Preparation and controlled drug delivery applications of mesoporous silica polymer nanocomposites
through the visible light induced surface-initiated ATRP

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Abstract

The mesoporous materials with large pore size, high specific surface area and high thermal stability have been widely utilized in a variety of fields ranging from environmental remediation to separation and biomedicine. However, surface modification of these silica nanomaterials is required to endow novel properties and achieve better performance for most of these applications. In this work, a new method has been established for surface modification of mesoporous silica nanoparticles (MSNs) that relied on the visible light induced atom transfer radical polymerization (ATRP). In the procedure, the copolymers composited with itaconic acid (IA) and poly(ethylene glycol)methyl acrylate (PEGMA) were grafted from MSNs using IA and PEGMA as the monomers and 10-Phenylphenothiazine(PTH) as the organic catalyst. The successful preparation of final polymer nanocomposites (named as MSNs-NH₂-poly(IA-*co*-PEGMA)) were evidenced by a series of characterization techniques. More importantly, the anticancer agent cisplatin can be effectively loaded on MSNs-NH₂-poly(IA-*co*-PEGMA) and controlled release it from the drug-loading composites with pH responsive behavior. As compared with conventional ATRP, the light induced surface-initiated ATRP could also be utilized for preparation of various silica polymer nanocomposites under rather benign conditions (e.g. absent of transition metal ions, low polymerization temperature and short polymerization time). Taken together, we have developed a rather promising strategy method for fabrication of multifunctional MSNs-NH₂-poly(IA-*co*-PEGMA) with great potential for biomedical applications.

Key words: Mesoporous silica nanoparticles, visible light induced polymerization, surface-initiated ATRP, controlled drug delivery

1. Introduction

Since Kresge and his colleagues reported a novel type of mesoporous silica nanomaterials (MSNs) which were called MCM41 in 1992, the research interest of mesoporous materials have attracted widespread attention for various applications.[1] Due to a variety of excellent properties of mesoporous silica materials, it possess extensive application prospect in the separation and purification, biological materials, chemical synthesis and transformation of catalysts, semiconductors, computers, sensors, nonlinear optical material and many other fields.[2-6] But the hydrophobic nature and lack of functional groups of unmodified MSNs still largely limit their practical applications especially in the biomedicine related fields. Therefore, surface modification of MSNs to endow their good water dispersity and novel functions have raised the most recent research attention.

There are many kinds methods have been reported for the surface modification of MSNs.[7-11] Among them, the surface functionalization of MSNs with polymers has proven to be a simple but effective method.[12-17] Different surface polymerization strategies such as atom transfer radical polymerization (ATRP), revisable additional-fragmentation chain transfer (RAFT) polymerization, nitroxide-mediated radical polymerization (NMP) have been demonstrated for preparation of a large number of polymer nanocomposites with different functionality, which could endow many interest properties or obviously enhanced the performance of resultant polymer composites.[18-30] Compared with other polymerization, ATRP provides a more concise and effective way in the synthesis of a variety of functional polymers, such as molecular weight of polymer, low molecular weight polymer and terminal functional high polymer, block copolymer. Thus ATRP has also regarded as one of the most useful and promising method for surface-initiated modification of different materials and surface for different applications.[31-35] However, to the best of our knowledge, traditional ATRP are required to using transition metal ions and organic ligand as the catalysts, which are toxic to living organisms and difficult to be completely removed from the final products.[36] Therefore, there is of great interest to develop novel ATRP method that need not involve in the metal ions and organic ligands.[37-39] A variety of metal-free catalyzed ATRP were discovered by scientists. It is one of the representative classes to modify MSNs by enzyme mimetic catalytic ATRP for controlled cargo release.[10]

In this contribution, a novel metal-free ATRP that based on the UV light induced polymerization using organic catalysts 10-Phenylphenothiazine (PTH) has been developed for surface modification of MSNs. As shown in **Scheme 1**, the MSNs were synthesized using cetyltrimethylammonium bromide

