The Dual-Stimulated Release of Size-Selected Cargos from Cyclodextrin-Covered Mesoporous Silica Nanoparticles

Lei Tan, Hai-Xia Wu, Mei-Yan Yang, Chuan-Jun Liu, Si-Xue Cheng, Ren-Xi Zhuo,*

1. Key Laboratory of Biomedical Polymers of Ministry of Education, College of Chemistry and Molecular Science, Wuhan University, Wuhan, 430072, P. R. China.

2. College of Chemistry and Chemical Engineering, Luoyang Normal University, Luoyang, 471022, P. R. China

Email:cjliu@whu.edu.cn

1. Chemicals and Materials. 5-hydroxy-2-nitrobenzyl alcohol (97 %, Aldrich), propargyl bromide (99 %, Aldrich), N, N'-diisopropylcarbodiimide (DIC) (99 %, Aladdin chemistry Co. Ltd), 4-(dimethylamino)pyridine (DMAP) (99 %, Aladdin chemistry Co. Ltd), ferrocenecarboxylic acid (FcA) (98 %, Aladdin chemistry Co. Ltd), methoxy poly(ethylene glycol) (PEG, Mn, GPC =550) (99 %, Alfa Aesar) were used as received. β-cyclodextrin (β-CD) sodium azide (99 %, NaN_3) and triphenylphosphine (PPh_3) were obtained from Sinopharm Chemical Reagent Co. Ltd. β-CD was dried at 100 ℃ for 24 h in vacuum oven before use. All solvents were treated with calcium hydride and distilled before use.

2. Characterizations.

^{1}H NMR spectra were determined with Mercury VX-300 spec-trometer at 300 MHz. Scanning electron microscopy (SEM, QUANTA 200, Holland) was operated at 30 kV. The surface area and pore size distributions were obtained by Brunauer–Emmett–Teller (BET) and Barrett–Joyner–Halenda (BJH) analysis (Micromeritics ASAP 2020).

3. Synthesis

3.1. Synthesis of per-6-azido-*β*-cyclodextrin.[1]

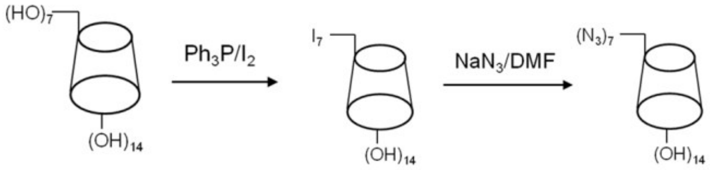

Figure S1 Synthesis route of per-6-Aazido-β-cyclodextrin

Per-6-Iodo-*β*-Cyclodextrin (per-I-β-CD) was prepared as follows: Ph_3P (18.4 g, 70 mmol) was dissolved in 100 mL anhydrous DMF, and then I_2 (17.8 g, 70 mmol) was added into the solution under stirring in 50 ℃ over 15 min. Subsequently, the dried β-CD (5.7 g, 5 mmol) was added into the reaction mixture, the temperature was raised to 70 ℃. The reaction was carried out in an argon atmosphere for 24 h. After that, a large proportion of solvent was removed under reduced pressure to about 35 mL. The sticky dark brown solution was stirring in ice water. Next, the pH of reaction was adjusted to 10 by the addition of NaOMe solution (30 mL, 3 mol / L). The color of solution changed from dark brown to light yellow. The solution was precipitated in 600 mL methanol, after filtering and drying in vacuum, the yellow powder was re-dissolved in DMF and precipitated in large amount of methanol again. The precipitate re-dissolved procedure was repeated for 4 times until the powder become white.

The per-6-azido-*β*-cyclodextrin was prepared as follows: To the solution of Per-6-Iodo-*β*-Cyclodextrin (216 mg) in DMF (5 mL), sodium azide (NaN_3) (74 mg, 1.1 mmol) was added subsequently. The reaction solution was stirred at 70 ℃ under argon atmosphere for 24 h. The solution was then condensed to 1 mL under reduced pressure. And then, the residue solution was precipitated in 600 mL DI water and filtered off. The yellow powder was washed with water for three times and dried in vacuum at 60 ℃ to yield a white product.

^{1}H-NMR (300 MHz, D_2O) in DMSO-d6, δ_H(ppm): 3.3–3.74 (m, 42H, H-2, H -3, H-4, H-5, H-6), 4.86 (d, 7H, H-1), 5.73 (d, 7H, OH), 5.88 (d, 7H, OH). (Figure S2). FT-IR (KBr): 1051, 1152, 1288, 1384, 1643, 2106 (N_3), 2926, 3434. (Figure S3).

