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Oligo(ethylene glycol) and quaternary ammonium-based block copolymer micelles: from tunable thermoresponse to dual salt response†

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P(St-*g*-QA)-*b*-P(MEO₂MA-co-OEGMA) copolymers were synthesized by RAFT and click chemistry. The micelles self-assembled from the amphiphilic copolymers showed tunable thermoresponse through alteration of the molar ratio of MEO₂MA and OEGMA. P(St-*g*-QA) and P(MEO₂MA-co-OEGMA) segments both presented salt response.

Recently, increasing interest has been attracted to the stimuli-responsive polymers due to their potential applications in a variety of fields such as drug delivery, sensors, nanotechnology and gene transport systems.^{1–3} These polymers would undergo reversible changes in response to external stimuli such as temperature, pH value, light, and redox potential.^{4–8} Among various stimuli-responsive polymers, thermoresponsive polymers are the most investigated.^{9–11} The copolymerization of two oligo(ethylene glycol) macromonomers of different chain-lengths leads to the formation of thermoresponsive copolymers with a tunable LCST. For instance, the random copolymers of 2-(2-methoxyethoxy)ethyl methacrylate (MEO₂MA) and oligo(ethylene glycol) methacrylate (OEGMA) exhibit a LCST in water, which can be finely tuned anywhere between 26 and 90 °C depending on OEGMA content.^{12–15} These poly(ethylene glycol)-based copolymers are water solubility, nontoxicity, biocompatibility, and anti-immunogenicity.

In order to broaden the applications of stimuli-responsive polymers, a great many efforts have been used to synthesize novel stimuli-responsive polymers, which could respond to other stimuli, such as ion strength of salt concentration. In general, salt responsive polymers are ionic polymers containing charged groups. They present varied solubility in aqueous

solution depending on the salt concentration.^{16–19} Liu and co-workers reported salt-responsive micellization behaviour based on a double hydrophilic sulfobetaine block copolymer.²⁰ The formation-dissociation of micelles was induced by salt solution. McCormick *et al.* reported pH/salt responses of poly(sodium 2-acrylamido-2-methyl-1-propanesulfonate-*block*-poly(*N*-acryloyl-L-alanine)) with the formation of shell cross-linked micelles.²¹ Tang *et al.* reported *N*-[3-hydroxypropyl]-*cis*-5-norbornene-*exo*-2,3-dicarboximide-*graft*-[poly(ε-caprolactone)-*co*-poly(ε-caprolactone-*graft*-quaternary ammonium)] (PNPH-*g*-[PCL-*co*-P(CL-*g*-QA)]) cationic bottle-brush polymers and observed the salt response of the copolymers.²² They also reported the degradable and salt-responsive poly(ε-caprolactone)-*co*-poly(ε-caprolactone-*graft*-quaternary ammonium) (PCL-*co*-P(CL-*g*-QA)) cationic random copolymers.²³ However, up to now, there are few reports on synthesis and self-assembly of the multi-stimuli responsive systems containing salt-response.

Herein, in this communication, a series of block copolymers of poly(styrene-*graft*-quaternary ammonium)-*block*-poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-oligo(ethylene glycol) methacrylate) (P(St-*g*-QA)-*b*-P(MEO₂MA-co-OEGMA)) with tunable thermoresponse and dual salt responses were synthesized by the combination of reversible addition-fragmentation chain transfer polymerization (RAFT) and click chemistry (Scheme S1, ESI†). Firstly, poly(*p*-chloromethylstyrene)(PCMS) was synthesized by RAFT with *S*-dodecyl-*S'*-(α,α'-dimethyl-α''-acetic acid) trithiocarbonate (DDMAT) as the RAFT agent. After reacting with sodium azide (NaN₃), poly(*p*-azidomethylstyrene) (PAMS) was obtained. Poly(*p*-azidomethylstyrene)-*block*-poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-oligo(ethylene glycol) methacrylate) (PAMS-*b*-P(MEO₂MA-co-OEGMA)) copolymers with different ratio of MEO₂MA to OEGMA were prepared by RAFT using PAMS as the macro-RAFT agent. Finally, P(St-*g*-QA)-*b*-P(MEO₂MA-co-OEGMA) copolymers were synthesized by click chemistry of PAMS-*b*-P(MEO₂MA-co-OEGMA) with propargyl quaternary ammonium salt. ATR FTIR, ¹H NMR and ¹³C NMR spectra of PCMS, PAMS, PAMS-*b*-P(MEO₂MA-co-OEGMA)

