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RESEARCH ARTICLE

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Synthesis of ultra-high molecular weight core cross-linked star (CCS) polymer using high molecular weight spherical nanoparticles and arm-first method

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Abstract

P (*N,N*-Dimethylacrylamide) -b-P (2-methoxyethyl acrylate) (PDMA-b-PMEA) and Poly (poly (ethylene glycol) methyl ether methacrylate) -b-P (2-methoxyethyl acrylate) (PPEGMA-b-PMEA) di-block copolymer nanoparticles are prepared by RAFT dispersion polymerization in water at 35°C. By changing the degree of polymerization (DP) of PMEA and the solid content of the reaction solution, only spherical nanoparticles are obtained. Using PDMA and PPEGMA as macromolecular chain transfer agents (Macro-CTA), the actual DP of PMEA block can be up to 11,520 and 17,000, respectively, the size of the obtained spherical nanoparticles can be close to 600 nm, and the molecular weight of the block copolymer can reach 10^6. Such large spheres may serve as model sterically stabilized particles for analytical centrifugation studies. In the mixed solvent of ethanol and water (1:1, v/v), we synthesize ultra-high molecular weight CCS polymer by the arm-first method. Star polymer with such high molecular weight and small particle size can be used for emulsification.

KEYWORDS
degree of polymerization, dispersion polymerization, morphology, ultra-high molecular weight

1 | INTRODUCTION

Polymer nanoparticles with different morphologies have different characteristics and have potential applications in catalysis,[1] therapy,[2] imaging,[3] and sensing.[4] Nowadays, self-assembly is often used to prepare particles with various shapes. Traditional self-assembly can only be carried out at a low concentration (<1%),[5–9] the preparation process is cumbersome and it is difficult to get other shapes besides spheres, so the application is limited. Controllable living radical polymerization,[10–16] especially RAFT polymerization combined with polymerization-induced

self-assembly, has become an important method to prepare various shapes of block polymer nanoparticles.[17–24]

CCS polymer contains high cross-linked core and many long arms around the core.[25]CCS polymer is usually tens of nanometers, making them similar with nanoparticles in size. We can regard CCS as an intermediate between common soluble polymer and polymer nanoparticles, which combines the size of nanoparticles and the flexibility of soluble polymers. Star polymers have been intensively studied for various applications such as drug delivery, imaging, catalysis, and polymer blends.[26–28]An has previously reported that core cross-linked star (CCS) polymers can be used as highly effective emulsifiers to form long-lasting stable emulsions.[29]

Synthesis of high molecular weight polymers by solution polymerization usually results in very high viscosities. Therefore, it is usually achieved by heterogeneous polymerization.[23,30–33] Chen[34] synthesized temperature and salt dual responsive CCS polymers using the arm-first method, which consist of poly (MEA_x-co-$PEGA_y$) (MEA is 2-methoxyethyl acrylate and PEGA is poly (ethylene glycol) acrylate)) of different compositions. Molecular weight of the CCS can be as high as 300 KDa. Jesson et al.[35] synthesized high molecular weight poly (glycerol monomethacrylate) via RAFT emulsion polymerization of iso-propylidene glycerol methacrylate. Molecular weight of the poly (glycerol monomethacrylate) can be as high as 160 KDa. Parker et al.[36] explored the upper size limit for poly (stearyl methacrylate)-poly (benzyl methacrylate) (PSMA-PBzMA) diblock copolymer nanoparticles in mineral oil. Well defined morphologies and narrow particle size distributions can be obtained for DP of PBzMA up to 3500, which corresponds to an upper particle size limit of 459 nm.

Poly (2-methoxyethyl acrylate) (PMEA) is a non-toxic material with good biocompatibility. The monomer MEA has good water solubility, but the polymer PMEA is water-insoluble.[37–41] Higher-order morphologies (worms and vesicles) for RAFT-mediated aqueous dispersion polymerization of MEA at 70°C using PEG_{113}-CTA as a steric stabilizer was reported by Sugihara et al.[42] The authors carefully tuned the BCP composition and solids, which led to higher-order morphologies. Galle Mellot et al.[43] reported a series of poly (*N,N*-dimethylacrylamide)-b-poly (2-methoxyethyl acrylate) (PDMAc-b-PMEA) diblock copolymers prepared by aqueous dispersion polymerization. They found the introduction of the templating bis-urea stickers into PISA greatly promotes the formation of fibers.