(CTAB) as template and tetraethyl orthosilicate (TEOS) as silica source. Then the surface of MSNs was modified with amino groups to obtain (MSNs-NH₂) via surface modification with 3-Aminopropyl triethoxysilane (APTES). The synthetic Br-containing MSNs-NH₂ (MSNs-NH₂-Br) was synthesized through amidation reaction and could be further utilized for surface polymerization with itaconic acid (IA) and poly(ethylene glycol)methyl acrylate (PEGMA) using an organic photoredox catalyst via a metal-free ATRP strategy. The resultant MSNs-NH₂-poly(IA-co-PEGMA) showed great water dispersity, non-toxicity and high drug loading capability, implying their great potential for biomedical applications. Yang et al. had done a lot of work to used modified mesoporous silicon materials in the biomedicine related fields.[40-43] Stoddart et al. used mesoporous silicon as carriers to control and release the drug with stimuli-responsive.[44-46] In this article, MSNs-NH₂-poly(IA-co-PEGMA) was used to develop pH-responsive material for the delivery of cisplatin. As compared conventional ATRP, the method described in this work provided a facile and effective route for fabrication of various multifunctional polymer nanocomposites. On the other hand, the light induced ATRP could elegant overcome the drawbacks of conventional ATRP such as residue of transition metal ions, long reaction time, high reaction temperature etc.[47]

Scheme 1 Synthesis route of MSNs-NH₂-poly (IA-co-PEGMA) via a metal-free ATRP, that could enhance the water dispersity and also potentially utilized for carrying drugs such as cisplatin.

2. Materials and experimental procedure

2.1 Materials and instruments

Cetyltrimethylammonium bromide (CTAB, M_w : 364.45 Da, 99%), tetraethyl orthosilicate (TEOS M_w : 208.33 Da, 99%) and (3-aminopropyl) triethoxysilane (APTES, M_w : 221.37 Da, 99%) were supplied by Alfa Aesar. N,N,N-triethylamine (TEA, M_w : 101.19 Da, 99%), poly(ethylene glycol) methyl ether methacrylate (PEGMA, M_w : 950 Da, 98%), itaconic acid (IA, M_w :

130.10 Da, 99%) and α -bromoisobutyryl bromide (M_w : 229.90 Da, 98%) were purchased from Aladdin (Shanghai, China). 10-phenylphenothiazine (PTH, M_w : 275 Da) was synthesized by using phenothiazine and iodobenzene. Acetone and toluene were obtained by Heowns (Tianjin, China). All chemical agents were of analytical grade and were used directly without any purification.

^1H NMR spectra were recorded on Bruker Avance-400 spectrometer with deuterium DMSO as the solvent. Fourier transform infrared (FT-IR) spectra were performed on a Nicolet 380 Fourier transform spectrometer with a resolution of 2 cm^{-1} . UV-Visible absorption spectra were obtained by Perkin Elmer LAMBDA35 UV/Vis spectroscopy. Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV, the tested specimens were made by placing a drop of the nanoparticles suspension on a carbon-coated copper grid. X-ray photoelectron spectra (XPS) were measured on a VGESCALAB 220-IXL spectrometer using an Al Ka X-ray source (1486.6 eV).

2.2 Synthesis of MSNs

MSNs were synthesized according to the previous report.[48] In brief, CTAB (1.37 mmol, 500 mg) and NaOH (3.75 mmol, 150 mg) were added to distilled water (250 mL) and introduced in a schlenk bottle with a magnetic stir bar at 80 °C for 0.5 h. Then TEOS (2.24 mmol, 0.5 mL) was added dropwise to the reaction mixture under vigorous stirring for 4 h. In the next moment, the impure MSNs and the final reaction mixture were separated by centrifugation at 8000 rpm for 3 min (Shuke Centrifuge TG16, Sichuan shuke instrument Co., Ltd., China). The crude product was washed with deionized water and methanol for three times and dried at the vacuum drying oven at 35 °C for 24 h.

2.3 Synthesis of MSNs-NH₂-2

MSNs-NH₂-2 was prepared according to the previous method.[48] The pure MSNs (1.5 g) were added in toluene (50 mL) and stirred for 20 min. APTES (3.2mmol, 0.75 mL) was added dropwise to the mixture solution. The reaction mixture was refluxed at 100 °C for 3 h. Then the MSNs of NH₂-contain (MSNs-NH₂-1) were separated by centrifugation at 8000 rpm for 3 min. The obtained MSNs-NH₂-1 was washed with toluene and isopropanol three times and dried at 40 °C for 3 h. To remove the surfactant CTAB, we refluxed 1.00 g of MSNs-NH₂-1 for 24 h in a methanolic solution of 6.00 mL of HCl (37.4%) in 100.00 mL of methanol. Then the reaction mixture was separated by centrifugation at 8000 rpm for 3 min. The centrifugal products were washed with distilled water and methanol three times and dried in vacuum drying oven at 35 °C to yield pure MSNs-NH₂-2.

