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Fine Chemical Technologies

- Theoretical Bases of Chemical Technology
- Chemistry and Technology of Organic Substances
- Chemistry and Technology of Medicinal Compounds and Biologically Active Substances
- Synthesis and Processing of Polymers and Polymeric Composites
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- Analytical Methods in Chemistry and Chemical Technology
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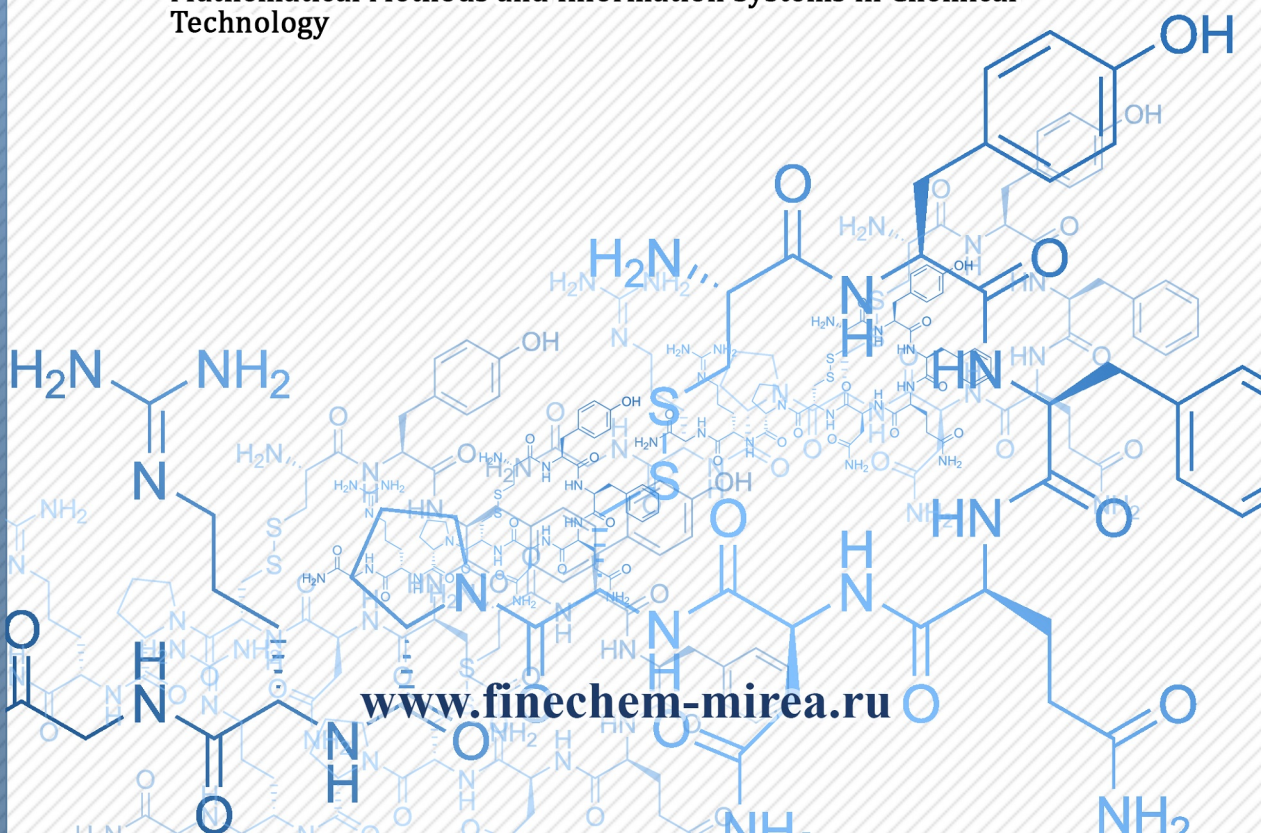

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Editor-in-Chief:
Dr. of Sci. (Engineering), Professor
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Editorial contacts:

Editor: Galina D. Seredina
+7 (495) 246-05-55 (#2-88), e-mail: vestnik@mitht.ru

Executive Editor: Olga V. Esipova
+7 (495) 246-05-55 (#9-33), e-mail: esipova@mirea.ru

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86, Vernadskogo pr., Moscow, 119571 Russia.
Phone: +7(495) 246-05-55 (#2-88)
E-mail: *vestnik@mitht.ru*

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119571, г. Москва, пр. Вернадского, 86, оф. Л-119.
Тел.: +7(495) 246-05-55 (#2-88)
E-mail: *vestnik@mitht.ru*

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Structural features of synthetic glycoconjugates and efficiency of their interaction with glycoprotein receptors on the surface of hepatocytes

Anastasiya S. Nosova[@], Ulyana A. Budanova, Yury L. Sebyakin

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow 119571, Russia
[@]Corresponding author, e-mail: c-221@yandex.ru

Objectives. *Over the last few years, medicinal chemistry research has been focusing on the creation of molecules that can target particular body systems, organs and tissues, thus abating systemic toxicity and side effects, and, most of all, boosting therapeutic potential. This goal can be achieved through the specific interaction of such drugs with active sites of cellular receptors. For example, glycoprotein receptors that can be found on cellular surfaces in neural tissues and liver parenchyma, selectively bind various glycoproteins and glycosides, facilitating their penetration into cells. This review describes how certain parameters of ligand structure (the nature and length of the spacer between carbohydrate and non-carbohydrate fragments of the molecule, number of carbohydrate residues per molecule, etc.) influence the penetration efficiency of synthetic glycoconjugates into liver cells.*

Methods. *This review article summarizes 75 research papers and discusses data from in vitro and in vivo experiments showing which structures of synthetic carbohydrate derivatives are optimal for targeted drug delivery into liver cells.*

Results. *The surface of liver cells (hepatocytes) contains a significant number of asialoglycoprotein receptors (ASGP-R) that are almost never found elsewhere. This makes ASGP-R an ideal target for the directed treatment of liver diseases, including such difficult, socially important conditions as hepatocellular carcinoma and Hepatitis C. A number of various ligands and targeted (to ASGP-R) delivery systems have been designed. Such molecules always contain derivatives of mono- and disaccharides, most commonly D-glucose, D-galactose, D-lactose and N-acetylglucosamines. This review contains the chemical structures of carbohydrate-based ligands.*

Conclusions. *Glycolipids based on D-carbohydrates, when in liposomes, facilitate penetration into liver cells by a receptor-mediated, clathrin-dependent endocytosis mechanism that is activated upon contact of the carbohydrate-containing ligand fragment with the active site of ASGP-R. It can be addressed by the use of monovalent derivatives of carbohydrates as well as polyvalent glycoconjugates. Alterations in the ligand structure and the number of liposomal modifications can boost the therapeutic effect. The distance between the liposomal surface and the carbohydrate residue (spacer length), as well as the hydrophilic-lipophilic balance of the ligand molecule, have a great effect on the affinity and cellular response.*

Ключевые слова: *glycoconjugates, asialoglycoprotein receptor, receptor-mediated endocytosis, targeted delivery, liver cells.*

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Структурные особенности синтетических гликоконъюгатов и эффективность их взаимодействия с гликопротеиновыми рецепторами на поверхности гепатоцитов

А.С. Носова[@], У.А. Буданова, Ю.Л. Себякин

МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва 119571, Россия
[@]Автор для переписки, e-mail: c-221@yandex.ru

Цели. *Последние несколько лет исследования в области медицинской химии уделяют большое внимание созданию молекул, направленно воздействующих на конкретные системы организма человека, органы и ткани, что помогает снизить общее токсическое воздействие препаратов на их основе, уменьшить степень проявления побочных эффектов, а самое главное – многократно усилить их терапевтический эффект. Это может быть достигнуто при помощи специфического взаимодействия подобных веществ с активными центрами клеточных рецепторов. Например, класс гликопротеиновых рецепторов, располагающихся на поверхности клеток нервной ткани и паренхимы печени, селективно связывает различные гликопротеины и гликозиды, способствуя их проникновению внутрь клеток. В обзоре рассмотрено влияние таких особенностей структуры лигандов, как природа и длина связующего звена (спейсера) между углеводной и неуглеводной частями молекулы, количество углеводных остатков в составе одной молекулы, а также ряда других, на эффективность проникновения синтетических гликоконъюгатов в клетки печени.*

Методы. *В обзоре проанализировано 75 публикаций и обобщены результаты исследований, в которых с помощью in vitro и in vivo экспериментов устанавливается, какая структура искусственно синтезированных производных углеводов окажется наиболее оптимальной для направленной доставки лекарственных средств в клетки печени.*

Результаты. *На поверхности гепатоцитов (клеток печени) в большом количестве представлен асиалогликопротеиновый рецептор (ASGP-R), который почти не встречается на других типах клеток, что делает его идеальным рецептором-мишенью для направленного лечения заболеваний печени, в том числе таких трудно излечимых социально значимых заболеваний, как гепатоцеллюлярная карцинома и гепатит С. Разработан ряд разнообразных лигандов и систем направленной доставки к ASGP-R. Такие молекулы обязательно имеют в составе производные моно- и дисахаридов, чаще всего применяются D-глюкоза, D-галактоза, D-лактоза и N-ацетилглюкозамины. В обзоре приводятся примеры химических структур углеводсодержащих лигандов.*

Заключение. *Гликолипиды на основе D-углеводов в составе липосом обеспечивают их проникновение в клетки печени по механизму рецептор-опосредованного клатрин-зависимого эндоцитоза, который активируется при контакте углеводсодержащей части лиганда с активным центром ASGP-R. Показано, что для этого можно использовать как моновалентные производные углеводов, так и поливалентные гликоконъюгаты. Варьируя структуру лиганда и количество добавляемых к липосоме модификаций, можно достичь наибольшего терапевтического эффекта. Большое влияние на аффинность и клеточный ответ оказывают расстояние от поверхности липосомы до углеводного остатка (длина спейсера) и гидрофильно-липофильный баланс молекулы лиганда.*

Keywords: *гликоконъюгаты, асиалогликопротеиновый рецептор, рецептор-опосредованный эндоцитоз, направленная доставка, клетки печени.*

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Novel pharmaceutical approaches in the design and development of medications are expected to lead to a rise in revolutionary drugs with high bioavailability, biocompatibility and efficacy, and low toxicity. One of the ways to solve the existing difficulties in drug design is the creation of nanoparticles that carry low yet efficient doses of medication. The great variety of nanosized delivery systems allows us to design therapeutic complexes with the required characteristics. A number of *in vitro* and *in vivo* studies have shown that liposomes (lipid vesicles with a two-layer membrane) possess all the necessary features to deliver any type of medication.

The liver's role in the metabolism of toxic substances implies that its cells (hepatocytes) are often affected by drugs, microbes and toxic molecules, which may lead to a number of liver diseases. Such diseases are the fifth most common cause of death. Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most deadly type of cancer [1, 2]. HCC development is driven by two major types of the hepatitis virus, Hepatitis B and Hepatitis C (HBV and HCV, respectively). Approximately 2 billion people across the world are infected by HBV and 320 000 cases are fatal every year [3], whereas 170 million people in the world are infected by HCV [4, 5]. Since HCC and other liver diseases, such as fibrosis and cirrhosis, mainly affect hepatocytes [6], the targeted delivery of therapeutics directly to these cells seems to be a most logical approach. In order to develop a hepatocyte-targeted delivery system, an asialoglycoprotein receptor (ASGP-R) [7] was selected as a target receptor. It is often found on the surface of hepatocytes but not as much on the membranes of other cells.

Today, research is focusing on the establishment of optimal glycolipid structures that will give liposomes "targeting" features. Several systems of gene delivery that are based on such ligands have shown exciting clinical results, attracting the attention of the scientific community and demonstrating the prospects of nanotherapeutics.

Structure and functions of the asialoglycoprotein receptor ASGP-R

ASGP-R, also known as the "Ashwell–Morell receptor," was the first mammalian cellular lectin discovered in the 1960s, during studies on the metabolism of plasma glycoproteins [8, 9]. The main function of this receptor is binding to cellular fibronectin, prothrombin components, liver lipoproteins and immunoglobulin A (IgA). The role of ASGP-R is to mediate the homeostasis of serum glycoproteins by balancing between binding to and the endocytosis of a wide range of glycoproteins that bear galactose residues or *N*-acetylgalactosamine at the termini [10]. These glycoproteins undergo endocytosis through clathrin-presenting areas, after which they are transported into lysosomes for acidic degradation. ASGP-R is widely present on the surface of parenchymal liver cells, making up to $(1–5)\times10^5$ of binding sites per cell [11]. Apart from this, the interaction of the receptor with cellular components of pathogens is a major reason for the generalization of certain liver diseases, particularly those caused by hepatitis viruses A and B, as well as the Marburg virus [12–15].

Mammalian ASGP-R consists of two homologous polypeptide subunits, main and auxiliary that are encoded by two genes [13, 16]. In humans, the main subunit H1 and the auxiliary subunit H2 are 46 and 50 kDa in size, respectively. Each subunit is a transmembrane *C*-type protein, with a short *N*-terminus in the cytoplasm; an internal part that runs throughout the membrane; and a *C*-terminus with a Ca^{2+}-dependent domain responsible for carbohydrate recognition, on the outer side of the membrane [17]. Combinations of different subunit ratios lead to functional homo- and heterooligomers with different receptor configurations. It has been established that the most common configuration is the conjugate of two H1 subunits and one H2 subunit (Fig. 1). This conjugate shows the highest affinity to the ASOR ligand (asialo-orosomucoid) that binds to ASGP-R, similarly to lactoferrin – serum glycoprotein [11, 18].

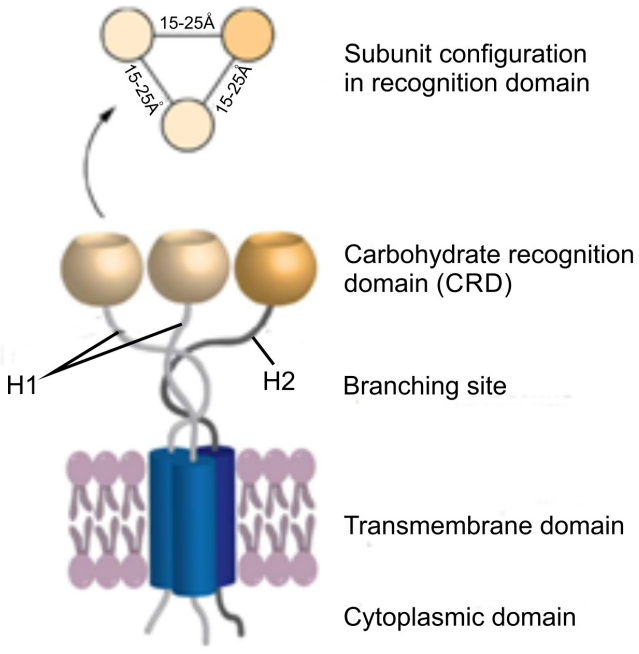


Fig. 1. Schematic depiction of ASGP-R that showing a heterooligomer made up of two H1 subunits and one H2 subunit. The figure shows the spatial arrangement of the receptor's binding sites [19].

The carbohydrate recognition domain (CRD) in ASGP-R subunits belongs to the C-type family (Ca^{2+}-dependent) [20]. The majority of CRD C-type domains selectively bind to D-mannose, D-glucose and their derivatives (Man-type ligands), or D-galactose and its derivatives (Gal-type ligands). The binding of D-galactose to the receptor (Fig. 2) occurs in the presence of Ca^{2+} ions under basic conditions [21–23].

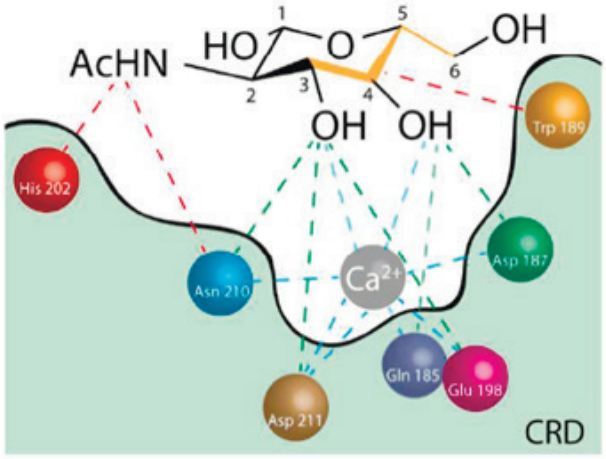


Fig. 2. Binding of the *N*-acetylgalactosamine (GalNAc) molecule to the recognition domain of ASGP-R. Between hydroxyl groups at 3 and 4 carbon atoms in the pyranose ring of GalNAc and ^{187}Asp, ^{198}Glu, ^{185}Gln, ^{211}Asp and ^{210}Asn amino acid residues, the interaction is due to hydrogen as well as coordination bonds (with the participation of the Ca^{2+} ion). The hydrogen atom in the amide bond and the nonpolar GalNAc region between 3 and 6 carbon atoms participate in the creation of hydrophobic interactions with ^{202}His and ^{189}Trp amino acid residues, respectively [19].

ASGP-R facilitates clathrin-mediated endocytosis [24]. This mechanism is used upon interaction with a transmembrane receptor that activates a signaling cascade and lets the particles through. Clathrin domains occupy only 0.5–2% of the total cell surface area, meaning that substance transport by a clathrin-mediated mechanism is quite selective. For successful recognition, liposomes and other substances should be first labelled by apolipoproteins that are commonly found in plasma [25]. After entering the cell, this aggregate is found inside an early endosome whose membrane later fuses with the outer layer of the liposome, maturing to form a late endosome. Depending on the structure of the parental liposome, its charge and presence/absence of specific ligands on the surface, the late endosome can either become a lysosome (upon enzymatic action) leading to the degradation of the whole complex, or its contents can be released into the cytoplasm where they can affect the organoids [26, 27]. Research on the mechanisms of endocytosis and ways of blocking it has shown that penetration of the cells does not occur at 4 °C, but the process of molecule recognition by receptors remains the same [28]. This is why it is possible to determine whether the transport is receptor-dependent and selective while using low temperatures for studying mechanisms of penetration for certain liposome structures. It has also been demonstrated that the human Hepatitis C virus enters hepatocytes via this mechanism [29].

ASGP-R has also been found on the surface of hepatocytes in other mammals, including rabbits [30], mice [31], and rats [32], although the size and number of subunits differ slightly between species. Despite the differences in receptor structure in various mammals, the amino acid sequence is rather conservative and, potentially, originates from the same common gene. For example, the H1 subunit is 80% identical to the rat lectin-1 (RHL1), and the H2 subunit is 62% identical to the RHL2 [33]. This fact allows us to project the *in vivo* experimental data on to the expected results of clinical studies.

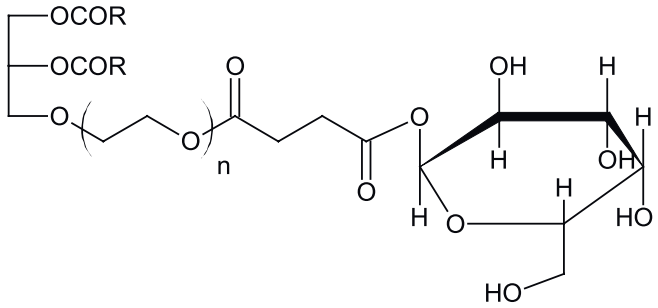
Principles of targeted drug delivery to liver cells

It is known that in chemotherapy more than 90% of molecules of cytotoxic agents are captured by healthy tissues and only 2–5% reach tumors [34]. This is why it is so important to create drug delivery systems that could be selective and would only reach target organs [35, 36]. Receptor-mediated endocytosis is a very promising approach for targeted drug delivery because it allows high drug concentrations in target cells to be reached, thus boosting efficacy and decreasing side effects.

Optimizing the ligand–receptor interaction has demonstrated that affinity is affected by a number of properties of the carbohydrate ligand. For example, it is known that the recognition domain binds cyclic D-galactose derivatives and acyclic D-galactosides equally well. The most efficient interaction with the receptor is observed for derivatives of D-galactose and D-glucose; lactose and D-mannose are less effective for hepatocytes, but they have a higher affinity for the receptors of Kupffer cells [37]. Affinity of D-galactose increases by 100–1000 times when the number of carbohydrate residues at the terminus of one ligand molecule grows from 1 to 3–4, due to the cluster effect [38]. To this end, monovalent and polyvalent ligands can be used to target ASGP-R.

The distance between the carbohydrate residue and the liposome surface is a crucial parameter for interaction with lectins [39, 40]. Construct design should take into account the minimal distance between

the carbohydrate and the surface of the carrier [41, 42]. If there is no hydrophobic spacer, carbohydrate residues are not exposed to the aqueous medium enough to bind to the active sites of receptors [43], but a spacer that is too long can prevent their interaction [44]. This effect has been observed in the binding studies of glycolipids **1a–c** with ConA (carbohydrate-binding protein extracted from vegetables) in the presence of glycogen [45].



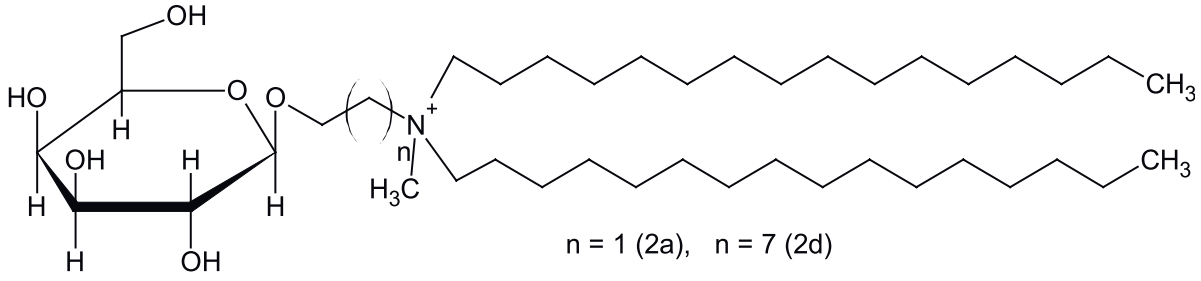
n = 10, R = $C_{15}H_{31}$ (1a)

n = 20, R = $C_{17}H_{35}$ (1b)

n = 40, R = $C_{17}H_{35}$ (1c)

1a–c

Theoretical calculations and experimental data have confirmed that a long spacer makes the carbohydrate residue more mobile (glycolipid **1c**), providing easier access to the binding site of the receptor protein. For example, D-galactosides with a 20 Å long spacer bind to the receptor even at low concentrations, whereas a 4 Å long spacer requires more active molecules [45]. Similar results have been obtained in experimental attempts to lower serum cholesterol: the effective dose of glycosides with a 20 Å long spacer is 30 times lower than that for compounds with a 4 Å long spacer [46]. For the spontaneous binding of carbohydrate residue to the receptor, the spacer length should be 25–30 Å on average, and if the carbohydrate residue is cyclic, a slightly longer distance to the nanoparticle surface is required [47]. At the same time, there are successful examples of shorter spacers, which are 15 Å [38], 11.05 Å [48], and 10.1 Å long [49]. It seems that there is no universal, ideal spacer length for all types of carbohydrate ligands, and this length depends on the spacer's nature and the type of carbohydrate residue. Studies on transfection activity of lipoplexes, which are based on aliphatic glycosides that contain a quaternary nitrogen atom, have shown that the cyclic form (**2a–e**) requires a spacer that is 6 methylene units long, and the acyclic form (**3a–e**) requires only 2 methylene units [50]. It has also been shown that pyranosides, which have a glycosidic bond at the C-6 atom out of plane, enter hepatocytes while "skipping" the lysosome stage, thus improving the drug's therapeutic effect [51].

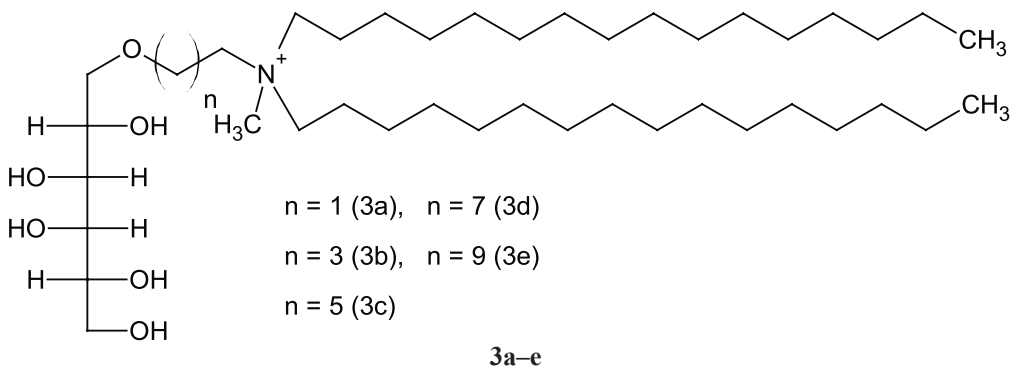


n = 1 (2a), n = 7 (2d)

n = 3 (2b), n = 9 (2e)

n = 5 (2c)

2a–e



n = 1 (3a), n = 7 (3d)

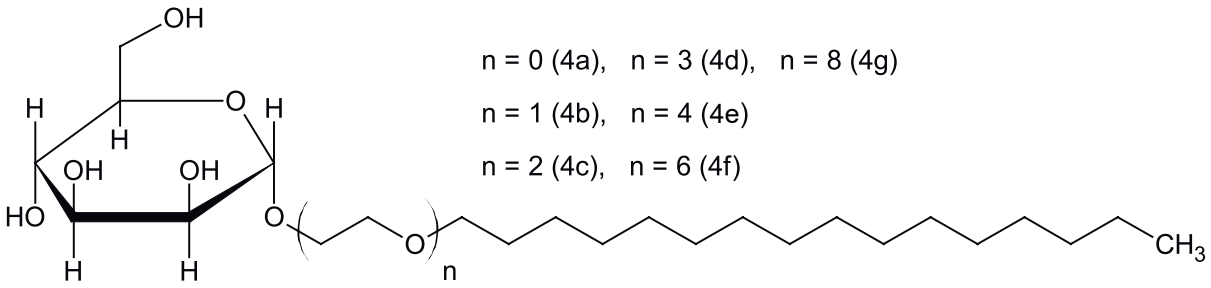
n = 3 (3b), n = 9 (3e)

n = 5 (3c)

3a–e

The effect of the configuration of the chirality center of the carbohydrate fragment has also been investigated; some studies show that α-glycosides have a higher activity towards the model plant receptor ConA [52] or cell line HepG2 derived from hepatocytes [53], in comparison with β-glycosides.

In addition, the use of liposomes as carriers requires a minimal effective share of carbohydrate ligands in the total lipid content; it is called the threshold effect [54]. *In vitro* data for the binding of D-mannose modified liposomes (**4a–g**) to the plant lectin ConA demonstrate that the minimal effective share of D-mannose is 28% for short spacers (2 oxyethylene units), whereas it is only 3% for a medium-long spacer (6 units).



n = 0 (4a), n = 3 (4d), n = 8 (4g)

n = 1 (4b), n = 4 (4e)

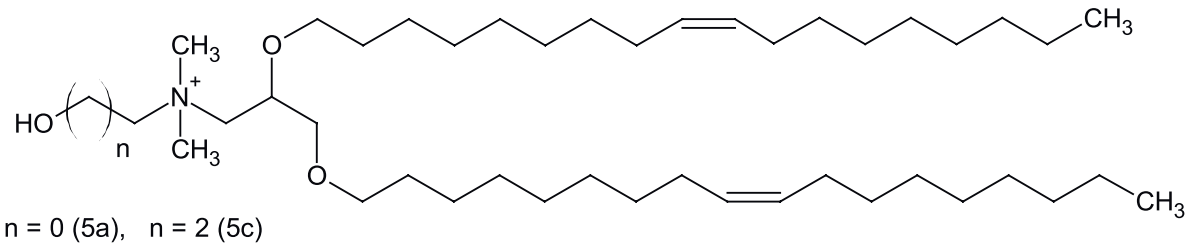
n = 2 (4c), n = 6 (4f)

4a–g

In the case of D-lactose based glycolipids with a hydrophobic unit that contains two alkyl chains and a succinic acid residue acting as a small linker, the threshold effect is observed upon addition of 5% of the resulting substance to the liposome composition [55]. In addition, there is evidence of a sharp increase in the uptake of carbohydrate-containing particles by macrophages after interaction with Gal/Fuc-recognizing receptors on their surfaces, if the modification rate reaches 50% [56]. The introduction of structuring lipids, such as cholesterol, into the liposomes decreases the carbohydrate threshold, and the use of unsaturated phosphatidylcholines as a lipid matrix increases it [57].

It is worth noting that oxyethylene groups, which are not found in nature, are able to replace natural monosaccharide residues, imitating a long polysaccharide chain. This effect has been established in studies on binding efficiency for three different glycolipids with the plant lectin RCA1 – binding efficiency increased in a series of aliphatic derivatives of D-galactose, D-lactose, and D-galactose, with a short hydroxyethylene spacer attached to it [43]. In addition, the use of longer polyethylene glycol chains (more than 10 units) creates the effect of steric surface protection of liposomes from blood proteins, leading to prolonged blood circulation of the complexes. An increase in ligand content in the lipid composition results in easier penetration into liver cells, and the presence of a long hydrophilic spacer slows down the removal of the complexes from the blood [44].

Hydroxyl groups at the terminus of a carbohydrate-containing ligand may facilitate the contacts between the modified liposome and the active site of ASGP-R, as well as improve the transfection activity of the complexes of such vesicles with nucleic acids. A number of *in vitro* studies on cationic liposome bioactivity, where the polar head of the lipid contains a hydroxyl group (**5a–d**), have shown that complexes formed with DNA are more stable, due to the formation of hydrogen bonds between the surface of the bilayer and the molecules of the nucleic acid [58]. The closer these groups are to the positively charged quaternary nitrogen atom (**5a**), the more effective complex formation is [59].



n = 0 (5a), n = 2 (5c)

n = 1 (5b), n = 3 (5d)

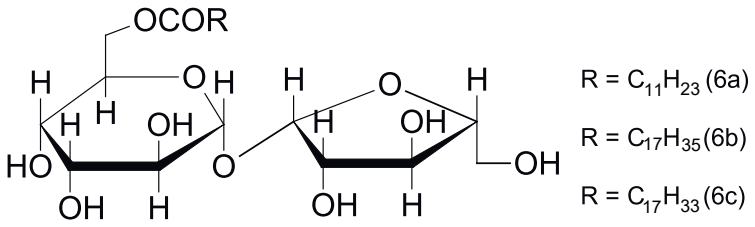
5a–d

An increase in the number of hydroxyl groups in cationic lipids also improves transfection efficiency [60]. Hydroxyl groups at lipid termini within the bilayer perform a function that is analogous to that of PEG (polyethylene glycole) chains, forming a small protective layer around the liposome, thus letting the glycoside-containing particles further circulate in the blood, in comparison with cationic dispersions [50].

In summary, the crucial parameters in the design of such ligands are spacer length, hydrophilic-lipophilic balance of the molecule, and its spatial geometry.

Success in developing liposomal medications for liver disease therapies

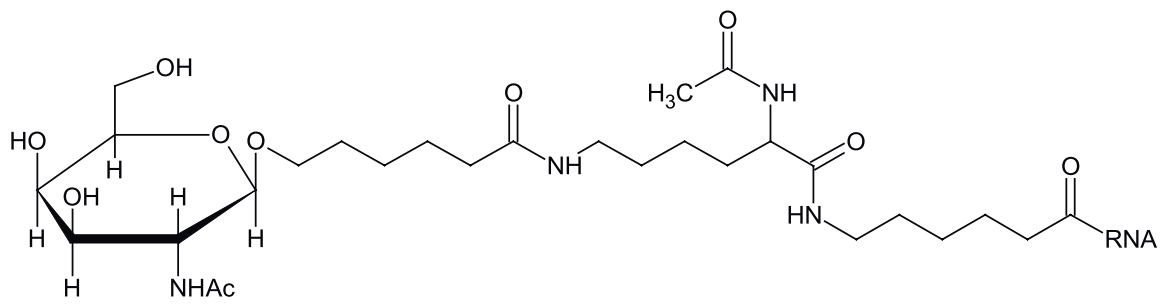
Cationic liposomes that contain analogs of natural lipids may have much higher efficacy of gene delivery, compared to liposomes based on phospholipids, thanks to their particular bilayer structure [61]. However, such conjugates require the presence of helper lipids that play an important role in lipoplex formation from cationic liposomes and nucleic acids, and determine their morphology [62]. One study suggests aliphatic esters of saccharose as helper lipids, where the hydrophobic domain is represented by residues of various fatty acids (**6a–c**). They have shown high efficacy by improving transfection activity of lipoplexes *in vitro* and *in vivo* [63]. The cellular uptake of modified cationic liposomes increased by 20–30%, whereas cytotoxicity decreased by 20–60%. However, the structure of such esters may have a great impact on the transfection efficiency and liposome toxicity; this is why the choice of length and type of fatty acid residue plays an important role. The existing data shows that liposome size gradually decreases with an increasing hydrophilic-lipophilic balance. On average, liposome diameter is lower for those particles that contain lauric acid residues (**6a**) than the diameter of liposomes with esters of stearic acid (**6b**), even with the same hydrophilic-lipophilic balance.



