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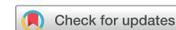
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RESEARCH ARTICLE



## Micellar solubilization of poorly water-soluble drugs: effect of surfactant and solubilize molecular structure

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### ABSTRACT

**Objective:** This study aims to clarify the role of surfactant and drug molecular structures on drug solubility in micellar surfactant solutions.

**Significance:** (1) Rationale for surfactant selection is provided; (2) the large data set can be used for validation of the drug solubility parameters used in oral absorption models.

**Methods:** Equilibrium solubility of two hydrophobic drugs and one model hydrophobic steroid in micellar solutions of 19 surfactants was measured by HPLC. The drug solubilization locus in the micelles was assessed by UV spectrometry.

**Results:** Danazol is solubilized much more efficiently than fenofibrate by ionic surfactants due to ion-dipole interactions between the charged surfactant head groups and the polar steroid backbone. Drug solubilization increases linearly with the increase of hydrophobic chain length for all studied surfactant types. Addition of 1–3 ethylene oxide (EO) units in the head group of dodecyl sulfate surfactants reduces significantly the solubilization of both studied drugs and decreases linearly the solubilization locus polarity of fenofibrate. The locus of fenofibrate solubilization is in the hydrophobic core of nonionic surfactant micelles and in the palisade layer of ionic surfactant micelles.

**Conclusions:** Highest drug solubility can be obtained by using surfactants molecules with long chain length coupled with hydrophilic head group that provides additional drug-surfactant interactions (i.e. ion-dipole) in the micelles.

### ARTICLE HISTORY

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hydrophilic head

### Introduction

Poor water solubility is characteristic for more than 40% of the new chemical entities that emerge from the modern drug discovery programs [1]. The slow and incomplete dissolution of such drugs in the gastro-intestinal fluids limits their oral bioavailability and is a major problem in drug development. One of the classical approaches to improve the water solubility of hydrophobic drugs that is still being used in the pharmaceutical industry is to solubilize them in surfactant micelles [2,3].

Surfactants are a large group of pharmaceutical excipients, which are used in a wide variety of drug delivery vehicles as solubilizers, emulsifiers, foamers, wetting agents, etc. [4]. Above the critical micelle concentration (CMC), the surfactant molecules form micelles [5]: colloidal aggregates with heterogeneous microstructure, which contain regions with different polarity. The varying polarity in the micelles facilitates the incorporation of poorly water-soluble drug molecules, which results in solubilization, *viz.* in an increase in the apparent aqueous solubility of the drug.

The micellar solubilization of drugs by surfactants is an extensively studied topic [6–19]. The effect of alkyl sulfates, polysorbates, ethoxylated alcohols, ethoxylated alkyl esters, and alkyl trimethyl ammonium bromides (TABs) on the solubility of different drugs has been investigated by a number of authors [8–19]. However, most studies usually report the drug solubilization effectiveness of a given surfactant (or set of surfactants), without considering the relationship between surfactant structure and

solubilization capacity. In several studies, the effects of surfactant charge [14,15], length and type of hydrophobic chain [16–18], and number of ethoxy (EO)-groups in the ethylene oxide (EO) chain [19] on drug solubility enhancement are particularly addressed.

Thus, Stephenson et al. [14] found that ibuprofen is solubilized most efficiently by cationic surfactants, followed by nonionic, whereas the anionic had the lowest solubilization capacity. Different trends were reported for erythromycin, where cationic and anionic surfactants had the same effect, which was bigger than that of nonionic surfactants [15]. The increase of the number of EO groups in ethoxylated alcohol surfactants was found to have very different effects, depending on the type of drug: for erythromycin, the solubilization capacity decreases [15], whereas the opposite is observed for four types of steroid drugs [19]. In contrast, the increase of EO groups of ethoxylated alkyl esters from 40 to 100 units had no effect on the solubility of timobesone acetate [16].

The solubilization capacity of the micelles increases significantly with the increase of hydrophobic chain length of the surfactant for erythromycin, timobesone acetate, and  $\beta$ -arteether [15–17]. However, Alkhamis et al. [18] demonstrated that the increase of the chain length of alkylsulfate surfactants decreases glyclazide solubilization, due to solubilization in the palisade layer of the micelles.

All studies described above illustrate the fact that surfactant molecular structure can have different effect on the solubilization capacity, depending on the type of drug. However, there is still no

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 Supplemental data for this article can be accessed [here](#).

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general consensus on the main mechanisms governing the strong effects of surfactant hydrophilic head and hydrophobic chain. Thus, regardless of the significant efforts that have been focused on the study of drug solubilization by surfactants, there is still a major lack of understanding of the molecular mechanisms and interactions that govern drug solubility in micellar surfactants solutions. The latter are essential for the development of advanced oral drug absorption simulators, which depend on the estimation of drug solubility in complex media [20].

Therefore, the major aim of this article is to clarify the link between the surfactant molecular structure and drug solubilization capacity by studying systematically the effect of 19 different surfactants on the solubility of two hydrophobic drugs of different polarity: fenofibrate and danazol. These two drugs were chosen as they both have solubility-limited absorption (BCS class II) and have similar molecular mass (361 and 338 g/mol for fenofibrate and danazol, respectively), which allows us to compare the effect of drug molecular structure on micellar solubilization. In addition, the model non-polar compound androstane was also studied to clarify the specific role of the ion–dipole interactions for the solubilization capacity of charged surfactant micelles. To gain additional information about the drug–surfactant interactions, the locus of fenofibrate solubilization inside the micelles of different surfactants was studied by UV absorption spectroscopy.

First, we describe the materials and methods used. Next, the main experimental results are presented. On this basis, the role of the various molecular characteristics for the solubilization capacity of the surfactant micelles is discussed afterwards. Finally, the main conclusions are summarized.

## Materials and methods

### Materials

#### Surfactants and drugs

A total of 19 surfactants were used to investigate the relationship between drug solubilization and surfactant molecular structure see Table 1. We studied systematically the effect of surfactant charge, head group type, and chain length. Two groups of nonionic surfactants were studied: polysorbates and alcohol ethoxylates. We have also studied homolog series of anionic surfactants of the alkyl sulfate type, with hydrophobic chain lengths of  $C_{10}$ ,  $C_{12}$ , and  $C_{14}$ . Additional anionic surfactants studied are the ethoxylated alkylsulfates, linear alkylbenzene sulfonate, and alpha olefin sulfonate. The cationic surfactants we have used are homolog series of TABs with hydrophobic chain lengths of  $C_{12}$ ,  $C_{14}$ , and  $C_{16}$ . The used abbreviations and properties of the studied surfactants are summarized in Table 1. Although some of these surfactants are toxic and rarely used in drug delivery, we included them in this study to clarify the general trends (*viz.* effect of surfactant charge).

