Zeolitic Imidazolate Framework-8 Capped Mesoporous Silica Nanoparticles for pH-Controlled Drug Release

Jiaxing Liu, Xianxian Yao, and Yufang Zhu*

School of Materials Science and Engineering, University of Shanghai for Science and Technology, 516 Jungong Road, Shanghai 200093, P. R. China

* Corresponding Author. Email: yfzhu@usst.edu.cn

Received January 12, 2018; Revised January 18, 2018

Citation: J. Liu, X. Yao, and Y. Zhu, Nano Adv., 2018, 3, 1-5.

We proposed a strategy to construct zeolitic imidazolate framework-8 (ZIF-8) capped mesoporous silica nanoparticles (MSN) for potential pH-controlled drug release. The structure, drug loading and release behavior of the ZIF-8 capped MSN nanoparticles were evaluated. The results showed that ZIF-8 capped MSN nanoparticles had a core-shell structure. Using camptothecin (CPT) as a model anticancer drug, the CPT-loaded MSN/ZIF-8 nanoparticles could release CPT rapidly in pH 4.5 solution, but very slow in pH 7.4 solution, indicating pH-dependent drug release behavior. Therefore, ZIF-8 capped MSN nanoparticles have great potential for cancer therapy with pH-controlled drug release.

KEYWORDS: Mesoporous silica; Zeolitic imidazolate framework-8; Nanocarrier; Controlled drug release

1. Introduction

Controlled drug release is of great important in drug delivery. To date, a variety of smart nanocarriers have been developed for controlled drug release.1 Among them, mesoporous silica nanoparticles (MSN) are promising candidate nanocarriers for drug delivery owing to their high surface area, large pore volume, good biocompatibility and ease of surface functionalization.2-4 Importantly, MSN nanoparticles can be functionalized to construct the responsive caps on the mesopores for controlled drug release. Many studies have reported the design of responsive caps, such as nanoparticles, polymers, supramolecular assemblies and biomolecules, to control drug release from MSN in response to different stimuli including pH, temperature, light, redox activation, enzymes, competitive binding, etc.5-11

Of the stimuli previously reported, the construction of pH-triggered caps was one of the most efficient strategies for controlled drug release due to the different pH environment in cells, tissue or body.14-17 For example, the interstitial or extracellular environment in tumors tends to be more acidic than the normal tissues, and the endosomes/lysosomes in cancer cells exhibit even lower pH values.18-20 To date, much effort has been made to develop pH-triggered drug release systems using MSN as nanocarriers.21-27 For example, Zou et al. proposed a natural gelatin capped MSN for intracellular anticancer drug controlled release.21 The gelatin capping layer could effectively block drug release at neutral pH, but the slightly acidic environment triggered drug release due to the enhanced electrostatic repulsion between the gelatin and MSN, resulting in uncapping of the gelatin layer.22 Chen et al. used i-motif quadruplex DNA to cap the mesopores of MSN and realized pH-controlled drug release based on the morphology change of the DNA chains.23 Huang et al. prepared graphene quantum dots (GQDs) grafted MSN nanocarriers (GQDs-MSN) through electrostatic interaction, and in vitro assay showed the release of aspirin from the aspirin-loaded GQDs-MSN was pH-dependent.24 Recently, our group developed a potential pH-controlled protein drug delivery system based on aldehyde-functionalized dendritic MSN as nanocarriers. Bovine serum albumin (BSA) was used as a model protein drug to load in MSN via the formation of imine bonds between aldehyde groups on MSN and primary amines of BSA molecules, and BSA release from MSN could be triggered by acidic environment owing to pH-sensitivity of imine bonds.25 However, most of developed strategies suffered from the complicated preparation procedures, unstable caps or difficulty in control manner. It is still a great challenge to develop novel pH-sensitive caps to construct pH-triggered drug release system based on MSN nanoparticles.

Zeolitic imidazolate framework-8 (ZIF-8) is one type of non-toxic and biocompatible metal-organic frameworks, which consist of inorganic zinc ions acting as nodes connected by 2-methylimidazolate linkers.28 Previous studies demonstrated that ZIF-8 is stable under physiological conditions and decomposes under acidic conditions, which could be used for...
pH-sensitive drug delivery or pH-sensitive caps. For example, Sun et al. loaded (5-fluorouracil) 5-Fu in ZIF-8 nanoparticles, and about 50% of 5-Fu was released via slow release during the early stage in pH 7.4 solution, but the 5-Fu release rate was significantly increased in pH 5.0 solution. Zheng et al. reported one-pot synthesis of ZIF-8 with encapsulated doxorubicin (DOX), and showed promising in pH-responsive drug delivery for cancer therapy. Song et al. encapsulated the photosensitizer zinc phthalocyanine (ZnPc) in ZIF-8 nanoparticles to improve the biocompatibility and passive cancer targeting of the photosensitizer ZnPc in photodynamic therapy, and the results indicated that the ZnPc-encapsulated ZIF-8 nanoparticles exhibited good pH-dependent release behaviour, and the ZnPc release could occur in the acidic environment of lysosomes. However, to the best of our knowledge, there are few reports on describing the preparation of ZIF-8 capped MSN nanoparticles for pH-controlled drug release.

