Polymerization-induced cooperative assembly (PICA) is reported to efficiently access inverse bicontinuous mesophases within particles consisting of amphiphilic block copolymers (BCPs) and solvophobic copolymers. Reversible addition-fragmentation chain transfer (RAFT) dispersion alternating copolymerization of styrene and pentafluorostyrene is conducted in 2% v/v toluene/ethanol by simultaneously using poly(N,N-dimethylacrylamide) (PDMA29) as a macromolecular chain transfer agent (macro-CTA) and small molecule CTA. The polymerization kinetics of PICA and polymerization-induced self-assembly (PISA) were compared, and the apparent rate constants observed in both systems were essentially the same. Gel permeation chromatography (GPC) indicated that PICA-synthesized amphiphilic BCPs/solvophobic copolymers had low dispersity. PICA syntheses were conducted by systematically varying the degree of polymerization of the core-forming block/solvophobic copolymer at different CTA molar ratios (x) and solid contents. The particle morphology was investigated by transmission electron microscopy (TEM), scanning electron microscopy (SEM), and small-angle X-ray scattering (SAXS). Inverse bicontinuous mesophases could be accessed at different x and solid contents, demonstrating that PICA promoted the formation of inverse bicontinuous mesophases more effectively, compared with PISA.

Keywords: block copolymers, bicontinuous mesophases, cubosomes, hexasomes, polymerization-induced self-assembly, polymerization-induced cooperative assembly, reversible addition-fragmentation chain transfer
Introduction

Particles with ordered inverse mesophases have shown great promise in biomaterials, nanotemplates, and bioractors due to their bicontinuous channels, high surface area, and high porosity. Polymer mesophase particles are typically prepared by solution self-assembly of highly asymmetric block copolymers (BCPs) for which the particle morphology is determined by the packing parameter $p = \frac{\nu}{\alpha c \lambda_c}$ (where $\nu$, $\alpha$, and $\lambda_c$ represent the volume of the core-forming block, the interfacial area, and the length of the core-forming block, respectively). By varying the $p$ values along with other conditions, various morphologies such as sphere, worm, vesicle, and lamellae can be accessed readily at $p \leq 1$. In principle, inverse bicontinuous mesophases such as cubosome and hexasome can also be accessed provided that the conditions for $p > 1$ are met. However, these inverse morphologies have been much less reported, presumably due to their elusive formation mechanism and complex assembly conditions.

Experimental Methods

Materials

Styrene analytical reagent (St AR) grade was purchased from Sinopharm Chemical Reagent (Shanghai, China), 2,3,4,5,6-pentafluorostyrene (PFS; 97%) and N,N-dimethylacrylamide (DMA; 99%) from J&K Scientific (Shanghai, China) were passed through an alkaline aluminum oxide column to remove the inhibitor. 2,2′-Azobis(2-methylpropionitrile) (AIBN; 99%) from Sigma-Aldrich (Shanghai, China) was recrystallized from ethanol before use. The 2-ethylnsulfanyltiocarbonylsulfanylpropionic acid methyl ester was synthesized according to a previous report. Ethanol (AR), N,N-dimethylformamide (DMF; AR), toluene (AR), tetrahydrofuran (THF; AR), and 1,4-dioxane (AR) from Sinopharm Chemical Reagent were used without further purification.

Characterization

Nuclear magnetic resonance spectroscopy

Proton nuclear magnetic resonance (1H NMR) spectroscopy was conducted on a Bruker AV 400 MHz spectrometer (Bruker, Switzerland) using CDCl$_3$ as the solvent. Chemical shifts were obtained using solvent residue as the reference. The monomer conversion was calculated from Sinopharm Chemical Reagent

Transmission electron microscopy

Transmission electron microscopy (TEM) was conducted on a JEM-1400 Plus Microscope (JEOL Ltd., Tokyo, Japan) at 120 kV, and high-resolution TEM was performed on a JEOL JEM2011F Microscope (Tokyo, Japan) at 200 kV. TEM samples were prepared by dropping 10 μL dispersion (0.05% or 0.1%, w/v) on a carbon-coated grid.
copper grid and dried at room temperature and then further dried under vacuum at 40 °C for 12 h.

