Supplementary Information

Thermoresponsive Physical Hydrogels of Poly(lactic acid)/Poly(ethylene glycol) Stereoblock Copolymers Tuned by Stereostructure and Sequence of Hydrophobic Blocks

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EXPERIMENTAL

Materials. Dihydroxyl-terminated PEG ($M_n = 10$ kg/mol) was purchased from Sigma-Aldrich. L- and D-lactide were purchased from Purac Co. (Gorinchem, the Netherlands) and *meso*-lactide (D,L-lactide) was purchased from Jinan Daigang Biomaterial Co., Ltd (China). All these lactides were recrystallized from ethyl acetate before use. Tin(II) 2-ethylhexanoate [Sn(Oct)₂, Sigma-Aldrich] and doxorubicin hydrochloride (DOX HCl, Beijing Huafeng United Technology Co.) were used as received. Toluene was dried by sodium and distilled after reflux for 48 h.

Synthesis of PLA/PEG Pentablock Copolymers. A typical procedure to prepare the pentablock copolymer having the expected M_n s of each PLLA and PDLA block of 2160 g/mol is described as below. In the first-step ring-opening polymerization (ROP), dried PEG (10.0 g, 1.0 mmol) and L-lactide (2.16 g, 15 mmol) were charged into a Schlenk flask and further dried under reduced pressure at 60 °C for 30 min. The flask was then pulped and purged with dry argon. After injection of 50 mL of anhydrous toluene, the mixture was fluxed and 20 mL of toluene was distilled off to remove the trace of water. Then, Sn(Oct)₂ (0.02 g, 0.05 mmol) dissolved in 1.0 mL of dry toluene was injected into the reaction mixture. The polymerization was allowed to proceed under reflux for 12 h. After polymerization, the reaction mixture was dissolved in dichloromethane and precipitated into excess of diethyl ether/*n*-hexane mixed solvent (v/v, 1/1). The product was isolated and dried *in vacco* at 60 °C for 12 h.

In the second-step ROP, 9.73 g of PLLA–PEG–PLLA triblock copolymer synthesized in the first step and 1.96 g of D-lactide (13.6 mmol) were added into a Schlenk flask and dried under reduced pressure at 80 $^{\circ}$ C for 30 min, which was then pulped and purged with dry argon. After injection of 50 mL of anhydrous toluene, 20 mL of toluene was distilled off under reflux to remove the trace of water. Then, 0.04 mmol of Sn(Oct)₂ solution was injected into the reaction mixture. The polymerization was allowed to proceed under reflux for 12 h. After the polymerization, the polymer was purified according to the method similar to that used in the first step. For comparison, PLA–PEG–PLA triblock copolymers comprised of isotactic PLLA, PDLA, and atactic PDLLA were synthesized by a similar method. *Meso*-lactide was used as the monomer for synthesizing PDLLA–PEG–PDLLA.

Measurements

Thermal properties of copolymers were measured on a NETZSCH 214 Polyma DSC (NETZSCH, Germany). The sample was first heated to 200 °C at a heating rate of 10 °C/min and held at this temperature for 2 min to eliminate the thermal history. Then, the sample was cooled to -70 °C at a cooling rate of 100 °C/min, followed by a reheating to 200 °C at a heating rate of 10 °C/min.

Dynamic light scattering (DLS) analysis was performed on a Zetasizer Nano ZS90 instrument with a laser light (wavelength = 633 nm) set at a scattering angle of 90°. To prepare the micelle solution, 20 mg of block copolymer was dissolved in 10 mL of THF at 25 °C and 20 mL of deionized water was added under continuous stirring. Then, THF in the copolymer solution was evaporated at room temperature to attain the micelle solution. The micelle solution (~0.1 wt%) was equilibrated at 20 °C for 24 h before measurement.

Fourier transform infrared (FTIR) spectrum was measured on a Nicolet iS50 spectrophotometer (ThermoElectron, Madison, U.S.A.) with 32 scans and a resolution of 2 cm^{-1} .



Fig. S1 Representative ¹H NMR spectra of PLA/PEG stereo pentablock copolymers. The peak at 4.3 ppm (indicated by asterisk) is assigned to the terminal methine proton of PLA blocks and the terminal methylene protons of PEG block that is connected to PLA.



Fig. S2 GPC traces of PEG, PLLA–PEG–PLLA precursor and PDLA–PLLA–PEG–PLLA– PDLA pentablock copolymer synthesized in the first and second-step ROP.



Fig. S3 DSC curves of PLA/PEG copolymers and their enantiomeric mixture collected in the heating process: (A) symmetric pentablock copolymers with different PLLA/PDLA block lengths; (B) pentablock copolymers with different PLLA/PDLA block ratios; (C) pentablock and triblock copolymers with different sequence structures. Before the heating process, the samples were cooled from 200 to -70 °C at a cooling rate of 100 °C/min.



Fig. S4 FTIR spectra in carbonyl stretching region of freeze-dried PLA/PEG copolymer gels: (A) symmetric pentablock copolymers with different PLLA/PDLA block lengths; (B) pentablock copolymers with different PLLA/PDLA block ratios; (C) pentablock and triblock copolymers with different sequence structures.



Fig. S5 Number-averaged hydrodynamic diameter (D_h) and its distribution for PLA/PEG pentablock and triblock copolymers in water (0.1wt%) at 25 °C: (A) 5L₅D₂₅, (B) 5L₁₀D₂₀, (C) 5L₁₅D₁₅, (D) 5L₂₀D₁₀, (E) 5L₂₅D₅, (F) 3L₃₀/D₃₀.



Fig. S6 SAXS profiles of PLA/PEG copolymer gels (12 wt%) at 20 °C: (A) symmetric pentablock copolymers with different PLLA/PDLA block lengths; (B) pentablock copolymers with different PLLA/PDLA block ratios; (C) pentablock and triblock copolymers with different sequence structures. The profiles were arbitrarily shifted in vertical direction for clarity. The sample-to-detector distance was 2.0 m in SAXS measurement.



Fig. S7 SAXS profiles of PLA/PEG copolymer gels with a copolymer concentration of 30 wt% at 20 °C: (A) pentablock copolymers with different PLLA/PDLA block ratios; (B) pentablock and triblock copolymers with different sequence structures. The profiles were arbitrarily shifted in vertical direction for clarity. The sample-to-detector distance was 2.0 m in SAXS measurement.



Fig. S8 Plots of loss modulus as a function of frequency for the PLA/PEG copolymer gels (12wt%) at 37 $\$ C: (A) pentablock copolymers with different PLLA/PDLA block ratios; (B) pentablock and triblock copolymers with different sequence structures.



Fig. S9 ¹H NMR spectra of PLA/PEG copolymer gels after partial degradation. A_a/A_b denotes the area ratio of peaks a to b after the partial degradation. Peaks a and b are assigned to the methylene protons of PEG and methyl protons of PLA, respectively.