

Supporting Information

Extremely Low Frequency Alternating Magnetic Field Triggered and MRI Traced Drug Delivery by Optimized Magnetic Zeolitic Imidazolate Framework-90 Nanoparticles

Jie Fang, Yong Yang, Wen Xiao, Bingwen Zheng, Yun-Bo Lv, Xiao-Li Liu and Jun Ding*

EXPERIMENTALS

Synthesis of 12 nm Fe₃O₄-OA nanoparticles:¹

synthesis of iron-oleate complex

10.8 g of FeCl₃·6H₂O (40 mmol) and 36.5 g of sodium oleate (120 mmol) was dissolved in a mixture solvent composed of 80 ml ethanol, 60 ml distilled water and 140 ml hexane. The resulting solution was heated to 70 °C and kept at that temperature for four hours. When the reaction was completed, the upper organic layer containing the iron-oleate complex was washed three times with 30 ml distilled water in a separatory funnel. After washing, hexane was evaporated off, resulting in iron-oleate complex in a waxy solid form.

synthesis of iron oxide nanocrystals

36 g (40 mmol) of the iron-oleate complex and 5.7 g of oleic acid (20 mmol) were dissolved in 200 g of 1-octadecene at room temperature. The reaction mixture was heated to 320 °C with a constant heating rate of 3.3 °C min⁻¹, and then kept at that temperature for 30 min. When the reaction temperature reached 320 °C, a severe reaction occurred and the initial transparent solution became turbid and brownish black. The resulting solution containing the nanocrystals was then cooled to room temperature, and 500 ml of ethanol was added to the solution to precipitate the nanocrystals. The nanocrystals were separated by centrifugation.

Synthesis of 3 nm Gd₂O₃-OA nanoparticles:²

Gadolinium acetate (1.0 mmol, 334.0 mg) was mixed with oleic acid (18.0 mmol, 5.1 g) and oleylamine (60.0 mmol, 16.1 g). The mixture was heated at 120 °C in a three neck flask for 1

h under mild N₂ flow to remove water. Then a reflux condenser was mounted to the flask and the temperature was raised to 280 °C immediately and maintained for another 6 h. After cooling down, the mixture was treated with ethanol for the product to crash out. The product was collected with centrifugation and washed with toluene and ethanol three more times. The final product was suspended and stored in 20 ml toluene or chloroform.

Ligand exchange:²

PVP (Mw=55000, 0.02 mmol, 1.0 g), Gd₂O₃-OA or Fe₃O₄-OA (0.25 mmol, 5.0 ml) stock solution in toluene and 25.0 ml DMF/DCM (volume ratio of 1:1) were mixed and refluxed at 80°C for 12 h under mild N₂ flow. The reaction solution was cooled down and added to 130 ml ethyl ether dropwise under vigorous stirring. Precipitate appeared immediately and was collected by centrifugation. The product was washed with toluene and ethyl ether three more times. And the final product was dispersed and kept in DI water.

Synthesis of ZIF-90:

3.5 g 2-ICA and 4.0 g PVP were mixed with 120 ml DI water. The mixture was heated at 90 °C until 2-ICA totally dissolved. Then immediately 120 ml 5 mM Zn(NO₃)₂ in 2-propanol or *n*-butanol or *tert*-butanol or ethylene glycol was poured into the above solution. The mixture was then left still for 18h. The product was collected by centrifugation and washed twice with DI water.

Synthesis of m-ZIF-90 and Gd-ZIF-90:

3.5 g 2-ICA, 4.0 g PVP and 2 ml 5.4 mM Fe₃O₄-PVP or 5 ml 2.0 mM Gd₂O₃-PVP were mixed with 120 ml DI water. The mixture was heated at 90 °C until 2-ICA totally dissolved. Then immediately 120 ml 5 mM Zn(NO₃)₂ in ethylene glycol was poured into the above solution. The mixture was then left still for 18h. The product was collected by centrifugation and washed twice with DI water.

