Methylene chloride	0.094	0.146	0.171	0.02	0.0014
10		0.059	0.112	0.057	0.03	0.0008
11		0.061	0.060	0.054	0.05	0.0005
12		0.058	0.051	0.046	0.02	0.0006
13	Acetone	0.067	0.092	0.05	0.02	0.0009
14		0.024	0.062	0.048	0.04	0.0006
15		0.015	0.047	0.051	0.03	0.0008
16		0.013	0.049	0.046	0.03	0.0007

resulting system was equated to zero and solved with respect to the coefficients A, B, C, and D. Thus, an approximation was constructed for the dependence of the amounts of each of the residual impurities on the normalized factors x and y. The plot of this fitting function comprises the response surface.

Processing of experimental data and mathematical modeling by multivariate analysis of multicriteria optimization was carried out using Wolfram Mathematica software (*Wolfram Research*, USA).

Carbon tetrachloride

According to the calculations for the carbon tetrachloride solvent, the following dependencies (F) of the impurity residues on the amount of added solvent (x) and settling time (y) were obtained. Figure 2 shows the level lines for each impurity. The solid line indicates the limit value, while the dotted line indicates the permissible values. Optimal points should be located in the area of intersection of lines of all colors:

1. $F_{\text{solvent}}(x,y) = (341.25 - 191.25x - 109.375y + 39.375xy) \cdot 0.0004\%$;

2. $F_{\text{HMDA}}(x,y) = (-18.19 + 40.77x - 11.795y - 7.245xy) \cdot 0.05\%$;

3. $F_{\text{GHC}}(x,y) = (-1.49 + 9.63x - 7.875y + 1.575xy) \cdot 0.05\%$;

4. $F_{\text{sulfate ash}}(x,y) = (-11.5 + 20.25x - 6.125y - 1.575xy) \cdot 0.1\%$;

5. $F_{\text{heavy metals}}(x,y) = (-3.8 + 9x - 1.05y - 3.15xy) \cdot 0.001\%$.

Table 4. Normalized experimental data

No.	Solvent	Normalized added volume	Normalized settling time
1	Chloroform	0.67	0.33
2		0.78	0.50
3		0.89	0.75
4		1.00	1.00
5	Carbon tetrachloride	0.67	0.29
6		0.78	0.57
7		0.89	0.86
8		1.00	1.00
9	Methylene chloride	0.68	0.44
10		0.78	0.67
11		0.89	0.78
12		1.00	1.00
13	Acetone	0.73	0.60
14		0.82	0.40
15		0.91	0.80
16		1.00	1.00

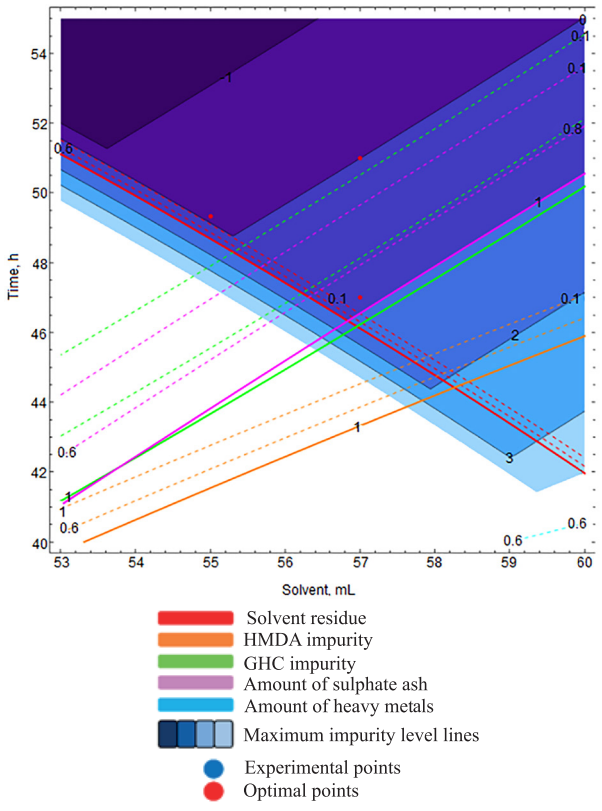

Fig. 2. Results of OHMG-HS optimization with carbon tetrachloride.

