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

The use of microfluidic hardware in the synthesis of oligohexamethylene guanidine derivatives

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Abstract

Objectives. *To develop a method for the microfluidic synthesis of oligohexamethylene guanidine salts in a flow-type reactor and to evaluate its effectiveness in relation to the synthesis in a traditional capacitive reactor and compare the purities of products obtained by these methods.*
Methods. *The synthesis of oligohexamethylene guanidine bihydrocarbonate (OHMG-BHC) was done using microfluidic hardware and the classical approach in volume. The purity and structure of the resulting product were confirmed by ^{13}C NMR spectroscopy and high-performance liquid chromatography (HPLC).*
Results. *The ^{13}C NMR spectrum of OHMG-BHC in classical bulk synthesis demonstrates that the product is unbranched and contains additionally unidentifiable impurities, in contrast to the sample obtained by the microfluidic method. Furthermore, the HPLC analysis showed that the OHMG-BHC sample synthesized using microfluidic technology has a 1.5-fold lower content than the initial monomers.*
Conclusions. *The advantage of synthesizing OHMG-BHC in a flow-type reactor compared to the traditional method of synthesis in volume is demonstrated since a product with a higher degree of purity is obtained.*

Keywords: *antimicrobial resistance, oligohexamethylene guanidine, bihydrocarbonate, microfluidic synthesis*

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НАУЧНАЯ СТАТЬЯ

Применение микрофлюидного аппаратного оснащения в синтезе производных олигогексаметиленгуанидина

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Аннотация

Цели. *Разработать методику микрофлюидного синтеза солей олигогексаметиленгуанидина в реакторе проточного типа и оценить ее эффективность по сравнению с синтезом в классическом емкостном реакторе, а также сравнить чистоту продуктов, полученных данными методами.*
Методы. *Синтез олигогексаметиленгуанидина дигидрокарбоната (ОГМГ-ДГК) проводили с применением микрофлюидного аппаратного оснащения и классическим методом в объеме. Подтверждение чистоты и структуры полученного продукта осуществляли с помощью ^{13}C ЯМР спектроскопии и высокоэффективной жидкостной хроматографии (ВЭЖХ).*
Результаты. *Спектр ^{13}C ЯМР ОГМГ-ДГК при классическом синтезе в объеме демонстрирует, что продукт является неразветвленным и содержит дополнительно неидентифицируемые примеси в отличие от образца, полученного микрофлюидным способом. Анализ методом ВЭЖХ показал, что образец ОГМГ-ДГК, синтезированный с помощью микрофлюидной технологии, имеет в 1.5 раза более низкое содержание исходных мономеров.*
Выводы. *Синтез ОГМГ-ДГК в проточном реакторе имеет преимущество по сравнению с классическим способом синтеза в объеме, поскольку выдает продукт с более высокой степенью чистоты.*

Ключевые слова: *резистентность к противомикробным препаратам, олигогексаметиленгуанидин, гидрокарбонат, микрофлюидный синтез*

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INTRODUCTION

According to the World Health Organization, antimicrobial resistance is a global threat to humanity[1]. The development of effective antibiotics in the 20th century is a direct result of the significant breakthroughs in antimicrobial therapy. Yet, the widespread use of antimicrobial drugs has contributed to the emergence of resistant pathogenic microflora, making it challenging to treat emerging infections and increasingly complex and expensive. Thus, an important task is searching and synthesizing new substances that exhibit antimicrobial activity [1, 2]. In this regard, compounds of several alkylene guanidines, in particular, oligohexamethylene guanidine (OHMG), with a wide spectrum of activity, a low toxicity class, and having a prolonged effect are promising [3, 4]. No bacterial resistance was detected for this class of compounds, and therefore they can be recommended for use, for example, as active pharmaceutical substances in ready-made dosage forms [5].

[1]https://www.who.int/drugresistance/documents/surveillancereport/en/ (Accessed April 04, 2021).

