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Aqueous Dispersion Polymerization of 2-Methoxyethyl Acrylate for the Synthesis of Biocompatible Nanoparticles Using a Hydrophilic RAFT Polymer and a Redox Initiator

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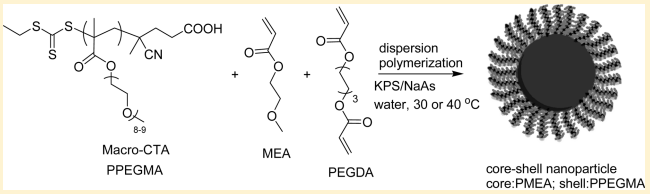
ABSTRACT: Aqueous dispersion polymerization systems mediated by reversible addition−fragmentation chain transfer (RAFT) process have been less studied in comparison with other heterogeneous polymerization systems due to limited number of monomer/polymer pairs that are suitable for such a condition. We report a novel dispersion polymerization system based on 2-methoxyethyl acrylate (MEA) which is highly water-soluble, but its polymer is not. Using a hydrophilic polymer, poly(poly(ethylene glycol) methyl ether methacrylate) (PPEGMA), as the macromolecular chain transfer agent (Macro-CTA), both solution and dispersion polymerization of MEA were studied. Chain extension by MEA from PPEGMA was successfully realized in DMF solution polymerization. In dispersion polymerization of MEA in water, PPEGMA was used as both a RAFT mediating species and a steric stabilizer for the formed nanoparticles. The dispersion polymerization of MEA in water was highly efficient using a redox initiator, potassium persulfate/sodium ascorbate, at low temperatures. Simultaneous control of both colloidal stability and RAFT process was realized. Block copolymers with small polydispersity indices were efficiently produced up to complete monomer conversion at solids content up to 32% w/v, in the form of nanoparticles of 40−60 nm diameter.



INTRODUCTION

Reversible addition−fragmentation chain transfer (RAFT) polymerization is one of the major controlled/living radical polymerization techniques that is widely used in the design and preparation of architecturally defined and functional macromolecules with predetermined molecular weight, composition, and narrow molecular weight distribution.[1−10] While RAFT polymerization is easily conducted in solution and bulk, its adaptation to aqueous dispersed systems is currently attracting significant efforts with aims to have broader industrial applications.[11−14] Early studies in aqueous dispersed systems typically used small molecular chain transfer agents (CTAs) to effect RAFT polymerization, which was proved to have limited success at least in part due to the difficulty for the CTAs to effectively transport through aqueous solutions. There is now a clear trend to use macromolecular CTAs (Macro-CTAs) to effect successful RAFT polymerizations in aqueous dispersed systems. These Macro-CTAs generally function as both RAFT polymerization mediating species, i.e. as CTAs, and steric/electrosteric stabilizers which endow colloidal stability for the formed latexes. For example, Gilbert et al. reported a self-assembly method to lock the CTA of the in-situ formed amphiphilic block copolymers into micelles under a starve feeding of butyl acrylate during the particle formation stage and then continued the emulsion polymerization at any desired feeding rate.[15,16] Successful batch emulsion polymerizations have also been reported using amphiphilic PEO-based Macro-CTA,[17,18] poly(acrylic acid)-*b*-polystyrene Macro-CTA,[19] poly(3-[2-(acryloyloxy)ethoxy]-3-oxopropyl(phenyl)phosphinic acid)-*b*-polystyrene Macro-CTA,[20] glucose-based Macro-CTA,[21] hydrophilic poly(acrylamide) Macro-CTA,[22] and both amphiphilic and hydrophilic poly(*N*,*N*′-dimethylacrylamide) Macro-CTAs.[23] While Macro-CTAs have been used to formulate miniemulsions with hydrophobes such as hexadecane,[24−26] it is noteworthy that miniemulsions free of both surfactants and hydrophobes were also reported by Hawkett et al. using appropriately designed amphiphilic Macro-CTAs,[27,28] a significant progress toward practical applications for RAFT miniemulsions.

RAFT-mediated dispersion polymerizations have been investigated in organic media[29−35] as well as in supercritical CO_2.[36−38] In comparison, RAFT dispersion polymerizations in water have been less investigated but have higher industrial impact. In dispersion polymerization, all the starting materials including the monomer, the polymerization mediating species (a CTA or Macro-CTA in the case of a RAFT process), and the initiator are soluble in water to form a homogeneous solution. As the polymerization proceeds to a critical point following initiation, the generated polymers become insoluble in water and thus form a separate phase existing in the form of stabilized latex. In 2007, one of us reported the RAFT precipitation/dispersion polymerization of *N*-isopropylacrylamide using water-soluble poly(*N*,*N*′-dimethylacrylamide) Macro-CTAs for the synthesis of core−shell thermoresponsive nanogels,[39] which were later

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demonstrated to be selectively functionalized in the core and the shell using orthogonal chemistry, nucleophilic thiol−ene, and alkyne−azide click.[40] We recently extended this approach to the synthesis of biocompatible, antifouling, and thermosensitive core−shell nanogels based on copolymerization of oligo(ethylene glycol) methacrylates of different side chain length.[41] Following a similar strategy, Charleux et al. studied the RAFT precipitation/dispersion polymerization of *N,N′*-diethylacrylamide, using a poly(ethylene glycol) (PEG) Macro-CTA, to form PEGylated nanogels.[42,43] Recently, PEGylated cationic nanogels of poly(*N,N′*-dimethylaminoethyl methacrylate) were also reported using an amphiphilic Macro-CTA.[44] On extending their work of dispersion polymerization of 2-hydroxypropyl methacrylate using conventional free radical chemistry,[45] Li and Armes reported the RAFT dispersion polymerization of 2-hydroxypropyl methacrylate for the formation of sterically stabilized nanolatexes and vesicles using a water-soluble poly(glycerol monomethacrylate) Macro-CTA.[46]

