

Synthesis, Self-assembly and pH Sensitivity of a Novel Fluorinated Triphilic Block Copolymer^{*}

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Abstract A novel fluorinated triblock copolymer incorporating 2-ethylhexyl methacrylate (EHMA), *tert*-butyl methacrylate (tBMA) and 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate (FA) (PEHMA-*b*-PtBMA-*b*-PFA) was first synthesized using three successive reversible addition fragmentation chain transfer (RAFT) polymerization and the subsequent hydrolyzing at acidic condition. The as-fabricated triblock copolymer exhibited an interesting morphology evolution from the multi-compartment rod-like structure to spherical structure along with the addition of a selective solution. At the same time, a visible phase separation domain could be seen in the core area due to the existence of fluorocarbon segments. Furthermore, the self-assembly behavior of the triphilic copolymer at different pH was also verified by transmission electron microscopy, as well as the dynamic light scattering. These stimuli-responsive multi-compartment nanostructures may have potential applications in drug delivery.

Keywords Triphilic block copolymer; Self-assembly; pH sensitivity; Fluorinated copolymer; Multi-compartment structure

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INTRODUCTION

Block copolymers are in general ideal precursors for a rich variety of nanostructures with different morphology and size^[1]. In an aqueous solution, the hydrophilic and hydrophobic blocks of the amphiphilic copolymer can respectively constitute the outer shell and inner core of the micelles. In fact, the lipid bilayers of living cells are also made from the self-assembly of phospholipids, such as the transport protein and serum albumin in blood. Therefore, the applications of self-assembly micelles in biomedical and bionics materials were typically highlighted^[2–4]. When they were used as drug delivery systems and carriers in gene therapy^[5, 6], the hydrophilic shell was an interface between the hydrophobic core and the biological environment, while the hydrophobic core served as a container for the hydrophobic drugs with the effect of hydrophobic interactions. In some cases, due to the different solubility of these blocks, special core-shell structures could be obtained and might possess unique advantages such as biocompatibility and biodegradability^[7]. Hence, the concept of multi-compartment micelles has been derived, which is believed to be the most potential micellar morphology for drug delivery.

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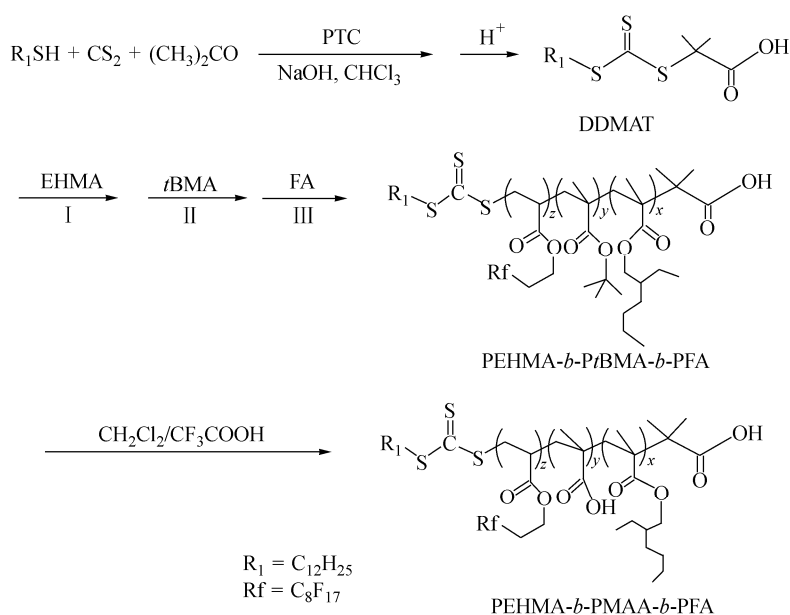
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However, the classical amphiphilic diblock copolymers are impossible to form the multi-compartment structure, as there is only one single hydrophobic domain in the core. Since the self-assembly is driven by a series of interaction forces^[8], the addition of third block can not only add new chemical and physical properties to the copolymer, but also increase the complexity of those interaction forces. Various multi-compartment nanostructures have been produced from the self-assembly of triblock copolymers, including sphere^[9, 10], soccer ball micelles^[10, 11], vesicles^[8, 12, 13], raspberry^[14–16], hamburger-like micelles^[17, 18], flower-like micelles^[18, 19] and some other morphology^[18, 20–22].

