Supporting Information

Doxorubicin Intercalated Copper Diethyldithiocarbamate Functionalized Layered Double Hydroxides Hybrid Nanoparticles for Targeted Therapy of Hepatocellular Carcinoma

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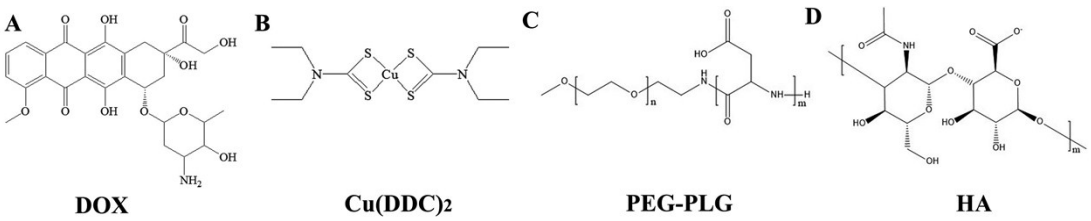


Figure S1. The structural formulas of DOX, $Cu(DDC)_2$, PEG-PLG and HA.

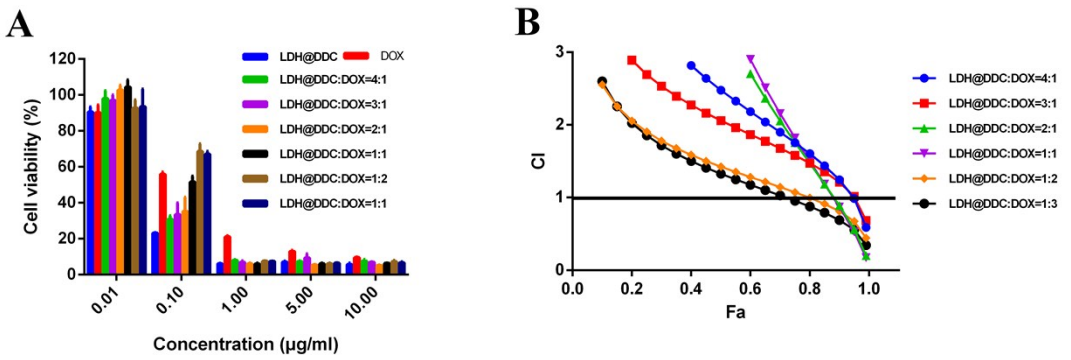


Figure S2. (A) Cytotoxicity of DOX and LDH@DDC samples at different concentrations and ratios on Hep G2 cells. B) Fa-CI graph of Hep G2 cells**.**

