ISSN 1070-3632, Russian Journal of General Chemistry, 2023, Vol. 93, No. 3, pp. 593–600. © The Author(s), 2023. This article is an open access publication.
Russian Text © The Author(s), 2023, published in Zhurnal Obshchei Khimii, 2023, Vol. 93, No. 3, pp. 483–492.

Biocompatible Microemulsions Based on Oleic Acid Modified with Piperidinium Surfactants

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Received January 19, 2023; revised February 6, 2023; accepted February 9, 2023

Abstract—A series of microemulsions based on oleic acid and Tween 80, modified with piperidinium surfactants, have been obtained and characterized. The effect of additives on the size, stability, and solubilization effect of the formed systems with respect to hydrophilic (rhodamine B) and hydrophobic (indomethacin) substances have been investigated. Varying of the components ratio has allowed preparation of the microemulsions with strongly different viscosity: from easy-flowing formulations to gels. Kinetic parameters describing release of the substrates from the microemulsions have been obtained. In vivo tests of the anti-inflammatory action of the microemulsions loaded with indomethacin have shown that the presence of piperidinium surfactants enhances the therapeutic effect of the drug.

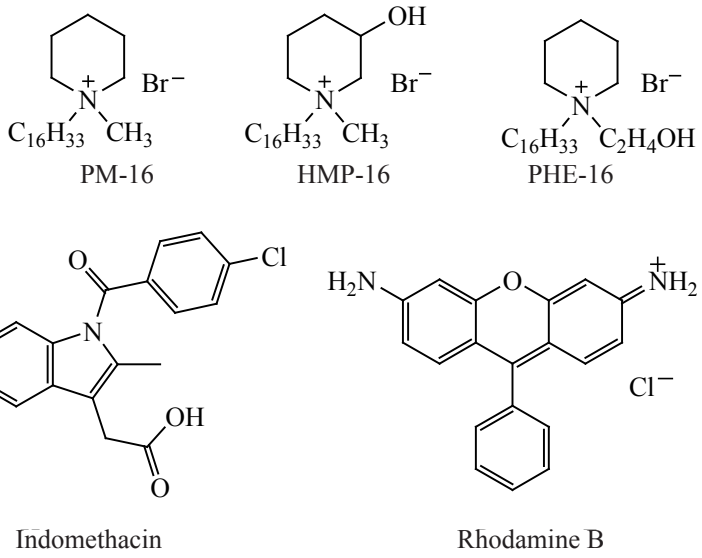
Keywords: microemulsion, piperidinium surfactants, viscosity, size, anti-inflammatory effect

DOI: 10.1134/S1070363223030167

Analysis of modern trends in the drug delivery systems formation and application in medicine and biology has revealed that the supramolecular formulations based on amphiphilic species (micelles, vesicles, micro- and nanoemulsions, liposomes, and solid lipid nanoparticles) open vast possibilities when used as carriers ensuring targeted action and bioavailability of drugs [1–4]. To ensure efficiency and safety of such systems, they should consist of biocompatible, nontoxic, and pharmaceutically acceptable species as well as correspond to a set of physico-chemical parameters. First, the size of the obtained carrier particles should be in the nanoscale range. The system should be stable, exhibit strong solubilizing action, and ensure prolonged release of the bound species. The increased viscosity of the systems turns important as far as its external use is concerned. These demands are to a large extent met in the case of microemulsions, which usually consist of aqueous and oil (hydrocarbon) phases separated by a layer of micelle-forming surfactant, sometimes in the presence of a co-surfactant [5–7]. Nonionic surfactants, which are low-toxic and compatible with many biologically active species, have been often used in the preparation of microemulsions intended for biomedical applications [8–10]. However, they have exhibited poorer performance in comparison with more toxic ionic surfactants. A combination of nonionic surfactant with cationic one can impart positive surface charge to disperse particles, which improves their stability, enhances the solubilizing action, and facilitates their interaction with negatively charged regions of the components of biological systems. The presence of cationic surfactants in microemulsions ensures especially high efficiency in the case of their external application, for instance, as ophthalmological and transdermal drug formulations [11–14].

This study is a continuation and development of our investigations of microemulsions based on oleic acid and Tween 80 used as drug carriers [15–17]. We aimed to widely vary the ratio of the components and partially substitute Tween 80 with piperidinium cationic surfactants. The choice of the latter was inspired by the fact that piperidinium surfactants have manifested themselves as species which can exhibit multifunctional activity and serve as antimicrobial agents and adjuvants improving the solubilizing action and transport properties of the formulations containing bioactive additives

Scheme 1.