An effective strategy towards the multi-compartment micelles is the introduction of fluorocarbon hydrophobic segments, which are poorly compatible with the hydrocarbon segments and can dramatically increase the Flory-Huggins interaction parameter (χ) between the core and shell chains^[23]. In the last decade, theoretical works on the fluorinated triblock copolymers have been constantly reported^[9–11, 18–20, 24–26], to the best of our knowledge mainly focusing on the influence of block length, chemical structures and the nature of solvents during their self-assembly process. There are also some practical progresses on the application of the fluorinated micelles in biotechnology, especially in drug delivery^[27, 28] and ¹⁹F-magnetic resonance imaging (¹⁹F-MRI) probes in cancer diagnose^[29, 30]. Since the organism environment is extremely complicated, stimuli-responsive multi-compartment micelles might have a wide application, as this kind of colloidal systems could stay stable under different temperature or pH conditions. For example, Synatschke *et al.*^[28] reported a pH-responsive multi-compartment structure derived from a well-designed triblock copolymer polybutadiene-block-poly(1-methyl-2-vinylpyridinium methyl sulfate)-block-poly(methacrylic acid), which can be an excellent drug delivery system in photodynamic therapy. But still there are not so many studies about the stimuli-responsive fluorinated block copolymers^[13, 18, 19, 31, 32].

Our team had studied the self-assembly of a novel fluorinated diblock triphilic copolymer poly(methyl methacrylate-*co*-methacrylic acid)-block-polyperfluoroalkyl ethyl methacrylate (P(MMA-*co*-MAA)-*b*-PFEMA) and reported a new nail-shaped structure^[20]. To continue this study, herein, we report the synthesis and self-assembly of a well-designed linear fluorinated triphilic copolymer poly(2-ethylhexyl methacrylate)-block-poly(methacrylic acid)-block-poly(1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate) (PEHMA-*b*-PMAA-*b*-PFA). In this copolymer PEHMA is the lipophilic block with a low T_g ; PMAA is the hydrophilic block; PFA is the fluorophilic block with a long fluorocarbon side chain. Scheme 1 shows the synthetic route of the copolymer.



Scheme 1 The synthetic procedure of the copolymer PEHMA-*b*-PMAA-*b*-PFA

Study on the self-assembly behavior of this triphilic copolymer was carried out in DMF/H₂O dispersion with increasing water contents and the morphology evolved from the multi-compartment rod-like structure to spherical structure. Since the hydrophilic block PMAA was a weak polyelectrolyte, the self-assembly aggregations could also undergo some changes of morphology and size under different pH conditions, owing to the deprotonation or protonation of the carboxyl groups.

EXPERIMENTAL

Materials

2-Ethylhexyl methacrylate (EHMA, Aladdin, 99%), *tert*-butyl methacrylate (*t*BMA, Aladdin, 99%) and 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate (FA, Aldrich, 97%) were rinsed orderly with 5 wt% NaOH aqueous solution and deionized water, then distilled under reduced pressure after drying with CaH₂ overnight. The reversible addition fragmentation chain transfer (RAFT) chain transfer agent (CTA) *S*-1-dodecyl-*S'*-(α,α' -dimethyl- α' -acetic acid) trithiocarbonate (DDMAT) was synthesized consulting a literature procedure under the phase transfer catalysis condition^[33], as specified in Figs. S1 and S2 (in the supporting information, SI). 2,2'-Azobisisobutyronitrile (AIBN, Aldrich, 98%) was re-crystallized from methanol and used as the thermal initiator. Toluene (SCRC, AR) was distilled after drying with CaH₂. α,α,α -Trifluorotoluene (TFT, Aladdin, 99%) was used as received. Other reagents and solvents were all obtained from SCRC and used without further purification.

