Electronic Supplementary Material (ESI) for Journal of Materials Chemistry B

Coumarin-containing photo-responsive nanocomposites for NIR light-triggered controlled drug release *via* a two-photon process

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Supplementary Information

Materials

Octadecyltrimethoxysilane, Methacryloyl chloride (C18), 2-(acryloyloxy)ethyl) trimethylammonium chloride (AETAC, 80 wt% in water), 2,2'-azobis(2-methylpropionamidine)dihybromide (V-50), hexadecyltrimethylammonium bromide (CTAB), and tetraethoxysilane (TEOS) were purchased from Aldrich. Methoxycarbonyl chloride and acetoacetic ester were purchased from TCI. Benzyl chloride, sodium methoxide, potassium ferricyanide were all purchased from Shanghai Chemical Reagent Co. Ltd. as analytical reagents and used without further purification. Other reagents were commercially available and used as received.

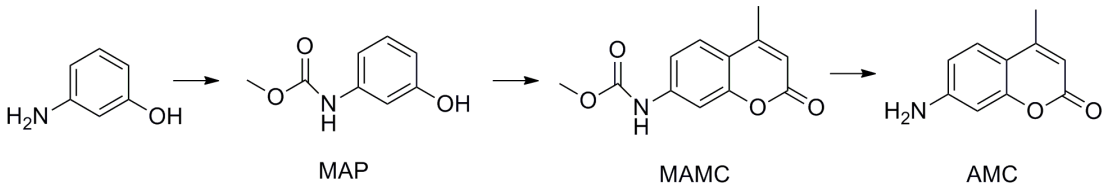
Synthesis of hollow mesoporous spherical particles (HMS)

To prepare the polystyrene latex templates, 1.0 g of AETAC (80 wt% in H_2O) was dissolved in 390.0 g water. 40.0 g styrene was added slowly to the solution and kept stirring at 800 rpm by mechanical raking for 30 min. The mixture was purged with nitrogen for 20 min and then heated to 90 ^{o}C. Afterwards, 10 mL of an aqueous solution containing 1.0 g V-50 was added and the emulsion was kept at 90 ^{o}C for 24 h under nitrogen. The polystyrene latex was obtained by centrifugation at 18000 rpm for 15 min, and washed with ethanol several times. To obtain the HMS, 0.8 g of CTAB was dissolved in a mixture of 29.0 g of water, 12.0 g of ethanol and 1.0 ml of aqueous ammonia solution. 930 mg of PS powders was dispersed in 10.0 g water by ultrasonication and then added dropwise to the above CTAB solution at room temperature under vigorous stirring, followed by ultrasonication for 10 min. The derived milky mixture was then magnetically stirred for 30 min before adding dropwise 4.0 g of TEOS. The resulting mixture was kept stirring at room temperature for 48 h before the mesoporous silica coated latex was harvested by centrifugation at 7000 rpm for 40 min. The precipitate was washed with copious amounts of ethanol and then dried at room temperature. Finally the material was calcined in air at 600 ^{o}C for 8 h using a heating rate at 3 ^{o}C min^{-1} to remove any organic matter.

Modification of the external surface of HMS with octadecyltrimethoxysilane (C18) (HMS@C18)

100 mg HMS was dispersed in 20 mL acetonitrile, following by adding 5 mL C18, and the obtained suspension was stirred for 24 h and collected by centrifugation, washed with acetonitrile and ethanol for several times, and dried under vacuum. The obtained white solid was denoted as HMS@C18.

Synthesis of 7-amino-4-methylcoumarin (AMC)



Scheme S1 Synthetic route of AMC

m-(N-Methoxycarbonylamino) phenol (MAP): A sample of methoxycarbonyl chloride (18mL, 234 mmol) was added dropwise in the course of 0.5 h with stirring and cooling to a suspension of m-aminophenol (22 g, 202 mmol) and $KHCO_3$ (25 g, 250 mmol) in 150 mL of ethyl acetate and 10 mL water. After which the mixture was stirred for 1 h, water (50 mL) was then added, and the mixture was stirred for another 3 h. The aqueous layer was separated, and the organic layer washed successively with water, 1 M H_2SO_4, water, and saturated NaCl solution, dried with $MgSO_4$, and evaporated. The crystalline residue was recrystallized from benzene to give 31.5 g (188 mmol, 94% yield) MAP.

7-Methoxycarbonylamino-4-methylcoumarin (MAMC) : A mixture of MAP (23 g, 137mmol) and 25 mL of acetoacetic ester was added in portions with stirring to 60 mL of concentrated H_2SO_4, after which the mixture was stirred for 2 h and diluted with a mixture of water and ice (300 mL). The diluted mixture was stirred until crystallization ceased, and the precipitate was removed by filtration, washed with water, methanol, and ether and dried to give 23.0 g (98.7 mmol, 87.5% yield) MAMC.

