Support Information

Inhalable Mucin-Permeable Nanomicelles Deliver Antibiotics for Effective Treatment of Chronic Pneumonia

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The synthesis of 2-(piperidin-1-yl)ethyl methacrylate (PEMA) monomers

Poly(ethyl methacrylate) (PEMA) monomer was synthesized following literature procedures. 2-(Piperidin-1-yl)ethanol (12.9 g, 0.1 mol), triethylamine (10.1 g, 0.1 mol), and phloroglucinol as an inhibitor (0.13 g, 0.001 mol) were stirred to dissolve in THF, and then methacryloyl chloride (10.4 g, 0.1 mol) was added dropwise into the round flask. The solution was heated under reflux (80℃) in THF overnight. Suction filtration was used to remove the precipitate, and the THF solvent was removed by a rotovap. The monomer was obtained through reduced pressure distillation (110℃) as a colorless liquid.

The synthesis of 2-(N-oxide-pentamethyleneimino)ethyl methacrylate (POEMA) monomers

PEMA (1.0 g, 5 mmol) was dissolved in 20 mL of anhydrous DCM in an ice bath. m-Chloroperoxybenzoic acid (mCPBA) (1.295 g, 7.5 mmol) was added into the round flask with stirring. The solution was allowed to warm to room temperature and stirred for another 2 h. The DCM solvent was removed by rotovap. The product was then dissolved in water and washed twice with diethyl ether in a separating funnel. After lyophilization, the resulting monomers showed a yellowish jelly-like appearance.

The synthesis of poly[2-(pentamethyleneimino)ethyl methacrylate] (PPEMA) and poly[2-(pentamethyleneimino)ethyl methacrylate]-*block*-poly[2-(N-oxide-pentamethyleneimino)ethyl methacrylate] (PPEMA-*b*-PPOEMA)

PPEMA and PPEMA-*b*-PPOEMA were synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization. A mixture of PEMA (1972.8 mg, 10 mmol), CPADB (111.75 mg, 0.4 mmol), and AIBN (16.42 mg, 0.12 mmol) were added to 2 mL of anhydrous DCM. The mixture was degassed by three freeze-pump-thaw cycles and then placed in a preheated oil bath at 70 ℃ for 12 h. The resulting product was dialyzed against absolute methanol(500 mL×3), and the methanol solvent was removed by vacuum drying. The final product obtained was a magenta viscous solid.

PPEMA after protonation was used as a macromolecular chain transfer agent to synthesize PPEMA-*b*-PPOEMA. POEMA (810 mg, 3.8 mmol), PPEMA (390 mg, 0.04 mmol), and ACVA (2.8 mg, 0.01 mmol) were added to deionized water, and the total volume was 2 mL. The mixture was degassed by three freeze-pump-thaw cycles and then placed in a preheated oil bath at 70 °C for 12 h. The production was dialyzed against alkaline PBS (500 mL×3) for 48 h to deprotonate. Then the product was dialyzed against methanol (500 mL×3). The methanol solvent was removed by vacuum drying. The product was a brown viscous solid.