We use the hydrophilic macromolecule transfer agent P (*N,N*-dimethylacrylamide) (PDMA) and poly (polyethylene glycol methyl ether methacrylate) (PPEGMA) to carry out the RAFT dispersion polymerization of MEA in water, and use the redox initiator KPS/NaAs at a low temperature. And finally spherical nanoparticles with good structure and uniform particle size are prepared. The DP of PMEA can be as high as more than 10,000, which corresponds to the upper limit of particle size around 600 nm. Although the size is large, the size distribution is quite narrow (PDI < 1.2). Then in the mixed solvent of ethanol and water (1:1, v/v), we synthesize ultra-high molecular weight CCS polymer by the arm-first method by using such a high molecular weight diblock copolymer as an arm.

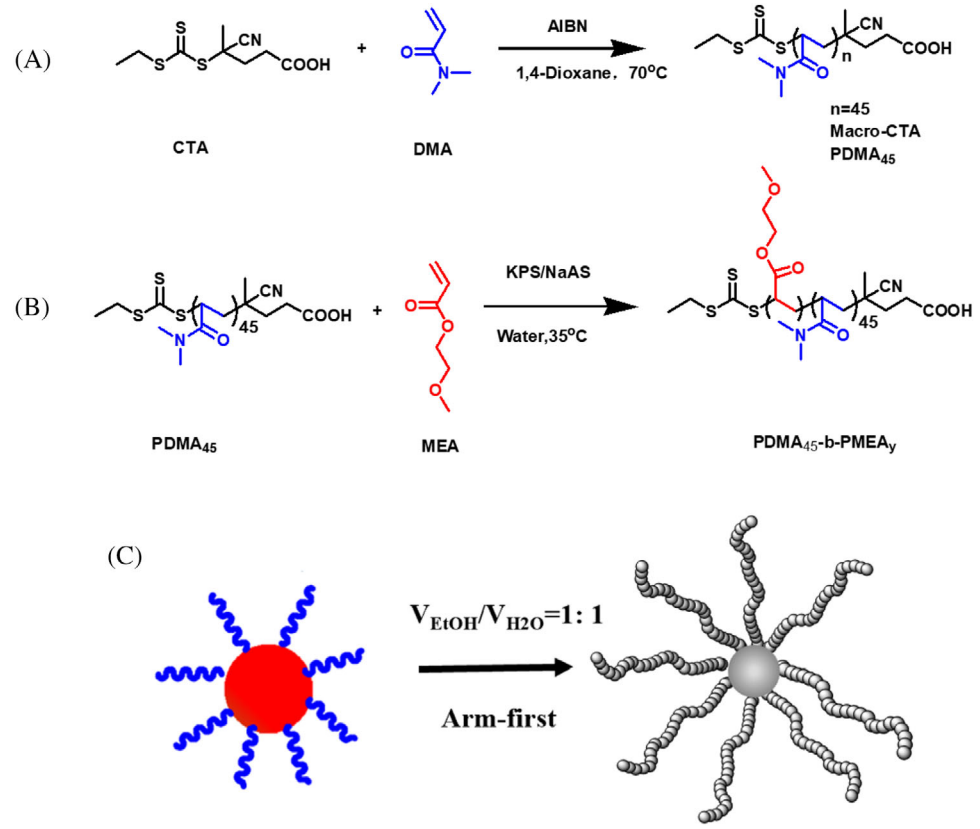
2 | EXPERIMENT

2.1 | Materials

2-Methoxyethyl acrylate (MEA, 98%), *N,N*-dimethylacrylamide (DMA, 98%) and L-Ascorbic acid sodium salt (NaAs, 99%) was purchased from Macklin. Poly (ethylene glycol) methyl ether methacrylate(PEGMA, M_n = 500) were purchased from Sigma-Aldrich. Potassium persulfate (KPS, AR), *N,N*-dimethylformamide (DMF, >99.5%), tetrahydrofuran (THF, >99%), and Azobisisobutyronitrile (AIBN, CP) were bought from Sinopharm Chemical Reagent Co. Ltd. AIBN was recrystallized twice in methanol. KPS was recrystallized in cold water. All monomers must be passed through an Al_2O_3 column before use to remove the inhibitor. 4-Cyano-4-(ethylthiocarbonothioylthio) pentanoic acid was prepared by referring to previous literature.