**Gel permeation chromatography**

Gel permeation chromatography (GPC) was performed on an Agilent 1260 Infinity with a Waters 2410 refractive index detector (Agilent, America). The calibration curve was determined using monodisperse poly(styrene) (PS) (molecular weight range from 5.8 x 10^3 to 8.53 x 10^5 g mol^-1) using THF as the mobile phase. The flow rate of THF was 1.0 mL min^-1 at 35 °C.

**Field-emission scanning electron microscopy**

Field-emission scanning electron microscopy (FESEM) was performed on a Zeiss Ultra 55 (Zeiss, Germany) at a working voltage of 20 kV. Dispersions were diluted to 0.1% v/v and dropped onto mica sheet attached to steel stubs using carbon adhesive and then dried under vacuum at 40 °C for 5 h. The samples were made conductive by sputtering a thin layer of gold.

**Small-angle X-ray scattering**

Small-angle X-ray scattering (SAXS) profiles were recorded on a France/Xenocs XeUSS2.0 (Xenocs, France), with microfocus liquid metal anodes Ga alloy at 70 kV. The experiments were carried out through X-ray radiation with a wavelength of λ = 1.34 Å at room temperature (25 °C). To prepare the SAXS samples, 0.5 mL BCP dispersions were dropped on glass slides and dried at room temperature for 12 h and then further dried under vacuum at 25 °C for 2 h.

**Synthetic procedures**

**Synthesis of PDMA29-b-P(St-alt-PFS)m BCP particles via PISA**

Poly(N,N-dimethylacrylamide) (PDMA29) b-P(St-b-PFS)m, BCP particles were synthesized by RAFT dispersion polymerization in toluene/ethanol (2/98, v/v) at 30% solid content and 70 °C. A typical procedure is described as follows: PDMA29 (26.2 mg, 0.0085 mmol), St (200.3 mg, 1.92 mmol), PFS (373.2 mg, 1.92 mmol), and AIBN (32 µL, 0.0131 g mL^-1 in 2% v/v toluene/ethanol, 2.56 µmol) were dissolved in 2% v/v toluene/ethanol (2 mL). The solution was then degassed with N2 for 15 min in an ice/water bath and heated to 70 °C for 48 h. More 2% v/v toluene/ethanol (5 mL) was added to the reaction solution (1 mL), followed by centrifugation (8000 rpm, 10 min). The solids were washed three times with 2% v/v toluene/ethanol to give the polymers for 1H NMR, 19F NMR, and GPC analysis. 1H NMR (400 MHz, CDCl3, δ [ppm]): 6.82–7.21 (br, Ha, Hb), 6.31–6.79 (br, Hg), 2.78–3.19 (Hb), 2.11–2.78 (br, Hg, Ha, Hb), 1.45–2.11 (Hb, Hg), 0.82–1.41 (Hc). Residual peak: 1.56 ppm was H2O. 19F NMR (376 MHz, CDCl3, δ [ppm]): –142 (Fg), –157 (Fb), –163 (Fh).

**Synthesis of PDMA29-b-P(St-alt-PFS)m/ P(St-alt-PFS)m BCP/solvophobic copolymer blend particles via PICA**

PDMA29-b-P(St-alt-PFS)m/P(St-alt-PFS)m blend particles were synthesized by RAFT dispersion polymerization in toluene/ethanol (2/98, v/v) at 70 °C. A typical procedure is described as follows: PDMA29 (21.0 mg, 0.0068 mmol), CTA (0.65 mg, 0.0029 mmol), St (201.9 mg, 1.94 mmol), PFS (376.4 mg, 1.94 mmol), and AIBN (28 µL, 0.0172 g mL^-1 in 2% v/v toluene/ethanol, 2.91 µmol) were dissolved in 2% v/v toluene/ethanol (2 mL). The solution was degassed with N2 for 15 min in an ice/water bath and heated to 70 °C for 48 h. More 2% v/v toluene/ethanol (5 mL) was added to the reaction solution (1 mL), followed by centrifugation (8000 rpm, 10 min). The solids were washed three times with 2% v/v toluene/ethanol to give the polymers for 1H NMR, 19F NMR, and GPC analysis. 1H NMR (400 MHz, CDCl3, δ [ppm]): 6.78–7.21 (br, Ha, Hb, Hg), 6.28–6.78 (br, Ha, Hg), 2.80–3.19 (Hb), 1.98–3.19 (br, Ha, Hc, Hg, Hb), 1.37–1.98 (Hb, Hg, Hb, Hb), 0.74–1.39 (Hc). 19F NMR (376 MHz, CDCl3, δ [ppm]): –159 to 143 (Fg, Fb), –154 to 160 (Fg, Fc), –161 to 165 (Fb, Fd).