As can be seen from the traces of residual impurities, the amount of residue after cleaning can fall below the maximum allowable values given the correct solvent ratio and sufficient time. This area on the chart marked in dark blue and purple is bounded by red, pink and green solid charts. Within this allowable area, 3 optimal points for the reaction were found (red dots on the graph) with integer values of the added amount of solvent (mL) and settling time (h, min):

1. x = 57 mL, y = 47 h;
2. x = 55 mL, y = 49 h 20 min;
3. x = 57 mL, y = 51 h.

Methylene chloride

Similar calculations were carried out for the methylene chloride solvent (Fig. 3):

1. $F_{solvent}(x,y) = (4.1 - x - 8.3y + 6.17xy) \cdot 0.06\%$

2. $F_{HMDA}(x,y) = (13.6 - 19x + 0.67y + 5.8xy) \cdot 0.05\%$;

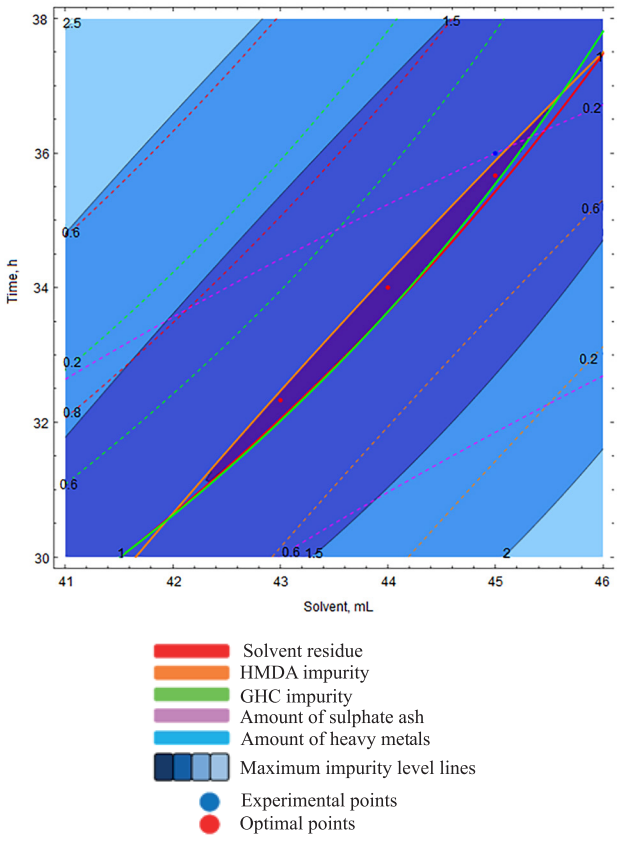

Fig. 3. Results of OHMG-HS optimization with methylene chloride.

