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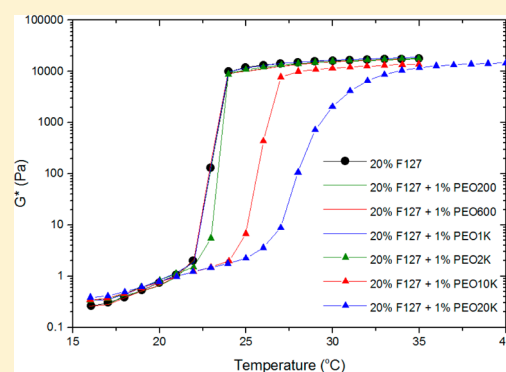
Effect of Chain Length of PEO on the Gelation and Micellization of the Pluronic F127 Copolymer Aqueous System

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S Supporting Information

ABSTRACT: The effect of adding homopolymer poly(ethylene oxide) (PEO) on the sol/gel behavior of amphiphilic triblock copolymer Pluronic F127 ((EO)₉₈(PO)₆₇(EO)₉₈) in aqueous media is explored. Emphasis is placed on the influence of the PEO molecular weight and concentration on micellization and gelation and the exploration of their correlation. PEO is always found to lower the critical micellization temperature modestly. However, short PEO chains promote the gelation of F127, and long chains delay or even curb gel formation. Micelle size measurements and cryo-TEM micrographs provide evidence for micellar aggregation via the bridging of long PEO chains or depletion flocculation, thereby impeding the ordering of micelles for gel formation.



1. INTRODUCTION

Pluronic is an amphiphilic nonionic triblock copolymer (ABA type) with poly(propylene oxide) (PPO) groups as the central block and poly(ethylene oxide) (PEO) groups as the outer blocks. The block lengths can be adjusted to produce Pluronics of various PPO and PEO chain lengths, and this series of triblock copolymers is called a Pluronic grid.¹ The ability of these polymers to form thermoreversible micelles and gels has created substantial interest in their use in pharmaceutical applications. The self-assembly of block copolymers is also used to produce nanostructures for many other applications.^{2–6} For example, thin films made of block copolymers can provide well-defined patterning of semiconductor surfaces because of their ability to produce ordered templates.^{7–10}

Among various Pluronic species, F127 is the most widely studied copolymer owing to its high stability, bioadhesive characteristics, thermoreversible gelling ability at room temperature, and nontoxic properties, which all make it a suitable vehicle for drug formulations.^{1,11,12} To tune the properties of F127 to match the particular needs of a specific application, different additives are incorporated into the F127 gel. For instance, the gel strength of F127 can be modified by adding inorganic salts and organic solvents, thereby influencing the drug release rate of the gel,^{13,14} and the local bioavailability can be increased by the addition of polymers such as methylcellulose and hydroxypropyl methylcellulose to F127.¹⁵ Apart from the above-mentioned gel property tuning, what is equally or more important is the modification of the critical micellization temperature (CMT) and the critical gelation temperature (CGT) because most of the pharmaceutical and pharmacological applications rely on the temperature dependence of self-assembly and its properties. Many additives (e.g., sodium chloride (NaCl), calcium chloride (CaCl₂), sodium

alginate, and Carbopol) have been reported to reduce the CGT of F127.^{11,16,17} In contrast, very few additives can increase the CGT; one among them is the PEO homopolymer.

Gilbert et al.¹⁸ were the first to report the rise in CGT of F127 in the presence of PEO homopolymer with molecular weights (MWs) of 2k, 10k and 20k g/mol based on the tube-inversion method. A similar finding for gelation suppression using rheometry¹⁹ was later documented along with a decrease in the storage modulus.²⁰ It was also reported that the solubility of a hydrophobic drug in the F127/water system can be increased by the addition of a small amount of PEO.²¹ For PEO with MW ≤ 1000 g/mol, however, the CGT of F127 was found to decline in the study by Zhang et al.,²² where PLGA-PEO-PLGA was the main copolymer in their investigation, with PLGA denoting poly(lactic acid-co-glycolic acid). They proposed and addressed several mechanisms to account for the experimentally observed effect of PEO. Despite the existence of the aforementioned gelation studies, there are only a few investigations on the micellization and its correlation with gelation of F127 in the presence of PEO. Only in a very recent work did Ricardo et al.²⁰ use dynamic light scattering to measure the micelle size of F127 with added PEO (MW = 6k and 35k) along with an examination of gelation by rheometry and small-angle X-ray scattering. They reported an increase in micelle size and a face-centered-cubic structure of the formed gels.

Whether it is the micellization/gelation aspect for pharmaceutical applications or the structural ordering aspect for lithographic applications, a sound understanding of the

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interaction and self-assembly behavior of Pluronic with additives is of utmost importance. To seek insight into the underlying mechanisms, we investigate the micellization and gelation of F127 with the addition of PEO homopolymer over a wide range of molecular weight (200–35k g/mol) in this study. The focus is placed on the effects of the chain length and concentration of PEO on CMT, micelle size, CGT, gelation time, and gel strength. We intend to explore how the added PEO affects the self-assembly behavior and microstructure and seek a correlation between micellization and gelation.