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and P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) were shown in Fig. S1–S6 (ESI[†]). GPC curves of PCMS and PAMS-*b*-P(MEO₂MA-*co*-OEGMA) were shown in Fig. S7.[†]

Amphiphilic PAMS-*b*-P(MEO₂MA-*co*-OEGMA) could self-assemble to micelles with PAMS core and P(MEO₂MA-*co*-OEGMA) shell (Scheme 1). The CMC of PAMS-*b*-P(MEO₂MA-*co*-OEGMA) was 0.065 mg mL^{−1} (Fig. S8(a)[†]). The spherical micelles could be observed in TEM image, as shown in Fig. 1(a). The average size was about 170 nm. It is worth noting that the P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) was still amphiphilic copolymer, although the hydrophilic QA molecules were linked to PAMS chains. The copolymer also could self-assemble to micelles. The CMC of P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) was 0.016 mg mL^{−1} (Fig. S8(b)[†]). TEM image showed that the micelles presented the average size of about 230 nm. For P(St-*g*-QA) chains, the presence of QA molecules endowed the chains with hydrophilicity. However, the hydrophobic benzene ring and 1,2,3-triazole groups ensured the hydrophobicity of this chain. Namely, P(St-*g*-QA) was amphiphilic polymer itself. Compared to the micelles self-assembled from PAMS-*b*-P(MEO₂MA-*co*-OEGMA), the micelles self-assembled from P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) presented larger sizes due to the loose core, as shown in Scheme 1.

In order to investigate the tunable thermoresponse of P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) micelles, the feed molar ratios of MEO₂MA to OEGMA were varied (95/5, 90/10 and 85/15) during the synthesis process. The actual molar ratios calculated from ¹H NMR spectra were 95/5, 91/9 and 86/14 (sample 1–3) respectively (Table S1, ESI[†]). Fig. 2(a) showed the transmittance curves of P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) micelle solutions (sample 1–3). It can be seen that the transmittance curves underwent sharp transition during heating processes. The LCST values of copolymer micelle solutions increased from 35.9, 41.9

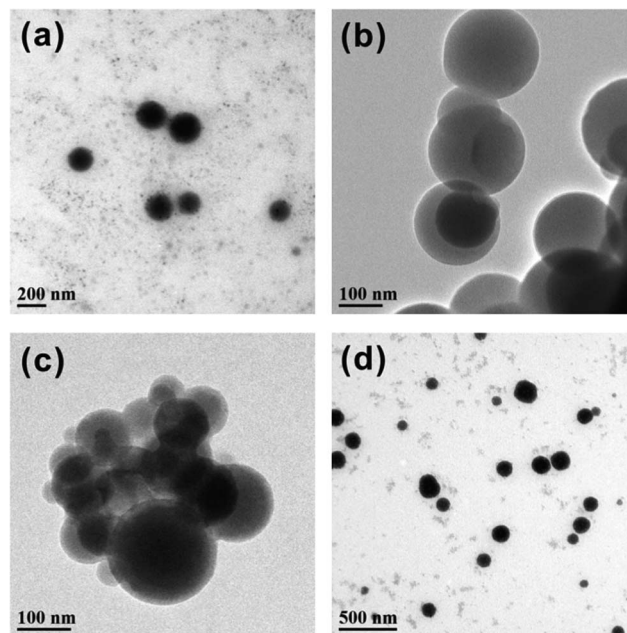
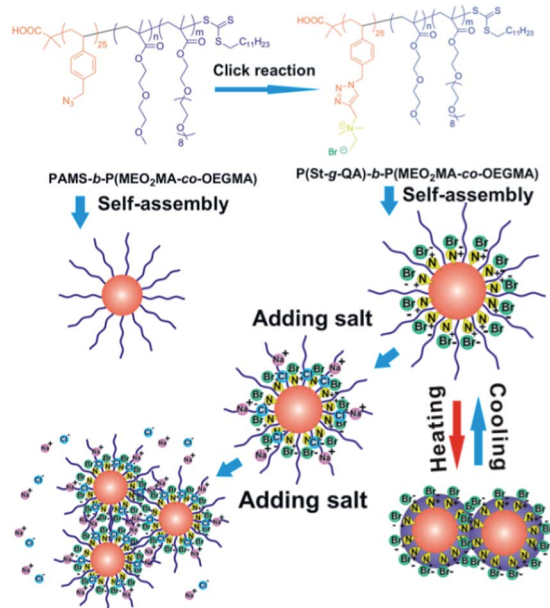


Fig. 1 TEM images of (a) PAMS-*b*-P(MEO₂MA-*co*-OEGMA) micelles at 25 °C, (b) P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) micelles (sample 2) at 25 °C, (c) P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) (sample 2) micelles at 50 °C, and (d) P(St-*g*-QA) micelles at 25 °C (concentration: 0.3 mg mL^{−1}).

to 47.1 °C with the increase of the molar ratio of OEGMA from 5, 9 to 14%, which means that the LCST of the copolymer micelle solutions can be tuned through altering the ratio of MEO₂MA



Scheme 1 Self-assembly of P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) and tunable thermoresponse and dual salt responses.

