

Electronic Supporting Information (ESI)

Doxorubicin-reinforced supramolecular hydrogels of RGD-derived peptide conjugates for pH-responsive drug delivery

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Table S1. Table of parameters of Ritger-Peppas models for drug release behavior of DOX/1-RGDH hydrogel at varying pH conditions.

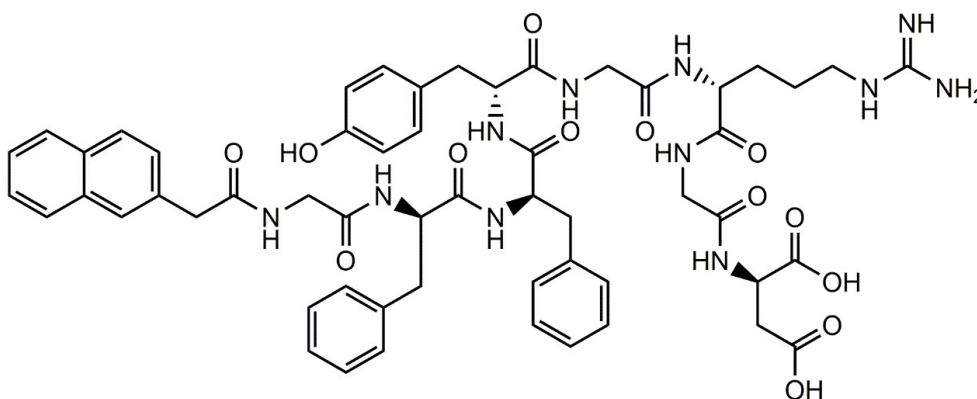


Figure S1.The chemical structure of 1-RGD.

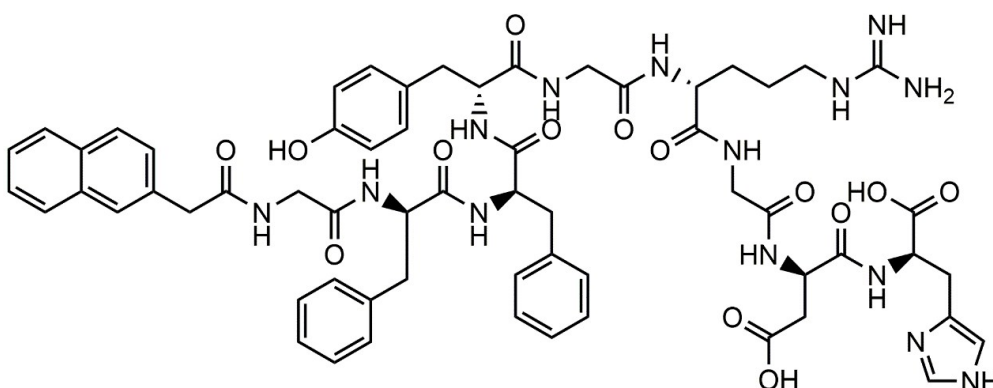


Figure S2.The chemical structure of 1-RGDH.

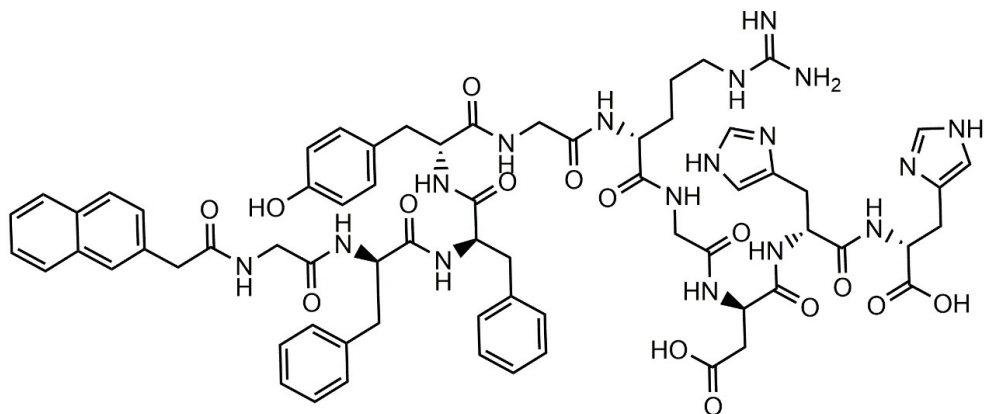


Figure S3. The chemical structure of 1-RGDHH.

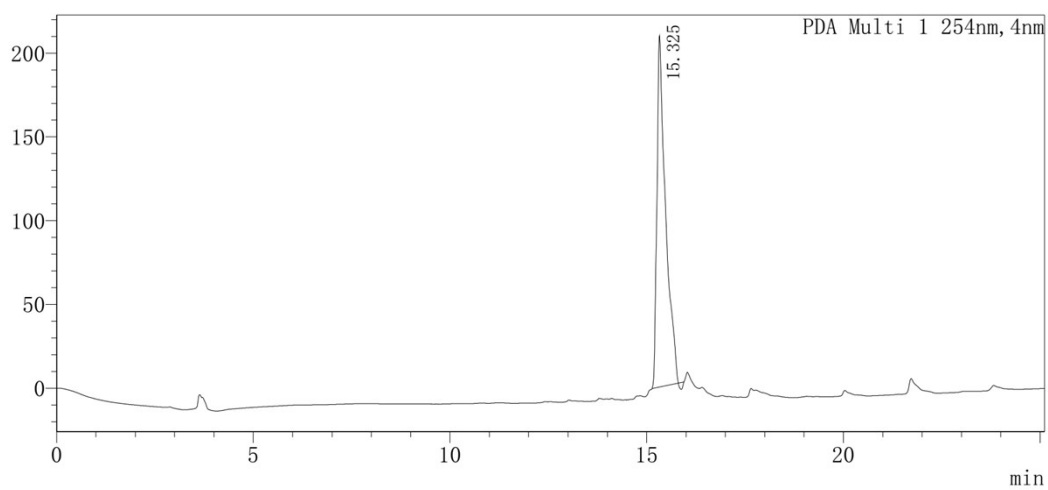


Figure S4. HPLC elution curve of 1-RGD.

