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Self-assembly of mixed systems based on nonionic and carbamate-bearing cationic surfactants as a tool for fabrication of biocompatible nanocontainers

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ABSTRACT

Aggregation behavior of mixed micellar solutions and microemulsions based on cationic carbamate-bearing surfactants with hexadecyl hydrophobic group and nonionic surfactants (Tween 80, Tween 20, and Triton X 100) has been studied. Critical micelle concentrations have been determined at varying component ratios, which demonstrated a negative deviation of surfactant systems from ideal behavior (synergetic effect). The electrokinetic potential and size of aggregates have been evaluated. Solubilizing effect of individual and mixed systems toward anti-inflammatory drug meloxicam possessing pH dependent solubility in aqueous solutions has been testified by spectrophotometry. It has been determined that nonionic surfactants slightly increase the solubility of meloxicam in water, while the carbamate-bearing surfactants with the concentration of nearly 0.1% provide more than a 10-fold increase in the solubility of this drug in weakly acidic media. Carbamate-bearing surfactants are referred to a class of moderately toxic substances. Their employment in binary compositions with nonionic surfactants has decreased the toxicity of the systems with the retention of the high degree of solubilizing effect. A transition to biocompatible Tween 80/oleic acid/water/ethyl alcohol microemulsions modified with carbamate-bearing surfactant additives has increased the solubility of meloxicam by the factor of 575 as compared to water.

1. Introduction

Surface-active substances are widely used in biotechnologies, pharmacology, and medicine as solubilizers, drug delivery systems, diagnostic tools, and antimicrobial agents [1–6]. Typical surfactant property responsible for their wide practical application is their ability of self-assembling with the formation of supramolecular aggregates. A simplest example of these aggregates is micelles, which represent self-organizing associates of diphilic molecules, which are formed in surfactant solutions at critical micelle concentration (CMC) [7,8]. Another important type of supramolecular systems based on surfactants is microemulsions. They represent a macroscopically homogeneous thermodynamically stable microdisperse system, which consists of water and oil (hydrocarbon) phases, which are separated by the layer of micelle-forming surfactants, which sometimes include cosurfactants [9,10]. The application of supramolecular systems in medicine and pharmacology poses the problems of safety and biocompatibility of the formed compositions and applies strict requirements, such as low toxicity, effectiveness at low concentrations and under mild conditions, high solubilizing capacity, and high performance and selectivity. These properties are intrinsic to a significant extent for low-toxic nonionic surfactants (Tween 20, Tween 80, Triton-X-100, Tyloxapol, amphiphilic block-copolymers, and others) [11–14], which determines their wide application as solubilizing agents during the preparation of drug compositions and the formation of delivery systems. However, these compounds are often inferior to more toxic ionic surfactants in their effectiveness. The latter exhibit higher solubilizing effect, which is provided not only due to hydrophobic, but also electrostatic forces; other types of interactions may be involved in the presence of functional fragments in surfactant molecules as exemplified by hydrogen bond formation [1,15–17]. The charge of micelle used as a drug delivery agent, often provides its better interaction with biosurfaces and bioorganisms thus increasing therapeutic effect. There are examples of successful employment of cationic surfactants to provide transdermal drug delivery [18–20]. Cationic surfactants also demonstrated numerous benefits in ophthalmology, because it provides prolonged retention of solubilizing preparations on the eye surface [21,22]. It can be anticipated that a successful choice and combination of two types of surfactant would develop the systems, which combine their advantages.

We previously synthesized a series of cationic surfactants with carbamate (urethane) moieties, which are superior to trimethylammonium counterparts by lower critical micelle concentrations, increased solubilizing effect, and lower toxicity [23,24]. In

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addition, the compounds bearing urethane residue (organic carbamates) are characterized by hydrolytic cleavage under physiological conditions, which may facilitate their removal from organism [25]. This work continues and develops our previous studies. Main emphasis is made in the study of the behavior of mixed micellar solutions and microemulsions based on carbamate-bearing and nonionic surfactants. Employment of mixed compositions based on various surfactants as effective solubilizing agents is rationalized in a number of works [26,27]. We considered that addition of nonionic surfactant provides a decrease in the toxicity and the concentration threshold of aggregation of the system without compromising its solubilizing effect. In this work, previously synthesized and new urethane surfactants with identical length of hydrophobic radical and various structures of head group were used. Tween 20, Tween 80, and Triton-X-100 were chosen as nonionic surfactants. A number of aggregation characteristics was obtained for binary solutions at varying component ratios. The solubilizing effect of individual and mixed micellar solutions with respect to meloxicam anti-inflammatory preparation, which is widely used in medicine, was investigated. The structure of the compounds is given in Fig. 1.

