ACS APPLIED MATERIALS & INTERFACES

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Glucose- and pH-Responsive Nanogated Ensemble Based on Polymeric Network Capped Mesoporous Silica

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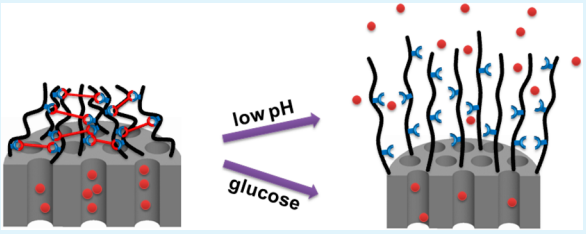
Supporting Information

ABSTRACT: In this paper, a glucose and pH-responsive release system based on polymeric network capped mesoporous silica nanoparticles (MSN) has been presented. The poly(acrylic acid) (PAA) brush on MSN was obtained through the surface-initiated atom transfer radical polymerization (SI-ATRP) of *t*-butyl acrylate and the subsequent hydrolysis of the ester bond. Then the PAA was glycosylated with glucosamine to obtain P(AA-AGA). To block the pore of silica, the P(AA-AGA) chains were cross-linked through the formation of boronate esters between 4,4-(ethylenedicarbamoyl)-phenylboronic acid (EPBA) and the hydroxyl groups of P(AA-AGA). The boronate esters disassociated in the presence of glucose or in acidic conditions, which lead to opening of the mesoporous channels and the release of loaded guest molecules. The rate of release could be tuned by varying the pH or the concentration of glucose in the environment. The combination of two stimuli exhibited an obvious enhanced release capacity in mild acidic conditions (pH 6.0).



KEYWORDS: *mesoporous silica nanoparticles, controlled drug release, pH response, glucose response, glycosylated polymer, core−shell nanoparticles*

INTRODUCTION

Controlled drug delivery systems (DDS) have attracted considerable interest in biomedical materials. To improve the treatment efficacy and reduce the side effects of drugs during chemotherapy, smart stimuli-responsive DDS were designed to release effective dosage drug at desired time.[1] Zero-premature release and triggered release properties are two essential preconditions for smart DDS.[2] In the past decades, a variety of DDS have been developed, such as liposomes,[3,4] micelles,[5,6] nanogel[7,8] and inorganic nanoparticles.[9,10] However, organic nanocarriers are usually physicochemically instable and lead to unexpected drug leakage.[11] In contrast, the inorganic nanoparticles are chemically stable, such as the mesoporous silica nanoparticles. Recently, the biocompatible mesoporous silica nanoparticles (MSN) were used as an ideal nanocarriers for DDS owing to their stable structure, tunable pore size, large surface area and well-defined surface.[12,13]

The capping system based on MSN has been proved as an excellent method for blocking the drug in the pore channel. Various DDS based on MSN were prepared by using different capping agents such as inorganic nanoparticles,[14,15] biomolecules,[16] supramolecule assemblies[17] and polymers.[18,19] These "smart caps" could be removed with different stimuli, such as pH,[20] temperature,[21] light,[22] redox[23] and competitive binding,[24] inducing the controlled release of the drug. As for dual-stimuli DDS, it offered multiple function during its application. Du et al. reported a pH- and glucose-responsive MSN system capped with protein, which have potential applications in diabetes and cancer treatment.[25] The polymer shell capped MSN system could provide better performance during the release process because the burst release was suppressed to a certain extent.[26] For example, Hong et al. reported a DDS system based on MSN, which was coated with a redox-responsive polymer, and the release of drug could be controlled by the disulfide-reducing agent DTT.[27]

It is known that the complexation between phenylboronic acid and glycosyl can be cleaved under a certain concentration of glucose or in mild acid conditions.[21] Many efforts have been devoted to decrease the pK_a of phenylboronic acid (PBA) to realize the glucose sensitivity of PBA under physiological conditions (pH 7.4, 1−3 g/L glucose). As reported, 4,4-(ethylenedicarbamoyl)phenylboronic acid (EPBA) with a pK_a of 7.8 was attributed to the electron-withdrawing groups at the para position of aryl boronic acid.[23] Besides, the coordination between unreacted carboxyl and phenylboronic acid induced the decrease of the pK_a of phenylboronic acid.[24]

We combined the advantages of a polymer capped MSN system and the responsive properties of boronate ester bond on

