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Effect of surfactant molecular structure on Progesterone solubilization

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ABSTRACT

Progesterone is a hydrophobic drug (LogP = 3.9) with solubility-limited oral bioavailability. One approach to improve its aqueous solubility is by solubilization in micellar surfactant solutions. We investigate systematically the effect of surfactant molecular structure on Progesterone solubility by using a set of 17 surfactants with different hydrophilic head group charge and variable hydrophobic chain length. Charged surfactants showed highest solubilization capacity, increasing Progesterone solubility from 0.01 mg/mL to above 3 mg/mL, whereas all nonionic surfactants had much smaller effect (0.5 −1 mg/mL Progesterone solubility). The high solubilization of Progesterone in charged surfactant micelles was explained by ion-dipole interactions in the micelle palisade layer. The increase of hydrophobic chain length improved drug solubilization for all studied surfactants, regardless of the type and charge of the hydrophilic head. In respect to the effect of hydrophilic head group, the solubilization capacity of C-12 surfactants decreased in the order SO_4^- > $E_1SO_4^-$ > $^+N(CH_3)_3$ > $E_3SO_4^-$ > $SorbEO_{20}$ = E_{10} = E_{23}. Therefore, the best candidates to improve oral Progesterone absorption through solubility enhancement are surfactants with long hydrophobic chain and charged hydrophilic head group (*e.g.* alkylsulfates).

1. Introduction

More than 40% of the new chemical entities that emerge from modern drug discovery programs and many well-known active pharmaceutical ingredients are characterized by poor aqueous solubility [1]. The slow and incomplete dissolution of such drugs in the gastro-intestinal fluids limits their oral bioavailability and presents a significant problem for drug formulation.

Progesterone is an endogenous steroid sex hormone used for therapy of various acute or chronic gynecological conditions [2]. Its highly hydrophobic nature (Log P = 3.9) results in very low aqueous solubility of 10 μg/mL [3]. Thus, Progesterone is labeled as "practically insoluble", according to the solubility classification adopted by USP and Ph. Eur, and is classified as Class II drug (poor solubility-high permeability) by the Biopharmaceutical Classification System (BCS) [4].

The poor solubility of Progesterone and its rapid hepatic metabolism hampered its wide therapeutical application until the development of micronized formulations [5]. Later, Progesterone bioavailability was further enhanced by the use of lipid-based drug delivery systems [6–8]. Thus, oral Progesterone is usually formulated as a solution or suspension of micronized Progesterone in vegetable oil and lipophilic surfactants, which is incorporated in softgels [9]. Opportunities to improve further Progesterone delivery by using microemulsions and self-emulsifying drug delivery systems are still being explored [10–12]. However, the drawback in using a lipid solution or suspension for oral drug delivery is that the product can be formulated only in softgels, which are usually a second choice compared to tablets (due to production cost). One of the classical approaches to improve the aqueous solubility of hydrophobic drugs, which could allow the development of tablets or granules with enhanced Progesterone oral bioavailability, is to use appropriate surfactants [13–16].

The effect of surfactant type on Progesterone solubility was addressed in a limited number of studies [17–20]. Barry et al. studied systematically the effect of alcohol ethoxylate surfactants and showed that the increase of ethylene oxide units in the head group resulted in increased molar solubilization capacity [17]. The latter was attributed to the increased number of micelles with increasing hydrophilic head group size. Miller et al. showed that 10 mM sodium dodecyl sulfate increased strongly Progesterone solubility to 0.4 mg/mL, whereas sodium taurocholate had much smaller effect (≈0.02 mg/mL Progesterone solubility), at the same concentration [18]. However, higher concentration of sodium

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glycocholate (110 mM) increased strongly drug solubility to *ca.* 0.4 mg/mL Progesterone [19]. In another study, Zughaid et al. investigated Progesterone solubilization by individual and mixed bile acids, and the effect of the bile acid-to-phospholipid ratio [20]. It was found that Progesterone is solubilized more efficiently by mixtures of bile acids (compared to the individual molecules) and that the higher fraction of phospholipids in the bile acid-phospholipid mixtures also improves drug solubilization. Highest Progesterone solubility of ≈0.23 mg/mL was obtained by a mixture of bile acids with total concentration of 30 mM.