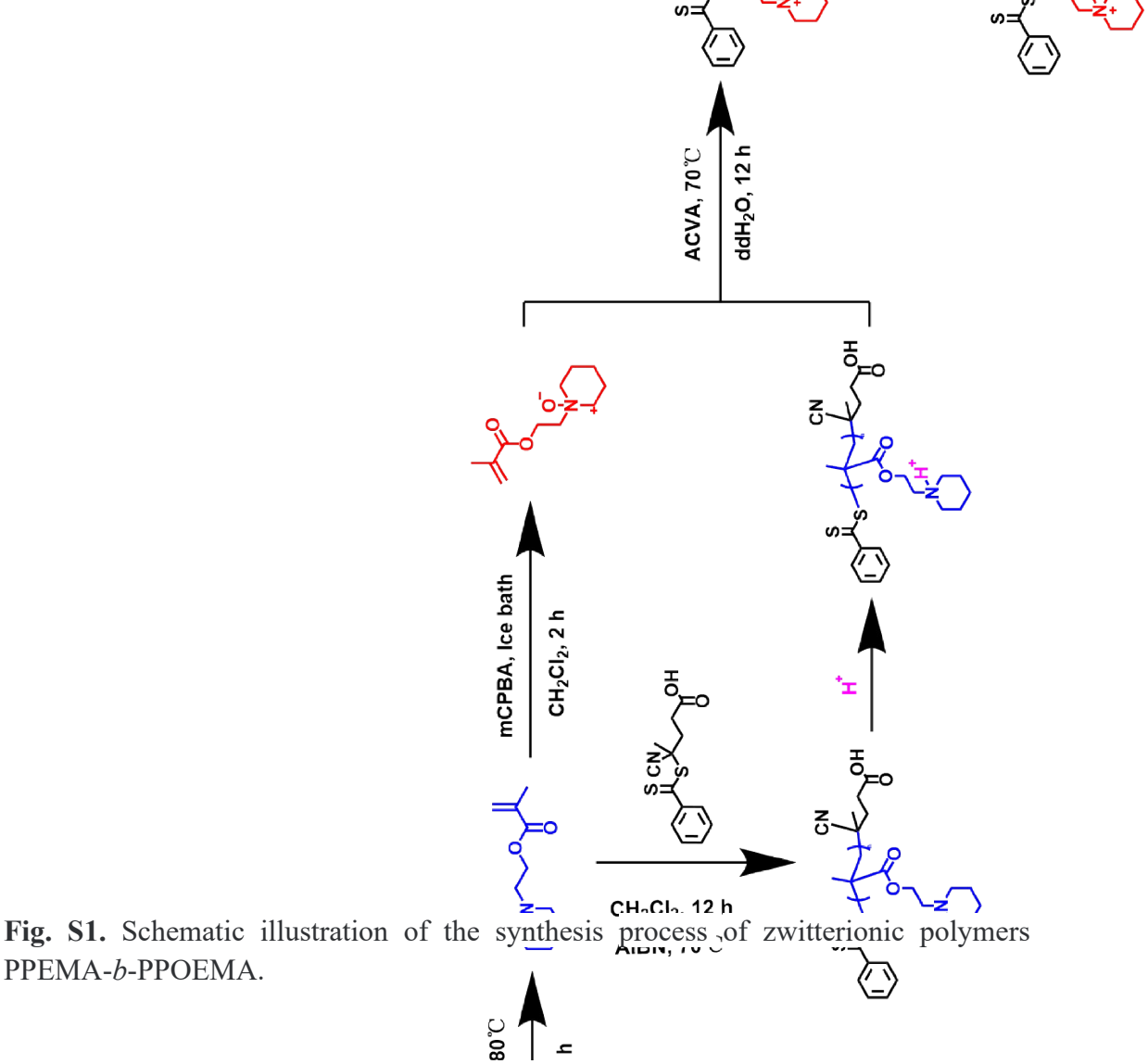

Fig. S1. Schematic illustration of the synthesis process of zwitterionic polymers PPEMA-*b*-PPOEMA.

