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- Theoretical Bases of Chemical Technology
- Chemistry and Technology of Organic Substances
- Chemistry and Technology of Medicinal Compounds and Biologically Active Substances
- Synthesis and Processing of Polymers and Polymeric Composites
- Chemistry and Technology of Inorganic Materials
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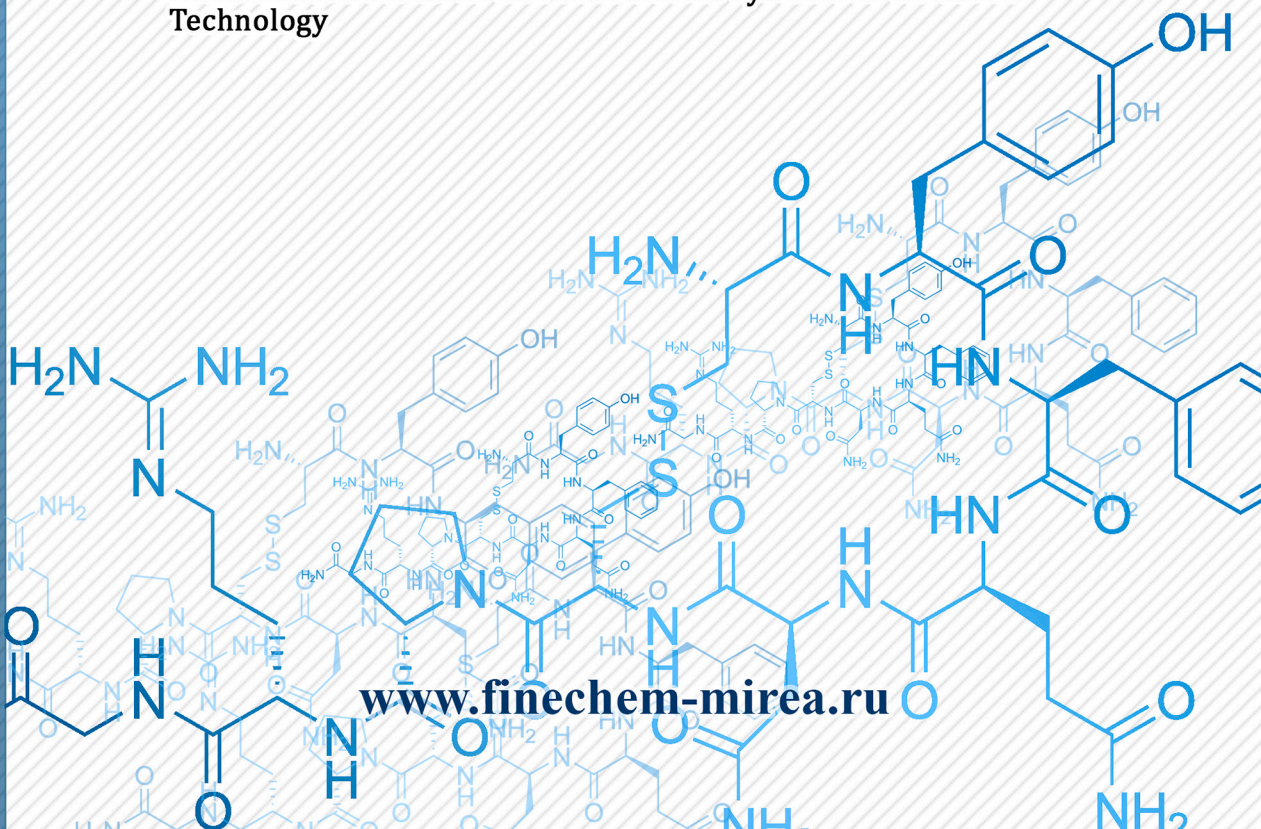

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86, Vernadskogo pr., Moscow, 119571, Russian Federation.
Phone: +7(495) 246-05-55 (#2-88)
E-mail: *seredina@mirea.ru*

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Тел.: +7(495) 246-05-55 (#2-88)
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RESEARCH ARTICLE

Development of an encapsulation process for toxic waste and hazardous chemicals in a fluidized bed

Yuri A. Eleev[@], Yulia S. Bogoyavlenskaya, Elena N. Glukhan, Vladimir F. Golovkov, Vladimir V. Afanasiev

State Research Institute of Organic Chemistry and Technology, Moscow, 111024 Russia
[@]Corresponding author, e-mail: 2553215@gmail.com, dir@gosniiokht.ru

Abstract

Objectives. *This paper presents research results on the encapsulation of a fluidized bed of liquid and solid toxic waste containing chemicals with a hazard class of 1–3.*

Methods. *Soils contaminated with hexachlorobenzene and hexachlorocyclohexane were used as the seed material. Ceresin was selected as the encapsulant, which was sprayed onto the fluidized bed through a pneumatic nozzle at a temperature of 135°C. Before the spraying of the ceresin, binders were introduced into the fluidized bed of the seed material through pneumatic nozzles in the form of a melt of high-temperature coal-tar pitch and wastewater containing sodium and arsenic salts as well as heavy metal oxides. The experiments were carried out using a modified GLATT AGT-150 laboratory unit.*

Results. *The results demonstrate that the mechanism for granule formation is a mixed mechanism. The binding of the seed material is carried out by both the pitch and salting out. In this case, the cavities in the agglomerates are partially filled with salt deposits, which increases the strength and integrity of the final product's structure. Ranges for the process parameter values were established at the point at which there was no unwanted agglomeration in the fluidized bed, and dust formation did not exceed 5%. When the ratio of the bed mass to the mass of ceresin is equal to unity, a moisture-resistant free-flowing product of hazard class 5 is obtained, which is suitable for transportation and long-term storage. The average diameters of the initial particles and encapsulated granules were 0.5 and 1.5 mm, respectively.*

Conclusions. *The present study demonstrates a potential process for the granulation–encapsulation of toxic waste and hazardous substances with a hazard class of 1–3 in a single fluid-bed apparatus, resulting in the formation of a moisture-resistant hazard class-5 granular product suitable for transportation and long-term storage. The results obtained can be used in the development of an industrial large-scale process for encapsulating waste of hazard classes 1–3.*

Keywords: *persistent organic pollutants, heavy metals, toxic wastes, wastewater, encapsulation, coal-tar pitch, ceresin*

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НАУЧНАЯ СТАТЬЯ

Разработка процесса инкапсуляции токсичных отходов и опасных химических веществ в псевдоожиженном слое

Ю.А. Елеев[@], Ю.С. Богоявленская, Е.Н. Глухан, В.Ф. Головков, В.В. Афанасьев

Государственный научно-исследовательский институт органической химии и технологии, Москва, 111024 Россия
[@]Автор для переписки, e-mail: 2553215@gmail.com, dir@gosniiokht.ru

Аннотация

Цели. *Исследование процесса инкапсуляции в условиях псевдоожиженного слоя жидких и твердых токсичных отходов, содержащих химические вещества 1–3 классов опасности.*
Методы. *Для исследований в качестве затравочного материала использовался грунт, загрязненный гексахлорбензолом и гексахлорциклогексаном. Инкапсулянтом выступал церезин, который при температуре 135 °C распылялся в псевдоожиженный слой через пневматическую форсунку. Эксперименты осуществлялись на модифицированной лабораторной установке GLATT AGT-150. Перед распылением церезина в грунт через пневматические форсунки вводились связующие – плав высокотемпературного каменноугольного пека и сточные воды, содержащие соли натрия, мышьяка, а также оксиды тяжелых металлов.*
Результаты. *Показано, что механизм гранулообразования носит смешанный характер. Связывание исходных частиц загрязненного грунта осуществляется как пеком, так и за счет высаливания. При этом полости в агломерате частично заполняются отложениями солей, что увеличивает прочность и целостность структуры конечного продукта. Установлены диапазоны значений управляющих параметров процесса, при которых в слое отсутствовала нежелательная агломерация, а пылеобразование не превышало 5%. При отношении массы слоя частиц (гранул) к массе поданного церезина, равном единице, получен влагоустойчивый сыпучий пригодный для транспортировки и длительного хранения продукт 5 класса опасности. Средние диаметры исходных частиц и капсулированных гранул соответственно составляют 0.5 мм и 1.5 мм.*
Выводы. *Выполненные исследования показали принципиальную возможность проведения в одном аппарате процесса сушки-грануляции-капсулирования токсичных отходов и опасных химических веществ 1–3 классов опасности с образованием сыпучего продукта 5 класса опасности, обладающего влагоустойчивостью, а также пригодного для транспортировки и длительного хранения. Полученные результаты могут быть использованы при разработке промышленного крупнотоннажного процесса инкапсуляции отходов 1–3 классов опасности.*

Ключевые слова: *стойкие органические загрязнители, тяжелые металлы, токсичные отходы, сточные воды, инкапсуляция, каменноугольный пек, церезин*

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INTRODUCTION

According to the official data of the Ministry of Natural Resources and Environment of the Russian Federation, there are currently more than 200 sites of accumulated environmental damage in Russia where toxic substances are stored or buried, including substances of hazard class 1 or 2 (in particular, persistent organic pollutants, POPs). The total volume of these substances is estimated to be in the millions of tons. It is also known that there are numerous unauthorized dumps and burial sites containing industrial waste.[1,2]

For the destruction of toxic substances classified as hazard class 1 or 2, the thermal high-temperature neutralization method has gained the greatest global popularity. Despite this method's high level of efficiency, its main drawback is the need to create an expensive gas cleaning system. At the same time, it is necessary to address the issue of wastewater disposal associated with this method [1, 2].

At the regional level, as a rule, the options considered for making relatively small landfill sites containing toxic substances/waste safe are either to establish a landfill for the appropriate hazard class in the immediate vicinity of the general-waste landfill site or to transfer the hazardous chemicals/waste to a specialized organization for further processing, disposal, or dumping.

The primary objective, both during the long-term storage and transportation of toxic waste, hazardous chemicals, and wastewater, is to minimize the likelihood of their penetration into the environment.

One of the industrial methods used for this purpose is encapsulation in a solid matrix. Concrete and bitumen are usually used as encapsulants [3]. A common disadvantage of both matrices is a significant increase in the weight and volume of the encapsulated waste as well as the observed leaching of toxic contents, the percentage of which depends both on the composition of the encapsulated substances and the encapsulator as well as on the storage conditions [4]. For example, the leaching of arsenic from concreted arsenic-containing waste over a period of 406 days under constant water exposure (at 10% of the maximum achievable arsenic content in the concrete matrix) has been calculated at 0.34% [5, 6]. In addition, experiments on the bituminization of ash from the incineration of toxic waste have demonstrated the leaching of heavy metals over 90 days at a level of 0.1–0.3%; the heavy metal concentration in the ash was 5–11 mg/kg and the ash content of the bitumen was up to 60% by weight [7]. The leaching of polycyclic aromatic hydrocarbons directly from bitumen can reach 1×10^{-4} mg/L over 64 days [8].

In the present study, ceresin, widely used as an insulating material in radio and electrical engineering, was proposed as an alternative encapsulant. Ceresin is a solid under normal conditions and is a water-insoluble and environmentally inert mixture of marginal hydrocarbons. Due to its relatively low melting point, density, and viscosity, ceresin can be easily sprayed through a mechanical or pneumatic nozzle into a fluidized bed of solid material to form a film on its surface.

To reduce the consumption of ceresin, the possibility of increasing the size of fluidized particles through granulation was investigated, which, in turn, would significantly reduce the total area of the encapsulated surface. Two mixtures were selected as binders: a high-temperature coal-tar and wastewater containing heavy metals and soluble sodium salts (including arsenite). This selection is based on the fact that these binders are also disposable and recyclable as waste, and therefore their use as raw materials is economically justified.

Thus, the aim of this study was to develop a process for encapsulation of toxic waste and hazardous chemicals using solid hydrocarbon waste and wastewater containing heavy metals and soluble salts as a binder in a product suitable for transportation and long-term storage without significantly increasing the initial weight and volume.

This study focused on hazard class-2 POP-contaminated soil removed from the Bolshie Izbishchi landfill site (Lipetsk oblast, Russia) and a hazard class-3 reaction mass, obtained by laboratory means from the wet cleaning stage of flue gases during the research of the thermal neutralization of hazard class-2 sludge sampled from the territory of the former *Srednevolzhsky Chemical Plant* (Chapaevsk, Russia).

The hazard class was determined using bioassay methods on hydrobionts in accordance with R 52.24.566-94.[3]

[1] Ministry of Natural Resources of Russia: The state register of objects of accumulated environmental damage (accessed April 13, 2021) (in Russ.). https://www.mnr.gov.ru/docs/docs/svedeniya_soderzhashchiesya_v_gosudarstvennom_reestre_obektov_nakoplennogo_vreda_okruzhayushchey_sr/?special_version=Y

[2] Rosprirodnadzor. Rosprirodnadzor reports on illegal landfills. Russia, Moscow; 2019 (published July 09, 2020, accessed Oct 8, 2020) (in Russ.). https://rpn.gov.ru/news/156/

[3] R 52.24.566-94. Recommendations. Methods for toxicological assessment of pollution of freshwater ecosystems. St. Petersburg: Gidrometeoizdat; 1994. 136 p.

MATERIALS AND METHODS

The composition of the POP-contaminated soil, sampled from the Bolshie Izbishchi landfill site, is presented in Table 1.

Table 1. The composition of the contaminated soil*

Component name	mass %
Water	17.45
Inert filler (talc, pyrophyllite, kaolin)	15.37
Hexachlorobenzene	0.004
Hexachlorocyclohexane (mixture of isomers including lindane)**	0.002
Soil	67.18
Total:	100.00

* Average particle diameter 0.5–0.6 mm.
** Lindane is classified as hazard class 1.

The wastewater composition is shown in Table 2.

High-temperature coal-tar with a melting point of ~116–120°C (CAS no. 65996-93-2)[4] was used as a binder to model the properties of waste from the production of coke and coal-tar pitch. Before use, the pitch was crushed in a laboratory ball mill to a particle size of less than 200 μm. The encapsulant was ceresin-75 (according to GOST 2488-79)[5], and air was used as a fluidizing agent. A schematic diagram of the laboratory unit developed for this study, based on GLATT AGT-150 (*Glatt GmbH*, Germany), is shown in Fig. 1.

The main geometric parameters of the installation are as follows: the diameter of the working chamber is 160 mm, the height of the cylindrical part of the working chamber is 450 mm, and the area of the gas distribution grid is 0.02 m^2.

The pitch spray nozzle (7) is installed at a height of 335 mm above the gas distribution grid (5), and the pneumatic spray nozzle for wastewater and ceresin (6) is installed at a height of 40 mm (nozzle direction up).

The design of the unit provides the ability for the selective discharge of the product into the collector (4)

Table 2. Wastewater composition

Component name	mass %
H_2O	77.55
PbO	0.02
ZnO	0.01
CdO	0.003
CoO	0.001
CuO	0.02
As_2O_3	0.02
Na_2CO_3	0.79
NaCl	20.69
Na_2SO_4	0.50
$NaNO_2$	0.33
Na_3AsO_3	0.07
Total:	100.00

through a sifter (3), in which the particles are segregated by weight by controlling the flow rate of the ascending air flow. The area of the slotted gap for the supply of air to the nozzles is 6.28×10^{-6} m^2.

The unit has a control panel for setting and controlling the operating parameters: the flow rate of the "processed" air and its temperature, the air pressure in the injectors, the flow rate and temperature of the supplied substances, and the pressure in the sifter of the finished product.

The laboratory unit's technological and design parameters were determined as the following:

– wastewater and ceresin consumption (G_{ww}, G_c): 0.6–3.0 kg/h;
– fluidizing agent consumption (G_{FA}): 40–400 m^3/h;
– pitch consumption (G_p): 0.5 kg/h;
– fluidizing agent temperature (T_{FA}): up to 260°C;
– spray air pressure in the injectors (P_{AA}): 1.4–3.6 bar;
– diameter of the spray nozzle of the injectors: 0.5 mm.

The experimental procedure is as follows. A specified amount of contaminated soil is loaded into the drying chamber (8). Then, using a fan (10) in the drying chamber (8), a fluidizing agent (air) of a specified temperature is introduced through the unit's

[4] CAS No. 65996-93-2. Coal-tar pitch, high temperature. Summary risk assessment report (accessed April 13, 2021). URL: https://echa.europa.eu/documents/10162/13630/trd_rar_env_netherlands_pitch_en.pdf
[5] GOST 2488-79. Geresin. Specifications. Moscow: Izd-vo standartov; 1980. 6 p.

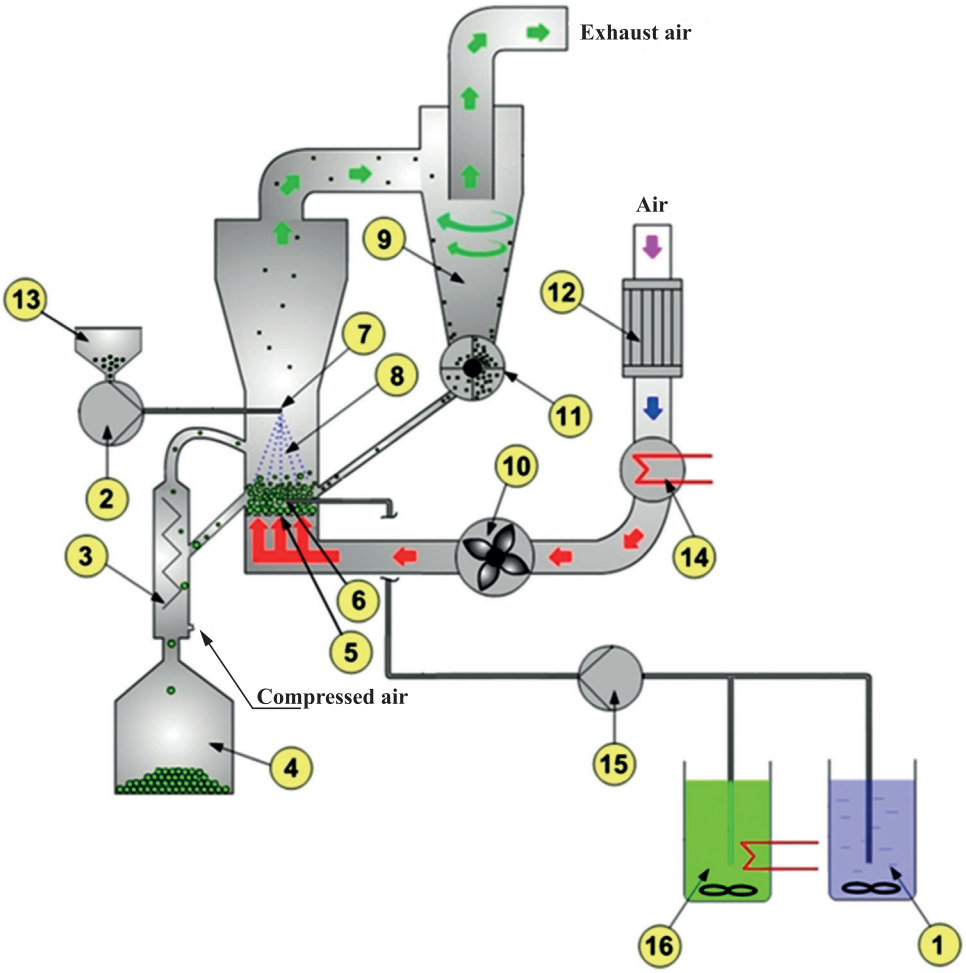


Fig. 1. Schematic diagram of the laboratory unit:
(1) tank with wastewater; (2) screw dispenser; (3) sifter; (4) product collector; (5) gas distribution grid; (6) nozzle for spraying wastewater and ceresin; (7) pitch feed nozzle; (8) drying-encapsulation chamber; (9) cyclone; (10) fan; (11) drum gateway; (12) refrigerator; (13) bunker with crushed pitch; (14) heater; (15) pump; (16) vessel with ceresin melt.

gas distribution grid (5), changing the contaminated soil/granulate bed into a fluidized state.

Wastewater (1), which is continuously agitated, is sprayed by a gerotor pump (15) through the pneumatic nozzle (6) into the drying chamber (8), where the moisture evaporates and the solids settle on the surface of the contaminated soil. At the same time, crushed pitch is fed from the hopper (1) via a screw dispenser (2) to the working chamber of the pneumatic nozzle (7). This chamber (7) is equipped with an electric heating element that converts the powdered pitch into a molten state (temperature ~200–210°C). The pitch melt is then fed from the working chamber to the nozzle for spraying using an integrated screw pump.

The exhaust air ascends to the top of the device and, after additional dust separation in the cyclone (9), is discharged into the supply and exhaust ventilation system. The fine particles separated in the cyclone are continuously discharged through the cellular rotary valve (11) back to the working area of the machine.

After the accumulation of granules of a given size in the bed, the temperature of the fluidizing agent is reduced to room temperature, and by means of a pneumatic nozzle (6), the molten ceresin is fed from the heated container (16) at a temperature of 135°C with constant stirring. As the molten ceresin is sprayed onto the fluidized bed, the previously formed granules form capsules covered with an inert solid shell.

The operating time of the single experiment is 1 h. At the end of the experiment, the unit is cooled to room temperature and the product is discharged from the drying chamber (8).

The experiments were carried out in three stages:

Stage 1: determination of the operating parameters of the dry granulation of wastewater on the surface of the contaminated soil,

Stage 2: determination of the operating parameters of the dry granulation of wastewater on the surface of the contaminated soil with the simultaneous spraying of pitch, and

Stage 3: determination of the operating parameters of the ceresin encapsulation of the granules obtained in Stage 2.

The resulting product was subjected to a sieve analysis. In addition, at Stage 3, the product was tested for moisture resistance by placing it in water (volume 2 L) at room temperature for 96 h and performing a chemical analysis on the extract, and biotesting on hydrobionts was conducted to determine the product's hazard class.

RESULTS AND DISCUSSION

The flow rate of the fluidizing agent was estimated using the calculation method described by N.A. Shakhova [9]. Thus, the minimum flow rate of the fluidizing agent at a temperature of 100°C, which provides fluidization of particles in the size range d_p = 0.5 mm (density 2165 kg/m^3), was 65 m^3/h (operating speed w_{FA} = 0.9 m/s).

It is known [10] that the values of the working speed of w_{FA} in the range of 0.8–1.4 m/s are routinely related to drying in a fluidized bed, whereas, in dry granulation, the speed of the fluidizing agent is usually 1.0–2.0 m/s. Therefore, it was also advisable to use the fluidizing agent flow rate of 110 m^3/h (w_{FA} = 1.53 m/s) during the experiments.

The calculation of the mass of layer M, which contains the particles d_p = 0.5 mm located in the nozzle flare zone, and the maximum height of layer l, which should not exceed the height of the working chamber (0.45 m), under conditions in which the operating speed of the fluidizing agent changes from 0.9 m/s to 1.53 m/s (a flow rate change from 65 m^3/h to 110 m^3/h), was also carried out according to the Shakhova method [9, 11].The results of the mass calculation are presented graphically in Fig. 2.

Based on the results of the calculated data presented in Fig. 2, we assumed that the amount of contaminated soil used as a seed with d_p = 0.5 mm can be in the range of M = 0.5–2.4 kg (w_{FA} = 0.9 m/s) and M = 0.4–1.7 kg (w_{FA} = 1.53 m/s).

The temperature of the fluidizing agent and the wastewater flow rate are among the main control parameters that regulate the moisture content in the layer and affect the nature of the interaction of the particles with each other [12].

The calculation of the dependence of the temperature of the fluidizing agent T_{FA} on the wastewater flow rate G_{ww} (in the range of 0.6–3.0 kg/h) while maintaining a constant temperature in the bed of 100°C (the highest moisture intake during drying) and fluidizing agent G_{FA} flow rates of 65 m^3/h and 110 m^3/h was carried out according to the heat

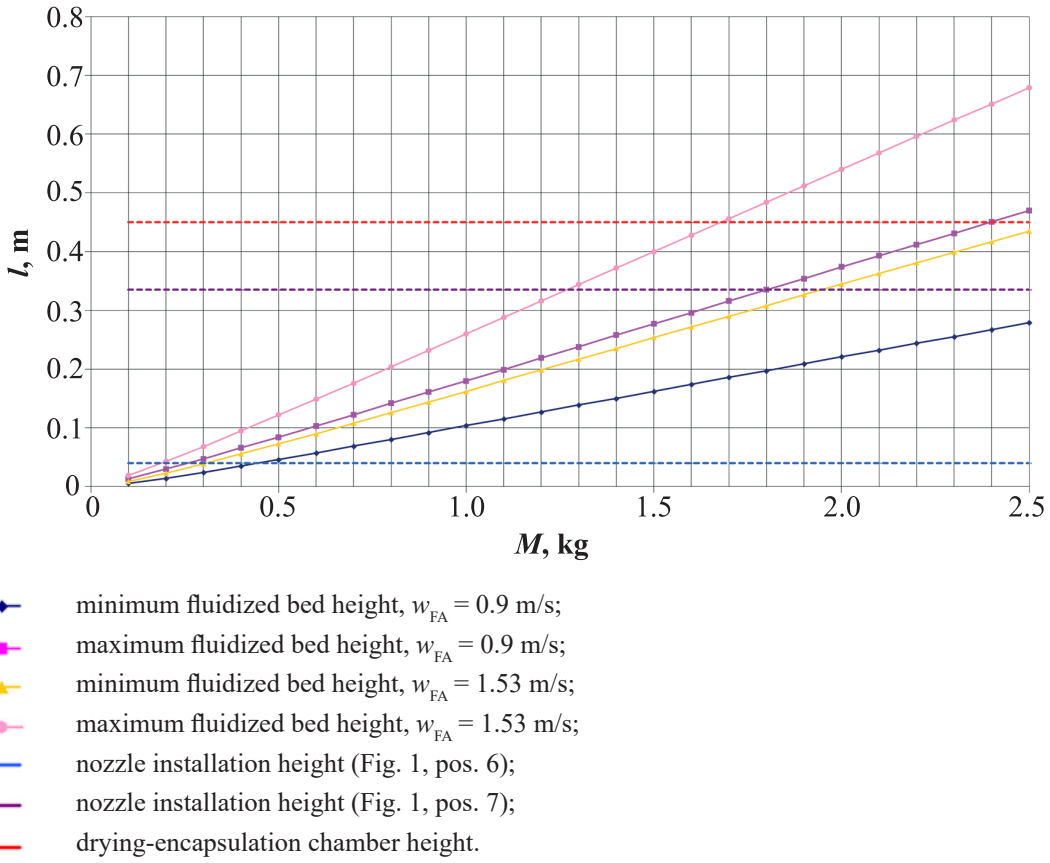


Fig. 2. Calculated dependence of the fluidized bed height on its mass (d_p = 0.5 mm).

balance equation given in P.G. Smith's monograph [13]. The values presented in Table 3 were used for the calculation.

The results of this calculation in graphical form are shown in Fig. 3.

As can be seen in the graph, with a fluidizing agent flow rate of 110 m^3/h, the potential capacity of the wastewater drying plant is significantly higher. However, it should be noted that an increase in the speed of the fluidizing agent increases the probability of particle abrasion, which, in turn, results in an increase in dust formation.

Thus, based on the calculated data, the initial temperature of the fluidizing agent in the laboratory experiments was T_{FA} = 118.5°C. The effect of pitch supply on the heat content of the layer was not taken into account since the main influence on the temperature of the latter is the amount of water supplied (and evaporated). In the ceresin spray mode, the fluidizing agent heating was turned off, and its temperature corresponded to room temperature.

The average diameter of wastewater droplets was calculated using the empirical K. Masters ratio [11, 14]. Recommended by Masters for pneumatic injectors, the "flow rate of the spraying agent/flow rate of the sprayed liquid" ratio is in the range of 0.1–10. In addition, the size of the droplets d_d, which is determined by this ratio, should be at least 10 times

Table 3. Values of constants for calculating the temperature of the fluidizing agent T_{FA} and determining the amount of moisture removed from wastewater G_{ww}

Parameter name	Dimension	Value
Heat capacity of the fluidizing agent (at 100°C)	kJ/(kg·K)	1.01
Heat capacity of wastewater (at 20°C)	kJ/(kg·K)	2.88
Wastewater supply temperature	°C	20.0
Salinity of wastewater	–	0.23
Heat loss	%	5.0

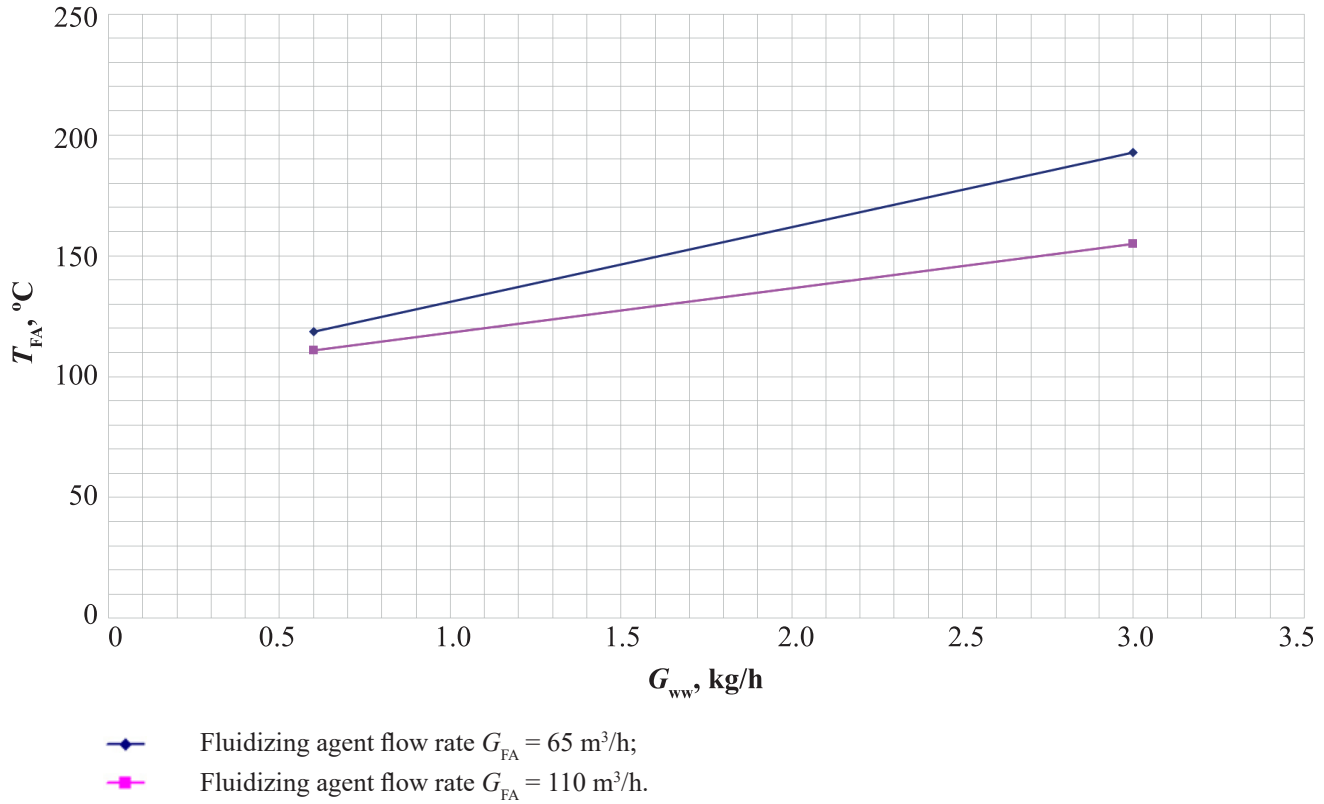


Fig. 3. Calculated dependence of the fluidizing agent temperature on the wastewater flow rate while maintaining a constant temperature in the bed 100°C.

smaller than the diameter of the particles on the surface being sprayed [15–18]. Since during the dry granulation–encapsulation process there is a constant growth of granules (i.e., the diameter of d_p increases), the maximum value of d_d was also assumed to be 0.2 mm (200 μm). The graph in Fig. 4 shows the calculated dependence of the size of the droplets of sprayed wastewater and pitch on the pressure of the atomizing agent.

Thus, the pressure range of the atomizing agent was assumed to be 1.4–2.4 bar at a wastewater flow rate of 0.6 to 3.0 kg/h and d_p = 0.5–2 mm. At d_p = 2 mm, a pressure of 1.4 bar is sufficient to spray the pitch, but, at d_p = 0.5 mm, the minimum pressure of the atomizing agent is at least 3 bar.

Taking into account the fact that the values of the physical properties of ceresin at a temperature of 135°C, which affect the nature of the droplet spraying, are comparable to wastewater [19], 1.4 bar was taken as the initial pressure value for the ceresin spray.

Tables 4, 5, and 6 set out the results of the experimental studies in which the results of the calculations are used as the initial operating parameters of the process.

In Experiment 2, dust formation was noted, which was visually observed, as well as discrepancies between the values of the expected amount of discharged granulate and the actual amount of more than 10%. An increase in the amount of seed material allowed the removal of unwanted dust formation and achieved the required performance for wastewater due to the increased contact surface between the liquid and solid phases (Experiment 3).