2. Experimental section

2.1. Materials

Commercially available Tween 20, Tween 80, Triton X 100, oleic acid, butyl isocyanate, ethyl isocyanate, diazobicyclooctane (DABCO), meloxicam, (Sigma, 99%) were used without preliminary purification. The carbamate-bearing surfactants under study are prepared by the reaction of alkylammonium surfactant bearing hydroxyethyl substituent at head group with butyl isocyanate (or ethyl isocyanate) using DABCO as a catalyst in accordance with [23]. The structure of the compounds was confirmed by elemental analysis, ESI mass spectrum, IR- and NMR-spectroscopy data. The data obtained presented in SI.

All solutions were prepared with double-distilled water purified by Direct-Q 5 UV apparatus; the water resistivity was 18.2 MΩ·cm at 25°C. Experimental temperatures were maintained at 25 ± 0.1 °C, unless otherwise indicated. All experiments were accurate within 4%.

2.2. Instruments and methods

Surface tension measurements were performed by the anchor-ring method using KRUSS 6 tensiometer. The cmc values were defined as the concentration corresponding to the breakpoints in the γ vs. logarithm of surfactant concentration plots.

UV–Vis spectra of meloxicam solutions were recorded in quartz cells using Specord 250 Plus (Analytik Jena) spectrophotometers equipped with a thermostated cell unit. The molar extinction coefficient (ε) of the drugs was determined from the optical density (D), measured at the wavelength corresponding to the absorption maximum from the relation $\varepsilon = D/L \times C$, where C is a concentration of the drug, and L is the path length. For the accurate estimation of the ε value, the dependence of absorbance versus meloxicam concentration was plotted for the samples of micellar systems or microemulsions loaded with the drug. Linear sections of the dependences within the absorbance range from 0.2 to 1.0 were taken into consideration. The average values of three to five independent measurements were used as final results.

The solubilizing capacity of individual or mixed micellar systems toward meloxicam was determined by following the change in the absorbance of their saturated solutions with concentration of the surfactant added. For this aim the excess of a crystalline probe was placed in the surfactant solution with known concentration at neutral pH, stirred vigorously for 1 h and then equilibrated for 48 h at 25 °C. The undissolved probe was filtered, and the filtrate was put to a cuvette, after which optical density at the maximum absorption was measured. The spectra were recorded in the range from 250 to 600 nm with Specord-250 Plus spectrophotometer using the thermostated quartz cells of a 0.5–1.0 cm path length. Solubilization capacity was estimated from

