Mixed systems based on the cationic surfactant with a butyl carbamate fragment and nonionic surfactant Tween 80: Aggregation behavior and solubilization properties

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Mixed micelles are formed in the binary compositions based on the cationic surfactant functionalized by the butyl carbamate fragment and nonionic surfactant Tween 80 in aqueous solutions. The aggregation parameters of the formed micelles (critical micelle concentration, size, and surface potential) depend on the component ratio in the system. The solubilization effect of individual and mixed micelles on the drugs of the heterocyclic series, indomethacin and 1-[5-(4-chlorophenyl)-3-phenylpyrrol-2-yl)]benzimidazol-2(3*H*)-one, was quantitatively characterized.

Key words: surfactants, aggregation, mixed micelles, solubilization, drugs.

Cationic surfactants find practical use as micellar catalysts, inhibitors of corrosion, remedies of drug and diagnostics delivery, and antimicrobial agents.[1—5] Their application in biotechnologies, pharmacology, and medicine cause a necessity to search for new nontoxic surfactants or efficient systems based on them that act under mild conditions in a low concentration range and characterized by a high solubilization capacity and ability to overcome biological barriers. The surfactants functionalized by the carbamate (urethane) moiety have certain advantages in this respect: the possibility of hydrogen bond formation can facilitate micelle formation processes in solutions and enhance the efficiency of binding guest molecules during solubilization. In addition, these compounds can undergo hydrolytic decomposition under physiological conditions and, when used as carriers, they can liberate active molecules after passing through biobarriers, which favorably distinguishes them from other cationic surfactants.[6,7] However, there are few literature data on the synthesis and application of the surfactants with the carbamate group.

We synthesized a new cationic surfactant containing the butyl carbamate fragment in the head group and hexadecyl radical as the hydrophobic component: *N*-{2-[(butylcarbamoyl)oxy]ethyl}-*N*-hexadecyl-*N*,*N*-dimethylammonium bromide (BCB-16).[8] This compound is shown to have a lower critical micelle concentration (CMC) than its trimethylammonium analog, namely, hexadecyltrimethylammonium bromide (CTAB). Micellar solutions of BCB-16 are characterized by a high solubilization effect, which was demonstrated toward polyaromatic pollutants naphthalene and anthracene.[8] In addition, this surfactant belongs to the class of moderately dangerous substances characterized by LD_{50} equal to 80—100 mg kg^{-1} (mice, intraperitoneal injection), whereas for CTAB at the same injection method LD_{50} is considerably lower: 27 mg kg^{-1}.[9]

The present work is a continuation and development of the previous studies. In this work, we concentrated attention on studying the behavior of mixed compositions of BCB-16 and nonionic surfactant Tween 80 in aqueous solutions. It was assumed that the addition of the nonionic surfactant, which is widely used in medicine and pharmacology, would make it possible to decrease the toxicity and concentration threshold of aggregation of the system without reducing its solubilization effect. A number of aggregation characteristics was obtained in the course of the work for binary solutions varying the component ratio. The solubilization effect of individual and mixed micellar solutions was tested toward biologically active substances of the heterocyclic series. Anti-inflammatory drug indomethacin and the benzimidazole derivative, *viz.*, 1-[5-(4-chlorophenyl)-3-phenylpyrrol-2-yl)]benzimidazol-2(3*H*)-one (PBI), were chosen as heterocyclic biologically active substances.[10—13] The pharmacophoric moieties in a PBI molecule allow one to expect biological

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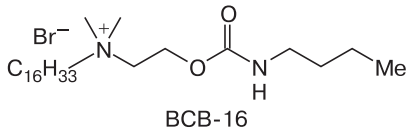
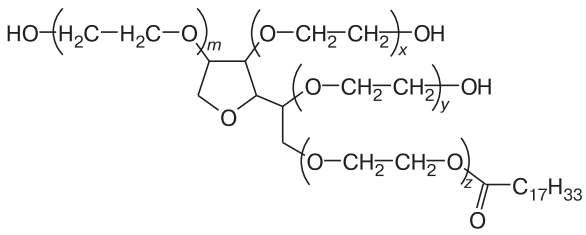
activity, in particular, the preliminary tests revealed the sugar-decreasing effect of this compound.

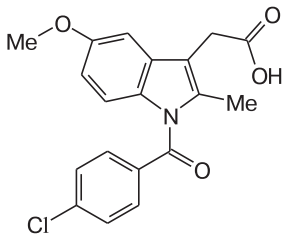
The formulas of the considered compounds are presented below.