[18–21]. 1-Methyl-1-hexadecylpiperidinium bromide (PM-16), 1-methyl-1-hexadecyl-3-hydroxypiperidinium bromide (HMP-16), and 1-(2-hydroxyethyl)-1-hexadecylpiperidinium bromide (PHE-16) were used as piperidinium cationic surfactants. The goals of the research were to characterize the size and stability of the obtained microemulsions and to obtain the systems differing in the viscosity. It was planned to use those systems for solubilization of hydrophilic (Rhodamine B) as well as hydrophobic (indomethacin) species, to estimate the rate of the encapsulates substances release, and to demonstrate the efficiency of the obtained microemulsions loaded with the anti-inflammatory in the in vivo tests. Structures of the considered cationic surfactants and the solubilizates are shown in Scheme 1.

The ME1 microemulsion studied in [10, 17], consisting of biocompatible components (oleic acid, water, Tween 80, and ethanol acting as the co-surfactant and aqueous phase modifier), was selected as the basic system in this research. To impart positive charge to the particles, improve the system stability, and enhance its solubilizing properties, its composition was modified with the hexadecylpiperidinium surfactant additives, including those bearing the hydroxy group in the structure. Moreover, it was possible to obtain the gel-like formulations, convenient for application at different surfaces, via variation of the components ratio. Compositions of the considered microemulsions are collected in Table 1.

The obtained liquid microemulsions (ME1–ME4) exhibited viscosity of 1.2 to 2 cP, which was somewhat reduced with the increase in the fraction of the cationic surfactant in the system (cf. note to Table 1). The most prominent decrease in the viscosity was observed in the case of the microemulsion containing PM-16, molecule of which did not bear the OH group. The dynamic light scattering data revealed unimodal particle size distribution in the case of sample ME1. The derivates systems ME2–ME5 contained two types of the particles (with hydrodynamic diameter of 4–6 and 16–26 nm), irrespectively of the structure of the introduced cationic surfactant. The increase in the content of the cationic surfactant led to decrease in the size of both types of the particles, the fraction of the smaller aggregates being increased. The considered microemulsions retained their transparency, macroscopic uniformity, and the particles distribution in the system during at least two months.

Change in the ratio of the components of the microemulsions and increase in the water content led to significant increase in the system viscosity. As an example, the compositions of a thicker microemulsion (ME6) and the gel-like formulations (ME7–ME9) are given in Table 1. It was found that, the components ratio being equal, denser gels were formed in the systems

Table 1. Composition of the considered microemulsions[a]

Component	Composition, wt %								
	ME1	ME2	ME3	ME4	ME5	ME6	ME7	ME8	ME9
Water	17.0	17.0	17.0	17.0	17.0	40.0	47.0	47.0	47.0
Tween 80	21.0	19.0	15.0	15.0	15.0	13.3	6.5	6.5	6.5
HMP-16	0	2.0	6.0	0	0	4.0	7.0	0	0
PHE-16	0	0	0	6.0	0	0	0	7.0	0
PM-16	0	0	0	0	6.0	0	0	0	7.0
Oleic acid	25.0	25.0	25.0	25.0	25.0	16.5	16.0	16.0	16.0
Ethanol	37.0	37.0	37.0	37.0	37.0	26.2	23.5	23.5	23.5

[a] Viscosity of the flowing microemulsions ME1, ME2, ME3, ME4, ME5, and ME6 was 1.88, 1.80, 1.78, 1.24, 1.48, and 6.3 cP, respectively.

containing the hydroxypiperidinium surfactants, whereas the analogous system containing PM-16 was a rather fluid gel. Likely, the possibility of formation of hydrogen bonds by the hydroxypiperidinium surfactants enhanced the interaction between the microemulsion components and led to its additional structuring, the difference in the location of the OH group in the molecule did not result in noticeably different behavior. It is interesting to note that when a formulation similar to ME7 contained only Tween 80, the microemulsion was not formed. Figure 1 displays the appearance of selected samples prepared in this study.