Post-synthesis modification:

5 mg ZIF-90 was suspended in 5ml Tetrahydrofuran (THF) under magnetic stirring followed by addition of 2 drops of 35% hydrazine. After 10 min, the precipitate was collected by centrifugation. The product was then washed twice with DI water, and then dispersed in 1ml 1xPBS.

2mg RSA was dissolved in 1ml 10 mM MES buffer solution. Then 6mg N-Hydroxysuccinimide (NHS) and 4mg 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was added, and the solution was kept on a shaker for 10min. Then the activated RSA solution was mixed with the above solution and left on the shaker overnight. The product was then collected by centrifugation and washed with 1xPBS twice.

Characterization:

SEM images were obtained on Hitachi S-4880 FESEM. The magnetic properties were characterized by using a vibrating sample magnetometer (VSM; LakeShore Model 7407). XRD patterns were collected by Bruker D8 advance. TEM images were obtained on JEOL FE-TEM 2010. FT-IR spectra were achieved on Agilent Cary 600 FTIR. UV-Vis absorption was measured on Shimadzu 1800 Spectrophotometer. Dynamic light scattering (DLS) and zeta potential measurements were carried out on Malvern Zetasizer Nano-ZS. Inductively coupled plasma (ICP) analysis was conducted with Dual-view Optima 5300 DV ICP-OES system.

For experimental determination of SAR, the magnetic nanoparticle dispersions were placed into a Cu coil. Temperature changes against the time of exposure to an AMF (amplitude, 27 kA m⁻¹; frequency, 488 kHz) were recorded with the software provided by the equipment (Ambrell, Easy Heat 4.2–10 kW) using an optical fiber connected to a multimeter. The SAR is obtained using the equation:

$$SAR = C \frac{\Delta T}{\Delta t} \frac{1}{m_{Fe}}$$

where C is the specific heat of the medium ($C_{\text{water}} = 4.18 \text{ J g}^{-1} \text{ }^{\circ}\text{C}^{-1}$), $\Delta T/\Delta t$ is the initial slope of the time-dependent temperature curve and m_{Fe} is the weight fraction of Fe in the medium.^{3,4}

MRI phantom study:

The samples for MRI phantom study were prepared with 5 concentrations of Fe or Gd in water. The control sample denoted as 0 mM. The longitudinal (T_1) and transverse (T_2) relaxation times of the samples were measured at 25 °C using a 63-mm volume RF coil on 7 T MRI system (Agilent Technologies, Santa Clara, CA). T_2 relaxation times were determined from a multi-echo spin-echo sequence of all bottles (6 echoes; TR: 1600 ms; TE: 9.1 ms-160 ms). T_1 was calculated using an inversion-recovery fast spin-echo sequence (TR= 5000ms, TE=7 ms; inversion-times (TIs) = 31, 150, 300, 700, 1200, 1800, 2400, 3000, 3600, 4000, 4500 and 4900 ms. The T_1 and T_2 relaxation time was computed using Vnmrj3.0 software (Agilent Technologies, Santa Clara, CA). Based on the T_1 and T_2 values, the specific relaxivities (r_1 and r_2), which are a measure of the induced change of the spin-lattice relaxation rate ($1/T_1$) and spin-spin relaxation rate ($1/T_2$), were calculated.

Extremely Low frequency alternating magnetic field setting-up:

The low frequency AC magnetic field was generated by a home set-up instrument comprised of an AC power source (NF EC750S) and a coil, with 100 V voltage, 10 A current and 20 Hz frequency. The measured AC magnetic field at the center of the coil is 200 Oe.

Drug loading and release study:

10 mg m-ZIF-90-RSA was soaked in 2 ml 5 mg/ml 5-Fu in methanol for 24 hours. Then the drug loaded m-ZIF-90-RSA was collected by centrifugation, and dried at room temperature. The drug loaded m-ZIF-90-RSA was then dispersed in 10 ml 1xPBS, and divided into two. Each one was loaded in a dialysis tube and sealed, and dialysis against 40 ml 1xPBS in a 50ml sealed plastic tube. One was treated with LF-AC MF for 20 min every one hour in the beginning 7 hours. The other one was kept still for comparison as control. 1ml dialysate was

withdrawn at intervals from both tubes for UV-Vis absorption spectrometer evaluation to determine the drug concentration, and 1ml fresh 1xPBS was recovered.