Given their simplicity and efficiency in the controlled preparation of architecturally defined core−shell nanoparticles/nanogels with a high degree of spatial precision in the location of functionalities, the nanoparticles/nanogels prepared using RAFT aqueous dispersion polymerization are desirable nanomaterials for biomedical applications such as drug delivery or imaging.[47−49] For biomedical applications, one of the most important requirements is biocompatibility of the nanoparticles. Judicious selection of the Macro-CTA stabilizer and the core polymer is therefore of critical importance in order to conform to this stringent rule. Poly(2-methoxyethyl acrylate) (PMEA) has been known to be blood compatible due to the formation of a layer of freezing bound water to the polymer surface[50−52] and has been used as a biomaterial in biomedical devices.[53] To our delight, MEA is highly water-soluble, and a survey of the literature indicated that PMEA is not water-soluble, although copolymers of MEA with more hydrophilic monomers are water-soluble and exhibit varied cloud points depending on their relative composition.[54,55] To our knowledge, aqueous dispersion polymerization of MEA under either conventional or controlled/living radical conditions, however, has not been reported. We therefore decided to study the RAFT dispersion polymerization of MEA for the preparation of biocompatible core−shell nanoparticles for potential biomedical applications. As linear PEG analogues, polymers based on poly(ethylene glycol) methyl ether (meth)acrylates are highly water-soluble and biocompatible[56] and have been used for polymer−protein/RNA conjugation,[57−59] drug delivery,[60,61] and imaging.[62] Furthermore, their molecular weight and functionality can be easily tailored using RAFT polymerization optionally in combination with other orthogonal chemistry,[63,64] an attribute contrasting favorably to the linear PEG polymers. Hence, we prepared a hydrophilic polymer of poly(ethylene glycol) methyl ether methacrylate (PPEGMA) as the Macro-CTA. Finally, we conferred one more feature in favor of potential biomedical applications to our RAFT aqueous dispersion polymerization system by using an efficient redox initiator, potassium persulfate (KPS)/sodium ascorbate (NaAs). Redox initiators have been widely used in heterogeneous conventional free radical polymerizations,[65−70] but their use in RAFT-mediated heterogeneous systems is rather limited.[25] The low activation energy of the redox initiator allows the polymerization to be carried out at low temperatures such that temperature-sensitive drugs or biomacromolecules could be potentially incorporated during the polymerization process. Indeed, redox initiators have been successfully used for RAFT polymerization in solutions or even under freezing conditions,[71−76] while their use in RAFT-mediated dispersed systems remains scarce.[25]

Herein, we report the first study of RAFT aqueous dispersion polymerization of MEA using hydrophilic PPEGMA as the Macro-CTA and KPS/NaAs as the initiator. This efficient, surfactant-free protocol produced biocompatible core−shell nanoparticles with excellent colloidal stability and amphiphilic block copolymers of PPEGMA-*b*-PMEA with excellent RAFT control.

EXPERIMENTAL SECTION

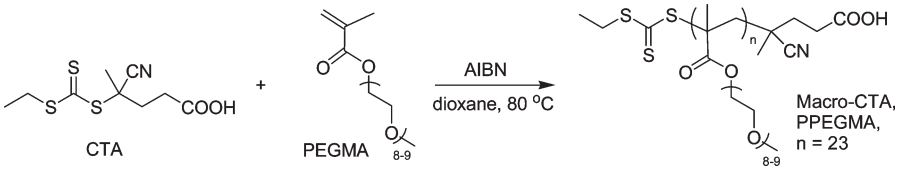
Materials. 2-Methoxyethyl acrylate (MEA, 98%), poly(ethylene glycol) diacrylate (PEGDA, M_n = 258), and poly(ethylene glycol) methyl ether methacrylate (PEGMA, M_n = 475) were purchased from Sigma-Aldrich. L-Ascorbic acid sodium salt (NaAs, 99%) was purchased from Alfa-Aesar. Potassium persulfate (KPS, AR), hydroquinone (AR), *N,N′*-dimethylformamide (DMF, 99.5+%), tetrahydrofuran (THF, 99+%), and 2,2′-azobis(2-methylpropionitrile) (AIBN, CP) were purchased from Sinopharm Chemical Reagent Co. Ltd. KPS was recrystallized from cold water. AIBN was recrystallized from methanol twice. All monomers were passed through a column of Al_2O_3 to remove the inhibitor before use. 4-Cyano-4-(ethylthiocarbonothioylthio)pentanoic acid was synthesized according to literature procedures.[77,78]

Characterization. NMR spectra were collected on a Bruker AV 500 MHz spectrometer, and chemical shifts were reported using the solvent residue as the reference. Gel permeation chromatography (GPC) was performed on a Waters Alliance e2695 GPC system, equipped with a styragel guard column, a Waters styragel HR3 (molecular weight range 5.0×10^2−3.0×10^4), a Waters styragel HR4 (molecular weight range 5.0×10^3−6.0×10^5), and a Waters styragel HR5 (molecular weight range 5.0×10^4−4.0×10^6). Detection was performed on a 2414 refractometer using DMF (HPLC grade, containing 1 mg/mL LiBr) as the eluent at a flow rate of 0.8 mL/min. The temperature of the columns was set at 65 °C, and the temperature of the refractometer was set at 45 °C. Analysis of molecular weight and polydispersity index of polymers was performed using Empower 2 software against PMMA standard (molecular weight range 2.4×10^2−1.0×10^6). Nanoparticle sizing was analyzed using dynamic light scattering (DLS) on a Malvern Zetasizer 3000HSA at 25 °C. Atomic force microscopy (AFM) was performed on a Shimadzu SPM-9600 in the tapping mode.

