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Supporting Information

Ligand-Metal-Drug Coordination Based Micelles for Efficient Intracellular Doxorubicin Delivery

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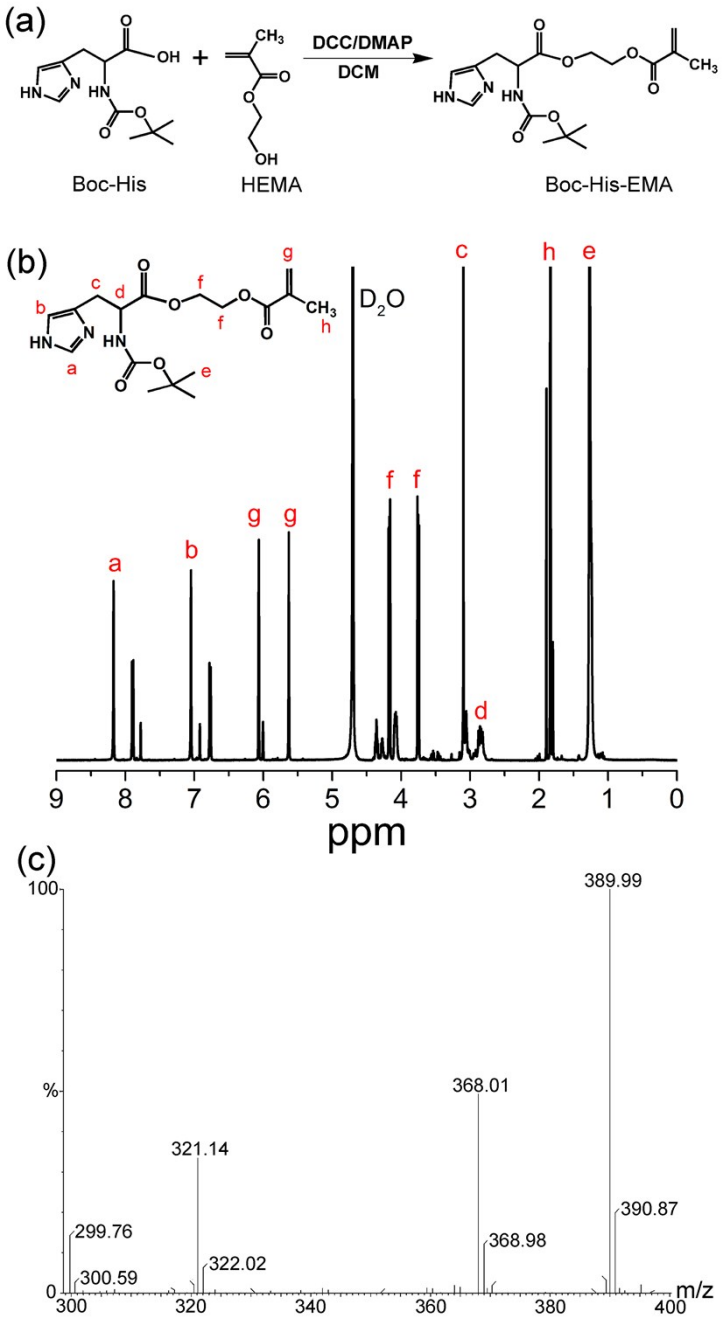

Fig. S1 (a) Synthetic route, (b)^{1}H NMR and (c) EIS-TOF MS spectra of Boc-His-EMA.