Therefore, Progesterone solubilization is studied only for a limited number of surfactants – alcohol ethoxylates, bile salts and phospholipids, and there are still no general rules for surfactant selection. In the current article we study systematically Progesterone solubility in surfactant solutions and aim (1) to establish the main structural properties of surfactants required for Progesterone solubilization and (2) to provide physicochemical explanation of the mechanisms of the observed effects. To achieve these aims we determined experimentally the effect of 17 surfactants with different charge, type of hydrophilic head group and hydrophobic chain length on Progesterone solubility. The non-polar steroid Androstane was used in several experiments to provide further mechanistic insight on Progesterone solubilization.

2. Materials and methods

2.1. Materials

Progesterone was obtained from TCI (purity > 98.0%) and 5α-androstane was obtained from Sigma-Aldrich (purity ≥ 99%). Their structures are presented in Fig. 1. The used surfactants and their properties are presented in Table 1. To check the effect of ionic strength we used NaCl (Sigma, purity > 99%). Deionized water from water-purification system Elix 3 (Millipore, USA) was used for preparation of all solutions. Methanol (Sigma, HPLC-grade) was used as a mobile phase component for HPLC.

2.2. Methods

2.2.1. Determination of drug solubility in different surfactant systems

Progesterone suspensions (10 mg/mL) were prepared by weighing the required amount of drug in an empty 20 mL bottle and adding 10 mL of 40 mM aqueous surfactant solution. For some of the experiments, the ionic strength of the surfactant solution was increased by addition of NaCl to obtain final NaCl concentration of 600 mM. The dispersions were placed in a thermostated water bath at 37 °C and stirred for 24 h with a magnetic stirrer at 350 rpm. After incubation, the obtained turbid Progesterone suspensions were filtered through 200 nm NYLON filter (thermostated at 37 °C). Finally, the concentration of the dissolved drug in the obtained clear filtrate was determined by HPLC. All experiments were performed at least in duplicate.

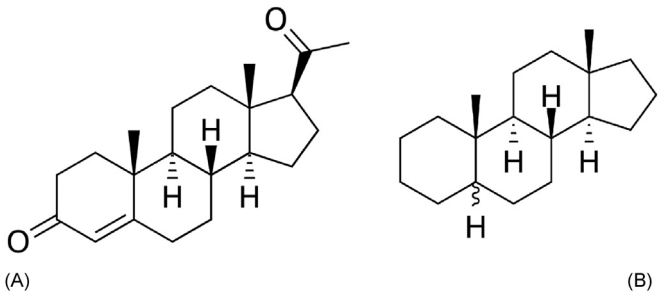


Fig. 1. Chemical structures of (A) Progesterone and (B) Androstane.

2.2.2. HPLC analysis

The method for quantitative determination of Progesterone was adapted from Pereira et al. [28]. The used mobile phase was water:methanol 30:70, pumped at a flow rate of 1.0 mL/min. XBridge C18 column (100 × 4.6 mm^2, 3.5 μm particle size) was used for analysis, the column temperature was set at 40 °C and the UV detector was set to measure the absorbance at 254 nm. The HPLC analysis was carried out on Shimadzu apparatus composed of two high-pressure mixing binary gradient pumps (LC-20AD), autosampler (SIL-10ADvp), four-line membrane degasser (DGU-14A), wide temperature range column oven (CTO-10ASvp) and a dual-wave length UV-VIS detector (SPD-10Avp).

The retention time of Progesterone was t_R = 6.1 min at all conditions studied (see Fig. S1 in Supplementary materials). The concentration of soluble drug was determined by using a standard curve, which was prepared by dissolving a known amount of drug in methanol (see Fig. S2 in Supplementary materials).

3. Results and discussion

3.1. Effect of surfactants on Progesterone solubility

The solubility of Progesterone in micellar surfactant solutions is presented in Fig. 2. One sees that drug solubility depends very strongly on solubilizer molecular structure: the determined Progesterone solubilities ranged from 0.25 to 3.3 mg/mL (25–300 times higher than Progesterone solubility in water) for the studied set of surfactants.

