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One-step synthesis of pegylated cationic nanogels of poly(*N*,*N*′-dimethylaminoethyl methacrylate) in aqueous solution via self-stabilizing micelles using an amphiphilic macroRAFT agent

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ABSTRACT

Cationic nanogels of Pegylated poly(*N*,*N*′-Dimethylaminoethyl methacrylate) (PEG-PDAEMA) have been synthesized in aqueous solution by a one-step surfactant-free reversible addition-fragmentation transfer (RAFT) process. A Pegylated amphiphilic macroRAFT agent ($mPEG_{550}$-TTC) with a hydrophobic dodecyl chain was utilized to stabilize the micelles and control the polymerization and crosslinking of DMAEMA in aqueous solution. ^{1}H NMR, GPC, Elemental analysis, Dynamic light scattering (DLS), Zeta potential and Atomic force microscopy (AFM) measurements confirmed the formation of the cationic nanogels in size of about 20 nm with a narrow distribution. It also revealed that the concentration of monomer and the kinds of crosslinker are the key factors to control the formation of nanogel. This cationic nanogel has potential application in gene delivery.

1. Introduction

Nanogel is a kind of crosslinked polymer in size of nanometers with attracting properties [1–3], which has potential application in biomaterials, such as the delivery system for protein, polypeptide, RNA and DNA [4–7]. Pegylated of nano-carriers for drug delivery have attracted special attention for PEG chain can improve the biocompatible and stability of the carriers in blood. There are several methods to induce the PEG chains into polymers. Kim et al. reported the synthesis of copolymer nanogel of a Pegylated poly(*N*-isopropyl acrylamide) (PNIPAM) by a PEG-macroinitiator in a mixture solvent of water/tetrahydrogenfuran or in pure water [8]. Leobandung et al. reported the synthesis of the Pegylated PNIPAM nanospheres by copolymerization of PEG macro-monomer with NIPAM, and the product showed both thermo-sensitivity and high insulin loading ability [9]. Deng et al. prepared a poly(acrylic acid)-g-PEG nanogel with pH-responsive properties, which made the drug of protein stable in stomach environment and has an efficient releasing of drug in high pH condition [10].

Generally, the synthesis of nanogel was carried out in diluted monomer solution or in heterogeneous media, such as micro- or mini-emulsion under the assistant of surfactant. Living radical polymerizations such as atom transfer radical polymerization (ATRP) [11], nitroxide-mediated polymerization (NMP) [12] and reversible addition-fragmentation transfer (RAFT) polymerization [13] have also been utilized for the synthesis of nanogels. Among them, a surfactant-free method has been paid much attention and developed by using an amphiphilic macroinitiator as surfactant, and the self-assembly of which results in the formation of micelles and makes it stable during polymerization [14]. Rieger and Charleux et al. recently prepared the Pegylated thermally responsive block copolymer micelles and nanogels of poly(*N*,*N*-diethylacrylamide) and poly(*N*,*N*-dimethylacrylamide) via an in situ RAFT aqueous dispersion polymerization [15]. However, they found that it always results in the formation of macroscopic gel when an amphiphilic PEO_{2000}-TTC macroRAFT agent was utilized to control the polymerization of monomer in the presence of crosslinker MBA (4.6 mol%), and they believed that the length of hydrophilic PEO_{2000} is not long enough to stabilize the micelles during polymerization [15]. So they developed a two-step strategy based on sequential addition of the monomer and MBA, and prepared PDEAAm nanogel in size of about 500–800 nm [15]. Another method they developed is increasing the hydrophilicity of the macroRAFT. They utilized mPEO-b-PDMAAm macroRAFT agent instead of PEO-TTC in a one-step reaction, and successfully prepared the nanogel of PDEAAm in size of tens of nanometer [15]. However, we think it is still possible to prepare nanogels in one-step process by the PEG-TTC macroRAFT agent using different monomer, crosslinker, controlling the concentrations of monomer, or shorting the length of

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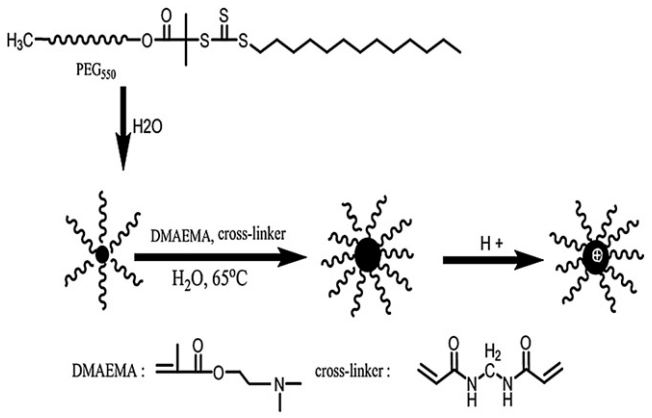
the PEG chain. In addition, the synthesis of Pegylated cationic nanogel is still an attractive topic for potential application in gene delivery [16,17].