Two hydrophobic drugs were used, both products of Sigma-Aldrich (St. Louis, MO): fenofibrate ( $M_W = 360.8$  g/mol, purity  $\geq 99\%$ ) and danazol ( $M_W = 337.5$  g/mol, purity  $\geq 98\%$ ). Both drugs have very low water solubility: 1 and 0.8  $\mu\text{g/mL}$  for danazol and fenofibrate, respectively [9,30], and belong to Class II of the Biopharmaceutical classification system [31]. The model non-polar substance 5 $\alpha$ -androstane was obtained from Sigma-Aldrich ( $M_W = 260.5$  g/mol, purity  $\geq 99\%$ ). The molecular structures of the three studied substances are presented in Figure 1.

#### Water, electrolytes, and organic solvents

Mobile phase solvents for HPLC analysis included methanol (HPLC grade, 99.9%) and deionized water, filtered through 450 nm

NYLON filter. All aqueous solutions and phases were prepared using deionized water from water-purification system Elix 3 (Millipore, Billerica, MA). Sodium chloride (99%) was obtained from Merck (Kenilworth, NJ). The organic solvents used to measure the absorption spectra of fenofibrate in media with different polarity were dodecane, hexadecane, and methanol (all obtained from Sigma-Aldrich, purity  $\geq 99\%$ ).

### Methods

#### Drug solubilization

To determine the equilibrium drug solubility in presence of surfactants, excess amount of drug (1.0 or 1.5 mg/mL, for danazol or fenofibrate, respectively) was added to 10 mL freshly prepared surfactant solution. For some of the experiments the aqueous phase contained 600 mM NaCl, in order to study the effect of ionic strength. The aqueous drug suspension was stirred with a magnetic stir bar at 400 rpm for 24 h at 37 °C. After incubation, the suspension was filtered through 200 nm NYLON syringe filter to eliminate all undissolved particles. Finally, the concentration of the solubilized drug in the obtained clear aqueous phase was determined by HPLC (see Supplemental information for experimental details). Every step of the procedure (including filtration) was performed at  $T = 37$  °C.

The drug solubilization efficiency of surfactant micelles was assessed by the molar solubilization capacity [2]:

$$x = \left( \frac{S_{\text{tot}} - S_W}{C_S - \text{CMC}} \right) \times 1000 \quad (1)$$

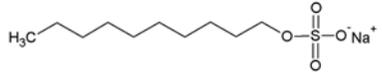
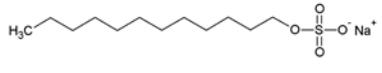
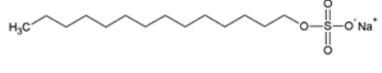
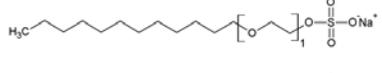
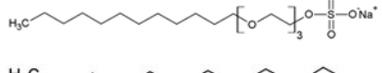
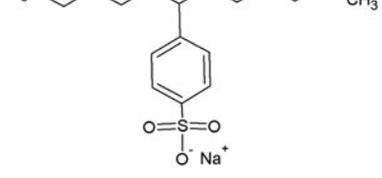
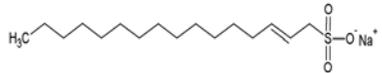
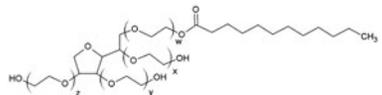
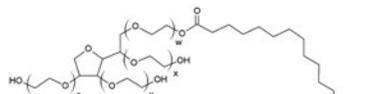
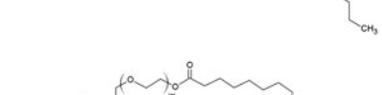
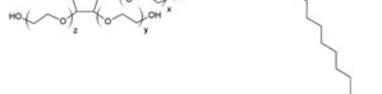
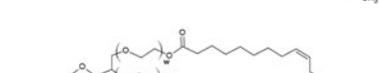
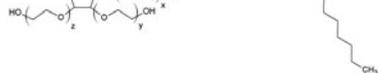
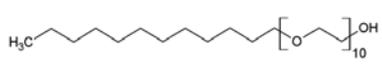
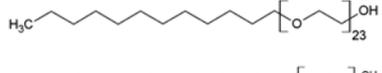
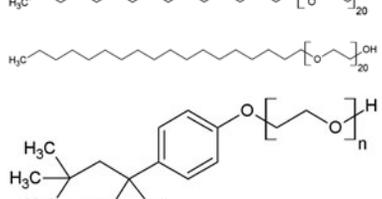
where  $S_{\text{tot}}$  is the measured molar drug solubility in the presence of surfactants,  $S_W$  is the intrinsic water solubility of the drug,  $C_S$  is the molar surfactant concentration, and  $\text{CMC}$  is the critical micelle concentration of the respective surfactant. Note that the subtraction of  $S_W$  from  $S_{\text{tot}}$  and of  $\text{CMC}$  from  $C_S$ , allows one to consider only the drug and surfactant molecules that are incorporated in the micelles (surfactant monomers and drug molecules dissolved in water are disregarded). Most of the experimental data points were obtained from multiple experiments at a single surfactant concentration (0.5 wt% for most surfactants), as drug solubility increased linearly with surfactant concentration (see Figures S4 and S5 in Supplemental data).

#### Determination of locus of drug solubilization

The locus of fenofibrate solubilization was assessed by UV–vis absorption spectrometry [18,32]. In this method, the shift of the absorption spectrum of the solubilized molecules is used to assess the polarity of their surroundings in the micelle. To determine the dependence of the spectral shift on solvent polarity, fenofibrate spectra were obtained in a series of solvents with increasing polarity (Figure S6 in Supplementary information): *n*-dodecane, *n*-octanol, methanol, and several water:methanol mixtures (the most polar medium studied was 70:30 water:methanol, vol./vol.). The solvent shift was characterized by the shift in the shoulder between  $\lambda = 300$  and 320 nm, determined at molar absorption coefficient of  $\epsilon_{\text{uv}} = 5 \text{ mM}^{-1} \cdot \text{cm}^{-1}$ , which provided higher sensitivity and resolution, compared to the shifts of the absorption maxima, see Figure S7 in the Supplementary information.