Received: January 21, 2015
Accepted: March 4, 2015
Published: March 4, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acsami.5b00631
ACS Appl. Mater. Interfaces 2015, 7, 6310−6316

pH and the glucose. The pH-responsive property of DDS is important in the field of cancer treatment because acidic extracellular pH is a major feature of tumor tissue. For diabetes treatment, the challenge is the glucose-responsive release of drug in blood. With the increase of concentration of the blood glucose, the sustained release of hypoglycemic drugs is necessary. Herein, we prepared a new glucose- and pH-responsive delivery system based on cross-linked polymeric network capped MSN. The P(AA-AGA) layer on MSN was prepared through the polymerization of *t*-butyl acrylate, and the subsequent hydrolysis and glycosylation. The atom transfer radical polymerization (ATRP) method was supposed to be capable of obtaining a dense and narrow dispersion polymer brush.[22] The polymer P(AA-AGA) chains were cross-linked through the reaction between hydroxyl groups along the P(AA-AGA) brush and the diboronic acid group of EPBA. The polymeric network could dissociate under a low concentration of glucose or in mild acid conditions, which lead to the release of trapped molecules.

EXPERIMENTAL SECTION

Materials. 3-Aminopropyltriethoxysilane (APTES, 99%), tetraethylorthosilicate (TEOS), 2-bromoisobutyryl bromide (BIBB, 99%), 2-bromoisobutyric acid ethyl ester (BAEE, 98%) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyl diethyl-enetriamine (PMDETA, 99%) were purchased from Sigma-Aldrich. D-Glucosamine hydrochloride and *t*-butyl acrylate (tBA) were purchased from Alfa. CuBr (Shanghai Chemical Reagent) was purified with ethylic acid at 80 °C overnight, washed with ethanol and dried in a vacuum. Rhodamine 6G (Rd6G), trifluoroacetic acid (TFA), and sulfoxide chloride were purchased from Shanghai Reagent Chemical Co., Ltd. and used as received.

Preparation of Amino-Modified MSN (MSN-NH_2). MSN was prepared according to a reported method:[34] 0.25 g of cetyltrimethylammonium bromide (CTAB) and 0.875 mL of NaOH solution (2 M) were added to the aqueous solution (120 mL), and the solution was stirred at 80 °C. Subsequently, 1.25 mL of tetraethylorthosilicate (TEOS) was added to the solution. The reaction was stirred at 80 °C for 2 h. The resulted product was filtered and washed with an amount of H_2O and methanol. As-prepared MSN was dried in a vacuum at 100 °C for 24 h before using.

270 mg of MSN was well-dispered in 35 mL of anhydrous toluene, and 2 mL of APTES was added. The reaction mixture was refluxed under an argon atmosphere for 24 h. The MSN was separated by centrifugation (10000 rpm, 10 min) and washed twice with toluene and ethanol. The CTAB template was extracted by stirring in 48 mL of methanol and 2.7 mL of concentrated hydrochloric acid at 60 °C for 24 h. The particles were centrifuged, washed with methanol and dried at 60 °C in a vacuum.

Preparation of ATRP Initiator-Modified MSN (MSN-Br). 150 mg of MSN-NH_2 and 0.24 mL of anhydrous triethylamine were added into 10 mL of anhydrous dichloromethane. Subsequently, 0.2 mL of BIBB was added dropwise into the mixture in an ice bath for 1 h, and then the solution was stirred at room temperature for 24 h. The MSN-Br was collected by centrifugation (10000 rpm, 10 min), washed with dichloromethane for three times and dried at 60 °C under vacuum overnight.

Preparation of Poly(acrylic acid) Grafted MSN (MSN-PAA). 100 mg of MSN-PAA-AGA, 0.1 mL of PMDETA, 3.2 g of tBA and 7 mL of acetone were added to a polymerization pipe. The solution was degassed by two freeze−pump−thaw cycles under argon. Subsequently, 36 mg of CuBr was added, and the solution was degassed two times. The sealed pipe was reacted at 60 °C for 72 h. The MSN-PAA particles were obtained after the hydrolysis of poly(*t*-butyl acrylate) grafted on MSN in the presence of TFA.[35]

Preparation of Partially Glucosamine-Modified MSN-PAA (MSN-PAA-AGA). 60 mg of MSN-PAA was suspended in 10 mL of deionized (DI) H_2O. Subsequently, 60 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 12 mg of *N*-hydroxysuccinimide (NHS) were added, and the solution was stirred at 0 °C for 1 h. Then, 80 mg of glucosamine was added into the solution, and the mixture was stirred under ambient temperature. The resulted particles were washed with water and dried under vacuum.

Drug Loading. 1 mg of Rd6G was added to 5 mL of DI H_2O containing 40 mg of MSN-PAA-AGA. The mixture was stirred at room temperature for 24 h. The solution of 60 mg of EPBA dissolved in 4 mL of dimethylformamide (DMF) was added to the suspension, and the solution was stirred for 48 h to seal the drug in the nanoparticles. To remove the absorbed drug, the final drug loaded particles were centrifugated from the suspension, and then washed with an amount of DMF and water until no fluorescence signal of rhodamine 6G in supernatant was observed.

