Electronic Supplementary Information (ESI) for

Preparation, characterization, biotoxicity, and biodistribution of thermo-responsive magnetic complex micelles formed by $Mn_{0.6}Zn_{0.4}Fe_2O_4$ and a PCL/PEG analogue copolymer for controlled drug delivery

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Experimental section

1. Materials

ε-Caprolactone (CL, 99%, Acros Organic) was purified with CaH_2 at 25°C for 72 h then distilled under reduced pressure before use. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, >92.5%, Sigma-Aldrich) was distilled under reduced pressure. Neopentyl glycol (NPG, 99%, Sigma-Aldrich) was dried in vacuo at 60°C for 24 h before use. 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA, 95%), oligo (ethylene glycol) methacrylate (OEGMA, M_n=475) and 2-hydroxyethyl methacrylate (HEMA, 97%) were purchased from Sigma-Aldrich and passed through a column of activated basic alumina to remove inhibitors. Cuprous bromide (CuBr, 99%, Alfa Aesar) was purified by stirring in acetic acid and washed with ethanol and then dried in vacuo. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and triethylamine (Et_3N) were dried by refluxing over CaH_2 and distilled before use. Dimethyl sulfoxide (DMSO) was dried by refluxing over CaH_2 and distilled under reduced pressure prior to use. *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA, 99%), 2-bromoisobutyryl bromide (BiBB, 98%), fluorescein isothiocyanate (FITC, 95%), oleic acid (OA, >90%), oleylamine (OAm, >70%) and 1,2-hexadecanediol (>98%) were purchased from TCI (Shanghai) Development Co., Ltd. without further purification. Iron (III) acetylacetonate ($Fe(acac)_3$, 99%), Manganese (II) acetylacetonate ($Mn(acac)_2$, 98%), Zinc (II) acetylacetonate ($Zn(acac)_2$, 98%) and benzyl ether (98%) were purchased from Alfa Aesar without further purification. Doxorubicin hydrochloride (DOX·HCl, 98%, Adamas-beta) and other common reagents obtained from Sinopharm Chemical Reagent Co., Ltd. were used as received.

Cell culture tests were carried out on the immortalized human normal hepatic cell line HL7702 obtained from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Dulbecco's modified Eagle's medium (DMEM, high glucose), fetal bovine serum (FBS), trypsin-EDTA, and penicillin-streptomycin were purchased from Gibco/BRL. Cell proliferation reagent (water-soluble tetrazolium salt, WST-1) and cytotoxictiy detection kit (lactate dehydrogenase, LDH) were obtained from Roche Molecular Biochemicals and other chemicals were purchased from Sigma-Aldrich and used without further purification.

For animal tests, ICR mice (Institute of Cancer Research strain mice, aging 7 weeks, 24-28 g) were obtained from Shanghai Experiment Animal Center, Chinese Academy of Sciences, and maintained at 25±2°C on a 12 h light-dark cycle with free access to food and water. All animal procedures were performed according to the protocol approved by the Institutional Animal Care and Use Committee of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

2. Synthesis of polymers

2.1 Synthesis of PCL-$(OH)_2$

Dually hydroxyl-terminated poly(ε-caprolactone) (PCL-$(OH)_2$) was synthesized by ring-opening polymerization (ROP) of CL initiated by neopentyl glycol (NPG) and catalyzed by $Sn(Oct)_2$. A typical procure was as follows. In a previously dried round-bottom flask, NPG (0.3586 g, 3.442 mmol) was dried to remove traces of water by three successive toluene azeotropic distillations before adding CL(19.64 g, 172.1 mmol) and a catalytic amount of $Sn(Oct)_2$. The round-bottom flask was degassed with three freeze-evacuate-thaw cycles. The bulk polymerization was carried out at 115°C for 24 h under an argon atmosphere with magnetic stirring and then cooled to room temperature. The crude polymer was dissolved in CH_2Cl_2 and precipitated in a large volume of cold methanol for three times. The purified polymer was filtrated and dried in vacuum at 40°C until constant weight.

$M_{n,NMR}$ = 6430, $M_{n,GPC}$ = 6250, M_w/M_n = 1.24.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.06 (t, $OCCH_2CH_2CH_2CH_2C\boldsymbol{H_2}O$), 3.88 (s, $OC\boldsymbol{H_2}(CH_3)C(CH_3)C\boldsymbol{H_2}O$), 3.65 (t, $OCCH_2CH_2CH_2CH_2C\boldsymbol{H_2}OH$), 2.31 (t, $OCC\boldsymbol{H_2}CH_2CH_2CH_2CH_2O$), 1.65 (tt, $OCCH_2C\boldsymbol{H_2}CH_2C\boldsymbol{H_2}CH_2O$), 1.39 (tt, $OCCH_2CH_2C\boldsymbol{H_2}CH_2CH_2O$), 0.97 (s, $OCH_2(C\boldsymbol{H_3})C(C\boldsymbol{H_3})CH_2O$).

2.2 Synthesis of PCL-$(Br)_2$ ATRP macroinitiator

The PCL-$(Br)_2$ macroinitiator was synthesized by the esterification reaction between the hydroxyl group of PCL-$(OH)_2$ and 2-bromoisobutyryl bromide (BiBB). A typical procure was as follows. In a previously dried round-bottom flask, the dried PCL-$(OH)_2$ (12.86 g, 4.000 mmol of hydroxyl groups) was dissolved in anhydrous CH_2Cl_2 (50 ml) with magnetic stirring. Et_3N (1.619 g, 16.00 mmol) was added to the solution under argon protection at room temperature, then the mixture solution was cooled to 0°C under stirring in an ice bath. BiBB (2.759 g, 12.00 mmol) diluted with anhydrous CH_2Cl_2 (20 mL) was added dropwise to the mixture solution within 60 min at 0°C. The reaction mixture was stirred for 2 h at 0°C and then stirred for 48 h at room temperature under an argon atmosphere. After filtering, the resulting product solution was washed with saturated $NaHCO_3$ aqueous solution (80 ml×2) and deionized water (80 ml×3), and then the collected organic phase was dried overnight with anhydrous $MgSO_4$. The crude polymer solution was collected by filtration, and concentrated on a rotary evaporator, then purified by precipitating in cold methanol for three times. The purified polymer was filtrated and dried in vacuum at 40°C until constant weight.