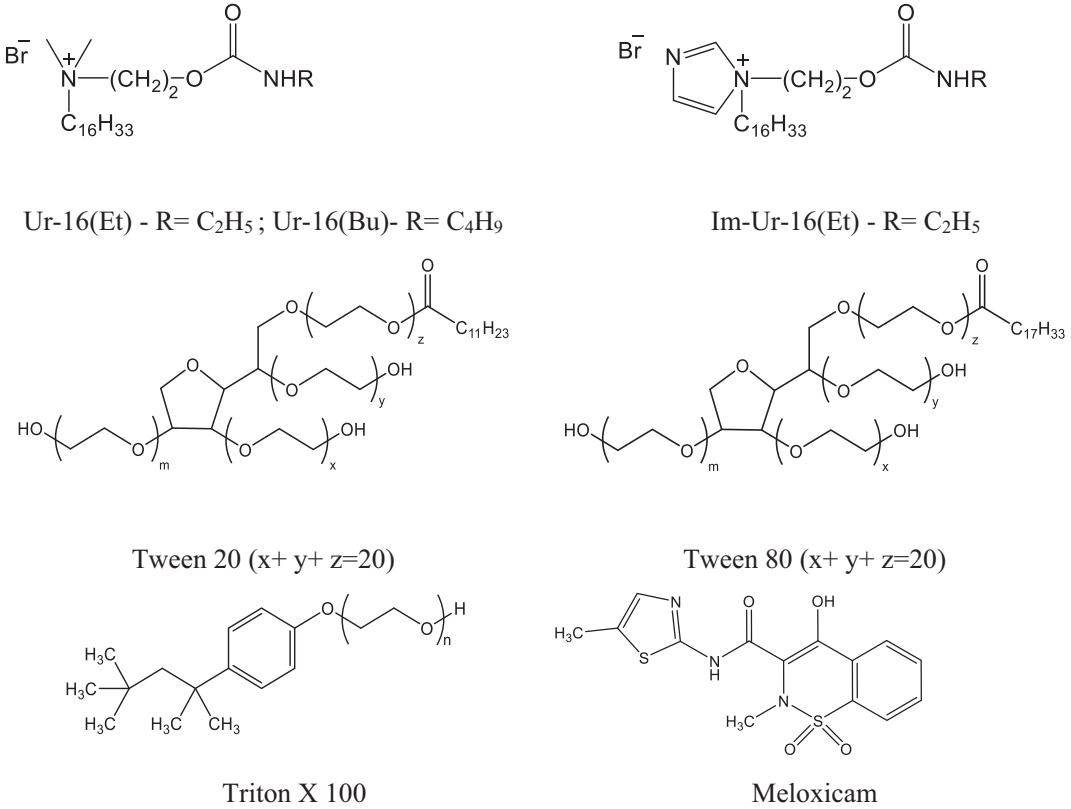

Fig. 1. Structural formulas of the compounds under study.

the D/L versus C_{surf} dependences. Concentration of meloxicam in microemulsions was determined spectrophotometrically based on equation $C = \varepsilon \times D \times L$, under conditions of saturation of the systems with the drug, as described above. The error of all experiments was <4%.

The mean of micelles size, zeta potential and polydispersity index were determined by dynamic light scattering (DLS) measurement using Malvern ZetaSizer Nano (Malvern Instruments, UK). The source of laser radiation was a He—Ne gas laser with the power of 10 mW and the wavelength of 633 nm. The light scattering angle is 173°. The pulse accumulation time is 5–8 min. The signals were analyzed using a single-plate multichannel correlator coupled with IBM PC compatible computer equipped with the software package for the evaluation of effective hydrodynamic radius of dispersed particles. All samples were analyzed in triplicate, the average error of measurements was approximately 4%.

The viscosity of microemulsions in study was determined according to Poiseuille method by measuring the duration of a liquid flow in a calibrated viscometer at an experimental temperature of 25°C.

3. Results and discussion

An interest in carbamate-bearing surfactants as solubilizing agents for drugs is caused by their advantages over analogous trimethylammonium surfactants, which are conventionally used as reference standards. 1. They possess lower critical micelle concentration (Table 1), because self-organization of these surfactants in solution, on the one hand, can be facilitated by hydrogen bond formation [28,29]; on the other hand, the presence of carbamate fragment alters charge distribution in the molecule and decreases unfavorable electrostatic interactions between head groups. The functional activity of carbamate-bearing surfactants manifests itself in their lower content in solutions due to low CMC. 2. They exhibit high solubilizing effect with respect to some hydrophobic compounds as exemplified by polyaromatic dyes and pollutants [24]; 3. Carbamate-beaning surfactants are identified as moderately toxic substances (LD_{50} 80–100 mg/kg, mice, oral) [23], while trimethylammonium surfactants are toxic; e.g. LD_{50} for CTAB is reported to be 27 mg/kg (mice, oral) [30]. These important characteristics are sometimes enhanced by the design of mixed compositions; we suggested that addition of nonionic amphiphiles to carbamate-bearing cationic surfactants would decrease the concentration threshold of aggregation of the system and its toxicity without compromising its solubilizing effect. At the first stage of investigation, CMC values of the mixed systems at varying ratios of ionogenic to nonionic surfactants (Table 1) were determined by tensiometry (Figs. 2, S 1–3). Experimental CMC values are given in Table 1 along with the values calculated according to the model for ideal surfactant behavior [31]:

$$\frac{1}{C^*} = \frac{\alpha_1}{C_1} + \frac{\alpha_2}{C_2}, \quad (1)$$

Table 1
CMC values of the mixed systems at varying ratios of ionic to nonionic surfactants, as well as CMC values calculated by Eq. (1).