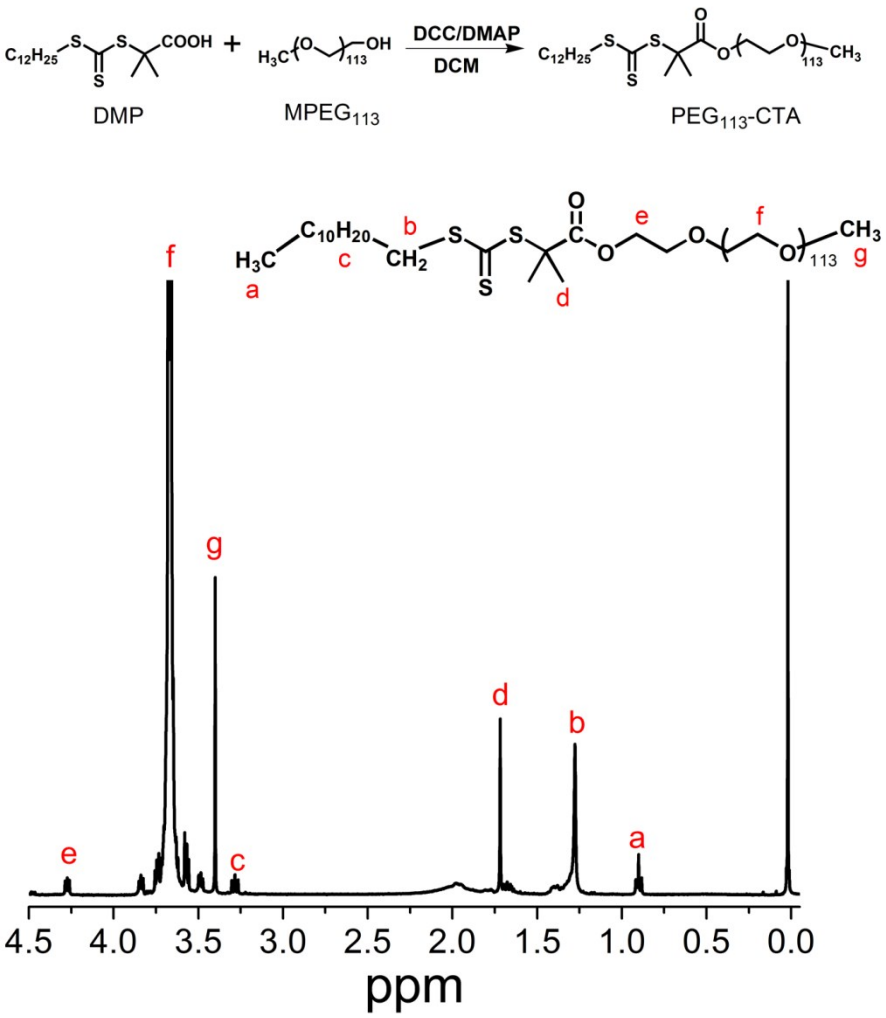

Fig. S2 Synthetic route and ^{1}H NMR spectrum of PEG_{113}-CTA.