Poly(*N*,*N*′-dimethylaminoethyl methacrylate), PDMAEMA, as one kind of cationic polymer, has both thermo- and pH-responsive behavior, which make it an attracting polymer for gene delivery [18]. There are many reports on the synthesis of PDMAEMA and various copolymers of it for gene delivery [19–21]. However, there is still seldom study on the synthesis of the nanogels of PDMAEMA, especially Pegylated PDAEMA nanogel [22].

Here, a Pegylated cationic PDMAEMA nanogel was tried to be prepared by a RAFT process in one-step in the absence of surfactant, and the polymerization and crosslinking of DMAEMA monomer were carried out in the micelles which were formed and stabilized by an amphiphilic Pegylated macroRAFT agent, $mPEG_{550}$-TTC.



Scheme 2. The synthesis sketch map of the Pegylated PDMAEMA nanogel controlled by the amphiphilic $mPEG_{550}$-TTC macroRAFT agent.

2. Experimental section

2.1. Materials

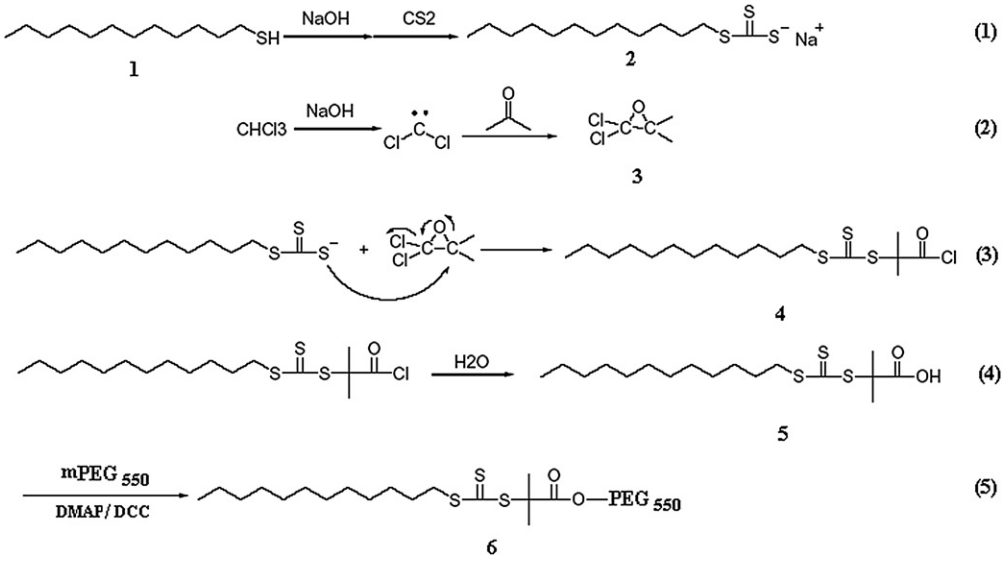
Acetone, Carbon disulfide, Isopropanol, Tetrabutyl ammonium bromide, Sodium hydroxide, Chloroform, Hexane, and Diethyl ether were purchased from Sinopharm Chemical Reagent (AR). *N*, *N*′-Dicyclohexylcarbodiimide (DCC, Shanghai Medpep, 99%), Dodecanethiol (Acros, 99%), $mPEG_{550}$ (Alfa Aesar, 98%), *N*,*N*′-dimethylamino pyridine (DMAP, Acros, 98%), 4,4′-Azobis (cyanovaleric acid (V501, Alfa Asear, 98%), and *N*,*N*′-Dimethylaminoethyl methacrylate (DMAEMA, Alfa Asear, 97%) were used directly as received. Azobisisobutyronitrile (AIBN, Shanghai First Reagent Co, 95%) was recrystallized from methanol. *N*,*N*′-methylenebisacrylamide (MBA, Sinopharm Chemical Reagent, 96%) was recrystallized twice from methanol before use. Ultra-pure water (18.2 MΩ) was produced by a Millipore System (Millipore Q, USA).