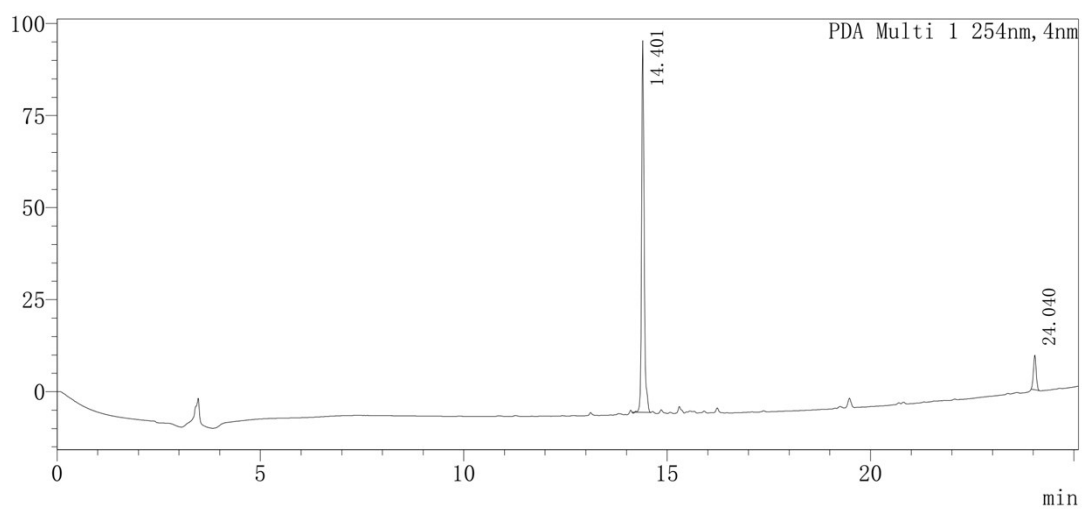


Figure S5. HPLC elution curve of 1-RGDH.

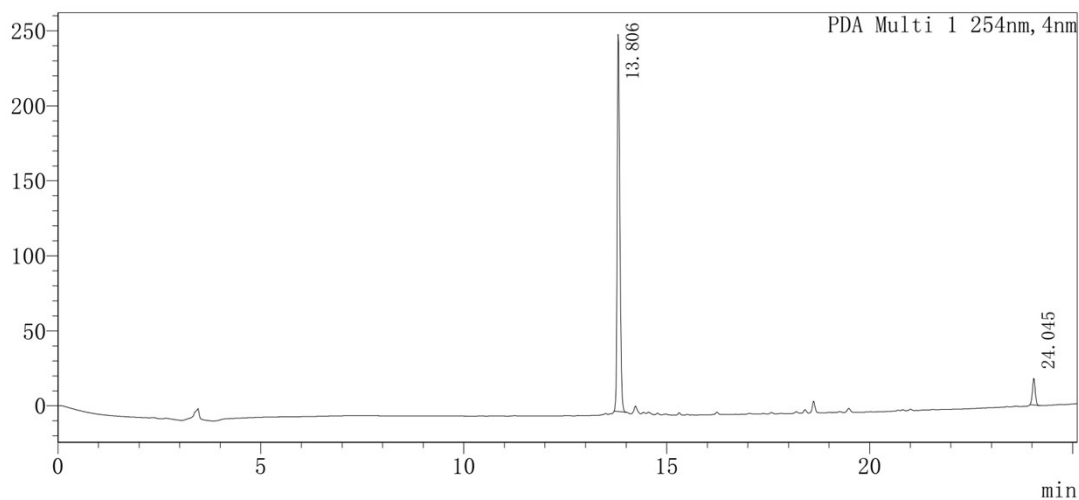


Figure S6. HPLC elution curve of 1-RGDH.