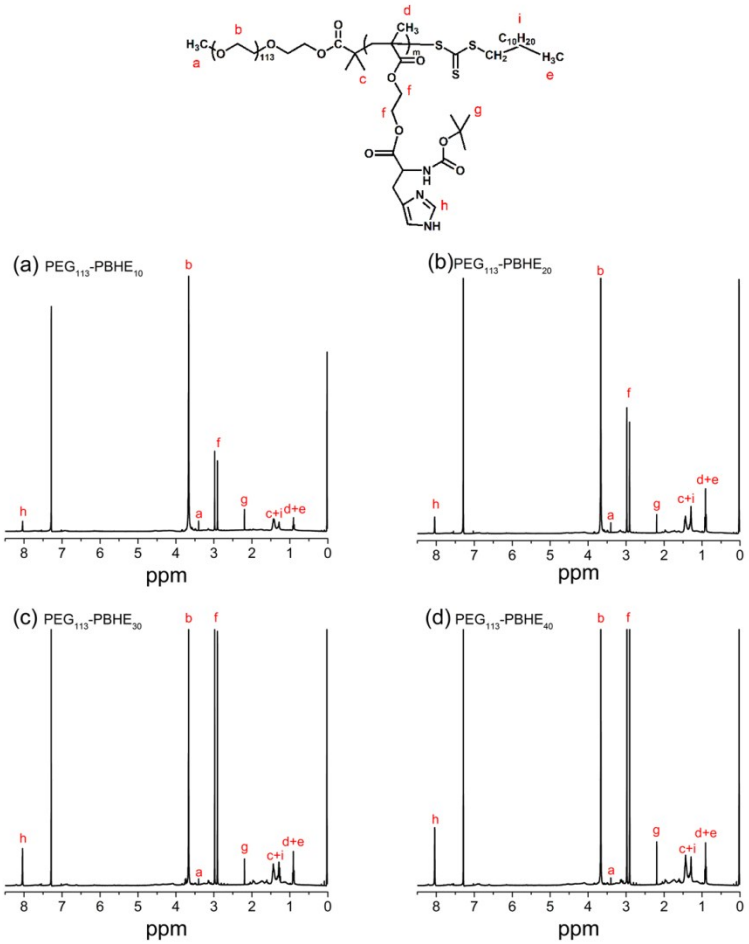

Fig. S3 ^{1}H NMR spectra of PEG_{113}-$PBHE_{m}$.

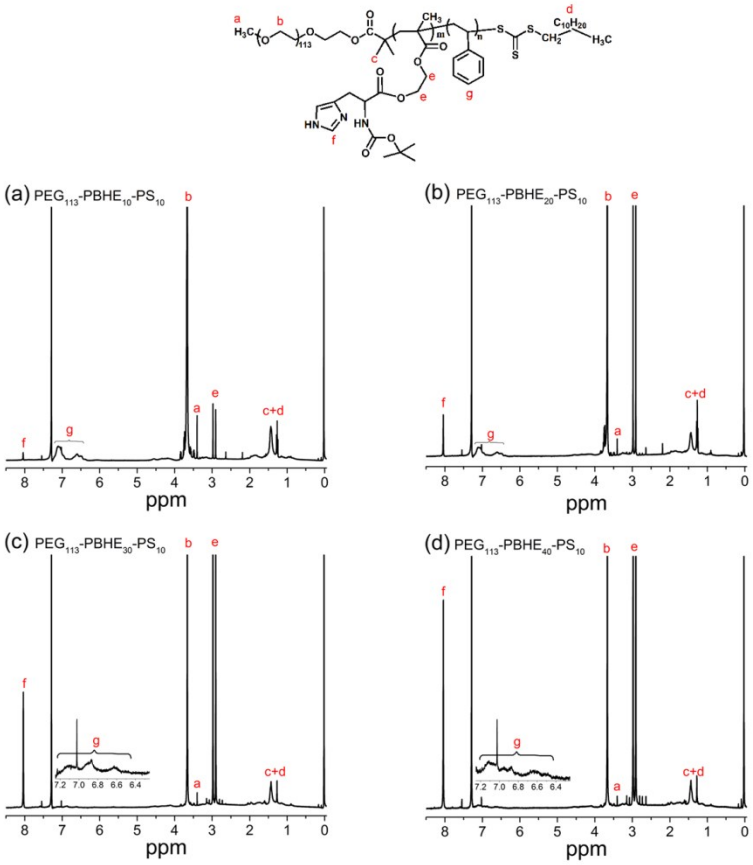

Fig. S4 ^{1}H NMR spectra of PEG_{113}-$PBHE_{m}$-PS_{n}.