$M_{n,NMR}$ = 6730, $M_{n,GPC}$ = 6520, M_w/M_n = 1.26.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.06 (t, $OCCH_2CH_2CH_2CH_2C\boldsymbol{H_2}O$), 3.88 (s, $OC\boldsymbol{H_2}(CH_3)C(CH_3)C\boldsymbol{H_2}O$), 2.31 (t, $OCC\boldsymbol{H_2}CH_2CH_2CH_2CH_2O$), 1.93 (s, $COC(C\boldsymbol{H_3})_2Br$), 1.65 (tt, $OCCH_2C\boldsymbol{H_2}CH_2C\boldsymbol{H_2}CH_2O$), 1.39 (tt, $OCCH_2CH_2C\boldsymbol{H_2}CH_2CH_2O$), 0.97 (s, $OCH_2(C\boldsymbol{H_3})C(C\boldsymbol{H_3})CH_2O$).

2.3 Synthesis of PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$

PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ block copolymer was synthesized by ATRP of MEO_2MA and OEGMA using PCL-$(Br)_2$ as macroinitiator and CuBr/PMDETA as catalytic system. The general procedure was as follows. In a previously dried round-bottom flask, PCL-$(Br)_2$ macroinitiator (1.211 g, containing 0.3600 mmol initiating group), MEO_2MA (3.537 g, 18.79 mmol), OEGMA (1.334 g, 2.808 mmol) were dissolved in anhydrous THF (20 ml) with magnetic stirring at room temperature. After three evacuate-argon-filling cycles, CuBr (67.20 mg, 0.4680 mmol) and PMDETA (97.72 μL, 0.4680 mmol) were added into the round-bottom flask. The flask was carefully degassed by three freeze-evacuate-thaw cycles and backfilled with argon. Then, the polymerization was carried out at 60°C under an argon atmosphere with magnetic stirring in an oil bath. After 5 h, the reaction system was cooled to room temperature and exposed to air to stop the polymerization. The reaction mixture was diluted with THF and passed through a neutral alumina oxide column to remove the residual copper catalysts. The filtered solution was concentrated by using a rotary evaporator and then purified by dialysis (molecular weight cut-off: 8000~14000 Da) against deionized water to remove unreacted MEO_2MA and OEGMA. The final product was collected by lyophilization.

$M_{n,NMR}$ = 20260, $M_{n,GPC}$ = 18640, M_w/M_n = 1.16.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.09-4.16 (t, COOC$\boldsymbol{H_2}$$CH_2O$ in $PMEO_2MA$ and POEGMA), 4.06 (t, $OCCH_2CH_2CH_2CH_2C\boldsymbol{H_2}O$ in PCL), 3.88 (s, $OC\boldsymbol{H_2}(CH_3)C(CH_3)C\boldsymbol{H_2}O$ in NPG), 3.53-3.75 (t, $C\boldsymbol{H_2}C\boldsymbol{H_2}O$ in $PMEO_2MA$ and POEGMA), 3.36-3.44 (s, $CH_2CH_2OC\boldsymbol{H_3}$ in $PMEO_2MA$ and POEGMA), 2.31 (t, $OCC\boldsymbol{H_2}CH_2CH_2CH_2CH_2O$ in PCL), 1.91 (s, $COC(C\boldsymbol{H_3})_2$), 1.81 (s, $C\boldsymbol{H_2}C(CH_3)$ in $PMEO_2MA$ and POEGMA), 1.65 (tt, $OCCH_2C\boldsymbol{H_2}CH_2C\boldsymbol{H_2}CH_2O$ in PCL), 1.39 (tt, $OCCH_2CH_2C\boldsymbol{H_2}CH_2CH_2O$ in PCL), 0.78-1.10 (m, $CH_2C(C\boldsymbol{H_3})$ in $PMEO_2MA$ and POEGMA), 0.97 (s, $OCH_2(C\boldsymbol{H_3})C(C\boldsymbol{H_3})CH_2O$ in NPG).

2.4 Synthesis of FITC-labeled PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$

FITC-labeled PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ copolymer, that is, PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-P(HEMA-FITC)]$_2$, was synthesized by two steps using HEMA as the auxiliary monomer.

PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-PHEMA]$_2$ block copolymer was prepared by ATRP of HEMA using PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ as macroinitiator and CuBr/PMDETA as catalytic system. The typical procedure is as follows. In a previously dried round-bottom flask, PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ (1.216 g, containing 0.1200 mmol initiating group), HEMA (0.1562 g, 1.200 mmol) were dissolved in anhydrous THF (23 ml) with magnetic stirring at room temperature. After three evacuate-argon-filling cycles, CuBr (22.38 mg, 0.1560 mmol) and PMDETA (32.57 μL, 0.1560 mmol) were added into the round-bottom flask. The flask was carefully

degassed by three freeze-evacuate-thaw cycles and backfilled with argon. The polymerization was carried out at 60°C under an argon atmosphere with magnetic stirring in an oil bath. After 5 h, the reaction system was cooled to room temperature and exposed to air to stop the polymerization. The reaction mixture was diluted with THF and passed through a neutral alumina oxide column to remove the residual copper catalysts. The filtered solution was concentrated by using a rotary evaporator and then purified by dialysis (molecular weight cut-off: 8000~14000 Da) against deionized water to remove unreacted HEMA. The final product was collected by lyophilization.

PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-P(HEMA-FITC)]$_2$ copolymer was synthesized by the chemical reaction between the hydroxyl group of PHEMA and fluorescein isothiocyanate (FITC). In a typical procedure, PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-PHEMA]$_2$ (0.8624 g, containing 0.400 mmol hydroxyl group) was dissolved in anhydrous DMSO (20 ml) and FITC (0.2336 g, 0.600 mmol) was added. The reaction mixture was stirred at 96°C for 2 h in the dark. After cooling to room temperature, the solution was diluted with DMSO (20 ml) and dialyzed (molecular weight cut-off: 8000~14000 Da) against deionized water to remove unreacted FITC. The final product was dried by lyophilization.

PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-PHEMA]$_2$: $M_{n,NMR}$ = 21560, $M_{n,GPC}$ = 20030, M_w/M_n = 1.16.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.09-4.16 (t, COOC***H*****$_2$**CH_2O in $PMEO_2MA$, POEGMA and PHEMA), 4.06 (t, $OCCH_2CH_2CH_2CH_2C$***H*****$_2$**O in PCL), 3.88 (s, OC***H*****$_2$**$(CH_3)C(CH_3)C$***H*****$_2$**O in NPG), 3.53-3.75 (t, C***H*****$_2$**C***H*****$_2$**O in $PMEO_2MA$, POEGMA and PHEMA), 3.36-3.44 (s, CH_2CH_2OC***H*****$_3$** in $PMEO_2MA$ and POEGMA), 2.31 (t, OCC***H*****$_2$**$CH_2CH_2CH_2CH_2O$ in PCL), 1.91 (s, $COC(C$***H*****$_3$**$)_2$), 1.81 (s, C***H*****$_2$**$C(CH_3)$ in $PMEO_2MA$, POEGMA and PHEMA), 1.65 (tt, $OCCH_2C$***H*****$_2$**CH_2C***H*****$_2$**CH_2O in PCL), 1.39 (tt, $OCCH_2CH_2C$***H*****$_2$**CH_2CH_2O in PCL), 0.78-1.10 (m, $CH_2C(C$***H*****$_3$**) in $PMEO_2MA$, POEGMA and PHEMA), 0.97 (s, $OCH_2(C$***H*****$_3$**$)C(C$***H*****$_3$**$)CH_2O$ in NPG).

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.76 (s, OCH_2CH_2O***H*** in PHEMA), 4.01-4.10 (t, COOC***H*****$_2$**CH_2O in $PMEO_2MA$, POEGMA and PHEMA), 3.98 (t, $OCCH_2CH_2CH_2CH_2C$***H*****$_2$**O in PCL), 3.82 (s, OC***H*****$_2$**$(CH_3)C(CH_3)C$***H*****$_2$**O in NPG), 3.39-3.70 (t, C***H*****$_2$**C***H*****$_2$**O in $PMEO_2MA$, POEGMA and PHEMA), 3.21-3.31 (s, CH_2CH_2OC***H*****$_3$** in $PMEO_2MA$ and POEGMA), 2.27 (t, OCC***H*****$_2$**$CH_2CH_2CH_2CH_2O$ in PCL), 1.83 (s, $COC(C$***H*****$_3$**$)_2$), 1.74 (s, C***H*****$_2$**$C(CH_3)$ in $PMEO_2MA$, POEGMA and PHEMA), 1.54 (tt, $OCCH_2C$***H*****$_2$**CH_2C***H*****$_2$**CH_2O in PCL), 1.29 (tt, $OCCH_2CH_2C$***H*****$_2$**CH_2CH_2O in PCL), 0.64-1.02 (m, $CH_2C(C$***H*****$_3$**) in $PMEO_2MA$, POEGMA and PHEMA), 0.90 (s, $OCH_2(C$***H*****$_3$**$)C(C$***H*****$_3$**$)CH_2O$ in NPG).

PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-P(HEMA-FITC)]$_2$: $M_{n,NMR}$ = 24670, $M_{n,GPC}$ = 23210, M_w/M_n = 1.32.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.32-8.23 (protons of FITC moiety), 4.76 (s, OCH_2CH_2O***H*** in PHEMA), 4.01-4.10 (t, COOC***H*****$_2$**CH_2O in $PMEO_2MA$, POEGMA and PHEMA), 3.98 (t,

$OCCH_2CH_2CH_2CH_2C\boldsymbol{H_2}O$ in PCL), 3.82 (s, $OC\boldsymbol{H_2}(CH_3)C(CH_3)C\boldsymbol{H_2}O$ in NPG), 3.39-3.70 (t, $C\boldsymbol{H_2}C\boldsymbol{H_2}O$ in $PMEO_2MA$, POEGMA and PHEMA), 3.21-3.31 (s, $CH_2CH_2OC\boldsymbol{H_3}$ in $PMEO_2MA$ and POEGMA), 2.27 (t, $OCC\boldsymbol{H_2}CH_2CH_2CH_2CH_2O$ in PCL), 1.83 (s, $COC(C\boldsymbol{H_3})_2$), 1.74 (s, $C\boldsymbol{H_2}C(CH_3)$ in $PMEO_2MA$, POEGMA and PHEMA), 1.54 (tt, $OCCH_2C\boldsymbol{H_2}CH_2C\boldsymbol{H_2}CH_2O$ in PCL), 1.29 (tt, $OCCH_2CH_2C\boldsymbol{H_2}CH_2CH_2O$ in PCL), 0.64-1.02 (m, $CH_2C(C\boldsymbol{H_3})$ in $PMEO_2MA$, POEGMA and PHEMA), 0.90 (s, $OCH_2(C\boldsymbol{H_3})C(C\boldsymbol{H_3})CH_2O$ in NPG).

3. Synthesis of $Mn_{0.6}Zn_{0.4}Fe_2O_4$ (MZF) nanoparticles

The oleic acid modified manganese and zinc doped ferrite (MZF, $Mn_{0.6}Zn_{0.4}Fe_2O_4$) nanoparticles were prepared according to the previous literatures.[1-3] Briefly, $Fe(acac)_3$ (0.7063 g, 2.000 mmol), $Mn(acac)_2$ (0.1519 g, 0.6000 mmol), and $Zn(acac)_2$ (0.1054 g, 0.4000 mmol) were mixed with 1,2-hexadecanediol (2.584 g, 10.00 mmol), oleic acid (1.695 g, 6.000 mmol), and oleylamine (1.605 g，6.000 mmol) in benzyl ether (20 mL) with magnetic stirring under dry and deoxidized argon atmosphere. The mixture was heated to 200°C for 2 h and then heated to reflux (~300°C) for another 1 h. After the mixture was cooled to room temperature by turning off the heating devices, ethanol was added into the mixture, then the dark-brown precipitates appeared in the solution and were separated via centrifugation (8000 rpm, 10 min) to obtain the crude product of MZF nanoparticles. The crude product was redispersed in hexane in the presence of oleic acid (0.050 mL) and oleylamine (0.050 mL), then purified via centrifugation (8000 rpm, 10 min) to remove any undispersed residue. After being reprecipitated with ethanol and centrifuged (8000 rpm, 10 min) to remove the solvent, the MZF nanoparticles were obtained. Finally, the MZF nanoparticles were dried in vacuum at 40°C until constant weight for storage.