2.2. Synthesis of S-1-dodecyl-S′-(α,α′-dimethyl-α″-acetic acid) trithiocarbonate (TTCA) RAFT agent

The TTCA RAFT agent was synthesized by a method reported in ref. [23]. In brief, 8.08 g dodecanethiol (40 mmol), 20 mL acetone, and 0.52 g tetrabutyl ammonium bromide (1.6 mmol) were added into a 100 mL flask, and it was bubbled with nitrogen gas for 30 min at 10 °C. After that, 3.35 g 50 wt% sodium hydroxide (42 mmol) aqueous solution was added slowly below 10 °C. After stirring for another 15 min, a carbon disulfide solution in acetone was added dropwise (CS_2: 3.05 g, 40 mmol; acetone: 4.03 g, 69 mmol). Next the system was stirred for another 15 min, and then 7.13 g chloroform (60 mmol) and 16 g of 50 wt% sodium hydroxide (200 mmol) were added below 10 °C. The ice bath was removed 30 min later, and the reaction was carried out for 12 h, and then 60 mL of distilled water and 10 mL of hydrochloric acid (13.6 M) were added. After 30 min, the system was distilled under reduced press to remove the volatile solvents and there appeared some yellow precipitation, and which was collected by filtration. Then the precipitation was dissolved into 200 mL isopropanol under strong stirring, and the undissolved residue was removed by filtration. After that, the filtrate was distilled under reduced press to remove isopropanol, and the residue was recrystallized in hexane and was dried in vacuum for 24 h. At the end, 9.1 g TTCA RAFT agent was obtained. ^{1}H NMR($CDCl_3$, δ ppm), 0.9 (t, 3H, $CH_2\boldsymbol{CH}_3$ of the $C_{12}H_{25}$ chain moiety), 1.23–1.47(m, 18H, $-CH_2(\boldsymbol{CH}_2)_9CH_3$), 1.67–1.75 (m, 8H, $-C(\boldsymbol{CH}_3)_2-SC(S)S-CH_2\boldsymbol{CH}_2(CH_2)_9CH_3$), 3.25(t, 2H, $-SC(S)S-\boldsymbol{CH}_2CH_2-$).

2.3. Synthesis of the amphiphilic $mPEG_{550}$-TTC macroRAFT agent

$mPEG_{550}$-TTC macroRAFT agent 6 was synthesized by the reaction of $mPEG_{550}$ and the TTCA (Scheme 1). Typically, 0.51 g $mPEG_{550}$



Scheme 1. Synthesis process of the amphiphilic $mPEG_{550}$-TTC macroRAFT agent.

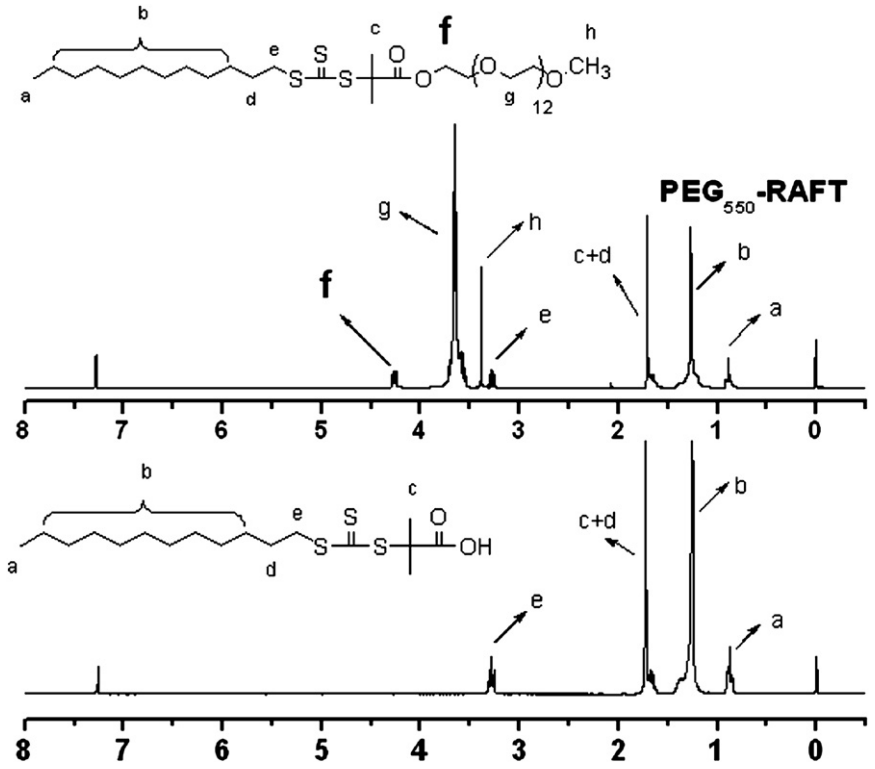


Fig. 1. ^{1}H NMR spectra of TTCA and the amphiphilic mPEG$_{550}$-TTC macroRAFT agent in $CDCl_3$.

(0.93 mmol) was dissolved into 150 mL toluene, and it was refluxed for 24 h. Then toluene was removed by distilling, and 50 mL of anhydride dichloromethane was added to dissolve PEG$_{550}$. After that, 0.728 g TTCA (2 mmol), 0.013 g DMAP (0.106 mmol) and 0.433 g DCC (2.1 mmol) were added into the flask, and the reaction was carried out 24 h at room temperature. Next dichloromethane was removed by distilling, and the product was purified by column chromatography using the mixture of dichloromethane, hexane and diethyl ether as eluent (2:1:1).