In recent years, one of the foremost perspectives taken by development actions for antimicrobial compounds is the synthesis of analogs and derivatives and the replacement of functional groups or parts of a molecule of already studied drugs, provided these parts meet the requirements for antimicrobial action and biological safety [6]. According to this approach, such derivatives of oligoalkylene guanidine as OHMG hydrochloride and OHMG hydrosuccinate were synthesized and studied. The studies have proved their effectiveness in dealing with pathogenic and opportunistic microorganisms compared to chlorohexidine and miramistin [5, 7]. Moreover, it is assumed that the new compounds of the OHMG class will also be highly effective against a wide range of pathogenic microflora. In this regard, the task of finding ways to obtain new derivatives of OHMG, for example, hydrocitrate, hydrosulfosalicylate, and hydrosalicylate, is urgent.

Traditionally, OHMG salts are obtained in capacitance-type reactors by polycondensing the initial monomers-hexamethylenediamine and guanidine bicarbonate or guanidine hydrochloride. Then, depending on the preferred guanidine salts, OHMG dihydrocarbonate (OHMG-BHC) or OHMG hydrochloride (OHMG-HC) are obtained, which are subsequently converted into other salt forms of OHMG (Fig. 1). However, the bulk synthesis approach, which is the traditional method, has many disadvantages; for example, this process's turbulent mixing regimes resulting in an uneven flow leads to a high content of residual monomers and anisotropy of the molecular mass characteristics of the resulting product [8–10].

Currently, microfluidics is a rapidly developing field of chemical synthesis. The primary advantage of microfluidic technology is its high efficiency due to improved mass and heat exchange provided by laminar flow and the ability to accurately control process parameters [11–16].

Previous studies have worked out the technology of microfluidic synthesis of OHMG-GC [17, 18], used as a semi-product for the production of other derivatives of OHMG, the synthesis of which was carried out according to scheme 1 (Fig. 1). However, as a disadvantage, it can be noted that in this scheme, additional stages are required for the further reaction: first, the preparation of the base of OHMG and/or OHMG-BHC, and then its corresponding salt (Fig. 1, Scheme 1). Alternatively, the implementation of synthesis through a semi-product of OHMG-BHC (Fig. 1, Scheme 2) can be considered. This, together with the use of microfluidic hardware, will reduce the number of stages and enhance the quality criteria in reference to its analog synthesized in volume. Thus, this study compares the effectiveness of methods for obtaining OHMG salt and the purity of the resulting product, based on the approach used – synthesis by the classical method in a capacitive reactor or microfluidics in a flow-type reactor.