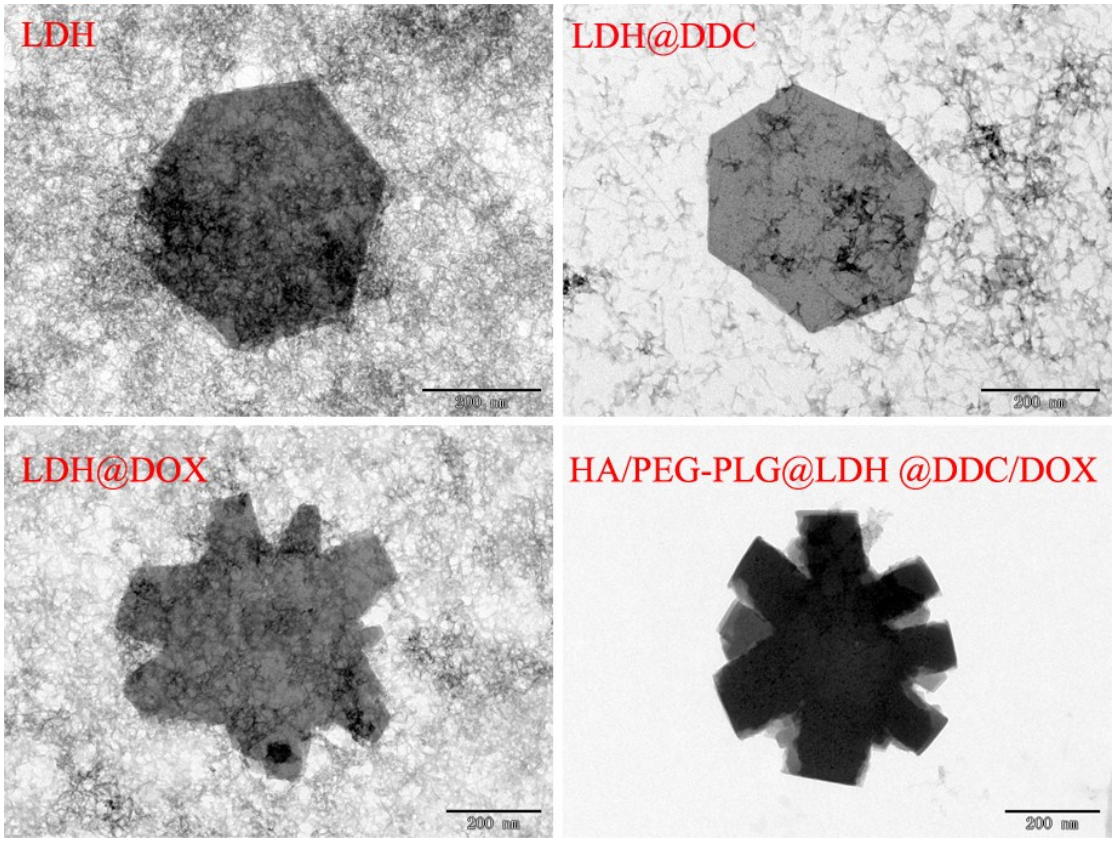


Figure S3. Bright field transmission electron micrographs of LDH, LDH@DDC, LDH@DOX and HA/PEG-PLG@LDH@DDC/DOX.

