

Ultrasound-responsive Homopolymer Nanoparticles

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Electronic Supplementary Information

Abstract Noninvasive ultrasound is a more effective strategy for on-demand drug delivery of polymeric nanoparticles than many other stimuli. However, the preparation of ultrasound-responsive homopolymer nanoparticles is still very challenging. In this study, we disclose the regulating factors of ultrasound responsiveness of homopolymer nanoparticles and the disaggregation behavior of homopolymer nanoparticle aggregates. Homopolymer nanoparticles such as vesicles and large compound micelles (LCMs) are self-assembled from poly(methoxyethyl methacrylate) (PMEMA) and poly(amic acid) (PAA), respectively. The ultrasound responsiveness of PAA vesicles at metastable state could be regulated by tuning the self-assembly temperature (T_s), and was optimized when T_s is around the glass transition temperature (T_g) of PAA. However, the PMEMA LCMs did not respond to ultrasound as they are at stable state. On the other hand, poly(2-(2-ethoxyethoxy)ethyl acrylate) (PEEA) could self-assemble into vesicle aggregates or complex micelle aggregates, which were dissociated upon sonication. Overall, the above findings provide us with a fresh insight for designing ultrasound-responsive polymeric nanoparticles.

Keywords Ultrasound responsiveness; Homopolymers; Vesicles; Micelles; Self-assembly

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INTRODUCTION

Amphiphilic block copolymers have been self-assembled to fabricate a range of nanostructures such as micelles, vesicles, nanodisks, hydrogels, etc.^[1–5] These polymeric nanoparticles may respond to external stimuli for targeted and controlled delivery of small molecules and biomacromolecules.^[6,7] External stimuli include: (1) physical stimuli such as ultrasound,^[8,9] light,^[10] temperature,^[11,12] etc.; (2) chemical stimuli such as pH,^[13,14] and redox;^[15,16] (3) biological stimuli such as glucose^[17,18] and enzymes.^[19] Among these stimuli, ultrasound is a noninvasive physical stimulus, and it is very convenient, adjustable, and easy accessible for biomedical applications.^[20–25] Therefore, a series of ultrasound-responsive nanoparticles have been prepared from amphiphilic block copolymers.^[8,20–26]

Recently, amphiphilic homopolymers have attracted more and more attention for their readily designable, one-step polymerization, and plenty types of self-assemblies such as micelles, vesicles, and etc.^[27–33] For example, Du and coworkers reported homopolymer nanobowls with controlled opening and internal holes of nanobowls as a result of the synergistic effect between the hydrogen bonding and π - π interaction of homopolymers.^[30] Those homopolymer nanoparticles have been extended for biomedical applications such as drug

delivery,^[29,34] living cell transport,^[35] and labelling and sensing of biomacromolecules.^[27,36,37] By further introducing stimuli such as pH,^[38] redox,^[34] and magnetic field,^[39] homopolymer nanoparticles can become “smart” vehicles. For example, Yan and coworkers reported amphiphilic branched homopolymer micelles with a multi-core/shell structure, which exhibited smart redox-responsive properties for efficient transportation of hydrophobic anticancer drug into the nuclei of tumor cell.^[34] However, ultrasound-responsive homopolymer nanoparticles with tunable responsiveness behavior need to be explored.

Herein, we report ultrasound-responsive homopolymer nanoparticles from PEEA, PAA, and PMEMA (Fig. 1): PMEMA LCMs did not respond to ultrasound while the ultrasound responsiveness of PAA vesicles could be regulated by tuning the T_s . The PEEA vesicle aggregates or complex micelle aggregates could respond to ultrasound, leading to the disaggregation of their nanoparticle aggregates.

EXPERIMENTAL

Materials

All monomers were purchased from Aladdin Chemistry, Co. and passed through a basic Al_2O_3 column before use. Tetrahydrofuran (THF), dimethylformamide (DMF), dioxane, *n*-hexane, and AIBN were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