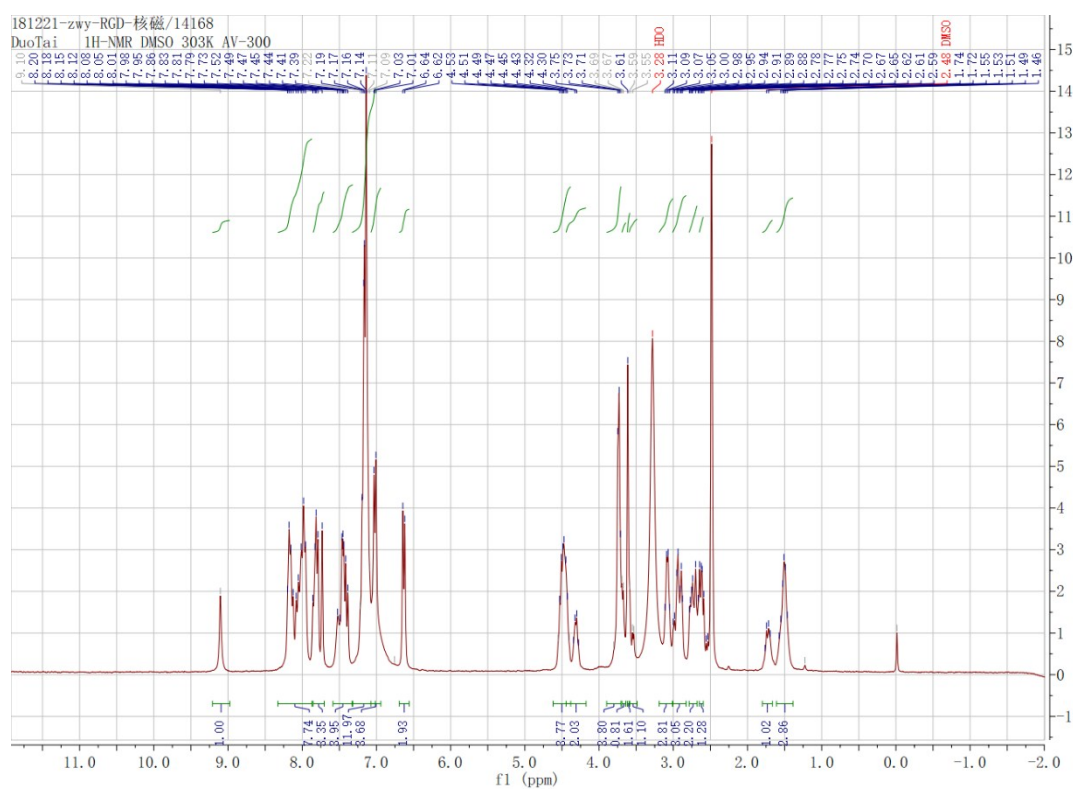


Figure S7. ^1H NMR spectrum of 1-RGD (300 MHz, DMSO).

^1H NMR (300 MHz, DMSO) δ 9.19 (s, 1H), 8.20 – 7.88 (m, 8H), 7.86 – 7.73 (m, 3H), 7.60-7.30 (m, 4H), 7.25 – 7.10 (m, 12H), 7.06-6.96 (d, J = 8.3 Hz, 4H), 6.66 (d, J = 8.3 Hz, 2H), 4.57 – 4.41 (m, 4H), 4.31 (d, J = 6 Hz, 2H), 3.74 (dd, J = 6, 12 Hz, 4H), 3.68 (s, 1H), 3.62 (s, 2H), 3.54 (d, J = 6 Hz, 1H), 3.08 (d, J = 6 Hz, 3H), 2.92 (ddd, J = 6, 6, 3 Hz, 3H), 2.71 – 2.69 (m, 2H), 2.65 – 2.61 (m, 1H), 1.80 – 1.67 (m, 1H), 1.52 (dd, J = 13.7, 8.5 Hz, 3H)

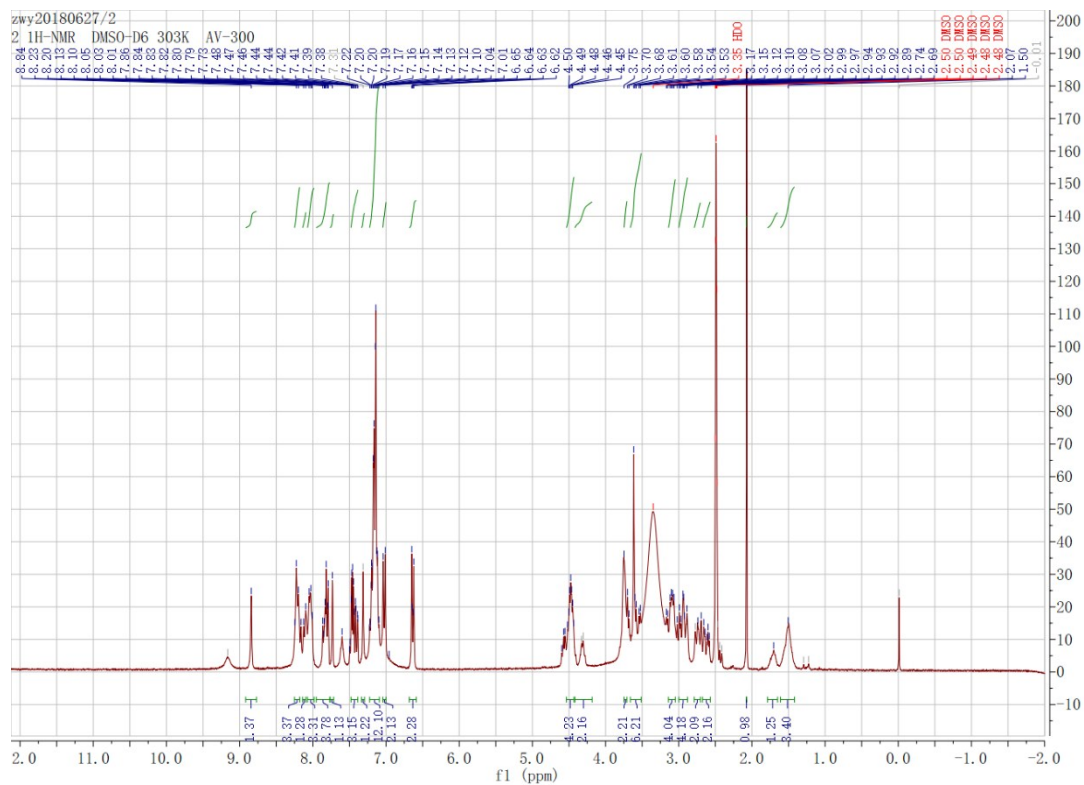


Figure S8. ¹HNMR spectrum of 1-RGDH (300 MHz, DMSO).