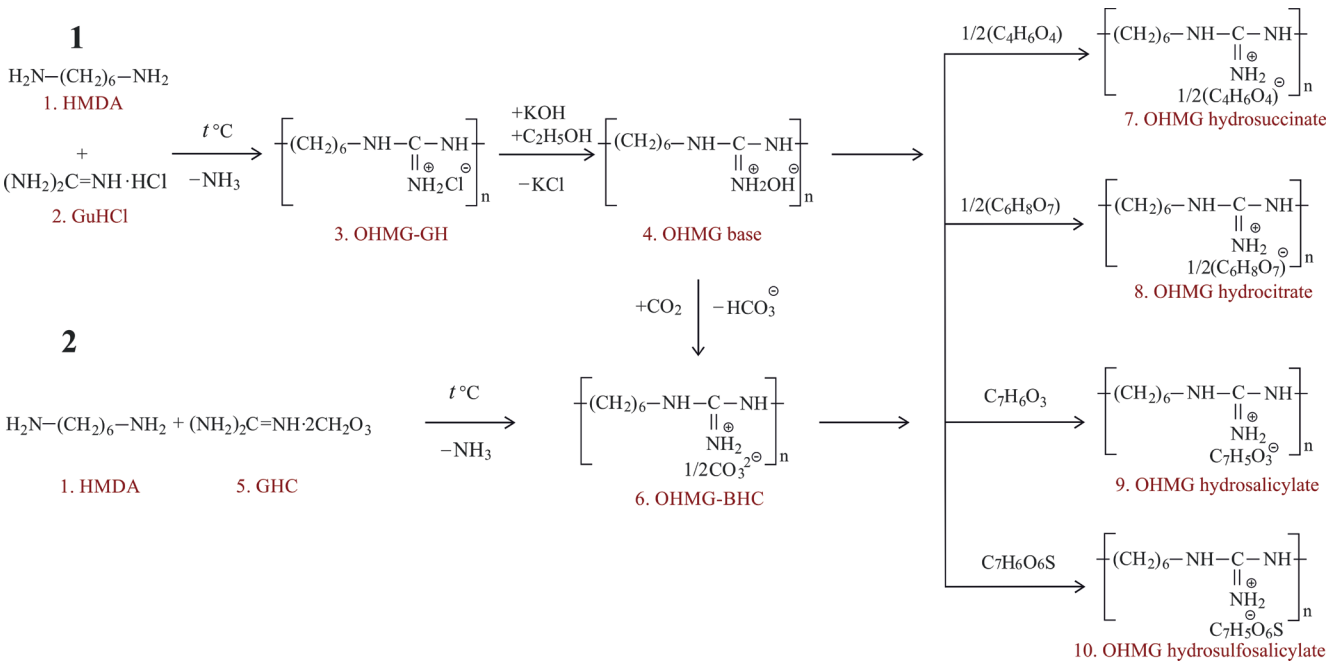

Fig. 1. Scheme synthesis of OHMG salts. HMDA – hexamethylenediamine; GuHCl – guanidine hydrochloride; OHMG base – the base of oligohexamethylene guanidine; GHC – guanidine hydrocarbonate.

EXPERIMENTAL

The following reagents were used in the experiment: Hexamethylenediamine (HMDA, *Acros Organics*, Belgium); guanidine hydrocarbonate (GHC, *Sigma-Aldrich*, USA). For microfluidic synthesis, a Qmix Pro Ext microreactor module from *Wingflow AG* (Switzerland) was used, consisting of syringe pumps (neMESYS MPM, Switzerland) and a capillary with a diameter of 1/8 inch (Qmix Q + HP flow, Switzerland) (Fig. 2). In addition, a rotary evaporator (IKA RV 10, Germany) was used to evaporate the water mixture.

OHMG-DHA was obtained in two ways—using traditional synthesis in volume and in a flow reactor.

Method 1-synthesis in a capacitive reactor. 1.55 g (1 mol) was mixed in a pre-weighed three-necked flask with a volume of 250 mL GHC and 1.0 g (1 mol) of HMDA. A flask with attachments of the initial components was installed on a heating plate, providing thermal insulation with asbestos cloth. Mixing the components was carried out using an upper-drive mixing device with a paddle stirrer immersed in the flask. The synthesis was started with simultaneous stirring and heating of the flask's contents at 90°C for 1 h. After that, the melt temperature was raised to 110°C, and polycondensation was carried out for 4 h. At the end of the process, the formed polymer was cooled to room temperature. A sample was taken for NMR analysis of the product and the quantitative content of related impurities [8].

Method 2-microfluidic synthesis in a flow reactor. In a pre-weighed glass, 1.55 g (1 mol) HHC, 1.0 g (1 mol) HMDA, and 11.5 g of water purified with a magnetic stirrer and an elliptical armature were mixed at room temperature until the substances were completely dissolved. The purified water acted as a solvent, which made it possible to avoid limiting the capillary throughput and, as a result, clogging it. The final concentration of the solution was 8.7% and 13.0% in the case of HMDA and GHC, respectively. The resulting mixture was continuously fed into the capillary using a syringe pump at about 0.01 mL/min rate. Polycondensation was carried out at 90°C for 1 h, after which the heating was increased to 110°C and the working mixture was maintained for 4 h. Thus, the OHMG salt was formed in the liquid flow as it moved along the length of the reactor at certain values of temperature and time. At the end of the synthesis, the working mixture was collected in a round-bottomed flask and transferred to the evaporation stage using a rotary evaporator at a temperature of 97°C. After the evaporation stage, a sample was taken from the formed polymer, which was subsequently analyzed by high-performance liquid chromatography (HPLC) and ^{13}C NMR.