2.4 Synthesis of MSNs-NH₂-Br

The initiator of Br-containing was synthesized by introducing α -bromoisobutyryl bromide to the surface of MSNs by amidation reaction. MSNs-NH₂-2 (300 mg) and TEA (0.59 mmol, 60 mg) was dissolved in toluene (40 mL) and introduced in a polymerization bottle with a magnetic stir bar and purged by nitrogen flow. When the temperature of the reaction mixture was reduced to 5 °C, a toluene solution of α -bromoisobutyryl bromide (30 μ L) in 10 mL of toluene was added dropwise into the polymerization bottle. Reaction mixture was stirred violently at 0-5 °C for 4 h and separated by centrifugation at 8000 rpm for 3 min. The centrifugal product was washed with acetone three times and dried in vacuum drying oven at 40 °C to yield MSNs-NH₂-Br.

2.5 Preparation of MSNs-NH₂-poly(IA-co-PEGMA)

Metal-free ATRP was used to modify MSNs. MSNs-NH₂-Br (250 mg), PEGMA (1.88 mmol, 1.786 g), IA (1.88 mmol, 245 mg) and PTH (0.04 mmol, 10 mg) were dispersed in 3 mL THF and purged by nitrogen flow. The reaction mixture were stirred vigorously and irradiated by LEDs (365 nm) for 7 h and then separated by centrifugation at 8000 rpm for 3 min. The centrifugal product was washed with distilled water and methanol three times and dried in vacuum drying oven at 40 °C for 12 h. The pure MSNs-NH₂-poly(IA-co-PEGMA) was obtained.

2.6 Cisplatin loading and release in vitro

MSNs-NH₂-poly(IA-co-PEGMA) (20 mg) was dispersed in phosphate buffer saline (PBS) (100 mL, pH = 7.4). Then a suspension mixture with 10 mg of cisplatin (cis-dichlorodiammineplatinum (II)) in PBS (2 mL, pH = 7.4) was added to the above reaction system. The final reaction mixture was stirred under the condition of avoiding light for 48 h and separated by centrifugation at 8000 rpm for 3 min. The concentration of the supernatant was measured, and the absorbance was obtained by subtraction method. The centrifugal solids are MSNs-NH₂-poly(IA-co-PEGMA)-CDDP. MSNs-NH₂-poly(IA-co-PEGMA)-CDDP complexes were dialyzed with PBS (100 mL, pH = 5.5 and 7.4) to evaluate the drug release behavior. The concentrations of cisplatin in PBS were measured at different interval up to 48 h. The release percentage of cisplatin from MSNs-NH₂-poly (IA-co-PEGMA)-CDDP complexes can be calculated from the concentrations of cisplatin in PBS.

3. Results and discussion

MSNs with desirable properties such as high specific surface areas, optical transparent, chemical inert and low toxicity have been extensively explored for various applications especially in biomedical fields.[49] However, the surface of MSNs is lack of functional groups and poor solution stability.

Therefore surface modification of MSNs with polymers is of great interest to endow novel functional and improve their performance. In this work, a novel metal-free surface-initiated ATRP was reported to introduce functional polymers on MSNs that relied on the light induced controlled living radical polymerization using PTH as the organic catalyst while IA and PEGMA as the model monomers. The successful preparation of MCM41 was first confirmed by a series of characterization techniques such as XRD, TEM, ^1H NMR, FT-IR, TGA and XPS. The low-angle XRD are commonly used to investigate the ordering of the ordered mesoporous materials. As presented in **Fig. S1**, a wide diffraction peak appears between 1 and 2 degree can be found. This indicated we have successfully synthesized MSNs with rather ordered mesoporous structure. The morphology of the MSNs and MSNs-NH₂-poly(IA-co-PEGMA) was characterized by TEM. Many spherical nanoparticles with diameter about 100 nm can be observed (**Fig. 1a**). **Fig. 1b** showed the high-magnification TEM images of MSNs, we can see a lot of small regular channels arranged on the silica nanoparticles. This gives the direct evidence for the successful synthesis of MSNs. However, after surface modification with polymer, the structure of MSNs-NH₂-poly(IA-co-PEGMA) seems blurry. Moreover, the polymer coatings on MSNs could also be observed. The above results implied that the copolymers were grafted on the MSNs through the light induced surface-initiated ATRP.