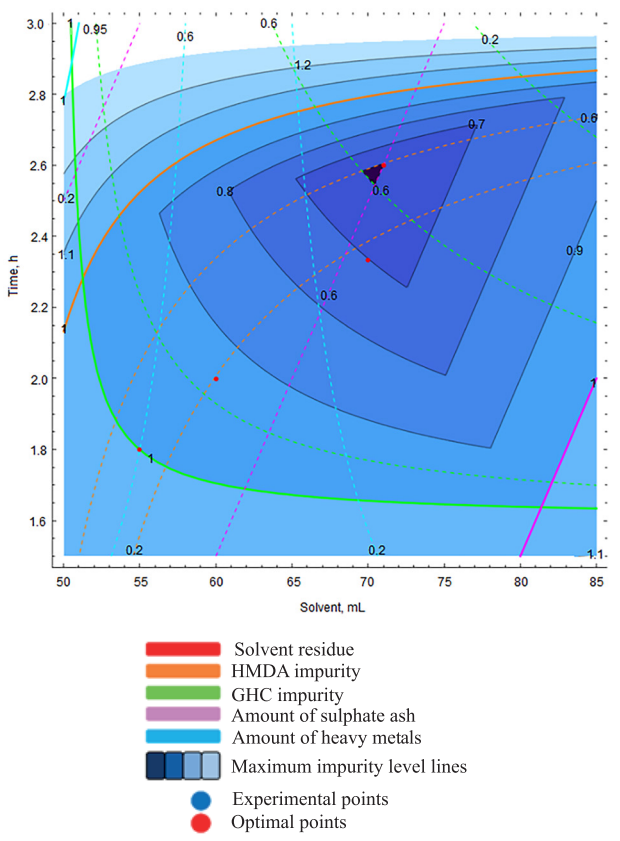

Fig. 4. Results of OHMG-GS optimization with chloroform.

3. $F_{GHC}(x,y) = (15.1 - 7.82x - 30.88y + 24.53xy) \cdot 0.05\%$;

4. $F_{sulfate\ ash}(x,y) =$
$= (-4.17 + 7.84x + 1.16y - 4.63xy) \cdot 0.1\%$;

5. $F_{heavy\ metals}(x,y) = (7.8 - 9x - 6.3y + 8.1xy) \cdot 0.001\%$.

Residual impurities plots show that, given the correct solvent ratio and sufficient time, the amount of residue after cleaning can fall below the acceptable limits (purple area bordered by orange, green, and red solid graphs). Within this allowable area, 3 red dots characterize the optimal (integer) values of the added amount of solvent and the settling time for carrying out the reaction:

1. $x = 44$ mL, $y = 34$ h;

2. $x = 43$ mL, $y = 32$ h 20 min;

3. $x = 45$ mL, $y = 35$ h 40 min.

Chloroform

Figure 4 shows the dependencies (F) of impurity residues on the amount of added solvent (x) and settling time (y) for the chloroform solvent in accordance with the calculations:

1. $F_{solvent}(x,y) = (26 - 48x + 32y - 9xy) \cdot 0.006\%$;

2. $F_{HMDA}(x,y) = (17.28 - 21.24x - 0.48y + 5.76xy) \cdot 0.05\%$;

3. $F_{GHC}(x,y) = (16.4 - 17.1x - 23.04y + 25.56xy) \cdot 0.05\%$;

4. $F_{sulfate\ ash}(x,y) = (-3.6 + 8.1x - 6y + 1.8xy) \cdot 0.1\%$;

5. $F_{heavy\ metals}(x,y) = (6.9 - 7.2x - 6y + 7.2xy) \cdot 0.001\%$.

In Fig. 4, the blue triangle (the darkest of those present), bounded by orange, green, and pink solid graphs, indicates the area where the amount of residue after cleaning can fall below the limit values at the desired ratio of solvent and time. Within this allowable range, the optimal (integer) values for the solvent amount added and the settling time are indicated by a red dot:

$x = 41$ mL, $y = 15$ h 20 min.

Acetone

Similar calculations for the acetone solvent are shown in Fig. 5:

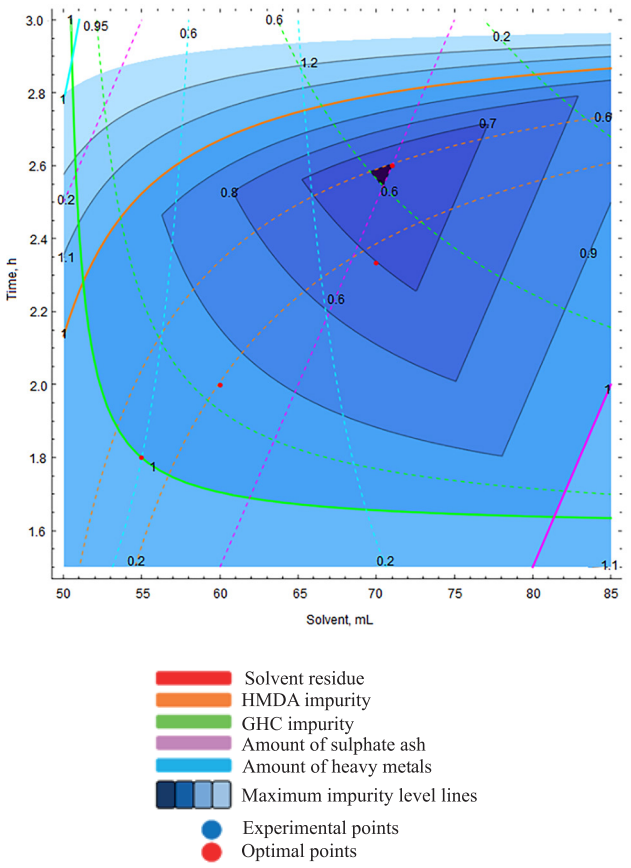

Fig. 5. Results of optimization of OHMG-GS with acetone.

1. $F_{solvent}(x,y) = (1.05 - 1.27x - 0.62y + 0.86xy) \cdot 0.5\%$;
2. $F_{HMDA}(x,y) = (11.32 - 12.41x - 8.3y + 10.37xy) \cdot 0.05\%$;
3. $F_{GHC}(x,y) = (-0.71 + 1.92x + 2.7y - 2.99xy) \cdot 0.05\%$;
4. $F_{sulfate\ ash}(x,y) = (-0.3 + 1.1x - 0.5y) \cdot 0.1\%$;
5. $F_{heavy\ metals}(x,y) =$
$= (-0.29 + 0.63x + 3.5y - 3.14xy) \cdot 0.001\%$.

As can be seen from the graphs of residual impurities, acetone is the best solvent, as it requires less settling time compared to chloroform, carbon tetrachloride, and methylene chloride. Four optimal points were proposed and approximated:

1. $x = 55$ mL, $y = 108$ min;
2. $x = 60$ mL, $y = 120$ min;
3. $x = 71$ mL, $y = 156$ min;
4. $x = 70$ mL, $y = 140$ min.

Table 5 indicates the values of the acceptance criteria calculated for points that meet the criteria.

From the data obtained by MAMO, it can be seen that the optimal points for OHMG-HS along with those for chloroform and methylene chloride solvents are on the border of the acceptance criteria in terms of HMDA and GHC impurities. From the location of the remaining proposed points for carbon tetrachloride and acetone solvents, it can be seen that the settling time of the mixture is reduced several times when using acetone in comparison with the use of carbon tetrachloride, which belongs to hazard class 1—highly toxic solvents (according to the State Pharmacopeia of the Russian Federation of the Russian Federation, carbon tetrachloride is used in pharmaceutical production in exceptional cases, when it is impossible to refuse its use). In this connection, the optimal method for purifying OHMG-HS is reprecipitation with acetone at the appropriate ratios of added solvent and mixture settling time:

1. 55 mL – 108 min;
2. 60 mL – 120 min;
3. 71 mL – 156 min;
4. 70 mL – 140 min.

After carrying out mathematical calculations, it was decided to reproduce control experiments that check the correctness of the obtained data (optimal points) (Figs. 6 and 7). The obtained experimental data are presented in Table 6.

Thus, based on a comparison of the experimental data with the MAMO data, the advanced hypothesis can be confirmed as valid, since for the methods of quantitative determination, the recovery factor (R) corresponds to an interval from 90% to 110%.

The precision of the technique was determined by the parameter of convergence (repeatability). For OHMG-HS, after selecting a single optimal point and performing the required number of experiments, the standard deviation and dispersion values were calculated for the results of HMDA, GHC, sulfate ash, and heavy metal impurities (Table 7).

The characteristics presented in the table indicate the compliance of the obtained results with the established acceptance criteria (Table 1) and the reproducibility of the technological stage of purification of OHMG-HS under the conditions selected using MAMO.

CONCLUSIONS

The obtained results were interpreted using MAMO according to the described algorithm.

