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Solubilisation of camptothecin by nonionic surfactants and alkyldimethylamine oxides

Research Article

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Abstract: The solubilisation of poorly soluble antineoplastic drug camptothecin by nonionic surfactants (polysorbates and octylphenol ethoxylates) and alkyldimethylamine oxide surfactants with the alkyl chain length 8 to 16 carbon atoms was investigated. The hydrophobicity of the solubilising agent turned out to be the primary structural parameter controlling the solubility efficiency of camptothecin in an aqueous solution. The quantitative parameter of solubilisation (drug loading coefficient) provided values in the range of 0.1 – 1.2% and 0.1 – 1.0% for alkyldimethylamine oxides and nonionic surfactants, respectively. The decreasing number of oxyethylene units and the extension of the hydrophobic part of nonionic surfactant molecule resulted in the increase of camptothecin solubility. From the dynamic light scattering measurements, the hydrodynamic diameter values of camptothecin-loaded alkyldimethylamine oxide and nonionic micelles were found in the range of 4 – 42 nm and 5 – 120 nm, respectively. The experimental values confirmed the increase in micellar size with the increasing alkyl chain length. The values of the packing parameter of camptothecin-loaded dodecyldimethylamine oxide micelles indicate their spherical shape at all the investigated surfactant concentrations. A simple computer model of camptothecin-loaded dodecyldimethylamine oxide micelle provided the diameter of the structure cross section which is consistent with the experimental values.

Keywords: Camptothecin • Alkyldimethylamine oxide • Solubilisation • Hydrodynamic diameter
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1. Introduction

Poorly soluble systems are often represented by new drug candidates, and result from the complex development technologies and plans. The absorption of a potential drug in its crystalline form through gastrointestinal tract is limited by its solubility. In the field of pharmaceutical technologies, procedures have been developed which result in a decrease in drug degradation, bioavailability increase and an increase in a drug concentration at the target site. The complexation of a drug with a surface-active agent proves to be a promising solution to poorly soluble drug transport to the target site.

Many anti-cancer drug candidates are only weakly soluble in water. If a drug shows good permeability through a membrane, it is usually poorly soluble in water. Camptothecin is a cytotoxic alkaloid originally isolated from the stem wood *Camptotheca acuminata*. The lactone ring in camptothecin molecule can be hydrolyzed to form the open carboxylate form of camptothecin. The chemical formula of biologically active camptothecin lactone form is shown below,
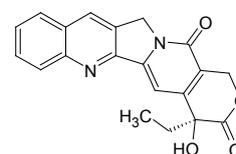
20-(S)-camptothecin and its analogues 9-nitrocamptothecin and 9-aminocamptothecin have been shown to be potent antineoplastic agents. Their activity against cancer includes human lung, colon, prostate, breast, stomach and ovarian carcinomas. The mechanism of camptothecin anti-tumoral activity is based on the inhibition of topoisomerase I which is a nuclear enzyme that plays an important role in the relaxation of DNA during replication and transcription. Very poor solubility and instability in a basic environment appears to be the major drawback of this potential drug.

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In the last decade, a lot of research has been done in the field of camptothecin solubilisation. Research works covering the area of camptothecin interaction with polymers were focused mostly on micellar solubilisation by nonionic surfactant Pluronic and its copolymers, *e.g.* with polyethylene glycol phosphatidyl ethanolamine conjugates [1,2], Pluronic covalently modified with polyacrylic acid [3], with polybutylcyanoacrylate [4], and with polyethylene glycol succinate [5]. Several studies focuses on camptothecin solubilisation by polyethylene glycol micelles with polyaspartic acid [6] and its derivatives [7-9], methylated polyethylene glycol [10], methoxy-polyethylene glycol-polycaprolactone [11] and polyvalerolactone [12] polymeric micelles. Micelles composed of phospholipids and polyethylene glycol turned out to be good vehicles for the delivery of poorly soluble camptothecin [13]. Another area of scientific work foucsses on camptothecin solubility improvement by cyclodextrins, mainly on their derivative hydroxypropyl-β-cyclodextrin approved by the US Federal Drug Administration. A strong solubility increase was observed upon the application of β-cyclodextrin to camptothecin [14,15] and an efficient hydroxypropyl-β-cyclodextrin formulation with high camptothecin solubility and stability was developed [16]. Cyclodextrin-based nanoparticles showed better camptothecin solubilisation capacity as compared to polymers [17,18] and durable protection of instable lactone camptothecin form from hydrolysis [19]. The application of other systems to increase the camptothecin solubility such as polysaccharides [20], lipids [21], dendrimers [22], inorganic nanoparticles [23,24] and nanocrystals [25] led to promising results. In the studies of surfactants as camptothecin solubilisers, focus was given to the application of the common anionic surfactant sodium dodecyl sulfate [26] and cationic ammonium surfactants dodecyltrimethylammonium bromide [27] and hexadecyltrimethylammonium bromide [28]. Due to known toxicity issues of cationic surfactants in pharmaceutical applications, the aim of the present paper is to investigate non-cationic agents (alkyldimethylamine oxides, nonionic surfactants) as potentially efficient camptothecin solubilisers.