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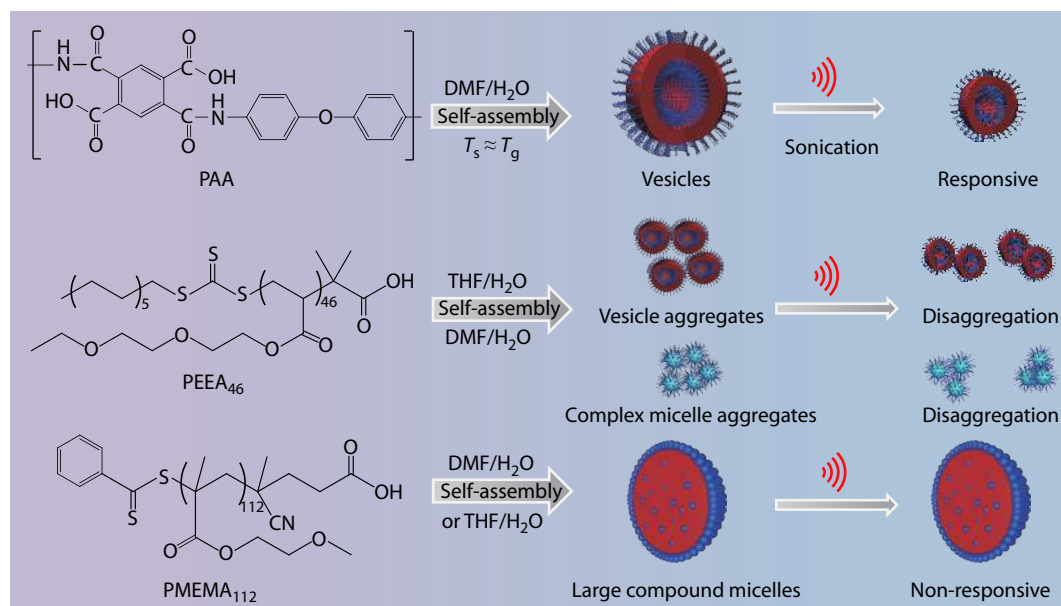


Fig. 1 Ultrasound-responsive homopolymer nanoparticles. PMEMA₁₁₂ LCMs (self-assembly solvent: THF/H₂O and DMF/H₂O) did not respond to ultrasound. PAA vesicles (self-assembly solvent: DMF/H₂O) could respond to ultrasound when the self-assembly temperature was around T_g of the PAA. PEEA₄₆ vesicle aggregates (self-assembly solvent: THF/H₂O) or complex micelle aggregates (self-assembly solvent: DMF/H₂O) could respond to ultrasound as a result of the disaggregation of the aggregates.

Synthesis of Homopolymers

Synthesis of poly(methoxyethyl methacrylate) (PMEMA)

Monomer MEMA (0.516 g, 3.58 mmol) and chain transfer agent 4-cyanopentanoic acid dithiobenzoate (CPAD, 20.0 mg, 70.0 μ mol) were dissolved in 0.5 mL of dioxane. The mixture was degassed by passing argon through for 30 min at room temperature. Then AIBN (2.30 mg, 14.3 μ mol) was quickly added into the flask and the reaction was carried out for 10 h at 70 °C with magnetic stirring. After polymerization, the mixture was precipitated in hexane for three times, followed by drying in a vacuum oven. Yield: > 70%.

Synthesis of poly(amic acid) (PAA)

PAA was synthesized according to literature.^[31] 4,4'-Oxydianiline was dissolved in dimethylformamide (DMF) at 25 °C, followed by batch-by-batch addition of equivalent pyromellitic dianhydride in DMF within one hour. The mixture was stirred for additional one hour and a viscous PAA solution was obtained. Then it was precipitated in acetone for 3 times and dried in a vacuum oven at 30 °C for 2 days. Yield > 95%.

Synthesis of poly(2-(2-ethoxyethoxy)ethyl acrylate) (PEEA)

PEEA was synthesized according to literature.^[29] Monomer EEA (1.00 g, 5.40 mmol) and chain transfer agent 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid (DDMAT, 39.0 mg, 106 μ mol) were dissolved in 1.5 mL of dioxane. The mixture was degassed by passing argon through for 30 min at room temperature. Then AIBN (2.0 mg, 12 μ mol) was quickly added into the flask and the reaction was carried out for 48 h at 80 °C with magnetic stirring. After polymerization, the mixture was precipitated in hexane for three times, followed by drying in a vacuum oven. Yield: > 70%.

Self-assembly of Homopolymers

Solvent-switch method was used to prepare nanoparticles such

as vesicles and micelles. Generally, the polymer was dissolved in THF or DMF with an initial concentration of 1.0 mg·mL⁻¹. Then distilled water was added dropwise under magnetic stirring (2/1, V/V) at desired self-assembly temperature T_g , followed by addition of the same volume of water at one stroke. Afterwards, THF or DMF was removed by dialysis against deionized water in a dialysis tubing with a molecular weight cut-off from 8.0×10^3 to 1.4×10^4 .