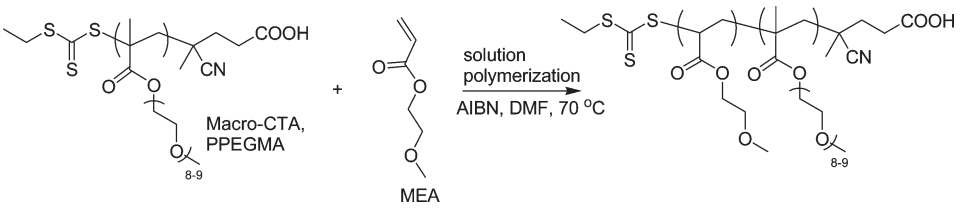
Synthesis of PPEGMA Macro-CTA. 4-Cyano-4-(ethylthiocarbonothioylthio)pentanoic acid (0.159 g, 0.60 mmol), PEGMA (8.586 g, 18.1 mmol), AIBN (0.020 g, 0.12 mmol), and DMF (0.154 g, 2.1 mmol, internal standard) were dissolved in dioxane (80 mL). The solution was degassed with nitrogen at 0 °C for 0.5 h before immersion into a preheated oil bath at 80 °C. The polymerization was conducted for 8 h at 71.4% monomer conversion as determined by ^{1}H NMR. The polymerization was quenched by immersing the polymerization flask into ice/water bath and exposing to air. The solution was concentrated on a rotary evaporator, and the polymer was precipitated into ethyl ether. The polymer was collected by centrifugation and purified one more time by precipitation of THF solution of the polymer into ethyl ether. 4.79 g of a yellow viscous liquid in 56% yield was obtained after drying the polymer under vacuum overnight. ^{1}H NMR (500 MHz, $CDCl_3$): 4.06 ppm (s, $COOCH_2-$), 3.78−3.50 ppm (m, $-O(CH_2)_2O-$), 3.37 ppm (s, $-OCH_3$), 2.5−1.5 ppm (backbone $-CH_2-$), 1.5−0.6 ppm (s, $-CH_3$). M_n = 11 100 (^{1}H NMR), M_n = 18 400 (GPC), M_w/M_n = 1.10 (GPC).

Solution Polymerization of MEA Using Macro-CTA in DMF. Macro-CTA PPEGMA (0.438 g, 0.039 mmol), MEA (0.512 g, 3.936 mmol), and 1,3,5-trioxane (35.4 mg, 0.393 mmol, internal standard) were dissolved in 2.5 mL of DMF. The solution was degassed

Scheme 1. RAFT Synthesis of Macro-CTA PPEGMA



Scheme 2. Solution Polymerization of MEA for the Synthesis of PPEGMA-*b*-PMEA in DMF



with nitrogen at 0 °C for 40 min before immersion into a preheated oil bath at 70 °C. After the temperature was stabilized, a degassed solution of AIBN (0.67 mg, 0.004 mmol) in DMF was injected via a microsyringe. Aliquots were sampled at predetermined time intervals for polymerization kinetics study. The conversion of monomer was calculated by comparing the vinyl signals of MEA at 6.40, 6.18, and 5.98 ppm with the signal of 1,3,5-trioxane at 5.16 ppm. The samples were diluted with DMF for GPC measurement.

Dispersion Polymerization of MEA in Water Using Macro-CTA. Dispersion polymerization of MEA in water was carried out at either 30 or 40 °C, at a constant molar ratio of [NaAs]:[KPS]:[PPEGMA] = 0.02:0.02:1, with target degrees of polymerization (DP) of 300, 400, and 500. A typical synthesis of dispersion polymerization of MEA at 10% w/v monomer feeding with a target DP of 400 is given as follows. Macro-CTA PPEGMA (0.107 g, 0.0096 mmol), MEA (0.50 g, 3.83 mmol), and a small amount of DMF (internal standard) were dissolved in 5 mL of water. The solution was degassed with nitrogen at 0 °C for at least 40 min before immersion into a preheated oil bath at 30 or 40 °C. After the temperature was stabilized, degassed solutions of NaAs (0.038 mg, 0.19 μmol) and KPS (0.052 mg, 0.19 μmol) were injected in that order via microsyringes. The polymerization was allowed to continue under protection of nitrogen. Aliquots were withdrawn at predetermined time intervals and were quenched with a small amount of hydroquinone. After polymerization was complete, a bluish dispersion was obtained. The conversion of monomer was calculated 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. For GPC measurement, the samples were dried via freeze-drying and dissolved in DMF. For DLS measurement, the samples were diluted with water directly.

