Microporous and Mesoporous Materials 152 (2012) 16–24

Contents lists available at SciVerse ScienceDirect

Microporous and Mesoporous Materials

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

# Hollow mesoporous silica nanoparticles conjugated with pH-sensitive amphiphilic diblock polymer for controlled drug release

Xiao Mei, Dongyun Chen, Najun Li *, Qingfeng Xu, Jianfeng Ge, Hua Li, Jianmei Lu *

*Laboratory of Absorbent Materials and Techniques for Environment, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China*

ARTICLE INFO

*Article history:*
Received 16 September 2011
Received in revised form 25 October 2011
Accepted 6 December 2011
Available online 13 December 2011

*Keywords:*
Hollow mesoporous silica nanoparticles
Atom transfer radical polymerization
pH-sensitive
Controlled drug release

ABSTRACT

A pH-sensitive amphiphilic diblock polymer (poly(PDM-*b*-PEGMA)) was grafted from the surface of hollow mesoporous silica nanoparticles (HMS) via atom transfer radical polymerization (ATRP). The morphology of the obtained core–shell nanocomposites, HMS@poly(PDM-*b*-PEGMA), was determined by transmission electron microscopy (TEM) and scanning electron microscope (SEM). The nanocomposites could be used as drug carriers due to the excellent biocompatibility with a high drug loading efficiency as 80%. Furthermore, less than 10 wt.% of DOX was released from the nanocomposites in neutral condition. When the solution is adjusted to acidic, more than 80 wt.% of DOX was released. In addition, *in vitro* experiments with human hepatoma 7402 cells and L02 lung cancer cells demonstrated that the nanocomposites could be internalized by both kinds of cells effectively but only release drug in cancer cells.


## 1. Introduction

As a kind of unique inorganic nanomaterials, mesoporous silica nanoparticles (MSNs) have received much attention in recent years. Due to their excellent biocompatibility, modifiable outer surface with abundant Si-OH and adjustable pore size [1–3], these materials have been increasingly used as biomedical materials, such as drug and gene delivery, cell imaging, biosensor, etc. [4–10]. In particular, the applications of MSNs in drug delivery have been focused in recent years. Many researchers have investigated the MSNs in natural sustained-release system (such as MCM-41 and SBA-15) [11–16]. However, in comparison with the sustained-release system, the stimuli-responsive controlled-release system can achieve regioselectivity and controlled release, which can improve the therapeutic effectiveness and reduce the toxicity of drugs on normal tissues. Therefore, several strategies are employed to modify the outer surface of MSNs and meet the requirement of "zero" drug release before the drug carriers reach at the target area. For instance, Kim and coworkers designed mesoporous silica particles blocked by the surface-grafted pH-responsive polyethyleneimine (PEI)/cyclodextrins (CD) polypseudorotaxane, which could trigger to release the drugs from the pores of the particles by reversible dethreading of CDs from the PEI chains [17]. Bein and co-workers prepared mesoporous silica nanoparticles with a gating system at the outer particle surface via a delayed co-condensation approach to achieve controlled drug release [18].

Nevertheless, ordinary mesoporous silica nanomaterials have some defects, such as low drug loading capacity, the blocking of the mesopore channels after adsorbing the drug molecules [19] and the irregular morphology which is also not perfect for drug delivery. To overcome these disadvantages, an unique mesoporous silica nanomaterial, hollow mesoporous silica nanoparticles (HMS) which have a special structure with hollow core and porous silica shell have been introduced [20–22]. In addition to all the advantages of MSN, HMS has other characters such as large specific surface area and high drug loading capacity. So many researchers pay attention to innovate the preparing methods of HMS. Guo and co-workers prepared the HMS with a mesoporous shell perforated by hexagonally arrayed cylindrical nanochannels [23], Wu and co-workers prepared the HMS without additional dissolution and a calcination process to remove the polystyrene cores [24], Du and co-workers prepared the HMS using a thermosensitive polymer as core template [25], and so on [26,27]. However, modification strategies in the outer surface of HMS with functional polymers for controlled drug release were rarely reported. To our best knowledge, only Shi and co-worker modified the surface of HMS using layer-by-layer (LbL) technique to achieve stimuli-responsive controlled drug release, which system would trigger release drug not only in acid environment but also release with different NaCl concentration [28].