Synthesis of the Novel Fluorinated Triphilic Block Copolymer

Synthesis of hydrophobic macro CTA-PEHMA

DDMAT (0.1823 g, 0.5 mmol), EHMA (11.8479 g, 60 mmol) and the initiator AIBN (0.0093 g, 0.05 mmol) were mixed in toluene (40 g), then injected into a dried round-bottomed flask. The flask was deoxygenated and continuously purged with N₂. After stirring for 10 h at 65 °C, the polymerization was stopped by cooling the flask in ice/water mixture. Then the polymer was isolated by precipitating in cold methanol. The obtained yellow gluey product was dissolved in THF and precipitated with methanol for three times, and finally dried under vacuum at 55 °C overnight.

Synthesis of diblock copolymer PEHMA-*b*-*t*BMA

Macro CTA-PEHMA (2.4109 g, 0.1 mmol), *t*BMA (0.6376 g, 4 mmol) and the initiator AIBN (0.0024 g, 0.01 mmol) were mixed in toluene (20 g), then injected into a dried, deoxygenated flask as described above. After stirring for 20 h at 65 °C in N₂ atmosphere, the polymerization was ceased. Then the polymer was isolated by precipitating in methanol. The obtained copolymer product was dissolved in THF and precipitated with methanol for three times, and finally dried under vacuum at 55 °C overnight.

Synthesis of triblock copolymer PEHMA-*b*-*t*BMA-*b*-PFA

PEHMA-*b*-*t*BMA (1.3502 g, 0.08 mmol), FA (0.6751 g, 1.2 mmol) and the initiator AIBN (0.0026 g, 0.016 mmol) were dissolved in a mixed solvent (toluene:TFT = 2:1, *V*:*V*, 20 g). Herein, the use of TFT was aimed at increasing the solubility of fluorinated blocks in the polymerization system^[11]. Then the mixture was injected into a dried, deoxygenated flask. After stirring for 36 h at 65 °C in N₂ atmosphere, the polymerization was ceased. And the copolymer was isolated by precipitation in methanol. The obtained white product was dissolved in THF and precipitated with methanol for three times, and finally dried under vacuum at 55 °C overnight.

Synthesis of triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA

Triblock copolymer PEHMA-*b*-*t*BMA-*b*-PFA was first dissolved in a mixed solvent (CF₃COOH:CH₂Cl₂ = 1:1, *V*:*V*) and then stirred at room temperature overnight. Part of the solvent was removed by rotary evaporation at 30 °C. After that, the concentrated solution was precipitated with methanol. Finally, the obtained powder was dried under vacuum at 55 °C overnight.

Self-assembly of the Triphilic Copolymer

To study the self-assembly morphology of PEHMA-*b*-PMAA-*b*-PFA in a dilute solution, the copolymer was first dissolved in DMF at a concentration of 0.5 mg/mL. Then deionized water (a selective solvent for PMAA) was added to the copolymer solution at a rate of 2 mL/h with continuously stirring for at least 6 h. After that, an excessive amount of water was added to the solution to kinetically freeze the aggregations. Finally, the micellar solution was dialyzed against deionized water for three days to remove all the DMF. Different recipes were designed to investigate the influence of the water content (the added water/DMF volume ratio) on the self-assembly behavior of the triphilic copolymer.

To study the pH sensitivity of this triphilic copolymer, PEHMA-*b*-PMAA-*b*-PFA was first dissolved in 10 mL of DMF at a concentration of 1 mg/mL, diluted by adding some deionized water under magnetic stirring. Then the diluted solution was dialyzed against water for three days to remove all the solvent. After that, the micellar aqueous solution was transferred to a 25 mL volumetric flask to immobilize its volume. Therefore, a 0.4 mg/mL copolymer micellar aqueous solution was successfully prepared. Next, 0.1 mL of HCl or NaOH solution was added to the 1 mL of micellar aqueous solution to adjust the pH value. A series of HCl/NaOH solutions with different concentration gradients were prepared to create different pH conditions.

