Sustained Drug Release on Temperature-responsive Polymer Hybrid Nanoporous Silica Composites

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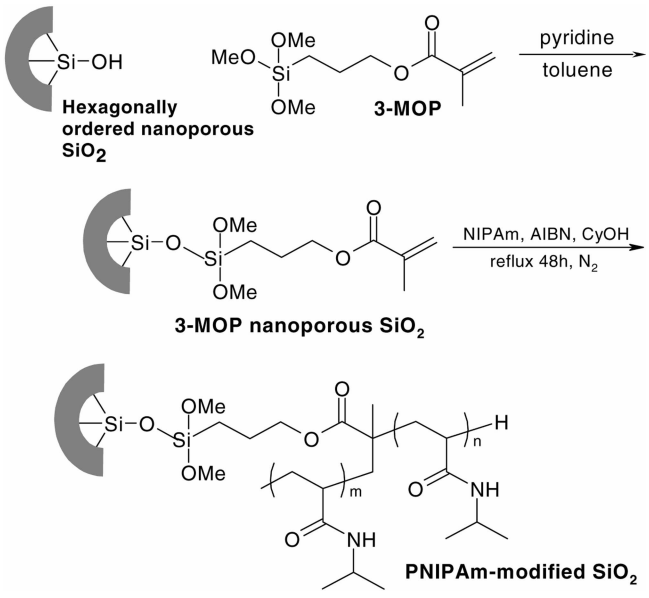
The discovery of ordered nanoporous materials using a surfactant-templated approach has opend a new era in the synthesis of ordered nanoscale materials.[1-4] Many investigations have been explored on the preparation of nanoporous materials with novel chemical composition,[5] on the fundamental understanding of the reaction processes,[6-8] and on the potential applications such as catalysis,[9-11] and separation technology[12,13] expected to open up further application possibilities. Interest in the structure of the pore network is necessarily concomitant with the formation of different structures including a hexagonal, cubic, and lamellar structure. The liquid crystal templating approach on these structures is based on the micellar or tubular structure. After templating, the inorganic precursor condenses to form a rigid cast of the underlying liquid crystal, and the organic phase can be removed to form an inorganic solid composed of a periodic nanoporous structure of uniform diameter and distribution. Although the feasibility of choosing the pore size offers a wide range of possibilities for hosting different molecules, references dealing with the drug delivery of oredered nanoporous materials are not abundant and usually involve structure modification.[14,15] Especially, the systematic drug-delivery study on the polymer hybrid nanoporous materials have not been reported yet.

Here we report the systematic application of the ordered nanoporous materials to smart controlled drug release using the thermoresponsive PNIPAm hybrid nanoporous structures with different pore sizes. Synthetic polymers that undergo discontinuous volume phase transitions in response to external stimuli have been especially focused for controlled drug delivery owing to their possible versatile application. This approach which involves co-assembly of a chemically-active polymer layer within the ordered porosity of a ceramic matrix holds promise for the novel application to drug delivery system or drug containers with high specificity and throughput.

The hexagonally ordered mesoporous silicas with different pore sizes (10, 17, 30 nm) were prepared by the reported procedure.[4,6] In a typical preparation of the nanoporous silica, 4.0 g of Pluronic P123 was dissolved in 30 g of water and 120 g of 2M-HCl, and then 8.5 g of tetraethyl orthosilicate (TEOS) was added into the solution at 40 °C. The mixture was aged in a bomb at 120 °C overnight without stirring. The solid product was filtered, washed with excess water, and air-dried at room temperature. Calcination was carried out at 550 °C for 6 hours. The PNIPAm hybridized nanoporous materials were prepared by the radical-initiated polymerization with NIPAm monomers and 2,2'-azobis(isobutyronitrile) (AIBN) with ammonium sulfate on [3-(methacryloyloxy)propyl]trimethoxysilane (3-MOP) modified nanoporous silica surface after modification of MOP on ordered nanoporous silicas with different pore sizes (10, 17, 30 nm) synthesized (Scheme 1). The dried PNIPAm hybrid nanoporous materials were immersed in a saturated solution of indomethacin in EtOH-water (8 : 2, v/v) overnight and dried over a period of 3 days at room temperature. The drug-loaded composites of the PNIPAm hybrid nanoporous silicas were immersed in 10 mL of phosphate buffer (PBS, pH 7.4, 10 mM). Solutions containing the drug-loaded composites were shaken in temperature-controlled shaker for stepwise temperature changes between 25 °C and 40 °C. The indomethacin concentration of the solution was measured using a UV-Vis. spectrophotometer (257 nm) at



Scheme 1. The preparation of PNIPAm-hybrid nanoporous silica materials.