6a–c

The length of the hydrophobic fragment may affect the stability and fluidity of liposomes as well. It has been shown that alkyl chains with 12 carbon atoms provide the best penetration into cells, in comparison with shorter (6–10 atoms) or longer (>14 atoms) chains [64]. Saccharose esters with short chains (lauric acid residues), whose hydrophilic-lipophilic balance is equal to 6, allow for the formation of liposomes, which provide high transfection efficiency for DNA plasmids and suppress tumor growth in mice [65].

There are a number of studies, which demonstrate that an increase in transfection efficiency and genetic silencing in liver cells may be achieved even by simple conjugation of the glycoside with a DNA or RNA molecule. It has been shown that the targeted delivery of genetic material for HCV treatment, when such a modification is used, increases the penetration of nucleic acid into the cells by 10 times [66]. The conjugation of an antisense oligonucleotide with even one GalNAc residue (**7**) significantly increases the efficiency of the delivery of the bioactive molecule. In this case, lysine has been used as a spacer and branching agent.

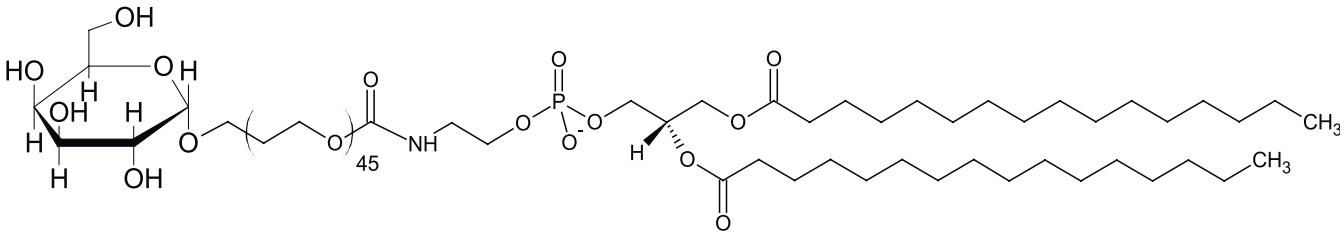


7

Apart from gene therapy agents, chemotherapy drugs have been quite successfully targeted into liver cells as well. In one study, cationic liposomes carrying doxorubicin were coated by D-galactose residues, at the stage of liposomal carrier formation. *In vitro* cytotoxicity experiments have shown that delivery to Huh-7 cells (human hepatocarcinoma) is selective; the cells have ASGP-R on the surface. The cytotoxicity is dose-dependent, increasing with a growing concentration of liposomes in the well of the plate [66].

In order to create another targeted anti-tumor drug, liposomes with encapsulated oxaliplatin have been engineered. Their surface was coated with lactobionic acid, a disaccharide polyhydroxy acid. The cytotoxic agent itself and the unmodified, carrying liposomes were used as comparator drugs. Fluorescent labelling allowed to detect that addition of carbohydrate onto the liposomal surface led to three-fold growth in vesicle concentration in hepatocellular carcinoma cells [68]. Oxaliplatin carried by targeting liposomes had a stronger cytotoxic effect on these cancer cells, in comparison to a "simple" drug and unmodified liposomes.

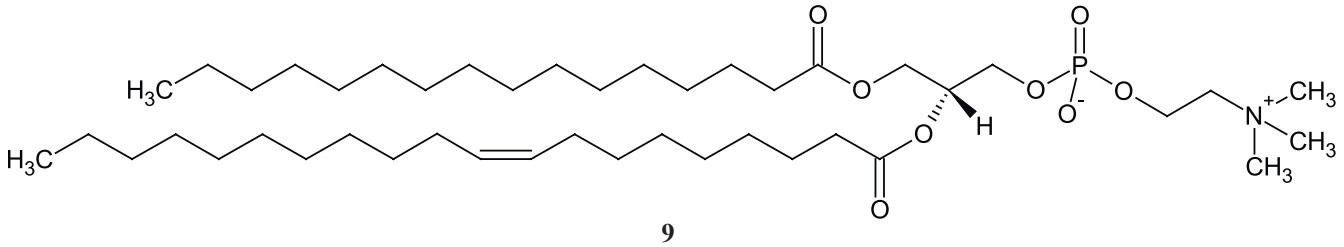
Confocal microscopy with contrast organoid staining allows the accumulation of liposomes in targeted cells to be investigated. The conjugation of D-galactose residues with the surface of cationic liposomes via the amino group of the DSPE lipid (**8**) leads to a significantly better uptake by HepG2 hepatocytes [69].



8

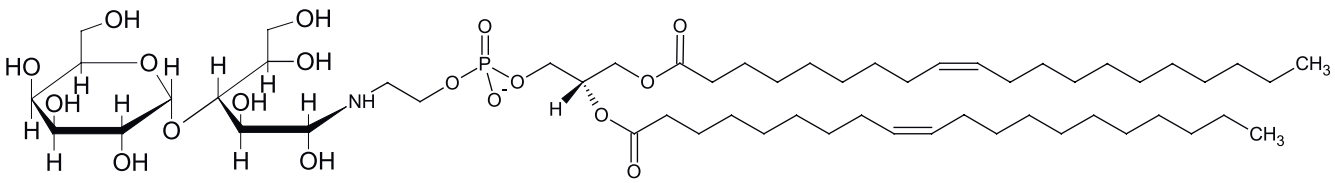
The co-incubation of cells with liposomes and specific conjugation inhibitors, such as indomethacin and chlorpromazine, has shown that adding these substances dramatically decreases the number of modified liposomes inside the cells [69]. It is known that chlorpromazine blocks clathrin-dependent endocytosis, and that indomethacin is caveolin-dependent. This is why the study confirms that penetration of carbohydrate-containing particles into hepatocytes occurs via a clathrin-mediated mechanism, and also shows that caveolin-dependent uptake, too, plays an important role. The latter process is responsible for the uptake of the majority of complex microorganisms and viruses.

There has been research on cationic liposomes containing D-galactolipid and the POPC helper lipid (**9**) in various ratios [70].



9

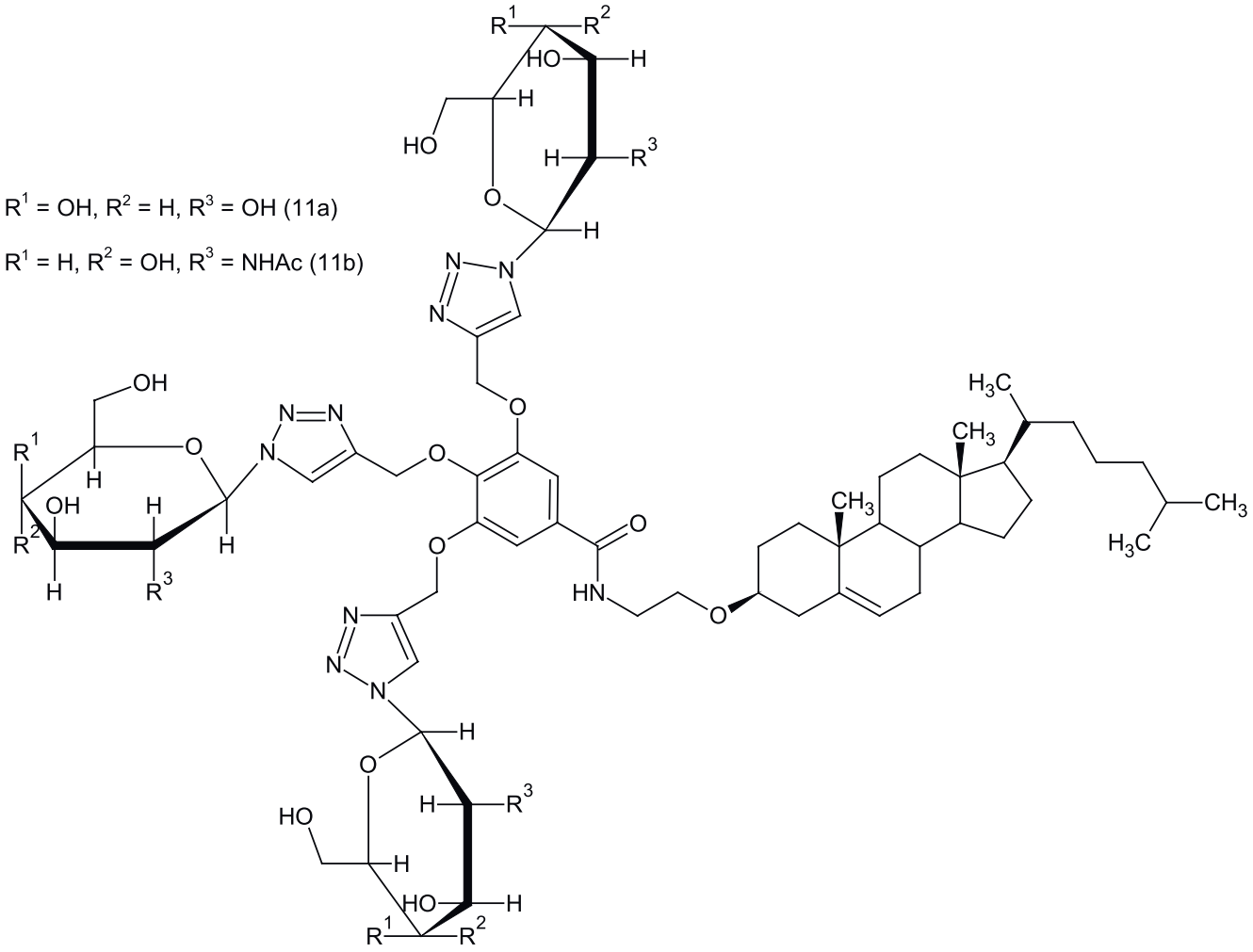
In vitro experiments have shown that liposome uptake by Huh-7 cells increases with a growing amount of a carbohydrate-containing lipid in the lipid matrix. Carbohydrate-containing liposomes resulted in nearly two times better silencing of VEGF genes, responsible for the development of squamous epithelium tumors, in comparison to "standard" cationic liposomes. The introduction of a glycolipid into the liposome, if that glycolipid has been obtained by a reaction between lactose and DOPE lipid (**10**), does not require any helper lipids for a successful exit from endosomes.



10

An *in vivo* pharmacokinetics study has shown that lipoplex uptake by liver cells occurs through a receptor-mediated mechanism, since just 5 minutes after the start of the experiment the majority of the modified complexes were found in the liver, whereas "standard" cationic liposomes remained in the plasma for the most part [70].

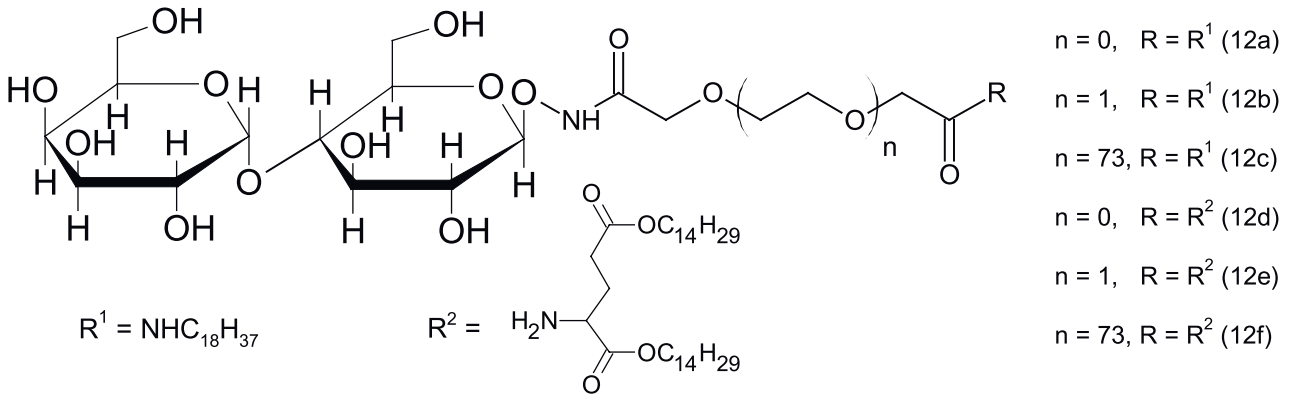
Another *in vivo* experiment with BALB/c mice has demonstrated the faster excretion of glycated liposomes, in comparison to cationic liposomes based on phosphatidylcholines and cholesterol [71]. For this study, two cholesterol-based glycoconjugates were synthesized; they contained D-galactose (**11a**) or *N*-acetyl-D-glucosamine (**11b**). In 20 minutes after the start of the experiment, the modified liposomes were almost absent in the blood, but were found in the liver, spleen, and kidneys. Additionally, liposomes with D-galactose residues on the surface reached the liver from the blood faster.



11a, b

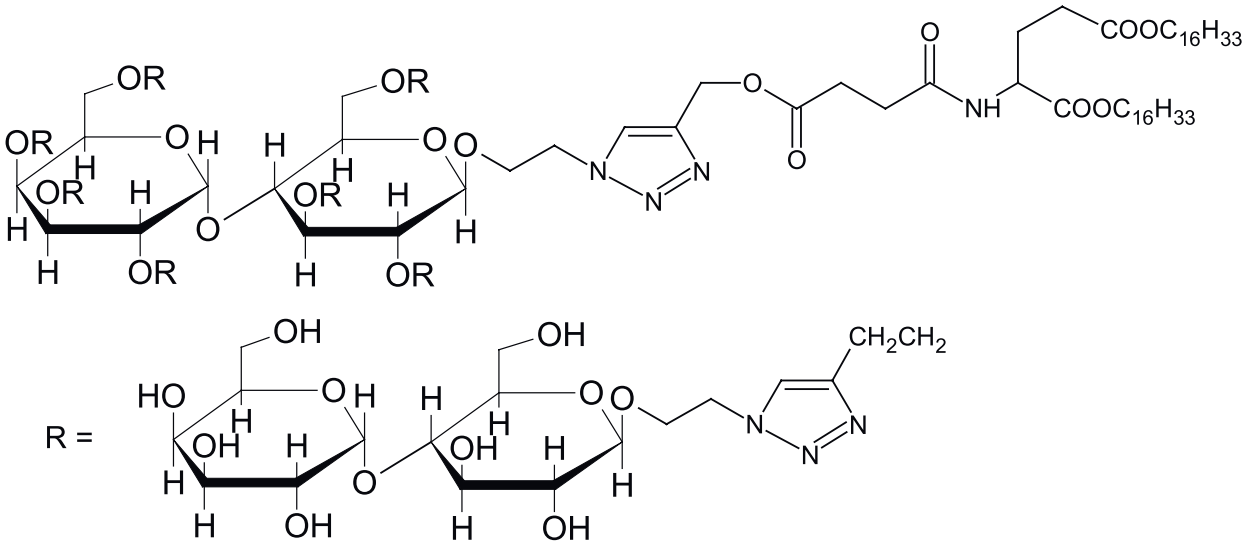
The synthesis of D-lactose based glycolipids has been reported; the molecules had spacers of various lengths, based on di-, tri-, and polyethylene glycol. These compounds (**12a–f**) were added to lipids, in the amount of 5%, during bilayer formation, after which the efficiency of binding of all three modified liposomes to the RCA1 receptor was evaluated [72].

It was expected that the longest spacer, PEG (**12c, f**), would provide the highest affinity of the complexes, due to the longer distance between the vesicle surface and the carbohydrate fragment. However, the *in vitro* results indicated that the most successful ligands were the ones with a triethylene glycol spacer (**12b, e**) [72]. The authors speculated that the PEG chains were too long, becoming a barrier between the receptors and the carbohydrate-containing ligands, thus preventing them from interaction. The same experiment was performed with a D-lactoside (**13**) containing 7 lactose residues linked with a lipopeptide through a 1,2,3-triazole cycle [73]. The results confirmed that polyvalent glycolipids also have good potential for generating targeted, modified liposomes.



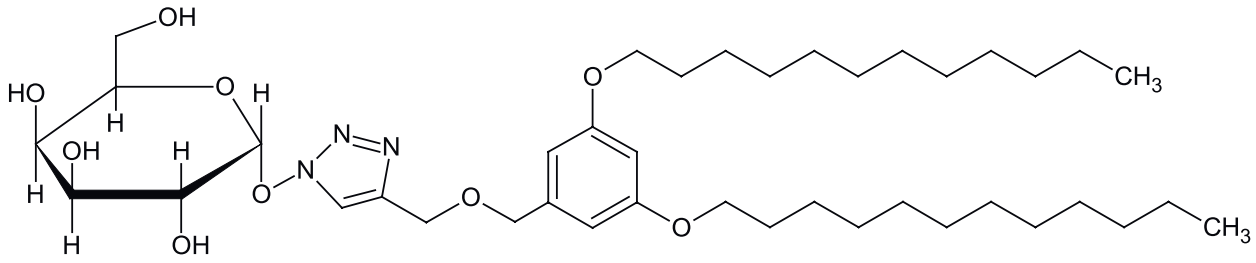
12a–f

Glycolipid **13** was used as a ligand in the structure of a cationic liposome to study its effect on the transfection efficiency for the HepG2 cell line (human hepatocellular carcinoma). Almost the same glycolipid, but with a single D-lactose residue, was used as a different ligand type. It was found that the branched ligand decreases transfection activity of the liposomal complex that carries the plasmid, due to steric hindrance and a shielding effect [74].



13

Studies of glycolipid-containing liposomes with a triazole cycle in the structure are presented in both Russian and foreign literature, indicating that such a link between the lipophilic and the hydrophilic fragments is convenient [23, 75]. In addition, D-galactose derivative **14** contains a benzene ring as a linker [75].



14

Conclusions

Liposomal delivery systems are well suited for carrying anti-tumor drugs as well as nucleic acids. They allow us to design stable and effective medications with fewer side effects, compared to "pure" active molecules. However, such delivery systems may cause toxic and immunological effects, due to unselective particle distribution in the body and the relatively large size (compared to other delivery systems), thus

activating a protective response. Apart from this, lipoplexes do not release their contents after entering the cell very effectively. It is necessary to achieve targeted drug delivery to the organ of interest by adding specific ligands to the liposomal surface. Glycolipids based on D-carbohydrates, when in the liposomes, facilitate penetration into liver cells by a receptor-mediated, clathrin-dependent endocytosis mechanism, which is activated upon contact of the carbohydrate-containing ligand fragment with the active site of the asialoglycoprotein receptor (ASGP-R). This can be addressed via the use of monovalent derivatives of carbohydrates as well as polyvalent glycoconjugates. Alterations in the ligand structure and the number of liposomal modifications can boost the therapeutic effect. The distance between the liposomal surface and the carbohydrate residue (spacer length), as well as the hydrophilic-lipophilic balance of the ligand molecule, have a great effect on affinity and the cellular response.

In summary, to ensure the minimal efficiency of the interaction between a modified particle and asialoglycoprotein receptors, it is required to add 5% of a specific ligand to the liposome, and the distance between the liposomal surface and the carbohydrate residue should be approximately 10 Å. The presence of glycolipids in a cationic liposome accelerates penetration into the cell, not only due to the receptor-mediated mechanism, but also because of the physicochemical changes in the particle's surface. A number of studies have confirmed that modified liposomal complexes exit the endosomes more easily than "standard" cationic liposomes; we can speculate that glycolipids play a helping role as well. Carbohydrate-containing liposomes are able to effectively deliver both genetic material and cytotoxic drugs into target cells, indicating that it is possible to use such compositions against a wide range of liver diseases.

Acknowledgments

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The authors declare no conflict of interest.

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About the authors:

Anastasiya S. Nosova, Master of the N.A. Preobrazhensky Chair of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). https://orcid.org/0000-0002-4905-8911

Ulyana A. Budanova, Cand. of Sci. (Chemistry), Assistant of Professor of the N.A. Preobrazhensky Chair of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). Scopus Author ID 14622352500, ResearcherID E-1659-2014, https://orcid.org/0000-0003-1702-9435

Yury L. Sebyakin, Dr. of Sci. (Chemistry), Professor, Professor of the N.A. Preobrazhensky Chair of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). Scopus Author ID 6701455145, ResearcherID T-2835-2019, https://orcid.org/ 0000-0002-7027-378X

Об авторах:

Носова Анастасия Сергеевна, магистр кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, д. 86). https://orcid.org/0000-0002-4905-8911

Буданова Ульяна Александровна, кандидат химических наук, ассистент кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, 86). Scopus Author ID 14622352500, ResearcherID E-1659-2014, https://orcid.org/0000-0003-1702-9435

Себякин Юрий Львович, доктор химических наук, профессор, профессор кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, 86). Scopus Author ID 6701455145, ResearcherID T-2835-2019, https://orcid.org/0000-0002-7027-378X

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New technological solutions in the production of high quality cyclohexanone

Svetlana V. Levanova[@], Evgeniya A. Martynenko, Alena A. Morgun, Ilya L. Glazko, Alexander B. Sokolov

Samara State Technical University, Samara 443031, Russia
[@] Corresponding author, e-mail: kinterm@mail.ru

Objectives. *The intensification of modern large-tonnage Russian technologies requires a deep investigation into the theoretical foundations of these processes and searching for ways that would significantly reduce the time and cost of their development, as well as to ensure the access of high-quality products on the world market. The aim of the work was to study the options regarding technological changes in the process of obtaining cyclohexanone at two stages: 1) oxidate (cyclohexane oxidation product after the stage of neutralization and removal of the main amount of unreacted cyclohexane) saponification and 2) end product rectification. The changes should ensure the high quality of the product without requiring significant energy and investment costs.*

Methods. *Studies of heterophase alkaline hydrolysis with NaOH solutions were carried out at 30–80 °C in the presence of and without a phase transfer catalyst (PTC) (saponification conditions in the industry are 70 °C). The homophase process was studied in the presence of KOH at 120 °C (industrial conditions for raw cyclohexanone rectification are 90–130 °C) on artificial mixtures based on industrial samples of the oxidate with the addition of model substances (oxygen-containing impurities with a main substance content of no less than 95%). Analysis of the initial and obtained products was carried out using gas-liquid chromatography and chromatography-mass spectrometry.*

Results. *The totality of the obtained data provides theoretical justification for the fact: 50–70% of esters and unsaponifiable impurities can be removed by using heterophase alkaline saponification in industrial environments. The post-treatment of crude cyclohexanone by rectification in the presence of KOH decreases the ester number by a factor of 3–5, however, the number of cyclohexanone condensation products in the bottom sharply increases. The amount of these substances varies from 10 to 20 kg/t of cyclohexanone depending on compliance with the conditions. In the presence of PTC, the conversion of esters at the saponification stage is 95–100%, aldehydes 100%, and unsaturated ketones 80%.*

Conclusions. *If the proposed technology for saponification in the presence of PTC is adopted there will be no need to use an alkali during the process of cyclohexanone rectification. This makes the process more stable, reduces the losses of cyclohexanone, reduces the amount of tars, and normalized indicators of cyclohexanone quality are attained.*

Keywords: *caprolactam, cyclohexanone, purification, impurities, phase-transfer catalysis.*

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Новые технологические решения в производстве циклогексанона высокого качества

С.В. Леванова[@], Е.А. Мартыненко, А.А. Моргун, И.Л. Глазко, А.Б. Соколов

Самарский государственный технический университет, г. Самара 443100, Россия
[@]Автор для переписки, e-mail: kinterm@mail.ru

Цели. *Интенсификация современных многотоннажных отечественных технологий требует глубокой проработки теоретических основ этих процессов и поиска путей, которые позволили бы существенно сократить сроки и затраты на их освоение и обеспечить выход на мировой рынок продукции высокого качества. Цель работы заключалась в исследовании вариантов технологических изменений процесса получения циклогексанона на стадиях омыления оксидата (продукта окисления циклогексана после отгонки основной части непрореагировавшего циклогексана) и ректификации целевого продукта, обеспечивающих его высокое качество, не требующих значительных энергетических и инвестиционных затрат.*

Методы. *Исследования гетерофазного щелочного гидролиза водными растворами NaOH проводили в интервале температур 30–80 °С в присутствии и без катализатора межфазного переноса (КМФП) (режим омыления в промышленности 70 °С); гомофазный процесс изучали в присутствии КОН при температуре 120 °С (промышленный режим ректификации циклогексанона-сырца 90–130 °С) на искусственных смесях, составленных на основе промышленных образцов оксидата с добавлением модельных веществ (кислородсодержащих примесей с содержанием основного вещества не менее 95%). Анализ исходных и полученных продуктов проводили с использованием газо-жидкостной хроматографии и хромато-масс-спектрометрии.*

Результаты. *Совокупность полученных данных дает теоретическое обоснование реальному факту: при гетерофазном щелочном омылении в промышленных условиях сложные эфиры и неомыляемые примеси могут быть удалены на 50–70%. Доочистка сырого циклогексанона при ректификации в присутствии КОН в 3–5 раз уменьшает эфирное число, однако в кубе резко возрастает количество продуктов конденсации циклогексанона, которое в зависимости от соблюдения режимов колеблется от 10 до 20 кг/т циклогексанона. В присутствии КМФП конверсия эфиров на стадии омыления составляет 95–100%, альдегидов 100%, непредельных кетонов 80%.*

Заключение. *В случае внедрения предложенной технологии омыления оксидата в присутствии КМФП отпадает необходимость использования щелочи в процессе ректификации сырого циклогексанона, что делает процесс более стабильным, сокращаются потери циклогексанона, уменьшается количество смол и достигаются нормированные показатели качества циклогексанона.*

Ключевые слова: *капролактам, циклогексанон, очистка, примеси, межфазный катализ.*

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Introduction

The intensification of modern large-tonnage Russian technologies requires an in-depth study of the theoretical basis of these processes, as well as a search for methods that would allow for a considerable reduction in the time and costs of their development and allow high-quality products to enter the world market [1–3].

The complexity of the situation regarding the production of caprolactam is that, as we know, when oxidizing cyclohexane, a large amount (more than 50) of oxygen-containing compounds (saponifiable and non-saponifiable) belonging to different classes and having different reactivity are formed. These are aldehydes, alcohols, ketones, peroxides, carboxylic acids, as well as their aliphatic and cyclohexyl esters [4–7].

The state of cyclohexanone and caprolactam can be evaluated by generally accepted quality indicators, which while rather sensitively, yet conditionally, indicate the presence of impurities of another

chemical nature. This is the permanganate index (PI) – an indicator of cyclohexanone and caprolactam quality characterizing the content of easily oxidizable compounds in the target product. For rectified cyclohexanone that meet the requirements of international standards, the permanganate index should be no more than 20 units[1] [2]. The quality of marketable caprolactam (PI: 4–5 units) directly depends on the quality of cyclohexanone. The purification of the latter in the production process has been attracting the attention of chemists and technology experts from around the world over the course of several decades with varying degrees of success [2, 8–21].

The Russian industrial production of cyclohexanone includes several successive stages to purify the oxidate obtained by cyclohexane liquid-phase oxidation in the presence of cobalt naphthenate: aqueous or aqueous-alkaline washing to remove acids, saponification (hydrolysis) of esters, and rectification of crude cyclohexanone in the presence of potassium hydroxide (0.01–1% wt. per reaction mass). The main disadvantage of the industrial purification methods is the lack of stable indicators and of control of the resulting high-boiling by-products, as well as high alkali consumption and the loss of the target product [2].

We have provided reasons about the possible options to make changes at the stage of oxidate saponification and cyclohexanone rectification to ensure its high quality. The suggested changes are based on an analysis of the available literature, from our previous studies [2, 3, 14, 17–19] and results obtained in this work. These changes do not require significant power consumption and investment expenditures.

Materials and Methods

An industrial sample of the reaction mass from the cyclohexane oxidation process obtained after the neutralization stage and removal of the basic amount of unreacted cyclohexane was used for the study, % wt.: cyclohexane – 38.8; cyclohexanone – 35.5; cyclohexanol – 24.0; impurities – 1.7.

The following compounds were chosen as models for the study: hexanal and cyclohexen-2-one as research objects among aldehydic and unsaturated/carbonyl impurities, respectively; dibutyl adipate (DBA) and dicyclohexyl adipate (DCHA), among other compounds. The latter was chosen as an ester that is most difficult to saponify.

[1]State Standard GOST 26743.7-86. Caprolactam. Method for determination of permanganate index. Moscow, Standartov Publ., 1981. 6 p. (in Russ.).

Dibutyl adipate (DBA) of at least 96% wt. purity produced by *Acros Organics* is a colorless transparent liquid, bp = 305 °C, ρ^{20} = 0.965 g/cm^3.

Dicyclohexyl adipate (DCHA) was obtained by the esterification of adipic acid (analytical grade) with cyclohexyl alcohol (chemically pure). The resulting product is a white powder, mp = 35.5 °C, bp = 324 °C, ρ^{20} = 1.037 g/cm^3. The purity of the obtained ester was at least 99.8% according to GLC.

Cyclohexen-2-ol was synthesized by cyclohexene bromination with N-bromosuccinimide followed by saponification with sodium bicarbonate according to the procedure [22]. The final product was of more than 85% wt. purity according to GLC, bp = 164–165 °C.

Cyclohexen-2-one and hexanal manufactured by *Sigma-Aldrich* were of at least 95.0 and 98.0% wt. purity, respectively.

The phase transfer catalyst, trioctylmethylammonium chloride (trade name: Aliquat-336) produced by *Acros Organics*, is a heavy, viscous, colorless liquid of more than 97.0% purity. Potassium and sodium hydroxides used in the work were chemically pure and of an analytical grade, respectively.

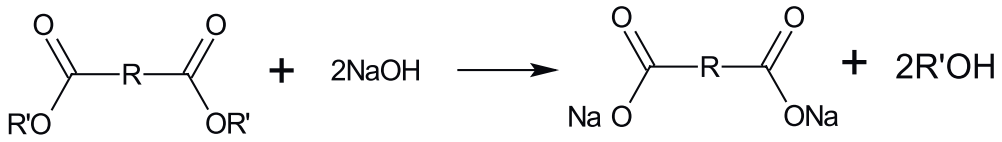
Artificial mixtures based on industrial samples of the oxidate with the addition of the studied objects in the temperature range of 30–90 °C (temperature close to the conditions of the saponification stage) in the presence of and without the phase transfer catalysts (PTC) were used in the studies.

The oxidate was analyzed chromatographically. The oxidation products were identified by chromatography-mass spectrometry. Analysis conditions: Shimadzu GCMS QP2010 Ultra apparatus, DB-1ms capillary column, 30 m × 0.25 mm; temperature control mode: 60 °C (5 min) – 10 °C/min – 260 °C; carrier gas: helium; split injection 1/100. The majority of impurities in the oxidate were identified on the basis of mass spectra available in the NIST database [23], while other components were identified according to the rules of molecular ion fragmentation [24].

Results and Discussion

The alkali-catalyzed hydrolysis of esters is irreversible. Due to this, it is widely used in industrial organic synthesis. Most esters are water-insoluble. So, hydrolysis with aqueous solutions of alkalis in a two-phase system proceeds very slowly, especially in the case of dicyclohexyl esters of dicarboxylic acids [5, 25].