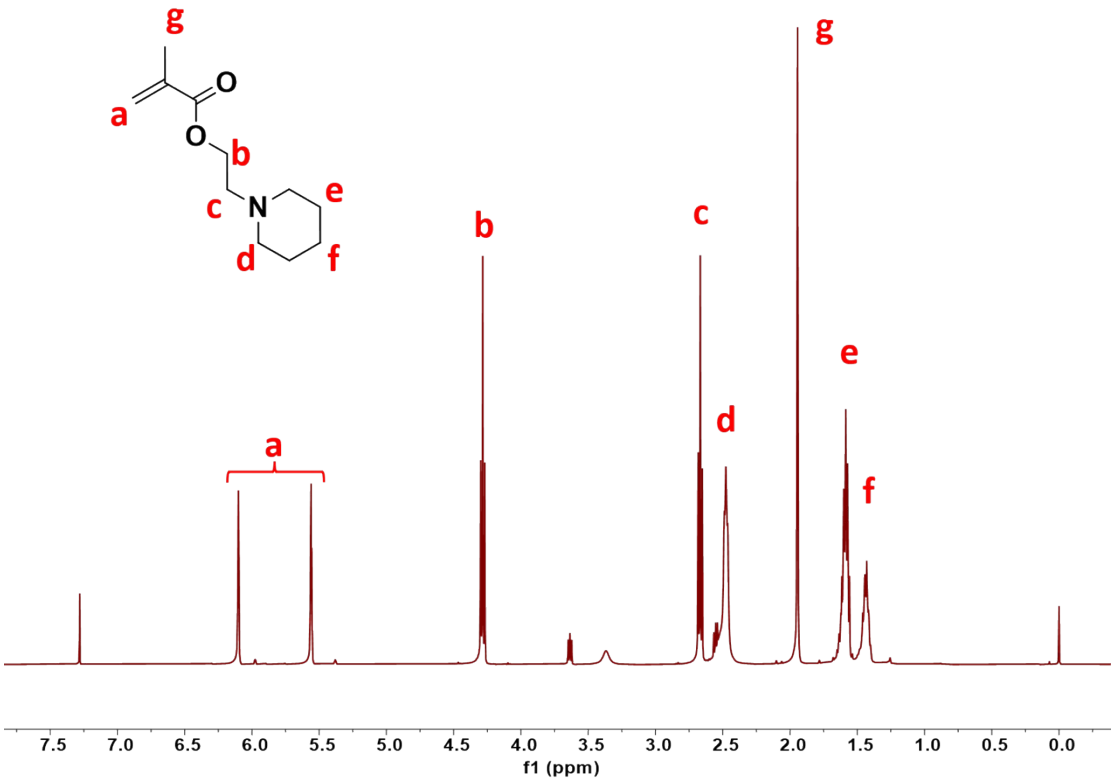

Fig. S2. The structure and corresponding ^{1}H NMR spectrum of PEMA in $CDCl_3$

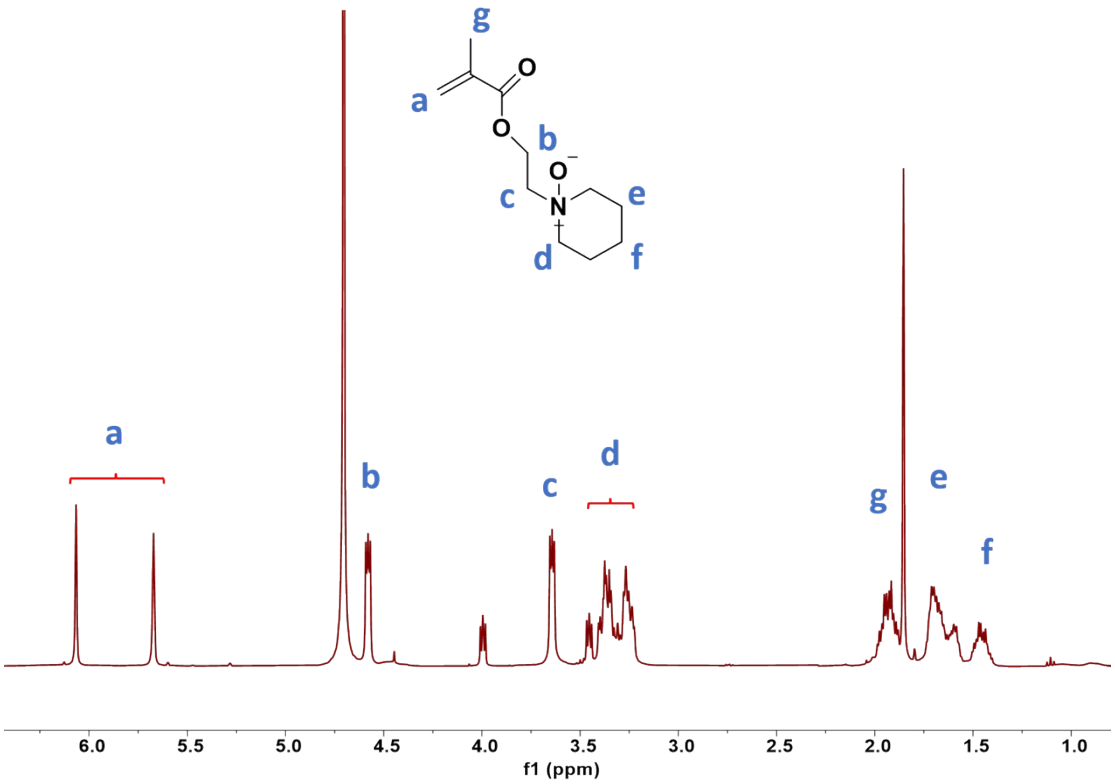

Fig. S3. The structure and corresponding 1H NMR spectrum of POEMA in D_2O.