2. EXPERIMENTAL SECTION

2.1. Materials and Sample Preparation. Pluronic F127 copolymer and PEO homopolymer of different MWs (200, 600, 1k, 2k, 10k, 20k, and 35k g/mol) were obtained from Sigma-Aldrich. The molecular weight dispersity of each PEO was examined with gel permeation chromatography and was found to be rather monodisperse (Table S1 in SI). Hereafter, each PEO is denoted by PEO#, with # being its MW. Millipore water with a resistivity of 18 M Ω cm was used throughout the study. All materials were used as received. An appropriate amount of F127 was dissolved in Millipore water or in an appropriate weight percentage of PEO solutions by cold method.¹ The solution was allowed to stand below 5 °C for 2 days prior to any experiment to remove air bubbles and to achieve equilibrium. All samples prepared in weight to weight percentages (w/w %).

2.2. Tube Inversion Technique. The critical gelation temperature (CGT) of each sample was determined using the tube-inversion technique in order to make a comparison with that inferred by rheometry. A test tube filled with the sample was immersed in a water bath at 15 °C. The temperature of the water bath was increased in steps of 0.1 °C and allowed to equilibrate for 10 min at each step. The test tube was tilted 90°, and the flow was observed visually. The temperature at which the sample does not flow is taken as the gelation point.

2.3. Dynamic Light Scattering (DLS). DLS measurements were made using a Zetasizer Nano ZS (Malvern), which applies back scattering to measure the intensity-weighted size distribution. The sample was filtered through a 0.2 μ m Millipore filter to prevent any dust particles from affecting the results. The temperature was controlled using a Peltier unit system with an accuracy of ± 0.1 °C at 25 °C and ± 0.5 °C at 90 °C. A waiting time of 10 min at an appropriate temperature was allowed prior to any experiment.

2.4. Differential Scanning Calorimetry (DSC). A Mettler Toledo DSC822 differential scanning calorimeter was used to study the critical micellization temperature (CMT) of the samples. An aluminum crucible was filled with 20 to 30 mg of the sample, and an empty crucible was used as the reference. Temperature scans were performed from 0 to 30 °C at a rate of 1 °C/min.

2.5. Oscillatory Rheometry. A Haake Rheo Stress 600 rheometer with cone and plate geometry (C60/4, diameter 60 mm and angle 4°) was used to characterize the rheological properties. In the linear viscoelastic regime, oscillatory temperature sweeps (1 Hz and 2 Pa) were carried out to find the CGT from the crossover of storage and loss moduli. A Peltier controller unit was used to control the temperature of the sample with an accuracy of 0.1 °C. Temperature was increased from 16 to 45 °C at a rate of 1 °C/min. Oscillatory stress sweeps (1 Hz and 37 °C) were also carried out to find the storage modulus plateau and the yield stress of the samples.

2.6. Nuclear Magnetic Resonance (NMR). NMR measurements were performed on a Bruker DRX 500 operating at 500 MHz for proton spectra and 125 MHz for carbon spectra. The temperature was controlled using a Bruker temperature control unit, and the samples were equilibrated at their respective temperatures for 15 min before every measurement.

2.7. Cryogenic Transmission Electron Microscopy (Cryo-TEM). Cryo-TEM micrographs were obtained using a Jeol JEM 2010F. Samples were prepared in the way mentioned by Lam et al.²³ and were maintained at 30 °C before they were frozen. A 3 μ L portion of the

sample was pipetted onto the grid maintained at high humidity in the FEI Vitrobot Mark IV. A blotting time of 5–10 s was used before the grid was plunged into liquid ethane. The sample was then transferred to the cryo-TEM using a Gatan cryoholder to keep the sample at liquid-nitrogen temperature.

3. RESULTS AND DISCUSSION

3.1. Gelation Temperature. The critical gelation temperature (CGT) can be determined by different methods, and the result can slightly vary from one method to another.²⁴ In this study, the crossover between the storage and loss moduli (G' and G'' , respectively) obtained from an oscillatory temperature sweep (1 Hz and 2 Pa) in the linear viscoelastic regime is taken to be the CGT.^{25,26} To illustrate the sharp change in mechanical properties upon gelation, we plot the complex modulus G^* against the temperature for F127 without and with added PEO in Figure 1. We observe that for high MW PEO

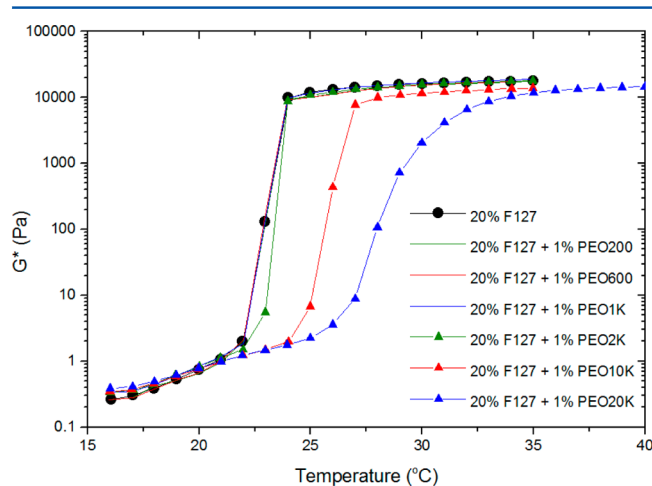


Figure 1. Effects of MW of PEO on the gelation of the F127/water system with F127 at 20 wt %.