2.4. Synthesis of mPEG$_{550}$-PDMAEMA linear diblock copolymer by mPEG$_{550}$-TTC macroRAFT agent in water

The linear diblock copolymer of mPEG$_{550}$-PDMAEMA was synthesized by aqueous dispersion polymerization of DMAEMA in the presence of the mPEG$_{550}$-TTC macroRAFT agent. In a typical experiment, 6.4 mmol of DMAEMA, 0.24 mmol of mPEG$_{550}$-TTC and 0.27 mmol of V501 were dissolved in 25 ml of water, and the solution was bubbled by nitrogen gas for 60 min. Then the reaction was carried out for 48 h at 65 °C, and the reaction was quenched by decreasing the temperature to 0 °C in an ice-bath. The product was dialyzed for two days with dialysis bag, and was freeze dried.

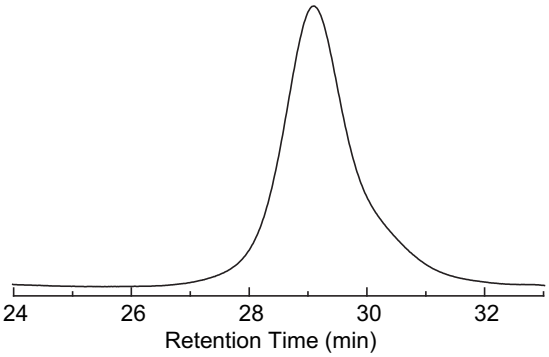


Fig. 2. GPC trace of mPEG$_{550}$-PDMAEMA linear copolymer.

2.5. Polymerization and crosslinking of DMAEMA controlled by the amphiphilic mPEG$_{550}$-TTC macroRAFT agent

The mPEG$_{550}$-TTC macroRAFT agent, initiator AIBN or V501, DMAEMA and crosslinker MBA with various ratios were added into deionized water, and the solution was bubbled by nitrogen gas for 60 min. Then the reaction was carried out for 48 h at 65 °C, and the reaction was quenched by decreasing the temperature to 0 °C in an ice-bath. The product was dialyzed for two days with dialysis bag (M_w:8000–10 000), and was freeze dried. The process was described in Scheme 2. The mPEG$_{550}$-TTC macroRAFT is amphiphilic and it produced micelle at suitable concentration in water. The self-assemble of the hydrophobic dodecyl groups forms the core while the PEG segment works as the shell, and the trithiocarbonate segment is at the interface. There formed a colloid when mixing the RAFT agent, monomer, crosslinker and initiator in water at 65 °C, and the polymerization of DMAEMA monomer was carried

Table 1
Reaction condition for the three sample preparation.

	Sample 1	Sample 2	Sample 3
DMAEMA	3 mmol	6 mmol	6.4 mmol
mPEG$_{550}$-TTC	0.14 mmol	0.28 mmol	0.24 mmol
Initiator	AIBN: 0.015 mmol	AIBN: 0.042 mmol	V501: 0.27 mmol
Crosslinker MBA	0.13 mmol	0.2 mmol	0.26 mmol
Water	4 mL	20 mL	25 mL
Monomer concentration	0.75 M	0.3 M	0.26 M
Product	Macroscopic gel	Nanogel	Nanogel

Fig. 3. Photography of the PDMAEMA macroscopic gel formed by the RAFT polymerization at high monomer concentration (0.75 M) and AIBN as initiator.

out at the interface. In the presence of the crosslinker, there should form a crosslinked region between the core and the shell, and result in the formation of nanogel. The complete ionization of the PDMAEMA segment in the product was carried out in 1 mM phosphate buffer at pH 4 at room temperature.