2.2 | Characterizations

^{1}H NMR spectra were recorded using a 400 MHz NMR instrument (referenced internally to Me_4Si). Gel permeation chromatography (GPC) was performed on a PL-GPC50 instrument, equipped with 4 × 300 mm column. The type of refractive index detector was RI Deflection detector. Using DMF (HPLC grade, containing 1 mg mL^{-1} LiBr) as the eluent at a flow rate of 1.0 mL min^{-1}. The temperature of the columns and the refractometer was set at 30°C. Analysis of molecular weight and polydispersity index of polymers was performed using CirrusTM software against PS standard. Colloid solutions were diluted to generate 0.05% dispersions for DLS and TEM characterization. Nanoparticle sizing was analyzed using dynamic light scattering (DLS) on a Nano Brook 90 Plus Zeta at 25°C. Transmission electron microscopy (TEM) was performed on a JEOL JEM-2100F. To prepare TEM samples, colloid solutions were dropped onto carbon-coated copper grids and dried in air. IKA RT 5 was used as heating instrument.



SCHEME 1 A, Synthesis of Macro-CTA $PDMA_{45}$; B, RAFT aqueous dispersion polymerization of MEA using $PDMA_{45}$ as Macro-CTA; C, Synthesis of CCS polymer by arm-first method

TABLE 1 Conditions and results of dispersion polymerization of MEA using $PDMA_{45}$ as macro-CTA in water[a]

Entry	MEA/$PDMA_{45}$	Solid (%w/v)[b]	T [°C]	Time [h]	Con. (%)[c]	M_n [kg mol^{-1}][d]	M_w [kg mol^{-1}]	M_w/M_n	D_h [nm][e]	PDI
1	1500	15	35	4	97.7 (4 h)	1162	1660	1.429	106.1	1.045
2	5000	15	35	4	96.5 (4 h)	1304	1529	1.173	221.7	1.139
3	7000	15	35	5	93.7 (5 h)	1657	1995	1.204	250.9	1.020
4	10000	15	35	6	94.8 (6 h)	1804	2304	1.277	490.6	1.274
5	12000	15	35	6	96.0 (6 h)	3351	3565	1.064	536.8	1.258
6	15000	15	35	6	Precipitation	/	/	/	/	/

[a][NaAs]:[KPS]:[PDMA] = 0.02: 0.02: 1. For Entry 4 and Entry 5, [NaAs]:[KPS]:[PDMA] = 0.05:0.05:1.
[b]Total polymer content relative to water: $(W_{Macro\text{-}CTA} + W_{polymer})/V_{water}$.
[c]Monomer conversion determined by ^1H NMR.
[d]M_n and M_w measured by GPC.
[e]Particle diameter determined by DLS.

3 | RESULTS AND DISCUSSION

3.1 | Effect of DP

Dispersion polymerization of MEA was carried out at solids content 15%w/v relative to water using $PDMA_{45}$ and $PPEGMA_{16}$ as both the RAFT controlling agent and the hydrophilic steric stabilizer (as shown in Scheme 1 and Scheme S1). KPS/NaAs was used as the radical initiator to allow efficient polymerization at 35°C. To study the influence of PMEA DP on morphology, the target DP of PMEA was adjusted for n (MEA):n ($PDMA_{45}$) = 1500-15,000 (Table 1) and n (MEA):n ($PPEGMA_{16}$) = 1500-40000 (Table S1), at a molar ratio of [NaAs]:[KPS]:[Macro-CTA] = 0.02:0.02:1, adjusting the reaction time 4-6 hours according to the monomer concentration. ^1H NMR was used to test monomer conversion, GPC was used to test relative molecular weight and polydispersity, DLS was used

