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Aqueous Dispersions of Poly(ethylene oxide)-*b*-poly(γ-methyl-ϵ-caprolactone) Block Copolymers

John A. Zupancich,[†] Frank S. Bates,*,[†] and Marc A. Hillmyer*,[‡]

Department of Chemical Engineering and Materials Science and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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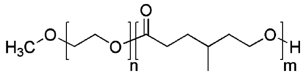
Amphiphilic block copolymer self-assembly has been utilized to fabricate a diverse array of structurally distinct nanoscale aggregates. The targeting of specific morphologies has been shown to be experimentally tractable through control of the copolymer composition[1,2] and the protocol employed in micelle preparation.[3,4] Spherical, cylindrical, and bilayered micelles, as well as more elaborate architectures, have been observed in dilute solutions of polymeric amphiphiles.[5,6] Desire to exploit the properties of block copolymer micelles in biomedical applications, namely the efficacious delivery of hydrophobic drugs sequestered within micellar cores, has roused interest in biocompatible and biodegradable amphiphiles.[7] The extreme hydrophobicity of typical block copolymer amphiphiles[8] and the semicrystalline and/or glassy nature of common degradable, hydrophobic polymers (e.g., the aliphatic polyesters polylactide and polycaprolactone) often necessitates the use of elevated temperature or an organic solvent to aid in dissolution and self-assembly.[9] Here, we demonstrate that spherical, cylindrical, and bilayered vesicle structures can be formed from dispersions of poly(ethylene oxide)-*b*-poly(γ-methyl-ϵ-caprolactone) (OMCL) in water. The micelles were generated at moderate temperatures (25−50 °C) without the use of a cosolvent and are comprised of a hydrophilic, biocompatible poly(ethylene oxide) block[10,11] and an amorphous, low-T_g (∼−60 °C) aliphatic polyester, poly(γ-methyl-ϵ-caprolactone) (PMCL).[12] The dependence of micelle structure on diblock composition was examined through the systematic variation of the PMCL block molecular weight. A continuous evolution of morphologies was observed, with coexistence of aggregate structures occurring in windows of composition intermediate to that of pure spheres, cylinders, and vesicles.

OMCL



Fourteen diblock copolymers (Table 1) were synthesized from a common α-methoxy-ω-hydroxypoly(ethylene oxide) (PEO, 1.9 kg mol^{-1}; Aldrich) by the aluminum-mediated ring-opening polymerization of γ-methyl-ϵ-caprolactone (MCL).[13] The PEO sample, characterized by MALDI time-of-flight mass spectrometry and SEC (Figure S1), was found to have a $M_n = 1.9$ kg mol^{-1} (MALDI) and a PDI of 1.08 by SEC and 1.02 by MALDI. The macroinitiator was prepared by the reaction of PEO with 1.1 equiv of triethylaluminum in the presence of pyridine. MCL was added directly to the macroinitiator solution, and polymerization yielded OMCL diblock copolymers characterized by monomodal molecular weight distributions (PDI < 1.3) (Figure S1) and varying PMCL block molecular weights (2.5k−9.5k) (Figure S2).[14] Aqueous solutions of OMCL diblocks were prepared by a thin-film hydration protocol in which OMCL was initially dissolved in methylene chloride and the solution was added to tared vials. Evaporation of the solvent yielded thin films on the sides of vials, and residual methylene chloride was removed from the polymer films by drying in vacuo overnight at 60 °C. An appropriate amount of Milli-Q water (Millipore Milli-Q system) was added to the dried films (1 wt % polymer in H_2O), and solutions were stirred in sealed vials at 25−50 °C for at least 1 week prior to analysis; identical results were obtained for all preparation temperatures.

Table 1. Molecular Characteristics of OMCL Diblock Copolymers

ID	M_n (kg mol^{-1})[a]	N_{PMCL}[b]	w_{PEO}[c]	PDI[d]	morphology[e]
OMCL1	11.4	74	0.17	1.25	V
OMCL2	10.3	66	0.18	1.23	V
OMCL3	9.9	63	0.19	1.19	V
OMCL4	9.6	60	0.20	1.20	V, C
OMCL5	8.9	55	0.21	1.28	V, C
OMCL6	8.3	50	0.23	1.22	C, V
OMCL7	7.9	47	0.24	1.22	C, V
OMCL8	7.3	42	0.26	1.20	C, V
OMCL9	6.8	38	0.28	1.22	C, V
OMCL10	6.4	35	0.30	1.23	C
OMCL11	5.8	30	0.33	1.20	C
OMCL12	5.6	29	0.34	1.23	C, S
OMCL13	5.2	26	0.36	1.20	S, C
OMCL14	4.4	16	0.43	1.20	S

[a] Number-average molecular weight of OMCL diblock copolymers as determined by ^{1}H NMR spectroscopy. [b] Number of monomer repeat units in PMCL block as determined by ^{1}H NMR spectroscopy. [c] Weight fraction of the PEO block as determined by ^{1}H NMR spectroscopy. [d] Polydispersity index determined from size exclusion chromatography. [e] Micelle structures formed in water identified with cryo-TEM: V = vesicles, C = cylinders, S = spheres. Predominant coexisting structure is listed first.

