Electronic Supplementary Information (ESI)

Lipase-catalyzed synthesis of oxidation-responsive poly(ethylene glycol)-*b*-poly(*β*-thioether ester) amphiphilic block copolymers

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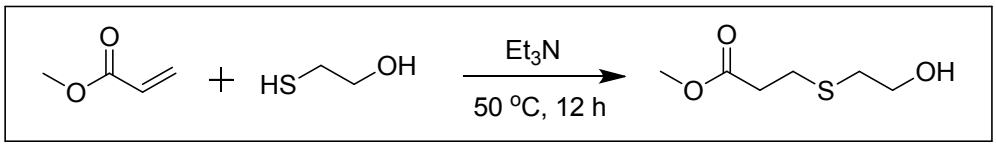
Synthesis and Characterization

Synthesis of methyl 3-((2-hydroxyethyl)thio)propanoate (MHETP)



2-mecarptoethanol (7.81 g, 0.1 mol) and methyl acrylate (9.0 ml, 0.1 mol) were added into a 50 mL flask, and then trimethylamine (0.2 ml, 1.4 mmol) was slowly added under magnetic stirring at room temperature. Subsequently, the reaction temperature was increased to 50 °C,

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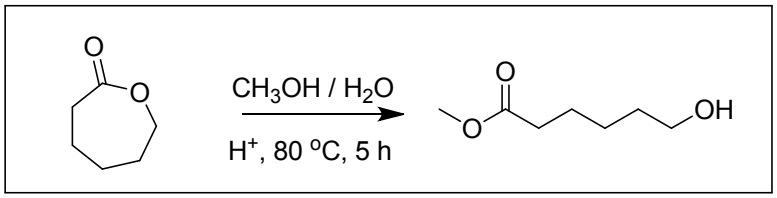
and the reaction was continued for 12 h. Trimethylamine removed in vacuo and the crude product was purified by chromatography on a silica gel column using petroleum ether/ethyl acetate = 4:1 as eluent. MHETP: Colourless liquid (9.08 g, Yield: 55 %).

^{1}H NMR (400MHz, $CDCl_3$), δ 2.63 (t, *J* = 7.2 Hz, 2H, SCH_2CH_2CO), 2.75 (t, *J* = 5.8 Hz, 2H, SCH_2CH_2O), 2.82 (t, *J* = 7.2 Hz, 2H, SCH_2CH_2CO), 3.71(s, 3H, CH_3O), 3.76 (t, *J* = 5.8 Hz, 2H, SCH_2CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$), δ 172.38, 60.57, 51.91, 35.41, 34.66, 26.64.

Synthesis of methyl 6-hydroxyhexanoate (MHH)



Concentrated aqueous sulfuric acid (0.1 mL) was dropwise added to a solution of ε-caprolactone (5.5 mL, 0.05 mol) in methanol (60 mL) and water (15 mL). The mixture was refluxed at 80 °C for 5h. Methanol removed in vacuo and the mixture was subsequently extracted with diethyl ether (150 mL) at three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on a silica gel column using petroleum ether/ethyl acetate = 2:1 as eluent. MHH: Colourless liquid (5.33 g, Yield: 73 %).

^{1}H NMR (400MHz, $CDCl_3$), δ 1.40 (m, 2H, $CH_2CH_2CH_2O$), 1.58 (m, 2H, CH_2CH_2O), 1.66 (m, 2H, CH_2CH_2CO), 2.33 (t, *J* = 7.4 Hz, 2H, CH_2CO), 2.36 (s, 1H, CH_2OH), 3.63 (t, *J* = 6.6 Hz, 2H, CH_2OH), 3.67 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.25, 62.31, 51.44, 33.93, 32.20, 25.25, 24.59.

