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Nontoxic antimicrobial micellar systems based on mono- and dicationic Dabco-surfactants and furazolidone: Structure-solubilization properties relationships

Tatiana N. Pashirova [a,*], Evgeniya A. Burilova [a], Svetlana S. Lukashenko [a], Nail K. Gaysin [b], Oleg I. Gnezdilov [c], Anastasia S. Sapunova [a], Ana R. Fernandes [d], Aleksandra D. Voloshina [a], Eliana B. Souto [d,e], Elena P. Zhiltsova [a], Lucia Ya. Zakharova [a]

[a] Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, Arbuzov St., 8, Kazan 420088, Russia
[b] Kazan National Research Technological University, Karl Marx St., 68, Kazan 420015, Russia
[c] Kazan E. K. Zavoisky Physical-Technical Institute, FRC Kazan Scientific Center, Russian Academy of Sciences, Sibirsky tract 10/7, Kazan 420029, Russia
[d] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra (FFUC), Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal
[e] CEB - Centre of Biological Engineering, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

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ABSTRACT

Self-assembly and solubilization properties of amphiphilic mono- and bisquaternized derivatives of 1,4-diazabicyclo[2.2.2]octane (mono-CS-n and di-CS-n, where CS – cationic surfactant, $n = 12, 14, 16, 18$) was investigated by nuclear magnetic resonance with magnetic field pulse gradient. The influence of Dabco-surfactant structure (head group and length of alkyl chains) on critical micelle concentration and aggregation number of micelles was studied. The CMC of mono-CS-n are lower than CMC of di-CS-n. The aggregation numbers of mono-CS-n micelles are higher than for di-CS-n micelles. The solubilization capacity of mono-CS-n is higher than di-CS-n. The solubilization capacity of mono-CS-16 is 2.5 times higher than CTAB in the case of Orange OT as a solute, and it is close to CTAB in the case of Sudan I. The solubility of a poorly water-soluble antibacterial drug furazolidone was improved by micellar solubilization based on mono- and di-Dabco-surfactants. Mono-CS-n is the best solubilizing agents toward furazolidone. The use of mixed composition mono-Dabco-16-furazolidone provides a significant increase in antimicrobial activity (by 2 times against bacteria and 8 times against fungi) and reduces by 2 times the dose of each of the components in combination formulation and causes <2% haemolysis of human red blood cells at the active dose.

1. Introduction

It is well known that cationic amphiphiles are vectors for gene transfection [1,2] and antimicrobial agents [3,4]. Recently, great attention has been paid to the development of positively charged particles, as new targeted delivery systems with improved stability, selectivity, and other properties [5–7]. The interactions of positively charged particles result in improved ocular bioavailability [8–10], skin penetration [11–13] and intranasal mucosal delivery [14]. Inflammatory activation of liposomes depends not only on the charge but also in the cationic surfactant structure [15]. Starting with the first and second generations of cationic charged liposomes [16], preclinical and clinical results testify the promising cationic liposomal therapy in the future [17,18]. However, as a rule, surface potential is a source of cytotoxicity. Therefore, it is important to find a compromise between benefits and toxicity of cationic surfactants. The synthesis of new non-toxic materials was performed and a new approach was implemented to improve the safety of delivery systems. For this purpose, cationic surfactants with low critical micelle concentrations such as gemini (dimeric) surfactants are the most attractive [19–26]. Cationic amphiphiles containing natural fragments, such as sugar- [27,28], peptide- [29,30] pyrimidine- [31,32] and amino acid-surfactants [33], biodegradable amphiphiles [34] are also promised. The long-chain cetalkonium chloride-cationic emulsions are attractive for reducing toxicity of cationic surfactants and for further development in eye drops [35] The increase of the antimicrobial efficacy by cationic nanoemulsions was shown [36].

Our research group focused on amphiphilic derivatives of 1,4-diazabicyclo[2.2.2]octane (Dabco) [37–39]. Some interesting features in self-assembly behavior and functional activity (high catalytic effect, solubilization properties, antimicrobial activity) of Dabco-surfactants

* Corresponding author at: A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8, ul. Arbuzov, 420088 Kazan, Russia.
E-mail address: tatyana_pashirova@mail.ru (T.N. Pashirova).

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were shown [40–43]. It should be noted that the hexadecyl derivative of Dabco is less toxic than the classic surfactant, cetyltrimethylammonium bromide, CTAB [41]. In addition, the hexadecyl derivative of Dabco is non-toxic in the presence of *N*-methyl-D-glucamine and has an antimicrobial activity [39].

This work was aimed at improving the solubility of a poorly water-soluble drug furazolidone by micellar solubilization of mono- and dicationic Dabco surfactants (Fig. 1). Furazolidone is an antibacterial drug against both gram-positive and gram-negative bacteria, used as a topical surface skin active component in prevention and treatment of burn wound infections. The bioavailability of furazolidone was improved by adding organic solvents and hydrotropes [44]. To avoid toxicity, furazolidone-loaded liposomal forms were prepared [45] and interaction with dimyristoylphosphatidylcholine was studied [46]. Liposomal forms of furazolidone open prospects against leishmaniasis [47] and *Helicobacter pylori* [45]. The process of micellar solubilization involves several factors [48]: the structure of surfactants (solubilizer) [49,50], the aggregation number [51], and the size and geometry of micelles [52]. A drug can be solubilized, not only in the inner core micelle by hydrophobic effect, but also in the peripheral area of micelle [53,54] by electrostatic and hydrogen bonding with the head groups of surfactants.

The goal of this work was to establish the relationship between Dabco-surfactant structures, aggregation number of micelles and solubilization properties toward poorly water-soluble optical dyes and an antimicrobial drug (furazolidone). Biological activity and toxicity analysis were performed for creation of non-toxic antimicrobial formulations based on derivatives of Dabco and furazolidone.

2. Materials and methods

2.1. Materials

Monocationic surfactants were prepared by reaction of Dabco with 1-bromoalkyles. Dicationic surfactants of 1,4-diazabicyclo[2.2.2]octane were made by quarterization of mono-CS with ethyl bromide. All details about syntheses were described earlier [38]. N-Methyl-D-glucamine (99%, ACROS Organics, NJ, USA), cetyltrimethylammonium bromide (CTAB, 99%, DK, Acros), 1-(o-tolylazo)-2-naphthol (75%, Orange OT, Aldrich, USA), 1-phenylazo-2-naphthol (Sudan I, Acros Organics), furazolidone (98%, Alfa Aesar, Heysham, England), hexamethyldisiloxane (HMDSO, Aldrich), Triton-X-100 (ACROS Organics, NJ, USA), Sodium dodecyl sulfate (SDS, 99%, ACROS Organics, NJ, USA) were used as purchased.