α_1[a]	CMC, mM									
	Ur-16 (Bu)/Triton X100		Ur-16 (Bu)/Tween 20		Ur-16 (Bu)/Tween 80		Ur-16 (Et)/Tween 80		Im-Ur-16 (Et)/Tween 80	
	Tenz	Ideal	Tenz	Ideal	Tenz	Ideal	Tenz	Ideal	Tenz	Ideal
0	0.21		0.10		0.15		0.15		0.15	
0.3	0.15	0.22	0.105	0.12	0.18	0.17	0.14	0.20	0.14	0.19
0.5	0.13	0.22	0.11	0.14	0.21	0.18	0.13	0.25	0.16	0.24
0.7	0.20	0.23	0.14	0.17	0.22	0.20	0.30	0.33	0.29	0.31
1.0	0.24		0.24		0.24		0.70		0.57	

[a] α_1 is the fraction of carbamate-bearing surfactant.

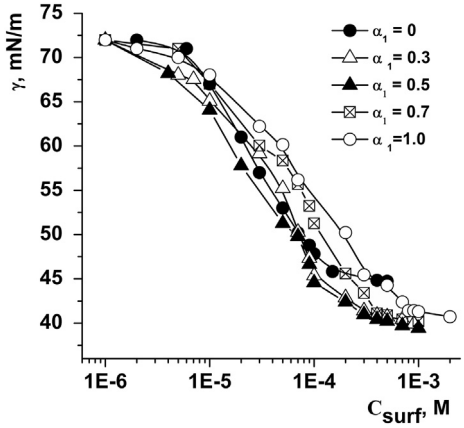

Fig. 2. Surface tension isotherms of the Im-Ur-16(Et)/Tween 80 system ($C_{surf} = C_{Tween\ 80}$ + CIm-Ur-16(Et), 25°C.

where α_1 and α_2 are the molar fractions of ionic and nonionic surfactant in solution and C^*, C_1, and C_2 are CMC values of the mixed system, as well as ionic and nonionic surfactants, respectively for ideal surfactant behavior.

Comparison of the data indicates negative deviation from the ideal mixing behavior, which shows the presence of mutual attraction between various types of surfactants in micelles (synergetic effect). This fact is particular clear in binary systems, where individual surfactants differ significantly according to their micelle forming ability as exemplified by Ur-16(Et)/Tween 80 and Im-Ur-16(Et)/Tween 80 (Fig. 3a, b); in this case, a synergetic effect is most representative in the range of α_1 from 0.3 to 0.6.

Formation of mixed aggregates can be confirmed by dynamic light scattering, which was carried out in the Im-Ur-16(Et)/Tween 80 system. Results of the analysis of the aggregate size distribution with the assumption of signal intensities of all particles in the solutions confirm that there are two types of particles in the specimens regardless of the component ratio, namely, small with the hydrodynamic diameter (D_h) of 2–15 nm and larger possessing the size of nearly 100 nm. However, analysis of autocorrelation function according to the number of light-scattering particles indicates that small particles predominate in the solutions (Fig. 4). Hydrodynamic diameter of aggregates increases with an increase in the content of nonionic surfactant, with the polydispersity index decreasing. An increase in the concentration of surfactant results in the increase in the population of large aggregates, which may represent agglomerates of several micelles.

Incorporation of nonionic surfactant presumably leads to the decrease in electrostatic repulsion of positively charged head groups of urethane surfactant, which is accompanied by the increase in micelle size. In addition, the charge of mixed micelles changes during their formation: electrokinetic potential of aggregates determined by electrophoretic light scattering in the Im-Ur-16(Et)/Tween 80 system corresponds to 20, 51, 67, and 76 mV at the fraction of cationic surfactant of 0.3, 0.5, 0.7, and 1.0, respectively. We previously recorded analogous changes of the surface potential of an Ur-16(Bu)/Tween-80 binary system; method of spectral probes showed that there is a linear drop of the surface potential from 106 to 0 mV with the growth of the fraction of nonionic surfactant in this system [32].

