

Mixed Block Copolymer Aggregates with Tunable Temperature Behavior

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A block copolymer of propylene oxide (PO) and ethoxyethyl glycidyl ether (EEGE), $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$, that has been found to possess lower critical solution temperature properties in water in the temperature range below 20 °C was mixed at 1:0.1, 1:1, and 1:10 weight ratios with commercially available Pluronic (L64 or P85) block copolymers. The cooperative association of the copolymers in aqueous solution was studied by dynamic light scattering over a wide temperature range (5–60 °C). At lower temperatures, the systems containing either L64 or P85 behave similarly irrespective of the composition: three species corresponding to $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ unimers, Pluronic-dominated mixed micelles, and large (50–60 nm in radius) composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ /Pluronic aggregates were identified. At a certain temperature, which is composition-dependent, the systems phase-separate [$(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ /L64 1:0.1], enter an interval of instability [$(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ /L64 1:1 and 1:10], or rearrange by dissociation of the large composite particles [$(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ /P85]. The presence of a Pluronic micellar peak in the relaxation time distribution at lower temperatures, the dimensions of the composite particles, and the different behavior of the systems at elevated temperatures are discussed. A possible application of the thermosensitive mixtures in delivery/release of active substances is suggested.

Introduction

The self-assembly of amphiphilic block copolymers in selective solvents is of particular academic interest with important industrial and medical applications. Block copolymers composed of moieties possessing a lower critical solution temperature (LCST) exhibit a pronounced temperature-induced transition from a soluble to an insoluble state resulting in micellization above a certain temperature.^{1–12} A recent paper¹³ describes the synthesis and aqueous solution properties of block copolymers of ethoxyethyl glycidyl ether (EEGE) and propylene oxide (PO). The chemical structures of the copolymers are presented in Figure 1. The constituent blocks exhibit an LCST in the low-temperature region.

The copolymers were found to form stable multichain core-corona aggregates in water at temperatures close to 0 °C. The micellar cores consist of PEEGE moieties, which are the more hydrophobic, whereas the relatively hydrophilic PPO chains interact with water and stabilize the cores against aggregation. Some penetration of PPO chains into the liquid cores is assumed. The aggregates are stable over a certain temperature interval. Upon being heated, however, a secondary aggregation that is found to produce rather compact and dense particles takes place. Upon further heating, milky-white opalescence appears indicating phase separation. The intervals in which the aggregates are stable and temperature-independent are relatively narrow. A natural continuation of the previous study is to find conditions that extend the temperature intervals of stability, that is, to inhibit the secondary aggregation. A possible way to achieve steric stabilization is by using block copolymer surfactants of ethylene

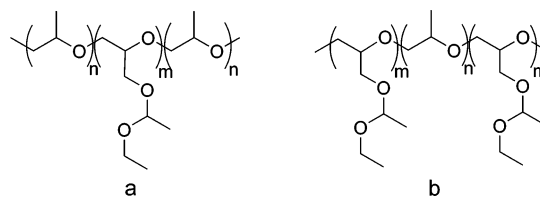


Figure 1. Chemical structures representing $(\text{PO})_n(\text{EEGE})_m(\text{PO})_n$ (a) and $(\text{EEGE})_m(\text{PO})_n(\text{EEGE})_m$ (b) block copolymer architectures.

oxide (EO) and PO. These copolymers are commercially available (Pluronics, BASF and Synperonics, ICI) and find a wide range of applications as emulsifiers, wetting agents, solubilizers, etc.¹⁴ Using this approach, composite particles consisting of distinct layers could be prepared. Such particles, referred to as onion-type micelles,¹⁵ are normally prepared using an ABC block copolymer¹⁶ or a pair of diblock copolymers with identical blocks (i.e., AB and BC diblock copolymers).¹⁵ Typically, the preparation of onion-type micelles involves changes of the solvent, pH, or dialysis.

In the present paper, we report the steric stabilization of an EEGE/PO block copolymer using commercially available EO/PO block copolymers. In contrast to the aforementioned onion-type micelles, dispersions were prepared simply by mixing the two copolymers in water at low (below 3 °C) temperatures. The changes of the particle dimensions with temperature were studied by dynamic light scattering (DLS).