In order to reduce the toxicity and side effects of drug for normal cells, the drug should be triggered released only in cancer cells. As we know the physiological pH value of normal cells is 7.4, whereas that early endosomes and late endosomes/lysosomes in the intracellular of cancer cells is around 6.0 and 5.0, respectively [29], so, pH-reponsitive drug release could be an effective way for cancer therapy. Herein, we designed a modified HMS, HMS@

* Corresponding authors. Tel./fax: +86 (0) 512 6588 0367.
*E-mail addresses:* linajun@suda.edu.cn (N. Li), lujm@suda.edu.cn (J. Lu).

1387-1811/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.micromeso.2011.12.015

poly(PDM-*b*-PEGMA), which was prepared by grafting pH-sensitive amphiphilic diblock copolymer (poly(PDM-*b*-PEGMA)) from the outer surface of HMS via ATRP technique. This strategy not only can overcome the disadvantage of low drug loading, but also can achieve drug stimuli-responsive controlled-release to improve the therapeutic efficacy. An easier silica nanoparticle initiator than before [30] had been synthesized by coupling HMS and 2-bromoisobutyryl bromide via 3-aminopropyltriethoxysilane (KH550). Then 2-phenyl-1, 3-dioxan-5-yl methacrylate (DM) and (ethylene glycol) methyl ether methacrylate (EGMA) were initiated, respectively. The as-synthesized nanocomposites HMS@poly(PDM-*b*-PEGMA) can load hydrophobic drug in hollow core, shell pores and hydrophobic segments of polymer shell. In a neutral aqueous environment, the hydrophobic segments shrink on the surface and cover the pores of HMS to prevent the release of hydrophobic drug. Under weakly acidic condition, the hydrophobic segments hydrolyzed into hydrophilic segments, resulting in the changes of hydrophobic–hydrophilic property, which is favorable for controlled drug release (Scheme 1).

