Supplementary Information

Facile synthesis of reduction-responsive amphiphilic triblock polymer via selective thiol-disulfide exchange reaction

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General

Materials

Acetic acid, mercaptoacetic acid, and p-toluenesulfonic acid were purchased from Sinopharm Chemical Reagent Co. Ltd. 2,2'-dithiodipyridine, 1,6-hexanedithiol, monomethoxy poly(ethylene glycol) (M_n= 1.9kDa, mPEG1.9k) were purchased from Aladdin Reagent Co. Ltd. Solvents were purified by standard procedures.

Instrumentation

NMR spectra were recorded on an INOVA-400 instrument using TMS as an internal standard. Gel permeation chromatography (GPC) of the obtained triblock copolymer was performed on a Waters 1515 GPC instrument in THF calibrated with standard polystyrene. Fluorescent spectra were recorded at room temperature with a HITACHI F-4600 fluorescence spectrophotometer with the excitation and emission slit widths at 5.0 and 5.0 nm respectively. Transmission electron microscopy (TEM) measurement was performed on a Tecnai G2 F20 S-twin TEM at 80 kV. Dynamic light scattering (DLS) measurements were carried out using a Nano-ZS90 zeta-potential and particle analyzer (Malvern, UK).

Synthesis of mPEG-SH

mPEG1.9k (9.5 g, 5 mmol), mercaptoacetic acid (4.6 g, 50 mmol) and p-toluenesulfonic acid (0.1 g, 0.58 mmol) were dissolved in toluene (120 mL). The solution was refluxed at 120 °C for 24 h and the reaction was driven forward by the continuous removal of water produced. Toluene was removed via evaporation on a rotovap. The resulting residue was dissolved in CH_2Cl_2 and precipitated in cold diethyl ether, then repeated twice. Then precipitate was dried under vacuum to give 7.9 g (4.0 mmol) of mPEG-SH. Yield: 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.0 (t, 0.9, SH), 3.25 (d, 1.9, CH_2S), 3.3 (s, 3, OCH_3), 4.25 (t, 2.1, CH_2-O-C(O)).

Synthesis of PDS(1)

In glove box, 2,2'-dithiodipyridine (2.0 g, 9.1 mmol) was dissolved in 2.5 ml dry CH_2Cl_2. To this stirring solution 1,6-hexanedithiol (1.31 mL, 8.7 mmol) and catalytic amount of acetic acid (0.1 mL) were added sequentially and the reaction mixture was stirred at room temperature for 2.5 h. Afterwards the reaction mixture was dissolved in $CHCl_3$ (2 mL) and precipitated from excess methanol. After re-dissolving the yellow precipitate in $CHCl_3$, it was re-precipitated from acetone and washed few times with acetone and dried under vacuum to obtain PDS(1) as yellowish white powder (0.95 g, 73%, M_n (^{1}H NMR) = 5.4 kDa).

Synthesis of mPEG-*b*-PDS(1)-*b*-mPEG

PDS(1) (324 mg, 0.06 mmol) was dissolved in 5 mL CH_2Cl_2. To this stirring solution, mPEG-SH (394 mg, 0.2 mmol) and acetic acid (0.5 mL) were added sequentially and the reaction mixture was stirred further at room temperature for 48 h. Then the reaction mixture was dialyzed against ethanol for 24 h (MWCO = 3.5 kDa). After dialysis, the reaction mixture was precipitated from excess diethyl ether and the precipitate was dried under vacuum to give 500 mg (0.053 mmol) of mPEG-*b*-PDS(1)-*b*-mPEG. Yield: 88%.

Preparation of micelles

Micelles of mPEG-*b*-PDS(1)-*b*-mPEG were prepared by a dialysis method. 10.0 mg copolymer was dissolved in DMF (2 mL), and then DI water (20 mL) was slowly added under vigorous stirring. After vigorous stirring for another 2 h at room temperature, the micelles were obtained and further dialyzed against DI water for 24 h to remove DMF (MWCO of 3.5 kDa). The final polymer concentration was adjusted to 0.2 mg/mL.

Determination of critical micelle concentration (CMC)

CMC of the micelle was determined using Nile Red (NR) as a fluorescence probe. NR in THF (0.1 mg mL^{-1}, 30 μL) was added to a glass vial via a microsyringe. After THF was evaporated, a micellar solution (2 mL) was added. The concentration of the micellar solution was varied from 0.2 to 2×10^{-3} mg mL^{-1}. Then the solution was stirred for 5 h. Finally, fluorescence measurements were taken at an excitation wavelength of 550 nm and the emission wavelength was monitored from 580 to 750 nm.

Reduction-triggered release experiments

The release profiles of mPEG-*b*-PDS(1)-*b*-mPEG micelles (0.2 mg mL^{-1}) with Nile Red concentration at about 1.5×10^{-3} mg mL^{-1} were studied in two different media, i.e. with or without 10 mM DTT. Fluorescence spectrophotometer measurement was used to monitor the whole process

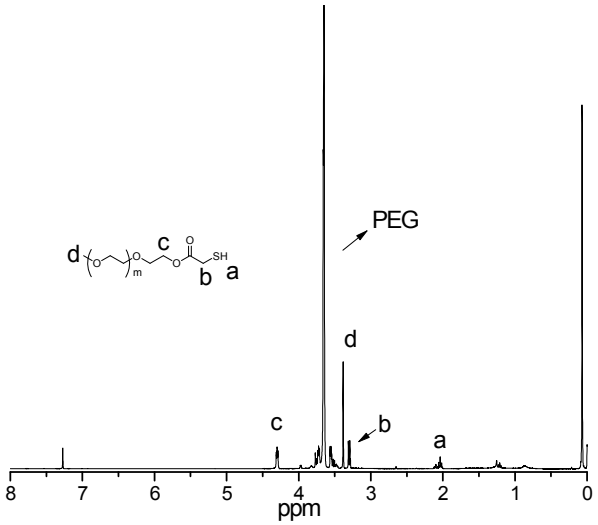

Figure S1. ^{1}H NMR spectrum of mPEG-SH.

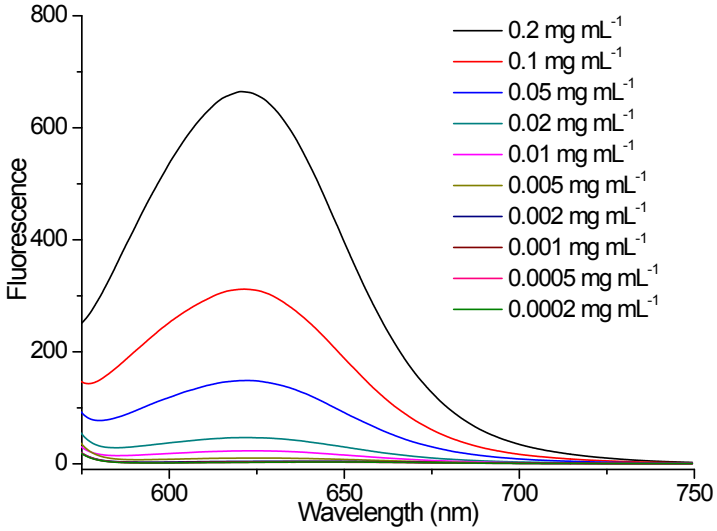

Figure S2 Fluorescence emission spectra of Nile Red in mPEG-*b*-PDS(1)-*b*-mPEG micelles of varying concentrations