Experimental Procedures

Materials. The EEGE/PO block copolymer with a composition $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ was synthesized by sequential anionic polymerization of EEGE followed by PO as described elsewhere.¹³ The Pluronic block copolymers, L64 and P85, were obtained from BASF Corp. and used as received. Table 1 lists

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TABLE 1: Molecular Weight and Composition Characterization Data of the Pluronic Copolymers Used in This Study

pluronic copolymer	molecular weight (Da)	EO/PO/EO
L64	2900	13/30/13
P85	4500	26/40/26

the molecular weights and compositions according to the manufacturer.

Sample Preparation. To achieve better mixing, the dispersions were prepared by codissolving $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ and the respective Pluronic copolymer in a chosen weight ratio in chloroform. Appropriate volumes of corresponding stock solutions in chloroform were placed in glass vials. Then, the chloroform was evaporated under a gentle stream of nitrogen, and the traces were removed under vacuum. Cold purified water (Millipore Super-Q-System) was added to the dry film. The resulting dispersions were stirred overnight at low (<3 °C) temperatures and filtered directly into dust-free light scattering cells using $0.25\ \mu\text{m}$ Millipore Sartorius Minisart filters.

Methods. Dynamic Light Scattering. The light scattering setup has been described previously.¹⁷ It consists of a 488 nm Ar ion laser and the detector optics with an ITT FW 130 photomultiplier and an ALV-PM-PD amplifier-discriminator connected to an ALV-5000 autocorrelator built into a computer. The cylindrical scattering cells were sealed and then immersed in a large-diameter thermostated bath containing the index matching fluid decalin. Measurements were made at different angles in the range of 50 – 130° and at different temperatures.

Analysis of the dynamic data was performed by fitting the experimentally measured $g_2(t)$, the normalized intensity autocorrelation function, which is related to the electrical field correlation function $g_1(t)$ by the Siegert relationship¹⁸

$$g_2(t) - 1 = \beta |g_1(t)|^2 \quad (1)$$

where β is a factor accounting for the deviation from ideal correlation. For polydisperse samples, $g_1(t)$ can be written as the inverse Laplace transform (ILT) of the relaxation time distribution, $\tau A(\tau)$

$$g_1(t) = \int \tau A(\tau) \exp(-t/\tau) d \ln \tau \quad (2)$$

where τ is the lag-time. The relaxation time distribution, $\tau A(\tau)$ was obtained by performing ILT using the constrained regularization algorithm REPES, which minimizes the sum of the squared differences between the experimental and the calculated $g_2(t)$.¹⁹ A mutual diffusion coefficient, D , was calculated from the position of each peak as $D = \Gamma/q^2$, where q is the magnitude of the scattering vector $q = (4\pi n/\lambda) \sin(\theta/2)$ and $\Gamma = 1/\tau$ is the relaxation rate of each mode. Here, θ is the scattering angle, n is the refractive index of the medium, and λ is the wavelength of the light in a vacuum. Since plots of Γ versus q^2 were found to be linear and pass through the origin, thereafter the values of the diffusion coefficients were evaluated from measurements at an angle of 90° .

Apparent hydrodynamic radii, R , were calculated using the Stokes–Einstein equation

$$R = kT/(6\pi\eta D) \quad (3)$$

Here, kT is the thermal energy factor, η is the temperature-dependent viscosity of the solvent, and D is the mutual diffusion coefficient at a fixed concentration.

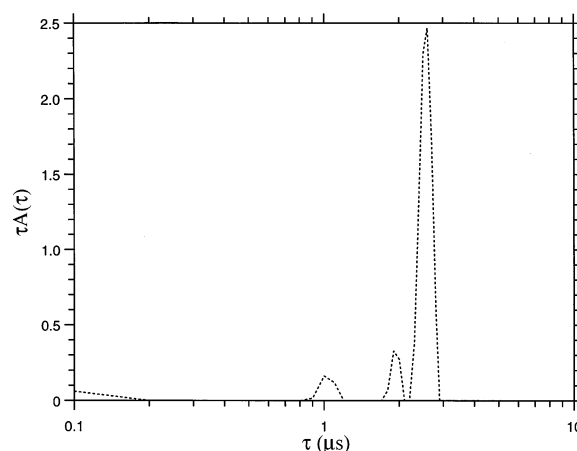


Figure 2. Relaxation time distribution measured at an angle of 90° of a $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ system at a 1:1 weight ratio and 26 °C. $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ concentration is $5.2\ \text{g/L}$.