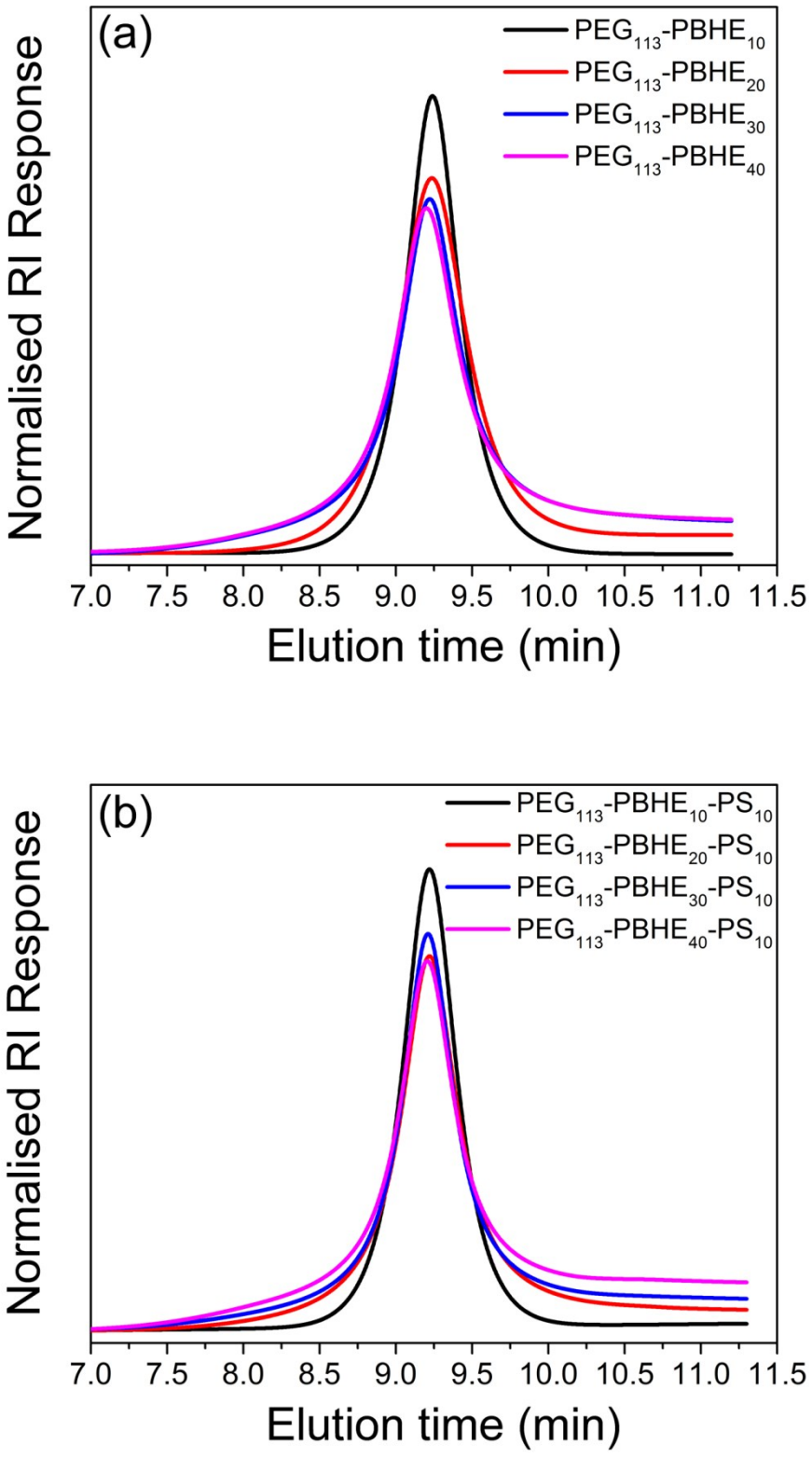

Fig. S5 GPC traces of (a) PEG_{113}-$PBHE_m$ and (b) PEG_{113}-$PBHE_m$-PS_n.

Table S1. Structural information of PEG_{113}-$PBHE_m$ and PEG_{113}-$PBHE_m$-PS_n