The values of the process parameters presented in Table 4 (Experiment 3) were used as the initial values at Stage 2 of the research.

In Experiment 4, intensive formation of large agglomerates in the bed was observed. An increase in the temperature in the bed and the pressure of the atomizing agent did not lead to a noticeable improvement in the results (Experiment 5).

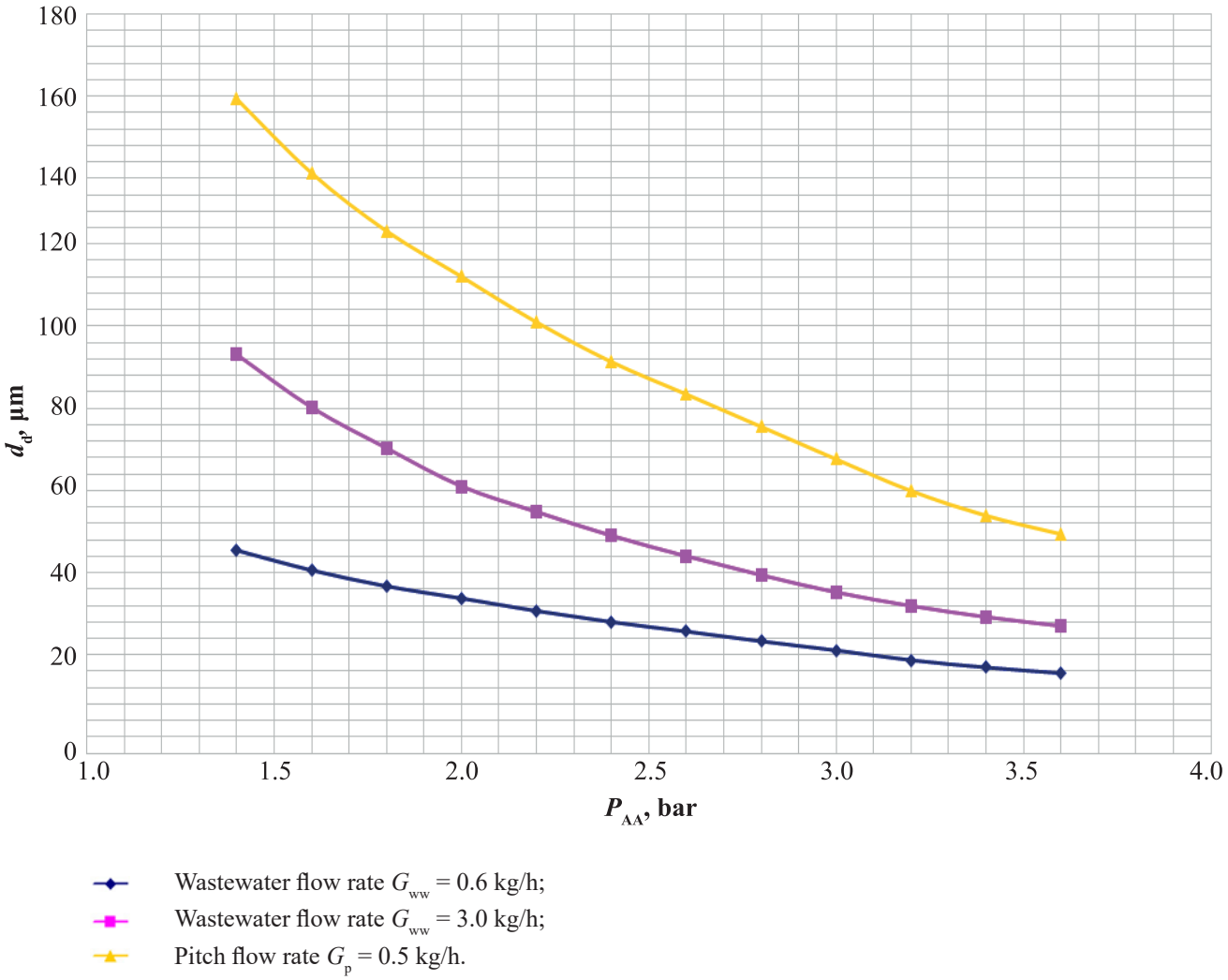


Fig. 4. Calculated dependence of the droplet size of sprayed wastewater and pitch on the pressure of the atomizing agent.

It is clear that one of the reasons for the formation of agglomerates was the insufficient velocity of the particles relative to each other, i.e., cohesive interparticle interaction forces were significantly greater than the crushing and grinding forces acting on the part of the fluidizing bed, which is probably primarily due to the sputtering of the pitch melt. In this regard, in subsequent experiments, the flow rate of the fluidizing agent was increased to 110 m^3/h.

Table 4. Summary table of the experimental results on the dry granulation of wastewater on the surface of contaminated soil (Stage 1)

No. exp.	Parameters							Notes
	M, kg	G_{FA}, m^3/h	T_{FA}, °C	T_B,** °C	T_{EA},** °C	P_{AA}, bar	G_{ww}, kg/h	
1	0.4	64–67	118–188	95–102	75–83	1.4–2.2	0.6–2.1	+*
2	0.4	63–68	187–192	90–101	77–82	2.2–2.4	2.1–3.0	Dust formation
3	0.5	61–67	185–198	88–104	76–84	2.2–2.4	1.5–3.0	+

* No unwanted dust formation and agglomeration.
** Temperature in the bed (T_B) and temperature of the exhaust gases (T_{EA}), respectively.

Table 5. Summary table of the experimental results on the dry granulation of wastewater on the surface of contaminated soil with simultaneous spraying of pitch (Stage 2)

No. exp.	Parameters									Notes
	M, kg	G_{FA}, m^3/h	T_{FA}, °C	T_B,** °C	T_{EA},** °C	$P_{AA(ww)}$*, bar	$P_{AA(p)}$*, bar	G_p, kg/h	G_{ww}, kg/h	
4	0.5	62–70	121–192	97–106	82–93	2.2–2.4	3.0–3.1	0.5	1.5–1.8	Unwanted agglomeration
5	0.5	63–65	117–190	95–103	81–90	2.4–2.8	3.3–3.6	0.5	1.5–1.8	Unwanted agglomeration
6	0.5	107–115	118–133	92–103	71–85	2.4–2.8	3.3–3.6	0.5	1.5–1.8	Dust formation
7	0.6	108–112	129–135	95–100	78–81	2.0–2.4	3.3–3.6	0.5	1.5–2.1	+
8	0.6	106–114	134–144	92–100	70–81	1.4–2.0	3.3–3.6	0.5	1.5–2.5	Dust formation
9	0.8	107–114	131–154	91–98	73–81	1.4–2.0	3.3–3.6	0.5	1.5–2.5	+
10	1.0	107–113	135–153	88–95	74–82	1.4–2.0	3.3–3.6	0.5	1.5–3.0	+
11	1.0	106–115	143–154	92–99	77–85	1.4–2.0	–	–	2.1–2.2	+
12	1.0	107–113	138–145	84–93	75–78	–	3.3–3.6	0.5	–	+

* Atomizing agent pressure for wastewater ($P_{AA(ww)}$) and pitch ($P_{AA(p)}$) spraying, respectively.
** Temperature in the bed (T_B) and temperature of the exhaust gases (T_{EA}), respectively.

In Experiment 6, the number of particles less than 0.5 mm in the unloaded product increased from 3.43 to 8.58 wt % in comparison with the experiments in Stage 1. At the same time, ~37% of the dust fraction was made up of pitch particles. It is likely that the growth of the dust fraction was associated with both the increased velocity of the fluidizing agent and with a reduction in the number of contacts between the solid particles in the bed and those sprayed with pitch (in the form of melt) due to the intensification of heat removal in the supra-bed space.

A gradual increase in the amount of contaminated soil to be loaded up to 1 kg (and, consequently, the minimum bed height), while reducing the pressure of the atomizing agent in the nozzle (Fig. 1, pos. 6) up to 1.4 bar at a wastewater flow rate of up to 3 kg/h, allowed a stable dry granulation process to be achieved without agglomerate formation (Experiment 10).

Comparative experiments were carried out feeding only wastewater into the bed (Experiment 11) and only pitch (Experiment 12). In both cases, the quantities of the loaded contaminated soil and the supplied solid fraction were 1 kg and 0.5 kg, respectively. The results of the sieve analysis of the product from Experiments 11–13 are shown in Table 6, and Fig. 5 shows the appearance of the granules. Images were taken using a Leica DM2500 microscope (*Leica Microsystems*, Germany).

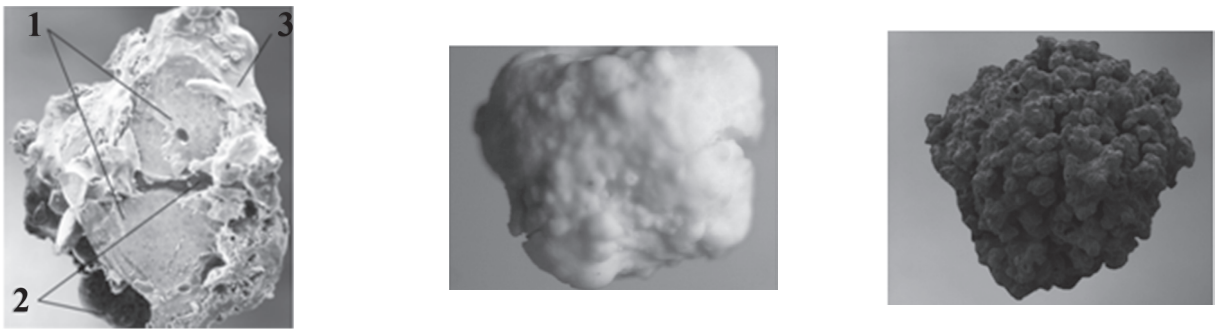
Based on the results of the analysis of the granulometric composition of the product, we assumed that the predominant mechanism for granule growth in Experiments 10 and 12 was agglomeration. This agrees with M. Hemati, *et al*. [20], who note that the growth of granules in a fluidized bed is due to agglomeration if the number of granules with a diameter two times larger than the diameter of the initial particles is more than 15% of the total number of particles in the bed during the process for 1 h.

Although the values of the surface tension and wetting angle of the pitch melt are comparable to water [21], the cohesive–adhesive interaction and wettability are mainly determined by the polarity of the substances in contact and the dispersion forces, and therefore the mechanisms for granule growth can differ markedly. In addition, the surface of the pellets during the spraying of wastewater is formed by salting out, and the size of the particles deposited on the surface of the contaminated soil is an order of magnitude smaller than that of the pitch particles. Figure 5c clearly shows the cavities, while the surface structure of the granule in Fig. 5b looks much more uniform.

Figure 5a shows a photo of the granules obtained in Experiment 10. Based on its internal structure, we can imagine that the granulation mechanism is of a

Table 6. Results of sieve analysis of the product were obtained by spraying wastewater and pitch melt into a fluidized bed of contaminated soil

Fraction, mm	Exp. 10, %	Exp. 11, %	Exp. 12, %
<0.25	0.17	0.12	2.42
0.25–0.49	1.88	2.54	3.33
0.50–0.99	70.51	94.29	76.47
1.00–1.99	26.42	2.87	17.41
≥2.00	1.02	0.18	0.37



a b c

Fig. 5. Fraction 1.00–1.99 mm: (a) granule from Experiment 10; (b) granule from Experiment 11; (c) granule from Experiment 12. At Fig. a: 1 – contaminated soil, 2 – pitch, 3 – deposits of salts containing heavy metals.

mixed nature. The binding of the initial particles of the contaminated soil is carried out by both pitch and salting. In this case, the cavities in the agglomerate are partially filled with salt deposits, which increases the strength and integrity of the structure of the final product. This can be seen by increasing the number of granules of 1.00–1.99 mm by more than 10% (Experiments 10 and 12) and by reducing dust formation.

At Stage 3 of the studies, a fraction of 1.00–1.24 mm was used for encapsulation with ceresin, which was previously produced at the specified technological parameters (Experiment 10).

We have made an approximate calculation of the minimum amount of ceresin to be fed into the bed under the following assumptions: ceresin is evenly distributed over the surface of the spherical particles; particle mass is 1 kg; bulk particle density is ~1250 kg/m^3; ceresin density is ~900 kg/m^3). The calculation results are shown in the graph in Fig. 6.

It should be noted that the amount of theoretically required ceresin strongly depends on the size of the particles in the bed. So, for example, for the coating of particles d_p = 1 mm with a ceresin film with a thickness of 200 μm, the ratio of the layer mass and the mass of the encapsulator is 1.0 : 0.9, and for d_p = 1.5 mm it is 1.0 : 0.6.

The results of Stage 3 of the experimental studies are presented in Table 7. When the consumption of ceresin G_c was 0.6 kg/h and 0.8 kg/h (Experiments 13 and 14), the resulting product did not pass the waterproofness test because chloride ions were found in the water extract as well as trace amounts of organic compounds that make up the pitch. This indicates an incompleteness/heterogeneity of encapsulation.

An increase in the flow rate to 1 kg/h (Experiment 15) made it possible to obtain a sealed, moisture-resistant product, which, according to the results of the bioassay on hydrobionts, was assigned to hazard class 5.

Unloading was carried out through a sifter, the pressure in which was set to 1.1 bar, which allowed particles less than 1 mm to be filtered out. The difference between the expected and actually unloaded product quantity was ~5%.

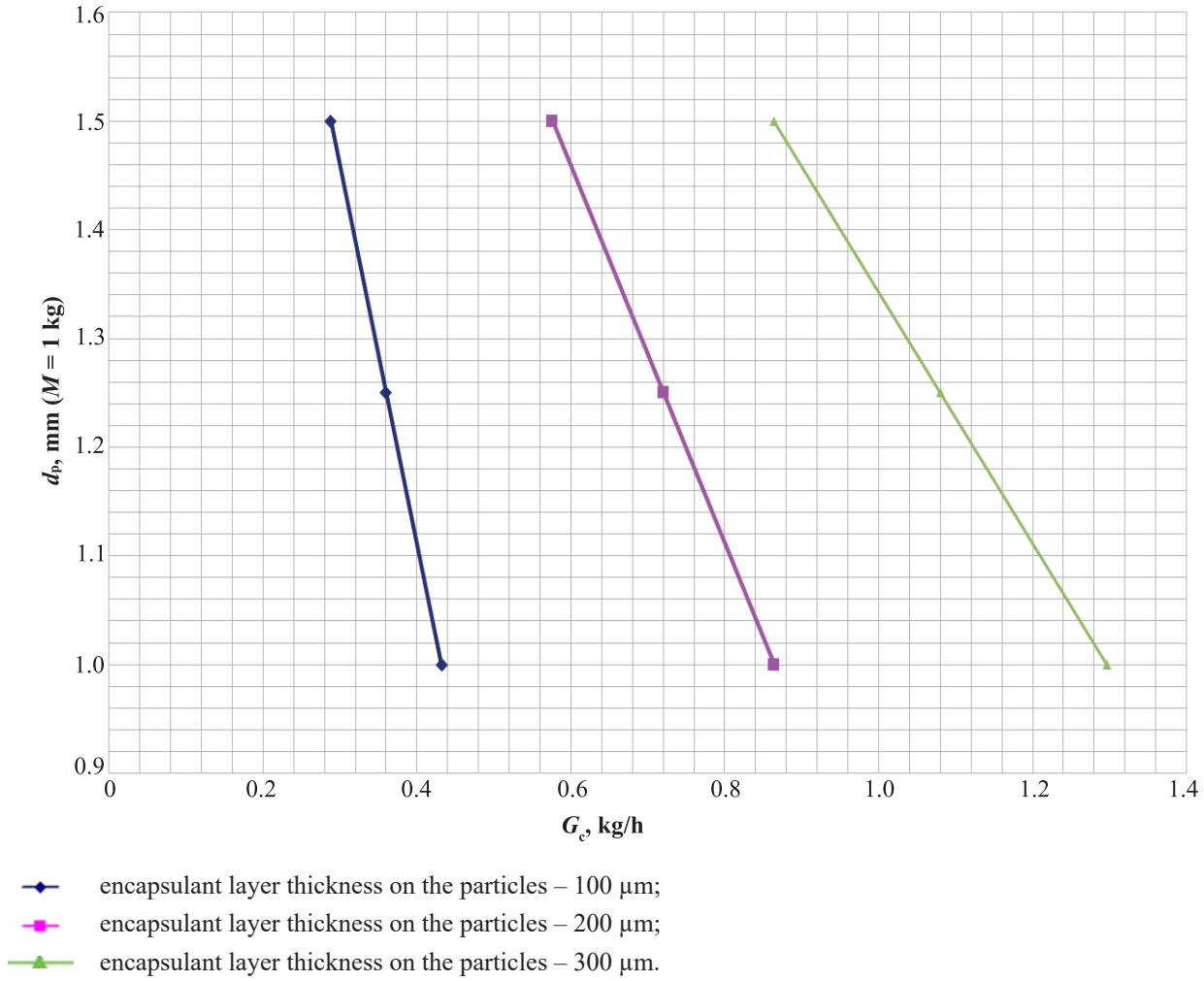


Fig. 6. Calculated dependence of the required encapsulant (ceresin) consumption on the initial particle size in the fluidized bed (the mass of the bed is 1 kg).

Table 7. Results of experiments on encapsulation of granulate with ceresin

No. exp.	Parameters							Notes
	M, kg	G_{FA}, m^3/h	T_{FA}, °C	T_B,* °C	T_{EA},* °C	P_{AA}, bar	G_c, kg/h	
13	1.0	107–114	18–23	18–30	15–24	1.4–2.0	0.6	Water resistance test failed
14	1.0	105–113	18–23	17–33	16–26	1.4–2.0	0.8	Water resistance test failed
15	1.0	103–115	18–23	17–35	15–29	1.4–2.0	1.0	Water resistance test passed

* Temperature in the bed (T_B) and temperature of the exhaust gases (T_{EA}), respectively.

Figure 7 shows the appearance of the resulting product. Image was taken using a Leica DM2500 microscope.

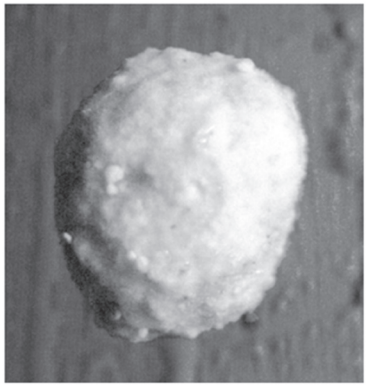


Fig. 7. Encapsulated waterproof hazard class-5 product (Experiment 15, fraction 1.25–1.99 mm).

CONCLUSIONS

In conclusion, the present study demonstrates the potential for a drying–granulation–encapsulation process for toxic waste and hazardous chemicals with a hazard class of 1–3 in one device, producing a bulk product of hazard class 5 that is moisture-resistant and suitable for transportation and long-term storage.

The technology for encapsulating toxic waste and wastewater can be implemented, for example, in an industrial continuous drying–granulation unit of the GLATT-GFG-500 type, which has been successfully used for the dry granulation of reaction masses obtained as a result of the alkaline hydrolysis of lewisite [11]. In industrial implementation, the ratio of the bed mass to the mass of the encapsulant is expected to change through a reduction in the amount of ceresin sprayed since, according to the experience with the GLATT-GFG-500 unit, the size of the salt particles produced and discharged reached 5–6 mm.

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Authors' contribution

Yu.A. Eleev – formulation of research goals and objectives, development of experimental methods, analysis of the results.

Yu.S. Bogoyavlenskaya – experimental research and primary processing of the obtained experimental data.

E.N. Glukhan – general management of the research process and preparation of materials for publication.

V.F. Golovkov – scientific support and assistance in the analysis of research results.

V.V. Afanasyev – scientific and technical support for the modernization and preparation of the experimental unit.

The authors declare no potential or actual conflicts of interest.

REFERENCES

1. Jiang X., Li Y., Yan J. Hazardous waste incineration in a rotary kiln: a review. *Waste Dispos. Sustain. Energy.* 2019;1(1):3–37. https://doi.org/10.1007/s42768-019-00001-3

2. Block C., Van Caneghem J., Van Brecht A., *et al.* Incineration of Hazardous Waste: A Sustainable Process? *Waste Biomass Valor.* 2015;6(2):137–145. https://doi.org/10.1007/s12649-014-9334-3

3. Sheu E.Y., Mullins O.C. (Eds.). *Asphaltenes: fundamentals and applications.* New York: Springer; 1995. 258 p. https://doi.org/10.1007/978-1-4757-9293-5

4. Spence R.D., Shi C. (Eds.). *Stabilization and Solidification of Hazardous, Radioactive, and Mixed Wastes.* Boca Raton: CRC Press; 2005. 391 p.

5. Leist M., Casey R.J., Caridi D. The fixation and leaching of cement stabilized arsenic. *Waste Manag.* 2003;23(4):353–359. https://doi.org/10.1016/S0956-053X(02)00116-2

6. Clancy T.M., Snyder K.V., Reddy R., Lanzirotti A., Amrose S.E., Raskin L., *et al*. Evaluating the cement stabilization of arsenic-bearing iron wastes from drinking water treatment. *J. Hazard. Mater.* 2015;300:522–529. https://doi.org/10.1016/j.jhazmat.2015.07.051

7. Shon J.S., Lee S.H., Kim G.N., Kim I.T., Shin H.S. Effect of Polyethylene as Additive on the Bituminized Waste Form with Hazardous Ash Waste. *Environ. Technol.* 2000;21(4):407–415. https://doi.org/10.1080/09593332108618100

8. Brandt H.C.A., De Groot P.C. Aqueous leaching of polycyclic aromatic hydrocarbons from bitumen and asphalt. *Wat. Res.* 2001;35(17):4200–4207. https://doi.org/10.1016/S0043-1354(01)00216-0

9. Shahova N.A. *Konstruirovanie i raschet apparatov s psevdoozhizhennym sloem: Uchebnoe posobie* (*Design and calculation of fluidized bed apparatuses: Tutorial*). Moscow: MIHM; 1978. 83 p. (in Russ.).

10. Parikh D.M. *Handbook of Pharmaceutical Granulation Technology*: 2nd ed. Boca Raton: Taylor & Francis Group; 2005. 654 p.

11. Eleev Yu.A., Glukhan E.N., Kazakov P.V., Belikov V.A. Features of the fluidized bed granulation scale-up process under the fundamental structural differences between model and industrial units. *Khim. Prom. Segodnya* (*Chem. Ind. Today*). 2016;6:34–44 (in Russ.).

12. Schæfer T., Wørts O. Control of fluidized bed granulation. III. Effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. *Arch. Pharm. Chem. Sci.* 1978;6:1–13.

13. Smith P.G. *Applications of fluidization to food processing.* Oxford: Blackwell; 2007. 258 p.

14. Masters K. Spray *Drying: An Introduction to Principles Operational Practice and Applications*. London: Leonard Hill Books; 1972. 668 p.

15. Knight P.C. An investigation of the kinetics of granulation using a high shear mixer. *Powder Technol.* 1993;77(2):159–169. https://doi.org/10.1016/0032-5910(93)80053-D

16. Dencs B., Ormós Z. Particle formation from solution in a gas fluidized bed. I. *Powder Technol.* 1982;31(1):85–91. https://doi.org/10.1016/0032-5910(82)80007-7

17. Crooks M.J., Schade H.W. Fluidized bed granulation of a microdose pharmaceutical powder. *Powder Technol.* 1978;19(1):103–108. https://doi.org/10.1016/0032-5910(78)80077-1

18. Waldie B. Growth mechanism and the dependence of granule size on drop size in fluidized-bed granulation. *Chem. Eng. Sci.* 1991;46(11):2781–2785. https://doi.org/10.1016/0009-2509(91)85147-P

19. Bayvel L., Orzechowski Z. *Liquid Atomization*. Washington: Taylor & Francis; 1993. 477 p.

20. Hemati M., Cherif R., Saleh K., Pont V. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. *Powder Technol.* 2003;130(1–3):18–34. https://doi.org/10.1016/S0032-5910(02)00221-8

21. Shornikova O.N., Malakho A.P., Govorov A.V., Galiguzov A.A., Nashchokin A.V., Avdeev V.V. Wetting of Carbon Fibers by Coal-Tar Pitch Melts. *Fibre Chem*. 2016;47(5):367–371. https://doi.org/10.1007/s10692-016-9694-5

About the authors:

Yuri A. Eleev, Cand. Sci. (Eng.), Assistant Professor, Head of Department, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, Shosse Entuziastov, Moscow, 111024, Russia). E-mail: 2553215@gmail.com, dir@gosniiokht.ru. https://orcid.org/0000-0001-8796-124X

Yulia S. Bogoyavlenskaya, Researcher, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, Shosse Entuziastov, Moscow, 111024, Russia). E-mail: dir@gosniiokht.ru. https://orcid.org/0000-0002-2500-5137

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

Vladimir F. Golovkov, Dr. Sci. (Chem.), Chief Researcher, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, Shosse Entuziastov, Moscow, 111024, Russia). E-mail: dir@gosniiokht.ru. Scopus Author ID 7005127502, https://orcid.org/0000-0001-9387-4003

Vladimir V. Afanasiev, Cand. Sci. (Eng.), Deputy Head of Department, State Research Institute of Organic Chemistry and Technology (GosNIIOKhT), State Scientific Center of the Russian Federation (23, Shosse Entuziastov, Moscow, 111024, Russia). E-mail: dir@gosniiokht.ru. https://orcid.org/0000-0003-0906-1072

Об авторах:

Елеев Юрий Александрович, к.т.н., доцент, 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: 2553215@gmail.com, dir@gosniiokht.ru. https://orcid.org/0000-0001-8796-124X

Богоявленская Юлия Сергеевна, научный сотрудник, 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. https://orcid.org/0000-0002-2500-5137

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, https://orcid.org/0000-0002-2369-5648

Головков Владимир Федорович, д.х.н., главный научный сотрудник, 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 7005127502, https://orcid.org/0000-0001-9387-4003

Афанасьев Владимир Васильевич, к.т.н., заместитель начальника 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: dir@gosniiokht.ru. https://orcid.org/0000-0003-0906-1072

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RESEARCH ARTICLE

Optimal modes of side-section flow in heat-pump-assisted extractive distillation systems for separating allyl alcohol–allyl acetate mixtures with butyl propionate

Pavel S. Klauzner[@], Danila G. Rudakov, Elena A. Anokhina, Andrey V. Timoshenko

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
[@]Corresponding author, e-mail: klauzner@mirea.ru

Abstract

Objectives. *To investigate the influence of side-section flow modes on the energy efficiency of a partially thermally coupled distillation sequence (PTCDS) with a vapor recompression heat pump for the extractive distillation of an allyl alcohol–allyl acetate mixture with n-butyl propionate and identify modes under which the combined use of a PTCDS and heat pump are the most efficient.*
Methods. *Mathematical modeling in the Aspen Plus V10 software package was used as the main research method. The local composition equation of the non-random two-liquid model was used as a model for describing the vapor–liquid equilibrium, while the Redlich–Kwong model was used to consider the non-ideal vapor phase. When modeling the conventional extractive distillation scheme and PTCDS, parametric optimization was carried out according to the criterion of the total energy costs in the column reboilers. For the economical evaluation, Aspen Process Economic Analyzer V10.1 tools were used.*
Results. *For extractive distillation of a mixture of allyl alcohol (30 wt %) and allyl acetate (70 wt %) with n-butyl propionate as an entrainer, the minimum energy consumption was achieved at the same side-section flow mode for the variants of a PTCDS with and without a heat pump. The reduction in energy costs relative to the conventional scheme was 20% for the sequence without a heat pump and 38% for that with a heat pump. An economic assessment was made of the best options in comparison with the conventional extractive distillation scheme. The PTCDS with a heat pump had an advantage over the sequence without a heat pump only for long periods of operation.*
Conclusions. *For the extractive distillation of an allyl alcohol–allyl acetate mixture, the optimal modes for the combined use of a PTCDS with a vapor recompression heat pump coincide with the optimal modes for a PTCDS without a heat pump.*

Keywords: *extractive distillation, heat pump, partially thermally coupled distillation sequence, energy saving*

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НАУЧНАЯ СТАТЬЯ

Оптимальные режимы бокового отбора в системах экстрактивной ректификации с тепловым насосом при разделении смеси аллиловый спирт–аллилацетат с бутилпропионатом

П.С. Клаузнер[@], Д.Г. Рудаков, Е.А. Анохина, А.В. Тимошенко

МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
[@]Автор для переписки, e-mail: klauzner@mirea.ru

Аннотация

Цели. *Исследовать влияние режимов бокового отбора на энергетическую эффективность комплекса с частично связанными тепловыми и материальными потоками (ЧСТМП) с тепловым насосом (ТН) открытого типа в экстрактивной ректификации смеси аллиловый спирт–аллилацетат с н-бутилпропионатом и выявить условия, при которых совместное применение комплекса с ЧСТМП совместно с ТН наиболее эффективно.*

Методы. *Математическое моделирование в программном комплексе Aspen Plus V10. Для моделирования парожидкостного равновесия применяли уравнение локальных составов модель Non-Random Two Liquid, а для учета неидеальности паровой фазы – модель Редлиха-Квонга. При моделировании традиционной схемы экстрактивной ректификации и комплекса с ЧСТМП проводили параметрическую оптимизацию по критерию суммарных энергетических затрат в кипятильниках колонн. Для экономической оценки применяли инструменты Aspen Process Economic Analyzer V10.1.*

Результаты. *Для экстрактивной ректификации смеси 30 мас. % аллилового спирта и 70 мас. % аллилацетата с н-бутилпропионатом в качестве разделяющего агента показано, что минимум энергозатрат достигается при одинаковом уровне и количестве бокового отбора как для варианта комплекса с ЧСТМП с ТН, так и без него. Снижение энергетических затрат относительно традиционной схемы для комплекса без ТН составляет 20%, а с ТН – 38%. Была произведена экономическая оценка наилучших вариантов по сравнению с традиционной схемой экстрактивной ректификации. Показано, что применение комплекса с ЧСТМП с ТН имеет преимущество только при длительных сроках эксплуатации.*

Выводы. *Показано, что для экстрактивной ректификации смеси аллиловый спирт–аллилацетат оптимальные режимы бокового отбора при совместном применении комплекса с ЧСТМП с ТН открытого типа и комплекса с ЧСТМП без ТН совпадают.*

Ключевые слова: *экстрактивная ректификация, тепловой насос, комплекс с частично связанными тепловыми и материальными потоками, энергосбережение*

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INTRODUCTION

Allyl alcohol (AAL) is a key product of the chemical technology of basic organic synthesis. It is used for the synthesis of glycidol, glycerol, allyl, glycidyl, and several other esters used in the production of fibers, paints and varnishes, sealants, molded products, fiberglass-reinforced plastics, polymers, food products, medicines, and perfumery products. There are several industrial methods for obtaining AAL from allyl acetate (AAC)—saponification, hydrolysis, alcoholysis [1], and a combined reaction–distillation process [2]. Regardless of the preparation method, during the preliminary separation of the reaction products, an AAL–AAC mixture is formed; it has an azeotrope with a minimum boiling point and an AAL content of 0.63 wt. fract. (0.75 mol. fract.). To separate this mixture, the authors in [3] have proposed using extractive distillation (ED) with ethylene glycol as an entrainer; this entrainer is distinguished by a sufficiently high selectivity, and in its presence, the relative volatilities are reversed. As an alternative, we propose n-butyl propionate (BP) as an entrainer in [4]. The maximum difference in boiling points is 100°C when using EG and 48°C when using BP.

In several cases, ED is characterized by a significantly lower energy consumption than that of other special separation methods. Despite this, the search for ways to reduce the energy cost of its implementation remains urgent since it is used in large-tonnage technologies of basic organic and petrochemical synthesis. Conventional ways to reduce energy costs in ED include using selective entrainers and parametric and structural scheme optimization. As with conventional distillation, heat integration [5–8] and methods based on the approach of distillation to thermodynamically reversible [9] can be used to improve the ED process, e.g., schemes with a completely [10] or partially thermally coupled distillation sequence (PTCDS) [11, 12]. Many works have been devoted to PTCDS schemes. The use of such schemes in the ED of various mixtures [13–15] has been investigated, and an empirical criterion for a preliminary assessment of the energy efficiency of PTCDS schemes in ED [16] and an optimization algorithm for such schemes [17] have been proposed. Another promising [18] method for improving the ED process is the use of various heat pumps (HPs). At present, few works have been devoted to this topic [19–22]. Since the use of HPs and PTCDS schemes is based on different principles, it is advisable to consider the possibility of their joint use and evaluate the effectiveness of this approach.