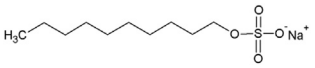
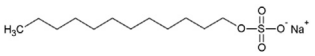
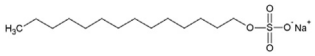
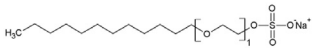
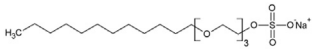
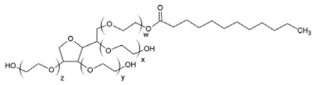
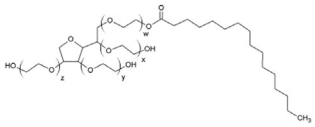
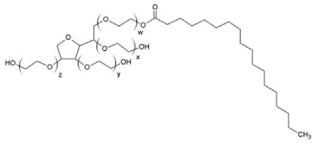
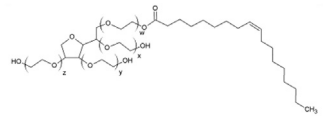
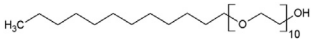
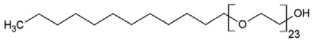
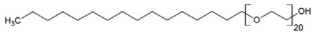
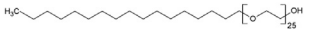
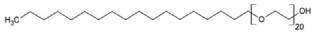
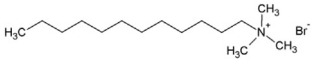
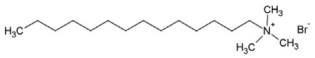
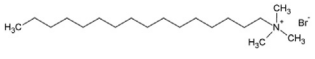
The strongly increased solubility of Progesterone can be expected to improve its oral bioavailability, since Progesterone is a low solubility-high permeability drug (BCS class II). However, the solubilization in surfactant micelles can also influence significantly the permeability of the drug, as shown by Dahan et al. [29,30]. Further experiments are required to determine how the various surfactants affect the permeability of the solubilized drug and the overall oral bioavailability.

Comparing the best surfactants of each class, anionics had greatest effect (Progesterone solubility of 3.3 mg/mL for $C_{14}SO_4$), followed by the cationics (2.3 mg/mL for C_{16}TAB) and finally the nonionics (1.0 mg/mL for $C_{18}E_{20}$). However, the solubility enhancement varied considerably among surfactants of the same class: for example, the solubility of Progesterone in solution of the anionic $C_{12}E_3SO_4$ (1.0 mg/mL) was more than three times lower than for $C_{14}SO_4$ (3.3 mg/mL). Similar differences were observed for pairs of cationic (e.g. C_{16}TAB vs. C_{12}TAB) or nonionic surfactants ($C_{12}E_{10}$ vs. $C_{18}E_{20}$). The different extent of drug solubilization is clearly determined by the specific chemistry of each surfactant. In the next subsection we aimed to clarify the effect of surfactant molecular structure on the measured increase of drug solubility.

3.2. Role of surfactant structure on Progesterone solubilization capacity

To assess the effect of the hydrophilic head group we compared surfactants with the same hydrophobic chain length, subsection (A). The effect of the hydrophobic chain length is discussed in the second subsection (B) by comparing sets of surfactants with identical hydrophilic head group. To account for the different critical micellar concentrations (CMC) of the studied surfactants and for drug solubility in pure water, we used the molar solubilization capacity [13]:

Table 1
Properties of the studied surfactants.

