

ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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The study of o/w emulsions using the rotating viscometer method and the method of spin probes

The rheological properties of o/w emulsions used as vehicles for semi-solid preparations (SSP) depend on the composition of o/w and w/o emulsifiers to a large extent, and it is related to the structure of their aggregates in emulsions. In order to control the rheological parameters of emulsions it is necessary to know the regularities of the influence of the composition and properties of emulsifiers on these parameters, as well as the mechanism of emulsion stabilization, which depends on the structure of the aggregates formed by emulsifiers.

Aim. To study the relationship between the structure of the aggregates formed by emulsifiers and the rheological properties of o/w emulsions.

Materials and methods. The objects of the study were o/w emulsions stabilized with macrogol-40 stearate (M40S), glyceryl monostearate 40-55 (type II) (GMS) and cetostearyl alcohol (CSA). The rheological studies were performed by the rotational viscometer method. The structure of aggregates of emulsifiers was studied by the spin probes method. Probes simulating o/w and w/o emulsifiers with different localization of the radical were used.

Results and discussion. The apparent viscosity of emulsions stabilized with the o/w emulsifier (M40S) and a mixture of w/o emulsifiers (GMS and CSA) is maximal at a certain ratio between o/w and w/o emulsifiers. The increase in the rheological parameters correlates with the increase in the packing density of emulsifier molecules in the polar part of their aggregates; it in this case practically does not change at the level of the 5 and 16 carbon atoms of alkyl chains. This indicates formation of non-spherical aggregates which form a coagulation structure in the emulsion.

Conclusions. The change in the ratio between o/w and w/o emulsifiers results in the change in the structure of their aggregates, and it affects the rheological properties of o/w emulsions. Based on the results of the studies it is possible to reasonably control the rheological parameters of preparations with emulsions as a vehicle.

Key words: *emulsion; emulsifier; apparent viscosity; spine probe; EPR spectrum; rotational correlation time*

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Дослідження емульсій м/в методами ротаційної віскозиметрії та спінових зондів

Реологічні властивості емульсій м/в, що застосовуються як основи для м'яких лікарських засобів (МЛЗ), багато в чому залежать від складу емульгаторів м/в та в/м, що пов'язано зі структурою їх агрегатів в емульсіях. Щоб управляти реопараметрами емульсій необхідно знати закономірності впливу на них складу та властивостей емульгаторів, а також механізм стабілізації емульсій, який залежить від структури агрегатів, утворених емульгаторами.

Мета роботи. Дослідити зв'язок між структурою агрегатів, утворених емульгаторами, і реологічними властивостями емульсій м/в.

Матеріали та методи. Об'єкти досліджень – емульсії м/в, стабілізовані макрогол-40 стеаратом (М40С), гліцерилмоностеаратом 40-55 (типу ІІ) (ГМС) і цетостеариловим спиртом (ЦСС). Реологічні дослідження проводили методом ротаційної віскозиметрії. Структуру агрегатів емульгаторів досліджували методом спінових зондів. Використовували зонди, що моделюють емульгатори м/в та в/м, з різною локалізацією радикалу.

Результати та їх обговорення. Структурна в'язкість емульсій, стабілізованих емульгатором м/в М40С і сумішшю емульгаторів в/м (ГМС і ЦСС), максимальна при певному співвідношенні між емульгаторами м/в та в/м. Збільшення реопараметрів корелює з підвищенням щільності упаковки молекул емульгаторів у полярній частині їх агрегатів, яка при цьому не змінюється на рівні 5 і 16 атомів вуглецю алкільних ланцюгів. Це свідчить про утворення агрегатів несферичної форми, з яких в емульсії формується коагуляційна структура.

Висновки. Зміна співвідношення між емульгаторами м/в та в/м змінює структуру їх агрегатів, що впливає на реологічні властивості емульсій м/в. За результатами досліджень можна обґрунтовано управляти реологічними параметрами препаратів на основі емульсій.