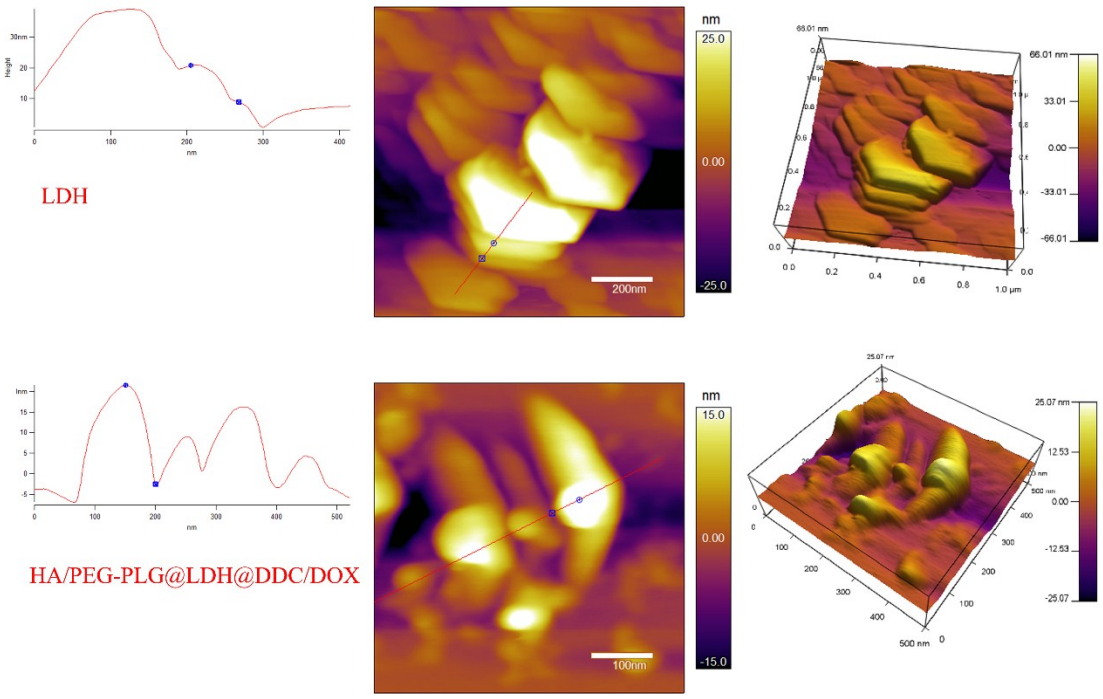


Figure S4. AFM image of LDH and HA/PEG-PLG@LDH@DDC/DOX.

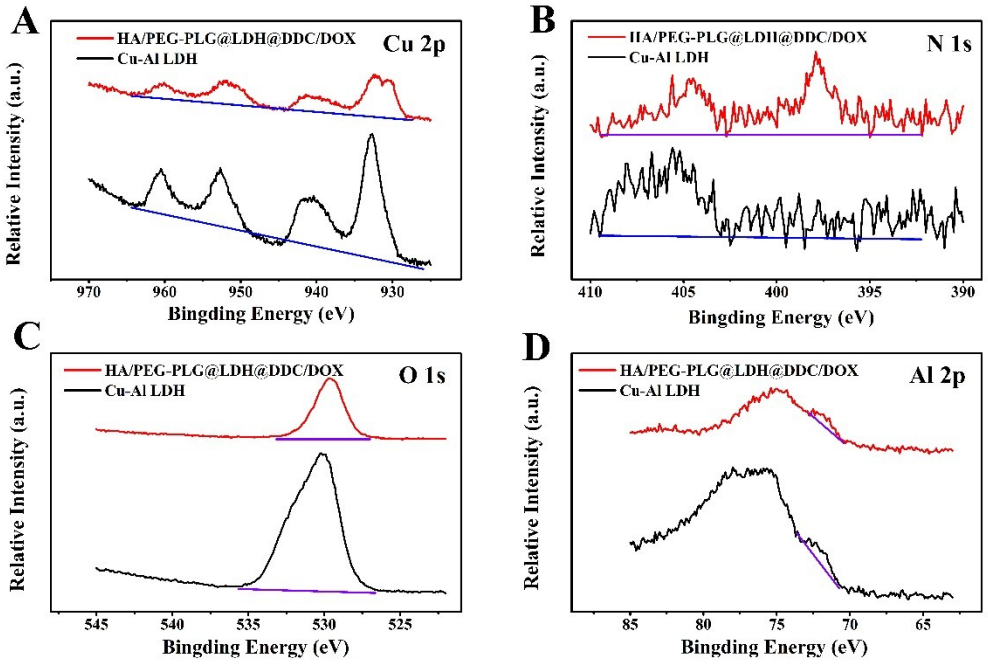


Figure S5. Narrow scan spectra of LDH and HA/PEG-PLG@LDH@DDC/DOX: (A) Cu 2p; (B) N 1s; (C) O 1s; (D) Al 2p.