Solution morphologies were characterized with cryogenic transmission electron microscopy (cryo-TEM) which allows for direct visualization of the aggregate structures formed in water. A controlled environment vitrification system (CEVS) was employed in the preparation of cryo-TEM samples.[15] A drop of micelle solution at 25 °C was placed on a lacey carbon-supported TEM grid which was held by tweezers and suspended within the water vapor saturated chamber of the CEVS. Excess solution was removed through blotting with a piece of filter paper, and the remaining solution, held as films spanning the holes in the lacey carbon film, was allowed to relax for ∼20 s prior to the grid being plunged into a reservoir of liquid ethane (∼90 K) cooled by liquid nitrogen. Vitrified specimens, stored in liquid nitrogen prior to transferring and mounting on a cryogenic sample holder (Gatan 626), were examined with a JEOL 1210 TEM operated at 120 kV. Images were recorded on a Gatan 724 multiscan CCD and processed with DigitalMicrographs version 3.3.1. Aliquots of the micelle solutions were taken periodically and analyzed by SEC to ensure that hydrolytic degradation of the PMCL block did not occur prior to examination of the aggregate structures with cryo-TEM.[16]

Spherical micelles observed in a 1% aqueous solution of OMCL14 ($w_{PEO} = 0.43$) are shown in Figure 1A. The micellar cores, composed of the hydrophobic PMCL block, appear as dark spheres with an average diameter of 19 nm; this is comparable to the 21 nm core diameter reported for spherical

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* Authors for correspondence: bates@cems.umn.edu (F.S.B), hillmyer@chem.umn.edu (M.A.H).
[†] Department of Chemical Engineering and Materials Science.
[‡] Department of Chemistry.

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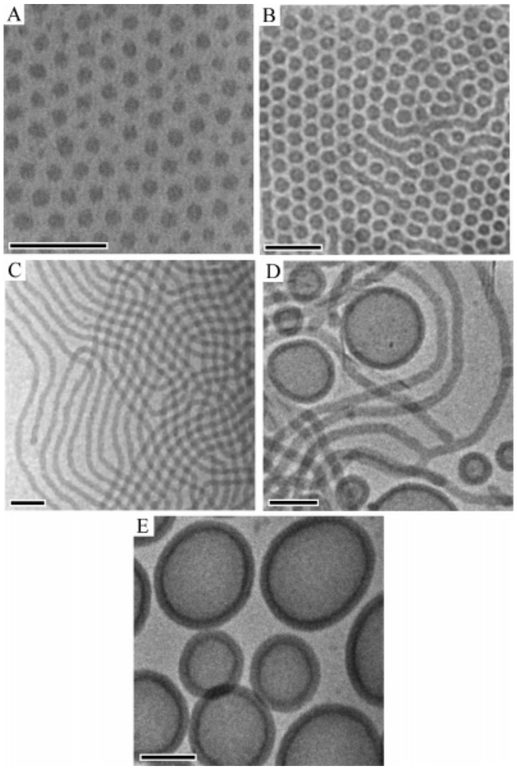

Figure 1. Cryo-TEM images obtained from 1 wt % H_2O solutions of (A) OMCL14 ($w_{PEO} = 0.43$), (B) OMCL13 ($w_{PEO} = 0.36$), (C) OMCL10 ($w_{PEO} = 0.30$), (D) OMCL7 ($w_{PEO} = 0.24$), or (E) OMCL1 ($w_{PEO} = 0.17$). Scale bars indicate100 nm.

micelles generated from poly(ethylene oxide)-*b*-poly(ϵ-caprolactone) containing the same number of core block repeat units.[17] The hydrated PEO chains that form the coronal domain do not provide enough contrast for direct observation, though their presence is evident by the apparent hexagonal packing of micelles confined to a single layer due to a film thickness that is comparable to the micellar diameter.

An increase in the molecular weight of the core block, and subsequent decrease in the diblock PEO weight fraction to 0.36, results in the onset of a shape transition from spherical to cylindrical aggregates. Figure 1B shows a set of fairly uniform spheres formed from a 1% solution of OMCL13. The spherical micelles have core diameters of 25 nm and are packed in a planar hexagonal geometry characterized by spacing comparable to the expected width of the coronal domain (~7 nm).[17,18] The coexistence of short cylindrical micelles with cross-sectional diameters of 18 nm is also evident. Undulations in the cross-sectional diameter of the cylinders suggest formation through coalescence of spherical micelles. The observed contour lengths of the cylinders are typically small, ranging from 70 to ~500 nm.