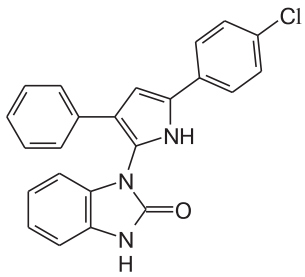
BCB-16



Tween 80 ($x + y + z = 20$)



Indomethacin



PBI

Experimental

Tween 80, poly(ethylene glycol) (molecular weights 1000 and 10 000), and indomethacin (Sigma—Aldrich, content of the major substance 99%) were used. Surfactant BCB-16 was synthesized by the reaction of dimethyl(2-hydroxyethyl)hexadecylammonium bromide and butyl isocyanate in the presence of 1,4-diazabicyclooctane by analogy to the previously described method.[8] Heterocyclic compound PBI was obtained using a known procedure.[14] The characteristics of the synthesized samples are consistent with the literature data. Water purified on a Direct-Q 5 UV setup (pH 6.8—7.0, $\chi = 2$—3 μS cm^{-1}) was used for the preparation of solutions.

Electronic spectra were recorded in temperature-maintained cells with an absorbing layer thickness of 1 cm on a Specord 250 Plus spectrophotometer. The solubilization effect of the micellar systems was evaluated by analogy to earlier works[15,16] determining the absorbance (D) of saturated solutions of indomethacin or PBI in the studied systems using the spectrophotometric method. The content of the solubilizing agent in a sample was determined from the obtained D values at the absorption maximum taking into account the molar absorption coefficients of the agents.

The surface potential of the aggregates was studied by the spectral method examining a change in the acid-base properties of the indicator (*p*-nitrophenol) depending in the surfactant concentration according to a previously described procedure.[17] The apparent pK_a value for *p*-nitrophenol (p$K_{a,app}$) was calculated by the Henderson—Hasselbalch equation

$$pK_{a,app} = pH + \log[\text{phenol}]/[\text{phenolate}].$$

The apparent dissociation constant at $C_{Surf} \to \infty$ was accepted to be the dissociation constant of *p*-nitrophenol in the micellar phase ($K_{a,m}$).

The sizes of the aggregates were determined on a Malvern ZetaSizer Nano photon correlation spectrometer of dynamic and electrophoretic light scattering (Malvern Instruments, Great Britain). A He—Ne laser (power 10 mW, wavelength 633 nm) served as a laser radiation source. The scattering angle of the light was 173°. The pulse acquisition time was 5—8 min. The signals were analyzed using a one-plate multichannel correlator, which is conjugated with an IBM PC compatible computer equipped with the program package for the estimation of the effective hydrodynamic particle diameter.

Results and Discussion

It was found by tensiometry that the CMC values for BCB-16 and Tween 80 are close to be $2.5 \cdot 10^{-4}$ and $1.5 \cdot 10^{-4}$ mmol L^{-1}, respectively. The CMC values determined for mixed compositions lie in a range between these values (Fig. 1, Table 1). As a rule, mixed micelles are formed in binary compositions of the cationic and nonionic surfactants. In the cases of BCB-16 and Tween 80, this can be demonstrated by the dynamic light scattering method. Regardless of the component ratio in the considered binary system, the particle size distribution is unimodal and has a low polydispersity index (0.1—0.2). The hydrodynamic diameter (D_h) of mixed micelles increases with an increase in the content of Tween 80 (Fig. 2). Probably, the incorporation of the nonionic surfactant results in a decrease in the electrostatic repulsion of positively charged head groups of BCB-16, which is ac-

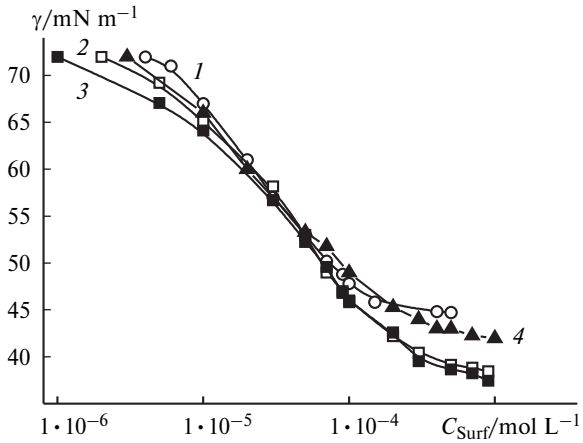


Fig. 1. Surface tension (γ) isotherms for the individual and binary systems at 25 °C: Tween 80 (*1*), BCB-16 (*2*), BCB-16 + + 5 m*M* PEG 10 000 (*3*), and BCB-16 + Tween 80, $\alpha = 0.5$ (*4*).