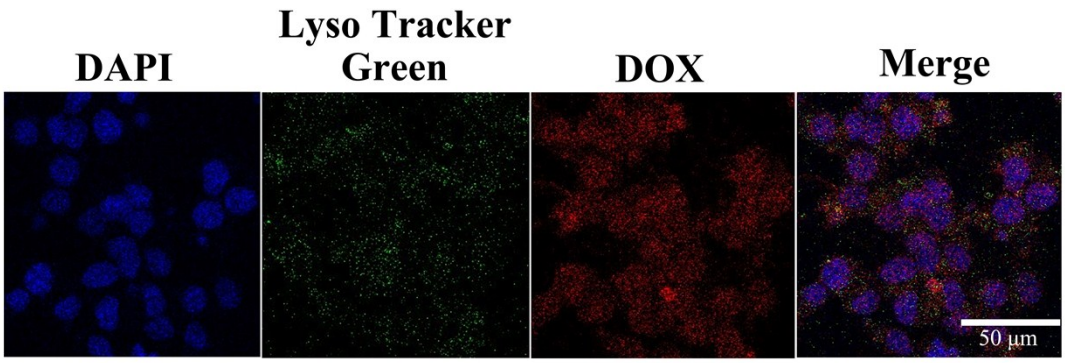


Figure S6. Confocal microscopic images of Hep G2 cells treated with HA/PEG-PLG@LDH@DDC/DOX at DOX concentration of 1 μg/mL for 1 h, followed by staining with 70 nM LysoTracker Green and 5 μg/mL DAPI.

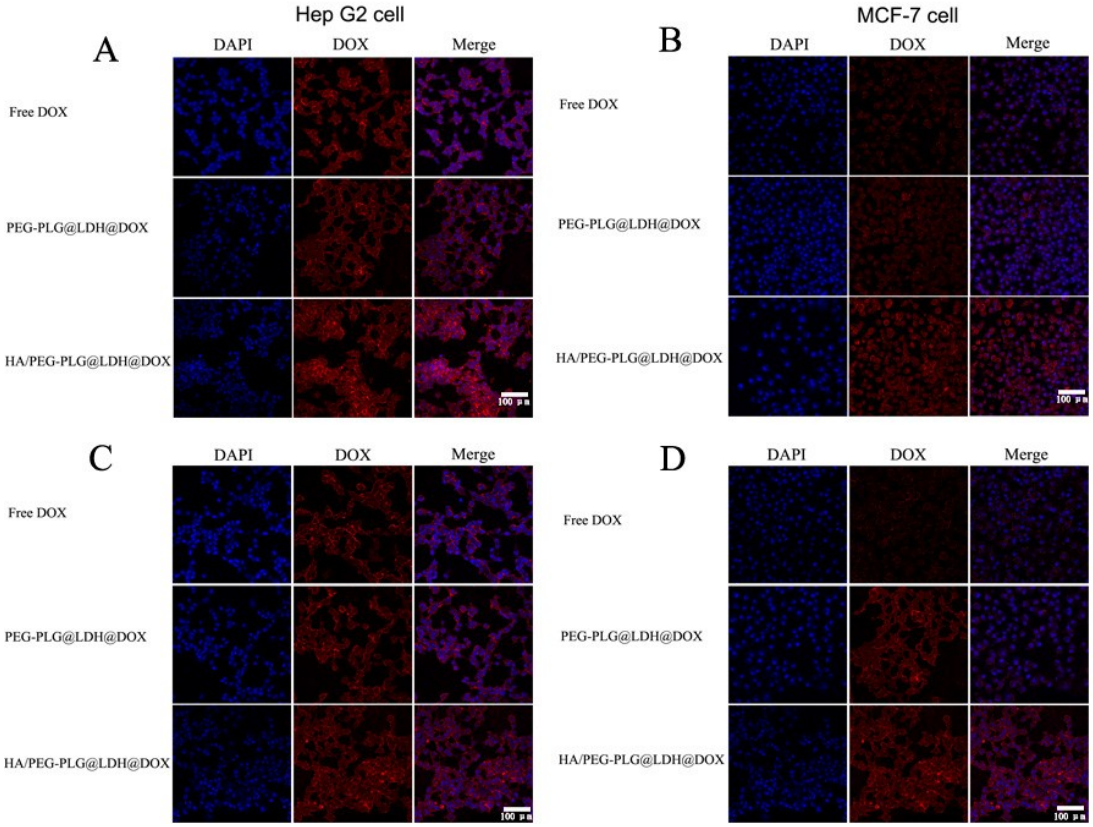


Figure S7. Laser scanning confocal microscopy images of Hep G2 cells and MCF-7cells after incubation with different samples for 2 and 4 h: (A) Hep G2 cells, 4 h; (B) MCF-7 cells, 4 h (C) Hep G2 cells, 2 h; (D) MCF-7 cells, 2 h.