Fig. 1 TEM images of MSNs. (a) Low-magnification, scale bar = 200 nm and (b) high-magnification, scale bar = 100 nm.

The successful surface modification of MSNs with polymers could also be evidenced by ^1H NMR spectrum. As shown in **Fig. 2**, a number of chemical information about the monomers of IA and PEGMA was observed. The detailed information of ^1H NMR (DMSO, δ , ppm) was described as follows. After IA was grafted on the MSNs, one methylene peak was appeared in 1.35 ppm, another methylene peak was appeared in 2.39 ppm due to the shielding effect of carboxyl. In the PEGMA monomer, a methyl peak was observed in 1.35 ppm, another methyl peak and two methylene peaks combined into a wide and strong peak in 3.2-3.6 ppm because of the electron withdrawing effect of

oxygen atom. The emergence of these peaks clearly indicates that IA and PEGMA have been successfully grafted on the MSNs via light induced ATRP.

Fig. 2 ^1H NMR spectrum of MSNs- NH_2 -poly(IA-co-PEGMA). The characteristic peaks referred to IA and PEGMA can be found in spectrum of MSNs- NH_2 -poly (IA-co-PEGMA), indicating that successful grafting of poly(IA-co-PEGMA) onto MSNs.

The MSNs- NH_2 -poly(IA-co-PEGMA) can be qualitatively confirmed by the FT-IR data in **Fig. 3**. The characteristic absorbance band at 1070 cm^{-1} of the MSNs suggests the existence of the silicon-oxygen bond (Si-O). The C-H stretching vibration is normally observed in the range between $2900\text{--}3000\text{ cm}^{-1}$, which can be evidenced the existence of CTAB in MSNs. However, the intensity of saturation C-H vibration has significantly decreased or almost completely disappeared in the sample of MSNs- NH_2 . This indicated that CTAB has been removed from the MSNs. On the other hand, a new characteristic absorbance band at 3480 cm^{-1} was emerged in the sample of MSNs- NH_2 . The change of characteristic absorbance bands suggested that MSNs were successfully grafted with $-\text{NH}_2$. After surface functionalized with polymers, the intensity of the following absorbance at 1660 cm^{-1} ($\text{C}=\text{O}$), 1410 cm^{-1} (C-H) was obviously increased. Additionally, two small peaks at about 2920 and 2840 cm^{-1} were also emerged in MSNs- NH_2 -poly(IA-co-PEGMA). This can be attributed to the CH_2 and CH_3 of poly(IA-co-PEGMA). All the above results further indicated that MSNs- NH_2 -poly(IA-co-PEGMA) have been successfully prepared via metal free light-initiated ATRP.

Fig. 3 FTIR spectra of MSNs, MSNs-NH₂ and MSNs-NH₂-poly(IA-co-PEGMA). The characteristic peak of Si-O can be found all the samples. On the other hand, the disappearance of signals between 2900-3000 cm⁻¹ in the sample of MSNs-NH₂ and re-emerged in the sample of MSNs-NH₂-poly(IA-co-PEGMA). This indicated that the surfactant CTAB has been removed from MSNs and poly(IA-co-PEGMA) has been grafted onto MSNs successfully. Moreover, the signal intensity at 1660 cm⁻¹ (C=O) has been obviously enhanced, further evidencing the immobilization of copolymers on MSNs through light induced surface-initiated ATRP.