Results

General Remarks. $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ is selected for the present study because of its suitable relaxation time distribution determined from DLS.¹³ At concentration $c = 5.2\ \text{g/L}$, which is above the critical micellization concentration, and temperatures up to 23 °C, the relaxation time distribution contains a low-amplitude fast mode and a dominant mode that contributes more than 90% of the overall scattered light intensity.¹³ The former mode is attributed to a small fraction of unassociated macromolecules, unimers, whereas the latter corresponds to multichain aggregates. The radii of the two species were 0.9 – 1 and 38 – $40\ \text{nm}$ for the unimers and aggregates, respectively. On the other hand, secondary aggregation leading to an abrupt increase of the particle size and eventually to phase separation was found to occur in the temperature interval of 23 – 29 °C.¹³ The behavior of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ is thus convenient for performing a comparative study of pure and stabilized by polymeric surfactants aggregates.

L64 and P85 were used as steric stabilizers. The two copolymers have similar EO contents but differ considerably in total molecular weight (Table 1). Dynamic light scattering measurements were done on dilute dispersions of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{Pluronic}$ at 1:0.1, 1:1, and 1:10 weight ratios. Changes in particle dimensions were monitored by following the changes of the radius of the particles from the decay rates measured at an angle of 90° .

The behavior of the systems stabilized with either L64 or P85 is similar at lower temperatures. Typically, the relaxation time distribution is trimodal. An example of relaxation time distribution observed for $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ at a 1:1 weight ratio and 26 °C is presented in Figure 2. There is a dominant mode, corresponding to particles of radius about $\geq 50\ \text{nm}$ (see also Figures 4 and 8), accompanied by two low-amplitude fast modes. The total amplitude of the latter two modes does not exceed 9%. The fastest mode corresponds to particles with dimensions of $1 \pm 0.2\ \text{nm}$ and is attributed to $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ unimers.¹³ The radius of the particles responsible for the intermediate mode was estimated to be ca. $12\ \text{nm}$, which is somewhat larger than that of pure L64 (typically 6 – $8\ \text{nm}$, although the quantities reported are very variable^{20–24}) or P85 (7.5 – $8.0\ \text{nm}$ ^{25–28}) micelles. Most likely these are Pluronic-dominated particles containing small amounts of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$. The weight concentrations of the three species were calculated using the approach given elsewhere.²⁹ According to this approach, the ratio of the weight concentrations is given

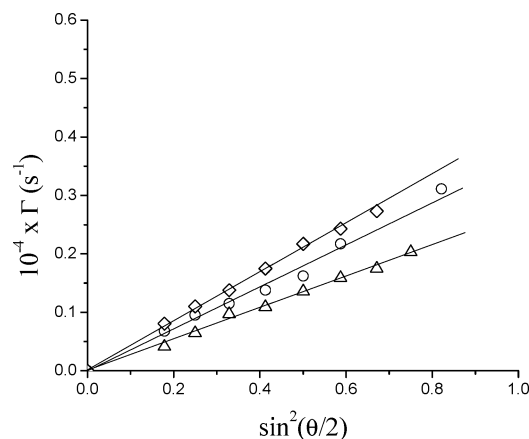


Figure 3. Relaxation rate, Γ , of the dominant modes of three dispersions at selected conditions as a function of $\sin^2(\theta/2)$. $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 1:10 at 10 °C (triangles), $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 1:0.1 at 10 °C (circles), and $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 1:10 at 50 °C (diamonds).