2.2. Methods

2.2.1. Tensiometry

Surface tension measurements were performed using the du Nouy ring detachment method (Kruss K6 Tensiometer, Hamburg, Germany). Briefly, the spherical ring was placed parallel to the air/water interface. Between two surface tension measurements, the ring was cleaned with Ultra-pure water, followed by soaking in ethanol for 5–7 min, rinsing again with Ultra-pure water, and finally flame-drying. Temperature was kept constant at 25 °C during all experiments.

2.2.2. Conductometry

Specific conductivity was measured using a WTW InoLabCond 720 precision conductivity meter (WTW GmbH, Weilheim, Germany). All measurements were carried out at 25 °C. Purified water (18.2 MΩ cm resistivity at 25 °C) from Direct-Q 5 UV equipment (Millipore S.A.S. 67120 Molsheim-France) was used for all sample preparations.

2.2.3. Spectrophotometry (dye and drug solubilization)

Solubilization of dyes (Orange OT, Sudan I) was performed by adding an excess of crystalline dyes to surfactant solutions. These solutions were allowed to equilibrate for about 48 h at 25 °C, followed by filtration. Then the absorbance was measured at 495 nm (Orange OT) and in the range 483–492 nm (Sudan I) on a spectrophotometer Specord 250 Plus (Analytik Jena AG, Germany). Quartz cuvettes (1 cm path length) were used. The solubilization capacity of associates (S), which corresponds to the number of moles of dye solubilized per mole of surfactant, was determined according to Eq. (1) [55]:

$$S = B/(\varepsilon_{ext} \times 1) \quad (1)$$

where B is the slope of the dye absorbance as a function of surfactant at concentration above the critical micelle concentration (CMC) and ε_{ext} is the extinction coefficient of Orange OT ($\varepsilon_{ext} = 18720\ M^{-1}\ cm^{-1}$) [56] and the extinction coefficient of Sudan I ($\varepsilon_{ext} = 8700\ M^{-1}\ cm^{-1}$) [57].

2.2.4. Particle size analysis

Size, zeta potential and polydispersity index of nanoparticles were determined by dynamic light scattering (DLS) measurements, using the Malvern Instrument Zetasizer Nano (Worcestershire, UK). Measured autocorrelation functions were analyzed by Malvern DTS software, applying the second-order cumulant expansion methods. The effective hydrodynamic radius (R_H) was calculated according to the Einstein-Stokes equation $D = k_BT / 6\pi\eta R_H$, where D is the self-diffusion coefficient, k_B is the Boltzmann constant, T is the absolute temperature, and η is the viscosity. The diffusion coefficient was measured at least three times for each sample. The average error of measurements was 4%. All samples were diluted with ultra-pure water to suitable concentration, and then, analyzed in triplicate.

2.2.5. NMR experiments for micellization study

Sample preparation for measurement of self-diffusion coefficients (SDC) are described earlier [40,58,59]. The solvent for surfactant

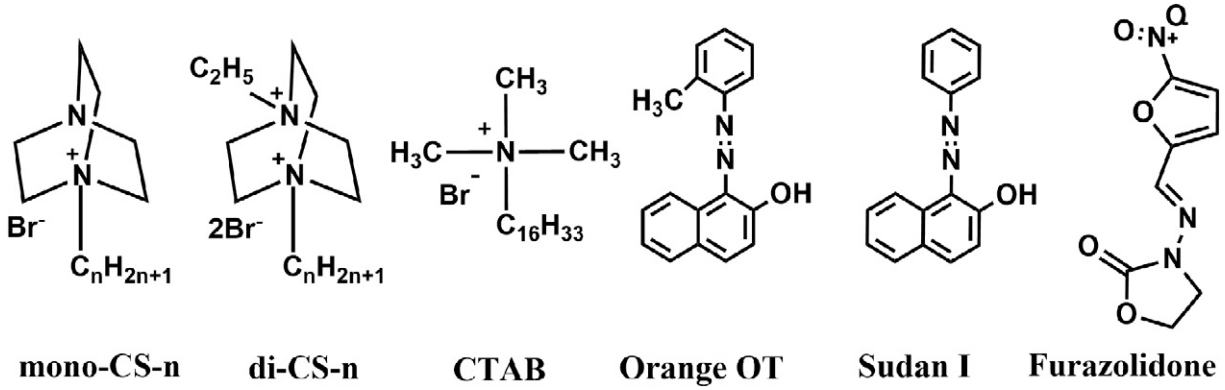

Fig. 1. Structural formulas of cationic surfactants, mono-(mono-CS-n) and bisquaternary (di-CS-n) ammonium derivative of 1,4-diazabicyclo[2.2.2]octane (Dabco-n where $n = 12, 14, 16, 18$), cetyltrimethylammonium bromide (CTAB), hydrophobic dyes (Orange OT, Sudan I) and drug (Furazolidone).

samples was deuterated water D_2O. The SDCs of surfactant in aqueous solutions were measured by using a Bruker AVANCE 400 NMR-spectrometer using a pulsed magnetic field gradient (G) of up to 0.53 T m^{-1}. The D values were derived from the decrease in the integral intensity of stimulated spin echo signals from protons of the different groups of alkyl and cyclic moieties of surfactants (Eq. (2)). These signals are due to changes in the field gradient in a series of three consecutive 90° pulses:

$$I(G) = I_0 \exp\left[-(\gamma\delta G)^2 D\left(\Delta - \frac{\delta}{3}\right)\right] \quad (2)$$

In Eq. (2), γ is the gyromagnetic ratio of proton, δ is the gradient pulse duration, and Δ is the time interval between gradient pulses. Depending on the self-diffusion coefficient the values of δ and Δ varied from 6 to 10 ms and from 50 to 70 ms, respectively. These times are substantially longer than the time needed for exchange of molecules between free and micellar components of the solution.

The SDC values were averaged from proton resonance signals of the different atomic groups of alkyl and cyclic moieties of surfactant. The error in SDC measurement at high surfactant concentration was about 2%, at low concentration - about 5%. The experimental studies were carried out at 25 °C controlled by the thermostabilized system of spectrometer. The concentration dependence of the SDC of surfactant molecules was simulated by using a pseudo-phase model of micellization, in which the critical micelle concentration is considered as a transition point between monomer (free) and aggregated states of surfactant in solution.

At concentration exceeding CMC, there is a fast exchange between free surfactant molecules and micellar surfactant molecules, so that the observed SDC of surfactant molecules D_{obs} represents the average quantity weighted between the SDC of these components:

$$D_{obs} = p_f D_f + p_m D_m \quad (3)$$

where p_f, D_f and p_m, D_m are the weights and the SDC of free and micellar components of surfactant in solution.