Characterization

Measurements

The compositions of the macro CTA, diblock and triblock copolymers were measured by ^1H -NMR spectroscopy on a Bruker AV400 nuclear magnetic resonance (NMR) spectrometer, using CDCl_3 as the solvent and TMS as a reference, while the triphilic copolymer was dissolved in the mixed solvent $\text{CDCl}_3/\text{DMSO}$. Fourier transform infrared spectra (FTIR) were recorded with KBr pellets on a Nicolet 6700 spectrometer. Molecular weight (M_n) and molecular weight distribution (M_w/M_n , PDI) were determined by gel permeation chromatography (GPC) equipped with a Waters 1515 isocratic HPLC pump, three Waters Styragel columns (Waters HT4, HT5E, and HT6) and a Waters 2414 refractive index detector (set at 35 °C), using tetrahydrofuran (THF) as an eluent at a flow rate 1.0 mL/min at 35 °C, and calibrated with polystyrene standards. The fluorine content of the triphilic copolymer was determined using the fluorine element analysis (F-EA)^[34].

The self-assembly morphology of PEHMA-*b*-PMAA-*b*-PFA was observed by transmission electron microscope (TEM). The micellar solution was dropped onto a copper grid coated with carbon and then placed at room temperature to fully eliminate all the solvent. The transmission electron microscope (JEM-1400) was used at an accelerating voltage of 200 kV. The turbidity was recorded on a UV-2550 UV-Vis spectrometer (SHIMADZU) using a quartz cell (path length: 1 cm) at the wavelength of 690 nm, which was far from the absorption of the copolymer. pH value was measured by a SIN-PH100 pH meter. Dynamic light scattering (DLS) was performed on a Malvern Zetasizer Nano ZS instrument, equipped with a 400 mW argon ion laser with wavelength of 532 nm. The test temperature was controlled at 25 °C and the scattering angle was 90°.

Turbidity measurement (OD)

The triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA was first dissolved in DMF, which was a good solvent for both PEHMA and PMAA blocks, at a concentration of 0.5 mg/mL. Then the selective solvent water was introduced to the 2 mL copolymer solution drop by drop (8 μL per drop) under magnetic stirring. After that, the solution was stirred for at least 1 min and set for equilibrium until the copolymer solution stabilized. The turbidity was then measured on the UV-Vis spectrometer until the optical density did not change anymore.

RESULTS AND DISCUSSION

Synthesis of the Novel Fluorinated Triphilic Copolymer

Three successive RAFT polymerizations were used to prepare the triblock copolymer PEHMA-*b*-P*t*BMA-*b*-PFA, starting with the monofunctional trithiocarbonate DDMAT (CTA), as shown in Scheme 1. The ^1H -NMR spectra of the hydrophobic macro CTA PEHMA and the diblock copolymer PEHMA-*b*-P*t*BMA in CDCl_3 were

specified in Fig. S3 (in SI). After hydrolyzing in acidic condition, the triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA was obtained. Figure 1(A) is the ^1H -NMR spectrum of PEHMA-*b*-PtBMA-*b*-PFA in CDCl_3 . The characteristic signals of PEHMA ($\delta = 3.83$, 2H, $-\text{OCH}_2-$), PtBMA ($\delta = 1.41$, 9H, $-\text{OC}(\text{CH}_3)_3$), PFA ($\delta = 4.35$, 2H, $-\text{OCH}_2-$) could all be found in the spectrum, which indicated the successful synthesis of the triblock copolymer. The ^1H -NMR spectrum of PEHMA-*b*-PMAA-*b*-PFA is given in Fig. 1(B). Compared to Fig. 1(A), new signal at $\delta = 12.26$ was assigned to the protons of the carboxyl groups from PMAA ($-\text{COOH}$). At the same time, the signal of tertiary butyl groups from PtBMA at $\delta = 1.41$ disappeared, proving that the tertiary butyl groups had been totally hydrolyzed and the fluorinated triphilic copolymer was successfully obtained.

FTIR measurement was also carried out here to prove the synthesis of the targeted copolymer PEHMA-*b*-PMAA-*b*-PFA. As shown in Fig. 2, the absorption at 1726 cm^{-1} corresponds to the stretching vibration of the ester bond ($-\text{C}=\text{O}$) and the absorption at 1139 cm^{-1} corresponds to the stretching vibration of the fluorinated side chain. After hydrolysis, the broad characteristic absorption of carboxylic acid shifted from 3200 cm^{-1} to