The weight percentage of polymers grafted on the silica nanoparticles was preliminarily investigated by TGA. **Fig. 4** displayed the TGA weight loss curve of pristine MSNs, MSNs-NH₂ and MSNs-NH₂-poly(IA-co-PEGMA). From **Fig. 4**, the weight loss of pristine MSNs was about 7.5% when the temperature was raised from 30 to 160 °C. It can be attributed to the loss of water that was physically adsorbed on MSNs. Moreover, MSNs were stable without evident weight loss from 160 to 800 °C. On the contrary, there was a weight loss stage between 100 and 600 °C for MSNs-NH₂ (12%). This weight loss can be resulted from the losing of functional groups on the surface of MSNs. Compared with pristine MSNs, the TGA curve of MSNs-NH₂-poly(IA-co-PEGMA) showed a major decomposition at a temperature range from 100 to 600 °C corresponding to IA and PEGMA layer on the surface of MSNs. Especially, the weight loss with temperature between 300-400 °C should be the decomposition of PEGMA, which is well consistent with the previous reports.

Fig. 4 TGA images of MSNs, MSNs-NH₂, and MSNs-NH₂-poly(IA-co-PEGMA).

To evaluate the chemical compositions of MSNs, the survey XPS spectra ranging from 0 to 1400 eV were examined and results were displayed in **Fig. 5**. In **Fig. 5A**, the element of Si and O can be found. It can be ascribed to the TEOS a hydrolysis reaction and generate Si-O. The peaks of the element of C and N were derived from the existence of CTAB. After the surface of MSNs was coated with APTES, the peak strength of the element of C and N increased significantly (**Fig. 5B**). **Fig. 5B** suggested that APTES had successfully grafted to the surface of the MSNs. Compared with **Fig. 5B**, the most obvious change is the appearance of the element of Br (**Fig. 5C**). It is no doubt that the element of Br came from CTAB. In the last picture (**Fig. 5D**), the element of Br had disappeared again, which may be ascribed to IA and PEGMA had successfully grafted on the MSNs-Br. The introduction of polymers on MSNs will lead to the decrease of Br content in the final MSNs-NH₂-poly(IA-co-PEGMA).

Fig. 5 Survey XPS spectra of MSNs, MSNs-NH₂, MSNs-Br and MSNs-NH₂-poly(IA-co-PEGMA).

The high resolution XPS spectra of C1s, N1s, O1s and Si2p were displayed in **Fig. 6**. Compared with the sample of MSNs, a stronger peak appeared in the sample of MSNs-NH₂. It indicated that the content of C was increased and the amino group was successfully grafted onto the MSNs. A new peak appeared between 287 and 290 eV in the sample of MSNs-NH₂-poly(IA-co-PEGMA), which suggested that there was a new chemical bond formation, it can be attributed to the success of monomers grafted on the MSNs (**Fig. 6A**). **Fig. 6B** is the high resolution XPS spectra of N1s, the peak positions of the three samples were respectively in 402-404 eV, 400-403 eV and 397-401 eV, which indicated that the three kinds of N were in different environments. In MSNs, the element of N was positively charged, and the bond polarity formed by the C element is relatively large. In MSNs-NH₂, the element of N mainly existed in the amino group. In MSNs-NH₂-poly(IA-co-PEGMA), the element of N basically existed in the peptide bond. Different kinds of N chemical bond information suggested that we successfully modified the MSNs with polymers. The element of O1s and Si2p were shown in the **Fig.**

6C-D. It can be seen that the intensity of O1s and Si2p was obviously decreased in the sample of MSNs-NH₂ and MSNs-NH₂-poly(IA-co-PEGMA). This give clearly evidence for the successful surface modification of MSNs with polymers.

Fig. 6 High resolution XPS spectra of MSNs, MSNs-NH₂ and MSNs-NH₂-poly(IA-co-PEGMA). (A) The region of C1s, (B) the region of N1s, (C) the region of O1s and (D) the region of Si2p.

The element contents of MSNs, MSNs-NH₂ and MSNs-NH₂-poly(IA-co-PEGMA) were calculated by XPS results. As shown in **Table 1**, the percentages of Si and O were calculated to be 22.42% and 51.24%, respectively. The existence of the element of C and N was due to the residual of CTAB. As compared with unmodified MSNs, the percentages of Si, C, O and N in the samples of MSNs-NH₂ were changed to 17.2%, 41.84%, 37.25% and 3.71%. The decrease of contents of Si and O as well as increase of N percentages suggested that APTES have been successfully immobilized on the MSNs by hydrolysis reaction. **Fig. S2** shows the Br3d spectra of unmodified MSNs and their composites. It can be seen that the element Br3d was emerged in the sample of MSNs-Br. This result clearly confirms that initiator has been successfully introduced on the surface of MSNs. Furthermore, the percentage of the C element was raised to 56.82%, but the content of Si was decreased significantly in the sample of MSNs-NH₂-poly(IA-co-PEGMA). These results indicated that IA and PEGMA were linked onto MSNs-NH₂ via surface-initiated light induced ATRP.