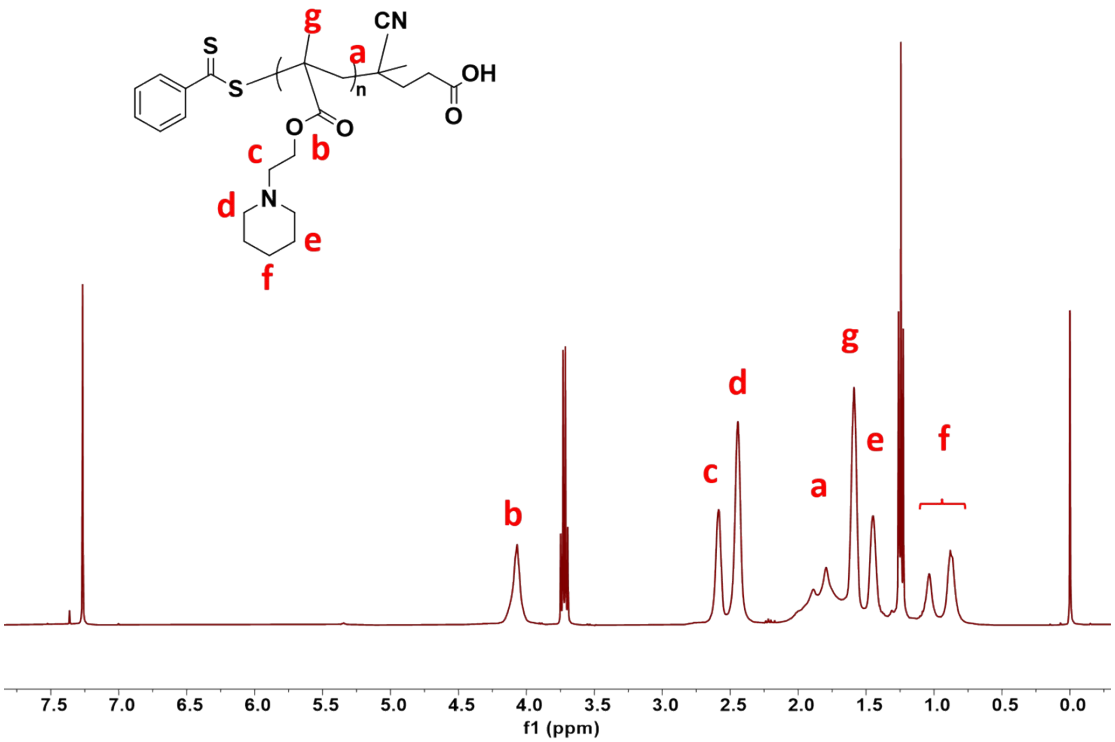

Fig. S4. The structure and corresponding 1H NMR spectrum of PPEMA in $CDCl_3$

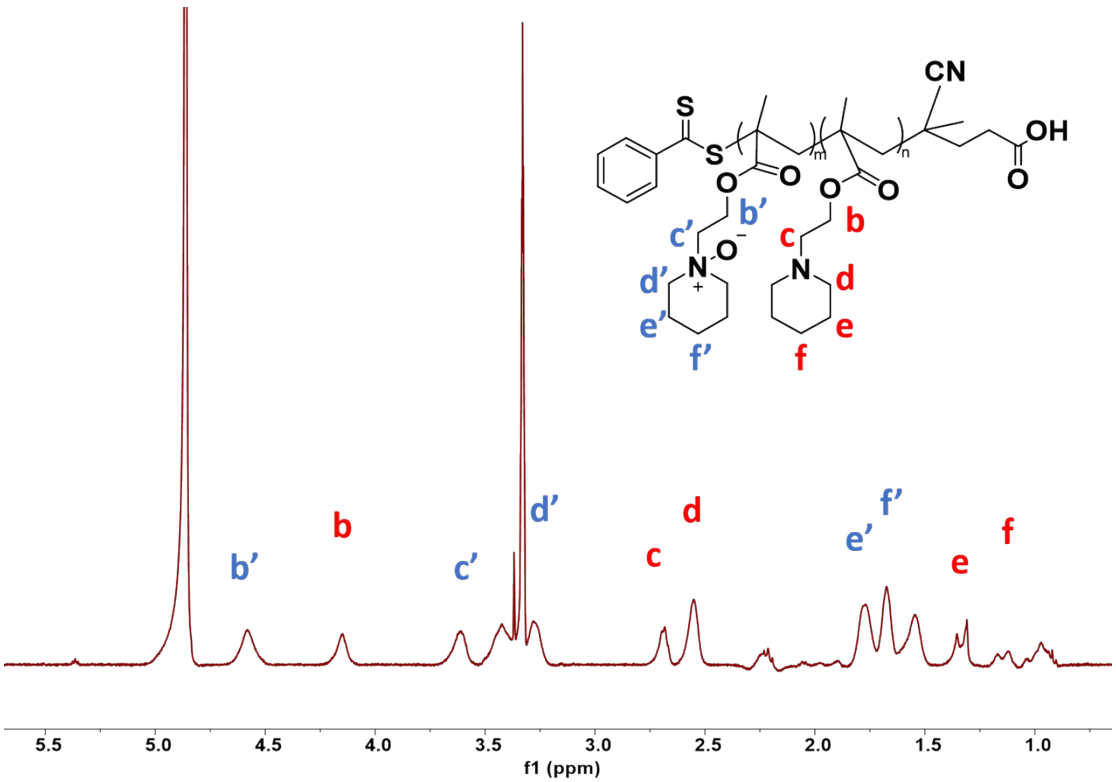

Fig. S5. The structure and corresponding 1H NMR spectrum of PPEMA-*b*-PPOEMA in methanol-D_4.