Ключові слова: *емульсія; емульгатор; уявна в'язкість; спіновий зонд; спектр ЕПР; час кореляції обертальної дифузії*

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Исследование эмульсий м/в методами ротационной вискозиметрии и спиновых зондов

Реологические свойства эмульсий м/в, применяемых в качестве основ для мягких лекарственных средств (МЛС), во многом зависят от состава эмульгаторов м/в и в/м, что связано со структурой их агрегатов в эмульсиях. Чтобы управлять реопараметрами эмульсий, необходимо знать закономерности влияния на них состава и свойств эмульгаторов, а также механизм стабилизации эмульсий, зависящий от структуры агрегатов, образованных эмульгаторами.

Цель. Исследовать связь между структурой агрегатов, образованных эмульгаторами, и реологическими свойствами эмульсий м/в.

Материалы и методы. Объекты исследований – эмульсии м/в, стабилизированные макрогол-40 стеаратом (М40С), глицерилмоностеаратом 40-55 (типа II) (ГМС) и цетостеариловым спиртом (ЦСС). Реологические исследования проводили методом ротационной вискозиметрии. Структуру агрегатов эмульгаторов исследовали методом спиновых зондов. Использовали зонды, моделирующие эмульгаторы м/в и в/м, с разной локализацией радикала.

Результаты и их обсуждение. Структурная вязкость эмульсий, стабилизированных эмульгатором м/в М40С и смесью эмульгаторов в/м (ГМС и ЦСС), максимальна при определенном соотношении между эмульгаторами м/в и в/м. Увеличение реопараметров коррелирует с повышением плотности упаковки молекул эмульгаторов в полярной части их агрегатов, которая при этом не изменяется на уровне 5 и 16 атомов углерода алкильных цепей. Это свидетельствует об образовании агрегатов несферической формы, из которых в эмульсии формируется коагуляционная структура.

Выводы. Изменение соотношения между эмульгаторами м/в и в/м изменяет структуру их агрегатов, что влияет на реологические свойства эмульсий м/в. На основании результатов исследований можно обоснованно управлять реологическими параметрами препаратов на основе эмульсий.

Ключевые слова: эмульсия; эмульгатор; кажущаяся вязкость; спиновый зонд; спектр ЭПР; время корреляции вращательной диффузии

O/w emulsions are used as a vehicle for drugs in various dosage forms, in particular for semi-solid preparations (SSPs) [1]. It is necessary that emulsions have the appropriate rheological properties taking into account the requirements for the medicinal product under development. Various emulsifiers are usually used to stabilize emulsions as disperse systems [2]. It is known that the structure of the mixed aggregates of o/w and w/o emulsifiers depends on their ratio, the molecular structure of emulsifiers and temperature. In the mixed aggregates of o/w emulsifiers and fatty alcohols as w/o emulsifiers the lateral phase separation takes place in a certain temperature range when along with the liquid regions of a hydrophilic surfactant two-dimensionally solid and one-dimensionally liquid sites of fatty alcohols are formed [3]. This is due to a very large difference in the hydrophilic-lipophilic balance (HLB) values of the o/w emulsifier and fatty alcohols ($HLB < 1$) [4]. Due to these properties of surfactants/fatty alcohol aggregates the coagulation structures determining a high apparent viscosity and stabilization of emulsions are formed [5].

The systematic studies of emulsions stabilized by surfactants and the w/o emulsifier with a higher HLB value of 3-6 or by a mixture of fatty alcohols and the w/o emulsifier with high HLB values are relevant for the technology of semi-solid preparations. Glyceryl monostearate (GMS) with HLB of 3.8 can be used as such emulsifier [2].

Materials and methods

The o/w emulsions containing the well-known excipients [2, 6] were studied. The oil phase of the emulsion consisted of isopropyl myristate (7 %), octyldode-

canol (7 %), hexyldecyl stearate (7 %) and dimethicone 100 (1 %), and the dispersion medium was composed of propylene glycol (6 %) and purified water (up to 100 %). An antimicrobial preservative phenoxyethanol (1%) was included to the o/w emulsion formulations. M40S ($HLB = 16.9$ [2]) was used as an o/w emulsifier and a mixture of GMS and CSA in the ratio of 10 : 1 was used as a w/o emulsifier. The HLB value of CSA calculated by the Davies method [4] was 0.825; therefore, the total HLB value of the mixture of w/o emulsifiers was 3.53. The ratio between M40S and the GMS/CSA mixture (10:1) varied. The total content of emulsifiers was 14 %. Emulsions were made according to the method described in the literature [6].

