Supporting Information For

Co-delivery of doxorubicin hydrochloride and verapamil hydrochloride by pH-sensitive polymersomes for the reversal of multidrug resistance

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Synthesis of triblock copolymer $mPEG_{2K}$-PCL_{4K}-PGA_{1K}

(1)The first step was to synthesize $mPEG_{2K}$-PCL_{4K}-OH: $mPEG_{2K}$ (2.0 g) and ε-caprolactone (4.0g) were interreacted at 120 °C for 12h using stannous octanoate as a catalyst. The polymerization mixture was cooled to room temperature and then the product was dissolved in CH_2Cl_2 and precipitated with an excess of diethyl ether. After filtration, the solid was dried in vacuo. (2) Secondly, the $mPEG_{2K}$-PCL_{4K}-OH was converted into $mPEG_{2K}$-PCL_{4K}-Phe-^{N}BOC: The $mPEG_{2K}$-PCL_{4K}-OH (6.0 g, 1 mmol), Phe-^{N}BOC (0.53 g, 2 mmol) and DMAP (0.025 g, 0.2 mmol) were dissolved in 20 ml dry CH_2Cl_2, and then 2 ml dry CH_2Cl_2 containing DCC (0.62 g, 3 mmol) was added dropwise. After reacting for 48 h at 0 °C, the dicyclohexylurea (produced by DCC after absorbing water) was removed by filtration. The filtrate was washed with

the saturated aqueous solution of $NaHCO_3$. Finally, the $mPEG_{2K}$-PCL_{4K}-Phe-NBOC in the CH_2Cl_2 solution was precipitated when poured into cold diethyl ether. (3) The third step is to remove the BOC group of $mPEG_{2K}$-PCL_{4K}-Phe-^{N}BOC and get $mPEG_{2K}$-PCL_{4K}-NH_2: $mPEG_{2K}$-PCL_{4K}-Phe-^{N}BOC was dissolved in the mixture of CH_2Cl_2 and trifluoroacetic acid (2:1, v/v) for 2 h at 0 °C. The product was washed with saturated aqueous $NaHCO_3$ and precipitated with diethyl ether. After filtration, the solid was dried in vacuo. (4) The fourth step is to produce $mPEG_{2K}$-PCL_{4K}-$PBLG_{1K}$ by ROP of the BLG-NCA: the $mPEG_{2K}$-PCL_{4K}-NH_2 (6.0 g, 1mmol) was reacted with BLG-NCA (2.37 g, 9 mmol) in a dried CH_2Cl_2 solution for 72 h at 30 °C. The product was precipitated with an excess of diethyl ether. After filtration, the purified $mPEG_{2K}$-PCL_{4K}-$PBLG_{1K}$ was obtained. (5) The last step was to get the final product $mPEG_{2K}$-PCL_{4K}-PGA_{1K}: $mPEG_{2K}$-PCL_{4K}-$PBLG_{1K}$ (1 g) was dissolved in a mixture of TFA (12 mL), TFMSA (1.2 mL) and thioanisole (1.4 mL). After reacting at 0 °C for 1 h and then at room temperature for 30 min to remove the benzyl protecting group, the reaction mixture was poured into cooled diethyl ether to obtain the white precipitate which was collected by filtration and dried in a vacuum to yield about 0.6 g of product.

The molecular weight of PCL was estimated to be 4K. They are determined by the ^{1}H NMR analysis. For example, the relative molecular mass of PEG is 2000 Da (PEG_{2000} was bought from Sigma-Aldrich) and the monomers is 44, thus the degree of polymerization of PEG is 45 (2000÷44≈45). Based on the peak areas of H in PEG (4H, $CH_3O\mathbf{CH_2CH_2}O$) and PCL (2H, $COC\mathbf{H_2}CH_2CH_2CH_2CH_2O$), the ratio of them was

about 2.6. Therefore, the number of H in PCL is 70 (45×4÷2.6≈70) and the degree of polymerization of PCL is 35 (70÷2=35). The relative molecular mass of monomer of PCL is 114, therefore the relative molecular weight of PCL is about 4000 (35×114=3990).