7-amino-4-methylcoumarin (AMC): A suspension of MAMC (28 g, 120 mmol) in 60 mL of 45 % KOH solution was stirred at 80 – 90 ^{o}C until a solution formed (15–20 min). The reaction mixture was cooled and diluted with water to 200 mL, and the solution was acidified cautiously with concentrated HCl to pH 5 – 6 with stirring and cooling. A solution of alkali was added to the resulting suspension to pH 8, and the mixture was stirred until crystallization ceased. The precipitate was removed by filtration, washed with water, methanol, and ether, and dried to give 17.4 g (99.4 mmol, 83% yield) AMC. ^{1}H NMR (DMSO, 400 MHz): δ7.42 (d, J=8.0 Hz, 1H, Ar-H), 6.58 (d, J=8.0 Hz, 1H, Ar-H), 6.42 (s, 1H, Ar-H), 6.11 (s, 2H, NH_2), 5.92 (s, 1H, Ar-H), 2.32 (s, 3H, CH_3).

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Synthesis of RAFT agent 4-cyanopentanoic acid dithiobenzoate (CAD)

CAD was synthesized according to the literature with some modifications. Briefly, 12.8 g of benzyl chloride was added dropwise to a sodium methoxide methanol solution (172 g, 12.6 wt%) containing 12.8 g of elemental sulfur. Subsequently, the obtained mixture was refluxed for 10 h under inert atmosphere. The crude sodium dithiobenzoate solution was extracted by diethyl ether, 1.0 M hydrochloric acid and sodium hydroxide aqueous solution, respectively and finally yielded a solution of sodium dithiobenzoate. Potassium ferricyanide solution (500 mL, 6.5 wt%) was added dropwise to the sodium dithiobenzoate over a period of 1 h with vigorous stirring. The obtained red precipitate was filtered, washed with deionized water, and dried in vacuum at room temperature overnight. Dithiobenzoyl disulfide (8.50 g, 0.28 mol) was added slowly to the distilled ethyl acetate (150.0 mL) solution containing 11.68 g of V-501 (0.42 mol). After refluxing for 18 h, the reaction solution was concentrated in vacuum and isolated by column chromatography (ethyl acetate:hexane = 2:3). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) : 7.91 (d, J=7.59 Hz, 2H, C_6H_4), 7.58 (t, J=7.47 Hz, 1H, C_6H_4), 7.41 (t, J=7.79 Hz, 2H, C_6H_4), 2.75 (m, 2H, CCH_2), 2.45 (m, 2H, $\underline{CH_2}COOH$), 1.95 (s, 3H, CH_3).

Table S1 Characteristics of HAMA-*b*-DDACMM with different ratio in feed

Weight ratio in feed HAMA:DDACMM	M_n	PDI	Polymer composition HAMA(y+z):DDACMM(x)
1:1	42400	1.33	1.25:1
2:1	45300	1.21	2.20:1
4:1	46200	1.43	5.98:1

Table S2 GPC data of HAMA, HAMA-*b*-DDACMM, HAMAFA-*b*-DDACMM

Sample Name	RT(min)	M_n	M_w	PDI
HAMA	27.1	41900	52000	1.24
HAMA-*b*-DDACMM*	26.5	46100	66000	1.43
HAMAFA-*b*-DDACMM	26.3	49900	71300	1.43

*The weight ratio in feed HAMA:DDACMM was 4:1

Table S3 Drug loading concent and drug loading efficiency

Theoretical drug loading concent (wt%)	Drug loading concent (wt%)	Drug loading efficency (%)
5	3.87	77.40
10	7.53	75.35
50	35.78	71.56