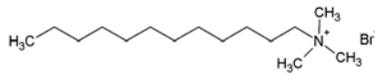
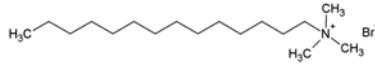
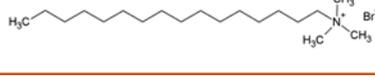
The absorption spectra were measured in the range from 200 to 400 nm by an Unicam 8625 UV–vis spectrophotometer (Scientific Equipment Repair, Mountain View, CA). All solutions of fenofibrate (both in solvents and in surfactants) were diluted in the respective media to obtain an absorption of  $1.0 \pm 0.2$  AU at

**Table 1.** Properties of the surfactants studied.

Trade name	Acronym used in text	Supplier, purity	CMC, mM	Molecular mass, g/mol	Surfactant structure
Sodium decyl sulfate	C <sub>10</sub> SO <sub>4</sub> Na	Merck, 99%	33.0 <sup>c</sup> [21]	260	
Sodium lauryl sulfate	C <sub>12</sub> SO <sub>4</sub> Na	Arcos, 99%	8.6 <sup>c</sup> [22]	288	
Sodium tetradecyl sulfate	C <sub>14</sub> SO <sub>4</sub> Na	Merck, 95%	2.2 <sup>c</sup> [22]	316	
Sodium lauryl ethoxy (1) sulfate	C <sub>12</sub> E <sub>1</sub> SO <sub>4</sub> Na	Stepan Co., 70%	3.9 <sup>b</sup> [23]	332	
Sodium lauryl ethoxy (3) sulfate	C <sub>12</sub> E <sub>3</sub> SO <sub>4</sub> Na	Stepan Co., 70%	2.0 <sup>d</sup> [24]	420	
Linear alkyl benzene sulfonate	LAS	Stepan Co., 92%	1.4 <sup>b</sup> [29]	348	
Alpha olefin sulfonate	AOS	Stepan Co., 90%	1.5 <sup>b</sup> [28]	341	
Tween 20	T20	Sigma-Aldrich	0.064 <sup>a</sup>	1228	
Tween 40	T40	Sigma	0.014 <sup>a</sup>	1277	
Tween 60	T60	Sigma-Aldrich	0.020 <sup>a</sup>	1309	
Tween 80	T80	Sigma-Aldrich	0.023 <sup>a</sup>	1310	
Polyoxyethylene (10) lauryl ether	C <sub>12</sub> E <sub>10</sub>	Sigma	0.015 <sup>a</sup>	627	
Polyoxyethylene (23) lauryl ether	C <sub>12</sub> E <sub>23</sub>	Sigma-Aldrich	0.053 <sup>e</sup>	1198	
Polyoxyethylene (20) cetyl ether	C <sub>16</sub> E <sub>20</sub>	Sigma	0.007 <sup>e</sup>	1124	
Polyoxyethylene (20) stearyl ether	C <sub>18</sub> E <sub>20</sub>	Sigma	0.003 <sup>e</sup>	1152	
Triton X-100	TX100	Merck	0.16 <sup>a</sup>	647	

(continued)

Table 1. Continued

Trade name	Acronym used in text	Supplier, purity	CMC, mM	Molecular mass, g/mol	Surfactant structure
Dodecyl trimethyl ammonium bromide	C <sub>12</sub> TAB	Sigma-Aldrich, 98%	16.0 <sup>b</sup> [25]	308	
Tetradecyl trimethyl ammonium bromide	C <sub>14</sub> TAB	Sigma, 99%	4.2 <sup>c</sup> [26]	336	
Cetyl trimethyl ammonium bromide	C <sub>16</sub> TAB	Merck, 99%	0.98 <sup>b</sup> [27]	364	

<sup>a</sup>Determined by laser light scattering in this study, see [Supplementary materials](#) for experimental details.

<sup>b</sup>CMC is measured at  $T = 25^\circ\text{C}$ .

<sup>c</sup>CMC is measured at  $T = 40^\circ\text{C}$ .

<sup>d</sup>CMC is measured at  $T = 50^\circ\text{C}$ .

<sup>e</sup>Damyanova et al. manuscript in preparation; CMC is measured at  $T = 25^\circ\text{C}$ .

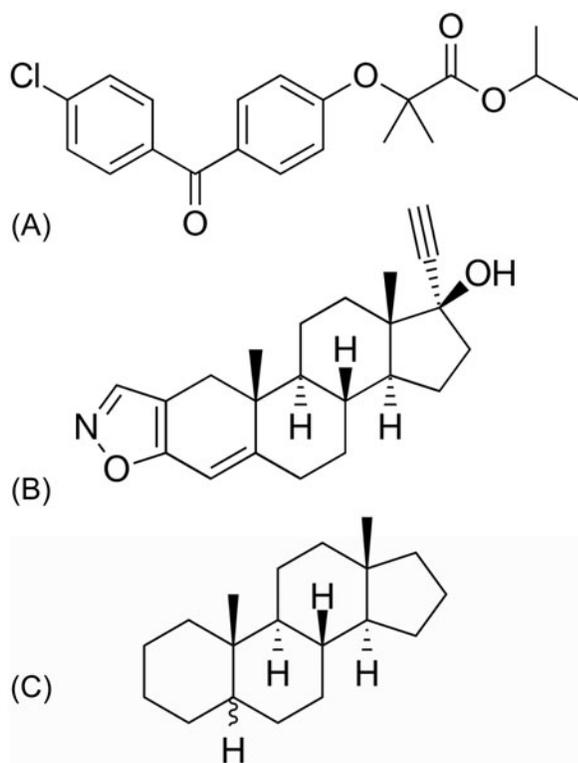


Figure 1. Molecular structures of (A) fenofibrate (B) danazol, and (C) androstane.

$\lambda_{\text{max}}$  in order to maximize the sensitivity and accuracy of the measurement.

## Experimental results

### Solubilization of fenofibrate and danazol in surfactant solutions

#### Effect of surfactant type

The drug solubilization capacity of the studied surfactant micelles is compared in [Figure 2](#). Two general trends are observed: (a) ionic surfactants solubilize danazol much more efficiently than fenofibrate and (b) the nonionic surfactants solubilize fenofibrate better than danazol. Thus, maximal solubilization capacity for fenofibrate ( $\chi_{\text{max}} \approx 50 \text{ mM/M}$ ) is attained by several nonionic (C<sub>18</sub>E<sub>20</sub>, T60, and T80) and one anionic surfactant (C<sub>14</sub>SO<sub>4</sub>Na). In contrast, danazol is

solubilized best by the ionic surfactants C<sub>14</sub>SO<sub>4</sub>Na and C<sub>14</sub>TAB and its maximal solubilization ( $\chi_{\text{max}} = 90\text{--}100 \text{ mM/M}$ ) is much higher than that of fenofibrate. The obtained results clearly demonstrate that the solubilization capacity is particularly sensitive to both drug and surfactant type.

The sizes of empty and drug-loaded micelles of several polysorbate surfactants were measured by dynamic light scattering (DLS) and it was found that the solubilization of drug molecules does not influence the size of the micelles (see [Figure S8 in the Supplementary materials](#)). The latter is most likely due to the very low number (1–2) of drug molecules per micelle, which do not increase the diameter of the aggregates to a measurable extent.

