pH/redox dual-responsive amphiphilic zwitterionic polymers with precisely controlled structure as anti-cancer drug carrier

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Supporting information

Experiments

1.1 Synthesis of PCL-ss-iBuBr

OH-ss-iBuBr which was synthesized previous as reported[1] was used to ring opening polymerization of ε-caprolactone(ε-CL). OH-ss-iBuBr(0.34 g, 1.80mmol) and ε-CL(5.14 g, 45.03mmol) were added in round flask. Oxygen and water in the reactor were removed by an exhaust–refill process using N2 for 3 times. Then the reaction was carried out at 120 °C under vacuum for 24 h. Crude product was dissolved in DCM and purified by precipitation via cold methanol. White powder polymer PCL-ss-iBuBr was obtained. Yield: 91.21%.

1.2 Synthesis of PCL-ss-P(DEA-r-MPC)

PCL-ss-P(DEA-r-MPC) was obtained by copolymerization of MPC and DEA. Macromolecular initiator PCL-ss-iBuBr (2.01 g, 0.63 mmol), MPC(2.34 g, 7.92 mmol), DEA (0.76 g, 4.12 mmol) and BPY (0.24 g, 1.51 mmol) were dissolved in 15 mL mixture of THF/CH_3OH(1/1,V/V). Bubble solution with nitrogen for 30 min. Thereafter, CuBr(0.11 g, 0.75 mmol) was added into reactor. With N_2 atmosphere, this polymerization was conducted under room temperature for 24 h. Then, the reaction mixture was purified by dialysis against pure water for 2 days. Product was obtained by freeze-drying. Yield:78.13%.

2.1 Synthesis of alkynyl-ss-OH

OH-ss-OH (0.58 g,3.74mmol) were dissolved in 5mL dried DCM.Under N_2 atmosphere, 5mL DCM mixture of 5-Hexynoicacid (0.38g,3.40mmol), DCC (0.77g, 3.74mmol) and DMAP (0.09g,0.75mmol) were added dropwise to the abovementioned solution after 2 h stirring for 5-Hexynoicacid activation. After that, the reaction was performed at 30 °C for 24 h. DCU by-product was removed by filtration. Subsequently, the mixture was concentrated by rotary evaporation, and the product was purified by silica column chromatograph with mixtures of petroleum ether/ethyl acetate (2/1, v/v). The product alkynyl-ss-OH was isolated by evaporation of the solvents and further dried in a vacuum oven at 40 °C overnight. Yield:52.36%.

2.2 Synthesis of alkynyl-ss-PCL

Alkynyl-ss-OH (0.54 g, 2.90 mmol), CL (8.60 g,75.35 mol) and catalytic amount of $Sn(Oct)_2$ were added into a dry polymeric flask. Oxygen and water in the reactor were removed by an exhaust–refill process using N2 for 3 times. Then the ring-open polymerization (ROP) of CL was carried out

at 120 °C under vacuum for 24 h. Crude product was dissolved in DCM and purified by precipitation via cold methanol. White powder polymer poly(ε-caprolactone) (PCL-OH) was obtained. Yield: 95.67%.

2.3 Synthesis of PMPC-PDEA-N_3

Intiator t-Butyl 2-bromo isobutyrate (0.10 g, 0.45mmol), monomer MPC (1.00 g,5.37 mmol) and Me6-TREN (0.20 g, 0.90 mmol) were were dissolved in 15 mL MeOH Bubble solution with nitrogen for 30 min. Thereafter, CuBr(0.065 g, 0.45 mmol) was added into reactor. With N_2 atmosphere, this polymerization was conducted under room temperature for 24 h. Then monomer DEA (0.54 g,2.91 mmol) was added in above reactor under N_2 atmosphere, and this reaction was preformed for 24h at room temperature too. the reaction mixture was purified by dialysis against pure water for 2 days and PMPC-PDEA-Br was obtained. Yield: 81.60%.

NaN_3 (0.17 g,2.6 mmol) and PMPC-PDEA-Br (1 g, 0.26 mmol) were dissolved in 15 mL MeOH under N_2 atmosphere, and this reaction was performed at 40 °C overnight. Remove the residual NaN_3 though filter, collect the filtrate and purify it by dialysis against pure water for 2 days, Target product PMPC-PDEA-N_3 was obtained though freeze-drying. Yield:94.16%.