At the next stage of our work, solubilizing effect of individual and mixed systems of carbamate-bearing cationic surfactants and nonionic surfactants was studied. A nonsteroidal meloxicam anti-inflammatory preparation was used as a solubilizing agent. In spite of a broad application and high effectiveness of this preparation, remarkable side effects prevent its more extensive use, in addition to low and pH dependent solubility in water, which is associated with its existence in various forms [33,34]. The pK value of 4.18 [35] of meloxicam characterizes dissociation of enolic OH group with the formation of anionic form of the

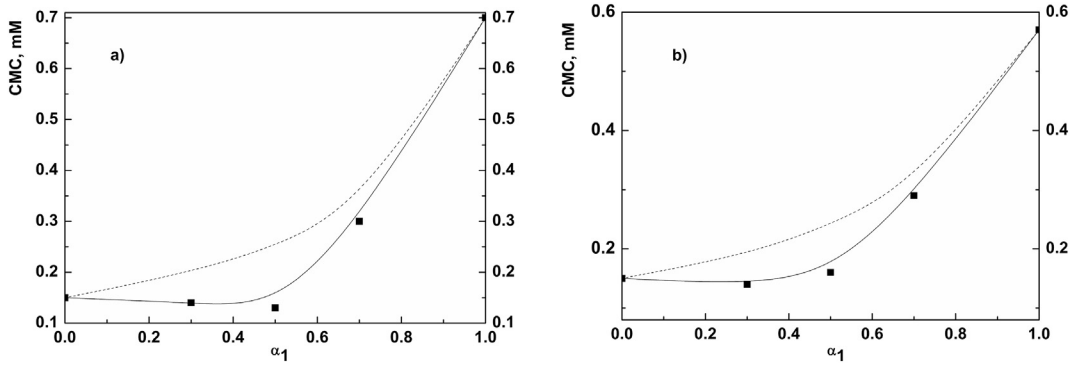

Fig. 3. (a, b) Nonideality in the CMC values for the studied systems Ur-16(Et)/Tween 80 (a), Im-Ur-16(Et)/Tween 80 (b). Dashed lines correspond to the CMCs predicted by the Eq. (1), α_1 is the fraction of carbamate-bearing surfactant.

drug. For this reason, the solubility of meloxicam in water is in the range of 0.001–0.003 mg/mL at pH 2 to 5, while at pH 6 it corresponds to 0.27 mg/mL [33]. This implies that the active ingredient dissolves and is absorbed only in intestine at peroral administration rather than in stomach, which slows down significantly its appearance in blood. Such delay is a huge drawback, because it may provoke patients to increase the dose of preparation not waiting until analgesic effect. An increase in the solubility of meloxicam at pH < 6 would increase its bioavailability and decrease therapeutic doses of drug and thus decrease its adverse effect. For this reason, we attempted to use the characteristics of micellar solutions of carbamate-bearing surfactants, which are related to their significant solubilizing effect.