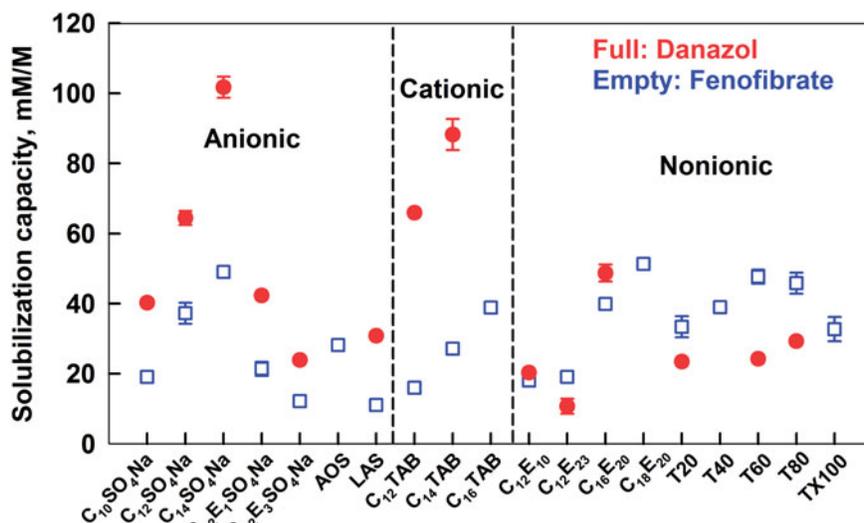
#### Effect of hydrophobic chain length

To analyze the effect of surfactant structure on solubilization, the solubilization capacity is plotted as a function of the hydrophobic chain length for the different surfactant head groups, see [Figure 3](#). For each of the plots in [Figure 3](#), the chain length is varied while the type of hydrophilic head is the same: trimethylammonium bromide for the cationics, sulfate for the anionics, and EO (20–23) for the nonionics. The increase of the chain length increases linearly the solubilization of both drugs for all surfactant types studied (nonionic, cationic, and anionic). Comparing the magnitude of solubilization capacity increase per CH<sub>2</sub>-group (*viz.* the slope of the lines in [Figure 3](#)), one sees that the effect is greater for danazol than for fenofibrate, for all surfactants studied ([Figure S9 in Supplementary materials](#)). In respect to the type of surfactant, the magnitude of the chain length effect decreases in the order C<sub>n</sub>SO<sub>4</sub>Na > C<sub>n</sub>TAB > C<sub>n</sub>E<sub>20–23</sub> for both drugs studied.

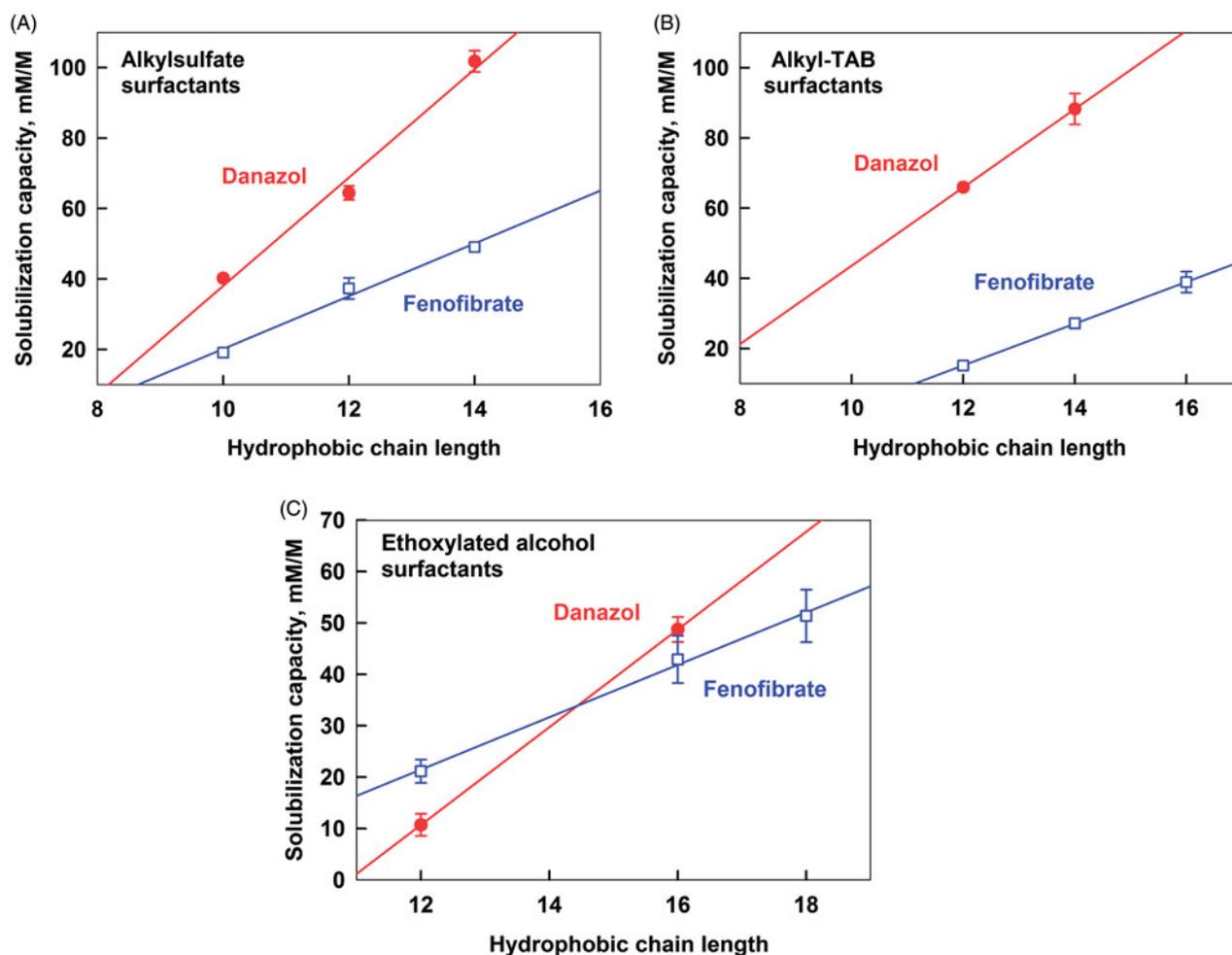
#### Effect of hydrophilic head group

The effect of the hydrophilic head on the solubilization capacity of surfactants with C<sub>12</sub> hydrophobic chain is compared in [Figure 4](#). As already explained, one sees that danazol is solubilized much more efficiently by ionic surfactants, compared to fenofibrate. The addition of electrolyte (600 mM NaCl) to the drug suspensions has no significant effect on the solubilization of fenofibrate by C<sub>12</sub>SO<sub>4</sub>Na, C<sub>12</sub>E<sub>1</sub>SO<sub>4</sub>Na, and C<sub>n</sub>TAB surfactants (see [Figure S10 in Supplementary materials](#)), whereas it decreases danazol solubilization by C<sub>12</sub>SO<sub>4</sub>Na from 64 to 36 mM/M. Explanations of these trends are given in the discussion section below.