The stage of ester saponification with 5–20% aqueous alkali solutions is as follows:

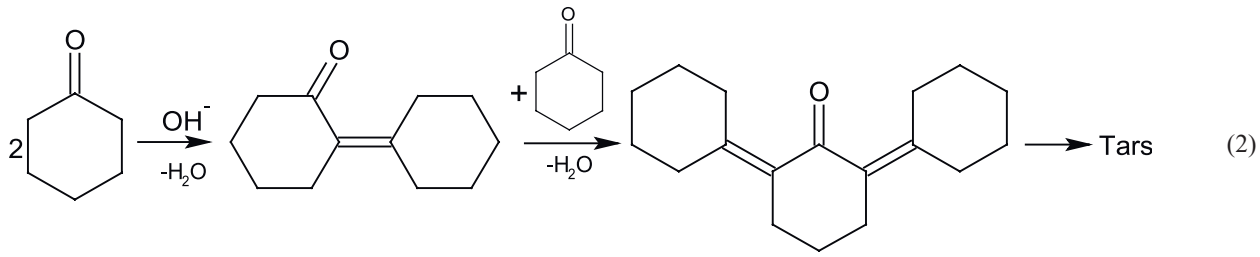


(1)

As shown by studies of industrial samples, esters can be removed at the saponification stage by only 50–70%, indicating its low efficiency. The non-catalytic reaction in the heterophase aqueous alkaline system has limitations due to the limit of the substrate solubility in the aqueous phase, which is inversely proportional to the concentration of the alkaline solution used [26]. It was assumed that the effect of the substrate dissolution in water-alkaline reactions increases, which is fundamental for intensifying the process in a perfect mixing reactor. We considered several options for a possible solution to the problem.

1) Changing the process's temperature conditions

It was shown in [17] that increasing the saponification temperature allows esters to be removed more completely. However, this results in the formation of cyclohexanone condensation products:



(2)

It was established that as the temperature increases from 30 to 120 °C, the amount of condensation products (tars) increases 10-fold.

An increase in temperature results in the need to carry out the process under pressure. This requires a change in the implementation process and, accordingly, high capital costs.

2) Reaction medium homogenization

The transition from a heterophase system to a homophase system when carrying out the process in a water-alcohol alkali solution results in a significant increase in the esters' hydrolysis rate even at lower temperatures (0–20 °C). The rate constants increase by 2–3 orders of magnitude [17]. So, the time to attain a 95% conversion of dicyclohexyl adipate (DCHA) in the case of heterophase hydrolysis is 6 hours, and in the case of homogeneous hydrolysis, 1 min. However, a disadvantage of this method is the use of a solvent for homogenization, which results in a change in the current technology and significant costs for the solvent's regeneration. Therefore, it is necessary to look for other ways of intensifying the process.

3) Using phase transfer catalysts

Phase-transfer catalysis is known to be a recognized method of intensifying heterophase processes including the saponification of esters [27, 28]. Our studies have shown [17] that the greatest increase in esters' hydrolysis rate was observed when using trioctylmethylammonium chloride $[N(C_8H_{17})_3CH_3]Cl$ (TOMAC) as a catalyst. In the concentration range of 0.2–1.4% wt. (optimally 0.5% wt.) it can be attributed to the class of phase-transfer catalysts not blocking the phase interface. When increasing concentration to more than 1.5% mass., tarring is observed. Using PTC increases the rate of esters' hydrolysis: the time to attain a 95% conversion of dicyclohexyl esters is 2 hours versus 6 hours in a non-catalytic process; the quantitative conversion of dibutyl adipate (DBA) is achieved in just a few minutes.

As mentioned above, the oxidate contains unsaponifiable impurities in addition to saponifiable products: about 6% mass. of the total amount of impurities. Among these, 3.1% are compounds containing an aldehyde group, 1.5% are compounds containing a keto group, 1.1% are hydrocarbons, and 0.1% are unsaturated compounds [18]. Under the conditions of nucleophilic catalysis, all of these compounds, except hydrocarbons, can theoretically undergo condensation and disproportionation

reactions forming high-boiling by-products. The latter should be removed from crude cyclohexanone.

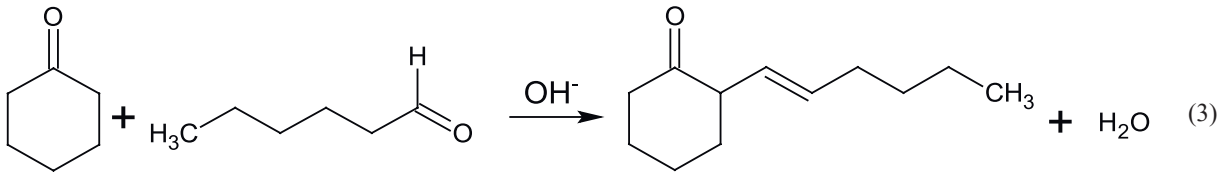
In [18], competing condensation reactions of cyclohexanone with unsaponifiable impurities were studied on model systems close to industrial conditions.

The studies were carried out under the conditions of heterophase alkaline hydrolysis with aqueous NaOH solutions in a temperature range of 30–80 °C in the presence of and without PTC (saponification mode is 70 °C), and also under homophase conditions in the presence of KOH at 120 °C (crude cyclohexanone rectification mode is 90–130 °C).

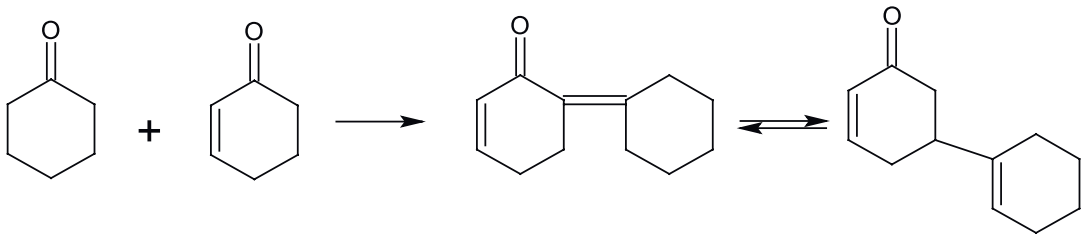
The results obtained allow us to draw the following conclusions:

– Linear aldehydes with a boiling point of 75–130 °C interact with cyclohexanone (reaction 3) under the conditions of alkaline catalysis with a conversion of 30–40% in the temperature range of 30–70 °C (saponification mode). In the presence of a PTC, the rate increases 2-fold, and the conversion reaches more than 80%.

– Unsaturated cyclic ketones behave similarly. Due to the presence of an active carbonyl group they interact with cyclohexanone at 50–70 °C. In the presence of a PTC at 70 °C, the reaction proceeds almost quantitatively (reaction 4).



(3)



(4)

The totality of the data obtained provides a theoretical justification for one fact: esters and unsaponifiable impurities cannot be completely removed under the conditions of oxidate saponification without a PTC. The oxidate PI before saponification is 350–400 units; after saponification, 80–130 units.

The further purification of crude cyclohexanone under industrial conditions is carried out by rectification in a plate column in the presence of potassium hydroxide (up to 1% wt. per reaction mass) at 90–130 °C (average temperature in the column). The reaction mixture residence time in the column is 2–2.5 hours. As shown in [14, 19, 29], the purity of crude cyclohexanone during rectification without alkali is 99.7–99.8%, the PI remains at a level of 80–100 units, and the content of readily oxidizable impurities averages $(0.3–0.5)\cdot10^{-5}$ mol of ester groups/g. If the alkali solution is supplied to the rectification column simultaneously with the feed in an amount equivalent to the content of readily oxidized impurities, then the PI will decrease to 10–20 units, and the ester number will decrease 3–5-fold $(0.1–0.3)\cdot10^{-5}$ mol of ester groups/g). However, the quantity of cyclohexanone condensation products – its dimers and trimers – dramatically increases in the rectifying still (up to 20–50 kg/t). Cyclohexanone dimers appear in the distillate and reduce the concentration of marketable cyclohexanone to 99.1–99.4%. To obtain normalized quality indicators, it is required to install an additional package or an additional rectification column [29]. However, in this case one will have to put up with the constant formation of heavy products. Their amount depends on compliance with rectification indicators (temperature, supplied alkali amounts, and hydrodynamic regimes in the column) and varies from 10 to 100 kg/t of cyclohexanone.

As the problem analysis shows, using PTC opens up a real opportunity to optimize the saponification stage, and there is no need to change the implementation process [18].

During the course of this study, a control experiment was carried out at the industrial oxidate saponification stage in the presence of and without a

PTC under the recommended conditions on the basis of kinetic studies [18]. The GLC and GC-MS analyses of reaction masses were performed before and after hydrolysis. The results are presented in the table. It can be seen that the conversion of esters including those difficult to saponify is 95–100%, aldehydes – 100%, and unsaturated ketones – 80%. In this case, rectification can be carried out without alkali.

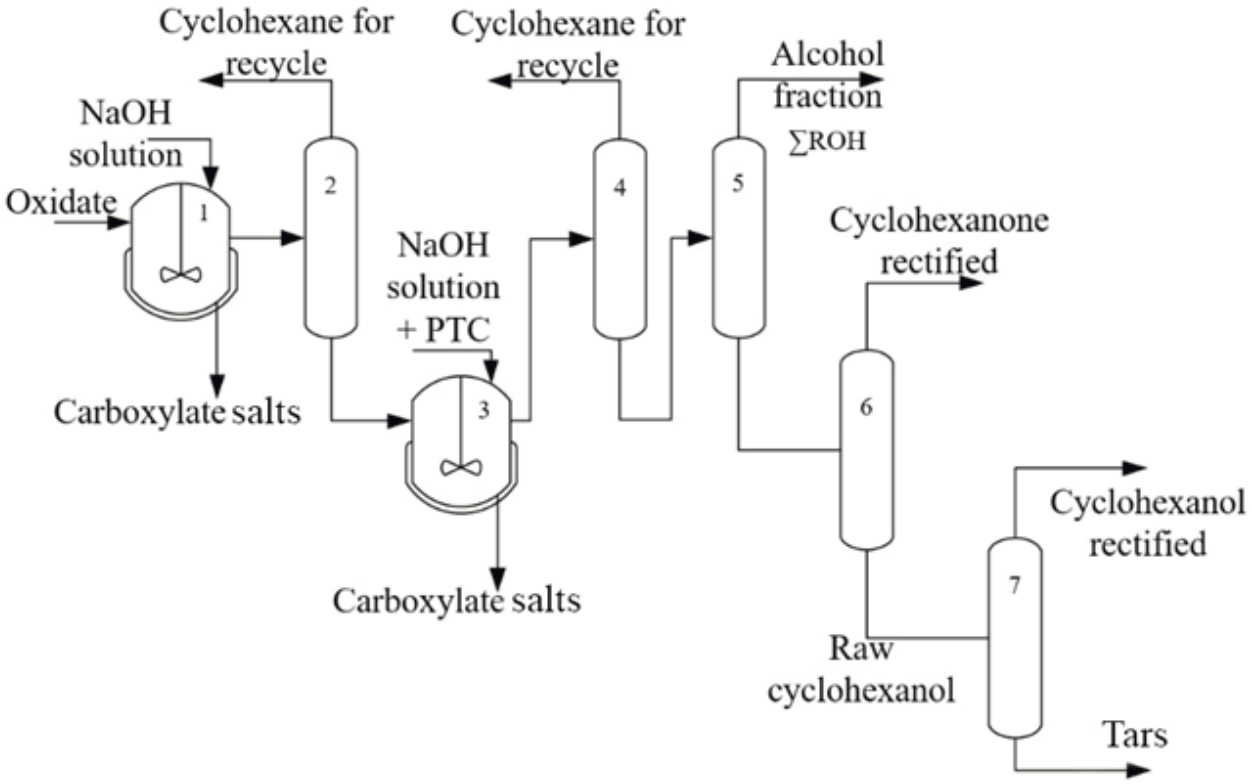
Results of the oxidate analysis before and after alkaline hydrolysis of esters under the conditions of phase-transfer catalysis

No.	Compound name	Concentration*, %	
		Before hydrolysis	After hydrolysis
1	**Ethanoic acid propyl ester**	**0.51**	**0.00**
2	Methylcyclohexane	1.38	0.82
3	Ethylcyclopentane	0.39	0.40
4	1-Pentanol	11.90	12.36
5	Toluene	1.03	1.14
6	Cyclopentanol	2.00	2.64
7	Hexanal	8.19	0.00
8	1,2-Epoxycyclohexane	4.58	1.49
9	2-Cyclohexen-1-one	3.33	0.00
10	**Methanoic acid cyclohexyl ester**	**0.39**	**0.00**
11	Hexanoic acid	0.43	0.00
12	1,5-Pentadiol	3.01	1.19
13	**Ethanoic acid cyclohexyl ester**	**1.01**	**0.00**
14	1,2-Cyclohexanediol	4.00	3.97
15	1,3-Cyclohexanediol	7.53	3.13
16	2-Ethylidenecyclohexanone	0.74	1.20
17	**Propanoic acid cyclohexyl ester**	**1.23**	**0.00**
18	**Pentanoic acid hexyl ester** **Hexanoic acid pentyl ester**	**0.63**	**0.00**
19	**Pentanoic acid cyclohexyl ester**	**0.66**	**0.00**
20	Hexadial-1,6	2.52	1.86
21	**Pentanoic acid cyclohexyl ester**	**4.19**	**0.00**
22	Hexylcyclohexyl ether	0.62	0.57
23	Dicyclohexyl ether	6.45	6.70
24	**Hexanedioic acid pentyl ester**	**0.62**	**0.00**
25	**Hexane acid cyclohexyl ester**	**0.83**	**0.00**
26	2-(1-Hydroxy-1-hexyl)cyclohexanone	13.74	7.70
27	2-Cyclohexenylcyclohexanol	0.72	2.82
28	[1,1'-Bicyclohexyl]-2-one	1.22	0.96
29	**Pentanedioc acid cyclohexyl ester**	**1.37**	**0.00**
30	2-Cyclohexylidenecyclohexanone	0.74	2.15
31	1,5-Octahydro-4a-methylnaphthalenedione-1,5	1.48	2.13
32	**Cyclopentanecarboxylic acid pentyl ester**	**1.08**	**0.00**
33	**Butanedioic acid dicyclohexyl ester**	**1.79**	**0.00**
34	1'-Hydroxy-[1,1'-bicyclohexyl]-one-2	0.92	40.42
35	1,2'-Dihydroxy-[1,1'-bicyclohexyl]	1.16	0.00
36	Bicyclohexyl-2,3'-dione	0.62	1.01
37	**Cyclopentanecarboxylic acid cyclohexyl ester**	**1.27**	**0.00**

Table. Continued

No.	Compound name	Concentration*, %	
		Before hydrolysis	After hydrolysis
38	Bicyclohexyldiones	2.41	5.33
39	**Hexanedioic acid dibutyl ester**	**1.28**	**0.00**
40	**Hexanedioic acid dicyclohexyl ester**	**2.01**	**0.00**
Σ		**100.0**	**100.0**

* The content is presented as a percentage of the total impurity content equal to 1.7%.



Scheme of an industrial process for cyclohexanone isolation and purification with the suggested optimization options.

The Figure shows a block diagram of an industrial process for cyclohexanone isolation and purification with the suggested optimization options at the oxidate saponification and crude cyclohexanone rectification stage.

After cyclohexane oxidation, the oxidate goes to the neutralization stage, where it is mixed with an aqueous alkali solution in a cascade of mixing apparatuses (item 1) at a temperature of 140–160 °C and a pressure of 1.3–1.65 MPa. The neutralization of organic acids and the partial hydrolysis of esters occur. Next, the organic layer enters the distillation column (item 2), where the bulk of the unreacted cyclohexane is distilled off. The distillation residue enters a cascade of apparatuses with stirrers (saponification reactors), where an aqueous solution of alkali with added PTC is supplied (item 3). The temperature in the reactors rises sequentially from 60 °C, and in the last reactor it reaches 90 °C. Under these conditions, the quantitative decomposition of non-readily saponifiable esters and the condensation of saturated and unsaturated aldehydes occur. After

saponification, the organic layer is sent to column 4 for residual cyclohexane removal. Along with other by-products, the reaction mixture contains alcohols: amyl alcohol, butyl alcohol, cyclopentanol, ketones, etc. (the alcohol fraction). They are distilled off in column 5 (a top pressure of no more than 0.01 MPa, the top temperature of the column is no more than 160 °C).

Distillation columns 6 and 7 are designed for the separation of cyclohexanone (bp = 155 °C) and cyclohexanol (bp = 160 °C). It was suggested on the basis of the study results to exclude alkali supply to column 6. Columns 6 and 7 operate under a vacuum at a column top pressure of no more than 10 kPa and 6.67 kPa, respectively. For rectified cyclohexanone distillation, the column's top temperature is no more than 90 °C, and the rectifying still temperature is no more than 125 °C. In column 7, rectified cyclohexanol is separated from high-boiling components (tars). The column's top temperature is 74–88 °C, and the rectifying still temperature is no more than 175 °C.

Conclusions

On the basis of the analysis, relevant Russian and foreign information, and our own research it was found that in the operation of existing industrial plants for cyclohexanone production:

1. The main disadvantage of industrial methods for cyclohexanone purification is the lack of stability indicators and of control over the resultant high-boiling by-products, high alkali consumption and target product loss.

2. The use of PTC makes it possible to optimize the saponification stage with no need to change the implementation process and no additional investment costs: the conversion of non-readily saponifiable esters increases 3–4-fold (up to 90–96%), and the carbonyl impurities condensation rate increases 2-fold.

3. This, in turn, enables one to avoid using alkali in crude cyclohexanone rectification, reduces the target product loss, and decreases the amount of tars 1.5–2-fold. The standard indicators of cyclohexanone quality are attained: purity more than 99.9% and PI 18–20 units.

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The authors declare no conflict of interest.

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About the authors:

Svetlana V. Levanova, Dr. of Sci. (Chemistry), Professor of the Chair "Technology of Organic and Petrochemical Synthesis", Samara State Technical University (244, Molodogvardeiskaya ul., Samara 443100, Russia).

Evgeniya A. Martynenko, Cand. of Sci. (Chemistry), Researcher of the Chair "Chemical Technology of Oil and Gas Refining", Samara State Technical University (244, Molodogvardeiskaya ul., Samara 443100, Russia).

Alena A. Morgun, Master's Degree Candidate, Engineer of the Chair "Technology of Organic and Petrochemical Synthesis", Samara State Technical University (244, Molodogvardeiskaya ul., Samara 443100, Russia).

Ilya L. Glazko, Cand. of Sci. (Chemistry), Associate Professor of the Chair "Technology of Organic and Petrochemical Synthesis", Samara State Technical University (244, Molodogvardeiskaya ul., Samara 443100, Russia).

Alexander B. Sokolov, Cand. of Sci. (Chemistry), Associate Professor of the Chair "Technology of Organic and Petrochemical Synthesis", Samara State Technical University (244, Molodogvardeiskaya ul., Samara 443100, Russia).

Об авторах:

Леванова Светлана Васильевна, доктор химических наук, профессор кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» (443100, г. Самара, ул. Молодогвардейская, д. 244).

Мартыненко Евгения Андреевна, кандидат химических наук, научный сотрудник кафедры «Химическая технология переработки нефти и газа» ФГБОУ ВО «Самарский государственный технический университет» (443100, г. Самара, ул. Молодогвардейская, д. 244).

Моргун Алена Александровна, магистрант, инженер кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» (443100, г. Самара, ул. Молодогвардейская, д. 244).

Глазко Илья Леонидович, кандидат химических наук, доцент кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» (443100, г. Самара, ул. Молодогвардейская, д. 244).

Соколов Александр Борисович, кандидат химических наук, доцент кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» (443100, г. Самара, ул. Молодогвардейская, д. 244).

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Influence of reactor temperature conditions on the recycle flow rate

Sergey L. Nazanskiy[@], Arkadiy V. Solokhin

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

Objectives. *The problem of optimizing chemical flow sheets according to energy costs associated with recycling flows is at present quite relevant. The current article investigates the influence of temperature conditions on the recycle flow rate, securing the specified conversion of the recycled flow sheet "reactor – separation unit."*
Methods. *The study's main method is the mathematical simulation of a recycled flow sheet based on material balance and chemical kinetics equations. This model assumes that the separation unit can form the recycle and outlet flows of any specified compositions.*
Results. *The mathematical model recycle flows provides the full reagent conversion of recycled flow sheet depends on the reactor type and the temperature conditions in it. It was established that the dependence of the recycle flow rate on the reactor temperature for endothermic reactions has monotonously decreasing shape. The most interesting are exothermic reactions for which the dependence of the recycle flow rate on the reactor temperature curve has a minimum. It is proved that the "reactor – separation unit" system with the plug flow reactor has lower optimal recycle flow rate than the recycled system with the continuous stirred tank reactor. For the adiabatic reactor the dependence of total conversion recycle flow rate on the inlet reactor temperature was investigated. It has been proven that the optimal recycle flow rate is equal to the minimum recycle flow rate for total conversion in the "reactor – separation unit" system.*
Conclusions. *It has been established that isothermal operation conditions are the best in terms of the recycle flow rate, securing the specified conversion for the system.*

Keywords: *recycled systems, reactor temperature conditions, recycle flows, conversion on system.*

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Влияние температурного режима реактора на величину рециркулирующего потока

С.Л. Назанский[@], А.В. Солохин

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

Цели. *Исследование влияние температурного режима в реакторе на величину рецикла, обеспечивающего заданную конверсию в рециркуляционной системе «реактор – блок разделения».*
Методы. *Математическое моделирование на основе уравнений материального баланса и химической кинетики. Предполагается, что блок разделения может создавать рецикл и выходной поток любого заданного состава.*
Результаты. *В вычислительном эксперименте определены величины рециклов, обеспечивающие 100%-ную конверсию в системе в зависимости от типа реактора и температурного режима в нем. Было установлено, что для эндотермических реакций зависимость величины рецикла от температуры имеет монотонно убывающий характер. Наибольший интерес представляет случай экзотермических реакций, для которых зависимость рецикла от температуры имеет вид кривой с минимумом. Показано, что для случая реактора идеального вытеснения оптимальный рециркулирующий поток меньше, чем для случая реактора идеального смешения. Для случая адиабатического реактора исследована зависимость рецикла, обеспечивающего 100%-ную конверсию в системе от температуры на входе в реактор. Установлено, что оптимальной является некоторая минимальная температура, ниже которой 100%-ная конверсия не может быть достигнута.*
Заключение. *Изотермический режим в реакторе идеального вытеснения является наилучшим с точки зрения величины рецикла, обеспечивающей заданную конверсию в системе «реактор – блок разделения».*

Ключевые слова: *рециркуляционные системы, температурный режим реактора, рецикловые потоки, конверсия в системе.*

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Introduction

In the vast majority of industrial chemical flow sheets (CFS) there are recirculating flows, the presence of which in some cases allows one to achieve high values of conversion and selectivity in the system [1–3]. On the other hand, the values of recirculating flows directly affect the energy costs of CFS associated with pumping flows and with a change in the flow aggregation state [4, 5]. The task of optimizing the CFS according to energy costs is relevant. At the pre-design development stage, it can be reduced to the problem of optimizing the CFS according to the recirculating flow value, which is necessary to achieve a given conversion rate in the system.

The present work is devoted to the nature of the recycle value relationship in the "reactor – separation unit" system with temperature conditions in various types of reactors for the simplest reversible reaction A⇔B. The system works in a stationary mode.

Mathematical model of a recycled system

The structure of the "reactor – separation unit" recycled system is shown in Fig. 1.

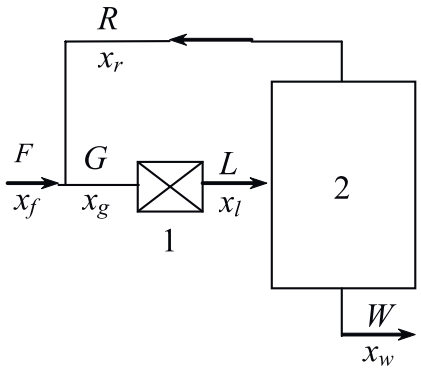

Fig. 1. "Reactor – separation unit" recycled system: 1 – chemical reactor; 2 – reaction separation unit (*See further down in the text for a list of symbols*).

To form a mathematical model of the system, we write material balances according to their elements (flow designations are shown in Fig. 1). We will use molar quantities, so flows will be measured in kmol/h, and concentrations in molar fractions.

Material balance for the mixer:

$$G = F + R \quad (1)$$

$$Gx_g = Fx_f + Rx_r \quad (2)$$

for the separation unit:

$$L = W + R \quad (3)$$

$$Lx_l = Wx_W + Rx_r \quad (4)$$

for the reactor:

$$G = L \quad (5)$$

$$Lx_l = Gx_g - P \quad (6)$$

and for the system:

$$Fx_f - Wx_w = P \quad (8)$$

$$F = W \quad (9)$$

In equations (6) and (8), P is the reactor productivity characterizing the amount of reagent converted into a product per unit time, kmol/h.

For further analysis of the system, the assumption is made that the separation unit is capable of creating recycle R and product W flows of any given composition, even up to pure components. Pure reagent A (x_f = 1) in the amount of F (kmol/h) is supplied to the system input. The recycle also consists of a pure reagent A (x_r = 1). The chemical reaction rate w obeys the power law in the form:

$$w = k^+x - k^-(1-x), \quad (10)$$

where x is the mole fraction of reagent A; $w = k^+$, k^- are the rate constants of the forward and reverse reactions, respectively, kmol/(m^3·h).

Under the condition of 100% conversion in the system, reagent A is absent in the product flow of the system, then x_w = 0. In this case, from (8) it follows

$$P = F, \quad (11)$$

that is, the reactor productivity corresponds to the amount of reagent supplied to the system input.

Recirculation system with a continuous ideally stirred-tank reactor

For a continuous ideally stirred-tank reactor (CISTR), in which the temperature and composition are identical throughout the entire volume, the expression for productivity is the multiplication of the volume by the reactor and the reaction rate, and with (10) in mind has the form:

$$P = Vw = V(k^+ + k^-)x_l - Vk^-. \quad (12)$$

Applying condition (11) to (12), we obtain the expression for the continuous ideally stirred-tank reactor's composition, which is realized at 100% conversion in the system:

$$x_l = x_{100} = \frac{F + Vk^-}{V(k^+ + k^-)}. \quad (13)$$

The material balance of the separation unit, taking into account (9), is written as:

$$L = F + R \quad (14)$$

$$Lx_l = Fx_W + Rx_r \quad (15)$$

Substituting expressions (14) and (13) in (15), and also assuming the assumption x_r = 1, we obtain:

$$(F + R_{100})\frac{F + Vk^-}{V(k^+ + k^-)} = R_{100}. \quad (16)$$

Let us express from (16) the value of the recycle corresponding to 100% conversion:

$$R_{100} = \frac{F(F + Vk^-)}{Vk^+ - F}. \quad (17)$$

As can be seen, the recycle value corresponding to 100% conversion in the system is determined by the amount of reagent F in the system inlet, the reactor volume, and the rate constants of the forward and reverse reactions, which, in turn, depend on the temperature in accordance with the Arrhenius equation:

$$k^+ = k_0^+ e^{-\frac{E^+}{R_g T}}, k^- = k_0^- e^{-\frac{E^-}{R_g T}}, \quad (18)$$

where k_0^+, k_0^- are pre-exponential factors for the rate constants of the forward and reverse reactions,

respectively, h^{-1}; E^+, E^- are activation energies for forward and reverse reactions, respectively, J/mol; R_g = 8.314 J/(mol·K) is the universal gas constant.

Substituting (18) into (17), we obtain an expression showing the temperature dependence of R_{100}:

$$R_{100} = \frac{F^2 + FVk_0^- e^{\frac{E^-}{R_g T}}}{Vk_0^+ e^{\frac{E^+}{R_g T}} - F}. \quad (19)$$

From (19) it follows that the positive recycle values R_{100} will be obtained with non-negative values of the denominator. So, for fixed values of the reactor volume, power flow, and the parameters of the Arrhenius equation, there is a minimum temperature in the reactor at which the desired reactor productivity and conversion in the system can be achieved:

$$T \geq T_{\min} = \frac{E^+}{R_g}\left[Ln\left(\frac{Vk_0^+}{F}\right)\right]^{-1}. \quad (20)$$

It is also seen from (19) that $R_{100} \to \infty$ at $T \to T_{\min}$. Therefore, the minimum temperature determined by (20) is the vertical asymptote of dependence (19).

During an unlimited increase in temperature, the recycle value R_{100} tends to the limit value:

$$R_{100}^{\infty} = \lim_{T\to\infty} R_{100} = \frac{F^2 + FVk_0^-}{Vk_0^+ - F}. \quad (21)$$

To identify the nature of the dependence $R_{100}(T)$ (19), we write the expressions for the derivative taking into account (18):

$$\frac{dR_{100}}{dT} = -\frac{(E^+ + E^-)F^2V(k^+ + k^-) + (E^+ - E^-)F^2V^2k^+k^-}{R_gT^2(Vk^+ - F)^2}. \quad (22)$$

It can be seen from (22), that for $E^+ \geq E^-$ the derivative is negative at any temperature; consequently, the dependence $R_{100}(T)$ has a monotonously decreasing character, shown in Fig. 2, curve a. In the case $E^+ < E^-$ the derivative can be both positive and negative, and then extrema can be on the dependence $R_{100}(T)$.

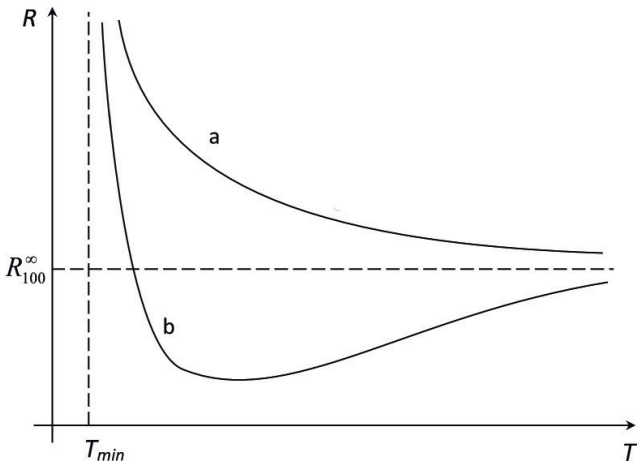

Fig. 2. Qualitative view of the temperature dependence of recycle value R_{100} in the continuous ideally stirred-tank reactor. Ratio of activation energies of forward and reverse reactions: a) $E^+ \geq E^-$; b) $E^+ < E^-$.

From published data [6] it is known that in the case of exothermic reactions (and this is just the case $E^+ < E^-$) the dependence of the reactor productivity on temperature, at fixed values of the reactor load and the reactor volume, has the form of a curve with a maximum, in other words, there is some optimal temperature corresponding to maximum performance. The presence of a maximum is explained by the fact that, in the case of $E^+ < E^-$ as the temperature increases, the rate constant k^- increases faster than the rate constant k^+. This leads to a greater increase in the rate of reverse reaction and, as a consequence, to a decrease in reactor productivity. On the other hand, at a fixed temperature, the productivity of the reactor is directly related to the reactor load G, which in our case, in accordance with (1), consists of power and recycle flows. So, it can be expected that at temperatures other than optimal, a higher recycle value will be required to achieve a given productivity value than at an optimum temperature. It follows that for the case of $E^+ < E^-$ the dependence curve $R_{100}(T)$ will have a minimum, as shown in Fig. 2, curve b.

Recirculation system in an ideal plug-flow reactor

Since the composition of the reaction mixture and, consequently, the reaction rate in an ideal plug-flow reactor (IPFR) are continuously changing along the length of the reactor, the expression for the productivity value has the form of:

$$P = \int_0^V w(u)du\,, \tag{23}$$

wher u is the current volume of the reactor, V is the total reactor volume.

At this stage, we are taking into consider the case of an isothermal reactor, in which the temperature is the same throughout the volume. We obtain the form of the speed dependence on the current reactor volume, which is a part of (23). From the material balance for an infinitely small element of volume it follows that:

$$-(F+R)dx - wdu = 0\,. \tag{24}$$

We express from (10) the mole fraction x:

$$x = \frac{w + k^-}{k^+ + k^-}\,. \tag{25}$$

Differentiating the left and right sides of (25), we obtain:

$$dx = \frac{1}{k^+ + k^-}dw\,. \tag{26}$$

Substituting (26) into (24), we obtain the differential equation with separable variables:

$$\frac{dw}{du} + \frac{k^+ + k^-}{F+R}w = 0\,,$$

whose solution with the initial condition of $w\,(u = 0) = w_0$ will have the form:

$$w = w_0 e^{-u\frac{k^+ + k^-}{F+R}}\,. \tag{27}$$

From (10) it follows that under the assumptions made on the feed and recycling, consisting of a pure reagent, the initial velocity will be equal to the rate constant of the forward reaction:

$$w_0 = k^+\,. \tag{28}$$

We substitute (27) and (28) into (23), after integration we obtain:

$$P = \frac{k^+(R+F)}{k^+ + k^-}\left[1 - e^{-\frac{V(k^+ + k^-)}{R+F}}\right]. \tag{29}$$

Combining (29) with the condition of 100% conversion (11), we obtain the equation for the recycle value R_{100}:

$$\frac{k^+(R_{100}+F)}{k^+ + k^-}\left[1 - e^{-\frac{V(k^+ + k^-)}{R_{100}+F}}\right] - F = 0\,. \tag{30}$$

From the form of equation (30) it follows that its solution with respect to the recycle value R_{100} is possible only via numerical methods.