Sonication Tests

The sonication tests were conducted with a power of 37.5 W and time of 3 min (the frequency of ultrasound is 20 kHz). In a typical sonication test, the ultrasound probe was placed in the middle of a bottle with 2.0 mL of diluted solution (0.1 mg·mL⁻¹). The bottle was placed in a water bath at 25 °C. The sonication was kept for 3 min with the power of 37.5 W. The hydrodynamic diameters (D_h^a , before sonication; D_h^b , after sonication) and the size distribution of nanoparticles were determined by dynamic light scattering (DLS) at each interval. Each test was repeated for three times.

$$\text{Size change percentage} = |D_h^a - D_h^b| / D_h^a \times 100\%$$

Characterization

The molecular weights and polydispersities were evaluated by size exclusion chromatography (SEC), which was performed at 40 °C with two linear Styragel columns and an Agilent differential refractive index (RI) detector (1200 Infinity Series from Agilent Technologies). High performance liquid chromatograph (HPLC) grade DMF was utilized as eluent with a flow rate of 0.8 mL·min⁻¹. PEO was used as standard.

¹H-NMR spectra were recorded using a Bruker AV 400 MHz spectrometer with CDCl₃ as the solvent.

DLS measurements were carried out at 25 °C with a fixed scattering angle of 90° and Zetasizer Nano series instrument

(Malvern Instruments ZS 90). Each measurement was conducted for three runs.

Differential scanning calorimetry (DSC) curves were recorded by DSC Q100 (TA Instruments). Samples were kept at $-40\text{ }^{\circ}\text{C}$ for 3 min ($-80\text{ }^{\circ}\text{C}$ for PEEA), heated to $80\text{ }^{\circ}\text{C}$ at a rate of $20\text{ }^{\circ}\text{C}\cdot\text{min}^{-1}$ ($120\text{ }^{\circ}\text{C}$ for PAA), cooled down to $-40\text{ }^{\circ}\text{C}$ (round 2), and then heated to $80\text{ }^{\circ}\text{C}$ at a rate of $20\text{ }^{\circ}\text{C}\cdot\text{min}^{-1}$ (round 3). The curve of round 3 was analyzed for T_g of homopolymers.

Transmission electron microscopy (TEM) images were obtained using a JEM-2100F electron microscope operating at an acceleration voltage of 200/80 kV equipped with a Gatan 894 Ultrascan 1k CCD camera. A carbon-coated copper grid was pre-disposed for 30 s with a plasma cleaner. The nanoparticle solution ($8.0\text{ }\mu\text{L}$) was dropped onto it and left dried at ambient temperature. The sample-loaded copper grid was then stained for 180 s with 1.0% neutral aqueous phosphotungstic acid solution.

Ultrasound probe (FS-250N $\Phi 6\text{ mm}$) was purchased from Shanghai Sonxi Ultrasonic Instrument Co., Ltd. with frequency of 20 kHz.

RESULTS AND DISCUSSION

Synthesis and Self-assembly of Homopolymers

The amphiphilic homopolymers were synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization and stepwise polymerization (Fig. S1 in the electronic supplementary information, ESI). The compositions, T_g of homopolymers, SEC results of copolymers, and the corresponding morphologies of nanostructures are summarized in Table 1. The compositions were determined by $^1\text{H-NMR}$ spectroscopy (Figs. S2–S5 in ESI).

Homopolymer nanoparticles were prepared by self-assem-

bly of homopolymers in THF/water or DMF/water (2/1, V/V), followed by dialysis against deionized water to remove THF or DMF. The morphologies of nanoparticles were revealed by TEM and their sizes were measured by DLS as well.

When THF or DMF was used as the organic cosolvent, PMEMA₁₁₂ was self-assembled into LCMs (Figs. 2a and 2b). By contrast, vesicles could be prepared from PAA in DMF/water^[31] (Fig. S6 in ESI). PEEA₄₆ could self-assemble into vesicle aggregates (Fig. S6 in ESI).^[29] Complex micelle aggregates could be observed from PEEA₄₆ in DMF/water (Fig. 2c).

Ultrasound Responsiveness of PMEMA₁₁₂ Nanoparticles

Self-assembly temperature and solvent have important influence on the self-assembly process for preparing nanoparticles as well as the ultrasound responsiveness of the resulting homopolymer nanoparticles. The sonication experiments were carried out in a water bath at a constant temperature of $25\text{ }^{\circ}\text{C}$.