4. Preparation of micelles

All micelles were prepared by self-assembly method.

4.1 Blank polymer micelles

5.0 mL of the PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ (or with FITC-labeled) polymer solution (20 mg/mL in THF) was added into 10 mL of deionized water (or normal saline for biological tests) within 5 min dropwise under ultrasonication. The mixture was dialyzed against deionized water (or normal saline) using an 8000-14000 MWCO dialysis bag at room temperature for 24 h, and the medium was refreshed every 6 h to remove THF during this period.

4.2 Magnetic complex micelles

The oleic acid modified MZF nanoparticles were dispersed in THF with the concentration of 5.0 mg/mL for subsequent use. 2.0 mL of the MZF/THF dispersion solution was added into 4.5 mL of the PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ (or with FITC-labeled) polymer solution (20 mg/mL in THF), followed by ultrasonication for 2 min.

The mixture solution was added into 10 mL of deionized water (or normal saline for biological tests) within 5 min dropwise under ultrasonication. The subsequent dialysis process was the same as the blank polymer micelles.

4.3 DOX-loaded magnetic complex micelles (DOX-MZF-micelles)

DOX·HCl (8.5 mg) and Et_3N (3.0 mL) were dissolved in THF (2.0 mL) completely, and the mixture was stirred overnight at room temperature. 2.0 mL of polymer/THF solution (20 mg/mL) was added into the mixture, followed by stirring for 30 min. Then 0.80 mL of the MZF/THF dispersion solution (5.0 mg/mL) was added into the above-mentioned mixture, followed by ultrasonication for 2 min. The final mixture solution was added into 10 mL of phosphate buffer solution (PBS, 10 mM, pH 7.4) within 5 min dropwise under ultrasonication, then dialyzed against PBS (10 mM, pH 7.4) using an 8000-14000 MWCO dialysis bag at room temperature for 16 h in the dark, and the medium was refreshed every 4 h to remove THF during this period.

5. Characterization methods

^{1}H NMR spectra of the samples were obtained on a Bruker DMX 500 NMR spectrometer operating at 400 MHz using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) as solvents. The chemical shifts were relative to tetramethylsilane(TMS).

Attenuated total reflection Fourier transform infrared (ATR FT-IR) spectra of the samples were recorded on an EQUINOXSS/HYPERION2000 FTIR spectrometer (Bruker, Germany).

The average molecular weight and polydipersity of each sample were measured on a gel permeation chromatograph (GPC) instrument equipped with a Waters 150C separations module and a Waters differential refractometer. The samples were dissolved in THF at a concentration of 1.0-2.0 mg/mL. The measurements were performed using THF to eluted through two Waters Styragel HT columns and a linear column at a flow rate of 1.0 mL/min at 30°C.

The structural formation of MZF nanoparticles was characterized by X-ray diffraction (XRD) on a Rigaku D/Max-2550 X-ray powder diffractometer with Cu Kα (1.54 Å) radiation (40 kV, 100 mA). The sample was scanned from $2\theta = 10°$ to 80° at a speed of 5° min^{-1}.

The morphology of polymer micelles was observed using a JEOL JEM-2010F transmission electron microscope (TEM) at an accelerating voltage of 120 kV. The samples for TEM observation were prepared by dropping 10 μL of 1.0 mg/mL micellar solution on the copper grid coated with thin films and carbon.

The hydrodynamic diameter (D_h) of micelles was measured on a Malvern Zetasizer Nano-ZS90 dynamic light scattering (DLS) spectrometer at 25°C. DLS was performed at a scattering angle of 90°. The D_h was obtained by a cumulant analysis.

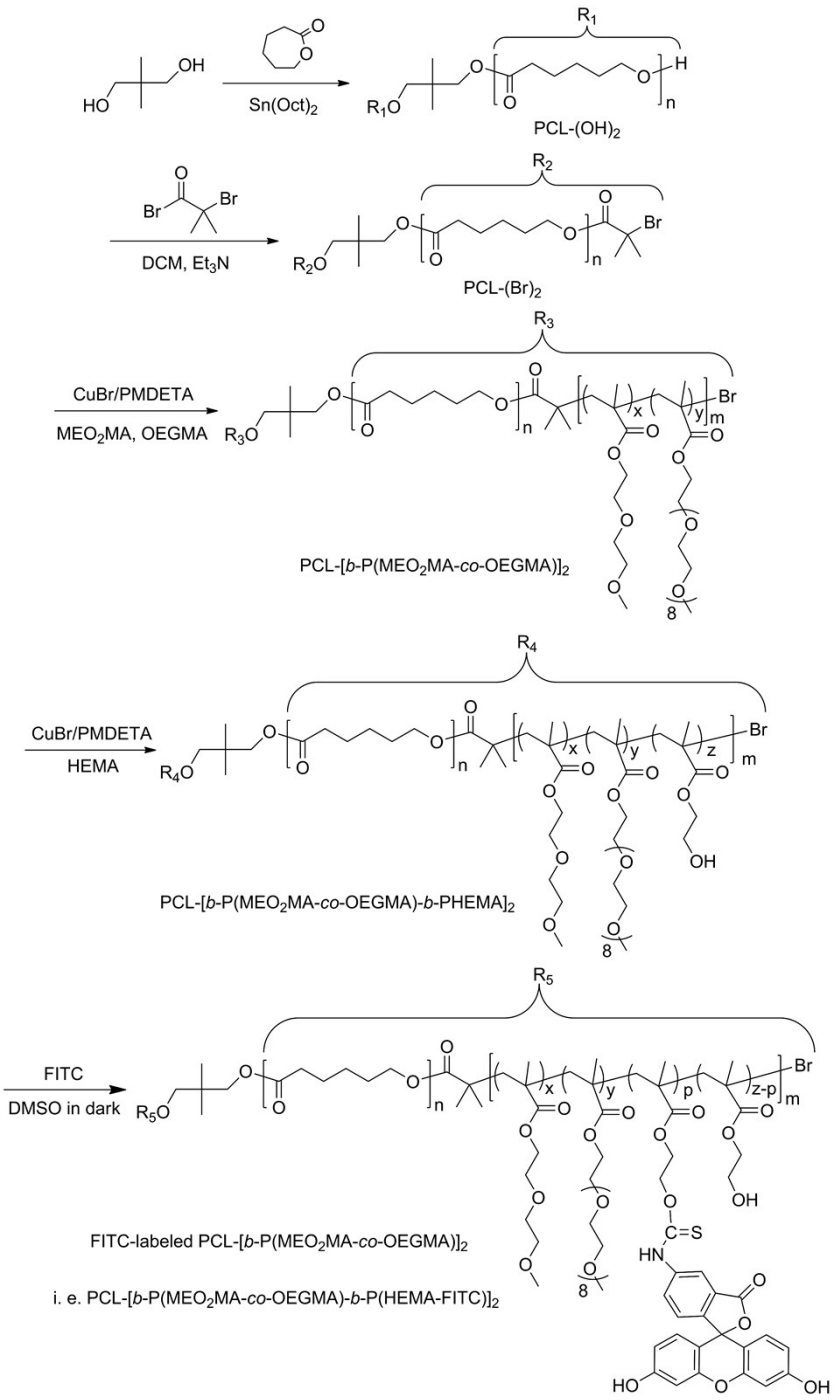
Thermogravimetric analysis (TGA) was performed on a TGA 2050 thermogravimetric analyzer with a heating rate of 10°C/min from room temperature to 600°C under a nitrogen atmosphere.

