

Effect of Increasing *N,N*-Dimethylformamide Concentration on the Structure of Polysorbate 80 Micelles

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Abstract: The structures of micelles of the surfactant polysorbate 80 (Tween 80) in 0-50% aqueous *N,N*-dimethylformamide (DMF) solutions (pH 7.2, ionic strength 2.44 mM) were investigated by means of small-angle X-ray scattering. At all the tested DMF concentrations, core-shell cylinder micelles formed; that is, increasing the concentration of DMF did not result in changes in the shape of the micelles. These results indicate that increasing the concentration of polar solvents does not always result in changes in the shapes of surfactant micelles.

Keywords: Micelle, small-angle X-ray scattering, micellar structure investigations, least-squares fit calculation, ternary system, core-shell cylinder micelles.

INTRODUCTION

In aqueous solution, surfactant molecules aggregate to form micelles at concentrations above the critical micelle concentration. The behavior of surfactant micelles in aqueous solution has been investigated extensively, but research on the behavior of micelles in aqueous solutions of polar solvents is limited. Polar solvents are soluble in both water and organic solvents. Clarification of how surfactant molecules form micelles and how changing the solvent from 100% water to mixtures of water and a polar solvent affects the shape and size of micelles is a desirable goal.

Polysorbate 80 (Tween 80), a hydrophilic non-ionic surfactant, is frequently used as an emulsifier and a dispersing agent for medicinal products designed for internal use. It contains hydrophilic groups (four polyoxyethylene groups and a tetrahydrofuran group) and a hydrophobic polyethylene tail (Fig. 1) [1].

In recent work, we used small-angle X-ray scattering (SAXS) to study the structures of polysorbate 80 micelles in 0-50% aqueous solutions of each of two polar solvents, 1,4-dioxane and dimethyl sulfoxide (DMSO), at pH 7.2 and ionic strength 2.44 mM. We found that polysorbate 80 micelles change from core-shell cylinder micelles to core-shell disc micelles between concentrations of 20 and 30% 1,4-dioxane, and from core-shell disc micelles to core-shell elliptical disc micelles between concentrations of 40 and 50% 1,4-dioxane. The micelles change from core-shell cylinder micelles to core-shell disc micelles between concentrations of 20 and 30% DMSO [2, 3]. That is, our results indicated that the concentration-dependent shape changes differ from these two polar solvents. Our findings suggest that additional polar solvents must be investigated individually

until enough information has been accumulated to allow predictions about untested solvents.

In this study, we therefore investigated the structures of polysorbate 80 micelles in *N,N*-dimethylformamide (DMF), a polar solvent that is used for the manufacture of Orlon and polyacrylic fibers and for the synthesis of organic compounds [4] and that has properties different from those of 1,4-dioxane and DMSO. We investigated the structure of polysorbate 80 micelles in aqueous DMF (pH 7.2, ionic strength 2.44 mM) by means of SAXS, which is the best technique for determining the three-dimensional structure of micelles in solution.

MATERIALS AND METHODOLOGY

Materials and Sample Preparation

Polysorbate 80 (Tween 80) and DMF were obtained from Nacalai Tesque (Kyoto, Japan), and disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) and sodium dihydrogen phosphate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) were obtained from Wako Pure Chemical Industries (Osaka, Japan). A mixture of 7.2 mmol $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 2.8 mmol $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ was dissolved in 1 L of water to give a 10 mM stock solution of sodium phosphate buffer (pH 7.2, ionic strength 24.4 mM). Polysorbate 80 was dissolved in the stock sodium phosphate buffer to give a 500 $\text{g} \cdot \text{L}^{-1}$ stock solution. The stock sodium phosphate buffer, stock polysorbate 80 solution, DMF, and water were mixed to give sample solutions that contained 0-50% DMF, 50 $\text{g} \cdot \text{L}^{-1}$ polysorbate 80, and 1 mM sodium phosphate buffer (pH 7.2, ionic strength 2.44 mM). In addition, the stock sodium phosphate buffer, DMF, and water were mixed to give reference solutions that contained 0-50% DMF and 1 mM sodium phosphate buffer.