For fenofibrate, the solubilization capacity decreases in the order SO<sub>4</sub>Na > E<sub>1</sub>SO<sub>4</sub>Na > E<sub>10</sub> ≈ E<sub>23</sub> ≈ TAB > E<sub>3</sub>SO<sub>4</sub>Na ≈ benz-SO<sub>3</sub>Na.



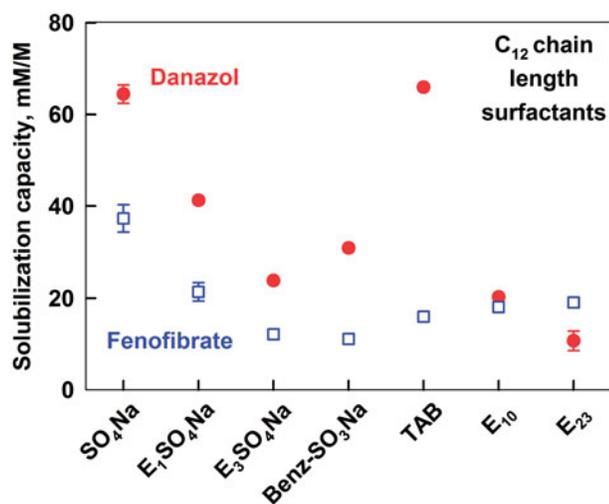
**Figure 2.** Solubilization capacity of fenofibrate (empty blue squares) and danazol (full red circles) as a function of the surfactant type. See Table 1 for surfactant abbreviations. The error bars can be smaller than the symbols.



**Figure 3.** Solubilization capacity of fenofibrate (empty blue squares) and danazol (full red circles) as a function of the hydrophobic chain length of (A) alkylsulfate (B) trimethylammonium bromide, and (C) ethoxylated alcohol ( $\approx 20$  ethylene oxide units) surfactants. The results are averaged over at least two independent measurements. The error bars can be smaller than the symbols.

Thus, best solubilization is achieved for the surfactant with sulfate head group. The addition of EO groups in between the sulfate group and the alkyl chain decreases very strongly the solubilization capacity:  $\chi = 37$  and 12 mM/M for C<sub>12</sub>SO<sub>4</sub>Na

and C<sub>12</sub>E<sub>3</sub>SO<sub>4</sub>Na, respectively. In contrast, the increase of EO units from 10 to 23 has no significant effect on the solubilization capacity of the nonionic alcohol ethoxylates ( $\chi = 18$ –19 mM/M).



**Figure 4.** Solubilization capacity of fenofibrate (blue squares) and danazol (red circles), as a function of the type of hydrophilic head for surfactants with hydrophobic chain length of C<sub>12</sub>. The error bars can be smaller than the symbols.

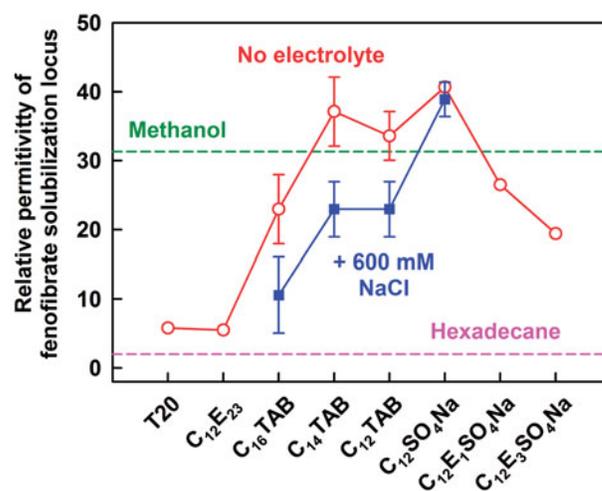
For danazol, the solubilization capacity decreases in the order SO<sub>4</sub>Na ≈ TAB > E<sub>1</sub>SO<sub>4</sub>Na > benz-SO<sub>3</sub>Na > E<sub>3</sub>SO<sub>4</sub>Na ≈ E<sub>10</sub> > E<sub>23</sub>. Best solubilization is obtained by surfactants with sulfate or TAB head group. On the other hand, all surfactants with nonionic hydrophilic head have low solubilization capacity. The solubilization effectiveness of the nonionics decreases with the increased number of EO units in the head group: from  $\chi = 20$  mM/M for E<sub>10</sub>, to  $\chi = 11$  mM/M for E<sub>23</sub>.

The head group of Tween 20 is not included in this consideration, as this surfactant is a technical mixture with different hydrophobic chain lengths. Only ≈40% of the molecular chains are C-12, while significant fraction of longer chains (C-14, C-16, and C-18) is also present. Therefore, no proper comparison is possible with this surfactant head group, as the chain length also affects the solubilization.

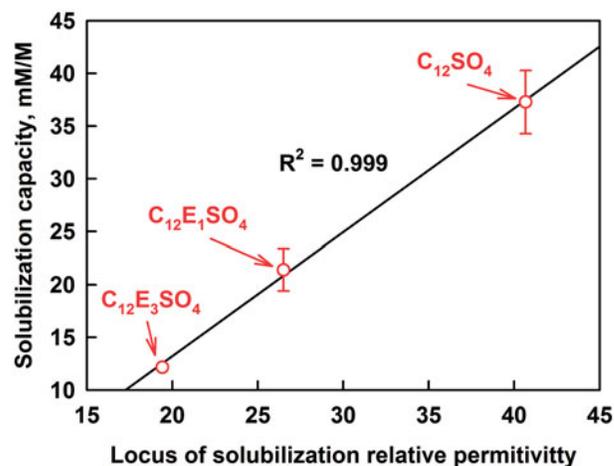
#### Relative polarity of fenofibrate solubilization locus in the micelles and correlation with solubilization capacity

The relative polarity of the microenvironment around the fenofibrate molecules, solubilized in the surfactant micelles, was assessed by the polarity shift of fenofibrate UV absorption spectrum. The characteristic absorption maxima of fenofibrate correspond to two  $\pi \rightarrow \pi^*$  electronic transitions at  $\lambda_{\max} = 262$  and 286 nm (Figure S6 in Supplementary information), which are caused by the benzene rings (benzenoid band) and the conjugation of the C=O bond of the linking carbonyl group with the C=C bonds of the two neighboring benzene rings (K-band) [33]. To characterize the polarity we used the shift in the shoulder after the two absorption maxima (see experimental methods section for more details). The measured shift in UV absorption spectrum provides information about the microenvironment of the aromatic part of the fenofibrate molecule.