RESULTS

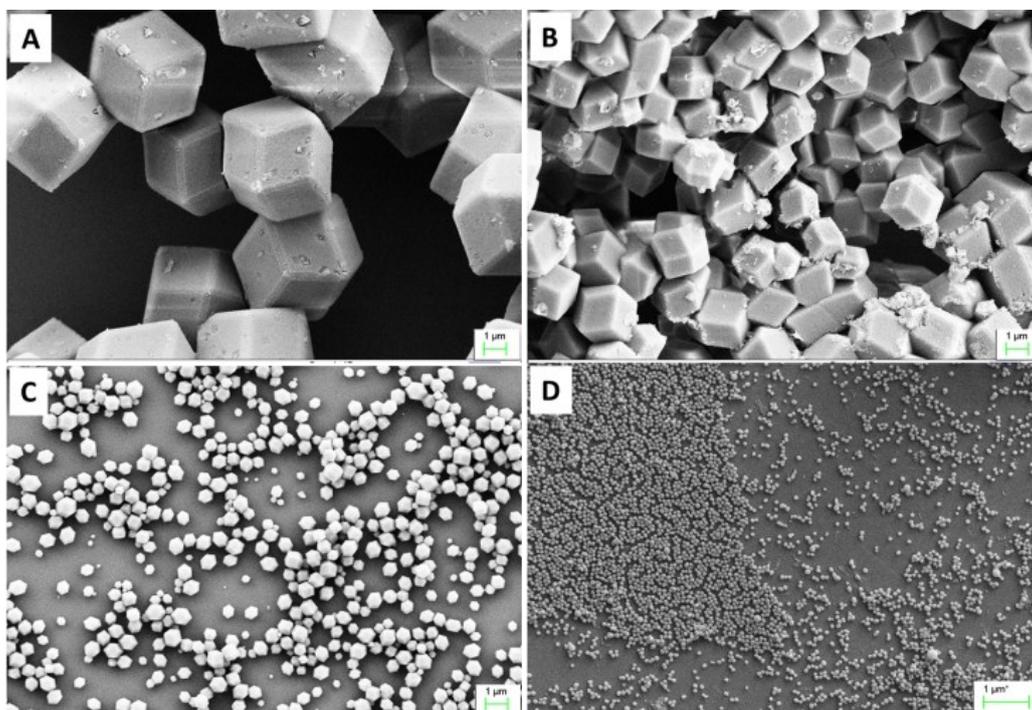


Figure S1. SEM images of ZIF-90 synthesized with (A)2-propanol, (B)*n*-butanol, (C)*tert*-butanol and (D)ethylene glycol as co-solvent.