Trade name	Acronym used in text	Supplier, purity	CMC, mM	Molecular mass, g/mol	Surfactant structure
Sodium decyl sulfate	$C_{10}SO_4Na$	Merck, 99%	33.0[c] [21]	260	
Sodium dodecyl sulfate	$C_{12}SO_4Na$	Arcos, 99%	8.6[c] [22]	288	
Sodium tetradecyl sulfate	$C_{14}SO_4Na$	Merck, 95%	2.2[c] [22]	316	
Sodium lauryl ethoxy (1) sulfate	$C_{12}E_1SO_4Na$	Stepan Co., 70%	3.9[b] [23]	332	
Sodium lauryl ethoxy (3) sulfate	$C_{12}E_3SO_4Na$	Stepan Co., 70%	2.0[d] [24]	420	
Tween 20	T20	Sigma – Aldrich	0.064[a]	1228	
Tween 40	T40	Sigma	0.014[a]	1277	
Tween 60	T60	Sigma – Aldrich	0.020[a]	1309	
Tween 80	T80	Sigma – Aldrich	0.023[a]	1310	
Polyoxyethylene (10) lauryl ether	$C_{12}E_{10}$	Sigma	0.015[a]	627	
Polyoxyethylene (23) lauryl ether	$C_{12}E_{23}$	Sigma – Aldrich	0.053[e]	1198	
Polyoxyethylene (20) cetyl ether	$C_{16}E_{20}$	Sigma	0.007[e]	1124	
Polyoxyethylene (25) cetostearyl ether	$C_{16\text{-}18}E_{25}$	Sigma	0.005[e]	1358	
Polyoxyethylene (20) stearyl ether	$C_{18}E_{20}$	Sigma	0.003	1152	
Dodecyl trimethyl ammonium bromide	$C_{12}TAB$	Sigma – Aldrich, 98%	16.0[b] [25]	308	
Tetradecyl trimethyl ammonium bromide	$C_{14}TAB$	Sigma, 99%	4.2[c] [26]	336	
Cetyl trimethyl ammonium bromide	$C_{16}TAB$	Merck, 99%	0.98[b] [27]	364	

[a] Vinarov et al. Micellar solubilization of poorly water-soluble drugs: effect of surfactant and solubilizate molecular structure, *Drug Dev. Ind. Pharm.* under review.
[b] CMC is measured at T = 25 °C.
[c] CMC is measured at T = 40 °C.
[d] CMC is measured at T = 50 °C.
[e] Damyanova et al. manuscript in preparation; CMC is measured at T = 25 °C.

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

where S_{tot} is the measured molar drug solubility in presence of surfactants, S_W is the intrinsic water solubility of the drug, C_S is the molar surfactant concentration and CMC is the critical micelle concentration of the respective surfactant. Thus, the solubilization capacity considers only the drug and surfactant molecules that are present in the micellar aggregates (without the contribution of surfactant monomers and the drug molecules dissolved in water).

3.2.1. *Effect of hydrophilic head group type and charge*

The effect of the type of hydrophilic head group for a series of

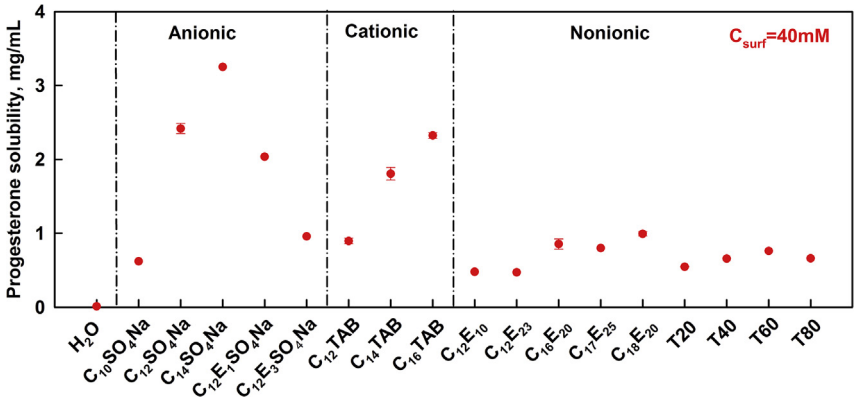


Fig. 2. Progesterone solubility as a function of surfactant type. All experiments are performed at surfactant concentration of 40 mM and T = 37 °C. The error bars can be smaller than the symbols (the number of experiments performed to determine each experimental point is n ≥ 2).

surfactants with the same hydrophobic chain length (C_{12}) is presented in Fig. 3. The highest solubilization capacity of the sulfate group (≈250 mM/M) decreased dramatically (to ≈ 40 mM/M) when it was replaced with uncharged E_{10}, E_{23} or sorbitan-E_{20} group. The addition of 1 or 3 ethylene oxide units in between the sulfate head group and the hydrophobic alkyl chain also decreased strongly the solubilization capacity. The trimethylammonium bromide (TAB) group had intermediate properties: smaller solubilization capacity compared to the sulfate group, but much higher than all uncharged groups. The increase of ethylene oxide units from 10 to 23 had no significant effect on the solubilization capacity of the nonionic alcohol ethoxylates, which was rather low (≈40 mM/M) and similar to that of the polyoxyethylene-sorbitan group.