Releasing Experiment. The release of loaded molecules was operated with the following: 5 mg of Rd6G loaded and polymer capped MSN-PAA-AGA was dispersed in 10 mL of phosphate buffered saline (PBS) solution (pH 7.4). To investigate the responsive behavior of MSN-PAA-AGA on glucose, the activation of nanogate was performed by adding different concentrations of glucose. As a function of time, 3 mL of supernatant was withdrawn and made up by another 3 mL fresh solution. The release profile of drug was obtained on the basis of concentration of Rd6G via the fluorescence intensity at 554 nm. As for the pH responsive properties of samples, the nanogate was also activated by adjusting the solution to different pH. The release study through the combination of low pH and glucose was also operated similarly.

Characterizations. Fourier transform infrared (FT-IR) spectra were determined with a PerkinElmer spectrometer. Transmission electron microscopy (TEM) images were collected on a high resolution transmission electron microscopy (HRTEM, JEOL, JEM-2010FEF, Japan) instrument with an accelerating voltage of 100 kV. Powder X-ray diffraction (PXRD, Bruker D8 ADVANCE, Germany) was conducted using Cu Kα radiation (λ = 1.540 56 Å). The fluorescence spectra of Rd6G were determined using a LS55 luminescence spectrometry instrument (PerkinElmer) with excitation at 483 nm. The thermal gravimetric analysis (TGA) was recorded by A TGS-2 thermogravimetric analyzer (PerkinElmer), using an N_2 atmosphere protection with a heating rate of 10 °C per minute from 323 to 1273 K. The surface area and pore size distributions were measured by Brunauer−Emmett−Teller (BET) and Barrett−Joyner−Halenda (BJH) analysis (Micromeritics ASAP 2020). X-ray photoelectron spectroscopy (XPS) was performed with KRATOS XSAM800 spectrometer.

RESULTS AND DISCUSSION

Preparation and Characterization of MSN. For the design of the glucose- and pH-responsive MSN system, mesoporous silica and glycosylate polymer were chosen as the carrier and capper, respectively. As shown in Figure 1, the model drug can be released by adding the glucose or reducing pH value of solution. The diameter of the MSN with ordered mesoporous structure was about 100 nm, as shown in the TEM images (Figure 2a,b). The polymer layer on the nanoparticles was observed after the introduction of polymers, as shown in Figure 2c,d. The polymer shells coated on MSN were uniform, and the thickness of cross-linked MSN-PAA-AGA was about 8 nm, indicating the successful modification of polymers on particles. Small-angle X-ray diffraction (XRD) analysis was employed to character the hexagonal array pores structure of the MSN, which was indexed as (100), (110) and (200) Bragg peaks (Figure 3). Compared to curve a in Figure 3, the decreased peaks of curves b−d were attributed to the introduction of polymers on the surface of the particles. The weakest peak intensity of curve d in Figure 3 was resulted from the cross-linkage of the polymer shell. Figure 4 illustrates the nitrogen adsorption−desorption isotherms of unmodified

DOI: 10.1021/acsami.5b00631
ACS Appl. Mater. Interfaces 2015, 7, 6310−6316

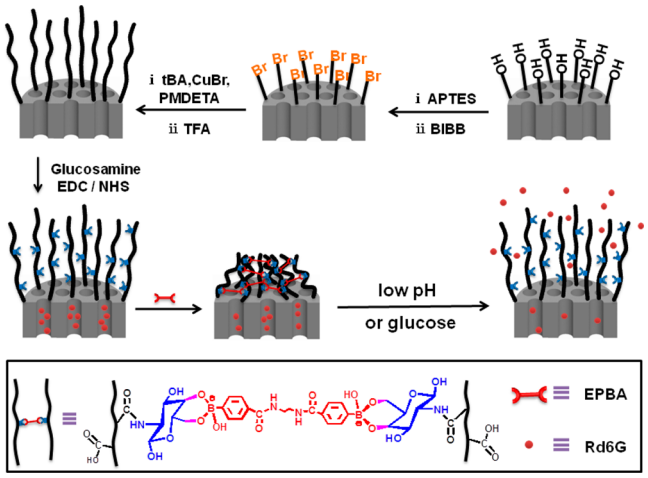


Figure 1. Schematic illustration of the preparation of cross-linked MSN-PAA-AGA and the dual-responsive drug release proccess.