The concentration of free p_f and micellar p_m components of surfactant can be expressed by Eq. (4) from the total concentration of surfactant in solution D_t, the observed SDC D_{obs}, the SDC of free molecules D_f, and the SDC of surfactant forming the micelles D_m:

$$p_f = 1 - p_m = (D_t - D_m)/(D_f - D_m) \quad (4)$$

The SDC of free molecules were calculated from Eq. (5) [59]:

$$D_f = D_{f,CMC}\left(1 + \frac{\varphi}{2}\right)^{-1} \quad (5)$$

where $D_{f,CMC}$ is the SDC of free molecules of surfactant near CMC and φ is the volumetric fraction of micellar surfactant. φ is determined by the Eq. (6):

$$\varphi = M_{ef}(C_t - CMC)/\rho V \quad (6)$$

where M_{ef} is the effective mass of surfactant micelles, $M_{ef} = 500$, determined taking into account the degree of binding with the counter-micelle (β) from [38], C_t is surfactant concentration in solution, ρ is the density of the micellar surfactant, V is volume of the solution.

Hexamethyldisiloxane (HMDSO) was used as a micellar solubilized molecule in order to determine the SDC of micelles. HMDSO molecules penetrate into micelles and diffuse together with them. Assuming that the presence of the HMDSO molecules in micelles does not cause notable errors in SDC and size of micelles at low concentration of HMDSO ($C_{HMDSO} \ll C_{surf}$), the SDC D_m was measured from the decay of NMR line attributed to HMDSO protons.

The aggregation numbers of micelles were estimated using the ratio of "dry" micelle volume $V_m = 4\pi R^3/3$, to volume of the surfactant molecule, $V_{mol} = M_{ef}/\rho N_A$, where, ρ – is the surfactant density in micelle (it is considered that density is close to that of surfactant in solid state 10^3 kg/m^3). The values of micelle SDC near CMC were estimated by extrapolation of the concentration dependence of D_m to the zero concentration of micelles. This extrapolation was performed on purpose of using the viscosity of the pure solvent in calculations.

Results obtained can be used to estimate the number of surfactant and solubilizate (Furazolidone) molecules in micelles [41]. The volume of a micelle (V_m) is the sum of volumes occupied by surfactant (V_{Surf}) and solubilizate ($V_{Fu,}$).

$$V_m = V_{surf} n_{surf} + V_{Fur} n_{Fur} \quad (7)$$

where $V_{Surf} = M_{ef\,Surf}/(\rho_{Surf} N_A)$ is the volume occupied by the surfactant molecule, $V_{Fur} = M_{Fur}/(\rho_{Fur} N_A)$ is the volume occupied by the solubilizate molecule in the micelle, $M_{ef\,Surf}$ and M_{Fur} are the molecular masses of surfactant and solubilizate, $M_{fur} = 225$, ρ_{Surf} and ρ_{Fur} are the densities of surfactant and solubilizate, n_{Surf} and n_{Fur} are the numbers of surfactant and solubilizate molecules in the micelle. With consideration to $N_{agg} = n_{Surf} + n_{Fur}$, Eq. (8) can be rewritten as follows:

$$\frac{V_m}{N_{agg}} = \frac{M_{surf}}{\rho_{surf} N_A}\frac{n_{surf}}{n_{surf} + n_{Fur}} + \frac{M_{Fur}}{\rho_{Fur} N_A}\frac{n_{Fur}}{n_{surf} + n_{Fur}} \quad (8)$$

If formula (8) is supplemented with a solubilization factor defined as $\beta = n_{Fur}/n_{Surf} = C_{m,Fur}/C_{m,Surf}$, where $C_{m,Fur}$ and $C_{m,Surf}$ are the concentrations of solubilizate and surfactant molecules in micelles, then the expression for the micelle aggregation number takes the form.

$$N_{agg} = V_m N_A (1 + \beta)/\left[M_{surf}/\rho_{surf} + (M_{Fur}/\rho_{Fur})\beta\right] \quad (9)$$

Finally, the number of solubilizate molecules in micelles was calculated by the formula $n_{Fur} = N_{agg}/(1 + 1/\beta)$.

2.3. Antibacterial and antifungal activity

In vitro antibacterial and antifungal activities of cationic surfactants and their compositions were evaluated against pathogenic representatives of Gram-positive bacteria *Staphylococcus aureus ATCC 209p* (*Sa*) and fungi *Candida albicans NCTC 885-653* (*Ca*). Minimal inhibitory concentrations (MICs) were estimated by conventional dilution methods for bacteria and fungi [60]. The antibacterial and antifungal assays were performed in Hottinger broth (HiMe-dia Laboratories Pvt. Ltd. Mumbai, India) and Sabouraud dextrose broth (HiMedia Laboratories Pvt. Ltd. Mumbai, India) (bacteria 3×10^5 cfu/mL and yeast 2×10^4 cfu/mL). The components of Hottinger broth (Lactalbumin hydrolysate (10 g), Peptone (10 g), NaCl (5 g)) were dissolved in 1 L of distilled water, autoclaved for 20 min at 121 °C. The pH was adjusted to 7.2 prior to autoclaving. The components of Sabouraud dextrose (Peptone (10 g), glucose (40 g)) were dissolved in 1 L of distilled water, autoclaved for 15 min at 121 °C. The pH was adjusted to 5.6 prior to autoclaving. The tests were repeated 3 times.

2.4. Hemolytic activity assay

Toxicity of cationic surfactants was tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC collected from heparinized blood were rinsed 3 times with 35 mM phosphate buffer containing 0.15 M NaCl, pH 7.3 (PBS). Each time, the suspension was centrifuged for 10 min at 800g, the supernatant discarded, and the pellet re-suspended in PBS. Test compound dissolved in PBS (concentrations 0.98–500 μg/mL) were then added to 0.5 mL of a suspension of hRBC in PBS to reach a final volume of 5 mL (final erythrocyte concentration was 10% v/v). The resulting suspension was incubated under gentle

stirring for 1 h at 37 °C. The samples were then centrifuged at 2000 rpm for 10 min. The release of hemoglobin from hRBC was monitored by measuring the supernatant absorbance at 540 nm. Controls for zero hemolysis (blank) and 100% hemolysis consisted of hRBC suspended in PBS and distilled water, respectively.

3. Results and discussion

3.1. Self-assembled properties and aggregation number of Dabco-surfactant micelles

The self-assembly of Dabco-surfactants was studied using NMR with magnetic field pulse gradient (NMR-MFPG) to understand the influence of Dabco-surfactant structure (head groups and length of alkyl chains) on the CMC and aggregation number of micelles. The dependence of self-diffusion coefficients on the concentration of surfactants is shown in Figs. 1S–3S. CMCs were determined from the dependence of D_{obs} on the reciprocal of concentration, $1/C_t$, according to [61]. The values of the CMC are presented in Fig. 2a. N_{agg} for mono-CS-n and di-CS-n are shown in Fig. 2b and c, respectively.