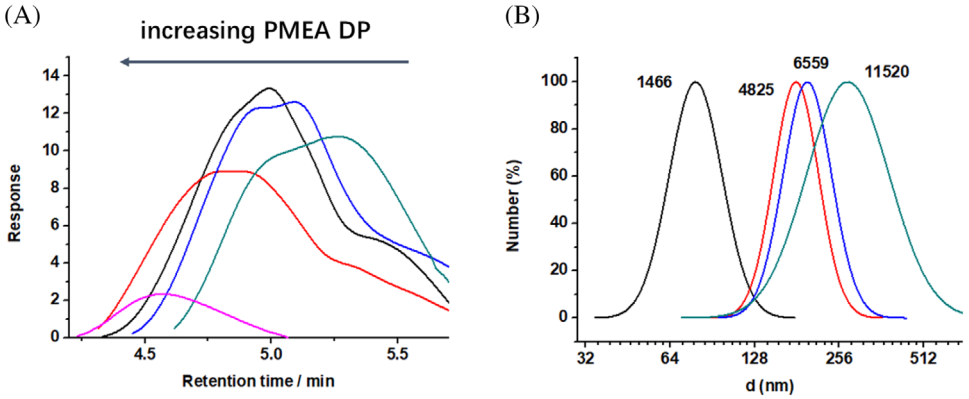


FIGURE 1 A, GPC chromatograms of PDMA-b-PMEA polymers with different DP of PMEA. B, DLS results of PDMA-b-PMEA polymers with different DP of PMEA.

to study the size of nanoparticles, and TEM was used to observe the morphology of nanoparticles.

We first synthesized $PDMA_{45}$ and $PPEGMA_{16}$ by RAFT solution polymerization, using 4-cyano-4-(ethylthiocarbonothioylthio) pentanoic acid as CTA, *N,N*-dimethylacrylamide (DMA) and poly (ethylene glycol) methyl ether methacrylate (PEGMA, M_n = 500) as monomer, respectively. After purification and drying, $PDMA_{45}$ and $PPEGMA_{16}$ were used in the subsequent RAFT dispersion polymerization as a macromolecular chain transfer agent and hydrophilic steric stabilizer.

When $PDMA_{45}$ is used as the macromolecular chain transfer agent, in order to study its maximum DP (when it precipitates), the target DP of PMEA was changed from 1500 to 15,000, the reaction time is extended as the target degree of polymerization increases (Table 1). Precipitation appeared when the DP reached 15,000, indicating that the macromolecular chain transfer agent cannot stabilize and sustain the increasing hydrophobic block PMEA. When using $PPEGMA_{16}$ as the macromolecular chain transfer agent, the target DP of PMEA was changed from 1500 to 40,000, and precipitation appeared when the DP reached 30,000. As can be seen from Table 1, the monomer conversion is measured by ^{1}H NMR, and the reaction time is adjusted according to the monomer concentration, so that the monomer conversion all reaches more than 90%.

We used GPC to determine the relative molecular weight and polydispersity of the polymer. Only smaller molecular weight polymers can be measured, because it was difficult for samples with larger molecular weight to pass 0.22 μm filter membrane after being dissolved in the eluent solvent DMF. As the actual DP of PMEA increases, both M_n and M_w increase, and both are larger than 10^6 g mol^{-1}. Although the molecular weight is large, the polydispersity is still below 1.5, indicating that the RAFT polymerization is well controlled. But from the GPC chromatographs shown in Figure 1A, we can see that at high monomer conversions, shoulders of higher molecular weights are present for the polymers with lower DP of PMEA, such higher molecular weight fractions may come from bimolecular radical termination and chain transfer to polymer. Also we can see a small amount of Macro-CTA left for the polymers with lower DP of PMEA. The remaining Macro-CTA in the final polymer products may possibly come from dead PDMA during its RAFT synthesis or from hydrolysis of PDMA Macro-CTA during dispersion polymerization in water.

Table 1 lists the particle size of the nanoparticles, measured by DLS. We can see that the size of the nanoparticles increases as the target DP of PMEA increases, at last reaching the size limit of more than 500 nm (also can be seen from Figure 1B). Continue to increase the degree of polymerization of PMEA will cause macroscopic precipitation. Although the particle size is large, the PDI is still less than 1.3 and the dispersion is still stable.

From Table S1, as the target DP of PMEA increases, the particle size of the nanoparticles also increases, with the maximum particle size close to 600 nm (also can be seen from Figure S1). The target DP exceeding 20,000, resulting in macroscopic precipitation. Although the particle size is large, the PDI is still less than 1.1. Compared with PDMA as a chain transfer agent, PDI is slightly smaller. The maximum DP of PMEA that can be achieved is 20,000, which is higher than the 12,000 that can be achieved with PDMA as chain transfer agent. The reason is that the hydrophilic chain of PDMA is short, and its stabilization effect is worse than that of PPEGMA. Comparing Entries 1, 2, and 5 in Table 1 and Entries 1, 3, and 7 in Table S1, respectively, when using different chain transfer agents, the size of the nanoparticles is not much different at similar DP of PMEA.