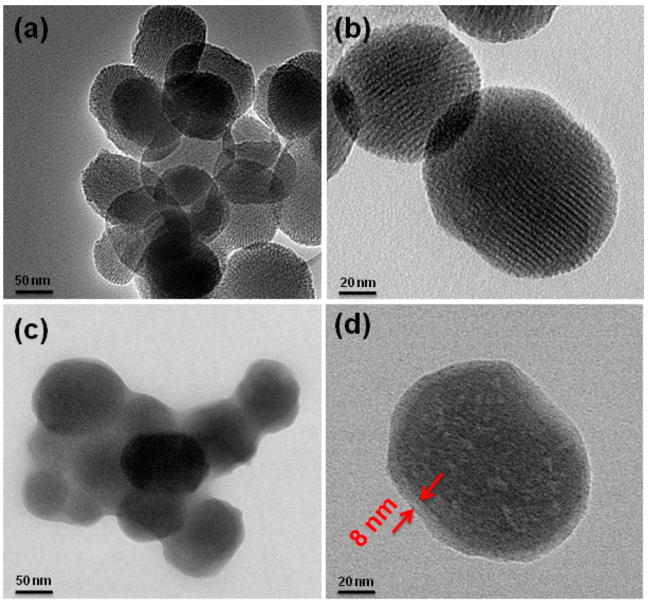


Figure 2. TEM images of MSN (a, b) and cross-linked MSN-PAA-AGA (c, d).

MSN. The type IV isotherm suggested the typical mesoporous property of the particles, and the size of mesopore was about 2.5 nm (as shown in Figure 4b). However, the isotherm became flat after the modification of the polymer shell, and the pore diameter could not be obtained. This is resulted from the covering of the polymer layer on the mesoporous of the MSN.

FT-IR spectra were used to monitor the process of the surface functionalization of MSN, as shown in Figure 5. The initiators were immobilized on the surface of MSN through the reaction between MSN-NH_2 and BIBB, which was demonstrated by the absorption band of amide group (secondary amide C═O stretching) at 1560 cm^{-1}. After the surface-initiated atom transfer radical polymerization (SI-ATRP) of tBA with MNS-Br, the MSN-PAA was obtained after the hydrolysis of poly(*t*-butyl acrylate) grafted on MSN in the presence of TFA. The absorption band of curve b in Figure 5 at 1726 cm^{-1} was attributed to the C═O bond from carboxyl group, indicating the successful grafting of poly(acrylic acid) brush. As shown in curve d in Figure 5, the intensity of the

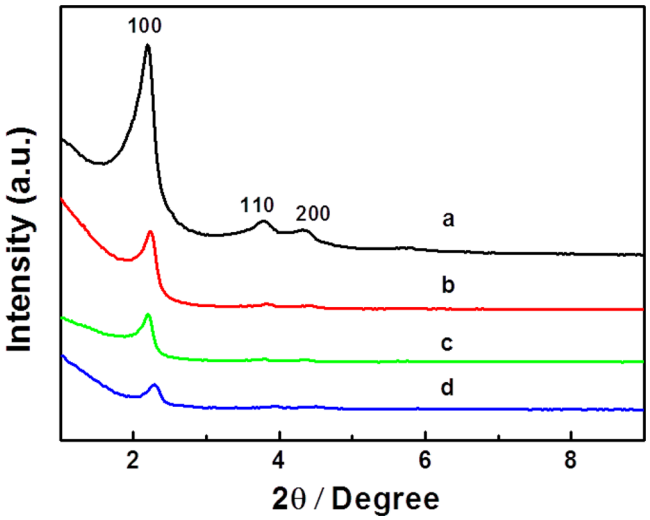


Figure 3. Low-angle XRD pattern of MSN (a), MSN-PAA (b), MSN-PAA-AGA (c), cross-linked MSN-PAA-AGA (d).

carboxyl stretching vibration at 1726 cm^{-1} decreased compared to MSN-PAA, which indicated the partially modification of glucosamine. It is known that boronic acid derivatives are capable of banding to diol moieties.[36,37] Thus, the glycosylated polymer could be cross-linked by diboronic acid derivatives. Herein, the diboronic acid-linker EPBA was introduced to block the nanopore of MSN through cross-linkage of MSN-PAA-AGA chain through the boronate esters. In curve e of Figure 5, the bands of B—O adsorption at 1272 and 1354 cm^{-1} were observed, respectively.[38,39]

To further confirm the successful modification of each step, the particles were characterized using XPS spectroscopy. As shown in Figure 6a and Table S2 (Supporting Information), the N and Br elements appeared at 404 and 74 eV in XPS spectra, which further proved the successful modification of $-NH_2$ and initiators. The percentage of Br was calculated to be 1.1%, whereas only C, O, and Si elements were observed in the component of MSN. The C element percentage of MSN-PAA increased compared with MSN-Br, while the percentage of Si element was decreased due to the shielding of the polymer layer on the surface. The N element percentage of MSN-PAA-AGA was increased compared with that of MSN-PAA, indicating the successful attachment of glucosamine onto MSN-PAA. The B 1s peak at 191 eV appeared in XPS spectra of cross-linked MSN-PAA-AGA, and the percentage of B element was calculated to be 1.2%, which proved that polymer brush was cross-linked with EPBA.