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Table 1. BET pore sizes (D) and surface areas (S) as a function of organic modification

Type	Samples	D_{ad} (nm)[a]	D_{de} (nm)[b]	S_{BET} (m^2/g)
Nanoporous silica	A1(10 nm)	8	5	712
	A2(17 nm)	17	7	656
	A3(30 nm)	29	15	630
MOP-hybrid silica	B1(10 nm)	5	4	320
	B2(17 nm)	9	5	380
	B2(30 nm)	23	15	310
PNIPAm-hybrid silica	C1(10 nm)	5	4	24
	C2(17 nm)	5	4	5
	C3(30 nm)	23	8	43

[a]Adsorption pore size, [b]Desorption pore size

different time intervals. After each measurement, 10 mL of PBS buffer was replaced.

The BET results obtained by N_2 sorption experiment indicated that the dramatical decrease of pore sizes and surface areas of PNIPAm modified nanoporous materials is caused by organic modification of the calcined original nanoporous structures (Table 1). The nanoporous materials with three different pore diameters were used: 8, 17, and 29 nm. They are referred to as A1 (10 nm), A2 (17 nm), and A3 (30 nm) nanoporous materials hereafter for simplicity. The transmission electron microscopy (TEM) images of the three nanoporous materials exhibited the hexagonally ordered structure and the quite uniform of the pore size: the 10 nm and 17 nm materials have uniform and ordered cylidrical pore channels, but the porosities in 30 nm material are almost completely disordered, and the pore sizes are more or less uniform (Fig. 1). The PNIPAm hybrid nanoporous structures obtained by polymerization have not distinct images in TEM measurement due to the polymeric characteristics. The pore size distribution and BET isotherms by modification of PNIPAm polymers changed the adsorption and desorption branch and microporous pattern of isotherm hysteresis (Fig. 2(a)). The FT-IR spectra proved the presence of the PNIPAm network with no other significant components in which bands were observed at 1645, 1370, and 2800-3000 cm^{-1} for the carbonyl group, isobutyl group, and

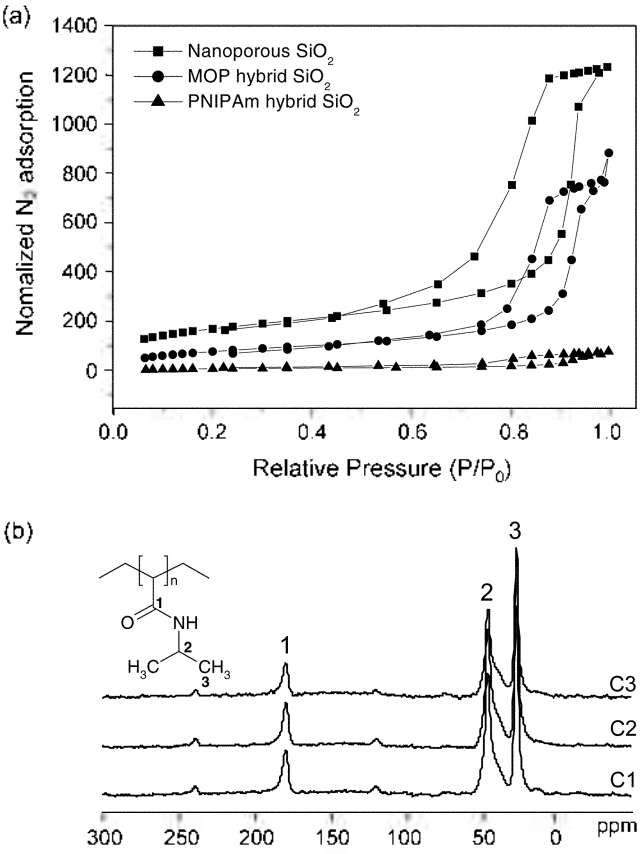

Figure 2. (a) BET isotherms as a function of surface modifications on 30 nm nanoporous silica and (b) solid-state ^{13}C CP-MAS spectra of PNIPAm hybrid nanoporous silicas.

