Supporting Information

Polyacrylic acid@Zeolitic Imidazolate Frameworks-8 Nanoparticles with Ultrahigh Drug Loading Capability for pH-sensitive Drug Release

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EXPERIMENTAL SECTION

Materials. Poly (acrylic acid sodium salt) (PAAS) (M_w=5100) and doxorubicin hydrochloride (DOX) were purchased from Sigma (USA). Methanol was purchased from Beijing Chemical Works. 2-methylimidazole (HMeIM) was purchased from Chengdu Kelong Chemical Reagent Company. $Zn(NO_3)_2$ was purchased from Tianjin Fengchun Chemical Reagent Technologies Co., Ltd. Isopropyl alcohol (IPA) was

purchased from Sinopharm Chemical Reagent Beijing Co., Ltd and used without further purification. Deionized water (DI-water) was used in all experiments.

Characterization. FTIR spectra were obtained on a Magna 560 FTIR spectrometer (Nicolet, USA). TEM was performed on a JEOL-2100F transmission electron microscope under 200 kV accelerating voltage. FE-SEM images and EDS were obtained using an XL30 ESEM-FEG field-emission scanning electron microscope (FEI Co.). X-ray diffraction (XRD) patterns were obtained on a D8 Focus diffractometer (Bruker) with Cu Kα radiation. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was measured with Leeman ICP-AES Prodigy. UV/Vis absorption spectroscopy was obtained on U-3010 spectrophotometer (Hitachi, Japan). Confocal laser scanning microscopy (CLSM) was operated on Olympus Fluoview FV1000. Fluorescence spectra were performed with Eclipse fluorescence spectrophotometer (Varian, USA).

Synthesis of PAAS Nanospheres (NPs). Well-dispersed PAAS NPs were prepared at room temperature while the volume ratio of PAAS DI-water (PAAS concentration of 0.01g mL^{-1}) to IPA is mixed at 1:19. Firstly, 0.1 g PAAS was mixed with 10 mL of DI-water by stirring. Subsequently, 190 mL IPA was dropwise added into the mixture solution by continuously stirring. The obtained PAAS NPs were kept at room temperature for further experiments.

Synthesis of PAA-Zn NPs. To synthesize the PAA-Zn NPs, 378 μL methanol solution of $Zn(NO_3)_2$ (0.1 M) was mixed with 4 mL as-prepared PAAS NPs under

stirring for 5 min. Then, the obtained PAA-Zn NPs were centrifuged and rinsed with methanol repeatedly.

Synthesis of PAA@ZIF-8 NPs. HmeIM (16 mg) was mixed with methanol (10 mL) at 70 ^{o}C for 10 min. Subsequently, PAA-Zn NPs (2.4 mL) was injected into the above methanol solution of HMeIM under stirring. After 0.5 h, the precipitates were separated by centrifugation, washed with methanol several times.

In vitro DOX loading into PAA@ZIF-8 NPs. 100 μg of PAA@ZIF-8 NPs were dispersed in 1 mL of DOX solution with the DOX concentration of 200 μg mL^{-1}. The mixture was centrifuged to collect the DOX-loaded PAA@ZIF-8 NPs after shaken for 24 h at room temperature. To calculate the amount of DOX loaded into the PAA@ZIF-8 NPs, the contents of original DOX and the supernatant were determined by UV/Vis measurements at 480 nm. The DOX loading efficiency (LE) can be calculated by Equation (1) :

$$LE\ (\%) = [m(\text{original DOX}) - m(\text{DOX in supernatant})] / m(\text{original DOX}) \times 100\% \quad (1)$$

In vitro release of DOX from DOX-loaded PAA@ZIF-8 NPs. A certain amount of DOX-loaded PAA@ZIF-8 NPs were immersed in phosphate-buffered saline (PBS, 1 mL, pH = 5.5 and 7.4) at 37 ^{o}C. The PBS solution was taken by centrifuging and replaced with fresh PBS solution at selected time interval. The amount of released DOX from DOX-loaded PAA@ZIF-8 NPs was measured by fluorescence spectrophotometer with emission at 591 nm and excitation at 479 nm.

In vitro cytotoxicity assay. The cell toxicity was quantified by standard 3-(4,5-dimethylthialzol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using

MCF-7 cells. MCF-7 cells were incubated at 37 ^{o}C in DMEM media containing 10% fetal bovine serum (FBS) under an atmosphere of 5 % CO_2 for 24 h. Then, free DOX, DOX-loaded PAA@ZIF-8 NPs and PAA@ZIF-8 NPs were added into the cells, respectively. After the incubation times, 20 μg of 5 mg mL^{-1} MTT solution in PBS (pH = 7.4) was added to each well and further incubated for 4 h. The supernatant in each well was aspirated and 150 μL DMSO was added to each well to dissolve the MTT formazan crystals. Afterward, the absorbance determinate was measured at 490 nm in a microplate reader. Cell viability was calculated as a percentage of viable cells after treated with DOX or DOX-loaded NPs compared with the untreated cells.