2.6. Characterization of products

^{1}H NMR spectra were measured by a Bruker spectrometer (Avance 300, 300 MHz) with $CDCl_3$ or D_2O as solvent. The number-average molar mass (M_n), the weight-average molar mass (M_w), and the molar mass distribution (M_w/M_n) were determined by gel permeation chromatography (GPC, Waters 2410) in THF at 1.0 mL/min using PS as the standard. For dynamic laser scattering measurement, a commercial spectrometer (ALV/DLS/SLS-5022F) equipped with multi-τ digital time correlation (ALV5000) and a cylindrical 22 mW UNIPHASE He–Ne laser ($\lambda_0 = 632$ nm) as the light source was used. The intensity–intensity time correlation function $G^{(2)}(t,q)$ was measured to determine the line-width distribution $G(\Gamma)$. For diffusive relaxation, Γ is related to the translational diffusion coefficient (D) of the scattering object (polymer chain or colloid particle) in dilute solution or dispersion by $D = (<\Gamma>/q^2)_{C\to 0, q\to 0}$ and further to hydrodynamic radius (R_h) from the Stokes–Einstein equation: $R_h = k_B T/(6\pi\eta D)$, where η, k_B, and T are the solvent viscosity, the Boltzmann constant, and the absolute temperature, respectively. Hydrodynamic radius distribution $f(R_h)$ was calculated from the Laplace inversion of a corresponding measured $G^{(2)}(t,q)$ using the CONTIN program. All dynamic LLS measurements were conducted at a small scattering angle (θ) of 15°. AFM images were captured in the tapping mode by a NanoScope IIIa MultiMode SPM (Digital Instruments Inc., Santa Barbara, CA) at room temperature. Silicon tip (model TESP, Nanoprobes, Digital Instruments) with cantilever length of 125 μm and resonant frequency of about 300 kHz was used. The scan rates were in between 0.5 and 1.0 Hz. Height image with 512 × 512 points were recorded and analyzed by using the AFM software, WSxM 4.0 (Nanotec Electronic S. L.) and Photoshop 5.0. Zeta potential of the nanogel was measured by laser doppler velocimetry (LDV) at 25 °C using a Zetasizer Nano ZS90 (Malvern Instruments, Malvern, UK), and the concentration of polymer is 0.1 mg mL^{-1}.

3. Results and discussion

The synthesis of the $mPEG_{550}$-TTC macroRAFT was carried out by the reaction of $mPEG_{550}$ with TTCA under the assistant of DMAP and DCC in toluene. Fig. 1 shows the ^{1}H NMR spectra of the TTCA and the as-prepared $mPEG_{550}$-TTC macroRAFT agent. Comparing to TTCA, there appears some new peaks for the product at 4.27 ppm, which correspond to the proton of $-CH_2-O-(C=O)$, and the signal at 3.6 ppm is assigned to the proton in the methylene of the mPEG chain. The chemical shift of the proton of the terminal methoxyl of the mPEG appears at 3.4 ppm. The ratios of A_f: A_a: A_e: A_h = 2:3:2:3, and the results confirmed the formation of $mPEG_{550}$-TTC macroRAFT agent [15].

The efficiency of $mPEG_{550}$-TTC in controlling the polymerization of DMAEMA in aqueous solution was studied, and Fig. 2 shows the GPC trace of the as-formed copolymer $mPEG_{550}$-PDMAEMA. The

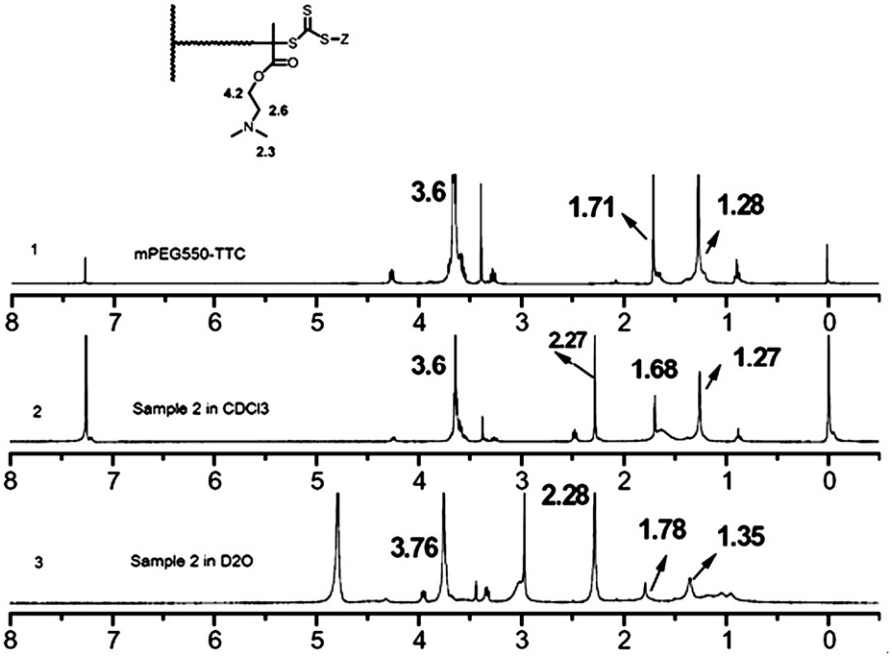


Fig. 4. ^{1}H NMR spectra of the $mPEG_{550}$-TTC macroRAFT agent (Curve 1), and Sample 2 in both $CDCl_3$ (Curve 2) and D_2O (Curve 3), respectively.

