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ARTICLE TYPE

Effects of Interfacial Tension on Formation of Poly(ethylene oxide)-*block*-Polystyrene Micelles from Emulsions

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In this report, we show that the structure of an amphiphilic block copolymer assembled through the emulsion and solvent evaporation method can be regulated by tuning the interfacial tension with a third solvent. Microspheres were obtained when a poly(ethylene oxide)-*block*-polystyrene copolymer was self-assembled by emulsification of its chloroform solution in water. Addition of water-miscible tetrahydrofuran or N,N-dimethylformamide into the aqueous phase by 20 vol% was shown to reduce the interfacial tension between chloroform and water significantly, and strings of vesicles became the dominant structure. Addition of ethanol by 15, 50 and 100 vol% was found to produce strings of vesicles, cylinders and microspheres, respectively. Introduction of cyclohexane, a hydrocarbon solvent, into the organic phase of 1,2-dichloroethane increased the interfacial tension with the aqueous phase, and vesicles were observed instead of the strings of spheres obtained previously. The different assembled structures are discussed in terms of interfacial curvature driven by variation in the interfacial tension.

Introduction

Amphiphilic block copolymers have attracted great interest as vehicles for diagnoses and/or therapies in biomedical applications.¹⁻⁴ Owing to their propensity to self-assemble in selective solvents into robust aggregates, amphiphilic copolymers can carry active ingredients that are either hydrophilic or hydrophobic. It was recently revealed that the biological fate of the delivery system is closely related to its structure. For instance, filaments with lengths of up to 18 μm exhibited a circulation time ten times longer than their spherical cousins.⁵⁻⁷ So far, spheres, cylinders, vesicles and other more exotic structures with tailored sizes have been prepared through careful manipulation of the interactions between the copolymer components and the solvent.^{8,9} Assembly is governed by the intrinsic properties of the copolymer, such as the architecture, the block ratio, the molecular weight and so on,^{4,10} as well as external conditions, including temperature, foreign reagents, external fields, solvents, etc.¹¹⁻¹⁵ The latter provide convenient control over structure without resorting to tedious synthesis and thus have become methods of choice.

While the dominant approach to block copolymer assemblies involves addition of a selective solvent into the copolymer solution to gradually decrease the solvent quality for one block,^{8,9} the emulsification and solvent evaporation method has generated considerable interest recently.¹⁶⁻²⁰ In this method, the amphiphilic copolymer solution in a water-immiscible organic solvent is poured into water, a selective solvent, and an emulsion is formed because of the immiscibility between the two solvents. The copolymer then assembles at the organic/water interface of the

emulsion and produces aggregates when the volatile organic solvent evaporates. This method brings some unique advantages. For example, giant worms can be obtained, which effectively encapsulate nanoparticles, and exotic structures with nanoscopic hydrophobic or aqueous domains evenly distributed over the worm-like micelles have been reported.^{17,18} So far, factors such as copolymer composition (through varying either block ratio or blend composition) and co-surfactant concentration have been utilized to regulate the structure of the micelles thus obtained.^{17,19} In the present study, we introduce a third solvent (in addition to water and the common organic solvent used to dissolve the copolymer) in the emulsification and solvent evaporation method to alter the interfacial tension between water and the organic phase and investigate its impact upon the structure of amphiphilic copolymers assembled.

Experimental Section

Materials. PEO_{7k}-*b*-PS_{23k} (poly(ethylene oxide)-*block*-polystyrene, the subscripts referring to the number-average molecular weight of the respective blocks, with a polydispersity index (PDI) of 1.05) was purchased from Polymer Source. PEO_{5k}-*b*-PS_{4.2k} (PDI~1.5) was synthesized following a procedure described in the literature.²¹ Poly(vinyl alcohol) (PVA, $M_w = 8.7\text{--}12.4$ kg/mol, 87~89% hydrolyzed) was purchased from Sigma-Aldrich. Sodium dodecyl sulfate (SDS) was obtained from J&K Scientific Ltd. Chloroform, 1,2-dichloroethane, tetrahydrofuran (THF), N,N-dimethylformamide (DMF), ethanol, and cyclohexane were purchased from Beijing Chemical Works. All materials were used without further purification. Ultrapure

water (18.2 M Ω -cm) was obtained from a PGeneral GWA-UN Pure Water System and used for all experiments.