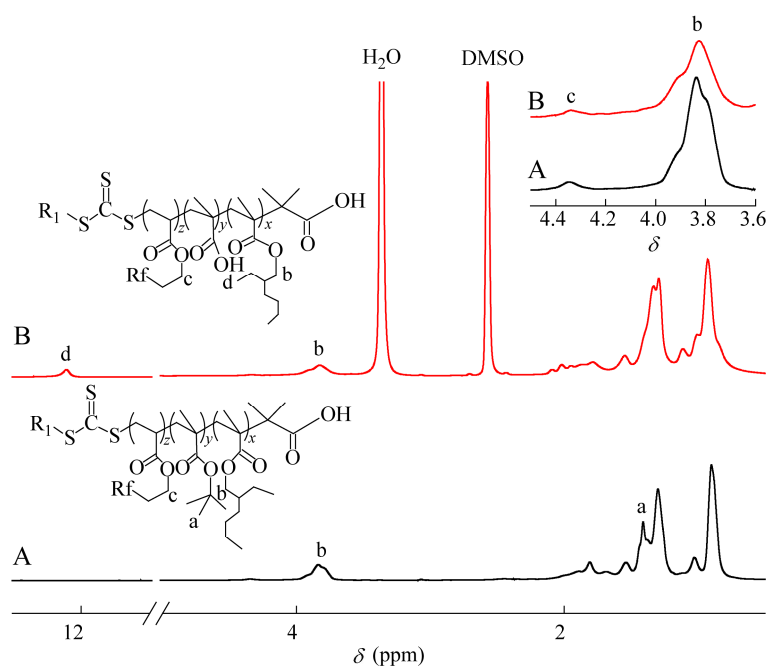


Fig. 1 ^1H -NMR spectra of PEHMA-*b*-PtBMA-*b*-PFA (A) and PEHMA-*b*-PMAA-*b*-PFA (B)

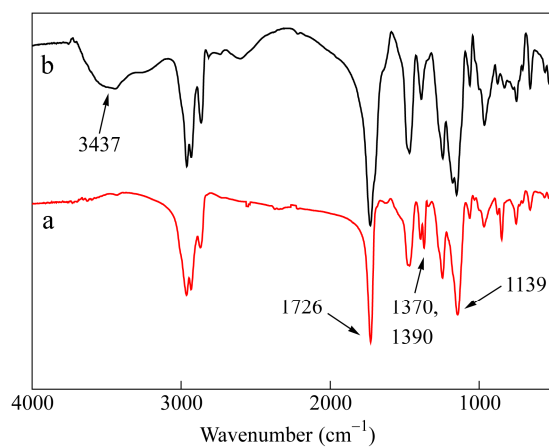


Fig. 2 The FTIR spectra of PEHMA-*b*-PtBMA-*b*-PFA (a) and PEHMA-*b*-PMAA-*b*-PFA (b)

3600 cm^{-1} , and at the same time, the absorption at 1370 and 1390 cm^{-1} , which was attributed to the symmetric bending vibration of the *tert*-butyl groups, was obviously weakened. Over all, the ^1H -NMR and FTIR spectra together revealed the successful synthesis and hydrolysis of the triblock copolymer.

Molecular weight and molecular weight distribution of the triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA and its precursors are presented in Table 1. As the used eluent THF was a poor solvent for PFA blocks, the fluorinated segments would probably associate even at a low concentration. Therefore, elemental analysis was performed to give the approximate content of PFA block. The fluorine content, combined with the molecular weight of the diblock copolymer, was used to determine the molecular weight of PEHMA-*b*-PMAA-*b*-PFA. All the results and calculation method are listed in Table 1.

Table 1 Molecular weight and molecular weight distribution of PEHMA-*b*-PMAA-*b*-PFA and its precursors

Sample	$M_n \times 10^{-4}$ (g/mol)	PDI ^a	F (wt%) ^b	DP
PEHMA	1.27 ^a	1.31	—	62 ^c
PEHMA- <i>b</i> -P _t BMA	1.69 ^a	1.29	—	30 ^c
PEHMA- <i>b</i> -P _t BMA- <i>b</i> -PFA	—	—	8.81	5 ^d
PEHMA- <i>b</i> -PMAA- <i>b</i> -PFA	1.79 ^e	—	—	—