Supplementary Figures and Tables

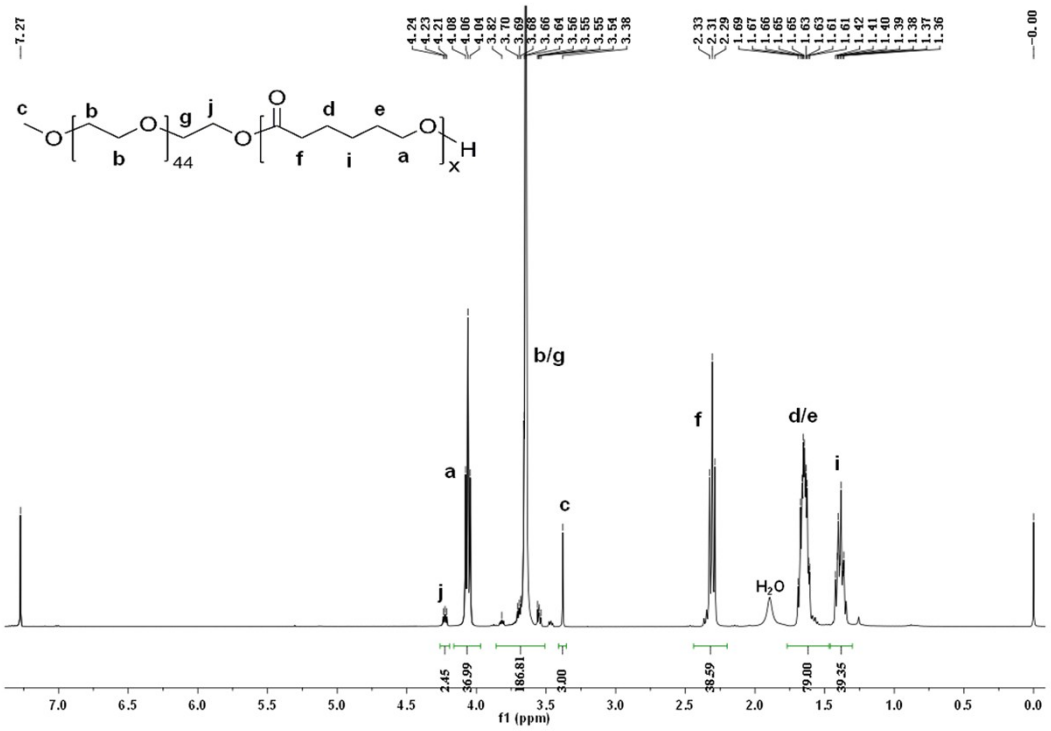


Fig. S1 ^{1}H NMR spectra of mPEG-*b*-PCL_{20} in $CDCl_3$.

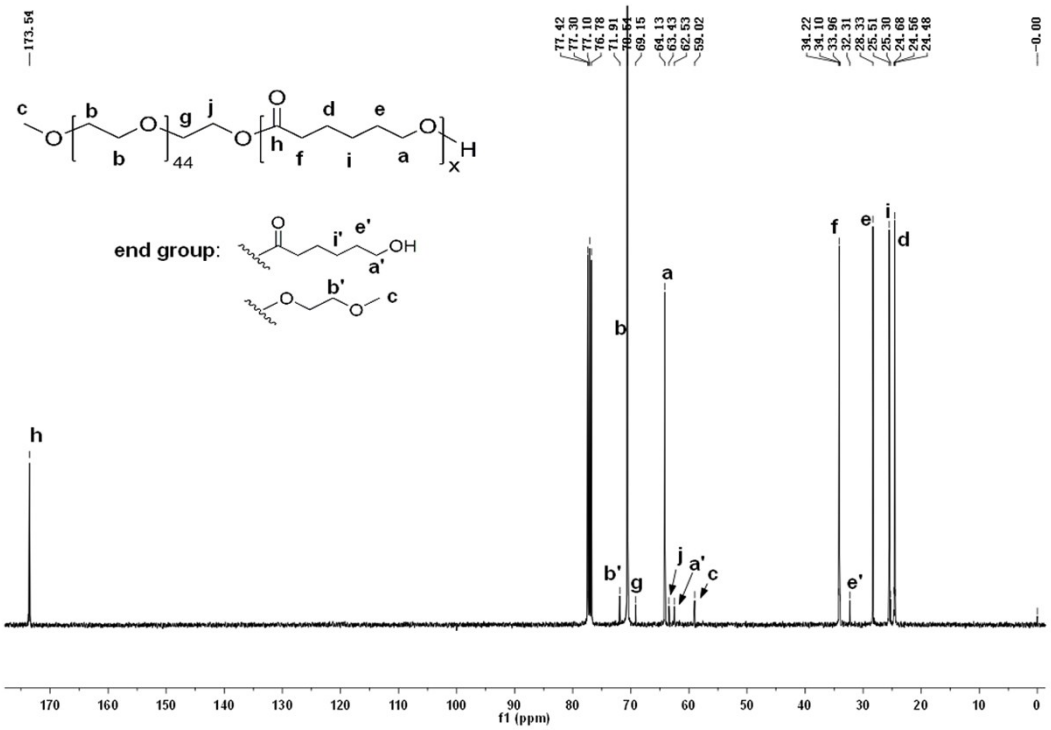


Fig. S2 ^{13}C NMR spectra of mPEG-*b*-PCL_{20} in $CDCl_3$.