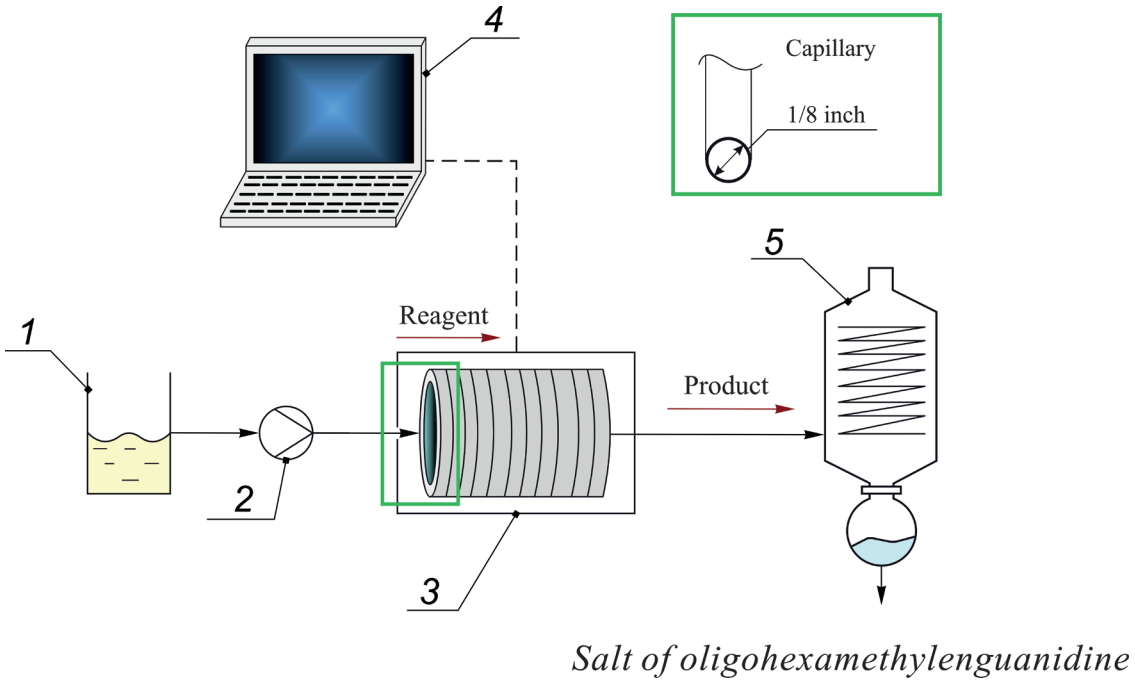

Fig. 2. Hardware diagram of microfluidic synthesis: *1* – an aqueous solution of GHC and HMDA; *2* – a syringe pump; *3* – a microreactor; *4* – a control computer; *5* – a rotary evaporator.

Spectra ^{13}C NMR samples of the synthesized compounds were recorded using the Bruker DPX NMR spectrometer (*Bruker*, Germany), deuterium oxide D_2O was used as a solvent, the resonant frequency was 75 MHz.

Quantitative determination of impurities in OHMG-BHC was carried out according to the State Pharmacopoeia of the Russian Federation of the 14th edition of the OFS.1.2.1.2.0005.15 "High-performance liquid chromatography" on the *Thermo Fisher Scientific* chromatograph (USA). The controlled limit of related impurities, namely HMDA and GHC, was determined according to the work of I.S. Ivanov[2] and amounted to 0.05 wt %. The concentrations of HMDA and GHC were determined chromatographically by external standards with UV detection at wavelengths of 205 nm and 264 nm, respectively[3].

The conditions for chromatographic determination of HMDA: column Luna C18(2) 5 µm, 150 × 4.6 mm; mobile phase A: water for chromatography; mobile phase B: acetonitrile; flow rate: 1 mL/min; temperature: 25°C; the volume of injected sample: 20.0 µL; analysis time: 30 min; gradient profile: 0–3 min, 0% B, 4–15 min, 90% B, 16–30 min, 0% B.

The conditions for chromatographic determination of GHC: column Luna C18(2) 5 µm, 250 × 4.6 mm; mobile phase A: water for chromatography; mobile phase B: acetonitrile; flow rate: 1 mL/min; temperature: 30°C; the volume loops – 100 µL; gradient profile: 0–1 min, 40% B, 10–16 min, 90% B, 17–20 min, 40% B.

