Acta Biomaterialia 51 (2017) 471–478

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Controlled release of silyl ether camptothecin from thiol-ene click chemistry-functionalized mesoporous silica nanoparticles

Yue Yan [a], Jie Fu [a,*], Tianfu Wang [b], Xiuyang Lu [a]

[a] Key Laboratory of Biomass Chemical Engineering of Ministry of Education, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, China
[b] Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi 830011, China

ARTICLE INFO

Article history:
Received 22 September 2016
Received in revised form 12 December 2016
Accepted 23 January 2017
Available online 25 January 2017

Keywords:
Drug delivery
Silyl ether
Click chemistry
Mesoporous silica nanoparticles

ABSTRACT

As efficient drug carriers, stimuli-responsive mesoporous silica nanoparticles are at the forefront of research on drug delivery systems. An acid-responsive system based on silyl ether has been applied to deliver a hybrid prodrug. Thiol-ene click chemistry has been successfully utilized for tethering this prodrug to mesoporous silica nanoparticles. Here, by altering the steric bulk of the substituent on the silicon atom, the release rate of a model drug, camptothecin, was controlled. The synthesized drug delivery system was investigated by analytical methods to confirm the functionalization and conjugation of the mesoporous silica nanoparticles. Herein, trimethyl silyl ether and triethyl silyl ether were selected to regulate the release rate. Under normal plasma conditions (pH 7.4), both types of camptothecin-loaded mesoporous silica nanoparticles (i.e., MSN-Me-CPT and MSN-Et-CPT) did not release the model drug. However, under *in vitro* acidic conditions (pH 4.0), based on a comparison of the release rates, camptothecin was released from MSN-Me-CPT more rapidly than from MSN-Et-CPT. To determine the biocompatibility of the modified mesoporous silica nanoparticles and the *in vivo* camptothecin uptake behavior, MTT assays with cancer cells and confocal microscopy observations were conducted, with positive results. These functionalized nanoparticles could be useful in clinical treatments requiring controlled drug release.

Statement of Significance

As the release rate of drug from drug-carrier plays important role in therapy effects, trimethyl silyl ether (TMS) and triethyl silyl ether (TES) were selected as acid-sensitive silanes to control the release rates of model drugs conjugated from MSNs by thiol-ene click chemistry. The kinetic profiles of TMS and TES materials have been studied. At pH 4.0, the release of camptothecin from MSN-Et-CPT occurred after 2 h, whereas MSN-Me-CPT showed immediate drug release. The results showed that silyl ether could be used to control release rates of drugs from MSNs under acid environment, which could be useful in clinical treatments requiring controlled drug release.

1. Introduction

Advances in utilizing mesoporous silica nanoparticles (MSNs) as vehicles for drug delivery have attracted interest over the past few decades [1–3]. MSNs have been shown to have high surface areas and large pore volumes, and furthermore, their surfaces are very easy to be functionalized. As such, MSNs provide a potential new strategy for drug delivery. Current drug treatment methods have limited efficacy and detrimental side effects. To overcome these disadvantages, MSNs could be used. The application of MSNs in drug delivery could be realized through the functionalization of the interior and exterior surfaces of the mesoporous material. Because of the high density of silanol, grafting of different organic silanes (i.e., $(RO)_3SiR'$) can be used to modify the surface to load various molecules and confer diverse functionalities in terms of responsiveness to stimulation [4–7].

Strategies and mechanisms for conferring different stimulation-responsive functions have been employed in a number of processes. For instance, stimuli-responsive systems have exploited changes in pH [8,9], light [10,11], temperature [12], enzyme concentrations [13], redox reactions [14], and magnetic field strengths

* Corresponding author.
E-mail address: jiefu@zju.edu.cn (J. Fu).

http://dx.doi.org/10.1016/j.actbio.2017.01.062
1742-7061/

[13]. Acid-activated release mechanisms are particularly attractive because acidic environments are present at most disease sites and in the endocytic pathways in tumor cells. The tethering of drugs onto the surfaces of carriers by acid-labile bonds, such as bonds involving trityls [15], vinyl ethers [16], poly(ketals) [17,18], hydrazone [19], thiopropionates [20], and poly(ortho esters) [21], has been demonstrated by a number of studies. However, these strategies have drawbacks, including poor tunability, complicated multistep syntheses, and toxic byproducts. To overcome these disadvantages, different bonds should be considered for drug delivery systems.

Silyl ethers are widely used to protect side groups in organic chemistry [22]. As such, silyl ethers could be exploited in the development of drug delivery vehicles for three reasons: (1) the degradation rate of silyl ethers can be modulated by altering the steric bulk surrounding the silicon atom, which may be useful for fine-tuning the properties of a drug delivery system; (2) upon degradation, silyl ethers do not produce toxic byproducts; and (3) the use of silyl ethers only requires a simple procedure and mild reaction conditions. One type of silyl ether used for the protection of 1,2- and 1,3-diols consists of a C–O–Si(R)$_2$–O–C linkage [23]. A less-hindered R group (*e.g.,* dimethyl) makes the silyl ether susceptible to acid-catalyzed hydrolysis, whereas a diethyl or diisopropyl R group provides steric protection. Parrott et al. constructed a system of monoclonal antibodies coupled with gemcitabine through silyl ether linkers and demonstrated selective release profiles at endosomal pH levels (pH 5.0) and stable profiles under systemic conditions (pH 7.4)[24]. The authors further reported that drug-loaded PRINT nanoparticles fabricated with bifunctional silyl ethers showed an acid-responsive functionality. By increasing the steric bulk of the alkyl substituent on the silicon atom, the authors decreased the release rates [25]. Thus, silyl ether linkers have been advantageously used in acid-responsive drug delivery applications.