Micelle Preparation. For water-miscible third solvents, 200 μ L THF or DMF was blended with 800 μ L aqueous solution of PVA (2 mg/mL) to give a mixture of 1 mL, while 150 μ L ethanol was mixed with 850 μ L PVA solution because of its high surface activity. Then, 100 μ L of the PEO-*b*-PS solution (10 mg/mL) in chloroform, a water-immiscible common solvent, was introduced into this mixture under stirring to produce an emulsion. The emulsion was stirred for overnight. For cyclohexane, a third solvent that is immiscible with water, the procedure was the same except that cyclohexane was added into the common solvent 1,2-dichloroethane. In experiments with SDS, the copolymer solution was added into the aqueous solution of SDS.

Characterization. Transmission electron microscopy (TEM) characterization was carried out on a JEOL JEM-1011 microscope operating at an accelerating voltage of 100 kV. A drop of the micelle solution was placed onto a carbon-coated copper grid and allowed to evaporate for 30 min, and the remaining solution was then blotted away using a strip of filter paper. The specimen was then negatively stained using a phosphotungstic acid solution (1 wt.%) for 2 min followed by drying in atmosphere at ambient temperature before TEM characterization. The interfacial tension was measured using the pendant drop method, where the drop profile is determined by a hydrodynamic balance between gravity and the surface force acting on the drop.^{22,23} Before each measurement, the solvents were brought into contact with each other at set ratios and allowed to equilibrate for several hours. The measurements were performed on a ramé-hart Instruments 200-F1 goniometer connected to a computer. A stainless steel needle with an external diameter of 0.45 mm was used. Detailed drop shape parameters and analyses are included in Supplementary Information.

Results and Discussion

Solvents greatly impact block copolymer assemblies, adjusting the stretching (deformation) of the blocks in the core, modifying the interface between the core and the solvent, and altering the repulsion among the blocks in the corona.¹⁴ The emulsification and evaporation method, where water and a water-immiscible organic solvent are involved, is no exception. As shown in Figure 1a, PEO_{7k}-*b*-PS_{23k} self-assembled into microspheres by emulsification of its chloroform solution in an aqueous phase containing PVA as a surfactant to stabilize the emulsion droplets,¹⁷ an outcome consistent with a literature report.²⁴ Then, a third solvent was introduced into the system in an attempt to regulate the structure of the micelles produced. The influence of two commonly used solvents, THF and DMF, was explored. Because both are miscible with water, each was added to the aqueous phase before the emulsification. As can be seen from the TEM images in Figures 1b and 1c, strings of vesicles were produced when the aqueous phase contains 20% THF or DMF. This variation from microspheres to strings of vesicles parallels the more commonly encountered vesicle-to-sphere transition in terms of interfacial curvature.

As listed in Table 1, the solubility parameter of THF is similar to that of chloroform, and both are close to that of PS. Thus the addition of THF is unlikely to alter the extent of stretching of the