by the relative amplitudes divided by the relative molar masses. Assuming that R is proportional to $M^{0.57}$ (where R and M refer to radii and molar masses, respectively), the relative weight concentrations, in particular for the distribution shown in Figure 2, are as follows: $C_S/C_I = 6.73$, $C_S/C_F = 4.16$, and $C_I/C_F = 0.62$, where the subscripts S , I , and F denote the slow, intermediate, and fast modes, respectively. Thus, the ratio of the weight concentrations is 17.3:10.7:72.0 for the particles responsible for the fast, intermediate, and slow modes, respectively. The weight proportions and particle dimensions slightly change with temperature and/or composition in the temperature intervals in which the trimodal distribution is manifested. The width of these intervals, however, is composition-dependent. They extend to maximum of 32 °C for $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /P85 1:0.1.

Measurements were made also at different angles (50–130°). A selection of angular dependences of the relaxation rates is presented in Figure 3. The selection shows linear dependence according to $\Gamma = Dq^2$ as expected for diffusive modes. All modes were found to be diffusive.

$(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64. The effect of temperature on the dimensions of the particles responsible for the dominant modes in the nonstabilized and stabilized systems is presented in Figure 4. Although the curve profiles are quite distinct, both initial and stabilized dispersions exhibit common features: temperature intervals in which the particle dimensions are not influenced by changes of temperature followed by a sharp increase of the dimensions at a certain temperature were observed for all compositions. The dimensions of the stabilized particles, however, are invariably larger than those of pure $(\text{PO})_2$ -(EEGE) $_6$ -($\text{PO})_2$ aggregates in the temperature interval of size stability; the compositions of 1:0.1 and 1:1 $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 weight ratios form aggregates that have practically equal particle dimensions, whereas the latter are even larger for the composition with a 1:10 weight ratio.

The clouding of the samples is also shifted toward higher temperatures. In the absence of a steric stabilizer, the $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ dispersion was found to become milky-white opalescent at 29 °C.¹³ In the presence of a small amount of L64 (e.g., at a 1:0.1 weight ratio), clouding appeared at 33 °C, whereas the dispersions of 1:1 and 1:10 weight ratios remained optically clear at temperatures as high as 58 and 60 °C, respectively. According to the manufacturer's technical data,³⁰ these temperatures correspond to the cloud points of L64 at

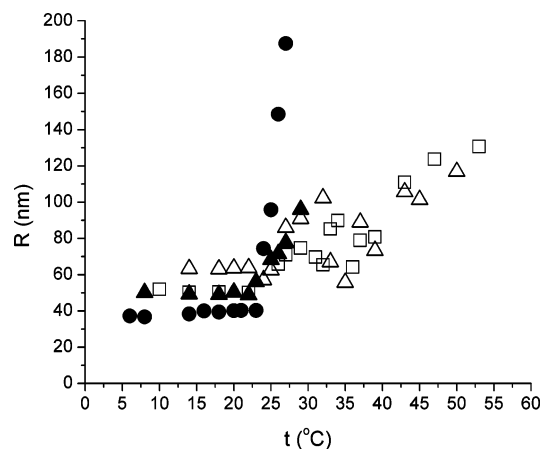


Figure 4. Temperature dependence of the hydrodynamic radii, R , of particles responsible for the dominant modes in binary, $(\text{PO})_2$ -(EEGE) $_6$ -($\text{PO})_2$ /water, and ternary, $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64/water, systems: pure $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ aggregates (circles); $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 aggregates at 1:0.1 (filled triangles); 1:1 (squares); and 1:10 (open triangles). $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ concentration is 5.2 g/L.

concentrations of 1 and 10 weight %, respectively. In addition, the abrupt increase of the particle dimensions, which follows the initial interval of size stability, is less pronounced for the stabilized dispersions (Figure 4).

At temperatures above 29 °C and weight ratios 1:1 and 1:10, an interval is entered in which the behavior of both systems is rather unsystematic: small changes in temperature cause large variations of the relaxation time distribution. Selected relaxation time distributions are depicted in Figure 5a,b. The unsystematic behavior and the low reproducibility of the experiments in this temperature range prevented us from acquiring the effects of, for example, composition or temperature. Obviously, opposite forces are in operation, and small environmental changes result in substantial shift of the equilibrium between the coexisting particles. With a further increase of temperature ($t > 40$ °C), the two systems return to more systematic behavior; the distributions become monomodal and are represented by narrow peaks (Figure 5c), and the results obtained are of good reproducibility. In this temperature range (40–60 °C), the particle dimensions were found to gradually increase with temperature (Figure 4).