2. Experimental procedure

2.1. Chemicals

Camptothecin (molecular weight 348.35, 98% purity) was purchased from Calbiochem, USA. Dimethyl sulfoxide (DMSO, Fluka) of analytical grade was used for camptothecin calibration. Amine oxides: N-octyl-N,N–dimethylamine N-oxide (C_8DAO), N-dodecyl-N,N–dimethylamine N-oxide ($C_{12}DAO$), N-tetradecyl-N,N–dimethylamine N-oxide ($C_{14}DAO$), N-hexadecyl-N,N–dimethylamine N-oxide ($C_{16}DAO$) were synthesized and purified in our laboratories as described previously [29]. Nonionic surfactants: Triton X-100 (ethoxylated octylphenol, 9 oxyethylene units) was purchased from Koch-Light Laboratories (UK), Triton X-405 (ethoxylated octylphenol, 20 oxyethylene units) was purchased from Technicon chemicals (Belgium), Tween 60 (polyethylene glycol sorbitan monostearate, 20 oxyethylene units) was purchased from Lachema (Czech republic), Brij 78 (ethoxylated stearylether, 20 oxyethylene units) and Brij 35 (ethoxylated dodecylether, 23 oxyethylene units) were purchased from Janssen Chimica (Belgium).

2.2. Preparation of camptothecin-surfactant mixtures

Mixtures of camptothecin and amine oxides were prepared by weighing 2 mg of camptothecin and respective amounts of nonionic surfactants and amine oxides to receive the relative concentration against the surfactant critical micelle concentration (CMC) – 5xCMC, 10xCMC, 15xCMC, and 20xCMC. The molar concentrations used in the solubilisation experiment are listed in Table 1 for all investigated surfactants. The CMC values for alkyldimethylamine oxides were taken from references [30-32]. The CMC of $C_{16}DAO$ was determined by the linear extrapolation of the log CMC *vs.* alkyl carbon number dependence. Due to the large amount of octyldimethylamine oxide (C_8DAO) required to prepare the 20xCMC concentration, this concentration step was omitted in the solubilisation experiment. The CMC values of nonionic surfactants were taken from previous work [33].

Solids were diluted by 10 mL of deionised water. Heterogeneous mixtures of camptothecin and surfactants were sonicated for 1 hour and subsequently homogenized by mechanical shaking for 48 hours at a speed of 250 rpm. After the homogenisation, the mixtures were centrifuged for 1 hour at a speed of 5500 rpm. The supernatant was filtered through a syringe filter with a pore diameter of 450 nm and the camptothecin concentration in micellar phase was spectroscopically determined.

2.3. Spectrophotometric measurements

The calibration of camptothecin was made in a dimethyl sulfoxide solution. UV absorbance of camptothecin at 368 nm (spectral plot shown in Fig. 1a) was plotted against the camptothecin molar concentration c_{CPT} (Fig. 1b).

The absorbance vs. concentration dependence was fit using a linear dependence with the fitting line equation absorbance equal to $0.014 + 25656 c_{CPT}$. From

Table 1. Molar concentrations of nonionic surfactants and alkyldimethylamine oxides (C_mDAO; m = 8, 12, 14, 16) used in the camptothecin solubilisation experiment.

Surfactant	5xCMC (mmol L⁻¹)	10xCMC (mmol L⁻¹)	15xCMC (mmol L⁻¹)	20xCMC (mmol L⁻¹)
C_8DAO	413.00	826.00	1239.00	-
C_{12}DAO	8.50	19.00	25.50	38.00
C_{14}DAO	0.70	1.40	2.10	2.80
C_{16}DAO	0.08	0.17	0.25	0.34
Brij 35	0.45	0.90	1.35	1.80
Brij 78	0.03	0.06	0.09	0.12
Triton X-100	1.20	2.40	3.60	4.80
Triton X-405	4.05	8.10	12.10	16.20
Tween 60	0.11	0.21	0.33	0.42
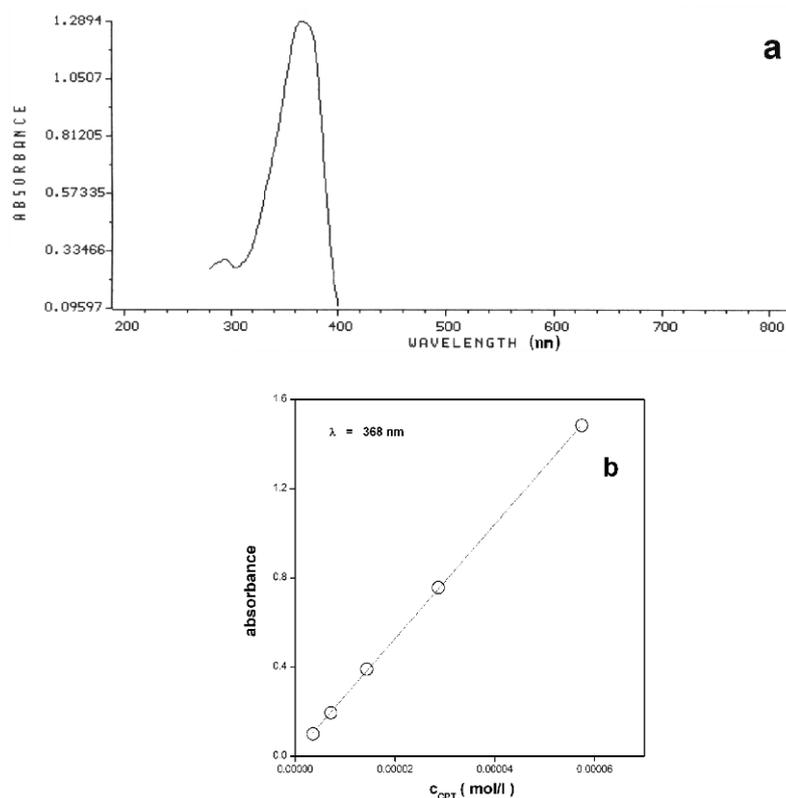
Figure 1. UV spectrum plot of camptothecin in dimethyl sulfoxide (a), calibration plot of camptothecin in dimethyl sulfoxide (b).

the absorbance values, the concentration of solubilised camptothecin in the surfactant micellar phase was calculated.