(2k–35k) the gelation is delayed to a higher temperature and the extent of this delay is higher for larger PEO MW. This behavior is in good agreement with that reported in the literature.^{18,19} For PEO with a shorter chain length (MW = 200–1k), 1% PEO did not make noticeable changes in the CGT. However, at higher concentration (8%) the CGT is decreased slightly, and the decline is more at lower molecular weight (Figure S1 in SI). The estimated CGT is presented in Tables 1 and S2 to show the effects of PEO MW and concentration, respectively.

Our finding contradicts the behavior reported by Zhang et al. in which the extent of CGT decline increases with PEO MW²² on the basis of tube inversion. To determine if the discrepancy arises from different methods to determine CGT, we also applied the tube-inversion method and included the results in parentheses in Table 1 for comparison. As seen, the trend remains unchanged although the CGT is slightly lower for each case. The higher CGT by rheometry is due to the temperature ramp speed.²⁴ On the basis of our finding of different trends for CGT, we classify the PEO studied in this work into two classes (A and B) for convenience as shown in Tables 1 and S2. The deviation of CGT from the value of the pure F127 solution always increases with increasing PEO concentration, regardless of the class (Table S2 in SI), but it generally requires a higher concentration for class A than for class B to see a noticeable deviation.

Table 1. Effects of Molecular Weight of PEO on CGT, t_{gel} , τ_{co} , and G_0' of 20 wt % F127^a

	PEO MW (g/mol)	CGT (°C)	t_{gel} (s)	τ_{co} (Pa)	G_0' (kPa)
20 wt % F127		23.0 (22.2)	137	310	21.4
class A PEO conc = 8 wt %	200	20.0 (18.8)	131	328	21.3
	600	20.3 (19.0)	133	281	17.9
	1k	21.0 (19.8)	135	245	16.4
class B PEO conc = 1 wt %	2k	23.5	138	283	19.4
	10k	25.6	229	226	14.9
	20k	28.5	606	180	12.0
	35k	33.0		12	1.5

^aEstimated uncertainties: CGT ± 0.5 °C (± 0.1 °C), $t_{\text{gel}} \pm 5.0$ s, $\tau_{\text{co}} \pm 5.0$ Pa, $G_0' \pm 1$ kPa.

3.2. Gelation Time and Gel Strength. To examine the effect of added PEO on the gel properties, we measure the gelation time and gel strength using oscillatory rheometry. The loss factor $\tan(\Theta) = G''/G'$ provides a gauge for the classification of a material: $\tan(\Theta) > 1$ for liquid, $0.1 < \tan(\Theta) < 1$ for a weak gel, and $\tan(\Theta) < 0.1$ for a strong gel.²⁷ The time interval between the point at which $\tan(\Theta)$ reaches the maximum and the point at which $\tan(\Theta)$ drops to 0.1 is taken as an estimate of the gelation time t_{gel} as illustrated in Figure S2 in SI. Note that the initial increase in the loss factor arises from the larger increase in the loss modulus with temperature prior to gelation. The effect of the molecular weight and concentration of PEO on the gelation time of F127 can be seen from the data in Tables 1 and S2.

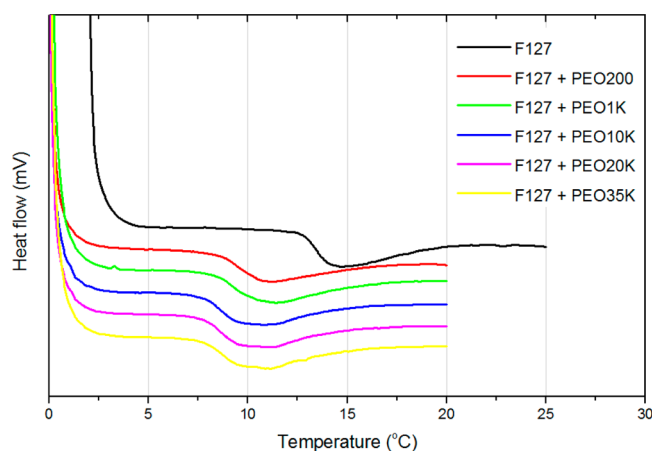
Class B PEO was found to increase the gelation time of F127, whereas class A appeared to reduce it slightly. The effect of MW on gelation time is similar to that on CGT of F127. With increasing MW, the gelation time becomes longer, implying that the presence of class B PEO hinders both the initial structural rearrangement of micelles and the subsequent caging to form a packed, ordered gel structure. As such, the mechanical properties could be affected accordingly. To gain a better understanding of this hindering effect of PEO, we investigate the rigidity and yielding behavior of the resulting gel by oscillatory stress sweep (1 Hz at 37 °C). The temperature is fixed at 37 °C because the gel has been developed to a state in which the complex modulus is nearly independent of temperature as seen in Figure 1. The apparent yield stress τ_{co} can be measured in a number of ways as documented in the literature.²⁸ In this study, the stress at the crossover of G' and G'' is adopted as the yield stress^{28,29} as depicted in Figure S3 in SI. The gel rigidity is gauged by the plateau storage modulus G_0' at small stress. The results of these mechanical properties are tabulated in Tables 1 and S2. Note that class B PEO showed a drastic change in the yield stress and rigidity with respect to those of PEO MW at 1 wt %, whereas class A PEO gave rise to much smaller changes at this concentration, although the results are not shown.