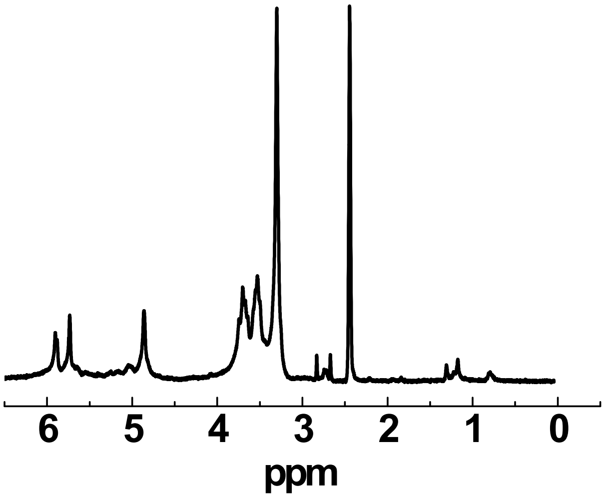

Figure S2 ^{1}H NMR spectrum of per-6-azido-β-cyclodextrin in DMSO-d6.

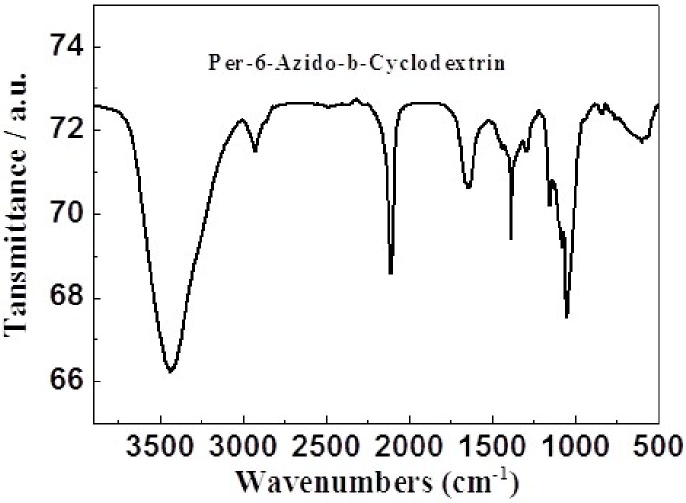

Figure S3 FT-IR spectrum of per-6-azido-β-cyclodextrin.

3.2 Synthesis of 5-propargylether-2-nitrobenzyl alcohol.[2]

5-hydroxy-2-nitrobenzyl alcohol (428 mg, 2.52 mmol) and 900 mg dry K_2CO_3 was dissolved in 7 mL anhydrous DMF and stirred in 60 ℃ for 1 h. And then, propargyl bromide (0.35 mL, 4.4 mmol) was then added into the reaction drop by drop and stirred under argon for 24 h. Thereafter, the DMF was removed by rotary evaporator.

The mixture was partly dissolved in ethyl acetate and extracted by the addition of water. The obtained light yellow product was recrystallizated from ethyl acetate into n-hexane. ^{1}H NMR (300MHz, DMSO-d6), δ_H(ppm): 3.68 (s, 1H, CH≡C-), 4.86 (s, 2H, HO-CH_2-Ph), 4.97 (s, 2H, -O-CH_2-C≡CH), 7.10 (d, 1H, -Ph-), 7.40 (s, 1H, -Ph-), 8.14 (d, 2H, -Ph-). (Figure S4). FT-IR (KBr, cm^{-1}):3436, 3266, 2922, 2125 (C≡C), 1608, 1509, 1243, 1078. (Figure S5).

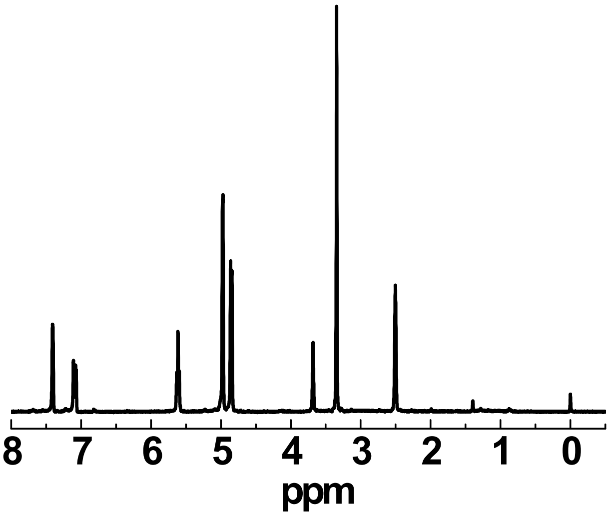

Figure S4 ^{1}H NMR spectrum of 5-propargylether-2-nitrobenzyl alcohol in DMSO-d6.