2.4 Synthesis of PCL-ss-PDEA-b-PMPC

The synthesis of PCL-ss-PDEA-b-PMPC was conducted by click reaction. alkynyl-ss-PCL(0.242 g, 0.078 mmol), PMPC-PDEA-N_3(0.30 g,0.078mmol) and BPY(29.35 mg,0.188 mmol) were added into the mixture of THF/MeOH(1/1,V/V), After purging oxygen with N_2 for 30 min, the catalyst CuBr 13.5 mg,0.094 mmol) was added into the flask under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 40 °C for 24 h. The product was concentrated and dialyzed against pure water for 3 days, PCL-ss-PDEA-b-PMPC was obtained by lyophilization method with yield 89.74%.

Figures and Tables:

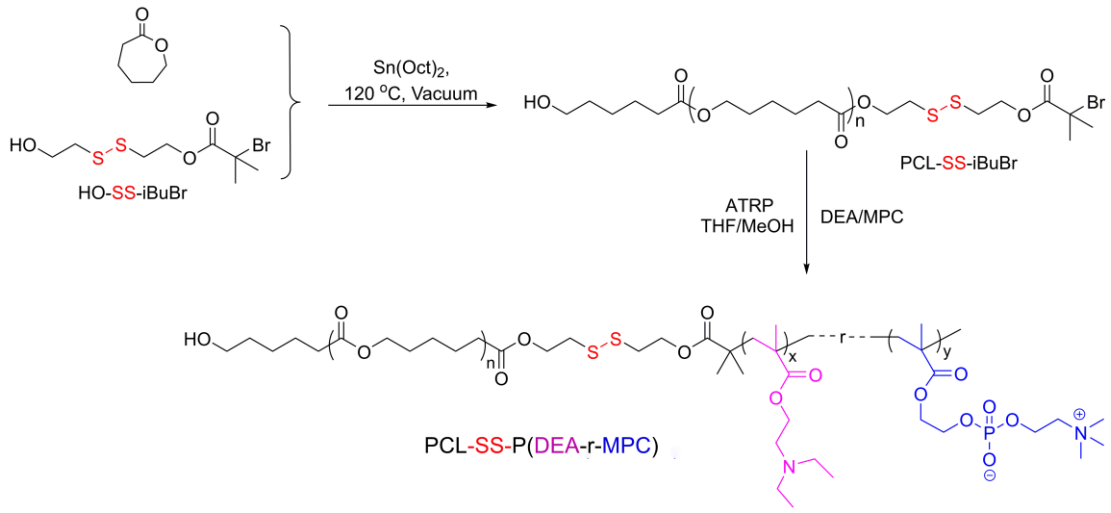

Fig.S1 Synthesis route of PCL-ss-P(DEA-r-MPC).