TABLE 2 Results of dispersion polymerization of MEA using $PDMA_{45}$ as macro-CTA at different solid concentration in water[a]

Entry	MEA/PDMA	Solid (%w/v)[b]	*T* [°C]	Time [h]	Con (%)[c]	D_h [nm][d]	PDI
1	10,000	20	35	7	97.7(6 h)	547.8	1.012
2	10,000	25	35	7	96.0(6 h)	555.9	1.102
3	10,000	30	35	7	Precipitation	/	/
4	10,000	35	35	6	Precipitation	/	/

[a][NaAs]: [KPS]: [PDMA] = 0.03: 0.03: 1.

[b]Total polymer content relative to water: $(W_{Macro\text{-}CTA} + W_{polymer})/V_{water}$.

[c]Monomer conversion determined by ^1H NMR.

[d]Particle diameter determined by DLS.

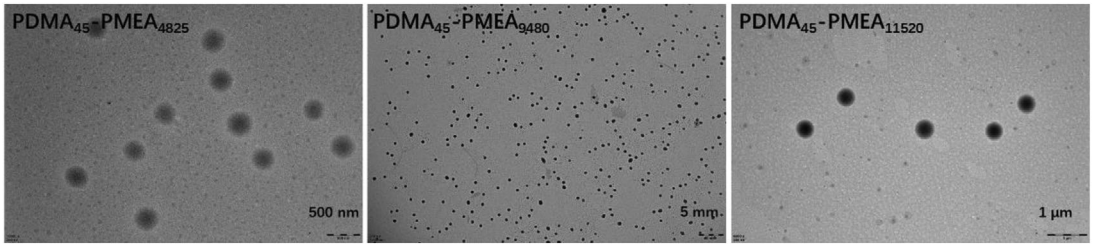


FIGURE 2 Representative transmission electron micrographs recorded for 0.05%w/v dispersions of selected $PDMA_{45}$-$PMEA_x$ nanoparticles (15%w/v, Entries 2, 4, 5 in Table 1)

3.2 | Effect of concentration

In order to study the effect of different solid content on the size of nanoparticles. We studied the morphology and particle size when using $PDMA_{45}$ as a macromolecular chain transfer agent, fixing the target DP of PMEA to 10,000, and then increased the solid content gradually. When the solid content exceeded 25%, macroscopic precipitation occurred. Comparing Entry 4 in Table 1 with Entries 1, 2 in Table 2, the solid content is increased from 15% to 25%, the particle size increased from 490.6 to 555.9 nm. As the solid content increases, the particle size also slightly increases when the actual DP of PMEA is close. When using $PPEGMA_{16}$ as a macromolecular chain transfer agent, fixing the target DP of PMEA to 15,000, and then increased the solid content gradually. When the solid content exceeded 25%, macroscopic precipitation occurred. From the comparison of Entry 7 in Table S1 with Entries 1 and 2 in Table S2, we have reached the same conclusion. The actual DP of PMEA is close, and the size of the nanoparticles slightly increases, when the solid content is increased from 15% to 25%.

3.3 | Morphology

We used TEM to observe the morphology of nanoparticles. Using $PDMA_{45}$ as the macromolecular chain transfer agent, gradually increased the DP of the hydrophobic block PMEA at 15%w/v. As shown in Figure 2, it can be seen that as the actual DP of PMEA increases, the particle size of the nanoparticles also increases. But the morphology has not changed. It is always monodispersed spheres, and uniform in particle size. Using $PPEGMA_{16}$ as the macromolecular chain transfer agent, gradually increasing the DP of the hydrophobic block PMEA at solid content of 15%, the same phenomenon was also observed, as shown in Figure S2.

In order to study the effect of concentration on the morphology of nanoparticles, we gradually increased the solid content of the reaction system and observed the changes in morphology. As can be seen in Figure 3, even the solid content is as high as 25%, DP of PMEA has exceeded or close to 10^4, the nanoparticles are still regular spheres.