Previously, in [4], we have considered the use of HPs in the ED of an azeotropic AAL–AAC mixture with a BP entrainer in conjunction with a PTCDS scheme. Relative to the conventional scheme, the reduction in energy costs of the combined scheme reached 50%. Since the energy efficiency and even the structure of the optimal technological scheme are a function of the initial composition of the food due to the process's irreversible nature, in this work, research is carried out on the initial composition with an AAL content of 30 wt %, significantly different from the previous study. It is known that the side-section flow mode, i.e., the position of the side-section tray (N_v) and the amount of side-section flow (V), has a significant effect on the energy efficiency of PTCDS schemes. Thus, the purpose of this work is to study the influence of these parameters on the energy efficiency of a PTCDS scheme with a vapor recompression HP and identify the conditions required for their joint use.

CALCULATIONS

All calculations were performed using Aspen Plus V10. As in [4], the non-random two-liquid equation was used to simulate the vapor–liquid equilibrium in this

[1] See the list of abbreviations at the end of the article for the introduced designations.

study, and the Redlich–Kwong equation was used to consider the imperfections of the vapor phase arising during vapor compression.

For all variants of the schemes, the separation of the initial mixture with an AAL–AAC feed rate of 1000 kg/h, temperature of 97°C, and pressure of 105.0 kPa was considered [3].

The pressure of the top of the columns was taken as equal to 101.3 kPa [3], and real trays with an efficiency of 0.65 and a pressure drop of 0.1013 kPa on each were considered. The calculations were carried out in the design and verification mode, with a fixed quality of the product flows. The concentration of AAL and AAC in the product flows was set as constant and equal to 99.5 wt %; the BP concentration was equal to 99.9 wt %.

The optimization criterion was the minimum total heat duty on Q_{total} reboilers. In general terms, it could be written as (1):

$$Q_{total} = \Sigma_{i=1}^{K} Q_{reb}^{i}, \quad (1)$$

where K is the total number of distillation columns, i is the column number in the scheme, and Q_{reb}^{i} is the reboiler duty of the i column..

Technological schemes with HPs differ significantly from conventional ones since they contain "hot" compressors and additional heat exchange equipment. The compressors can be driven using both steam and electricity. To compare the energy costs in technological systems with dissimilar equipment, the consumption of equivalent fuel or an economic assessment of operating costs can be applied. In the case of using HPs in distillation processes, the authors of [23] proposed a simple formula (2) for assessing energy efficiency through reduced energy costs (Q_{red}):

$$Q_{red} = Q_{total} + 3W_{comp}, \quad (2)$$

where Q_{total} is the total energy consumption in the column reboilers (kW) and W_{comp} is the compressor power consumption (kW).

To compare the options for organizing a process that includes dissimilar technological equipment, the total annual cost (TAC) criterion is usually used (3):

$$TAC = OC + \frac{CC}{OT}, \quad (3)$$

where OT is the operating time of the unit in years; CC is the capital costs, USD; and OC is the operating costs, USD/year.

Since changes in the service life significantly affect the TAC value, the criterion calculations were carried out for 10- and 20-year periods.

Aspen Process Economic Analyzer V10.1 was used to calculate the capital and operating costs. The energy prices are given in Table 1.

Table 1. Utility costs (USD)

Utility	Cost, USD
Electricity, kW	0.0775
Cooling water, t	0.03
Steam, kg	0.017

Modeling and optimization of the conventional ED scheme

The conventional ED scheme (Scheme I) is shown in Fig. 1 and consisted of two columns—an ED column (EC) and an entrainer regeneration column (RC).

For the conventional version of the ED organization according to the algorithm proposed in [17], the optimal operating parameters were determined. In the optimization process, the total number of trays in both columns, the position of the feed plates to the EC and RC columns, the position of the entrainer feed plate to the EC, and the amount of entrainer flow were determined. For the optimization,

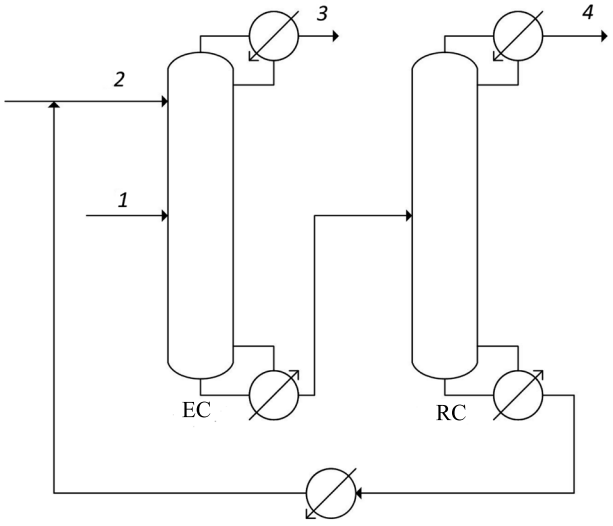

Fig. 1. Conventional ED scheme of AAL–AAC mixture with BP as the entrainer. EC is ED column, RC is entrainer regeneration column. Hereinafter: (1) feed, (2) entrainer, (3) AAL, (4) AAC.

the built-in tools of the Aspen Plus software package were used, which implemented the sequential enumeration of parameters and optimization via sequential quadratic programming (SQP).

The final operating parameters of the conventional ED scheme at a given composition (30-wt % AAC) of the initial mixture are presented in Table 2.

Modeling and optimization of a PTCDS scheme

The authors of [16] proposed a rule of thumb by which the use of PTCDS schemes is inappropriate when the reflux ratio in the RC is much lower than one. In this case, the value of RRC was 4.0, implying the achievement of a significant energy effect. Based on the conventional ED scheme, we simulated the scheme with a PTCDS (Scheme II), as shown in Fig. 2.

Table 2. Operating parameters of conventional ED scheme

Operating parameters	Columns	
	EC	RC
N_{total}	46	28
N_F	35	17
N_S	12	–
Q_{reb}, kW	299	375
Q_{cond}, kW	−275	−357
R	3.7	4.0
T_{cond}, °C	96.81	104.0
T_{reb}, °C	128.4	145.9
P_{cond}, kPa	101.3	101.3
P_{reb}, kPa	105.8	104.0
S, kg/h	2450	–
T_S, °C	120.0	–

The diagram in Fig. 2 was obtained by transforming the conventional scheme (Fig. 1) according to different algorithms [11, 12, 24]; it is a single complex column with a reinforcing side section. In the next stage, according to the algorithm proposed in [17],

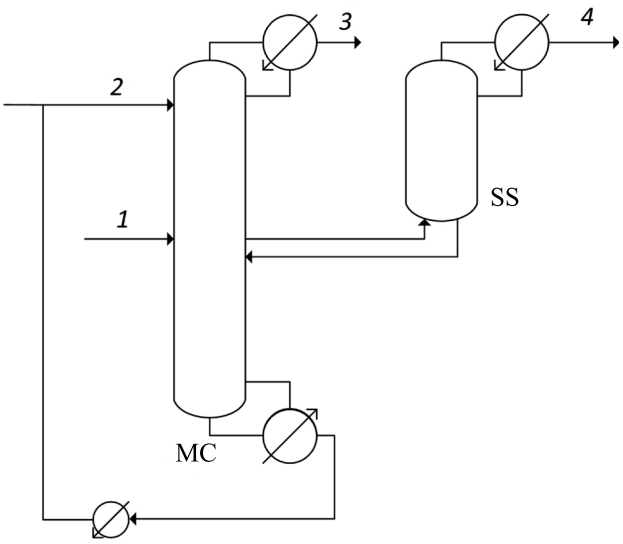

Fig. 2. PTCDS scheme: MC – main column, SS – side section.

the values of the flow and supply level of the side-section flow were determined. According to several studies, the optimal values of other variables, e.g., the number of feed plates, the entrainer feed plate, and the entrainer flow, in PTCDS schemes either do not differ or differ insignificantly from the corresponding parameters of the conventional scheme [12, 24]. Therefore, the optimization of PTCDS schemes to reduce the dimension tasks on these parameters may not have to be carried out. For several of the side-section trays, the SQP Optimization tool was used to determine the value corresponding to the minimum duty on the Q_{reb} reboiler. The data obtained at this stage are shown in Table 3.

The minimum lateral withdrawal flow was observed at N_V = 47, and the minimum energy consumption in the reboiler was observed at N_V = 48. The optimal operating parameters of the PTCDS scheme are presented in Table 4.

Combined use of a PTCDS scheme and HP

Based on the PTCDS scheme considered above, a scheme for the joint use of a PTCDS with a vapor recompression HP (Scheme III) was synthesized, as shown in Fig. 3.

For a preliminary assessment of the efficiency of using HPs based on the expression of the efficiency of a Carnot heat engine and an equation for calculating the heat required for separation, the authors of [25] proposed the efficiency factor of HPs, C_{ef}:

$$C_{ef} = \frac{Q_{reb}}{A} = \frac{T_{reb}}{(T_{reb} - T_{cond})}, \quad (4)$$

Table 3. Operation parameters optimization of PTCDS. Q units are [kW]

N_V	V, kg/h	Q_{reb}^{MC}	Q_{cond}^{SS}	R^{MC}	Q_{cond}^{SS}	R^{SS}
44	1721	611	−337	4.4	−162	1.4
45	1645	569	−335	4.2	−157	1.4
46	1622	532	−339	3.9	−154	1.4
47	1612	522	−327	3.7	−156	1.2
48	**1692**	**521**	**−318**	**3.6**	**−161**	**1.3**
49	1858	528	−311	3.4	−176	1.5
50	2214	560	−313	3.4	−206	1.9
51	2901	608	−305	3.4	−262	2.8

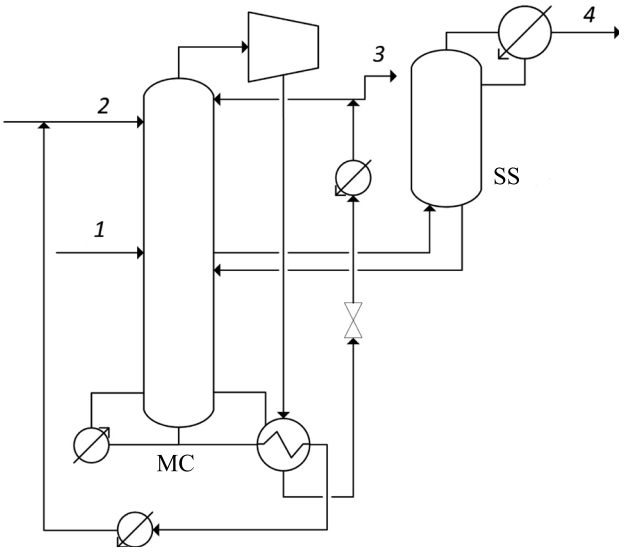

Fig. 3. PTCDS scheme with open type:
MC – main column, SS – side section.

where Q_{reb} is the column reboiler duty, A is the thermodynamic work, and T_{cond} and T_{reb} are the absolute temperatures in the condenser and reboiler of the EC, respectively.

Based on the data in Table 4, for the PTCDS scheme, C_{ef} equaled 8.3. In [25], it was noted that the use of HPs may be advisable at values of $C_{ef} > 5$.

It should be noted that when deriving Eq. (4), several assumptions were initially made to assess the applicability of HPs in the separation of zeotropic mixtures. Despite this, in several works, the criterion has also been used for PTCDS schemes with HPs in the separation of azeotropic mixtures, including ED [20, 26, 27].

Table 4. Optimal operating parameters of PTCDS

Operating parameters	Columns	
	MC	SS
N_{total}	57	17
N_F	35	–
N_V	48	–
N_S	12	–
V, kg/h	1692	–
Q_{reb}, kW	521	–
Q_{cond}, kW	−318	−161
R	3.6	1.3
T_{cond}, °C	96.8	104.9
T_{reb}, °C	147.0	–
P_{cond}, kPa	101.3	104.0
P_{reb}, kPa	107.5	–
S, kg/h	2450	–
T_S, °C	120.0	–

The steam flow of the main column was chosen as the working fluid for the HP since its heat content was higher than that of the upper steam flow of the side section. Simultaneously, the temperature of the steam flow required for effective heating of the column bottom was provided at a compression ratio in the compressor equal to 5.2. It is known that high economic efficiency from the use of HPs is achieved when this ratio is less than three [28, 29]. Thus, for an accurate comparison of the considered schemes, the following economic assessment was required.

For several positions of the side-section tray, N_V, and the corresponding optimal amount of side-section flow, V, considered when optimizing the PTCDS scheme, the operating parameters of an open-type HP were selected. The results are presented in Table 5.

In this case, Q_{reb}^{MC} и Q_{cond}^{MC} were duties on the auxiliary reboiler and condenser, respectively, W_{comp} was the compressor power consumption, Q_{HE} was the heat transferred in the heat exchanger of the HP, and Q_{HE} was the heat transferred in the heat exchanger of the HP, and Q_{red}^{HP} was the reduced energy cost determined by Eq. (2).

RESULTS AND DISCUSSION

According to the calculated data (Tables 3 and 5), the final dependences of the duty on the reboiler of the PTCDS scheme and the reduced energy consumption when using a PTCDS with an HP on the position and amount of side-section flow are shown in Fig. 4.

Table 5 and Fig. 4 show that as the N_V increased, the efficiency of the HP decreased; however, the minimum reduced energy costs, Q_{red}^{HP}, were observed at the same N_V and V values as the minimum energy costs of the PTCDS scheme without an HP. The comparison of the energy costs of the conventional scheme and the best options for the complex with PTCDS and the combined use of a PTCDS and HP are presented in Table 6.

As already indicated, for an accurate comparison of the considered solutions, it was necessary to perform an economic assessment. To do this, we evaluated several design parameters of the distillation columns, i.e., the diameter of the column (D) and the height of the trayed (packed) section (H), and selected the types of contact device. This assessment was made using the Aspen Plus software package; the results are presented in Table 7.

The general results of the economic assessment carried out with the Aspen Process Economic Analyzer and the *TAC* values calculated according to Eq. (3) based on these results are shown in Table 8.

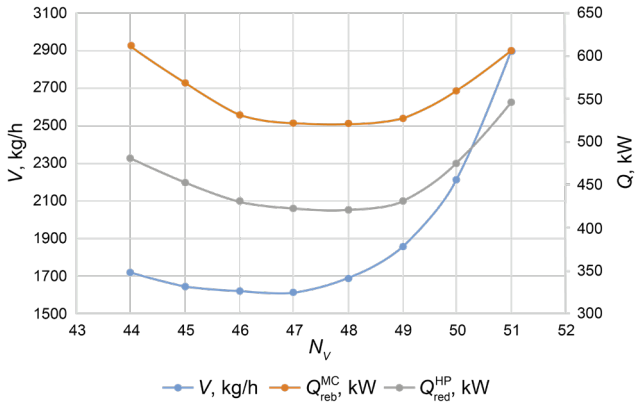

Fig. 4. PTCDS heat duty (Q_{reb}^{MC}, kW), PTCDS with HP reduced heat duty (Q_{red}^{HP}, kW) and V, kg/h dependence on side-stream stage (N_V).

Table 5. Operation parameters' dependence on N_V and V for HP schemes. Q and W units are [kW]

N_V	V, kg/h	Q_{reb}^{MC}	Q_{cond}^{SS}	R^{MS}	W_{comp}	Q_{HE}	Q_{red}^{HP}
44	1721	295	−86	4.4	62	331	481
45	1645	273	−81	4.2	60	302	453
46	1622	269	−74	3.9	54	276	431
47	1612	267	−71	3.7	52	263	423
48	**1692**	**274**	**−68**	**3.6**	**49**	**248**	**421**
49	1858	287	−66	3.4	48	240	431
50	2214	335	−66	3.4	47	230	476
51	2901	409	−65	3.4	46	224	547

Table 6. Energy duties of optimal PTCDS (II) and PTCDS with HP (III) schemes in comparison with conventional ED scheme (I)

Energy duties	Scheme		
	I	II	III
Q_{total}, kW	674	521	274
W_{comp}, kW	0	0	49
Q_{red}, kW	674	521	421
ΔQ_{red}, %	0	22	38

Table 7. Construction parameters of columns

Column	EC	RC	MC	SS
***D*, м**	0.6	0.75	0.7	0.45
***H*, м**	19	11	23	3
Tray/pack type	Valve trays	Valve trays	Valve trays	Raschig rings

Table 8. Economical evaluation

Economic parameters	Scheme		
	I	II	III
OC, USD/year	222420	179493	132675
Δ*OC*, %	0	19.3	40.3
CC, USD	502400	368000	1077100
*TAC*10	272660	216293	240385
*TAC*20	247540	197893	186530
Δ*TAC*10, %	0	20.7	11.8
Δ*TAC*20, %	0	20.1	24.7

CONCLUSIONS

The study showed that for the ED process of a mixture of AAL (30 wt %) and AAC (70 wt %) with BP, the use of a PTCDS scheme and that same scheme with an HP can significantly reduce energy expenses. Moreover, it was found that the change in the main variables (the level of the supply and the value of the lateral withdrawal flow), which affects the energy efficiency of the PTCDS scheme, also affects the efficiency of the HPs in the complex. However, in the case considered, the minimum energy costs were achieved under the same conditions in the PTCDS schemes both with and without an HP. A decrease in the concentration in the initial mixture of the component released in the distillate of the EC led to a decrease in the energy and economic efficiency of using the HP. According to the results of the economic

assessment performed based on the *TAC* criterion with a unit operation time of 10 years, it would be more expedient to use a PTCDS scheme without an HP. However, with an operation time of 20 years, a *TAC* reduction of 24% would be provided by the scheme with an HP, and a reduction of 20.1% would be provided by the PTCDS scheme without an HP.

Abbreviations

A – hermodynamic work;
C_{ef} – efficiency factor;
CC – capital costs;
D – diameter;
H – height;
N – plate number;
K – total number of columns;
OC – operating costs;
OT – operating time;
P – absolute pressure;
Q – heat duty;
R – reflux ratio;
S – flow rate of an entrainer;
T – temperature;
TAC – total annual costs;
*TAC*10 – total annual costs with a 10-year operating life;
*TAC*20 – total annual costs with a 20-year operating life;
V – side flow;
W – power consumption;
AAL – allyl alcohol;
AAC – allyl acetate;
SS – side section;
BP – *n*-butyl propionate;
MC – main column;
RC – entrainer regeneration column;
HP – heat pump;
PTCDS – partially thermally coupled distillation sequence;
EC – extractive distillation column;
ED – extractive distillation.

Indices

comp – compressor;
cond – condenser;
i – numbers of the column;
F – feed;
HE – heat exchanger;
HP – heat pump;
min – the minimum value;
opt – optimal value;
reb – reboiler;
red – reduced;
S – entrainer.

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Authors' contributions

P.S. Klauzner – planning and conducting research, analyzing research materials, writing the manuscript;

D.G Rudakov – conducting research, analyzing research materials;

E.A. Anokhina – management and scientific consulting;

A.V. Timoshenko – formulation of the scientific concept, general management.

The authors declare no conflicts of interest.

REFERENCES

1. Grigoriev A.A., Katsman E.A. Allylacetate and Syntheses on Its Basis. *Kataliz i neftekhimiya = Catalysis and Petrochemistry.* 2001;7:27–39 (in Russ.).

2. Anokhina E.A., Kardona K., Pisarenko Y.A., Saksonova O.I., Ponomarev V.N. The main stages of the combined processes development on the example of NSRRP for the production of allyl alcohol by butanolysis of allyl acetate. Part 1. *Khim. Prom. = Chem. Ind.* 1996;9:3–9 (in Russ.).

3. Anokhina E.A., Kardona K., Pisarenko Y.A., Saksonova O.I., Ponomarev V.N. The main stages of the combined processes development on the example of NSRRP for the production of allyl alcohol by butanolysis of allyl acetate. Part 2. *Khim. Prom. = Chem. Ind.* 1996;11:689–693 (in Russ.).

4. Klauzner P.S., Rudakov D.G., Anokhina E.A., Timoshenko A.V. Application of a complex with patricianly coupled thermal and energy flows and heat pumps in extractive distillation of allyl alcohol–allyl acetate mixture with *n*-butylpropionate. *Chem. Technol. of Org. Subst.* 2020;4(16):42–56 (in Russ.).

5. You X., Rodriguez-Donis I., Gerbaud V. Improved design and efficiency of the extractive distillation process for acetone–methanol with water. *Ind. Eng. Chem. Res.* 2015;54(1):491–501. https://doi.org/10.1021/ie503973a

6. Luyben W.L. Distillation column pressure selection. *Sep. Purif. Technol.* 2016;168:62–67. https://doi.org/10.1016/j.seppur.2016.05.015

7. Luyben W.L. Control of heat-integrated extractive distillation processes. *Comp. Chem. Eng.* 2018;111:267–277. https://doi.org/10.1016/j.compchemeng.2017.12.008

8. Tiverios P.G., van Brunt V. Extractive distillation solvent characterization and shortcut design procedure for methylcyclohexane–toluene mixtures. *Ind. Eng. Chem. Res.* 2000;39(6):1614–1623. https://doi.org/10.1021/ie990654k

9. Petlyuk F.B., Serafimov L.A. *Mnogokomponentnaya rektifikatsiya. Teoriya i raschet* (*Distillation of Multicomponent Mixtures. Theory and Calculation*). Moscow: Khimiya; 1983. 304 p. (in Russ.).

10. Petlyuk F.B., Platonov B.M., Slavinskii D.M. The thermodynamic optimal methods of separation of multicomponent mixtures. *Khim. Prom. = Chem. Ind.* 1965;3:206–211 (in Russ.).

11. Timoshenko A.V., Morgunov A.V., Anokhina E.A. Flowsheet synthesis for extractive distillation of azeotropic mixtures in systems consisting of columns with partially coupled heat and material flows. *Theor. Found. Chem. Eng.* 2007;41(6):845–850. https://doi.org/10.1134/S0040579507060097

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12. Anokhina E.A. Energy saving in extractive distillation. *Vestnik MITHT* (*Tonk. Khim. Tekhnol. = Fine Chem. Technol.*) 2013;8(5):3–19. (in Russ.).

13. Wang C., Guang C., Cui Y., Wang C., Zhang Z. Compared novel thermally coupled extractive distillation sequences for separating multi-azeotropic mixture of acetonitrile/benzene/methanol. *Chem. Eng. Res. Des.* 2018;136:513–528. https://doi.org/10.1016/j.cherd.2018.06.017

СПИСОК ЛИТЕРАТУРЫ

1. Григорьев А.А., Кацман Е.А. Аллилацетат и синтезы на его основе. *Катализ и нефтехимия.* 2001;7:27–39.

2. Анохина Е.А., Кардона К., Писаренко Ю.А., Саксонова О.И., Пономарев В.Н. Основные этапы разработки совмещенных процессов на примере НСРРП получения аллилового спирта бутанолизом аллилацетата. Часть 1. *Хим. пром.* 1996;9:3–9.

3. Анохина Е.А., Кардона К., Писаренко Ю.А., Саксонова О.И., Пономарев В.Н. Основные этапы разработки совмещенных процессов на примере НСРРП получения аллилового спирта бутанолизом аллилацетата. Часть 2. *Хим. пром.* 1996;11:689–693.

4. Клаузнер П.С., Рудаков Д.Г., Анохина Е.А., Тимошенко А.В. Применение комплекса с частично связанными тепловыми и материальными потоками и тепловых насосов в экстрактивной ректификации смеси аллиловый спирт – аллилацетат с *н*-бутилпропионатом. *Химия и технол. орг. вещ.* 2020;4(16):42–56.

5. You X., Rodriguez-Donis I., Gerbaud V. Improved design and efficiency of the extractive distillation process for acetone–methanol with water. *Ind. Eng. Chem. Res.* 2015;54(1):491–501. https://doi.org/10.1021/ie503973a

6. Luyben W.L. Distillation column pressure selection. *Sep. Purif. Technol.* 2016;168:62–67. https://doi.org/10.1016/j.seppur.2016.05.015

7. Luyben W.L. Control of heat-integrated extractive distillation processes. *Comp. Chem. Eng.* 2018;111:267–277. https://doi.org/10.1016/j.compchemeng.2017.12.008

8. Tiverios P.G., van Brunt V. Extractive distillation solvent characterization and shortcut design procedure for methylcyclohexane–toluene mixtures. *Ind. Eng. Chem. Res.* 2000;39(6):1614–1623. https://doi.org/10.1021/ie990654k

9. Петлюк Ф.Б., Серафимов Л.А. *Многокомпонентная ректификация, теория и расчет.* М.: Химия; 1983. 304 с.

10. Петлюк Ф.Б., Платонов В.М., Славинский Д.М. Термодинамически оптимальный способ разделения многокомпонентных смесей. *Хим. пром.* 1965;3:206–211.

11. Тимошенко А.В., Моргунов А.В., Анохина Е.А. Синтез схем экстрактивной ректификации азеотропных смесей в комплексах колонн с частично связанными тепловыми и материальными потоками. *Теор. основы хим. технол.* 2007;41(6):649–654.

12. Анохина Е.А. Энергосбережение в процессах экстрактивной ректификации. Вестник МИТХТ. 2013;8(5):3–19.

13. Wang C., Guang C., Cui Y., Wang C., Zhang Z. Compared novel thermally coupled extractive distillation sequences for separating multi-azeotropic mixture of acetonitrile/benzene/methanol. *Chem. Eng. Res. Des.* 2018;136:513–528. https://doi.org/10.1016/j.cherd.2018.06.017

14. Gutierrez-Guerra R., Segovia-Hernández J.G., Hernandez S., Bonilla-Petriciolet A., Hernández H. Design and Optimization of Thermally Coupled Extractive Distillation Sequences. *Comp. Aid. Chem. Eng.* 2009;26:189–194. https://doi.org/10.1016/S1570-7946(09)70032-X

15. Yang A., Sy Y, Chien I.L., Jin S., Yan C., Wei S., Shen W., *et al*. Investigation of an energy-saving double-thermally coupled extractive distillation for separating ternary system benzene/toluene/cyclohexane. *Energy.* 2019;186:115756. https://doi.org/10.1016/j.energy.2019.07.086

16. Anokhina E., Timoshenko A. Criterion of the energy effectiveness of extractive distillation in the partially thermally coupled columns. *Chem. Eng. Res. Des.* 2015;99:65–175. https://doi.org/10.1016/j.cherd.2015.03.006

14. Gutierrez-Guerra R., Segovia-Hernández J.G., Hernandez S., Bonilla-Petriciolet A., Hernández H. Design and Optimization of Thermally Coupled Extractive Distillation Sequences. *Comp. Aid. Chem. Eng.* 2009;26:189–194. https://doi.org/10.1016/S1570-7946(09)70032-X

15. Yang A., Sy Y., Chien I.L., Jin S., Yan C., Wei S., Shen W., *et al*. Investigation of an energy-saving double-thermally coupled extractive distillation for separating ternary system benzene/toluene/cyclohexane. *Energy.* 2019;186:115756. https://doi.org/10.1016/j.energy.2019.07.086

16. Anokhina E., Timoshenko A. Criterion of the energy effectiveness of extractive distillation in the partially thermally coupled columns. *Chem. Eng. Res. Des.* 2015;99:65–175. https://doi.org/10.1016/j.cherd.2015.03.006

17. Anokhina E.A., Timoshenko A.V., Akishin A.Y., Remizova A.V. Benzene purification from thiophene using dimethylformamide as an entrainer in thermally coupled extractive distillation columns. *Chem. Eng. Res. Des.* 2019;146(5):391–403. https://doi.org/10.1016/j.cherd.2019.04.003

18. Gerbaud V., Rodriguez-Donis I., Hegelyc L., Langc P., Denis F., Youe X.Q. Review of extractive distillation. Process design, operation, optimization and control. *Chem. Eng. Res. Des.* 2019;141:229–271. https://doi.org/10.1016/j.cherd.2018.09.020

19. You X., Rodriguez-Donis I., Gerbaud V. Reducing process cost and CO_2 emissions for extractive distillation by double-effect heat integration and mechanical heat pump. *App. Energy.* 2016;166:128–140. https://doi.org/10.1016/j.apenergy.2016.01.028

20. Luo H., Bildea C.S., Kiss A.A. Novel Heat-pump-assisted extractive distillation for bioethanol purification. *Ind. Eng. Chem. Res.* 2015;54(7):2208–2213. https://doi.org/10.1021/ie504459c

21. Wang C., Zhuang Y., Liu L., Zhang L., Du J. Heat pump assisted extractive distillation sequences with intermediate-boiling entrainer. *App. Therm. Eng.* 2021;186:116511. https://doi.org/10.1016/j.applthermaleng.2020.116511

22. Gu J., You X., Tao C., Li J. Analysis of heat integration, intermediate reboiler and vapor recompression for the extractive distillation of ternary mixture with two binary azeotropes. *Chem. Eng. Process.* 2019;142:107546. https://doi.org/10.1016/j.cep.2019.107546

23. Aurangzeb Md., Jana A.K. Vapor recompression with interreboiler in a ternary dividing wall column: Improving energy efficiency and savings, and economic performance. *App. Therm. Eng.* 2018;147:1009–1023. https://doi.org/10.1016/j.applthermaleng.2018.11.008

24. Timoshenko A.V., Anokhina E.A., Rudakov D.G., Timofeev V.S., Tatsievskaya G.I., Matyushenkova Yu.V. Power saving in distillation using complexes with coupled flows. *Vestnik MITHT* (*Tonk. Khim. Tekhnol. = Fine Chem. Technol.*) 2011;6(4):28–39 (in Russ.).

25. Plesu V., Bonet-Ruiz A.E., Bonet J., Llorens J. Simple equation for suitability of heat pump use in distillation. *Comp. Aided Chem. Eng.* 2014;33:1327–1332. https://doi.org/10.1016/B978-0-444-63455-9.50056-8

26. Patraşcu I., Bildea C. S., Kiss A. A. Eco-efficient Downstream Processing of Biobutanol by Enhanced Process Intensification and Integration. *ACS Sustain. Chem. Eng.* 2018;6(4):5452–5461. https://doi.org/10.1021/acssuschemeng.8b00320

27. Shi P., Zhang Q., Zeng A., Ma Y., Yuan X. Eco-efficient vapor recompression-assisted pressure-swing distillation process for the separation of a maximum-boiling azeotrope. *Energy.* 2020;196(13):117095. https://doi.org/10.1016/j.energy.2020.117095

17. Anokhina E.A., Timoshenko A.V., Akishin A.Y., Remizova A.V. Benzene purification from thiophene using dimethylformamide as an entrainer in thermally coupled extractive distillation columns. *Chem. Eng. Res. Des.* 2019;146(5):391–403. https://doi.org/10.1016/j.cherd.2019.04.003

18. Gerbaud V., Rodriguez-Donis I., Hegelyc L., Langc P., Denis F., Youe X.Q. Review of extractive distillation. Process design, operation, optimization and control. *Chem. Eng. Res. Des.* 2019;141:229–271. https://doi.org/10.1016/j.cherd.2018.09.020

19. You X., Rodriguez-Donis I., Gerbaud V. Reducing process cost and CO_2 emissions for extractive distillation by double-effect heat integration and mechanical heat pump. *App. Energy.* 2016;166:128–140. https://doi.org/10.1016/j.apenergy.2016.01.028

20. Luo H., Bildea C.S., Kiss A.A. Novel Heat-pump-assisted extractive distillation for bioethanol purification. *Ind. Eng. Chem. Res.* 2015;54(7):2208–2213. https://doi.org/10.1021/ie504459c

21. Wang C., Zhuang Y., Liu L., Zhang L., Du J. Heat pump assisted extractive distillation sequences with intermediate-boiling entrainer. *App. Therm. Eng.* 2021;186:116511. https://doi.org/10.1016/j.applthermaleng.2020.116511

22. Gu J., You X., Tao C., Li J. Analysis of heat integration, intermediate reboiler and vapor recompression for the extractive distillation of ternary mixture with two binary azeotropes. *Chem. Eng. Process.* 2019;142:107546. https://doi.org/10.1016/j.cep.2019.107546

23. Aurangzeb Md., Jana A.K. Vapor recompression with interreboiler in a ternary dividing wall column: Improving energy efficiency and savings, and economic performance. *App. Therm. Eng.* 2018;147:1009–1023. https://doi.org/10.1016/j.applthermaleng.2018.11.008

24. Тимошенко А.В., Анохина Е.А., Рудаков Д.Г., Тимофеев В.С., Тациевская Г.И., Матюшенкова Ю.В. Энергосбережение в ректификации с использованием комплексов со связанными потоками. *Вестник МИТХТ.* 2011;6(4):28–39.