When THF/H₂O was used as the solvent, LCMs of PMEMA₁₁₂ homopolymer were formed (Fig. 2a), which did not respond to ultrasound, no matter how T_s was varied, as shown in Fig. 3(A) and Table S1 (in ESI). This is because the solid LCMs were at their thermodynamically stable state. After sonication, the micellar morphology kept unchanged (Fig. S7 in ESI). The SEC traces and $^1\text{H-NMR}$ spectra of PMEMA₁₁₂ before and after sonication kept unchanged (Figs. 3C and 3D), confirming that no chemical changes occurred after sonication.

When DMF/H₂O was used as the solvent, LCMs were also observed (Fig. 2b), indicating that the type of self-assembly solvent had no influence on the morphology of PMEMA₁₁₂ homopolymer. Tuning the T_s exerted no effect on the ultrasound responsiveness of LCMs (Fig. 3B and Table S2 in ESI), indicating a thermodynamically stable state of LCMs.

LCMs from PMEMA with different molecular weights (Fig.

Table 1 Summary of homopolymers and the corresponding morphologies at different self-assembly conditions.

Homopolymer	Full name	T_g ($^{\circ}\text{C}$)	M_n (Da)	$\bar{D}$	Morphologies (TEM images)	
					THF/H ₂ O	DMF/H ₂ O
PMEMA ₁₁₂	Poly(methoxyethyl methacrylate)	32	9.3×10^3	1.05	Large compound micelles (Fig. 2a)	Large compound micelles (Fig. 2b)
PAA ^a	Poly(amic acid)	61	3.5×10^4	1.28	–	Vesicles (Fig. S6a in ESI)
PEEA ₄₆	Poly(2-(2-ethoxyethoxy)ethyl acrylate)	-51	3.7×10^3	1.21	Vesicle aggregates (Fig. S6b in ESI)	Complex micelle aggregates (Fig. 2c)

^a Synthesized according to literature.^[31]

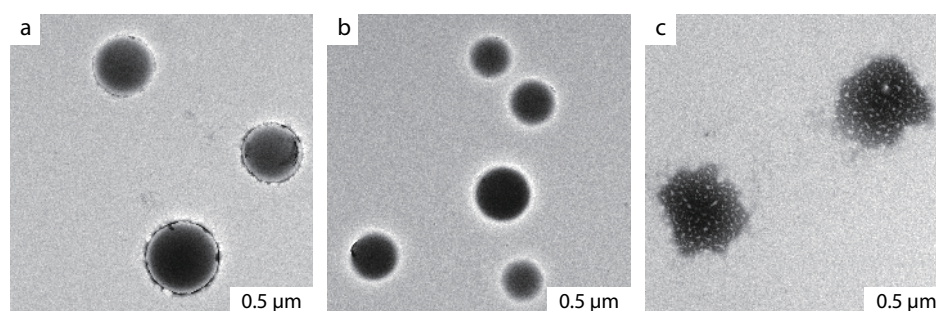


Fig. 2 TEM images of homopolymer nanoparticles after removing organic solvents by dialysis before sonication. (a) LCMs prepared with PMEMA₁₁₂ in THF/H₂O; (b) LCMs prepared with PMEMA₁₁₂ in DMF/H₂O; (c) Complex micelle aggregates prepared with PEEA₄₆ in DMF/H₂O. TEM images of vesicles prepared with PAA in DMF/H₂O^[31] and vesicle aggregates prepared with PEEA₄₆ in THF/H₂O^[29] are shown in Fig. S5 (in ESI). The self-assembly temperature (T_s) is $25\text{ }^{\circ}\text{C}$.