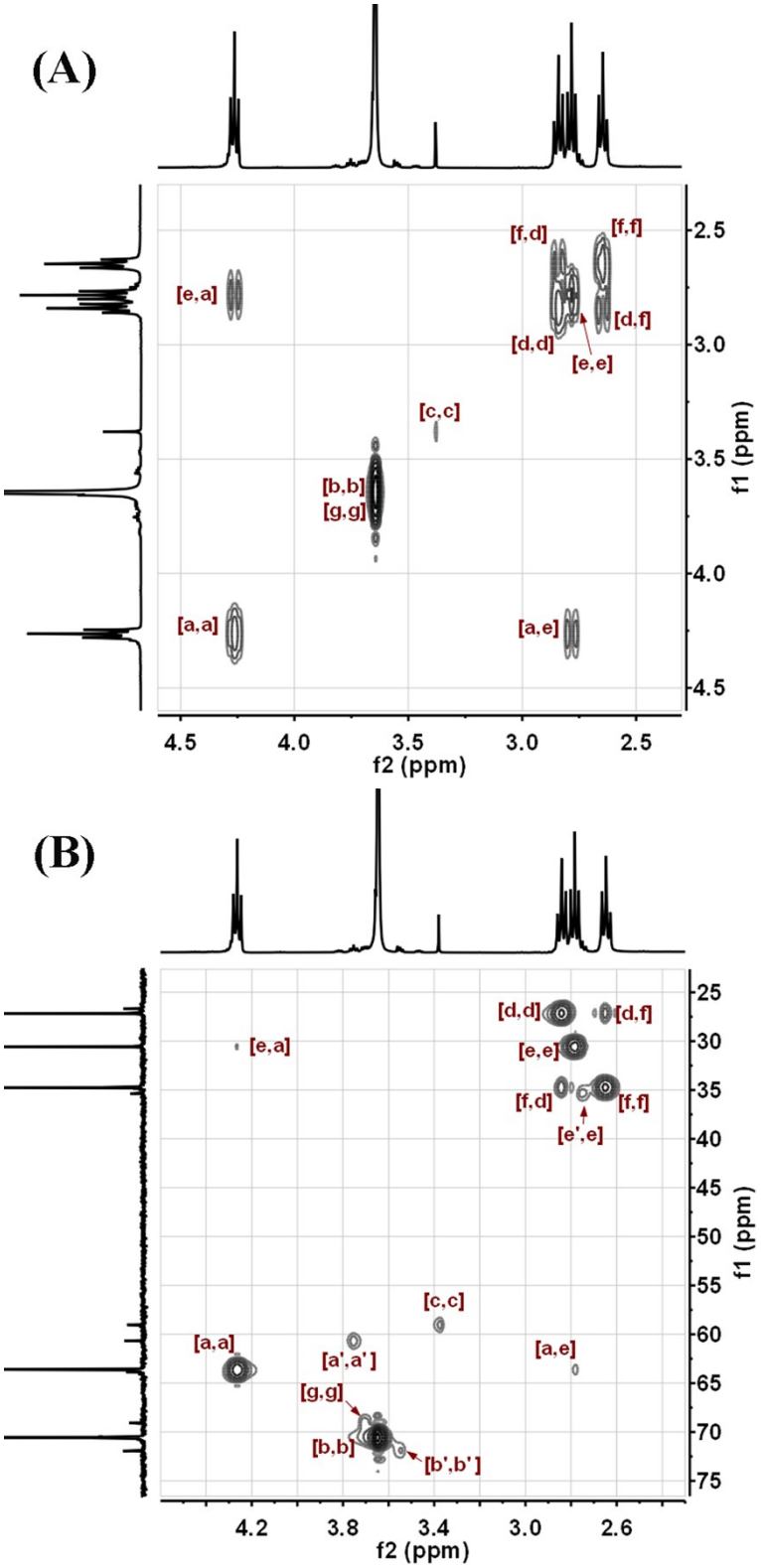


Fig. S3 (A) 2D COSY NMR spectra and (B) ^{13}C, ^{1}H-HSQC spectra of mPEG-*b*-PTE_{20} in $CDCl_3$.

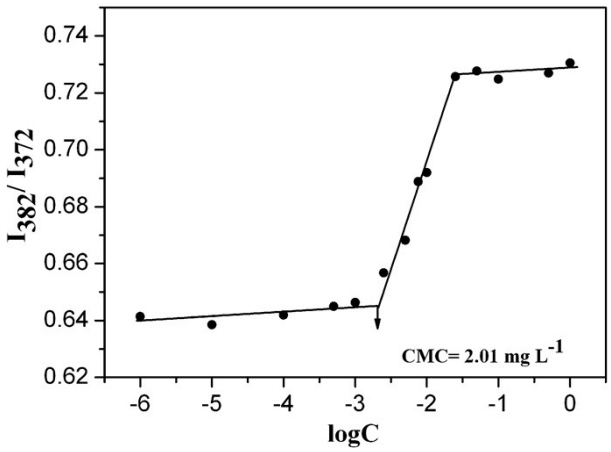


Fig. S4 Plots of the intensity ratio I_{382}/I_{372} from the pyrene emission spectra versus the logarithm of the concentration for self-assembling micelles in aqueous media from mPEG-*b*-PCL_{20}.