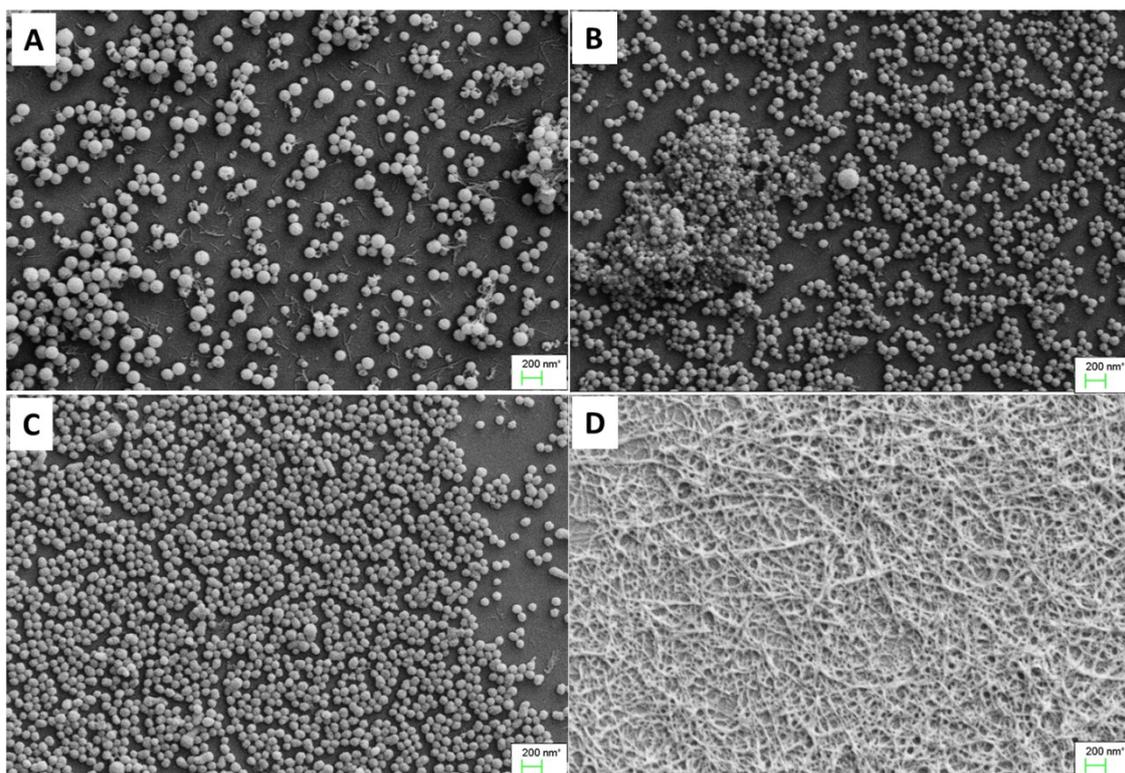


Figure S2. SEM images of ZIF-90 synthesized with (A) no PVP, (B) 0.8 g PVP, (C) 4 g PVP, (D) 1:1 of 2-ICA and Zn(NO₃)₂.

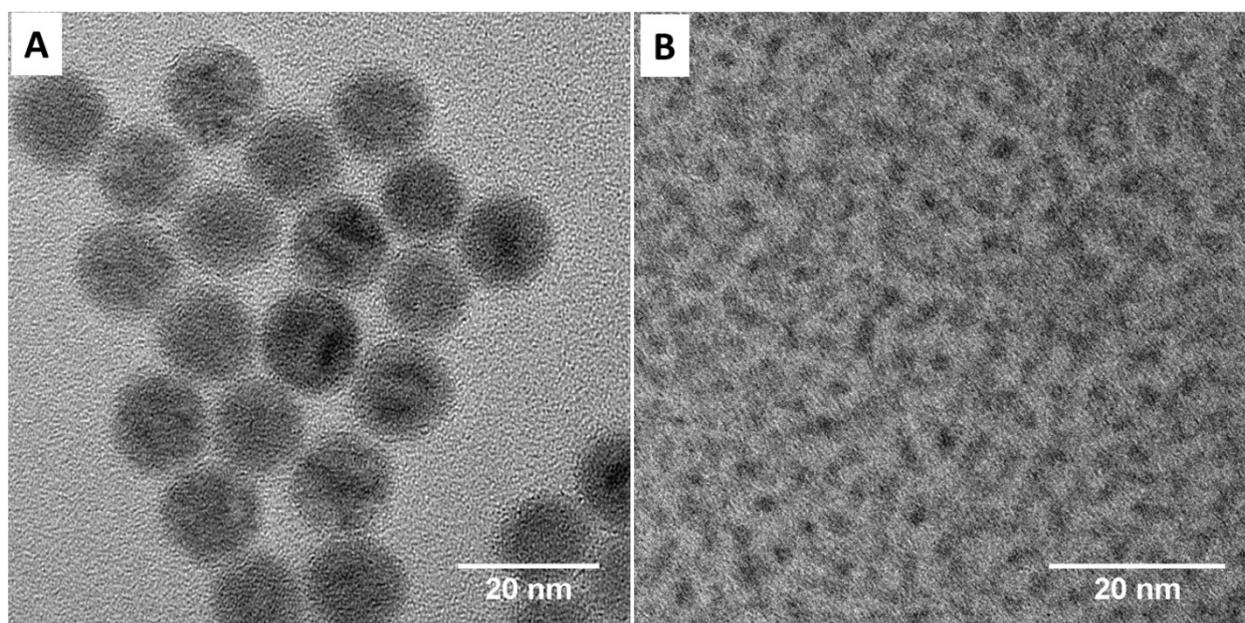


Figure S3. TEM images of 12 nm Fe₃O₄ and 3 nm Gd₂O₃ nanoparticles.