2.4. Concentration determination of solubilised camptothecin

The drug loading coefficient (DLC) [11] represents the amount of poorly soluble substance which is solubilised by the amount of surfactant forming the micellar phase. In this case, it is expressed as the ratio of the amount of solubilised camptothecin in the micellar phase of supernatant and the total amount of camptothecin and surfactant forming the micellar phase, *i.e.*, $c_{CPT}/(c_0+c_{surf} - CMC)$. The respective percentage is expressed as follows

$$DLC = 100\ c_{CPT}/(c_0 + c_{surf} - CMC) \qquad (1)$$

where c_{CPT} is the concentration of solubilised camptothecin in the micellar phase, c_0 is the total
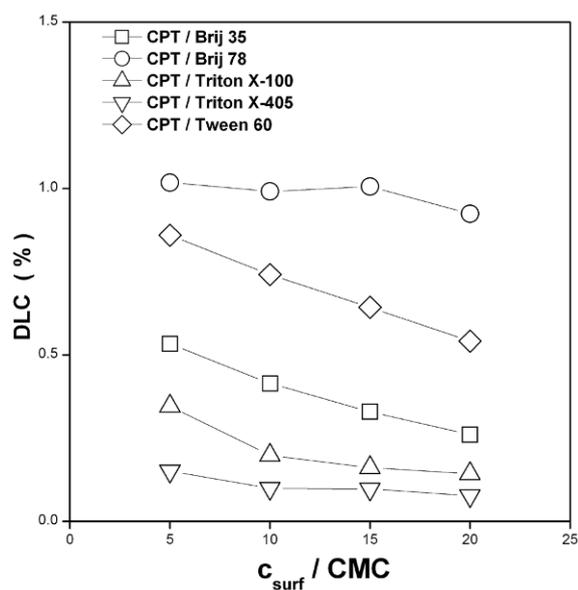
Figure 2. Dependence of the drug loading coefficient (DLC) *vs.* nonionic surfactant concentration c_{surf} relative to surfactant CMC.

amount of camptothecin divided by the volume of the mixture, c_{surf} – CMC is the concentration of surfactant in the micellar phase.

2.5. Size determination of camptothecin-loaded surfactant micelles

The hydrodynamic diameter of the surfactant micelles containing camptothecin was determined using a dynamic light scattering equipment (Brookhaven BI 9000 digital correlator, Brookhaven SM 200 goniometer, Lexel argon laser). The argon laser at 514.5 nm wavelength was used as the incident light source. The intensity time fluctuations of the scattered light were detected at a scattering angle of 90° and a temperature 25°C and autocorrelated in the BI 9000 correlator card where the time autocorrelation function was built. All measurements were taken five times for each surfactant concentration and the mean values and standard deviations from the determined quantities were calculated. Hydrodynamic diameter of surfactant micelles containing camptothecin were determined from the size distribution spectra which were obtained from the autocorrelation function using the CONTIN numerical algorithm [34].

2.6. Molecular model calculations

The molecular model calculations were performed on a O2 SGI workstation using Sybyl 8.0 software. The three-dimensional models of dodecyldimethylamine oxide ($C_{12}DAO$) molecule and camptothecin molecule with the stereogenic centre in S-configuration were built

in the sketch module using standard atomic geometry parameters. The structures were optimized with MM+ force field and RMS gradient 0.01 kcal $Å^{-1}$ mol^{-1}) without any constrains. The Connolly molecular surface was computed utilizing a sphere probe of 0.14 nm radii as it is implemented in the Sybyl 8.0 package [35].

3. Results and discussion

3.1. Solubilisation by nonionic surfactants

In Fig. 2, surfactant concentration dependence of the drug loading coefficient (DLC) for camptothecin-loaded nonionic micelles is shown.

The DLC represents the solubilisation capacity of the respective surfactant in the process of solubilisation of a weakly soluble drug which, along with the total drug amount, also takes into account the amount of solubilising agent and the surfactant micellar properties (represented by surfactant concentration and CMC concentration, respectively), as it follows from the DLC definition discussed in section 2.4.

3.1.1. Hydrophobic effect

From the DLC concentration curves shown in Fig. 2 , the solubilisation capacity does not change or moderately decreases with the increase in the nonionic surfactant concentration. The analysis of the hydrophobic parts of the surfactant molecules from the studied nonionic surfactants provides the alkyl chain length of individual nonionics and is shown in the Table 2.

By correlating alkyl chain length with the DLC results (Fig. 2), it is obvious that the highest solubilisation capacity was found for the Brij 78 and Tween 60 surfactants. This could be attributed to these surfactants having the longest hydrophobic tail (18 carbon atoms). This finding indicates that the solubilisation mechanism is primarily governed by the hydrophobic interaction between the weakly soluble drug and surfactant, *i.e.*, it mainly depends on the length of hydrophobic part of surfactant molecule. Solubilisation capacity decreases monotonically with the decreasing number of carbon atoms in the alkyl chain of surfactant molecule for all investigated surfactant concentrations in the following order: DLC (Brij 78, C_{18}) > DLC (Tween 60, C_{18}) > DLC (Brij 35, C_{12}) > DLC (Triton X-100, C_8) > DLC (Triton X-405, C_8).