$(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /P85. The EO content and the total molecular weight of P85 are higher than those of L64 (Table 1), and as expected, the behavior of the $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /P85 systems is considerably different from the corresponding systems stabilized with L64. The first and main difference is that the dispersions did not cloud and remained optically clear over the whole temperature interval studied (5–60 °C). In contrast to the $(\text{PO})_2$ -(EEGE) $_6$ ($\text{PO})_2$ /L64 systems at moderate temperatures for which an interval of instability was entered, the systems with P85 are relatively stable although the relaxation time distributions change abruptly from trimodal to bimodal at temperatures higher than 23, 26, and 32 °C for the dispersions of 1:10, 1:1, and 1:0.1 weight ratios, respectively. Such a bimodal distribution is presented in Figure 6 and is typical for broad temperature intervals. Interestingly, the amplitude of the slow mode, which is dominant at lower temperatures, was found to decrease with increasing temperature (Figure 7). The slow mode amplitude decreases more rapidly for the system of higher P85 content. As seen, at 60 °C and a 1:1 weight ratio, the slow mode was not detected (i.e., the relaxation time distribution was clearly monomodal), whereas at a 1:0.1 weight ratio and 60

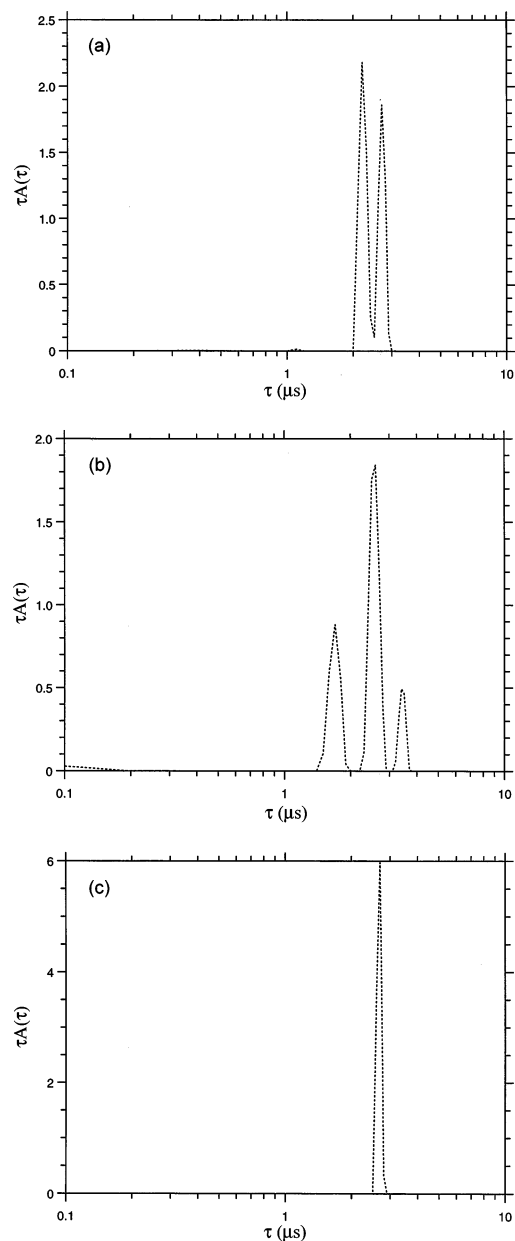


Figure 5. Relaxation time distributions measured at an angle of 90° of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{L64}$ systems at a weight ratio 1:1 and 34°C (a), 1:10 and 37°C (b), and 1:10 and 50°C (c). $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ concentration is 5.2 g/L.

$^\circ\text{C}$, a slow mode with amplitude about 27% was still present (Figure 7).