The thermal gravimetric analysis (TGA) curves of different MSN are displayed in Figure 7. The weight losses of MSN-Br, MSN-PAA, MSN-PAA-AGA and cross-linked MSN-PAA-AGA were 63%, 58%, 54% and 50% after they were heated to 800 °C under N_2 atmosphere, respectively. The percentages of poly(acrylic acid) and glucosamine on the nanoparticles were estimated to be 6% and 4%, Thus, the mole percentage of glucosamine modified on the poly(acrylic acid) of MSN-PAA was estimated to be 22.4%. The percentage of EPBA on nanoparticles is about 4%, which further demonstrated the reaction of EPBA and glycosylate polymer.

Drug Loading and Release. We chose Rd6G as a model drug to investigate the pH- and glucose-responsive release from the cross-linked MSN-PAA-AGA. The Rd6G can diffuse through the hydrophilic PAA-AGA brush layer into the pore

DOI: 10.1021/acsami.5b00631
ACS Appl. Mater. Interfaces 2015, 7, 6310−6316

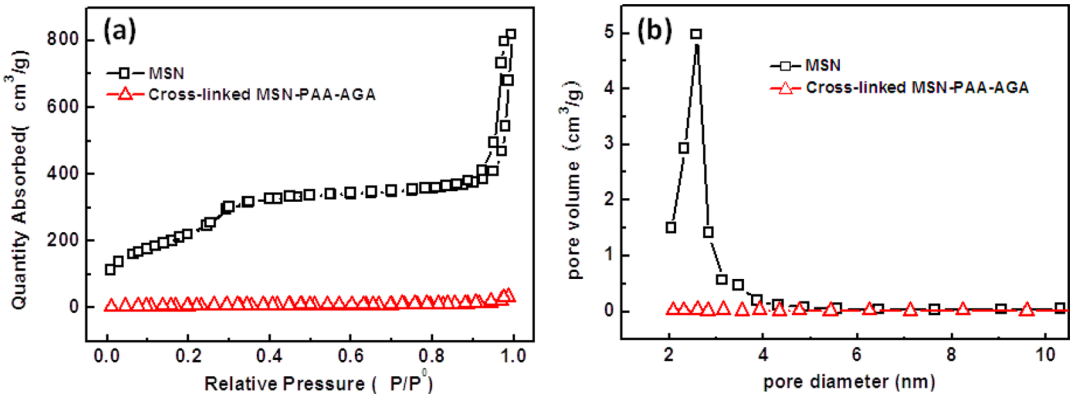


Figure 4. (a) Nitrogen adsorption−desorption isotherms of MSN and cross-linked MSN-PAA-AGA. (b) Pore size distribution of MSN and cross-linked MSN-PAA-AGA.

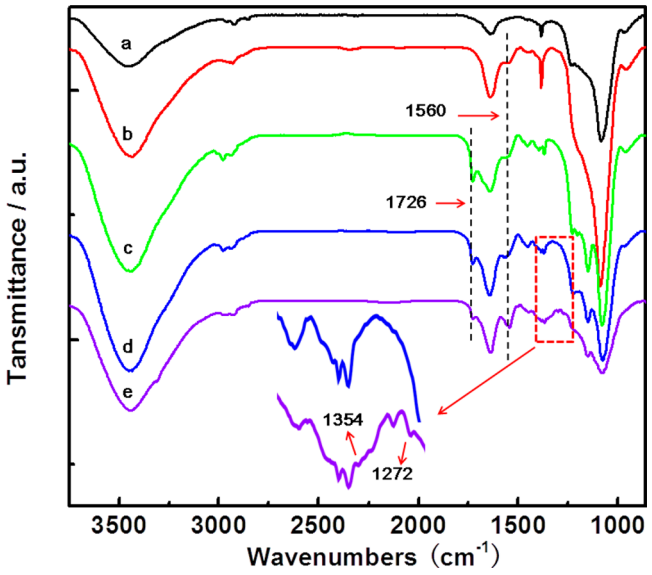


Figure 5. FTIR spectra of MSN (a), MSN-Br (b), MSN-PAA (c), MSN-PAA-AGA (d) and cross-linked MSN-PAA-AGA (e).