¹H NMR (300 MHz, DMSO) δ 8.84 (s, 1H), 8.25-8.20 (m, 3H), 8.13-8.09 (m, 1H), 8.05-8.01 (m, 3H), 7.87-7.79 (m, 4H), 7.73 (s, 1H), 7.50-7.44 (m, 3H), 7.31 (s, 1H), 7.23-7.10 (m, 12H), 7.03 (d, J = 9 Hz, 2H), 6.65-6.62 (d, J = 9 Hz, 2H), 4.53-4.44 (m, 4H), 4.41-4.19 (m, 2H), 3.70 (s, 2H), 3.60 (d, J = 9 Hz, 6H), 3.10 (d, J = 3 Hz, 4H), 2.93 (d, J = 6 Hz, 2H), 2.89 (d, J = 30 Hz, 2H), 2.63 (d, J = 21 Hz, 2H), 2.07 (s, 1H), 1.80–1.67 (m, 1H), 1.52 (dd, J = 13.7, 8.5 Hz, 3H),

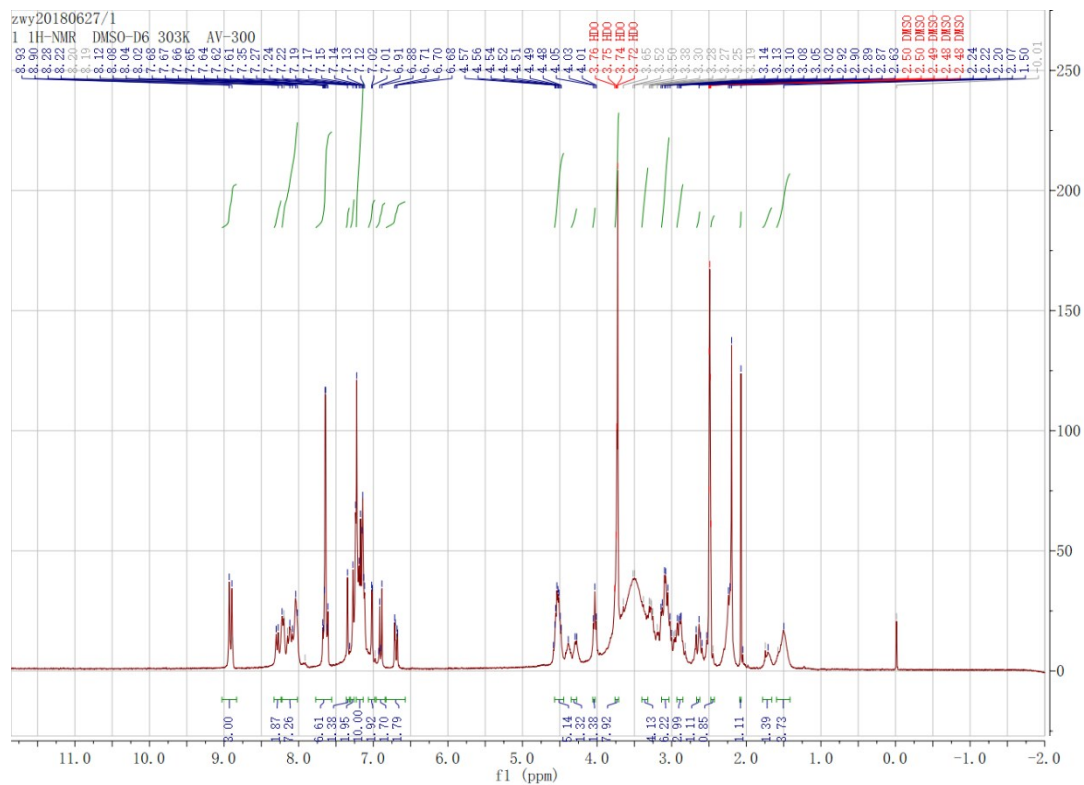


Figure S9. ^1H NMR spectrum of 1-RGDHH (300 MHz, DMSO).

^1H NMR (300 MHz, DMSO) δ 8.92 (d, J = 9 Hz, 3H), 8.29 (d, J = 6 Hz, 2H), 8.22-8.02 (m, 7H), 7.68-7.61 (m, 7H), 7.35 (s, 1H), 7.28 (s, 2H), 7.23-7.13 (m, 12H), 7.02 (d, J = 3Hz, 1H), 6.91 (dd, J = 6 Hz, J = 9 Hz, 2H), 6.69 (dd, J = 3 Hz, J = 3 Hz, 2H), 4.58-4.48 (m, 5H), 4.28 (m, 1H), 4.03 (t, J = 6 Hz, 2H), 3.76-3.72 (m, 8H), 3.14-3.02 (m, 4H), 2.48-2.42 (s, 1H), 2.07 (s, 1H), 1.80–1.67 (m, 1H), 1.52 (dd, J = 13.7, 8.5 Hz, 3H).