6. Determination of critical micelle concentration (CMC)

The CMC of PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ copolymer was determined using pyrene as a fluorescence probe. 10 μL of pyrene/acetone solution (0.50 mg/mL) was added into each container, and the acetone was allowed to evaporate. 2.0 mL of aqueous polymer solutions ranging from 0.49 mg/L to 1000 mg/L was added into each container which contained the pyrene residue respectively. Upon ultrasonication for 10 min, the solutions were kept at room temperature for 24 h to reach the solubilization of pyrene in the aqueous phase before fluorescent emission measurements. The fluorescence spectra were recorded on a Hitachi F-2700 fluorescence spectrophotometer with the excitation wavelength of 340 nm, and the emission spectra were recorded ranging from 350 nm to 600 nm. The slit widths were set at 5 nm for both excitation and emission. From the pyrene emission spectra, the intensities (peak height) of the first band ($I_{373\ nm}$) and the third band ($I_{393\ nm}$) were selected to analyze the CMC.[4,5] The CMC was estimated as the cross-point when extrapolating the intensity at low and high concentration regions.

7. Transmittance measurements and determination of the LCST

The transmittance of the PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ copolymer micelle solutions (5.0 mg/mL) at various temperatures was measured at 500 nm on a UV-Vis spectrophotometer (U-3310, Hitachi, Japan) fitted with the temperature controller. Sample cell was thermostated at different temperatures ranging from 30 to 50°C prior to measurements using the temperature controller. The lower critical solution temperature (LCST) was defined as the temperature exhibiting an optical transmittance of 50%.



Scheme S1 Synthesis of unlabeled and FITC-labeled PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ copolymers

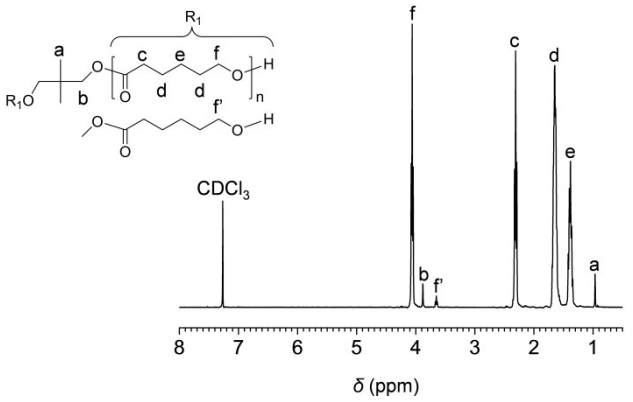


Fig. S1 ^{1}H NMR spectrum of PCL-$(OH)_2$ in $CDCl_3$.

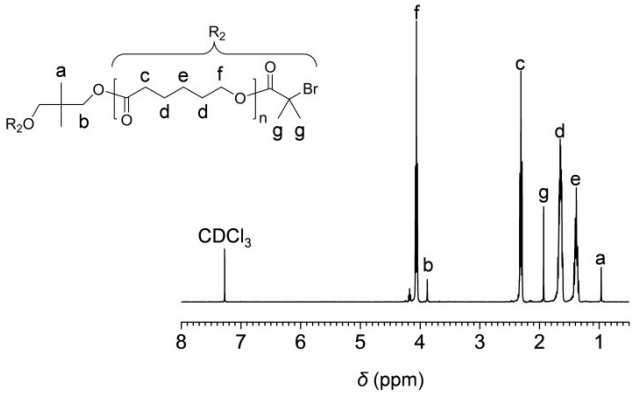


Fig. S2 ^{1}H NMR spectrum of PCL-$(Br)_2$ in $CDCl_3$.

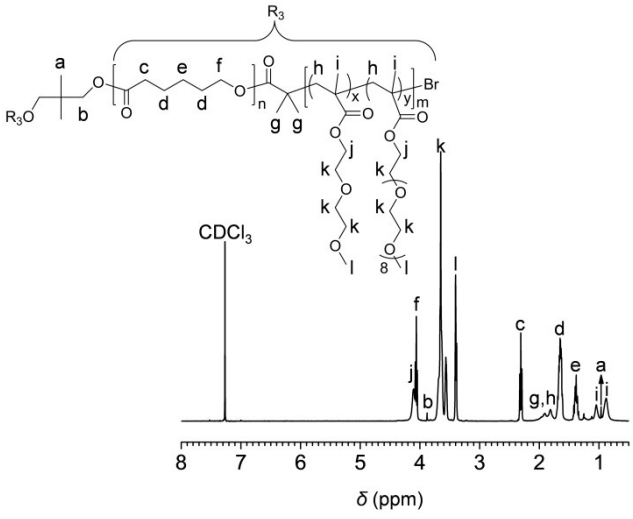


Fig. S3 ^{1}H NMR spectrum of PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ in $CDCl_3$.