A closer examination of the relaxation time distributions, shown in Figures 2 and 6, suggests that the particles responsible for the fast mode at elevated temperatures (at which a bimodal distribution is manifested) can be assigned to P85-dominated micelles. In other words, the intermediate mode in Figure 2 and the fast mode in Figure 6 reflect motions of related particles. The position of the latter mode is shifted toward the shorter relaxation times as seen from the decrease of the hydrodynamic radii from 10 to 12 nm at lower temperatures to 7–8 nm at elevated temperatures (Figure 8). Such significant contraction of the particle size is not characteristic for Pluronic copolymer micelles. Typically, the size of these particles slightly changes with temperature due to compensation effects between an increase of the aggregation number and a decrease in coronal swelling. More significant reduction of the particle radius has

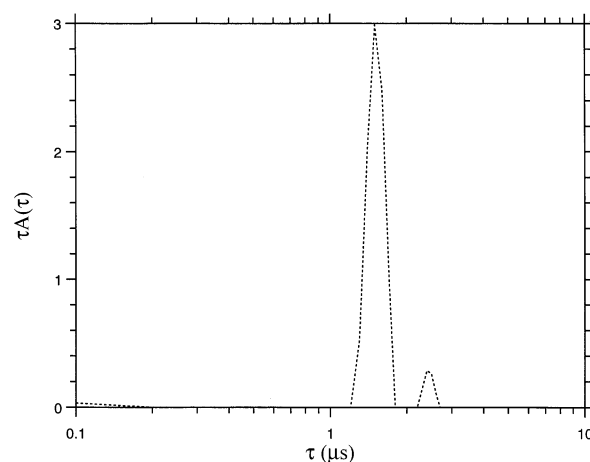


Figure 6. Relaxation time distribution measured at an angle of 90° of a $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ system at a weight ratio 1:1 and 40°C . $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ concentration is 5.2 g/L.

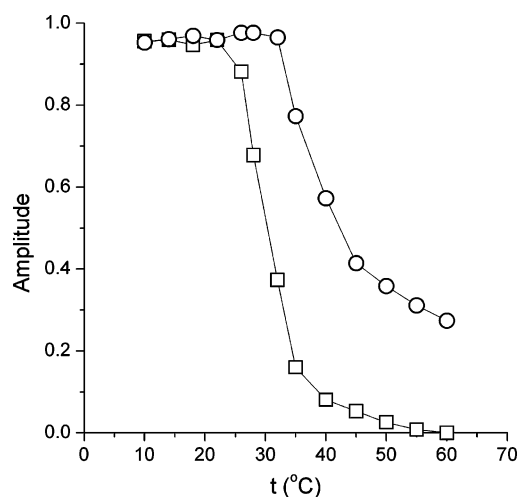


Figure 7. Variations of slow mode amplitudes of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ systems at weight ratios 1:1 (squares) and 1:0.1 (circles) with temperature. $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ concentration is 5.2 g/L.

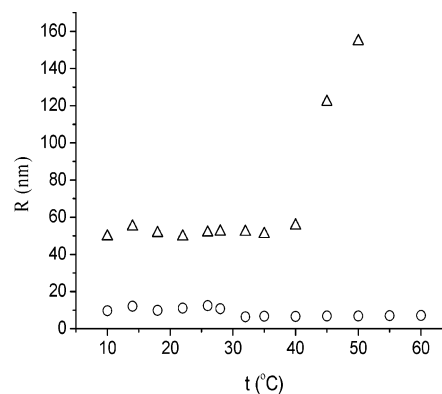


Figure 8. Temperature dependence of the hydrodynamic radii, R , of particles responsible for the intermediate and fast modes at lower and elevated temperatures, respectively (circles), and composite particles (triangles) for $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ at a weight ratio 1:1. $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ concentration is 5.2 g/L. See text for more information.

been observed for PEG-based copolymers bearing short blocks of lipid-mimetic repeating units.³¹ The contraction of the aggregates composed of these copolymers has been attributed to the presence of PEG-water domains in the aggregate cores. Thus, at elevated temperatures, both the shrinkage of the PEG-water domains in the core and the decrease of the corona

thickness contribute to the overall contraction of the particles. If the changes of the size are considered to be related only to the dehydration of the PEG corona, then the particle size reduction would be considerably smaller—6–7%.³² Returning to the present Pluronic-dominated particles, responsible for the intermediate mode in Figure 2 and the fast mode in Figure 6, it appears that the shrinkage of the particles is quite significant to be attributed only to changes in the PEG corona. To explain this finding, we must assume that the initial Pluronic-dominated particles contain substantial amounts of water that is pumped out at elevated temperatures.