Except for the system with PEO200, an increase in the MW of either class progressively decreased the yield stress and the plateau storage modulus of the F127 gel. This indicates that the presence of PEO perturbs the F127 gel structure and hence weakens the network. This disturbing effect is a strong function of the PEO MW. In fact, the sample with added 1 wt % PEO35k has no measurable storage modulus or yield stress at 37 °C, revealing the absence of a gel network. (The system remains in the sol state.) From the investigation of gelation

time and strength, we can conclude that by increasing the chain length of PEO added to F127 solution the gelation rate and gel strength are reduced. Therefore, the addition of PEO not only has an effect on the kinetics of gel formation involving micellar rearrangement but also affects the gel network structure after this process is complete.

3.3. Micellization Temperature (CMT). Because micellization is the prerequisite for the gelation of F127, it is essential to study the former process and characterize micellar samples to seek its correlation with the latter.

Differential scanning calorimetry (DSC) measurements were carried out for 20 wt % F127 with PEO homopolymers of different chain lengths and concentrations, and the thermograms are shown in Figure 2. We see a broad endothermic peak

**Figure 2.** Thermograms of F127 in the presence of PEO of different MWs. F127 conc = 20 wt % and PEO conc = 6 wt %.

in the spectrum as a result of the dehydration of the PPO block of F127 when the temperature becomes high enough.³⁰ Because the dehydration of the PPO block is the driving force for micelle formation, the endothermic peak can be used to characterize the CMT. The temperature for the onset of the endothermic peak is taken as the CMT. The effects of the molecular weight and concentration of PEO on the CMT of 20 wt % F127 are provided in Figure 3. The obtained CMT of pure 20 wt % F127 is 12.6 °C, in good agreement with the reported value in the literature.¹⁶

We find that the presence of PEO decreases the CMT of F127 for both classes and that this decline increases with increasing chain length (Figure 3 left) or concentration (Figure 3 right) of the PEO homopolymer. The decrease in CMT is expected for class A PEO because it also decreases the CGT of F127. For class B, however, the reason for this behavior was not yet clear at first glance. A detailed comparison also revealed that the change in CMT is much smaller than that in CGT with the addition of PEO. For example, the addition of 2 wt % PEO20k decreased the CMT of 20 wt % F127 by ~ 1.5 °C only, but gelation became completely absent, in contrast. This indicates that more facile micelle formation due to the addition of PEO does not necessarily promote gelation. The decrease in CMT was also observed by adding the PEO homopolymer to another Pluronic P105.

For F127 at low concentrations, DSC is not sensitive enough to detect the weak heat flow change. The micellization of such samples can be characterized by a light-scattering method because the unimer–micelle transition will cause a sharp

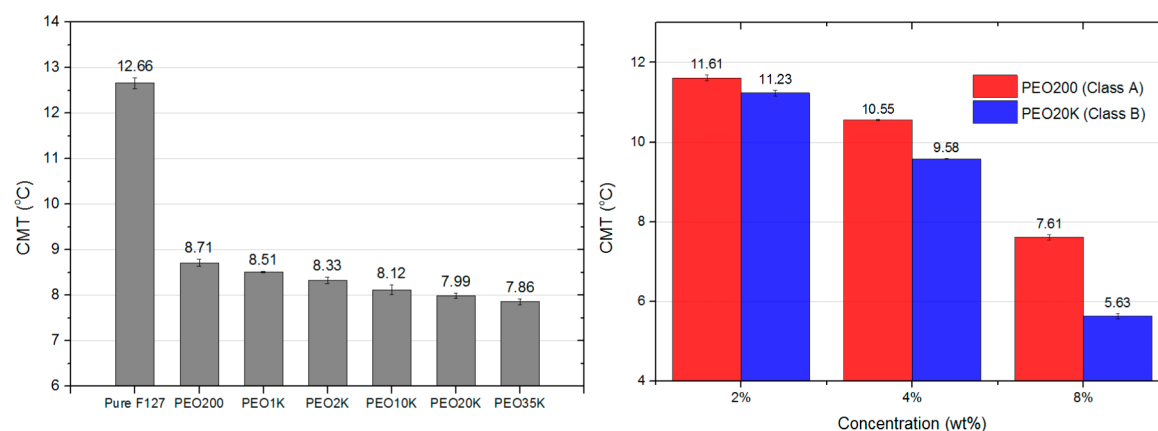


Figure 3. Effect of MW of PEO on CMT of 20 wt % F127 (left); PEO conc = 6 wt %. Effect of PEO concentration on CMT of 20 wt % F127 (right); CMT of 20 wt % F127 = 12.6 ± 0.1 °C.