Light absorbance of meloxicam solutions in UV region provides its quantitative determination in the specimens. The spectrum of freshly prepared solutions of this drug in water is characterized by two absorption bands at 275 nm (ε 9000 $mol^{-1}L\ cm^{-1}$) and 366 nm (ε 14,700 $mol^{-1}L\ cm^{-1}$), which almost do not shift with the change of pH from 4 to 8, as well as with the addition of surfactant (Figs. S4, S5). However, with a transition to more acidic range, there is a marginal bathochromic shift of the absorption band, which is caused by the decrease in the content of anionic form of meloxicam. It should be noted that such shift is observed at lower pH in micellar solutions of carbamate-bearing surfactants, which indicates the effect of surfactant on pK of this compound. A decrease in pK induced by cationic surfactants is a typical phenomenon for hydrophobic compounds [36,37]. Solubilizing effect of individual and mixed compositions of nonionic and carbamate-bearing surfactants was evaluated at pH 4.4 (acetate buffer) at varying component ratios. Assuming that meloxicam is weakly soluble in water under these conditions, an increase in the absorbance (D) of its saturated solutions with the addition of surfactant at the concentration higher than CMC is related to the solubilization of this hydrophobic substance by micelles. In Fig. 5, the results reflecting the change of meloxicam absorbance in micellar systems of individual carbamate-bearing surfactants under study are given. The plots $D/l = f(C_{surf})$ laid the foundation for the determination of the solubilizing capacity (S) of the micellar system: S = b/ε, where b is the slope of the linear part of the dependence and ε is the molecular extinction coefficient of meloxicam. As follows from the data in Fig. 5 and Table 2, carbamate-bearing surfactants significantly increase the solubility of meloxicam in contrast to nonionic amphiphiles; in this case, Ur-16(Bu) is the most effective: this compound with the concentration of 1 mM provides a 30-fold increase in the content of the preparation in solution as compared to water. It can be suggested that cationic surfactant solubilize meloxicam not only due to hydrophobic, but also electrostatic interactions. In addition, the fact that cationic surfactants usually affect acid-base characteristics of solubilized compounds decreasing their pK_a [36,37] may be a reason for an increase in the fraction of anionic form of meloxicam, which is highly soluble in water, in the presence of urethane surfactants. Comparison of the effect of Ur-16(Bu) and its unfunctionalized counterpart CTAB reveals that the latter possesses lower solubilizing capacity. This contradicts to the fact that CTAB possesses higher zeta-potential, which would anticipate higher electrostatic binding to meloxicam than in the case of urethane surfactants. Higher effectiveness of these compounds is presumably caused by the presence of the fragment, which is capable of hydrogen bonding, which would involve additional mechanisms of interaction between drug and micelle, which facilitates solubilizing processes. Thus, an increase in the solubility of meloxicam in carbamate-bearing surfactant solutions reflects the combined effect of several factors.

Then, the solubilizing effect of carbamate-bearing surfactants in mixed systems with nontoxic nonionic surfactants at varying component ratios in the systems was studied (Fig. 6, Table 2). As follows from the data, the solubilizing capacity of binary system increases

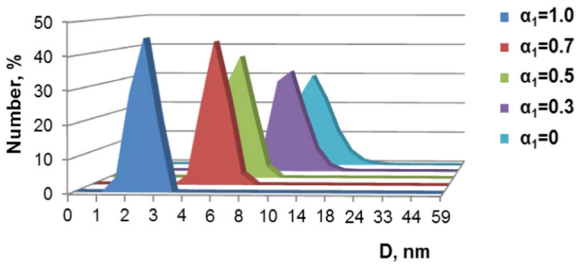

Fig. 4. Particle size distribution (averaged by the number of particles) in micellar solutions of Im-Ur-16(Et)/Tween 80 at varying component ratios; α_1 is the fraction of cationic surfactant.

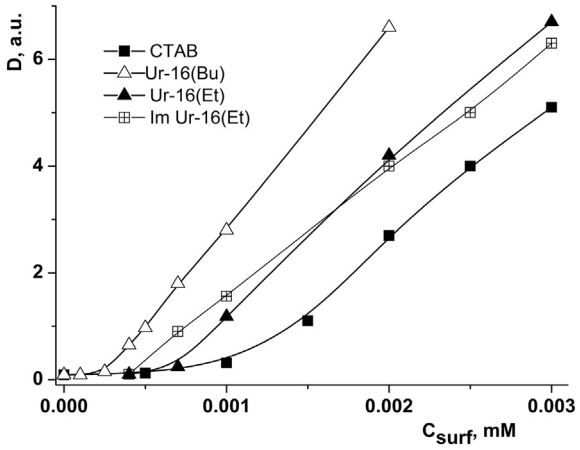

Fig. 5. Dependence of the absorbance of micellar solutions saturated with meloxicam at 366 nm vs. concentration of carbamate-bearing surfactants and reference cationic surfactant CTAB.

Table 2
Solubilizing capacity (S) of individual and mixed micellar systems with respect to meloxicam (pH 4.4, 25 °C).