Some of the prepared microemulsions were used as the carriers of hydrophilic (Rhodamine B, a dye often used in diagnostics as sensitive fluorescent probe) and hydrophobic organic substances (anti-inflammatory drug indomethacin, solubility of which in water is of ~0.001 wt % [22, 23]). In the case of indomethacin, we aimed to prepare a system with high content of the drug, prone to its prolonged release. In the case of Rhodamine B, we aimed to ensure retarded release of the dye solubilized in the microemulsion into the external medium. For both substances, their content in the systems was quantitatively determined by means of spectrophotometry. The following absorption bands were used as the analytical signal: at 320 nm (ε 7200 L mol^{-1} cm^{-1}) for indomethacin and at 554 nm (ε 94000 L mol^{-1} cm^{-1}) for Rhodamine B. The solubilizates release from the microemulsions was monitored by means of dialysis under conditions similar to the physiological ones: pH 6.86 (phosphate buffered solution) and temperature 37°C.

The use of the obtained microemulsions allowed significant increase in the indomethacin solubility in aqueous systems, the formulations with the hydroxypiperidinium surfactants revealing somewhat higher solubilization capacity. The limiting content of the drug was of 1.3, 1.5, 1.4, and 1.2 wt % for the ME1, ME3, ME4, and ME5 formulations, respectively. Accurate determination of the indomethacin solubility was technically challenging in the case of the gel-like microemulsions. Therefore, the systems containing 0.5 wt % of indomethacin were used in further experiments. The data reflecting kinetics of the drug release from the considered microemulsions are shown in Fig. 2. From the obtained data it followed that the release was slow: the indomethacin release during a day did not exceed 20%, whereas the release of the free drug loaded into the dialysis bag as the aqueous-alcoholic solution was complete under the same conditions within approximately within 4 h. The indomethacin release from the gel-like

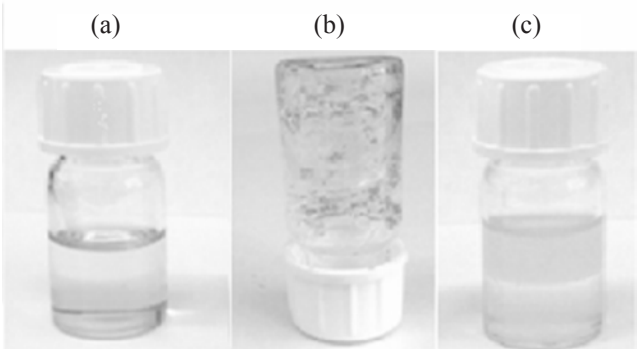


Fig. 1. Appearance of the samples prepared in the study: (a) liquid microemulsion ME2, (b) gel-like system ME7, and (c) layered formulation analogous to ME7, with Tween 80 instead of the cationic surfactant.

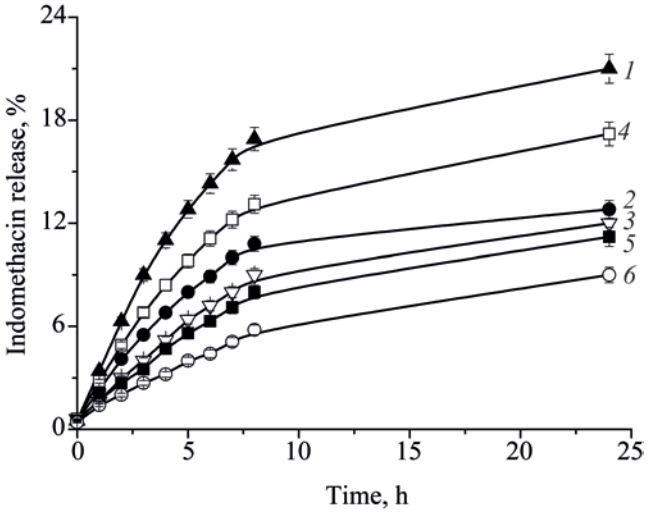


Fig. 2. Kinetic curves of indomethacin release from microemulsions (pH 6.86, 37°C). (*1*) ME1, (*2*) ME3, (*3*) ME4, (*4*) ME5, (*5*) ME7, and (*6*) ME8.