In this study, we proposed a concept to develop ZIF-8 capped MSN nanoparticles (MSN/ZIF-8) as nanocarriers for potential pH-controlled drug release. As shown in Figure 1, MSN nanoparticles are functionalized with carboxyl groups to form carboxyl-functionalized MSN nanoparticles (MSN-COOH). After loading drug, MSN-COOH nanoparticles are capped by ZIF-8 layer through the deposition of zinc ion and 2-methylimidazole for capping the mesopores. When applied in acidic environment, the loaded drug could be triggered to release from MSN nanoparticles due to the decomposition of ZIF-8 layer.

2. Experimental

2.1 Materials and chemicals

Tetraethyl orthosilicate (TEOS), triethanolamine (TEA), zinc nitrate hexahydrate (Zn(NO$_3$)$_2$·6H$_2$O), ethanol, dimethylformamide were obtained from Sinopharm Chemical Reagent Co. Ltd. PBS (pH 7.4) and camptothecin (CPT) were obtained from Sangon Biotech (Shanghai) Co. Ltd. Hexadecyltrimethylammonium p-toluenesulfonate (CTAT), 2-methylimidazole, 3-aminopropyltriethoxysilane (APTES), succinimide anhydride were obtained from Sigma-Aldrich. Ultrapure water was obtained from Millipore pure water system. All other chemicals were of analytical-reagent grade and used without further purification.

2.2 Preparation of carboxyl-functionalized mesoporous silica nanoparticles (MSN-COOH)

MSN nanoparticles were prepared according to our reported method with some modification. Briefly, CTAT (0.6836 g) and TEA (0.4 g) were dissolved in water (60 mL) under stirring and heated to 80 °C. After vigorous stirring for 30 min, 2 mL of TEOS was added into the above solution, and continue to stir for another 2 h. Then, the white precipitates were collected by centrifugation, washed with water and ethanol for several times, and then dried in vacuum at 60 °C for 12 h. Finally, MSN nanoparticles were obtained by the calcination of white precipitates at 650 °C for 6 h to remove the organic templates.

Carboxyl-functionalized MSN nanoparticles (MSN-COOH) were obtained as follows. 5 mL of 3-aminopropyltriethoxysilane (APTES) and 2.5 g of succinic anhydride were dispersed in 30 mL DMF, and allowed to react for 3 h at 30 °C. Subsequently, 0.5 g of MSN nanoparticles were dispersed in 40 mL DMF, and the suspension was added into the above solution under magnetic stirring. After stirring for 12 h, the suspension was collected by centrifugation and extensively washed with DMF. Finally, MSN-COOH nanoparticles were obtained after dried in vacuum at 60 °C for 24 h.

2.3 Preparation of CPT-loaded MSN/ZIF-8 nanoparticles (CPT-MSN/ZIF-8)

Typically, 50 mg of MSN-COOH nanoparticles was dispersed in 10 mL of CPT solution (0.5 mg/mL in ethanol), the suspension was stirred under dark condition at room temperature for 24 h.
In vitro release of CPT from CPT-MSN/ZIF-8 nanoparticles

In vitro release of CPT from CPT-MSN/ZIF-8 nanoparticles were performed in the release solution of pH 7.4 or pH 4.5 with shaking at 100 rpm. The temperature of the release solution was kept at 37 °C. Typically, 10 mg of CPT-MSN/ZIF-8 nanoparticles were dispersed in 1.0 ml of PBS solution with pH 7.4 or pH 4.5 at 37 °C. At predetermined time intervals, the release system was centrifuged and 20 μL of the supernatant solution was taken out for UV-vis analysis to determine the released CPT amount, and replaced with the same amount of fresh solution each time. Before determination, a calibration curve was recorded by measuring the absorbance values at the absorbance of CPT at 365 nm.

2.5 Characterization

Scanning electron microscopy (SEM) was carried out on an FEI Quanta 450 field emission scanning electron microscope. Transmission electron microscopy (TEM) images were obtained with a Tecnai G2 F30 electron microscope operated at an acceleration voltage of 300 kV. Powder X-ray diffraction (XRD) patterns were obtained on a D8 ADVANCE powder diffractometer using Cu Kα1 radiation (0.15405 nm). N₂ adsorption–desorption isotherms were obtained on a Quadrasorb SI automated surface area and pore size analyzer at -196 °C under continuous adsorption condition. UV–vis analysis was performed on a Nanodrop 2000C spectrophotometer.