25. Plesu V., Bonet-Ruiz A.E., Bonet J., Llorens J. Simple equation for suitability of heat pump use in distillation. *Comp. Aided Chem. Eng.* 2014;33:1327–1332. https://doi.org/10.1016/B978-0-444-63455-9.50056-8

26. Patraşcu I., Bildea C.S., Kiss A.A. Eco-efficient Downstream Processing of Biobutanol by Enhanced Process Intensification and Integration. *ACS Sustain. Chem. Eng.* 2018;6(4):5452–5461. https://doi.org/10.1021/acssuschemeng.8b00320

27. Shi P., Zhang Q., Zeng A., Ma Y., Yuan X. Eco-efficient vapor recompression-assisted pressure-swing distillation process for the separation of a maximum-boiling azeotrope. *Energy.* 2020;196(13):117095. https://doi.org/10.1016/j.energy.2020.117095

28. Reay D.A., Macmichael D. *Heat pumps. Design and applications.* UK: Pergamon Press; 1979. 302 p.

29. Kiss A.A., Ferreira C.A. *Heat Pumps in Chemical Process Industry.* US-FL: CRC Press; 2016. 442 p. https://doi.org/10.1201/9781315371030

28. Reay D.A., Macmichael D. *Heat pumps. Design and applications.* UK: Pergamon Press; 1979. 302 p.

29. Kiss A.A., Ferreira C.A. *Heat Pumps in Chemical Process Industry.* US-FL: CRC Press; 2016. 442 p. https://doi.org/10.1201/9781315371030

About the authors:

Pavel S. Klauzner, Assistant, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: klauzner@mirea.ru. ResearcherID AAJ-7842-2021, https://orcid.org/0000-0001-5844-549X

Danila G. Rudakov, Cand. Sci. (Eng.), Associate Professor, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: rudakov@mitht.ru. Scopus Author ID 37018548000, ResearcherID M-5241-2014, https://orcid.org/0000-0002-9892-7909

Elena A. Anokhina, Cand. Sci. (Eng.), Associate Professor, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: anokhina.ea@mail.ru. Scopus Author ID 6701718055, ResearcherID E-5022-2016.

Andrey V. Timoshenko, Dr. Sci. (Eng.), Professor, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: timoshenko@mitht.ru. Scopus Author ID 56576076700, ResearcherID Y-8709-2018.

Об авторах:

Клаузнер Павел Сергеевич, ассистент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: klauzner@mirea.ru. ResearcherID AAJ-7842-2021, https://orcid.org/0000-0001-5844-549X

Рудаков Данила Григорьевич, к.т.н., доцент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: rudakov@mitht.ru. Scopus Author ID 37018548000, ResearcherID M-5241-2014, https://orcid.org/0000-0002-9892-7909

Анохина Елена Анатольевна, к.т.н., доцент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: anokhina.ea@mail.ru. Scopus Author ID 6701718055, ResearcherID E-5022-2016.

Тимошенко Андрей Всеволодович, д.т.н., профессор кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: timoshenko@mitht.ru. Scopus Author ID 56576076700, ResearcherID Y-8709-2018.

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ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Specificities of multi-primer polymerase chain reaction optimization for the detection of infectious pneumonia agents in human

Ekaterina S. Klochikhina[@], Valeriy E. Shershov, Viktoria E. Kuznetsova, Sergey A. Lapa, Alexander V. Chudinov

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991 Russia

[@]Corresponding author, e-mail: arctickate@yandex.ru

Abstract

Objectives. *The objectives of this work are the development of a multi-primer system based on the polymerase chain reaction (PCR) aimed at the simultaneous detection of six bacterial pathogens that cause human pneumonia and the determination of the parameters important for the optimization of this multi-primer system, including solid-phase PCR systems (biological microarrays).*

Methods. *To determine the optimal parameters of the system, PCR methods were used in monoplex and multiplex formats.*

Results. *Primers for Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenza, Legionella pneumophila, Klebsiella pneumoniae, and Streptococcus pneumoniae detection were designed, and the PCR cycling conditions were optimized. The patterns of primer design for solid-phase PCR were revealed.*

Conclusions. *The developed prototype of a system specifically identifies six clinically significant bacterial pathogens. It could be expanded for the analysis of viral and fungal pathogens and used in clinical diagnostics. A prototype of a system for pathogenic agent detection in the immobilized phase (biological microarray) was created.*

Keywords: *infectious pneumonia, multiplex PCR, biochips, COVID-19*

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НАУЧНАЯ СТАТЬЯ

Особенности оптимизации мультипраймерной ПЦР для выявления возбудителей инфекционной пневмонии человека

Е.С. Клочихина[@], В.Е. Шершов, В.Е. Кузнецова, С.А. Лапа, А.В. Чудинов

Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук, Москва, 119991 Россия
[@]Автор для переписки, e-mail: arctickate@yandex.ru

Аннотация

Цели. *Разработка мультипраймерной системы на основе полимеразной цепной реакции (ПЦР), направленной на одновременное выявление шести основных бактериальных возбудителей пневмонии человека; выявление параметров и закономерностей, имеющих важное значение для оптимизации мультипраймерной системы, в том числе для разработки систем ПЦР в иммобилизованной фазе (на биологическом микрочипе).*
Методы. *Для определения оптимальных параметров системы использовали методы ПЦР в т.н. «моноплексном» и мультиплексном форматах.*
Результаты. *Сконструированы праймеры, и оптимизирован температурно-временной профиль проведения ПЦР в объеме для выявления Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenza, Legionella pneumophila, Klebsiella pneumoniae и Streptococcus pneumoniae. Выявлены закономерности конструирования праймеров для ПЦР в иммобилизованной фазе.*
Выводы. *Изученные закономерности особенностей оптимизации мультипраймерных систем позволили разработать прототип системы, способной специфично выявлять шесть клинически значимых возбудителей пневмонии человека. Прототип системы может быть расширен для анализа вирусных и грибковых патогенов и применяться в клинической диагностике. Результаты изучения особенностей мультиплексной ПЦР в иммобилизованной фазе привели к созданию прототипа системы для выявления патогенных агентов на биологическом микрочипе.*

Ключевые слова: *инфекционная пневмония, мультиплексная ПЦР, биочипы, COVID-19*

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INTRODUCTION

The term “infectious pneumonia” covers a spectrum of diseases of the respiratory system that differ in etiology and pathogenesis [1]. Accurate and timely identification of the causative agent of the lesion is important for the development of successful treatment regimens [2], as well as for the control of the infection. This has become an urgent problem in the context of the COVID-19 pandemic, when, in addition to a viral disease, patients entering medical institutions are faced with secondary nosocomial infections [3].

To identify the causative agents of pneumonia, which can be viruses, bacteria, or fungi, possible standard methods can be used for etiological diagnosis, for example, inoculation. This is often inconvenient due to the limitations of working

with biological samples, as well as the lengthy and laborious work involved in cultivation, isolation, and further determination of the pathogenic agents [4, 5]. For these reasons, more accurate and faster identification is often required for correct treatment [6].

Currently, molecular genetic methods of analysis, such as the polymerase chain reaction (PCR) variations, are becoming more widespread. Their application is favorably notable for relative ease, accuracy, and sensitivity of the results, as well as speed [4], which is important for treating diseases with a highly dynamic pathological development process.

This work is devoted to the development and optimization of PCR for the simultaneous detection of six bacterial pathogens of human pneumonia: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Legionella pneumophila*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*. In the described approach, regions of marker genes of pathogens were amplified in one common volume, the resulting products being separated by the electrophoretic method. The lengths of the detected amplified fragments were used to identify the specific pathogen.

Using the developed system as an example, important features for the optimization of multi-primer PCR are described, including those for use in the immobilized phase.

EXPERIMENTAL

Strains

We used the decontaminated genome-wide DNA of bacterial strains from the collection of the State Scientific Center for Applied Microbiology and Biotechnology (Obolensk, Serpukhov, Moscow oblast, Russia). DNA isolation from the cell cultures was completed using the cetyltrimethylammonium bromide method [7].

Primers

Multiple alignment of the genomic target sequences was performed using the ClustalW[1] algorithm. The primers were designed using the Integrated DNA Technologies[2] network resource, and the specificity analysis was performed using the basic local alignment search tool (BLAST)[3] algorithm (National Institutes of Health, USA). The sequences, species specificities, genetic targets, and lengths of the PCR products for all of the primer pairs used are shown below:

S. aureus, ebpS gene, direct ebpS-f (5'-ACTCGACTGAGGATAAAGCGTCT-3'), reverse ebpS-r (5'-CCTCCAAATATCGCTAATGCACC-3'), PCR product length: 283 base pairs (bp), nested reverse R1 (5'-NH_2-CCTCCAAATATCGCTAATGCACC-3'), R2 (5'-NH_2-GGTAACAATACTTTGGCCATGCCACC-3'), nested direct F1(5'-CTGCCGCTTCAAAACCACATGCC-3), F2 (5'-AAAAGGTGGCATGGCCAAAGT-3'), F3 (5'-AGCAAGTAATAGTGCTTCTGCCG-3').

S. pneumonia, cpsB gene, direct cpsB-f1 (5'-TTGATGTAGATGACGGTCCCAAG-3'), reverse cpsB-r1 (5'-TATATCTCTGCGCCATAAGCAAT-3'), PCR product length: 217 bp, nested reverse R3 (5'-NH_2-TATATCTCTGCGCCATAAGCAAT-3'), R4 (5'-NH_2-CGAACCTGAAGAAAGTTTTCTG-3'), R5 (5'-NH_2-GCAATGACTAAATCATCTGCCAC-3'), nested direct F4 (5'-GCGAACCATTGTCTCTACCTCTC-3'), F5 (5'-TCTACCTCTCACCGTCGCAAGGG-3'), F6 (5'-TGGCAGAATCCTACAGGCAGG-3').

L. pneumophila, sidA gene, direct sidA-f (5'-TTCCACTGGTGGGTGGGGTTTTG-3'), reverse sidA-r (5'-TCATGTTGGAGTTCTATGGCACG-3'), PCR product length: 369 bp.

H. influenza, fucK gene, direct fucK-f (5'-TGCTCACTCAACGCTTAACTGGT-3'), reverse fucK-r (5'-TTCTGGGCTAATGGTGTACGTAA-3'), PCR product length: 193 bp.

P. aeruginosa, oprL gene, direct oprL-f (5'-GCGTGCGATCACCACCTTCTACT-3'), reverse oprL-r (5'-TTCTTCAGCTCGACGCGACGGTT-3'), PCR product length: 321 bp.

K. pneumonia, rmpA gene, direct rmpA-f (5'-ATCAATAGCAATTAAGCACAAAA-3'), reverse rmpA-r (5'-TCATAATCACACCCTTTAGGATA-3'), PCR product length: 177 bp.

Multiplex PCR

The reaction mixture (30 μL) contained 1.5 units of Taq polymerase (*Thermo Scientific*, United States) in the buffer produced by the same company, dNTP at a concentration of 200 μM each, five pairs of specific primers, and a genome-wide bacterial template (or a mixture of bacterial DNA). The reaction was carried out in a MiniCycler DNA amplifier (*MJResearch*, USA) under the following conditions: 95°C for 5 min (initial denaturation), 30 cycles of 20 s at 95°C, 30 s at 66°C, and 30 s at 72°C; the final incubation was 5 min at 72°C. Gradient PCR and determination of the system sensitivity using real-time PCR were performed in an IQ5 amplifier (*Bio-Rad*, USA). The PCR products were separated in 4% agarose gel and colored with ethidium bromide. The lengths of the amplification products in ultraviolet light were used to determine the type of analyzed DNA.

[1] Clustal: Multiple Sequence Alignment. URL: www.clustal.org (accessed December 15, 2020).
[2] Integrated DNA Technologies. URL: www.idtdna.com (accessed December 17, 2020).
[3] Basic Local Alignment Search Tool. URL: https://blast.ncbi.nlm.nih.gov/Blast.cgi (accessed December 15, 2020)

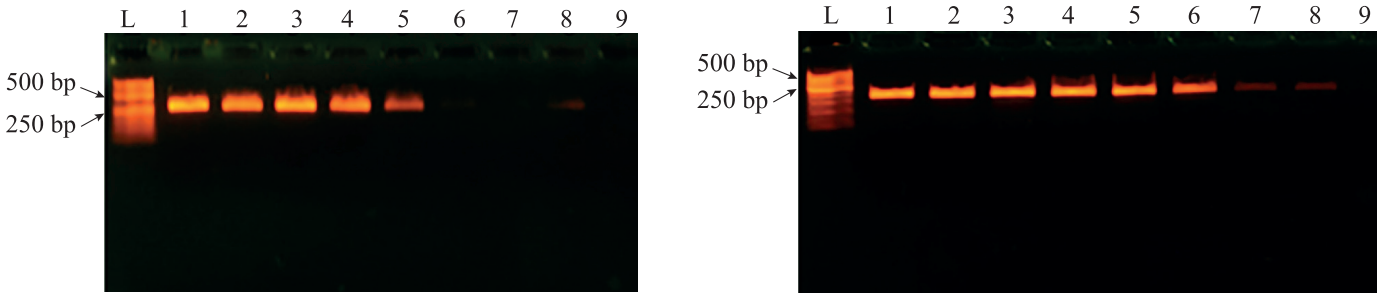

Fig. 1. Electropherograms of PCR products of gradient PCR. L – GeneRuler 50bp length marker (*Thermo Scientific*, USA). 4% agarose gel, coloring with ethidium bromide.
(a) *S. aureus*. Primers annealing temperatures: Well 1: 65.0°C, Well 2: 65.6°C, Well 3: 66.5°C, Well 4: 67.7°C, Well 5: 69.5°C, Well 6: 70.8°C, Well 7: 71.7°C, Well 8: 72.0°C, Well 9: negative control;
(b) *L. pneumophila*. Primers annealing temperatures: Well 1: 57.0°C, Well 2: 58.2°C, Well 3: 60.0°C, Well 4: 62.7°C, Well 5: 66.5°C, Well 6: 69.3°C, Well 7: 71.0°C, Well 8: 72.0°C, Well 9: negative control.

RESULTS AND DISCUSSION

Genetic targets were selected for the six most important causative agents of pneumonia, and primers were designed for multiplex PCR [8–16].

We were guided by the general requirements when designing the primer sequences: species specificity and intraspecific conservatism of the selected regions of the genetic targets. The primer annealing sites were manually selected. Additionally, the need to obtain different lengths of PCR products for the convenient subsequent detection of pathogens by electrophoretic separation was taken into account. The physicochemical characteristics were determined for each oligonucleotide sequence; a BLAST analysis was then performed and examined for the formation of dimers, hairpins, and other secondary structures.

The initial amplification conditions for subsequent optimization were chosen as follows: denaturation at 95°C and 30 cycles of 20 s at 95°C, 30 s at 57°C, and 30 s at 72°C. For the pathogens *S. aureus* and *L. pneumophila*, gradient "monoplex" PCRs were performed. The results revealed that the annealing temperature of the latter was increased to 66°C (Fig. 1).

In a new temperature–time cycle, monoplex PCR variants were carried out for the remaining four pathogens. The primer effects were checked, comparing the lengths of the PCR products with the theoretical ones. Then, in the mode of a mixture of the DNA templates (Fig. 2) of several pathogens, their specificity and ability to detect only their pathogens without providing false-positive results were confirmed.

The result of differential detection of a pathogen's DNA in a sample by multiplex PCR is shown in Fig. 3.

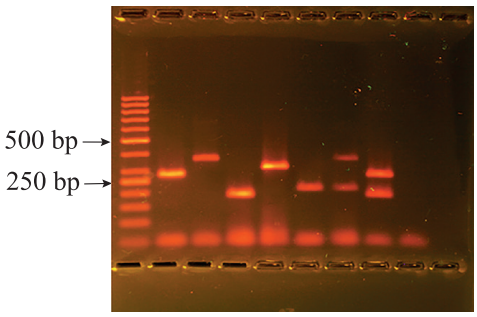

Fig. 2. Electrophoretic separation of PCR products by multiplex PCR with a mixture of primers.
(1) GeneRuler 50bp length marker (*Thermo Sientific*, USA), (2) *S. aureus*, (3) *L. pneumophila*, (4) *H. influenzae*, (5) *P. aeruginosa*, (6) *S. pneumoniae*, (7) *L. pneumophila* + *S pneumoniae*, (8) *S. pneumoniae* + *H. Influenzae* + *S. aureus*.
The PCR products were separated in 4% agarose gel and colored with ethidium bromide.

In the cases of *S. aureus* and *S. pneumoniae*, specific primers were designed for subsequent immobilization on a biochip incorporating fluorescently labeled nucleotides into the immobilized growing chain. The above principles were also used in this work. The high sensitivity of the primers designed for immobilization was confirmed by volumetric PCR undertaken under the conditions of the previously found optimal temperature–time profile. The results of the monoplex PCRs in volume for *S. aureus* and *S. pneumoniae* are shown in Figs. 4 and 5. It can be seen from the pherograms that the lengths of the PCR products obtained using various combinations of primers were in good agreement with the theoretical ones.

When analyzing the pherograms, primers showing insufficient sensitivity or specificity were re-analyzed

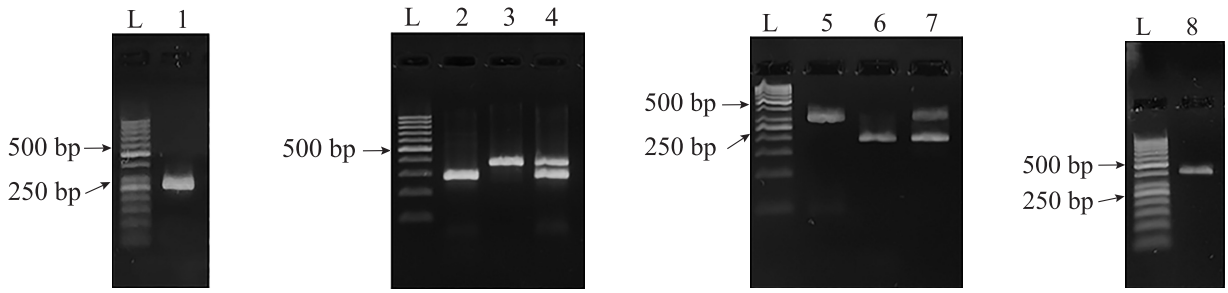

Fig. 3. Determination of the pathogen DNA by electrophoretic separation of PCR products. L – GeneRuler 50bp length marker (*Thermo Scientific*, USA), (1) *S. pneumoniae*, (2) *S. aureus*, (3) *L. pneumophila*, (4) *S. aureus* + *L. pneumophila*, (5) *H. influenzae*, (6) *P. aeruginosa*, (7) *H. influenzae* + *P. aeruginosa*, (8) *K. pneumoniae*. The PCR products were separated in 4% agarose gel and colored with ethidium bromide.

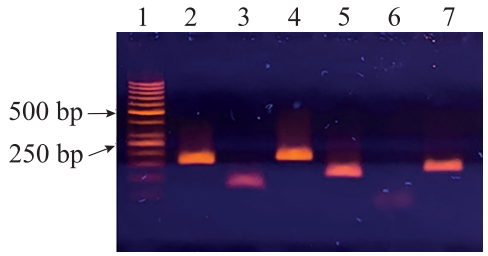

Fig. 4. Electrophoretic separation of *S. aureus* PCR products. (1) GeneRuler 50bp length marker (*Thermo Sientific*, USA), (2) R1 + F1 (163 base pairs (bp)), (3) R1 + F2 (78 bp), (4) R1 + F3 (180 bp), (5) R2 + F1 (115 bp), (6) R2 + F2 (30 bp), (7) R2 + F3 (132 bp). The letters "R" and "F" indicate the numerical indexes used to designate various primers. The theoretical length of the corresponding PCR product is indicated in parentheses.

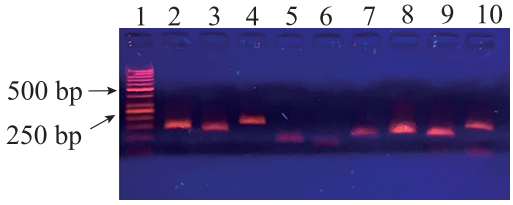

Fig. 5. Electrophoretic separation of PCR products of *S. pneumoniae.* (1) GeneRuler 50bp length marker (*Thermo Sientific*, USA); (2) R3 + F4 (144 bp); (3) R3 + F5 (131 bp); (4) R3 + F6 (169 bp); (5) R4 + F4 (87 bp); (6) R4 + F5 (74 bp); (7) R4 + F6 (112 bp); (8) R5 + F4 (126 bp); (9) R5 + F5 (113 bp); (10) R5 + F6 (151 bp). The letters "R" and "F" indicate the numerical indexes used to designate various primers. The theoretical length of the corresponding PCR product is indicated in parentheses.

for the presence of secondary structures (both intramolecular and intermolecular). If correction by "shifting" the primer along the complementary strand or varying its length or melting temperature to change the structures formed was impossible, the primer was replaced with one that was newly designed.

CONCLUSIONS

PCR for the simultaneous detection of six clinically important bacterial pathogens of human pneumonia was designed and optimized.

Currently, the design of primers for immobilization is being undertaken, and a test system based on biochips is being developed. In the future, the system could have an expanded range of diagnosed pathogenic agents of infectious pneumonia and could be used in accelerated clinical diagnostics.

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Authors' contribution

E.S. Klochikhina – research, preparation of the manuscript.

V.E. Shershov – synthesis of fluorescently labeled dNTPs.

V.E. Kuznetsova – synthesis of fluorescently labeled dNTPs.

S.A. Lapa – planning experiments, editing the manuscript.

A.V. Chudinov – academic advising.

The authors declare no conflicts of interest.

REFERENCES

1. Nair G.B., Niederman M.S. Community-acquired pneumonia: an unfinished battle. *Med. Clin. North Am.* 2011;95(6):1143–1161. https://doi.org/10.1016/j.mcna.2011.08.007

2. Harris M., Clark J., Coote N., Fletcher P., Harnden A., McKean M., Thomson A. British Thoracic Society Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax.* 2011;66:ii1–ii23(Suppl. 2). https://doi.org/10.1136/thoraxjnl-2011-200598

3. Rawson T.M., Wilson R.C., Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. *Clin. Microbiol. Infect.* 2021;27(1):9–11. https://doi.org/10.1016/j.cmi.2020.09.025

4. Chuchalin A.G., Sinopal'nikov A.I., Kozlov R.S., Avdeev S.N., Tyurin I.E., Rudnov V.A., Rachina S.A., Fesenko O.V. Russian Respiratory Society Interregional association on clinical microbiology and antimicrobial chemotherapy Clinical guidelines on diagnosis, treatment and prevention of severe community acquired pneumonia in adults. *PULMONOLOGIYA*. 2014;(4):13–48 (in Russ.). https://doi.org/10.18093/0869-0189-2014-0-4-13-48

5. Tartakovskii I.S. Modern approaches to the diagnosis of atypical pneumonia. *Klin. Mikrobiol. Antimikrob. Khimioterap. = Clin. Microbiol. Antimicrob. Chemotherapy.* 2000;2(1):60–68 (in Russ.). Available from URL: https://cmac-journal.ru/en/publication/2000/1/cmac-2000-t02-n1-p060/cmac-2000-t02-n1-p060.pdf

6. Brusnigina N.F., Mazepa V.N., Samokhina L.P., *et al.* Etiological structure of community-acquired pneumonia. *Med. Al'manakh = Med. Alm*. 2009;2(7):118–121 (in Russ.).

7. Doyle J.J., Doyle J.L. A Rapid DNA Isolation Procedure for Small Quantities of Fresh Leaf Tissue. *Phytochemical Bullettin.* 1987;19(1):11–15.

8. Morona J.K., Morona R., Miller D.C., Paton J.C. *Streptococcus pneumoniae* capsule biosynthesis protein CpsB is a novel manganese-dependent phosphotyrosine-protein phosphatase. *J. Bacteriol.* 2002;184(2):577–583. https://doi.org/10.1128/JB.184.2.577-583.2002

9. Liu Y., Cao Y., Wang T., Dong Q., Li J., Niu C. Detection of 12 Common Food-Borne Bacterial Pathogens by TaqMan Real-Time PCR Using a Single Set of Reaction Conditions. *Front Microbiol.* 2019;10:222. https://doi.org/10.3389/fmicb.2019.00222

10. Xirogianni A., Tzanakaki G., Karagianni E., Markoulatos P., Kourea-Kremastinou J. Development of a single-tube polymerase chain reaction assay for the simultaneous detection of *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus* spp. directly in clinical samples. *Diagn. Microbiol. Infect. Dis.* 2009;63(2):121–126. https://doi.org/10.1016/j.diagmicrobio.2008.09.017

11. Huletsky A., Giroux R., Rossbach V., Gagnon M., Vaillancourt M., Bernier M., Gagnon F., Truchon K., Bastien M., Picard F.J, van Belkum A., Ouellette M., Roy P.H., Bergeron M.G. New real-time PCR assay for rapid detection of methicillin-resistant *Staphylococcus aureus* directly from specimens containing a mixture of staphylococci. *J. Clin. Microbiol.* 2004;42(5):1875–1884. https://doi.org/10.1128/JCM.42.5.1875-1884.2004

12. Morrison K.E., Lake D., Crook J., Carlone G.M., Ades E., Facklam R., Sampson J.S. Confirmation of psaA in all 90 serotypes of *Streptococcus pneumoniae* by PCR and potential of this assay for identification and diagnosis. *J. Clin. Microbiol.* 2000;38(1):434–437. https://doi.org/10.1128/jcm.38.1.434-437.2000

13. Binks M.J., Temple B., Kirkham L.-A., Wiertsema S.P., Dunne E.M., *et al*. Molecular Surveillance of True Nontypeable *Haemophilus influenzae*: An Evaluation of PCR Screening Assays. *PLoS ONE.* 2012;7(3):e34083. https://doi.org/10.1371/journal.pone.0034083

14. De Vos D., Lim A.Jr., Pirnay J.P., *et al*. Direct detection and identification of *Pseudomonas aeruginosa* in clinical samples such as skin biopsy specimens and expectorations by multiplex PCR based on two outer membrane lipoprotein genes, oprI and oprL. *J. Clin. Microbiol.* 1997;35(6):1295–1299. https://doi.org/10.1128/jcm.35.6.1295-1299.1997

15. Tabatabaei M., Hemati Z., Moezzi M.O., Azimzadeh N. Isolation and identification of *Legionella* spp. from different aquatic sources in south-west of Iran by molecular &culture methods. *Mol. Biol. Res. Commun.* 2016;5(4):215–223. https://dx.doi.org/10.22099/mbrc.2016.3858

16. Turton J.F., Perry C., Elgohari S., Hampton C.V. PCR characterization and typing of *Klebsiella pneumoniae* using capsular type-specific, variable number tandem repeat and virulence gene targets. *J. Med. Microbiol.* 2010;59(5):541–547. https://doi.org/10.1099/jmm.0.015198-0

About the authors:

Ekaterina S. Klochikhina, Laboratory Assistant, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (32, Vavilova ul., Moscow, 119991, Russia). E-mail: arctickate@yandex.ru. https://orcid.org/0000-0002-9485-3068

Valeriy E. Shershov, Researcher, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (32, Vavilova ul., Moscow, 119991, Russia). E-mail: shershov@list.ru. https://orcid.org/0000-0003-3308-7133

Viktoria E. Kuznetsova, Cand. Sci. (Chem.), Researcher, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (32, Vavilova ul., Moscow, 119991, Russia). E-mail: kuzneimb@gmail.com. https://orcid.org/0000-0002-8204-4132

Sergey A. Lapa, Cand. Sci. (Biol.), Senior Researcher, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (32, Vavilova ul., Moscow, 119991, Russia). E-mail: lapa@biochip.ru. Scopus Author ID 6603461000, https://orcid.org/0000-0002-9011-134X

Alexander V. Chudinov, Cand. Sci. (Chem.), Head of the Laboratory, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (32, Vavilova ul., Moscow, 119991, Russia). E-mail: chud@eimb.ru. Scopus Author ID 7003833018, https://orcid.org/0000-0001-5468-4119

Об авторах:

Клочихина Екатерина Сергеевна, лаборант, ФГБУН Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук (119991, Россия, Москва, ул. Вавилова, д. 32). E-mail: arctickate@yandex.ru. https://orcid.org/0000-0002-9485-3068

Шершов Валерий Евгеньевич, научный сотрудник, ФГБУН Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук (119991, Россия, Москва, ул. Вавилова, д. 32). E-mail: shershov@list.ru. https://orcid.org/0000-0003-3308-7133

Кузнецова Виктория Евгеньевна, к.х.н., научный сотрудник, ФГБУН Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук (119991, Россия, Москва, ул. Вавилова, д. 32). E-mail: kuzneimb@gmail.com. https://orcid.org/0000-0002-8204-4132

Лапа Сергей Анатольевич, к.б.н., старший научный сотрудник, ФГБУН Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук (119991, Россия, Москва, ул. Вавилова, д. 32). E-mail: lapa@biochip.ru. Scopus Author ID 6603461000, https://orcid.org/0000-0002-9011-134X

Чудинов Александр Васильевич, к.х.н., заведующий лабораторией, ФГБУН Институт молекулярной биологии им. В.А. Энгельгардта Российской академии наук (119991, Россия, Москва, ул. Вавилова, д. 32). E-mail: chud@eimb.ru. Scopus Author ID 7003833018, https://orcid.org/0000-0001-5468-4119

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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

Combination of *Phyllanthus amarus* Schum. & Thonn. and *Gymnema sylvestre* R. Br. for treatment of diabetes and its long-term complications

Tan M. Le[1,2], Chinh D.P. Nguyen[1,2], Anh C. Ha[1,2,@]

[1]Faculty of Chemical Engineering, Ho Chi Minh City University of Technology, 268 Ly Thuong Kiet Street, Ho Chi Minh City, Vietnam
[2]Vietnam National University Ho Chi Minh City, Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam
[@]Corresponding author, e-mail: hcanh@hcmut.edu.vn

Abstract

Objectives. *The amount of patients with diabetes is increasing, and such patients experience several long-term complications. Therefore, finding a method to treat the disease and its complications is an urgent issue worldwide. In Vietnam, Phyllanthus amarus Schum. & Thonn. (PA) and Gymnema sylvestre R. Br. (GS) are common herbs used in traditional therapy including diabetes treatment. This study aimed to combine PA and GS to extend their bioactivities in antidiabetes, antioxidant, and anti-inflammatory treatments.*

Methods. *Here, PA and GS powders were mixed at different ratios for extraction. Ethanolic extract was used to detect bioactive compounds, bioactivities, and appropriate ratios of the mixtures.*

Results. *The optimal ratio for the PA and GS combination was 2 : 1 (g/g). The ethanolic extraction of the 2 : 1 sample at 50°C over two hours with a solid/liquid ratio of 1 : 10 achieved a high yield of 14.37%. This sample exhibited good α-glucosidase inhibition activity with a half-maximal inhibitory concentration (IC50) of 9.74 μg/mL, antioxidant activity with an IC50 of 29.87 μg/mL, and anti-inflammatory activity with an IC15 of 400 μg/mL.*

Conclusions. *The study confirmed that combining PA and GS can have high α-glucosidase inhibition as well as antioxidant and anti-inflammatory effects.*

Keywords: *antidiabetes, antioxidant, anti-inflammatory, Phyllanthus amarus Schum. & Thonn, Gymnema sylvestre R. Br., integration*

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НАУЧНАЯ СТАТЬЯ

Комбинация *Phyllanthus amarus* Schum. & Thonn. и *Gymnema sylvestre* R. Br. для лечения диабета и его долгосрочных осложнений

Т.М. Ле[1,2], Ч.Д.П. Нгуен[1,2], А.К. Ха[1,2,@]

[1]Химико-технологический факультет, Технологический университет Хошимина, 268 Ли Тхыонг Кьет ул., г. Хошимин, Вьетнам
[2]Вьетнамский национальный университет, Район Тхёк, г. Хошимин, Вьетнам
[@]Автор для переписки, e-mail: hcanh@hcmut.edu.vn

Аннотация

Цели. *Количество пациентов с диабетом растет, у них часто возникают долгосрочные осложнения, поэтому поиск методов лечения этого заболевания и коррекции его осложнений является важным для всего мирового медицинского сообщества. Phyllanthus amarus Schum. & Thonn. (PA) и Gymnema sylvestre R. Br. (GS) – распространенные во Вьетнаме лекарственные растения, используемые в традиционной медицине, включая лечение диабета. Цель данного исследования – скомбинировать PA и GS, чтобы расширить их биологическую активность и усилить антидиабетический, антиоксидантный и противовоспалительный эффект.*

Методы. *Порошки листьев PA и GS смешивали в различных соотношениях и экстрагировали 95% этанолом. Полученные этанольные экстракты использовались для определения биологически активных соединений, биологической активности и оптимального соотношения компонентов смеси.*

Результаты. *Оптимальное соотношение PA и GS, определенное в исследовании, равно 2 : 1 (г/г). Экстракция 95% этанолом данного образца (2 : 1) при 50 °C в течение двух часов при соотношении сырье/эстрагент 1 : 10 позволила получить высокий выход экстрактивных веществ, равный 14.37%. Этот образец продемонстрировал хорошую активность ингибирования α-глюкозидазы с половинной максимальной ингибирующей концентрацией (IC50) 9.74 мкг/мл, антиоксидантную активность с IC50 29.87 мкг/мл и противовоспалительную активность с IC15 400 мкг/мл.*

Выводы. *Исследование подтвердило, что сочетание PA и GS может значительно ингибировать α-глюкозидазу, а также обладает антиоксидантным и противовоспалительным эффектами.*

Ключевые слова: *антидиабетическое, антиоксидантное, противовоспалительное, Phyllanthus amarus Schum. & Thonn, Gymnema sylvestre R. Br., интеграция*

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1. INTRODUCTION

Diabetes mellitus is an endocrine disorder disease characterized by a hereditary or acquired deficiency in insulin excretion as well as reduced responsiveness of organs to the produced insulin [1]. According to International Diabetes Federation reports, there were about 463 million adults with diabetes in 2019, and the number is predicted to rise to 630 million by 2045 [2, 3]. Patients with diabetes mellitus are likely to have long-term complications, e.g., impaired wound healing, retinopathy, atherosclerosis, cataract, neuropathy, and nephropathy [4]. Inflammation and oxidation are the most common complications of diabetes [5]. Therefore, a medicine or drug for treating diabetes and its complications is being researched worldwide [1]. In these efforts, the use of natural compounds with antidiabetic properties has attracted much attention. However, the major drawback of herb-based medicine is that the bioactivities of the plants depend on the extraction conditions. A solution for this issue can be found in traditional medicine. For example, in traditional Vietnamese medicine, several human diseases can be treated using a combination of various herbs. Certain plants play the main role in treating the disease, while the others are used for treating the complications. However, the development of pharmaceutical preparations has led to lower and less efficient quantities of herbs being used in medication for human diseases. The traditional method shows promise in creating more valuable disease treatments, especially diabetes.