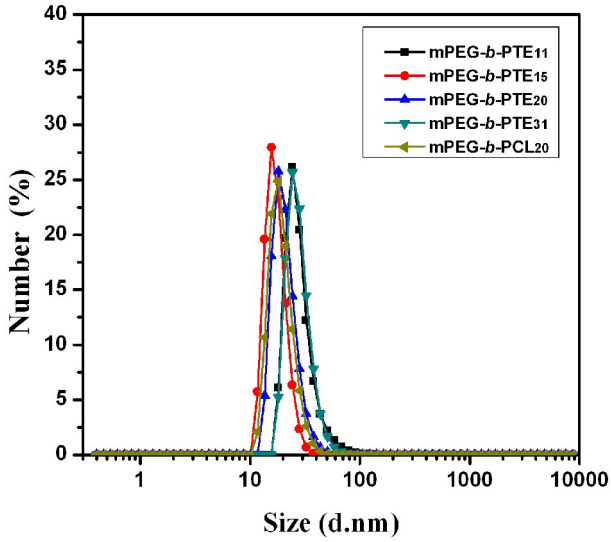


Fig. S5. DLS plots of mPEG-*b*-PTE and mPEG-*b*-PCL_{20} micelles at a concentration of 1 mg mL^{-1} prepared by the direct dissolution method.

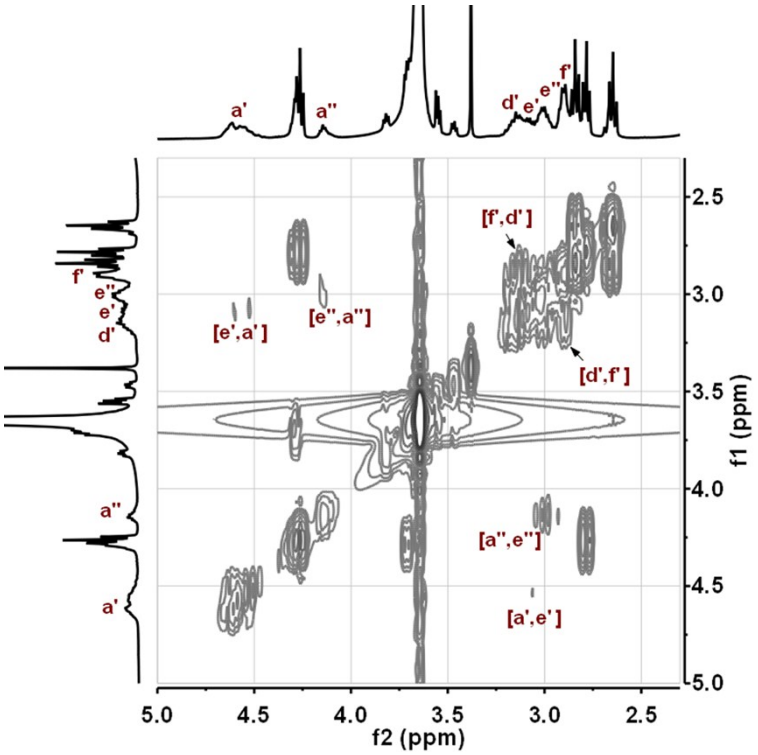


Fig. S6. 2D COSY NMR spectra of mPEG-*b*-PTE_{20} treated with 1% (w/v) H_2O_2 for 24h.

Table S1. GPC data of mPEG-*b*-PTE_{20} and mPEG-*b*-PCL_{20} treated with H_2O_2

Polymer	Oxidation condition	Mw	Mn	Mw/Mn
mPEG-*b*-PTE_{20}	0 h	4780	3700	1.29
	24 h, 0% (w/v) H_2O_2	4810	3680	1.31
	2 h, 1% (w/v) H_2O_2	5040	3710	1.36
	8 h, 1% (w/v) H_2O_2	4030	2830	1.42
	24 h, 1% (w/v) H_2O_2	1950 (peak 1)	1860	1.05
		370 (peak 2)	300	1.23
mPEG-*b*-PCL_{20}	0 h	6190	4360	1.42
	24 h, 1% (w/v) H_2O_2	6190	4180	1.48