The large composite particles are stable and temperature independent up to 40 °C (Figure 8). With a further increase of temperature they, similarly to $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{L64}$ at weight ratios 1:1 and 1:10, increase in size. The size increase is accompanied, as already mentioned, with a decrease of the amplitude of these particles in the relaxation time distribution, which implies that their weight fraction rapidly decreases. The other two systems, $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ at 1:0.1 and 1:10, were found to behave analogically.

Discussion

The results indicate that when mixed at lower temperatures with L64 or P85 Pluronic copolymers, $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ forms particles with different dimensions and compositions. Three species were found to coexist and were assigned as follows: one to $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ unimers, the second to Pluronic-dominated micelles, and the third to composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{Pluronic}$ aggregates. The upper limit of the low-temperature intervals in which a trimodal relaxation time distribution (Figure 2) is observed is composition-dependent. The presence of a Pluronic micellar peak in the relaxation time distribution was unexpected since Pluronic copolymers usually dissolve as unimers at those temperatures. However, as shown elsewhere,^{33–37} the presence of a solute greatly enhances the micellization of block copolymers in selective solvents and decreases their critical micellization concentration. Furthermore, the introduction of low concentrations of vegetable oil has been shown to stabilize Pluronic micelles against dissociation upon dilution.³⁸ It is plausible, therefore, to assume that the $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ unimers serve as nucleation centers for the micellization of the Pluronic copolymer, thereby lowering the critical micellization concentration and temperature of the latter.

The slow moving particles are clearly composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{Pluronic}$ aggregates. The dimensions of these probably Pluronic-coated aggregates are comparable to, but invariably larger than, those of the pure $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ aggregates. As can be clearly seen from Figure 4, the hydrodynamic radii of the composite particles at different temperatures are normally 10–12 nm larger than those of the pure nonstabilized $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ aggregates. Certainly, an increase of the radii of the Pluronic-coated aggregates is to be expected if we assume a model of Pluronic copolymer molecules anchored on the $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ aggregate surface via their poly(oxypropylene) blocks and poly(oxyethylene) chains interacting with water and preventing particles from further aggregation. It appears, however, that the difference between the radii of the composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{Pluronic}$ particles and the pure $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ aggregates is up to 100% larger than the length of a fully extended poly(oxyethylene) chain of any of the two stabilizing Pluronic copolymers. To explain this controversial result, we must assume that the number of associated $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ molecules is greater in the composite particles than in the pure $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$ ag-

gregates. As shown elsewhere,³⁹ the presence of PEG results in depression of the LCST of poly(*N*-isopropyl acryl amide) because the former orders water molecules, which, in turn, makes the entropy of mixing more negative. The Pluronic copolymer may have a similar effect on the LCST of $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$, and an increase of the aggregation number of the latter is thus anticipated. Other possible explanations are polydispersity of the particles, which is known to lead to overestimation of the radius and that some poly(oxypropylene) chains of the Pluronic copolymer are partly pulled into the corona region. The latter would imply that the stabilizing layer is not always monomolecular. The sample preparation (i.e., hydration of a dry mixed polymer film) may favor the formation of a nonmonomolecular layer. From the information available, we are not able to distinguish the size-determining factor. Possibly, a combination of the aforementioned reasons contributes to a varying extent to the apparent increase of the size of the composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{Pluronic}$ particles.

