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Hybrid drug carriers with temperature-controlled on–off release: A simple and reliable synthesis of PNIPAM-functionalized mesoporous silica nanoparticles

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ABSTRACT

MCM-41-like mesoporous silica nanoparticles (MSNs) grafted with a thermoresponsive copolymer of N-isopropylacrylamide were synthesized, fully characterized and tested to assess their efficiency as drug delivery systems. The hybrid nanoparticles were prepared by carrying out the optimized copolymer synthesis within the mesopores of MSNs after infiltration of monomers and initiator. Polymerization and grafting of the thermoresponsive copolymer occurred simultaneously by exploiting the reactive sites of the 3-methacryloxypropyltrimethoxysilane comonomer which carries a polymerizable group and alkoxysilane groups prone to condensation with surface silanols on silica. The grafted copolymer through its coil-to-globule transition acts as a gatekeeper for the temperature-controlled release of ibuprofen molecules loaded inside the pores. Significant difference in the quantitative release of ibuprofen was observed at 25 and 40 °C, which are below and above the lower critical solution temperature of the thermoresponsive copolymer. Importantly, the ordered mesoporous structure of the MSNs remained intact in all synthetic steps, loading of drug and during the in vitro release tests.

1. Introduction

Mediated transport of drugs has emerged as a powerful methodology for the treatment of various diseases. The possibility to address therapeutic substances to target tissues or cells, to control their release kinetics and to protect drugs from the attack of biological, chemical and physical agents has been receiving growing attention, and many attempts have been made in the last decades to design drug delivery systems exhibiting one of these properties or a combination of them. In this context mesoporous silica nanoparticles (MSNs) are growing in importance due to their biocompatibility, nontoxicity, controllable mesopore structure and ease of surface modification. In recent years, the use of mesoporous materials for hosting and further delivering of a variety of pharmaceutical compounds has been described [1–6]. It has been shown that both small and large molecular drugs can be entrapped within the mesopores by an impregnation process and released via a diffusion-controlled mechanism. MCM-41 type silica nanoparticles having high surface area, relatively large pore volume, tunable pore size and good chemical and thermal stability are potentially suitable for various drug delivery applications and have been proposed as drug delivery systems since 2001 [7]. Many attempts have been made to test the efficiency of these types of nanoparticles in delivery of drugs either as such or with chemical modifications [8–10]. A variety of functional groups and polymers have been attached on the nanoparticle surface in order to increase drug loading and to modulate rate and duration of drug release. Much more interesting is the possibility to precisely control where and when the drug will be released and eventually to dose it by application of an external stimulus. To this aim mesoporous silica nanoparticles need to be functionalized with appropriate release triggers, specifically reacting to perturbations from chemicals [11–13], temperature [14,15], pH [16–19], light [20], magnetic field [21,22], ultrasounds [23], etc.

Among thermoresponsive polymers, Poly(N-isopropylacrylamide) (PNIPAM) has been widely investigated [24,25]. The thermosensitivity of NIPAM-based polymers is due to a coil-to-globule transition of the polymer chains in aqueous solution, which takes place at the lower critical solution temperature (LCST). Above the LCST the extended and hydrated polymer chains in solution shrink into a very compact mass. The range of temperature at which the coil-to-globule transition of PNIPAM occurs (i.e. 30–35 °C) is interesting for drug delivery applications.

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Recently, different strategies have been proposed to synthesize silica/PNIPAM mesoporous particles with thermoresponsive properties with the final aim of governing the opening and closing of the pores through thermal cycles, thus controlling the release of loaded molecules [26–28]. These strategies generally include surface activation, the use of grafting agents, initiators, co-initiators, chain transfer agents and other chemicals required in post-synthesis functionalization of MSNs. Although these methods allow an efficient grafting of PNIPAM chains on the silica surface and a fine control of polymer chains at a compositional and molecular level, most of these strategies appear too complex and imply the use of several substances whose fate in in vivo trials has not been fully disclosed. Moreover, most of the reported thermoresponsive MSNs are based on materials with larger mesopores than MCM-41. This is intended to allow an efficient encapsulation of drugs with higher molecular weight, but at the same time larger mesopores increase the risk of significant drug leakage at room temperature.

Here, we present a simple, efficient and convenient method to obtain hybrid silica/PNIPAM thermoresponsive nanoparticles with ordered, highly dense nanopores which can be opened and closed by changing the temperature. Grafting of the thermoresponsive copolymer on MSNs is achieved by carrying out the free radical copolymerization of NIPAM and 3-methacryloxypropyltrimethoxysilane (MPS) inside the mesopores of MCM-41-like nanoparticles, after infiltration of monomers and initiator into the mesopores. The hybrid mesoporous nanoparticles obtained following this one-step synthesis exhibit a temperature dependent on–off drug release that can facilitate the in-situ dosage of drugs and the reduction of dose frequency.

2. Experimental section

2.1. Materials and methods

All reagents and solvents were purchased from Sigma-Aldrich and used as received.

MCM-41-like nanoparticles with an average diameter of approximately 100 ± 23 nm were prepared according to literature procedures using cetyltrimethylammoniumbromide (CTAB) as a structure directing agent [29,30].