RESULTS AND DISCUSSION

The authenticity of the synthesized compounds was confirmed by comparing the signals in a typical ^{13}C NMR spectrum of OHMG-BHC (according to the abovementioned work of Ivanov, Fig. 3) with signals in the spectra of the obtained samples (Fig. 4 and 5). The ^{13}C NMR spectrum analysis (Table 1) showed that in the case of a sample obtained by the classical method in volume, there is no signal at 156 ppm characterizing the branched structure of OHMG-BHC. In addition, signals from unidentifiable impurities were present in

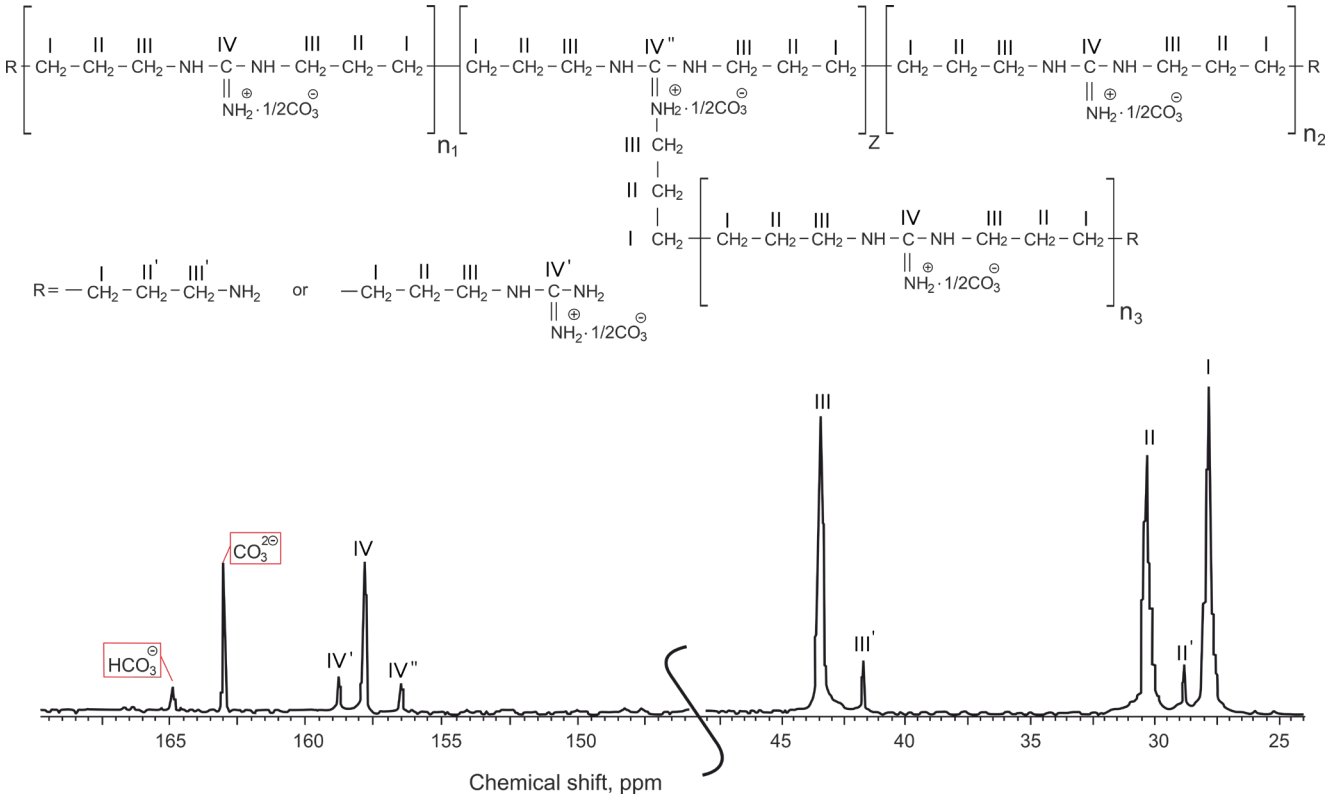

Fig. 3. Typical OHMG-BHC ^{13}C NMR spectrum (the signals in the spectrum are indicated according to the numbering of the atoms in the structural formula of the compound shown in the figure).

[2] Ivanov I.S. Microfluidic synthesis of the substance oligohexamethylene guanidine hydrosuccinate and the creation of an ophthalmic drug based on it. Cand. Thesis (Pharm.). Moscow: RTU MIREA; 2021. 118 p., 38–40.