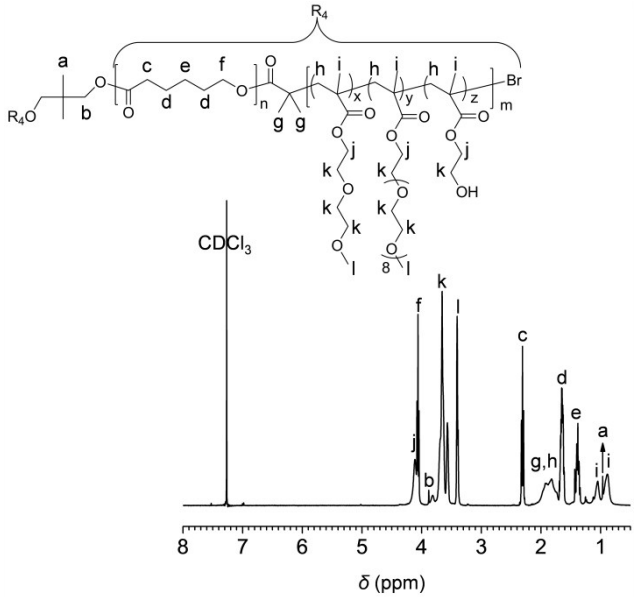


Fig. S4 ^{1}H NMR spectrum of PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)-*b*-PHEMA]$_2$ in $CDCl_3$.

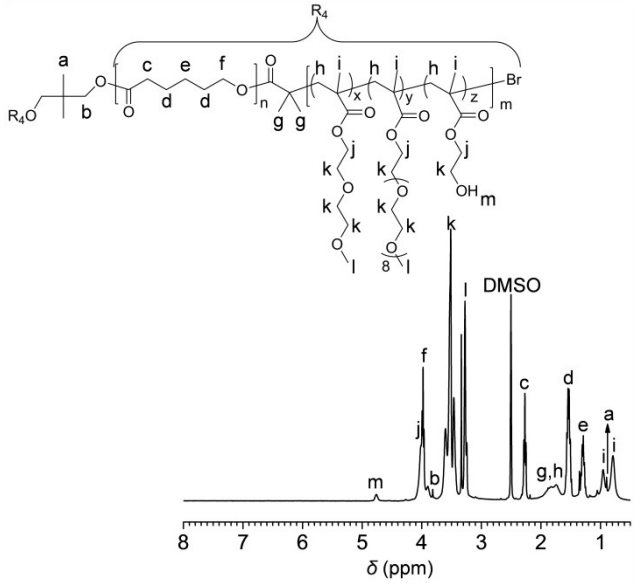


Fig. S5 ^{1}H NMR spectrum of PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)-*b*-PHEMA]$_2$ in DMSO-d_6.

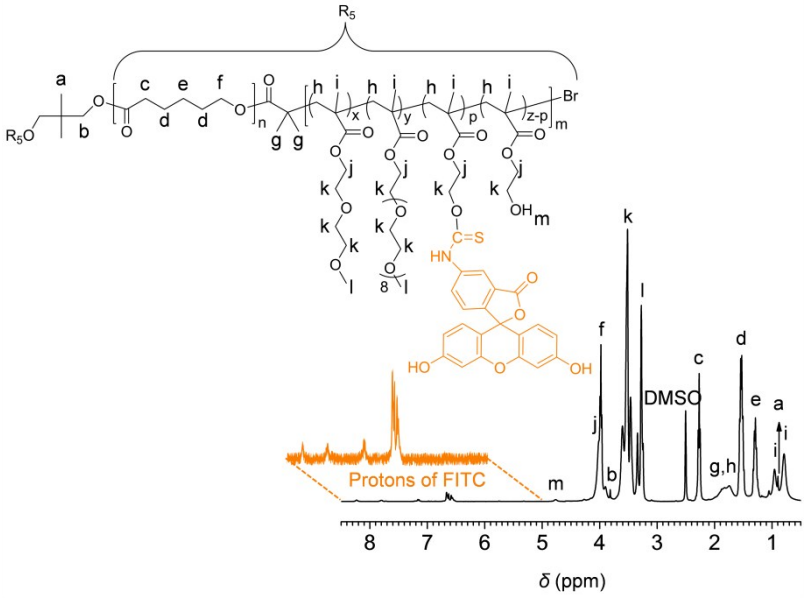


Fig. S6 ^{1}H NMR spectrum of FITC-labeled PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)]$_2$ in DMSO-d_6.

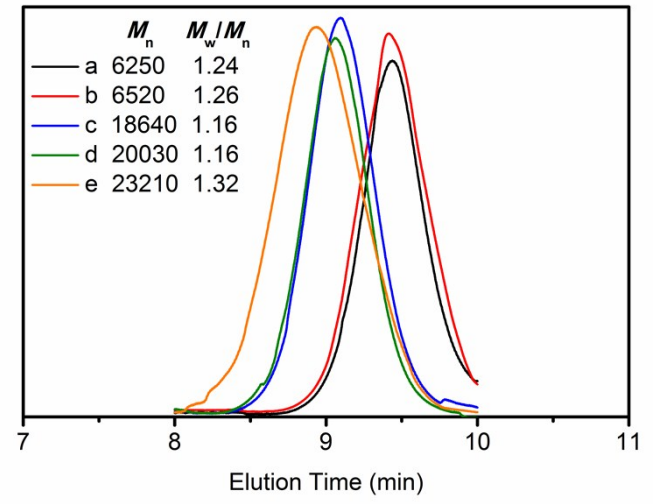


Fig. S7 GPC traces of (a) PCL-(OH)$_2$, (b) PCL-(Br)$_2$, (c) PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)]$_2$, (d) PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)-*b*-PHEMA]$_2$ and (e) FITC-labeled PCL-[*b*-P(MEO$_2$MA-*co*-OEGMA)]$_2$.

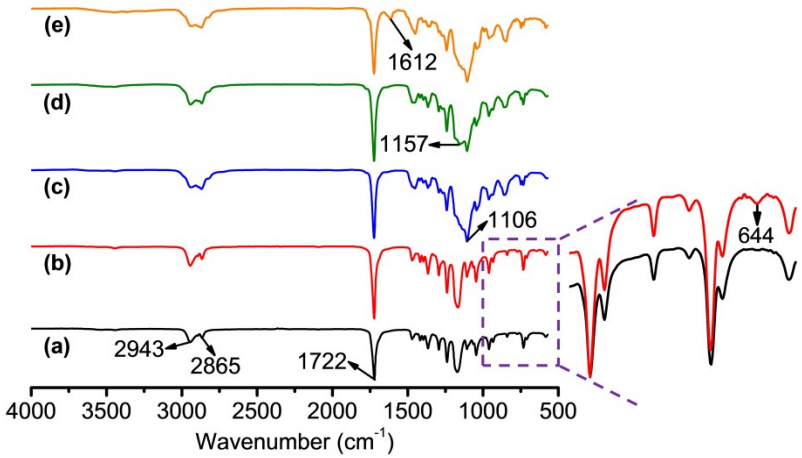


Fig. S8 FT-IR spectra of (a) PCL-$(OH)_2$, (b) PCL-$(Br)_2$, (c) PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$, (d) PCL-[*b*-P(MEO_2MA-*co*-OEGMA)-*b*-PHEMA]$_2$ and (e) FITC-labeled PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$.