SAXS Measurements and Analysis of SAXS Data

SAXS equipment for solution analysis, including optics and a detector system, were used for this study. The SAXS equipment is installed at the Energy Accelerator Research Organization in Tsukuba, Japan, and the specifications of

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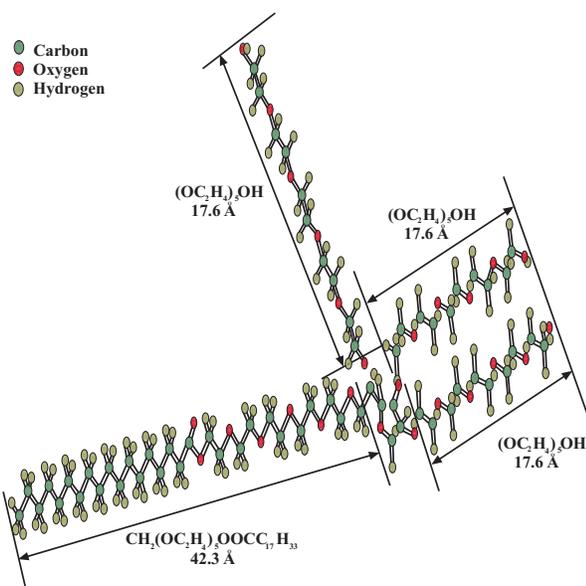


Fig. (1). Molecular structure of polysorbate 80.

this equipment have been reported in detail elsewhere [5, 6]. SAXS intensities were measured for 600 s for each surfactant solution and for a reference solution. By means of a previously described method [2], the intensities were calibrated and transformed into scattering cross-sections, $SCS(q)$, where q is the scattering vector [$q = (4\pi/\lambda) \sin \theta$, where λ is the wavelength of the X-rays and 2θ is the scattering angle].

Because polysorbate 80 forms core-shell cylinder micelles in 100% water [2], we also attempted to fit the SAXS data obtained at DMF concentrations between 0 and 50% to the core-shell cylinder model for dilute particle solutions. The core-shell cylinder model for dilute particle solutions is described mathematically below [2].

The scattering cross-section, $SCS(q)$, which does not take into account the structure factor (in dilute particle solutions), is given by

$$SCS(q) = nV^2 \Delta\beta^2 F(q)^2 \quad (1)$$

where n , $\Delta\beta$, and V are the number density of particles, the difference in scattering length density between the particles and the solvent or matrix, and the volume of particles, respectively; and $F(q)$ is the form factor. For the core-shell cylinder, V and $\Delta\beta^2 F(q)^2$ are given by

$$V = \pi(R + d)^2 H \quad (2)$$

and

$$\Delta\beta^2 F(q)^2 = \int_0^1 \{ [CF_1(q) + CF_2(q)] / CF_3(q) \}^2 dx \quad (3)$$

where

$$CF_1(q) = \{ 4R(\beta_{\text{core}} - \beta_{\text{shell}}) J_1[qR(1-x^2)^{1/2}] \sin(qHx/2) \} / [q^2 x(1-x^2)^{1/2}] \quad (4)$$

and

$$CF_2(q) = \{ 4(R+d)(\beta_{\text{shell}} - \beta_{\text{solvent}}) J_1[q(R+d)(1-x^2)^{1/2}] \sin(qHx/2) \} / [q^2 x(1-x^2)^{1/2}] \quad (5)$$

and

$$CF_3(q) = R^2 H(\beta_{\text{core}} - \beta_{\text{shell}}) + (R+d)^2 H(\beta_{\text{shell}} - \beta_{\text{solvent}}) \quad (6)$$

where R and β_{core} are the radius of the circular base of the core cylinder and the scattering length density of the core, respectively; d and β_{shell} are the length and the scattering length density of the shell, respectively; H is the height of the core-shell cylinder; β_{solvent} is the scattering length density of the solvent; $J_1(x)$ is first order Bessel function and x is distance on the x axis.

Six parameters (n , R , d , H , β_{core} , and β_{shell}) for equations (1) to (6) were determined by least-squares fit of the SAXS data to the model. Rough values of β_{core} and β_{shell} were estimated, and the exact value of β_{solvent} was determined from the density and the number of electrons in polysorbate 80 and the mixed solvents [2]. β_{core} is given by $(\rho_{\text{core}} N_{\text{e}_{\text{core}}} \text{Th} N_{\text{A}}) / M_{\text{core}}$, where ρ_{core} is the density of the core, $N_{\text{e}_{\text{core}}}$ is the number of electrons in the core molecule, N_{A} is Avogadro's number, Th is the Thomson radius, and M_{core} is the molecular weight of the core. β_{shell} is given by $(\rho_{\text{shell}} N_{\text{e}_{\text{shell}}} \text{Th} N_{\text{A}}) / M_{\text{shell}}$, where ρ_{shell} is the density of the shell, $N_{\text{e}_{\text{shell}}}$ is the number of electrons in the shell molecule, and M_{shell} is the molecular weight of the shell. β_{solvent} is given by $(\rho_{\text{solvent}} N_{\text{e}_{\text{solvent}}} \text{Th} N_{\text{A}}) / M_{\text{solvent}}$, where ρ_{solvent} is the density of the solvent, $N_{\text{e}_{\text{solvent}}}$ is the number of electrons in the solvent molecule, and M_{solvent} is the molecular weight of the solvent.

