Bicontinuous, Thermoresponsive, L_3-Phase Silica Nanocomposites and Their Smart Drug-Delivery Applications

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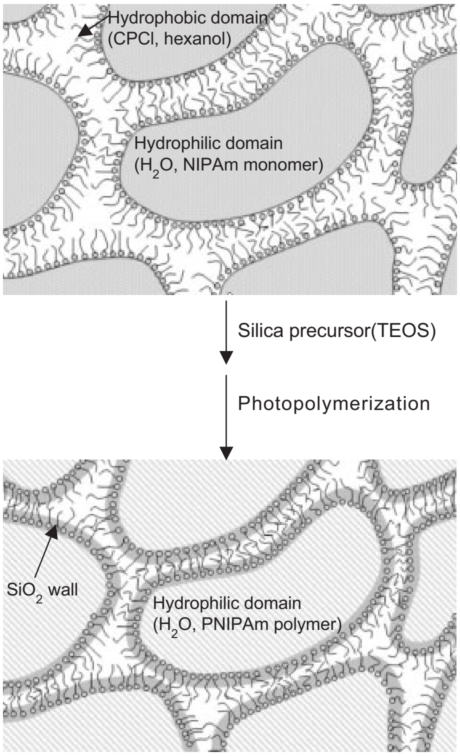
The discovery that ordered nanoporous materials can be produced using a surfactant-templated approach has opened up a new era in the synthesis of ordered nanoscale materials.[1–4] Many investigations have explored the preparation of nanoporous materials with novel chemical composition,[5] the fundamental nature of the reaction processes,[6–8] and potential applications, such as catalysis[9–11] and separation technology,[12,13] which is 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 hexagonal, cubic, and lamellar structures. The liquid-crystal templating approach to these structures is based on a 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 leave an inorganic solid composed of a periodic nanoporous structure with uniform diameter and distribution. Although the feasibility of choosing the pore size offers a wide range of possibilities for hosting different molecules, reports on the drug-delivery behavior of ordered nanoporous materials are not abundant and usually involve structural modification.[6] In particular, a systematic drug-delivery study on the porous geometrical shapes of nanoporous materials has yet not been reported.

Here we report the smart drug-delivery application of synthesized L_3-phase (sponge-phase) nanoporous materials in highly controlled drug release, upon integration of a thermoresponsive polymer, poly(*N*-isopropylacryl amide) (PNIPAm). The L_3 phase is formed by the self-assembly of amphiphilic templates during the formation of nanoporous inorganic materials, and it consists of a three-dimensional random packing of a multiply connected bilayer of the surfactant and cosurfactant that divides the space into two subspaces filled with solvent, based on the liposome structure. The pore size and the distance between the silicate layers in the porous structure were controlled by changing the hydrophilic domain, for example, by varying the amount of water. The aim of this work is to explore a new potential application of the bicontinuous, disordered, L_3-phase nanoporous structure and its capability of acting as a convenient reservoir for controlled drug release. For this purpose, we introduced indomethacin (IMC), an antipyretic and analgesic drug, into the non-calcined, silicified L_3 gels and L_3-integrated thermosensitive PNIPAm polymer gels (L_3-PNIPAm), and subsequently demonstrated the in-vitro drug-release process by a step-wise temperature change.

The synthesis of silicified L_3 gels was achieved using a method that was a slight modification of one previously reported,[14] in which the order of mixing of the three components of the L_3 phase was not important, but it was necessary to maintain the correct ratio of hexanol to the surfactant, 1-hexadecyl pyridinium chloride (CPCl), in order to ensure phase purity and stability. The formation of bicontinuous, thermosensitive, L_3-phase silica nanocomposites is schematically illustrated in Scheme 1. The surfactant–water system first formed the surfactant L_3 phase. The PNIPAm polymer gel formed in the hydrophilic region of the surfactant L_3 phase, and then condensation of the silica network at the surfactant–water interface completed the preparation of the interpenetrating nanoscale network of silica and polymer gel. A series of silicified L_3-PNIPAm gels containing 60, 80, and 95 wt.-% water were prepared by UV-initiated polymerization.

Results from Brunauer–Emmett–Teller (BET) measurements, obtained from N_2 adsorption–desorption experiments, indicated that the dramatic decrease of the surface areas of



Scheme 1. The formation of bicontinuous, thermosensitive, L_3-phase silica nanocomposites.