All of the described trends are reproduced very well when the comparison is made per unit mass (mg Progesterone solubilized per gram of surfactant), see Fig. S3 in the Supplementary materials. The differences between the charged and uncharged head groups is even more pronounced: for example, the solubilization capacity of the sulfate head group is 266 mg/g, compared to only 11 mg/g for the polyoxyethylene-sorbitan group of Tween 20.

The strong impact of the hydrophilic head group type on Progesterone solubilization capacity clearly indicates that the drug molecules are solubilized in the palisade layer of the surfactant micelles. Effects of such magnitude are not expected for molecules that are solubilized in the anhydrous hydrophobic core of the micelles, where hydrophobic and dispersion interactions govern the solubilization capacity [31]. Furthermore, only molecules with very simple aliphatic structure have been shown to be located in the hydrophobic core of the micelles [31,32–34], whereas polar molecules such as Progesterone are usually solubilized in the palisade layer [35–40].

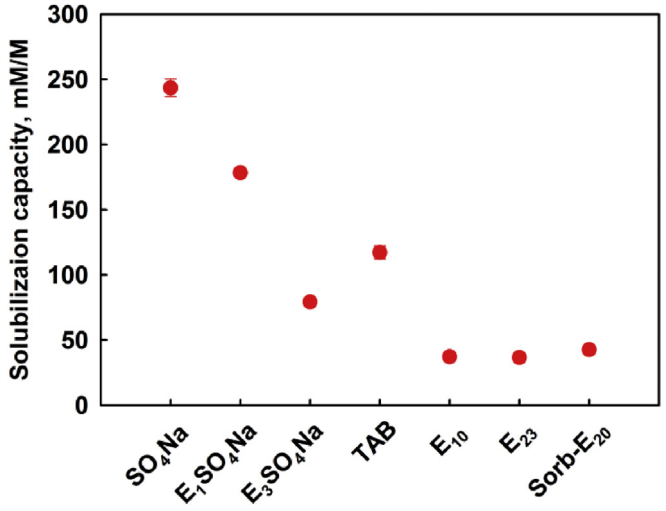


Fig. 3. Progesterone solubilization capacity as a function of hydrophilic head group type forsurfactants with the same hydrophobic chain length (C-12). The error bars can be smaller than the symbols (n ≥ 2).

To gain further insight about the micellar microenvironment of solubilized Progesterone and the main intermolecular interactions that determine the solubilization capacity, we can examine additional details of the experimental data. Best solubilization is observed in charged surfactants micelles, which suggests that electrostatic interactions play a key role in solubilization. As Progesterone molecules are not charged, the interactions are most likely of the ion-dipole type. The latter explanation suggests that the lower solubilization capacity of the positively charged TAB group is due to lower binding energy (*viz.* weaker ion-dipole interactions) of the TAB group to Progesterone. In support of the latter suggestion, the sulfate group of alkylsulfate surfactants was shown experimentally to bind water molecules via ion-dipole interactions much more strongly than the TAB group [41].

The validity of the ion-dipole interaction hypothesis was checked by solubilization experiments with Androstane: a hydrophobic molecule with simple steroid structure, which in contrast to Progesterone does not contain any polar atoms (O, N, S) or unsaturated groups (C=C, C≡C). If the proposed hypothesis is correct, one would expect low solubilization capacity of Androstane in ionic surfactant micelles, due to the very low dipole moment of Androstane, which results in very weak ion-dipole interactions. The results for Androstane solubilization in $C_{12}SO_4Na$, $C_{12}TAB$ and Tween 20 surfactants are presented in Fig. 4A. One sees that indeed, the solubilization capacity of the ionic surfactants for Androstane is much lower than for Progesterone. Therefore, ion-dipole interactions between Progesterone and surfactant head groups are key for the micellar solubilization capacity.