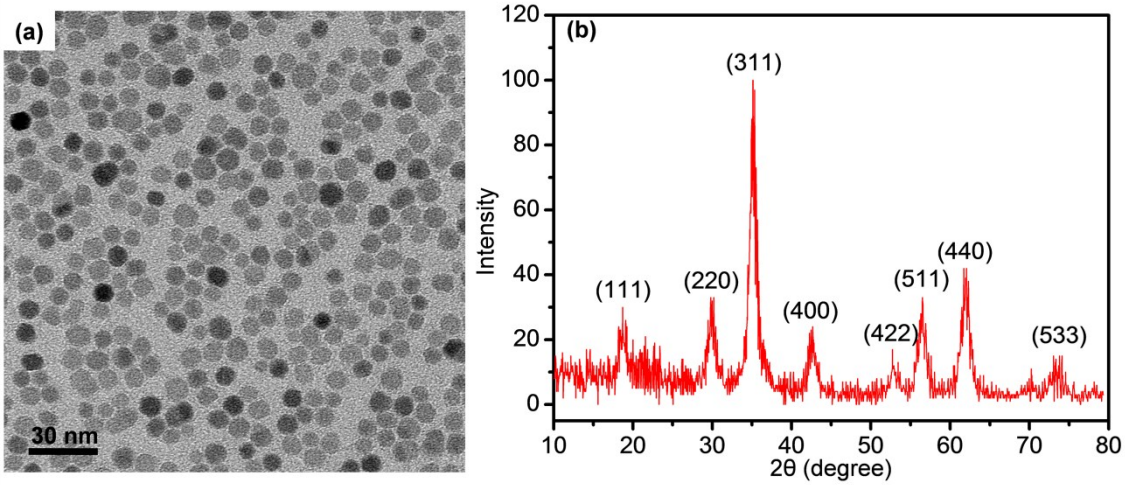


Fig. S9 (a) TEM image and (b) XRD pattern of oleic acid modified $Mn_{0.6}Zn_{0.4}Fe_2O_4$ nanoparticles.

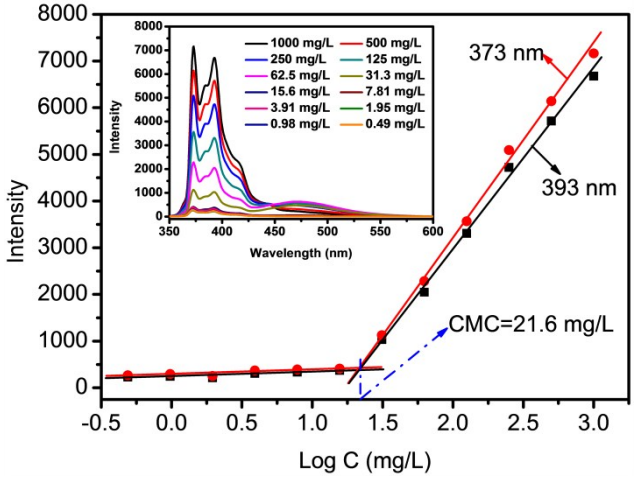


Fig. S10 CMC measurements of PCL-[*b*-P(MEO_2MA-*co*-OEGMA)]$_2$ using the fluorescence emission spectra of pyrene at the wavelengths of 373 nm and 393 nm.

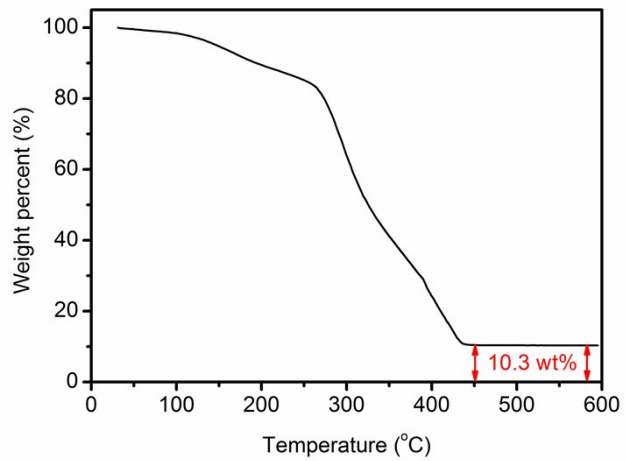


Fig. S11 TGA curves of the magnetic complex micelles.

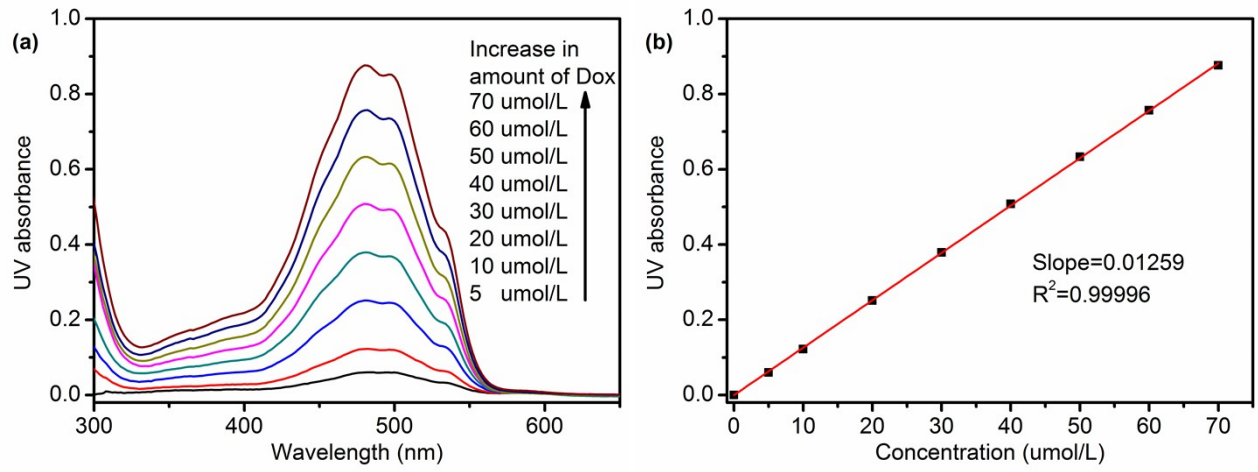


Fig. S12 (a) UV spectra of DOX at different concentrations in DMF and (b) the standard curve of absorbance vs. concentration of DOX in DMF.