Phyllanthus amarus Schum. & Thonn (PA) is a small tropical herb in the *Phyllanthus* genus of the *Euphorbiaceae* family and can be found in Nigeria, India, China, Vietnam, and Thailand [6]. Its leaves are commonly used and highly valued in traditional medicine because of their beneficial properties [7]; several researchers have extracted and isolated bioactive compounds, such as polyphenols, flavonoids, tannins, triterpenes, sterols, and alkaloids, from PA leaves [8]. Because of these valuable ingredients, the leaves have been confirmed to have several potential bioactive applications, such as antihepatitis [9], antioxidant [10], anticancer [11], anti-inflammatory [12], antimalarial [13], antimicrobial [14], and antidiabetes [15].

Gymnema sylvestre R. Br. (GS), a plant in the *Asclepiadaceae* family, is commonly found across Asia, Africa, and Australia [16]. Its leaves are used in numerous traditional therapies for patients with diabetes and various other diseases [17]. The plant reportedly has potent anti-obesity activities, e.g., it may help lower weight gain and fat accumulation [18]. Isolated bioactive compounds of GS indicate the gymnemic acid group is the main active compound responsible for the plant's antidiabetes activity. In addition, GS leaves have been reported to have diverse antiviral [19], antibiotic [20], and anticancer [21] bioactivities among others [16]. Similar to those of PA, most bioactivities of GS do not concurrently exist under the same extraction conditions. The plant has also been used in the production of tea brews, tea bags, and confections as well as in the management of sugar homeostasis and maintenance of obesity and blood cholesterol levels in a various foods [22].

Owing to their diverse bioactivities, PA and GS show potential for use in treating diabetes and its complications. Therefore, in this study, they are mixed at different ratios to improve their antidiabetes, antioxidant, and anti-inflammatory activities. The antidiabetes activity is measured via α-glucosidase inhibition, whereas the antioxidant and anti-inflammatory effects are determined via 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and albumin denaturation, respectively. Following traditional medicine, the herbs play the main role in the mixtures' antidiabetes activity, as verified via ethanolic extraction for further research.

2. MATERIALS AND METHODS

2.1. Materials

The PA and GS leaves were harvested from Binh Chanh District, Ho Chi Minh City, Vietnam, in October 2020. The identification was done at the Department of Ecology and Evolutionary Biology of the Faculty of Biology and Biotechnology, Ho Chi Minh City University of Science, Vietnam National University. After being harvested, the samples were rinsed with water, dried at room temperature, ground into a powder with a particle size of 3–5 mm, and stored in sealed bags.

The following pure-grade chemicals were purchased from commercial suppliers: ethanol (EtOH), methanol (MeOH), distilled water, sodium nitrite, sodium carbonate (Na_2CO_3), sodium hydroxide, aluminum chloride, and dimethyl sulfoxide (DMSO). The Folin–Ciocalteu reagent, quercetin, gallic acid (GA), *para*-nitrophenyl *α*-D-glucopyranoside (*p*-NPG), *α*-glucosidase, acarbose, bovine albumin, and DPPH were provided by *Sigma-Aldrich*, Singapore.

2.2. Preparation of extracts

A total of 50.00 g of the PA and GS powder mixture was extracted at different ratios with 500 mL EtOH 95% over two hours at 50°C and a solid/liquid ratio of 1 : 10 g/mL. Afterward, the extracts were filtered using filter paper (15–20 μm) under vacuum conditions. The herbal residue was recycled for subsequent extraction under the same conditions. The two extractions were mixed and concentrated via rotary vacuum evaporation at 55°C (Buchi R-215 Rotavapor). The moisture content of the extracts and powders were determined using Sartorius moisture analyzer MA37.

All experiments were performed in triplicate. The extraction yield was determined using Eq. 1:

$$Extraction\ yield\ (\%) = \frac{m_{extract}}{m_{sample}} \times 100\%, \quad (1)$$

where $m_{extract}$ is the dry weight of the extract (g) and m_{sample} is the dry weight of the sample (g).

2.3. Phytochemical screening

Phytochemical screening of the PA and GS was conducted to detect the presence of alkaloids, flavonoids, tannins, saponins, terpenoids, cardiac glycosides, and polyphenols [23–27]. The reagents, test method, and results are shown in table.

2.4. Determination of the total polyphenol excreted (TPE)

The phenolic level was determined by Folin–Ciocalteu assay, as described by McDonald *et al*. [28]. A total of 40 μL of each extract was dissolved in DMSO, and 200 μL of Folin–Ciocalteu reagent was mixed and homogenized in a sonication bath for five minutes at room temperature. Afterward, 600 μL of 20% Na_2CO_3 and 3160 μL of distilled water were added to the mixture. An extract without reagents was used as a sample. After incubating all samples at room temperature for 30 min, their absorbance was measured at 760 nm using a UV–Vis spectrophotometer (*Thermometer*, USA). The calibration curve for GA was created to calculate the phenolic content. The TPE was shown as the milligrams GA equivalent (GAE) per gram of the extract (dry weight). The equation of the calibration curve was $y = 1.2003x - 0.0034$, where $R^2 = 0.9979$.

2.5. *In vitro* α-glucosidase inhibitory assay

The antidiabetes activity of the extracts *in vitro* was measured via the α-glucosidase inhibition activity because the α-glucosidase enzyme plays an important catalytic role in converting polysaccharides to monosaccharides (glucose). Thus, inhibition of α-glucosidase lowers the glucose content.

The investigation regarding the α-glucosidase enzyme inhibitory activity of the extract was conducted following Liu's method [29]. The test was performed on 96 well plates. The extracts were dissolved in DMSO before the test, and 40 and 20 μL of the sample solution and α-glucosidase enzyme (1 U/mL), respectively, were added to the wells. Next, 100 μL of phosphate buffer (pH 6.8) was added to the mixture. The plate was incubated for five minutes at 37°C. Then, 40 μL of 0.1 mM *p*-NPG was added to the reacting mixture, which was continuously incubated for 30 min at 37°C. Subsequently, ~100 μL of 0.1 M Na_2CO_3 was added to terminate the reaction. The sample absorbance was measured at 405 nm using the UV–Vis spectrophotometer. Acarbose was employed as a positive control. The percent inhibition of the α-glucosidase reaction was calculated as follows:

$$I\% = \left(\frac{A - B}{A}\right) \times 100\%, \quad (2)$$

where A is the absorbance at 405 nm of the blank (α-glucosidase and the substrate) and B is the absorbance at 405 nm of the extract (α-glucosidase, the substrate, and the sample).

The concentrations of the extracts resulting in the half-maximal inhibitory concentration (IC_{50}) of the enzyme activity were determined graphically.

2.6. *In vitro* antioxidant assay

The oxidation is one of the main complications of diabetes; thus, finding an agent with antioxidant and antidiabetes activities is a necessity. The antioxidant activity of the samples was investigated via DPPH free radical scavenging assay according to Stagos' method, with slight modifications [30]. A total of 120 μL of sample was added to 180 μL of DPPH dissolved in 80% MeOH. The mixture was incubated for 30 min at 30°C in the dark. Then, the absorbance was measured at 517 nm using the UV–Vis spectrophotometer. Here, MeOH and ascorbic acid were used as the negative control and positive control, respectively. The percentage inhibition (I%) was calculated using Eq. 3:

$$I\% = \left(\frac{A - B}{A}\right) \times 100\%, \quad (3)$$

where A is the absorbance at 517 nm of the DPPH radical of the negative control and B is the absorbance at 517 nm of the DPPH radical solution mixed with the sample.

The antioxidant activity was expressed by the IC_{50} value, representing the sample concentration required to inhibit 50% of the free radical scavenging activity.

2.7. *In vitro* anti-inflammatory assay

Inflammation is a complex process associated with the reaction of body tissues to infection, irritation, or other injuries. Therefore, it is involved in various diseases, including diabetes [31]. The *in vitro* anti-inflammatory activity of the extracts was evaluated via the extracts' protective activity against albumin denaturation, as described in previous studies with slight modifications [32]. The extracts were serially diluted in DMSO, which was used as the negative control.

The reaction mixture was prepared by adding 3 mL of bovine albumin dissolved in phosphate buffer with a pH of 6.4 into 2 mL of tested extract. The mixture was incubated for 5 min at 70°C. After cooling to room temperature, the sample absorbance was measured at 660 nm using a UV-Vis spectrophotometer (*Jasco*, USA).

The percentage inhibition of the protein denaturation was calculated using Eq. 4:

$$I\% = \frac{A_{control} - A_{sample}}{A_{control}} \times 100\%, \quad (4)$$

where $A_{control}$ is the absorbance of the negative control (DMSO) and A_{sample} is the absorbance of the extract.

2.8. Statistical analysis

All analyses were performed in triplicate, and the data were expressed as the mean value ± standard deviation for each measurement.

3. RESULTS AND DISCUSSION

3.1. Phytochemical studies of PA and GS

Ethanol is a polar solvent commonly used in phytochemical extraction because EtOH has been suggested to extract the maximum amount of bioactive compounds from plants [33, 34]. According to the phytochemical screening results presented in table, all previously mentioned bioactive compounds were detected in both PA and GS. Alkaloids and terpenoids were present in large quantities in both herbs, which indicated that the plants have potent antidiabetes and antioxidant activities because of the specific activities of these biocompounds. In particular, the strong presence of tannins in the PA extract suggested the probability of such bioactivities. Tannins have been shown to have antibacterial, antiviral, antifungal, antidiabetic, and antioxidant activities and promote tissue recovery in cases of superficial burn injuries [35]. Furthermore, the existence of flavonoids in the PA extract suggested the ability to enhance the current therapy options for type 2 diabetes mellitus [36]. The GS extract had a more vigorous reaction with the saponin and cardiac glycoside reagents than the PA extract. Saponins have been shown to exhibit hemolytic, antimicrobial, insecticidal, anthelmintic, analgesic, anti-inflammatory, sedative, and antitumor bioactivities [37]. The use of cardiac glycoside in clinical trials for the treatment of heart disease and atrial arrhythmia has been confirmed [38]. Because of the robust amount of key biocompounds possessing antidiabetes activity, the PA extract was predicted to exhibit better antidiabetes activity than the GS extract.

3.2. Effect of different PA and GS ratios on extraction yield and TPE

The TPE and extraction yields of the PA and GS mixtures of various ratios are presented in Fig. 1. The results showed that the differences in the extraction yield were insignificant (approximately 1%). The extraction yield was in the range of 13.77% (GS) to 15.22% (PA), increasing with the increase in the PA content in the powder. The GS content increased when the TPE of the extracts decreased, except in the 2 : 1 sample. In general, the TPE of all samples was in the range of 65–71 mgGAE/g and the difference was statistically significant. The TPE reached a maximum value of 71.06 mgGAE/g at the PA/GS ratio of 2 : 1, with the highest extraction yield from the PA. Phenolics are the primary bioactive materials in nature and have been reported to have multiple biological effects, including antidiabetes effects [39]. Thus, the high TPE values illustrated the extracts' potential antidiabetes activity.

Phytochemical screening of PA and GS extracted with EtOH solvents

Bioactive compounds	Test	Extracts	
		PA	GS
Alkaloid	Dragendroff [24]	++	++
	Bouchardat [24]	++	++
Flavonoid	Lead acetate 10% [24]	+	–
	Sulfuric acid 98% [26]	+	+
Tannin	Gelatin 1% [25]	++	+
Saponin	Foam [23]	+	++
	Liebermann–Burchard [27]	+	++
Terpenoid	Salkowski [26]	++	++
Cardiac glycoside	Keller–Kiliani [25]	–	+
Polyphenol	Ferric (III) chloride [25]	++	++

– Not detected; + Slightly positive reaction; and ++ Strong positive reaction

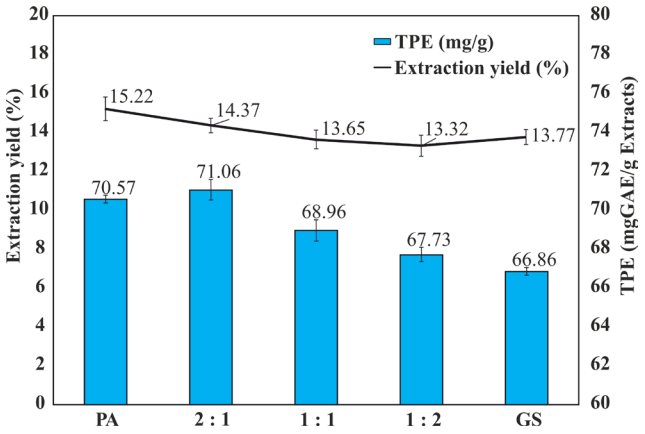
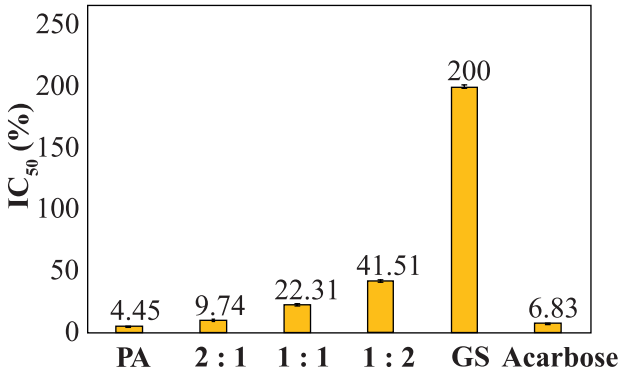


Fig. 1. Extraction yield and TPE in the PA and GS mixtures of various ratios. Here, 2 : 1 refers to the PA/GS ratio of 2 : 1, and from right to left, the PA content gradually decreases.

3.3. The effect of the different ratios of PA and GS on their bioactivities

Figure 2 displays the bioactivities of the various extracts at different herbal powder ratios. The PA extracts showed strong inhibitory effects on α-glucosidase, with an IC_{50} value of 4.45 μg/mL lower than that of the positive control acarbose (6.83 μg/mL). The antioxidant and anti-inflammatory activities of the PA samples were lower than those of the GS samples, but the PA's antioxidant activity was still higher than that of numerous herbs in the existing literature [40]. The GS extract exhibited the most antioxidant activity, with an IC_{50} value of 22.12 μg/mL, as well as anti-inflammatory activity, with an IC_{15} value of 200 μg/mL. Here, IC_{15} was used to evaluate the anti-inflammatory activity because all extracts' inflammatory inhibition was lower than 20%. William *et al.* reported that extracts with inflammatory inhibition above 20% following albumin denaturation can be considered anti-inflammatory agents [41].

The efficiency of the plants' combination was determined using the bioactivities of the combined samples. The results indicated significant biological activity changes compared with the raw materials. The PA content was an important factor in the antidiabetes activity, and a decrease in PA led to a reduction of the activity in the extract. Mixing the PA with the GS powder significantly improved the α-glucosidase inhibition activity of the latter, which was demonstrated via the increased antidiabetes activity of samples 2 : 1, 1 : 1, and 1 : 2 compared with the GS powder alone. The PA/GS ratio of 2 : 1 showed antidiabetes activity (IC_{50} 9.47 μg/mL) 21 times higher



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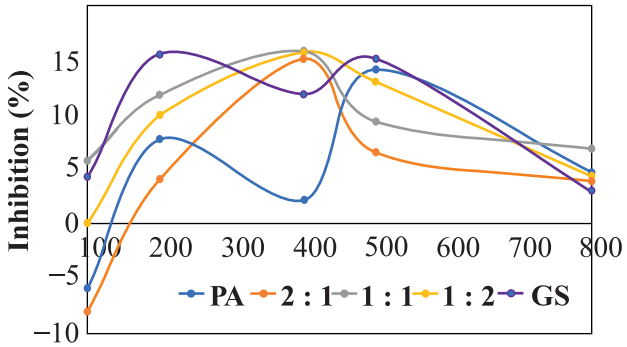

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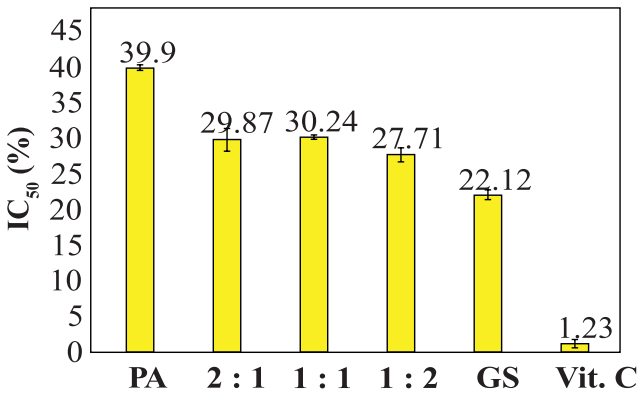

c

Fig. 2. Bioactivities of the various extracts at different PA/GS ratios: (a) *α*-glucosidase inhibition activity, (b) anti-inflammatory activity, and (c) antioxidant activity.

than that of the GS extract alone. Moreover, the GS content was responsible for improving the antioxidant and anti-inflammatory activities of the mixture. The radical scavenging activity increased as the GS content increased in the samples at the ratios of 2 : 1, 1 : 1, and 1 : 2, with IC_{50} values of 29.87, 30.24, and 27.71 μg/mL, respectively. The combination of PA and GS enhanced the antioxidant activities approximately 1.7-fold compared with the PA extract alone. Increasing the GS concentration in the mixture had no discernible effect on the anti-inflammatory properties. Compared with the PA extract, the IC_{15} value of samples 2 : 1, 1 : 1, and 1 : 2 was almost 400 μg/mL, a 1.8-fold improvement. The enhancement of the bioactivities verified that the integration of PA and GS led to the discovery of a novel agent for treating diabetes and its complications.

The extraction yields and bioactivities of the five samples are shown in Fig. 3 to determine the optimal ratio for integration. The results illustrated that the PA extract exhibited the highest antidiabetes activity and extraction yield but the lowest antioxidant and anti-inflammatory activities. However, the GS extract exhibited high antioxidant and anti-inflammatory activities. The samples with a PA/GS ratio of 1 : 2 and 1 : 1 exhibited nearly equivalent activities, but their antidiabetes activity was lower than that of sample 2 : 1. Therefore, the powder with a PA/GS ratio of 2 : 1 was concluded to be suitable for developing a new agent with strong antidiabetes activity to treat diabetes and its complications.

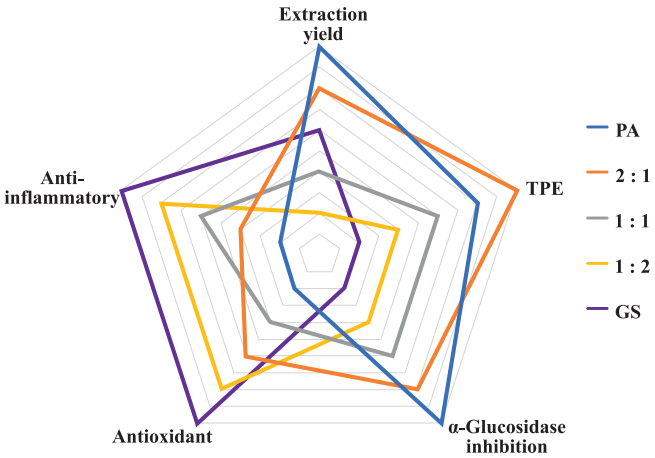

Fig. 3. Comparison of the samples' bioactivities, extraction yields, and TPE.

4. CONCLUSIONS

The present study reported the extraction of PA and GS and the creation of mixtures of different ratios using EtOH. The combination of PA and GS achieved high bioactivities, such as antidiabetes, antioxidant, and anti-inflammatory. In the mixtures, PA played the main role in the antidiabetes activity, whereas GS yielded high antioxidant and anti-inflammatory activities. The mixture with the PA/GS ratio of 2 : 1 was the best sample because of its high TPE and antidiabetes and related bioactivities. The optimization of the bioactivities of this mixture will be reported in the next phase. In future work, the PA and GS combining extracts need to be studied *in vivo* for a comprehensive assessment for the plants' integration before practical application.

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Authors' contribution

Tan M. Le *– conceptualization, formal analysis, conducting research, and writing the manuscript;*

Chinh D.P. Nguyen *– conducting research, writing the review, and editing the text;*

Anh C. Ha *– supervision, methodology, and conceptualization; writing the review and editing the text.*

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

REFERENCES

1. Do N.H.N., Le T.M., Nguyen C.D.P., Ha A.C. Optimization of total flavonoid content of ethanolic extract of *Persicaria pulchra* (Bl.) Soják for the inhibition of α-glucosidase enzyme. *Fine Chem. Technol.* 2020;15(4):39–50. https://doi.org/10.32362/2410-6593-2020-15-4-39-50

2. Andersson E., Persson S., Hallén N., Ericsson Å., Thielke D., Lindgren P., *et al*. Costs of diabetes complications: hospital-based care and absence from work for 392,200 people with type 2 diabetes and matched control participants in Sweden. *Diabetologia.* 2020;63(12):2582–2594. https://doi.org/10.1007/s00125-020-05277-3

3. Shaw J.E., Sicree R.A., Zimmet P.Z. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010;87(1):4–14. https://doi.org/10.1016/j.diabres.2009.10.007

4. Ahmed N. Advanced glycation endproducts—role in pathology of diabetic complications. *Diabetes Res. Clin. Pract.* 2005;67(1):3–21. https://doi.org/10.1016/j.diabres.2004.09.004

5. Oguntibeju O.O. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int. J. Physiol. Pathophysiol. Pharmacol.* 2019;11(3):45–63.

6. Nguyen V.T., Van Vuong Q., Bowyer M.C., Van Altena I.A., Scarlett C.J. Effects of different drying methods on bioactive compound yield and antioxidant capacity of *Phyllanthus amarus*. *Dry. Technol.* 2015;33(8):1006–1017. https://doi.org/10.1080/07373937.2015.1013197

7. Appiah-Opong R., Nyarko A.K., Dodoo D., Gyang F.N., Koram K.A., Ayisi N.K. Antiplasmodial activity of extracts of *Tridax procumbens* and *Phyllanthus amarus* in *in vitro Plasmodium falciparum* culture systems. *Ghana Med. J.* 2011;45(4):143–150.

8. Patel J.R., Tripathi P., Sharma V., Chauhan N.S., Dixit V.K. *Phyllanthus amarus*: Ethnomedicinal uses, phytochemistry and pharmacology: A review. *J. Ethnopharmacol.* 2011;138(2):286–313. https://doi.org/10.1016/j.jep.2011.09.040

9. Ogunmoyole T., Awodooju M., Idowu S., Daramola O. *Phyllanthus amarus* extract restored deranged biochemical parameters in rat model of hepatotoxicity and nephrotoxicity. *Heliyon.* 2020;6(12):e05670. https://doi.org/10.1016/j.heliyon.2020.e05670

10. Nguyen V.T., Sakoff J.A., Scarlett C.J. Physicochemical properties, antioxidant and cytotoxic activities of crude extracts and fractions from *Phyllanthus amarus*. *Medicines.* 2017;4(2):42. https://doi.org/10.3390/medicines4020042

11. Noor N.A.M., Nafiah M.A., Tuan Johari S.A.T., Hasnan M.H.H., Tan S.P., Liew S.Y., *et al*. Anticancer Effect of Hypophyllanthin, Niranthin and Lintetralin From *Phyllanthus amarus* on HeLa Cells And NIH/3T3 Cells. *Int. J. Recent Technol. Eng.* 2019;8(2S7):106–110. https://doi.org/10.35940/ijrte.B1024.0782S719

12. Harikrishnan H., Jantan I., Haque M.A., Kumolosasi E. Anti-inflammatory effects of *Phyllanthus amarus* Schum. & Thonn. through inhibition of NF-κB, MAPK, and PI3K-Akt signaling pathways in LPS-induced human macrophages. BMC Complement. *Altern. Med.* 2018;18(1):224. https://doi.org/10.1186/s12906-018-2289-3

13. Ojezele M.O., Moke E.G., Onyesom I. Impact of generic antimalarial or *Phyllanthus amarus* and vitamin co-administration on antioxidant status of experimental mice infested with *Plasmodium berghei. Beni-Suef Univ. J. Basic Appl. Sci.* 2017;6(3):260–265. https://doi.org/10.1016/j.bjbas.2017.04.008

14. Ajitha B., Reddy Y.A.K., Jeon H.-J., Ahn C.W. Synthesis of silver nanoparticles in an eco-friendly way using *Phyllanthus amarus* leaf extract: Antimicrobial and catalytic activity. *Adv. Powder Technol.* 2018;29(1):86–93. https://doi.org/10.1016/j.apt.2017.10.015

15. Kumar J., Kumar M. Ethnobotanical study of *Phyllanthus amarus* used in treating diabetes mellitus in Patna district of Bihar, India. *Int. J. Instifut. Indust. Resear.* 2018;3(1):130–132.

16. Khan F., Sarker M., Rahman M., Ming L.C., Mohamed I.N., Zhao C., *et al*. Comprehensive review on phytochemicals, pharmacological and clinical potentials of *Gymnema sylvestre*. *Front. Pharmacol*. 2019;10:1223. https://doi.org/10.3389/fphar.2019.01223

17. Chen G., Guo M. Rapid screening for α-glucosidase inhibitors from *Gymnema sylvestre* by affinity ultrafiltration–HPLC-MS. *Front. Pharmacol.* 2017;8:228. https://doi.org/10.3389/fphar.2017.00228

18. Manimegalai B., Velavan S. Evaluation of anti-obesity activity of *Gymnema sylvestre* leaves extract. *J. Pharmacogn. Phytochem.* 2019;8(3):2170–2173. https://www.phytojournal.com/archives/2019/vol8issue3/PartAC/8-2-542-354.pdf

19. Porchezhian E., Dobriyal R.M. An overview on the advances of *Gymnema sylvestre*: chemistry, pharmacology and patents. Die Pharm. *Int. J. Pharm Sci.* 2003;58(1):5–12.

20. Arora D.S., Sood H. *In vitro* antimicrobial potential of extracts and phytoconstituents from *Gymnema sylvestre* R. Br. leaves and their biosafety evaluation. *AMB Express*. 2017;7(1):115. https://doi.org/10.1186/s13568-017-0416-z

21. Karthikeyan M., Ahamed A.J., Karthikeyan C., Kumar P.V. Enhancement of antibacterial and anticancer properties of pure and REM doped ZnO nanoparticles synthesized using *Gymnema sylvestre* leaves extract. *SN Appl. Sci.* 2019;1(4):355. https://doi.org/10.1007/s42452-019-0375-x

22. Tung P.H.T. Targeted classification, identification and metabolite profiling of triterpenoids in the genus *Gymnema* and *Gynostemma* by developing a building block strategy using UHPLC-QTOF/MS. *Seoul Nation. Univ. Grad. School*; 2019. 174 p. http://dcollection.snu.ac.kr/common/orgView/000000157619

23. Das P.E., Abu-Yousef I.A., Majdalawieh A.F., Narasimhan S., Poltronieri P. Green synthesis of encapsulated copper nanoparticles using a hydroalcoholic extract of *Moringa oleifera* leaves and assessment of their antioxidant and antimicrobial activities. *Molecules*. 2020;25(3):555. https://doi.org/10.3390/molecules25030555

24. Uc R., Nair V.M.G. Phytochemical analysis of successive reextracts of the leaves of *Moringa oleifera* Lam. *Int. J. Pharm. Pharm. Sci.* 2013;5(S3):629–634.

25. Ghosh N., Ghosal S., Bhattacharyya D.K. Phytochemical Screening and Antioxidative Activity of Oil Extracted from Indian Carp Fish (Labeo Rohita) Skin. *Int. Res. J. Eng. Tech.* 2019;6(2):1414–1420.

26. Dharmadhas J.S., *et al.* Preliminary Studies on Phytochemicals and Antimicrobial Activity of Solvent Extracts of Medicinal Plant Lawsonia Inermis. *Int. J. Adv. Res.* 2019;7(10):887–896. http://dx.doi.org/10.21474/IJAR01/9904

27. Vu Q. Phytochemical Screening from Parts of *Tacca Leontopetalodes* (L.) Kuntze Collected from AN Giang province, Vietnam. In: *The 12th SEATUC symposium*. IEEE; 2018.

28. McDonald S., Prenzler P.D., Antolovich M., Robards K. Phenolic content and antioxidant activity of olive extracts. *Food Chem.* 2001;73(1):73–84. https://doi.org/10.1016/S0308-8146(00)00288-0

29. Liu F., Ma H., Wang G., Liu W., Seeram N.P., Mu Y., *et al*. Phenolics from *Eugenia jambolana* seeds with advanced glycation endproduct formation and alpha-glucosidase inhibitory activities. *Food Funct.* 2018;9(8):4246–4254. https://doi.org/10.1039/C8FO00583D

30. Stagos D. Antioxidant activity of polyphenolic plant extracts. *Antioxidants.* 2020;9(1):19. https://doi.org/10.3390/antiox9010019

31. Pedersen B.K. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur. J. Clin. Invest.* 2017;47(8):600–611. https://doi.org/10.1111/eci.12781

32. Eshwarappa R.S.B., Ramachandra Y.L., Subaramaihha S.R., Subbaiah S.G.P., Austin R.S., Dhananjaya B.L. Anti-Lipoxygenase activity of leaf gall extracts of *Terminalia chebula* (Gaertn.) Retz.(Combretaceae). *Pharmacognosy Res.* 2016;8(1):78–82. https://doi.org/10.4103/0974-8490.171103

33. Nobossé P., Fombang E.N., Mbofung C.M.F. Effects of age and extraction solvent on phytochemical content and antioxidant activity of fresh *Moringa oleifera* L. leaves. *Food Sci. Nutr.* 2018;6(8):2188–2198. https://doi.org/10.1002/fsn3.783

34. Seo J., Lee S., Elam M.L., Johnson S.A., Kang J., Arjmandi B.H. Study to find the best extraction solvent for use with guava leaves (*Psidium guajava* L.) for high antioxidant efficacy. *Food Sci. Nutr.* 2014;2(2):174–180. https://doi.org/10.1002/fsn3.91

35. Dah-Nouvlessounon D., Adoukonou-Sagbadja H., Diarrassouba N., Sina H., Adjanohoun A., Inoussa M., *et al.* Phytochemical Analysis and Biological Activities of *Cola nitida* Bark. *Biochem. Res. Int.* 2015;2015:493879. https://doi.org/10.1155/2015/493879

36. Ahmed Q.U., Sarian M.N., Mat So'ad S.Z., Latip J., Arief Ichwan S.J., Hussein N.N., *et al*. Methylation and acetylation enhanced the antidiabetic activity of some selected flavonoids: *in Vitro*, molecular modelling and structure activity relationship-based study. *Biomolecules.* 2018;8(4):149. https://doi.org/10.3390/biom8040149

37. Hassan H.S., Sule M..I, Musa A.M., Musa K.Y., Abubakar M.S., Hassan A.S. Anti-inflammatory activity of crude saponin extracts from five Nigerian medicinal plants. *Afric. J. Tradit. Complement. Altern. Med.* 2012;9(2):250–255. https://doi.org/10.4314/ajtcam.v9i2.10

38. Prassas I., Diamandis E.P. Novel therapeutic applications of cardiac glycosides. *Nat. Rev. Drug Discov.* 2008;7(11):926–935. https://doi.org/10.1038/nrd2682

39. Zhang H., Wang G., Dong J. Inhibitory properties of aqueous ethanol extracts of propolis on alpha-glucosidase. *Evid.-Based Complement. Altern. Med.* 2015;2015:587383. https://doi.org/10.1155/2015/587383

40. Neffati N., Aloui Z., Karoui H., Guizani I., Boussaid M., Zaouali Y. Phytochemical composition and antioxidant activity of medicinal plants collected from the Tunisian flora. *Nat. Prod. Res.* 2017;31(13):1583–1588. https://doi.org/10.1080/14786419.2017.1280490

41. Williams L.A.D., O'Connar A., Latore L., Dennis O., Ringer S., Whittaker J.A., *et al*. The in Vitro anti-denaturation effects induced by natural products and non-steroidal compounds in heat treated (immunogenic) bovine serum albumin is proposed as a screening assay for the detection of anti-inflammatory compounds, without the use of animals. *West Indian Med. J.* 2008;57(4):327–331.