To further clarify the role of surfactant charge and electrostatic interactions we performed additional experiments at high ionic strength of 600 mM NaCl with one cationic, anionic and nonionic C-12 chain-length surfactant, see Fig. 4B. The solubilization capacity of the charged surfactants decreased very strongly, whereas no effect was observed for the nonionic surfactant. The lack of effect of ionic strength for the nonionic surfactants is not surprising, as their head groups are uncharged. However, screening the charged surfactant head groups (sulfate and TAB) resulted in drastic decrease of the solubilization capacity, due to the decreased ion-dipole interactions strength. Note that the change in the number of micelles

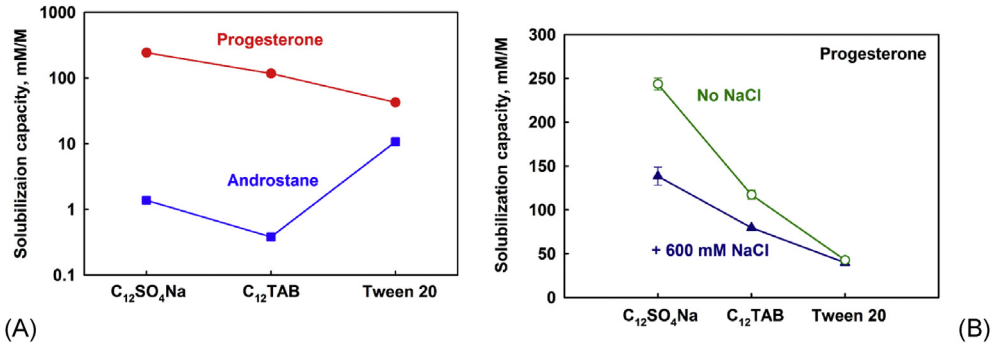


Fig. 4. Solubilization capacity of sodium dodecyl sulfate, dodecyl trimethylammoinum bromide and Tween 20 for (A) Progesterone (red circles) and Androstane (blue squares) and (B) Progesterone in absence of NaCl (empty green circles) and at high ionic strength of 600 mM NaCl (full dark blue triangles). The error bars can be smaller than the symbols ($n \geq 2$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(*viz.* the CMC) is accounted for in the calculation of the solubilization capacity and thus cannot explain the observed decrease.

The influence of the hydrophilic head group on Progesterone solubilization can be analyzed further by discussing two additional trends observed in Fig. 3: (1) the decreased solubilization upon addition of ethylene oxide units to the sulfate head group and (2) the low solubilization by all nonionic surfactants.

We analyzed in more detail the strong decrease of solubilization capacity with the addition of ethylene oxide units to the sulfate head group of dodecyl sulfate surfactants (Fig. 3). One of the possible explanations is that the ion-dipole interaction energy of the sulfate head group with Progesterone decreases significantly upon addition of ethylene oxide units. The latter claim is supported by the decreased electrostatic attraction between the head groups of ethoxylated dodecyl sulfates and Ca^{2+} ions [42]. However, ion-dipole interactions are not important for Androstane and its solubilization also decreases with the addition of ethylene oxide units, thus refuting this hypothesis.

Another possible explanation is geometric incompatibility between Progesterone and the micelles, due to the presence of ethylene oxide units between the alkane chain and the sulfate head group. The latter is supported by the decrease of aggregation number with increasing number of ethylene oxide units in ethoxylated dodecyl sulfates [43], which indicates increasingly difficult packing of the surfactant molecules in the micelles.

The small solubilization capacity of nonionic surfactants could be explained by two factors: (1) the lack of head group charge, which makes impossible the ion-dipole interactions that increase substantially the solubilization for the ionic surfactants and (2) the difficult penetration of Progesterone through the polyoxyethylene shell, which probably results in the drug molecule not being able to reach the hydrophobic alkane chain and decreases the strength of the hydrophobic interactions.