The relative polarity of the fenofibrate microenvironment, measured in micelles of several surfactants, is presented in Figure 5. The relative polarity of the nonionic surfactant micelles solubilization locus ( $\epsilon_r \approx 5.5$ ) is comparable to that of *n*-dodecane ( $\epsilon_r = 2.0$ ). In contrast, the relative polarity of charged surfactant micelles in the absence of electrolyte is much higher ( $\epsilon_r \geq 19$ ) and reaches values characteristic for polar solvents, such as methanol and methanol-water mixtures. The increase of the chain length of



**Figure 5.** Apparent relative dielectric permittivity of the locus of fenofibrate solubilization in different surfactant micelles, as determined by UV absorption spectroscopy and solvent calibration. The experiments were performed in absence of electrolyte (empty red circles) and in presence of 600 mM NaCl (full blue squares).



**Figure 6.** Solubilization capacity for fenofibrate as a function of solubilization locus relative permittivity of dodecyl sulfate micelles in water.

C<sub>n</sub>TAB surfactants from C = 14 to 16 decreases  $\epsilon_r$  from ≈35 to 23, whereas the increase from C-12 to C-14 has no effect on  $\epsilon_r$ .

Addition of EO units to C<sub>12</sub>SO<sub>4</sub>Na also decreases strongly the polarity of the solubilization locus: from  $\epsilon_r = 41$  (no EO units) to  $\epsilon_r = 19$  for three EO units.

High electrolyte concentration (600 mM NaCl) decreases significantly the solubilization locus polarity for C<sub>n</sub>TAB surfactant micelles, whereas no such effect is observed for C<sub>12</sub>SO<sub>4</sub>Na micelles.

To check whether the polarity of fenofibrate microenvironment in the micelles has direct influence on the extent of its solubilization, we plotted the measured solubilization capacity as a function of the determined solubilization locus polarity. No general correlation is observed between these two parameters, see Figure S11 in Supplementary information. Only for the solubilization capacity of the ethoxylated dodecyl sulfate surfactants we observed a linear increase with the increase of solubilization locus polarity, Figure 6.

## Discussion

The systematic study of fenofibrate and danazol solubilization in micellar surfactant solutions reveals several important general

trends of the effect of surfactant structure on its solubilization capacity and several intriguing differences between the two studied drugs. In this section, these trends are interpreted at a molecular level, considering the main physicochemical factors affecting solubilization.

#### Locus of fenofibrate solubilization in surfactant micelles

The location of the solubilized molecule inside the surfactant micelles is one of the factors that is expected to have a major influence on the micellar solubilization capacity. Our experimental results show that, for the nonionic surfactant micelles (Tween 20 and  $C_{12}E_{23}$ ), the aromatic part of fenofibrate is located in a medium with relative polarity similar to that of normal hydrocarbons (Figure 5). This result evidences that the locus of fenofibrate solubilization in these micelles is in the anhydrous hydrophobic core, Figure 7(A). In contrast, the much higher relative polarity measured for ionic surfactant micelles in the absence of electrolyte shows that the drug is located in the transition region between the anhydrous hydrophobic core and the micelle surface, *viz.* in the palisade layer, Figure 7(B). Note that danazol molecules are more polar than those of fenofibrate which means that danazol is solubilized predominantly in the palisade layer, at least for the ionic surfactant micelles.

The screening of electrostatic interactions at high ionic strength decreases the relative polarity of the locus of fenofibrate solubilization for TAB micelles, which could be explained by a reduced repulsion between the charged head groups, resulting in improved packing of the surfactant molecules in the micelles [5], and decreased penetration of water. The lack of similar electrolyte effect on the solubilization locus polarity for  $C_{12}SO_4Na$  micelles is somewhat surprising, because the electrolytes are known to affect the micellar properties of this surfactant [34]. Obviously, the fenofibrate molecules are able to accommodate well in the palisade layer of  $C_{12}SO_4Na$  (e.g. by shifting their relative position with respect to the micelle center), even in the presence of electrolytes with high concentration, thus minimizing the electrolyte effect in this particular system.

The decreased solubilization locus polarity when the chain length of  $C_nTAB$  surfactants is increased from C-14 to C-16 is certainly due to a deeper penetration of the fenofibrate aromatic scaffold into the core of the surfactant micelles. Note that the  $C_{16}TAB$  molecule is longer than the extended conformation of the fenofibrate molecule (see Figure S12 in the Supplementary materials). Therefore, one could expect that the fenofibrate molecules can find their preferred position inside the palisade layer of the respective micelles.

The location of the solubilized molecule inside the surfactant micelles is determined by the polarity of the medium preferred by the solubilize and should be related to the solubilization capacity. Indeed, excellent linear dependence between the solubilization locus polarity and the solubilization capacity was observed for the ethoxylated dodecyl sulfates (Figure 6). The decreased polarity with increasing EO units could be explained by the partially hydrophobic character of these units when their number is low [35]. However, if the EO units are considered as completely hydrophobic, the decreased solubilization capacity is in an apparent contradiction with the positive effect of the hydrophobic chain length (Figure 3). The reason for this apparent discrepancy is most likely due to difference in the conformation of the EO ( $OC_2H_4$ )<sub>n</sub> and ethylene ( $C_2H_4$ )<sub>n</sub> units. The EO units are bulkier, which perturbs the packing of surfactant molecules in the micelles and hinders