Figure 3 shows the results of solution (19) and (30) with the following initial data: the system power flow is F = 100 kmol/h; the reactor volume is V = 1 m^3; the Arrhenius equation parameters for the forward reaction rate constant are $k_0^+ = 4.75\cdot10^{14}$ kmol/(m^3·h), E^+ = 78 000 J/mol, for the reverse reaction $k_0^- = 2.37\cdot10^{18}$ kmol/(m^3·h), and E^- = 107 000 J/mol.

Figure 3 shows that in the temperature range under consideration, the dependences of the recycle value on temperature for both types of reactors have a characteristic minimum. It should also be noted that the minimum R_{100} recycle value for the case of an ideal plug flow reactor is less (curve a) than for the case of a continuous ideally stirred-tank reactor (curve b). This is due to the fact that for the same volume and load values, an ideal plug flow reactor is characterized by higher productivity; therefore, to achieve a given productivity, it requires a lower load, and, therefore, a recycle.

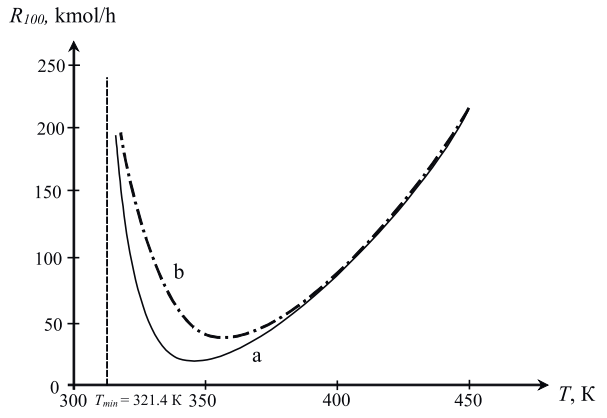

Fig. 3. Temperature dependence of the recycle value R_{100} on the recirculation system with isothermal reactors of various types: a) an ideal plug-flow reactor; b) a continuous ideally stirred-tank reactor.

Recirculation system in an adiabatic plug-flow reactor (under ideal conditions)

In the case of an adiabatic plug-flow reactor, the temperature along the length of the reactor changes in accordance with the thermal effect of the reaction, and therefore, the equation (30) cannot be used to find the recycle value. For this case, the mathematical model includes non-linear differential equations for material and heat balance with respect to composition and temperature, which cannot be solved analytically. Therefore, the adiabatic reactor with recycle was simulated in the Aspen Plus software package in accordance with the scheme shown in Fig. 4.

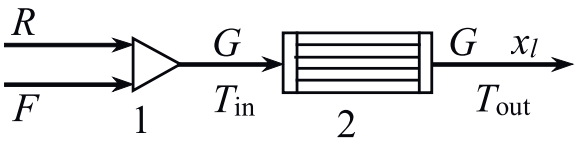

Fig. 4. Scheme of an adiabatic plug-flow reactor: 1 – mixer; 2 – reactor.

The reactor was modeled as a tubular one with a tube diameter of 0.05 m and a tube length of 3 m. The power value F, kinetic parameters, and the reactor volume were set to be the same as in the previous calculation for an isothermal reactor. The change in the reaction's enthalpy is ΔH = –30 000 J/mol. In the course of calculations, at various values of the temperature of the incoming flow T_{in}, the value of the recycle R was determined in which the condition (31) was satisfied:

$$G(1-x_l) = F\,, \qquad (31)$$

which, in turn, corresponds to the condition of 100% conversion in the system (11). The calculation results are presented in Fig. 5.

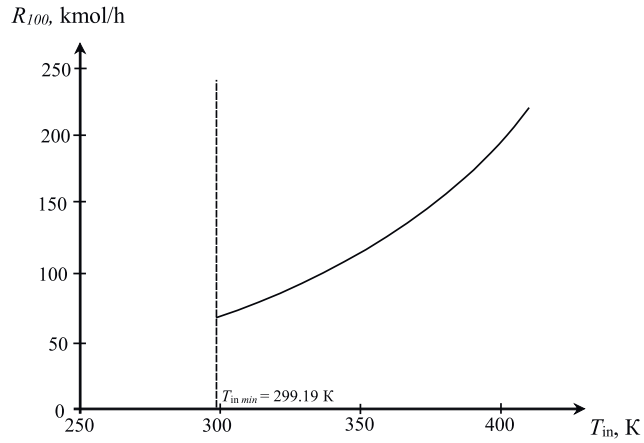

Fig. 5. Temperature dependence of the recycle value R_{100} for a recirculation system with an adiabatic plug-flow reactor.

Figure 5 shows that the optimal recycle value R_{100} for the temperature at the reactor's inlet corresponds to a minimum temperature $T_{in\ min}$, below which the reactor's productivity corresponding to the condition in (31) is not achieved. Therefore, at $T < T_{in}$ min the achieving of 100% conversion is impossible in a system with an adiabatic plug-flow reactor of a given volume. Figure 6 shows the temperature and reagent concentration profiles along the length of the reactor with optimal recycling.

Figure 6 shows that a change in temperature and composition occurs along the entire length of the reactor, and the rate of change of temperature is consistent with the rate of change in the composition. The result obtained indicates the effective work of the entire reactor volume. For comparison, Figure 7 shows the temperature and composition profiles at T_{in} = 310 K and R_{100} = 76.6 kmol/h.

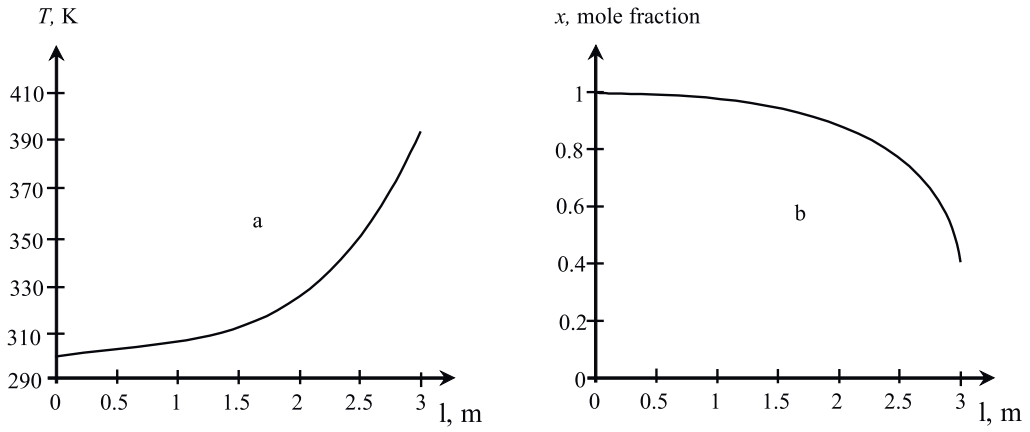

Fig. 6. Temperature (a) and composition (b) profiles along the length of the reactor at an optimal recycle value R_{100} = 68.4 kmol/h and $T_{in} = T_{in\ min}$ = 299.19 K.

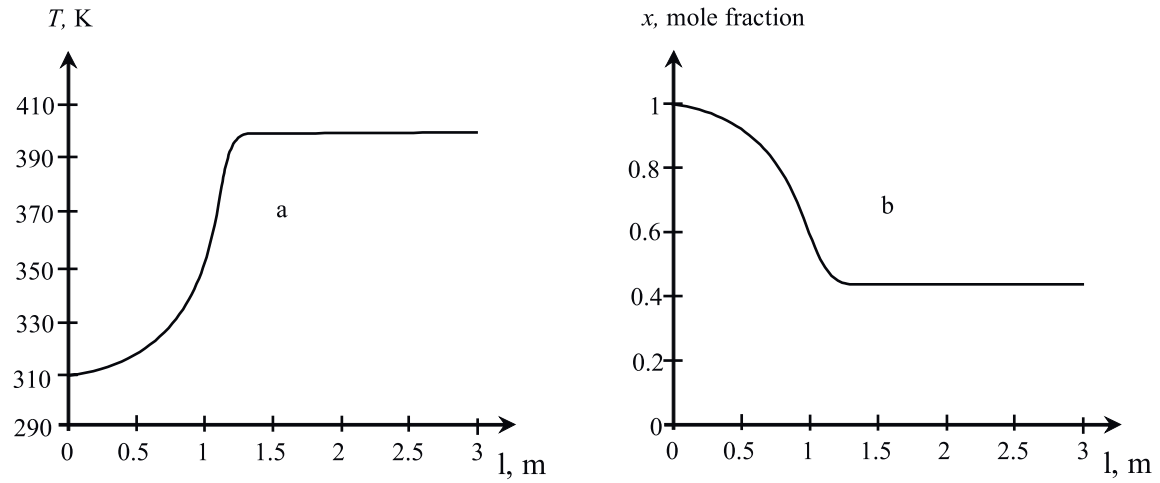

Fig. 7. Temperature (a) and composition (b) profiles along the length of the reactor with a recycle value R_{100} = 76.6 kmol/h and T_{in} = 310 K.

It can be seen from Fig. 7 that, at a reactor length of $l > 1.3$ m, the temperature and composition cease to change. This is due to the fact that the composition in the reactor becomes almost equilibrium and the rate of chemical conversion is close to zero. Therefore, this part of the length of the reactor does not consume the reagent and does not produce the product, in other words, it does not operate. Thus, with an increase in the temperature of the inlet flow, the desired reactor productivity can be achieved with a smaller reactor volume, but this requires a large recycle value. From the result obtained, it can be concluded that the optimal value of the recycle necessary to achieve a given conversion corresponds to the most efficient reactor work. It should be noted that this conclusion is valid under the assumption made on an idealized separation unit forming the recycle of a certain composition.

A comparison of the results presented in Figs. 3 and 5 shows that for the isothermal plug-flow reactor (under ideal conditions), the optimal value of R_{100} is less than for the adiabatic reactor (under ideal conditions). Therefore, in order to achieve the optimal recycle value corresponding to the given conversion in the system, it is necessary to maintain the isothermal mode in the reactor. It should be noted that for reactions with a significant thermal effect, it is much more difficult to achieve an isothermal mode in the reactor than an adiabatic one. In addition, with a lower recycle value for an isothermal reactor, there will be additional costs for the refrigerant supplied to the annulus of the reactor to remove the heat of the reaction.

Conclusions

So, according to a reversible reaction A⇔B with a fixed recycle composition, a correlation between the recycle value securing the given conversion in the "reactor – separation unit" system and the temperature in the reactor has been revealed. For an exothermic reaction, the possibility of the existence of an optimum temperature corresponding to the minimum value of the recycle is shown.

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The authors declare no conflict of interest.

List of symbols used in this article: A, B – reaction mixture components; E^+, E^- – activation energy of forward and reverse reactions, respectively, J/mol; F – power flow of the "reactor – separation unit" system, kmol/h; G – flow entering the reactor, kmol/h; k^+, k^- – rate constant of forward and reverse reactions, respectively, kmol/(m^3·h); k_0^+, k_0^- – pre-exponential factor in the Arrhenius equation for the forward and reverse reactions, respectively, kmol/(m^3·h); l – reactor length, m; L – flow, leaving the reactor, kmol/h; P – reactor productivity, kmol/h; R – recycle flow, kmol/h; R_{100} – recycle flow value corresponding to 100% conversion, kmol/h; R_{100}^{∞} – recycle limit corresponding to infinite temperature, kmol/h; R_g – universal gas constant, 8.314 J/(mol·K); T – temperature, K; T_{min} – the minimum temperature in the reactor at which it is possible to achieve 100% conversion in the "reactor – separation unit" system, K; T_{in} – adiabatic reactor inlet temperature, K; T_{out} – adiabatic reactor outlet temperature , K; $T_{in\ min}$ – minimum adiabatic reactor inlet temperature, at which 100% conversion in the "reactor – separation unit" system is possible, K; u – current reactor volume, integration variable (23), m^3; V – total reactor volume, m^3; W – the flow leaving the "reactor – separation unit" system, kmol/h; x – molar fraction of reagent A in the reaction mass; x_f – molar fraction of reagent A in the feed flow of the "reactor – separation unit" system; x_g – molar fraction of reagent A in the flow entering the reactor; x_l – molar fraction of reagent A in the flow leaving the reactor; x_r – molar fraction of reagent A in the recycle flow; x_w – molar fraction of reagent A in the flow leaving the "reactor – separation unit" system.

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About the authors:

Sergey L. Nazanskiy, Cand. of Sci. (Engineering), Associate Professor of the Chair 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). https://orcid.org/0000-0002-6612-4343. E-mail: nazanski@yandex.ru

Arkadiy V. Solokhin, Dr. of Sci. (Engineering), Professor of the Chair 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). https://orcid.org/0000-0002-6613-6489. E-mail: ark.solokhin@yandex.ru

Об авторах:

Назанский Сергей Леонидович, кандидат технических наук, доцент кафедры основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). https://orcid.org/0000-0002-6612-4343. E-mail: nazanski@yandex.ru

Солохин Аркадий Викторович, доктор технических наук, профессор кафедры основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). https://orcid.org/0000-0002-6613-6489. E-mail: ark.solokhin@yandex.ru

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Flow and mixing processes in a passive mixing microfluidic chip: Parameters' estimation and colorimetric analysis

Kirill A. Sarbashev[1,2], Marina V. Nikiforova[1,3,@], Darya P. Shulga[1,3], Margarita A. Shishkina[1], Sergey A. Tarasov[1,4]

[1]Materia Medica Holding, Moscow 129272, Russia
[2]Russian State Agrarian University – Timiryazev Moscow Agricultural Academy, Moscow 127550, Russia
[3]Peoples' Friendship University of Russia (RUDN), Moscow 117198, Russia
[4]Institute of General Pathology and Pathophysiology, Moscow 125315, Russia
[@]Corresponding author, e-mail: nauka@materiamedica.ru

Objectives. *The development of microfluidic systems is one of the promising areas of science and technology. In most procedures performed using microfluidic systems, effective mixing in microfluidic channels of microreactors (chips) is of particular importance, because it has an effect on the sensitivity and speed of analytical procedures. The aim of this study is to describe and evaluate the major parameters of the flow and mixing processes in a passive microfluidic micromixer, and to develop an information-measuring system to monitor the dynamics of flow (mixing) of liquids.*

Methods. *This article provides an overview of the concept of microfluidic mixing chips (micromixers) and their classification, and analyzes the kinds of points of mixing and microfluidic channels for mixing. The article presents the description and calculations of the hydrodynamic similarity criteria (Reynolds, Dean and Peclet numbers), which are the critical parameters for creating and optimizing micromixers (for example, straight and curved channels in the flow rate range between 100 and 1000 μl/min). We have developed an information-measuring system to monitor the dynamics of flow (mixing) of liquids in a microfluidic channel, which consists of a microscope with a digital eyepiece (LOMO MIB, Russia), an Atlas syringe pump (Syrris Ltd., UK) and a passive mixing microfluidic chip of interest (made of clear glass). This system was designed to quickly illustrate the principles of mixing in microfluidic channels of different configurations.*

Results. *The developed system has allowed carrying out a colorimetric analysis of the modes and dynamics of mixing two liquids (5% aqueous solution of azorubine dye and water) at the T-shaped mixing point, at the straight and curved (double-bend shaped) sections of the microfluidic channel of the passive-type micromixer with flow rates varying from 100 to 400 μl/min.*

Conclusions. *According to the obtained calculations, the share of the advective mixing processes (formation of vortex flows and increase in the contact area of the mixed substances) in flowing*

liquids is significantly higher in curved microchannels. The developed information-measuring system to monitor the dynamics of flow (mixing) of liquids in a microfluidic channel is a convenient tool for optimizing the mixing modes in the channels of micromixers, and for designing new configurations of channels in microchips. It would allow intensifying processes and increasing the performance of microfluidic systems.

Keywords: *microfluidics, microfluidic chip, passive micromixer, criteria of hydrodynamic similarity, colorimetric analysis.*

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Процессы течения и перемешивания в микрофлюидном чипе пассивного смешивания: оценка параметров и цветометрический анализ

К.А. Сарбашев[1,2], М.В. Никифорова[1,3,@], Д.П. Шульга[1,3], М.А. Шишкина[1], С.А. Тарасов[1,4]

[1]ООО «НПФ «Материа Медика Холдинг», Москва 129272, Россия
[2]Российский государственный аграрный университет – МСХА им. К.А. Тимирязева, Москва 127550, Россия
[3]Российский университет дружбы народов, Москва 117198, Россия
[4]Научно-исследовательский институт общей патологии и патофизиологии, Москва 125315, Россия
[@]Автор для переписки, e-mail: nauka@materiamedica.ru

Цели. *Разработка микрофлюидных систем является одним из перспективных направлений развития науки и техники. В большинстве процедур, проводимых с помощью микрофлюидных систем, важное значение имеет эффективное перемешивание в микрофлюидных каналах микрореакторов (чипов), которое влияет на чувствительность и быстроту аналитических процедур. Целью работы являлись описание и оценка основных параметров течения и смешивания в микрофлюидном микросмесителе пассивного смешивания и разработка информационно-измерительной системы контроля динамики протекания (перемешивания) жидкостей в нем.*

Методы. *Данная статья содержит обзор концепции микрофлюидных чипов смешивания (микросмесителей), их классификацию, обсуждены разновидности точек смешивания и микрофлюидных каналов смешивания. Приведены описание и расчеты критериев гидродинамического подобия (числа Рейнольдса, Пекле и Дина), являющихся критическими параметрами для разработки и оптимизации микросмесителей (на примере прямого и изогнутого каналов в диапазоне скоростей потоков от 100 до 1000 мкл/мин). Разработана информационно-измерительная система контроля динамики протекания (перемешивания) жидкостей в микрофлюидном канале, состоящая из микроскопа с цифровым окуляром («ЛОМО» МИБ, Россия), шприцевого насоса Atlas (Syrris Ltd., Великобритания) и исследуемого микрофлюидного чипа пассивного смешивания, изготовленного из прозрачного стекла. Данная система предназначена для того, чтобы оперативно проиллюстрировать принципы перемешивания в микрофлюидных каналах разной конфигурации.*

Результаты. *С помощью разработанной системы проведен цветометрический анализ режимов и динамики перемешивания двух жидкостей (5% водного раствора красителя азорубина и воды) в Т-образной точке смешивания, на прямом и изогнутых (в форме змеевика) участках микрофлюидного канала микросмесителя пассивного типа при варьировании скорости потоков от 100 до 400 мкл/мин.*

Заключение. *Согласно полученным расчетам, доля адвективных процессов смешивания (образование вихревых потоков и увеличение площади контакта смешиваемых веществ) в протекающих жидкостях существенно выше в изогнутых микроканалах*

микрочипов. Разработанная информационно-измерительная система контроля динамики протекания (перемешивания) жидкостей в микрофлюидном канале является удобным инструментом для работ по оптимизации режимов смешивания в каналах микросмесителей и для проектирования новых конфигураций каналов в микрочипах, что позволяет интенсифицировать процессы и увеличить производительность микрофлюидных систем.

Ключевые слова: *микрофлюидика, микрофлюидный чип, микросмеситель пассивного смешивания, критерии гидродинамического подобия, цветометрический анализ.*

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Innovative approaches in chemical and biological analyses, in order to simplify and speed up their procedures as well as boost their performance, are in high demand. Microfluidic systems are in the focus of researchers, because such systems can be used in various fields of science and technology, including chemical and biochemical analytical procedures. The driving force behind the active development of microfluidics was the creation of microelectromechanical systems (MEMS) which received the name "System-on-a-Chip," and which allow to place several functional components on a single microdevice. It is also in line with the general tendency to miniaturize devices, to elevate their performance and sensitivity for chemical and biological studies and analytical procedures [1]. Such miniaturized total analysis systems (μTASs) are used in chemistry, biology and medicine, and they are called a lab-on-a-chip (LoC) [2, 3]. A microfluidic chip (microreactor) is a device that combines several functions, when working with a reagent-to-product or sample-to-analysis pipeline, in a single complex system whose size varies from several millimeters to several square centimeters [4].

The main difference between microfluidic systems and other currently employed analytical laboratory equipment is the use of microvolumes (microliters) in microfluidics, allowing the use of reagents and electricity, as well as the amount of the analyte or biomaterial to be significantly minimized, thus making the analysis cheaper. Microfluidic systems are the tools that we can use to develop multifunctional automated analytical and manufacturing devices in a small scale, allowing various chemical and biochemical reactions to be performed quickly, in a small volume and with the minimal human involvement. The use of small volumes of substance solutions leads to the necessity of investigating flow processes in microfluidic systems in terms of both molecular dynamics and continuum mechanics. Special microfluidic microreactors have been developed, allowing to perform several actions with liquids on a single chip, for example, mixing, separation, fragmentation, sampling, etc. [2–10]. Other microfluidic chips, which perform only a single procedure, for example, mixing (one of the most important operations, involved in almost all chemical and biochemical analytical procedures), exist as well [11–14].

Microfluidic chips for mixing, the so-called micromixers, are used to control and accelerate the process of mixing [13, 14]. There are two kinds of micromixers, active and passive. To intensify the process, active micromixers require additional equipment that acts on the liquid flow externally. For example, it can be a piezoacoustic transducer, which creates shear stress in the liquid flow by ultrasound waves, and induces fluctuations in the velocity field, thus intensifying the mixing. Another example is magnetic particles in a certain area of the microfluidic chip, which mix the liquid flows by their own active movements [14].

The design of active micromixers and their integration into microfluidic systems is quite expensive and difficult. On the contrary, passive micromixers are easier and cheaper. When creating passive micromixers, it is necessary to take into account the geometrical parameters of the micromixer channels and the flow behavior of the liquid [4]. In passive micromixers, the mixing of liquid flows is intensified by various construction features of the microfluidic channels that allow increasing the contact surface between the liquids and decreasing the diffusion distance. For example, the micromixer channels may be equipped with obstacles, or have curved configurations, allowing to abruptly change the direction of flow, make the flows collide, create vortex flows, thus making the mixing process more effective [15, 16]. Superhydrophobic surfaces may also be used in the chip channels, making the sliding of the liquids better at the sides of the channels and increasing the velocity of the flow [17].

The aim of this study was to describe and evaluate the major parameters of the flow and mixing processes in a passive microfluidic micromixer, and to develop an information-measuring system to monitor the dynamics of flow (mixing) of liquids.

Evaluation of the hydrodynamic similarity criteria of flow and mixing processes in a passive mixing microfluidic chip

The efficiency of mixing processes in a passive mixing microfluidic chip, in accordance with the abovementioned description, depends on the construction features of the channels. The key zones in the chip structure, which facilitate effective mixing, are the point of mixing and the channel of mixing. The point of mixing is a certain place in the chip where two or more channels are joined (where liquids are supplied for further mixing). The channel where the liquids are flowing together is called the channel of mixing (Fig. 1).

By changing the geometry of these chip zones, developers of microfluidic systems achieve the maximal efficiency of mixing for various solutions. The point of mixing can be T-shaped, Y-shaped or arrow-shaped (Fig. 2).

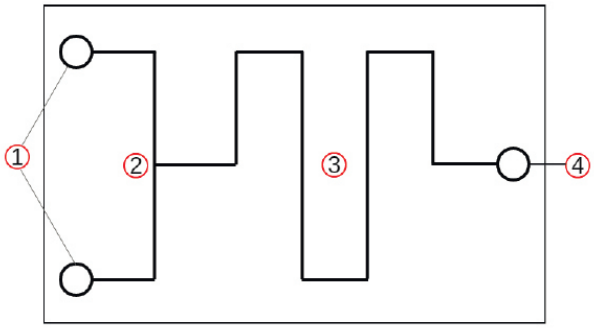
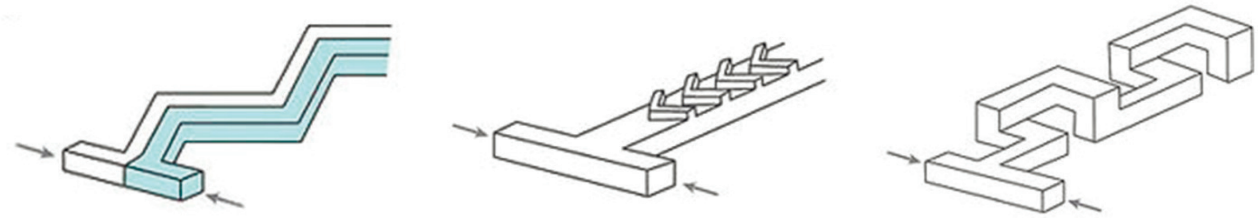


Fig. 1. Scheme of a microfluidic chip (micromixer):
1 – two points of entry of the liquids;
2 – the point of mixing;
3 – the channel of mixing;
4 – the point of exit of the resulting solution.

T- junction *Y- junction* *Arrow-shaped junction*

Fig. 2. Channel configurations at the point of mixing in passive mixing microfluidic chips.

Channels of mixing in passive micromixers can have various configurations, such as a double-bend shaped channel; a flat channel with staggered-herringbone grooves; a three-dimensional, connected out-of-plane channel (Fig. 3); and many more configurations [4].



a b c

Fig. 3. Examples of channel configurations in passive microfluidic chips:
a) Zigzag-shaped channel for chaotic mixing at high Reynolds numbers;
b) Staggered-herringbone grooves for chaotic mixing at low Reynolds numbers;
c) Three-dimensional L-shaped channel for chaotic mixing at intermediate Reynold numbers [4].

The mixing process in solutions is influenced by the parameters of the dissolved substances, such as viscosity, diffusion coefficient and the supply rate of the liquids. Other important factors, which affect the mixing process, are the material of the microfluidic chip and the characteristics of the chip itself, such as the roughness of the channel sides, length and angles of the channel.

In order to describe the mixing in microfluidic chips, it is necessary to use the following parameters

of hydrodynamic similarity: the Peclet number (Pe) that characterizes the ratio of the advective processes in the flow to diffusion; the Prandtl number (Pr) that characterizes the thermodynamics of the mixed liquids; the Reynolds number (Re) that characterizes the flow mode of the liquid; the Dean number (Dn) that characterizes the occurring transversal flows at the curves and bends of the channels (Fig. 4).

We calculated these parameters in order to analyze the mixing process in channels of passive microfluidic chips with T-shaped junction in two configurations, straight and double-bend shaped.

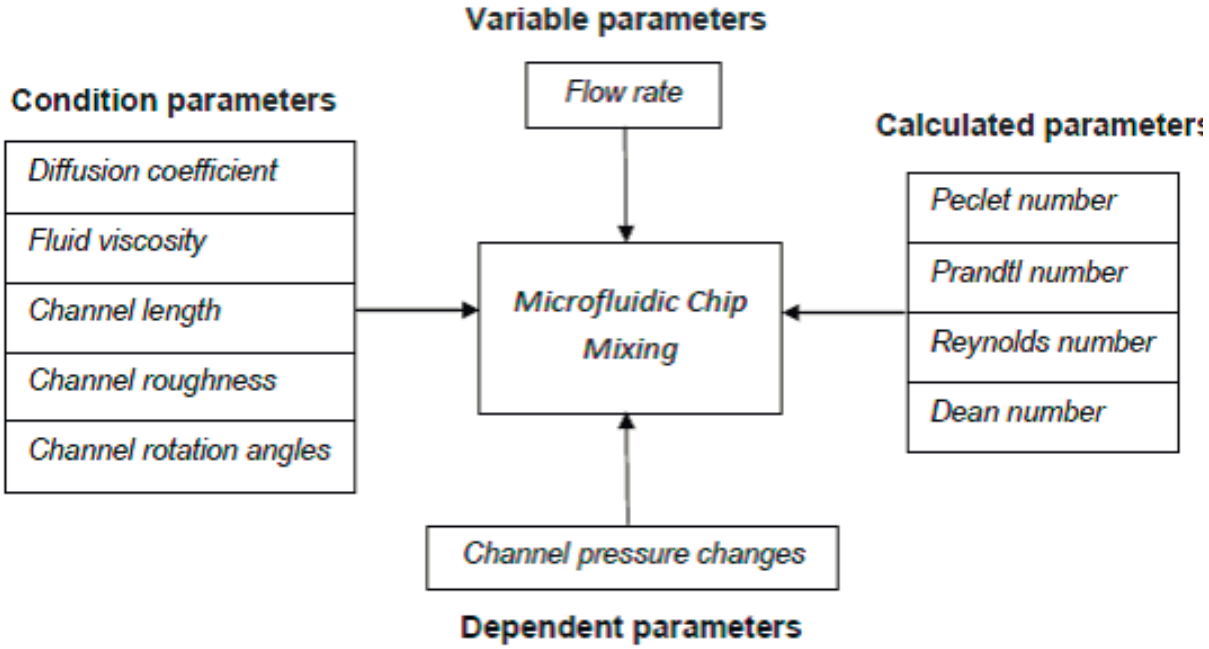


Fig. 4. Scheme of parameters for mixing of solutions in a passive microfluidic chip.

Let us consider the following setup, where we use a microfluidic chip to mix 5% aqueous solution of azorubine (carmoisine, food coloring E122; red dye supplied by *Roha Dyechem Pvt. Ltd.*, catalog number RD-09, India) and bidistilled deionized water (generated by Milli-Q Integral 5, *Merck Millipore*, France; further referred to as "Milli-Q water"), making a dilution of the starting dye solution with water to produce a homogeneous solution. The microfluidic channel has the same cross-section area of 1 mm^2 throughout the whole chip, and its length is 1080 mm. Two solutions are supplied to the micromixer channels at the rate of 400 µl/min.

The Reynolds number can be calculated by the following formula (1) [18]:

$$\mathrm{Re} = \frac{pvd}{\eta}, \qquad (1)$$

where ρ – density of the medium, kg/m^3;

v – characteristic velocity, m/s;

d – hydraulic diameter, m;

η – dynamic viscosity of the medium, kg/(m·s)

As a result, the Re number (in a straight channel) at the flow rate of 400 µl/min equals to 6.6.

In this mass transfer process, when mixing a dye solution with water, it is more important and descriptive to analyze the ratio of advective processes to diffusion, i.e. the ratio of the mass transfer caused by the movement of the medium to the mass transfer caused by the chaotic thermal movement of molecules. It can be characterized by the Peclet number according to the formula (2) [18]:

$$\mathrm{Pe} = \mathrm{Re} \times \mathrm{Pr}. \qquad (2)$$

The Prandtl number (Pr) equals to 7.02 for the flow of azorubine aqueous solution at 20 °C [19].

Therefore, for the liquid flow with Re = 6.6 (the flow rate is 400 μl/min) in a straight channel, the Peclet number equals to 46.33.

When flowing in a double-bend shaped channel, the liquid changes its direction at the bends of the channel. As we can see from the scheme of this channel (Fig. 5), the flow changes its direction twice. As a result of the centrifugal force action, the layers of the liquid begin to flow irregularly, the flow separates into layers, thus intensifying the mixing.

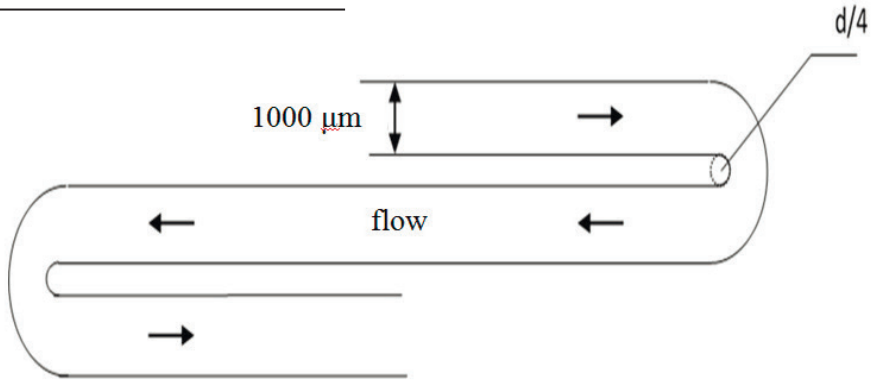


Fig. 5. Scheme of a part of a double-bend shaped channel.