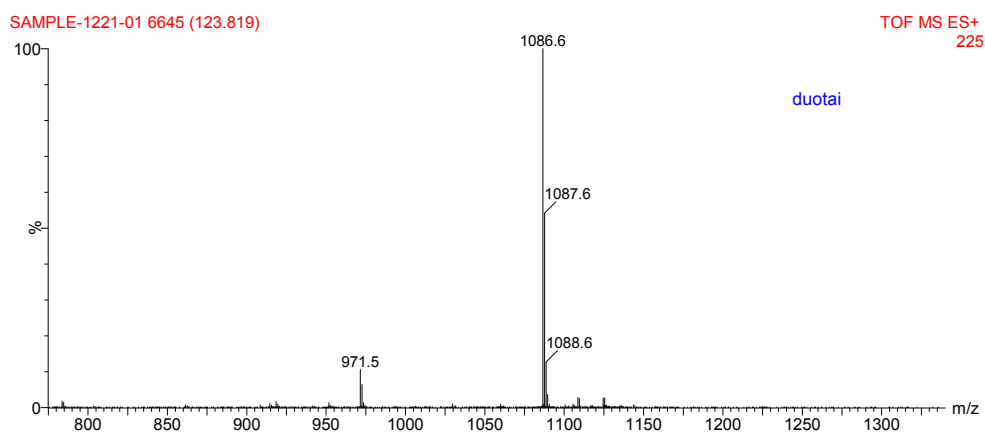


Figure S10. TOF-MS spectrum of 1-RGD. MS: calc.: $[M-H] = 1086$, obsvd.: $[M+H] = 1086.6$.

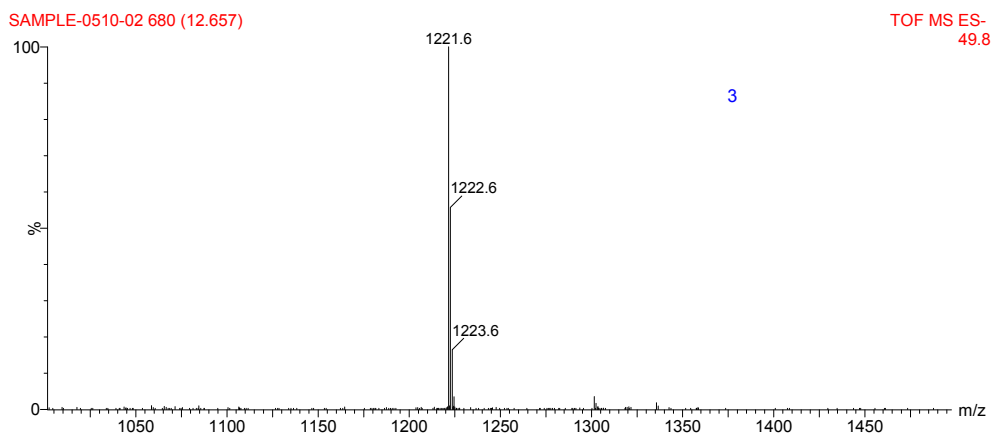


Figure S11. TOF-MS spectrum of 1-RGDH. MS: calc.: [M-H] = 1222, obsvd.: [M-H] = 1221.6.

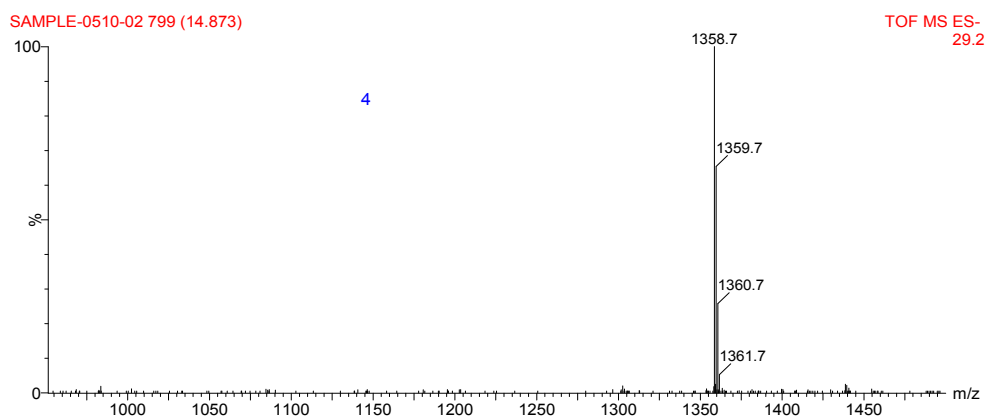


Figure S12. TOF-MS spectrum of 1-RGDHH. MS: calc.: [M-H] = 1359, obsvd.: [M-H] = 1358.7.

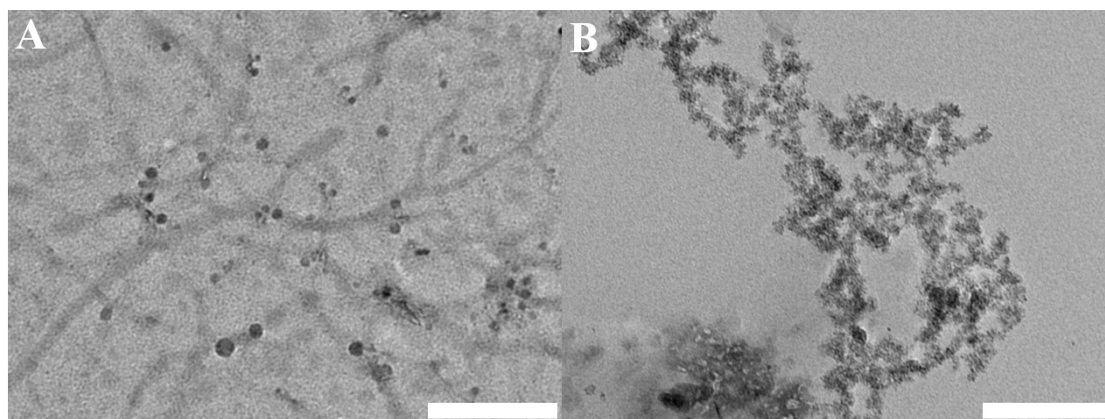


Figure S13. TEM images of 1-RGDH solution (1-RGDH, 0.1 wt.%; DOX, 0.1 equiv.) at pH 6.5 (A) and pH 5.5 (B). Bar, 200 nm.