Block polymers		Feed ratio[a]	$C_{monomer}$ (%)[b]	M_n[b][kgmol^{-1}]	M_n[c][kgmol^{-1}]	PDI[c]
Theoretical	Experimental					
PEG_{113}-$PBHE_{10}$	PEG_{113}-$PBHE_{12}$	1:15:0.1	80	9409	6584	1.32
PEG_{113}-$PBHE_{20}$	PEG_{113}-$PBHE_{20}$	1:30:0.15	66.7	12348	10745	1.47
PEG_{113}-$PBHE_{30}$	PEG_{113}-$PBHE_{32}$	1:60:0.3	53.3	16756	17712	1.85
PEG_{113}-$PBHE_{40}$	PEG_{113}-$PBHE_{40}$	1:90:0.45	44.4	19696	19990	1.93
PEG_{113}-$PBHE_{10}$-PS_{10}	PEG_{113}-$PBHE_{12}$-PS_{13}	1:15:0.1	86.6	10762	7198	1.33
PEG_{113}-$PBHE_{20}$-PS_{10}	PEG_{113}-$PBHE_{20}$-PS_{14}	1:20:0.1	70	13805	13056	1.55
PEG_{113}-$PBHE_{30}$-PS_{10}	PEG_{113}-$PBHE_{30}$-PS_{12}	1:20:0.1	60	16964	18930	1.88
PEG_{113}-$PBHE_{40}$-PS_{10}	PEG_{113}-$PBHE_{40}$-PS_{10}	1:20:0.1	50	20737	20079	2.01

a [PEG_{113}-CTA]:[BHE]:[AIBN] for diblock polymer; [PEG_{113}-$PBHE_m$-CTA]:[styene]:[AIBN] for triblock polymer.

b Conversion of monomer calculated by ^{1}H NMR results.

c Measured by GPC.

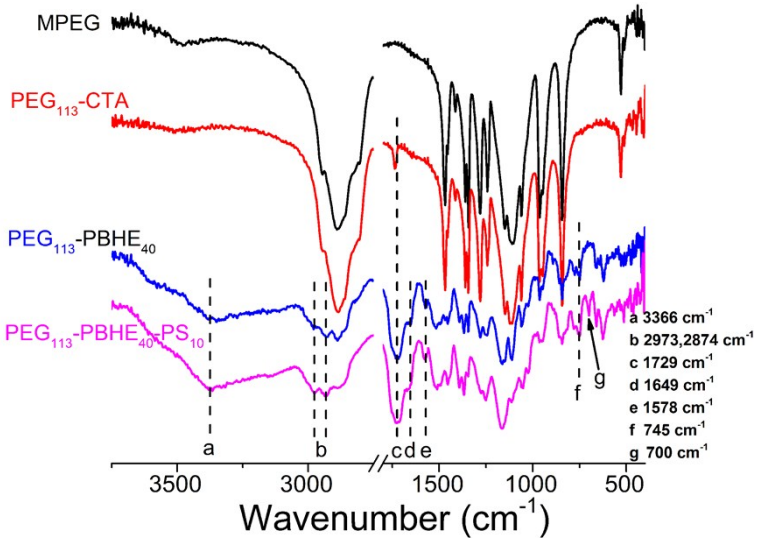

Fig. S6 FT-IR spectra of MPEG, PEG_{113}-CTA, PEG_{113}-$PBHE_{40}$ and PEG_{113}-$PBHE_{40}$-PS_{10}

The weak peak at 1729 cm^{-1} of PEG_{113}-CTA was attributed to the C=O stretching vibration of terminal carboxy group. The peaks at the same position of PEG_{113}-$PBHE_{40}$ and PEG_{113}-$PBHE_{40}$-PS_{10} became much stronger than that of PEG_{113}-CTA, due to the increasing amount of C=O bonds of PBHE blocks. The peaks at 3366 cm^{-1} (N-H stretching vibration of Boc- protected primary amine of His), 2973/2874 cm^{-1}(C-H stretching vibration of imidazole ring), 1649 cm^{-1}(C-N stretching vibration of imidazole), 1578 cm^{-1}(C=N stretching vibration of imidazole) and 745 cm^{-1} (C-H bending vibration of imidazole ring) of PEG_{113}-$PBHE_{40}$ and PEG_{113}-$PBHE_{40}$-PS_{10} were also the characteristic signals of PBHE blocks. And the peak of PEG_{113}-$PBHE_{40}$-PS_{10} at 700 cm^{-1} was assigned to the C-H bending vibration of benzene ring, suggesting the presence of PS blocks.