Table 5. Acceptance criteria at the optimal points for the OHMG-HS

Solvent	Amount of solvent, mL, and settling mixture time	Amount of solvent after cleaning, %	HMDA, %	GHC, %	Sulphate ash, %	Heavy metals, %
Chloroform	41 mL, 15 h 20 min	0.0000	0.0490	0.0490	0.0990	0.0007
Methylene chloride	44 mL, 34 h	0.0590	0.0480	0.0700	0.0320	0.0005
	43 mL, 33 h 20 min	0.0590	0.0490	0.0470	0.0390	0.0005
	45 mL, 35 h 40 min	0.0590	0.0480	0.0490	0.0230	0.0006
Carbon tetrachloride	57 mL, 47 h	0.0000	0.0100	0.0430	0.0870	0.0001
	55 mL, 49 h 20	0.0000	0.0160	0.0210	0.0170	0.0003
	57 mL, 51 h	0.0000	0.0110	0.0110	0.0120	0.0004
Acetone	55 mL, 108 min	0.0000	0.0200	0.0500	0.0440	0.0006
	60 mL, 120 min	0.0000	0.0090	0.0470	0.0500	0.0005
	71 mL, 156 min	0.0000	0.0290	0.0280	0.0600	0.0000
	70 mL, 140 min	0.0000	0.0050	0.0350	0.0630	0.0000

Table 6. Experimental (practical) and calculated (theoretical) data obtained during the OHMG-HS purification of in acetone

Specifications	No. 1	No. 2	No. 3	No. 4	Recovery factor *R* theor./pract.
Volume of added solvent (mL) and settling time (min)	55 mL, 108 min	60 mL, 120 min	71 mL, 156 min	70 mL, 140 min	–
Amount of solvent after cleaning, theor., %	0.0000	0.0000	0.0000	0.0000	100%
Amount of solvent after cleaning, pract., %	0.0000	0.0000	0.0000	0.0000	
HMDA, theor., %	0.0200	0.0090	0.0050	0.0290	91.3%
HMDA, pract., %	0.0210	0.0070	0.0090	0.0320	
GHC, theor., %	0.0500	0.0470	0.0280	0.0350	98.2%
GHC, pract., %	0.0410	0.0390	0.0420	0.0410	
Sulphate ash, theor., %	0.0440	0.0500	0.0600	0.0630	96.4%
Sulphate ash, pract., %	0.0460	0.0510	0.0630	0.0650	
Heavy metals, theor., %	0.0006	0.0005	0.0000	0.0000	100%
Heavy metals, pract., %	0.0005	0.0003	0.0002	0.0001	