Table 1. Aggregation characteristics and solubilization capacity of individual and binary solutions of the surfactants toward indomethacin and PBI

System*	CMC /mmol L^{-1}	pK_a	Surface potential/mV	Solubilization capacity	
				Indomethacin	PBI
BCB-16—Tween 80, α = 0	0.15	7.6	0	0.058	0.0082
BCB-16—Tween 80, α = 0.3	0.18	7.2	24	0.089	0.0074
BCB-16—Tween 80, α = 0.5	0.21	6.6	59	0.102	—
BCB-16—Tween 80, α = 0.7	0.23	6.2	83	0.205	0.0061
BCB-16—Tween 80, α = 1.0	0.24	5.8	106	0.375	0.0051
BCB-16—5 m*M* PEG 1000	0.26	5.8	106	0.297	0.0060
BCB-16—5 m*M* PEG 10000	0.25	5.9	101	0.394	0.0048

* α is the fraction of the cationic surfactant in the system.

companied by an increase in the aggregation numbers and appears as an increase in the micelle size. In addition, the surface charge changes upon the formation of mixed micelles. The method providing the study of the spectral properties of hydrophilic probe molecules capable of participating in acid-base equilibria was used for measuring the surface potential of micelles.[17] *p*-Nitrophenol was chosen as such a probe, and its pK_a value was determined by the variation of the component ratio in a BCB-16—Tween 80 system (see Table 1). The shift of pK_a of this compound in surfactant solutions depends first on the electrostatic interactions, the strength of which is determined by the surface potential of a micelle. The surface potential values were estimated using the equation[17]

$$pK_{a,m} = pK_{a,0} - F\Psi/(2.303RT),$$

where p$K_{a,0}$ is the nonelectrostatic component, *i.e.*, p$K_{a,m}$ in micellar solutions based on nonionic surfactants (p$K_{a,0}$ of *p*-nitrophenol in micelles of Tween 80 is 7.6); F = 96 485 C mol^{-1} is Faraday's constant; and R = = 8.314 J K^{-1} mol^{-1} is the gas constant.

The values obtained for the surface potential in a mixed system are presented in Table 1. Note that for individual micelles of BCB-16 the Ψ value is somewhat lower than that for its trimethylammonium analog.[18] Probably, the presence of the carbamate moiety leads to a change in the character of binding of counterions and charge distribution in the Stern layer of the micelle. As the content of the nonionic surfactant increases in the mixed mixture, the surface potential decreases, which can be described by the linear equation

$$\Psi\ (mV) = 111.7\ \alpha - 1.1\ (R = 0.991).$$

The replacement of the micelle forming nonionic surfactant by its hydrophilic polyoxyethylene analogs makes impossible the formation of mixed micelles with cationic surfactants, which leads to differences in the behavior of binary compositions. For example, we showed that the introduction of poly(ethylene glycol) (PEG) in a concentration of 5 mmol L^{-1} into a micellar solution of BCB-16 exerts almost no effect on the values of the CMC, size, and surface potential (see Table 1). The molecular weight of the polymer does not play a significant role. Some deviations of the aggregation parameters from the values obtained for individual systems are caused, most likely, by a change in the properties of the bulk medium.

The ability to solubilize low-polarity compounds is the most important practically significant property of micellar solutions. The solubilization process occurs due to the transition of the hydrophobic compound to the disperse phase, resulting in an increase in its content in aqueous systems. A guest can be retained in a micelle compound—guest due to electrostatic and hydrophobic interactions. Interactions of other types, in particular, hydrogen bond formation, can be involved in the process if a surfactant molecule contains functional groups.