The partial replacement of GMS on CSA is due to a significant increase in the rheological parameters of emulsions, which makes it possible to reduce the content of emulsifiers in the drug composition. Thus, the apparent viscosity of the emulsion was 9.4 Pa·s (at $Dr = 14.55 \text{ s}^{-1}$) if GMS alone was used as a w/o emulsifier in the concentration of 13.0 %, and the apparent viscosity of the emulsion was 28.8 Pa·s when the GMS/CSA mixture (10 : 1) was used in the same concentration 13.0 %. Therefore, the apparent viscosity increased by 3.06 times and was maximal with the M40S content of 1.0 % when the GMS/CSA ratio was exactly 10 : 1.

The rheograms representing the relationship between the shear stress (τ_r , Pa) and the shear rate (Dr , s^{-1}) were obtained at the temperature of 25 °C using a “Rheolab QC” coaxial double-cylinder viscometer (“Anton Paar”). The flow type, the presence and extent of the thixotropic properties and the yield stress were determined from the

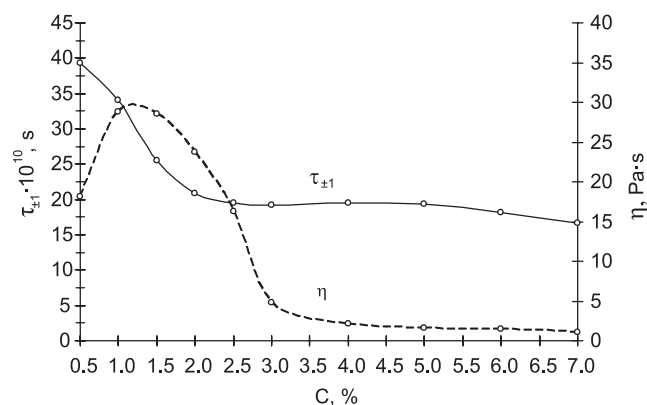


Fig. 1. The dependence of the apparent viscosity (η) (at $D_r = 14.55 \text{ s}^{-1}$) of emulsions and the rotational correlation time ($\tau_{\pm 1}$) of spin probe 1 in these emulsions on the M40S content (C)

rheograms; the apparent viscosity (η , Pa·s) was calculated by the formula:

$$\eta = \tau_r / D_r \quad (1)$$

The following spin probes were used in the experiments:

- spin probe 1: 4-(N,N-dimethyl-N-hexadecyl)ammonio)-2,2,6,6-tetramethylpiperidine-1-oxyl iodide (Mr 551,65; CAS 114199-16-5);
- spin probe 2: 4-palmitamido-2,2,6,6-tetramethylpiperidine-1-oxyl (Mr 409,67; CAS 22977-65-7);
- spin probe 3: 5-doxy-stearic acid (Mr 384,57; CAS 29545-48-0);
- spin probe 4: 16-doxy-stearic acid (Mr 384,57; CAS 53034-38-1).

Spin probe 1 simulates the o/w emulsifier, while spin probes 2, 3 and 4 are w/o emulsifier models.

The spin probes were incorporated into the emulsion in the concentration of 10^{-4} mol/l . The spectra of the electron paramagnetic resonance (EPR spectra) were obtained at the temperature of 25°C using an EPR spectrometer "ESR Spectrometer CMS8400" ("Adani"). The isotropic constant (A_N) characterizing the polarity of the radical surroundings, the component intensity, as well as the width of the component at low-field (ΔH_{+1}), the central component (ΔH_0) and the component at high-field (ΔH_{-1}) were determined by the EPR spectra; the rotational correlation time of the probes ($\tau_{\pm 1}$) was calculated by the formula [7]:

$$\tau_{\pm 1} = \left(\sqrt{\frac{h_{+1}}{h_{-1}}} - 1 \right) \cdot \Delta H_{+1} \cdot 6.65 \cdot 10^{-10}, \quad (2)$$

where: h_{+1} and h_{-1} are intensities of the components at low-field and at high-field of the EPR spectrum, and ΔH_{+1} is the width of the component at low-field.

According to the Stokes-Einstein equation the rotational correlation time (τ) is directly proportional to the effective radius of the molecule and the microviscosity of its local surroundings and is inversely proportional to the absolute temperature [7].