About the authors:

Tan M. Le, BEng., Postgraduate Student, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: lmtan.sdh20@hcmut.edu.vn. https://orcid.org/0000-0002-7956-1067

Chinh D.P. Nguyen, BEng., Postgraduate Student, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: npdchinh.sdh19@hcmut.edu.vn. https://orcid.org/0000-0002-2820-3913

Anh C. Ha, PhD, Dr. of Chemical Engineering, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: hcanh@hcmut.edu.vn. https://orcid.org/0000-0001-7919-4028

Об авторах:

Тан М. Ле, аспирант, Химико-технологический факультет, Технологический университет Хошимина (268 Ли Тхыонг Кьет ул., Район 10, г. Хошимин, Вьетнам); Вьетнамский национальный университет Хошимина (Линь Чунг Уорд, Район Тхёк, г. Хошимин, Вьетнам). E-mail: lmtan.sdh20@hcmut.edu.vn. https://orcid.org/0000-0002-7956-1067

Чин Д.П. Нгуен, аспирант, Химико-технологический факультет, Технологический университет Хошимина (268 Ли Тхыонг Кьет ул., Район 10, г. Хошимин, Вьетнам); Вьетнамский национальный университет Хошимина (Линь Чунг Уорд, Район Тхёк, г. Хошимин, Вьетнам). E-mail: npdchinh.sdh19@hcmut.edu.vn. https://orcid.org/0000-0002-2820-3913

Ань К. Ха, PhD, к.х.н., Химико-технологический факультет, Технологический университет Хошимина (268 Ли Тхыонг Кьет ул., Район 10, г. Хошимин, Вьетнам); Вьетнамский национальный университет Хошимина (Линь Чунг Уорд, Район Тхёк, г. Хошимин, Вьетнам). E-mail: hcanh@hcmut.edu.vn. https://orcid.org/0000-0001-7919-4028

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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

Stabilisation of cosmetic compositions using combined emulsifiers

Valentina V. Korypaeva, Evgeniya F. Bukanova, Evgeniya V. Eskova[@], Vera A. Sokhraneva

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia

[@]Corresponding author, e-mail: eskova@mirea.ru

Abstract

Objectives. *This study investigated the surface properties and micelle formation of combined stabilizers, which are a mixture of ionic and nonionic surfactants or different nonionic surfactants, to establish a correlation between the composition of stabilizers and the colloidal–chemical properties of direct emulsions obtained in their presence.*

Methods. *The surface tension at the interface between the aqueous solutions of the combined stabilizers with air and toluene was measured using a digital tensiometer. The sedimentation stability of the emulsions was assessed by the volume of the exfoliated water and oil phases for seven days. The particle sizes of the dispersed phase were determined using an Olympus CX3 bright field microscope equipped with a universal serial bus video camera connection. The rheological properties of the emulsions were evaluated using a rotary viscometer.*

Results. *According to the isotherms of the surface tension of aqueous surfactant solutions at the interface with air and toluene at emulsion preparation temperatures of 50 and 65°C, a mixture of nonionic surfactants exhibited a higher surface activity and lower critical micelle concentration at the interface with toluene. The optimal amount of stabilizers providing stability to the compositions for one month was 4 mass % for a mixture of anionic surfactants and nonionic surfactants and 7 mass % for mixtures of different nonionic surfactants. Emulsions obtained in the presence of a mixture of anionic and nonionic surfactants exhibited higher kinetic sedimentation stability values due to the formation of electrostatic and steric stabilization factors in the system. The developed compositions were microheterogeneous systems, the average droplet diameter of which varied within the range of 1.0–5.7 μm. In terms of rheological properties, emulsions were classified as liquid-like structured systems with coagulation structures; the strength of single contacts between particles of the dispersed phase was (1.6–27.0) × 10^{-10} N.*

Conclusions. *A comparison of the physicochemical characteristics of the compositions obtained in the presence of organic emulsifiers showed that emulsions stabilized using a mixture of ionic and nonionic surfactants, which form mixed adsorption layers, exhibited the best set of properties.*

Keywords: *nonionic surfactant, anionic surfactant, surfactant mixture, adsorption, critical micelle concentration, emulsification, particle size, viscosity, kinetic sedimentation stability*

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НАУЧНАЯ СТАТЬЯ

Стабилизация косметических композиций комбинированными эмульгаторами

В.В. Корыпаева, Е.Ф. Буканова, Е.В. Еськова[@], В.А. Сохранева

МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
[@]Автор для переписки, e-mail: eskova@mirea.ru

Аннотация

Цели. *Изучить поверхностные свойства и мицеллообразование комбинированных стабилизаторов, являющихся смесью ионных и неионых поверхностно активных веществ (ПАВ) или смесью неионных ПАВ. Установить корреляцию между составом стабилизаторов и коллоидно-химическими свойствами прямых эмульсий, полученных в их присутствии.*
Методы. *Поверхностное натяжение на границе раздела фаз водных растворов комбинированных стабилизаторов с воздухом и толуолом измеряли на цифровом тензиометре. Седиментационную устойчивость эмульсий оценивали по объему отслоившихся водной и масляной фаз в течение 7 дней. Размеры частиц дисперсной фазы определяли с использованием микроскопа Olympus CX3, предназначенным для работы в светлом поле, снабженным соединением для USB видеокамеры. Реологические свойства эмульсий оценивали с помощью ротационного вискозиметра.*
Результаты. *По изотермам поверхностного натяжения водных растворов ПАВ на границе с воздухом и толуолом при температурах приготовления эмульсий (50 и 65 °C) установлено, что большей поверхностной активностью и меньшей критической концентрации мицеллообразования на границе с толуолом обладает смесь неионных ПАВ. Оптимальное количество стабилизаторов, обеспечивающих устойчивость композиций в течение 1 месяца, составляет 4 мас. % смеси АПАВ и НПАВ и 7 мас. % смеси НПАВ. Эмульсии, полученные в присутствии смеси анионных и неионных ПАВ, имеют более высокие значения кинетической седиментационной устойчивости за счет формирования в системе электростатического и стерического факторов стабилизации. Разработанные композиции являются микрогетерогенными системами, средний диаметр капель которых изменяется в пределах 1.0–5.7 мкм. По реологическим свойствам эмульсии относятся к жидкообразным структурированным системам с коагуляционными структурами, прочность единичных контактов между частицами дисперсной фазы которых составляет (1.6–27.0) × 10^{-10} Н.*

Выводы. *Сравнение физико-химических характеристик композиций, полученных в присутствии органических эмульгаторов, показало, что лучшим комплексом свойств обладают эмульсии, стабилизированные смесью ионных и неионных ПАВ, образующих смешанные адсорбционные слои.*

Ключевые слова: *неионные ПАВ, анионные ПАВ, смеси ПАВ, адсорбция, критическая концентрация мицеллообразования, эмульгирование, размер частиц, вязкость, кинетическая седиментационная устойчивость*

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INTRODUCTION

Emulsions comprising two immiscible liquids are the primary materials for the production of products in various industries, particularly for the production of cosmetic and hygiene products [1], in which various substances of natural origin and those synthesized from natural raw materials are used [2, 3]. However, thermodynamic and sedimentation instability or delamination is a problem of all emulsion compositions, ultimately leading to their destruction [4].

To ensure the stability of the system, surfactants are introduced to the emulsion, and their role is to 1) reduce interfacial tension to 5 mJ/m^2; 2) create the ability to quickly adsorb on droplets, creating a thin layer that does not change when droplets collide and prevent coalescence; 3) provide good solubility in a dispersion medium; 4) provide the emulsion a degree of electrokinetic potential; 5) influence the viscosity of the emulsion; 6) introduce emulsifying properties even at low concentrations [5, 6].

To stabilize emulsions for various purposes, surfactant compositions of different or identical nature are commonly used. At specific component ratios, these compositions show the synergistic effect of reducing critical micelle concentration (CMC) and increasing surface activity due to the formation of mixed micelles. Adsorption layers of surfactant mixtures at the oil–water boundary include molecules of all surfactant components, ensuring the high stability of dispersed systems [7, 8]. Currently, in the production of cosmetic emulsions, there is a tendency to use readymade complex semifinished emulsifiers. Information regarding the colloidal–chemical properties of combined emulsifiers, which are mixtures of various natural surfactants, and the physicochemical characteristics of the final product, eliminate the requirement of performing a large number of experiments to predict the final results, thus remarkably simplifying the procedure for developing compositions that meet consumer properties.

MATERIALS AND METHODS

In this work, industrial-combined emulsifiers were used as stabilizers for direct emulsions: Blanova Muls Eco 2277, a mixture of anionic and nonionic surfactants (*Azelis Rus*, Russia), and Remiwax SE containing a composition of nonionic surfactants (*Revada*, Russia).

Table 1 presents the information regarding the components that constitute the combined emulsifiers.

The surface and interfacial tensions of the aqueous solutions of surfactant mixtures at emulsion preparation temperatures were measured using a K9 digital tensiometer (*Krüss AG*, Germany). The stability of the emulsions was evaluated by the volume of the exfoliated water and oil phases within seven days. The colloidal stability of emulsions was determined using a Type 310 b high-speed centrifuge (*Mechanika Precyzyna*, Poland). The particle sizes of the dispersed phase were determined using an Olympus CX31 microscope (*Olympus*, Japan), which is designed for working within a bright field and is equipped with a connection for a universal serial bus video camera. The rheological properties of emulsions were studied using a Polymer RPE-1M (*Khimpribor-1*, Russia) rotary viscometer. For preparing the compositions, the so-called “hot/hot” standard method was selected for preparing emulsions. Emulsions were prepared at 50°C (mixture of nonionic surfactants) and 65°C

Table 1. General characteristics of the emulsifier components

International Nomenclature of Cosmetic Ingredients – INCI Registry number CAS	Hydrophilic-lipophilic balance – HLB	*M*, g/mol
A mixture of anionic and nonionic surfactants (Blanova Muls Eco 2277). Molecular weight ~346 g/mol		
Glyceryl Stearate CAS Number 123-94-4	3–6	358
Stearyl Alcohol CAS Number 112-92-5	15.5	270
Sodium Stearoyl Lactylate CAS Number: 25383-99-7	8.3	450
Glyceryl Stearate Citrate CAS Number: 50825-78-0	3.4	306
Nonionic surfactant mixture (Remiwax SE PF). Molecular weight ~600 g/mol		
Glyceryl Stearate CAS Number: 31566-31-1	2.5	358
Ceteareth-20, Ceteareth-12 CAS Number: 68439-49-6	13.2 15.5	1136 784
Cetearyl Alcohol CAS Number: 67762-27-0	15.5	242.2
Cetyl Palmitate CAS Number: 540-10-3	10	480

(mixture of anionic and nonionic surfactants) using a Polytron PT 1200 E homogenizer (*Kinematica AG*, Switzerland). The mixing speed was 6000 rpm, and the homogenization time was 3 min. The ratio of the oil and water phases was 1 : 4. The concentration of the emulsifier was varied from 0.5–7% (wt).

RESULTS AND DISCUSSION

The type and stability of emulsions depend on the ratio (balance) of hydrophilic and hydrophobic (or lipophilic) functional groups among the surfactant molecules. To obtain direct «oil-in-water» emulsions, using emulsifiers with hydrophilic–lipophilic balance (HLB) numbers ranging from 8–13 was necessary [9]. The numbers of HLB stabilizers were experimentally determined using the Davies method. For a mixture of nonionic surfactants, this number was equal to 10.5; for a mixture of anionic and nonionic surfactants, it was 13.5. An ester of polyglyceride and fatty acids with an HLB number of 4 was used as a surfactant with a known HLB number. Based on the data obtained, refined sunflower oil with a close HLB number was selected as the nonpolar phase [5].

A K9 digital tensiometer was used to measure the surface tension of the combined stabilizers at the aqueous solution–gas and aqueous solution–toluene interface, which was selected as a model for the nonpolar phase. The surface isotherms, interfacial tension of nonionic surfactant mixtures, and the mixtures of anionic and nonionic surfactants at emulsion preparation temperatures are shown in Fig. 1.

The obtained surface and interfacial tension isotherms were used to determine the surface activity and CMC, and the parameters for the monolayers of stabilizers were calculated [10]. The results are presented in Table 2.

The data presented indicates that at the aqueous solution–air interface, the mixture of anionic and nonionic surfactants will have higher surface activity values, maximum adsorption, and a lower CMC value compared with a mixture of nonionic surfactants nondissociating in water, which is associated with the

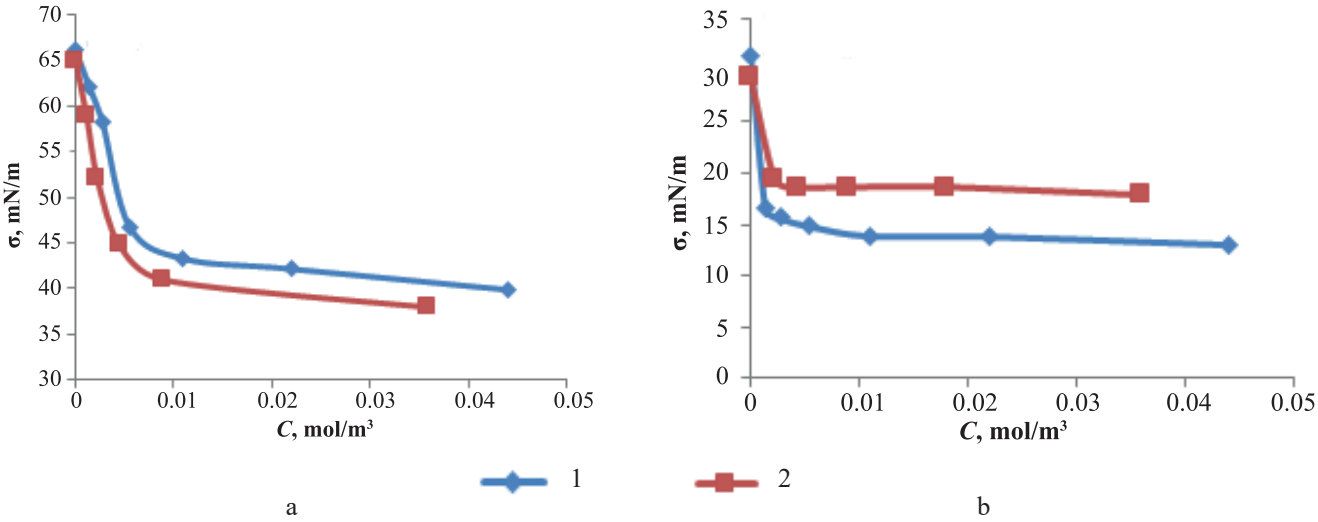


Fig. 1. Surface tension isotherms of surfactants in aqueous solutions containing mixtures of different nonionic surfactants (1); anionic and nonionic surfactants (2) at different interfaces, i.e., (a) air and (b) toluene.

Table 2. Surface activity values, critical micelle formation concentration, and the parameters of the adsorption layers of surfactant mixtures

Name of surfactants	Adsorption characteristics of surfactants					
	G, J·m/mol	$\sigma_{min} \times 10^3$, J/m²	$\Gamma_{max} \times 10^6$, mol/m²	$S_0 \times 10^{19}$, m²	$\delta \times 10^9$, m²	C_{CCM}, mol/m³
Aqueous solution–air boundary						
A mixture of anionic and nonionic surfactants	4.86	37.0	5.10	3.25	1.76	0.0045
A mixture of nonionic surfactants	3.80	40.0	7.80	2.95	2.94	0.0064
Aqueous solution–toluene boundary						
A mixture of anionic and nonionic surfactants	4.70	17.8	4.60	3.60	1.60	0.0037
A mixture of nonionic surfactants	8.80	13.0	6.80	2.44	4.08	0.0025

Note: G – surface activity;
σ_{min} – minimum surface tension;
Γ_{max} – maximum adsorption value;
S_0 – area occupied by a surfactant molecule in a saturated monolayer;
δ – the thickness of the adsorption layer;
C_{CCM} – the value of the critical concentration of micelle formation.

formation of mixed micelles in the solution [6]. At the boundary of the aqueous solution–toluene, an emulsifier with the best surface-active properties is a mixture of nonionic surfactants.

Notably, low values of σ_{min} at the interface between toluene and aqueous solutions of surfactant mixtures contributed to the formation of stable direct emulsions.

To calculate the temperature coefficients of the surface tension of the combined stabilizers, the σ values for aqueous solutions of surfactant mixtures of the same concentration were measured at different temperatures. For a mixture of anionic and nonionic surfactants, the value of $d\sigma/dT$ was −0.044 mJ/m^2; for a mixture of nonionic surfactants, the value of $d\sigma/dT$ was −0.037 mJ/m^2. The values of the temperature coefficient of surface tension allowed for predicting the behavior of the emulsifier at different temperatures and enabled selecting the conditions for mixing the phases.

The sedimentation stability of the emulsion was assessed by the volume of the exfoliated water and oil phases for seven days. The colloidal stability of the emulsions was determined according to the standard method[1] in an ultracentrifuge at a speed of 6000 rpm, from which it followed that the emulsion would be considered stable if, after centrifugation, in a test tube, no more than one drop of the aqueous phase and/or 0.5 cm of the oil layer were released.

The compositions differed in terms of the type of emulsifier and its concentration. Based on the results obtained, histograms of the ratios of the emulsion and exfoliated phases were plotted according to the concentration in the compositions stabilized with a mixture of anionic and nonionic surfactants and a mixture of different nonionic surfactants (Figs. 2 and 3).

With an increase in the concentration of the added stabilizer for all samples, the amount of stable emulsion increased. Compositions had high stability with the introduction of an emulsifier, starting from 3% for a mixture of anionic and nonionic surfactants and 5% for a mixture of different nonionic surfactants.

The influence of negative temperatures on the stability of emulsions was investigated, which enabled determining the stability of the emulsion at low temperatures and predicting the behavior of finished product during transportation in adverse weather conditions. It was found that at temperature drops, the loss of stability was determined to be 1–2%, which did not affect the consumer properties of the product.

As a result of the experiments, the following outcomes were observed:

– The optimal percentage of the input of the emulsifier for preparing the cosmetic composition was 4% by weight for an anionic and nonionic surfactant mixture and 7% weight for a nonionic surfactant mixture. Emulsions with these properties were sufficiently stable to withstand mechanical stress and did not collapse when exposed to a centrifugal field and negative temperatures.

[1] GOST 31460-2012. Interstate standard. Cosmetic creams. General specifications. Moscow: Standartinform; 2013.

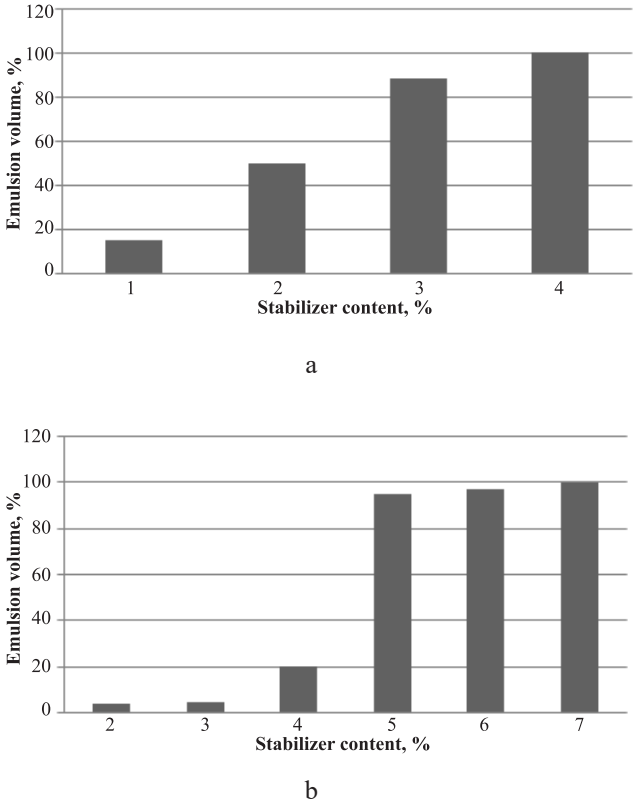
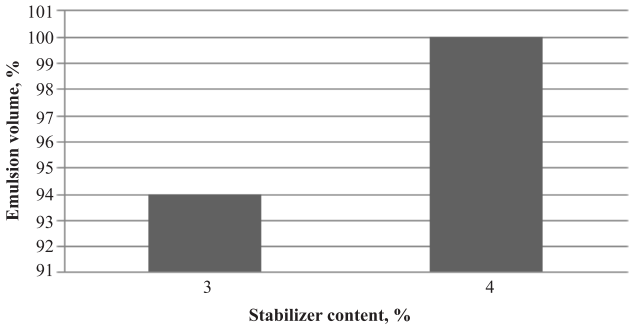


Fig. 2. Influence of the concentration of stabilizers comprising a mixture of anionic and nonionic surfactants (a) and a mixture of nonionic surfactants (b) on the stability of emulsions in a gravitational field.

– The use of a stabilizer in the form of a mixture of nonionic surfactants enabled obtaining cosmetic products for various purposes; with the introduction of a 2–3% emulsifying base, a liquid emulsion was obtained that could be used to prepare cosmetic milk and lotions. To obtain cosmetic creams and masks while preparing emulsions, the percentage of input should range from 5 to 7%.

– The high stability of the obtained emulsions in the presence of anionic and nonionic surfactant mixtures resulted from confounding stability factors in dispersed systems; the presence of ionic surfactants in a system provided electrostatic stabilization, and the presence of a nonionic surfactant provided steric stabilization (electrosteric stabilization) [5]. When using a combined stabilizer, i.e., a mixture of nonionic surfactants, only the steric factor of stability was realized in the system [11, 12].

Particle size in the dispersed phase is one of the defining characteristics of emulsion compositions, which was determined using the light microscopy method. Figure 4 shows the differential curves of the particle size distribution of emulsions obtained in the presence of nonionic surfactants. Similar data were obtained for compositions stabilized with a mixture of anionic and nonionic surfactants.



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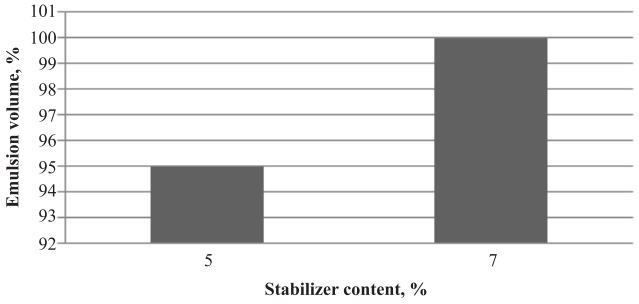

b

Fig. 3. Influence of the concentration of stabilizers comprising a mixture of anionic and nonionic surfactants (a) and a mixture of nonionic surfactants (b) on the stability of emulsions in a centrifugal field.

The presented data show that the obtained emulsions were polydispersed microheterogeneous systems. The diameters of various fractions varied from 1 to 5 μm for a mixture of anionic surfactants and nonionic surfactants, and from 3.3 to 16.6 μm for a mixture of different nonionic surfactants. The degree of polydispersity, equal to the ratio of the maximum diameter to the most probable diameter ranged from 1.75 to 4.25.

Rheological characteristics that determined the consumer properties of cosmetic compositions (absorbency, spreadability, moisturizing ability) [13, 14] were measured using a Polymer RPE-1M rotational viscometer. The flow curves of emulsions stabilized using different amounts of a mixture of ionic and nonionic surfactants and the dependence of viscosity on shear stress are shown in Figs. 5 and 6.

Based on the presented graphs, the developed compositions were liquid structured systems with a yield point. Similar dependences of the shear stress on the strain rate were obtained for emulsions stabilized with a mixture of nonionic surfactants. The rheological

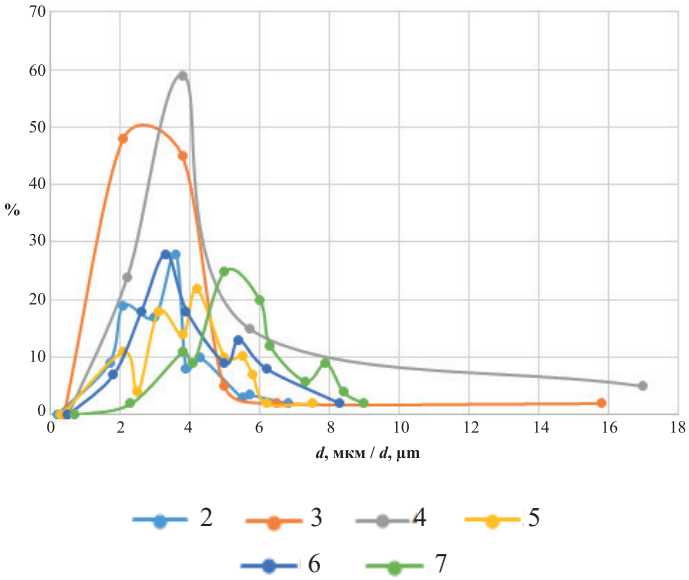

Fig. 4. Drop-size distribution of emulsions stabilized with various amounts of a mixture of nonionic surfactants (2–7 g per 100 mL of the composition).

behavior of such emulsions can be described using the Ostwald–de Waele and Herschel–Bulkley equations [15], which include the value of the ultimate shear stress (P_{str}), the form of which is expressed as follows:

$$P = P_{str} + \eta_{pl} \cdot \gamma^{n}, \quad (1)$$

where P_{str} is shear yield stress; η_{pl} is plastic viscosity; γ is strain rate; n is a constant that characterizes the degree of deviation in fluid properties from a Newtonian liquid.

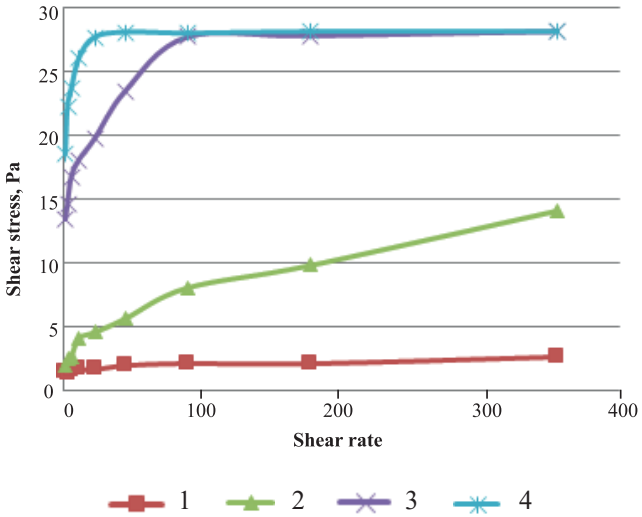

Fig. 5. Curves of the flow of emulsions stabilized using various amounts of a combination of anionic and nonionic surfactants (1–4 g per 100 mL of composition).

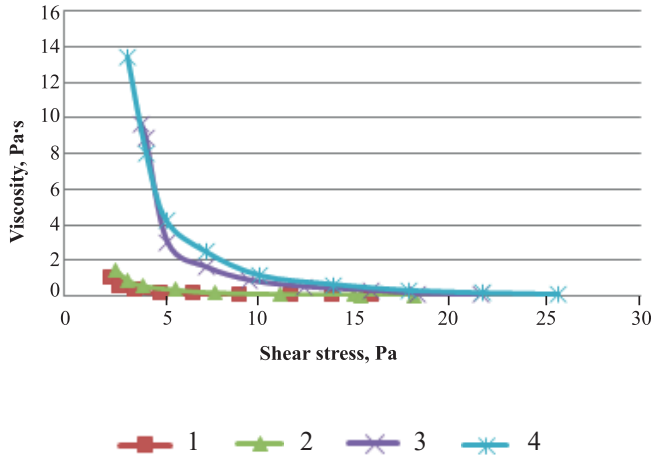

Fig. 6. Influence of the stabilizer content from a mixture of anionic and nonionic surfactants on the viscosity of emulsions.

The structural and mechanical properties of emulsions depended on the strength of a single contact between particles of the dispersed phase, which determined the nature of the contact (phase or coagulation). The availability of data on the strength of a single contact determines the ability of the system to resist destruction under the influence of external forces. According to Kuhn's model [16], which considers the yield point, the strength of a single contact was estimated for the compositions developed by us as follows:

$$F_1 = \frac{P_{str} 3\pi d^2}{2\varphi}, \quad (2)$$

where F_1 is single contact strength (N); φ is volume fraction; d is emulsion droplet diameter (m).

The strength values of single contacts (Table 3) showed that coagulation contacts were formed in emulsions, ensuring the restoration of the structure after destruction.

Table 3. Structural-mechanical and molecular-kinetic properties of emulsions

No.	Stabilizer content, g/100 mL	Yield strength P_{str}, single contact strength F_1, and plastic emulsion viscosity η_2			Sedimentation rate U and kinetic sedimentation stability (KSS) of emulsions			
		P_{str}, Pa	$F_1 \times 10^{10}$, N	η_2, Pa·s	$U_1 \times 10^7$, m/s	$KSS_1 \times 10^{-7}$, s	$U_2 \times 10^{10}$, m/s	$KSS_2 \times 10^{-10}$, s
A mixture of anionic and nonionic surfactants								
1	1.0	1.4	1.59	0.90	2.01	4.91	2.23	4.41
2	2.0	2.0	1.88	1.45	1.66	5.92	1.17	8.73
3	3.0	13.4	3.15	8.00	0.41	2.41	5.20	1.91
4	4.0	18.5	6.27	13.40	0.59	1.60	4.47	2.24
A mixture of nonionic surfactants								
1	2.0	1.8	4.61	1.31	4.53	2.16	3.74	2.62
2	3.0	2.4	6.53	1.78	4.81	2.04	2.70	3.63
3	4.0	2.7	9.67	1.95	6.33	1.55	2.98	3.28
4	5.0	3.3	1.30	2.40	6.99	1.40	2.91	3.37
5	6.0	3.3	1.24	2.40	6.62	1.48	2.68	3.66
6	7.0	3.6	2.75	2.60	10.80	0.90	4.15	2.36

Note: index 1 refers to values calculated considering the viscosity of the dispersion medium; index 2 refers to the values calculated considering the viscosity of the compositions.

The speed of movement of individual drops under the action of gravitational forces was proportional to the difference in the densities of the dispersed phase and the dispersion medium, ρ_1 and ρ_2, as well as the square of the radius of the drops, and it was inversely proportional to the viscosity of the dispersion medium [4]. Kinetic sedimentation stability (KSS) was the reciprocal of the sedimentation constant.

Using the experimentally obtained values of the particle size and viscosity of the developed compositions, the reverse sedimentation rates of direct emulsions were calculated, considering only the viscosities of water and taking into account the viscosity of real systems, as well as the KSS of emulsions (Table 3).

The calculations made enabled quantifying the effect of the stabilizer on the stability of the compositions. As concluded from the data given in Table 3, the rate of emulsion sedimentation in the presence of a stabilizer decreased, and the KSS increased 1000 times. The presence of combined stabilizers considerably increased the viscosity of emulsions, providing an additional hydrodynamic stability factor, and made enabled obtaining compositions stable for almost an unlimited time.

Analysis of the rheological characteristics of direct concentrated emulsions showed that these compositions were pseudoplastic systems with a yield point, the value of which depended on the type and amount of stabilizer. Varying the content of the emulsifier allowed gaining a line of cosmetics including different products ranging from milk to creams for various purposes. An emulsion obtained using stabilizer that is a mixture of anionic and nonionic surfactants, and which form mixed adsorption layers providing electrostatic and steric stability factors, is preferable in terms of structural and mechanical properties. The calculated values of the strengths of single contacts were in the range of 10^{-10}–10^{-9} N, which confirmed the presence of coagulation contacts between the particles of the dispersed phase.

CONCLUSIONS

The parameters of the adsorption layers of various natural surfactant mixtures were calculated. The maximum adsorption value at the interface with toluene and the thickness of the saturated adsorption layer of the nonionic surfactant mixture at this interface increased compared with the analogous value at the solution–air interface, which indicated an increase in the hydration layer around the oil droplets. The interfacial tension was reduced to 15 mN/m, which contributed to an increase in the stability of emulsions.

The optimal content of the emulsifier was established as 4% for a mixture of ionic and nonionic surfactants and 7% for a mixture for different nonionic surfactants. In the presence of stabilizers, the values of KSS increased by 1000 times.

Compositions stabilized using a combination of anionic and nonionic surfactants were microheterogeneous systems with an average droplet diameter of 1.0–5.0 μm, based on the surfactant content; for a mixture of nonionic surfactants, this value ranged from 4.0 to 8.0 μm and included a small number of fractions with sizes ranging from 10.0 to 16.5 μm.

The compositions were pseudoplastic fluids with a yield point. The calculated strength of single contacts between particles of the dispersed phase indicated the presence of coagulation contacts in dispersed systems.