increase in the scattering intensity.³⁰ Figure 4 illustrates the change in scattered light intensity with temperature for 0.5 wt

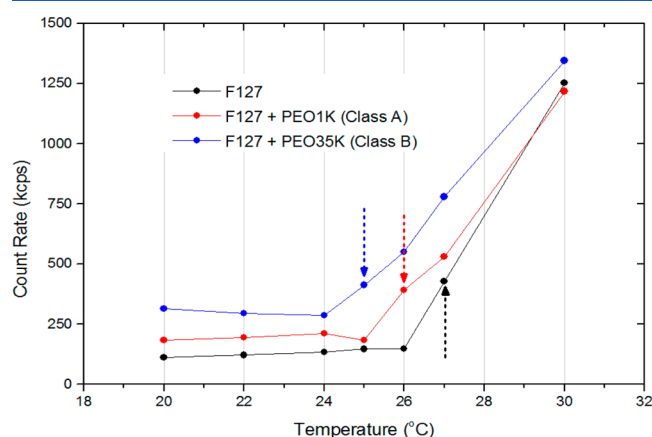


Figure 4. Plot of count rate against temperature from DLS. Arrows mark the CMTs of three different samples with F127 at 0.5 wt % and PEO at 4 wt %.

% F127. As seen, the CMT for F127/PEO1k is around 1 °C below that for the pure F127 solution and is around 2 °C lower for F127/PEO35k.

As described above, the presence of the PEO homopolymer (classes A and B) always decreases the CMT of F127; the longer the chain, the greater the decline. This trend is in overt contrast to the gelation behavior for which the CGT may be increased or decreased, depending on the PEO MW. The effect of additives on micellization can be elucidated by the change in F127 solubility. It has been known that the solubilization of F127 in water arises primarily from hydrogen bonding between the hydrogen atoms of water and the oxygen atoms in the polymer backbone. These oxygen atoms act as proton acceptors during H bonding. At raised temperature, this bonding (hydration) is weakened, and this behavior has been successfully inferred from changes in water self-diffusion measured with an NMR spin-echo pulsed field gradient method for Pluronic³¹ and nonionic surfactant/PEO.³² The study on solute-solvent interactions in a mixed solvent of PEO and water by Singh et al.³³ has found that the mixed solvent shows a decreased hydrogen bond donating (HBD) ability but an increased hydrogen bond accepting (HBA) ability when compared to the behavior of pure water. These changes are also

found to be more pronounced with increasing PEO concentration and molecular weight. Therefore, a PEO/water mixed solvent can decrease the extent of hydrogen bonding with F127, increasing the tendency for F127 to form micelles at raised temperature and leading to a lower CMT. According to Singh et al.,³³ the HBD ability of PEO/water mixed solvent depends more strongly on PEO concentration than on its MW, ranging from 200 to 6000 g/mol in their study. Interestingly, our findings also show that the decline in CMT is a weak increasing function of PEO MW when compared to the concentration dependence. In view of this consistency in the trend and dependence, we believe that the change in the solvent HBD ability (or solvency) due to the presence of PEO is one of the possible mechanisms for the observed CMT behavior.

The other plausible explanation rests on how the added PEO affects the water structure. For the addition of alcohol to water, methanol and ethanol were found to exert a structure-breaking effect on water whereas butanol showed the opposite behavior. The CMT of Pluronics was increased in the presence of the former two alcohol species but was decreased when the latter was added.^{34,35} Similar to butanol, the PEO homopolymer was reported to have a structure-promoting effect on water.^{36,37} because of its ability to fit into the tetrahedral water structure. This results in enhanced self-hydration of the PEO homopolymer in water, leading to the stronger hydrophobicity of F127 in such an environment and an increased ease of micellization.

3.4. Micelle Characterization. Because gelation has been thought to relate to micellar rearrangement and association to form an ordered network, it is important to characterize micelles with the addition of PEO. For DLS experiments, the F127 concentration must be low enough to avoid multiple scattering. Figure 5 shows the temperature dependence of the average micelle size for 0.5 wt % F127. For the pure F127 solution, the hydrodynamic radius increases suddenly to about 22 nm at 27 °C indicating the formation of micelles, in agreement with what is observed in Figure 4. When the temperature is raised further, the micelle size will decrease until reaching a constant (~ 12.5 nm). We think that this temperature rise ΔT above CMT facilitates the formation of a compact stable micellar structure (i.e., a transition from loose to compact micelles). A similar increase and then decrease in micelle size with increasing temperature has recently been reported for Pluronic L44 by Naskar et al.³⁸ They attributed the