By using similarity coefficients, flow in channels with turns can be characterized by the Dean number [18]:

$$Dn = \frac{\nu}{\upsilon} \times \sqrt{\frac{L^3}{2 \times r}}, \quad (3)$$

where υ – kinematic viscosity, m^2/s;
v – flow velocity/rate, m/s;
L – characteristic length, m;
r – radius of curvature, m.

The Dean number can also be calculated using the Reynolds number [18]:

$$Dn = \mathrm{Re} \times \sqrt{\frac{L}{r}}. \quad (4)$$

Then the Pe number for this type of mixing channel can be expressed by the following formula:

$$\mathrm{Pe} = (\mathrm{Re}_1 \times \mathrm{Re}_2) \times \mathrm{Pr}, \quad (5)$$

$$\mathrm{Re}_2 = 2 \times \left(\frac{Dn}{\sqrt{\frac{L}{r}}} \right), \quad (6)$$

where Re_2 characterizes the movement of the liquid at the bends of the double-bend shaped channel (the multiplier 2 is the number of bends in the double-bend shaped channel); Re_1 – the Reynolds number for the straight part of the channel.

The resulting number (Re_1+ Re_2) for this channel will be equal to 35.5. Therefore, the Pe number for the double-bend shaped channel will be equal to 250.6. The results of these calculations are shown in Table.

Similarity criteria for the straight channel and the double-bend shaped channel

Similarity criteria	Straight channel	Double-bend shaped channel
Re (Reynolds number)	6.6	35.5
Pe (Peclet number)	46.33	250.6

The calculations described above confirm that the share of advective mixing processes is much higher in the double-bend shaped channel than in the straight channel. It indicates that more bends in microfluidic channels are required for fast and effective mixing of liquids. Similarly, we calculated Peclet and Dean numbers for the straight channel and the double-bend shaped channel at various flow rates. The resulting dependencies of these similarity criteria on flow rates are shown in Fig. 6.

According to these graphs, for the double-bend shaped channel, the increase in the Pe number (that characterizes the ratio of the advective processes in the flow to diffusion) is directly proportional to the Re number, i.e. there is a significant dependency on the flow rate. More vortex flows at the bends of the mixing channel lead to larger contact areas of the liquids and more effective mixing.

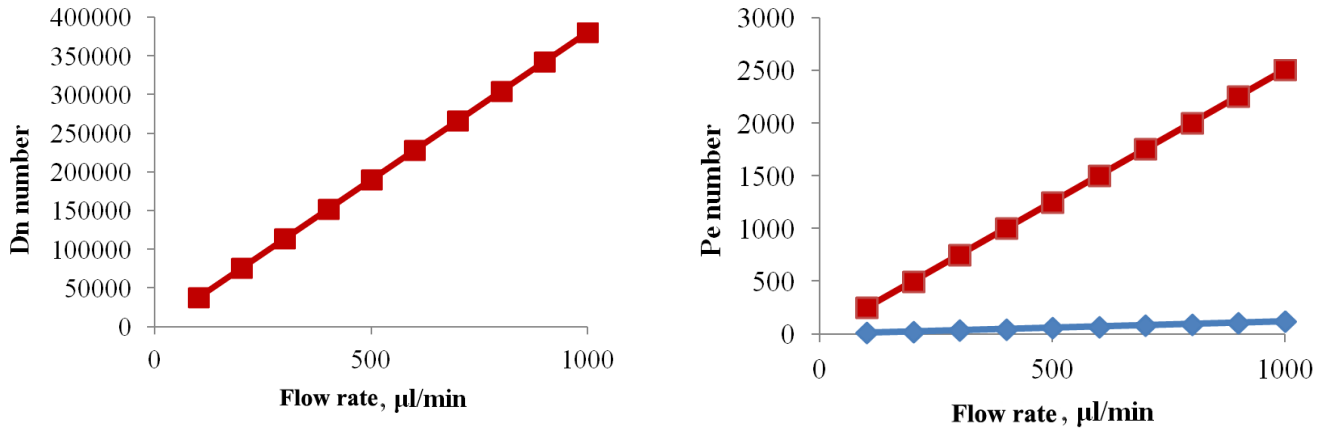


Fig. 6. Dependency of Dn and Pe numbers on flow rates for the mixing of azorubine aqueous solution with Milli-Q water. *Left*, double-bend shaped channel; *Right*, straight channel (diamonds, blue line) and double-bend shaped channel (squares, red line).

Colorimetric analysis of liquid flow in microchannels

In order to analyze the flow and mixing processes in passive microfluidic chips, we have developed an information-measuring system (IMS) to monitor the dynamics of liquid flow. The IMS (Fig. 7) consists of a microscope with a digital eyepiece (to take photographs and record videos when connected to a computer; *LOMO MIB*, Russia); an Atlas syringe pump (to supply liquids at a certain rate into the microfluidic chip; *Syrris Ltd.*, United Kingdom); and a passive mixing microfluidic chip of interest (a double-bend shaped channel, made of clear glass).

In preliminary experiments, we obtained a series of microscopic photographs that showed the mixing process of 5% aqueous solution of azorubine (red dye) with Milli-Q water. We used an algorithm designed with AutoHotKey script language for colorimetric analysis. The results obtained in the RGB color space were transformed into the CIE Lab color coordinate system. The red chromaticity was calculated by division of the "a" coordinate (green–red) by the "L" coordinate (brightness) [19].

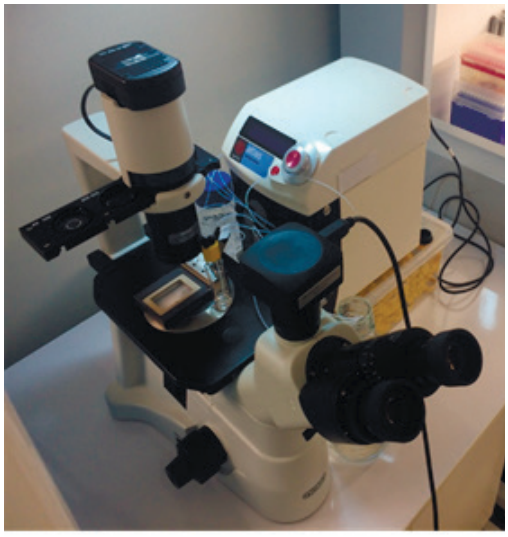


Fig. 7. View of the information-measuring system (IMS) for monitoring of the dynamics of liquid flow in a microfluidic chip.

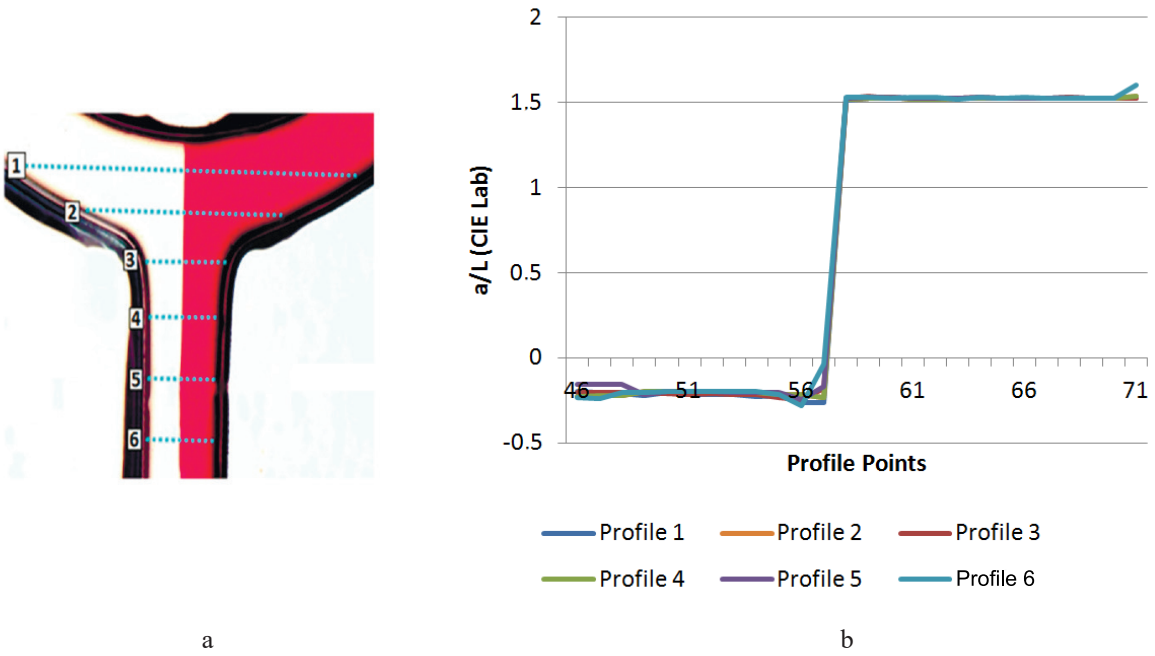
Using this IMS, we performed a colorimetric flow analysis (at the flow rate of 400 µl/min) at the T-shaped mixing point of the microfluidic chip for 5% aqueous solution of azorubine (bright red) and Milli-Q water (Fig. 8).

As we can see, the intensity of red chromaticity is always constant and there is a clear boundary between the flows. We can assume that the concentration also does not change, meaning that there is no convection mass transfer at the mixing point. Previously, a similar curve for distribution of concentrations was obtained by mathematical modeling [20, 21].

When we decrease the rate of one of the flows to 100 µl/min, we observe channel blocking (Fig. 9) caused by excess density of one of the flows; it is not optimal because mixing does not occur in this case.

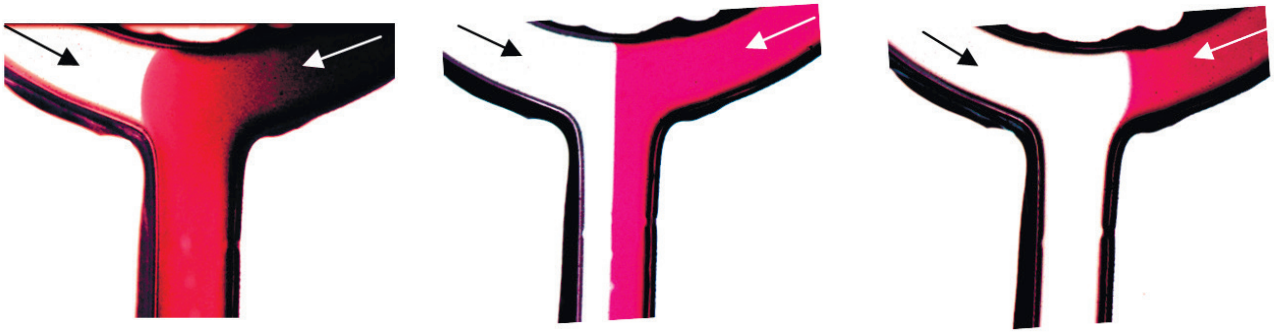
The colorimetric profile of dye distribution for flow in a straight channel is shown in Fig. 10.

The resulting curve for distribution of chromaticity intensity clearly has fluctuations of values at the sides, and shows formation of heterogeneity in azorubine concentration due to the interaction between dye molecules and sides of the channel. The profile of flow rates is parabolic, because the flow in the channel consists of a fast center and slow sides. The resulting curve for distribution of chromaticity intensity in the channel (Fig. 10) looks like the curve obtained in [20] by mathematical flow modeling for a straight channel, using methods of molecular dynamics (Fig. 11). It has been suggested that heterogeneity in flow rates may cause heterogeneity in concentration of the dissolved substance in the cross-section of the channel [20].



a b

Fig. 8. a) Microscopic photograph (4× magnified) of the T-shaped mixing point, with flows of 5% aqueous solution of azorubine and Milli-Q water. Dotted lines show colorimetric profiles – lines where chromaticity changes; b) Chromaticity curves.



a) Left channel blocking. Flow rates: solvent (left) – 100 µl/min, dye (right) – 400 µl/min

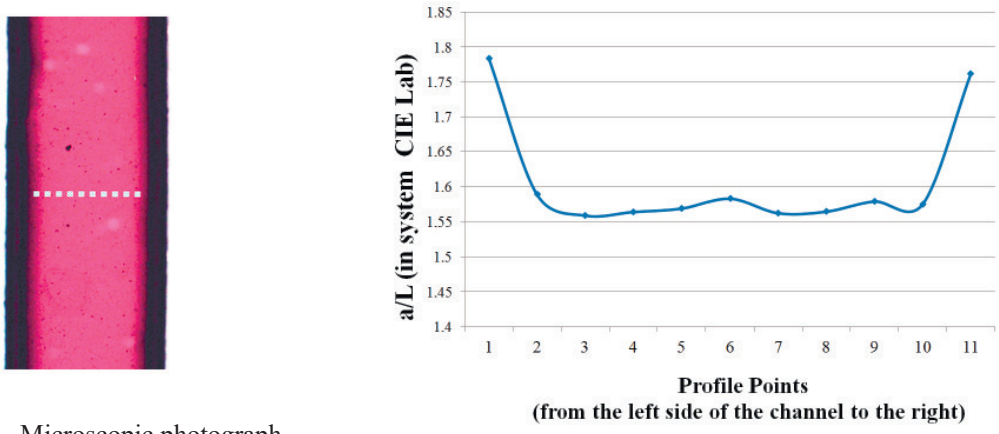
b) Uniform flow. Flow rates: solvent (left) – 100 µl/min, dye (right) – 100 µl/min

c) Right channel blocking. Flow rates: solvent (left) – 400 µl/min, dye (right) – 100 µl/min

Fig. 9. Microscopic photographs (4× magnified) for various flow modes of 5% aqueous solution of azorubine and Milli-Q water at the T-shaped mixing point of the microfluidic chip. Arrows show directions of flow.

It is known that, when both flow rates decrease, the flow is stabilized, the mixing mode is disrupted, the flow becomes laminar, and separates into layers without mixing [22]. For colorimetric analysis of mixing modes, we supplied 5% aqueous solution of azorubine and Milli-Q water to a double-bend shaped micromixer at the following flow rates: 100, 200, 300, 400 µl/min. We obtained microscopic photographs and curves for distribution of intensity of chromaticity (Fig. 12).

As we can see from these graphs of colorimetric profiles, the decrease in flow rate causes stratification of the flow. At flow rate of 400 µl/min, the colored solution fills the whole cross-section of the bent channel quite uniformly, indicating the effective mixing of the two flows. The reddish flow at 300 µl/min indicates that a gradient of dye concentration occurs, and the dye concentrates in the right part of channel. At 200 µl/min, we observe the unstable, yet appearing plateau of dye concentration. The curve of chromaticity intensity at



Microscopic photograph (4×magnified)

Distribution curve for intensity of chromaticity in the channel

Fig. 10. Colorimetric profile of flow in a straight channel for 5% aqueous solution of azorubine.

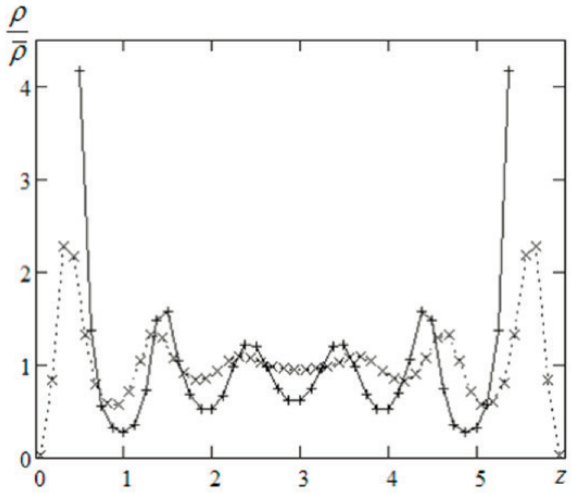
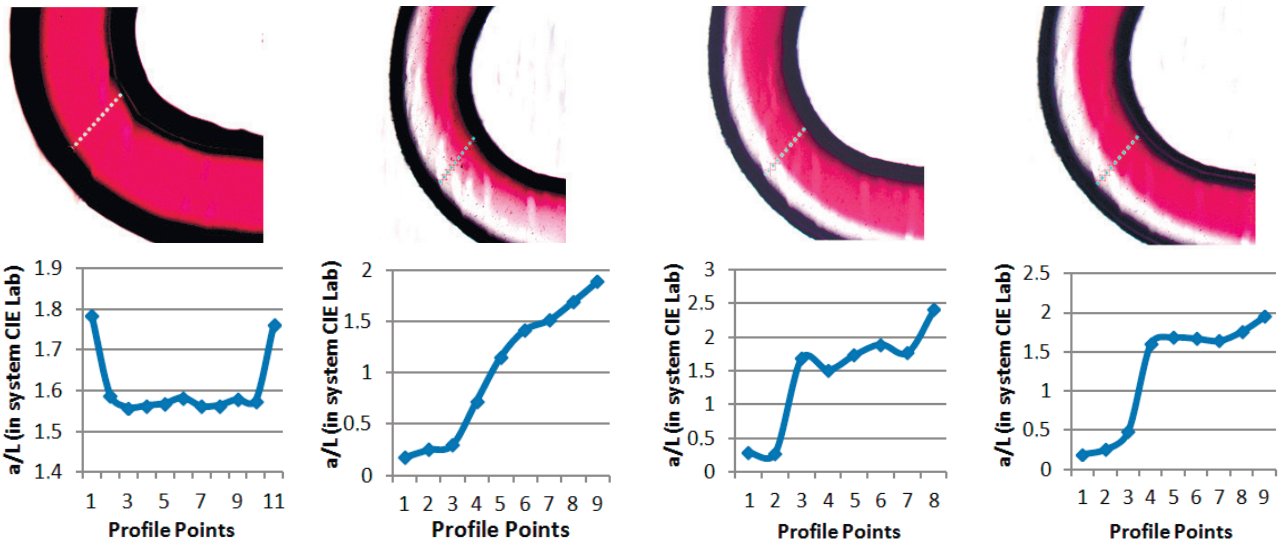


Fig. 11. Profile of flow density in the cross-section of a straight channel for molecules whose interaction is described: by the potential of hard spheres (+); by the Lennard-Jones potential (×) [20].



a) Flow rate: 400 µl/min b) Flow rate: 300 µl/min c) Flow rate: 200 µl/min d) Flow rate: 100 µl/min

Fig. 12. Microscopic photographs and curves of distribution of chromaticity intensity for mixing in a bent channel of a micromixer, while decreasing rate in both flows – azorubine solution and Milli-Q water (see from left to right – from a to d).

100 µl/min shows that the flow is stabilized as two laminar flows; the dye concentration in the right flow is uniform, which can be seen in the graph as a clear plateau between profile points 4 and 8.

We have also analyzed the mode of flow at 100 µl/min of dye solution in the bends of the channel filled with Milli-Q water (Fig. 13).

We can see that the dye fills up the central area first, i.e. the core of the flow. The change in the flow trajectory is caused by the appearing centrifugal force that acts on the flow, since its velocity is much higher than that of the side layers. By comparing the colorimetric profiles 1 and 2, we can see that the flow is shifted after the bend of the channel. At high flow rates, the destabilizing effect is higher, and active mixing occurs.

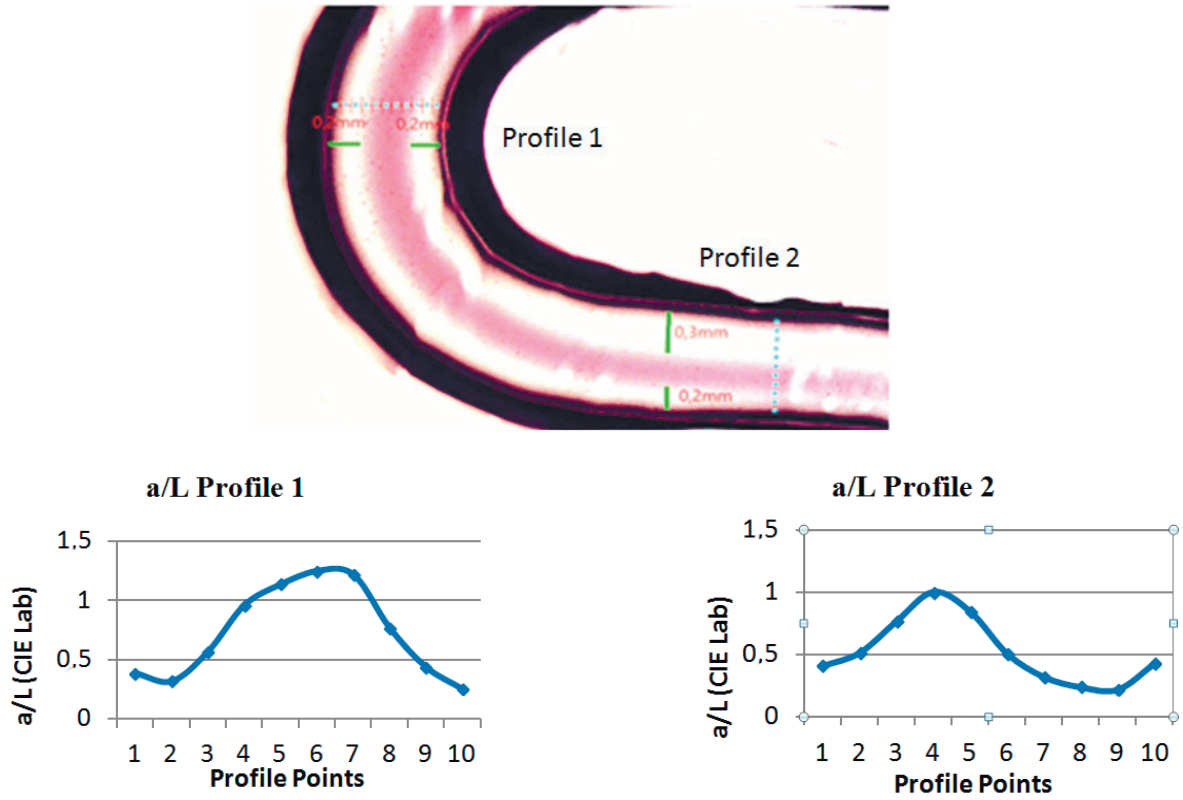


Fig. 13. Analysis of dye flow in a channel already filled with water.

Conclusions

We can conclude that the criteria of hydrodynamic similarity, which are Reynolds, Peclet and Dean numbers, are crucial for development and optimization of microfluidic mixers. These parameters are markers for prompt evaluation and correction of flow modes in various micromixers in order to ensure effective mixing.

We have developed an information-measuring system to monitor the dynamics of flow (mixing) in a microfluidic channel. It allows the principles of mixing in microfluidic channels of different configurations to be quickly illustrated, and modes and dynamics of mixing in various parts of the channels of various microfluidic chips to be evaluated. Using the IMS, we have shown that the flow rate of 400 µl/min is enough for effective mixing in the micromixer used in this study. It is a confirmation of the fact, previously described in research papers, that fast and effective mixing can be achieved in microfluidic micromixers at low Reynolds numbers. The developed IMS is a convenient tool for optimization of mixing modes in channels of micromixers and for development of novel channel configurations in microchips, which allow intensifying processes and boosting the performance of microfluidic systems.

Conflict of interests. *The authors of this article are employed by OOO "NPF "MATERIA MEDICA HOLDING", a company sponsoring this study.*

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About the authors:

Kirill A. Sarbashev, Technologist, Research Laboratory, OOO "NPF "MATERIA MEDICA HOLDING" (47-1, Trifonovskaya ul., Moscow 129272, Russia); Postgraduate Student, Chair of Storage and Processing Technologies of Animal Origin Products, Russian State Agrarian University – Timiryazev Moscow Agricultural Academy (49, Timiryazevskaya ul., Moscow 127550, Russia). E-mail: SarbashevKA@materiamedica.ru. ResearcherID X-1340-2019, https://orcid.org/0000-0002-2368-5562

Marina V. Nikiforova, Pharmaceutical Technology Project Manager, Research and Analytical Department, OOO "NPF "MATERIA MEDICA HOLDING" (47-1, Trifonovskaya ul., Moscow 129272, Russia); Postgraduate Student, Chair of Pharmaceutical and Toxicological Chemistry, Peoples' Friendship University of Russia (RUDN) (6, Miklukho-Maklaya ul., Moscow 117198, Russia). E-mail: nauka@materiamedica.ru. ResearcherID X-3703-2019, https://orcid.org/0000-0002-9139-7255

Darya P. Shulga, Junior Researcher, Research Laboratory, OOO "NPF "MATERIA MEDICA HOLDING" (47-1, Trifonovskaya ul., Moscow 129272, Russia); Postgraduate Student, Chair of Pharmaceutical and Toxicological Chemistry, Peoples' Friendship University of Russia (RUDN) (6, Miklukho-Maklaya ul., Moscow 117198, Russia). E-mail: Shulgadp@materiamedica.ru. ResearcherID X-3272-2019, https://orcid.org/0000-0002-5158-9500

Margarita A. Shishkina, Senior Researcher, Research Laboratory, OOO "NPF "MATERIA MEDICA HOLDING" (47-1, Trifonovskaya ul., Moscow 129272, Russia). E-mail: KanareykinaMA@materiamedica.ru. ResearcherID O-8014-2014, https://orcid.org/0000-0001-9508-2384

Sergey A. Tarasov, Cand. of Sci. (Medicine), Director of Research & Development Department, OOO "NPF "MATERIA MEDICA HOLDING" (47-1, Trifonovskaya ul., Moscow 129272, Russia); Leading Research Associate, Laboratory of Physiologically Active Substances, Institute of General Pathology and Pathophysiology (8, Baltiiskaya ul., Moscow 125315, Russia). E-mail: TarasovSA@materiamedica.ru. ResearcherID X-2509-2018, https://orcid.org/0000-0002-2425-174X

Об авторах:

Сарбашев Кирилл Артемович, технолог научно-исследовательской лаборатории ООО «НПФ «МАТЕРИА МЕДИКА ХОЛДИНГ» (129272, Россия, Москва, ул. Трифоновская, д. 47, стр. 1); аспирант кафедры технологии хранения и переработки продуктов животноводства ФГБОУ ВО Российского государственного аграрного университета – МСХА им. К.А. Тимирязева (127550, Россия, Москва, ул. Тимирязевская, д. 49). E-mail: SarbashevKA@materiamedica.ru. ResearcherID X-1340-2019, https://orcid.org/0000-0002-2368-5562

Никифорова Марина Владимировна, руководитель проектов по фармацевтическим технологиям научно-аналитического отдела ООО «НПФ «МАТЕРИА МЕДИКА ХОЛДИНГ» (129272, Россия, Москва, ул. Трифоновская, д. 47, стр. 1); аспирант кафедры фармацевтической и токсикологической химии ФГАОУ ВО «Российский университет дружбы народов» (1171981, Россия, Москва, ул. Миклухо-Маклая, д. 6). E-mail: nauka@materiamedica.ru. ResearcherID X-3703-2019, https://orcid.org/0000-0002-9139-7255

Шульга Дарья Петровна, младший научный сотрудник научно-исследовательской лаборатории ООО «НПФ «МАТЕРИА МЕДИКА ХОЛДИНГ» (129272, Россия, Москва, ул. Трифоновская, д. 47, стр. 1); аспирант кафедры фармацевтической и токсикологической химии ФГАОУ ВО «Российский университет дружбы народов» (1171981, Россия, Москва, ул. Миклухо-Маклая, д. 6). E-mail: Shulgadp@materiamedica.ru. ResearcherID X-3272-2019, https://orcid.org/0000-0002-5158-9500

Шишкина Маргарита Андреевна, старший научный сотрудник научно-исследовательской лаборатории ООО «НПФ «МАТЕРИА МЕДИКА ХОЛДИНГ» (129272, Россия, Москва, ул. Трифоновская, д. 47, стр. 1). E-mail: KanareykinaMA@materiamedica.ru. ResearcherID O-8014-2014, https://orcid.org/0000-0001-9508-2384

Тарасов Сергей Александрович, кандидат медицинских наук, директор департамента научных исследований и разработок ООО «НПФ «МАТЕРИА МЕДИКА ХОЛДИНГ» (129272, Россия, Москва, ул. Трифоновская, д. 47, стр. 1); ведущий научный сотрудник лаборатории физиологически активных веществ ФГБНУ «Научно-исследовательский институт общей патологии и патофизиологии» (125315, Россия, Москва, ул. Балтийская, д. 8). E-mail: TarasovSA@materiamedica.ru. ResearcherID X-2509-2018, https://orcid.org/0000-0002-2425-174X

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Comparison of alternative methods for methyl acetate + methanol + acetic acid + acetic anhydride mixture separation

Anastasiya V. Frolkova[1,@], Yuliya I. Shashkova[2], Alla K. Frolkova[1], Mark A. Mayevskiy[1]

[1]MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow 119571, Russia
[2]Chimmed, Moscow 115230 Russia
[@]Corresponding author, e-mail: frolkova_nastya@mail.ru

Objectives. *The paper is a comparative analysis of methyl acetate + methanol + acetic acid + acetic anhydride industrial mixture separation flowsheets based on the use of special distillation methods (extractive distillation and pressure-swing distillation). The results obtained illustrate the variability of the structure of the technological separation flowsheet.*
Methods. *Mathematical modeling using the software package Aspen Plus V. 10.0 was chosen as the research method. The simulation was based on the local composition equation NRTL and the Hayden–O'Connell equation of state. The relative uncertainties of phase equilibrium description do not exceed 3%.*
Results. *The vapor–liquid diagram of the quaternary mixture of methyl acetate + methanol + acetic acid + acetic anhydride was studied using thermodynamic topological analysis. It was shown that the system contains one binary azeotrope and is characterized by one distillation region. Although the structure is not complex, there is a possibility of using several methods for mixture separation: pressure-swing distillation, and extractive distillation with different entrainers. Twelve flowsheets with different structure were proposed, and 29 variants of separation were compared.*
Conclusions. *It was shown that the most perspective structure for the separation of a methyl acetate + methanol + acetic acid + acetic anhydride mixture is a combination of distributed sequence separation and extractive distillation.*

Keywords: *azeotrope, extractive distillation, pressure-swing distillation, separation flowsheet.*

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Сравнение альтернативных методов разделения смеси метилацетат – метанол – уксусная кислота – уксусный ангидрид

А.В. Фролкова[1,@], Ю.И. Шашкова[2], А.К. Фролкова[1], М.А. Маевский[1]

[1]МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва 119571, Россия
[2]ТД «Химмед», Москва 115230, Россия
[@]Автор для переписки, e-mail: frolkova_nastya@mail.ru

Цели. *Целью работы является сравнительный анализ технологических схем разделения промышленной смеси метилацетат – метанол – уксусная кислота – уксусный ангидрид, основанных на использовании специальных методов разделения: экстрактивная ректификация и варьирование давления. Полученные результаты иллюстрируют вариативность структуры технологической схемы разделения.*
Методы. *В качестве метода исследования выбрано математическое моделирование в программном комплексе Aspen Plus V. 10.0. Моделирование основывалось на уравнении локального состава NRTL и уравнении состояния Хейдена–О'Коннелла. Относительные ошибки описания фазового равновесия не превышают 3%.*
Результаты. *С помощью термодинамико-топологического анализа изучена диаграмма парожидкостного равновесия четырехкомпонентной системы метилацетат – метанол – уксусная кислота – уксусный ангидрид. Показано, что система содержит один бинарный азеотроп и характеризуется одной областью дистилляции. Несмотря на то, что структура не является сложной, существует возможность использования нескольких методов разделения смеси: ректификация с варьированием давления, экстрактивная ректификация с различными разделяющими агентами. Предложено 12 технологических схем различной структуры и проведен сравнительный анализ 29 вариантов разделения.*
Заключение. *Показано, что наиболее эффективным для разделения смеси метилацетат – метанол – уксусная кислота – уксусный ангидрид является сочетание промежуточного режима разделения смеси и экстрактивной ректификации.*

Ключевые слова: *метилацетат, азеотроп, экстрактивная ректификация, варьирование давления, схема разделения.*

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Introduction

Distillation is the most widely used method for the separation of liquid mixtures. The possibility of separation depends on the presence of azeotropes (minimum-boiling, maximum-boiling, homogeneous and heterogeneous). The existence of azeotropes might limit recovery or even make separation unfeasible, unless a special distillation method (for example, pressure-swing distillation [1], extractive distillation [2, 3], heteroazeotropic [4] distillation, or a combination of different methods [5–9]) is applied. Each method has its advantages and disadvantages. For example, pressure-swing distillation does not require the addition of a new component (solvent or entrainer), which could contaminate the product. However, this method is limited to systems, in which pressure has a significant effect on the azeotrope's composition. Extractive distillation is a process, in which an entrainer (a new component) favorably changes the relative volatility of azeotrope-forming components.