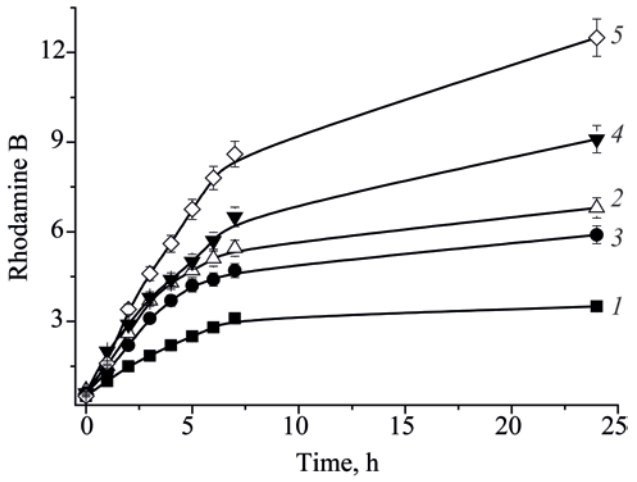


Fig. 3. Kinetic curves of Rhodamine B release from microemulsions (pH 6.86, 37°C). (*1*) ME1, (*2*) ME3, (*3*) ME4, (*4*) ME7, and (*5*) ME8.

systems was slower than from the liquid ones, and the structure of the piperidinium surfactant modifier did not significantly affect the kinetics.

The hydrophilic dye, Rhodamine B, was readily soluble in the obtained microemulsions. The systems containing 0.05 wt % of Rhodamine B were chosen for the experiments. As in the case of indomethacin, the release of the dye from microemulsions (Fig. 3) was slower than from the aqueous solution. For example, Rhodamine B dissolved in water was almost completely released into the external medium within 4 h, whereas no more than 8% of the dye was released during the same period from the microemulsions. Hence, it could be stated that the microemulsions could retain hydrophilic as well as hydrophobic solubilizates, thus ensuring their prolonged action, for example, when used in pharmacological formulations.

To investigate the mechanism of indomethacin and Rhodamine B release from the microemulsions modified with the cationic surfactants, the obtained kinetic curves (Figs. 2 and 3) were fitted using three most widely used mathematical approximations: the first-order model, the Higuchi model, and the Korsmeyer–Peppas model [16, 24, 25]. The underlying equations and the results obtained vis the experimental data processing are given in Table 2. The model affording the best description of the substrate release from the microemulsions could be chosen basing on the values of the correlation coefficient (R^2). That was the Korsmeyer–Peppas equation showing $R^2 \geq 0.99$ in the cases of both indomethacin and Rhodamine B release. This is a semiempirical model used in the case of spherical delivery systems, based on the assumption that the incorporated substance release can occur via its diffusion from the carrier into the solution as well as via the carrier decomposition [26, 27]. The slope (n) of the fitted curve reflects the process mechanism: at $n = 0.45$, the release occurs via the Fick diffusion; at n ranging between 0.5 and 1, the process is controlled via the diffusion as well as the carrier decomposition; if n exceeds 1, the substrate is primarily released via the carrier decomposition. From the n values (Table 2) obtained for the considered microemulsions, it could be stated that the diffusion of both substrates was accompanied by gradual decomposition of the carrier. For the systems incorporating indomethacin, the decrease of the k parameter for the ME3–ME5 formulations in comparison with the basic microemulsion ME1 evidenced the fact that the presence of the cationic surfactants led to additional binding of the dye and retardation of its release, which can ensure their prolonged action as the delivery systems. It should be noticed that indomethacin was somewhat stronger bound in the formulations containing the surfactants bearing the OH group, the gel-like microemulsions retaining the drug better than the liquid ones. On the contrary, Rhodamine B revealed

Table 2. Results of quantitative analysis of the dependences shown in Figs. 2 and 3 using different mathematical models

System	First-order model $\ln(1-Q) = -k_1 t$		Higuchi model $Q = k_H t^{1/2}$		Korsmeyer–Peppas model $Q = k_{KP} t^n$		
	$[R^2]$	k_1	$[R^2]$	k_H	$[R^2]$	k_{KP}	n
Indomethacin							
Free substrate	0.9960	0.660	0.8457	45.56	0.946	47.2	0.46
ME1	0.9436	0.026	0.9283	5.69	0.9939	3.97	0.72
ME2	0.9593	0.015	0.9627	3.5	0.9989	2.5	0.71
ME3	0.9845	0.012	0.9336	2.8	0.9987	1.7	0.80
ME4	0.9174	0.019	0.9392	4.3	0.9959	3.15	0.69
ME7	0.9783	0.011	0.9418	2.5	0.9984	1.6	0.78
ME8	0.9664	0.008	0.9490	1.8	0.9951	1.2	0.75
Rhodamine B							
Free substrate	0.8859	0.92	0.8318	54.56	0.9239	58.65	0.41
ME1	0.7489	0.0050	0.9838	1.12	0.9989	0.98	0.58
ME2	0.7462	0.0093	0.9610	2.06	0.9728	1.80	0.59
ME3	0.8158	0.0081	0.9271	1.77	0.9549	1.42	0.64
ME7	0.8104	0.010	0.9685	2.27	0.9926	1.90	0.61
ME8	0.9469	0.0140	0.9201	2.97	0.9985	2.04	0.74