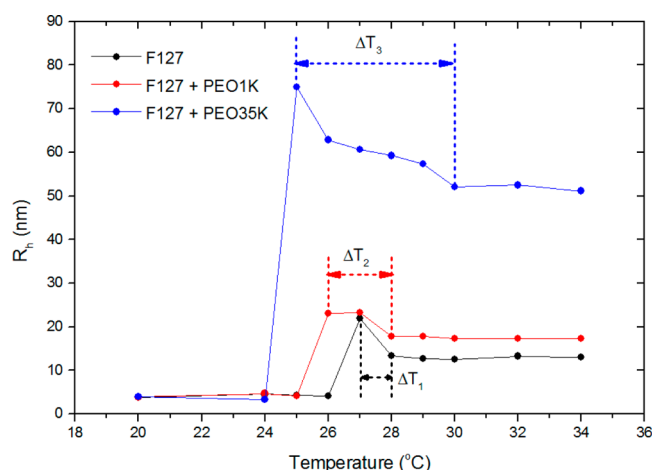


Figure 5. Plot of average hydrodynamic radius against temperature for 0.5 wt % F127 with PEO at 4 wt %.

decrease to the transition of larger to smaller aggregates. Wei et al.³⁹ reported a similar size variation just above the CMC of a synthesized surfactant (ibuprofen–poly(ethylene glycol)). For our samples, this behavior is also observed for cases involving the addition of PEO. However, ΔT becomes larger when PEO is added, as found from Figure 5, and increases with the PEO MW.

To further examine the effects of PEO MW and concentration on the micelle size and size distribution, we conducted DLS for 1 wt % F127 at 40 °C to ensure the formation of stable micellar structure. The obtained mean hydrodynamic micelle size for pure 1 wt % F127 at 40 °C is ~ 12 nm, in good agreement with the literature.²⁴ The effect of PEO of classes A and B on the size distribution based on light intensity is shown in Figures S4 and 6, respectively. The small

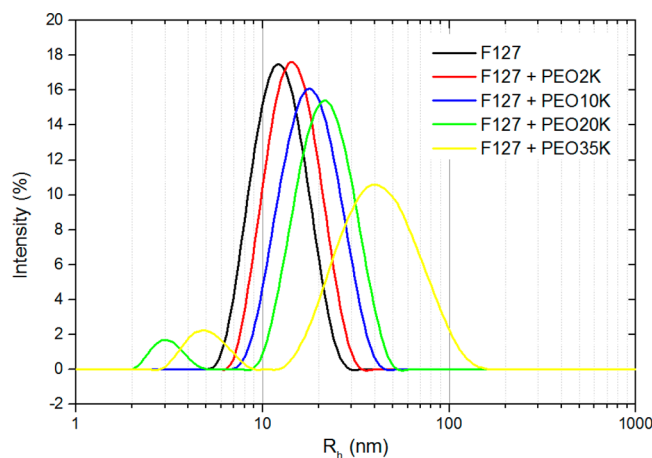


Figure 6. Effect of the molecular weight of class B PEO on the intensity distribution of the F127/water system; PEO conc = 2 wt % and F127 conc = 1 wt %.

peaks at around 3 and 5 nm for MW = 20k and 35k, respectively, are attributed to the scattering of the PEO homopolymer in the bulk solution. This has been confirmed by carrying out DLS for PEO solutions without F127, showing similarly sized peaks. Bimodal distributions have also been reported for PEO with other nonionic surfactant/water systems.^{40,41}

The quantitative data on micelle size are provided in Tables 2 and 3. It should be noted that these results are obtained from

Table 2. Effect of Molecular Weight of PEO on the Hydrodynamic Size of 1 wt % F127

	PEO MW (g/mol)	hydrodynamic radius (nm)	PDI (no units)
pure F127		12.18 ± 0.18	0.067 ± 0.01
class A PEO conc = 4 wt %	200	14.38 ± 0.20	0.066 ± 0.01
	600	15.58 ± 0.68	0.105 ± 0.02
	1k	16.71 ± 0.38	0.120 ± 0.02
class B PEO conc = 2 wt %	2k	14.11 ± 0.19	0.099 ± 0.01
	10k	18.92 ± 0.19	0.175 ± 0.01
	20k	21.91 ± 0.21	0.223 ± 0.01
	35k	39.41 ± 1.0	0.359 ± 0.08

Table 3. Effect of PEO Concentration on the Hydrodynamic Size of 1 wt % F127

	concentration of PEO (wt %)	hydrodynamic radius (nm)
pure F127		12.18 ± 0.18
class A PEO200	2	13.06 ± 0.07
	4	14.38 ± 0.20
	8	16.99 ± 0.32
class B PEO20k	1	16.34 ± 0.23
	2	21.91 ± 0.21
	4	34.03 ± 0.38

micelle diffusion in water. The presence of free PEO may impede the micelle diffusion and hence increase the obtained hydrodynamic radius. In SI, we assess this effect by measuring the viscosity of each PEO solution without F127 and correcting the micelle hydrodynamic size accordingly. This correction, however, requires the PEO solution to be treated as a continuum, which is not valid for high-MW PEO because the molecules are not much smaller than the micelles as seen in Figure 6. As such, the correction exercise in this way provides a lower bound, and we find the qualitative trend to remain unchanged. In what follows, we discuss the size results based on the water viscosity.