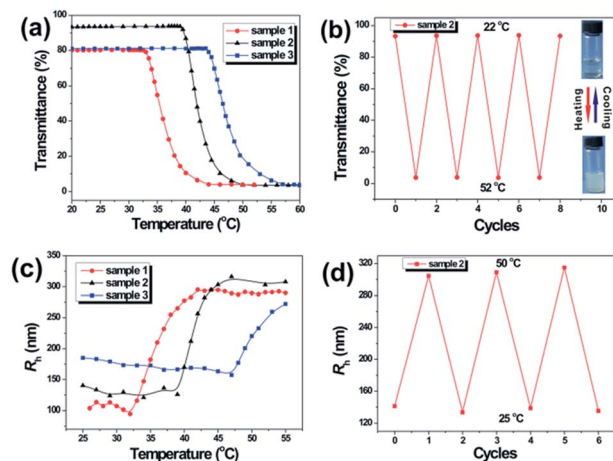


Fig. 2 (a) Temperature dependence of transmittance for the P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) micelle solutions of sample 1–3 (concentration: 1.0 mg mL^{−1}), (b) plots of transmittance as a function of temperature for the micelle solution of sample 2 (insert photographs: the reversible transparency-turbidity transition of copolymer micelle solution after heating-cooling cycle) (concentration: 1.0 mg mL^{−1}), (c) temperature dependence of hydrodynamic radius (*R*_h) for P(St-*g*-QA)-*b*-P(MEO₂MA-*co*-OEGMA) micelles (sample 1–3) (concentration: 0.3 mg mL^{−1}); (d) plots of *R*_h as a function of temperature for the micelles of sample 2 (concentration: 0.3 mg mL^{−1}).

and OEGMA of copolymers. As shown in Fig. 2(b), reversible transformation of transparency and turbidity occurred in P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) micelle solution during the reversible heating and cooling cycles. Obviously, the phase transition of the micelles was reversible, indicating that the copolymer micelles could undertake a reversible change of swelling and collapse. Fig. 2(c) showed the hydrodynamic radius (R_h) of micelles of sample 1–3 as a function of temperature. In the low temperature ranges, the R_h values were relatively small and changed slightly. For example, the R_h value of sample 2 was 140.4 nm at 25 °C. In contrast, the values increased drastically in the high temperature ranges. At 45 °C, the R_h value of sample 2 was 303.1 nm. At low temperature ranges, P(MEO₂MA-co-OEGMA) segments in copolymers existed in random coil conformation owing to the hydrogen-bonding interaction between ether oxygen of P(MEO₂MA-co-OEGMA) and water molecules. When the temperature increased to a critical value, P(MEO₂MA-co-OEGMA) chains shrank into a globular structure as the hydrogen bonds between ether oxygen and water collapsed and became hydrophobic. Therefore, the intermolecular hydrophobic attractions were thermodynamically favoured and the micelle aggregation occurred, which resulted in the increase of R_h . The TEM image of micelles at 50 °C also confirmed the shrinkage and aggregation of micelles (Fig. 1(c)), as depicted in Scheme 1. Fig. 2(d) showed the plots of R_h as a function of temperature for the micelles. Result revealed that the change of micelle size was reversible during the reversible heating and cooling cycles.