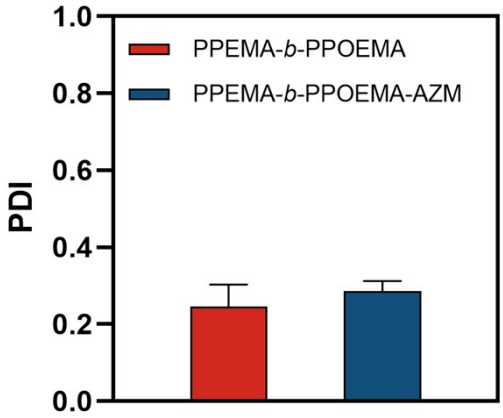

Fig. S6. The polydispersity index (PDI) of PPOEMA-*b*-PPOEMA and PPEMA-*b*-PPOEMA-AZM.

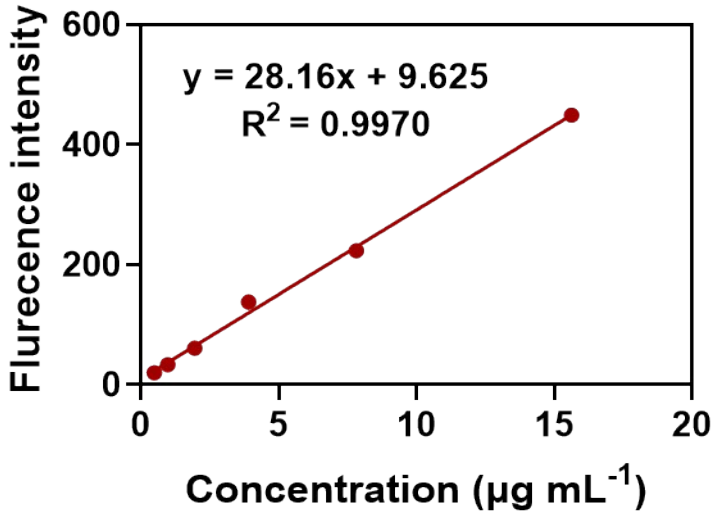

Fig. S7. Standard curve of Nile red in acetonitrile:PBS=1:1 solution.