α_1	S, mol of drug/mol of surfactant				
	Ur-16 (Bu)/Tween 80	Ur-16 (Bu)/Tween 20	Ur-16 (Bu)/Triton X100	Ur-16 (Et)/Tween 80	Im-Ur-16 (Et)/Tween 80
0	0.0026	0.0022	0.0025	0.0026	0.0026
0.3	0.011	0.0105	0.011	0.010	0.009
0.5	0.068	0.041	0.064	0.059	0.037
0.7	0.130	0.118	0.115	0.115	0.061
1.0	0.226	0.226	0.226	0.186	0.137

with an increase in the fraction of cationic surfactant (α_1); in this case, its performance is determined by the structure of carbamate-bearing surfactant and almost does not depend on the features of tested nonionic amphiphiles. Thus, the composition of mixed compositions bearing meloxicam should be optimized during their design and application and the balance should be found between the decrease in their toxicity due to increase in the fraction of nonionic surfactant and achievement of the high concentration of preparation due to the increase in the content of carbamate surfactant.

Microemulsions were used along with micellar systems in this work. Their features as drug delivery agents are related to the fact that can effectively solubilize both lipophilic and hydrophilic compounds [38–40]. Small size of drops and a highly developed interface provide redistribution of the preparation between the disperse phase and the dispersion medium of microemulsions, which provides a constant concentration of drug. In order to increase the solubility of meloxicam, we took oil/water microemulsions, which were suggested in [41] to solubilize rifampicin drug. They include Tween 80, oleic acid, water, and ethyl alcohol, which act as cosurfactant and modifier of water phase in microdrop core. To extend the existence ranges of microemulsions, as well as to acquire charge of the particles, a series of microemulsions with the addition of Ur-16(Bu) carbamate surfactant, which exhibited high solubilizing effect in micelles, was prepared and characterized at varying component ratios. Compositions of the formed microemulsions and their characteristics are given in Table 3.

Using dynamic light scattering, it was shown that there are two types of aggregates in ME-1 bearing Tween 80, as well as derivatives ME 2 and ME 3, where nonionic surfactant is partially replaced by Ur-16(Bu), namely, those possessing hydrodynamic diameters of 3–5 nm and 14–25 nm (Fig. 7).

With an increase in the fraction of Ur-16(Bu), the size of both types of aggregates diminishes, and the contribution of small aggregates

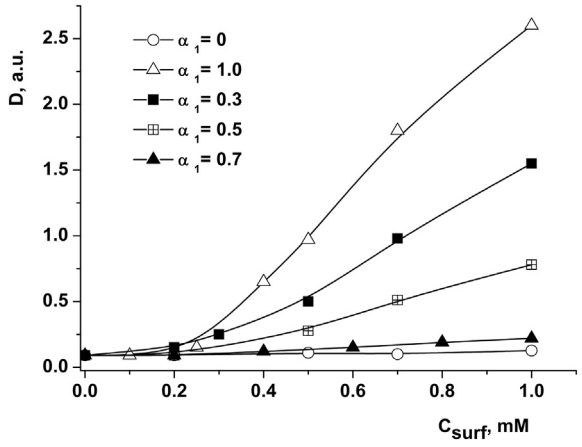

Fig. 6. Dependence of the absorbance of mixed micellar solutions saturated with meloxicam at 366 nm on the concentration of mixed surfactant ($C_{surf} = C_{Tween\ 80} + C_{Ur\text{-}16(Bu)}$); α_1 is the fraction of cationic surfactant.

Table 3
Composition of Tween 80/Ur-16(Bu)/oleic acid/water/ethyl alcohol microemulsions, their viscosity, and maximum allowable concentration of meloxicam (C_{mel}).

Components	ME1	ME 2	ME 3	ME 4	ME 5	ME 6
Composition, wt%						
Water[a]	17.0	17.0	17.0	24.5	40.0	45.6
Tween 80	21.0	18.0	15.0	16.4	15.0	5.3
Ur-16(Bu)	0	3.0	6.0	2.7	6.0	7.1
Oleic acid	25.0	25.0	25.0	22.7	17.0	14.7
Alcohol	37.0	37.0	37.0	33.7	22.0	27.3
Characteristics						
Viscosity × 10^3, Pa × s	1.81	1.80	1.72	2.22	3.02	3.10
C_{mel}, mM	2.0	2.1	2.3	1.7	1.1	0.94

[a] Water acetate buffer, pH 4.4.

increases along with reducing in the polydispersity index (from 0.316 to 0.117). It should be noted that we used the viscosity values of freshly prepared microemulsions upon the processing the correlation function by Stokes–Einstein equation (Table 3). The form of particle size distribution in the microemulsions does not change upon their long-term (more than one month) storage.