Cellular uptake. For CLSM, the MCF-7 cells were seed onto clean cover slips in 6-well culture plates in DMEM medium containing 10 % FBS overnight incubation in 5 % CO_2 at 37 ^{o}C. DOX-loaded PAA@ZIF-8 NPs were added into the MCF-7 cells at 37 ^{o}C for different times. Thereafter, the medium was removed and the cell monolayer was washed three times with PBS (pH = 7.4), fixed with formaldehyde (1 mL in each well) for 10 min, and then rinsed with PBS three times again. Subsequently, the cells were treated with Hoechst 33342 to stain the nucleus for 15 min and the rinsed with PBS three times. Finally, the glass cover slips were placed on a glass microscope slide and the observations were performed by using CLSM.

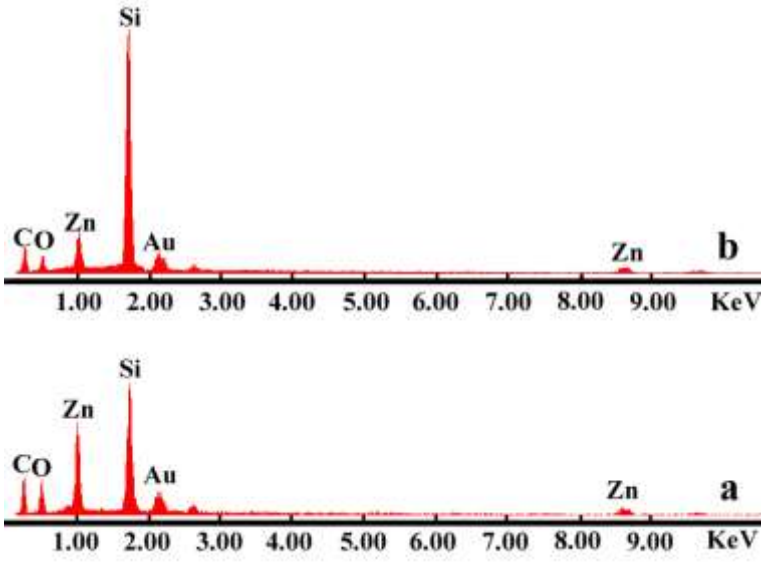

Fig. S1 EDS of (a) PAA-Zn NPs and (b) PAA@ZIF-8 NPs.

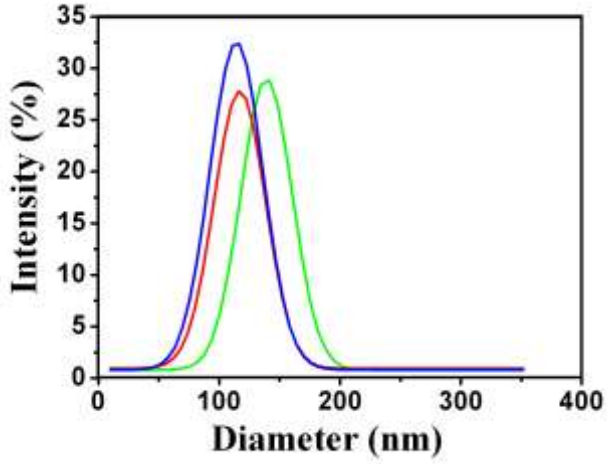

Fig. S2 The size distributions of (blue line) PAAS, (red line) PAA-Zn and (green line) PAA@ZIF-8 NPs with an average size of 111.7, 109.4 and 138.6 nm, respectively.

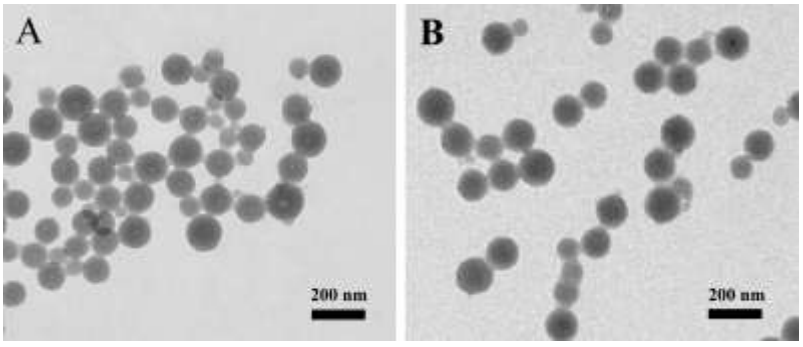

Fig. S3 TEM images of PAA@ZIF-8 NPs (A) in water and (B) in serum.