Table 1 Element content of MSNs, MSNs-NH₂, MSNs-Br, MSNs-NH₂-poly(IA-co-PEGMA)

	Si(%)	C(%)	N(%)	O(%)	Br(%)
MSNs	22.42	25.17	1.4	51.01	0
MSNs-NH ₂	17.64	41.09	4.25	37.02	0
MSNs-Br	16.5	44.34	3.54	34.21	1.41
MSNs-NH ₂ -poly(IA-co-PEGMA)	7.05	58.59	1.95	32.41	0

Because of the introduction of carboxyl groups on the surface of MSNs, the potential utilization of MSNs-NH₂-poly(IA-co-PEGMA) for loading and controlled release of cisplatin was further conducted. It is well known that cisplatin can be coordinated with carboxyl groups and be loaded on the drug carriers with high efficiency. On the other hand, the cisplatin can be released from MSNs-NH₂-poly(IA-co-PEGMA)-CDDP complexes under acidic environment. The cisplatin concentrations released from MSNs-NH₂-poly(IA-co-PEGMA)-CDDP complexes can be determined by UV-Vis spectroscopy with the maximum absorption wavelength at 705 nm, which is the absorbance of cisplatin and 1, 2-diaminobenzene complexes. The standard curve based on the UV absorbance was listed in **Fig. S3**. On the basis of the equation and the absorbance of the supernatant, the amount of cisplatin on the MSNs-NH₂-poly(IA-co-PEGMA) was calculated to be about 226 mg/g. **Fig. 7** shows the cisplatin release behavior of MSNs-NH₂-poly(IA-co-PEGMA)-CDDP complexes under the pH 5.5 and 7.4. It can be inferred that at the beginning of the release, the amount of drug release increased rapidly over time. The amount of drug release increased slowly between 2 and 20 h at pH = 5.5. After 25 h later, the percentage of drug release has reached 60%, the percentage of drug released was no longer increased over time. Compared with the percentage of drug release at pH = 5.5, the percentage of drug release at pH = 7.4 is less than 10%. The above results implied that MSNs-NH₂-poly(IA-co-PEGMA) can be used for carrying cisplatin and release it with pH responsiveness. More importantly, the drug loading capability of MSNs-NH₂-poly(IA-co-PEGMA) can also be adjusted through tuning the monomer IA feed ratio and the polymerization conditions. It is therefore, we can we adjusted the final performance of MSNs-NH₂-poly(IA-co-PEGMA) through the light induced metal free ATRP.

Fig. 7 The release behavior of cisplatin from the MSNs-NH₂-poly(IA-*co*-PEGMA)-CDDP complexes at pH values of 5.5 and 7.4. It can be seen that the drug release ratio at pH = 5.5 is much faster than that at 7.4. The above results indicated that the cisplatin can be controlled release from MSNs-NH₂-poly(IA-*co*-PEGMA)-CDDP complexes with pH responsiveness.

4. Conclusions

In summary, we have developed a mild and efficient method for surface **modification** of MSNs using an organic photoredox catalyst via a light induced metal-free ATRP. The results demonstrated that MSNs-NH₂-poly(IA-*co*-PEGMA) can be successfully prepared through the simple and effective light induced ATRP. As compared with the traditional ATRP, the light induced surface-initiate ATRP could avoid the using metal catalysts and organic ligands. On the other hand, the polymerization temperature is relative low and the polymerization speed is much faster. The resultant MSNs-NH₂-poly(IA-*co*-PEGMA) display good dispersity in water and organic solvents. More importantly, the anticancer agent cisplatin could be effectively loaded on MSNs-NH₂-poly(IA-*co*-PEGMA). The cisplatin loading capability is as high as 226 mg/g. Furthermore, the cisplatin can be released from MSNs-NH₂-poly(IA-*co*-PEGMA)-CDDP complexes faster in the acidic environment. Therefore, we can conclude that the light induced surface-initiated ATRP is a very promising method for fabrication of multifunctional MSNs composites, which possess many interest properties for biomedical applications.

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