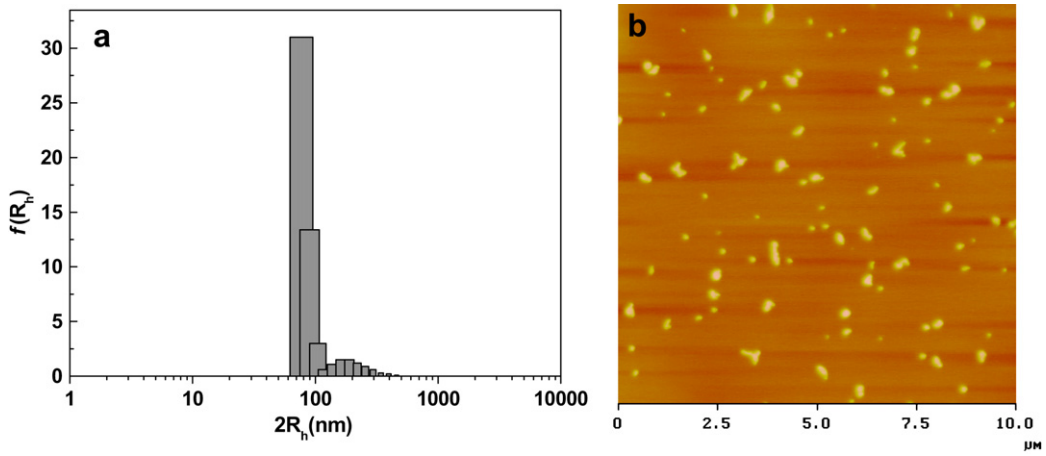


Fig. 5. a) Hydrodynamic radii (R_h) and its distribution (f(R_h)) of Sample 2 (0.5 mg mL^{-1}) in water; b) Typical AFM height image of the nanogel of Sample 2 at the surface of the new cleaved mica in air.

diblock copolymer exhibits an unimodal and narrow distribution, and the $M_n = 4.7 \times 10^3$, $M_w = 5.1 \times 10^3$ ($M_w/M_n = 1.1$), indicating the living radical polymerization of DMAEMA.

The as-prepared mPEG$_{550}$-TTC macroRAFT agent is an amphiphilic and could form micelles in aqueous solution. In experiment, DMAEMA monomer, crosslinker MBA, PEG-RAFT agent and the initiator AIBN were added into water to form a colloid of micelles under stirring. The ratios of DMAEMA: MBA: mPEG$_{550}$-TTC macroRAFT agent: initiator are listed in Table 1. For Sample 1, the concentration of DMAEMA is 0.115 g mL^{-1}, and the mixture was heated at 65 °C for 3 h for the polymerization. There formed a macroscopic gel in yellow-light color as shown in Fig. 3, indicates the damage of the micelles and the crosslinking of neighboring micelles. Riger and Charleux found the similar result in the polymerization of DEAAm controlled by the mPEO$_{2000}$-TTC macroRAFT agent, and they suggested that the hydrophilicity of PEO$_{2000}$ is too weak to stabilize the nanogel [15]. However, for PEO$_{2000}$ the number of the repeat units is 45 while there are 12 carbons as the hydrophobic segment, and it makes the macroRAFT more hydrophilicity. It will be different if mPEG$_{550}$-TTC macroRAFT agent was utilized for its ratio of the hydrophilic to hydrophobic segments is near 1. Another key factor is the concentration of monomer, and a low concentration should be helpful for avoiding the formation of macroscopic gel. Thereafter, a new mixture of reactants with ratio of DMAEMA:MBA:mPEG$_{550}$-TTC:initiator = 6:0.2:0.28:0.042 was prepared, and it was polymerized and crosslinked at 65 °C for 3 h (Sample 2). No apparent macroscopic gel appeared and there obtained a homogeneous turbid emulsion. After it was dialyzed at room temperature and freeze dried, some powder was obtained. Elemental analysis result shows that the ratio of N:C:H of the powder is 0.28:4.19:9.09. Then the molar ratio of mPEG and PDMAEMA in the product can be calculated by following equation:

$$n/(15n + 80m) = \mathrm{N} : \mathrm{H}$$

where n is the number of DMAEMA unit in the product, and m is the number of PEG-RAFT. The calculated n:m equals 4.6 for Sample 2, indicates the molar ratio of PDMAEMA and PEG segments in the polymer is 4.6.