Since Sharpless et al. introduced the concept to facilitate organic reactions with high selectivity, few side products, and mild reaction conditions in 2001 [26], click reactions have been used in a wide range of applications in materials science and synthetic chemistry. A light-mediated thiol-ene [27] radical reaction has recently drawn interest. The reaction is characterized by rapid reaction rates, benign catalysts, insensitivity to oxygen and water, and eco-friendly solvents. These properties have popularized the reaction. As shown in Fig. 1, the reactive carbon-carbon double bonds (ene) on functionalized silyl ether provide the possibility for incorporation with thiol-enes. To the best of our knowledge, no reports have combined the advantages of both silyl ethers as acid-responsive bonds and facile, highly efficient click chemistry. This controllable drug delivery system comprises sensitive linkers (silyl ethers), mild bridging bonds (thiol-enes via click chemistry) and biocompatible carriers (MSNs) and could be used as a drug carrier for cancer treatment.

In this study, we chose trimethyl silyl ether (TMS) and triethyl silyl ether (TES) as acid-sensitive silanes to control the rates of release of a model drug from MSNs by thiol-ene click chemistry. The synthesized carriers, that is, MSN-Me-CPT and MSN-Et-CPT, were characterized by cross-polarization/magic angle spinning ^{13}C nuclear magnetic resonance (CP/MAS ^{13}C NMR), Fourier transform infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), X-ray photoelectron spectroscopy (XPS), and Brunauer-Emmett-Teller (BET) analysis to identify the different silyl ether structures. We explored the release profiles of these two types of MSNs *in vitro* under normal plasma pH conditions and under acidic conditions. MTT assays with cancer cells and confocal microscopy were utilized to study the biocompatibility of the modified MSNs and the *in vivo* camptothecin uptake behavior. The results showed that silyl ether could be used to control the rates of release of drugs from MSNs by thiol-ene click chemistry.

2. Experimental procedures

The following reagents were used in this study as received, without further purification: N-cetyltrimethylammonium bromide (CTAB, Aldrich, ⩾99.0%), fluorescein isothiocyanate (FITC, Aldrich, ⩾98.0%), tetraethoxysilane (TEOS, Aldrich, ⩾99.0%), 3-mercapto propyltrimethoxysilane (MPTMS, Aldrich, ⩾97.0%), sodium hydroxide (Sinopharm, ⩾96.0%), hydrochloric acid (Sinopharm, 36.0%-38.0%), methanol (Sinopharm, ⩾99.5%), 4-dimethylaminopyridine (Aldrich, ⩾99.0%), imidazole (Aldrich, ⩾99.0%), N,N-dimethylformamide (Aldrich, ⩾99.0%), dichlorodimethylsilane (Aldrich, ⩾98.5%), hydroxyethyl acrylate (Aldrich, ⩾99.0%), dichlorodiethylsilane (Aldrich, ⩾97.0%), ethyl acetate (Sinopharm, ⩾99.5%), hexane (Sinopharm, ⩾99.5%), dichloromethane (Sinopharm, ⩾99.5%), hydroxyethyl acrylate (Aldrich, ⩾99.0%), sodium chloride (Sinopharm, ⩾96.0%), and benzoin dimethyl ether (DMAP, Aladdin, ⩾99.0%).

2.1. Synthesis of MSN-SH

To synthesize MSN-SH, a co-condensation method was utilized. Briefly, 3.50 mL of a 2.00 M sodium hydroxide aqueous solution was added to 480 mL of deionized water, and 1.00 g of CTAB (2.74 mmol) was dissolved in the solution. The solution temperature was increased to 353 K, and the solution was stirred at 600 rpm using an Isotemp digital stirring hot plate. Then,

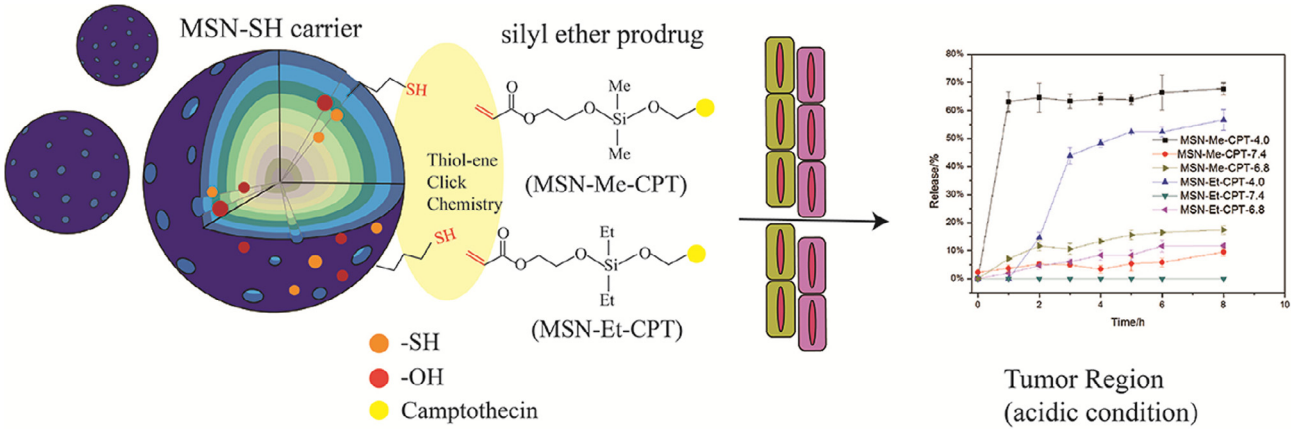

Fig. 1. Illustration of an acid-responsive silyl ether prodrug being released from an MSN-SH nanocarrier.