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Effect of Oligomerization of Sodium 10-Undecenoate on the Solubilization of a Hydrophobic Substrate

Clifford E. Larrabee, Jr., Mary R. Warmin
University of Cincinnati Clermont College
Batavia, Ohio, USA
cliff.larrabee@uc.edu; warminmr@ucmail.uc.edu

Chelsea N. Iles
University of Cincinnati
Cincinnati, Ohio, USA
ilescn@mail.uc.edu

Abstract **-** Most of the micellar drug delivery systems currently in clinical or preclinical investigation are based on amphiphilic polymers. This is due in part to the thermodynamic instability of micelles formed from low molecular weight surfactants below their critical micelle concentrations (CMCs). Here we show that an oligomeric micelle is capable of solubilizing a hydrophobic substrate at concentrations very much lower the CMC of its monomeric analogue. A direct comparison of the solubilization of a hydrophobic substrate by monomeric and oligomeric sodium 10-undecenoate micelles yielded CMCs of 0.100 and 0.006 mol dm^{-3} respectively. The results show that oligomerization can be a worthwhile parameter in the design of effective micellar drug delivery systems.

Keywords**:** Micelle, Oligomer, Solubilization, Model system, Drug delivery.

1. Introduction

One of the challenges of chemotherapy is the delivery of appropriate doses of drugs to targeted areas of the body. (Brewer, et al., 2011) Solubilization of hydrophobic drugs by micelle-forming surfactants offers a number of benefits, including increased bioavailability, reduction of toxicity, and enhanced permeability across physiological barriers. (Torchilin, 2001) Their sizes are generally smaller than polymeric micelles and this can be an advantage in designing systems based on size-dependent biodistribution. (Yue, et al., 2013) However, surfactant micelles have a serious disadvantage. They are thermodynamically stable only above the critical micelle concentration (CMC). Below that concentration they are subject to dissociation and the resulting precipitation of any dissolved substrate.

To date, the most successful way to avoid the instability of surfactant micelles has been to employ amphiphilic polymers. (Wang, et al., 2012) An alternative approach is to employ low molecular weight oligomers of ordinary surfactants. Laschewsky, et al. (2005) have reported much lower CMCs for H-type oligomers (joined at the headgroup) than the monomeric surfactant, and a general decrease in CMC with increasing degree of oligomerization.

The purpose of the research described here was to study the effect of oligomerization on a simple model system. Sodium 10-undecenoate, NaU, was chosen for the model system because it is a T-type (joined at the tail) oligomerizable surfactant (Larrabee and Sprague, 1979) with a well-defined CMC of 0.117 ± 0.001 mol kg^{-1} (Sprague, et al., 1983). Free radical oligomerization of aqueous solutions above the CMC yields polydisperse oligomers with a number average degree of oligomerization of 6.1 ± 0.2. (Denton, et al., 1993). Both monomeric NaU and oligomeric NaU form micelles with essentially the same aggregation number, 45 ± 3 monomer units, and the same spherical diameter, 2.08 ± 0.02 nm. (Denton, et al., 1993) Oil Blue N was chosen for the hydrophobic substrate because of its structural similarity to the cancer drug Mitoxantrone, see Figure 1.

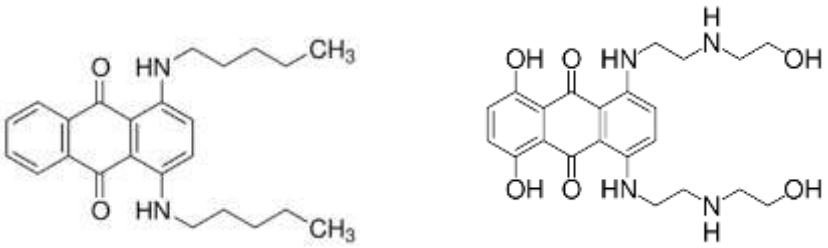

Fig. 1. Molecular structures of Oil Blue N (left) and Mitoxantrone (right)

2. Results and Discussion

2. 1. Micelle Formation

All solutions were made up with ACS Reagent Grade Type I water (Thermo Scientific). Sodium 10-undecenoate solutions were prepared by neutralization of 10-undecenoic acid (Acros, 99%) with sodium hydroxide (Fisher, ACS) after standardizing with potassium hydrogen phthalate (Acros, ACS reagent). The CMC was determined by the conductivity method described by Sprague, et al. (1983). Conductance was measured at 298.2 ± 0.3 K using an Amber Science Model 1056 conductivity meter and P/N 515 cell. Results are shown in Figure 2.