3. Results and discussion

Figure 2 shows XRD patterns of CPT-loaded MSN-COOH nanoparticles before and after ZIF-8 coating. It can be observed that CPT-loaded MSN-COOH nanoparticles had no diffraction peaks appearing on the XRD pattern except for a broad reflection at 2θ = 15–30°, which indicates the amorphous phase of MSN nanoparticles. After coating with ZIF-8 layer on the surface of MSN nanoparticles, the characteristic diffraction peaks of ZIF-8 component were detected, which confirmed the ZIF-8 component had formed during the deposition process of zinc ion and 2-methylimidazole.

The representative SEM and TEM images of CPT-MSN/ZIF-8 nanoparticles are shown in Figure 3. CPT-MSN/ZIF-8 nanoparticles are spherical and uniform, and the average particle size is about 100 nm. As shown in TEM image, the core-shell structure of CPT-MSN/ZIF-8 nanoparticles can be clearly observed, and MSN nanoparticles as cores are coated by a thin layer (ca. 10 nm). Together with the XRD results, the thin layer could be assigned to ZIF-8 component. Therefore, ZIF-8 layer could coat on the surface of MSN nanoparticles through the deposition of zinc ion and 2-methylimidazole, and thereby provide the possibility for pH-controlled drug release.

To verify the CPT loading in MSN/ZIF-8 nanoparticles, UV-vis analysis and N₂ physiosorption measurement were used in this study. Figure 4 shows UV-vis absorbance spectra of CPT, CPT-loaded MSN-COOH and CPT-MSN/ZIF-8 nanoparticles. It
can be seen that the CPT loaded in MSN-COOH nanoparticles did not change the characteristic absorbance peaks. After coating with ZIF-8 layer on the surface of CPT-loaded MSN-COOH nanoparticles, the characteristic absorbance peak at 365 nm can also be observed, suggesting the CPT loading in CPT-MSN/ZIF-8 nanoparticles. The loading capacity of CPT was estimated to be about 30 μg/mg by UV-vis analysis. Figure 5 shows N\textsubscript{2} adsorption-desorption isotherms and the corresponding pore size distributions for MSN/ZIF-8 and CPT-MSN/ZIF-8 nanoparticles. It is obvious that both types of nanoparticles exhibited the typical microporous isotherm, suggesting the coating of ZIF-8 layer on MSN nanoparticles. MSN/ZIF-8 nanoparticles had a BET surface area of 768.5 m\textsuperscript{2}/g and a pore volume of 0.57 cm\textsuperscript{3}/g, respectively. While for CPT-MSN/ZIF-8 nanoparticles, the N\textsubscript{2} adsorbed amount decreased significantly, and the BET surface area and pore volume decreased to be 530.4 m\textsuperscript{2}/g and 0.36 cm\textsuperscript{3}/g respectively. The decreases in surface area and pore volume of CPT-MSN/ZIF-8 nanoparticles could be attributed to the CPT loading in MSN/ZIF-8 nanoparticles, which is in accordance with the result of UV-vis analysis.

The release of CPT from CPT-MSN/ZIF-8 nanoparticles were performed at 37 °C in PBS buffer with pH 7.4 and pH 4.5, respectively. As shown in Figure 6, the CPT release from CPT-MSN/ZIF-8 nanoparticles was very low and ca. 3.6% of CPT was released after 10 h in pH 7.4 solution. In contrast, the CPT release rate exhibited a significant increase in pH 4.5 solution, and ca. 25.6% of CPT was released after 10 h. It indicated the pH-controlled release of CPT from CPT-MSN/ZIF-8 nanoparticles. Generally, the pH environment of cells is nearly pH 7.4, while that of the endosomes/lysosomes in cells is estimated to be pH 4.5–6.0. Therefore, CPT-MSN/ZIF-8 nanoparticles could be applied for intracellular drug delivery due to the pH-sensitive ZIF-8 layer on MSN nanoparticles, which could enhance the drug delivery efficiency and decrease the side effect of toxic drug.
4. Conclusions

In this study, a pH-controlled release nanocarrier based on ZIF-8 capped MSN nanoparticles has been successfully developed. The results showed that CPT, a model anticancer drug, was loaded in MSN nanoparticles and could be blocked by ZIF-8 layer under neutral condition. CPT release could be controlled by pH-triggered decomposition of ZIF-8 layer under acidic condition. Therefore, ZIF-8 capped MSN nanoparticles could be a promising nanocarrier for potential pH-controlled drug release.

Acknowledgements

The authors gratefully acknowledge the support by National Natural Science Foundation of China (no. 51572172).

Notes and references

15. X. Ma, O. S. Ong and Y. Zhao, Biomater. Sci., 2013, 1, 912.