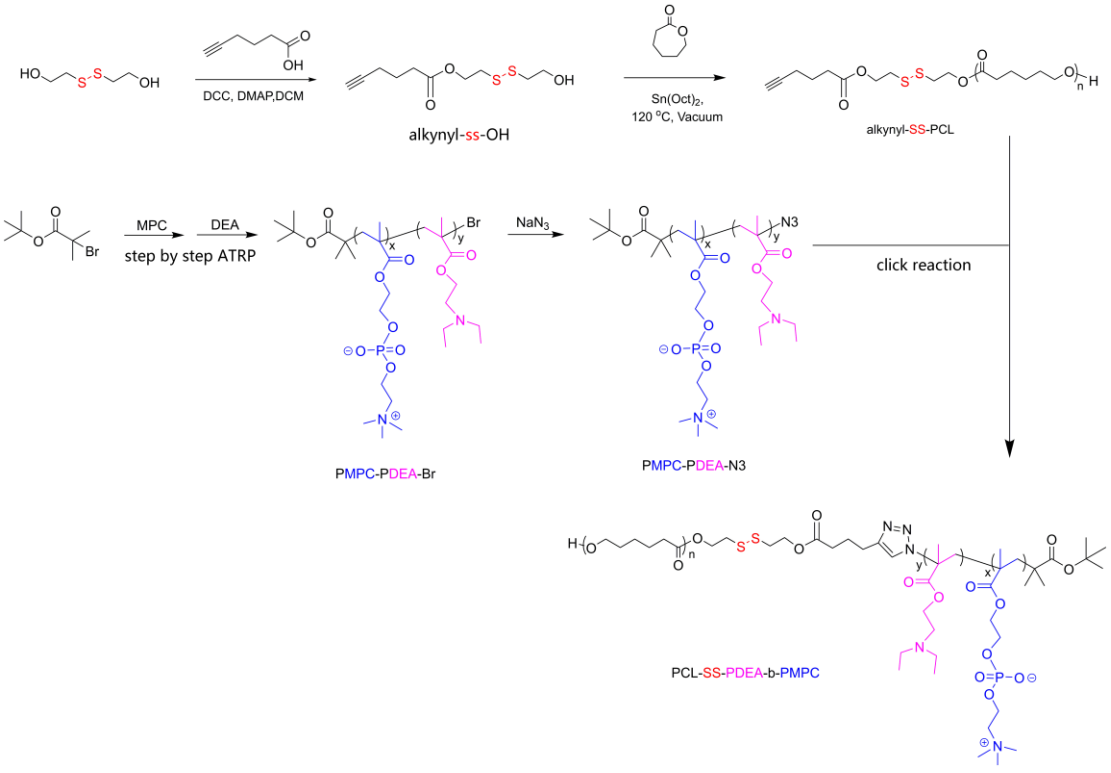

Fig.S2 Synthesis route of PCL-ss-PDEA-b-PMPC.

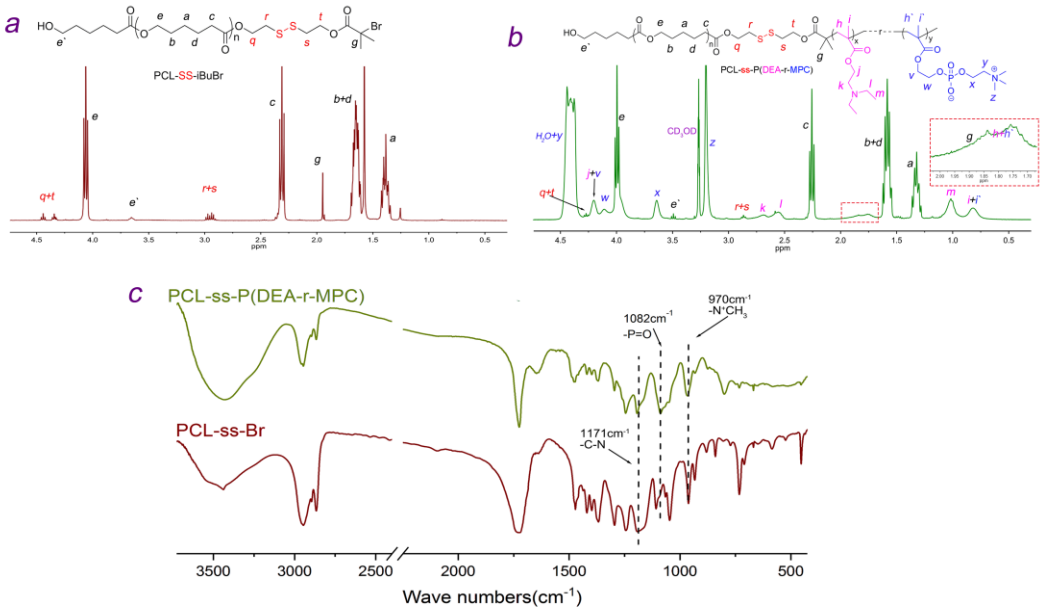

Fig.S3. ^{1}H NMR spectra of PCL-ss-iBuBr in $CDCL_3$(a), and PCL-ss-P(DEA-r-PMPC) in $CDCL_3/CD_3OD$=1/1(v/v) (f) and their FT-IR spectra (c).