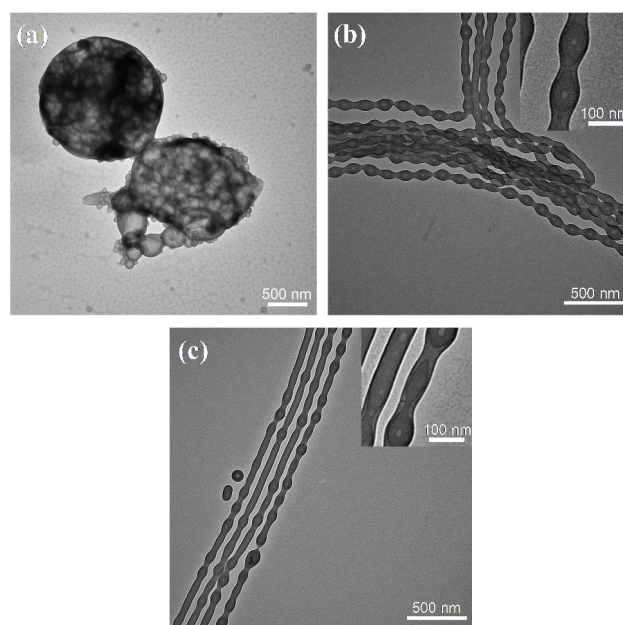


Figure 1. TEM images of PEO_{7k}-*b*-PS_{23k} micelles formed by emulsification of its chloroform solution in a PVA solution (a) in the absence of a third solvent, and with 20% v/v (b) THF and (c) DMF as a third solvent in the aqueous phase, respectively. Insets are enlarged views of the vesicles.

Table 1. Relevant Parameters of Different Solvents.

solvent	γ (mN m ⁻¹)	T_b (°C)	δ ([MPa] ^{1/2})
ethanol		79	26.4
THF		66	18.6
DMF		153	24.8
chloroform	32.8	61	19.0
1,2-dichloroethane	28.4	83	20.0
cyclohexane	50.2	81	14.7

γ : interfacial tension between the solvent and water; T_b : boiling temperature; δ : solubility parameter. δ_{PS} and δ_{PEO} were 18.7 and 20.3 [MPa]^{1/2}, respectively.²⁵

PS blocks in the core. On the other hand, it has been reported in the literature that introduction of a surface active solvent such as acetone and acetic acid into a water/oil system can greatly decrease the interfacial tension.²⁶ THF, a polar molecule composed of a hydrophilic ether group and a hydrocarbon part, is expected to decrease the interfacial tension between water and oil. As measured by the pendant drop method, the interfacial tension between chloroform and water was 33 mN/m, whereas addition of 20% THF (volume fraction) into the water phase reduced this value to \sim 9 mN/m (Supplementary Information). In addition, the presence of THF also decreases the interfacial tension between PS and water.²⁷ Therefore, addition of THF into water would reduce the interfacial tension between the solvent-swollen core and water, and as a result, the interfacial area per copolymer chain increases to relieve the repulsion between the blocks in the shell, leading to a higher curvature of the interface. From the above discussion, we conclude that the decrease in the interfacial tension is responsible for the morphology change from microspheres to strings of vesicles, a transition accompanied by increase in the interfacial curvature. The same argument applies

to DMF; addition of 20% DMF into water reduced the interfacial tension between chloroform and water to ~ 14 mN/m (Supplementary Information), and led to similar interfacial curvature increase and morphology change. However, the effects of DMF were more pronounced, with many more cylinders in the structure produced (Figure 1c). According to the solubility parameters in Table 1 and previous experimental results,²⁸ DMF is not as good a solvent for PS as either chloroform or THF, and so the swelling of the PS core or the stretching of the PS blocks in the core is reduced when DMF is introduced as compared to in chloroform or chloroform/THF. In addition, DMF is much less volatile than THF, as judged by the boiling points in Table 1, and remains in the system at a higher content than THF to lower the interfacial tension during the assembly process. These two factors contributed to the higher cylinder contents observed when DMF was employed.

However, when THF or DMF is employed as the third solvent for the chloroform/water system, the extent of modification is limited because the micelles disassemble at high THF or DMF contents. Ethanol, on the other hand, is a non-solvent for PS and a good solvent for PEO at mild temperatures or in the presence of a small amount of water²⁹ and can be used to further regulate the structure of the copolymer assembly. As given in Figure 2, strings of vesicles, cylinders, and spheres were obtained when ethanol was added to the aqueous phase with a volume fraction of 15, 50, and 100%, respectively, indicating that additional structures are made available by this approach. It is also interesting to compare the effects of ethanol with THF and DMF as the third solvent. While the interfacial tension between chloroform and water in the presence of 15% ethanol was 15 mN/m, slightly higher than that with THF and DMF (Supplementary Information), the fraction of cylindrical structure in Figure 2a is higher than that produced