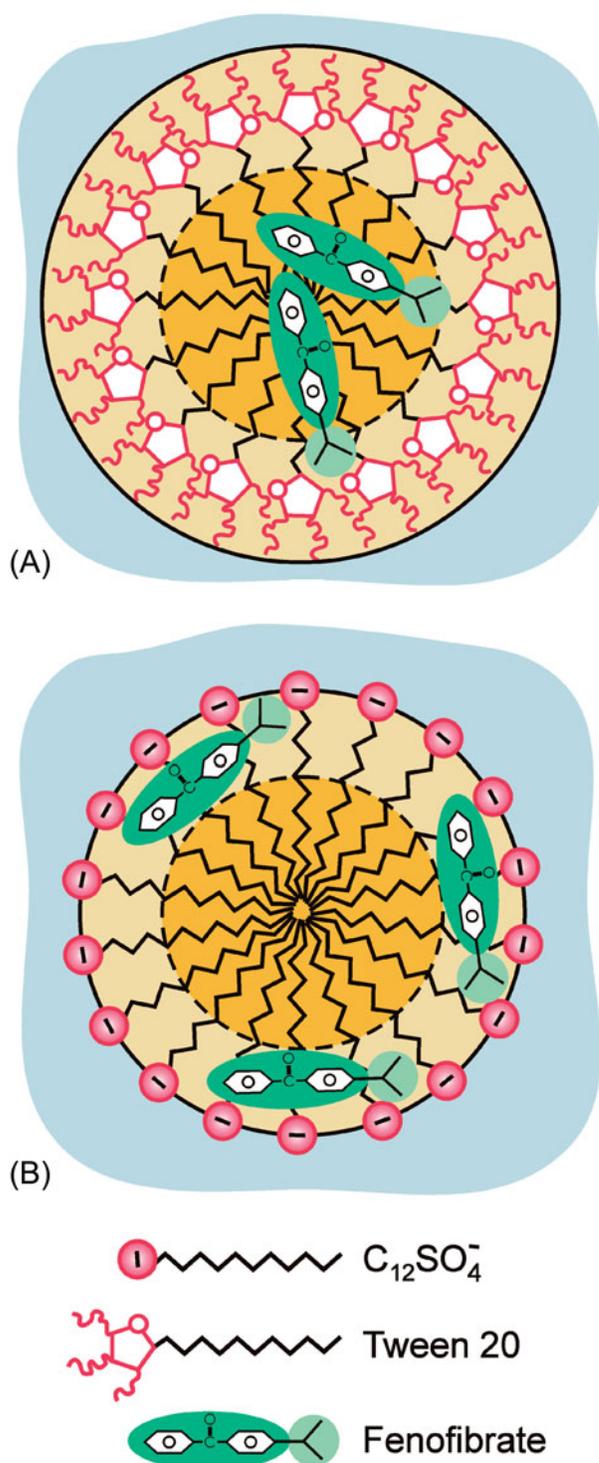


Figure 7. Schematic illustration of the fenofibrate solubilization: (A) inside the core of the micelles of nonionic surfactants and (B) in the palisade layer of the micelles of ionic surfactants.

the accommodation of guest molecules (*viz.* decreases the solubilization capacity).

Such general correlation was not observed for the other surfactants with the same chain length (see Figure S11 in the Supplementary materials), which demonstrates that the specific geometric constraints (*viz.* packing of the drugs and surfactant molecules in the micelles) also play an important role in drug solubilization.

### Effect of hydrophobic chain

Linear increase of surfactant solubilization capacity with the increase of hydrophobic chain length was observed for both studied drugs (Figure 3). The effect is present for all studied surfactants: nonionic (ethoxylated alcohols, polysorbates), anionic (alkylsulfates), and cationic (TABs). Similar results were obtained for drug molecules with very different structures, such as erythromycin [15], timobesone acetate [16],  $\beta$ -arteether [17], and mefenamic acid [36]. Thus, the improved solubilization with increasing surfactant hydrophobic chain length, which is a well-established effect for non-polar molecules [37], can be extended also to polar drug molecules. There is only one report of the opposite effect (decrease of solubilization capacity with increasing chain length): gliclazide in presence of alkylsulfate surfactants [18], which indicates the importance of some specific molecular characteristics (e.g. shape and/or charge distribution in the gliclazide molecule) for this particular system.

The presence of double bond in the hydrophobic chain of polysorbates has no significant effect on the solubilization of both danazol and fenofibrate, as demonstrated by the similar solubilization capacity of T60 and T80 (Figure 2).

The mechanism of improved solubilization at longer chain length for non-polar or slightly polar molecules is the increased volume of the hydrophobic core, where the solubilize is located [5,37]. Similar mechanism can be pictured for polar molecules like fenofibrate and danazol, which are solubilized in the palisade layer of ionic surfactants: increase of the hydrophobic chain length leads to bigger volume of the palisade layer and thus increases the space available for solubilization (Figure 7(B)). In agreement with the latter explanation, very good correlation is observed between the palisade layer volume and the solubilization capacity, see Figure 8. To calculate the volume of the palisade layer we assumed constant depth of penetration of water molecules in the micelle (the first three methylene groups of micellized surfactant [38,39]), whereas the approximation of Tanford (see the discussion in [40]) was used to calculate the total length of the surfactant hydrophobic chain. Therefore, the increased solubilization capacity with increasing surfactant chain length can be explained by the bigger volume of the palisade layer.

Calculation of the thermodynamic parameters of solubilization (see Figure S13 in Supplementary materials) shows that the standard energy of transfer of one drug molecule from the aqueous environment into the micelle increases by 0.05–0.30  $kT$  per

additional  $\text{CH}_2$ -group in the surfactant hydrophobic chain. The latter is more than five times smaller than the same parameter for surfactant molecules, which is  $0.8\text{--}1.2 \times kT/\text{CH}_2\text{-group}$  [40]. Most likely, the smaller energy gain is due to the mismatch of the drug and surfactant molecular structures, which hinders the close packing of the molecules in the micelle. This problem is absent for surfactant self-association, where the micelles are formed by similar flexible molecules which have the same hydrophobic chains and hydrophilic heads and thus can form better-packed aggregates.

### Effect of hydrophilic head

The micellar solubilization capacity of the polar fenofibrate and danazol molecules was affected dramatically by the surfactant head group (Figure 4). Notably, it was shown that the ionic surfactants have very high solubilization capacity for danazol, whereas they are less effective for fenofibrate.

Therefore, the mechanism of the effect should include electrostatic interactions which are specific for danazol and not for fenofibrate. Such interactions must arise from differences in the molecular structure of the two compounds (Figure 1): for example danazol has a steroid structure, in contrast to the planar aromatic structure of fenofibrate. The latter should result in different packing and orientation of the solubilized molecule in the micelle. In another study [41], we showed that the steroid progesterone is also solubilized preferentially by charged surfactants, which was explained via ion–dipole interactions in the micelle. Thus, the high solubilization of danazol in the ionic surfactant micelles is most likely due to ion–dipole interactions, like in the case of progesterone.