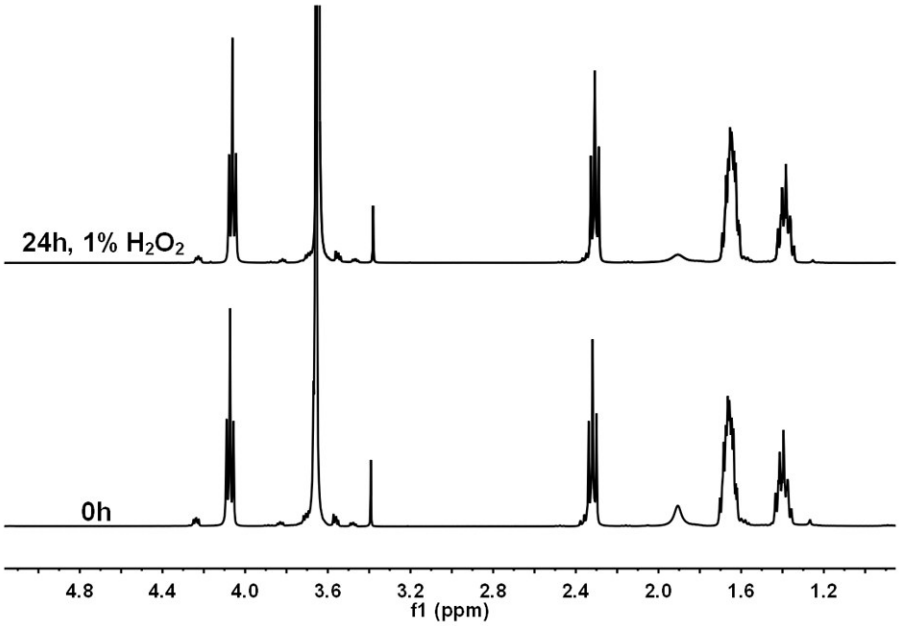


Fig. S7. ^{1}H NMR spectra of mPEG-*b*-PCL_{20} treated with 1% (w/v) H_2O_2 for 24h.

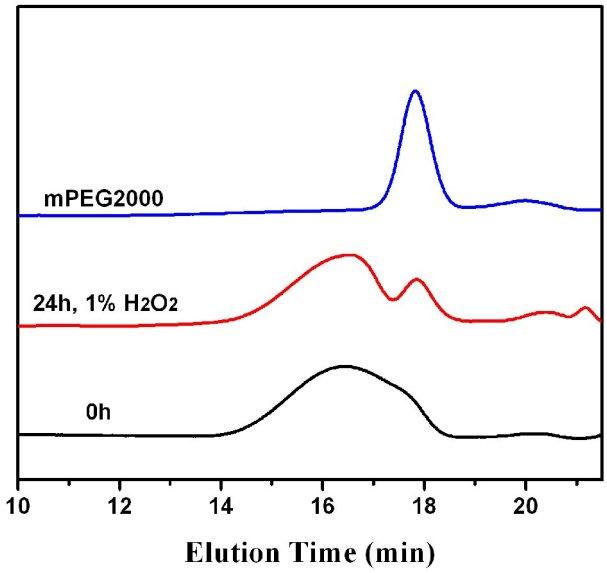


Fig. S8. GPC traces of mPEG-*b*-PCL_{20} treated with 1% (w/v) H_2O_2 for 24h.