At the same time with rising of the cationic surfactant concentration in microemulsion, their solubilizing effect increases both with respect to hydrophilic substances (water) and hydrophobic meloxicam drug (Table 3, Figs. 8, S8).

In the ME-3 system, whose water phase represents acetate buffer solution possessing pH 4.4, the maximum allowable concentration of meloxicam is 575 times as large as that in water at same pH. Electrostatic interaction of meloxicam with positively charged head groups of cationic surfactants, as well as the possible contribution of hydrogen bonding between the preparation and carbamate-bearing surfactant, can be a reason for the fact that ME-3 possesses largest solubilizing effect.

Subsequently, we formed and tested the microemulsions with the higher water content (ME 4, ME 5, ME 6, Table 3). These MEs are stable and characterized by the higher viscosity and lower solubilizing capacity than ME-1 - ME-3. Analyzing the data, it can be stated that a decrease in the total surfactant content and the fraction of cationic surfactant is the most unfavorable factor, which affects the solubilizing capacity of the system. Assuming low solubility of meloxicam in water, alcohol, and oleic acid [33,42] it can be suggested that an increase in the solubility in microemulsion is primarily related to the incorporation of the preparation into the interface layer.

4. Conclusions

Thus, for mixed micellar solutions and microemulsions of cationic carbamate-bearing surfactants with hexadecyl hydrophobic tail and nonionic surfactants (Tween 80, Tween 20, Triton X 100), a number of characteristics have been obtained, which reflect their aggregation

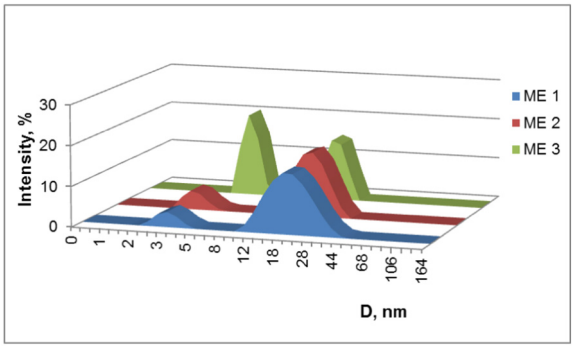

Fig. 7. Size distribution analysis (averaged by intensity) for ME-1, ME-2, and ME-3 microemulsions.

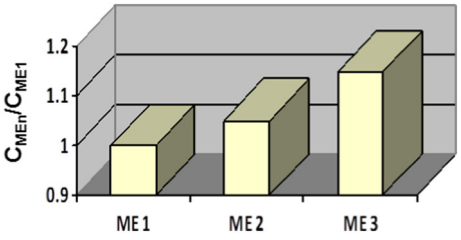

Fig. 8. An increase in meloxicam solubility in basic Tween 80/oleic acid/water/ethyl alcohol microemulsion (ME-1), which is achieved by partial replacement of nonionic surfactant by Ur-16(Bu).

behavior in solutions. Critical micelle concentrations have been determined at varying component ratios, which revealed a negative deviation from ideal mixing behavior (synergetic effect). Electrokinetic potential and aggregate sizes in the system have been determined. Using spectrophotometry, the solubilizing effect of individual and mixed systems with respect to meloxicam anti-inflammatory drug possessing pH-dependent solubility in aqueous solutions has been evaluated. It has been determined that nonionic surfactants (Tween 80, Tween 20, Triton X 100) weakly increase the solubility of meloxicam in water, while the carbamate-bearing surfactants provide more than a 10-fold increase in the solubility of meloxicam in weakly acidic medium at the concentration of nearly 0.1%. To design and fabricate nanocontainers for the drug solubilization with improved bioavailability, composition of mixed systems should be optimized with a focus on the balance between low toxicity allowed by nonionic surfactants and high solubilization effect allowed by carbamate-bearing surfactant. A transition to stable biocompatible Tween 80/oleic acid/water/ethyl alcohol microemulsions modified with the additives of carbamate-bearing surfactants provides an increase in the solubility of meloxicam by the factor of 575, which makes these systems promising in medicine and pharmacology.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2019.111407.

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