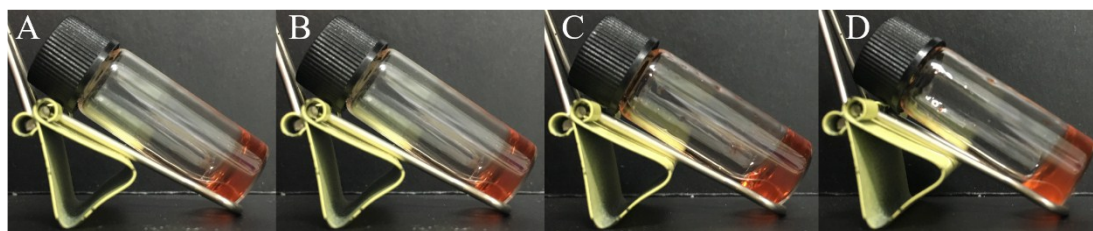


Figure S14. Optical images of the 1wt% 1-RGDH/DOX hydrogel before (A) and after addition of 0.4M imidazole (B), histidine (C) and EDTA (D).



Figure S15. Optical images of the 1wt% 1-RGDH/DOX with 0 (A), 0.5 (B), 1 (C), and 2 (D) mol/L of NaCl.

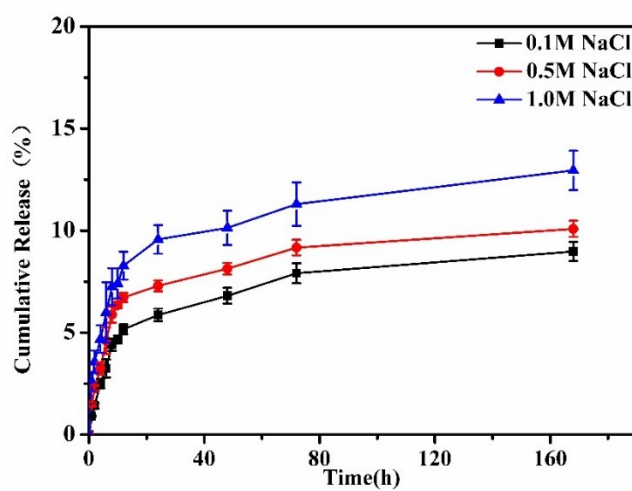


Figure S16. Cumulative release of doxorubicin from hydrogels at different concentration of NaCl (1-RGDH: 1 wt.%; DOX, 0.1 equiv.).

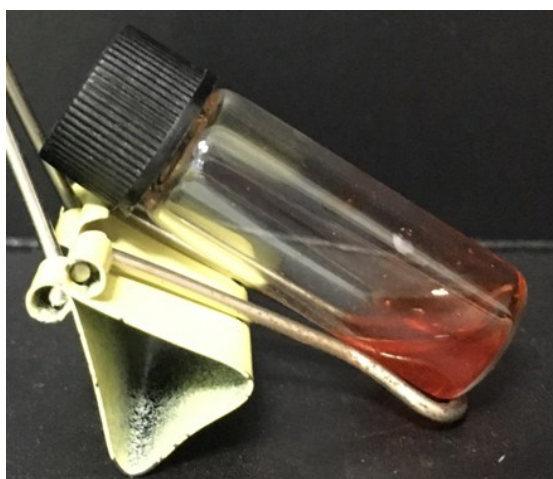


Figure S17. Optical images of the 1 wt.% RGD solution with 0.1. equiv. DOX.

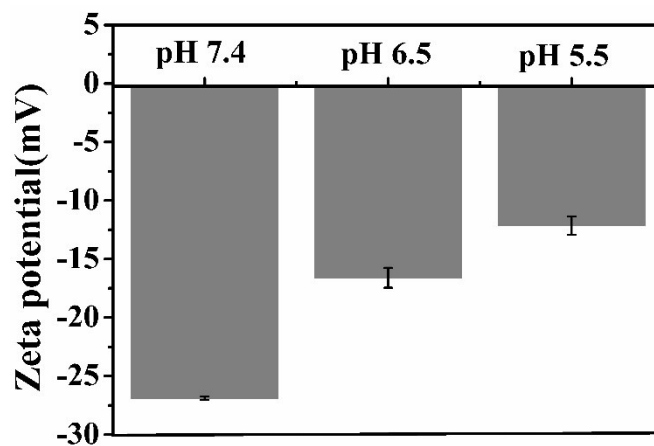


Figure S18. Zeta potentials of 1-RGDH solution (1-RGDH, 0.05 wt.%; DOX, 0.1 equiv.) at pH 7.4, 6.5 and 5.5.