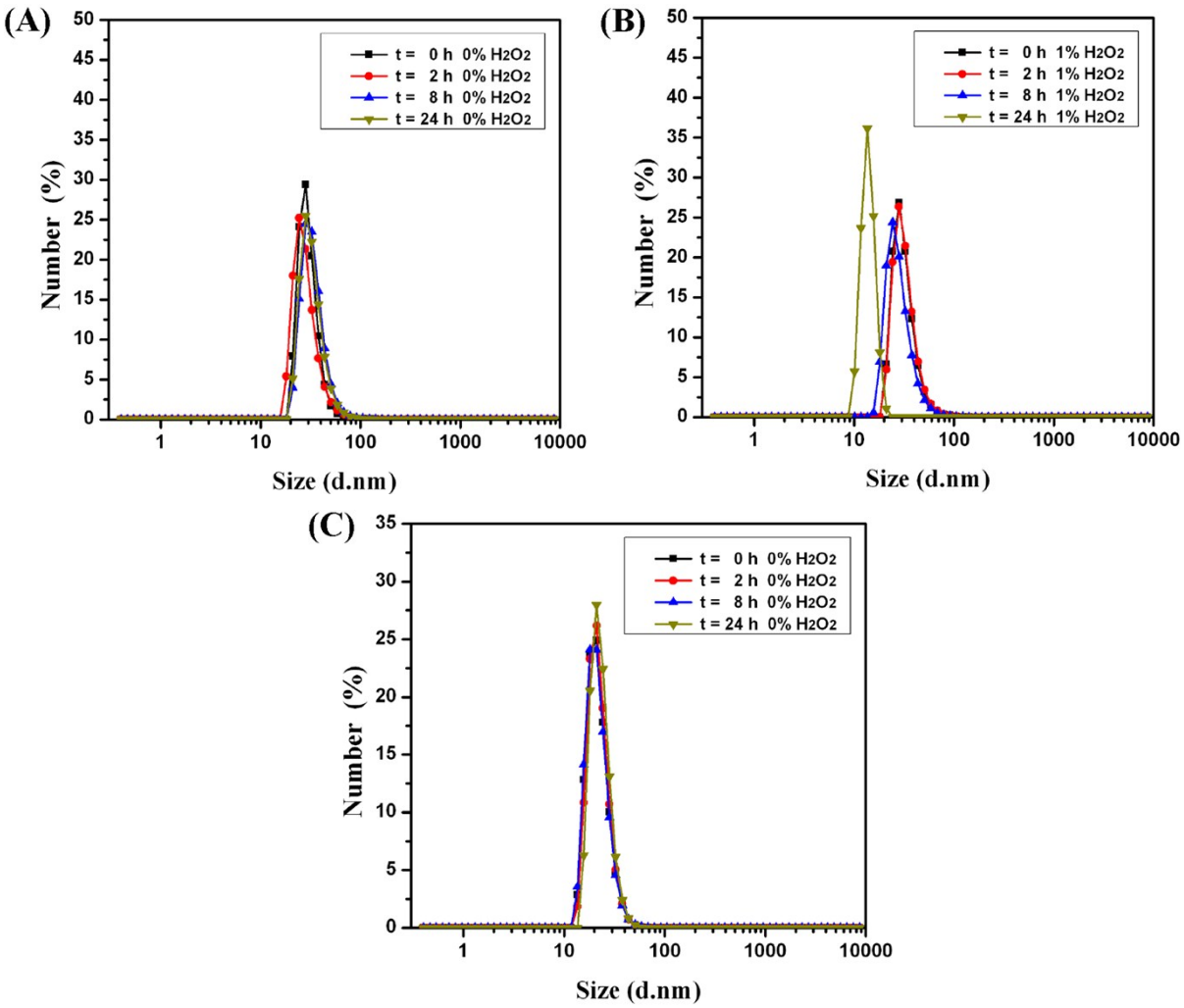


Fig. S9. DLS plots of (A) mPEG-*b*-PTE_{20} treated with 0% (w/v) H_2O_2 (B) mPEG-*b*-PTE_{20} treated with 1% (w/v) H_2O_2 and (C) mPEG-*b*-PCL_{20} copolymers treated with 0% (w/v) H_2O_2.

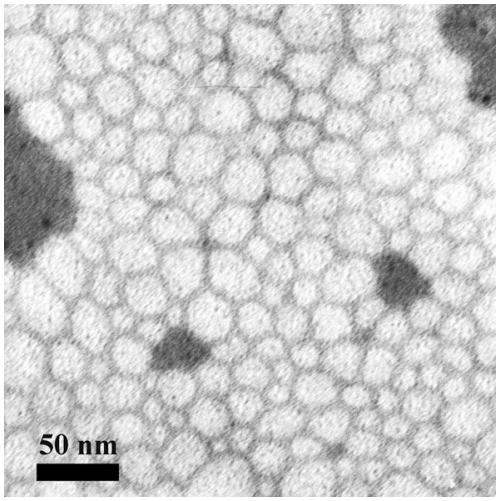


Fig. S10. TEM of mPEG-*b*-PCL_{20} micelles treated with 5% (w/v) H_2O_2 at 37 °C for 24 h.

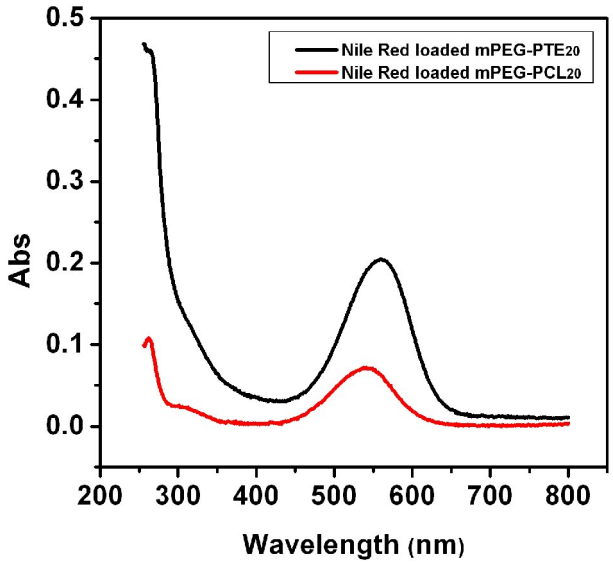


Fig. S11. UV absorption spectra of Nile Red loaded mPEG-*b*-PTE_{20} micelles (2 mg mL^{-1}) and mPEG-*b*-PCL_{20} micelles (0.25 mg mL^{-1}).