A further decrease in PEO composition reveals diblock self-assembly into extended cylindrical aggregates. In Figure 1C long, entangled cylindrical or wormlike micelles formed in a 1% aqueous solution of OMCL10 ($w_{PEO} = 0.30$) are clearly visible. These cylindrical micelles have an apparent core cross-sectional diameter of 21 nm and micelle lengths of at least several microns.[19] We could not obtain an average length due to the limited size of the images; however, lengths in excess of 5 μm were observed (Figure 2). Examination of large area micrographs shows long cylinders to be the dominant species in solution, with only occasional branch points or Y-junctions evident.[20]

Aqueous solutions of diblocks varying in PEO composition from 0.28 to 0.20 are marked by the presence of cylinders in conjunction with bilayered or vesicular aggregates. The coexistence of wormlike micelles with vesicles is shown in Figure 1D for a 1% solution of OMCL7 ($w_{PEO} = 0.24$). Extended cylinders with cross-sectional diameters of 23 nm were observed to be the majority species in solution. The cylindrical micelles are typically microns in length, though the occurrence of branching within wormlike micellar networks formed from diblocks with lower PEO composition is more frequent relative to wormlike micelles formed from OMCL10 ($w_{PEO} = 0.30$). The vesicles observed in a 1% aqueous solution of OMCL7 were generally spherical in shape and characterized by a bilayer thickness[21] of 16 nm and vesicle diameters typically less than 300 nm.

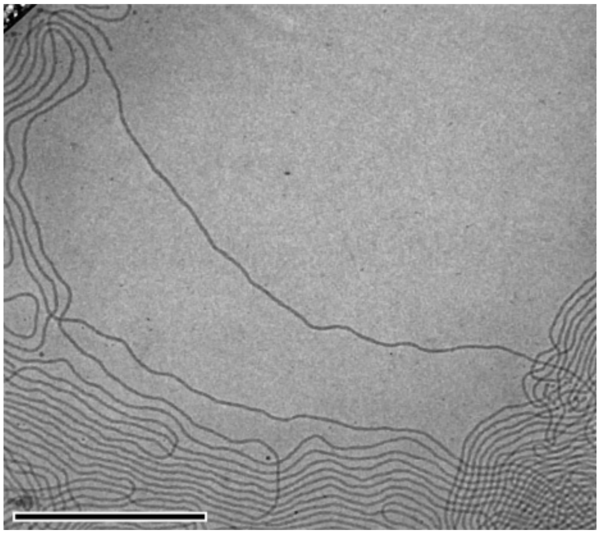

Figure 2. Cryo-TEM image of extended cylindrical micelles formed from OMCL10 ($w_{PEO} = 0.30$). Scale bar indicates 1 μm.

As the composition of OMCL diblocks falls below $w_{PEO} = 0.20$, bilayer structures emerge as the predominant species in solution. The shape and size of observed aggregates vary considerably; vesicles and bilayer sheets have widths that range from 100 nm to in excess of a micron. The vesicles evident in Figure 1E for a 1% solution of OMCL1 ($w_{PEO} = 0.17$) represent the more diminutive aggregate structures observed. However, the bilayer thickness, determined to be 18 nm for vesicles formed from OMCL1, was found to be independent of aggregate size.[22]

The evolution of aggregate structures formed from the self-assembly of OMCL diblock copolymers in water is analogous to that reported for other polymeric amphiphile systems.[20,23] As the hydrophobic content of the amphiphile is increased through the addition of PMCL, micelles develop morphologies with decreasing interfacial curvature, namely the progression from spheres to cylinders to bilayers. The progression of aggregate structure in polymeric amphiphiles through distinct regions of mixed morphology has been documented,[2,24] and coexistence is thought arise from the extremely hydrophobic nature of macromolecular surfactants and the inability of material exchange between aggregates to facilitate the achievement of global equilibrium.[25,26] Polydispersity of the constituent polymer molecules from which the aggregate is comprised may also contribute to the persistence of mixed morphologies;[26,27] however, the origin of coexistence is more likely a consequence of the kinetic trapping of structures formed upon dissolution of the polymer in selective solvent.

Previous efforts to generate self-assembled structures from polycaprolactone-based amphiphiles have typically utilized block copolymers containing a large hydrophilic component and resulted in the formation of spherical micelles.[17,28–30] Recently, poly(ethylene oxide)-*b*-poly(ϵ-caprolactone) block copolymers, in which the hydrophilic block was a minority component, were used to create cylindrical micelles and vesicles. In the case of cylindrical micelles ($w_{PEO} = 0.42$), a cosolvent was required for self-assembly,[19] whereas heating above the melting transitions of both blocks facilitated the formation of vesicles ($w_{PEO} = 0.14$).[22] OMCL diblock copolymers, comprised of a methyl-substituted, amorphous poly(ϵ-caprolactone) derivative, have only been used to prepare spherical micelles.[17,28] The results described in this report identify a promising approach for producing biocompatible and biodegradable dispersions under physiological conditions.

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Supporting Information Available: Figures S1 and S2 and the experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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