Fig. 4 shows the ^{1}H NMR spectra of the mPEG$_{550}$-TTC macroRAFT (Curve 1) agent and the product in both D_2O (Curve 2) and $CDCl_3$ (Curve 3), respectively. The characteristic signal of the methylene proton in PEG (~3.6 ppm) was appeared in every spectrum. However, there appears apparent difference for the spectra measured in D_2O and $CDCl_3$. In D_2O the signal of PDMAEMA is clear at 3.9 ppm, 3.3 ppm and 2.9 ppm, which are attributed to oxymethylene, azamethylene and the terminal methyl protons, respectively [24]. But the signals are very weak in $CDCl_3$. In addition, the area ratio of protons signal of PDMAEMA to PEG are smaller than the values measured by elemental analysis, indicates the mobility of the PDMAEMA chains in the products are limited. The result revealed that there may form crosslinking of PDMAEMA segments. The signal of the proton in PEG segment is strong,

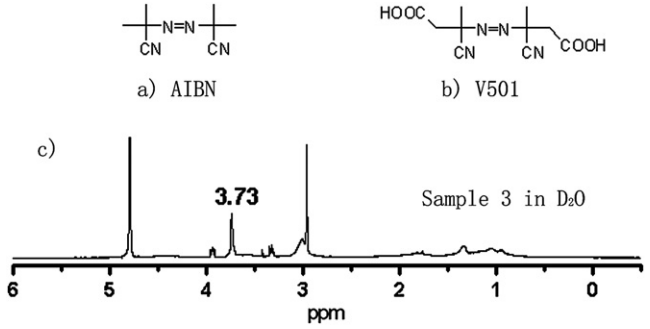


Fig. 6. The chemical structure of initiator AIBN (a) and V501 (b), and the ^{1}H-NMR spectrum of Sample 3 in D_2O (c).

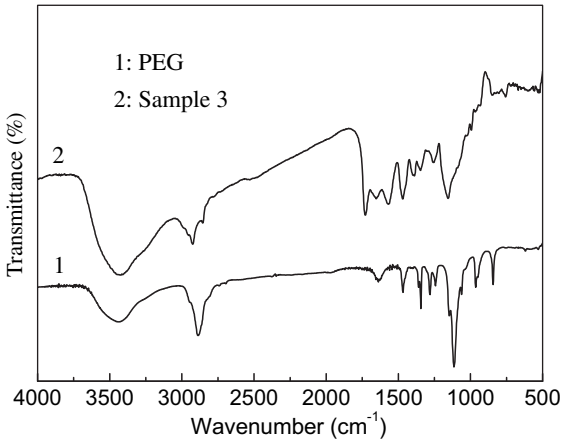


Fig. 7. FT-IR spectra of pure PEG (Curve 1) and Sample 3 (Curve 2).

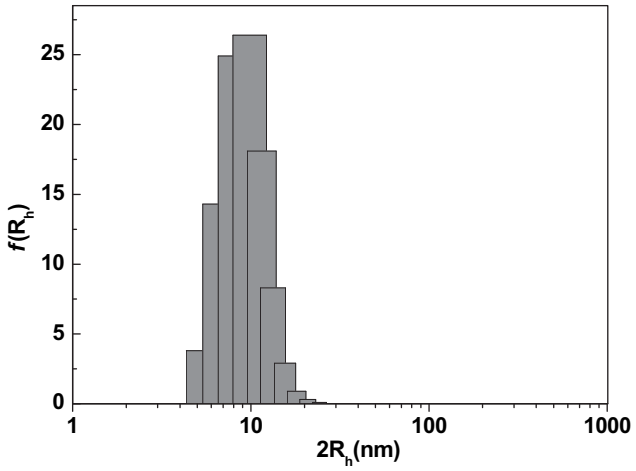


Fig. 8. Hydrodynamic radii (R_h) and its distribution (f(R_h)) of Sample 3 (0.5 mg mL^{-1}) in water.

indicates the free extend of PEG chains, and it suggested that the PEG chains surround the crosslinked PDMAEMA core [23].

Fig. 5a shows the hydrodynamic radii (R_h) and their distribution (f(R_h)) of Sample 2 measured by the dynamic laser scattering. The polymer owns a wide distribution of size in aqueous solution, and the major particles are in size of about 75 nm while there are some particles in size of about 200 nm in radii. The result revealed that there formed nanogel of PDMAEMA. However, the size of the nanogels is in a wide distribution. Fig. 5b shows the AFM image of the nanogels of Sample 2 on the surface of substrate, and the particles are also in a wide distribution, and the result is consistent with the DLS result.