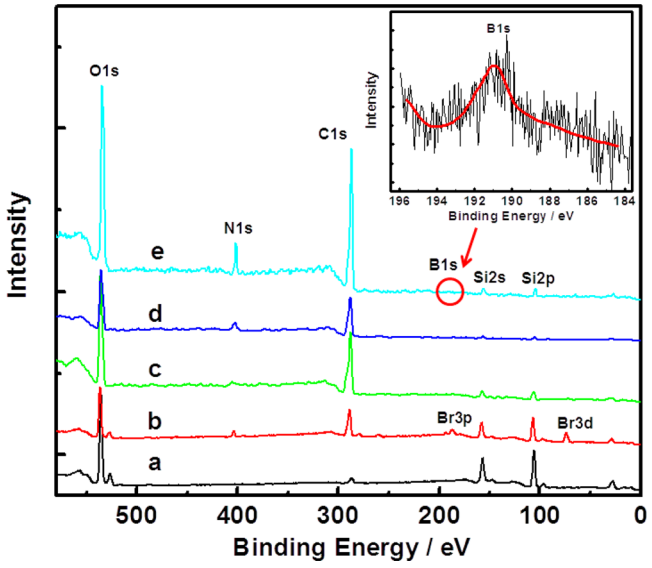


Figure 6. FTIR spectra of MSN (a), MSN-Br (b), MSN-PAA (c), MSN-PAA-AGA (d) and cross-linked MSN-PAA-AGA (e).

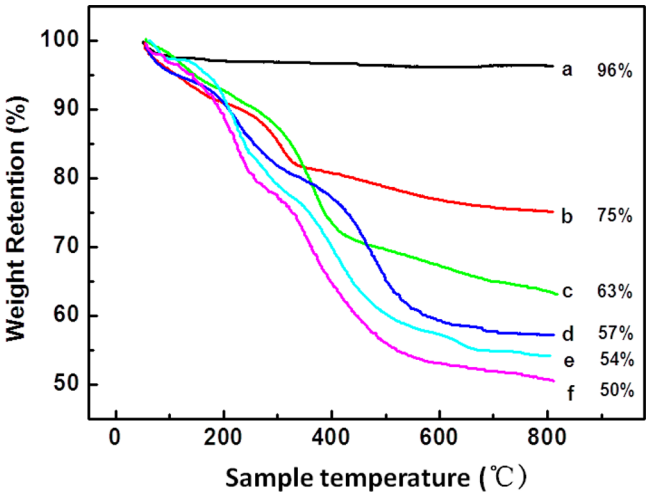


Figure 7. TGA curves of MSN (a), MSN-NH_2 (b), MSN-Br (c), MSN-PAA (d), MSN-PAA-AGA (e) and cross-linked MSN-PAA-AGA (f).

channel or stay among the polymer shells. First, 40 mg of MSN-PAA-AGA was dispersed in 5 mL of DI H_2O containing 1 mg of Rd6G. Then the cross-linker EPBA was added to the mixture, and the solution was stirred for 48 h. Afterward, it was washed with DMF and water to remove adsorbed Rd6G and unreacted EPBA. The loading content was 1.5%, determined using the fluorescence emission spectra. It was calculated through the following equation: loading content = (initial weight of Rd6G − supernatant weight of Rd6G)/weight of particles × 100%.

To investigate the pH-responsive release of Rd6G in vitro, three aliquots of 5 mg of cross-linked Rd6G-loaded MSN-PAA-AGA were placed in PBS solution with pH 7.4 for 40 h. At desired time intervals, the supernatant solution was collected to measure the fluorescence intensity and calculate the accumulative release amount of the loaded Rd6G (λ_{ex} = 483 nm). As shown in Figure 8, only 2% Rd6G was released in three groups after 40 h, which indicated that almost no drug premature released to the PBS (pH 7.4) solution. The zero-premature release behavior exhibited the excellent blocking performance of polymer-capping MSN systems. Subsequently, the pH values of two samples were adjusted to pH 6.0 and pH 5.0, respectively. The release of Rd6G was observed immediately after the change of pH value of the solution. The cumulative amount of Rd6G is up to 45% at pH 6.0 and 84% at pH 5.0

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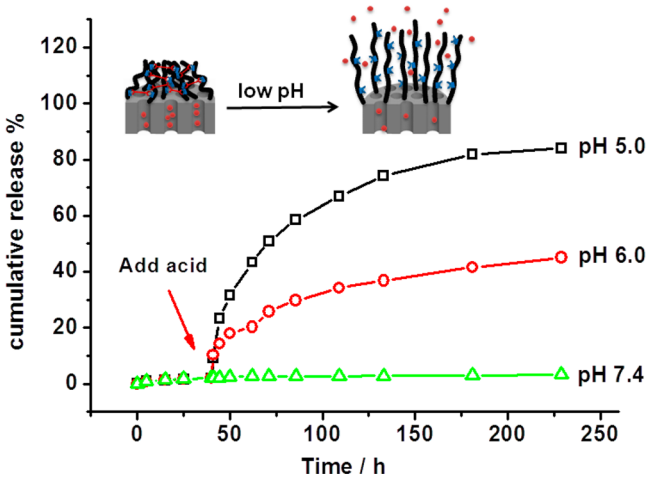