The hydrodynamic radius of F127 micelles in the presence of PEO of class A is larger than the counterpart without PEO addition. The modest enlargement increases with increasing molecular weight of PEO. For PEO of class B, the increase in the average size is more pronounced, showing a stronger dependence on the MW of PEO, and the size distribution becomes wider, indicative of increased polydispersity in size as seen in Table 2. Also, the size increase becomes more significant at higher PEO concentration, irrespective of the class as seen in Table 3. For the addition of PEO35k, the size distribution is broadened with the main peak centered at 39.4 nm and extends up to about 147 nm. Because the contour length of an F127 molecule (MW = 12.5k) is much shorter than 147 nm, this molecule is very unlikely to attain spherical micelles with a radius of ~ 147 nm even with the incorporation of PEO onto the micelles. The probability of forming rodlike micelles is also low, according to the TEM images that will be shown later. This implies that a number of micelles should have been associated or even merged into a larger one in the presence of PEO at higher MW.

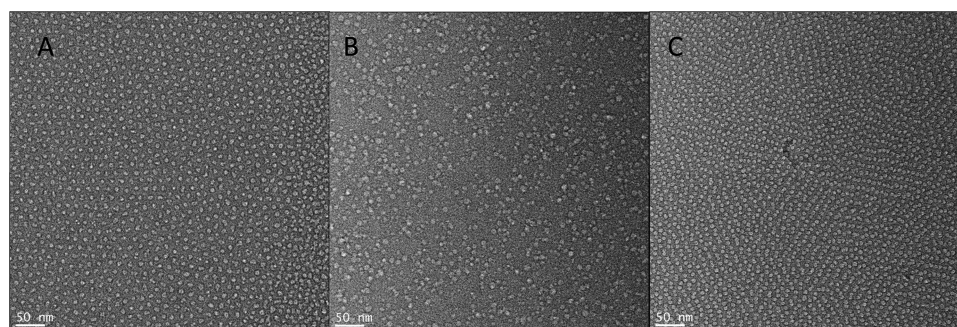


Figure 7. Cryo-TEM micrographs of (A) 10% F127, (B) 10% F127 + 5% PEO35k, and (C) 10% F127 + 5% PEO200.

Similar to class B PEO, methanol and ethanol have been reported to suppress the gelation of F127.³⁵ The addition of ethanol to F127 solutions is found to hinder the formation of F127 micelles.^{35,42,43} At a sufficient concentration of ethanol, the peak in the hydrodynamic radius was reported to shift to about 3 nm when compared to 12 nm for pure F127 solution. This considerable size reduction was attributed to the F127 unimers without micellization.⁴² Hence, the increased difficulty encountered by F127 in self-assembling into micelles in the presence of ethanol can account for the higher CGT. In contrast to ethanol, the addition of PEO of either class always shifts the size peak to higher values, implying that the micellization is never suppressed, consistent with the declining CMT obtained from DSC. Therefore, the mechanism underlying the ethanol effect cannot explain the suppressed gelation of F127 with class B PEO.

Apart from the effect at the onset of micellization, PEO also plays a role in the micellar interactions. As observed, PEO of class A increases the micelle size of F127 slightly, whereas PEO of class B appears to cause the aggregation/merger of the micelles. The degree of aggregation seems to increase with increasing chain length of PEO. The earlier belief that neutral polymers do not bind to the nonionic micelles⁴⁴ has been disproven by later research reporting that the neutral polymer (PEO) can interact with nonionic surfactant micelles to form complexes.^{40,41,45,46} These studies used isothermal titration calorimetry and time-resolved fluorescence quenching to study the interaction to find that the nonionic soluble polymer can interact with the nonionic surfactant micelle in two ways: (1) nonionic homopolymer chains can bind to the hydrophilic micelle corona or may even penetrate the corona as driven by hydrogen bonding and (2) polymer chains can thread through the hydrophobic micellar core, forming strings of beads.

For our system, the PPO and PEO blocks constitute the micelle core and corona, respectively. In the PEO/water system, there already exist four types of hydrogen bonding in terms of proton donor–acceptor: water–PEO, water–water, PEO–water, and PEO–PEO.⁴⁷ The PEO–PEO hydrogen bonding involves an end hydroxyl of one PEO and an ether oxygen of the other PEO. In the F127/PEO/water system, therefore, hydrogen bonds can also form between the corona EO groups of F127 and homopolymer PEO. Because some hydroxyl groups of F127 may stay on the outer surface of the corona, they can attract PEO homopolymers onto the micellar surface. However, PEO homopolymers could penetrate into the hydrophilic corona to behave as proton donors. Therefore, short homopolymer chains may each bind to the corona of one micelle, thereby making the micelle larger. When they are sufficiently long, to the contrary, each may bind to more than

one micelle and hence link the micelles to facilitate their aggregation or clustering as reported for comparable systems.^{40,41} Besides, the high-MW PEO homopolymers in the bulk solution can also result in a depletion zone between two micelles, where the osmotic pressure becomes lower than in the bulk, and can give rise to flocculation.