RESULTS AND DISCUSSION

Synthesis of Macro-CTA PPEGMA. As shown in Scheme 1, the Macro-CTA PPEGMA was synthesized by RAFT polymerization of PEGMA in dioxane using 4-cyano-4-(ethylthiocarbonothioylthio)pentanoic acid as the CTA[77,78] and AIBN as the initiator. The polymerization was stopped at 71% monomer conversion to ensure a high degree of end-group functionalization. The prepared PPEGMA had a number-average degree of polymerization (DP) of 23, calculated from the monomer conversion. GPC measurement using PMMA standard gave M_n = 18 400 and M_w/M_n = 1.10, indicating that PPEGMA was synthesized via a successful RAFT process.

Solution Polymerization of MEA in DMF. In order to check the efficiency of PPEGMA as Macro-CTA and to obtain results for comparison with dispersion polymerization in water, solution polymerization of MEA via chain extension of PPEGMA was conducted in DMF (Scheme 2) at 70 °C. The monomer concentration was 20% w/v, and the molar ratio of PPEGMA:AIBN was 10:1.

As shown in Figure 1A, conversion of MEA increases rapidly to 82.5% within the first 2 h and then gradually levels off at conversions above 90%. The GPC molecular weights of the produced block copolymers, PPEGMA-*b*-PMEA, linearly increase with MEA conversion up to high monomer conversion (93%) (Figure 1B), though the GPC molecular weights using PMMA standard are higher than those estimated from monomer conversion determined by ^{1}H NMR. All the produced block copolymers have low polydispersity indices (<1.20). A linear fit is also obtained for $\ln(M_0/M)$ vs time (Figure 1C), suggesting a pseudo-first-order kinetics of polymerization. The GPC chromatographs in Figure 1D show clear shift of the traces to smaller elution time (higher molecular weight) with monomer conversion, and all the traces are monomodal up to 90% monomer conversion. At monomer conversions above 90%, shoulders at the higher molecular weight side of the traces are increasingly clear. It is known that side reactions in RAFT or broadly speaking in controlled/living radical polymerizations are more significant at high monomer conversions.[79] Previous studies on RAFT solution polymerization have shown that higher molecular weight shoulders due to bimolecular radical termination can occur.[80−82] Therefore, such higher molecular weight shoulders in the GPC traces of PPEGMA-*b*-PMEA can be partially attributed to bimolecular radical termination. Also known for acrylate polymerization is that chain transfer to polymer leading to branched structure can occur in RAFT polymerization, although to a lower extent than in traditional free radical polymerization.[83,84] Nevertheless, the low polydispersity index (1.18) for the block copolymer produced at 93.7% MEA conversion indicates that side reactions such as bimolecular radical termination and chain transfer to polymer indeed only occur to a very low extent. These results collectively suggest that PPEGMA is an effective Macro-CTA for MEA polymerization, which is thus qualified for use in RAFT dispersion polymerization of MEA in water.

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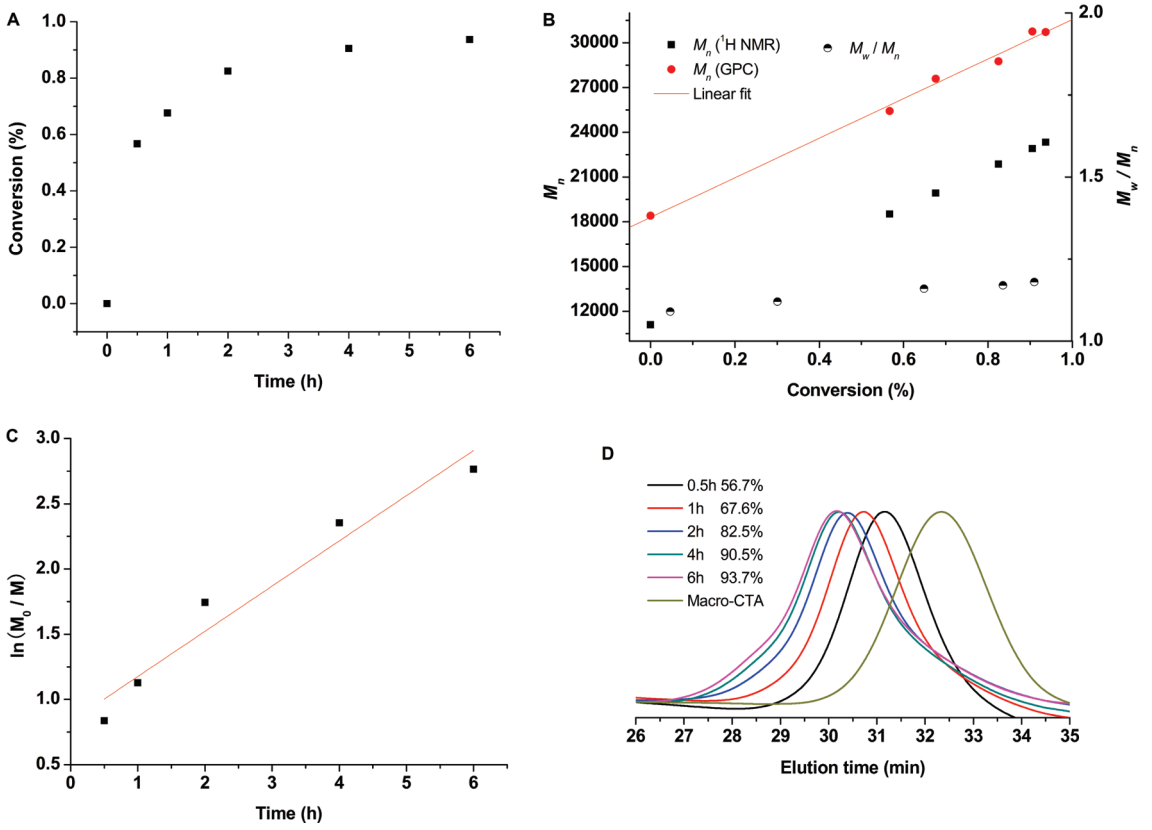
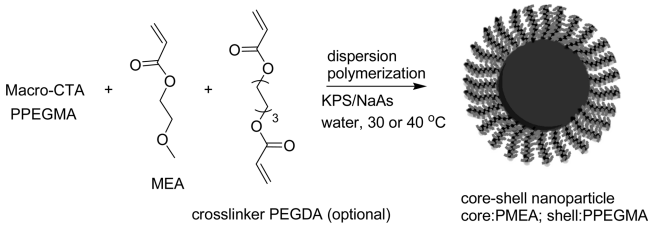