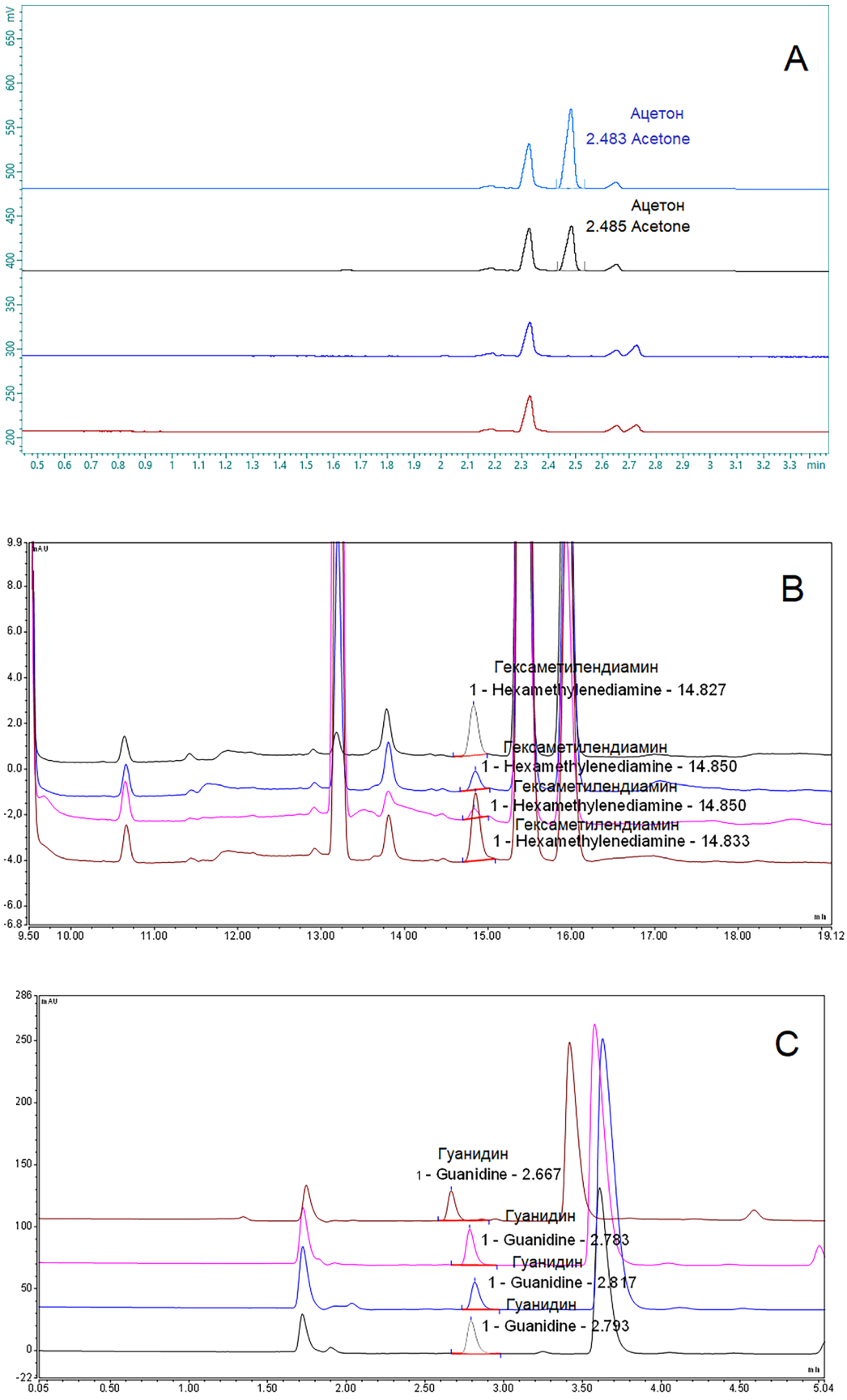

Fig. 6. HPLC analysis results for the content of acetone (A), HMDA (B), and GHC (C) admixtures for OHMG-HS samples No. 1–2.