In the course of experiments the temperature of the emulsion samples were thermostated using a F12-ED refrigerated/heating circulator ("Julabo") with an accuracy of $\pm 0.1^\circ \text{C}$.

Table 1

Parameters of the EPR-spectra of spin probe 1 in emulsions with the different content (C) M40S

C M40S, %	A_N , mT	ΔH_{+1} , mT	ΔH_0 , mT	ΔH_{-1} , mT	$\tau_{\pm 1} \cdot 10^{10}$, s	The spectrum form
0.5	1.59	0.66	0.41	0.86	39.4	triplet
1.5	1.56	0.56	0.38	0.80	25.5	triplet
2.5	1.54	0.36	0.36	0.64	19.5	triplet
4.0	1.54	0.35	0.32	0.59	19.5	triplet
6.0	1.57	0.34	0.33	0.60	18.2	triplet

Results and discussion

Fig. 1 shows the dependence of the apparent viscosity (η) of emulsions on the M40S content, i.e. the dependence of the apparent viscosity (η) on the ratio between the M40S content and the content of the GMS/CSA mixture provided that their total content is 14 %.

As it follows from Fig. 1, the apparent viscosity of emulsions increases from $4.7 \text{ Pa}\cdot\text{s}$ to $28.8 \text{ Pa}\cdot\text{s}$ (approximately 6 times) if the M40S content decreases from 3 % to 1 %; the apparent viscosity curve has the maximum. The increase in the apparent viscosity with the decrease in the M40S content from 2.5% to 1.0% correlates with the increase of $\tau_{\pm 1}$ for spin probe 1. The nitroxyl radical of spin probe 1 is localized in the polar part of aggregates of the emulsifiers as evidenced by the rather large values of the isotropic constant (A_N) of the EPR spectra of this probe (Tab. 1). Therefore, if the content of the

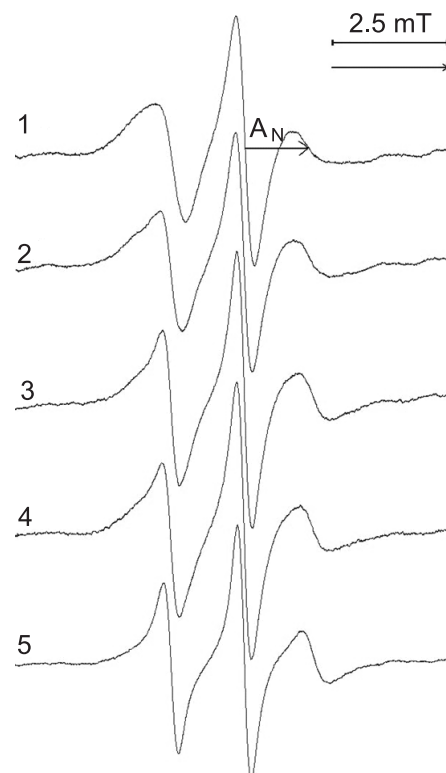


Fig. 2. The EPR spectra of probe 1 in emulsions with the different content of M40S: 1 – 0.5 %; 2 – 1.5 %; 3 – 2.5 %; 4 – 4.0 %; 5 – 6.0 %

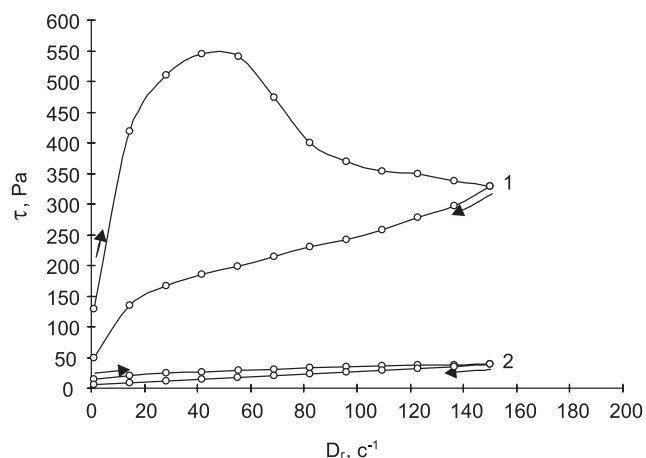


Fig. 3. Rheograms of emulsions with the different content of M40S: 1 – 1.0 % and 2 – 6.0 %

hydrophilic surfactant decreases, the microviscosity of the polar part of the aggregates formed from the molecules of the emulsifiers increases.