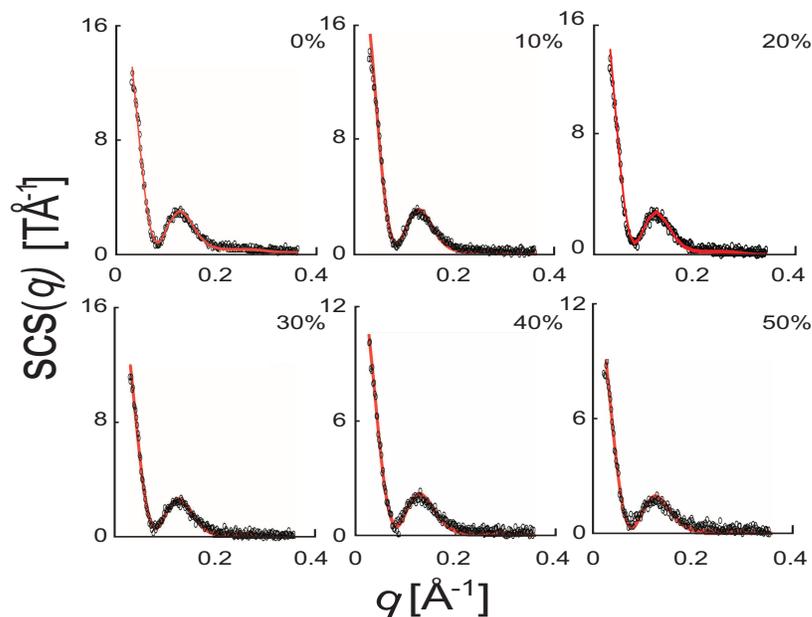
The density ($1.073 \text{ g}\cdot\text{cm}^{-3}$) of polysorbate 80 and the densities of the reference solvents were determined with a pycnometer, and the scattering length density ($10.12 \mu\text{Å}^{-2}$) of polysorbate 80 and the scattering length densities of the reference solvents were calculated from the above equation for β_{solvent} . The densities and scattering length densities are listed in Table 1. The least-squares fit calculation methods for the model and the SAXS data are described elsewhere [2].

RESULTS AND DISCUSSION

Because polysorbate 80 forms core-shell cylinder micelles in 100% water [2], we attempted to fit the SAXS data obtained at DMF concentrations between 0 and 50% to the core-shell cylinder model for dilute particle solutions. Scattering data obtained at these concentrations are shown in Fig. (2), along with curves fitted with the core-shell cylinder model. The DMF concentrations and shape parameters cal-

Table 1. Densities and Scattering Length Densities of the Reference Solvent

| DMF concentration (%) | 0 | 10 | 20 | 30 | 40 | 50 |
|---|-------|-------|-------|-------|-------|-------|
| Density (g·cm ⁻³) | 0.996 | 0.996 | 0.997 | 0.998 | 0.998 | 0.998 |
| Scattering length density (μÅ ⁻²) | 9.216 | 9.210 | 9.208 | 9.209 | 9.199 | 9.190 |

**Fig. (2).** Scattering data (circles) obtained at DMF concentrations between 0 and 50%, along with curves fitted to the core-shell cylinder model, $SCS(q) = 1$ (lines).

culated from the core-shell cylinder model for dilute particle solutions are listed in Table 2. This model provided the best fit for the SAXS data at 0-50% DMF. The SAXS data indicated that at concentrations of 0-50% DMF, polysorbate 80 formed core-shell cylinder micelles.