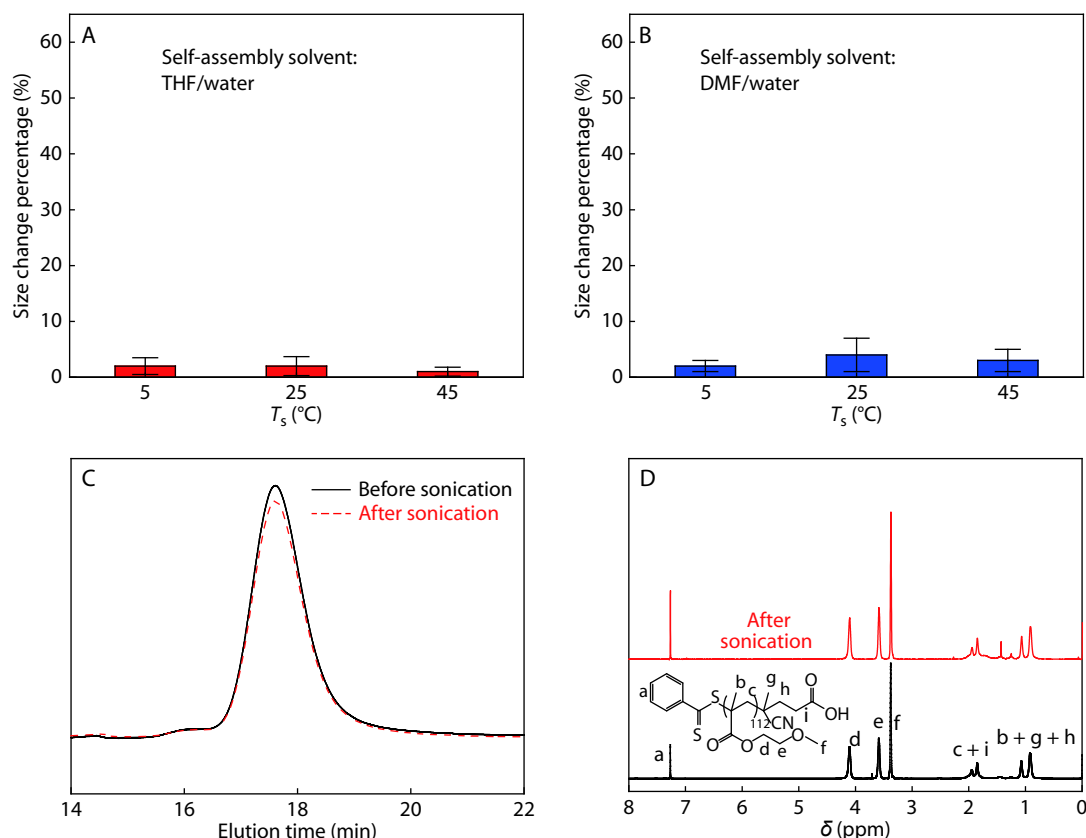


Fig. 3 (A, B) Regulating ultrasound responsiveness of PMEMA₁₁₂ LCMs by tuning the T_s ; (C) DMF SEC traces and (D) ¹H-NMR spectra (in CDCl₃) of PMEMA₁₁₂ frozen dried from its aqueous LCMs solutions before and after sonication tests, confirming no chemical changes.

S8 in ESI) did not respond to ultrasound either. For example, PMEMA₄₃ and PMEMA₁₅₈ LCMs showed no ultrasound responsiveness whether self-assembled in THF/H₂O or DMF/H₂O (Fig. S9 in ESI).

Based on the above results, we conclude that solid homopolymer nanoparticles at stable states have no ultrasound responsiveness, and this rule also applies to other homopolymer nanoparticles. For example, nanobowls with solid structure self-assembled from poly(2-hydroxy-3-((4-(phenyldiazenyl)phenyl)amino)propyl methacrylate)^[30] did not respond to ultrasound even at different T_s 's (Fig. S10 in ESI).

Ultrasound Responsiveness of PAA Vesicles

To reveal whether the ultrasound responsiveness of homopolymer vesicles can be regulated by T_s , we prepared PAA vesicles according to literature.^[31] When T_s was much lower than T_g of the PAA homopolymer, vesicles did not respond to ultrasound (the size of vesicles kept around 210 nm at $T_s = 25$ °C); raising T_s to 60 °C (around the T_g of PAA), the hydrodynamic diameter of vesicles^[40] increased to 525 ± 28 nm (516 ± 95 nm by TEM) and vesicles become responsive to ultrasound with 15% size decrease but unchanged morphology (Fig. 4, Figs. S11 and S12 and Table S3 in ESI).

These results confirm that the ultrasound responsiveness of homopolymer vesicles can be tuned by T_s . When T_s is far below T_g of PAA, the polymer chains are frozen at the glassy states with poor chain mobility, thus leading to stable vesicles without ultrasound responsiveness. When T_s is around T_g

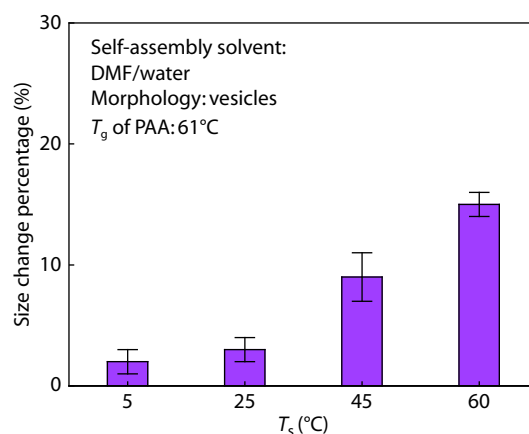


Fig. 4 Regulating ultrasound responsiveness of PAA vesicles (prepared in DMF/H₂O) by tuning the T_s .

of PAA, the increased polymer chain mobility can result in metastable vesicles with certain ultrasound responsiveness.