If the multicomponent azeotropic mixture has to be separated, a set of flowsheets with different structures may be proposed for this purpose [10]. Each flowsheet will be characterized by its sequence of components separation (direct, indirect, or distributed sequence), and also by the use of special methods. The pressure choice in distillation columns in the pressure-swing distillation complex will affect the change of the azeotrope's composition and hence the amount of recycle flows. The same azeotropic mixture can be separated by extractive distillation with different solvents: heavy [11–14], light [15], or mixed [16] entrainers. Thus, each flowsheet will be characterized by its energy consumption. It is not always possible to say in advance what flowsheet design is optimal.

This study illustrates the variability of separation flowsheets using the example of industrial mixture forming in the production of methyl acetate via acetic anhydride esterification with methanol [17]. The comparison of 29 separation variants revealed the optimal

structure of the flowsheet. Mathematical modeling (Aspen simulation) and thermodynamical topological analysis [10] were used in this work.

Mathematical modeling and thermodynamic topological analysis of phase diagram

The object of this study is a quaternary mixture containing methyl acetate (MA), methanol (M), acetic acid (AA) and acetic anhydride (AAh). The composition (x) and amount (F) of the mixture coming from the synthesis stage were taken from [17]: x_{MA} = 0.391, x_{M} = 0.157, x_{AA} = 0.178, x_{AAh} = 0.274 mol. frac; F = 775 kmol/h. All binary constituents are well studied. There is the information about vapor–liquid equilibrium (VLE) and azeotropic data at different pressures [13, 18–20]. This information is sufficient to verify the adequacy of mathematical modeling. The presence of associating compounds in the mixture determined the choice of the property model. The non-random two-liquid (NRTL) thermodynamic model [21] and the Hayden–O'Connell equation of state [22] were applied to calculate VLE. The parameters were taken from the NIST database. The relative uncertainties of VLE and description of azeotropic characteristics are given in Table 1.

Table 1. Relative uncertainties of VLE in binary constituents and description of azeotropic (Az) characteristics in a methyl acetate (MA) + methanol (M) + acetic acid (AA) + acetic anhydride (AAh) system

Vapor–liquid equilibrium						
Constituent	MA+M	MA+AA	MA+AAh	M+AA	M+AAh	AA+AAh
for y_1, %	1.33	1.10	1.60	3.46	0.29	2.97
for T, %	0.05	0.95	0.73	0.49	0.49	0.29
Methyl acetate + methanol azeotrope						
Pressure, kPa	26.3	53.7	80.0	140.8	395.2	787.3
for x_{MA}^{Az}, %	1.98	1.39	0.55	2.58	2.49	3.54
for T^{Az}, %	1.58	0.59	0.34	0.56	2.35	2.67

The vapor–liquid equilibrium diagram is characterized by a rather simple structure (Fig. 1): the system contains one binary azeotrope MA+M, which is an unstable node, and all distillation lines are directed to AAh (maximum boiling point – stable node).

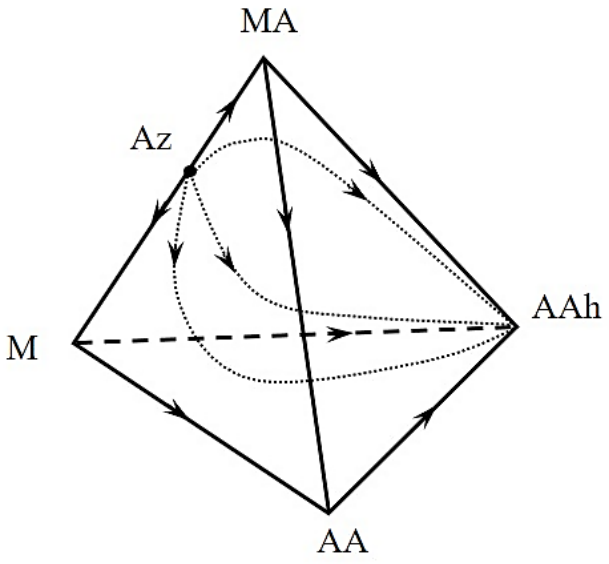

Fig. 1. VLE diagram of a methyl acetate (MA) + methanol (M) + acetic acid (AA) + acetic anhydride (AAh) system.

Other points are of a saddle type. The composition tetrahedron contains one distillation region. In this way, it is possible to realize separation of the mixture via direct (distillate flow will contain a mixture of MA+M of azeotropic composition), indirect (bottom flow will contain AAh), or distributed (MA+M at the top of the column and AA+AAh at the bottom) sequence.

The change in pressure has a significant effect on the methyl acetate + methanol azeotrope's composition (Fig. 2). So, it is possible to use pressure swing distillation to separate this mixture.

Additionally, extractive distillation can be used for the separation of an azeotropic binary mixture. Ethylene glycol (EG) and dimethyl sulfoxide (DMSO) [23] were recommended as selective solvents. The study of methyl acetate + methanol's relative volatility in the presence of these entrainers showed that it is more profitable to carry out the process of extractive distillation at a pressure of 50.7 kPa (an increase in the volatility by 2 and 1.5 times for EG and DMSO are observed respectively) [6].

It is possible to separate MA from the quaternary MA+M+AA+AAh, ternary MA+M+AA, or binary MA+M mixture. Table 2 shows the effect of the entrainer concentration on MA+M's relative volatility at a pressure of 50.7 kPa.

The data obtained show (Table 2) that the relative volatility increases with the increase of entrainer

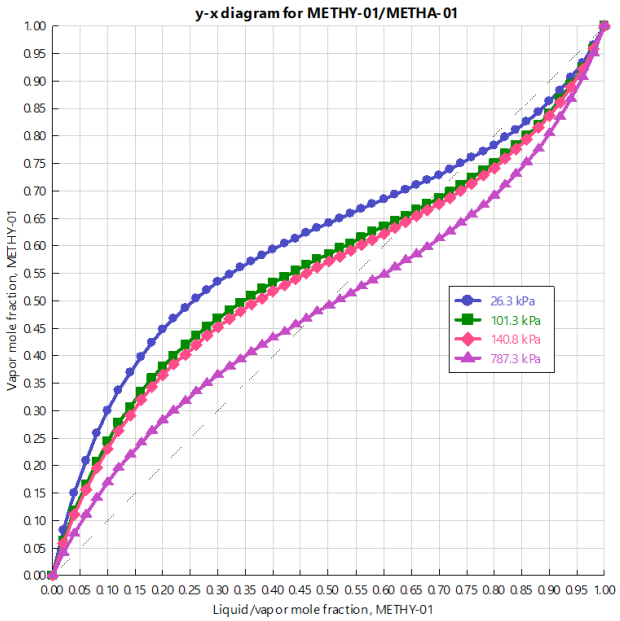

Fig. 2. VLE diagram of methyl acetate + methanol binary system at different pressures.

concentration. The coefficients in the case of extractive distillation of the binary mixture are higher, and in the case of the ternary and quaternary system they are lower due to the mixture's dilution.

Design of separation flowsheet

The design of separation flowsheets was based on the use of direct (separation of methyl acetate + methanol azeotrope as a distillate product), indirect (separation of acetic anhydride as a bottom product), and distributed (distillate flow containing methyl acetate + methanol, bottom flow containing acetic acid + acetic anhydride) sequence and different special methods: extractive distillation (ED) with EG (or DMSO) or pressure-swing distillation (PSD) (26.34–787.30 kPa). Twelve flowsheets with different structures were designed to separate the quaternary mixture (Figs 3–5).

Taking into account the different ranges of pressure (26.34–101.32; 53.70–101.32; 101.32–395.17; 101.32–787.30 kPa) and extractive agents (EG and DMSO) 29 cases were considered. Material balances were calculated, and the column working conditions were determined using simulation in AspenPlus (Table 3).

Table 2. Effect of entrainer concentration on the relative volatility of methyl acetate + methanol mixture components at 50.7 kPa

Initial mixture	Entrainer concentration, mole frac.			
	0.2	0.4	0.6	0.8
	Ethylene glycol			
MA+M+AA+AAh	1.50	1.82	2.38	3.38
MA+M+AA	1.82	2.45	3.42	4.46
MA+M	1.84	2.93	4.56	6.48
	Dimethyl sulfoxide			
MA+M+AA+AAh	1.64	2.18	2.86	3.31
MA+M+AA	1.70	2.39	3.22	3.46
MA+M	1.72	2.60	3.60	4.27

Table 3. Column working conditions and energy consumption

Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW	Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW
Figure 3 (a)											
1	23.34	28	10	3	36.1	1	53.70	29	10	1.5	49.5
2	101.32	30	16	3.5	47.0	2	101.32	30	16	3.5	80.1
3	101.32	27	10	2	3.9	3	101.32	27	10	2	3.9
4	101.32	50	26	5	5.4	4	101.32	50	26	5	5.4
1	101.32	30	15	3	41.6	1	101.32	30	16	3.5	34.0
2	395.17	30	20	5	54.6	2	787.30	30	20	4	24.3
3	101.32	27	10	2	3.9	3	101.32	27	10	2	3.9
4	101.32	50	26	5	5.4	4	101.32	50	26	5	5.4

Table 3. Continued

Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW	Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW
Figure 3 (b)											
1	23.34	28	10	3	36.1	1	53.70	29	10	1.5	49.5
2	101.32	30	16	3.5	47.0	2	101.32	30	16	3.5	80.9
3	101.32	33	18	3.5	10.3	3	101.32	33	18	3.5	10.3
4	101.32	15	6	1.5	3.1	4	101.32	15	6	1.5	3.1
1	101.32	30	15	3	41.6	1	101.32	30	16	3.5	34.0
2	395.17	30	20	5	54.6	2	787.30	30	20	4	24.3
3	101.32	33	18	3.5	10.3	3	101.32	33	18	3.5	10.3
4	101.32	15	6	1.5	3.1	4	101.32	15	6	1.5	3.1
Figure 3 (c), EA = EG						Figure 3 (d), EA = EG					
1	50.66	30	14(4)	4	7.4	1	50.66	30	14(4)	4	7.4
2	101.32	24	12	1	13.7	2	101.32	24	12	1	13.7
3	101.32	30	6	3	5.1	3	101.32	33	18	3.5	10.3
4	101.32	50	26	5	5.4	4	101.32	15	6	1.5	3.1
Figure 4 (a), EA = EG						Figure 4 (a), EA = DMSO					
1	101.32	49	27	4.5	18.0	1	101.32	49	27	4.5	18.0
2	50.66	29	20(4)	2.5	4.3	2	50.66	28	20(4)	2	5.3
3	101.32	14	8	0.5	4.7	3	30.40	12	6	1.5	3.9
4	101.32	15	6	3	2.4	4	101.32	15	6	3	2.4
5	101.32	50	26	5	5.4	5	101.32	50	26	5	5.4
Figure 4 (b), EA = EG						Figure 4 (b), EA = DMSO					
1	101.32	49	27	4.5	18.0	1	101.32	49	27	4.5	18.0
2	50.66	29	20(4)	2.5	4.3	2	50.66	28	20(4)	2	5.3
3	101.32	14	8	0.5	4.7	3	30.40	12	6	1.5	3.9
4	101.32	38	20	4.5	8.8	4	101.32	38	20	4.5	8.8
5	101.32	19	10	1.5	1.4	5	101.32	19	10	1.5	1.4
Figure 4 (c)											
1	101.32	30	15	3	20.7	1	101.32	30	15	3	20.7
2	101.32	14	5	0.5	5.4	2	101.32	14	5	0.5	5.4
3	23.34	28	20	3	41.4	3	101.32	30	16	3	45.2
4	101.32	30	15	5	37	4	395.17	30	17	4	39.5
Figure 4 (c)						Figure 4 (d)					
1	101.32	30	15	3	20.7	1	101.32	30	17	3	20.7
2	101.32	14	5	0.5	5.4	2	101.32	40	24	3.5	42.8
3	101.32	29	22	3	28.7	3	23.34	29	20	2	41.8
4	787.30	30	20	4	24.3	4	101.32	18	10	0.5	4.0
Figure 4 (d)											
1	101.32	30	17	3	20.7	1	101.32	30	17	3	20.7
2	101.32	34	20	3.5	67.3	2	395.17	30	15	3.5	39.7
3	53.70	28	15	2	47.8	3	101.32	29	16	5	41.8
4	101.32	18	10	0.5	4.0	4	101.32	18	10	0.5	4.0

Table 3. Continued

Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW	Column (F/F_{EA})	P, kPa	Number of stages	Feed stage (EA stage)	Reflux ratio	Q, MW
Figure 4 (d)						Figure 5 (a), EA = EG					
1	101.32	30	17	3	20.7	1	101.32	30	15	3	20.7
2	787.30	30	15	2.5	23.9	2	101.32	14	5	0.5	5.4
3	101.32	36	24	4	21.7	3	50.66	25	16(4)	2.5	5.6
4	101.32	18	10	0.5	4.0	4	101.32	15	9	0.5	4.8
Figure 5 (a), EA = DMSO						Figure 5 (b), EA = EG					
1	101.32	30	15	3	20.7	1	101.32	30	15	3	20.7
2	101.32	14	5	0.5	5.4	2	50.66	29	17(4)	2.5	6.4
3	50.66	35	22(4)	2.5	6.1	3	101.32	17	7	0.5	5.0
4	30.40	15	4	2	4.7	4	101.32	29	10	4.5	5.3
Figure 5 (c)											
1	101.32	23	10	1	8.6	1	101.32	23	10	1	5.6
2	101.32	49	26	5	5.4	2	101.32	49	26	5	5.4
3	23.34	28	20	3	41.4	3	101.32	30	16	3	41.2
4	101.32	30	15	5	37	4	395.17	30	17	4	38.5
Figure 5 (c)						Figure 5 (d), EA = EG					
1	101.32	23	10	1	8.6	1	101.32	23	10	1	8.2
2	101.32	49	26	5	5.4	2	101.32	49	26	5	5.4
3	101.32	29	22	3	28.7	3	50.66	25	16(4)	2.5	5.8
4	787.30	30	20	4	24.3	4	101.32	15	9	0.5	5.1
Figure 5 (d), EA = DMSO											
1	101.32	23	10	1	8.2						
2	101.32	49	26	5	5.4						
3	50.66	35	22(4)	2.5	8.2						
4	30.40	15	4	2	4.6						

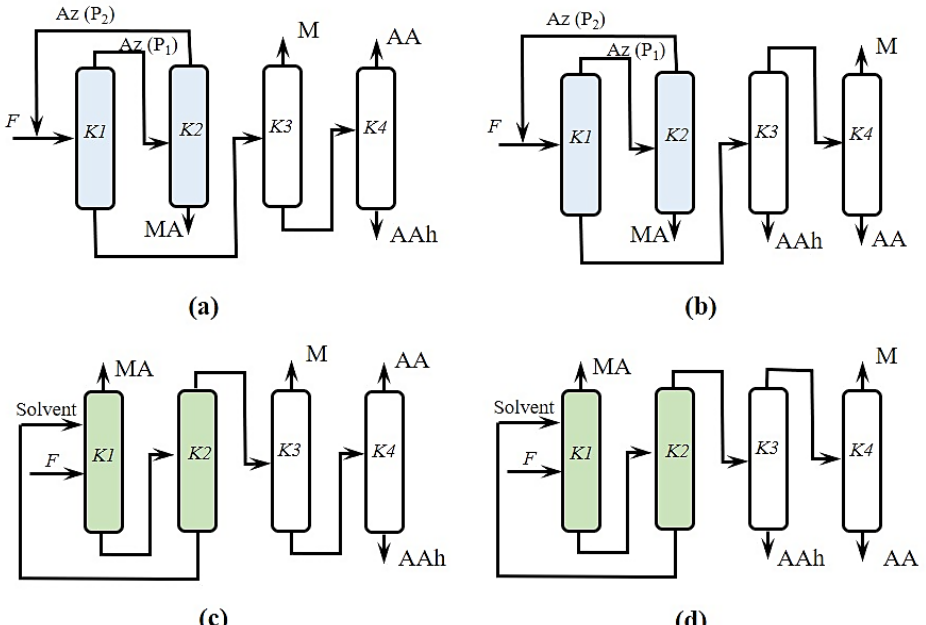

Fig. 3. Flowsheets for methyl acetate (MA) + methanol (M) + acetic acid (AA) + acetic anhydride (AAh) quaternary mixture separation:
(a), (b) – Direct sequence in *K1* + PSD; (c), (d) – ED.

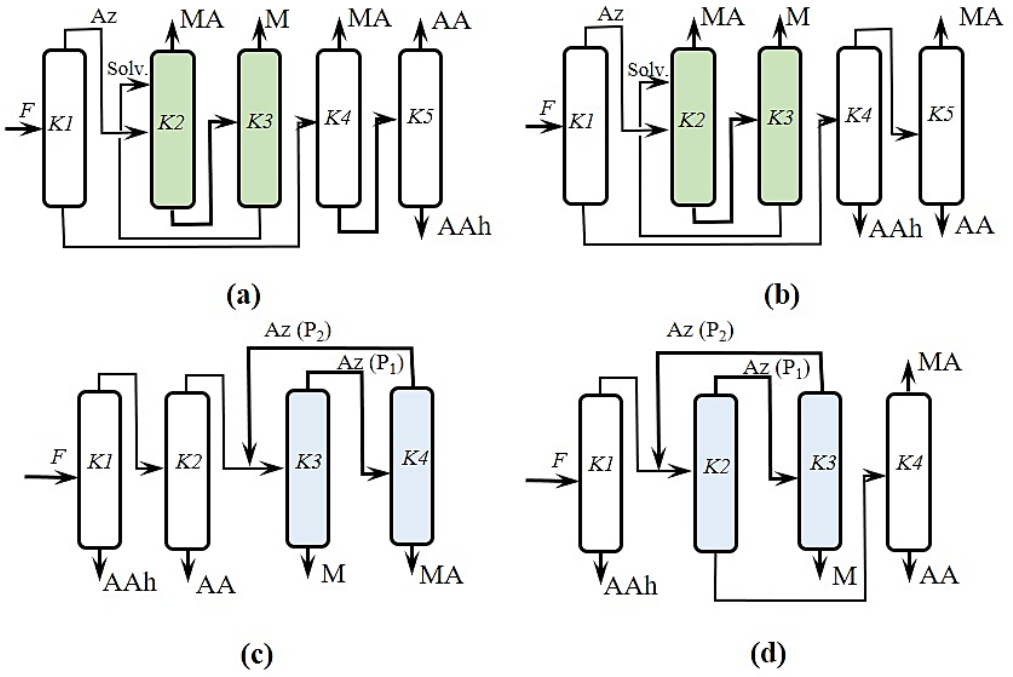

Fig. 4. Separation flowsheets for methyl acetate (MA) + methanol (M) + acetic acid (AA) + acetic anhydride (AAh) quaternary mixture separation:
(a), (b) – Direct sequence in *K1* + ED; (c), (d) – Indirect sequence in *K1* + PSD.

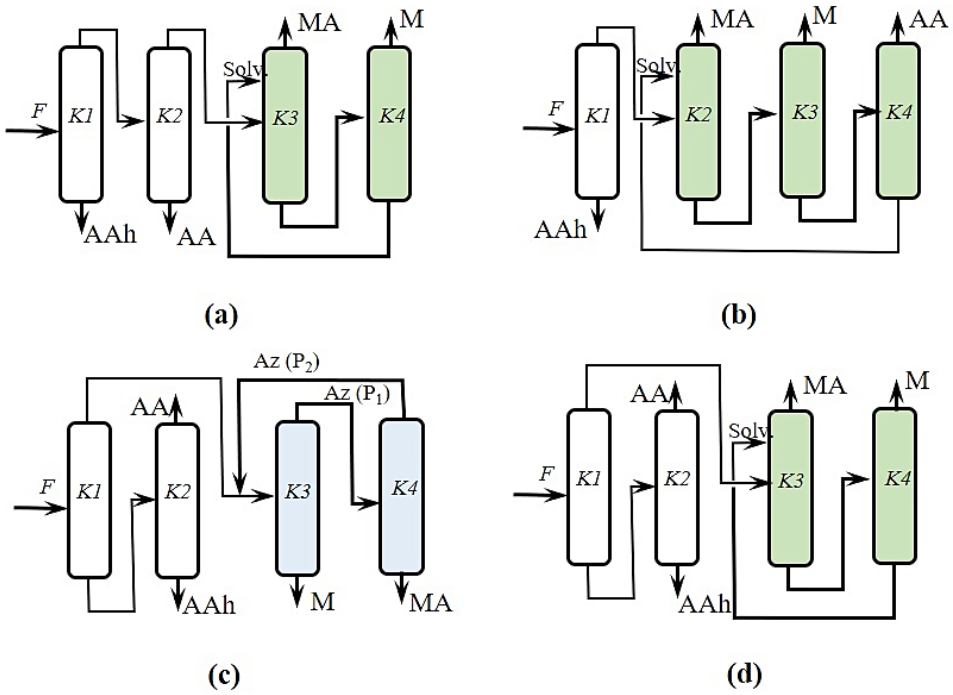

Fig. 5. Separation flowsheets for methyl acetate (MA) + methanol (M) + acetic acid (AA) + acetic anhydride (AAh) quaternary mixture separation:
(a), (b) – Indirect sequence in *K1* + ED; (c) – Distributed sequence in *K1* + PSD;
(d) – Distributed sequence in *K1* + ED.

The comparison of the amount of recycle flow and energy consumption is given in Table 4 and in histograms presented in Fig. 6 (for pressure-swing distillation) and in Fig. 7 (for extractive distillation).

Table 4. Comparison of energy consumption

Figure	Method of separation	Pressure, kPa (EA)	Δx_1^{Az}, mole frac.	Recycle amount, kmol/h	Q, MW
3 (a)	Pressure-swing distillation (*K1–K2*) + Direct dist. (*K3*)	26.34–101.32	0.0872	863.2	92.5
		53.70–101.32	0.0453	1941.9	139.6
		101.32–395.17	0.1130	899.9	105.6
		101.32–787.30	0.1766	575.8	67.6
3 (b)	Pressure-swing distillation (*K1–K2*) + Indirect dist. (*K3*)	26.34–101.32	0.0872	863.2	96.5
		53.70–101.32	0.0453	1941.9	144.2
		101.32–395.17	0.1130	899.9	109.6
		101.32–787.30	0.1766	575.8	71.7
3 (c)	ED (*K1-K2*) + Direct dist. (*K3*)	50.66–101.32 (EG)	–	775.0	31.6
3 (d)	ED (*K1–K2*) + Indirect dist. (*K3*)	50.66–101.32 (EG)	–	775.0	34.5
4 (a)	Direct dist. + ED (*K2–K3*) + Direct dist.	50.66–101.32 (EG)	–	543.8	34.9
		50.66–30.40 (DMSO)	–	543.8	35.1
4 (b)	Direct dist. + ED (*K2–K3*) + Indirect dist.	50.66–101.32 (EG)	–	543.8	37.3
		50.66–30.40 (DMSO)	–	543.8	37.5
4 (c)	Indirect dist. + Pressure-swing distillation (*K3–K4*)	26.34–101.32	0.0872	863.2	104.5
		101.32–395.17	0.1130	899.9	111.0
		101.32–787.30	0.1766	575.8	79.1
4 (d)	Indirect dist. + Pressure-swing distillation (*K2–K4*)	101.32–26.34	0.0872	927.1	109.3
		101.32–53.70	0.0453	1784.6	139.8
		395.17–101.32	0.1130	593.7	107.2
		787.30–101.32	0.1766	336.1	70.3
5 (a)	Indirect dist. + ED (*K3–K4*)	50.66–101.32 (EG)	–	637.1	36.5
		50.66–30.40 (DMSO)	–	637.1	36.9
5 (b)	Indirect dist. + ED (*K2–K3–K4*)	50.66–101.32 (EG)	–	562.7	37.4
5 (c)	Distr. dist. (*K1*) + Pressure-swing distillation (*K3–K4*)	26.34–101.32	0.0872	863.2	92.4
		101.32–395.17	0.1130	899.9	90.7
		101.32–787.30	0.1766	575.8	67.0
5 (d)	Distr. dist. (*K1*) + ED (*K3–K4*)	50.66–101.32 (EG)	–	637.1	24.5
		50.66–30.40 (DMSO)	–	637.1	26.3

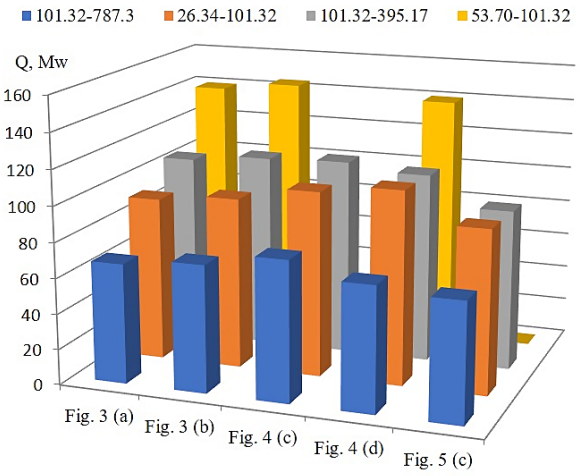

Fig. 6. Histogram showing the comparison of energy consumption in flowsheets based on the pressure-swing distillation.

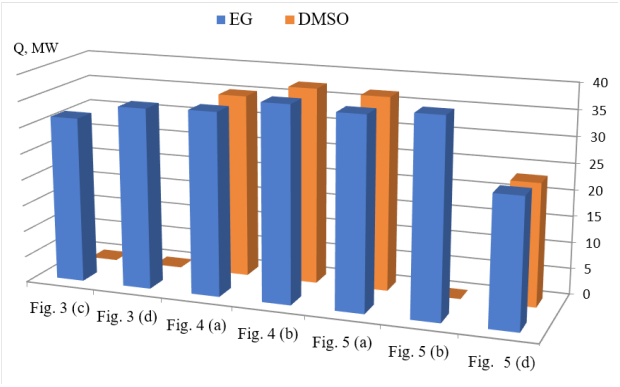

Fig. 7. Histogram showing the comparison of energy consumption in flowsheets based on the extractive distillation.

Conclusions

The amount of recycle flow depends on the mixture composition (feed to the pressure-swing distillation complex) and on the difference between azeotropic composition at chosen pressures. The results of Tables 3 and 4 show that the smaller this difference, the greater the amount of the recycle and hence energy consumption (for example, flowsheet in Fig. 3(a): $Q_{101.32–395.17} > Q_{101.32–787.30}$). It should be noted that an increase (decrease) in the value of the azeotrope composition changed by k times will result in a change in the value of the recycle and energy consumption by $k \pm 15\%$ times.

Direct distillation is preferable in comparison with indirect distillation (for example, $Q_{Fig.3(a)} > Q_{Fig.3(b)}$: energy saving varies from 13 to 31%).

The use of extractive distillation allows energy consumption to be reduced by 47–63% in comparison with pressure-swing distillation. Energy savings are achieved by increasing the relative volatility of the azeotrope-forming components (methyl acetate and methanol) by adding a solvent. Both extractive agents (EG and DMSO) give similar results, but the use of DMSO is limited to some flowsheets (except for cases presented in Fig. 3 (c), (d), and Fig. 5 (b)).

The most energy effective flowsheet is based on the combination of distributed sequence separation and extractive distillation (Fig. 5 (d)): there is a decrease in energy consumption by 1.3–5 times in comparison with other flowsheets.

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The authors declare no conflict of interest.

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About the authors:

Anastasiya V. Frolkova, Cand of Sci. (Engineering), Associate Professor, Chair 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: frolkova_nastya@mail.ru. ORCID 0000-0001-5675-5777, ResearcherID N-4517-2014

Yuliya I. Shashkova, Manager, Company Chimmed (9, bild. 3, Kashirskoe shosse, Moscow 115230, Russia). E-mail: juliashashkova82@gmail.com

Alla K. Frolkova, Dr. of Sci. (Engineering), Professor, Head of the Chair 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: frolkova@gmail.com. ORCID 0000-0002-9763-4717, ResearcherID G-7001-2018

Mark A. Maevskiy, Postgraduate Student, Chair 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: markhirurg@list.ru.

Об авторах:

Фролкова Анастасия Валериевна, кандидат технических наук, доцент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, д. 86). E-mail: frolkova_nastya@mail.ru. ORCID 0000-0001-5675-5777, ResearcherID N-4517-2014

Шашкова Юлия Игоревна, менеджер, ТД «ХИММЕД» (Россия, 115230, Москва, Каширское шоссе, дом 9, корп. 3). E-mail: juliashashkova82@gmail.com

Фролкова Алла Константиновна, доктор технических наук, профессор, заведующий кафедрой химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, д. 86). E-mail: frolkova@gmail.com. ORCID 0000-0002-9763-4717, ResearcherID G-7001-2018

Маевский Марк Александрович, аспирант кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (Россия, 119571, Москва, пр. Вернадского, д. 86). E-mail: markhirurg@list.ru

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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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Novel polymer surfactants based on the branched silatrane-containing polyesters and polyethers

Vladislav V. Istratov[1,@], Vitaly I. Gomzyak[2], Olga V. Yamskova[1], Gali D. Markova[1], Lyudmila G. Komarova[1], Boris A. Izmaylov[1], Valerii A. Vasnev[1]

[1]A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991, Russia

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

[@]Corresponding author, e-mail: slav@ineos.ac.ru

Objectives. *Biologically active polymeric surfactants are a new promising class of macromolecules that can find application in medicine, cosmetology, and agriculture. In this study, a number of new biologically active amphiphilic polymers based on branched silatrane-containing polyesters and polyethers were obtained, and their surface-active properties were investigated.*

Methods. *The branched polymers were represented by polyethers and polyesters, obtained respectively via the anionic polymerization of 1,2-epoxypropanol or a combination of equilibrium polycondensation and ring opening polymerization. The polymers were modified with 3-isocyanopropylsilatrane and trimethylethoxysilane to obtain the amphiphilic compounds containing silatrane groups bonded to the polymer backbone by the urethane bond. The structure of the synthesized polymer silatranes was confirmed via nuclear magnetic resonance spectroscopy and gel permeation chromatography. The surface active properties of all the copolymers obtained were investigated in connection with their obvious amphiphilicity. In particular, the formation of micelles in aqueous solutions is such a property. The critical micelle concentrations were determined by a method of quenching the fluorescence of the polymers.*

Results. *It was shown that the values of the critical micelle concentrations and the hydrophilic-lipophilic balance values of polymers determined by the Griffin equation correlate well with each other. A linear relationship between the hydrophilic-lipophilic balance and the critical micelle concentrations was established. At the same time, polyether-based polymers generally showed higher critical micelle concentrations than polyester-based polymers, although the hydrophilic-lipophilic balance values for polymers of different series, but with close degrees of substitution, were close. It was found that the use of all synthesized polymers as stabilizers of direct and reverse emulsions leads to an increase in the aggregative stability of both types of emulsions. The stability of emulsions depended both on the degree of substitution of peripheral hydroxyl groups of polymers by silatranes and on the molecular weight and structure of the branched block of polymers. The stability of direct emulsions increased for all polymers, while that of inverse emulsions decreased with an increasing degree of substitution of hydroxyl groups by silatranes. The increase of the branched block molecular weight led to an increase of droplet sizes for both direct and inverse emulsions. The smallest droplet size for direct and inverse emulsions was obtained using polymers with low molecular weight branched polyester blocks as surfactants.*

Conclusions. *The results obtained prove the possibility of creating polymer surfactants containing silatrane groups. By varying the structure of the polymer, its molecular weight and the degree of substitution of peripheral functional groups, it is possible to obtain surfactants with desired surface properties.*

Keywords: *branched polymers, silatranes, micellization, emulsions.*

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Новые полимерные ПАВ на основе разветвленных силатрансодержащих полиэфиров

В.В. Истратов[1,@], В.И. Гомзяк[2], О.В. Ямскова[1], Г.Д. Маркова[1], Л.Г. Комарова[1], Б.А. Измайлов[1], В.А. Васнёв[1]

[1]Институт элементоорганических соединений имени А.Н. Несмеянова РАН, Москва 119991, Россия
[2]МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва 119571, Россия
[@]Автор для переписки, e-mail: slav@ineos.ac.ru

Цели. *Биологически активные полимерные ПАВ являются новым многообещающим классом макромолекул, которые могут найти применение в медицине, косметологии, сельском хозяйстве. В данном исследовании был получен ряд новых амфифильных полимеров на основе разветвленных силатрансодержащих полиэфиров и исследованы их поверхностно-активные свойства.*

Методы. *Разветвленные полимеры были представлены простыми и сложными полиэфирами, которые получали соответственно способом анионной полимеризации 1,2-эпоксипропанола либо комбинацией равновесной поликонденсации и полимеризации с раскрытием цикла. Для получения амфифильных соединений, содержащих силатрановые группы, связанные с полимерным каркасом уретановой связью, полимеры были модифицированы 3-изоцианопропилсилатраном и триметилэтоксисиланом. Структура синтезированных полимерных силатранов была подтверждена методами ЯМР-спектроскопии и гель-проникающей хроматографии. Поверхностно-активные свойства всех полученных сополимеров были исследованы в связи с их очевидной амфифильностью, в частности, таким свойством является образование мицелл в водных растворах. Методом гашения флуоресценции полимеров были определены величины критических концентраций мицеллообразования (ККМ).*

Результаты. *Показано, что величины ККМ и определенные в соответствие с уравнением Гриффина величины гидрофильно-липофильного баланса (ГЛБ) для полимеров коррелируют, при этом была установлена линейная зависимость между указанными величинами. Полимеры на основе простых полиэфиров в целом показывали более высокие значения ККМ, чем полимеры на основе сложных полиэфиров, хотя величины ГЛБ для полимеров разных серий, но с близкими степенями замещения были близки. Было обнаружено, что использование всех синтезированных полимеров в качестве стабилизаторов прямых и обратных эмульсий приводит к увеличению агрегативной устойчивости эмульсий обоих типов. Устойчивость эмульсий зависела как от степени замещения периферийных гидроксильных групп полимеров силатранами, так и от молекулярной массы и строения разветвленного блока полимеров. Для всех полимеров устойчивость прямых эмульсий возрастала, а обратных эмульсий – снижалась с увеличением степени замещения гидроксильных групп силатранами. С увеличением молекулярной массы разветвленного блока размеры капель как прямых, так и обратных эмульсий увеличивались. Наименьший размер капель прямой и обратной эмульсии был получен при использовании в качестве ПАВ полимеров с низкомолекулярными разветвленными блоками на основе сложных эфиров.*

Заключение. *Полученные результаты показывают возможность создания полимерных ПАВ, содержащих силатрановые группы. Варьируя строение полимера, его молекулярную массу и степень замещения периферийных функциональных групп, возможно получение ПАВ с заданными поверхностными свойствами.*

Ключевые слова: *разветвленные полимеры, силатраны, мицеллообразование, эмульсии.*

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Introduction

Today, surface active substances (surfactants) are widely used in the food, cosmetic, perfume, and pharmacological industries. Moreover, for biomedical polymer surfactants, properties such as biocompatibility and the ability to decompose into non-toxic and easily released compounds are highly desirable [1]. Polymers, which are surface active substances, in the synthesis of which hydroxy acids – lactic, glycolic, etc. were used as reagents, are the most interesting from the point of view of environmental safety, since when they decompose, substances are formed that are products of the metabolism of living organisms [2, 3]. The attention of many scientists has been attracted not only by the preparation of biocompatible surfactants, but also by the synthesis and study of biologically active surfactants [4]. Such compounds can be the components of dosage forms combining high physiological activity and pronounced transport properties. A number of industrially important surfactants containing heterocyclic fragments and exhibiting bactericidal and antimicrobial activity can serve as an example [8–13]. In addition to the medical industry, the main consumer of biologically active surfactants, these compounds may be used in veterinary medicine and agriculture.