Figure 1. Results of solution polymerization of MEA (20% w/v) using PPEGMA Macro-CTA in DMF at 70 °C, [AIBN]:[PPEGMA]:[MEA] = 0.1:1:100. (A) Polymerization kinetics; (B) molecular weights and polydispersity indices of PPEGMA-*b*-PMEA polymers with increasing monomer conversion; (C) plot of pseudo-first-order kinetics of polymerization; (D) GPC chromatograms of PPEGMA-*b*-PMEA polymers at different monomer conversions.

Scheme 3. Dispersion Polymerization of MEA Using PPEGMA Macro-CTA in Water



Dispersion Polymerization of MEA in Water. As shown in Scheme 3, dispersion polymerization of MEA was carried out at solids content >10% w/v relative to water (Table 1), using PPEGMA as both the RAFT controlling agent and the hydrophilic steric stabilizer. KPS/NaAs was used as the radical initiator to allow efficient polymerization at low temperatures, either 30 or 40 °C. Since MEA and PPEGMA are highly soluble in water, chain extension of PPEGMA is expected to occur in the homogeneous solution. After PMEA grows to a certain length, the produced amphiphilic block copolymer PPEGM−PMEA assembles into core−shell nanoparticles. Given its high water solubility and the expected good solubility in its own polymer, MEA will partition in both nanoparticles and water. As polymerization continues in the nanoparticles, MEA in the nanoparticles is gradually consumed, which is continuously supplied from the aqueous solution. To produce cross-linked nanoparticles, a water-soluble cross-linker poly(ethylene glycol) diacrylate (PEGDA) is used at a constant molar ratio of PEGDA:PPEGMA = 3:1.

As can be seen from Figure 2A, dispersion polymerization of MEA using redox initiator KPS/NaAs is highly efficient at both 30 and 40 °C with no inhibition period being observed in both cases. The polymerization kinetics is essentially the same with the polymerization rate at 40 °C is only slightly higher than that at 30 °C. Within 1 h, MEA conversion is reached over 90%. The polymerization levels off after 1 h, and near-quantitative monomer conversion is achieved within 3 h. It should be noted that in dispersion polymerization the concentration of the monomer (10% w/v), the molar ratio of initiator/PPEGMA (0.02:1), and the temperature (30 or 40 °C) are all much lower than those used in solution polymerization in DMF. The polymerization rate in dispersion polymerization is, however, much higher than that in solution polymerization, clearly demonstrating the advantages of aqueous dispersion polymerization of MEA under such conditions.

As shown in Figure 2B, the M_n (GPC, PMMA standard) of the produced amphiphilic block copolymers (PPEGMA-*b*-PMEA) increases with MEA conversion, and an excellent linear relationship between M_n and conversion is clearly observed. The polydispersity indices (M_w/M_n) of the polymers remain below 1.25 throughout the polymerization with monomer conversion up to 100% (Figure 2B and Table 1). For MEA conversions below 80%, the molecular weights of PPEGMA-*b*-PMEA produced at 40 °C correlate very well with those produced at 30 °C.

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Table 1. Conditions and Results of Dispersion Polymerization of MEA in Water[a]

entry	MEA/Macro-CTA	monomer (% w/v)[b]	solid (% w/v)[c]	T (°C)	conv (%)[d]	M_n (kg/mol)[e]	M_w/M_n[e]	D_h (nm)[f]	PDI[f]	Macro-CTA incorporation (%)[g]
1	300	10	12.9	40	95	92.2	1.16	43	0.12	98.3
2	400	10	12.1	40	100	124.3	1.25	57	0.12	97.4
3	500	10	11.7	40	94	137.7	1.25	63	0.14	98.7
4	300	10	12.9	30	97	90.5	1.13	46	0.13	98.0
5	400	10	12.1	30	94	115.9	1.19	49	0.11	98.4
6	500	10	11.7	30	90	129.3	1.19	53	0.14	97.5
7	300	15	19.3	30	99	92.7	1.13	44	0.26	97.4
8	300	20	25.7	30	98	93.8	1.12	50	0.18	96.9
9	300	25	32.0	30	98	92.8	1.10	42	0.11	97.3
10	300 (KL)[h]	10	12.9	30	90			42	0.10	
11	400 (KL)[h]	10	12.1	30	94			54	0.06	
12	500 (KL)[h]	10	11.7	30	93			59	0.06	

[a] [NaAs]:[KPS]:[PPEGMA] = 0.02:0.02:1. [b] Monomer content relative to water: $W_{monomer}/V_{water}$. [c] Total polymer content relative to water: $(W_{Macro\text{-}CTA} + W_{polymer})/V_{water}$. [d] Monomer conversion determined by ^{1}H NMR. [e] Determined by GPC using DMF as the eluent and PMMA as the standard. [f] Particle diameter determined by DLS. [g] Percentage of Macro-CTA incorporated into nanoparticles by comparison of the integrated area of the polymers measured by GPC: $A_{block\ copolymer}/(A_{Macro\text{-}CTA} + A_{block\ copolymer})$. [h] Cross-linked nanoparticles with the molar ratio of PEGDA to Macro-CTA at 3:1.