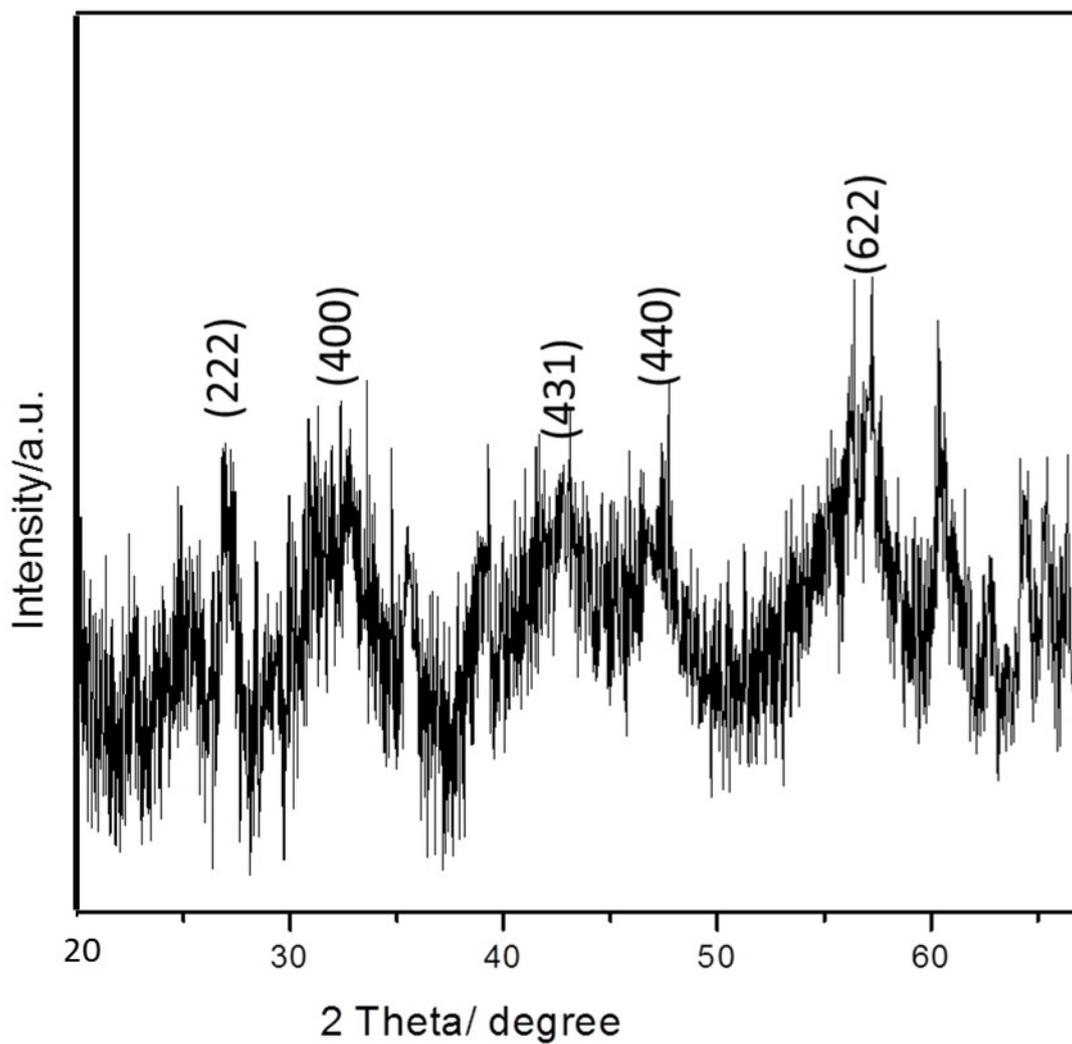


Figure S4. XRD pattern of Gd_2O_3 nanoparticles.