the strongest binding with the microemulsion containing no cationic surfactant (ME1), its release from the gel-like microemulsions being somewhat faster in comparison with the liquid ones. That fact was likely due to different localization of the hydrophilic and hydrophobic substrates in the system. As seen from the data in Table 2, the release of both free indomethacin and Rhodamine B occurred as the Fick diffusion ($n = 0.46$) but the values of k were almost an order of magnitude higher in comparison with the formulated substrates. Likely, in the case of microemulsions, the bound substrates were first released from the nanoparticles in the dispersion medium, following its diffusion into the external receiving solution through the pores of the dialysis bag.

At the next stage of the research, the in vitro experiments were extended to the in vivo tests. Being a non-steroidal anti-inflammatory drug, indomethacin has been widely used as a component of pharmacy ointments for external application. Using the carrageenan-induced edema model on rats, we compared the anti-inflammatory action of three systems containing 0.5 wt % of indomethacin: microemulsion ME1 containing no cationic surfactant, gel-like microemulsion ME7 containing 7 wt % of HMP-16, and a pharmacy ointment. The data on the change in the rat paw volume for the group receiving no therapy and the groups receiving the tested formulations are shown in Table 3 and Fig. 4.

It was found that in the control group the mean volume of the displaced liquid prior to the carrageenan administration equaled 1.05 mL, which was taken as 100%. The edema was gradually increased upon the carrageenan administration; the maximum value exceeding the starting one by 58.1% was achieved within 4 h. The edema was then gradually decreased, yet being not vanished completely even 24 h upon the experiment start (Fig. 4, curve *1*).

When applying the bandage impregnated with the unmodified microemulsion ME1, the edema was increased during 2 h, then its development was decelerated, and it was completely vanished 24 h upon the experiment start (Fig. 4, curve *2*).

In the group treated with the gel-like ME7 loaded with indomethacin, the edema increase upon 2 h was as low as 3.4% of the starting value, whereas 5 h upon the experiment start the volume of the displaced liquid was equal to the starting value, which evidenced complete removal of the inflammation (Fig. 4, curve *4*). It should be noted that the gel-like form of the considered formulation

Table 3. Influence of microemulsions loaded with indomethacin on the carrageenan-induced edema of rats[a]

System	Rat paw volume, mL						
	0 h	1 h	2 h	3 h	4 h	5 h	24 h
Control[b]	1.05±0.06	1.42±0.05	1.48±0.08	1.60±0.08	1.66 ± 0.1	1.55 ±0.1	1.05±0.06
ME1	1.76±0.1	2.04±0.09	2.03±0.08	2.03±0.07	1.86±0.12	1.77±0.09	1.76±0.1
ME7	1.42±0.05	1.49±0.04	1.49±0.06	1.5±0.07	1.48±0.07	1.45±0.55	1.42±0.05
Ointment[b]	0.98±0.03	1.07±0.02	1.12±0.03	1.16±0.02	1.19±0.04	1.20±0.04	0.98±0.03

[a] Each tested group consisted of 6 animals. The obtained data were treated by means of non-parametric analysis.

[b] The data were published in [16].

made its application at the wound surface easier and allowed its retention at the skin even without a bandage.

For the sake of comparison, we tested the "Indomethacin" ointment diluted with Vaseline so that the drug content in it was 0.5 wt %, i.e. equal to that in the formulated systems. The obtained results (Fig. 4, curve *3*) showed that in that case the inflammation was not so fast and the edema volume was not so large as in the control group, yet the recovery was significantly slower in comparison with the ME7 formulation. Hence, the studied microemulsions could serve as efficient carriers of anti-inflammatory drugs.