[3] Shatalov D.O. Development and standardization of quality control methods for branched oligohexamethylene guanidine hydrochloride. Cand. Thesis (Pharm.). Samara: Sam. gos. med. un-t; 2015. 137 p., 67–70.

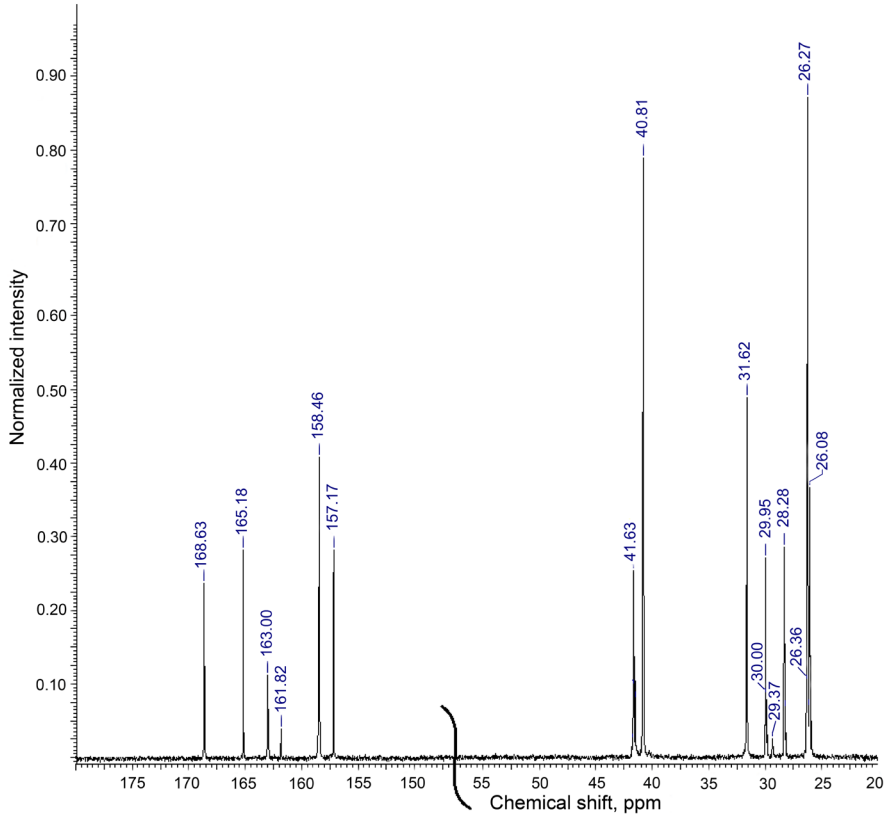

Fig. 4. ^{13}C NMR spectrum of OHMG-BHC obtained in volume.