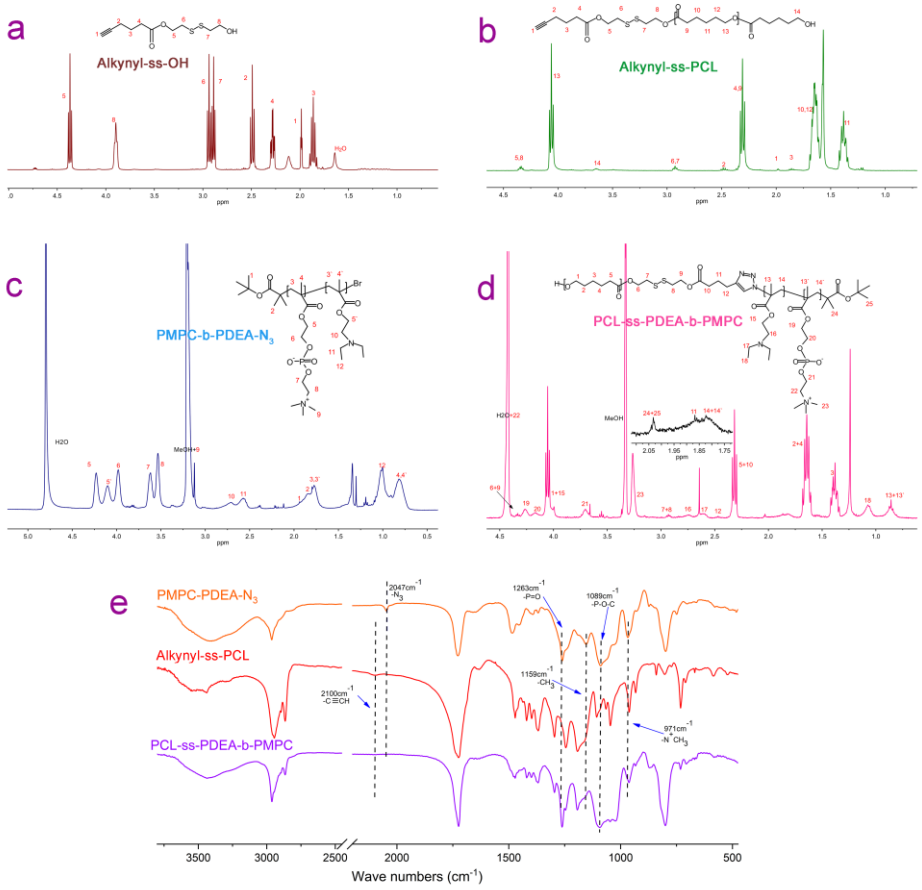

Fig.S4. ^{1}H NMR spectra of Alkynyl-ss-OH $CDCL_3$(a), Alkynyl-ss-PCL in $CDCL_3$(b), PMPC-b-PDEA-N_3 in CD_3OD (c) and PCL-ss-PDEA-b-PMPC in $CDCL_3/CD_3OD$=1/1(v/v) (d) and their FT-IR spectra (e).

Table S1. Element analysis of pH /reduction sensitive cell membrane inspired amphiphilic three block copolymers

Sample		N %	C %	H %	S %
PCL_{25}-ss-($PDEA_6$-r-$PMPC_{11}$)	(SDRM)	2.787	50.699	11.291	0.498
PCL_{25}-ss-$PCL_{5.5}$-b-$PMPC_{11}$	(SDBM)	2.027	47.541	9.335	0.502
PCL_{25}-$PDEA_6$-ss-$PMPC_{12}$	(DSM)	2.802	52.531	10.044	0.509

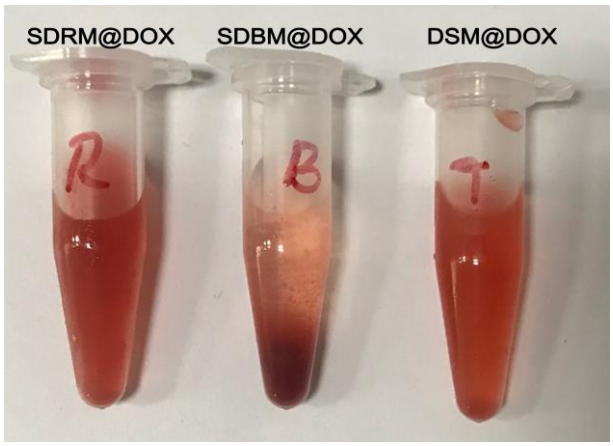

Fig.S5. Photos of DOX loaded micelles SDRM@DOX, SDBM@DOX and DSM@DOX.