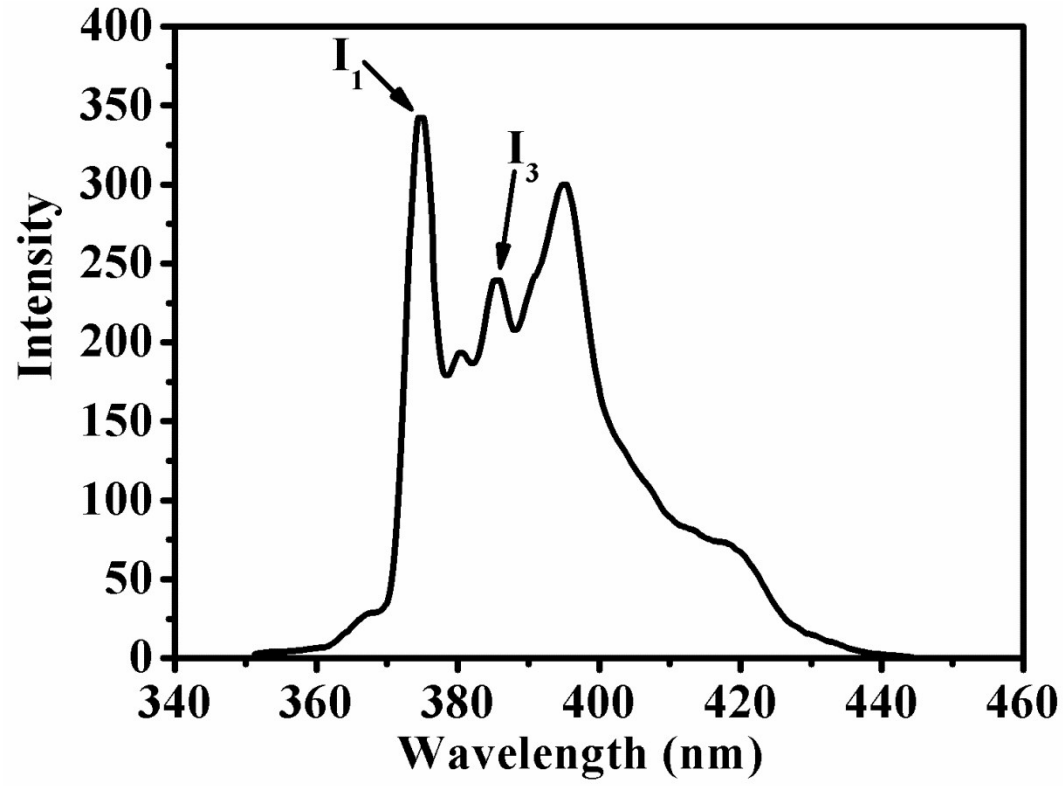

Fig. S1 The representative fluorescence spectra of pyrene.

Table S1 The EE and DL of poly(DOX+VER) with different ratio of feeding drugs

(DOX+VER) mg	(0.5+1.0) mg	(0.5+1.5) mg	(0.5+2.0) mg	(1.0+1.0) mg	(1.0+1.5) mg	(1.0+2.0) mg
DL %	DOX:2.36±0.39	DOX:2.93±0.04	DOX:3.11±0.26	DOX:5.41±0.49	DOX:5.05+0.26	DOX:3.99±0.20
	VER:6.41±0.82	VER:12.63±0.13	VER:13.08±0.38	VER:6.14±0.24	VER:10.72±1.08	VER:13.02±2.86
EE %	DOX:51.67±7.74	DOX:69.32±0.64	DOX:74.10±5.17	DOX:61.19±5.98	DOX:59.89±3.40	DOX:48.11±0.91
	VER:70.28±9.51	VER:99.71±1.14	VER:78.05±2.73	VER:69.37±3.11	VER:84.82±9.52	VER:78.43±7.79