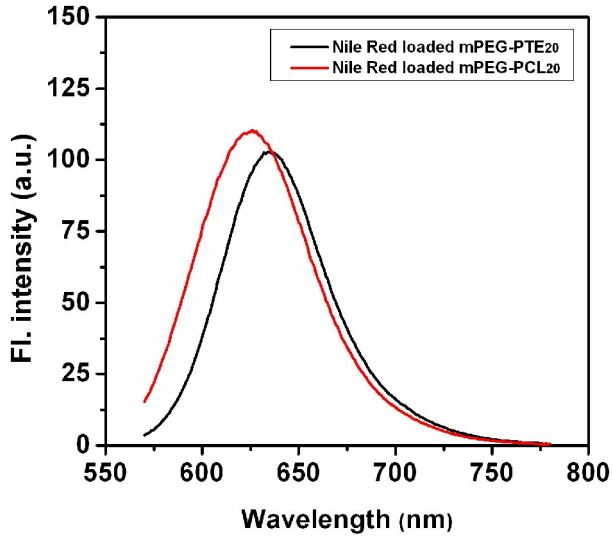


Fig. S12. Fluorescent emission spectra of Nile Red loaded mPEG-*b*-PTE_{20} micelles (2 mg mL^{-1}) and mPEG-*b*-PCL_{20} micelles (0.25 mg mL^{-1}) with the excitation wavelength of 557 nm.

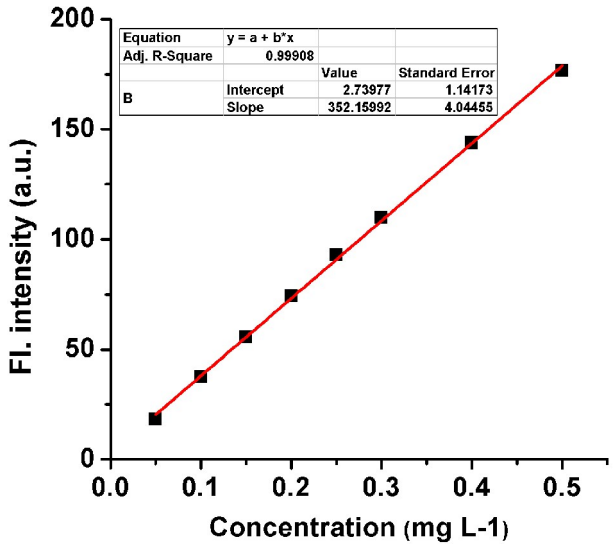


Fig. S13. Standard calibration curve of Nile Red measured in 90% DMF.