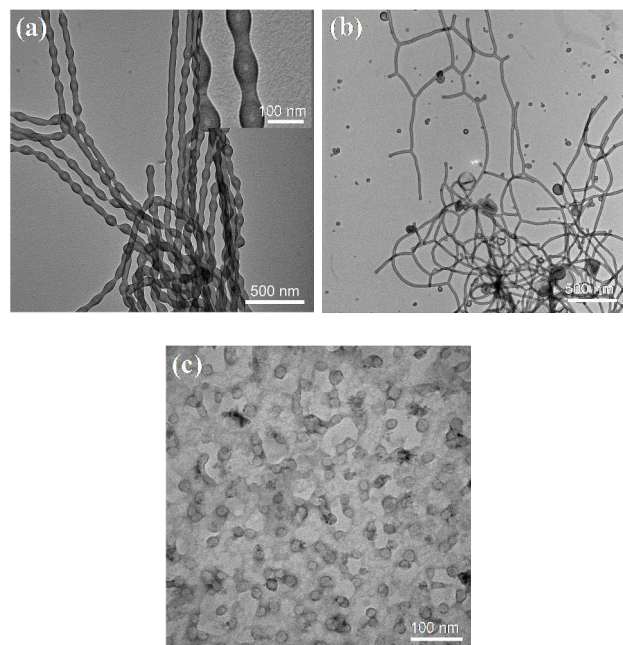


Figure 2. TEM images of PEO_{7k}-*b*-PS_{23k} micelles formed by emulsification of its chloroform solution in a PVA solution containing ethanol as a third solvent with a volume fraction of (a) 15%, (b) 50%, and (c) 100%, respectively. Inset in (a) is an enlarged view of the vesicles.

with THF (Figure 1b) and lower than that with DMF (Figure 1c). This again may be rationalized on the basis of the boiling temperatures in Table 1. A more volatile solvent evaporates faster and its reduction of the interfacial tension during the assembly process becomes less significant. In addition, it should be mentioned that at high ethanol concentrations chloroform can diffuse into the aqueous phase due to its compatibility with ethanol, and the conformational adjustment of the copolymer is arrested quickly. In other words, the acquisition of cylinders or spheres is partially influenced by the kinetics in addition to the thermodynamic modification of the interfacial tension.

The results and discussion thus far have demonstrated that the reduction of the interfacial tension can lead to copolymer assemblies with higher interfacial curvatures. Analogously, increasing the interfacial tension is expected to drive assembly in the opposite direction. Here, added into the common solvent rather than the aqueous phase due to miscibility consideration, a hydrocarbon was employed as a third solvent to increase the interfacial tension between the aqueous and oil phases. In particular, 1,2-dichloroethane and cyclohexane was chosen as the common solvent and the third solvent, respectively, which exhibits similar volatility (Table 1) so that the solvent composition variation over the micelle formation process should be insignificant. As seen in the TEM micrographs in Figure 3, PEO_{7k}-*b*-PS_{23k} assembled into strings of spherical micelles by emulsification of its 1,2-dichloroethane solution in an aqueous phase containing SDS as a surfactant, whereas vesicles were produced when cyclohexane was added to the 1,2-dichloroethane with a volume fraction of 40%, which raised the interfacial tension between the oil and the water from 28.4 mN/m to 33 mN/m (Supplementary Information). When the volume fraction