It can be seen, that the CMC decreases linearly with increasing the length of alkyl chains of Dabco-surfactants from dodecyl to octadecyl homologues by 2 orders, and 30 times for mono-CS-n and di-CS-n, respectively. There is a good linear dependence with correlation coefficients (0.998, 0.995) for mono-Dabco and di-Dabco-surfactant series, respectively. Slopes are decreasing from monocationic Dabco-n (0.35) to dicationic surfactants (0.254). Likely, the increase in CMC difference between mono-CS-n and di-CS-n (Fig. 2a) is due to more unfavorable thermodynamic process of di-CS-n micelle formation compared to mono-CS-n. The CMC of mono-CS-n are lower than CMC of di-CS-n with the same alkyl chain. This indicates that the polarity of these mono-Dabco and di-Dabco-surfactants are different. It is plausible that the electrostatic repulsion between the headgroups of di-CS-n is much stronger than for mono-CS-n. The values of N_{agg} support this hypothesis. As we can see in Fig. 2b and c, N_{agg} decreases upon increasing size of surfactant head group. By tensiometry, it was found that the minimal surface area per mono-CS-n surfactant molecule is less than per di-CS-n surfactant [38]. The reduction of mutual repulsion in micelle permits closer packing of the head groups, leading to a significant increase in N_{agg}. This trend remains with increasing the chain length of mono-CS-n surfactants. Usually N_{agg} increases with growing alkyl chain length in the homologous series of classical surfactants (*n*-alkyltrimethylammonium bromides and chlorides) and imidazolium ionic liquids [62–65].

N_{agg} increase with increasing mono-CS-n and di-CS-n surfactant concentrations. N_{agg} of mono-CS-14 and di-CS-14 surfactants in our present work are in good agreement with values obtained by means of fluorescence techniques earlier [38,59]. In numerous works, micelle aggregation numbers of typical cationic surfactants are concentration independent in the range extending from the CMC to 0.1 M and even above for certain investigated surfactants [64–66]. However, spherical micelles with variable aggregation numbers were also reported in literature [67,68]. Increasing N_{agg} with concentration can be explained by several hypotheses. The variable character of their N_{agg} is obvious for non-spherical micelles. The increase of N_{agg} with concentration could indicate that the spherical micelles present at low concentration change shape at higher concentration [69]. A much stronger tendency for micellar growth and formation of aggregates of lower curvature and formation of threadlike micelles for gemini surfactants was shown [70]. Increase in the polydispersity index of systems and formation of two types of aggregates could also be the cause [71].

3.2. Micellar solubilization of poorly water soluble dyes and drug (furazolidone)

Absorption spectra of poorly water-soluble dyes (Orange OT and Sudan I) in Dabco-surfactant solutions are presented in Figs. S4–S15. The optical density increases with increasing surfactant concentration for all Dabco-surfactants. Fig. 3 shows the absorption of dyes in Dabco-surfactant solutions at λ_{max}. The increase in absorption above CMC is associated with the solubilization of the dye in the hydrophobic core of surfactant self-assembled structures. In the case of di-CS-n (Fig. 3b, c), the increase of optical density is observed at concentrations below CMC di-Dabco-n surfactants. Despite the fact that the structure of both azo dyes is very similar, the formation of surfactant-Sudan I

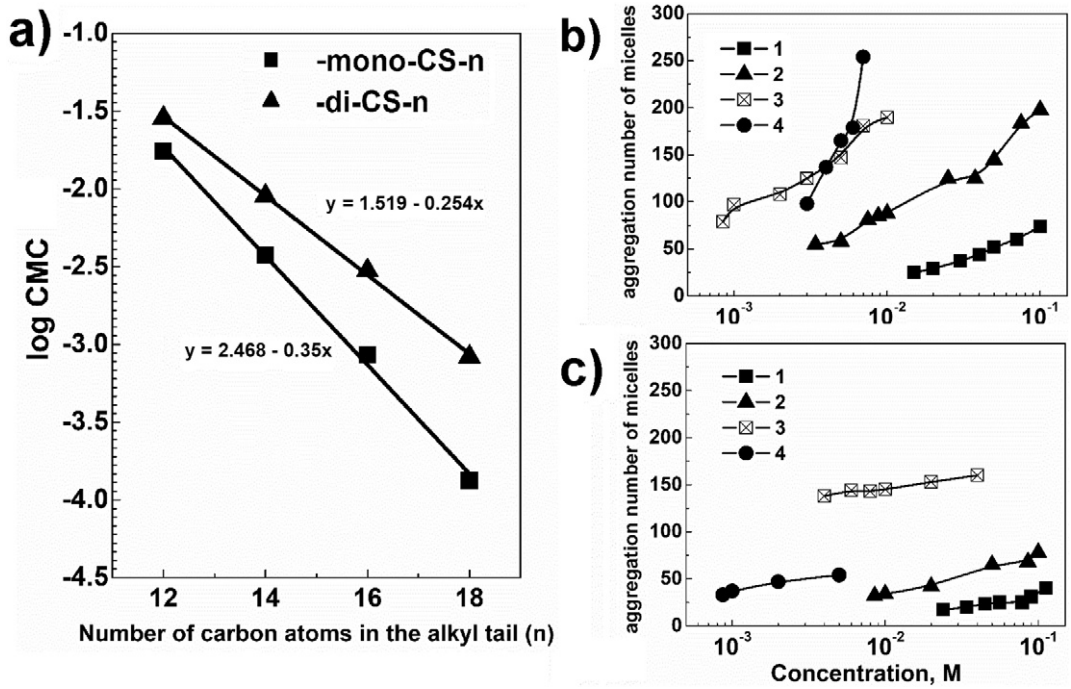

Fig. 2. CMC of Dabco-surfactants (a); aggregation number of micelles for mono-CS-n (b) and di-CS-n (c), where $n = 12^a$ (1), 14 (2), 16 (3), 18 (4) at 30 °C. a - Data from ref. [58].