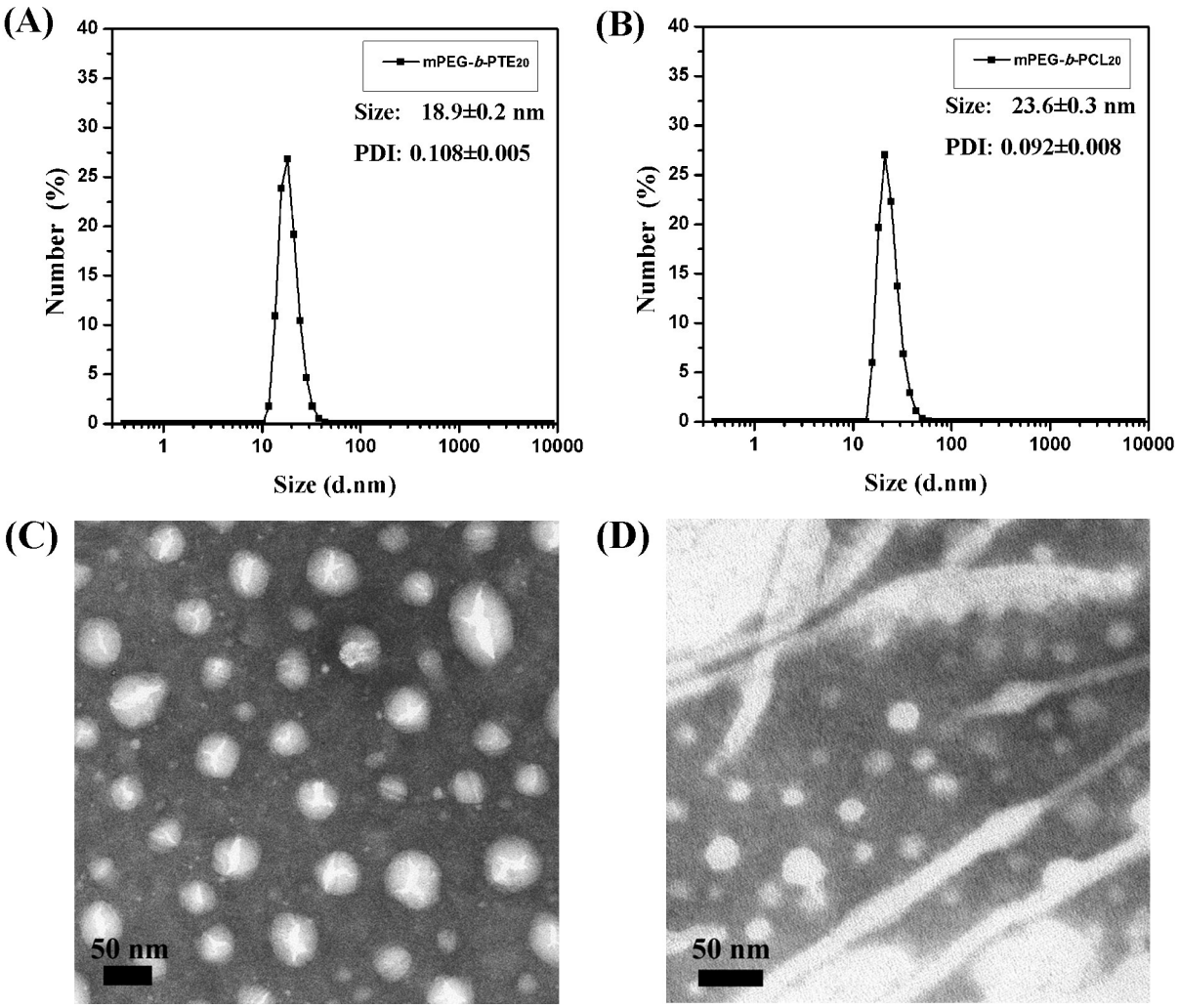


Fig. S14. DLS plots and TEM of (A, C) mPEG-*b*-PTE_{20} and (B, D) mPEG-*b*-PCL_{20} blank micelles prepared by a film hydration method.

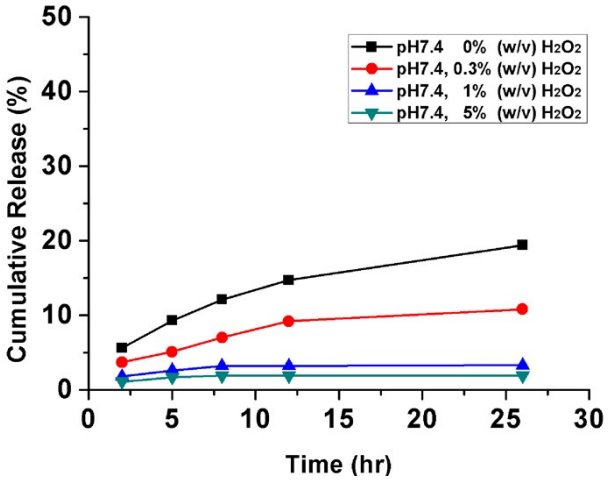


Fig. S15. Cumulative paclitaxel release profile from paclitaxel-loaded micelles

Experimental procedure: 50 mg of the mPEG-*b*-PTE_{26} block copolymer and 3 mg of paclitaxel were co-dissolved in THF for preparation. The loading amount and encapsulation efficiency of paclitaxel were 5.4 wt% and 96.5%, respectively, using HPLC analysis. To determine the release kinetics of drug from micelles, 1.0 mL of 2 mg mL^{-1} paclitaxel-loaded micelle solution was placed in a dialysis bag (molecular weight cutoff, 3.5 kDa). Dialysis bags were incubated in 20 mL of phosphate buffer solution (PBS, pH=7.4) with and without H_2O_2 at 37 °C under gentle shaking. At predetermined time points, the incubation medium was replaced with 20 mL fresh incubation medium. The amount of released paclitaxel in the incubation medium was quantified by determining absorbance at 227 nm using HPLC.