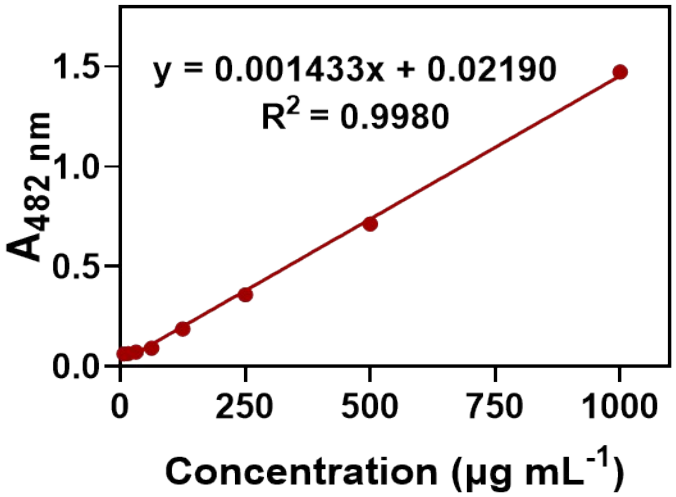

Fig. S8. Standard curve of azithromycin in methanol:PBS=1:1 solution.

	Drug loading rate (wt. %)
PPEMA-*b*-PPOEMA-AZM	19.2% - 22.8%
PPEMA-*b*-PPOEMA-Nilered	6.4%

Fig. S9. Drug loading rates of Nile red and AZM on PPEMA-*b*-PPOEMA.

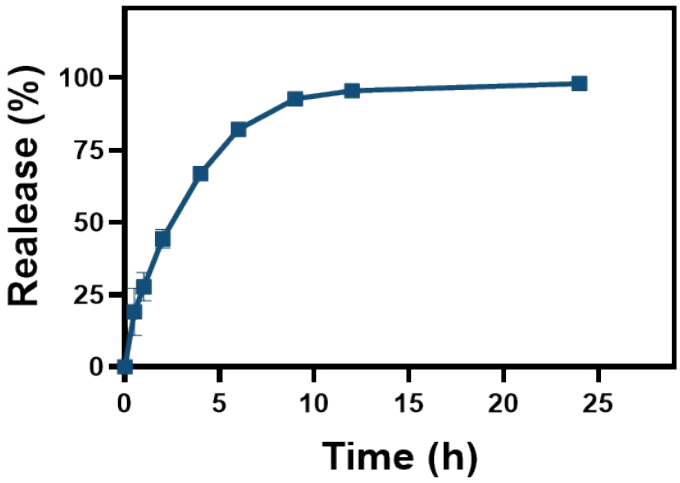

Fig. S10. AZM cumulative release curves of AZM loaded PPEMA-*b*-PPOEMA micelles in PBS.

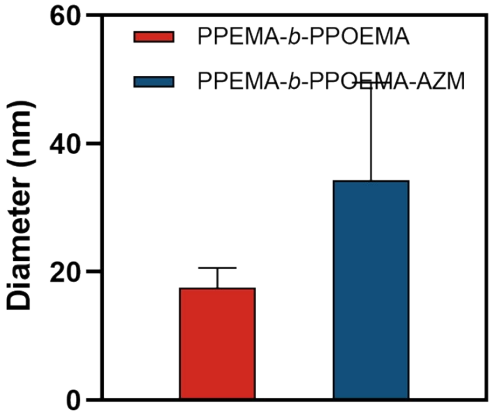

Fig. S11. Micellar diameter was measured after 100 micellar TEM images.

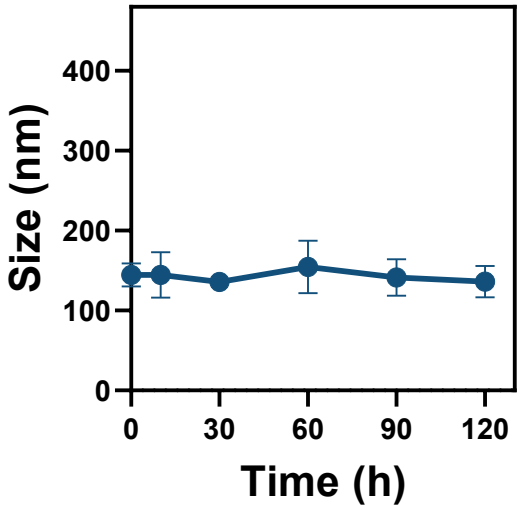

Fig. S12. Particle size changes after 2 h of incubation with artificial mucus.