Both untethered and tethered Poly(NIPAM-*co*-MPS) chains were prepared by AIBN-initiated radical polymerization. Untethered copolymers with different compositions were synthesized by changing the monomer to initiator molar ratio and the relative amount of the comonomer pair in the feed. The main molecular characteristics and properties of synthesized copolymers are reported in Table 1.

The same synthesis conditions used for the untethered polymers were also applied to the synthesis of Poly(NIPAM-*co*-MPS)-modified MSNs. Before initiation of the polymerization reactants were infiltrated into the MSNs in order to assure the presence of the thermoresponsive polymer not only on the nanoparticle surface but also inside the pores. Once infiltrated in the mesopores reactants were assumed to polymerize as in homogeneous solution and to give Poly(NIPAM-*co*-MPS) chains with similar composition and properties of the untethered polymer. As detailed below in Section 3, this assumption is supported by both FTIR spectra and critical coil-to-globule transition temperatures (T_c) of tethered and untethered copolymers, which are basically the same. Reactivity of trimethoxysilane groups of MPS with hydroxyl groups of the silica surface was exploited to anchor Poly(NIPAM-*co*-MPS) chains to the MSNs.

2.2. Synthesis of untethered Poly(NIPAM-co-MPS)

Poly(NIPAM-*co*-MPS) copolymers were synthesized by free radical polymerization of NIPAM and MPS initiated by AIBN. Copolymerization conditions are listed in Table 1. Polymerization was carried out in absolute ethanol at 70 °C for 16 h under nitrogen atmosphere. Then products were purified by three dissolution/precipitation cycles from acetone into hexane and were dried overnight at room temperature (RT).

Molecular weight, solubility and coil-to-globule transition temperature were modulated by changing the monomer to initiator molar ratio and relative amount of the comonomer pair in the feed, thus obtaining the series of copolymers whose main molecular characteristics and properties are reported in Table 1.

NMR and ATR-FTIR data of representative sample 5 are shown below.

^{1}H NMR (D_2O) δ = 1.0–1.2 ($CH(\underline{CH_3})_2$, $C(\underline{CH_3})$), 1.5–1.8 (main chain CH_2, $O–CH_2–\underline{CH_2}–CH_2$), 1.9–2.1 (main chain CH), 3.6 ($Si–O–\underline{CH_3}$), 3.8–4.0 ($N–\underline{CH}(CH_3)_2$, $O–\underline{CH_2}–CH_2$).

ATR-FTIR: 3290 (νN–H), 2970 ($\nu_{as}CH_3$), 2933 ($\nu_{as}CH_2$), 2874 (ν_sCH_3), 1720 (νC═O, MPS), 1638 (νC═O amide I), 1537 (νC–N + δNH amide II), 1458 ($\delta_{as}CH_3$), 1386–1367 ($\delta_sCH(CH_3)_2$), 1172 (νC–C), 1130 ($\rho CH(CH_3)_2$), 1086 cm^{-1} (νC–O).

2.3. Synthesis of hybrid Poly(NIPAM-co-MPS)/MSNs

Hybrid mesoporous nanoparticles were obtained by carrying out the synthesis of copolymer 5 in an ethanol dispersion of MSNs. In a typical reaction 280 mg of nanoparticles was used and dispersed in 10 mL of ethanol solution of NIPAM and AIBN by sonication at room temperature. The NIPAM/MSN weight ratio was 1:4. After 30 min MPS was added into the suspension and dispersed evenly by sonication for another 30 min. The dispersion was then injected in a three neck round bottom flask equipped with condenser and nitrogen inlet. The injected suspension was then heated at 70 °C under nitrogen for 16 h. The product was dried by nitrogen flow, washed three times with deionized water and recovered by centrifugation.

2.4. Characterization of untethered Poly(NIPAM-co-MPS)

NMR spectra were recorded with a JEOL EX 400 spectrometer (1H operating frequency 400 MHz) at 298 K; data were treated by Jeol Delta Software. 1H chemical shifts are relative to TMS (δ = 0 ppm) and referenced against solvent residual peaks (D_2O at 4.79 ppm).

Fourier Transform Infrared Spectroscopy (FTIR) spectra were collected with a Thermo-Nicolet FTIR Nexus instrument equipped with an attenuated total reflectance (ATR) device (Thermo Nicolet Smart Endurance) and with a DTGS detector. Spectra were collected in the range of 4000–400 cm^{-1} and with a resolution of 4 cm^{-1}.

A Q200 (TA instruments) differential scanning calorimeter was used to determine glass transition temperatures (T_g) and critical coil-to-globule transition temperatures (T_c). For T_g measurements analyses

Table 1
Synthesis conditions and properties of Poly(NIPAM-*co*-MPS) samples.

Sample	NIPAM/MPS	NIPAM/AIBN	M_n	M_w	PDI	T_g (°C)	T_c (°C)	Solubility	
								DMF	Water
1	10/1	20/1				126		−	−
2	20/1	20/1				115		+/−	−
3	40/1	20/1	2500	7200	2.9	93		+	+/−
4	10/1	30/1				119		−	−
5	20/1	30/1	8500	19,000	2.2	116	36	+	+
6	40/1	30/1	4800	12,000	2.5	107	36	+	+

+: soluble; −: non-soluble; +/−: partially soluble.