A comparison of the physicochemical characteristics of the compositions obtained in the presence of industrial organic emulsifiers showed that emulsions stabilized using a mixture of ionic and nonionic surfactants, which provided stability because of electrostatic and steric stability factors, exhibited the best combination of properties.

Authors' contribution

V.V. Korypaeva – conducting an experiment to study the colloidal-chemical properties of surfactant mixtures, studying the rheological properties of emulsions, collecting and processing material, writing the text of the article.

E.F. Bukanova – scientific consulting at all stages of the work.

E.V. Eskova – consultation during the individual stages of research and processing of the results obtained.

V.A. Sokhraneva – conducting an experiment to obtain emulsions and study their stability.

The authors declare no conflicts of interest.

REFERENCES

1. Lu M., Behnke K. Thin emulsion base for cosmetics: US Pat. US2019/0192390A1. Filed 12.10.2018; pub. 27.06.2019.

2. Franca C.C., Ueno H.M. Green cosmetics: perspectives and challenges in the context of green chemistry. *Desenvolv. Meio Ambiente.* 2020;53:133–150. http://dx.doi.org/10.5380/dma.v53i0.62322

СПИСОК ЛИТЕРАТУРЫ

1. Lu M., Behnke K. Thin emulsion base for cosmetics: US Pat. US2019/0192390A1. Filed 12.10.2018; pub. 27.06.2019.

2. Franca C.C., Ueno H.M. Green cosmetics: perspectives and challenges in the context of green chemistry. *Desenvolv. Meio Ambiente.* 2020;53:133–150. http://dx.doi.org/10.5380/dma.v53i0.62322

3. Puchkova T. *Entsiklopediya kosmeticheskikh ingredientov* (*Encyclopedia of cosmetic ingredients*). Moscow: Shkola kosmeticheskikh khimikov; 2015. 408 p. (in Russ.). ISBN 978-5-903338-02-3

4. Fridrikhsberg D.A. *Kurs kolloidnoi khimii* (*Colloidal chemistry course*). St. Petersburg: Lan'; 2010. 416 p. (in Russ.). ISBN 978-5-8114-1070-5. https://e.lanbook.com/book/4027

5. Holmberg K., Jönsson B., Kronberg B., Lindman B. *Poverkhnostno-aktivnye veshchestva i polimery v vodnykh rastvorakh* (*Surface-active substances and polymers in aqueous solutions*). Moscow: Binom; 2010. 528 p. (in Russ.). ISBN 978-5-9963-2942-7

6. Tadros Th. F. Emulsions. *Formation, Stability, Industrial Applications*. Berlin/Boston: Walter de Gruyter GmbH; 2016. 243 p. https://doi.org/10.1515/9783110452242

7. Rosen M.J. *Surfactants and Interfacial Phenomena*: 3rd ed. New York: John Wiley; 2004. 457 p. http://dx.doi.org/10.1002/0471670561

8. Bukanova E.F., Filippenkov V.M., Revina Yu.V. Mixtures of non-ionic surfactants for cleaning compositions. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2017;12(3):21–27 (in Russ.). https://doi.org/10.32362/2410-6593-2017-12-3-21-27

9. Garti N., Lutz R. Recent Progress in Double Emulsions. In: Petsev D.N. (Ed.). *Interface Science and Technology*. V. 4. *Emulsions: Structure Stability and Interactions. Amsterdam*: Elsevier; 2004. 557–605. https://doi.org/10.1016/S1573-4285(04)80016-4

10. Kulichikhin V.G. (Ed.). *Praktikum po kolloidnoi khimii* (*Workshop on colloidal chemistry*); Moscow: INFRA-M –2012; 287 p. (in Russ.). ISBN 978-5-9558-0217-6

11. Taylor P. Ostwald ripening in emulsions: estimation of solution thermodynamics of the disperse phase. *Adv. Colloid Interface Sci.* 2003;106(1–3):261–285. https://doi.org/10.1016/S0001-8686(03)00113-1

12. Babchin A.J., Schramm L.L. Osmotic repulsion force due to adsorbed surfactants. *Colloids Surf. B: Biointerfaces.* 2012;91(1):137–143. https://doi.org/10.1016/j.colsurfb.2011.10.050

13. Nour A.H. Emulsion types, stability mechanism and rheology: A review. *International Journal of Innovative Research and Scientific Studies* (*IJIRSS*). 2018;1(1):14–21. https://ssrn.com/abstract=3324905

14. Anuchina A.S., Avramenko G.V., Chudinova N.N., Tikhonova T.V., Kienskaya K.I. Consideration of some colloidal-chemical patterns in the development of cosmetic creams. *Khim. Prom. Segodnya = Chem. Ind. Today.* 2012;(8):40–49 (in Russ.).

15. Kirsanov E.A., Matveenko V.N. *Nen'yutonovskoe povedenie strukturirovannykh system* (*Non-Newtonian behavior of structured systems*). M.: TEKhNOSFERA; 2016. 384 p. (in Russ.). ISBN 978-5-94836-461-2

16. Matveenko V.N., Kirsanov E.A. The viscosity and structure of dispersed systems. *Mosc. Univ. Bull.* 2011;66(4)199–228. https://doi.org/10.3103/S0027131411040079

[Original Russian Text: Matveenko V.N., Kirsanov E.A. The viscosity and structure of dispersed systems. *Vestn. Mosk. Univ. Ser. 2. Khim*. 2011;52(4):243–276 (in Russ.).]

3. Пучкова Т. *Энциклопедия косметических ингредиентов.* М.: Школа косметических химиков; 2015. 408 с. ISBN 978-5-903338-02-3

4. Фридрихсберг Д.А. *Курс коллоидной химии.* СПб.: Лань; 2010. 416 с. ISBN 978-5-8114-1070-5. https://e.lanbook.com/book/4027

5. Холмберг К., Йёнссон Б., Кронберг Б., Линдман Б. *Поверхностно-активные вещества и полимеры в водных растворах*. М.: Бином; 2010. 528 с. ISBN 978-5-9963-2942-7

6. Tadros Th. F. Emulsions. *Formation, Stability, Industrial Applications*. Berlin/Boston: Walter de Gruyter GmbH; 2016. 243 p. https://doi.org/10.1515/9783110452242

7. Rosen M.J. *Surfactants and Interfacial Phenomena*: 3rd ed. New York: John Wiley; 2004. 457 p. http://dx.doi.org/10.1002/0471670561

8. Буканова Е.Ф., Филиппенков В.М., Ревина Ю.В. Смеси неионных ПАВ для получения чистящих композиций. *Тонк. хим. технол.* 2017;12(3):21–27. https://doi.org/10.32362/2410-6593-2017-12-3-21-27

9. Garti N., Lutz R. Recent Progress in Double Emulsions. In: Petsev D.N. (Ed.). *Interface Science and Technology*. V. 4. Emulsions: *Structure Stability and Interactions. Amsterdam*: Elsevier; 2004. 557–605. https://doi.org/10.1016/S1573-4285(04)80016-4

10. Куличихин В.Г. (ред.). *Практикум по коллоидной химии*. М.: ИНФРА-М; 2012. 287 с. ISBN 978-5-9558-0217-6

11. Taylor P. Ostwald ripening in emulsions: estimation of solution thermodynamics of the disperse phase. *Adv. Colloid Interface Sci.* 2003;106(1–3):261–285. https://doi.org/10.1016/S0001-8686(03)00113-1

12. Babchin A.J., Schramm L.L. Osmotic repulsion force due to adsorbed surfactants. *Colloids Surf. B: Biointerfaces.* 2012;91(1):137–143. https://doi.org/10.1016/j.colsurfb.2011.10.050

13. Nour A.H. Emulsion types, stability mechanism and rheology: A review. *International Journal of Innovative Research and Scientific Studies* (*IJIRSS*). 2018;1(1):14–21. https://ssrn.com/abstract=3324905

14. Анучина А.С., Авраменко Г.В., Чудинова Н.Н., Тихонова Т.В., Киенская К.И. Учет некоторых коллоидно-химических закономерностей при разработке косметических кремов. *Хим. пром. сегодня*. 2012;(8):40–49.

15. Кирсанов Е.А., Матвеенко В.Н. Неньютоновское поведение структурированных систем. М.: ТЕХНОСФЕРА; 2016. 384 с. ISBN 978-5-94836-461-2

16. Матвеенко В.Н., Кирсанов Е.А. Вязкость и структура дисперсных систем. *Вестн. Моск. Ун-та. Сер. 2. Химия*. 2011;52(4):243–276.

About the authors:

Valentina V. Korypaeva, Postgraduate Student, Department of General Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: vvkorypaeva@mitht.ru. https://orcid.org/0000-0002-9501-9403

Evgeniya F. Bukanova, Cand. Sci. (Chem.), Associate Professor, Department of Colloidal Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: bukanova@mirea.ru. https://orcid.org/0000-0002-9989-2437

Evgeniya V. Eskova, Senior Lecturer, Department of Colloidal Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: eskova@mirea.ru. https://orcid.org/0000-0003-2536-1884

Vera A. Sokhraneva, Student, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: sokhraneva.v@mail.ru. https://orcid.org/0000-0003-0930-5604

Об авторах:

Корыпаева Валентина Владимировна, аспирант кафедры общей химической технологии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: vvkorypaeva@mitht.ru. https://orcid.org/0000-0002-9501-9403

Буканова Евгения Федоровна, к.х.н., доцент кафедры коллоидной химии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: bukanova@mirea.ru. https://orcid.org/0000-0002-9989-2437

Еськова Евгения Владимировна, ст. преподаватель кафедры коллоидной химии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: eskova@mirea.ru. https://orcid.org/0000-0003-2536-1884

Сохранева Вера Александровна, студент Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: sokhraneva.v@mail.ru. https://orcid.org/0000-0003-0930-5604

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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

Quality management of the chemical-technological process for continuous synthesis of pharmaceutical substances of medicinal compounds in flow microreactors

Valery F. Kornyushko, Olga M. Nikolaeva@, Alexey V. Panov, Rem R. Biglov, Andrei S. Kuznetsov

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
@Corresponding author, e-mail: polyakova@mitht.ru

Abstract

Objectives. *The introduction of digital tools for the development of medicines, intelligent management systems, and quality control is stipulated not only by modern requirements for the chemical and pharmaceutical industry but also by strict regulatory requirements for manufactured products. This principle ensures the release of a quality product on the first attempt. The aim of this study is to develop information support for the intelligent quality management system for the production of active pharmaceutical substances (APSs) for medicines using a fundamentally new technology: continuous synthesis in flow microreactors. To develop the necessary information support, we developed appropriate systemic, informational, and mathematical models; algorithms for the online management of the experiment; and techniques and algorithms to qualitatively assess whether the product meets official regulatory documents.*

Methods. *System analysis techniques, information and mathematical modeling techniques with multireference regression models, and online optimization using the Hook–Jeevs algorithm (a method of expert evaluation based on the concordance factor) were used to solve the problems formulated.*

Results. *To manage the quality of the process of continuous APS synthesis in the flow microreactor, we developed theoretic multiple system models that were designed to build the digital information environment for the process of experimental research. We developed algorithms for mathematical modeling and optimization of the control process based on multiresponse regression models and*

an online optimization algorithm that allows the process to be managed step by step, taking into account the limitations. Our results show that the degree of conversion is higher in reactions that contain bromodiphenylmethan.

Conclusions. *Based on mathematical modeling method algorithms for the quality control of the process of continuous APS synthesis on a fundamentally new microreactor system, Qmix were developed. The applicability of the proposed methods and algorithms in the production of the drug diphenhydramine from chlorobenzohydrol and bromobenzohydrol as initial substances was proven by an experimental study. The built models were statistically adequate and valid.*

Keywords: *continuous synthesis in flow microreactors, active pharmaceutical substance, theoretic multiple system models, multicell regression models, online optimization, Hook–Jeeves method, expert evaluation, concordance factor, diphenhydramine drug*

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НАУЧНАЯ СТАТЬЯ

Управление качеством химико-технологического процесса непрерывного синтеза активной фармацевтической субстанции лекарственных соединений в проточных микрореакторах

В.Ф. Корнюшко, О.М. Николаева[@], А.В. Панов, Р.Р. Биглов, А.С. Кузнецов

МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
[@]Автор для переписки, e-mail: polyakova@mitht.ru

Аннотация

Цели. *Внедрение цифровых инструментов в разработку лекарственных препаратов, интеллектуальных систем управления и контроля качества обусловлено не только современными требованиями к химико-фармацевтической отрасли, но и строгими регламентированными требованиями к выпускаемой продукции. При этом повышение эффективности разработки и производства лекарственных средств на всех этапах их жизненного цикла опирается на системное применение принципа Quality-by-Design (QbD) – «качество, запланированное при разработке». Это системный подход к разработке лекарственных препаратов, который начинается с четко определенных целей и оканчивается получением лекарственного препарата, с учетом понимания его процесса изготовления и стратегии контроля, основываясь на надежных научных данных и оценке рисков, связанных с качеством. Применение этого принципа позволяет гарантировать выпуск качественного продукта «правильно с первого раза». Это достигается применением на всех стадиях новых технологий цифровизации всех систем сбора, обработки и хранения информации. Целью работы является разработка информационной поддержки интеллектуальной системы управления качеством получения активных фармацевтических субстанций (АФС) лекарственных средств с помощью принципиально новой технологии непрерывного синтеза на микрореакторах проточного типа. Использование этих микрореакторов имеет ряд серьезных преимуществ по сравнению с традиционными периодическими процессами. Среди них возможность подключения аналитического оборудования*

в проточном режиме, что позволяет обеспечить высокий уровень компьютеризации управления синтезом. Для разработки необходимого информационного обеспечения были разработаны соответствующие системные, информационные и математические модели, алгоритмы online управления экспериментом, методики и алгоритмы оценки качества продукта на основе официальных регламентных документов.

Методы. *Для решения поставленных задач были использованы методы системного анализа, методы информационного и математического моделирования с построением многоотказных регрессионных моделей и online оптимизации по алгоритму Хука-Дживса, метод экспертного оценивания на основе коэффициента конкордации. Приведенное алгоритмическое обеспечение реализовано с помощью программной среды SciLab.*

Результаты. *Для управления качеством процесса непрерывного синтеза АФС на проточном микрореакторе построены теоретико-множественные системные модели, служащие для построения цифровой информационной среды процесса экспериментальных исследований. Разработаны алгоритмы математического моделирования и оптимизации процесса управления на основе многоотказных регрессионных моделей и online алгоритма оптимизации, позволяющие осуществлять пошаговое управление процессом с учетом ограничений. Разработан алгоритм экспертного оценивания качества процесса синтеза на основе анализа эффективности и риска разрабатываемого лекарственного средства. Проведены тестовые испытания системы управления на микрореакторной системе Qmix на примере получения АФС дифенгидрамина при применении в качестве исходных веществ хлордифенилметана и бромдифенилметана. Показано, что степень конверсии выше в реакции, где участвует бромдифенилметан. В этом случае в полученной реакционной массе не остается примесей исходных реагентов.*

Выводы. *На основе методов математического моделирования разработаны алгоритмы управления качеством процесса непрерывного синтеза АФС с использованием принципиально новой микрореакторной системе Qmix. Экспериментальными исследованиями доказана работоспособность предложенных методов и алгоритмов в производстве лекарственного средства димедрола из исходных веществ хлорбензогидрола и бромбензогидрола, показана статистическая адекватность и состоятельность построенных моделей.*

Ключевые слова: *непрерывный синтез на проточных микрореакторах, активная фармацевтическая субстанция, системные теоретико-множественные модели, многоотказные регрессионные модели, online оптимизация методом Хука-Дживса, экспертное оценивание, коэффициент конкордации, лекарственное средство димедрол*

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INTRODUCTION

The standard methodology for developing and manufacturing a new medicinal product (MP) usually takes 11–12 years (Fig. 1) [1]. An obvious method to increase the efficiency of drug development is to reduce the duration of the full life cycle, i.e., from development to industrial production, of a drug.

Ensuring that the drug is effective and causes minimal side effects is laid in the development stage, and these factors are tested at the stages of preclinical and clinical testing. It is possible to divide the entire life cycle of drug production into four stages:

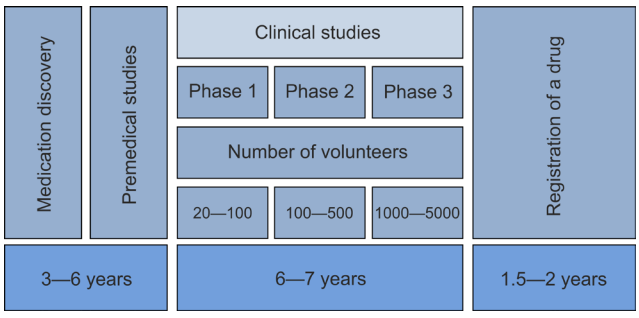

Fig. 1. Development and research of the drug over time.

– nanoscale or computer modeling and screening of molecules;

– microscale—composition (formulation) creation—the stage of pharmaceutical development;

– preclinical and clinical studies and drug registration [2].

An obvious way to significantly reduce total production time is to decrease the time it takes to conduct preclinical and clinical studies. However, it should be noted that reducing the length of preclinical and clinical trials will not be effective if there is an error in the development stage, especially if said error is not identified until the stage of clinical testing. In this case, it will be necessary to return to the stage of pharmaceutical development (microlevel) because it is during that stage that the mean active pharmaceutical substance found at the nanoscale is finally selected, a technological platform for obtaining a ready-made drug form is developed, and the necessary equipment and instrumentation are selected[1] [3].

METHODS

In this study, at the stage of drug development, a relatively new approach was used based on the widespread use of the quality by design (QbD) principle [4, 5]. Applying this principle guarantees the release of a quality product on the first attempt. This is achieved by applying a systematic approach to the development of quality management systems at each stage of the drug's life cycle. It is worth noting that, according to Demming's definition [6], the projected product quality management system will be optimal from a systematic point of view if its constituent links are optimal. In this particular case, these are the stages of a drug production's life cycle. To date, all the stages, with the exception of the pharmaceutical development stage, are certified and have quality management systems.

The pharmaceutical development stage consists of two substages that are fairly autonomous, i.e., they are usually developed by different research teams who are often part of separate organizations.

A systematic approach to the pharmaceutical development stage of a new drug includes [7–10]:

– the application of new innovative technologies for obtaining high-quality products in the form of active pharmaceutical ingredients (APIs) and ready-made drugs;

– the creation of a digital environment for research, including the analysis of information flow at the stage of pharmaceutical development (from the standpoint of system integration—the identification of interrelations between basic concepts and terms);

– the construction of systematic and functional models to determine solutions in the information environment; digitalize information acquisition, processing, and storage; develop databases and knowledge bases; and create intelligent information systems;

– mathematical modeling and software development for research planning and management, the estimation of the relationship between controlled parameters, and the quality of manufactured products.

Analysis of the development of information support for the second substage—the development of a finished product—is fully described in the literature [11]. Therefore, below, we will consider a systematic approach to building a quality management system for the substage of the synthesis of an active pharmaceutical ingredient since, to date, it is in that stage that innovative solutions regarding the synthesis of APIs have been found. A multistage scheme of set-theoretic models described in the form of tuples was chosen as the system model (Fig. 2).

Tuples of the third level and up are constructed in a similar way.

One of the main obstacles to successfully applying the QbD approach at all stages of drug development and production is forming an effective strategy to control the quality of the manufactured product.

The main principle of the QbD concept is that the main development goal is the finished product and its consumer (patient). This is primarily due to the risk assessment of applying a new engineering design for consumers. All possible production hazards associated with the raw materials and the process technology are eliminated only in reverse order during development. Therefore, the quality of the developed medicinal product is ultimately determined during the production stage despite the fact that quality assessment is performed at each stage[2].

In its most general form, the formation of the criterion is based on the following postulates. Each variant of control solution X is evaluated by a set of criteria K characterizing the quality of the found solution: $K = \{ki\}$, where $i = 1,\ldots, n$, where n is the number of criteria. The goal of research is described by the integral criterion G characterizing, from the viewpoint of the chemical–pharmaceutical development of drugs, the quality of the obtained drug, the risk of its use, and its commercial efficacy.

[1] On the approval of the Rules for the organization of production and quality control of medicines: Order of the Ministry of Industry and Trade of Russia of June 14, 2013, No. 916 (Registered at the Russian Ministry of Justice on September 10, 2013, No. 29938).

[2] On the circulation of medicines with additions and changes of 2015: Federal Law of the Russian Federation of 12.04.2010, No. 61-ФЗ.

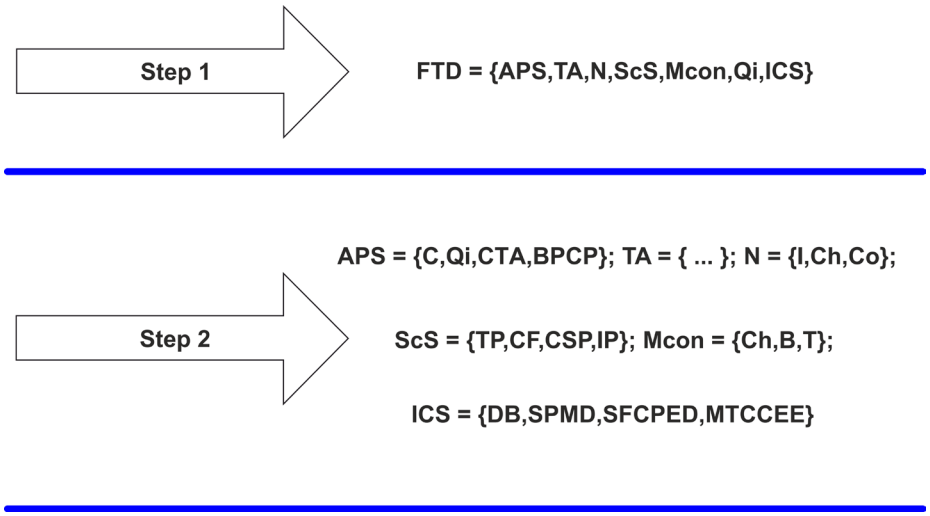

Fig. 2. The structure of the set-theoretic model used to form a task for the development of a system for medication synthesis control.

***Abbreviations*:**
FTD – forming a task to develop a system for medication synthesis control;
APS – active pharmaceutical suspension;
C – composition;
Qi – quality indicators according to regulatory documents;
TA – technical assignment for the development of an APS of a medication;
CTA – compliance with TA;
BPCP – basic physical and chemical properties;
N – name of the medication;
I – international;
Chm – chemical;
Co – commercial;
ScS – scheme of synthesis;
TP – technological process;
CF – control of the feedstock;
CSP – critical stages of the process;
IP – intermediate products;
Mcon – control methods;
Ch – chemical;
B – biotechnological;
T – technological;
ICS – intellectual control systems;
DB – databases;
SPMD – system for preparing management decisions;
SFCPED – subsystem for collecting and processing experimental data;
MTCCEE – means of telecommunication for communication with the external environment.

Let us formulate in general terms the quality criterion of a drug under development:

$$OptimG \rightarrow G\{Q;R;C\}, \quad (1)$$

where Q, R and C indicate the efficiency, risk, and commercial value of the developed drug, respectively.

By "the optimum of the global criterion" we mean the optimal assessment, made by an expert community, of the highest efficiency, lowest risk, and commercial component of a drug being developed in some uncertainty under external conditions. The indicators of the effectiveness of drug use and commercial assessment are quantitative, and the risk criterion is qualitative, i.e., it determines the conditions of drug inapplicability (allergic reaction, patient conditions such as colds, pressure, etc.), side effects, etc. The uncertainty of external conditions lies in the fact that when clinically testing a drug, it is not possible to identify all pathologies in which it should not be used. Only on the basis of long-term use would it be possible to more accurately assess the effectiveness a drug used under various conditions.

Criterion (1) is formed by experts after clinical trials and pilot industrial production. However, at each stage of the development life cycle, a range of conditions is set under which research is to be carried out. With regard to each condition, the quality of the drug obtained is assessed based on a local criterion, which is in turn assessed by its own group of experts.

The value of each of the local criterion K^j_{exp} assessing the quality of the product at each stage of the drug's development and production life cycle is evaluated by a group of experts according to the methodology approved by the Ministry of Health of the Russian Federation[3]. In addition, each stage has its own (technological or environmental–technological) criterion D^m_j, which serves to select the optimal parameters in the technological process.

Thus, the scheme of a criteria-based approach to qualitatively assess the stage of APS synthesis is as follows (2):

$$D \subset K \subset G, \quad (2)$$

where $G\{(R;Q;C)_{TA}; S^j_{exp}; W; \text{IES}\}$ is a global criterion for evaluating a drug under development; $(R;Q;C)_{TA}$ are the components of the global criterion, which are assessed by experts on the basis of quantitative and qualitative indicators of the drug under development according to the work request (R is risk, Q is quality [efficiency], and C is the commercial component); S^j_{exp} is a local criterion for assessing the quality of APS at stage j of the drug development life cycle according to experts; W is the concordance coefficient estimating the degree of agreement among experts; and IES is an intelligent expert system for assessing risk, efficiency, and commercial expediency according to the TA. This system is determined by experts during development and clinical trials as follows:

$$K^j_{exp.}\{E^j_i, W, D\} \subset S^j_{exp.}. \quad (3)$$

In (3), K^j_{exp} is the local criterion for assessing quality at stage j. The criterion is determined by the opinion of each ith expert E and depends on a particular technological criterion D. $D(Y,X,Z)$ is a particular technological criterion assessing the dependence of the objective function of the synthesis process Y on the vector of control parameters X and the constraint vector Z.

Typically, particular criteria include economic, environmental, and technological criteria. For example, at the substage of APS synthesis, the maximum value of the resulting mixture conversion degree Y is used as such a technological criterion along with control parameters X and constraints on the composition Z.

It should be noted that the method of expert evaluation is used to evaluate both the results of a complete drug preparation assessment during the entire life cycle and the quality of products at individual stages.

A fraction of the indicators for the expert assessment of a stage of drug APS synthesis is presented in the table below.

Figure 3 shows an algorithm for the formation of a private criterion of obtaining a drug with the use of the expert assessment method according to the expert tasks seen in the table[4].

RESULTS AND DISCUSSION

The solution to the problem of controlling APS synthesis is explored through a specific drug, diphenhydramine (dimedrol). This drug is well known in the field of pharmacy, and its synthesis is used to demonstrate the development of control algorithms [12]. Currently, in Russia, as in the rest of the world, the synthesis of active pharmaceutical ingredients found in drugs is carried out in capacitive reactors [13]. Only in the last few years have innovative continuous synthesis plants emerged. Figure 4 shows a general view and technical characteristics of the Qmix microreactor system (*Wingflow AG*, Switzerland), and Fig. 5 shows an instrumental scheme for the synthesis of diphenhydramine at this microreactor.

The characteristics of the Qmix system are as follows: the power supply unit is one Qmix Base module with a power of 600 W. The unit includes four neMESYS MPM precision medium-pressure syringe pump modules for generating two continuous streams with pressures up to 200 bar; one microreactor module Qmix Q+2MR with two separate thermostatic zones for two microreactors (temperature range from 20 to 250°C, pressure up to 20 bar); one Qmix P pressure

[3] Appendix No. 3 to the Order of the Ministry of Health of the Russian Federation of August 24, 2017, No. 558н "On the approval of the Rules for the examination of medicines for medical use and the special aspects of the expertize of certain types of medicines for medical use (reference medicines, generic medicines, biological medicines, bioanalog (biosimilar) medicinal products (bioanalogs), homeopathic medicinal products, herbal medicinal products, combinations of medicinal products), forms of expert committee findings" (Conclusion of the expert commission on the results of the examination of the proposed methods for controlling the quality of the medicinal product and the quality of the submitted samples of the medicinal product using these methods, examination of the ratio of the expected benefit /form/).

[4] Order of the Ministry of Health of the Russian Federation of August 24, 2017 No. 558н.

Table. Expert assessment and conclusions on the indicators of the medication submitted for the quality examination

Assessment number according to the Order of the Ministry of Health of the Russian Federation	Designation in the algorithm	Index content
4.1.1.2.	C_1	Assessment of the chemical scheme of synthesis, of the description of the technological process for the production of a pharmaceutical substance and its development including the control of raw materials, critical stages of production and intermediate products and the assessment of the production processes validation.
4.1.1.3.	C_2	Evaluation of the methods proposed by the applicant to explain the chemical and pharmaceutical properties of a pharmaceutical substance.
4.1.1.4.	C_3	Evaluation of the choice of quality indicators of a pharmaceutical substance and standards.
4.1.1.5.	C_4	Evaluation of profiles of a pharmaceutical substance impurities (organic, inorganic, biological).
4.1.1.6.	C_5	Assessment of the standard samples selection.
4.1.1.7.	C_6	Assessment of the methods of quality control of pharmaceutical substances proposed by the applicant.
4.1.1.8.	C_7	Evaluation of the materials submitted by the applicant for the validation of analytical methods for quality control of a pharmaceutical substance.
4.1.1.9.	C_8	The presence or absence of correspondence between the results of laboratory analysis submitted by the applicant for examination of samples of a pharmaceutical substance and the quality indicators included in the regulatory documentation.

Table. Continued

Assessment number according to the Order of the Ministry of Health of the Russian Federation	Designation in the algorithm	Index content
4.1.1.10.	C_9	Evaluation of the data provided by the applicant on the stability of the pharmaceutical substance in all declared types of primary packaging of data according to the pharmaceutical substance shelf life establishment by the applicant for all the declared types of primary packaging, assessment of the justification of the pharmaceutical substance storage conditions established by the applicant.

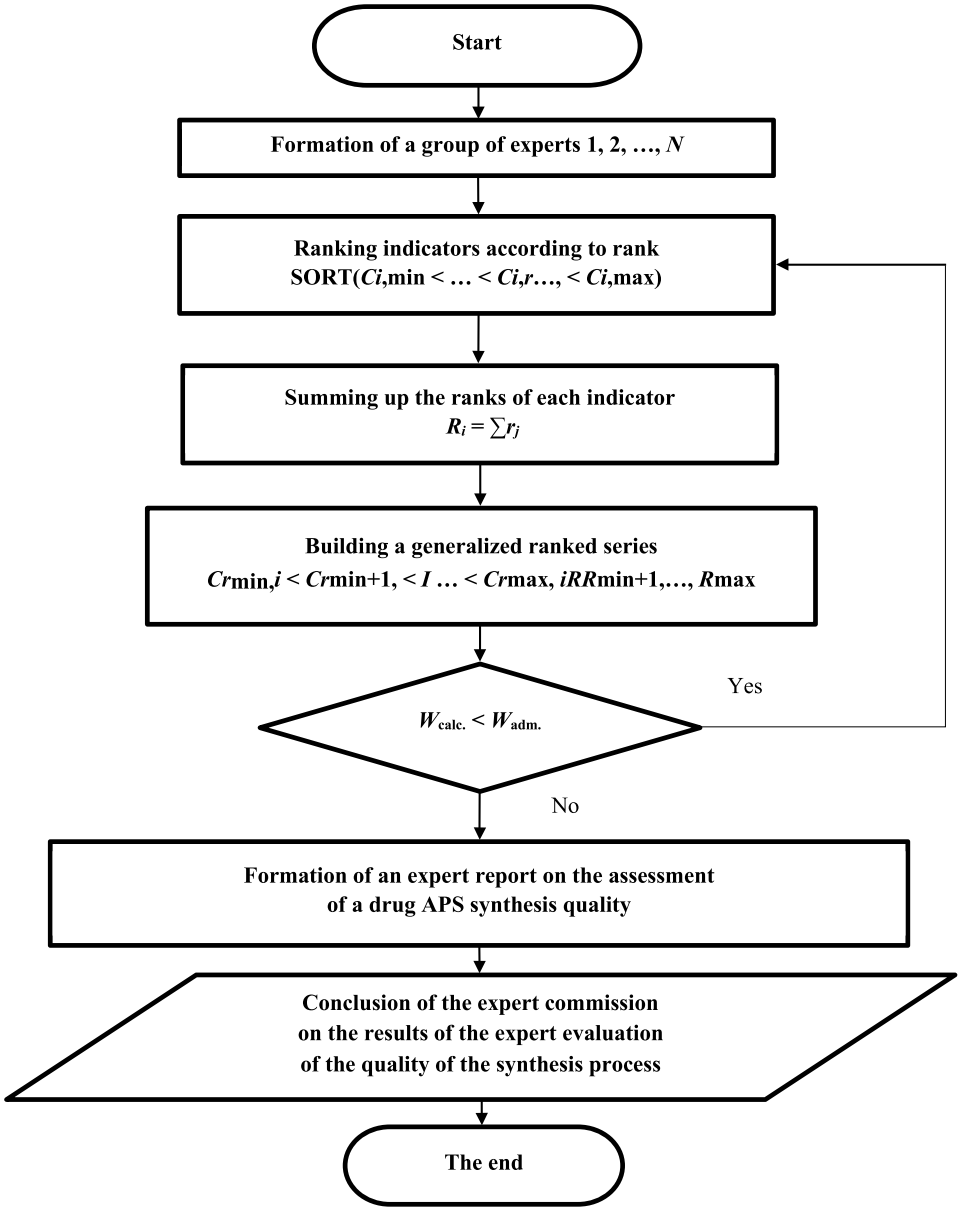

Fig. 3. Block diagram of the algorithm for forming a particular criterion.