In the reaction of synthesizing CCS polymer, we found that the double bond peak of monomer disappeared by measuring the Nuclear Magnetic Resonance Spectroscopy after 18 hours of reaction. Both the spacer monomer BA and the cross-linking agent PEGDA participated in the reaction. The star polymer was obtained in a water-ethanol solution (1:1, v/v). The morphology was observed through the transmission electron microscope. It is found that all spheres with a particle size of less than 100 nm are finally obtained. As can be seen from Figure 4, Because the molecular weight is too large, GPC cannot be tested, so there are no GPC traces.

From Table 1 and Figure 1B, we can see the DLS results of nanoparticles. As the degree of PMEA increases, the particle size becomes larger and larger, PDI also tends to become larger, and the size distribution becomes wider.

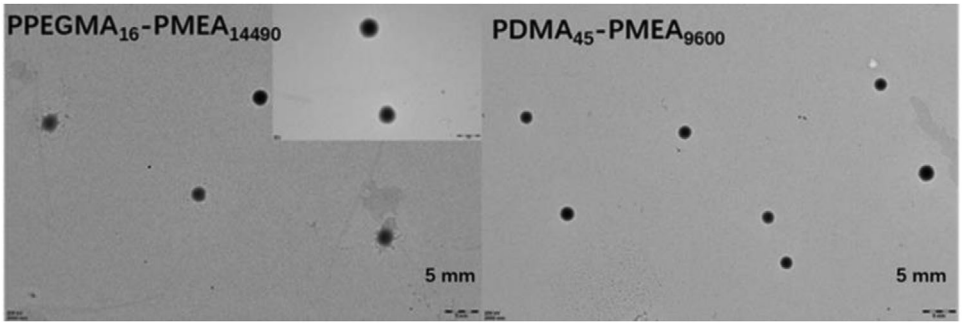


FIGURE 3 Representative transmission electron micrographs recorded for 0.05% w/v dispersions (25% w/v, Entry 2 in Table S2 and Entry 2 in Table 2)

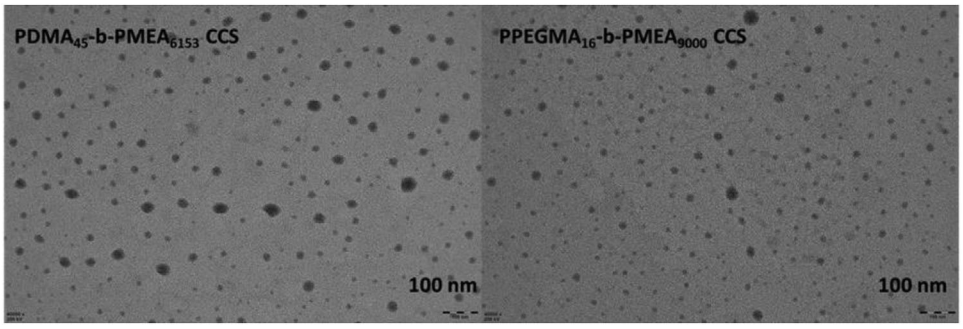


FIGURE 4 Representative transmission electron micrographs for 0.05% w/v dispersions

Because the degree of PMEA is already quite large, the stabilization effect of the Macro-CTA will become worse, and the RAFT control will become worse, which affects the size uniformity of the particles. We observed the morphology of the nanoparticles by TEM, and the particle size obtained is different from the DLS results. It may be caused by the collapse of the nanoparticles during the TEM sample preparation and air-drying process, so the particle size obtained by TEM is larger, and the particle size distribution is also non-uniform, as is seen in Figures S3-S5.

4 | CONCLUSIONS

We used PDMA and PPEGMA as macromolecular chain transfer agents to carry out RAFT aqueous dispersion polymerization of MEA at 35°C. We only got spherical morphology but no other morphologies when increasing the DP of PMEA or increasing the solid content of the polymerization system. Perhaps because the comb-like macromolecular chain transfer agent has excellent stability, also low glass transition temperature of PMEA is not prone to morphological transformation. We studied the effect of DP of PMEA on morphology. While using PDMA as a macromolecular chain transfer agent, the maximum actual DP of PMEA can reach 11,520. Using PPEGMA as a macromolecular chain transfer agent, the maximum actual DP of PMEA can reach 17,000. As the DP of PMEA increases, the particle size of the nanoparticles also increases, reaching a maximum of 600 nm. We studied the effect of the solid content of the polymerization system on morphology. It is found that increasing of the solid content has a small effect on the particle size of the nanoparticle when the actual DP of PMEA is close. We have obtained PDMA-b-PMEA and PPEGMA-b-PMEA polymer nanoparticles with such a large particle size and a molecular weight exceeding 10^6 g mol^{-1} via a "one-pot" method, which may serve as model sterically stabilized particles for analytical centrifugation studies. Using the arm-first method to synthesize ultra-high molecular weight CCS polymer, which are spheres with particle size of less than 100 nm by transmission electron microscope.