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the L_3-PNIPAm gels (387, 450, and 522 $m^2 g^{-1}$ for the L_3 gels, and 30, 34, and 35 $m^2 g^{-1}$ for the L_3-PNIPAm gels, each type of gel with 60, 80, and 95 wt.-% water contents, respectively) was caused by modification of the original L_3 gels by the PNIPAm polymer. When the water content increased from 60 to 95 wt.-%, during the synthesis of the silicified L_3 gels, the surface areas were increased, as observed by the larger number of surface silanol groups, but they were almost the same after PNIPAm polymerization. The Fourier-transform infrared (FTIR) spectra—in which bands were observed at 1645, 1370, and 2800–3000 cm^{-1} for the carbonyl group, isobutyl group, and aliphatic hydrocarbons of PNIPAm, respectively, and at 3070 cm^{-1} and 1080 cm^{-1} for CPCl and the SiO_2 network, respectively—proved the presence of the CPCl and PNIPAm network, with no other significant components. Thermogravimetric (TG) analysis under argon for the silicified L_3 gels and L_3-PNIPAm gels was conducted up to 500 °C (at a rate of 10 °C min^{-1}) under vacuum after drying in air. A significant weight loss was detected for the silicified L_3 gels (39, 40, and 39 % for gels with 60, 80, and 95 wt.-% water contents, respectively). As the temperature approached 300 °C, the CPCl surfactant began to decompose rapidly after evaporation of most of the water during the air-drying stage. The decomposition of CPCl and PNIPAm was slower in the L_3-PNIPAm gels (58, 57, and 59 % for gels with 60, 80, and 95 wt.-% water content, respectively) because of the presence of the silica wall encompassing the surfactant and polymer. The similar values of 39–40 % and 57–59 % indicate that the same amount of organic polymer and CPCl surfactants were present after vacuum drying. At 500 °C, most of the PNIPAm polymer would be expected to have decomposed.

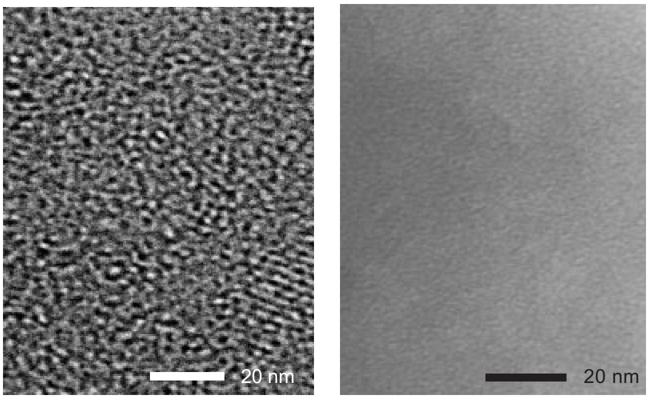

Figure 1. TEM micrographs of a) silicified L_3 gel and b) L_3-PNIPAm gel with a water content of 80 wt.-%.

The continuity of the pore network was confirmed by transmission electron microscopy (TEM) measurements, in combination with other characterization techniques such as small-angle X-ray diffraction (SAXRD), solid-state ^{29}Si NMR and FTIR spectroscopies, and BET N_2 adsorption–desorption studies, which showed that the structure formed by the silicified L_3 gel was highly uniform, with apparently high degrees of continuity in the pore structure and the network walls. Even though the pores of the L_3-PNIPAm gel were covered by the PNIPAm polymer, the porous structure was still multiply connected (Fig. 1). The estimated pore sizes for the silicified L_3 gel and the L_3-PNIPAm gel are approximately 5 nm and 3 nm, respectively. The SAXRD data (Fig. 2) support this, as they show one diffraction peak, in the 2θ range of 1–6°, for each of the silicified and L_3-PNIPAm gels with water contents of 60, 80, and 95 wt.-%. The respective d parameters extracted are 51.8, 53.8, and 54.4 Å for the silicified L_3 gels, and 29.0, 30.7, and 32.8 Å, for the L_3-PNIPAm gels. The d parameters of the silicified L_3 and L_3-PNIPAm gels with water contents of 95 wt.-% are larger than the others due to the relatively high occupancy of the hydrophilic domains by water; the d parameters of the L_3-PNIPAm gels were smaller due to the expansion of the polymeric PNIPAm domains upon photopolymerization. Solid-state ^{29}Si magic-angle-spinning (MAS) NMR spectra provided chemical information about the localized silicon environments. Three resonances are seen in the formation of the L_3-PNIPAm gels (Fig. 3a), at $\delta = -91$, -102, and -112 ppm, corresponding to $(OH)_2\mathit{Si}(OSi)_2$ (Q_2), $HO\mathit{Si}(OSi)_3$ (Q_3), and $\mathit{Si}(OSi)_4$ (Q_4) silicate layers, respectively. The ratio of the relative peak areas of the Q_4 and Q_3 signals for gels with 60, 80, and 95 wt.-% water-contents are 0.272, 0.231, and 0.226, respectively. An increase of the Q_4 resonance intensity is associated with an increased layer thickness since more $-(OSi)_4$ segments were formed.