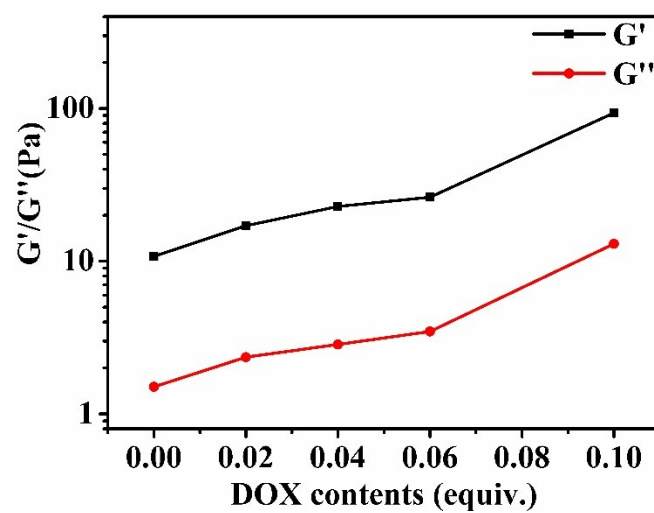


Figure S19. Storage moduli (G') and loss moduli (G'') of 1-RGDH hydrogel with varying ratio of DOX (1-RGDH: 1 wt.%; 0 - 0.1 equiv. DOX).

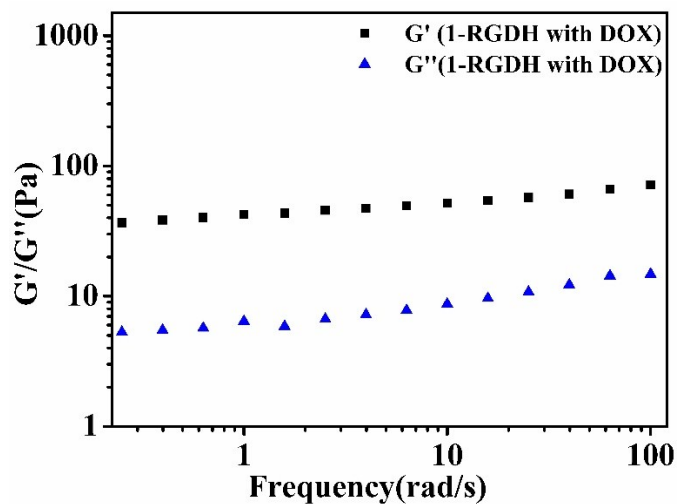


Figure S20. Dynamic frequency sweep of 1-RGDH/DOX hybrid hydrogels (1-RGDH: 1 wt.%; 0.1 equiv. DOX).

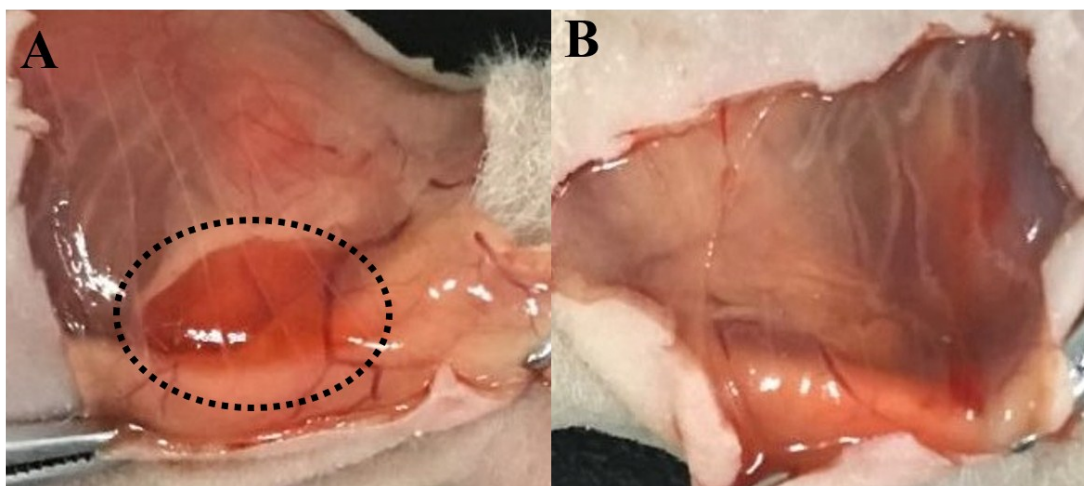


Figure S21. Subcutaneous injections of 1 wt.% 1-RGDH/DOX hydrogel (0.1 equiv. DOX) (A) and DOX solution (B).

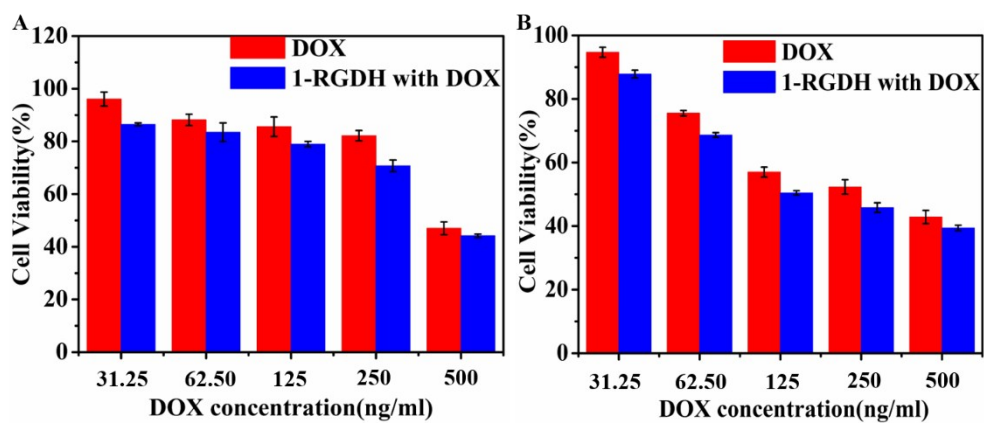


Figure S22. Cell viabilities of MCF-7 (A) and HeLa (B) after treatment of 1-RGDH/DOX or free DOX for 48 h.