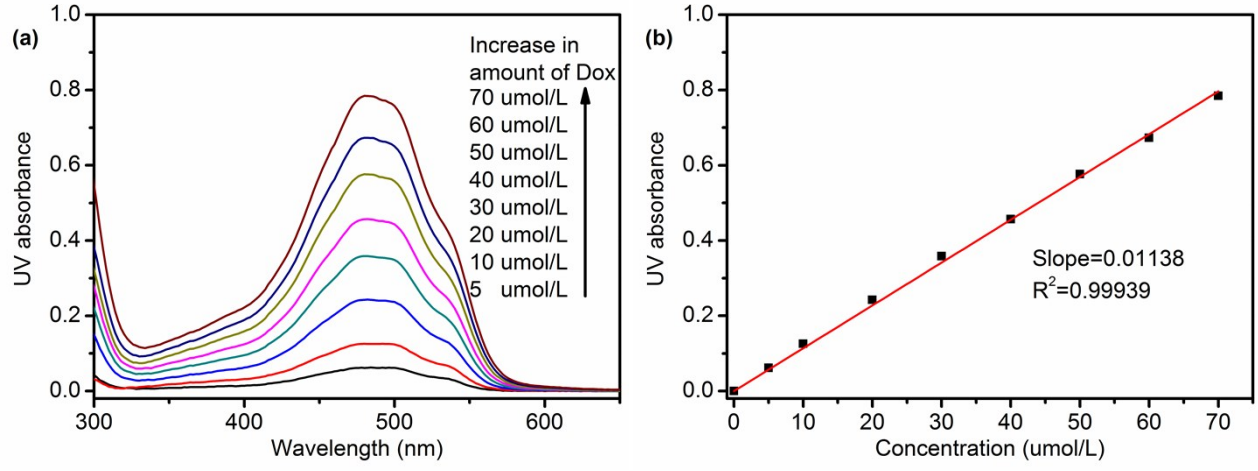


Fig. S13 (a) UV spectra of DOX at different concentrations in PBS and (b) the standard curve of absorbance vs. concentration of DOX in PBS.

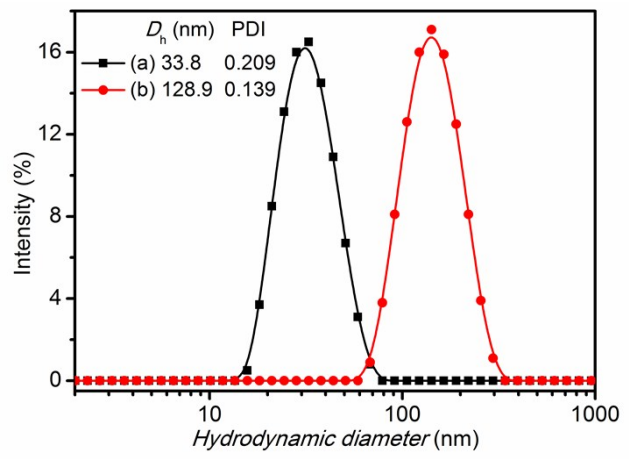


Fig. S14 DLS data of (a) blank polymer micelles and (b) magnetic complex micelles for quantitative analysis before being kept at 4°C for 30 days in NS.

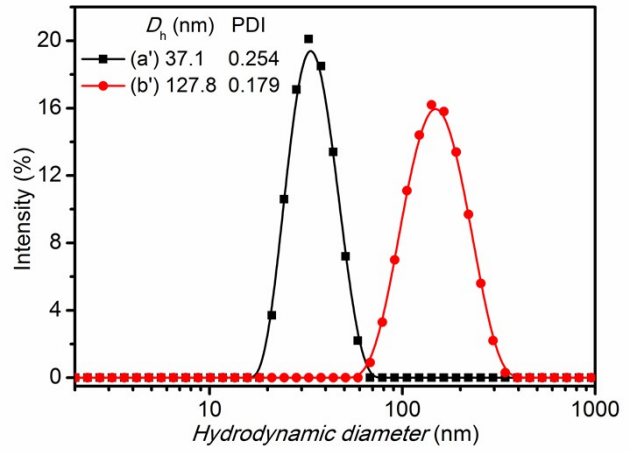


Fig. S15 DLS data of (a') blank polymer micelles and (b') magnetic complex micelles for quantitative analysis after being kept at 4°C for 30 days in NS.

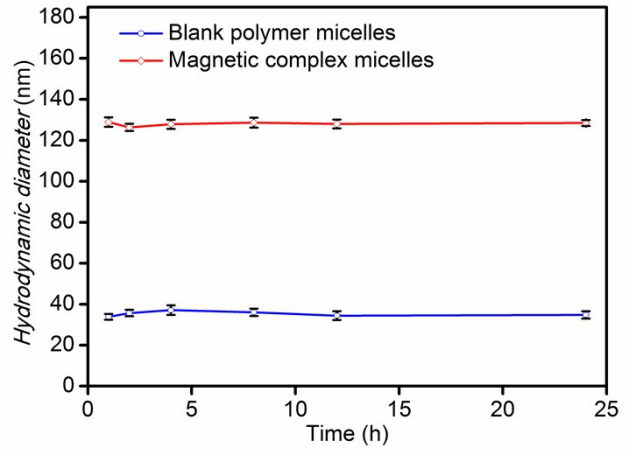


Fig. S16 Variations in hydrodynamic diameters (D_h) of blank polymer micelles and magnetic complex micelles in 50% FBS over 24 h (n=3, mean±SD).

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