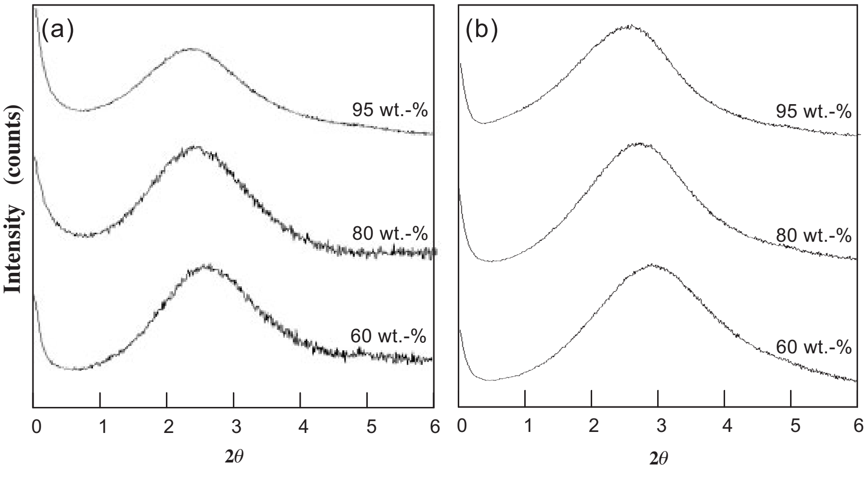

Figure 2. SAXRD patterns of a) silicified L_3 gels and b) L_3-PNIPAm gels with water contents of 60, 80, and 95 wt.-%.

The swelling degrees of the pure PNIPAm and L_3-PNIPAm gels were also studied with respect to temperature. The swell-

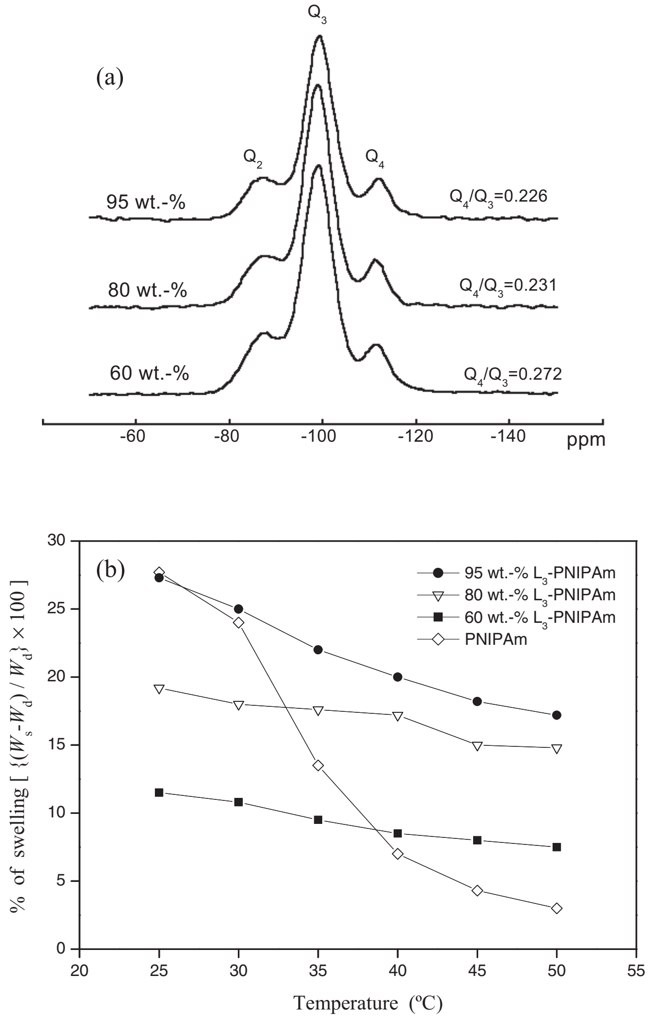

Figure 3. a) ^{29}Si solid-state MAS NMR spectra of L_3-PNIPAm gels, and b) the swelling ratio of pure PNIPAm and L_3-PNIPAm gels.