## 2. Experiment

### 2.1. Materials

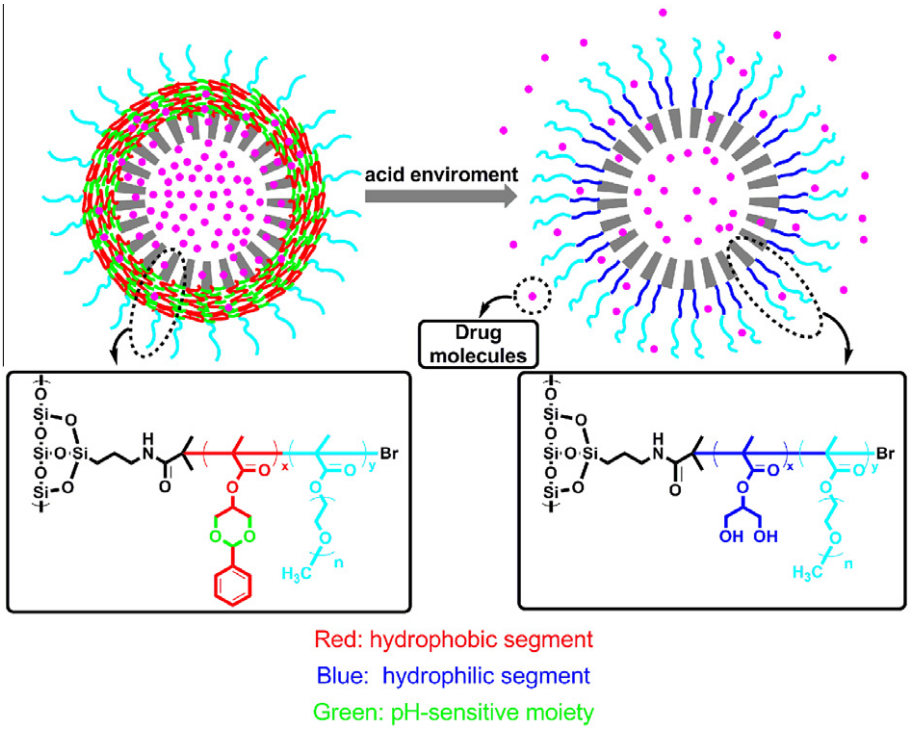
(2-(Acryloyloxy)ethyl) trimethylammonium chloride (AETAC, 80 wt.% in water), 2,2′-azobis(2-methylpropionamidine) dihydrochloride (V-50, >97.0%), hexadecyltrimethylammonium bromide (CTAB, >99.0%). Poly(ethylene glycol) methyl ether methacrylate (PEGMA, Mn = 475) were purchased from Aldrich. 2-Bromoisobutyryl bromide was purchased from Alfa. Benzaldehyde, glycerol, *p*-toluenesulfonic acid, triethylamine were purchased from Shanghai chemical reagent Co. Ltd. All chemicals above were used without further purification. Styrene (St, >99.0%) was washed through an inhibitor remover column for removing tert-butylcatechol and then distilled under reduced pressure prior to use. Tetraethyl orthosilicate (TEOS) and 3-aminopropyltriethoxysilane (KH550) were distilled under vacuum and stored at −15 °C under an inert gas atmosphere. Tetrahydrofuran (THF) and cyclohexanone were purified by reduced pressure distillation. CuBr was purified until colorless by stirring in glacial acetic acid, consecutive washing with absolute ethanol and diethyl ether and keeping under vacuum. Other reagents were commercially available and used as received.

### 2.2. Synthesis of hollow mesoporous spherical (HMS) particles

The hollow mesoporous spherical particles were synthesized according to the literature [27] with some modifications. To prepare the polystyrene latex templates, 1.0 g of AETAC (80 wt.% in $H_2O$) was dissolved in 390.0 g of water in a 500 mL round-bottom flask. Then 40.0 g of styrene was added slowly to the solution and kept stirring at 800 rpm for 30 min. The mixture was purged with nitrogen for 20 min and then heated to 90 °C in an oil bath. Afterwards, 10 mL of an aqueous solution containing 1.0 g V-50 was added. The emulsion was kept at 90 °C for 24 h under nitrogen to complete the polymerization. The polystyrene latex was collected by centrifugation at 18,000 rpm for 15 min, and washed with ethanol for several times. To get the HMS, 0.8 g of CTAB was dissolved in a mixture of 29.0 g of water, 12.0 g of ethanol and 1.0 mL of ammonium hydroxide solution. Nine hundred and thirty milligrams of PS powders was dispersed in 10.0 g water by sonication and then added dropwise to the above CTAB solution at room temperature under vigorous stirring, followed by sonication for 10 min. The derived milky mixture was then stirred for 30 min before adding 4.0 g of TEOS. The mixture was kept stirring at room temperature for 48 h before the mesoporous silica coated latex was harvested by centrifugation at 7000 rpm for 40 min. The precipitate was washed with amounts of ethanol and then dried at room temperature. Finally the material was calcined in air at 600 °C for 8 h at a heating rate of 3 °C/min.

### 2.3. Modification of ATRP initiator on the surface of HMS particles (HMS-Br)

Hundred microliters of KH-550 was added to the HMS toluene (50 mL) solution and stirred for 24 h. The resulting aminated nano-




**Scheme 1.** Schematic depiction of structure of HMS-copolymer nanocomposites and controlled release by degradation under weakly acidic conditions.