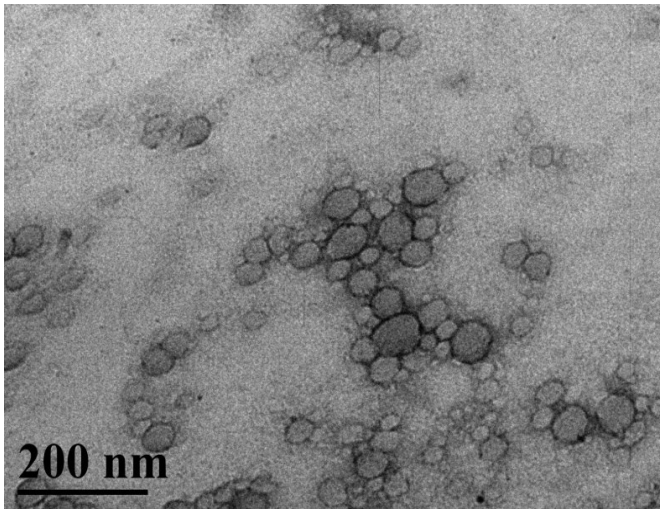

Fig. S2 The morphology of $mPEG_{2K}$-PCL_{4K}-PGA_{1K} self-assembly in water.

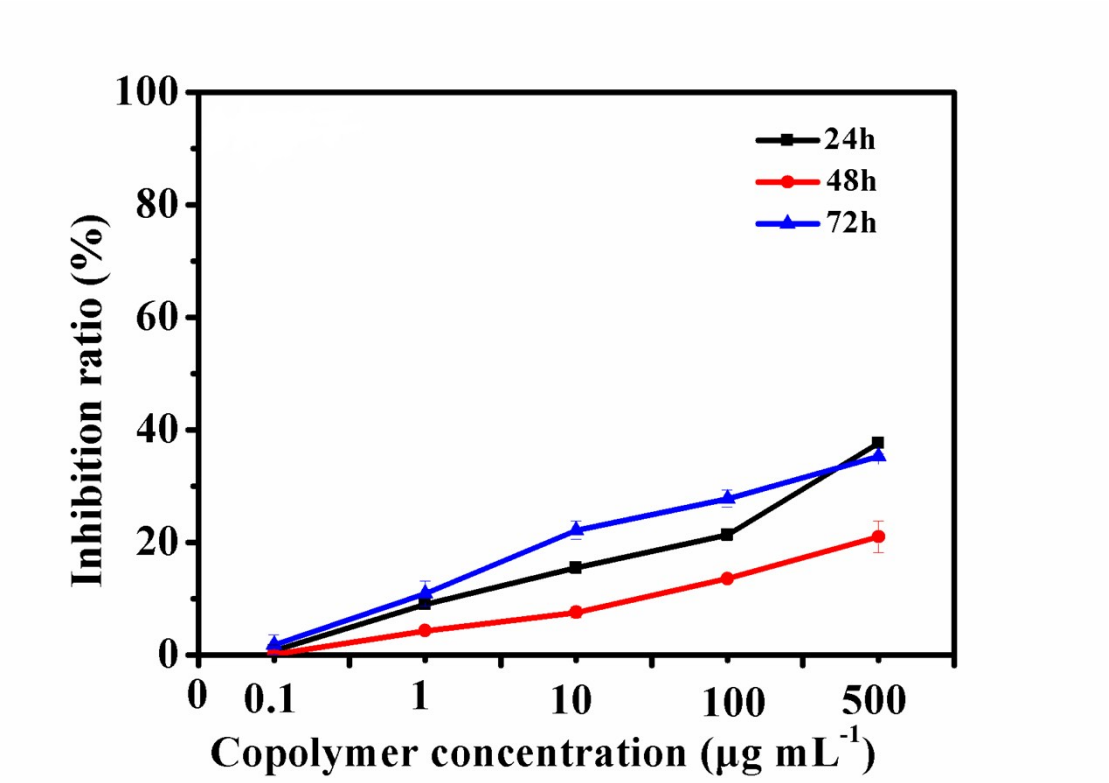

Fig. S3 The in vitro cytotoxicity of blank polymersomes against MCF-7 cells incubation for different times.