Another possibility could be the interaction between PEO homopolymers and the core PPO of F127 micelles. Phase behavior studies on the PEO/PPO/water system showed that the system remained in one phase at either high or low water content, whereas phase separation/immiscibility was observed at intermediate water content.⁴⁸ To detect if there exists an interaction between the PEO homopolymer and F127, we carried out ¹H and ¹³C NMR investigations. From ¹H NMR studies (Figures S6 and S7 in the SI), no interaction was found between PPO blocks of F127 and the PEO homopolymer. Our ¹³C NMR results also could not detect any noticeable conformation change in PPO or PEO blocks with the addition of homopolymer when compared to the signal peaks for the pure F127 solution at the same temperature. This finding suggests the possibility of depletion flocculation, which could lead to micelle merger and increased aggregation number.

To seek more clues, we used cryo-TEM to capture the microstructure. The micrographs of 10 wt % F127 without and with the addition of PEO 200 (class A) and PEO 35 000 (class B) are presented in Figure 7. The brighter spots are micelles, which are surrounded by water appearing in a grayish tone.²³ Pluronic F127 is found to have an ordered structure in the gel state.^{49,50} Although our tested concentration is below the critical gelation concentration (CGC = 15 wt %), the microstructure of the pure F127 sample exhibits long-range order, and each micelle is well separated from surrounding neighbors. This is attributed to a slight increase in the volume fraction of micelles due to the removal of some water during sample preparation.²³ In the presence of PEO of class A, the microstructure ordering does not show a discernible change. However, the addition of PEO of class B strongly disrupts the micellar arrangement to a disordered state, in which micellar aggregation can also be observed.

3.5. Correlation between Micellization and Gelation.

It is interesting to relate the PEO effects on micellization to the gelation behavior. As discussed above, the addition of PEO can (1) decrease the HBD ability of the mixed solvent or promote the water structure and (2) increase the average micelle size and the polydispersity via bridging micelles or depletion flocculation of the micelles. Mezmarich and Love²⁴ found that an increase in micellar monodispersity arising from the addition of a hydrophobic drug (methylparaben) could aid the gelation of F127 because the micelles would face fewer sizing defects

when undergoing structural ordering during gelation. Suggestively, an increase in the size polydispersity of micelles would lead to lattice disruption and hence suppress the gelation as speculated previously by Malmsten and Lindman,¹⁹ who measured the CGT of F127 with added PEO but did not provide any direct evidence to corroborate this thought.

In our opinion, the relative importance between the two aforementioned effects of PEO depends on its molecular weight. For class A PEO, the solvency effect dominates and manifests at high enough concentrations because the homopolymer is short-chained. The mixture of water and PEO decreases the solvency for F127, making it easier to form micelles as well as gel at lower temperatures. For class B PEO, apart from the solvency effect, the bridging/flocculation effect becomes equally or even more important. The formation of micellar clusters by bridging or larger micelles via merger increases the size polydispersity inferred from DLS, leading to more sizing defects for the micellar ordering/rearrangement process as evidenced by the cryo-TEM images and the decreased gel strength from oscillatory rheology. This obstacle is more pronounced with increasing PEO concentration and chain length, accounting for the experimentally observed trend in gelation suppression.

4. CONCLUSIONS

The micellization, gelation, and rheology of amphiphilic Pluronic triblock copolymer F127 have been investigated in the presence of homopolymer PEO, focusing on the effects of their chain length and concentration. Our DSC studies revealed that the CMT of F127 is always decreased irrespective of the chain length of the homopolymer. The decline increases with the chain length and the concentration. This promotion of micellization is attributed to the decreased HBD ability of the mixed solvent and/or the structure-promoting effect of PEO on water, namely, the solvency effect.

To the contrary, the rheological studies show that the PEO influence on CGT depends strongly on the MW. Short-chain-length PEO (MW ≤ 1000) decreases the CGT, whereas longer-chain-length PEO (MW ≥ 2000) either delays the gelation to a higher temperature or prevents it from happening. The change in CGT in the presence of PEO with low MW is weak when compared to that instigated by PEO of longer chain length. The delay or loss of gelation in the presence of high-MW PEO is attributed to the formation of micellar clusters or merged micelles with heterogeneity of size as evidenced by DLS and the consequent hindering effect on the micellar ordering as evidenced by cryo-TEM micrographs and reduced gel strength from oscillatory rheology. Future work using isothermal titration calorimetry (ITC), SANS, SAXS, and time-resolved fluorescence quenching is suggested to gain more insight into the interaction between Pluronic micelles and nonionic homopolymers.

■ ASSOCIATED CONTENT

■ Supporting Information

Polymer molecular weight dispersities obtained by GPC. Effects of PEO concentration on CGT, t_{gel} , and τ_{co} and G'_0 of 20 wt % F127. Effect of medium viscosity on micelle size. Effects of concentration of class A PEO on the gelation of the F127/water system. Loss factor $\tan(\Theta)$ versus temperature for 20 wt % F127. G' and G'' as a function of stress for 20 wt % F127 in the presence of class B PEO homopolymers at 37 °C. Effect of molecular weight of class A PEO on the intensity distribution of

the F127/water system. FE-TEM micrographs of 1% F127 and 1% F127 + 4% PEO 35k. ¹H NMR spectra of 1% F127 in D₂O at various temperatures. ¹H NMR spectra of F127/PEO200/D₂O (left) and F127/PEO35k/D₂O at various temperatures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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