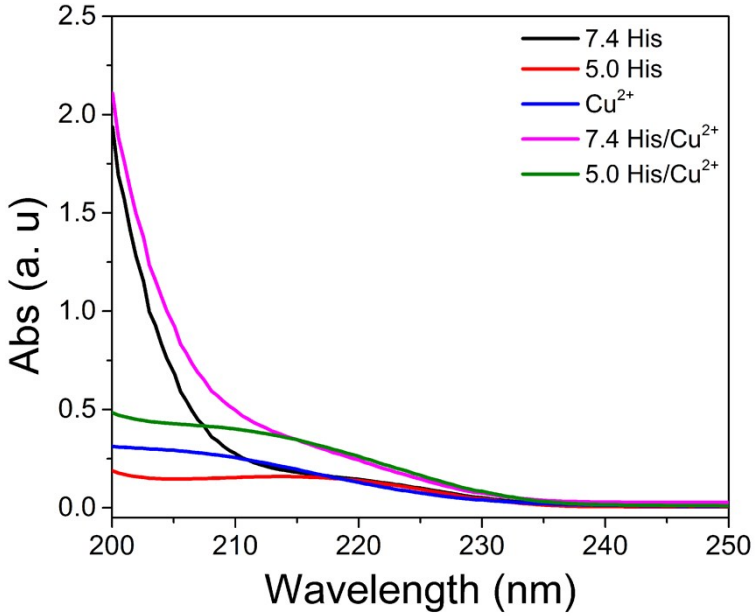

Fig. S7 UV-Vis spectra of His and His/Cu^{2+} aqueous solution at pH 7.4 and 5.0.

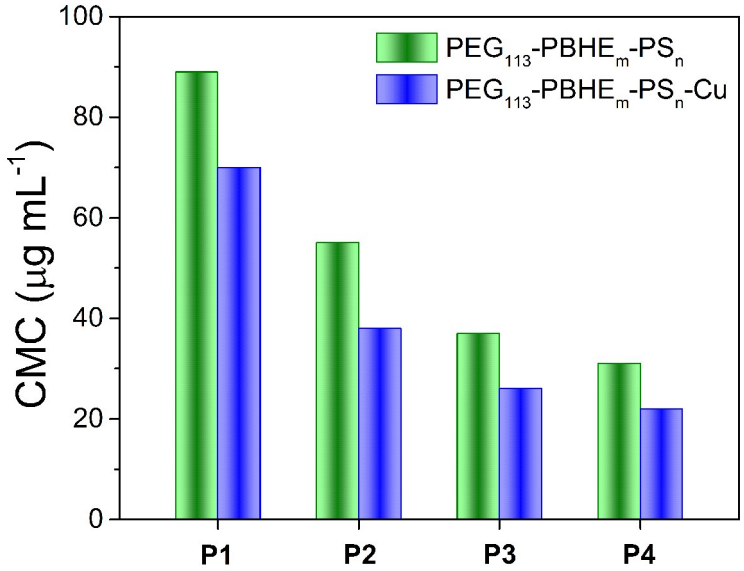

Fig. S8 CMC of PEG_{113}-$PBHE_m$-PS_n and PEG_{113}-$PBHE_m$-PS_n-Cu micelles at pH 7.4.