Disaggregation of PEEA₄₆ Nanoparticles under Sonication

The above results reveal that tuning T_s can regulate the ultrasound responsiveness of homopolymer vesicles but have no influence on that of homopolymer micelles. It is noteworthy that the influence of homopolymer structure on the ultrasound responsiveness derives mainly from the corresponding T_g and

morphologies (e.g., solid micelles or hollow vesicles). Different homopolymers may afford different morphologies. For a single solid nanoparticle such as a micelle, it does not respond to ultrasound because it is quite stable. As for vesicles, they can respond to ultrasound at metastable states when the self-assembly temperature is around T_g of the homopolymer. Besides these homopolymer nanoparticles, homopolymer nanoparticle aggregates can also respond to ultrasound.

Vesicle aggregates can be prepared from PEEA₄₆ in THF/H₂O.^[29] These vesicle aggregates could respond to ultrasound with more than 80% size decrease (Fig. 5A and Table S4 in ESI) but unchanged morphologies (Fig. S13 in ESI). This physical process is also confirmed by the unchanged SEC traces and ¹H-NMR spectra of PEEA₄₆ before and after sonication (Figs. 5C and 5D), indicating that no chemical changes occurred after sonication. By varying T_s , these vesicle aggregates could still respond to ultrasound (Fig. 5A and Table S4 in ESI). This phenomenon can be also observed from complex micelle aggregates prepared in DMF/H₂O (Fig. 5B and Table S5 in ESI).

The large size decrease is not the size change of nanoparticle itself, but the disaggregation of nanoparticle aggregates. The size of an individual vesicle was 66 ± 15 nm, much smaller than the results measured by DLS (580 ± 11 nm), indicating an aggregation behavior of vesicles in solution.

After sonication, the diameter of these vesicle aggregates was 142 ± 1 nm by DLS, but the diameter of a single vesicle was almost unchanged (60 ± 24 nm), suggesting a disaggregation process under sonication. These vesicles after sonication could aggregate again with size increasing to 308 ± 4 nm (further proving the aggregation behavior of vesicles) and could respond to ultrasound again with size decreasing to 219 ± 2 nm (Figs. 6a and 6b). Complex micelle aggregates showed similar reversible aggregation/disaggregation behavior (Figs. 6c and 6d).

This disaggregation behavior of PEEA₄₆ nanoparticle aggregates under sonication is different from the ultrasound responsiveness of single nanoparticle such as PAA vesicle, which can be regulated by the self-assembly temperature. Firstly, the disaggregation of PEEA₄₆ nanoparticle aggregates is not originated from their temperature-responsiveness but induced by ultrasound because the size of PEEA₄₆ vesicle or complex micelle aggregates increased upon raising temperature (Figs. 7a and 7c). Secondly, the disaggregation behavior may be caused by the destruction of hydrophobic effect after sonication. The temperature-responsiveness of PEEA₄₆ vesicle or complex micelle aggregates is driven by the hydrophobic effect because there exists a hydrophilicity-hydrophobicity rocking of oligo(ethyleneoxy) side chains (OEs) in water at different temperatures.^[29] The temperature-respons-