**Results and Discussion**

As an extension to PISA, PICA can facilitate morphological transitions via simultaneous use of macromolecular chain transfer agents (macro-CTAs) and small molecule CTAs, leading to the generation of amphiphilic BCPs and solvophobic copolymers that cooperatively assemble in the same particles. As depicted in Schemes 1a and 1b, a trithiocarbonate was used as a small molecule CTA, and PDMA29 (Mn = 3.1 kg/mol, D = 1.10), synthesized via RAFT polymerization from the same CTA, was used as a solvophilic macro-CTA or stabilizer. Mixtures of the small molecule CTA and PDMA29 macro-CTA were used to mediate RAFT dispersion alternating copolymerization of electron-rich St and electron-deficient PFS at 70 °C. Thus, this PICA approach generated colloidal particles consisting of PDMA-b-P(St-alt-PFS) BCPs and P(St-alt-PFS) copolymers in the same particles. PICA was conducted in 2% v/v toluene/ethanol since this solvent composition has been demonstrated previously to be effective in PISA to obtain ordered inverse mesophases based on dispersion alternating copolymerization of St and PFS.

PICA was first conducted at a total solid content of 30% w/v using 0.3 equiv. AIBN by controlling the molar ratio of small molecule CTA (x) at x = 0.3. The comparison of polymerization kinetics of PICA versus PISA is shown in Figure 1a. Both PICA and PISA synthesizes...
exhibited pseudo-first-order kinetics, indicating the presence of a constant radical concentration in both cases. Multistaged polymerization kinetics are often observed in some PISA systems because of polymerization locus transitions from solution to particles of different morphologies. However, multistaged transitions in polymerization kinetics were not observed in PISA or PISA, presumably due to the fast nucleation of the fluorine-containing core-forming block/solvophobic copolymer. The apparent polymerization rate constant for PICA ($k = 0.128 \text{ h}^{-1}$) was quite close to that for the PISA synthesis ($k = 0.121 \text{ h}^{-1}$), which means that the BCPs and solvophobic copolymers grew at the same rate considering that the AIBN concentration used for PICA (2.56 mmol L$^{-1}$) and PISA (2.58 mmol L$^{-1}$) was almost the same. Therefore, it is safe to assume that both PDMA$_{29}$-b-P(St-alt-PFS)$_m$ BCPs and P(St-alt-PFS)$_m$ copolymers possessed nearly the same degree of polymerization (DP) during PICA. PICA syntheses ($x = 0.3$) targeting DPs in the range 100-400 all resulted in stable particles with near-quantitative monomer conversions ($\geq 95\%$) (Supporting Information Table S1). Although a mixture of BCPs and solvophobic copolymers was present in the PICA-generated particles, the overall molecular weight distribution was relatively low ($D \leq 1.20$), as indicated by GPC measurements (Figure 1b). This suggests that PICA proceeds with good RAFT control, and the difference in molecular weight between BCPs and solvophobic copolymers was relatively small due to the low molecular weight of PDMA$_{29}$. $^1$H NMR spectroscopy analysis (Supporting Information Figure S1) indicated that PICA-generated particles had a higher integration ratio of aromatic protons (6.2-7.2 ppm) to N-methyl protons (2.8-3.2 ppm) than the corresponding PISA-generated particles. An apparent increase in the $^{19}$F signal was observed in $^{19}$F NMR spectra for the PICA sample relative to the PISA sample. These results confirmed that both PDMA$_{29}$-b-P(St-alt-PFS)$_m$ BCPs and P(St-alt-PFS)$_m$ copolymers were produced in PICA.