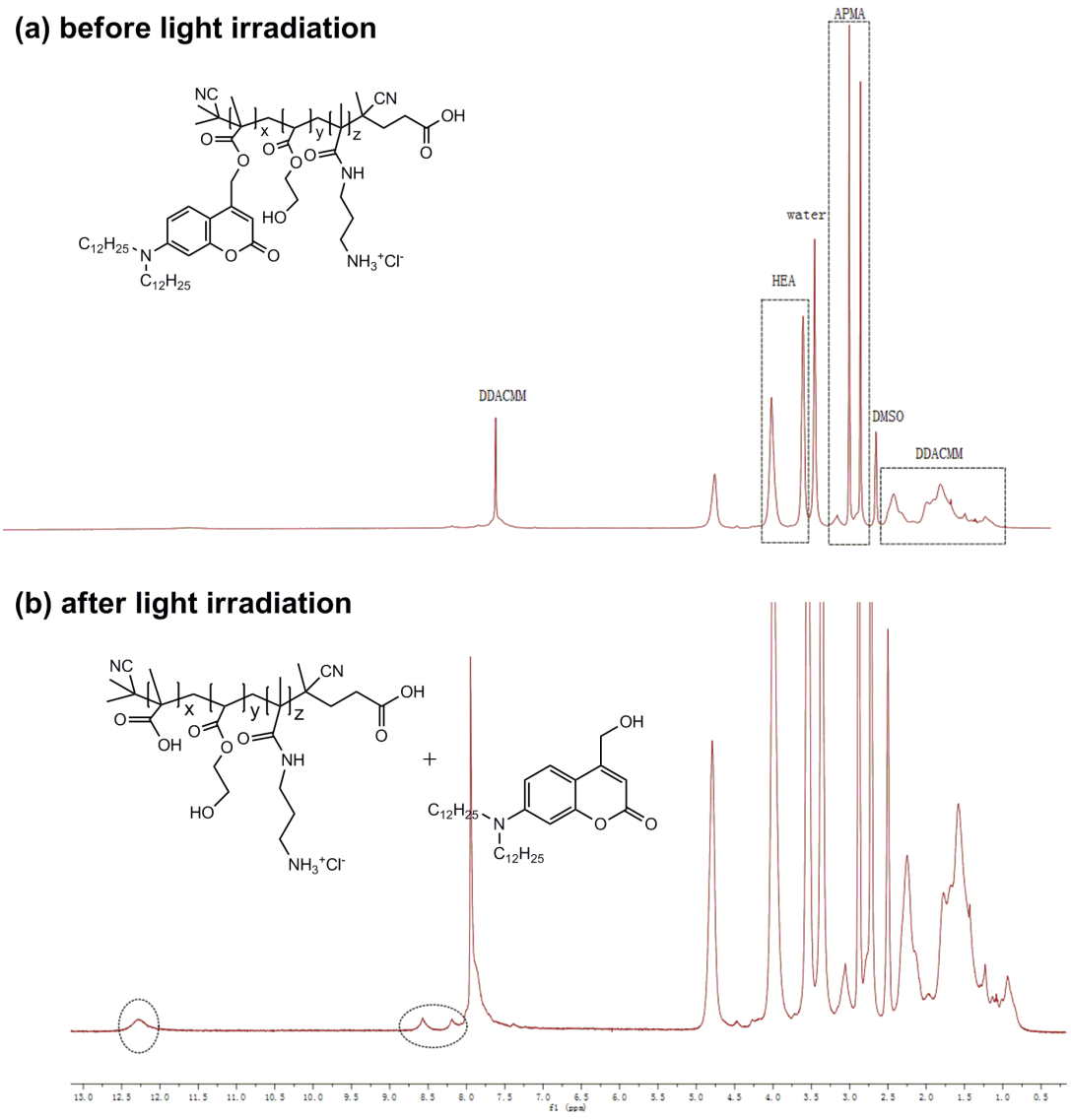

Figure S1 ^{1}H NMR spectrum of HAMA-b-DDACMM before and after light irradiation.

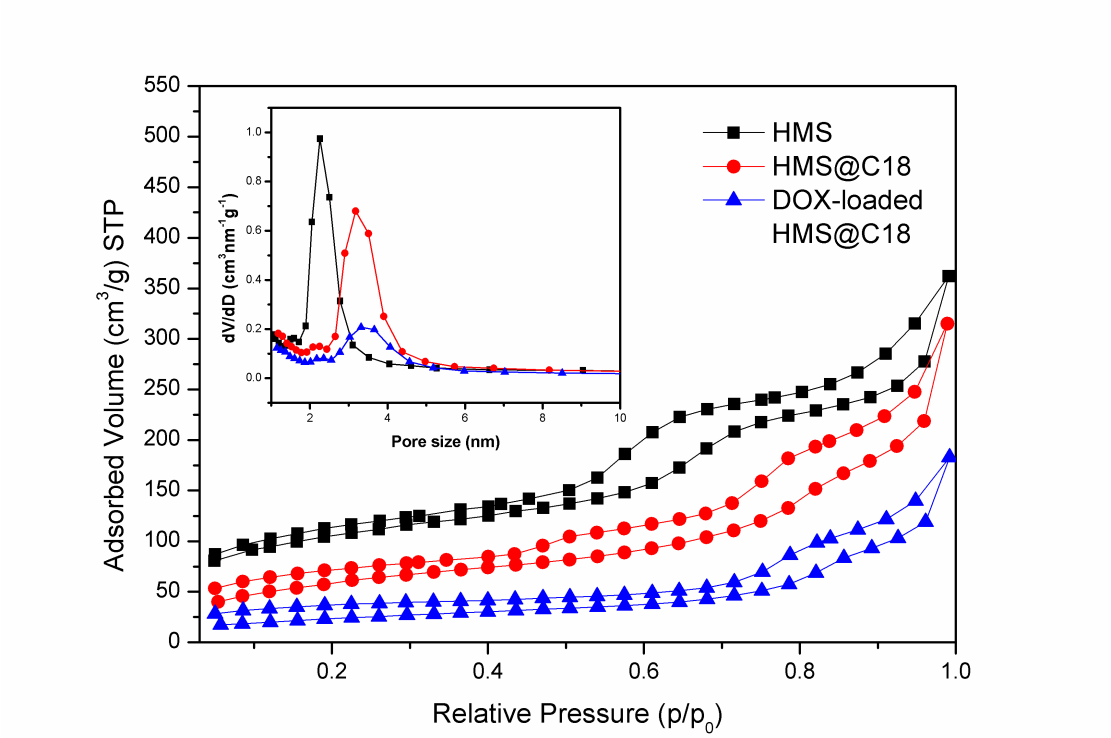

Figure S2 N_2 adsorption-desorption isotherm and the corresponding pore size distribution inset of HMS, HMS@C18, DOX-loaded HMS@C18.