In summary, stable microemulsions modified with piperidinium surfactant additives, exhibiting strong solubilizing action, were formulated based on the biocompatible components. Varying the components ratio afforded the formulations strongly differing in the viscosity (from easy-flowing formulations to gels) which were used as carriers of hydrophilic (Rhodamine B) and hydrophobic (indomethacin) substrates. The gel-like systems exhibited the slowest release of the substrates and hence can be considered the prolonged drug delivery systems. Addition of the piperidinium surfactants in the microemulsions gave the formulations with improved physico-chemical properties and strong therapeutic action exceeding the activity of the known drug forms. The obtained results evidenced the promises of the application of the obtained systems for the development of novel formulations, primarily for the external use. It is important to underscore that varying of the structure factors and optimization of the physico-chemical properties of the nanosized carriers (surface charge, size, and viscosity) can be used as an efficient mean to manage the functional activity of the encapsulated drugs, including the prolonged action and therapeutic effects.

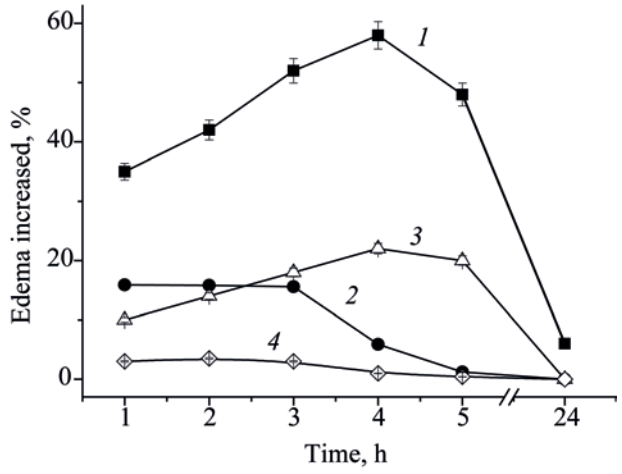


Fig. 4. Dynamics of the development of carrageenan-induced inflammation in rats and the results of the action of different formulations containing 0.5 wt % of indomethacin: (*1*) control (no treatment), (*2*) ME1, (*3*) pharmacy ointment, and (*4*) ME7.

EXPERIMENTAL

Tween 80, oleic acid, indomethacin, Rhodamine B, and carrageenan (Sigma-Aldrich) containing 99% of the major component were used. The cationic piperidinium surfactants were synthesized via the interaction of the corresponding *N*-alkylpiperidine with hexadecyl bromide in acetonitrile, followed by recrystallization of the reaction mixture, as described elsewhere [18, 19]. The microemulsions were obtained via sequential mixing of oleic acid, surfactant, ethanol, and water in the ratios listed in Table 1.

The particle size in the microemulsions was determined using a Malvern ZetaSizer Nano photon-correlation spectrometer of dynamic and electrophoretic light scattering (Malvern Instruments, Great Britain) equipped

with a He-Ne gas laser (power 10 mW, wavelength 633 nm). The light scattering angle was 173°.

Solubilizing action of the microemulsions with respect to indomethacin was assessed by means of spectrophotometry [18]. To do so, absorbance (D) at 320 nm of the microemulsions saturated with indomethacin was determined using a Specord 250 Plus instrument, and the limiting concentration (C) of the drug in the system was calculated using the Beer's law (Eq. (1)).

$$D = \varepsilon \cdot L \cdot C, \quad (1)$$

with L being the optical path length.

Viscosity of the studied microemulsions was determined via the Poiseuille method (measuring of the time for a fluid to flow in a calibrated viscometer) at 25°C.

Release of indomethacin from the microemulsions was monitored at 37°C by means of dialysis as described elsewhere [16]. The dialysis bags with cutoff limit 12–14 kDa were used. Phosphate buffered solution (pH 6.86) was used as the external medium.

Anti-inflammatory activity of the indomethacin-containing formulations was studied on the Wistar rats using the model of carrageenan-induced edema as described elsewhere [16]. The edema development was assessed using a Plethysmometer instrument (Ugo Basile) by measuring the volume of water displaced by the animal paw from the measuring cell. The experiments with animals were conducted according to the recommendations stated in Directive 2010/63/EU of the European Parliament; the experiments protocol was approved by the Commission on Bioethics, Federal Research Center "Kazan Scientific Center of RAS".

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CONFLICT OF INTEREST

L.Ya. Zakharova is a member of Editorial Board of Russian Journal of General Chemistry. Other authors declare that they have no conflicts of interest.

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