Silatranes are intra-organosilicon esters; their study was started by academician M.G. Voronkov in the 1960s [14]. Due to silatranes' unique antifungal, antibacterial, anti-inflammatory, antiviral and antitumor activity, as well as their pronounced activity in the regulation of plant growth [14–18], these compounds are used in medicine, cosmetology, and agriculture. For example, chloromethylsilatran is known as a highly effective, practically non-toxic, and easily biodegradable stimulator of crop growth and productivity [18–20].

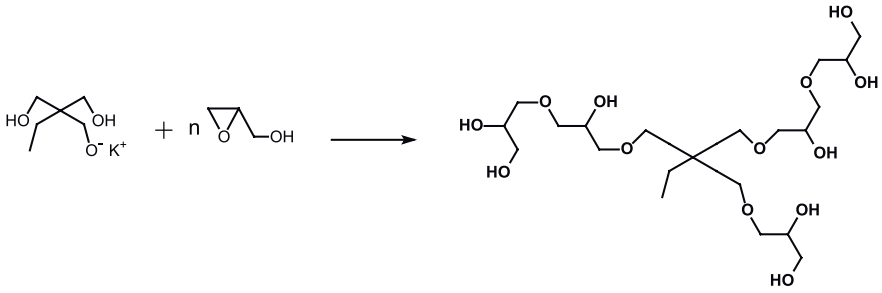
However, in the vast majority of studies, the structure, physicochemical properties, and biological activity of low molecular weight silatranes were studied. To date, there are practically no publications on the biological activity of polymers containing silatrane fragments, while the study of polymeric substances including silatrane groups is of great interest from the point of view of obtaining new bioactive and surface active polymers, as well as expanding the range of available pharmacological agents. To solve this problem, we synthesized a number of amphiphilic branched polymers containing polar lateral silatrane fragments, and evaluated their surface activity.

Materials and Methods

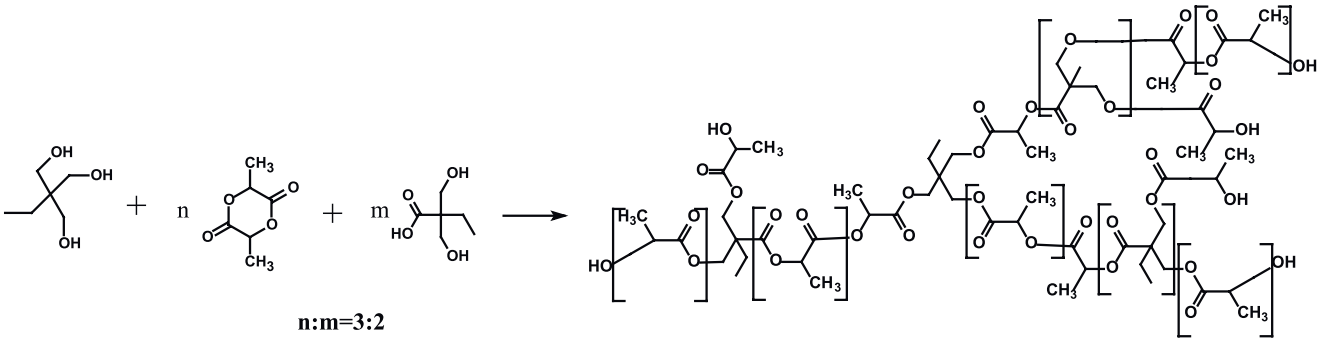
We used 3-isocyanopropyltriethoxysilane (98%), potassium *tert*-butanolate (97%) (*abcr GmbH*, Germany), triethanolamine ("pure"), diglyme ("pure") (*Chimmed*, Russia), 1,2-epoxypropanol (96%, *Sigma-Aldrich*, USA), 1.1.1-tris(hydroxymethyl)propane (97%), tin(II) 2-ethylhexanoate (Sn(Oct)2) (97%), trimethylethoxysilane (97%) (*Acros Organics*, USA), 2.2-bis(hydroxymethyl)butanoic acid (98%, Acros Organics, USA), diethyltin dicaprylate (DEDCO, 98%, *Abika*, Russia) without additional processing. Tetrahydrofuran (THF), benzene, methylene chloride (*Chimmed*, Russia), L-lactide (98%, *Sigma-Aldrich*, USA) were purified by standard methods [21].

As objects of study, biocompatible branched polymers were obtained that have different structures and molecular weights. These polymers were either polyethers (Scheme 1) or polyesters (Scheme 2), most of whose functional groups were on the peripheral part of the macromolecule. The synthesis was carried out, respectively, by the method of anionic polymerization of 1,2-epoxypropanol according to the aforementioned method [22] (Scheme 1), or by a combination of equilibrium polycondensation and polymerization with ring opening according to the procedure [23] (Scheme 2).

The synthesis of low molecular weight silatrane was carried out by modifying the method described in [24] (Scheme 3): a solution of 3-isocyanopropyltriethoxysilane (27.3 g, 0.11 mol) was added to a mixture of triethanolamine (15.0 ml, 16.8 g, 0.11 mol) in benzene (20 ml) and a catalytic amount (5 mg) of potassium *tert*-butanolate. The resulting mixture was heated to 80 °C and silatrane was synthesized for 10 hours by distillation of an azeotropic mixture of benzene and ethanol, at the same time adding to the reaction mixture an equivalent distilled-off amount of dry benzene. After the reaction, the silatrane was left in the form of a 2.2 M solution obtained in the synthesis process, without being isolated as a solid.



Scheme 1



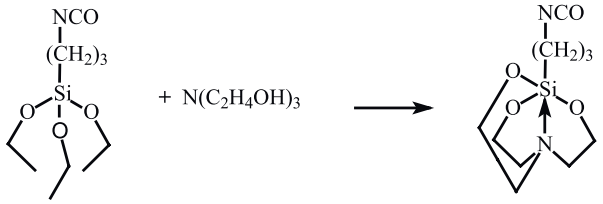
Scheme 2

In the next step, the synthesized polymers were modified with 3-isocyanopropylsilatrane and trimethylethoxysilane (Schemes 4, 5) to obtain amphiphilic compounds.

By varying the ratios of the branched polymer and silatrane used for the synthesis, we obtained polymers with different average degrees of substitution of the hydrophilic groups of branched macromolecules by silatranes. The reactions were carried out in THF with constant stirring and a temperature of 25 °C for 4 hours. In a 50 ml round bottom two-necked flask with a magnetic stirrer, inert gas injection and reflux condenser, the hydroxyl-containing polymer and the calculated amount of DEDCO in 10 ml of THF were dissolved with stirring, after which a solution of 3-isocyanopropylsilatran in THF was added. The synthesis was carried out for 60 min at 66 °C, after which a solution of trimethylethoxysilane excess was added and boiled for another 60 min. After completion of the reaction, the solvent was removed and the polymer was purified via dialysis (THF solvent, "ZelluTrans" dialysis membrane, MVCO 1000 Da) for 24 hours.

The nuclear magnetic resonance (NMR) spectra were recorded for 10% copolymer solutions in $CDCl_3$ on a Brucker spectrometer with an operating frequency of ^1H – 600.22 MHz and ^{13}C – 150.94 MHz (internal standard is tetramethylsilane) at the Center for Molecule Composition Studies of the Institute of Organoelement Compounds of the Russian Academy of Sciences (INEOS RAS).

Gel permeation chromatography (GPC) of the copolymers was carried out on a Waters 150 chromatograph, eluent was THF, the flow rate was 1 ml/min, with the PL-GEL 5u MIXC column (300 × 7.5 mm), at the Center for



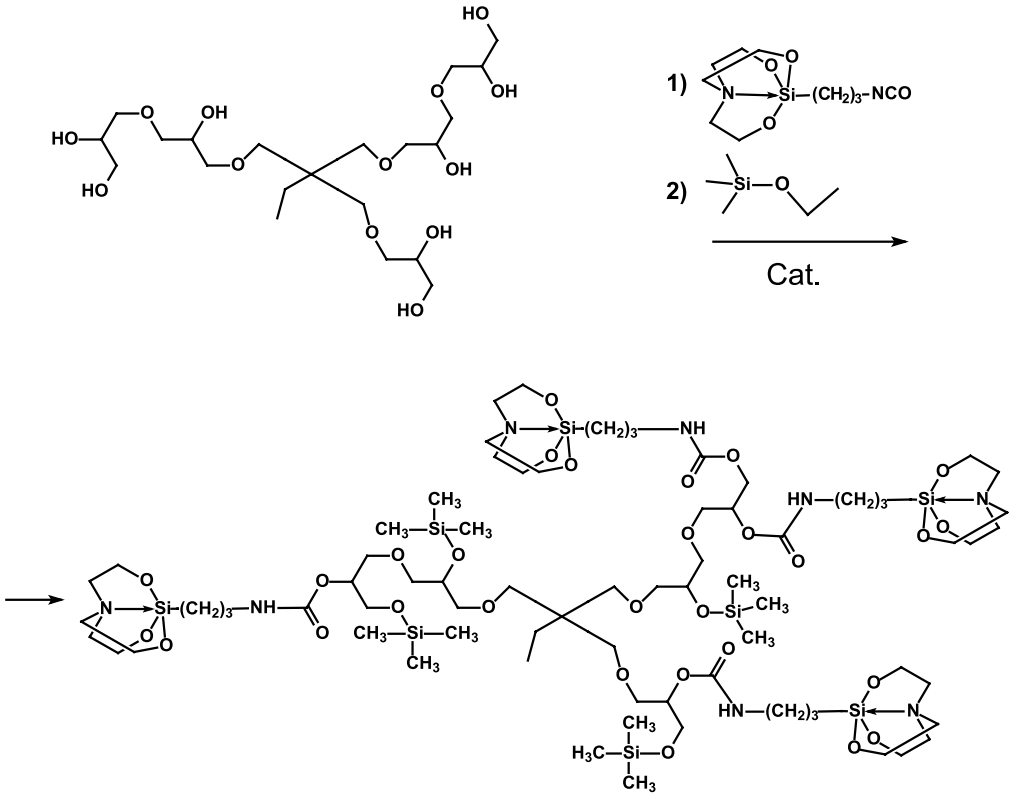
Scheme 3

Molecule Composition Studies of the INEOS RAS.

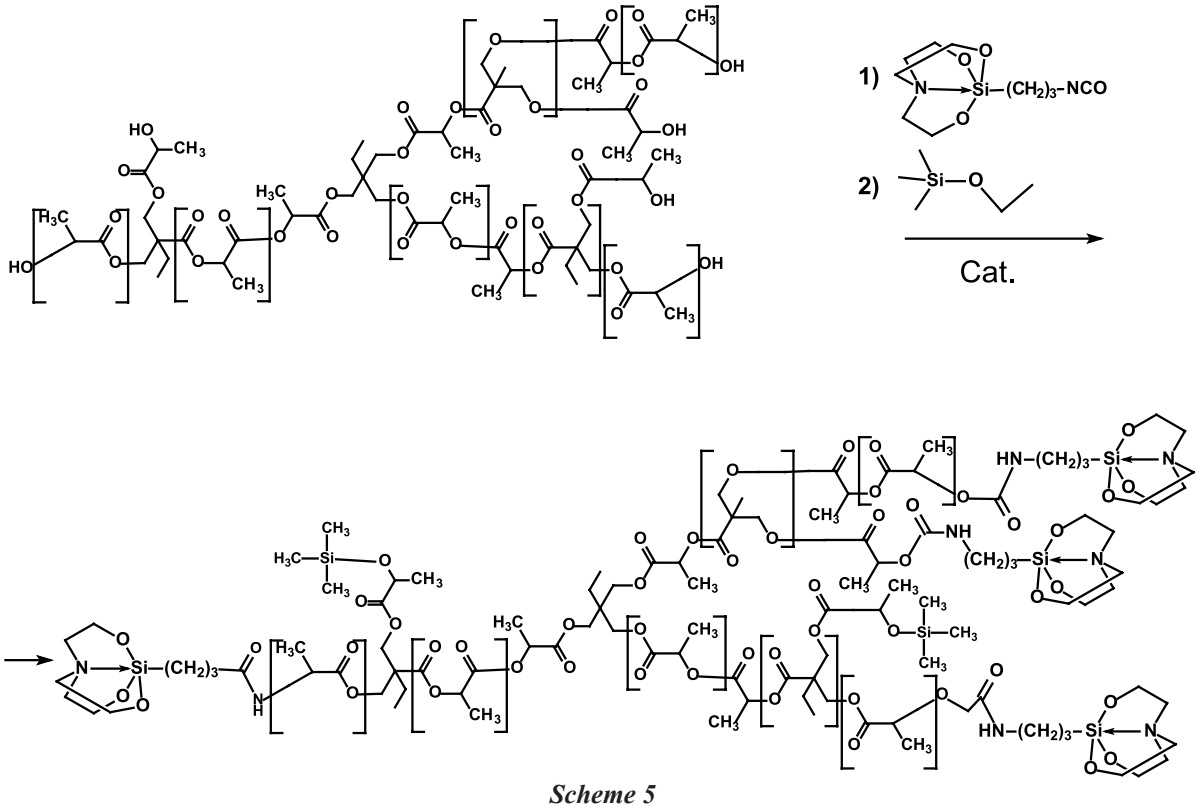
The value of the hydrophilic-lipophilic balance (HLB) for the polymer was determined according to Griffin [25]. The analytical expression of HLB for surfactant molecules is HLB = $20(M_h/M)$, where M_h and M are the molecular weights of the hydrophobic fragment and the whole molecule. For all the polymers studied, the branched macromolecular backbone was considered as hydrophobic.

The determination of critical micelle concentration (CMC) was carried out via a method of increasing the fluorescence in accordance with the procedure [26], using diphenylhexatriene as a fluorescent label. The fluorescence spectra were obtained at an excitation wavelength of 366 nm and a recording wavelength of 430 nm.

Direct emulsions were obtained by dispersing 4 ml of a 5% copolymer solution in methylene chloride in 40 ml of water (ultrasonic disperser UZDN-A, 30 s, 15 W). The concentration in water of all the copolymers for the resulting emulsions exceeded CMC two-fold. Reverse emulsions were also obtained by ultrasonic treatment, while 0.1 ml of water was dispersed in 10 ml of a 5% copolymer solution (ultrasonic disperser UZDN-A, 30 s, 15 W).



Scheme 4



Scheme 5

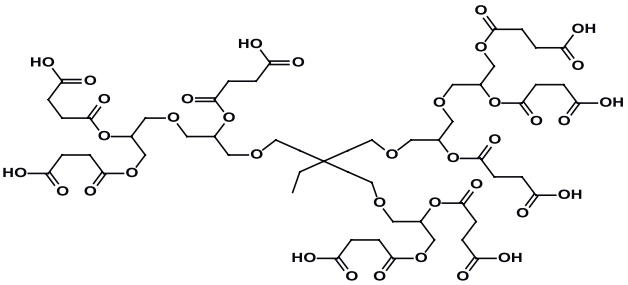
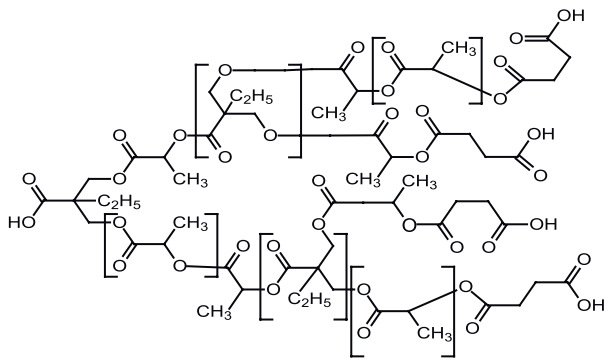
To determine the average droplet size of the emulsion, we used a Photocor-FC correlation spectrophotometer (*Photocor Instruments Inc*., USA) with a He-Ne laser radiation source (*Coherent*, USA, Model 31-2082, 632.8 nm, 10 mW).

Results and Discussion

The branched polymers **I–IV** were obtained in the form of yellowish solids, readily soluble in THF and chloroform. The ^{1}H-NMR spectra of polyethers **I** and **II**

contain signals of the macromolecule branched core protons for $–CH_2–CH_3$ (0.88 ppm) and $–CH_2–CH_3$ (1.37 ppm), characteristic of polyglycerol groups, as well as a wide multiplet peak typical for signals of the $–CH_2–O–$ and –CH< groups (at 3.00–4.20 ppm). The ^{1}H-NMR spectra of polyesters **III, IV** contain signals of proton groups –CH< and $–CH_3$ polylactide units at 5.04 and 1.45 ppm, respectively, as well as signals characteristic of the protons for the $–CH_2$ and $–CH_3$ groups of 2,2-bis-(hydroxymethyl)butanoic acid (1.23 and 0.90 ppm, respectively). Since the signals of the characteristic groups did not overlap in the spectra of all polymers and it was possible to integrate them, the ratio of the corresponding groups in the polymer, the monomer composition, and the molecular weight of the studied macromolecules were determined based on integrated signal intensities characteristic for various comonomers. As can be seen in Table 1, all branched polymers were obtained in high yield, which implies the completeness of the synthesis reaction.

Table 1. Characteristics of synthesized branched polymers

No.	Structure of branched polymer	Yield,%	M_n of copolymer, g/mol		M_w/M_n**
			M_n^{NMR}*	M_n^{GPC} **	
I		99	2300	2350	1.4
II		98	4800	4950	1.5
III		98	2000	2200	1.9
IV		96	5200	5800	2.3

*Determined from the NMR data;
**Determined from the GPC data.

As a result of the reaction of isocyanatopropylsilatrane with branched polymers, two series of amphiphilic compounds with a different structure and composition of the main polymer chains, as well as with an amount of side silatrane and trimethylsilyl fragments were obtained. These polymers were white solid materials, the solubility of which in water depended strongly on the content of silatrane fragments. Thus, polymers with an insignificant (about 10%) content of silatrane groups were poorly soluble in water, while polymers with 97–100% substitution of hydroxyl groups with silatrane groups were easily soluble in water. All amphiphilic polymers were characterized by NMR spectroscopy and GPC. The degree of substitution of free hydroxyl groups was characterized using ^{1}H and quantitative ^{13}C NMR spectroscopy (Table 2). The experimentally determined and theoretically calculated amounts of carboxyl groups substituted by silatranes have close values, which confirms the correspondence of the proposed polymer structures to those obtained.

As a result, we obtained polymers with a branched core formed by polyethers (polymers **1–6**) or polyesters (polymers **7–12**) with low (polymers **1–3**, **7–9**) or high (polymers **4–6**, **10–12**) molecular weight. In this case, polymers **1, 4, 7, 10; 2, 5, 8, 11** and **3, 6, 9, 12** differed in the structure and mass of the branched block, while the degree of substitution of the hydrophilic groups of the branched block by silatranes in these series of polymers were similar.

Table 2. Characteristics of synthesized polymeric silatranes

Sample No.	Branched polymer	Yield, %	Substitution degree*		M_n**	M_w/M_n**
			Calculated	Measured		
1	**I**	97	30	29	3300	2.3
2		95	60	57	4300	2.4
3		96	100	97	5550	2.3
4	**II**	93	30	28	6950	2.6
5		95	60	57	8900	2.8
6		92	100	93	11550	3.1
7	**III**	94	30	28	2700	2.8
8		96	60	57	3200	2.6
9		96	100	97	3800	2.7
10	**IV**	97	30	29	11100	3.2
11		97	60	58	16500	3.1
12		95	100	94	17400	3.4

*Degree of substitution of polymer hydroxyl groups by the silatrane fragments, determined via monomer ratios (Calculated) and from the NMR data (Measured).

**Values, determined from the GPC data.

In view of the amphiphilicity of the obtained compounds, their ability to form micelles in aqueous solutions and the properties of their surface activity were studied. CMC values were determined by quenching the fluorescence of polymers. The results are presented in Table 3 together with the HLB values determined by the Griffin equation. Based on the data obtained, it may be noted that the hydrophilic-lipophilic balance of the copolymers within each series changed systematically, while the HLB and CMC values of almost all polymers correlate well with each other, showing a linear relationship between HLB and CMC. Moreover, polymers based on polyethers (polymers **1–6**) generally showed higher CMCs than polymers based on polyesters (polymers **7–12**); although the HLB values for polymers of different series but with similar degrees of substitution were close.

Table 3. Surface-active properties of polymeric silatranes

Polymer	HLB	CMC, mol/L	Polymer	HLB	CMC, mol/L
1	6.1	2.2×10^{-5}	**7**	3.7	1.2×10^{-6}
2	9.3	3.2×10^{-3}	**8**	6.3	8.1×10^{-4}
3	11.7	5.8×10^{-1}	**9**	8.4	2.6×10^{-1}
4	6.2	3.1×10^{-4}	**10**	9.5	9.6×10^{-7}
5	9.2	6.3×10^{-3}	**11**	13.0	8.7×10^{-3}
6	11.7	7.1×10^{-1}	**12**	13.3	1.4×10^{-2}

Since one of the possible applications for synthesized copolymers is their use as surfactants during micro- and nanocapsulation, the study of the aggregative stability of emulsions stabilized by such compounds is of great importance. In connection with this, we evaluated the stability of direct and reverse emulsions stabilized by polymers **1–12** (Table 4).

It was found that all the copolymers studied were able to increase the aggregative stability of inverse emulsions: the size of inverse emulsion droplets in the presence of polymers **1–12** increased 2.1–6.1 times in 30 minutes, while without the use of polymers the size of the drops of the emulsion increased by 14.5 times. The stability of inverse emulsions depended both on the degree of substitution of peripheral hydroxyl groups of polymers with silatranes and on the molecular weight and structure of the branched block of polymers. The smallest emulsion droplets were obtained when polymers with a low molecular weight polyester branched block were used as surfactants. The size of the droplets of the emulsions increased when increasing the molecular weight of the branched block. A similar dependence in

Table 4. Size of the emulsion droplets, obtained from the solutions of polymeric silatranes

Polymer	Size of the reverse emulsion droplets (nm), after			Size of the direct emulsion droplets (nm), after		
	1 min	10 min	30 min	1 min	10 min	30 min
– *	58	490	840	175	1080	–**
1	57	211	270	179	580	870
2	58	227	285	175	471	552
3	62	254	328	188	338	470
4	54	191	242	184	479	690
5	56	218	280	180	434	537
6	57	270	350	188	371	430
7	56	118	140	200	437	727
8	55	169	210	191	377	464
9	58	199	250	205	350	416
10	56	209	265	212	570	760
11	56	231	297	200	532	687
12	57	247	321	196	422	596

*Emulsions, obtained without surfactants.

**Water release as a separate phase was observed.

the size of the inverse emulsion's droplets on the size of the branched block was also observed in polymers with a branched block based on simple ether (polymers **1–6**). For all the polymers, the stability of reverse emulsions decreased with increasing degree of substitution of hydroxyl groups with silatranes.

All the copolymers studied were able to increase the aggregative stability of direct emulsions as well: the sizes of direct emulsion droplets in the presence of **1–12** polymers increased 2.1–4.6 times in 30 minutes, which is much less than the increase in emulsion droplets without using polymers. The stability of direct emulsions, as well as reverse ones, depended both on the degree of substitution of peripheral hydroxyl groups of polymers with silatranes and on the molecular weight and structure of the branched block of polymers. When polymers with low molecular weight branched polyester blocks were used as surfactants, emulsions with the smallest droplet size were obtained: with increasing the molecular weight of the branched block, the size of the droplets of the emulsions increased. A similar dependence in the size of direct emulsion droplets on the size of a branched block was also observed in the case of polymers with a branched block based on ether (polymers **1–6**); although for these polymers the decrease in the droplet size of the emulsion with an increase in the branched polymer core was less pronounced. For all the polymers, the stability of direct emulsions increased with an increase in the degree of substitution of hydroxyl groups with silatranes.

Thus, the obtained results show the possibility of creating polymer surfactants containing silatrane groups. By varying the structure of the polymer, its molecular weight and the degree of substitution of peripheral functional groups, it is possible to obtain surfactants with the desired surface properties.

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The authors declare no conflict of interest.

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About the authors:

Vladislav V. Istratov, Cand. of Sci. (Chemistry), Senior Researcher of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences (28, Vavilova ul., Moscow, 119991, Russia). E-mail: slav@ineos.ac.ru, Scopus Author ID 17136964600, Researcher ID J-7017-2014

Vitaly I. Gomzyak, Cand. of Sci. (Chemistry), Senior Lecturer of the Medvedev Chair of Chemistry and Technology of Macromolecular Compounds, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: vgomzyak@gmail.com. Scopus Author ID 55841680300, Researcher ID E-4518-2017

Olga V. Yamskova, Cand. of Sci. (Chemistry), Researcher of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences (28, Vavilova ul., Moscow, 119991, Russia). E-mail: olga_yamskova@mail.ru. Scopus Author ID 56816874700

Gali D. Markova, Cand. of Sci. (Chemistry), Senior Researcher of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences (28, Vavilov ul., Moscow, 119991, Russia). E-mail: mgaly@yandex.ru. Scopus Author ID 7003815520

Lyudmila G. Komarova, Cand. of Sci. (Chemistry), Senior Researcher of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences (28, Vavilova ul., Moscow, 119991, Russia). Scopus Author ID 7102405938

Boris A. Izmaylov, Dr. of Sci. (Chemistry), Professor, Leading Researcher of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences (28, Vavilova ul., Moscow, 119991, Russia). E-mail: izmaylov38@yandex.ru. Scopus Author ID 24610651200

Valerii A. Vasnev, Dr. of Sci. (Chemistry), Professor, Head of the Laboratory of Heterochain Polymers, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences (28, Vavilova ul., Moscow, 119991, Russia). E-mail: vasnev@ineos.ac.ru. Scopus Author ID 7004556739

Об авторах:

Истратов Владислав Викторович, кандидат химических наук, старший научный сотрудник лаборатории гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). E-mail: slav@ineos.ac.ru. Scopus Author ID 17136964600, Researcher ID J-7017-2014

Гомзяк Виталий Иванович, кандидат химических наук, старший преподаватель кафедры химии и технологии высокомолекулярных соединений им. С.С. Медведева Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: vgomzyak@gmail.com. Scopus Author ID 55841680300, Researcher ID E-4518-2017

Ямскова Ольга Васильевна, кандидат химических наук, научный сотрудник лаборатории гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). E-mail: olga_yamskova@mail.ru. Scopus Author ID 56816874700

Маркова Гали Дмитриевна, кандидат химических наук, старший научный сотрудник лаборатории гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). E-mail: mgaly@yandex.ru. Scopus Author ID 7003815520

Комарова Людмила Григорьевна, кандидат химических наук, старший научный сотрудник лаборатории гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). Scopus Author ID 7102405938

Измайлов Борис Александрович, доктор химических наук, профессор, ведущий научный сотрудник лаборатории гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). E-mail: izmaylov38@yandex.ru. Scopus Author ID 24610651200

Васнев Валерий Александрович, доктор химических наук, профессор, заведующий лабораторией гетероцепных полимеров Института элементоорганических соединений им. А.Н. Несмеянова РАН (119991, Россия, Москва, ул. Вавилова, д. 28). E-mail: vasnev@ineos.ac.ru. Scopus Author ID 7004556739

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СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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Effect of polyethylene glycol mixtures as ointment base on the physicochemical properties of Lavsan atraumatic wound dressings

Anastasiya A. Korolchuk[1], Elena S. Zhavoronok[1], Olga A. Legonkova[2], Stanislav A. Kedik[1]

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

[2]A.V. Vishnevsky National Medical Research Center of Surgery, Moscow 117997, Russia

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

Objectives. *Modern atraumatic wound dressings are based on polyethylene terephthalate, or Lavsan, which is shaped to form threads. The aim of the study was to determine the reasons for Lavsan woven nets' hardening and becoming more trauma-prone during storage, and to find ways of eliminating these effects.*

Methods. *We used differential scanning calorimetry, performed on a NETZSCH DSC 204 F1 Phoenix device, in a dynamic mode with a temperature range from 20 to 300 °C in argon flow to determine phase states, glass transition temperatures, and melting temperatures of Lavsan fibers (including those treated with polyethylene glycol mixtures). We performed rheoviscometry studies on a Brookfield DV2TLV rotational viscometer, with a SC4-16 thermostatic control unit, at the following temperatures: 25, 36.6, 40, 45, 50, and 55 °C, with shear rates ranging from 120 to 200 s–1 to determine dynamic viscosity and investigate the mixing characteristics of polyethylene glycols with different molecular weights.*

Results. *We have established that samples of Lavsan woven nets, stored long-term in laboratory conditions (up to 2, 3, and 16 years), are in the crystalline state with a high degree of crystallinity. Upon heating these nets to 300 °C, it is possible to reduce the degree of crystallinity by 19–32%, but it does not completely eliminate the effect. Polyethylene glycols and their mixtures which exhibit non-Newtonian flow behavior and are used as an ointment base, have a significant effect on Lavsan's crystallinity. We have determined that the optimal ratio of polyethylene glycols for the modification of Lavsan nets is PEG-400:PEG-1500 = 80:20 wt %. Upon storing Lavsan woven nets in this mixture at room temperature, the Lavsan's crystallinity is greatly reduced, and upon heating the system, the crystallinity practically disappears.*

Conclusions. *The effect of polyethylene glycol mixtures (the base for therapeutic ointments) with various molecular weights on the phase organization of Lavsan has been evaluated. As a result of this study, we can offer a new approach to reduce the injuring effect of synthetic (Lavsan) bases of atraumatic wound dressings.*

Keywords: *wound dressing, ointment base, polyethylene terephthalate, polyethylene glycol, melting point, degree of crystallinity, viscosity.*

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Влияние смесей полиэтиленгликолей в качестве мазевой основы на физико-химические свойства лавсановых атравматичных раневых повязок

А.А. Корольчук[1], Е.С. Жаворонок[1], О.А. Легонькова[2], С.А. Кедик[1]

[1]МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва 119571, Россия
[2]Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского, Москва 117997, Россия
[@]Автор для переписки, e-mail: nastya.corolchuk@yandex.ru

Цели. *Основой современных атравматичных раневых повязок является полиэтилентерефталат (или лавсан), которому придают вид нитей. Целью работы являлось определение причин увеличения жесткости и травматичности лавсановых тканых сеток при хранении и поиск путей устранения этого эффекта.*
Методы. *Для определения фазового состояния, температуры стеклования и плавления лавсановых волокон, в том числе после обработки смесями полиэтиленгликолей, использовали дифференциальную сканирующую калориметрию, которую проводили на приборе NETZSCH DSC 204 F1 Phoenix в динамическом режиме в диапазоне температур от 20 до 300 °C в токе аргона. Для определения динамической вязкости и оценки характера смешения полиэтиленгликолей разной молекулярной массы применяли метод реовискозиметрии, которую осуществляли на ротационном вискозиметре Brookfield DV2TLV с термостатируемым рабочим узлом SC4-16 при температурах: 25, 36.6, 40, 45, 50 и 55 °C в диапазоне скоростей сдвига от 120 до 200 $с^{-1}$.*
Результаты. *Установлено, что длительно выдержанные в лабораторных условиях (до 2, 3 и 16 лет) образцы лавсановых тканых сеток находятся в кристаллическом состоянии с высокой степенью кристалличности. Прогрев этих сеток до 300 °C позволяет снизить степень кристалличности на 19–32%, но не устраняет ее полностью. Полиэтиленгликоли и их смеси, которые используют в качестве мазевой основы, проявляющие неньютоновское поведение при течении, оказывают заметное влияние на степень кристалличности лавсана. Установлено оптимальное соотношение полиэтиленгликолей для модификации лавсановых сеток: ПЭГ-400:ПЭГ-1500 = 80:20 мас. ч. После выдерживания лавсановой тканой сетки в этой смеси при комнатной температуре степень кристалличности лавсана сильно снижается, а после прогрева такой системы кристалличность практически исчезает.*
Заключение. *Оценено влияние на фазовую организацию лавсана смесей полиэтиленгликолей различной молекулярной массы, являющихся основой лечебных мазей. В результате проведенной работы предложен новый подход для уменьшения травматичности синтетических (лавсановых) основ атравматичных раневых повязок.*

Ключевые слова: *раневое покрытие, мазевая основа, полиэтилентерефталат, полиэтиленгликоль, температура плавления, степень кристалличности, вязкость.*

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Introduction

Atraumatic wound dressings is just one type of bandage material meant to gently protect wounds from exposure to harmful environmental factors [1]. Such dressings are based on fibers, threads, tissues, films, and nonwoven materials [2] and should prevent damaged areas from coming into contact with external irritants, foreign objects and infections, as well protect the wound from possible new injuries [2, 3].