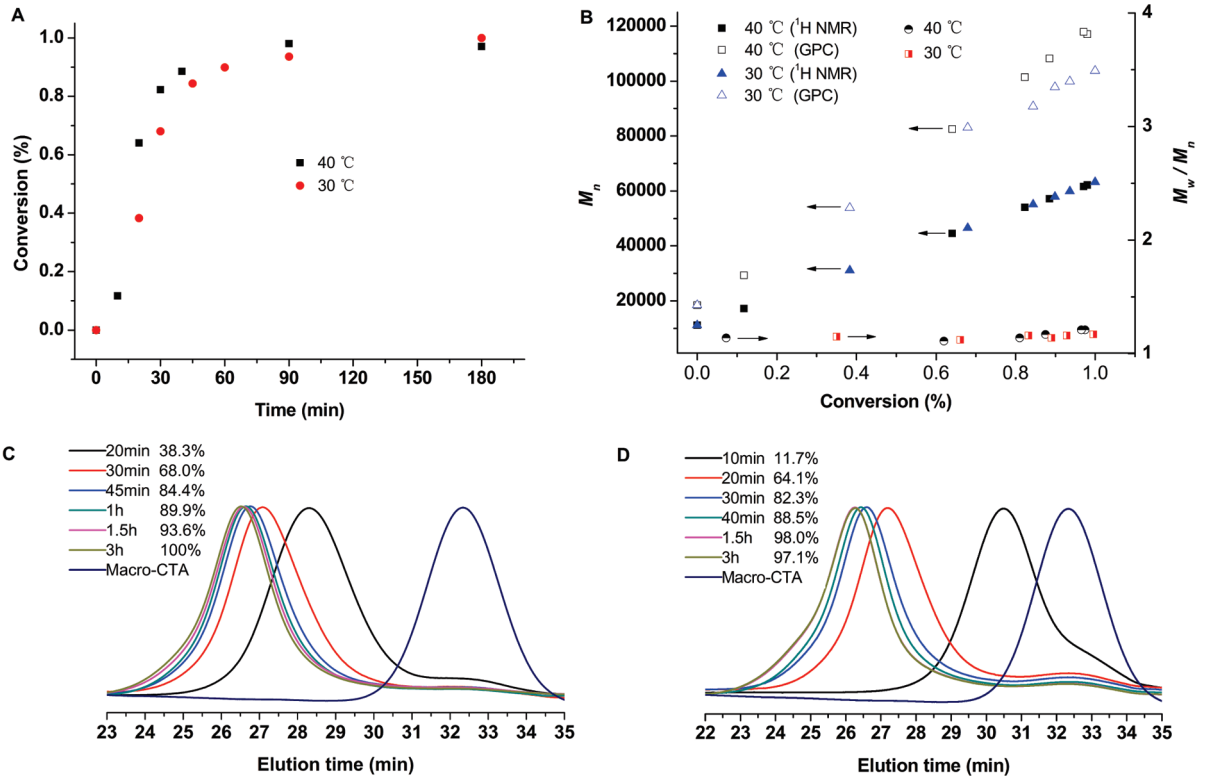

Figure 2. Results of dispersion polymerization of MEA (10% w/v) using PPEGMA Macro-CTA in water. [NaAs]:[KPS]:[PPEGMA]:[MEA] = 0.02:0.02:1:300. (A) Polymerization kinetics; (B) molecular weights and polydispersity indices of PPEGMA-*b*-PMEA polymers with increasing monomer conversion; (C) GPC chromatograms of PPEGMA-*b*-PMEA polymers at different monomer conversions synthesized at 30 °C; (D) GPC chromatograms of PPEGMA-*b*-PMEA polymers at different monomer conversions synthesized at 40 °C.

However, for MEA conversions above 80%, the molecular weights of the polymers produced at 40 °C are higher than those produced at 30 °C. From the GPC chromatographs shown in Figure 2C,D, we can see that at high monomer conversions shoulders of higher molecular weights are present for the polymers produced at 40 °C, whereas there are no obvious shoulders present for the polymers produced at 30 °C. As a result, the molecular weights measured by GPC for the polymers produced at 40 °C are higher than those produced at 30 °C. As discussed earlier for solution polymerization in DMF, such higher molecular weight fractions may come from bimolecular radical termination and chain transfer to polymer. Because higher temperature favors chain transfer to polymer,[79,84] the shoulders observed for the polymers produced at 40 °C, in comparison with

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those produced at 30 °C, may be mainly due to chain transfer to polymer. Figure 2C,D also shows that Macro-CTA is gradually consumed as MEA conversion increases. For dispersion polymerization at 30 °C, the GPC trace of 38.3% monomer conversion shows a clear shift to higher molecular weight direction with only a small amount of Macro-CTA left. GPC traces of higher monomer conversions show high degrees of Macro-CTA incorporation with only minimal amounts left. For dispersion polymerization at 40 °C, the GPC traces exhibit a similar trend with somehow slightly higher amounts of Macro-CTA left. The remaining Macro-CTA in the final polymer products may possibly come from dead PPEGMA during its RAFT synthesis or from hydrolysis of PPEGMA Macro-CTA during dispersion polymerization in water. Nevertheless, in all cases, quantification of the amounts of the produced polymers and the Macro-CTA indicates high degrees of Macro-CTA incorporation (>97%) into the final nanoparticles (Table 1).