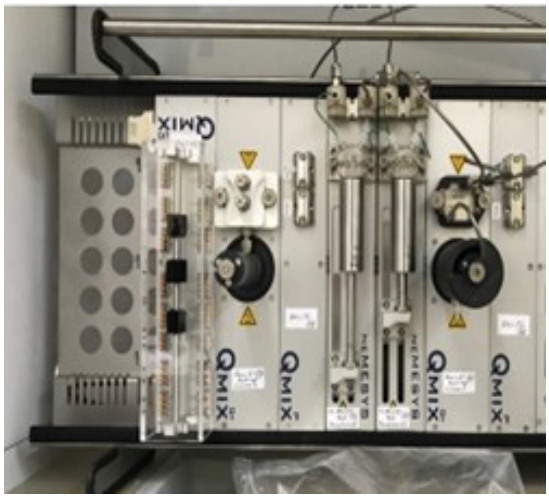

Fig. 4. Appearance of the Qmix microreactor system.

control module for two channels (pressure up to 200 bar); x-Factory microchips measuring 35 × 35 × 3.3 mm; 2-, 5-, 10-, and 50-mL syringes made of special steel; and 1-, 10-, and 50-mL syringes made of borosilicate glass. Capillary material: special 3.175-mm steel. The set of capillaries consists of 6.35-mm fittings (28UNF), 6.35-mm ferrules (28UNF), and 6.35-mm tees (28UNF). Qmix Elements software was used.

Diphenhydramine synthesis technology is described in detail in [13]. A brief description is given below. Using syringe pumps, chlorodiphenylmethane (2.0 M) and pure dimethylaminoethanol are fed into a 19.5-μL microfluidic reactor. Mixing occurs in the first section of the reactor. Immediately after the reactants are mixed, the reactor sections create a turbulent flow to ensure fast and efficient mixing.

Before the mixture enters the second section, it is diluted with acetonitrile.

The mixture is then fed to a pressure transducer and back pressure regulator through the reactor outlet connected to a 2-liter injection valve. The reactor is used to carry out reactions at pressures ranging from 10 to 20 bar.

The outlet is connected to a valve capable of dividing the flow between collection, waste, and an air using a split flow crystallizer.

Since the material exiting the reactor has a concentration of approximately 1.0 M, dilution with acetonitrile is performed in the stream. For the rapid delivery of droplets from the reactor to the mass spectrometer, segmented N_2 (g) droplets were obtained using an electronic pressure regulator. This made it possible to increase the data collection rate and reduce the amount of material consumed during the mass spectrometer data collection. The control system includes a phototransistor, a video microscope, and an optical sensor. Mass spectrometer analysis was performed using an inductive electrospray ionization source (iESI-MS) [14–17].

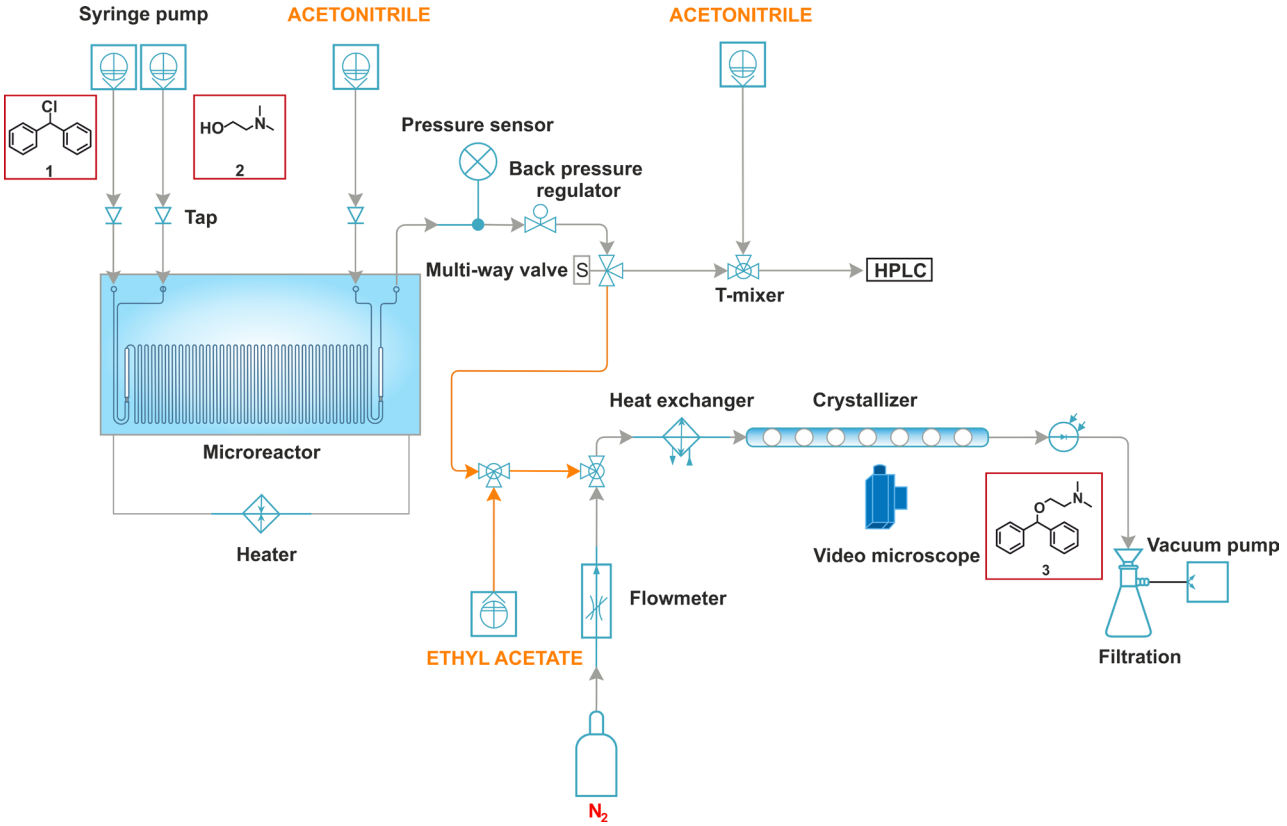

Fig. 5. Apparatus scheme for the synthesis of diphenhydramine.

An information model of the synthesis process in a flow microreactor was considered in [7–9].

When describing the criteria for assessing the quality of the synthesis process, it is indicated that the structure of the particular criterion includes the technological criterion $D(Y,X,Z)$. This criterion estimates the dependence of the objective function of the synthesis process Y on the control parameters vector X and the constraint vector Z.

The task is formulated as follows: it is necessary to construct a step-by-step algorithm to optimize the process of diphenhydramine synthesis in a flow reactor by searching for the maximum target product conversion degree by varying the following control variables x_1 is (t, °C), x_2 is time (min), and x_3 is the substituent in the ingredients Br or Cl with constraints to the permissible composition values. The permissible values of the composition components are as follows: z_1 is benzhydrol (Cl), z_2 is benzhydrol (Br), z_3 is diphenylmethyl (Cl), and z_4 is bis-diphenylmethyl (Br).

To study the dependence of the maximum conversion degree $Y(x_1,x_2,x_3)$ on the control parameters, i.e., x_1, x_2, and x_3, the simplest linear regression model of the criterion $Y(x_1,x_2,x_3)$ dependent on the controlled parameters x_1, x_2, x_3 was chosen (4).

$$Y(x_1,x_2,x_3) = b_1 \times x_{i1} + b_2 \times x_{i2} + b_3 \times x_{i3} (i = 1,2,3,...,n) \quad (4)$$

To solve the optimization problem using this model, it was necessary to formulate equations for the constraints, which are the composition values measured with a chromatograph [18].

For this purpose, we used a system of linear regression multiresponse equations interrelating the control variables x_1, x_2, and x_3 with the composition indices Z_j.

$$Z_j(x_{i1},x_{i2},x_{i3}) \le Z_{\text{adm}}, \quad (5)$$

where x_1, x_2, and x_3 are temperature t (°C), time (min), and the substituent in the ingredients, Br or Cl, respectively, and $Z_{j\text{adm}}$ consists of the admissible values of the composition components: z_1, z_2, z_3, and z_4.

Accordingly, regression equations (5) for assessing the conversion degree and describing constraints in matrix form are as follows:

$$A = (X \times X^t)^{-1} \times (X^t \times Y) \quad (6)$$

$$B = (X \times X^t)^{-1} \times (X^t \times Z) \quad (7)$$

In (6) and (7), A is the column vector of regression coefficients of dimension (1:N); X is the matrix of controlled parameters x_1, x_2, and x_3 of dimension (N:3); Y is the column vector of the values of the objective function of dimension (N:1); N is the number of experiments; $Z(z_1,z_2,z_3,z_4)$ is the matrix of the values of composition components of dimension (N:4); and B is the matrix of regression coefficients of dimensions (3:4).

The regression equations constructed during the first stage via a passive experiment made it possible to solve the optimization problem during the second stage considering the constraints. The purpose of the third stage is to build an online optimization algorithm: at each step j, a plan for changing the controlled variables x_1, x_2, and x_3 is determined such that the values of $D(x_1,x_2,x_3)$ (1) increase in the course of the synthesis, and the constraints (5) do not exceed the admissible limits $Z_j(x_{1j},x_{2j},x_{3j}) \le Z_{j\text{adm}}$.

One of the modifications of the coordinate-wise search for the optimum, the Hook–Jeeves algorithm [19], was chosen as the optimization algorithm. It is important to note that the new values of the objective function for a new point j, $Y(x_{1j},x_{2j},x_{3j})$, are not determined experimentally: they are found as predicted values according to model (1). After determining the maximum value of the objective function $Y_j(x_1,x_2,x_3)$ at this step using the Hook–Jeeves algorithm, the values of $Z_j(x_{1j},x_{2j},x_{3j})$ are calculated using model (2) and transmitted to the researcher, thus allowing them to make the final decision of the synthesis control.

Figure 6 shows the block diagram of an algorithm for optimizing control over the continuous synthesis of diphenhydramine in a Qmix microreactor system using an online optimization algorithm and regression models.

Figure 7 shows the partial results of a study carried out using the suggested algorithms in a Qmix microreactor system. Chlorobenzohydrol and bromobenzohydrol were used as starting components at temperature T = 100–180°C and reaction time t = 2–20 min. The resulting mixture composition was measured using high-performance liquid chromatography.

This graph shows that the conversion degree is higher in the reaction that contains bromodiphenylmethane. In this case, no impurities remain in the resulting reaction mass as starting reagents. Thus, when choosing dimedrol from two starting materials for the synthesis of APS, bromodiphenylmethane is preferred at this stage.

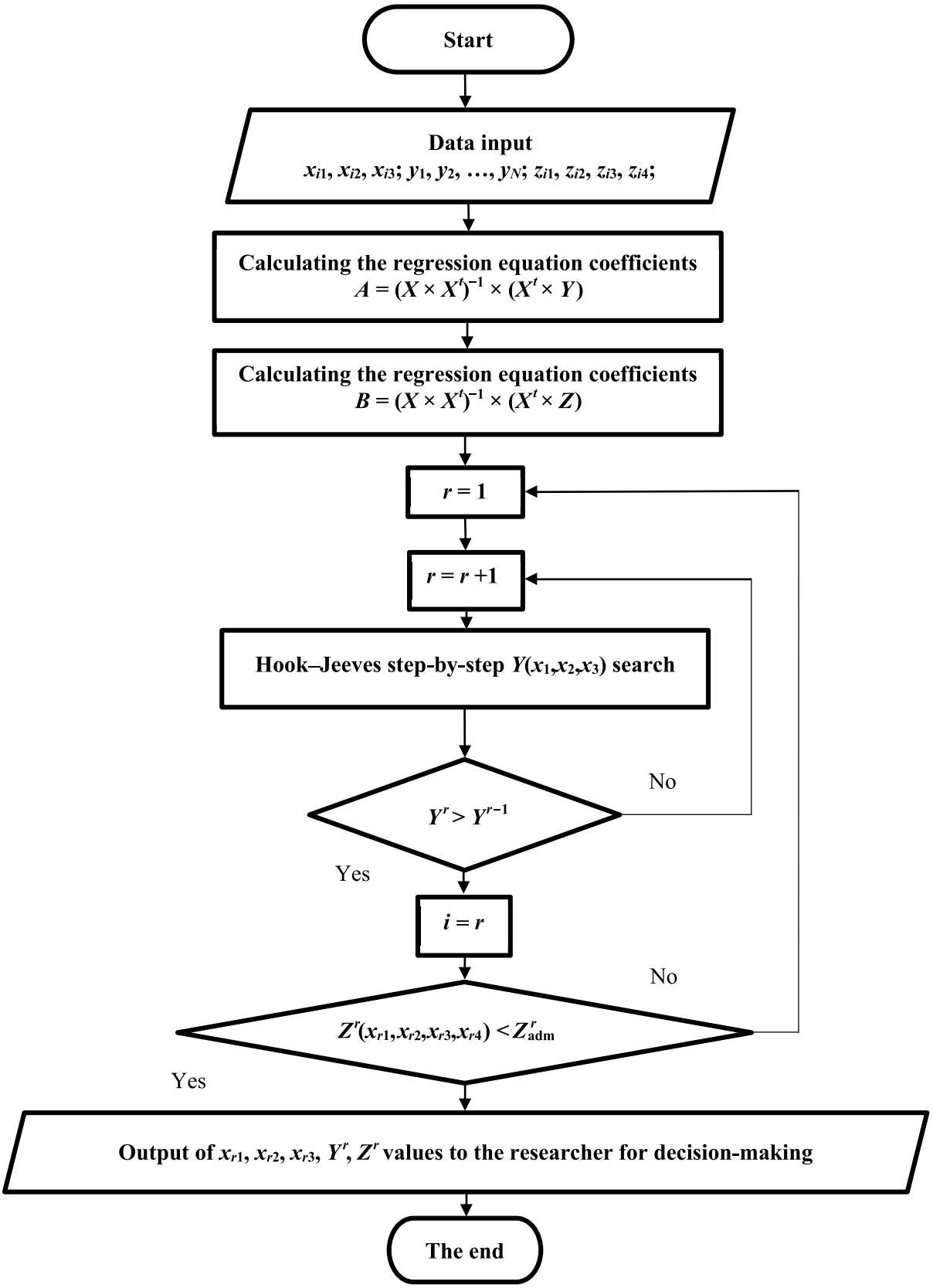

Fig. 6. Block diagram for optimizing the algorithm of control over the continuous synthesis of diphenhydramine in a Qmix microreactor system.

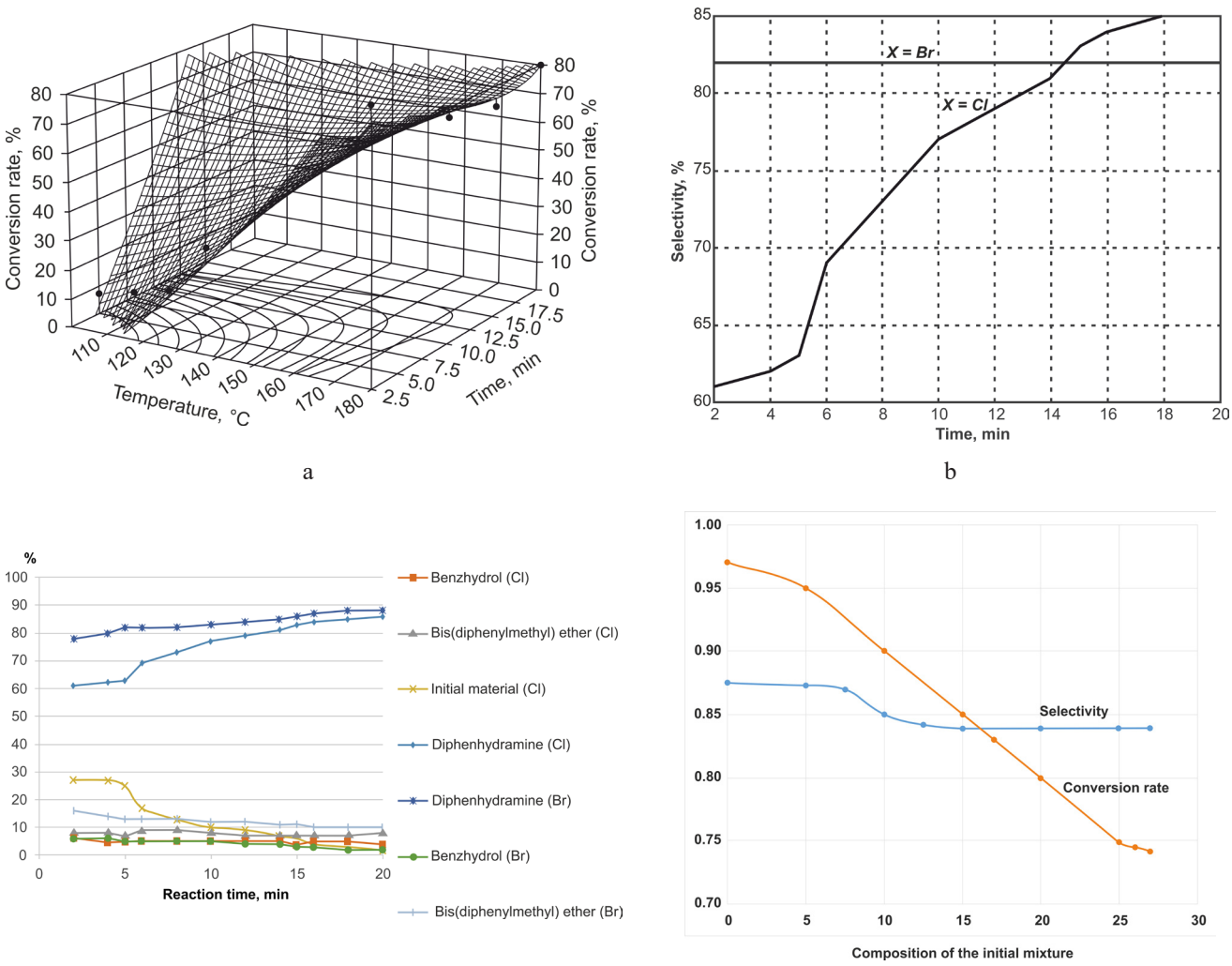

Fig. 7. Graph of the change in the degree of conversion during the synthesis of diphenhydramine APS: (a) dependence of conversion on the reaction temperature and treatment time; (b) selectivity of the process vs. the time of treatment with bromobenzohydrol and chlorobenzohydrol, respectively; (c) product yield vs. processing time; (d) degree of conversion and selectivity of the process vs. the initial mixture composition.

CONCLUSIONS

1. A systematic analysis of a quality management system for the substage of active pharmaceutical ingredient synthesis was carried out in this study because, to date, it is in this stage that innovative solutions in the synthesis of APS have been found. A multistage scheme of set-theoretic models described in the form of tuples was chosen as the system model.

2. The tasks of the criterial approach for assessing the quality of the drug under development were formulated. A methodology and an algorithm for calculating global and local quality assessment criteria based on regulatory documents of the Ministry of Health of the Russian Federation were suggested.

3. A description of the innovative process of the synthesis of an active pharmaceutical substance of a medicinal product in a flow microreactor system Qmix was given. It was found that the system significantly increases the efficiency of the synthesis process.

4. Mathematical modeling of the continuous synthesis process in a flow microreactor based on regression analysis was carried out.

5. The block diagram of an online optimization algorithm for continuous synthesis in a Qmix microreactor system was developed. The synthesis of the active pharmaceutical substance diphenhydramine was used to test the algorithm.

Authors' contribution

All authors equally contributed to the research work.

The authors declare no conflicts of interest.

REFERENCES

1. Bykov V.A., Beregovykh V.V., Shvets V.I., Samylina I.A., Pyatigorskaya N.V., Meshkovskii A.P., Topnikov I.V. On the specialty "Industrial Pharmacy." *Farmatsiya = Pharmacy.* 2007;1:45–47 (in Russ.).

2. Taptunov V.N., Guseva E.V., Batin S.E., Menshutina N.V., Zhukov D.J., Matasov A.V. Information intellectual system for conceptual design of technological schemes for solid dosage forms production. In: *Proceedings 19th International Congress of Chemical and Process Engineering* (*CHISA'2010*). Prague: Czech Republic; 2010. P. 132.

3. Matasov A.V., Kozlov A.I., Mozgunov V.A., Batin S.E., Menshutina N.V. Implementation of quality by design approach in CAD systems of solid dosage pharmaceutical forms production. In: *Proceedings 19th International Congress of Chemical and Process Engineering* (*CHISA'2010*). Prague: Czech Republic; 2010. P. 130.

4. Am Ende D., Bronk K.S., Mustakis J., O'Connor G., Santa Maria Ch.L., Nosal R., Watson T.J.N. API quality by design example from the Torcetrapib manufacturing process. *J. Pharm. Innov.* 2007;2(3–4):71–76. https://doi.org/10.1007/s12247-007-9015-x

5. Ende D.J. *Proizvodstvo lekarstvennykh sredstv. Khimicheskaya tekhnologiya ot R&D do proizvodstva* (*Production of drugs. Chemical technology from R&D to production*). St. Peterburg: Professiya; 2015. 1280 p. (in Russ.). ISBN 978-5-91884-071-9

[Ende A.D.J. Production of drugs. Chemical technology from R&D to production. Cambridge Press; 2014.]

6. Henry N.R. *Prostranstvo doktora Deminga = The Deming dimension: Printsipy postroeniya ustoichivogo biznesa* (*The Deming dimension: Principles of building a sustainable business*). Moscow: Al'pina Biznes Buks; 2005. 370 p. (in Russ.). ISBN 5-9614-0238-X

[Henry N.R. The Deming dimension. Knoxville, Tenn.: SPC Press; 1990. 440 p.]

7. Kornushko V.F., Panov A.V., Bogunova I.V., Nikolaeva O.M., Flid A.A. System approach to informational support of pharmaceutical development of finished medicinal products. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2018;13(2):91–99 (in Russ.). https://doi.org/10.32362/2410-6593-2018-13-2-91-99

8. Kornyushko V.F., Bogunova I.V., Flid A.A., Nikolaeva O.M., Grebenschikov A.A. Information – algorithmic support for the development of solid pharmaceutical form. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2018;13(5):73–81. https://doi.org/10.32362/2410-6593-2018-13-5-73-81

9. Kornushko V.F., Bogunova I.V., Panov A.V., Nikolaeva O.M., Flid A.A. The application of the system approach for building the information space for the development of the production of ready medicines. *Prikl. Inform. = J. Appl. Informatics.* 2018;13(3–75):83–100 (in Russ.).

10. Trofimova E.O., Del'vig T.Yu. New prospects for innovative development of the domestic pharmaceutical industry. *Farm Ekspress.* 2008;5:43–44 (in Russ.).

11. Lebedev E.A., Voynovskiy A.A., Matasov A.V. Menshutina N.V. Dispersion Process Modeling and Equipment Design. In: *Proceedings 20th European Symposium on Computer Aided Process Engineering* (*ESCAPE20*). 2010. P. 1859–1864.

12. Chueshov V.I., Gladukh E.V., Lyapunova O.A., Saiko I.V., Sichkar' A.A., Ruban E.A., Krutskikh T.V. *Promyshlennaya tekhnologiya lekarstv: elektronnyi uchebnik* (*Industrial Drugs Technology*). Kharkiv: National University of Pharmacy; 2010. (in Russ.).

СПИСОК ЛИТЕРАТУРЫ

1. Быков В.А., Береговых В.В., Швец В.И., Самылина И.А., Пятигорская Н.В., Мешковский А.П., Топников И.В. О специальности «Промышленная фармация». *Фармация*. 2007;1:45–47.

2. Taptunov V.N., Guseva E.V., Batin S.E., Menshutina N.V., Zhukov D.J., Matasov A.V. Information intellectual system for conceptual design of technological schemes for solid dosage forms production. In: *Proceedings 19th International Congress of Chemical and Process Engineering* (*CHISA'2010*). Prague: Czech Republic; 2010. P. 132.

3. Matasov A.V., Kozlov A.I., Mozgunov V.A., Batin S.E., Menshutina N.V. Implementation of quality by design approach in CAD systems of solid dosage pharmaceutical forms production. In: *Proceedings 19th International Congress of Chemical and Process Engineering* (*CHISA'2010*). Prague: Czech Republic; 2010. P. 130.

4. Am Ende D., Bronk K.S., Mustakis J., O'Connor G., Santa Maria Ch.L., Nosal R., Watson T.J.N. API quality by design example from the Torcetrapib manufacturing process. *J. Pharm. Innov.* 2007;2(3–4):71–76. https://doi.org/10.1007/s12247-007-9015-x

5. Энде Д.Дж. П*роизводство лекарственных средств. Химическая технология от R&D до производства*: пер. с англ. СПб: Профессия; 2015. 1280 с. ISBN 978-5-91884-071-9.

[Am Ende D.J. Production of drugs. Chemical technology from R&D to production. Cambridge Press; 2014.]

6. Нив Генри Р. *Пространство доктора Деминга = The Deming dimension: Принципы построения устойчивого бизнеса*. М.: Альпина Бизнес Букс; 2005. 370 с. ISBN 5-9614-0238-X

7. Корнюшко В.Ф., Панов А.В., Богунова И.В., Николаева О.М., Флид А.А. Системный подход к информационной поддержке фармацевтической разработки готовых лекарственных средств. *Тонкие химические технологии.* 2018;13(2):91–99. https://doi.org/10.32362/2410-6593-2018-13-2-91-99

8. Корнюшко В.Ф., Богунова И.В., Флид А.А., Николаева О.М., Гребенщиков А.А. Информационно-алгоритмическая поддержка разработки твердых лекарственных форм. *Тонкие химические технологии*. 2018;13(5):73–81. https://doi.org/10.32362/2410-6593-2018-13-5-73-81

9. Корнюшко В.Ф., Богунова И.В., Панов А.В., Николаева О.М., Флид А.А. Применение системного подхода для построения информационного пространства разработки состава готовых лекарственных форм. *Прикладная информатика*. 2018;13(3–75):83–100.

10. Трофимова Е.О., Дельвиг Т.Ю. Новые перспективы инновационного пути развития отечественной фармацевтической отрасли. *Фарм Экспресс.* 2008;5:43–44.

11. Lebedev E.A., Voynovskiy A.A., Matasov A.V. Menshutina N.V. Dispersion Process Modeling and Equipment Design. In: *Proceedings 20th European Symposium on Computer Aided Process Engineering* (*ESCAPE20*). 2010. P. 1859–1864.

12. Чуешов В.И., Гладух Е.В., Ляпунова О.А., Сайко И.В., Сичкарь А.А., Рубан Е.А., Крутских Т.В. *Промышленная технология лекарств*: электронный учебник. Харьков: Национальный фармацевтический университет; 2010.

13. Snead D.R., Jamison T.F. End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts. *Chemical Science.* 2013;4(7):2822–2827. https://doi.org/10.1039/C3SC50859E

13. Snead D.R., Jamison T.F. End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts. *Chemical Science.* 2013;4(7):2822–2827. https://doi.org/10.1039/C3SC50859E

14. Lengauer T., Lemmen C., Rarey M., Zimmerman M. Novel technologies for virtual screening. *Drug Discov. Today.* 2004;9(1):27–34. https://doi.org/10.1016/s1359-6446(04)02939-3

15. Kornyushko V.F., Nikolaeva O.M., Bogunova I.V., Kuznetsov A.S., Panov A.V. Software and algorithmic support for the intelligent control system of active pharmaceutical ingredient synthesis. *Program. Prod. i Sist. = Software & Systems.* 2020;33(1):132–143 (in Russ.). http://dx.doi.org/10.15827/0236-235X.129.132-143

16. Krasnyuk I.I., Mikhailova G.V., Chizhova E.T. *Farmatsevticheskaya tekhnologiya. Tekhnologiya lekarstvennykh form* (*Pharmaceutical Technology. Technology of dosage forms*). Moscow: Akademiya; 2006. 424 p. (in Russ.).

17. Roberge D.M., Ducry L., Bieler N., Cretton P., Zimmermann B. Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries? *Chem. Eng. Technol.* 2005;28(3):318–323. https://doi.org/10.1002/ceat.200407128

18. Zhilyakova E.T., Zinchenko A.A., Novikov O.O., Popov N.N. The development of a methods for the determination of miramistin and dimedrol in the new prolonged eye drops for treatment of bacterial conjunctivitis. *Nauch. Vedom. Belgorod. Gos. Univ. Ser. Medicina, Farm. = Belgorod State Univ. Sci. Bull. Med. Pharm.* 2015;10(207):211–214 (in Russ.).

19. Hook R., Jeeves T. «Direct Search» Solution of Numerical and Statistical Problems. *ACM J.* 1961;8(2):212–229. https://doi.org/10.1145/321062.321069

13. Snead D.R., Jamison T.F. End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts. *Chemical Science.* 2013;4(7):2822–2827. https://doi.org/10.1039/C3SC50859E

14. Lengauer T., Lemmen C., Rarey M., Zimmerman M. Novel technologies for virtual screening. *Drug Discov. Today.* 2004;9(1):27–34. https://doi.org/10.1016/s1359-6446(04)02939-3

15. Корнюшко В.Ф., Николаева О.М., Богунова И.В., Кузнецов А.С., Панов А.В. Программно-аналитическая поддержка интеллектуальной системы управления синтезом активных фармацевтических ингредиентов. *Программные продукты и системы.* 2020;33(1):132–143. http://dx.doi.org/10.15827/0236-235X.129.132-143

16. Краснюк И.И., Михайлова Г.В., Чижова Е.Т. *Фармацевтическая технология. Технология лекарственных форм*. М.: Академия; 2006. 424 с.

17. Roberge D.M., Ducry L., Bieler N., Cretton P., Zimmermann B. Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries? *Chem. Eng. Tecnol.* 2005;28(3):318–323. https://doi.org/10.1002/ceat.200407128

18. Жилякова Е.Т., Зинченко А.А., Новиков О.О., Попов Н.Н. Разработка методики определения мирамистина и димедрола в новых пролонгированных глазных каплях для лечения бактериальных конъюнктивитов. *Науч. Ведом. Белгород. Гос. У-та. Сер. Медицина. Фармация.* 2015;10(207):211–217.

19. Hook R., Jeeves T. «Direct Search» Solution of Numerical and Statistical Problems. *ACM J.* 1961;8(2):212–229. https://doi.org/10.1145/321062.321069

About the authors:

Valery F. Kornyushko, Dr. Sci. (Eng.), Professor, Department of Information Systems in Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: vfk256@mail.ru. Scopus Author ID 57205055432, ResearcherID C-4089-2017, https://orcid.org/0000-0002-2323-186X

Olga M. Nikolaeva, Cand. Sci. (Eng.), Assistant, Department of Information Systems in Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: polyakova@mitht.ru. https://orcid.org/0000-0003-3884-5028

Alexey V. Panov, Cand. Sci (Chem.), Docent, Department of Information Systems in Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: panov@mitht.ru. Scopus Author ID 57203160969, ResearcherID C-4251-2018, https://orcid.org/0000-0002-1603-143X

Rem R. Biglov, Cand. Sci. (Eng.), Docent, Department of Information Systems in Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: biglov@mitht.ru. Scopus Author ID 57218597730, ResearcherID C-4057-2018, https://orcid.org/0000-0002-1296-1058

Andrei S. Kuznetsov, Cand. Sci. (Eng.), Docent, Department of Information Systems in Chemical Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: askuznetsov@mitht.ru. Scopus Author ID 57215101046, Researcher ID C-4035-2018, https://orcid.org/0000-0003-1569-4765

Об авторах:

Корнюшко Валерий Федорович, д.т.н., профессор, профессор кафедры информационных систем в химической технологии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: vfk256@mail.ru. Scopus Author ID 57205055432, ResearcherID C-4089-2017, https://orcid.org/0000-0002-2323-186X

Николаева Ольга Михайловна, к.т.н., ассистент кафедры информационных систем в химической технологии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: polyakova@mitht.ru. https://orcid.org/0000-0003-3884-5028

Панов Алексей Валерьевич, к.х.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. Вернадского, д. 86). E-mail: panov@mitht.ru. Scopus Author ID 57203160969, ResearcherID C-4251-2018, https://orcid.org/0000-0002-1603-143X

Биглов Рем Равильевич, к.т.н., доцент, доцент кафедры информационных систем в химической технологии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: biglov@mitht.ru. Researcher ID C-4057-2018, https://orcid.org/0000-0002-1296-1058

Кузнецов Андрей Сергеевич, к.т.н., доцент кафедры информационных систем в химической технологии Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр. Вернадского, д. 86). E-mail: askuznetsov@mitht.ru. https://orcid.org/0000-0003-1569-4765

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