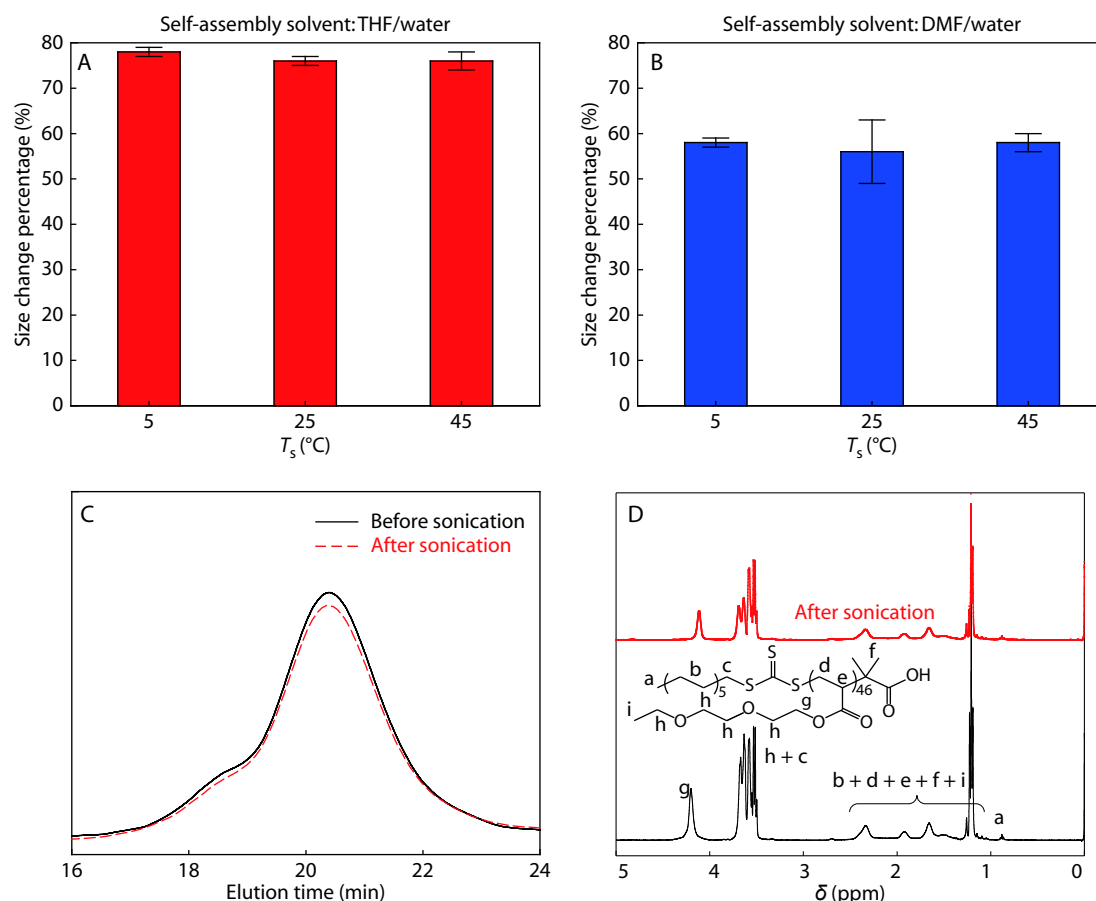


Fig. 5 PEEA₄₆ (A) vesicle aggregates and (B) complex micelle aggregates responding to ultrasound at different T_s ; (C) DMF SEC traces and (D) ¹H-NMR spectra (CDCl₃) of PEEA₄₆ frozen dried from its aqueous vesicle aggregates solutions before and after sonication tests, showing that no chemical changes occurred.

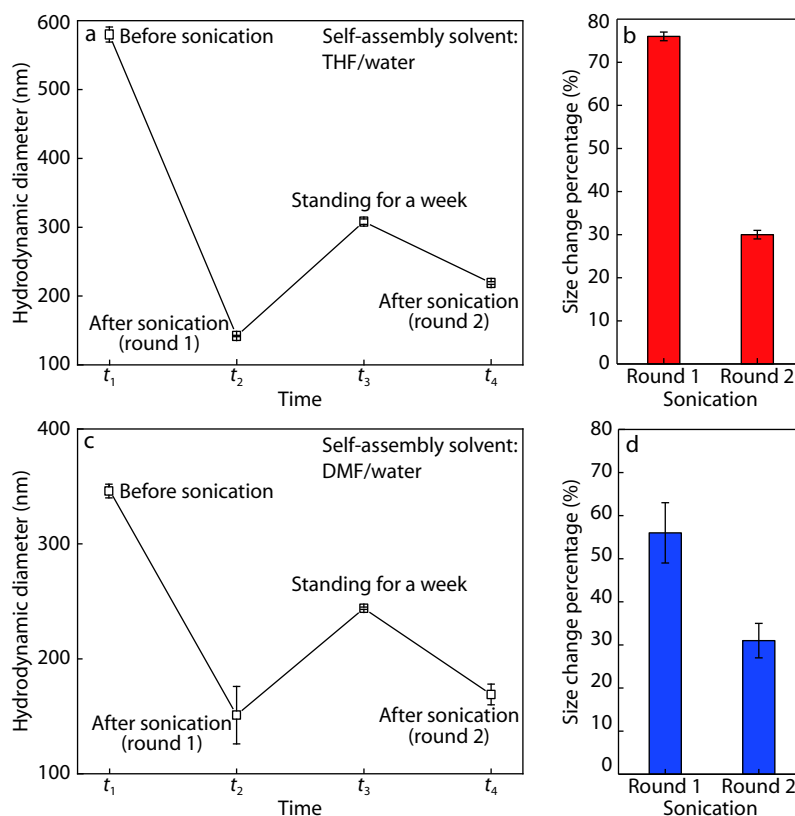


Fig. 6 Disaggregation and re-aggregation of (a, b) vesicle aggregates and (c, d) complex micelle aggregates by DLS.