Historically, the first materials used to stop bleeding and mechanically protect wounds, were cotton tissues [2]. However, this material has a

number of disadvantages, and a major one is the heterogeneity of cotton threads. Microscopic strands, which are characteristic for cotton, get into the wound, thus irritating the injured area and affecting the healing of the wound [3]. This has led to research on alternative dressings that could be chemically inert and have homogenous threads. Polymeric materials such as polyethylene terephthalate (PET) fulfill these requirements.

Polyethylene terephthalate, or Lavsan, is a complex polyester that is shaped as threads for convenience [4, 5]. The main reasons for Lavsan to be used as wound dressings are its mechanical characteristics and relatively low cost [5]. Lavsan fibers are very strong and durable, elastic and resistant to chemicals, and biocompatible; Lavsan is a polymer with a low rate of biodegradation [6, 7]. However, the prolonged storage of Lavsan nets makes them harder and more trauma-prone, which is unacceptable for wound dressings [8, 9]. The aim of this study is to investigate the reasons for Lavsan woven nets' hardening and becoming more prone to trauma during storage, and to find ways of eliminating these effects.

Materials and Methods

We used Lavsan woven nets made of polyethylene terephthalate with a nominal molecular weight of NMW = 30 kDa, stored in a laboratory for up to τ_{aging} = 2, 3, 16 years. The samples differed in their aging time, as well as in the weaving (see Table 1). To investigate the effect of ointment base on the nets, we used model oligomers: polyethylene glycols (PEGs) PEG-400, PEG-1500 and their mixtures in various ratios. The mixing of PEGs was performed at room temperature, followed by heating to 80 °C for 10 minutes until homogeneous viscous mixtures were obtained. The nets were soaked for 1, 7, or 28 days in PEG-400 or PEG-400:PEG-1500 = 80:20 wt % mixture, at room temperature, and subsequently studied.

Over the course of this work, we used differential scanning calorimetry (DSC) and rheoviscometry. Thermograms were recorded on a NETZSCH DSC 204 F1 Phoenix device, in a dynamic mode with the temperature range from 20 to 300 °C in argon flow. The dynamic viscosity of PEGs and their mixtures was studied on a Brookfield DV2TLV rotational viscometer, with a SC4-16 thermostatic operating unit, at the following temperatures: 25, 36.6, 40, 45, 50, and 55 °C, with shear rates ranging from 120 to 200 s^{-1}.

Results and Discussion

The results of DSC studies of Lavsan woven nets are shown in Fig. 1.

The analyzed samples have a clear endothermal peak in the 240–280 °C temperature range that can be interpreted as a melting of polyethylene terephthalate crystals, according to [10]. It is evident that this peak area becomes smaller in the second DSC experiment, but in the 60–80 °C temperature range there is a characteristic "step" indicating that devitrification occurs and an amorphous phase is present. In the second scanning, we observe an additional, sharp exothermal peak in the 140–160 °C temperature range, which can be interpreted as crystallization of the amorphous part of the sample, according to [10].

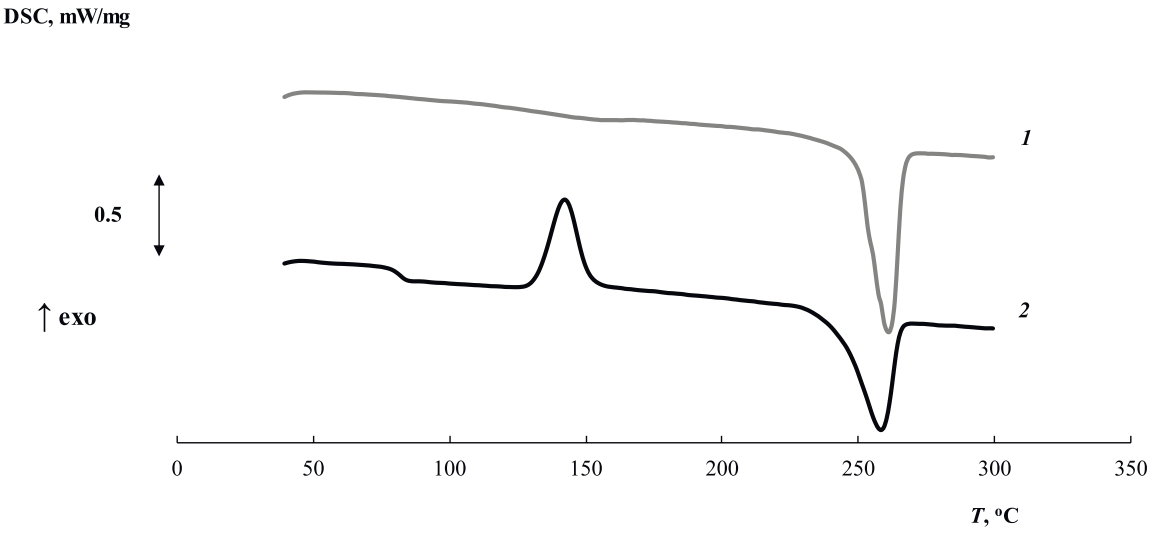

Fig. 1. Typical DSC diagram for Lavsan woven nets; shown here is the diagram for PET-207 at w^+ = 10 K/min: *1* – initial heating; *2* – secondary heating.

The thermophysical characteristics of the studied samples are presented in Table 1. We may conclude that samples stored at room temperature for a long time are in crystallized state, and the amorphous phase content is very low, but it increases upon heating of the sample.

The areas of endothermal melting peaks allowed us to estimate the degree of crystallinity, in our first approximation. We set the degree of crystallinity at 100% for those samples that did not exhibit vitrification, according to their DSC thermograms, and calculated the degree of crystallinity of the re-heated samples using the following formula [11]:

$$\alpha = \frac{\Delta S''}{\Delta S'} \times 100\% , \quad (1)$$

where α is the crystalline phase content, ΔS′ is the melting peak area of the crystalline phase in the first scanning, ΔS″ is the melting peak area of the crystalline phase in the second scanning.

The calculated values of α are shown in Table 1. We can see that the degree of crystallinity is between 68% and 81% even for the re-heated samples.

The ointment base can have a significant effect on the phase state of polyethylene terephthalate; this is why we investigated some ointment bases. A common ointment base is PEG mixtures, with molecular weights of 400 and 1500, used in various ratios [11]. The experimental viscosity–velocity curves (Fig. 2) show the PEG mixtures that look homogeneous do exhibit non-Newtonian behavior.

When PEG-1500 concentration increases, we observe viscosity hysteresis (rheopexy type) that enhances over time. This may indicate that the PEG mixture has a heterogeneous structure, despite it looking homogeneous. Figure 2 shows that when a PEG-1500 concentration in PEG-400 increases, the dynamic viscosity of the mixtures is elevated.

Temperature is an important parameter that influences the viscosity of oligomers and their mixtures. As we can see from experimental data in Fig. 3, the viscosity of the sample decreases when the temperature increases, and the non-Newtonian behavior becomes less obvious; for example, at 55 ºC we observe almost Newtonian behavior of the samples.

Our analysis of the results obtained at different temperatures allows us to estimate the activation energy of viscous flow for pure ethylene glycols and their mixtures using the Arrhenius–Frenkel–Eyring equation:

$$\eta = A \times e^{\frac{-E_a}{R}} , \quad (2)$$

where η is the effective dynamic viscosity at 55 s^{-1}; E_a is the activation energy of viscous flow; R is the universal gas constant; T is the absolute temperature; A is the pre-exponential factor that takes into account the probability that an elementary act of viscous flow happens.

The dependency of the apparent activation energy on the PEG ratio in their mixture is shown in Fig. 4. We can see that the activation energy of viscous flow is low and almost does not depend on the PEG mixture's composition. This indicates that the mixing of PEGs with different molecular weights (containing the same monomer) is athermal.

To sum up, when PEG-1500 content in PEG-400 is up to 50 wt %, the mixture of these oligomers

Table 1. Thermophysical parameters for Lavsan woven materials samples

Sample	τ_{aging}, years	T_g, ºC	T_{cryst}, ºC		$\lvert\Delta S_{cryst}\rvert$, J/g		T_{melt}, ºC		$\lvert\Delta S_{melt}\rvert$, J/g		α, %
			1 scan	2 scan	1 scan	2 scan	1 scan	2 scan	1 scan	2 scan	
PET-208*	2	80	–	145	–	36	261	256	62	44	71
PET-207**	3	80	–	–	–	–	262	257	79	54	68
PET-206*	3	80	–	148	–	69	260	257	115	90	78
PET-205**	16	83	–	–	–	–	262	258	74	51	69
PET-204*	16	82	–	142	–	37	261	258	72	58	81

* Weaving: "honeycombs".

** Weaving: "squares". Apparently, the difference in the weaving means the difference in the degree of Lavsan fiber elongation during the formation of the woven net, therefore the nets of the same age, but with different weaving, have different properties.

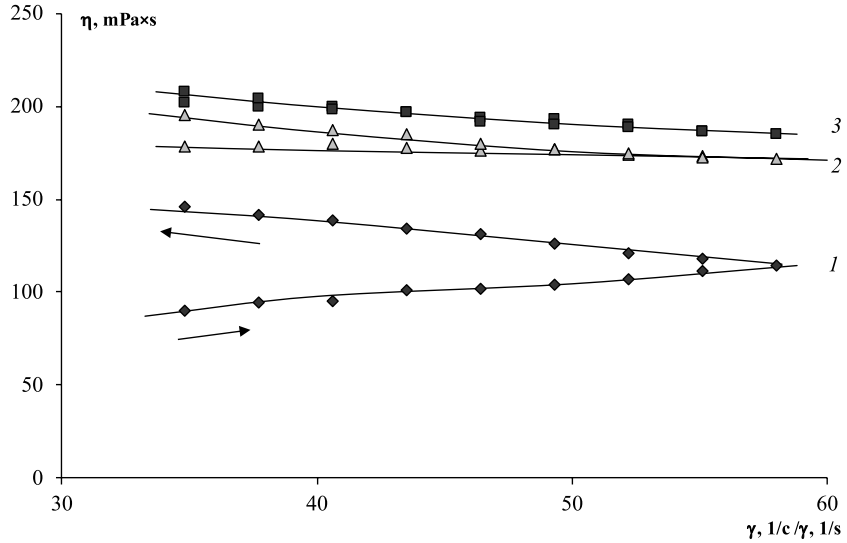

Fig. 2. Typical viscosity–velocity curves obtained at 25 ºC for PEG-400 and PEG-1500 mixtures, with PEG-400 content, wt %: 70 (*1*); 80 (*2*); 90 (*3*).

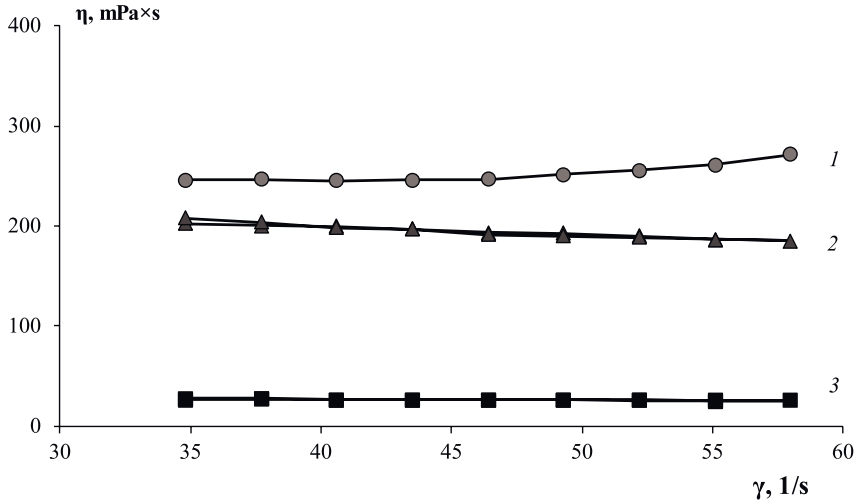

Fig. 3. Typical viscosity–velocity curves for the PEG-400:PEG-1500 = 80:20 wt % mixture, obtained at the following temperatures, ºC: 25 (*1*); 36.6 (*2*); 55 (*3*).

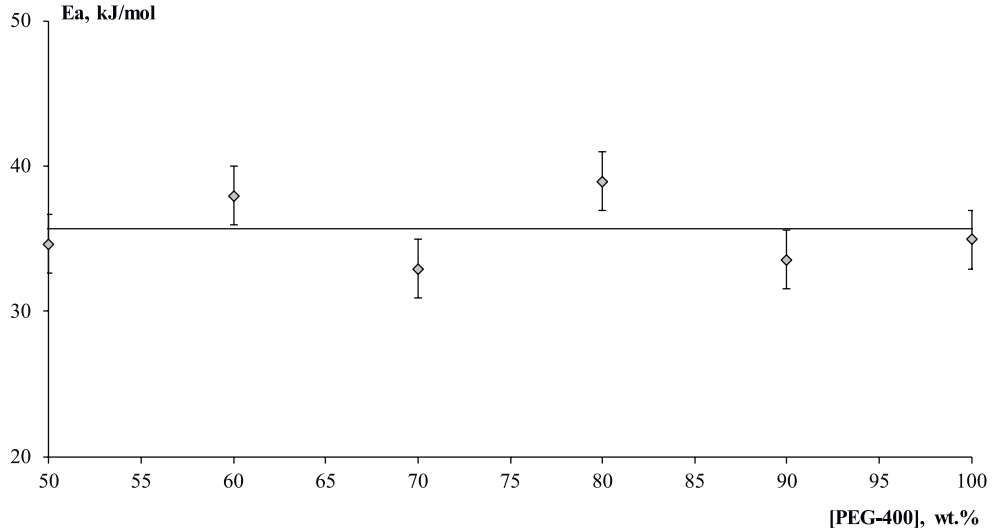

Fig. 4. Dependency of the apparent activation energy of viscous flow on the composition of PEG-400:PEG-1500 mixtures.

behaves the same. This is why we selected the PEG-400:PEG-1500 = 80:20 wt % composition for further study; this composition is widely used in ointment bases for atraumatic wound dressings, according to [12, 13]. We used the DSC method to investigate the effect of this composition on the phase state of Lavsan woven nets. The thermograms obtained are presented in Fig. 5.

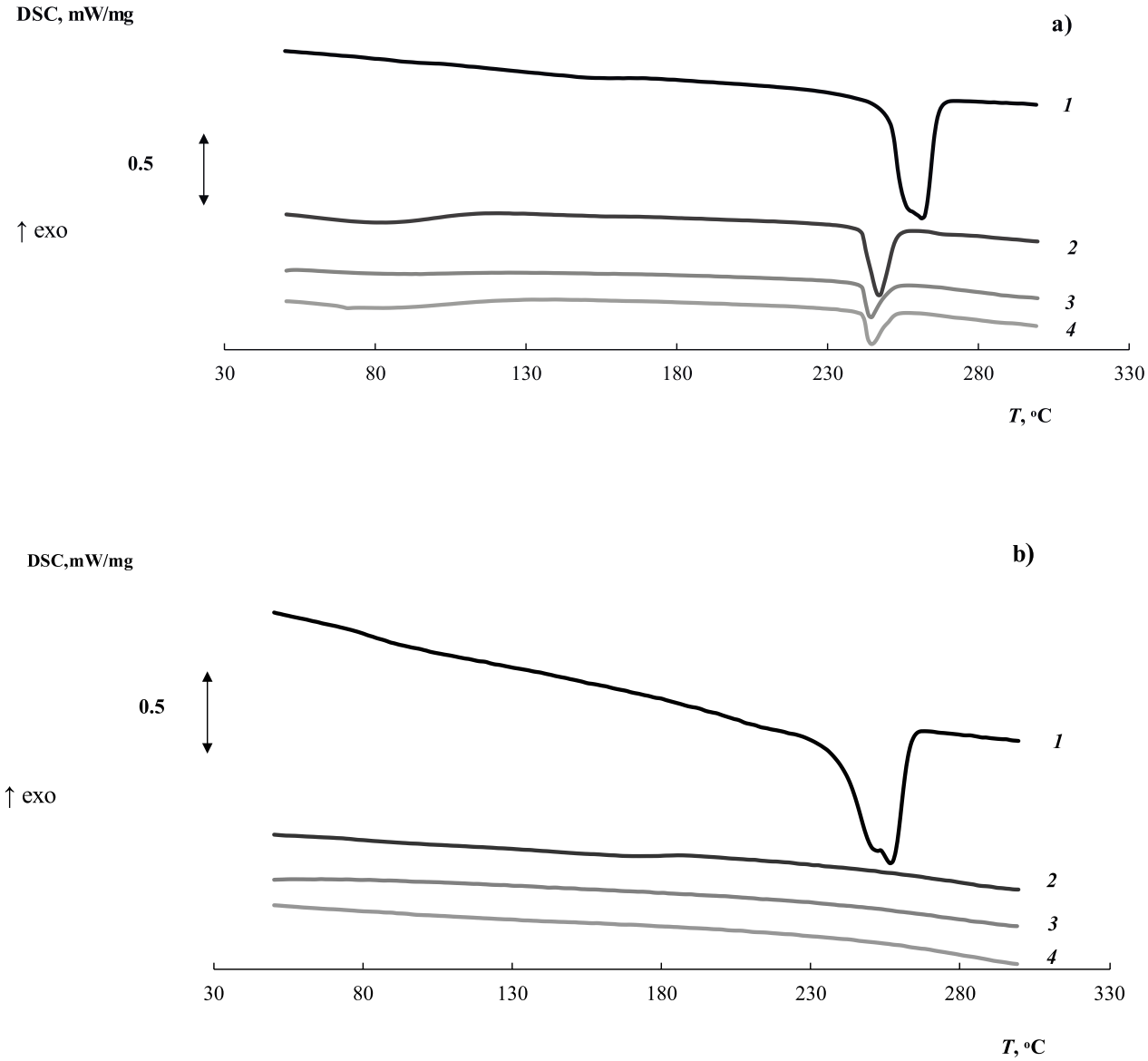

Fig. 5. Typical DSC thermograms for initial PET-204 (*1*) and for PET-204 incubated in the PEG-400:PEG-1500 = 80:20 wt % composition for 1 day (*2*), 7 days (*3*) and 28 days (*4*). Results of the first (a) and the second (b) scanning, at w^+ = 10 K/min, are shown here.

The analysis of these thermograms shows that the incubation of Lavsan woven nets in PEG mixtures results in an expected decrease in the area of the endothermal peak in the 250–280 ºC temperature range. At the same time, in the low temperature range (80–100 ºC) we observe a "step" resembling vitrification. It means that the degree of crystallinity decreases; calculations using formula (1) show that the degree of crystallinity for incubated samples goes down to 14% in 28 days (Table 2). However, even after this prolonged incubation the degree of crystallinity still remains significant. At the same time, the re-heating of such samples (Fig. 5b) leads to the complete disappearance of the endothermal melting peak. Clearly, it happens because PEG molecules penetrate into polyethylene terephthalate, but the woven net does not change its appearance and commercial properties.

Table 2. Thermophysical parameters for samples of PET-204 incubated in PEG-400 and its mixture with PEG-1500

Incubation time, days	PEG-400		PEG-400:PEG-1500 = 80:20 wt %	
	$\|\Delta S_{melt}\|$, J/g	α, %	$\|\Delta S_{melt}\|$, J/g	α, %
1	46	58	25	32
7	11	22	11	14
28	17	14	11	14

Conclusions

We have shown that Lavsan nets aged in natural conditions are partially crystallized, with a high crystalline content. Upon their incubation in PEG mixtures commonly used as ointment bases and whose optimal composition was selected based on rheoviscometry, the degree of crystallinity decreases significantly at room temperature, and the crystallinity almost disappears upon heating. This provides an opportunity to prolong the shelf life of Lavsan nets.

The authors declare no conflict of interest.

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About the authors:

Anastasiya A. Korolchuk, Student of the Chair of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow 119571, Russia).

Elena S. Zhavoronok, Cand. of Sci. (Chemistry), Associate Professor of the Chair of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). Scopus Author ID 7801409746, ResearcherID H-9420-2013, https://orcid.org/0000-0002-7235-3361

Olga A. Legonkova, Dr. of Sci. (Engineering), Head of the Department of Dressings, Suture and Polymer Materials in Surgery, A.V. Vishnevsky National Medical Research Center of Surgery of the Ministry of Health of the Russian Federation (27, Bolshaya Serpukhovskaya ul., Moscow 117997, Russia). Scopus Author ID 18437207900

Stanislav A. Kedik, Dr. of Sci. (Engineering), Professor, Head of the Chair of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow 119571, Russia). https://orcid.org/0000-0003-2610-8493

Об авторах:

Корольчук Анастасия Александровна, студент кафедры биотехнологии и промышленной фармации Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86).

Жаворонок Елена Сергеевна, кандидат химических наук, доцент кафедры биотехнологии и промышленной фармации Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). Scopus Author ID 7801409746, ResearcherID H-9420-2013, https://orcid.org/0000-0002-7235-3361

Легонькова Ольга Александровна, доктор технических наук, руководитель отдела перевязочных, шовных и полимерных материалов в хирургии ФГБУ «Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского» Министерства здравоохранения Российской Федерации (117997, Россия, Москва, ул. Большая Серпуховская, д. 27). Scopus Author ID 18437207900

Кедик Станислав Анатольевич, доктор технических наук, профессор, заведующий кафедрой биотехнологии и промышленной фармации Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). https://orcid.org/0000-0003-2610-8493

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In memory of the Master

On the occasion of the 90th birthday of Leonid Antonovich Serafimov

Alla K. Frolkova

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

@Corresponding author, e-mail: frolkova@mitht.ru

The article is dedicated to the 90th birthday of Leonid Antonovich Serafimov, an outstanding scientist, Doctor of Engineering Sciences, professor at the M.V. Lomonosov Moscow State University of Fine Chemical Technologies. Serafimov made an invaluable contribution to the development of the theoretical foundations of chemical technology. The article briefly describes the research conducted by the scientific school "Theoretical Foundations and Technological Principles of Mass-Transfer and Combined Processes of Organic Synthesis" founded and led by him. Special attention is given to the ideological component of his scientific and pedagogical activity; and his active civil position, encyclopedic knowledge and remarkable personal qualities are also duly noted.

Keywords: *Leonid A. Serafimov, scientific school, theory of combined reaction-mass transfer processes, thermodynamic-topological analysis of phase diagrams.*

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Памяти Учителя

К 90-летию со дня рождения Леонида Антоновича Серафимова

А.К. Фролкова

МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва 119571, Россия

@Автор для переписки, e-mail: frolkova@mitht.ru

Статья посвящена 90-летию со дня рождения выдающегося ученого, доктора технических наук, профессора МИТХТ им. М.В. Ломоносова Леонида Антоновича Серафимова, внесшего неоценимый вклад в развитие теоретических основ химической технологии. Кратко описаны исследования, проводимые научной школой «Теоретические основы и технологические принципы массообменных и совмещенных процессов органического синтеза», основанной и возглавляемой им; обращено внимание на мировоззренческую составляющую в его научно-педагогической деятельности; отмечены его активная гражданская позиция, энциклопедические знания и замечательные личностные качества.

Ключевые слова: *Серафимов Л.А., научная школа, теория совмещенных реакционно-массообменных процессов, термодинамико-топологический анализ фазовых диаграмм.*

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On September 29, 2019, Leonid Antonovich Serafimov, Doctor of Technical Engineering Sciences, professor, and world-famous scientist would have turned 90 years old. His entire life was associated with the M.V. Lomonosov Moscow State University of Fine Chemical Technologies (MITHT in Russian abbreviation), where he rose from a student, Stalin scholarship holder to a professor and head of a department. L.A. Serafimov worked for 13 years in the Ministry of Higher and Specialized Secondary Education of the Russian Soviet Federative Socialist Republic. He headed the General Directorate of Universities, Economic and Law Institutes and was a member of the ministry collegiate organ.

L.A. Serafimov was the founder of the scientific school "Theoretical Foundations and Technological Principles of Mass Transfer and Combined Processes of Organic Synthesis." He discovered the fundamental laws of heterogeneous equilibria and used these laws as a basis for an original thermodynamic-topological analysis of phase diagrams and dynamic rectification systems. This analysis is a stem for developing resource-saving schemes for the separation of complex mixtures in basic organic and petrochemical synthesis.

Professor L.A. Serafimov created the theory of combined reaction and mass-transfer processes and the theory of transformation of the structures of phase equilibrium diagrams based on boundary and internal tangential azeotropy. He actively developed the physicochemical fundamentals in the functioning of energy-efficient complexes for azeotropic mixture separation.

The studies of the scientific school headed by him were 15–20 years ahead of the work of foreign scientists, ensuring the stable priority of Russian science in the aforementioned field. Professor Serafimov placed great emphasis in his works on introducing various mathematical methods in studies on heterogeneous systems thermodynamics. His scientific results were used abroad to create modern program-oriented modeling systems for computers.

It is worth mentioning separately the worldview component in the scientific and pedagogical activity of L.A. Serafimov. He considered it absolutely necessary to include philosophical issues in lecture courses, to illustrate the relationship between natural science laws and philosophical ones and thought a lot about the impact of technology on society. His scientific works on the development of theoretical foundations for chemical technology applied to technological problems reveal the concepts of research intensity, ideality, infinity, homology and isomerism, invariants of phase diagram structures, mathematical modeling as a method of scientific knowledge, etc.

Professor Serafimov had a phenomenal capacity for work. As a professor at the Department of Chemistry and Technology of Basic Organic Synthesis he gave original lecture courses created by him, which have no analogues in the world. He was engaged in scientific work, wrote articles and left scientific notes for his students until the very end of his life. He possessed an amazing ability to gather young promising scientists around him and captivate them with his scientific ideas, to set specific tasks for them and helped to realize themselves in the form of defenses of qualification works of different levels.

L.A. Serafimov prepared 14 doctors and 75 candidates of sciences, as well as more than 30 masters. L.A. Serafimov is the author of more than 800 scientific papers. Among them are 6 scientific monographs, 44 copyright certificates and patents, and 520 scientific articles, the majority of which were published in leading journals in Russia and abroad.

For many years, Leonid Antonovich was the scientific director of the Laboratory of Problems of the Higher School of MITHT, which on the basis of original methodological works allowed the university to take its rightful place in modern higher education. He published about 40 articles on the modernization of higher education in Russia. The merits of Professor L.A. Serafimov were recognized by the scientific community: he was a two-time winner of the prize of the International Academic Publishing Company *Science* for a series of publications in the journal *Theoretical Foundations of Chemical Technology* published by the Russian Academy of Sciences; he was also Academician of the Russian and International Engineering Academies; Honored Worker of Science and Technology of the RSFSR; Honored Worker in Higher Professional Education of Russia; Honored Inventor of the USSR; Honorary Professor of MITHT named after M.V. Lomonosov; Honorary Doctor of the Association of the Russian Federation "Basic Processes and Technique of Industrial Technologies." He was also awarded orders and medals.

L.A. Serafimov was an excellent lecturer and a brilliant speaker. He was repeatedly invited to lecture at foreign universities and firms (Rostock and Dortmund Universities, Germany; University of Rennes, France; Prof. Dr. Assen Zlatarov University, Bulgaria; BASF, Stuttgart). He held master classes for students, postgraduates and colleagues from different universities. The Moscow scientific workshop on phase equilibria was created at his initiative.

L.A. Serafimov carried out a lot of scientific and organizational work. For a long time he was a member of the European Engineering and Chemical Working Group on Distillation, Absorption and Extraction, a member of the Expert Council of the Higher Attestation Commission, a member of three dissertation councils, an expert of the Russian Foundation for Basic Research, a member of the RAS Council for the Scientific Fundamentals of Chemical Technology, a member of the organizing committees of international conferences "Chemical Thermodynamics in Russia," "Science-Intensive Chemical Technologies," etc.

He worked as a member of the editorial boards of the journals *Theoretical Foundations of Chemical Technology* and *Fine Chemical Technologies* (*Vestnik MITHT*). Leonid Antonovich Serafimov was a demanding and at the same time benevolent reviewer: he always supported extraordinary publications made by talented scientists; he gave reasoned critical reviews; he published his fundamental results making a significant contribution to the formation of a positive reputation of magazines.

The scientific authority of Professor L.A. Serafimov was indisputable. He was respected both as a scientist and as a teacher by his colleagues, disciples, and students.

Leonid Antonovich's professional path as a scientist and professor is a great example of serving his work! This is the work of an active creator of the achievements of MITHT and higher education in Russia. He made a significant contribution to the history of our institute, academy, and university. An ardent admirer of his Alma Mater, he was always proud of our regalia: the name of Mikhail Vasilyevich Lomonosov and the Order of the Red Banner of Labor, which at various times marked the merits of the staff of the Moscow Institute of Fine Chemical Technologies.

Leonid Antonovich's active role in civil society, encyclopedic knowledge, and personal qualities attracted people of all ages and positions to him. His fidelity to principle and his responsibility always served the interests of MITHT named after M.V. Lomonosov.

We are proud that we lived and worked side by side with this man.

We will always remember him.

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