Fig. 3(a) showed the transmittance curves of P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) micelle solution (sample 2) at different ion strength of NaCl solutions. With the increase of ion strength of NaCl solutions from 0.2, 0.4, 0.6, 0.8 to 1.0 M, the LCST values decreased from 37.2, 33.9, 30.8, 28.7 to 25.7 °C. The photographs of micelle solutions at 26 °C and at different ion strength of NaCl solutions were shown in Fig. 3(b). It can be seen that the micelle solutions were transparent when the ion strength of NaCl solutions was less than 1.0 M at this temperature. At 1.0 M, the solution transformed to turbid at 26 °C. These results were in accordance with the results of Fig. 3(a). Lutz *et al.* found that the typical salting-out effect was observed in P(MEO₂MA-co-OEGMA) solutions.¹² They considered that the presence of NaCl led to a partial dehydration of the macromolecules and consequently to a decrease of the LCST. As a result, the solution phase transition should partly attributed to the salt-response of P(MEO₂MA-co-OEGMA) chains. Moreover, the salt-response of QA molecules in P(St-g-QA) segments also made contributions to the salt-responsive properties of P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) micelle systems. In order to confirm the salt-response of P(St-g-QA) segments, P(St-g-QA) was synthesized (Scheme S2, Fig. S9, ESI†). P(St-g-QA) could self-assemble to spherical micelles (Fig. 1(d)), further indicating that P(St-g-QA) was amphiphilic polymer. Without adding NaCl, R_h of the micelles was 165.8 nm (PDI = 0.372) (Fig. 3(c)). The value of R_h of the micelles increased to 278.0 nm (PDI = 0.923) when the ion strength of NaCl solution was 1.5 M. Obviously, P(St-g-QA) could reveal salt response. The size increase of micelles should be

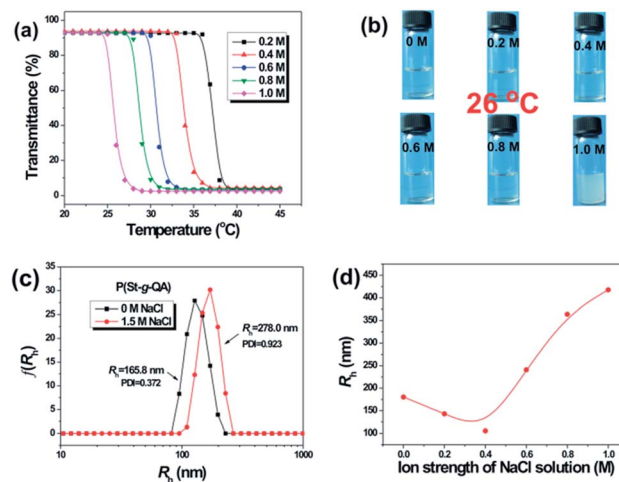


Fig. 3 (a) Temperature dependence of transmittance for the P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) micelle solution (sample 2) at different ion strength of NaCl solutions (concentration: 1.0 mg mL⁻¹), (b) photographs of transparency and turbidity of micelle solution (sample 2) at 26 °C and at different ion strength of NaCl solutions (concentration: 1.0 mg mL⁻¹); (c) dependence of hydrodynamic radius distribution, $f(R_h)$, obtained from 0 M and 1.5 M of NaCl solutions for the micelle solutions of P(St-g-QA) (concentration: 0.3 mg mL⁻¹), (d) ion strength of NaCl solution dependence of hydrodynamic radius (R_h) for P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) micelles (sample 3) (concentration: 0.3 mg mL⁻¹).

attributed to the further dehydration of P(St-g-QA) and the aggregation of micelles. Fig. 3(d) showed the R_h of micelles of P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) (sample 3) in water as a function of ion strength of NaCl solution. At low ion strength (0 to 0.4 M), the R_h values decreased from 180.2 to 105.7 nm. However, the R_h values increased from 105.7 to 417.8 nm when the ion strength increased from 0.4 to 1.0 M. At low ion strength, P(MEO₂MA-co-OEGMA) and P(St-g-QA) segments were partial dehydrated and the hydrophobicity of the copolymer increased. Therefore, both P(MEO₂MA-co-OEGMA) shell and P(St-g-QA) core were shrunk, which led to the decrease of the size of micelles. With the increase of ion strength, the dehydration of P(MEO₂MA-co-OEGMA) and P(St-g-QA) increased, leading to the further increase of hydrophobicity of micelles. As a result, the micelles aggregated to aggregates with larger size, as shown in Scheme 1.

In conclusion, P(St-g-QA)-*b*-P(MEO₂MA-co-OEGMA) copolymers with different molar ratio of MEO₂MA and OEGMA were synthesized by RAFT and click chemistry. The micelles self-assembled from the copolymers showed the reversible thermoresponse and the LCST could be tuned through altering the molar ratio of MEO₂MA and OEGMA. Furthermore, the transmittance and DLS investigations indicated that the P(St-g-QA) and P(MEO₂MA-co-OEGMA) segments both processed salt-response. The copolymer micelles with tunable thermoresponse and dual salt responses have the potential applications in biomedical fields (such as anticancer drug delivery owing to the fact that the tumor tissues show high salt concentration. The long-acting release

and controlled release of thermo-salt responsive micelles can be achieved) and nano-sensor due to the reversible thermo-salt responses of the micelles. The controlled drug release property of the multi-responsive micelles will be investigated in our future work.

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