3.1.2. Hydrophilic oxyethylene groups

When analyzing nonionic surfactant molecules with respect to the number of hydrophilic oxyethylene (EO) units, the results presented in Table 3 were found.

Table 2. Comparison of nonionic surfactants as a function of the alkyl chain length.

Brij 35	Brij 78	Triton X-100	Triton X-405	Tween 60
C_{12}	C_{18}	C_8	C_8	C_{18}

Table 3. Comparison of nonionic surfactants as a function of the number of oxyethylene groups.

Brij 35	Brij 78	Triton X-100	Triton X-405	Tween 60
23 EO	20 EO	9 EO	40 EO	20 EO

By comparing the DLC of the surfactants with longer hydrophobic parts (Brij 78, Tween 60), the difference result from the predominant hydrophobic interaction. If one compares surfactant molecules which have identical hydrophobic part, but differ from each other in the number of oxyethylene units, the influence of the hydrophilicity of surfactant molecule on camptothecin solubilisation can be analysed. This is the case of surfactants Triton X-100 (9 EO units, C_8 alkyl chain) and Triton X-405 (40 EO units, C_8 alkyl chain). As follows from Fig. 2, the solubilisation capacity of the more hydrophilic Triton X-405 (40 EO units) is significantly lower than that of the less hydrophilic Triton X-100 (9 EO units) for all investigated surfactant concentrations. Along with the found hydrophilicity feature negatively affecting the solubilisation capacity of the surfactants, both surfactants comply with the general trend of solubilisation capacity increase with the increasing alkyl chain length. The curves for both surfactants give the lowest DLC values (Fig. 2) due to the short octyl chain in the molecules.

3.2. Solubilisation by alkyldimethylamine oxides

The solubilisation capacity of camptothecin by alkyldimethylamine oxides monotonically increases as the alkyl chain length of alkyldimethylamine oxides increases for all surfactant concentrations investigated (Fig. 3).

The C_{16}DAO with the longest hexadecyl chain was found to be the most efficient camptothecin solubiliser (Fig. 3). By comparing the DLC values for a pair of surfactants consisting of a nonionic surfactant and an alkyldimethylamine oxide with both surfactants having the same alkyl chain length, the results indicate the predominant effect is a result of the alkyl chain length regardless of the surfactant molecular structure. As follows from Fig. 4, the DLC values for a pair of Triton
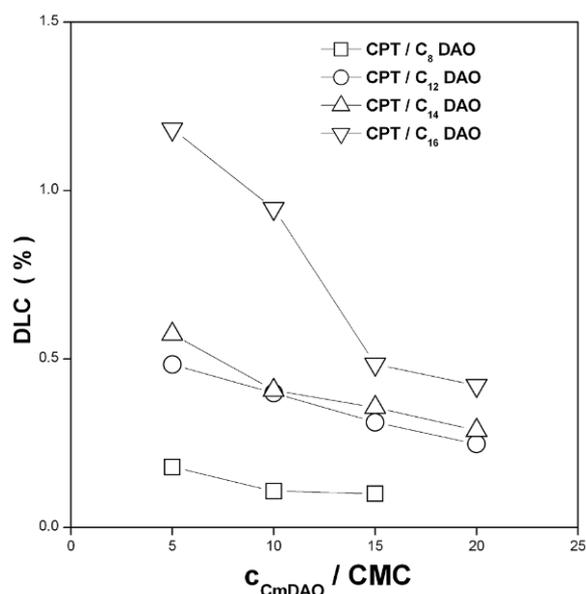

Figure 3. Dependence of the drug loading coefficient DLC vs. alkyldimethylamine oxide concentration c_{CmDAO} relative to its CMC for the alkyl tail length m = 8, 12, 14, 16.
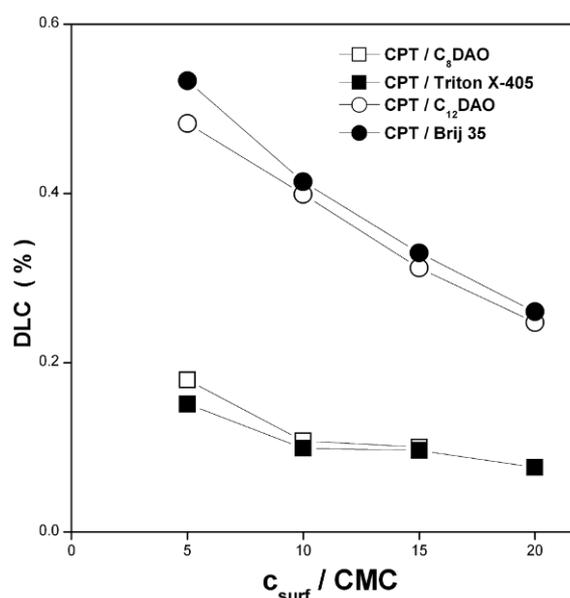
Figure 4. Comparison of DLC values for the pair nonionic surfactant – alkyldimethylamine oxide of identical alkyl chain length.

X-405/C_8DAO (octyl chains) are very similar and even show overlapping curves.

This also applies for the DLC values of a pair of dodecyl chain surfactants - Brij 35/C_{12}DAO. This finding confirms again the role of hydrophobic interaction between weakly soluble drug and solubiliser as the main mechanism controlling the solubilisation process.