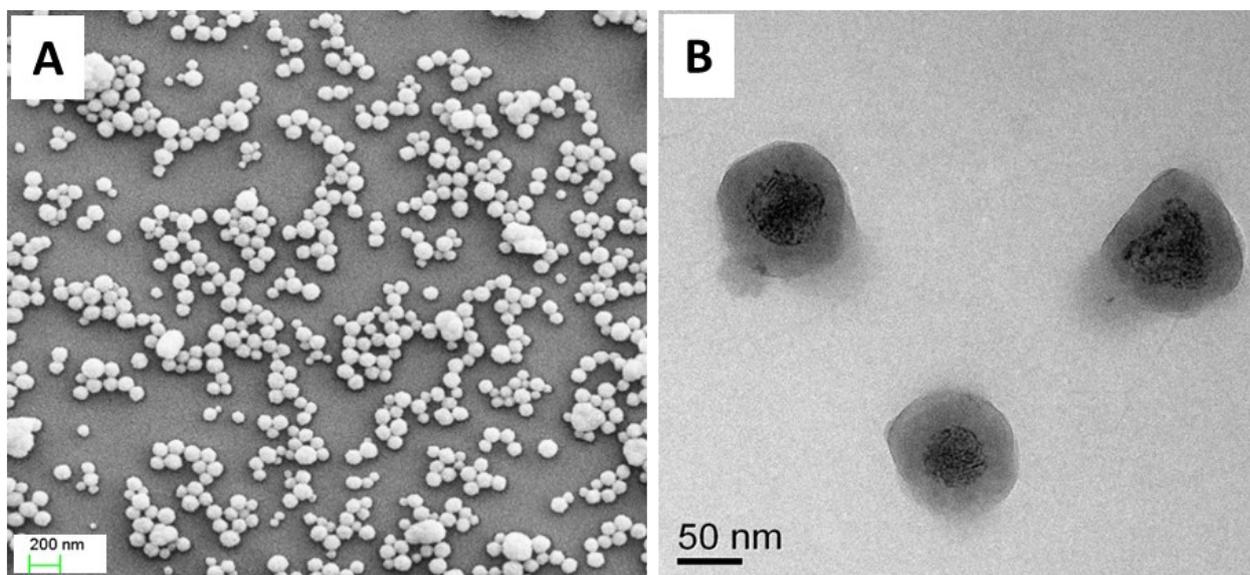


Figure S5. SEM and TEM images of Gd-ZIF-90.