The formation of core-shell cylinder micelles from polysorbate 80 molecules is illustrated in Fig. (3). The molecules of polysorbate 80 adopt crown-like shapes, and when two of the crown-shaped molecules connect to each other, the hydrophobic polyethylene group of one molecule enters the space created by the four hydrophilic polyoxyethylene groups of the other molecule. The molecules aggregate into a “cylindrical” layer comprising four long chains entangled with one another through intra- and intermolecular interactions. The outer core-shell cylinder is covered with hydrophilic groups. There is a natural division between hydropho-

bicity and hydrophilicity in the inner region of the micelle because surfactants are amphipathic; that is, they contain both a hydrophobic group and a hydrophilic group. Polysorbate 80 molecules form hydrophobic-core/hydrophilic-shell micelles that are stable in aqueous solutions.

As the concentration of DMF was increased, the structures of the core-shell cylinder micelles did not change. This result confirms that increasing the concentration of a polar solvent does not always result in a change in the structures of the micelles and that further investigation will be required before micelle behavior in polar solvents can be predicted.

It is a commonly held belief among chemical physicists that because the hydrodynamically stable shape of a bubble in aqueous solutions is a sphere or an ellipsoid, the normal shape of an aqueous micelle is also a sphere or an ellipsoid. However, the thermodynamically favorable shape of mi-

Table 2. Shape Parameters for the Core-Shell Cylinder Model [$SCS(q) = 1$] at Various DMF Concentrations

| Concentration (%) | n (aÅ ⁻³) | R (Å) | d (Å) | H (Å) | β_{core} (μÅ ⁻²) | β_{shell} (μÅ ⁻²) |
|-------------------|-------------------------|---------|---------|---------|---|--|
| 0 | 57 | 10 | 32 | 55 | 7.656 | 9.497 |
| 10 | 67 | 10 | 32 | 57 | 7.656 | 9.497 |
| 20 | 63 | 9 | 31 | 53 | 7.656 | 9.497 |
| 30 | 63 | 9 | 31 | 53 | 7.656 | 9.497 |
| 40 | 51 | 9 | 30 | 55 | 7.656 | 9.497 |
| 50 | 45 | 10 | 29 | 61 | 7.656 | 9.497 |

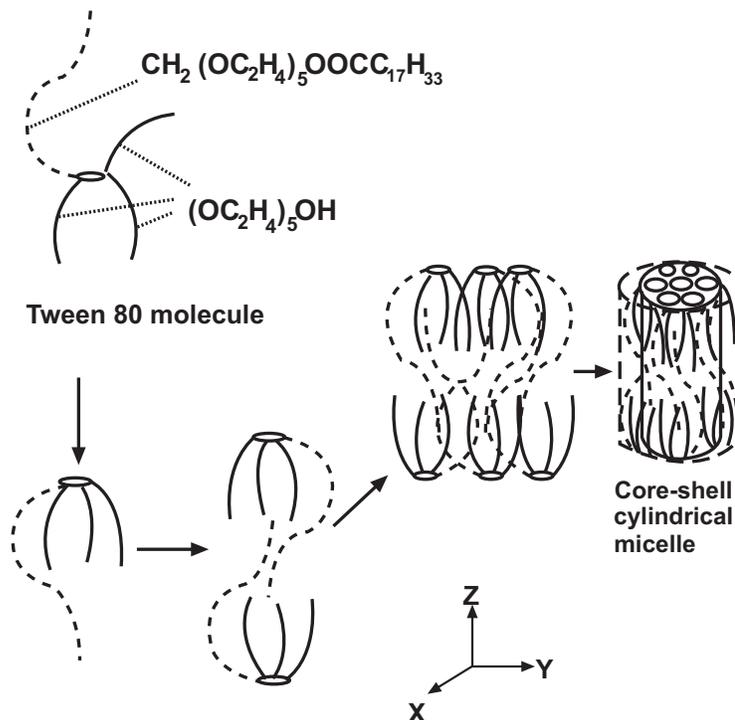


Fig. (3). Formation of micelles from polysorbate 80 molecules.

celles in aqueous DMF solutions (sphere, ellipsoid, or core-shell discus) cannot be predicted. Molecular dynamic simulation would be the method for predicting micelle shape and could corroborate the results described above. We hope to be able to carry out such simulation in future work.

CONCLUSION

The surfactant polysorbate 80 formed core-shell cylinder micelles in 0-50% aqueous DMF solutions (pH 7.2, ionic strength 2.44 mM); that is, increasing the concentration of DMF did not result in changes in the shape of the micelles. These results indicate that increasing the concentration of polar solvents does not always result in changes in the shapes of surfactant micelles.

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