The previous considerations were made under the assumption that the particles are spherical. It seems possible, however, that complicated structures (i.e., oblate spherical, ellipsoidal, cylindrical, etc.) could also produce similar observations. At this stage of investigation, however, information supporting nonsphericity of the particles is not available. On the contrary, a picture of isolated spherical particles was derived from the simultaneous static and dynamic light scattering as well as scanning electron microscopy performed previously on dilute dispersions of PO/EEGE copolymers.¹³

As it was already shown, the two stabilized systems behave similarly at lower temperatures. Upon increasing the temperature, the systems display a substantially different behavior: while the systems stabilized with L64 enter an interval of instability or phase-separate [$(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{L64}$ 1:0.1], the large composite $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{P85}$ aggregates gradually disappear (Figures 2, 6, and 7). At first sight, the different behavior may be attributed to different solubilization capacities of the Pluronic copolymers. A higher solubilization capacity is expected for P85 as compared to L64 because of its longer PPO block and higher total molecular weight, which have been found to favor solubilization.³³ The different behavior upon increasing temperature can also be understood in terms of PEG chain mobility. The mobility of the stabilizing Pluronic layer stems from the surface motion of the hydrated flexible poly(oxyethylene) chains. The latter has been found to be chain length dependent: the longer the chain, the faster its motion.⁴⁰ At lower temperatures, at which the particles were prepared, the poly(oxyethylene) chain mobility is low, which favors formation of particles of lower curvature. Upon heating, enhancement of the mobility of the poly(oxyethylene) chains is expected, which can increase lateral repulsions of the chains in the adsorption layer. Enhanced lateral repulsion can induce transition to particles of higher curvature since curving the surface would reduce the lateral tension and would allow the poly(oxyethylene) chains greater freedom of motion. The previous effects are opposed by the well-known reverse solubility of PEG-based materials: with increasing temperature, the hydrophobicity of the copolymer is enhanced, and the swelling of the poly(oxyethylene) block is decreased (i.e., as shown elsewhere,⁴¹ lower curvature structures are favored under these conditions). Experimentally, we can identify which process determines the behavior of the systems. In the case of P85, obviously the effect of the enhanced mobility dominates over the effect of decreased swelling. Therefore, small particles, that is, those of higher curvature, are eventually formed. In contrast, the interval of instability that

the $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2/\text{L64}$ systems enter at about 30 °C most probably reflects the competition between the two opposing processes. With a further increase of temperature (above 40 °C), the dehydration of the poly(oxyethylene) chains takes over, which results in an even further decrease of curvature: particles larger than the initial ones are formed at these temperatures (Figure 4).

Concluding Remarks and Implications for Controlled Release of Active Substances.

Simply by mixing in water a block copolymer composed of blocks exhibiting LCST in the low-temperature range (<20 °C), $(\text{PO})_2(\text{EEGE})_6(\text{PO})_2$, with the commercially available Pluronic block copolymers, L64 or P85, thermosensitive compositions have been prepared and investigated by dynamic light scattering. Although there are a number of similarities mainly in the low-temperature range, upon heating the systems exhibit distinctly different behavior depending on the Pluronic type and the weight ratio. This implies that by varying the type of the Pluronic copolymer and the concentration, we are able to influence the temperature behavior of the composite aggregates and control the temperature interval in which the rearrangement of the latter takes place. The rearrangement of the composite particles in particular may have potential applications in areas such as the delivery and release of active substances. If we assume that an active substance is entrapped in the PEEGE-dominated core of the Pluronic-coated composite aggregates then, upon the rearrangement of the particles at certain temperature, the active substance can be released. By changing the type of the EEGE/PO copolymer as well as the stabilizing Pluronic copolymer and the ratio between them, we can control the temperature at which the rearrangement, and consequently the release of the active substance, takes place. A suitable temperature behavior of the composite aggregates in aqueous solution does not, of course, necessarily ensure their utilization in drug delivery since much work in this direction must be carried out. This study is restricted to two systems at different compositions. We conclude from the present results that we may affect the temperature at which the rearrangement takes place by varying the type and the concentration of the Pluronic copolymer. With a study that has already been initiated by the present results, we aim to elucidate the role of the Pluronic-dominated micelles detected at lower temperatures in the rearrangement process, to investigate the thermoreversibility of the rearrangement, the release, and the time dependence of the release of model active substances at certain, for example, physiological, temperatures.

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