Having established that RAFT dispersion PICA of PDMA$_{29}$-b-P(St-alt-PFS)$_m$/P(St-alt-PFS)$_m$ could produce colloidally stable particles with well-controlled composition and molecular weight, we next focused our attention on the particle morphologies, which were investigated by TEM and scanning electron microscopy (SEM). For the convenience of comparison, the TEM micrographs for the PISA-generated particles are provided in Supporting Information Figure S2. At $x = 0.3$ and 30% w/v solid content, the morphological transition with increasing DPs of the core-forming block/solvophobic
copolymer of PICA-generated particles underwent with a sequence of a sphere–worm–vesicle–sponge–inverse bicontinuous mesophase (Figures 2a–2i), similar to that observed in PISA. Specifically, spheres with a diameter of 36.2 ± 7.5 nm, worms with a diameter of 32.7 ± 5.6 nm, vesicles with diameters of 434.6 ± 121.7 nm, and a wall thickness of 48.6 ± 13.5 nm were observed at DPs of 100, 130, and 180, respectively. Sponge-like particles started to form when DP increased to 250, beyond which the formation of inverse bicontinuous mesophases at DP ≥ 300 was evident. High-resolution TEM confirmed the presence of ordered mesophases with a solvophobic polymer channel diameter of 26.5 ± 4.8 nm and a hollow channel diameter of 33.4 ± 5.2 nm. SEM indicated that the bicontinuous structures were wrapped by a rough surface membrane (~32 nm). Noticeably, inverse bicontinuous mesophases started to form at a lower DP for PICA (DP 300) than for PISA (DP 450), demonstrating that PICA was more efficient in accessing inverse bicontinuous mesophases than PISA.

Unlike PISA, it was possible to adjust the molar ratio of CTA to modulate particle morphology in PICA, which led us to examine varying two more CTA molar ratios (x = 0.1 and 0.6) at the same solid content (30% w/v).

The TEM micrographs for PICA conducted at x = 0.1 are shown in Figures 3a–3i. The morphological transition for this series of particles is similar to that for PISA, as might be expected considering the relatively low CTA molar ratio. However, the effect of PICA on promoting morphological transition was still discernable even at this low CTA molar ratio (x = 0.1). For instance, sponge-like particles formed at DP 300 for PICA (x = 0.1), whereas DP 400 was required to create the same PISA morphology. Obviously, a higher CTA molar ratio had a more profound effect on promoting morphological transition, as inverse mesophases were observed at a DP as low as 300 for PICA conducted at x = 0.3, but inverse mesophases were obtained at DPs ≥ 400 for PICA (x = 0.1), as judged from the rim of the micron-sized particles and high-resolution TEM.

The TEM micrographs for PICA conducted at x = 0.6 are shown in Figures 4a–4f. Such a high CTA molar ratio showed a more significant effect on promoting morphological transition than CTA molar ratios of 0.1 and 0.3. Sponge-like morphology occurred at a much lower DP of 180. Inverse mesophases, albeit less ordered, appeared more readily at DP of 250 (Supporting Information Figure S4). As the DP further increased to 300, the internal mesophase became more ordered than those obtained at lower DPs within this series (x = 0.6, 30% w/v), as revealed by high-resolution TEM (inset of Figure 4e).

We reported previously that high solid contents, at least 30% w/v, were required to obtain inverse bicontinuous mesophases for PISA. To further illustrate the capacity of PICA for promoting morphological transition, we decided to conduct PICA syntheses at lower solid contents to see if inverse mesophases could still be achieved. Two series of PICA (x = 0.3) syntheses were conducted at 20% and 10% w/v solid content, respectively, and their TEM micrographs are presented in Figures 5a–5f and 6a–6f. For all PICA (x = 0.3) conducted at 30–10% w/v, the morphological transition sequence followed the same pattern, but increasingly higher DPs were required to obtain the same morphology due to decreasing solid content, and thus, lower probability of inelastic collision between particles. For instance, at DP 130, worms were observed for both 30% and 20% w/v solid contents, but spheres were observed for 10% w/v solid content. A higher DP 180 was required for 10% w/v solid content to reach the worm phase, and
Figure 2 | TEM (a–h) and SEM (i) micrographs of PICA-synthesized particles at $x = 0.3$ and 30% w/v solid content. TEM, transmission electron microscopy; SEM, scanning electron microscopy; PICA, polymerization-induced cooperative assembly.