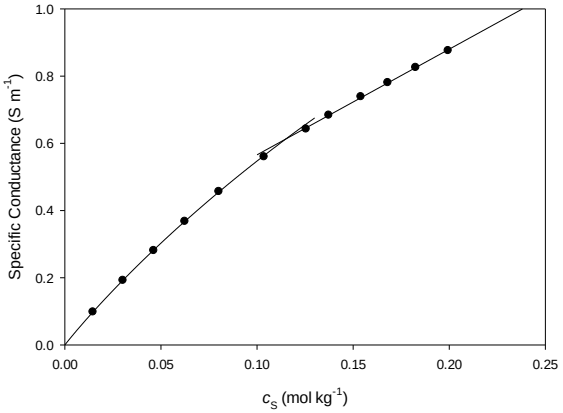

Fig. 2. Specific conductance as a function of surfactant concentration for sodium 10-undecenoate.

The CMC, 0.115 ± 0.007 mol kg^{-1}, is given by the intersection of the two lines in Figure 2. This value is indistinguishable from the value, 0.117 ± 0.001 mol kg^{-1}, reported by Sprague, et al. (1983) ($t = 0.61$, $p = 0.55$).

2. 2. Oligomerization

Sodium 10-undecenoate oligomers were prepared by persulfate-initiated, free-radical oligomerization of a 0.94 mol kg^{-1} solution of the monomer. (Duraraj and Blum, 1998) The product was isolated by precipitation in ethanol, and the absence of carbon-carbon double bonds in the product was confirmed by infrared spectrometry (Nicolet IR200 FT-IR). A portion of the product was converted to its methyl ester (Larrabee and Sprague, 1979), and the molecular weight of the ester was determined by boiling point elevation in ethyl acetate (Acros, 99.9%).

The number average molecular weight of the oligomer was 1200 ± 400 Da corresponding to a degree of oligomerization of 6 ± 2. This is in agreement with a number average degree of oligomerization of 6.1 ± 0.2 for oligomers prepared by γ-ray initiated, free-radical oligomerization of 0.20 mol kg^{-1} solution. (Denton, et al., 1993)

2. 3. Solubilization

Solutions were prepared by adding excess Oil Blue N (MP Biomedicals) to the surfactant solutions, sonicating for 30 minutes, allowing to settle overnight, and filtering (Millipore PVDF 0.45 μm) into glass cuvettes. Absorbance measurements were made at 600 nm with an Ocean Optics USB4000 UV/Visible spectrometer. All measurements were made at room temperature, 296 ± 2 K. The CMC values and solubilization powers, SP, were determined following the general approach described by Tehrani-Bagha and Holmberg (2013). The concentration of the dye, c_D, was plotted as a function of surfactant concentration, c_S, and a straight-line fit gave an x-intercepts equal to the CMCs and slopes equal to the SPs.

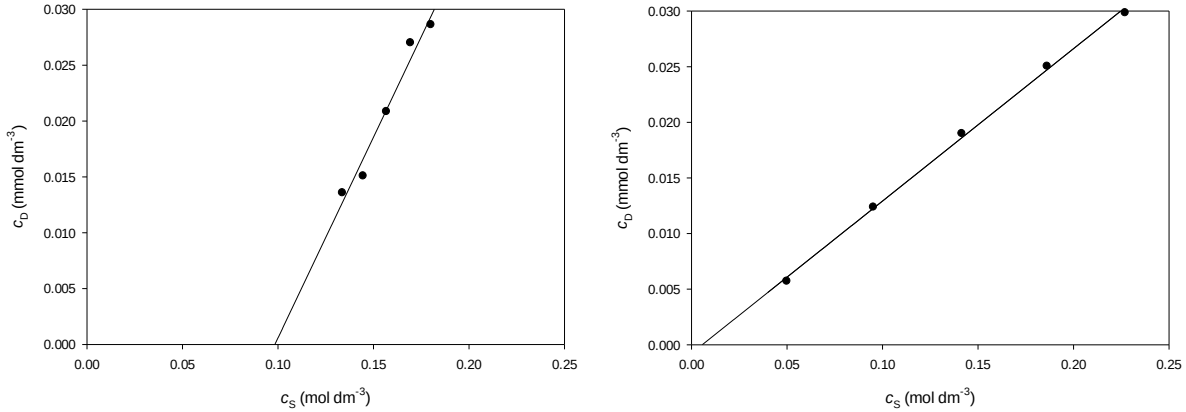

Figure 3. Dye solubilization as a function of concentration for monomeric NaU (left) and oligomeric NaU (right).