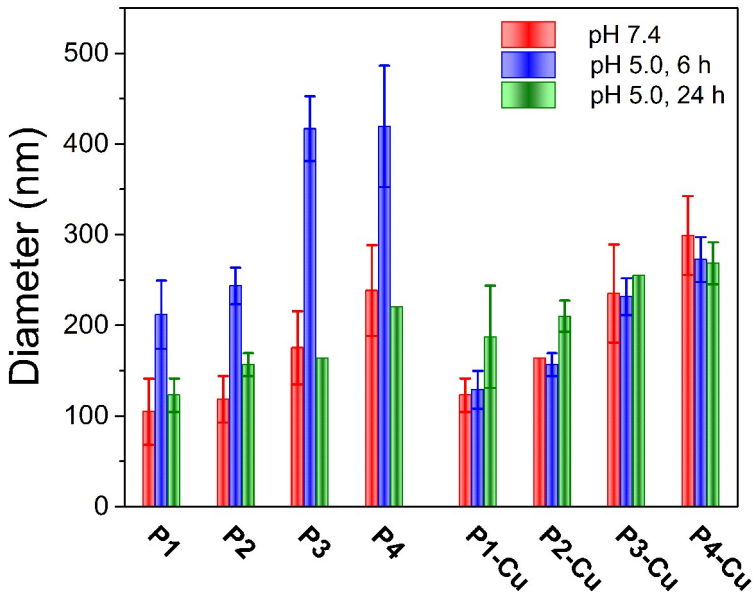

Fig. S9 Diameters of DOX-loaded PEG_{113}-$PBHE_m$-PS_n and PEG_{113}-$PBHE_m$-PS_n-Cu micelles.

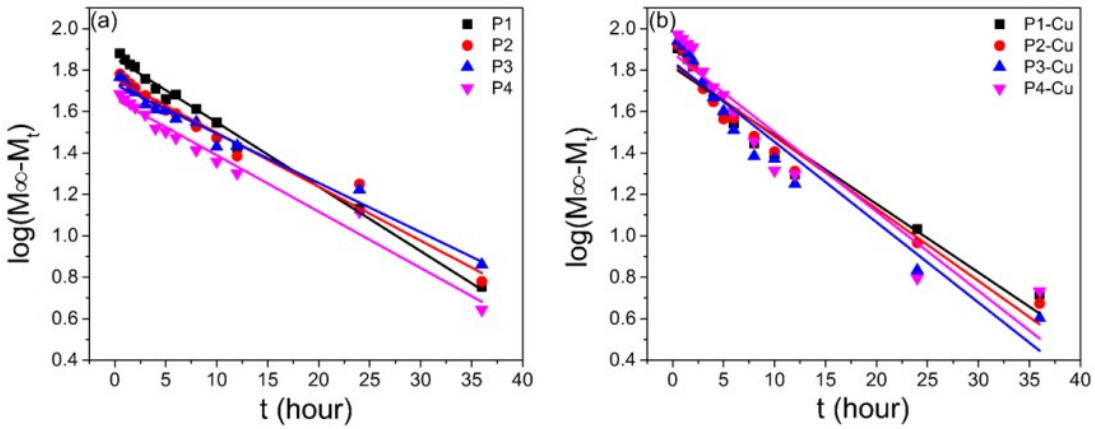

Fig. S10 Linear regression curves of release data of (a) PEG_{113}-$PBHE_m$-PS_n and (b) PEG_{113}-$PBHE_m$-PS_n-Cu micelles fitted by first-order kinetic model (pH 5.0).