Table 4. Hydrodynamic diameter values d_{hCONT} of the camptothecin-loaded micelles of alkyldimethylamine oxides C_mDAO, m = 8, 12, 14, 16.

c_{CmDAO}	$C_8DAO\ d_{hCONT}$ (nm)	$C_{12}DAO\ d_{hCONT}$ (nm)	$C_{14}DAO\ d_{hCONT}$ (nm)	$C_{16}DAO\ d_{hCONT}$ (nm)
5xCMC	6.2	5.5	11.0	27.8
10xCMC	6.2	5.4	14.4	28.6
15xCMC	6.1	4.2	14.4	30.8
20xCMC	-	5.0	14.6	41.7
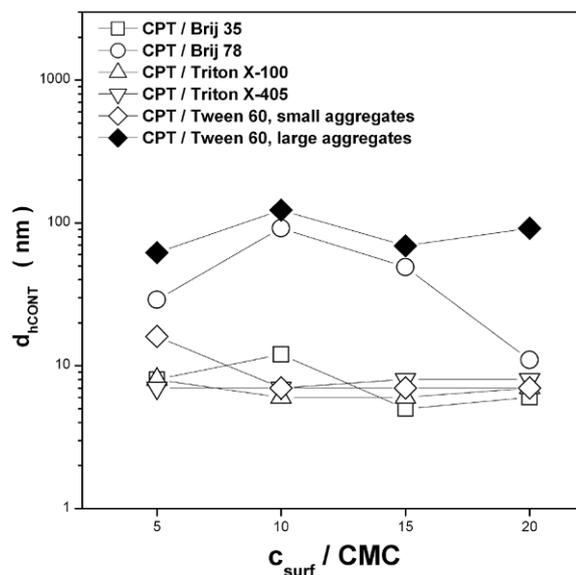
Figure 5. Dependence of the hydrodynamic diameter d_{hCONT} of camptothecin-loaded micelles on the nonionic surfactant concentration c_{surf} relative to surfactant CMC.

3.3. Size and shape of camptothecin-loaded micelles

The surfactant concentration dependences of the hydrodynamic diameter d_{hCONT} of camptothecin-loaded nonionic micelles are shown in Fig. 5. These results are from a series of dynamic light scattering measurements and data analysis utilizing the CONTIN algorithm (Fig. 6).

The results from the data shown in Fig. 5 and from the size distribution plots shown in Fig. 6 indicate that the micelles are small, spherical aggregates in the size range between 5 – 120 nm. Increasing the hydrophobic part of surfactant molecule results in an increase in micelle size in the following manner: d_{hCONT} (Triton X-405, C_8) ~ d_{hCONT} (Triton X-100, C_8) ≤ d_{hCONT} (Brij 35, C_{12}) < d_{hCONT} (Brij 78, C_{18}) < d_{hCONT} (Tween 60, C_{18}). Triton X-100 and X-405 form small micelles of 7 - 8 nm size. Brij 78 and Tween 60 form larger aggregates in the size range between 50 and 100 nm. From Fig. 6e, the size spectra shows bimodal size distribution for Tween 60, with small micelles of 7 nm diameter and larger aggregates lying in the size range 60 – 120 nm. It is interesting to note

that the bimodality in the CONTIN size spectra clearly appeared with all investigated surfactant concentrations (5x, 10x, 15x and 20xCMC). A bimodal size distribution pattern was also observed for the Tween 80 micelles with a soybean phospholipid solubilising a weakly soluble anti-cancer drug paclitaxel. The peaks in the size distribution spectra were observed at 10 and 100 nm and the larger size was attributed to the micelle-to-vesicle transition [36]. The transition towards vesicular aggregates may be also the cause of the bimodality of in the presented size distributions of Tween 60 aggregates with solubilised camptothecin.

A similar result was found for camptothecin-loaded micelles of alkyldimethylamine oxides. The dependence of the micellar hydrodynamic diameter on the alkyldimethylamine oxide concentration (Fig. 7) shows a constant micellar size or a moderate increase through the inspected alkyldimethylamine oxide concentration region.

C_mDAO molecules aggregate into small spherical micelles with a weak concentration dependence. Short-chained molecules C_8DAO and $C_{12}DAO$ aggregate into the micelles which are 6 nm in size. For $C_{14}DAO$, a moderate micelle size increase up to 11-15 nm was observed. $C_{16}DAO$ with the longest alkyl tail forms camptothecin-loaded micelles with a diameter range between 25 to 45 nm. The numerical values of the hydrodynamic sizes for the camptothecin-loaded C_mDAO micelles are summarized in Table 4.

The numerical size distributions of the camptothecin-loaded C_mDAO micelles at the specific amine oxide concentration (15xCMC) confirm the unimodal size distribution of alkyldimethylamine oxide micelles up to the longest alkyl chain investigated $C_{16}DAO$ (Fig. 8).