Figure 8. Cumulative release of Rd6G from cross-linked MSN-PAA-AGA in different pH without glucose.

after 189 h. However, there is only 3.4% of drug release was observed in the control group. This result demonstrated that the polymeric network capped on MSN can be cleaved under mild acid environment. The release mechanism can be explained by that the complexation between phenylboronic acid and diol binding can be cleaved under mild acid condition.[29]

Moreover, the glucose-responsive property of Rd6G-loaded MSN-PAA-AGA was also studied. Three aliquots of 5 mg samples were placed in PBS solution with pH 7.4 for 40 h. From Figure 9, it was found that there was about 1.9% Rd6G

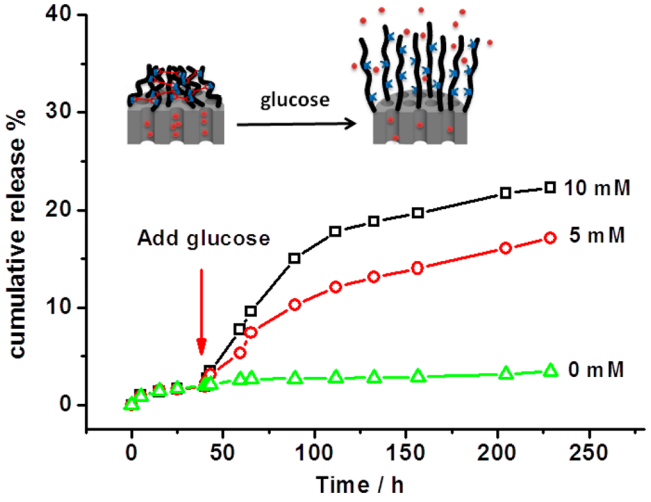

Figure 9. Cumulative release of Rd6G from MSN-PAA-AGA in PBS (pH 7.4) with different concentration of glucose.

released in the absence of glucose during 40 h, indicating the efficient confinement of drug in particles. However, after different amounts of glucose were added to the two samples, over 188 h, 17% and 22% of drug was released under 5 mM and 10 mM glucose PBS solutions, respectively. However, there was nearly no leakage of drug if glucose was not added, due to the great blocking effect of the polymer shell. The glucose-triggered release of drug was attributed to the competitive binding of glucose to the EPBA in comparison with glycosyl in polymer brush. Besides, the coordination between PBA and unreacted carboxyl also induced the decease of pK_a.[33]

To analyze the sensitivity of polymer capped systems with different pH values and concentrations of glucose, the average release rates of Rd6G in different conditions were calculated from the release profiles. As illustrated in Figure 10, minimum

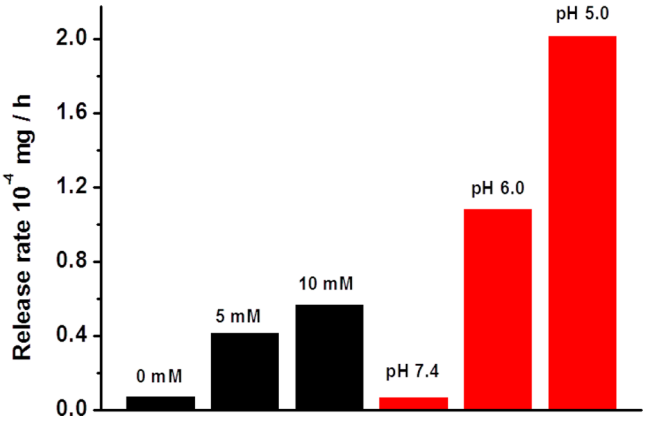

Figure 10. Release rate of Rd6G from cross-linked MSN-PAA-AGA under different stimuli conditions.

release rates were observed in the environment of pH 7.4 and without glucose. By increasing the glucose concentrations to 5 mM and 10 mM, the release rate increased to 0.49 and 0.57 × 10^{-4} mg/h, respectively. The release rates were faster compared to glucose conditions when the pH values of solutions were adjusted to pH 6.0 and pH 5.0. The release rates reached to 1.08 and 2.02 × 10^{-4} mg/h, respectively. The cleavage of the phenylboric acid ester bond in the polymer shell may be more rapid relatively in the acid conditions.