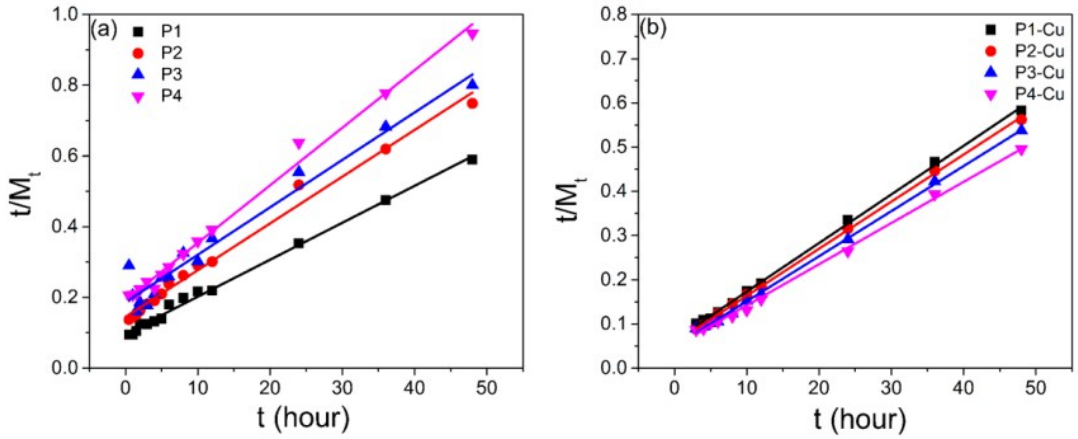

Fig. S11 Linear regression curves of release data of (a) PEG_{113}-$PBHE_m$-PS_n and (b) PEG_{113}-$PBHE_m$-PS_n-Cu micelles fitted by pseudo-second-order kinetic model (pH 5.0).

Table S2. First-order rate and second-order rate constants for DOX release from PEG_{113}-$PBHE_m$-PS_n and PEG_{113}-$PBHE_m$-PS_n-Cu micelles.

Sample	First-order				Second-order		
	M_∞[a](%)	k_1	M_∞[b](%)	R^2	k_2	M_∞[c](%)	R^2
P1	75.6	0.0715	72.1	0.9912	0.000109	95.6	0.9944
P2	64.1	0.0599	57.2	0.9715	0.000175	75.6	0.9881
P3	60.0	0.0547	53.8	0.9800	0.000180	74.5	0.9563
P4	50.7	0.0626	45.7	0.9765	0.000265	61.4	0.9927
P1-Cu	82.3	0.0761	65.3	0.9349	0.000121	90.9	0.9987
P2-Cu	85.3	0.0803	67.3	0.9487	0.000113	93.8	0.9992
P3-Cu	89.2	0.0892	69.3	0.9316	0.000104	98.1	0.9987
P4-Cu	96.4	0.0881	76.2	0.8987	0.000087	107.2	0.9971

a Experimental cumulative drug release amount at infinite time.

b Theoretical cumulative drug release amount at infinite time calculated from first-order kinetic model.

c Theoretical cumulative drug release amount at infinite time calculated from pseudo-second-order kinetic model.

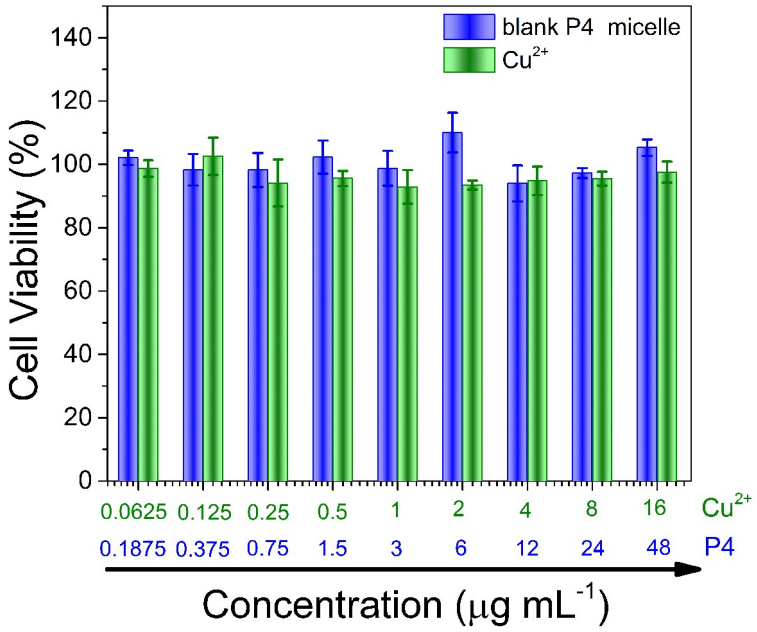

Fig. S12 Viability of HeLa cells after incubation with blank P4 micelles and Cu^{2+} for 48 h incubation.