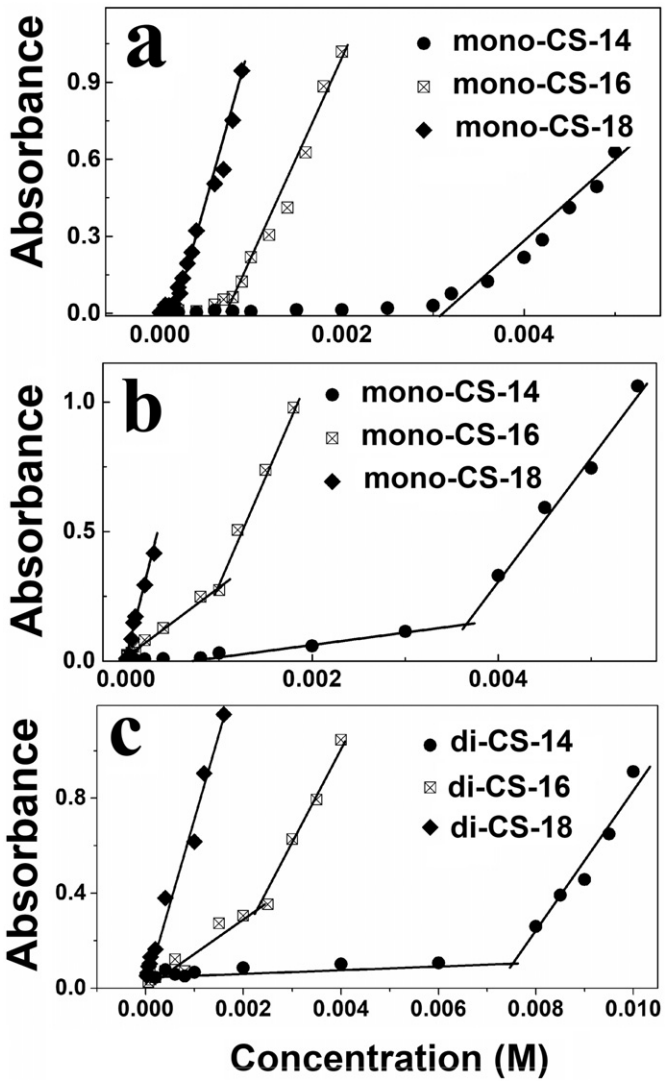

Fig. 3. Absorbance of Orange OT (a) and Sudan I (b, c) in surfactant solutions, at λ_{max} = 495 nm (a), 483–492 nm (b, c), L = 1 cm.

structures below CMC may be due to much higher conformational flexibility of Sudan I compared to Orange OT.

Solubilization capacity data, calculated through formula (1) are presented in Fig. 4. Solubilization ability allows one to quantify the ability of surfactants to solubilize the hydrophobic dye. Solubility of dyes linearly increases with alkyl chain length of CS-n and follows the relations:

$$S = -0.0899 + 0.00843n,\ r = 0.997\ (\text{Orange OT in mono}-\text{CS}-\text{n solution}),$$

$$S = -0.2096 + 0.0195n,\ r = 0.997\ (\text{Sudan I in mono}-\text{CS}-\text{n solution}),$$

$$S = -0.08767 + 0.00902n,\ r = 0.97\ (\text{Sudan I in di}-\text{CS}-\text{n solution}).$$

The solubilizing capacity depends on both surfactant chain length and nature of surfactant head group. Unlike mono-CS-n, the decrease in solubilization capability of di-CS-n with the same alkyl chain may result from their lower aggregation numbers and lower packaging in di-CS-n micelles. The incorporation of solubilizate in the hydrocarbon core of micelles is the result of the hydrophobic effect, but also of adsorption through other non-covalent interactions between dye and surfactant. It should be noted that the solubilizing properties depend on the nature of the solubilizate. The solubilization capacity of mono-Dabco surfactant is much higher with Sudan I than with Orange OT as

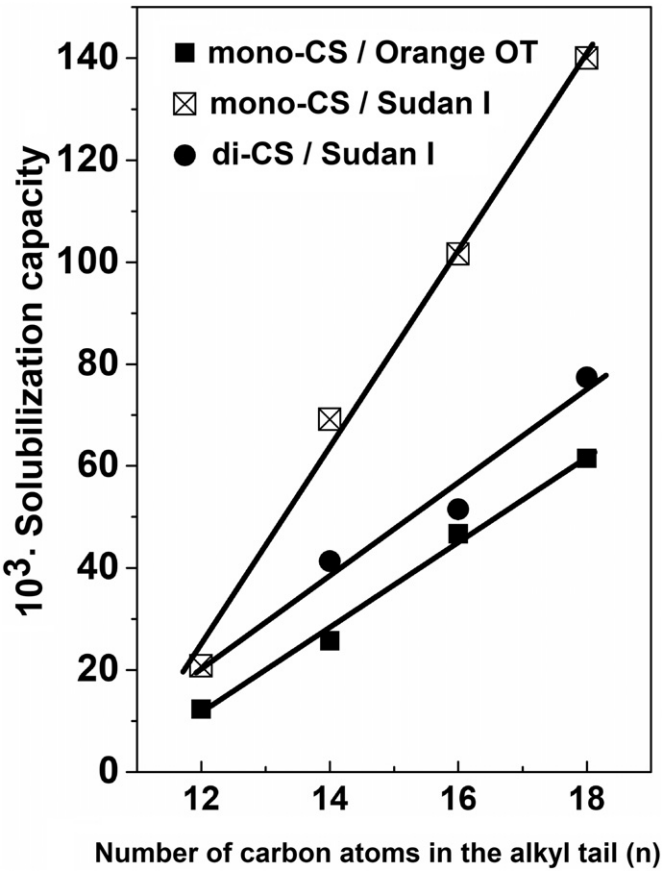

Fig. 4. Solubilization capacity of surfactants toward hydrophobic dyes Orange OT and Sudan I as a function of the number of carbon atoms of mono-Dabco and di-Dabco-surfactants.

solubilizates. The structure of dyes plays an important role in determining the solubilization capacity [72]. Further, the solubilization capacity of Dabco-surfactants with a hexadecyl chain and the classical surfactant cetyltrimethylammonium bromide (CTAB) were compared. In the case of Orange OT as a solute, the solubilization capacity of mono-CS-16 is 2.5 times higher than that of CTAB (S = 0.0159 [57]). In the case of Sudan I as a solubilizate, the solubilization capacity of mono-CS-16 and the solubilization capacity of CTAB (S = 0.107 [73]) are very close.

The solubility of furazolidone in different surfactant solution is shown in Fig. 5.

The concentration of solubilized furazolidone was calculated from the absorbance values with the aid of a calibration curve in organic solvent. Furazolidone is slightly soluble in water (solubility of 0.25 mM). As can be seen in Fig. 5, furazolidone dissolves better in cationic surfactant solutions. The solubility of furazolidone at 5 mM surfactant is 1.2 times better in CTAB solutions, 1.4 times better in mono-CS-16 solutions and 1.25 times better in di-CS-16 solutions than in water. The same solubility of furazolidone in mono-CS-12 and in SDS solutions is observed for a concentration of surfactants by 10 times higher. An increase of drug solubility may occur in the case of formation of mixed drug-surfactant self-assemblies. The micellization properties and thermodynamics of micelle formation may change in the presence of drugs [74–79]. The effect of furazolidone on the CMC of surfactant solutions was analyzed by tensiometry and conductometry. The surface tension isotherms of surfactant solutions in the absence and presence of furazolidone are presented in Fig. 6.