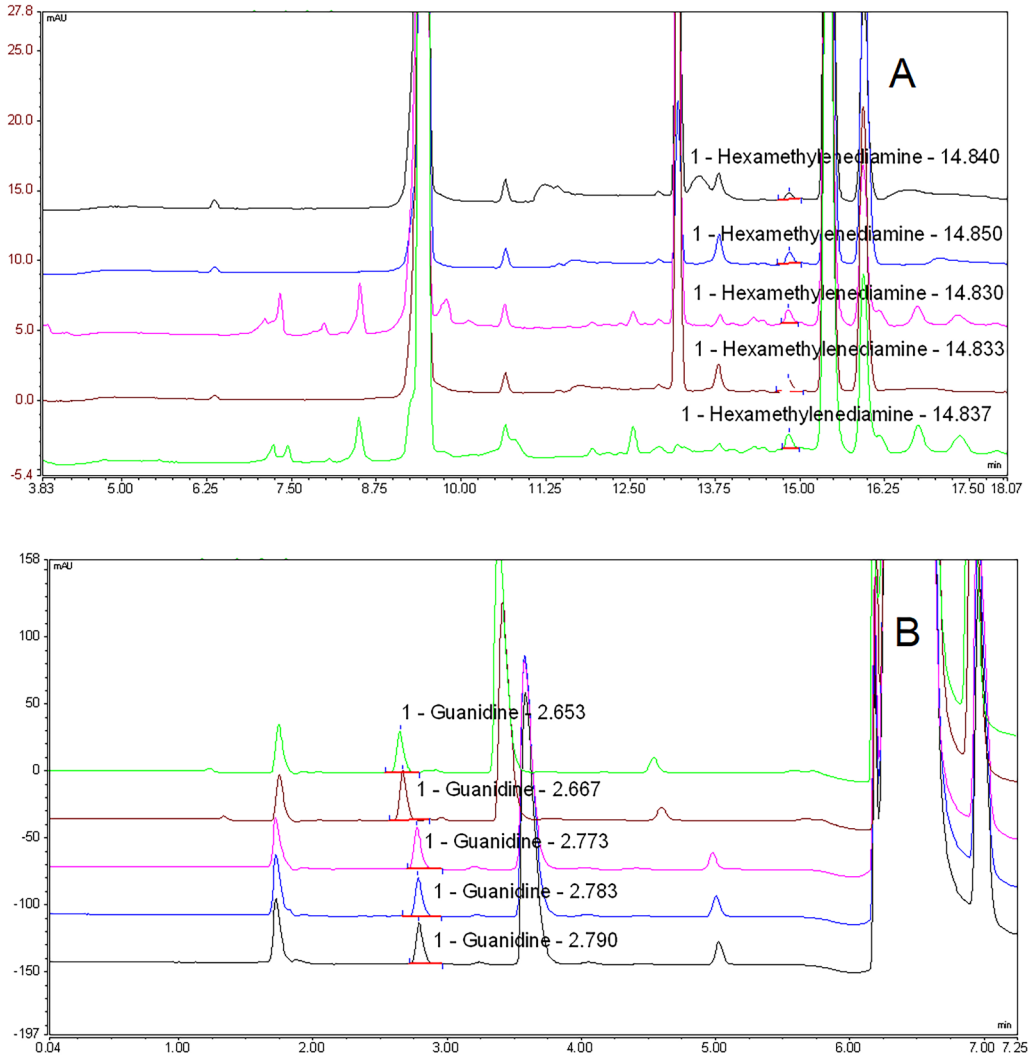

Fig. 7. HPLC analysis results for the content of HMDA (A) and GHC (B) admixtures for OHMG-HS obtained in the convergence study (5 repeats).

Table 7. Results of the convergence method checking

No.	Cleaning conditions		Quality criteria			
	solvent, mL	Settling time, min	HMDA, %	GHC, %	Sulphate ash, %	Heavy metals, %
1	70	140	0.011	0.045	0.063	0.0002
2			0.012	0.044	0.059	0.0001
3			0.007	0.043	0.062	0.0003
4			0.008	0.042	0.063	0.0001
5			0.009	0.041	0.061	0.0002
$\bar{A} \pm \sigma$			0.009 ± 0.002	0.043 ± 0.002	0.061 ± 0.002	0.0002 ± 0.0001

* $\bar{A} \pm \sigma$ – Standard deviation and dispersion.

As a result, dependencies of the influence of the ratio of the added amount of solvent and the settling time of the mixture on the final content of impurities in the target product were revealed. For the highest quality purification of OHMG-HS, the use of acetone solvent is advisable, since this reduces the process time to several hours while minimizing the quantity of impurities. Using statistical methods, the validity and repeatability of the proposed algorithmic model was substantiated. The use of MAMO for predicting the results and plotting the dependencies of the parameters and criteria of the reaction confirmed its feasibility as a means of reducing the time and material costs involved in experiments.

Authors' contributions

D.O. Shatalov – study concept;

K.N. Trachuk – writing and editing the text of the article, implementation of the analytical stage in the experimental studies, literature review;

A.V. Aydakova – conducting experiments;

D.A. Akhmedova – conducting experiments, writing and editing the text of the article;

I.S. Ivanov – conducting experiments;

D.S. Minenkov – processing experimental data;

I.Yu. Blazhevich – processing experimental data;

S.A. Kedik – developing a technological base for research.

The authors declare no actual or potential conflicts of interest in relation to this article.