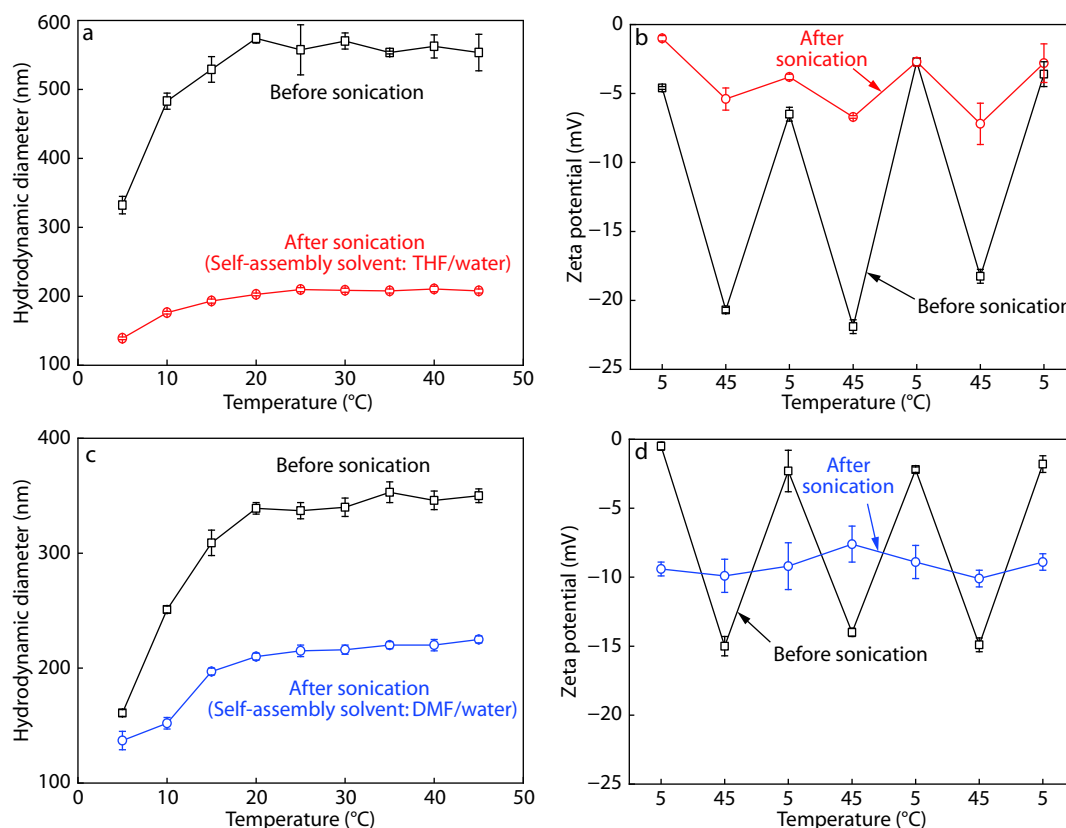


Fig. 7 Temperature dependence of (a, c) size and (b, d) zeta potential of (a, b) PEEA₄₆ vesicle aggregates and (c, d) PEEA₄₆ complex micelle aggregates.

iveness will be greatly affected after sonication as indicated by the size change (Figs. 7a and 7c) and the zeta potentials (Figs. 7b and 7d) against temperature. These results confirm that ultrasound may destroy the hydrophobic effect of OEs and thus lead to the disaggregation of PEEA₄₆ nanoparticle aggregates.

CONCLUSIONS

In conclusion, ultrasound-responsive homopolymer nanoparticles were prepared from PAA and PEEA homopolymers. LCMs from PMEMA homopolymers did not respond to ultrasound. By tuning T_g around T_g of PAA, the ultrasound responsiveness of PAA vesicles could be optimized. Different from the ultrasound responsiveness of single homopolymer nanoparticle, the PEEA vesicle aggregates or complex micelle aggregates could respond to ultrasound due to the disaggregation of nanoparticle aggregates. Overall, our study has provided a fresh insight for designing ultrasound-responsive homopolymer nanoparticles, which may have promising potential applications in nanomedicine and other fields.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://dx.doi.org/10.1007/s10118-020-2345-6>.

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