aliphatic hydrocarbon of PNIPAm, and 1080 cm^{-1} for the SiO_2 network, respectively. Thermogravimetric analysis for PNIPAm hybridized materials (C1-C3) was conducted up to 500 °C (10 °C/min). A significant weight losses in the materials (49, 50 and 47% for C1, C2, and C3, respectively) were detected by TGA in Ar and a large endothermic dissociation at 324 °C in the DTG, caused by the endothermic dissociation of organic PNIPAm polymer.

^{13}C solid-state cross polarization (CP) magic angle spinning (MAS) nuclear magnetic resonance (NMR) spectra were also obtained to further illustrate the chemical environments

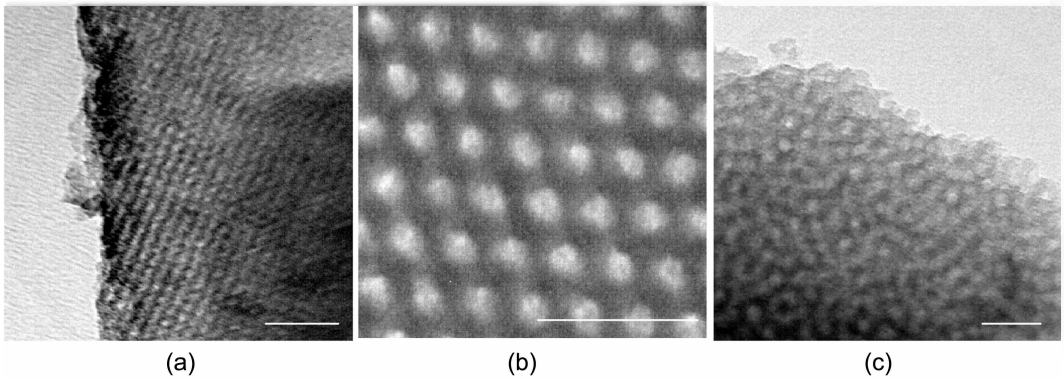

Figure 1. TEM micrographs of (a) 10 nm, (b) 17 nm, and (c) 30 nm nanoporous silicas. (scale bar: 100 nm)