The quantitative analysis of the shape of camptothecin-loaded micelles is demonstrated by the calculation of the packing parameter (p) which is expressed as the volume of hydrophobic groups in the micellar core (v_h) divided by the product of the length of the hydrophobic group in the core and the cross-sectional area occupied by the hydrophilic group at the micelle–solution interface $l_c\ a_0$, $p = v_h / l_c a_0$ [37]. Its value determines the micellar shape. For dodecyldimethylamine oxide micelles, the volume
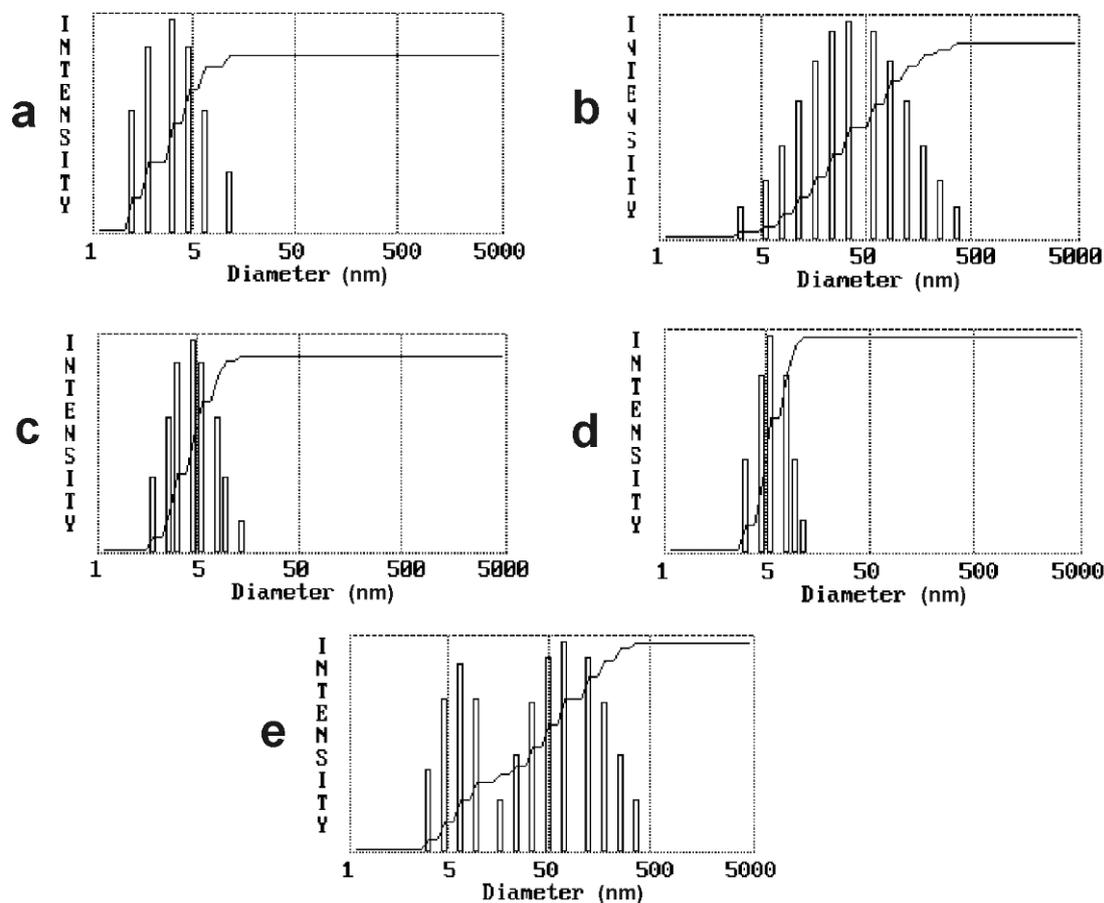
Figure 6. Particle size spectra of camptothecin-loaded nonionic micelles at the surfactant concentration 15xCMC. a -Brij 35, b – Brij 78, c – Triton X-100, d- Triton X-405, e - Tween 60.
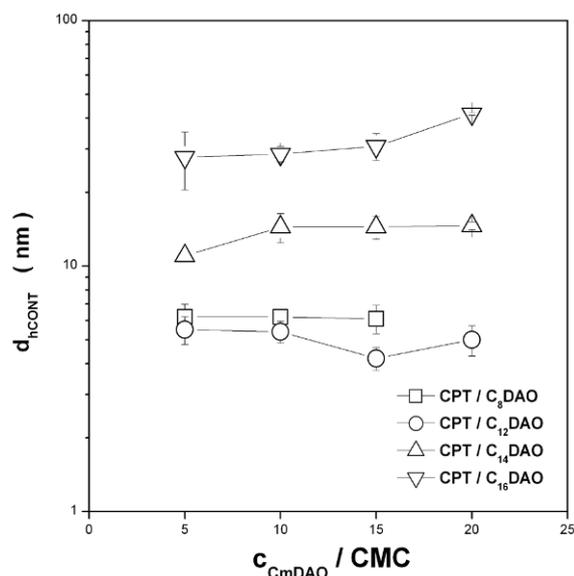

Figure 7. Dependence of the hydrodynamic diameter d_{hCONT} of camptothecin-loaded micelles on the alkyldimethylamine oxide concentration c_{CmDAO} relative to its CMC for the alkyl tail length m = 8, 12, 14, 16.