3.2.2. *Effect of hydrophobic chain length*

The effect of hydrophobic chain length on the solubilization capacity of alkylsulfate, alkyltrimethylammonium bromide (TAB), alcoholethoxylate and polyoxyethylene sorbitan ester surfactants is presented in Fig. 5. The increase of hydrophobic chain length increases linearly the solubilization capacity of all studied types of surfactants. The effect is most pronounced for the surfactants with charged head group (alkylsulfates and alkyl-TABs), whereas it is much smaller for the nonionics. The different intercept of the curves illustrates the effect of the hydrophilic head group type on solubilization capacity, which was already discussed in the previous subsection.

The effect of hydrophobic chain length on drug solubilization is

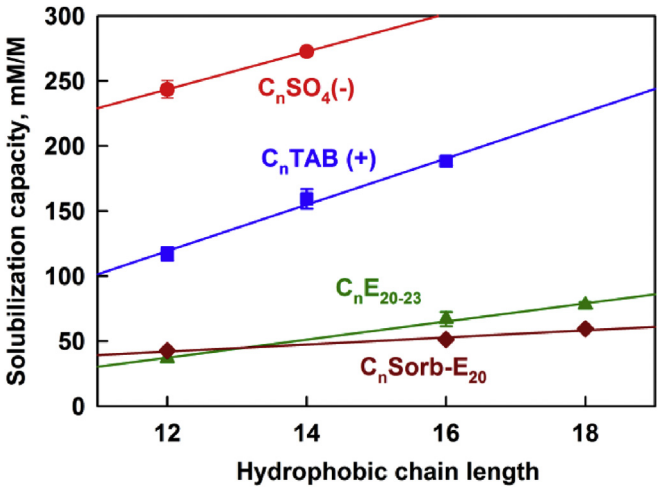


Fig. 5. Molar Progesterone solubilization capacity as a function of surfactant hydrophobic chain length for alkylsulfate (red circles), alkyltrimethylammonium bromide (blue squares), alcoholethoxylate (green triangles) and polyoxyethylene sorbitan ester (brown diamonds) surfactants. The error bars can be smaller than the symbols ($n \geq 2$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

well documented in literature and is usually explained with the decrease of CMC or the increase of the micellar hydrophobic core volume [24]. However, the differences in CMC have been accounted for in the calculation of the solubilization capacity and thus cannot explain the obtained results. On the other hand, the large effect of surfactant hydrophilic head on solubilization showed that the locus of Progesterone solubilization is most likely in the palisade layer, hence, the increase of hydrophobic core volume cannot explain the observed increase in the solubilization capacity. Most likely, the improved solubilization is due to increased palisade layer volume.

4. Conclusions

The solubilization of Progesterone by 17 surfactants with variety of hydrophilic head groups and hydrophobic chain lengths was studied. Charged surfactants showed highest solubilization capacity, increasing Progesterone solubility above 3 mg/mL, whereas all nonionic surfactants had much smaller effect (0.5–1 mg/mL Progesterone solubility). The high solubilization of Progesterone in charged surfactant micelles was explained by ion-dipole interactions. The increase of hydrophobic chain length improved drug solubilization for all studied surfactants, regardless of the type

and charge of the hydrophilic head. In respect to the effect of hydrophilic head group, the solubilization capacity of C-12 surfactants decreased in the order SO_4^- > $E_1SO_4^-$ > $^+N(CH_3)_3$ > $E_3SO_4^-$ > $SorbEO_{20}$ = E_{10} = E_{23}. All obtained results indicate that the locus of Progesterone solubilization is in the micelle palisade layer, where electrostatic ion-dipole interactions with charged surfactant head groups, combined with hydrophobic interactions between the hydrophobic moiety of the Progesterone molecule and the alkane chain of the surfactant, lead to high solubilization capacity. Therefore, the best candidates to improve oral Progesterone absorption through solubility enhancement are surfactants with long hydrophobic chain and charged hydrophilic head group (*e.g.* alkylsulfates).

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Conflict of interest statement

Conflicts of interest: none.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jddst.2017.09.014.

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