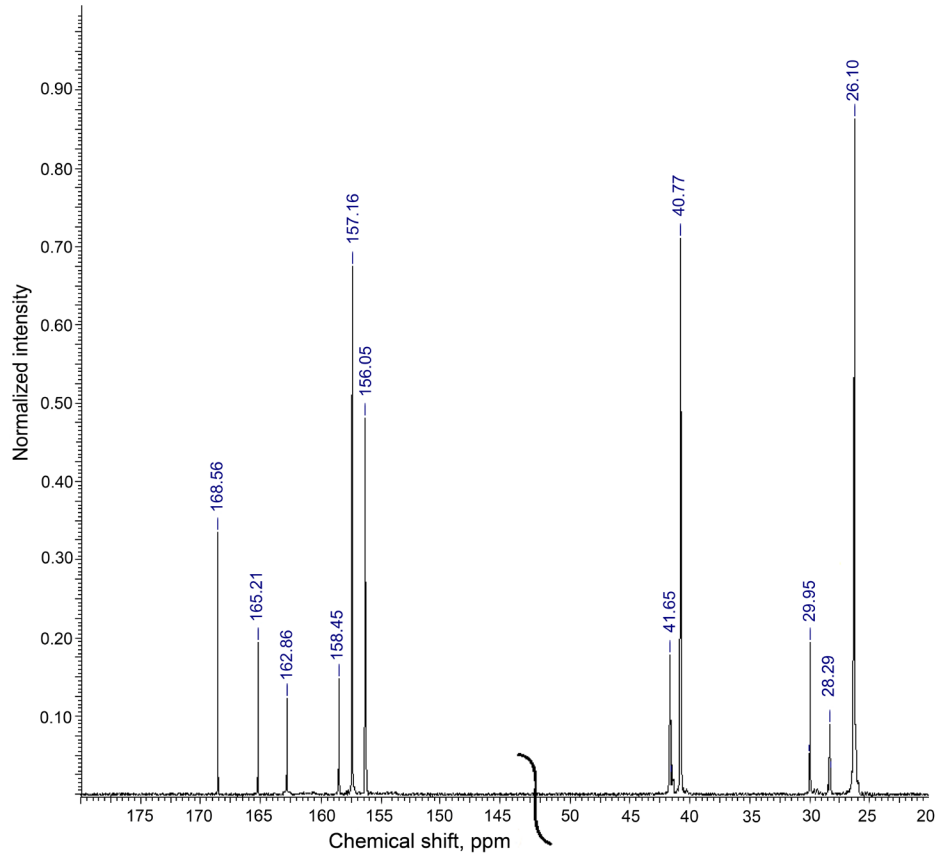

Fig. 5. ^{13}C NMR spectrum of OHMG-BHC obtained by microfluidic synthesis.

Table 1. Position of signals in the ^{13}C NMR spectrum of OHMG-BHC samples

Designation	Chemical shift, ppm		
	Typical spectrum	Volume synthesis	Microfluidic synthesis
I	26.0	26.27	26.10
II/	28.5	28.28	28.29
II	30.0	29.95	29.95
III/	40.0	40.81	40.77
III	41.5	41.63	41.65
IV//	156.0	–	156.05
IV	157.5	157.17	157.16
IV/	158.0	158.46	158.45
CO_3^{2-}	163.0	163.00	162.86
HCO_3	165.0	165.18	165.21
Impurity signals	–	168.63/161.82 31.82/30.00/29.37/26.36/26.08	168.56

the spectrum. However, microfluidic technology makes it possible to achieve branching of the OHMG-BHC oligomeric chain, which contributes to an increase in antimicrobial activity [19].

It could be seen from the HPLC analysis of samples of OHMG bicarbonate obtained by the two methods that the product contains the initial monomers GHC (Fig. 6) and HMDA (Fig. 7) with retention times of 14.38 min and 4.07 min, respectively. However, the analysis of results indicates (Table. 2) that OHMG-BHC, obtained from microfluidic technology, showed about 1.5 times lower content of the initial monomers—HMDA and GHC, thus indicating a more complete reaction the consumption of reagents. Nevertheless, the results show the need for further purification of the product, irrespective of the choice of the synthesis method.