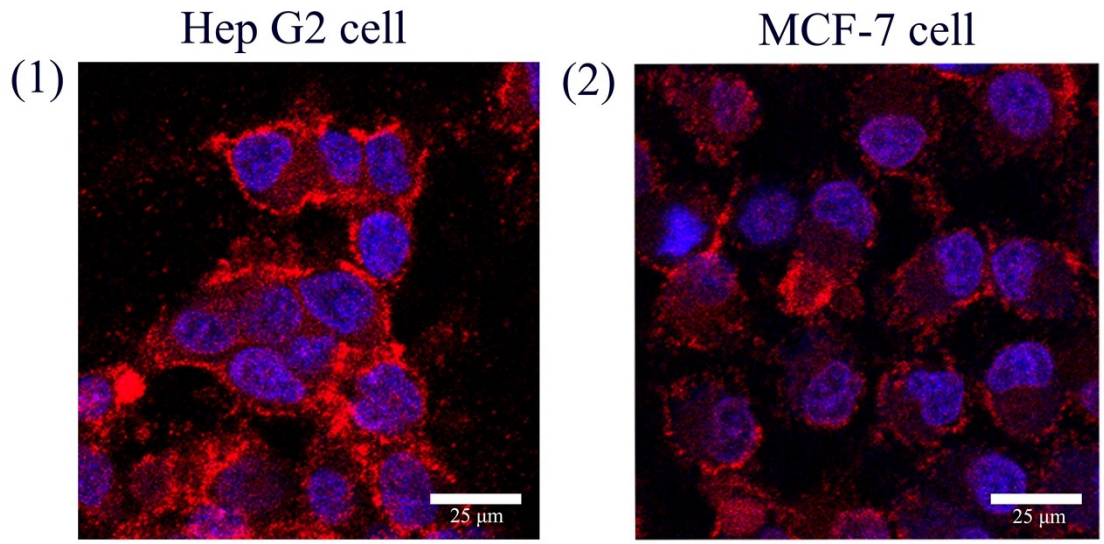
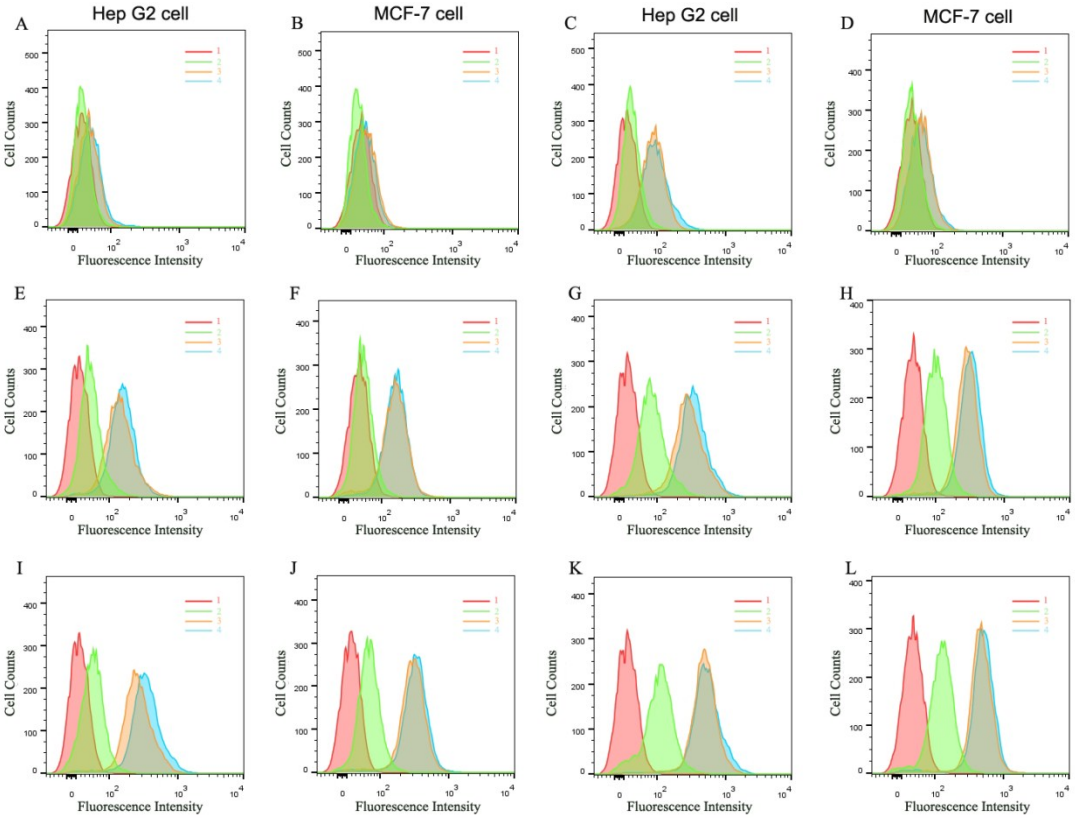