We studied the solubilization effect of a BCB-16—Tween 80 system at the variation of the component ratio. Biologically active substances of the heterocyclic series were chosen as solubilizing agents: indomethacin and the benzimidazole derivative PBI. These compounds are characterized by a very low solubility in water, which decreases their bioaccessibility. As a consequence, the

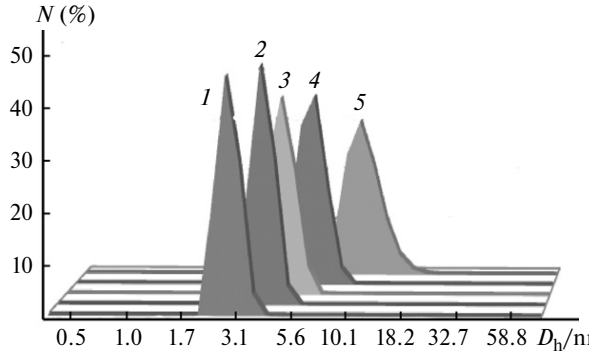


Fig. 2. Particle size distribution in BCB-16—Tween 80 micellar solutions under the conditions of variation of the component ratio: α = 1 (*1*), 0.7 (*2*), 0.5 (*3*), 0.3 (*4*), and 0 (*5*); *N* is the particle number.

therapeutic effect of the drugs becomes weaker. The use of surfactants in medicine and pharmacology is an efficient tool for increasing the content of drugs in aqueous compoundings.[19–21] Lowly toxic nonionic surfactants (Tween, Tyloxapol) should be mentioned among the most known solubilizing agent.[22–24] However, the cationic surfactants often turn out to be more efficient for transdermal drug delivery applied in ophthalmology.[25,26] It can be expected that a combination of both types of surfactants would enable one to prepare a system combining their advantages.

Electronic spectroscopy that makes it possible to simply and reliably detect the content of studied drugs in solutions was used in this work to determine the solubilization capacity of individual and mixed micellar systems. We have previously[15,16] shown that in neutral media the indomethacin content can be determined by the absorption maximum at 327 nm (ε = 5800 L mol^{-1} cm^{-1}), which insignificantly changes on going to micellar solutions of surfactants. In the case of PBI, the absorption band characterized by the maximum at 305 nm (ε = = 22 000 L mol^{-1} cm^{-1}) is convenient for these purposes. In micellar solutions of a surfactants, in the range of concentrations exceeding the CMC, the solubilities of both indomethacin and PBI increase with an increase in the surfactant content in the system (Fig. 3), which is a convincing argument in favor of the principal role of solubilization of hydrophobic compounds by micelles.

The dependences characterizing the change in the absorbance of saturated solutions of the studied drugs at the absorption maximum are presented in Fig. 4. They were used for the determination of the solubilization capacity (S). The values of this parameter were calculated by the equation $S = b/\varepsilon$, where b is the slope of the linear section of the plot of the reduced absorbance *vs* surfactant concentration. The data obtained (see Table 1) show that the solubility of indomethacin changes strongly on going from the cationic to nonionic surfactant: the S value in solutions of BCB-16 is almost an order of magnitude higher than that for Tween 80, and the mixed compositions are characterized by intermediate values of this parameter. Other tendencies are observed in the case of PBI: Tween 80 turns out to be more efficient, and the total micellar