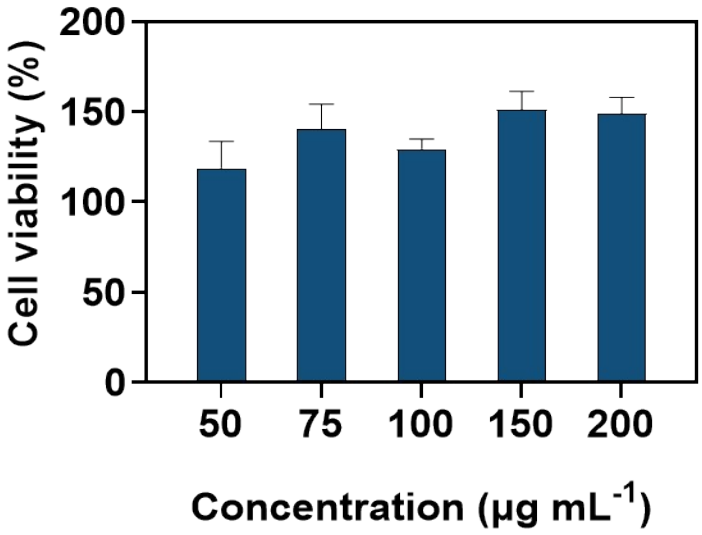

Figure S13. Viability of Raw 264.7 cells incubated with PPEMA-*b*-PPOEMA micelles.

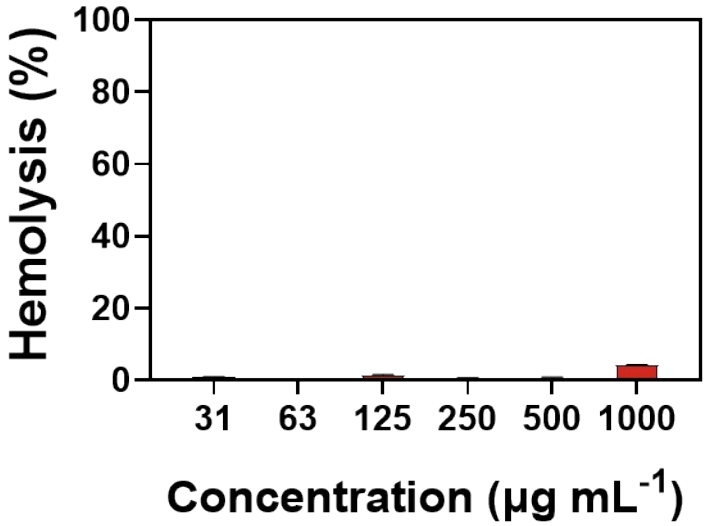

Figure S14. Statistical result of hemolysis evaluation of PPEMA-*b*-PPOEMA micelles.

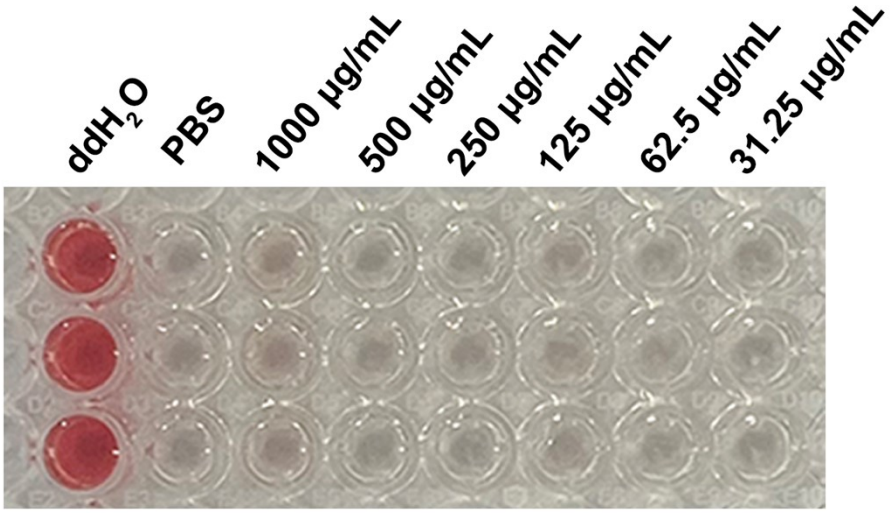

Figure S15. Image of hemolysis evaluation of PPEMA-*b*-PPOEMA micelles.