Figure S8. Laser scanning confocal microscopy images of Hep G2 cells and MCF-7cells with higher magnification after incubation with HA/PEG-PLG@LDH@DOX for 4 h.



(A) 0.1 μg mL^{-1} (2 h)	(B) 0.1 μg mL^{-1} (2 h)	(C) 0.1 μg mL^{-1} (4 h)	(D) 0.1 μg mL^{-1} (4 h)
(E) 0.5 μg mL^{-1} (2 h)	(F) 0.5 μg mL^{-1} (2 h)	(G) 0.5 μg mL^{-1} (4 h)	(H) 0.5 μg mL^{-1} (4 h)
(I) 1.0 μg mL^{-1} (2 h)	(J) 1.0 μg mL^{-1} (2 h)	(K) 1.0 μg mL^{-1} (4 h)	(L) 1.0 μg mL^{-1} (4 h)

Figure S9. Intracellular fluorescence with different samples recorded by flow cytometer: (1) control, (2) free DOX (3) PEG-PLG@LDH@DOX, (4) HA/PEG-PLG@LDH@DOX. The corresponding sample concentration and uptake time are shown in the above table.

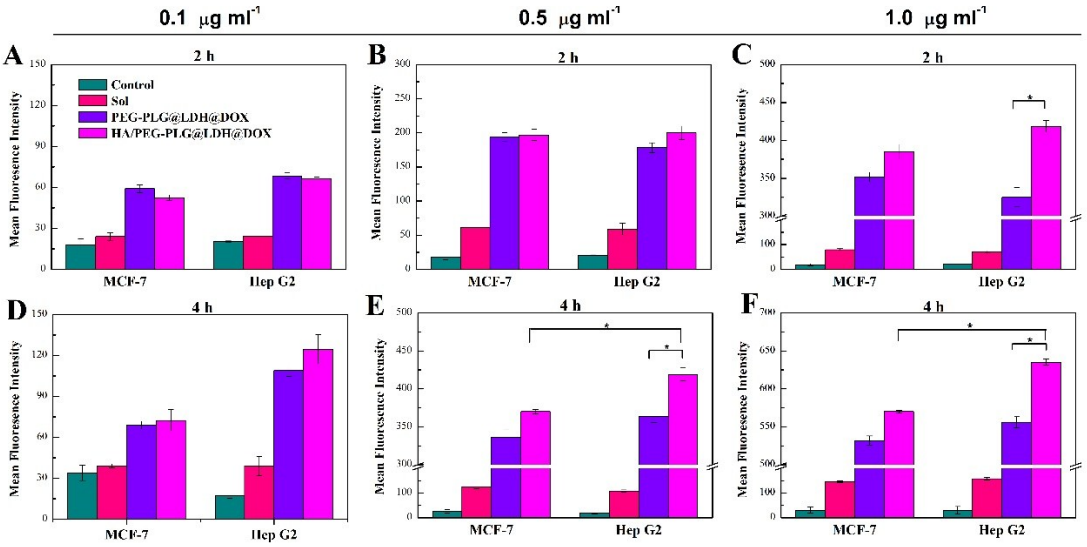


Figure S10. Corresponding normalized fluorescence intensity.

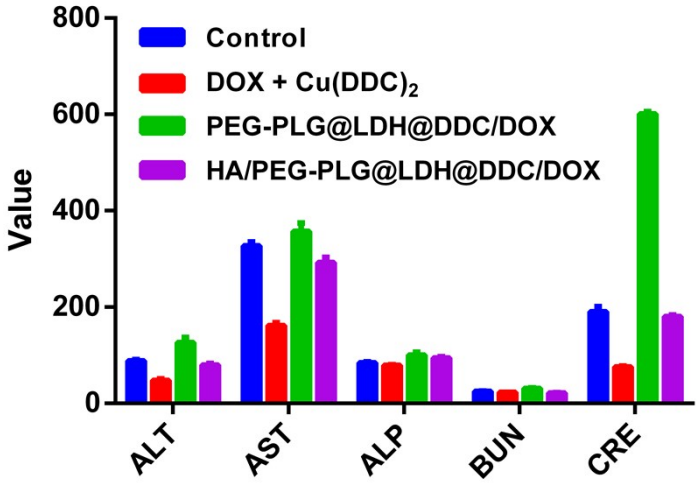


Figure S11. Liver and kidney function indexes of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN) and creatinine (CRE) for PEG-PLG@LDH@DDC/DOX, HA/PEG-PLG@LDH@DDC/DOX and DOX+$Cu(DDC)_2$ group.