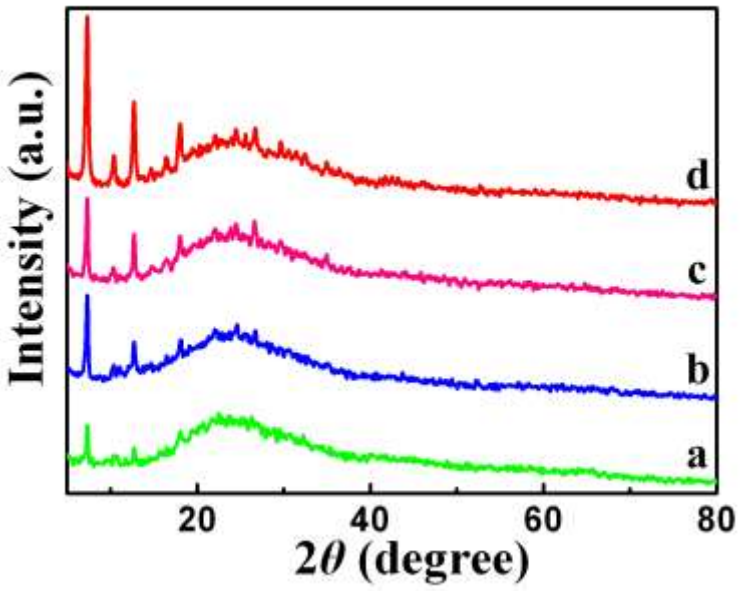

Fig. S4 XRD spectra of PAA@ZIF-8 NPs fabricated at 70 ^{o}C for (a) 0.5, (b) 12, (c) 24 and (d) 36 h, respectively.

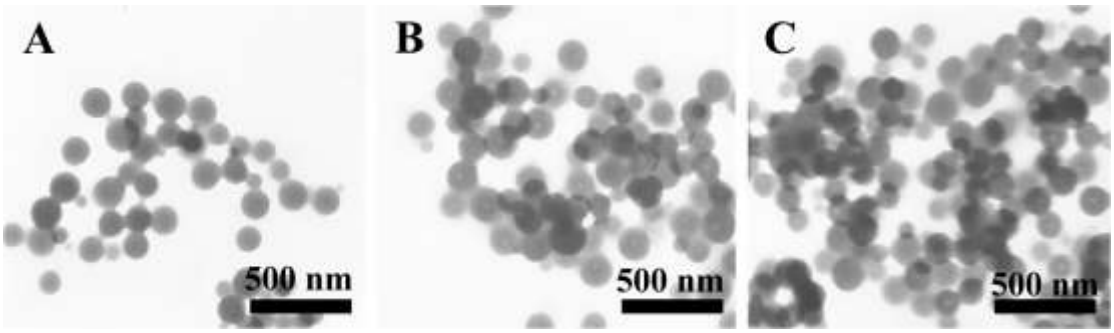

Fig. S5 TEM images of PAA@ZIF-8 NPs fabricated at 70 ^{o}C for (a) 12, (b) 24 and (c) 36 h, respectively.

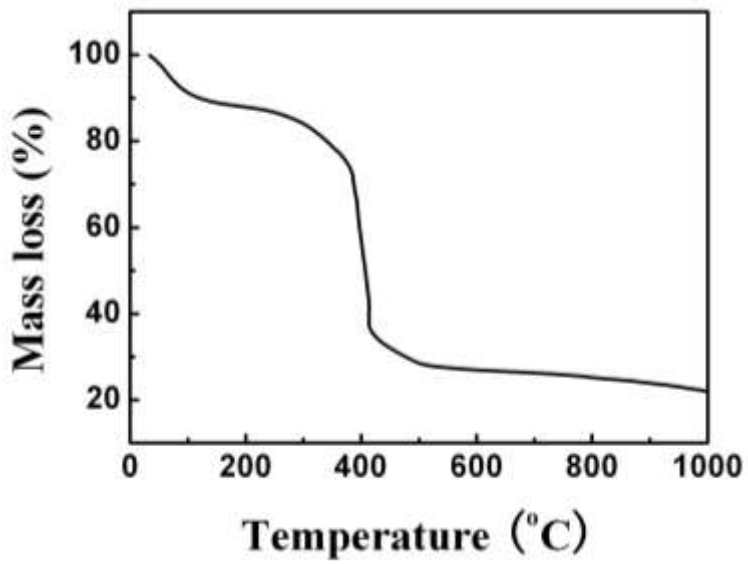

Fig. S6 TG curve of PAA@ZIF-8 NPs.