(v_h) and the length of the dodecyl chain (l_c)is denoted as v_{hC12} and l_{C12} , respectively. With the cross-sectional area of the amine oxide hydrophilic group a_{C12DAO} , the packing parameter is expressed as follows,

$$p = v_{hC12} / (a_{C12DAO} \, l_{C12}) \tag{2}$$

According to Tanford [38], the length of the straight conformation of hydrophobic alkyl chain (l_m) in nanometers can be expressed as the linear function of the alkyl chain length,

$$l_m = 0.15 + 0.1265 \, m \tag{3}$$

where, m, is the number of carbon atoms in the alkyl chain. Using Eq. 3 with a m value of 12, the length of the straight dodecyl chain l_{C12} is equal to 1.67 nm. The value of v_{hC12} which is the volume of the straight conformation of dodecyl chain in cubic nanometers, can be calculated according to the Tanford empiric formula,

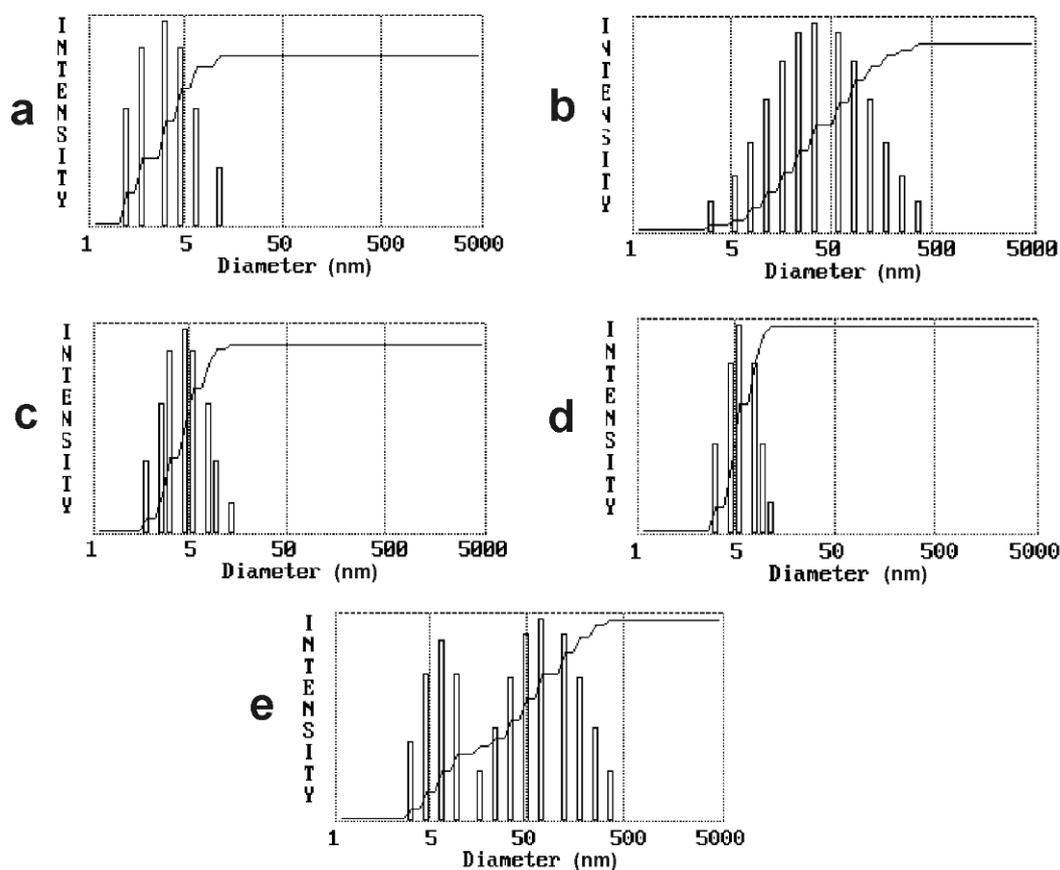$$v_{hC12} = 0.0274 + 0.0269 \, x12 \tag{4}$$

Figure 8. Particle size spectra of camptothecin-loaded alkyldimethylamine oxide micelles at the alkyldimethylamine oxide concentration 15xCMC. a – C_8DAO, b – $C_{12}DAO$, c – $C_{14}DAO$, d - $C_{16}DAO$.

Table 5. Camptothecin – dodecyldimethylamine oxide micellar parameters. c_{C12DAO} - $C_{12}DAO$ molar concentration, d_{hCONT} - $C_{12}DAO$ micellar hydrodynamic diameter, a_{C12DAO} - area of $C_{12}DAO$ molecule in the micellar shell, p – packing parameter, v_{CPT} - Connolly volume of camptothecin molecule, v_{hMIC} - volume of $C_{12}DAO$ micellar hydrophobic core.

c_{C12DAO} (mol L^{-1})	d_{hCONT} (nm)	a_{C12DAO} (nm^2)	p	v_{hMIC} (nm^3)	v_{CPT}/v_{hMIC}
0.0095	5.5	1.22	0.17	58.5	0.005
0.0190	5.4	1.17	0.18	54.9	0.006
0.0285	4.2	0.71	0.30	22.8	0.014
0.0380	5.0	1.01	0.21	42.1	0.008

thus giving the value v_{hC12} = 0.350 nm^3 for a straight dodecyl chain conformation. By definition, a_{C12DAO} is the area of $C_{12}DAO$ surfactant molecule at the air/water the interface or in the micellar shell and can be calculated from the micelle hydrodynamic diameter and aggregation number as follows,

$$a_{C12DAO} = \pi \, (d_{hCONT})^2 \, / \, N_{agg} \qquad (5)$$

N_{agg} is the aggregation number of $C_{12}DAO$ micelle equal to 78 [39]. The micellar hydrodynamic diameter value d_{hCONT} for $C_{12}DAO$ is taken from Table 4. The results are given in Table 5.