In addition to the production of well-defined polymers with high efficiency, relatively high DPs can be targeted under dispersion polymerizations. For this purpose, we prepared block copolymers with DPs of 300, 400, and 500. In all cases, the monomer conversions were above 90% and polymers with low polydispersity indices were obtained (Table 1 and Figure 3). Similarly, the polymers produced at 30 °C have better quality than those produced at 40 °C due to the reduced extent of chain transfer to polymer.

Dispersion polymerization of MEA using PPEGMA Macro-CTA produced amphiphilic block copolymers PPEGMA-*b*-PMEA in the form of core−shell nanoparticles with the hydrophilic PPEGMA as the stabilizing shell and the hydrophobic PMEA as the core. Dispersion polymerizations of MEA were carried out with monomer feeding in the range of 10−25% w/v and total solids content in the range of 11.7−32.0% w/v. In all cases, stable colloids were obtained with nanoparticle diameters in the range 40−60 nm (Table 1). Increasing the molar ratio of MEA/Macro-CTA increases the size of the nanoparticles. While maintaining the molar ratio of MEA/Macro-CTA but increasing the total solids content, the size of the nanoparticles in most cases remains the same. This result is consistent with that reported by Rieger and co-workers on nanogel formation via dispersion polymerization of *N*,*N*′-diethylacrylamide mediated by water-soluble Macro-CTAs.[43]

Interestingly, dispersion polymerization of MEA can be conducted at monomer feedings higher than its solubility, and the formed nanoparticles exhibit the same level of colloidal stability and polydispersity. When the monomer feedings were ≤15% w/v, homogeneous solutions were formed before polymerization. However, when the monomer feedings were ≥20% w/v (entries 8 and 9, Table 1), turbid inhomogeneous solutions were initially formed, which became clear in a few minutes after polymerization was initiated and then gradually turned into bluish, indicating the formation of nanoparticles. The formed nanoparticles under such conditions showed similar size and polydispersity with those produced at lower monomer feedings when the same MEA/Macro-CTA ratio was used. On the basis of these results for polymerizations above the monomer

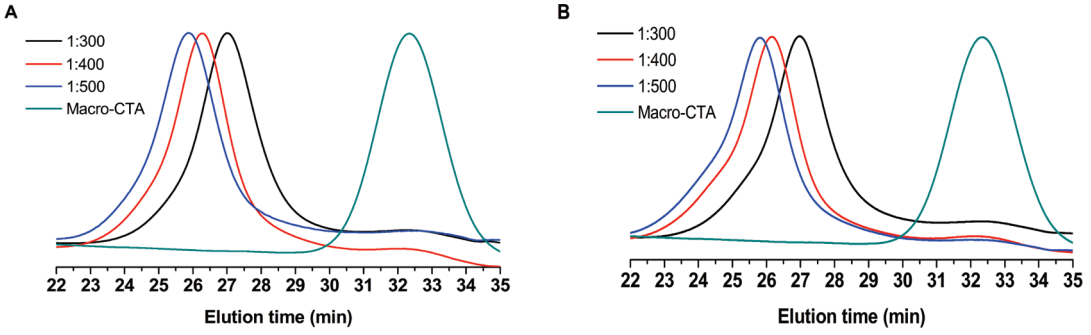

Figure 3. GPC chromatograms of PPEGMA-*b*-PMEA polymers of different degree of polymerization. MEA (10 wt/v %), [NaAs]:[KPS]:[PPEGMA] = 0.02:0.02:1. (A) 30 °C and (B) 40 °C.

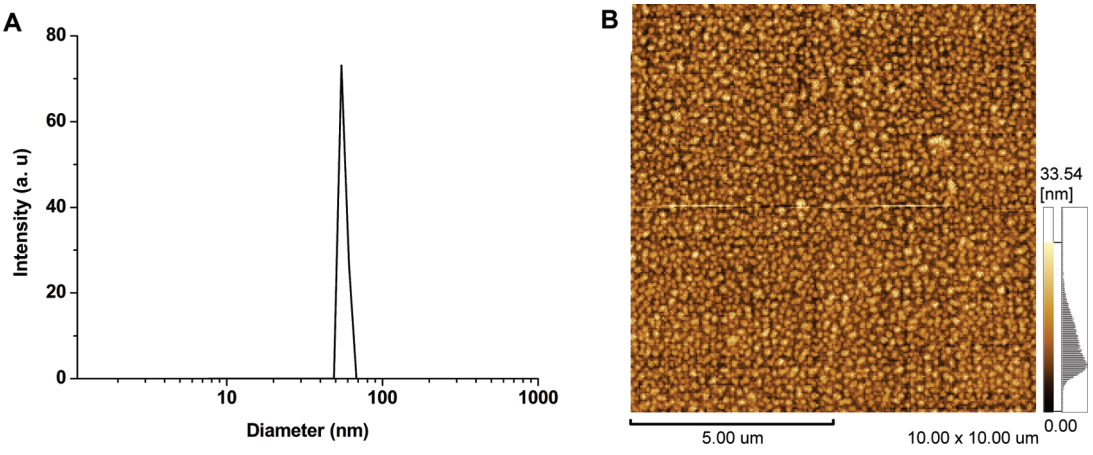

Figure 4. (A) Dynamic light scattering (DLS) result and (B) atomic force microscopy (AFM) micrograph of cross-linked nanoparticles (entry 11, Table 1).

