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Reversible crosslinking terpolymer shell-based mesoporous silica nanoparticles as on-off nanocarriers for pyrene-releasing application

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ABSTRACT

Mesoporous silica nanoparticles (MSNs) were successfully endowed with on-off transport ability and stimuli-responsive property through surface modification. The MSNs with large specific surface areas were synthesized using optimized Stöber method, and then successively modified by amino- and 2-bromoisobutyrate-functionalization. Finally, MSNs grafted with reversible crosslinking terpolymer (MSNs-g-PDMV) were achieved through surface-initiated atom transfer radical polymerization. The resultant MSNs-g-PDMV and their intermediates were confirmed by TEM, SEM, XPS, FTIR, and so on. Pyrene was chosen to evaluate their drug loading and controlled release properties. Owning to crosslinkage and de-crosslinkage of coumarin unit in PDMV under different ultraviolet (UV) irradiations, the polymeric chains substantially acted as on-off gate of MSNs to control the transport channel in mesoporous silica shell. The pyrene encapsulation percentage (31.6%) of MSNs-g-PDMV under the irradiation at 365 nm was only half of that under dark condition (60.3%). Cumulative release efficiency under the irradiation at 365 nm was obviously lower than that at 254 nm at the same temperature. In addition, thermal-responsive property of PDMV offered polymeric MSNs temperature sensitivity. Compared with pyrene-releasing experiment at 25 °C, a moderate drop in release efficiency occurred at 45 °C regardless of 254 nm or 365 nm UV irradiation.

1. Introduction

As one of the hottest research areas in Nano science, mesoporous nanoparticles have presented tremendous development in sorbents [1], catalyst carriers [2,3], dyes [4], and drug delivery systems [5–7] due to their ordered pore structure, high surface area, and tunable pore size. In recent years, the drug and gene delivery systems of mesoporous silica nanoparticles (MSNs) have also been extensively explored because the silica materials are of low toxicity, high permeability, and good biocompatibility [8–17]. For example, Yang et al. [11] have presented a review of significant research from poly (glycidyl methacrylate) (PGMA)-based drug delivery systems to MSN@PGMAs hybrid nanocarriers, and their bioapplications especially in the field of stimuli-responsive drug release are highlighted. The fabrication of MSNs is simple, scalable, controllable, and cost-effective, so MSNs hold the promise to be developed as versatile drug delivery systems arming toward clinical production [5,18].

Based on MSNs, further efforts have been devoted to organic/inorganic hybrid preparation, the regulation of pore structure, and surface modification [19–23]. Surface modification of MSNs plays pivotal role in altering the surface reactivity, improving the biocompatibility, and introducing the environmental responsiveness. Because of existence of abundant silanol groups, MSNs can be regulated by different surface functionalization via amino (-NH_2), phenyl (-Ph), carboxyl (-COOH), and methyl phosphonate groups [5,24]. Among them, endowing MSNs with on-off transport ability and stimuli-responsive property through surface modification is the most interesting. In order to meet this requirement, smart stimuli-responsive (pH, light, ultrasound, redox, enzymes, magnetic field, and so on) “decorations” have been widely introduced into MSNs. The photo-responsive constituent of “decorations” includes coumarin derivatives [25–27], spiropyran derivatives [28–30], azobenzene derivatives [31–33], and others [34–37]. For instance, Zink et al. [38] used the photocontrollable static and dynamic properties of azobenzene derivatives in and on mesopores to prepare MSNs hybrid materials, which enabled them to be externally controlled so that the expulsion of dye molecules from the mesopores could be started and stopped at will.

In addition, MSNs grafted with light-responsive polymer on the outer surface are developed as novel nanocarrier. Copolymer poly

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(N-isopropylacrylamide-co-2- nitrobenzyl acrylate), bearing photo-cleavable hydrophobic 2-nitrobenzyl groups, was grafted on the surface of MSNs by Zhao et al. [39]. The system possessed advantages such as non-invasive and high spatiotemporal resolution resulting from the using of light stimulus, as well as good biocompatibility and facile functionalization. Li et al. [40] fabricated a light-responsive nanocarrier based on hollow silica nanoparticle modified with spiropyran-containing polymer via a simple self-assembly process. The spiropyran-containing amphiphilic copolymer could shift its hydrophilic-hydrophobic balance to become hydrophilic upon UV ($\lambda = 365$ nm) irradiation, followed by the uncaging and release of the pre-loaded anticancer drug. However, to the best of our knowledge, encapsulation and release of guest molecules from MSNs modified with photo-responsive reversible crosslinking terpolymer is rarely reported.

In the present work, we designed polymeric MSNs, in which photo-responsive coumarin derivatives were chemically incorporated into the system at the molecular level. The MSNs were synthesized by using cetyltrimethylammonium bromide (CTAB) as the structure-directing agent and tetraethoxysilane (TEOS) as the silicon source, and then successively modified by amino-functionalization and 2-bromoisobutyrate-functionalization. Subsequently, poly (2-(dimethylamino)ethyl methacrylate-co-methyl methacrylate-co-7-(4-inylbenzyloxyl)-4-methylcoumarin) P(DMAEMA-co-MMA-co-VM) (PDMV), was grafted on the surface of MSNs via surface-initiated atom transfer radical polymerization (SI-ATRP) [29,41]. Typical fluorescent dye pyrene was chosen to investigate the loading capacity of the composited nanoparticles through encapsulation into the pore channels of MSNs. Moreover, photo-responsive groups of VM in PDMV make the crosslinkage and decrosslinkage of polymeric MSNs occur easily under the irradiation at 365 nm and 254 nm, respectively. The PDMV grafting chains can act as on-off gate to control encapsulating and releasing process of MSNs. The polar groups of MMA side chains can form intermolecular hydrogen bonds, thereby improving the stability of the grafting chains. In addition, thermal-responsive property of DMAEMA in PDMV offers polymeric MSNs temperature sensitivity. Control over temperature facilitates us to investigate the effect of the collapse of the grafting chains on releasing pyrene of MSNs.