AIBN is a typical hydrophobic initiator, and it may interact with the hydrophobic core of the formed micelle and makes it unstable, especially during the polymerization. So a more hydrophilic initiator may be good to control the distribution of the size of nanogels. Here, V501, a carboxyl modified AIBN was utilized for the preparation of Sample 3, and a mixture reactant with the ratio of DMAEMA:MBA:mPEG$_{550}$-TTC:initiator = 6.4:0.26:0.24:0.27 was prepared and polymerized. Fig. 6 shows the ^{1}H NMR spectrum of Sample 3 in D_2O, and the signal of protons in the PEG segments are clearly showed while the signals of protons for PDMAEMA are weak, and the result is similar to that of Sample 2, indicates the limitation of mobility of the PDMAEMA chains in product. Elemental analysis measurement showed that the ratio of N:C:H = 0.32:4.27:8.87 for the as-prepared product, and the calculated n:m equals 6.4. So in the product the molar ratio of the repeated unit of DMAEMA to PEG is 6.4, indicates a successful polymerization

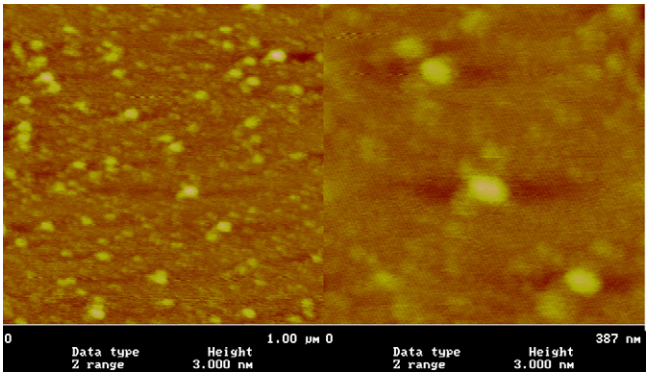


Fig. 9. Typical AFM height images of the nanogel of Sample 3 at the surface of the new cleaved mica in air.

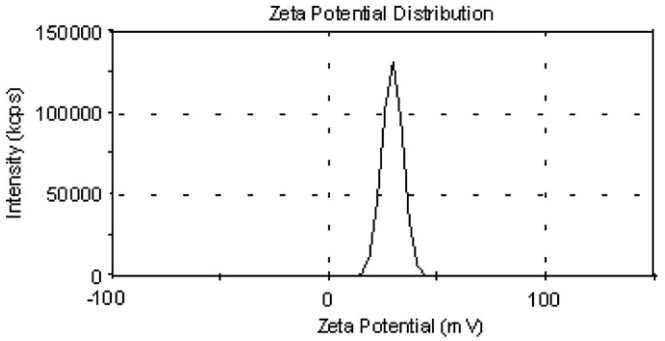


Fig. 10. Zeta potential of Sample 3 in water.

of DMAEMA monomer into the particles. Comparing with Sample 2, the PDMAEMA segments in Sample 3 increased. Beside the difference of the hydrophilicity for AIBN and V501, the other possible key factor is the half-life ($t_{1/2}$) of the initiators, and they are 10 h for AIBN and 29 h for V501 at 65 °C. So the slow decomposition rate for V501 may be the key point to control the polymerization of DMAEMA, and result in the formation of small nanogels. The detail should be studied in near future.

Fig. 7 shows the FT-IR spectra of PEG and Sample 3. Comparing with the spectrum of pure PEG (Curve 1), the Curve 2 has the characteristic peaks of PEG. In addition, there appears some new peaks at 2856 cm^{-1} for the C–H stretching of the –N(CH$_3$)$_2$ group, at 1728 cm^{-1} for the carbonyl group, at 1140 cm^{-1} for the C–N stretching, and at 1476 cm^{-1} for the N-(CH$_3$)$_3$ deformational stretch vibration [25], also indicate the polymerization of DMAEMA monomer in Sample 3.

Fig. 8 shows the hydrodynamic radii (R_h) and their distribution (f(R_h)) of Sample 3 measured by the dynamic laser scattering. The average size of the nanogel is about 10 nm, and the distribution is narrow. The result revealed that Pegylated nanogels of PDMAEMA with a narrow distribution can be prepared by using V501 as the initiator.

Fig. 9 shows the typical AFM height images of Sample 3 after depositing its suspension onto the surface of the new cleaved mica by a spin-coater (3000 rpm) at room temperature. There appear many particles and the size of the particles is about 20 nm in diameter, which is consistent with the DLS result.

It is well known that PDMAEMA is positive, and it is expected that the as-prepared nanogel should also be positive. Fig. 10 shows the Zeta potential measurement of Sample 3 with a complete ionization, and the zeta potential is +30 mV.

4. Conclusion

Here, a simple method was reported to synthesize the Pegylated cationic nanogel of PDMAEMA in one-step via the in situ formation of micelle by an amphiphilic trithiocarbonate macroRAFT agent (mPEG$_{550}$-TTC). Elemental analysis, dynamic laser scattering and atomic force microscopy studies confirmed the formation of the nanogels of PDMAEMA, and their size depended strongly on the monomer concentration and the kinds of initiator. The as-prepared nanogel initiated by V501 is in size of about 10 nm in radii and its zeta potential is about +30 eV, which is a potential gene delivery system for further biomedical application.

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