As it follows from Fig. 2 and Tab. 1, with a decrease in the concentration of the o/w emulsifier (M40S) from 2.5 % to 0.5 % there is a significant increase in the width of the components of the EPR spectra and an increase in the rotational correlation time of spin probe 1. However, at the same time the EPR spectra remain as triplets, it indicates a uniform distribution of the emulsifier molecules in the plane of aggregates.

It is evident from Fig. 3, with the reduced content of the hydrophilic surfactant from 6 % to 1 %, in addi-

Table 2
Some parameters of the EPR spectra of various spin probes in emulsions (see Fig. 4)

Spin probes	M40S content, %	A_N , mT	$\tau_{\pm 1} \cdot 10^{10}$, s	The spectrum form
1	1.0	1.55	44.9	triplet
1	6.0	1.57	14.9	triplet
2	1.0	1.58	5.3	triplet
2	6.0	1.58	4.2	triplet
3	1.0	1.41	13.5	triplet
3	6.0	1.42	12.9	triplet
4	1.0	1.45	3.9	triplet
4	6.0	1.45	4.3	triplet

tion to the increase of the apparent viscosity and the yield stress there is a change in the emulsion flow type and the extent of the thixotropic properties. It was interesting to study the structure of the emulsifier aggregates in emulsions differing significantly in their rheological properties. Fig. 4 shows the EPR spectra of four probes with different localization of radicals in their molecules incorporated into the emulsions studied. Some parameters of these spectra are presented in Tab. 2.

As it follows from Fig. 4 and data presented in Tab. 2, all EPR-spectra are triplets, but not superpositions of signals. It indicates that there is no lateral phase separation in contrast to emulsions stabilized by a colloidal