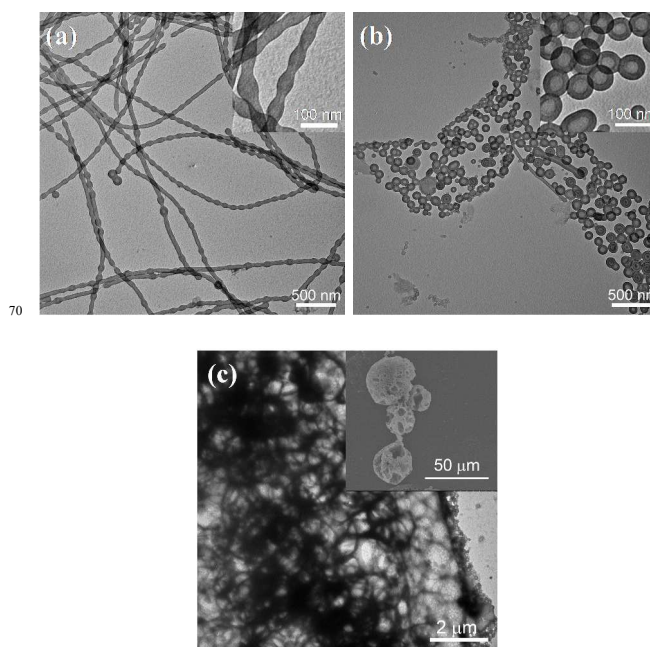


Figure 3. TEM images of PEO_{7k}-*b*-PS_{23k} micelles formed by emulsification of its solution in 1,2-dichloroethane containing (a) 0, (b) 40, and (c) 60% cyclohexane in water with 0.8 mg/mL SDS. Insets in (a) and (b) show enlarged views of strings of spheres and vesicles, respectively, and the inset in (c) is a global view of the microspheres.

of cyclohexane was further increased to 60%, microspheres were observed. These results clearly show interfacial curvature decreasing in the presence of cyclohexane. Since cyclohexane is not as good a solvent for the PS block as 1,2-dichloroethane, judged from the solubility parameters (Table 1), the presence of cyclohexane in the organic phase should suppress the stretching of the PS core block and thus lead to a higher interfacial curvature. Therefore, the opposite trend observed can only be attributed to the increase in the interfacial tension between the organic and aqueous phases with the introduction of cyclohexane, the contact area between the core and water further reduced to minimize the surface energy. In a separate experiment without SDS, cylindrical micelles of PEO_{5k}-*b*-PS_{4.2k} were found to dominate when the common solvent was 1,2-dichloroethane, and in contrast, a significant fraction of vesicles was observed in the presence of cyclohexane (Figure 4), again indicating the impact of a higher interfacial tension to the structure of the copolymer assembly.

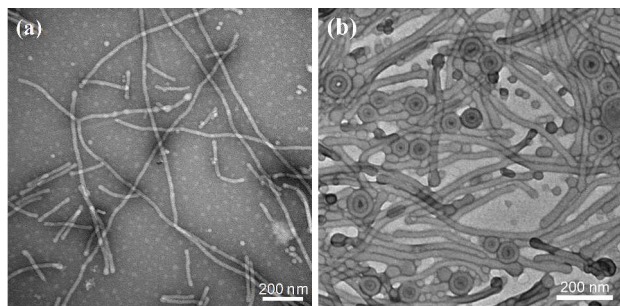


Figure 4. TEM images of PEO_{5k}-*b*-PS_{4.2k} assembled by emulsification in water without SDS of its solution in 1,2-dichloroethane containing (a) 0 and (b) 40% cyclohexane.

Conclusions

We have demonstrated experimentally that a third solvent, by modifying the interfacial tension between the oil and aqueous phases, can be harnessed to manipulate the structure of amphiphilic block copolymer assemblies obtained through the emulsification and solvent evaporation method. Upon addition of THF or DMF into the aqueous phase, the reduced interfacial tension drives microspheres into strings of vesicles, a transformation accompanied by an increase in the interfacial curvature. On the other hand, the presence of a hydrocarbon in the organic phase increased the interfacial tension, and in the case of cyclohexane with 1,2-dichloroethane, vesicles were produced instead of strings of spherical micelles, which paralleled a decrease in the interfacial curvature. This work largely expands the scope and the flexibility of the emulsion and solvent evaporation method while providing a facile approach to structure regulation for block copolymer assemblies with potential application in various fields.

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Notes and references

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