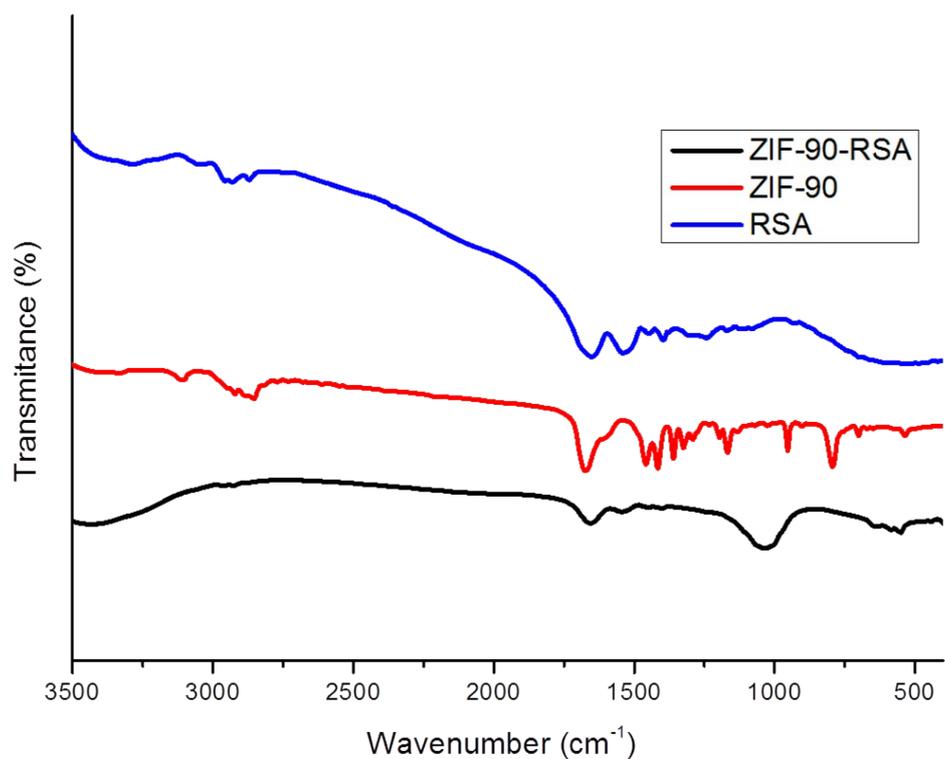


Figure S6. FT-IR spectra of RSA, ZIF-90 and ZIF-90-RSA.

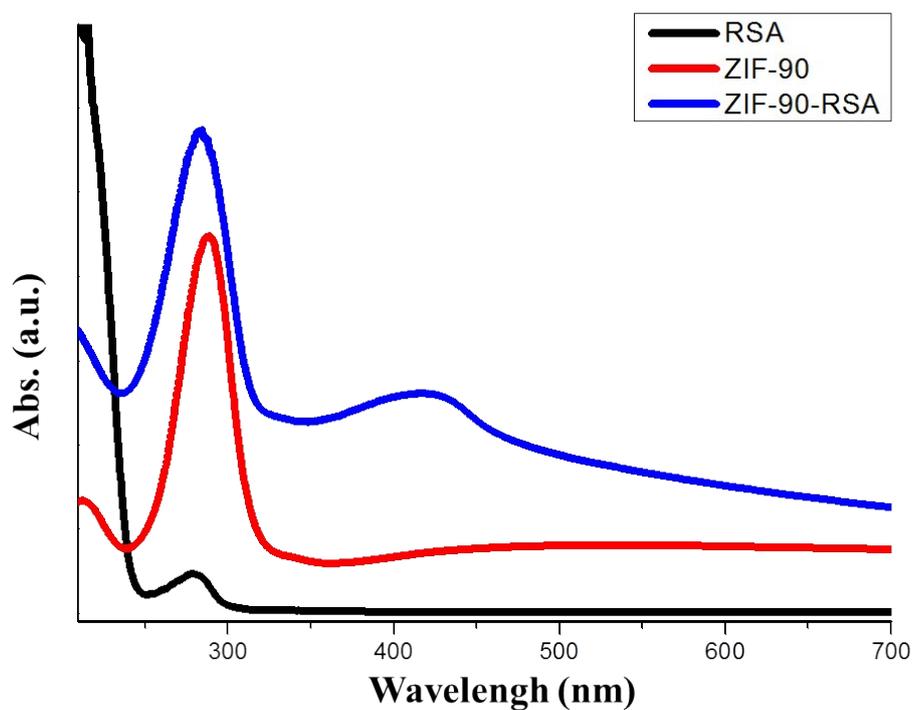


Figure S7. UV-Vis absorption spectra of RSA, ZIF-90 and ZIF-90-RSA.