To support the latter hypothesis, we performed solubilization experiments with androstane (Figure 1(C)): a hydrophobic molecule with simple steroid structure which, in contrast to danazol, does not contain polar atoms (O, N, S) or unsaturated groups ( $\text{C}=\text{C}$ ,  $\text{C}\equiv\text{C}$ ). If the ion–dipole interactions are important for solubilization, one would expect much lower solubilization of androstane in ionic surfactant micelles, due to the apolar structure of androstane molecules, which results in very weak ion–dipole interactions. The results for androstane solubilization in  $\text{C}_{12}\text{SO}_4\text{Na}$ ,  $\text{C}_{12}\text{TAB}$ , and Tween 20 surfactants are compared in Figure 9 with those for danazol. As predicted, the solubilization capacity of the ionic surfactants for androstane is much lower than that for danazol. Therefore, the ion–dipole interactions between danazol and

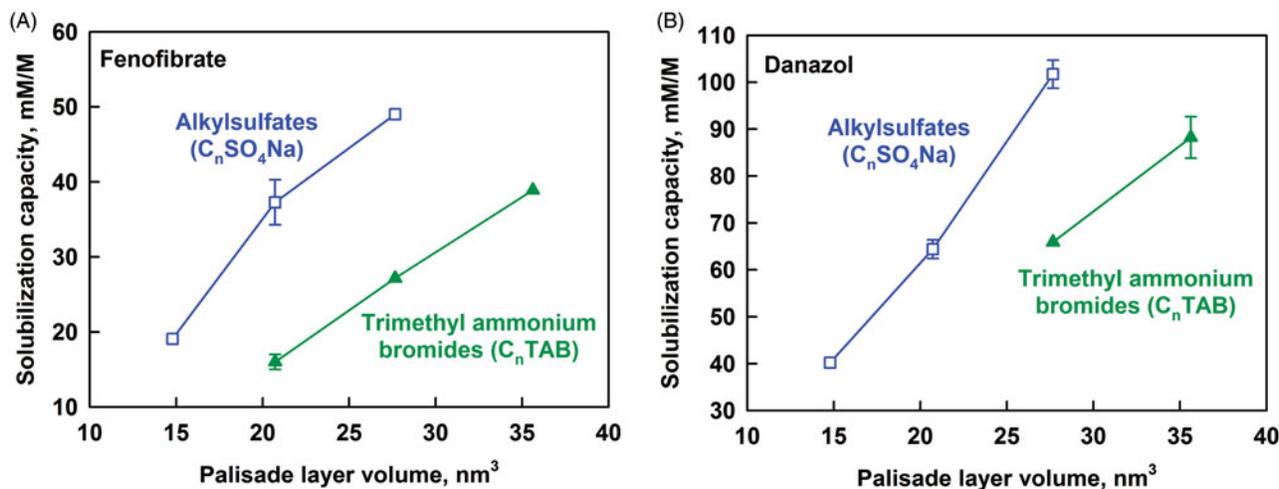


Figure 8. Solubilization capacity of (A) fenofibrate and (B) danazol, as a function of the palisade layer volume for alkylsulfate (empty blue squares) and trimethylammonium bromide (full green triangles) surfactants. The error bars can be smaller than the symbols.

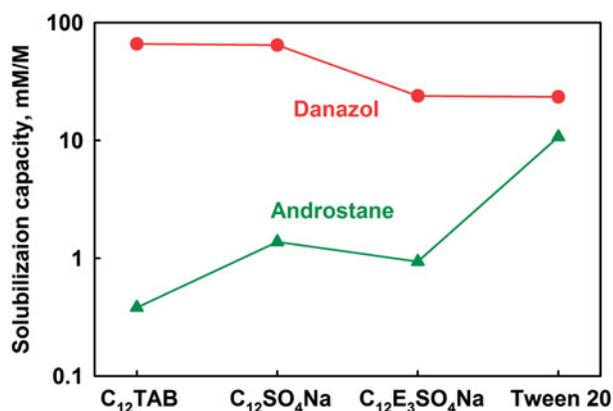


Figure 9. Solubilization capacity of danazol (red circles) and androstane (green triangles), as a function of the type of surfactant type.

surfactant head groups are key for the observed high solubilization capacity of the ionic micelles. The latter conclusion is supported further by the decreased solubilization of danazol in anionic surfactant micelles at high ionic strength.

Another interesting effect is the strong decrease of solubilization for both studied drugs when EO units are added to C<sub>12</sub>SO<sub>4</sub>Na (Figure 4). Zoeller and Blankschtein [42] investigated the micellar properties of this surfactant series by light scattering and viscosity measurements and showed that increasing the number of EO units in dodecyl sulfates decreases the surfactant aggregation number in presence of various NaCl concentrations. In absence of salt, the aggregation number was shown to decrease from 75 surfactant molecules-per-micelle for C<sub>12</sub>SO<sub>4</sub>Na to 66 molecules-per-micelle for C<sub>12</sub>E<sub>3</sub>SO<sub>4</sub>Na [35]. This result indicates that the ethoxylation hinders the packing of dodecyl sulfate molecules in the micelles, due to the incorporation of bulky EO units in the surfactant head group. The latter affects also the location of the solubilized molecule, as demonstrated by the decreased solubilization locus polarity of fenofibrate (Figure 5). Therefore, the decreased solubilization capacity of ethoxylated dodecyl sulfates is due to more difficult packing of the surfactant and drug molecules in the micelles of ethoxylated surfactants.

The presence of an aromatic moiety in the molecule of alkyl benzene sulfonate (LAS) surfactant did not result in higher solubilization of fenofibrate. This result suggests that the drug-surfactant packing inside the mixed micelles does not favor  $\pi$ -stacking interactions in the micelles, which otherwise would result in decrease of the free energy and enhanced solubilization.

### Summary

The effect of 19 surfactants on the solubilization of two poorly water-soluble drugs (fenofibrate and danazol) and one model non-polar steroid substance (androstane) was studied. On the basis of the obtained results, the relationship between surfactant molecular structure and the drug solubilization capacity was analyzed. The main conclusions are as follows:

1. Danazol is solubilized much better than fenofibrate and androstane by the ionic surfactants. The effect is due to ion-dipole interactions between the polar danazol molecules and the charged surfactant head-groups.
2. Ethoxylation of dodecyl sulfate decreases significantly the solubilization capacity of both studied drugs, which is explained by the hindered packing of the surfactant and drug molecules in the palisade layer of the micelles.

3. The solubilization locus polarity of dodecyl sulfate surfactant micelles decreases with the addition of ethoxy groups to the surfactant head group, due to their partially hydrophobic character, and is in excellent correlation with the decreased solubilization capacity.
4. Drug solubilization increases linearly with the increase of hydrophobic chain length for all types of surfactants (non-ionic, cationic, and anionic). The effect is due to the increased volume for solubilization in the micelles. The locus of fenofibrate solubilization is in the palisade layer of ionic surfactant micelles and in the hydrophobic core of the nonionic surfactant micelles.

The performed study demonstrates the strong dependence of drug solubilization on the surfactant molecular structure and provides molecular-based insight on the probable mechanisms and interactions that control the observed effects. The obtained knowledge about the relationship between surfactant structure and solubilization capacity can be used for validation of the drug solubility parameters used in oral absorption models.

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### Disclosure statement

The authors report no conflicts of interest in this work.

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