CMC of surfactants do not change in the presence of furazolidone, except for SDS. For SDS, the shift of CMC to lower concentrations and a decrease of surface tension are observed. This could be the result of different mechanism of binding furazolidone with anionic and cationic

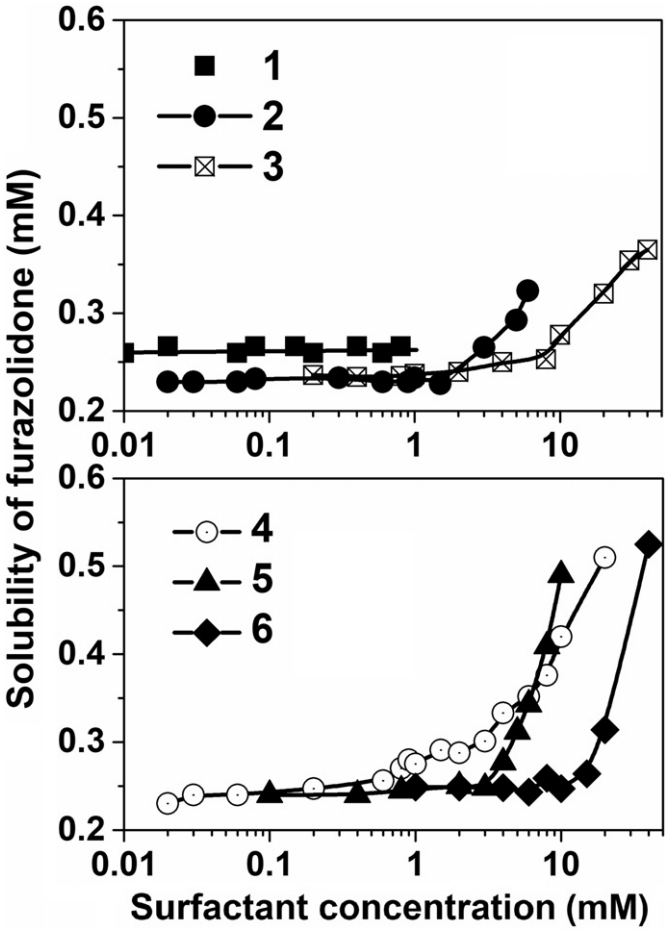

Fig. 5. Solubility of furazolidone as a function of surfactant concentration, Triton-X-100 (1), CTAB (2), SDS (3), mono-CS-16 (4), di-CS-16 (5), mono-CS-12 (6) pH 6.0, 25 °C.

surfactants. The formation of pre-micellar aggregates also could cause this behavior at air-water interface. Adsorption parameters determined from adsorption and conductometric data are presented in Table 1.

The values of surface excess (Γ_{max}), the surface area per molecule (A_{min}); the standard free energy of micellization per mole of monomer unit (ΔG_m) and the standard free energy of interfacial adsorption at the air/saturated monolayer interface (ΔG_{ad}) were calculated using Eqs. (7)–(11) [80–83]. Therefore, the constant m = 2 was used for monomeric ionic surfactant, where the surfactant ion and the counterion are univalent, while m = 3 was assumed for dicationic surfactants. This issue is thoroughly discussed in ref. [82].

$$\Gamma_{\max} = -\frac{1}{2.3mRT}\lim_{C\to cmc}(d\pi/d\log C) \quad (7)$$

$$A_{\min} = 10^{18}/(N_A \times \Gamma_{\max}) \quad (8)$$

$$\Delta G_{ad} = \Delta G_m - (\pi_{CMC}/\Gamma_{\max}) \quad (9)$$

$$\Delta G_m = RT(1+\beta)\ \ln(CMC), \quad (10)$$

$$\Delta G_m = RT(0.5+\beta)\ \ln(CMC) - [RT(\ln 2)/2] \quad (11)$$

Adsorption parameters, the values of surface excess and minimum surface area per molecule at the interface, A_{min}, suggest the formation of closely packed monolayer at the air-solution interface except for di-CS-16. The ΔG_{mic} values for di-CS-16/furazolidone and SDS/furazolidone mixed systems become increasingly more negative compared to pure surfactant. This indicates that micelle formation in mixed systems

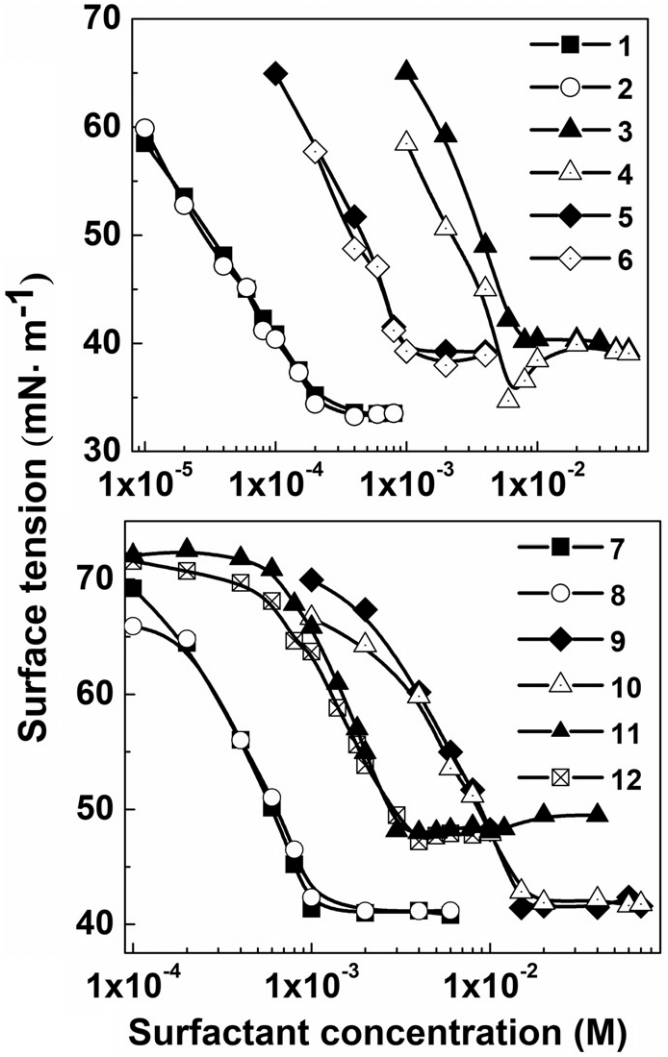

Fig. 6. Surface tension isotherms of surfactant solutions of Triton-X-100 (1, 2), SDS (3, 4), CTAB (5, 6), mono-CS-16 (7, 8), mono-CS-12 (9, 10), di-CS-16 (11, 12) in the absence (1, 3, 5, 7, 9, 11) and presence (2, 4, 6, 8, 10, 12) of furazolidone, 25 °C.

is easier. Likely, solubility of furazolidone is due to a combination of different mechanisms, including electrostatic and specific interactions with surfactants.