^a Determined by GPC with PS standard in THF at 35 °C; ^b Determined by F-EA; ^c Degree of polymerization calculated based on the equation: $DP = (M_n \text{ Polymer} - MW_{CTA})/MW_{\text{Monomer}}$; ^d Degree of polymerization of FA, calculated based on the equation: $F\% = (DP_F \times 17 \times 19)/(M_n \text{ PEHMA-}b\text{-P}t\text{BMA} + DP_F \times 532.19)$, 17 was the number of fluorine atoms in FA, 19 was the relative atomic weight of the fluorine atom, 532.19 was the molecular weight of FA; ^e Calculated with the equation: $M_n \text{ PEHMA-}b\text{-PMAA-}b\text{-PFA} = M_n \text{ PEHMA} + DP_{t\text{BMA}} \times 86.09 + DP_{\text{FA}} \times 532.19$, 86.09 was the molecular weight of MAA.

Turbidity Measurement (OD)

The turbidity of the copolymer solution will change with the morphology transition of the aggregates^[35]. Therefore, measurement of turbidity is an effective way to reflect the self-assembly process of the copolymer. Figure 3 shows the UV absorbance change of the triphilic copolymer solution along with different water contents. The triphilic copolymer was first dissolved in DMF, which formed a transparent homogeneous solution. When deionized water was gradually added to the dispersion, the hydrophobic PEHMA and PFA blocks started to aggregate. With the increasing water content, the amount of micelles increased as well; thus the turbidity increased. The sudden change of turbidity was related to the self-assembly process and the formation of aggregations during the addition of water. There were two obvious changes in accordance with the two kinds of morphologies at the water content 6 vol% and 22 vol%, which will be discussed in the following section.

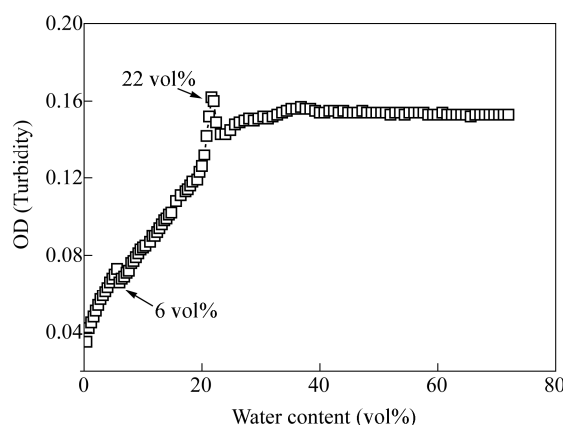


Fig. 3 The turbidity curve of the triphilic copolymer in DMF/water dispersion

Self-assembly of the Triphilic Copolymer in DMF/Water Dispersion

Self-assembly of triphilic copolymers in diluted solution is an efficient way to obtain various nanostructures. The morphology of these aggregations is controlled by a series of interaction forces, which could be tuned by block sequence, chemical composition of the copolymers and the outside solvent. In this study, we focused on the

influence of the selective solvent and its content on the self-assembly process. With the addition of water, which is a poor solvent for both PEHMA and PFA blocks, the inter-molecular repulsive force between water and the hydrophobic chains drove the self-assembly process, which formed the core of the aggregates. At the same time, the water-soluble PMAA block formed the corona.

Figure 4 shows the aggregation morphology of the triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA in different water contents. The morphology changed from multi-compartment rod-like structures (Fig. 4b) to spherical structures (Fig. 4d) as the water content increased from 10 vol% to 50 vol%, which was in accordance with the turbidity results in Fig. 3. Since the fluorinated block could not dissolve completely in DMF, the fluorocarbon side chain tended to associate in the copolymer DMF solution, as shown in Fig. 4(a). When deionized water was added to the solution drop by drop, the hydrophobic blocks started to aggregate and formed a visible phase separation region with the fluorinated blocks (see arrows in Figs. 4b and 4c). At the same time, the interaction parameter (χ) between the copolymer and solution changed along with the water content, which resulted in the morphology transformation of the aggregations.