2. Experimental

2.1. Materials

7-(4-Vinylbenzyloxyl)-4-methylcoumarin (VM) was synthesized according to methods described in the literatures [42–45]. 2-(Dimethylamino)ethyl methacrylate (DMAEMA, 99%, Aladdin) and methyl methacrylate (MMA, 99%, Adamas) were passed through a basic alumina column to remove inhibitors before use. Ethyl 2-bromoisobutyrate (EBIB, 98%, TCI) as the initiator, copper(I) bromide (CuBr, 99%, Aladdin) as the catalyst, *N,N,N′,N″,N‴*-pentamethyldiethylenetriamine (PMDETA, 98%, TCI) as the ligand, cetyltrimethylammonium bromide (CTAB, 99%+), tetraethoxysilane (TEOS, 99.5%), 3-aminopropyl-triethoxysilane (APTES, 99%+), 2-bromoisobutyryl bromide (BIBB, 97%, TCI), tetrahydrofuran (THF, 99%), pyrene (98%), ammonium hydroxide (25%), ethanol, pyridine, toluene, sodium hydroxide (NaOH), and ammonium nitrate (NH_4NO_3) were all used as received.

2.2. Preparation of initiator-functionalized mesoporous silica nanoparticles

The initiator-functionalized MSNs were prepared by using CTAB as the structure-directing agent and BIBB as the initiator source under mild conditions. The synthesis and modification procedure of MSNs was shown in Scheme 1.

2.2.1. Synthesis of mesoporous silica nanoparticles (MSNs)

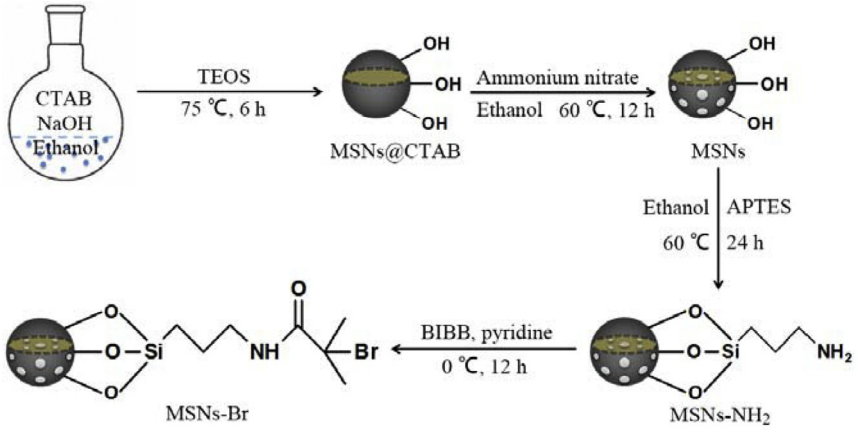
Stöber method with some optimizations was used to synthesis MSNs under mild conditions [46,47]. In a typical procedure, 360 ml CTAB (aq, 2.25 $g \cdot l^{-1}$), 40 ml ethanol and 0.224 g NaOH in sequence were added into a closed vessel under vigorous stirring at 75 °C. After the mixed solution became clear and homogeneous, 17 ml TEOS as the silicon source was added quickly and stirred continuously for 6 h. The as-synthesized materials (labelled as MSNs@CTAB) were centrifugated (8000 rpm), washed for five times with large amount of ethanol, and then dried overnight under vacuum at 40 °C. In order to remove CTAB and other redundant components, the final products were washed deeply by a mixture of NH_4NO_3 and ethanol (1 g NH_4NO_3: 100 ml ethanol) at 60 °C for 12 h to obtain the MSNs.

2.2.2. Synthesis of amino-functionalized mesoporous silica nanoparticles (MSNs-NH_2)

2 g MSNs was dispersed in 100 ml ethanol and then transferred to a 250 ml round-bottom flask in oil bath at 60 °C. 0.1 ml ammonium hydroxide and 1 ml APTES were added into reaction system dropwise. Vigorous stirring was continued for 24 h. The product (MSNs-NH_2) was centrifugated, successively washed with ethanol and toluene for five times, and then dispersed in 100 ml toluene.

2.2.3. Synthesis of 2-bromoisobutyrate-functionalized mesoporous silica nanoparticles (MSNs-Br)

The MSNs-NH_2 suspension (45 ml) and pyridine (0.3 ml) were placed into a 100 ml flat-bottom flask in an ice-water bath. Then, 0.3 ml BIBB was added dropwise and the mixture was stirred continuously for 12 h at 0 °C. In order to purify the nanoparticles, the



Scheme 1. Schematic illustration for the synthesis and modification procedure of MSNs.

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