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About the authors:

Denis O. Shatalov, Can. Sci. (Pharm.), Associate Professor, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: shat-05@mail.ru. ResearcherID H-9408-2013, Scopus Author ID 57060435900, RSCI SPIN-code 3453-9987, https://orcid.org/0000-0003-4510-1721

Kirill N. Trachuk, Student, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: trachuk98@yandex.ru. RSCI SPIN-code 9210-8024, https://orcid.org/0000-0002-2061-0274

Anna V. Aydakova, Technologist, Institute of Pharmaceutical Technologies (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: ann.reznikova2012@yandex.ru. RSCI SPIN-code 9925-5381, https://orcid.org/0000-0002-2560-5028

Diana A. Akhmedova, Postgraduate Student, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: akhmedova.diana.a@gmail.com. Scopus Author ID 57218775331, https://orcid.org/0000-0002-0951-939X

Ivan S. Ivanov, Technologist, Institute of Pharmaceutical Technologies (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: ivan.ivanov1994@gmail.com. Scopus Author ID 57372716000, RSCI SPIN-code 1899-6495, https://orcid.org/0000-0002-1346-7588

Dmitry S. Minenkov, Cand. Sci. (Phys.-Math.), Ishlinsky Institute for Problems in Mechanics, Russian Academy of Sciences (101, Vernadskogo pr., Moscow, 119526, Russia). E-mail: minenkov.ds@gmail.com. ResearcherID M-8037-2015, Scopus Author ID 36010696700, RSCI SPIN-code 6424-1334, https://orcid.org/0000-0001-6432-8134

Igor Yu. Blazhevich, Student, Faculty of Mechanics and Mathematics, Lomonosov Moscow State University (1, Kolmogorova ul., Moscow, 119234, Russia). E-mail: blazhevich-igor@mail.ru. https://orcid.org/0000-0002-3217-473X

Stanislav A. Kedik, Dr. Sci. (Eng.), Professor, Head of the Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia); General Director of the Institute of Pharmaceutical Technologies (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: doctorkedik@yandex.ru. Scopus Author ID 7801632547, https://orcid.org/0000-0003-2610-8493

Об авторах:

Шаталов Денис Олегович, к.фарм.н., доцент, доцент кафедры биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: shat-05@mail.ru. ResearcherID H-9408-2013, Scopus Author ID 57060435900, SPIN-код РИНЦ 3453-9987, https://orcid.org/0000-0003-4510-1721

Трачук Кирилл Николаевич, студент, кафедра биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86); E-mail: trachuk98@yandex.ru. SPIN-код РИНЦ 9210-8024, https://orcid.org/0000-0002-2061-0274

Айдакова Анна Викторовна, технолог, АО «Институт фармацевтических технологий» (121353, Россия, Москва, пр-т Вернадского, д. 86). E-mail: ann.reznikova2012@yandex.ru. SPIN-код РИНЦ 9925-5381, https://orcid.org/0000-0002-2560-5028

Ахмедова Диана Александровна, аспирант, кафедра биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: akhmedova.diana.a@gmail.com. Scopus Author ID 57218775331, https://orcid.org/0000-0002-0951-939X

Иванов Иван Сергеевич, технолог, АО «Институт фармацевтических технологий» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: ivan.ivanov1994@gmail.com. Scopus Author ID 57372716000, SPIN-код РИНЦ 1899-6495, https://orcid.org/0000-0002-1346-7588

Миненков Дмитрий Сергеевич, к.ф.-м.н., старший научный сотрудник, Институт проблем механики им. А.Ю. Ишлинского Российской академии наук (119526, Россия, Москва, пр. Вернадского, 101, к. 1) E-mail: minenkov.ds@gmail.com. ResearcherID M-8037-2015, Scopus Author ID 36010696700, SPIN-код РИНЦ 6424-1334, https://orcid.org/0000-0001-6432-8134

Блажевич Игорь Юрьевич, студент, механико-математический факультет ФГБОУ ВО «Московский государственный университет им. М.В. Ломоносова» (119234, Россия, Москва, ул. Колмогорова, 1). E-mail: blazhevich-igor@mail.ru. https://orcid.org/0000-0002-3217-473X

Кедик Станислав Анатольевич, д.т.н., профессор, заведующий кафедрой биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86); Генеральный директор АО «Институт фармацевтических технологий» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: doctorkedik@yandex.ru. Scopus Author ID 7801632547, https://orcid.org/0000-0003-2610-8493

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