The results from Table 5, show that the packing parameter, p, is smaller than 1/3 [37] for $C_{12}DAO$ micelles at all surfactant concentrations investigated thus indicating that $C_{12}DAO$ micelle keeps its spherical shape even if it contains solubilised camptothecin molecule. According to the published dynamic light scattering data on the non-protonated $C_{12}DAO$ micelle hydrodynamic diameter without the solubilized drug, a micelle diameter value of approximately 4 nm was found and was constant over the broad range of electrolyte concentration [40]. With respect to the diameter values of $C_{12}DAO$ micelles with solubilised camptothecin lying in the range 4.2 - 5.5 nm (Table 5), it is obvious that
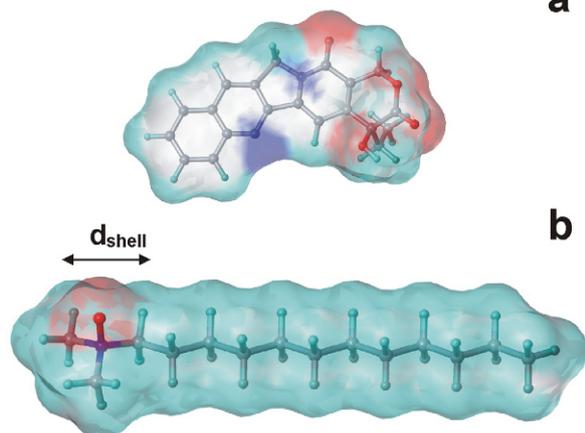
Figure 9. Three-dimensional model of camptothecin molecule (a), C_{12}DAO (b).
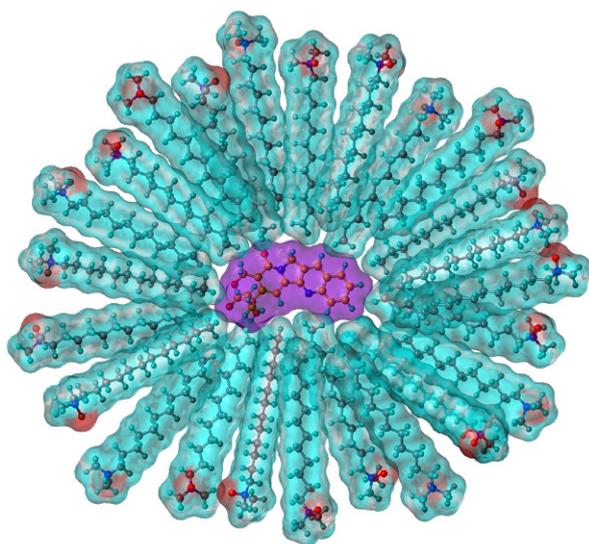

Figure 10. Simple phenomenological model of camptothecin molecule solubilised in C_{12}DAO micelle generated by spatial Connolly molecular volumes.

the camptothecin molecule inclusion into the micelle core represents an increase by 0.2 – 1.3 nm in the micelle size.

From the camptothecin molecular geometry analysis based on the optimised three-dimensional model (Fig. 9a), the Connolly volume of camptothecin molecule v_{CPT} is equal to 0.318 nm³ . A common way to represent three-dimensional structures of molecules, shapes, volumes and surfaces is using the Connolly surface method. This method provides the calculatation of the coordinates of points on the solvent accessible surface of molecules as well as their visualisation utilizing the vector computer graphics system in order to examine the structure and interactions of studied molecule with a solvent probe - water molecule of the radius 0.14 nm

[41]. The volume of hydrophobic core of a spherical C_{12}DAO micelle v_{hMIC} is given by the relation,

$$v_{hMIC} = 4/3 \; \pi \; (d_{hCONT}/2 - d_{shell})^3 \qquad (6)$$

where d_{shell} is the size of the dodecyldimethylamine oxide hydrophilic head. Based on the molecular model of C_{12}DAO shown in Fig. 9b, its value was found to be 0.34 nm.

The low values for the ratio v_{CPT} / v_{hMIC} (Table 5) indicate that camptothecin molecule occupies a small portion of the hydrophobic micellar core volume. The low v_{CPT} / v_{hMIC} values result partially from the large value of v_{hMIC} . The volume of v_{hMIC} is a function of the experimentally determined micellar hydrodynamic diameter (Eq. 6) which value also reflects the hydration layer of dodecyldimethylamine oxide micelle thereby increasing the volume of the micelle. The following illustration model (Fig. 10) depicts the cross section of a camptothecin-loaded C_{12}DAO micelle.

The diameter of the computer-generated micellar structure shown in Fig. 10 is equal to 5.0 nm which falls into the range of the found hydrodynamic diameters of camptothecin-loaded C_{12}DAO micelles 4.2 – 5.5 nm (Table 5).

4. Conclusions

These result indicate that the primary structural parameter controlling the solubility efficiency of poorly soluble systems is the hydrophobicity of the solubilising agent. The decrease of hydrophilicity represented by the decreasing number of oxyethylene units in a nonionic surfactant molecule and the extension of its hydrophobic part results in the camptothecin solubilisation efficiency improvement. The determination of hydrodynamic diameters of camptothecin-loaded surfactant micelles by dynamic light scattering measurements confirmed the increase in micellar size with the increasing alkyl chain length. The values of the packing parameter of camptothecin-loaded dodecyldimethylamine oxide micelles indicate their spherical shape at all investigated surfactant concentrations. A simple computer model of camptothecin-loaded dodecyldimethylamine oxide micelle provides the diameter of the structure cross section which fits the experimentally found micellar diameter values. Due to the lower toxicity against cationic polymers and surfactants, nonionic surfactants and alkyldimethylamine oxides represent a suitable alternative to convenient solubilisers of poorly soluble drugs while maintaining satisfactory level of the solubilisation efficiency.

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