5 | EXPERIMENTAL SECTION/METHODS

5.1 | Synthesis of $PDMA_{45}$ Macro-CTA

4-Cyano-4-(ethylthiocarbonothioylthio) pentanoic acid (0.071 g, 0.27 mmol), DMA (2.0 g, 20 mmol), AIBN (0.004 g, 0.027 mmol), and DMF (0.189 g, 2.6 mmol, internal standard) are dissolved in dioxane (4.2 mL), and placed in freezing water, deoxygenated with nitrogen for

30 minutes. AIBN (0.004 g, 0.027 mmol) is dissolved in dioxane and deoxygenated by the same method for 30 minutes. The reaction solution is immersed in 70°C oil bath and heated. After the temperature stabilizes, the dioxane solution containing a certain amount of AIBN is injected with a micro syringe to start the reaction. After reacting for 2 hours, the reaction vessel is immersed in an ice/water bath and exposed to air to quench polymerization. Measured by ^{1}H NMR, the monomer conversion is 60.0%. The polymerization solution is concentrated with a rotary evaporator and precipitated in ethyl ether. After centrifugation, the polymer is collected, re-dissolved in THF and precipitated in ethyl ether. Repeat it for two or three times, and collect the polymer. After vacuum drying, 1.26 g of yellow powder is obtained. ^{1}H NMR (400 MHz, $CDCl_3$): 3.2-2.75 ppm (m, $-N(CH_3)_2$), 2.75-2.25 ppm (m, $-(CO)CHCH_2-$), 1.85-1.1 ppm (backbone $-CH_2-$), $Mn = 4724$ (by ^{1}H NMR)

5.2 | Dispersion polymerization of MEA in water using Macro-CTA $PDMA_{45}$

MEA is polymerized by RAFT aqueous dispersion polymerization at 35°C, and the target DP is 1500-15,000. The following example is dispersion polymerization of MEA when the solid content is 15%w/v and the target DP of MEA is 7000. Dissolve Macro-CTA $PDMA_{45}$ (0.0037 g, 0.0008 mmol), MEA (0.714 g, 5.483 mmol) and a small amount of DMF (internal standard) in 4.78 mL of water. Degas the solution with nitrogen at 0°C for at least 40 minutes. NaAs (0.0031 mg, 0.016 μmol) and KPS (0.0042 mg, 0.016 μmol) are dissolved in water and deoxygenated with nitrogen at 0°C for 40 minutes. The reaction solution is placed on a heater at 35°C, and after the temperature stabilizes, an aqueous solution containing a certain amount of NaAs and KPS is sequentially injected with a micro syringe, so that the polymerization begins under the protection of nitrogen. After the polymerization is completed, a blue dispersion is obtained. By comparing the vinyl signals of MEA at 6.40, 6.18, and 5.98 ppm with the methyl signals of DMF at 2.99 and 2.82 ppm, the monomer conversion is calculated. The samples are freeze-dried and dissolved in DMF for GPC testing. The sample is directly diluted with water and tested for DLS and TEM.

5.3 | Synthesis of PDMA-b-PMEA CCS polymer

PDMA-b-PMEA CCS polymer is synthesized in water-ethanol solution. The example is as follows. PDMA-b-PMEA Macro CTA with Mn 805475 (263.7 mg, 0.33 μmol), PEGDA (0.65 mg, 1.6 μmol), BA (0.42 mg, 3.3 μmol) are dissolved in water-ethanol solution (1:1, v/v, 4 mL). After the mixture is degassed with nitrogen for 40 minutes in ice/water bath; then, immersed in a 70°C preheated oil bath. Pre-degassed V-50 solution (0.09 mg, 0.33 μmol) is injected via microsyringe. It continues for 18 hours under nitrogen protection. The CCS polymer is synthesized in 91% yield.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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