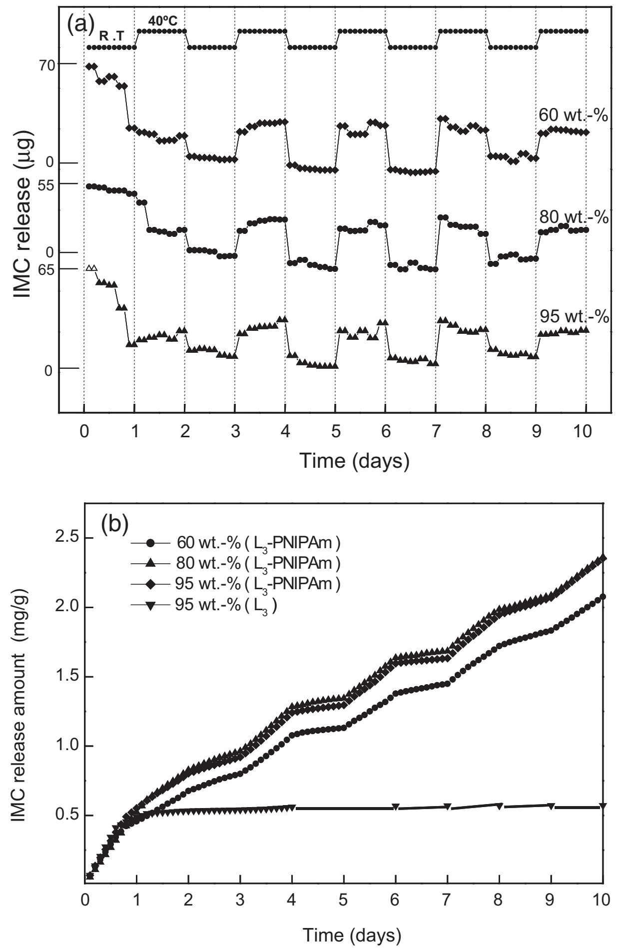

Figure 4. a) The highly controlled IMC release profile of L_3-PNIPAm gels and b) comparison of cumulative IMC release profiles of L_3-PNIPAm and silicified L_3 gels (95 wt.-% water-content) in response to stepwise temperature changes in PBS (pH 7.4).

ing studies were performed by immersing weighed blocks of dry silicified L_3 and L_3-PNIPAm gels in water for 24 h. The swollen blocks were lifted, patted dry, and weighed at regular intervals until equilibrium was attained. The percentage of swelling degree at equilibrium was calculated from the swollen (W_s) and dry (W_d) weights of the pure PNIPAm and L_3-PNIPAm gels (Fig. 3b).[15,16] Although the PNIPAm gel showed a drastic deswelling at 35–40 °C due to its lower critical solution temperature (LCST), the L_3-PNIPAm gels showed only a slight deswelling at increased temperatures due to the existence of L_3 ceramic structures. Moreover, the large porosity values obtained from BET measurements on the L_3-PNIPAm gel with 95 wt.-% water content is because of the swelling induced by the water-rich environment of the sparse, interconnected, polymer (PNIPAm) structure.

IMC was used to study the thermosensitive release properties of L_3-PNIPAm gels during stepwise temperature changes between 25 °C and 40 °C (Fig. 4a). To gain a clear understanding of these results, each measurement was not normalized, and shows consistency with the positive squeezing mechanism when the temperature was increased and the release rate was also increased. The release profiles of previous studies[17,18] using thermosensitive polymers or polymer-hybridized materials show that the release rate of each cycle gradually decreased over a period of 60–100 h. However, the L_3-PNIPAm system has an overall release rate that can be sustained over a much longer period of time. The cumulative IMC release-profile exhibits the release effectiveness as a function of time and step-wise temperature change (Fig. 4b). The sustained drug-release patterns of the L_3-PNIPAm gels with water contents of 80 and 95 wt.-% are more controlled, within the error range, than that of the L_3-PNIPAm gel with 60 wt.-% water-content due to the large domains of the water-soluble PNIPAm polymer. Extremely sustained release patterns were observed for the L_3-PNIPAm gels, but not for the silicified L_3 gels. The total IMC release in the L_3-PNIPAm gels was evaluated by solid-state UV–vis spectroscopy before and after 10 days; the amounts of released drug, as a function of time, were just 2.07, 2.29, and 2.35 mg g^{-1} for the L_3-PNIPAm gels with water contents of 60, 80, and 95 wt.-%, respectively, when the temperature was varied between 25 and 40 °C. The drug-release profiles of the L_3-PNIPAm gels did not vary much with water content up to 10 days, but showed a different pattern for long-period release in a further study which took place over three months. It will be reported in this further work, that the controlled release of the higher-water-content L_3-PNIPAm gels showed higher temperature-sensitivity. The favorable thermosensitive release mechanism is explained by the fact that the polymers are swollen, and therefore prevent significant amounts of the drug from being released into the medium at low temperatures. However, the polymers shrink and squeeze the drug into the L_3 porous channels, thereby opening the pore structure when the temperature is increased above the LCST of PNIPAm. The overall delivery of the drug into the medium is controlled by diffusion through the porous channels.