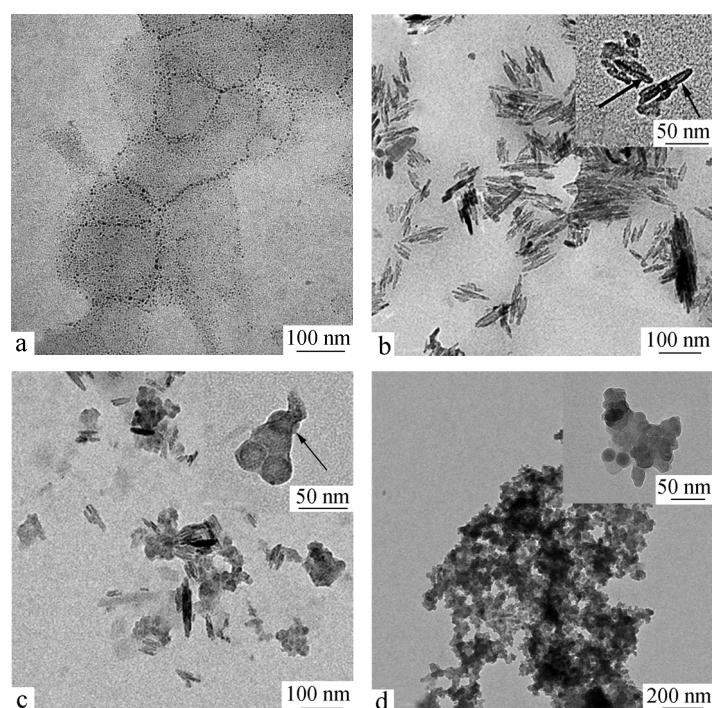


Fig. 4 TEM images of the PEHMA-*b*-PMAA-*b*-PFA aggregates in different water contents: 0 vol% (a); 10 vol% (b); 30 vol% (c); 50 vol% (d)

The morphology transformation mechanism was explained in terms of the effect of a series force balance. With the increase of water content, the local hydrophobic blocks were driven to aggregate-in while the hydrophilic PMAA block was driven to stretch-out. At a low water content, the inter-molecular force between the selective solvent and the copolymer chains was only able to compress the hydrophobic block and lead to rod-like aggregates. Meanwhile the fluorocarbon segments were poorly compatible with the hydrocarbon segments, so visible fluorocarbon separation domains^[17] could be found in the multi-compartment rod-like aggregations (see arrow in Fig. 4b). This internal structure was attributed to the side chain crystallization of the used fluorinated acrylate monomer. Since we could only observe 2D images in TEM, the exact structure of the phase separation region could not be identified, which could be a lamellar or cylinder structure. Along with the continuous addition of water, the inter-molecular force increased and the size of the polymer aggregations decreased as the hydrophobic blocks constantly aggregated inwards (see Fig. 4c).

Besides the inter-molecular force, interfacial tension also influenced the morphology transformation. As the selective solvent water was more polar than DMF, the interfacial tension between the solvent and the core-forming blocks would increase along with the addition of water. In order to stabilize the whole aggregation system, the morphology would transform into spheres to decrease the total interfacial tension by reducing the superficial area of the aggregations (Fig. 4c). Finally the aggregation system kept stable of the spherical morphology when the water content arrived at 50% (Fig. 4d).

pH Sensitivity of the Triphilic Block Copolymer

Since PMAA was a weak polyelectrolyte, the triphilic copolymer could be influenced by the pH change of the solution, owing to the deprotonation or protonation of the carboxyl groups. Therefore the pH sensitivity study was carried out with the addition of HCl or NaOH solution and aimed at fully neutralizing the whole protons in PMAA blocks. Five different pH values from 3 to 10 were designed to observe the size and morphology change of the aggregations in different pH conditions.

Results of size and size distribution of the copolymer aggregations were exhibited in Fig. S4 (in SI). Figure 5 shows the change of the aggregation size along with different pH, which reflected the stimuli-responding of the triphilic copolymer. As we can see, the size of the aggregations decreased when the pH increased from 3 to 5, which was probably ascribed to the hydrogen bond among the protonated PMAA shell^[36]. When the pH increased from 5 to 8, PMAA groups started to deprotonate and the electrostatic repulsion between the hydrophilic shells simultaneously increased the aggregation size. At the end, pH of the micellar solution reached 10. At this time, protons of the PMAA blocks were fully neutralized and the aggregation size was supposed to be the biggest. But Fig. 5 shows a decrease and this could be rationally explained as follows. When the PMAA block was fully deprotonated, the repulsive force between the hydrophilic shells was dramatically increased. This made the aggregations become unstable and would partly disintegrate^[19], which finally resulted in the decrease of the aggregation size.