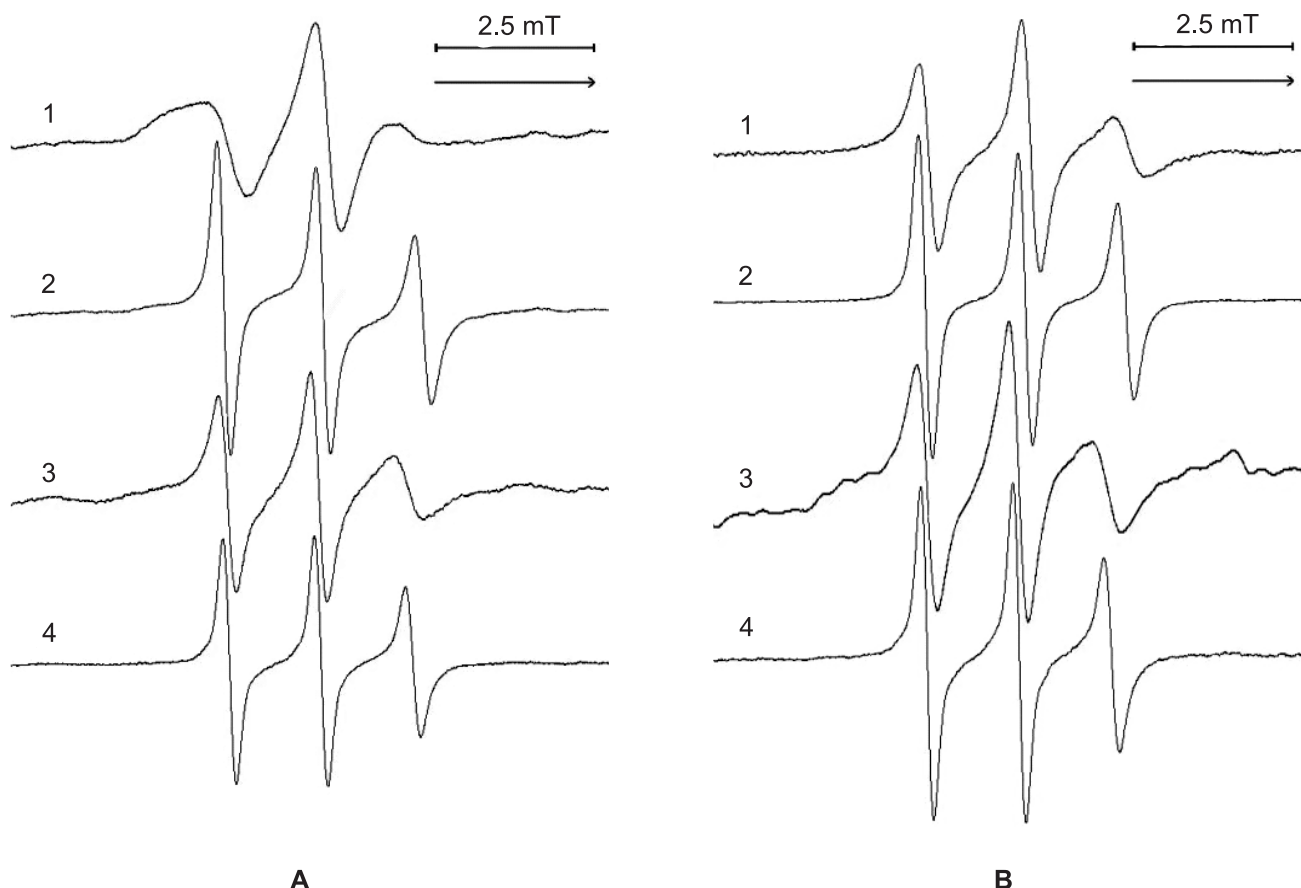


Fig. 4. The EPR spectra of spin probes 1, 2, 3 and 4 in emulsions with the M40S content of 1 % (A) and 6 % (B) and the w/o emulsifier content of 13 % and 8 %, respectively

surfactant and CSA [3]. Different ratios between the o/w emulsifier content and the content of w/o emulsifier mixture in these two emulsions (Fig. 3) led to different values of $\tau_{\pm 1}$ differing 3.0 times and 1.3 times for probes 1 and 2, respectively.

Nitroxyl radicals of spin probes 1 and 2 are localized in the hydrophilic parts of the emulsifier aggregates or at the boundary between the hydrophilic and lipophilic parts. The rotational correlation times of both spin probes 3 and 4 are almost identical in these two emulsions (Tab. 2). In the case of spin probe 4, the value of $\tau_{\pm 1}$ in the most viscous emulsion even decreased by 10 %. The A_N and $\tau_{\pm 1}$ values indicate that the most lipophilic medium surrounds the radical at the level of the 5 carbon atom of the alkyl chains, which packing density at this level is rather significant (Tab. 2). The radical surrounding at the level of the 16 carbon atom of the alkyl chains is also lipophilic, but the microviscosity of its surrounding is lower approximately 3 times. It can be assumed that at this level the alkyl chains are dissolved in the oil phase.

According to the results of the research it is obvious that with the decrease of the total HLB value of the emulsifiers the packing of their molecules in the aggregates at the level of the 1-5 carbon atoms of the alkyl chains changes. The aggregates of emulsifiers can have a spherical shape with a wedge-shaped packing, as well as various nonspherical forms. Moreover, hydrophilicity of the emulsifier aggregates also decreases. The maxi-

mum value of the apparent viscosity (Fig. 1) indicates the achievement of the optimal conditions for formation of a coagulation structure from aggregates of emulsifiers [5]. High HLB values of the w/o emulsifier are not an obstacle to formation of coagulation structures in emulsions.

CONCLUSIONS

1. When stabilizing o/w emulsions by a hydrophilic surfactant and the w/o emulsifier with a high HLB value no lateral phase separation in the aggregates of emulsifiers has been detected by the method of spin probes in contrast to emulsions stabilized by the o/w emulsifier and fatty alcohols.

2. It has been shown that at certain ratios between a hydrophilic surfactant and a w/o emulsifier with a high HLB value the rheological properties of emulsions change, and the apparent viscosity curve passes through the maximum due to formation of coagulation structures from the aggregates of emulsifiers.

3. The variation of the ratio between the hydrophilic surfactant and the w/o emulsifier with a high HLB value causes the change in the structure of their aggregates in the polar part and at the level of the 1-5 carbon atoms of the alkyl chains. This structure affects the rheological properties of emulsions, based on this it is possible to reasonably control their rheological parameters.

Conflict of Interests: authors have no conflicts of interests to declare.

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