We have shown that the release of drug can be controlled by varying pH or glucose concentration, respectively. We further investigated the combination effects of acidification and glucose. From Figure 11a,b, at 10 mM glucose or pH = 6 conditions, only 22% and 45% of drug were released, respectively. When 10 mM glucose in mild acidic conditions (pH 6.0) was employed, the cumulative release of Rd6G reached to 65% for the same time period. The obvious increased release rate may be attributed to the combination effects of glucose competitive binding and slight protonation of EPBA in mild acidic conditions. However, when 10 mM glucose was introduced to the solution with pH = 5.0, the dual-stimuli release profile was similar to the one in the solution with pH = 5.0, as shown in Figure 11c. It could be explained by the fact that the high protonation of EPBA in acid conditions (pH 5.0) had already cleaved the boronate esters completely. As shown in Figure 11c,d, the combined effect of acidic conditions (pH 5.0) and glucose was exhibited. The release rate was mainly dependent on the pH of solution. When in mild acidic condition, the introduction of glucose could increase the release rate. While in more acidic conditions (pH 5.0), the release rate mainly depended on the pH of solution, and the additional glucose only slightly increased the release rate.

CONCLUSION

A glucose and pH-responsive release system based on polymeric network capped mesoporous silica (MSN) has been prepared. The cross-linkage between EPBA and glycosylated polymer successfully blocked the drug from premature release. We have demonstrated that a low concentration of glucose and mild acidic conditions could

DOI: 10.1021/acsami.5b00631
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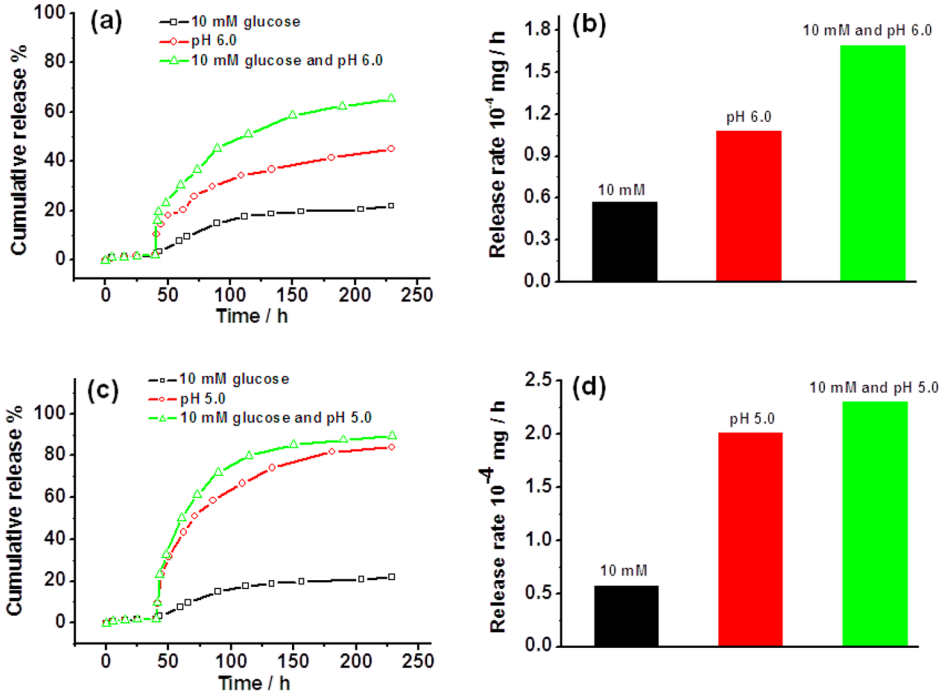

Figure 11. Release profiles of Rd6G from cross-linked MSN-PAA-AGA at pH 6.0 (a, b) and at pH 5.0 (c, d) in the presence of 10 mM glucose solution.

induce the disassociation of cross-linked polymer shell grafted on MSN. The release rate was increased with the glucose concentration. In the acidic conditions, we found for a lower pH, the release rate is faster. However, the combination of two stimuli exhibited an obvious enhanced release capacity in mild acidic conditions (pH 6.0). We believe this glucose and pH-responsive release system provides valuable information for the development of cancer and diabetes treatment.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and the characterization of EPBA; nitrogen adsorption−desorption isotherms, pore size distribution and BET, BJH parameters; ζ-potential; size distributions; XPS measurement of different MSN; GPC information on grafted polymers; cytotoxicity of materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by National Natural Science Foundation of China (21204070) and the National Key Basic Research Program of China (2011CB606202).

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DOI: 10.1021/acsami.5b00631
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