The formation of particles of size about 200 nm within the region of concentration 0.08–1.5 mM for cationic surfactants-furazolidone and about 80 nm for the SDS/furazolidone system within the region of

Table 1
CMC determined by tensiometry (Tens) and spectrophotometry (Spectr) and adsorption parameters for micellar surfactant systems in the absence and presence of furazolidone (Fur).

Systems	CMC, mM	CMC, mM	$10^6\ \Gamma_{max}$, mol m^{-2}	A_{min}, nm^2	ΔG_{ad}, kJ mol^{-1}	ΔG_{mic}, kJ mol^{-1}
	Spectr	Tenz				
CTAB	–	1	2.48	0.67	−49.5	−36.1
CTAB/Fur	2	1	3.1	0.536	−41.9	−31.4
Mono-CS-16[a]	–	1	2.37	0.70	−46.6	−34.1
Mono-CS-16/Fur	0.7	1.1	3.24	0.513	−42.4	−32.9
Di-CS-16	–	3	2.29	0.726	−33.5	−23.0
Di-CS-16/Fur	3	3.5	1.63	1.019	−38.3	−23.4
SDS	–	8	2.46	0.676	−38.3	−22.1
SDS/Fur	6	7	2.5	0.66	−41.1	−24.3

[a] Calculation according to ref. [38].

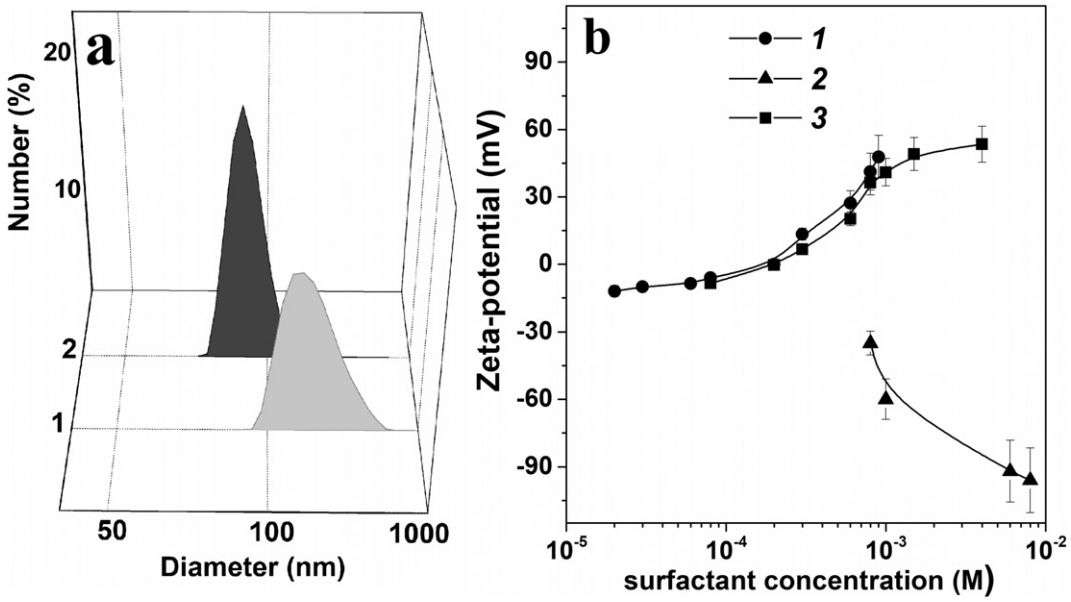

Fig. 7. Particle size distribution (a) using the number parameters for SDS/furazolidone (2 mM) and CTAB/furazolidone (0.08 mM) and zeta-potential (b) of CTAB/furazolidone (1), SDS/furazolidone (2) and mono-CS-16/furazolidone (3) mixed systems, 25 °C.

concentration 2–8 mM was established by dynamic light scattering (Fig. 7a).

A change in surface charge (zeta potential) of self-assembling surfactant-furazolidone structures from negative to positive with increasing surfactant concentration confirmed the formation of mixed structures (Fig. 7b). Zeta potential is changed and pre-micellar drug/surfactant structures are observed below the CMC. A high polydispersity of solutions >0.5 and additional aggregates of 2–3 nm size are observed at concentration above CMC.

Plots showing diffusion coefficients D of surfactant di-CS-16 and solubilizate (furazolidone) in D_2O vs. total concentration (A) and reciprocal total concentration (B) of surfactant C_t are shown in Fig. 8.

The SDC of surfactant is practically constant and close to the value of SDC_{CMC} at concentration below the CMC. It indicates that the influence of the interaction of surfactant molecules with each other on their translational motion is very weak. In contrast, the SDC of furazolidone is not constant and decreases with increasing surfactant concentration, approaching the SDC of surfactant molecules at CMC. It can be stated that this is an effect of surfactant molecules on the movement of furazolidone molecules and the formation of premicellar associates surfactant-furazolidone. The concentration dependences of the SDC of surfactant molecules in the absence and in presence of furazolidone and furazolidone, are the same in concentration range above CMC. All of parameters calculated using Eqs. (3)–(9) are presented in Table 2.

It can be seen that increasing concentration of surfactant in solution increases the relative fraction of surfactant molecules in micelles, the total concentration of micelle bound furazolidone molecules, and the radius and aggregation number of micelles but decreases the number of solubilizate molecules in micelles. The self-diffusion coefficient values and aggregation number of micelles in the absence and presence of solubilizate above CMC are almost the same. The difference in the aggregation numbers is high when the number of solubilizate molecules in surfactant micelles is high. Likely, in this case drug-surfactant micelles are looser than empty surfactant micelles. This indicates that solubilizate almost does not affect the size and the shapes of micelles. The partition coefficient of the solubilizate between the micellar and aqueous phases determined from the ratio of corresponding molar concentrations: $C_{m,fur} / (C_{total,fur} - C_{m,fur})$ [84], where $C_{total,fur}$ is the total concentration of furazolidone (0.4 mM). It can be seen in Fig. S16 that the fraction of furazolidone bound micelles on the initial segment of the plot is a linearly increasing function of surfactant concentration