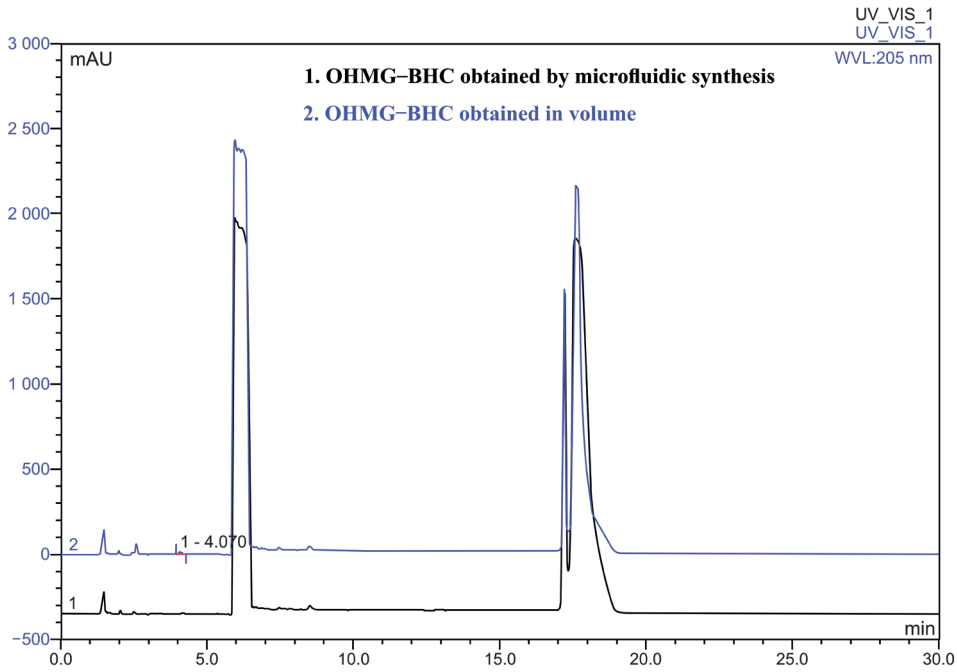

Fig. 6. Two methods obtained chromatograms for determining the quantitative content of GC in OHMG-BHC samples.

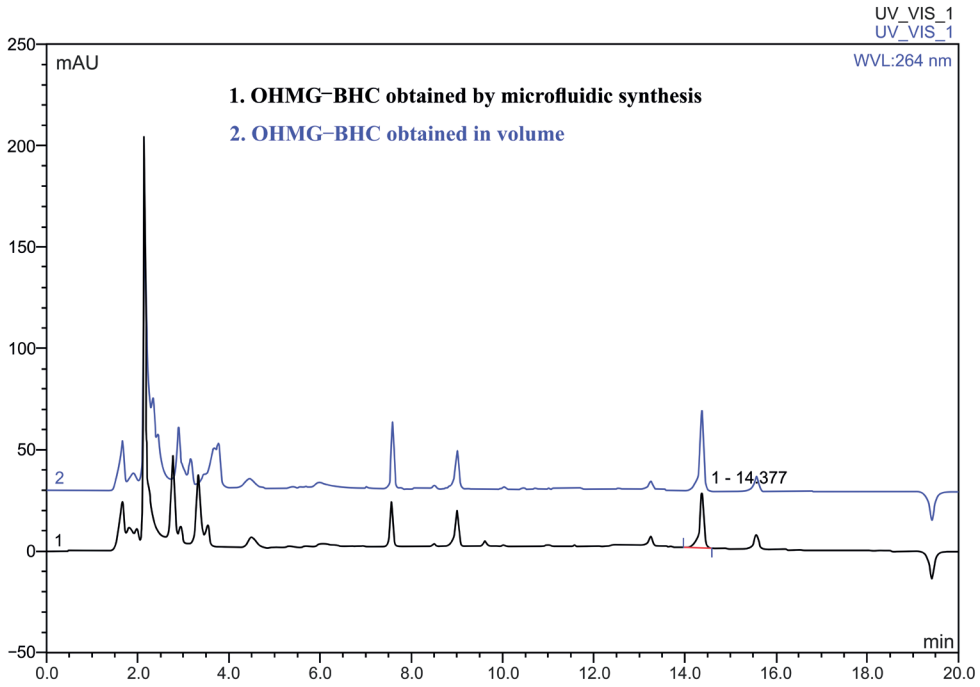

Fig. 7. Two methods obtained chromatograms for determining the quantitative content of HMDA in OHMG-BHC samples.

Table 2. The content of impurities in OHMG–BHC

Synthesis	GHC, wt %	HMDA, wt %
Voluminous	1.372	0.628
Microfluidic	0.821	0.451

CONCLUSIONS

The initial stages of the study showed the advantage of using microfluidic hardware in synthesizing OHMG-BHC compared to the classical method in volume. Therefore, the application of microfluidic technology results in higher purity products, which can be used as a semi-product for the production of other salts of OHMG, expanding the range of biologically active compounds with antimicrobial activity and the scope of their application.

Authors' contributions

D.A. Akhmedova – preparing the original project, conducting experiments, managing the project;

D.O. Shatalov – creating a research concept, implementation of the analytical stage in experimental studies;

I.S. Ivanov – methodology development, preparing the original project, conducting experiments;

A.V. Aydakova – conducting experiments;

A. Herbst – development of a technological base for conducting research; analysis of literary sources, writing and editing the text of the article;

L. Greiner – development of a technological base for conducting research; analysis of literary sources, writing and editing the text of the article;

A.P. Kaplun – processing experimental data, adjustment of experimental studies;

A.S. Zhurbenko – conducting experiments;

S.A. Kedik – creating a research concept, development of a technological base for conducting research.

The authors declare no conflicts of interest.

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