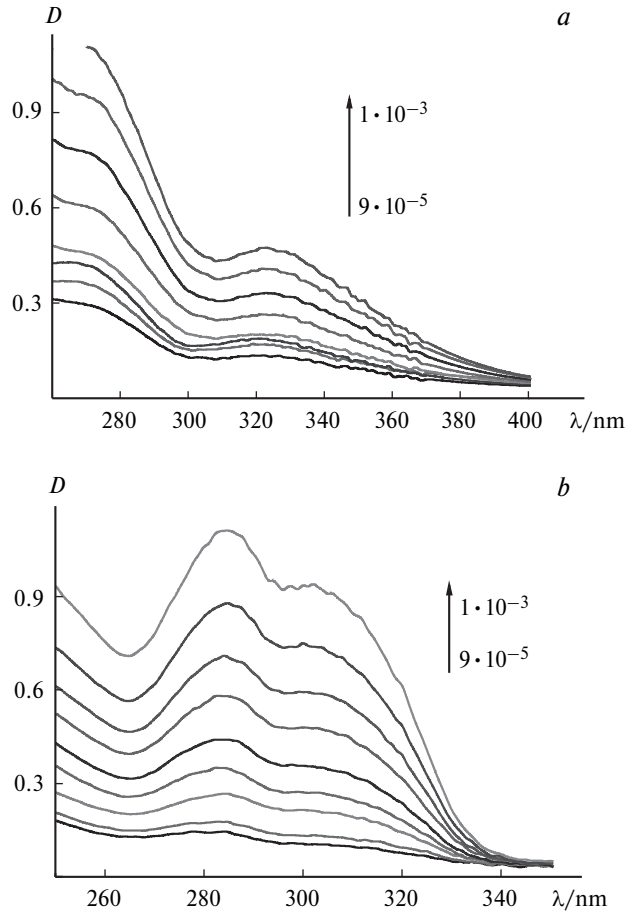


Fig. 3. Absorption spectra of saturated solutions of indomethacin (*a*) and PBI (*b*) in the presence of the cationic surfactant BCB-16 in the concentration range from $9 \cdot 10^{-5}$ to $1 \cdot 10^{-3}$ mol L^{-1}.

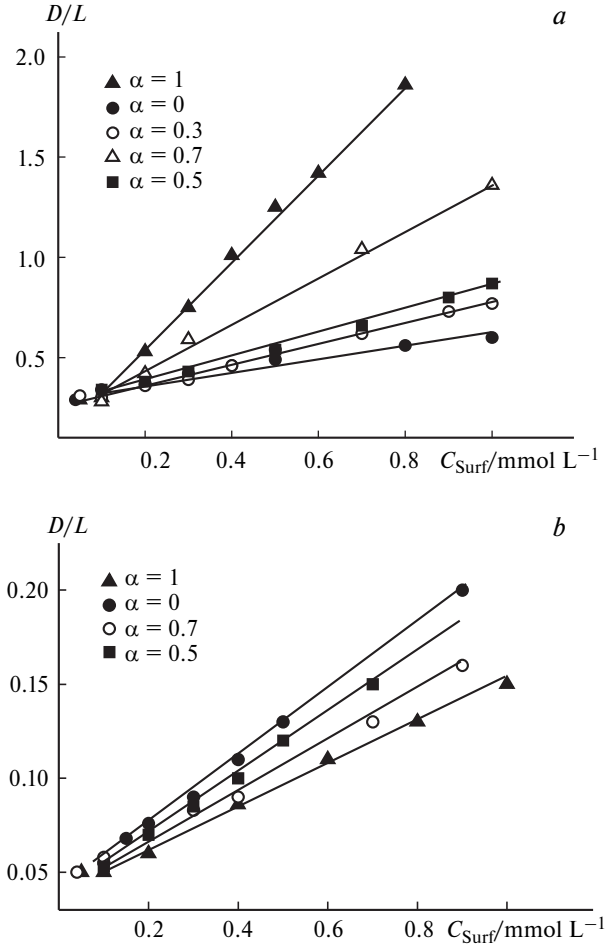


Fig. 4. Absorbance of micellar solutions saturated with indomethacin at 327 nm (*a*) or PBI at 305 nm (*b*) *vs* surfactant concentration ($C_{Surf} = C_{Tween\ 80} + C_{BCB\text{-}16}$).

effect is somewhat lower. This difference is related, most likely, to the presence of the carboxyl group in the indomethacin molecule characterized by $pK_a = 4.5$.[27] Thus, in neutral solutions the compound exists predominantly in the anionic form, which provides its concentrating at the positively charged micelles and contributes to an increase in the solubility of indomethacin in water. This is consistent with a change in the solubilization effect of the mixed compositions BCB-16—Tween 80, which increases with an increase in the surface potential of the micelles.

For the solubilization of an uncharged PBI molecule. The contribution of the hydrophobic component predominates and Tween 80 turns out to be most efficient. The addition of cationic BCB-16 to Tween 80 insignificantly (not more than by 1.5 times) decreases the solubilization capacity of the system.

No appreciable change in the solubilization effect of the cationic surfactant on the studied substances is observed in the binary compositions of BCB-16 with PEG (see Table 1).

To conclude, the quantitative characteristics of the aggregation and solubilization activity of the mixed micelles based on the cationic surfactants containing the butyl carbamate fragment and nonionic surfactant Tween 80. The use of the binary systems enables one to control and optimize practically significant properties of the aggregates: the size, surface charge, and solubilization capacity. Selective binding of various substrates by individual micelles should be mentioned, since it can play an important role in the development of transporting agents acting according to the molecular recognition principle. This provides a substantial biotechnological potential of nanosystems and makes it possible to combine advantages of both amphiphilic components and to recommend them as nanocontainers for enhancing solubility of hydrophobic guest molecules.

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