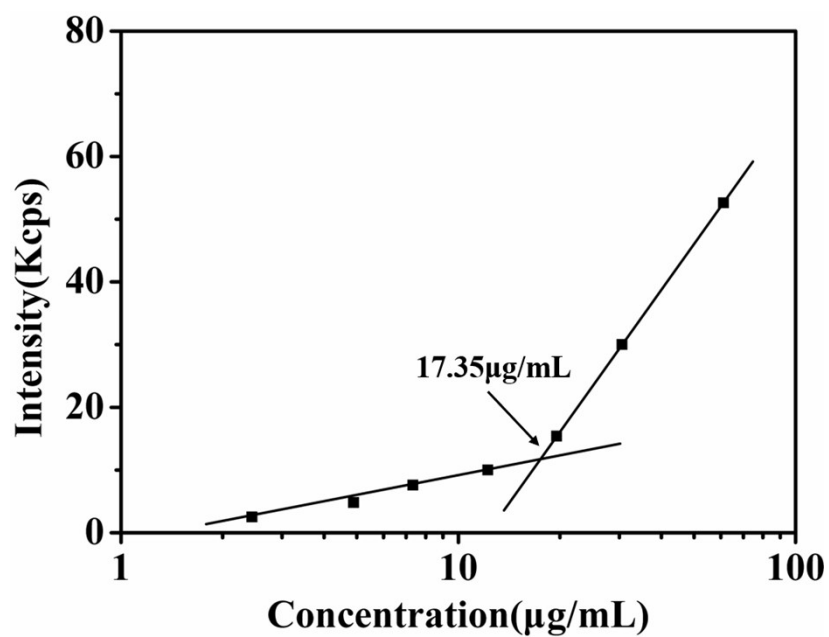


Figure S23. The calculation of CMC value of 1-RGDH/DOX hydrogel (1-RGDH: 1 wt.%; with 0.1 equiv. DOX).

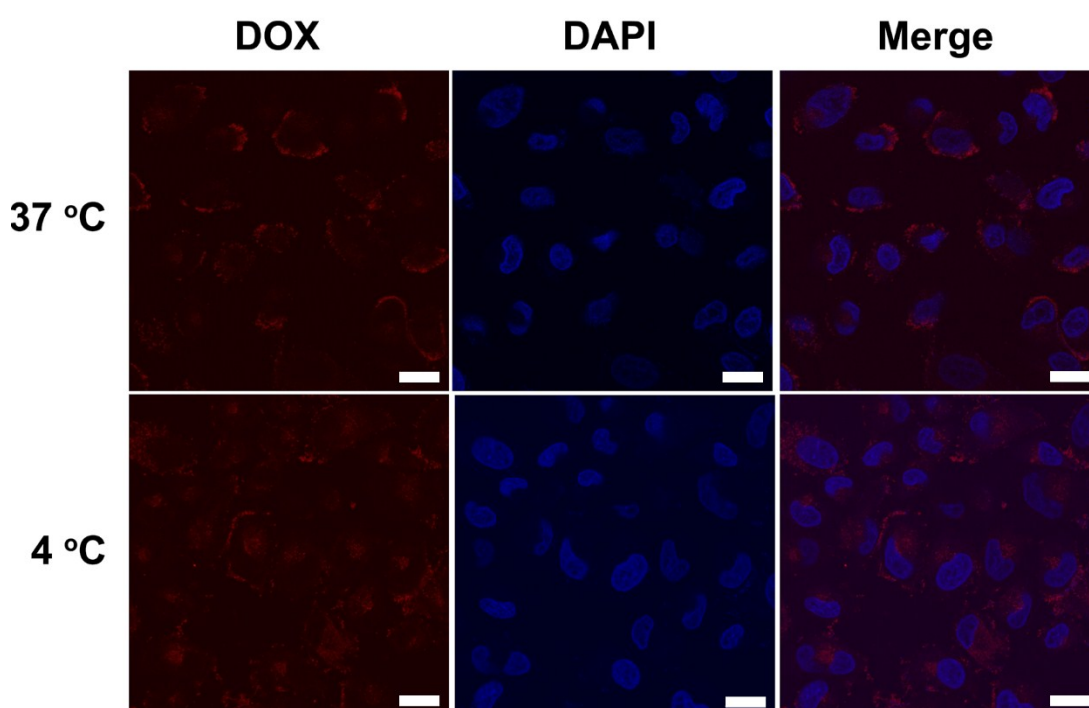


Figure S24. Confocal laser scanning microscopy (CLSM) images of A549 cells with incubation of aqueous solution of DOX at 37 °C or 4 °C. Red, DOX stain; blue, DAPI stain for cell nuclei. Bar, 20 µm.

Table S1. Table of parameters of Ritger-Peppas models for drug release behavior of 1-RGDH/DOX hydrogel at varying pH conditions (Stage I : 0-12h; Stage II : 24-168h).

	Stage	k	R ²	n
pH5.5	Stage I	0.0342	0.9905	0.8084
	Stage II	0.1374	0.9832	0.2265
pH6.5	Stage I	0.0185	0.9990	0.7946
	Stage II	0.0766	0.9926	0.2039
pH7.4	Stage I	0.0127	0.9846	0.7768
	Stage II	0.0471	0.9994	0.2189