Figure 3 | (a–i) TEM micrographs of PICA-synthesized particles at $x = 0.1$ and 30% w/v solid content. TEM, transmission electron microscopy; PICA, polymerization-induced cooperative assembly.
the worms were shorter than those for 30% and 20% solid contents. Nevertheless, it is remarkable to see that inverse mesophases could be accessed even when the solid content was lowered. Inverse mesophases occurred at DP 250 and 350 for 20% and 10% w/v solid content, respectively. Note that as the solid content decreased, the mesophases became less ordered, as revealed by high-resolution TEM. We also conducted PICA ($x = 0.6$) synthesis by lowering the solid content from 30% to 10% w/w. A similar trend was observed, and inverse mesophases were again observed at 10% w/v solid content (Supporting Information Figure S5).

We elucidated the PICA-generated particles’ internal mesophasic structures by performing SAXS and SAXS profiles for some of the representative samples are shown in Figure 7. We reported earlier that the mesophases of PISA-generated particles evolved from $Im\overline{3}m$ to mixed $Im\overline{3}m$ and $p6 \text{mm}$ structures as the DP of the core-forming block increased. In this study, all the PICA-generated particles possessed mixed $Im\overline{3}m$ and
p6 mm symmetries. Noteworthily, only one peak (q₁), assigned to the 10 faces of p6 mm, appeared in all these particles. In principle, a specific mesophasic structure could not be explicitly assigned based on only one SAXS peak. This somewhat arbitrary assignment of q₁ to p6 mm is based on the mixed Im3m and p6 mm structures observed in the PISA-generated particles and different microdomains in the PICA-generated particles, as revealed by high-resolution TEM. In Figure 7b, in addition to the q₁ peak assigned to p6 mm, the SAXS profile also shows two other distinct peaks (q₃ and q₄) with a defined q² ratio of 1/2, which could be assigned to Im3m phase. Particles with well-defined Im3m phase typically possesses ordered pores on the surface. 9,74,75 However, the surface of these particles did not possess any pores but showed some parallel aligned valleys, indicating that Im3m may be present at a minor fraction than p6 mm. This point was supported by the fact that hexagonally packed cylinders lying perpendicular to the page at the periphery of the particles, as well as cylinders aligning parallel to the page, could be observed. Literature reports also indicate that SAXS peaks of p6 mm phase were relatively less resolved than those for Im3m phase, even though p6 mm structures were observed by TEM. 14,76 Therefore, although peaks corresponding to Im3m phase appeared in the SAXS spectra; it is likely that Im3m phase-only accounted for a minor fraction, and the major fraction should be assigned to the p6 mm phase. The SAXS peaks in Figures 7a and 7c were less resolved, indicating the mesophases generated at x = 0.1

**Figure 6** | (a–f) TEM micrographs of PICA-synthesized particles at x = 0.3 and 10% w/v solid content. TEM, transmission electron microscopy; PICA, polymerization-induced cooperative assembly.

**Figure 7** | (a–c) SAXS profiles of representative PICA-generated particles with inverse bicontinuous mesophases (q in red color is for p6 mm and q in the black color is for Im3m). SAXS, small-angle X-ray scattering; transmission electron microscopy; PICA, polymerization-induced cooperative assembly.
and 0.6 were less ordered, consistent with the observation from TEM.

Conclusion

We have investigated PICA of PDMA-b-P(St-alt-PFS)/P(St-alt-PFS) systematically by varying the CTA molar ratio (χ), DP of the core-forming block/solvophobic copolymer, and the solid content (Supporting Information Table S7). PICA exhibited pseudo-first-order polymerization kinetic behavior with an apparent polymerization rate constant close to that of PISA, suggesting equal polymerization rates of BCPs and solvophobic copolymers, and thus, a uniform distribution of polymer chains within the particles. As DP of the core-forming block/solvophobic copolymer increased, morphological transitions followed the sequence of a sphere-worm-vesicle-large compound vesicle-sponge-inverse bicontinuous mesophase. Mixed inverse bicontinuous mesophases, Im3m and p6 mm were observed in all PICA syntheses conducted at different x (0.1, 0.3, and 0.6) and solid contents (10%, 20%, and 30% w/v), among which the mesophases obtained at x = 0.3 and 30% w/v showed the highest order. Therefore, we inferred that PICA could promote morphological transition and, especially, provide an effective method for generating particles with inverse bicontinuous mesophases. Future work will be dedicated to improving the purity and order of inverse bicontinuous mesophases, which could be achieved by careful optimization of the synthetic conditions.

Supporting Information

Supporting Information is available.

Conflict of Interest

The authors declare no competing interest.

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