Table S1. Parameters of combination index.

Sample	ED50	ED75	ED90	Dm	m	r
LDH@DDC	N/A	N/A	N/A	0.07027	0.69021	0.91342
DOX	N/A	N/A	N/A	0.2108	0.63603	0.98926
LDH@DDC : DOX=4:1	2.47728	1.75424	1.24367	0.16069	0.87443	0.90281
LDH@DDC : DOX=3:1	2.05959	1.5787	1.21189	0.13025	0.82074	0.90898
LDH@DDC : DOX=2:1	3.47838	1.75677	0.88907	0.2095	1.18527	0.90312
LDH@DDC : DOX=1:1	3.81267	1.8175	0.86919	0.20093	1.24411	0.91431
LDH@DDC : DOX=1:2	1.42511	1.07204	0.8099	0.06008	0.80836	0.95925
LDH@DDC : DOX=1:3	1.32712	0.95468	0.6899	0.04663	0.82739	0.96178

Table S2. XPS statistics of different elements on the surface of LDH and HA/PEG-PLG@LDH@DDC/DOX.

Name	Start BE	Peak BE	End BE	Height CPS	FWHM eV	Area (P) CPS.eV
LDH						
O1s	538.1	530.29	523.7	58433.17	3.68	220236.98
N1s	409.9	405.45	395.7	1061.87	0.98	4597.84
Al2p	73.25	71.61	68.35	475.08	0.17	467.48
Cu2p	965.6	932.78	925.1	34954.4	2.96	306133.93
HA/PEG-PLG@LDH@DDC/DOX.						
O1s	536.2	529.62	522.1	25966.6	2.18	65350.81
N1s	409.9	397.83	391.7	977.89	1.03	4706.00
Al2p	73.1	71.4	66.7	270.32	0.07	96.59
Cu2p	965.6	931.69	925.1	10975.25	4.6	123858.85