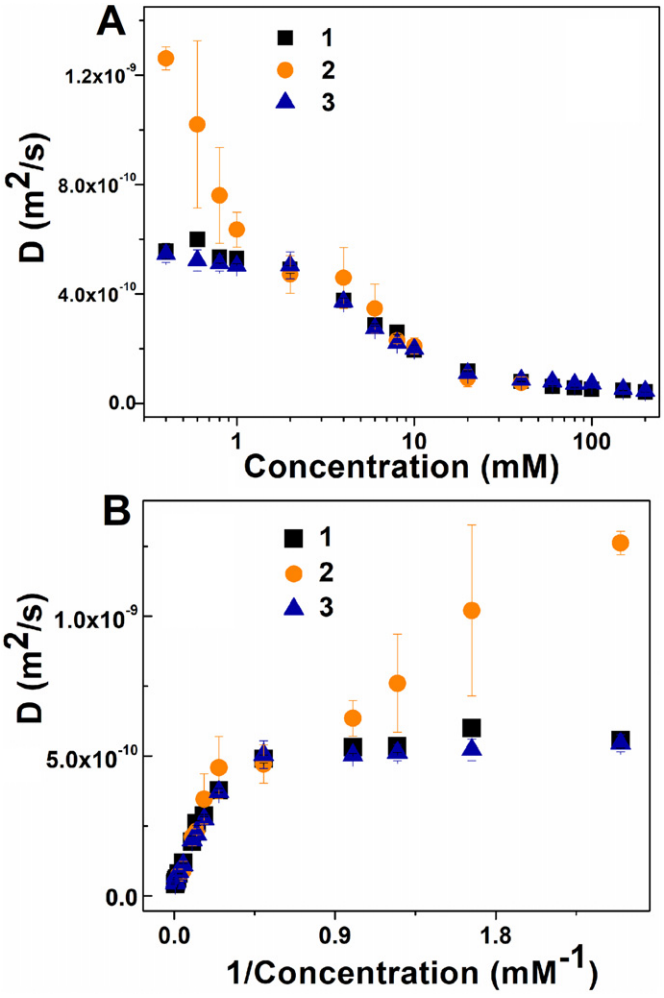

Fig. 8. The self-diffusion coefficient of cationic surfactant di-CS-16 in absence (1) and in the presence furazolidone (3), furazolidone (2) vs. surfactant concentration (A) and reciprocal concentration (B) at 30 °C (C_{Fur} = 0.4 mM).

Table 2
Parameters of di-CS-16 in the presence and in absence furazolidone, where n_{Fur} is the numbers of solubilizate molecules, D_2O at 30 °C.

C_t, mM	$C_{m\ surf}$, mM	$C_{m\ Fur}$, mM	D, sm^2/s	R (R[a]), nm	β	N_{agg} (N_{agg}[a])	n_{Fur}
4	1.42	0.132	8.2×10^{-7}	2.6 (3.04)	0.093	92 (138)	9
6	3.35	0.223	8.0×10^{-7}	2.6 (3.06)	0.067	97 (144)	6
8	5.41	0.27	7.8×10^{-7}	2.7 (3.05)	0.05	104 (143)	5
10	7.3	0.292	7.6×10^{-7}	2.8 (3.06)	0.04	113 (145)	4
20	18.23	0.364	7.3×10^{-7}	2.9 (3.12)	0.02	120 (153)	2
40	38.33	0.382	6.8×10^{-7}	3.02 (3.16)	0.01	140 (160)	1

[a] The hydrodynamic radius of micelles of surfactant in absence furazolidone.

Table 3
Antibacterial and antifungal activities of surfactant, furazolidone (Fur) and their mixed micellar systems.

Systems	Ratio Surf/drug	Bacteriostatic and fungistatic activity (μg·mL^{-1})		Bactericidal and fungicidal activity (μg·mL^{-1})		Haemolysis of human red blood cells (%)					
		Sa	*Ca*	*Sa*	*Ca*	The concentration of system (μg/mL)					
						0.48	0.98	1.8	3.9	7.8	31.3
Mono-CS-16 [39]	100/0	0.48 ± 0.05	3.1 ± 0.3	0.98 ± 0.1	6.3 ± 0.6	0	–	–	2.8	–	–
Fur	0/100	0.98 ± 0.09	31.3 ± 3	0.98 ± 0.1	31.3 ± 3	0	0	0.2	0.43		0.3
Mono-CS-16/Fur	50/50	0.48 ± 0.05	3.9 ± 0.4	0.48 ± 0.05	7.8 ± 0.78	0	0.2	0.9	1.8	8.6	51.2
Mono-CS-16/Fur/NmDg	25/50/25	1.9 ± 0.02	7.8 ± 0.8	1.9 ± 0.02	15.6 ± 1.5	0	0	0	0.8	0.63	100

until 10 mM. The partition coefficient calculated from the slope of the linear segment, considering $V_{surf} = 0.3$ L/mol is 1223.

3.3. Biological activity

The antimicrobial activity of mono-CS-16, furazolidone and their mixed systems was tested against a gram-positive bacteria *Staphylococcus aureus ATCC 209p* (*Sa*) and a fungus *Candida albicans/NCTC 885-653* (*Ca*). The minimum inhibitory concentrations (MIC), the minimal bactericidal concentrations (MBC) and the minimal fungicidal concentrations (MFC) are reported in Table 3. The combination of furazolidone with mono-Dabco-16 cationic surfactant improves antimicrobial activity (bacterial in 2 times and fungistatic in 8 times) with reducing their dose. It is known that furazolidone binds bacterial DNA [85,86] It is probable mono-Dabco-16 surfactant can facilitate the mechanism of action of furazolidone, for example, by internalization into microbial cells. The toxicity of mixed systems against human red blood cells is <2% at active dose and even less toxic in the presence *N*-methyl-d-glucamine (NmDg) additive.

4. Conclusions

Self-assembly of mono- and dicationic Dabco-surfactants was investigated to establish the relationship between the structure - solubilizing properties of these compounds toward poorly water-soluble dyes and the antimicrobial drug furazolidone. Aggregation number decreases upon increasing charge of surfactant head group Dabco-surfactants. This trend remains for all di-Dabco surfactant analogs. The deterioration of the solubilizing properties of dicationic Dabco-surfactants toward dyes Orange OT and Sudan I is associated with their low aggregation numbers and looser packaging micelles. To improve the solubility of drug (furazolidone), micellar solubilization was applied. Furazolidone dissolves better in cationic surfactant solutions. The solubility of furazolidone at 5 mM surfactants is 1.2 times better in CTAB solutions, 1.4 times better in mono-CS-16 solutions and 1.25 times better in di-CS-16 solutions than in water. The self-diffusion coefficient values and aggregation number of di-CS-16 micelle in the absence and presence of solubilizate, and solubilizate above CMC are almost the same. This indicates that solubilizate does not affect the size and shape of di-CS-16 micelles. Antimicrobial mixed compositions based on mono-Dabco-surfactant, displaying the best solubilization properties, were made. The use of mixed composition mono-Dabco-16/furazolidone improves not only the solubility of drug, but also provides a significant increase in the level of antimicrobial activity (MIC at the value 0.48 ± 0.05 and 3.9 ± 0.4 μg·mL^{-1} against bacterium *Staphylococcus aureus* and a fungus *Candida albicans*) and reduces the dose of each of the components in the formulation and decreases the toxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2019.112062.

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