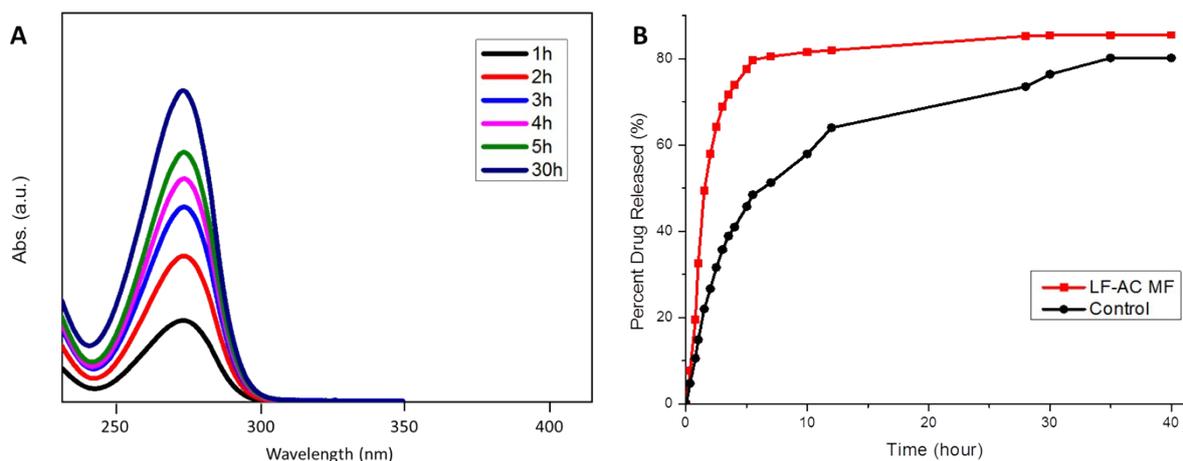


Figure S8. A, UV-Vis absorption spectra of dialysate withdrawn from ELF-AMF treated sample at different time. B, 5-Fu release profile with and without ELF-AMF.

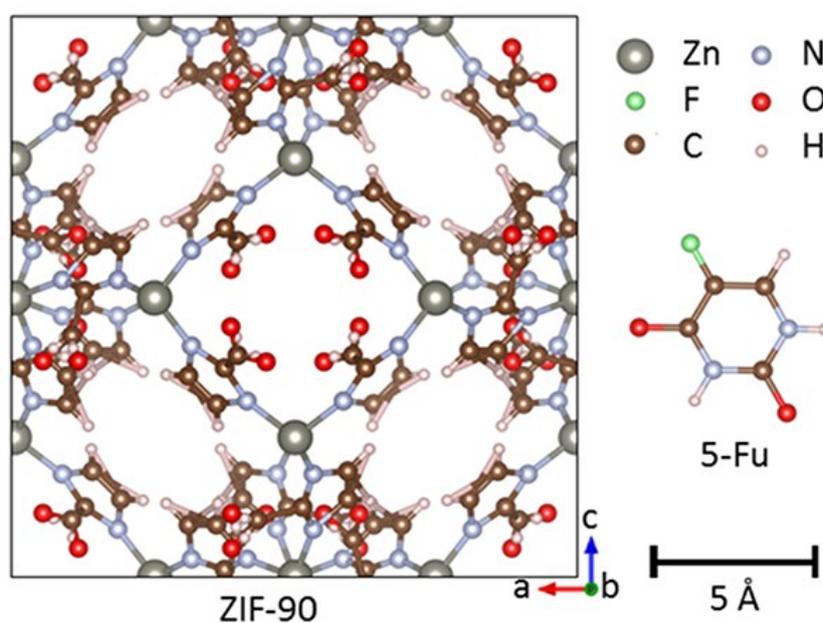


Figure S9. Molecular models of ZIF-90 and 5-Fu.

REFERENCES

- 1 J. Park, K. An, Y. Hwang, J.-G. Park, H.-J. Noh, J.-Y. Kim, J.-H. Park, N.-M. Hwang, T. Hyeon, *Nat. Mater.* 2004, **3**, 891.
- 2 J. Fang, P. Chandrasekharan, X.-L. Liu, Y. Yang, Y.-B. Lv, C.-T. Yang, J. Ding, *Biomater.* 2014, **35**, 1636.
- 3 X. L. Liu, H. M. Fan, J. B. Yi, Y. Yang, E. S. G. Choo, J. M. Xue, D. D. Fan, J. Ding, *J. Mater. Chem.* 2012, **22**, 8235.

4 B. A. Bornstein, P. S. Zouranjian, J. L. Hansen, S. M. Fraser, L. A. Gelwan, B. A. Teicher, G. K. Svensson, *Int. J. Radiat. Oncol. Biol. Phys.* 1993, **25**, 79.