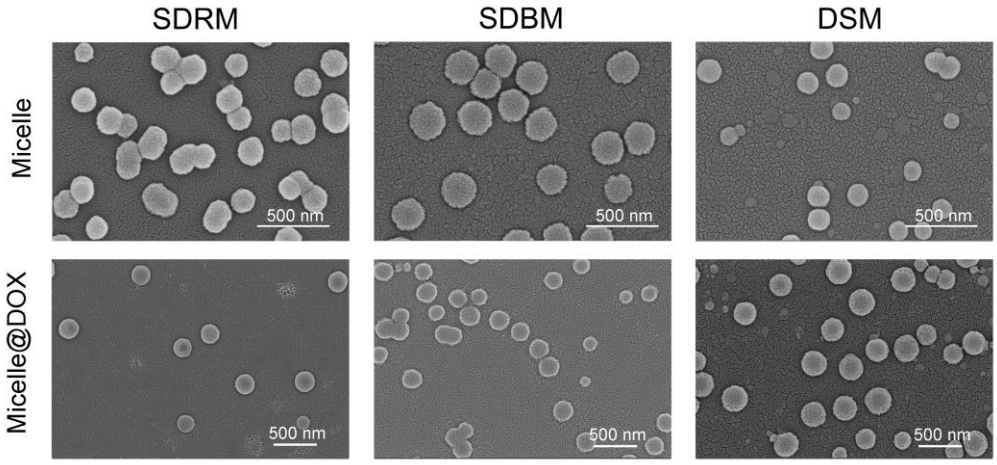

Fig.S6. SEM of blank and DOX loaded micelles.

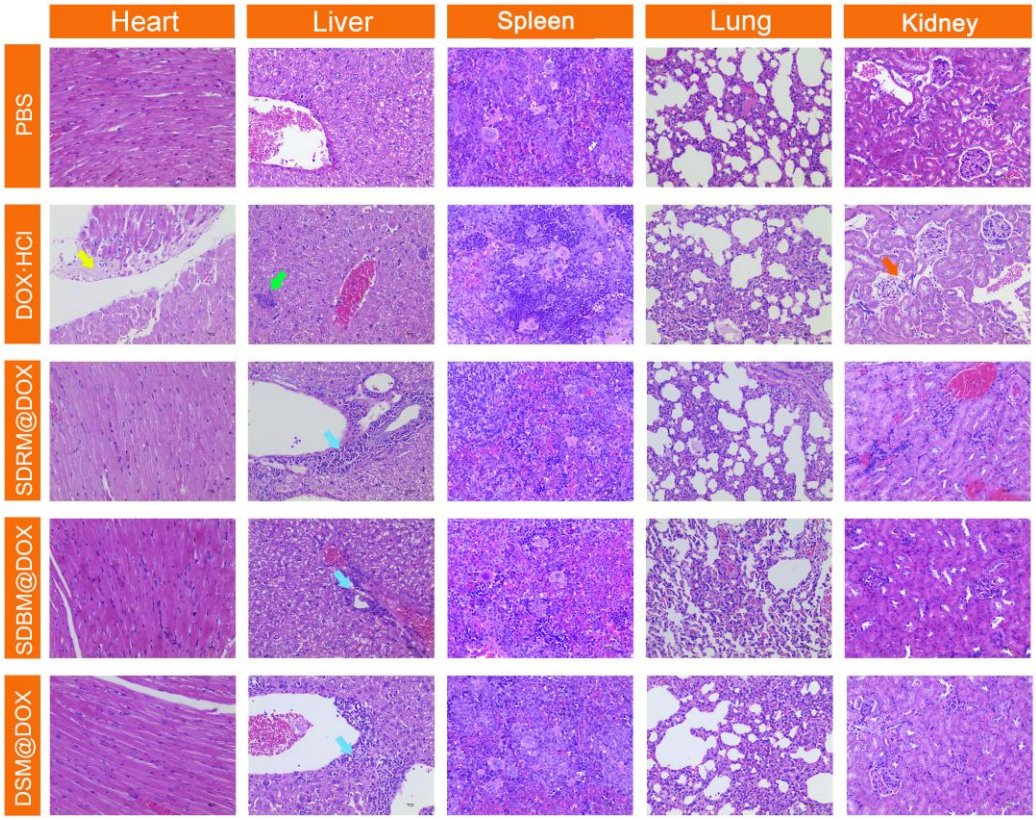

Fig.S7. H&E stain of major organ sections of BALB/c mice after treated with PBS, DOX·HCl solution, SDRM@DOX, SDBM@DOX and DSM@DOX。

Reference

1. M. Cai, M. Leng, A. Lu, L. He, X. Xie, L. Huang, Y. Ma, J. Cao, Y. Chen and X. Luo, *Colloids and surfaces. B, Biointerfaces*, 2015, **126**, 1-9.