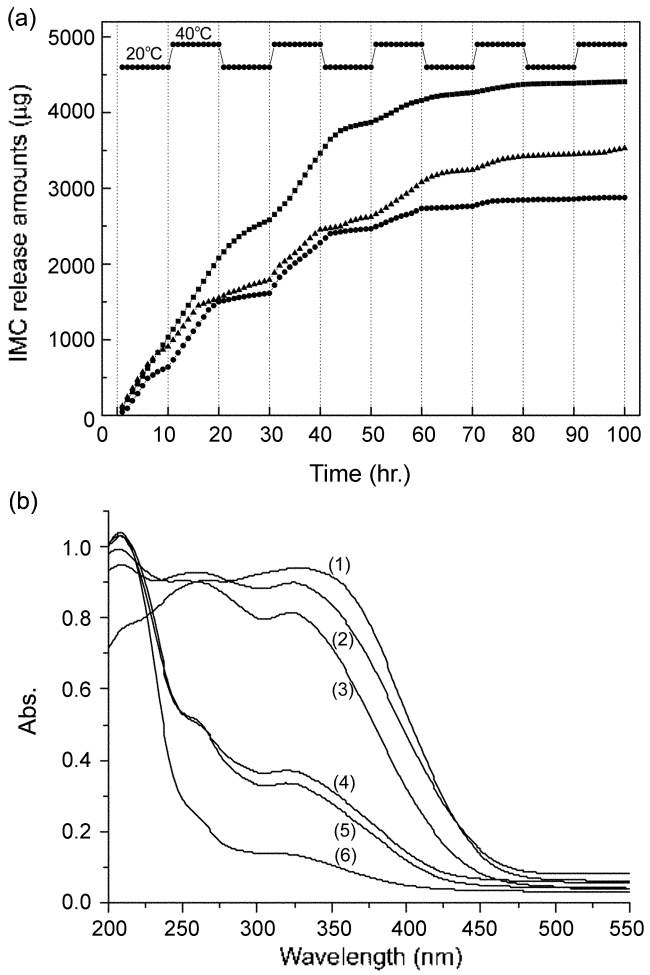

Figure 3. (a) Sustained release of Indomethacin from PNIPAm hybrid nanoporous materials (■ : C1, ▲ : C2, and ● : C3) in response to stepwise temperature changes in PBS (pH 7.4). (b) solid-state UV-Vis. spectra for comparison of drug-loaded and drug-released after 100 hr PNIPAm hybrid nanoporous materials: (1) drug-loaded C1, (2) drug-loaded C2, (3) drug-loaded C3, (4) drug-released C2, (5) drug-released C1, and (6) drug-released C3.

of the modified PNIPAm on interfacial region of the nanoporous materials (Fig. 2(b)). The spectra showed a well-resolved resonance peak at 178 ppm for carbonyl group of the PNIPAm in which the integration value of this peak implies the amount of the modified PNIPAm. As the pore size increases from C1 to C3, the resonance peaks at 12-17 ppm, associated with first carbon of the modified group bound to the silica surface, should be sensitive to the conformational arrangement of the pore size. The groups are most likely entangled and constrained in the small pore (C1), but the molecular chains are more organized, so the peak was broadened in large pores (C2, and C3).

Indomethacin, known as an antipyretic and analgesic drug, was used to study thermosensitive drug release on PNIPAm hybrid nanoporous materials. For PNIPAm hybrid materials, drug loaded and released pattern were depended on the pore confinement of the nanoporous structure by weak hydrogen bonding between surface hydroxy group (-OH) of SiO_2 and carboxyl group (-COOH) of indomethacin including a surface area and pore size that showed the larger pores provide a good drug-container. Indomethacin release from PNIPAm hybrid nanoporous materials (C1-C3) was investigated during stepwise temperature changes between 25 °C and 40 °C (Fig. 3(a)). The results were consistent with the positive squeezing mechanism reported: when the temperature was increased and maintained at 40 °C, nearly constant release pattern was observed. However, no significantly sustained, but rapidly decreased release was observed on the temperature change to 25 °C. The favorable thermosensitive release profile could be also explained by the nanodiffusion mechanism: At low temperature, the drug is trapped in the polymer and in the porous structures, and the polymers are swelled to prevent the drug from being significantly released into the media. When the temperature is increased above the lower critical solution temperature (LCST) of PNIPAm, the polymers shrink to squeeze the drug into the porous channels, and open the pore structure. The overall delivery of the drug into the media is controlled by diffusion through the porous channels. In the nanodiffusion mechanism, diffusion in the nanoporous channels of different sizes, rather than in the surface area or in the gel phase, is controlling mechanism. The diffusion rate in the small nanochannels is severly hindered (C1) while that in large pore channel (C3) approaches the rate of bulk diffusion. Therefore the drug can be easily extruded in C3 channel, but in C1 channel. A slight variation in pore dimension and the gel density along the pores will cause the fine nanoporous channels to be clogged before the drug has a chance to be extruded.

The total loaded amount and released amount after 100 hours of indomethacin in each material (C1-C3) were determined by the reflective method of solid-state UV-Vis. spectrophotometer (Fig. 3(b)). This result showed that the 94, 90, and 82 mg of indeomethacin was loaded per g of each material (C1-C3), and 58, 63, and 82% of the drug released for 100 hrs. for C1, C2, and C3, respectively.

In conclusion, this work describes the potential bio-application of hierarchically ordered nanoporous materials for the smart drug delivery system that involves a self-assembly process at the molecular level based upon thermo-responsive polymers. Thermosensitive polymer hybrid nanoporous materials were developed based on tailoring network of PNIPAm for smart drug release, and showed a sustained positive thermoresponsive drug release profile in which the overall release amount was controlled by change of the pore channel size. The use of biodegradable/thermo-responsive polymers in hierarchically ordered nanoporous structure can be useful for smart drug delivery applications.

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