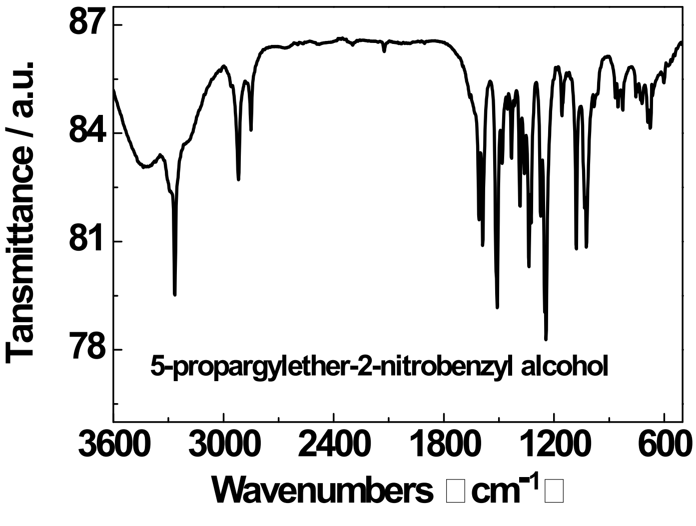

Figure S5 FT-IR spectrum of 5-propargylether-2-nitrobenzyl alcohol.

3.3 Synthesis of poly (ethylene glycol)-ferrocenecarboxylate (PEG-FcA).[3]

It was prepared as follows: PEG (1.1 g, 2 mmol, Mn = 550 kg/mol), FcA (0.506 g, 2.2 mmol), and DMAP (24 mg, 0.2 mmol) were stirred in 20 mL of anhydrous dichloromethane for 30min at 0 ℃. Subsequently, DCC (0.442 g, 2.2 mmol) was added to the solution. The reaction was reacted at room temperature for 48 h under argon atmosphere. Thereafter, we filtered solution and removed the solvent by evaporation. The solid was dissolved in dichloromethane, and the solution was extracted with NaOH aqueous solution (pH = 10, 10 mL) to remove unreacted FcA. The solution was further precipitation into diethyl ether. The final black product was dried in vacuum. ^{1}H NMR (300MHz, $CDCl_3$), δ_H(ppm): 4.81 (s, 2H, =*CH*C (COOH)*CH*=), 4.39 (s, 2H, -*CH*=*CH*-), 4.16 (s, 5H, another cyclopentyl), 3.64 (m, 84H, -OCH_2CH_2O-), 3.37 (s, 3H, terminal CH_3O-). (Figure S6). FT-IR (KBr, cm^{-1}): 2927 , 2853, 1710 (νC=O), 1628 (νC=C in ferrocene). (Figure S7).

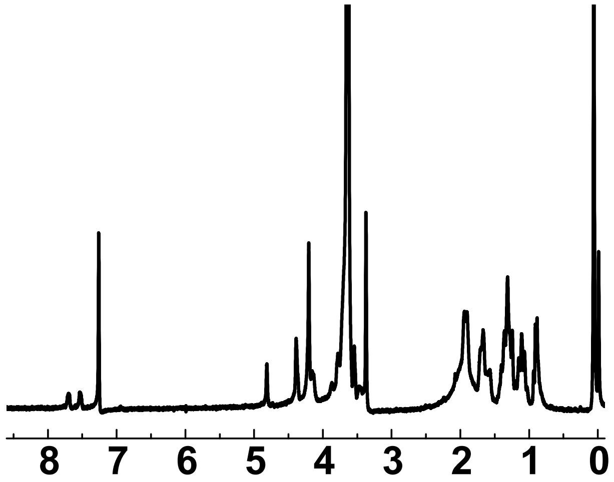

Figure S6 ^{1}H NMR spectrum of PEG-FcA in DMSO-d6

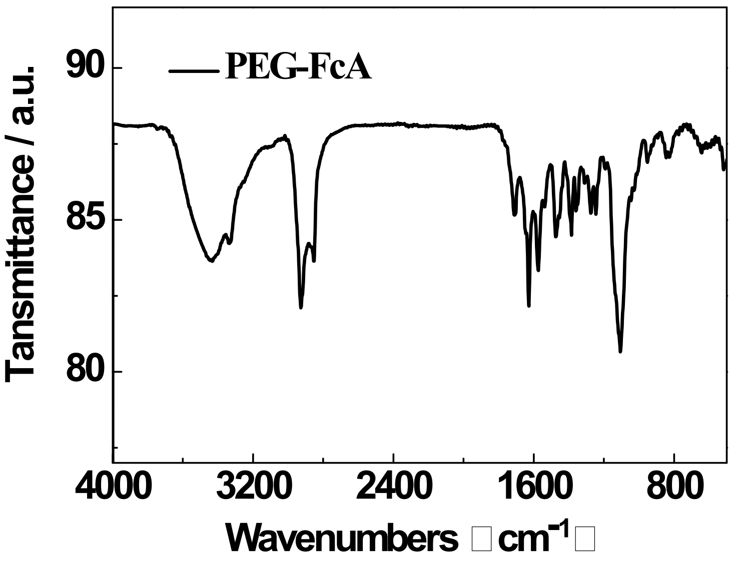

Figure S7 FT-IR spectrum of PEG-FcA.