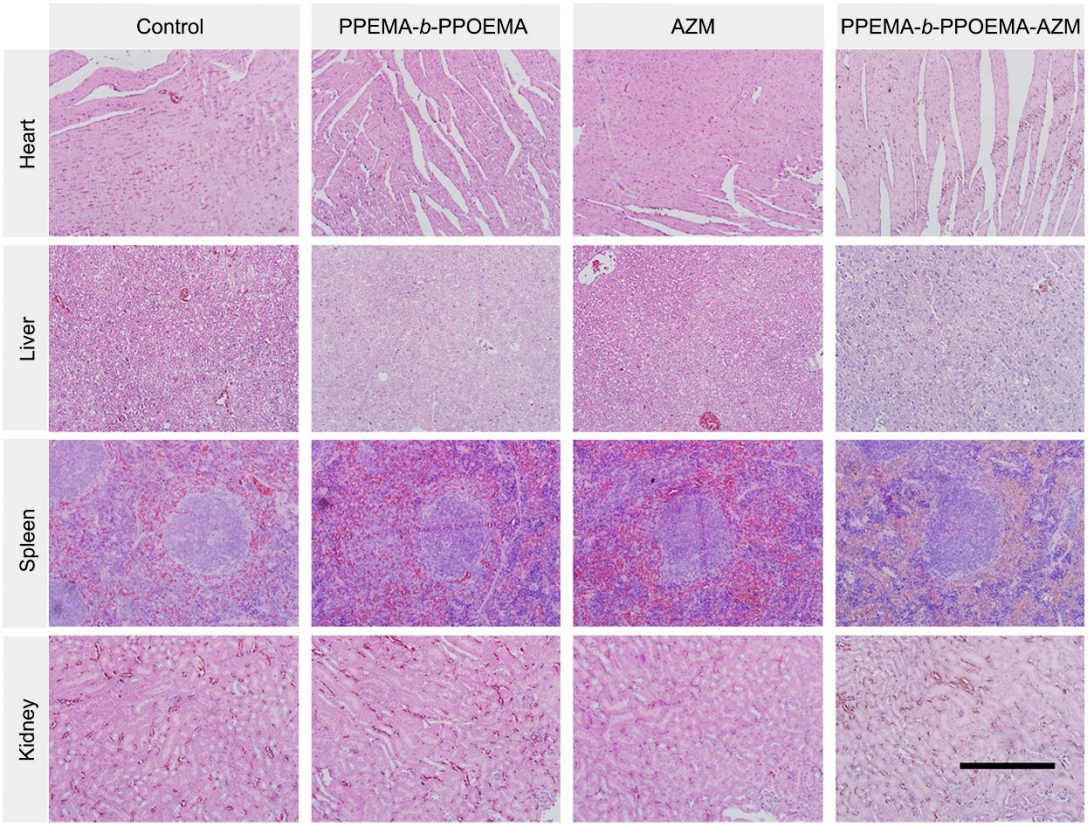

Figure S16. Images of mouse heart, liver, spleen, and kidney stained with H&E. Scale bar, 50 μm.

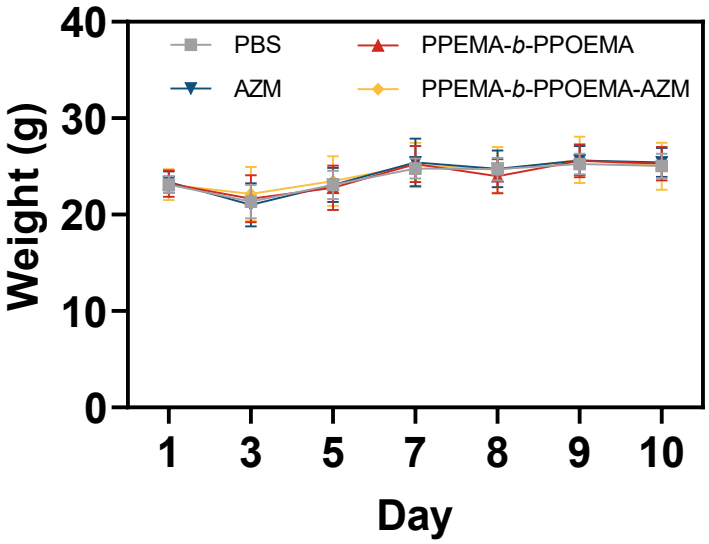

Figure S17. Changes in body weight of mice during the experiment.