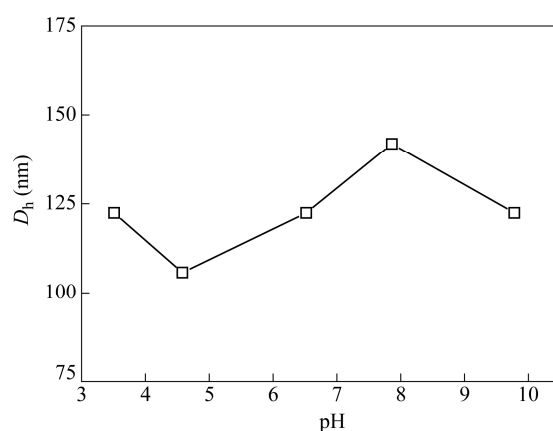


Fig. 5 The influence of pH on the aggregation size

Figure 6 shows the morphology of the aggregates in different pH conditions. The sizes in TEM images were smaller than the DLS results because the hydrophilic shell could not be seen in these images. Figure 6(b) presents the morphology of the copolymer aggregates without the addition of HCl or NaOH, where the rod-like and spherical mixed morphologies had been discussed in the previous section. Figures 6(a) and 6(c) exhibit the morphology of the copolymer aggregates with the addition of HCl and NaOH respectively. The addition of acid and base would dramatically increase the interfacial tension, which resulted in the disappearance of the rod-like structure. At the same time, obvious micro-phase fluorinated separation section can also be found in the core of the copolymer aggregates. But this time, the phase separation section was discontinuous and we assumed that the continuous crystallization of the fluorinated blocks was broken by the out-struggling force of the hydrophilic blocks.

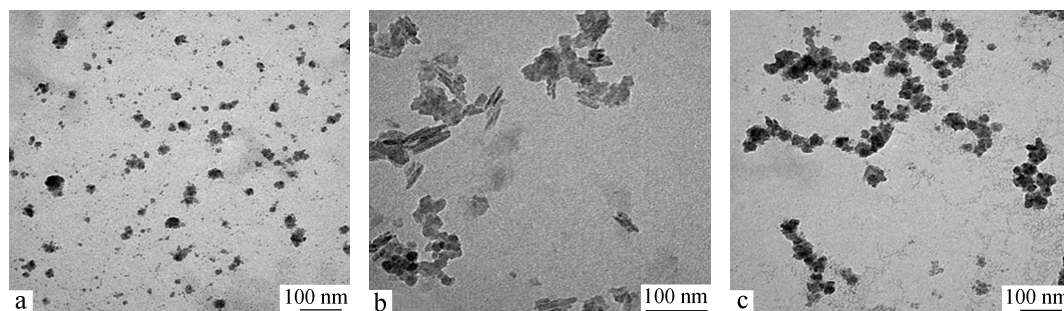


Fig. 6 TEM images of the aggregates under different pH conditions: 4.58 (a); 6.52 (b); 7.86 (c)

CONCLUSIONS

In this work, RAFT polymerization was used to synthesize a linear triphilic copolymer PEHMA-*b*-PMAA-*b*-PFA. ¹H-NMR, FTIR, and GPC were used to provide evidence for the successful synthesis of these well-defined copolymers. Turbidity measurement and the TEM images revealed a morphology evolution from the multi-compartment rod-like structure to spherical structure in different ratios of DMF/water dispersions. At the same time, on account of the poor compatibility between the hydrocarbon and the fluorocarbon blocks, visible micro-phase separation could be obtained in the core section. The morphology transformation mechanism was explained in terms of the effect of a series force balance, including the inter-molecular force and the interfacial tension. Followed by this, pH sensitivity study of the triphilic copolymer showed changes of morphology and aggregation size along with the addition of HCl or NaOH solution, which proved the triphilic copolymer to be pH sensitive. These stimuli-responsive multi-compartment nanostructures may have potential applications in drug delivery with a further study.

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