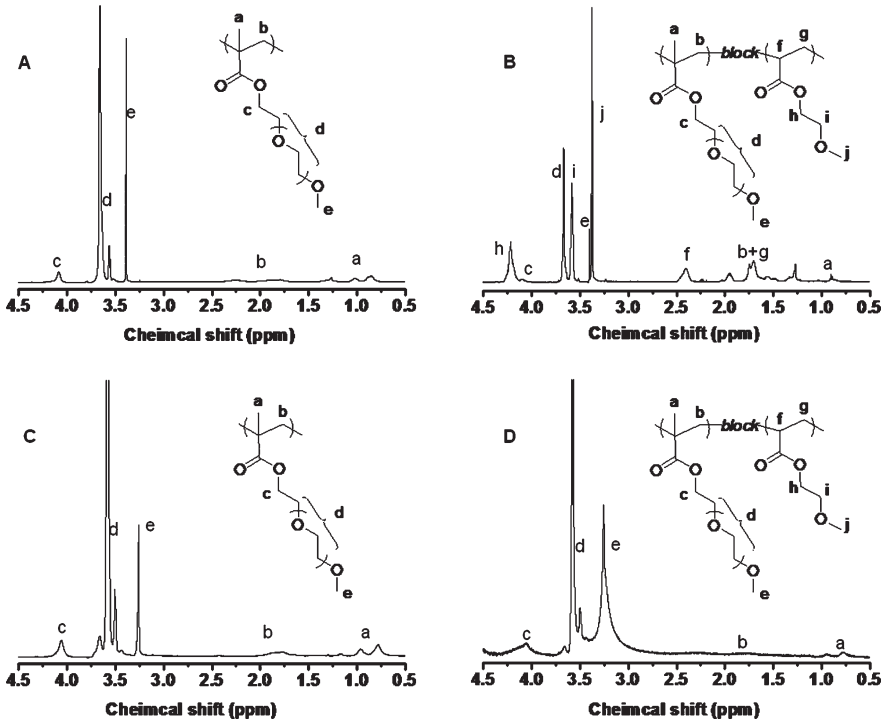

Figure 5. ^{1}H NMR spectra in $CDCl_3$ of (A) PPEGMA and (B) PPEGMA-*b*-PMEA synthesized via dispersion polymerization. ^{1}H NMR spectra in D_2O of (C) PPEGMA and (D) core−shell nanoparticles synthesized via dispersion polymerization.

solubility, it is reasonable to deduce that initiation still occurs in the aqueous solution like in a normal dispersion polymerization because the monomer has a high solubility in water (at least 15% w/v). After initiation, chain extension to Macro-CTA occurs, and the formed amphiphilic block copolymers assemble into nanoparticle seeds, which effectively solubilize excess monomer, and therefore, the solution becomes clear within a short period of time after initiation. After this initiation and monomer equilibration stage, the polymerization then behaves like a normal dispersion polymerization.

Cross-linked nanoparticles were also obtained by dispersion copolymerization of MEA and the cross-linker poly(ethylene glycol) diacrylate (PEGDA, M_n = 258) (entries 10−12, Table 1). For these experiments, the molar ratio of PEGDA/Macro-CTA was controlled at 3:1. The cross-linked nanoparticles had similar sizes as those without cross-linker but had smaller polydispersities. Figure 4 illustrates the DLS size distribution (D_h = 54 nm, PDI = 0.06) and the AFM image of the cross-linked nanoparticles (entry 11, Table 1). These results indeed demonstrate that the formed nanoparticles are highly monodisperse.

To elucidate the core−shell architecture of the nanoparticles, we performed NMR analysis of Macro-CTA and the produced block copolymers in $CDCl_3$, which is a good solvent for both, and of Macro-CTA and the resulting nanoparticles in D_2O, which is a solvent selective for PPEGMA (Figure 5). In $CDCl_3$, all the proton signals corresponding to PPEGMA and PMEA are clearly resolved. In contrast, in D_2O, only the proton signals corresponding to PPEGMA can be seen whereas the signals corresponding to the hydrophobic PMEA almost disappeared, indicating that indeed PPEGMA functions as the stabilizing shell polymer whereas the hydrophobic PMEA consists of the nanoparticle core.

CONCLUSION

A novel aqueous dispersion polymerization system based on MEA was developed using a hydrophilic RAFT polymer as both the stabilizing agent and the RAFT controlling species. Both solution polymerization in DMF and dispersion polymerization in water were studied, which demonstrated that well-defined block copolymers were effectively synthesized via chain extension of Macro-CTA. In comparison with solution polymerization, dispersion polymerization proceeded at higher polymerization rate but at lower temperatures using lower concentration of redox initiator KPS/NaAs. Lower polymerization temperature in dispersion polymerization resulted in the formation of polymers with narrower polydispersity possibly due to lower extent of chain transfer to polymer. Dispersion polymerizations of MEA with optional cross-linker were performed at high solids content (up to 32% w/v), and in all cases stable colloids were obtained.

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