Table 1. Critical micelle concentration and solubilization power for monomeric and oligomeric NaU

	CMC (mol dm^{-3})	Std. Error	SP x 10^3	Std. Error x 10^3
Monomer	0.100	0.006	0.37	0.04
Oligomer	0.006	0.003	0.14	0.01

The CMC of the monomer determined by solubilization is not significantly different from that determined by conductance measurements ($t = 0.3$, $p = 0.8$). This agreement indicates that there is no significant change in micelle formation in the presence of the Oil Blue N substrate. The CMC of the oligomer is very much less than that of the monomer ($t = 20$, $p = 5 \times 10^{-7}$). The SP of the oligomer is also less than the SP of the monomer ($t = 8$. $P = 1 \times 10^{-4}$).

The closest study for comparison of solubilization by oligomeric surfactants is from Laschewsky, et al. (2005) and Wattebled, et al. (2006). They synthesized and characterized dimers, trimers, and tetramers based on dodecyltrimethylammonium chloride and benzyldodecyldimethylammonium chloride. Like NaU these oligomers aggregate to form small micelles in aqueous solution with aggregation numbers of 10.5 to 32 ± 0.5 monomer units per micelle. Unlike oligomeric NaU, where monomers are linked at the end of the hydrocarbon tails (T-type) these oligomers were formed with short spacer groups connecting the ammonium headgroups (H-type). The results of Laschewsky, et al. include a general systematic trend in CMC lowering with increasing degree of oligomerization consistent with the results for NaU oligomers. However, they did not observe any significant trend in SP with degree of oligomerization for the hydrophobic dye pinacyanol. The difference in location of oligomer bonding could explain the difference in trends of SP with degree of oligomerization. The ability to accommodate the substrate in the micelle core can be expected to be impaired by the restriction of movement of the hydrophobic tails in the T-type oligomer lowering its SP relative to the unrestricted interior of an H-type oligomeric micelle.

3. Conclusions

Oligomerization of NaU leads to micelle formation at a much lower CMC and as a result allows stable solubilization of Oil Blue N at much lower surfactant concentrations. This result is consistent with other reports of solubilization by oligomeric micelles and is probably a general tendency for oligomers of ordinary surfactants.

The SP of oligomeric NaU is lower than monomeric NaU for the relatively large and rigid substrate, Oil Blue N. This result may be limited to small, T-type oligomers and could potentially be an advantage in designing carriers for smaller substrates.

References

Brewer, E., Coleman, J., Lowman, A. (2011). Emerging Technologies of Polymeric Nanoparticles in Cancer Drug Delivery. Journal of Nanomaterials, 2011, 1-10.

Denton, J.M., Duecker, D.C., Sprague, E.D. (1993). Size and Solution Behavior of Sodium 10-undecenoate Oligomers. Journal of Physical Chemistry, 97, 756-762.

Durairaj, B., Blum, F.D. (1989) Synthesis and Dynamics of Oligomeric Micelles. Langmuir, 5, 370-372.

Larrabee, Jr., C.E., and Sprague, E.D. (1979). Radiation-Induced Polymerization of Sodium 10-Undecenoate in Aqueous Micelle Solutions. Journal of Polymer Science Part C Polymer Letters, 17, 749-757.

Laschewsky, A., Wattebled, L., Arotcarena, M., Habib-Jiwan, J.-L., Rakotoaly, R., H. (2005). Synthesis and Properties of Cationic Oligomeric Surfactants. Langmuir, 21, 7170-7179.

Sprague, E.D., Duecker, D.C., Larrabee Jr., C.E. (1983). The Effect of a Terminal Double Bond on the Micellization of a Simple Ionic Surfactant. Journal of Colloid and Interface Science, 92, 416-421.

Torchilin, V.P. (2001). Structure and design of polymeric surfactant-based drug delivery systems. Journal of Controlled Release 73, 137–172.

Tehrani-Bagha, A.R., Holmberg, K. (2013). Solubilization of Hydrophobic Dyes in Surfactant Solutions. Materials, 6, 580-608.

Wang, Z.W., Langer, R., Farokhzad, O.C. (2012). Nanoparticle Delivery of Cancer Drugs. Annual Review of Medicine, 63, 185-198.

Wattebled, L., Laschewsky, A., Mooussa, A, Habib-Jiwan, J.-L. (2006). Aggregation Numbers of Cationic Oligomeric Surfactants: A Time-Resolved Fluorescence Quenching Study. Langmuir, 22, 2551-2557.

Yue, J., Liu, S., Xie, Z., Xing, Y, Jing, X. (2013). Size-dependent biodistribution and antitumor efficacy of polymer micelle drug delivery systems. Journal of Materials Chemistry B, 1, 4273-4280.