In conclusion, silicified L_3-phase gels based on a liposome structure have been prepared, which allow the fabrication of L_3-PNIPAm gels by integration of a thermosensitive polymer with a high degree of continuity in the pore and the network walls. A nanodiffusion mechanism related to the polymer shrinkage and 3D interconnected pores is proposed to explain the remarkable thermosensitive, on–off regulation for IMC delivery by L_3-PNIPAm gels, in which the overall release rate can be sustained over a much longer period of time with a constant release rate. This preliminary study demonstrates the feasibility of designing highly controlled drug-delivery systems, which could be applied to chemotherapy in hard-tissue engineering by using appropriate choices of the porous ceramic matrix (which can include a porous bone material) and the stimuli-sensitive or biodegradable polymers.

Experimental

In a typical procedure for preparing an L_3-PNIPAm gel containing 80 wt.-% water, 1.46 g of CPCl surfactant and 0.34 g of 1-hexanol in 5.07 g of 0.02 M HCl solution were combined and aged overnight. To this thick phase, 3.47 g of NIPAm monomer (recrystallized from *n*-hexane) and 0.10 g of *N,N′*-methylenebisacryl amide (NMBA) were added and then shaken until a homogeneous phase had formed. Then, 10.88 g of tetraethylorthosilicate (TEOS, silica precursor) was added. The hydrolysis of TEOS caused the temperature of the solution to rise. After the solution had cooled to room temperature, it was purged with nitrogen gas for 2 h. Irradiation of the solution with a UV lamp (Osram, Ultra-vitalux, 300 W) for 1 h caused polymerization and formation of a soft gel. This gel was cured at 60 °C for 5 days to condense the silicate to a hard gel. Other silicified L_3-PNIPAm gels containing 60 and 95 wt.-% water were also prepared by varying the water content of the initial mixture. The L_3-PNIPAm gels were washed five times with ethanol to remove unreacted residues, and then dried in air. The dried hard gel was immersed in a saturated indomethacin solution in ethanol (0.05 M, 100 mL) overnight and then dried for 3 days at room temperature. The total amount of impregnated IMC was calculated from the solid-state UV–vis spectrum (Jasco V-550 spectrophotometer) to be 14.5, 14.1, and 14.4 mg for L_3-PNIPAm gels with 60, 80, and 95 wt.-% water content, respectively. The drug-loaded L_3-PNIPAm gels were immersed in 10 mL phosphate buffer (PBS, pH 7.4, 10 mM). Solutions containing the drug-loaded L_3-PNIPAm gel were kept in a temperature-controlled shaker for making stepwise temperature changes between 25 °C and 40 °C. The IMC concentration of the solution was measured with a UV–vis spectrophotometer at different time intervals. After each measurement, 10 mL of PBS buffer was replaced.

The N_2 adsorption–desorption BET isotherms were measured with a Quantachrome Nova system. The sample was pretreated at 100 °C overnight in the vacuum line. The pore size distributions were calculated from the analysis of the adsorption branch of the isotherm using the Barrett–Joyner–Halenda (BJH) method. The pore volume was taken at five points of P/P_0. The 59 MHz ^{29}Si solid-state NMR experiment was performed with a Chemagnetics spectrometer (300 MHz, 89 mm wide-bore Oxford magnet). The samples were loaded into 7 mm Zirconia PENCIL rotors and spun at 3–4 kHz. TEM images (JEM-4010) were obtained at 400 kV, and SAXRD data were collected on a diffractometer with Cu Kα radiation and a graphite monochromator.

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