3.4 The uniform feature of the MSN was confirmed by SEM.

The feature of MSN was proved to be uniform spherical, and the particle size was about 100 nm, which is correspond with the result of TEM.

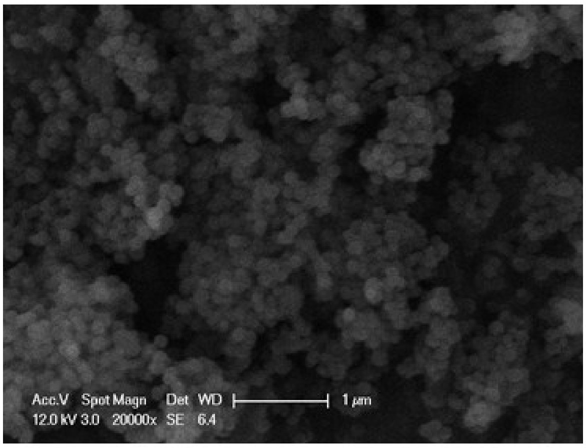

Figure S8 SEM image of MSN.

3.5 **Size distributions of MSNs and MSN-2 obtained by DLS instrument.**

The average sizes of MSNs and MSN-2 were measured as 189, 162 nm respectively, which indicated the particles were dispersible in water.

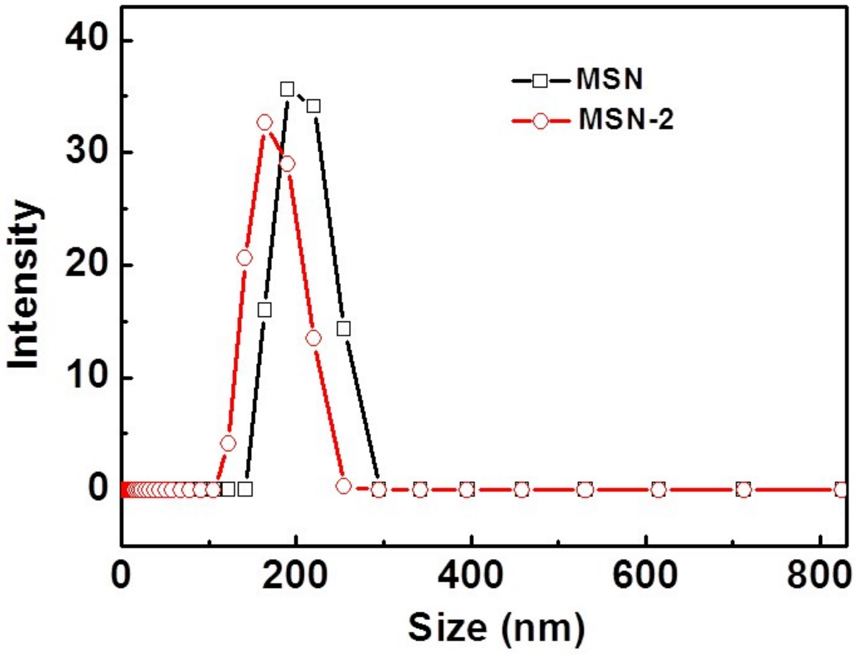

Figure S9 Size distributions of different MSNs.

3.6 The surface area, pore volume and pore size distributions of different samples were collected by nitrogen adsorption–desorption isotherms.

A high surface area of 898.14 m^2 g^{-1}, pore volume of 0.95cm^3 g^{-1}, and a mesopore diameter of 2.5 nm for MSN were measured by Brunauer-Emmett-Teller (BET) analysis and Barret-Joyner-Halenda (BJH) analysis. After the modifications, the surface area and pore volume were reduced, and the pore diameter cannot be obtained because of the blocking of nanopore.

Table S1. BET and BJH parameters of different nanoparticles

Samples	BET surface area S_{BET} (m^2/g)	BET pore volume V_p (cm^3/g)	BJH pore diameter V_{BJH} (nm)
MSN	993.23	1.29	2.5

MSN-1	173.64	0.41	/
MSN-2	26.55	0.07	/

References

S1. J. J. Deng, N. Li, K. J. Mai, C. A. Yang, L. Yan and L. M. Zhang, *J. Mater. Chem.*, **21**, 5273-5281.

S2. C. Park, K. Lee and C. Kim, *Angew. Chem. Inter. Ed.*, 2009, **48**, 1275-1278.

S3. Q. Yan, J. Y. Yuan, Z. N. Cai, Y. Xin, Y. Kang and Y. W. Yin, *J. Am. Chem. Soc.*, 2010, **132**, 9268-9270.