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ORIGINAL ARTICLE

# Silica nanoparticle-crosslinked thermosensitive hybrid hydrogels as potential drug-release carriers

Md Ashraful Alam[1,2], Makoto Takafuji[1] and Hirotaka Ihara[3,4]

**Thermosensitive hybrid hydrogels were prepared by chemical crosslinking using poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)] (*p*NS) copolymer chains as the backbone and silica nanoparticles (SiP) as crosslinkers. The preparation of these hybrid hydrogels involved mixing a reactive side chain-branched copolymer (*p*NS) solution with a SiP suspension at 25 °C. During the mixing of these components, caffeine was added as a model drug to form a thermo-responsive drug delivery system. The as-prepared caffeine-loaded hydrogels do not require any further processing. The effects of temperature on the equilibrium swelling ratios and on the release of caffeine from these hybrid hydrogels at different temperatures and with different hydrogel compositions were thoroughly investigated. We found that this novel system provides controllable drug loading and a positive drug-release pattern. More than 90% of the loaded drugs were released at both high and low temperatures, with a faster release rate at higher temperatures.**
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**Keywords:** colloidal silica; controlled release; drug delivery; multiple cross-linking point; polymer network; swelling; thermosensitive hydrogels

## INTRODUCTION

Hydrogels are three-dimensional polymer networks that can absorb and retain large amounts of water.[1] Some hydrogels undergo substantial volume changes in response to environmental stimuli, such as temperature, pH, electric field and ionic strength.[2–5] These responsive hydrogels have attracted considerable interest in the design of novel drug-release systems,[6–9] artificial organs[10] and gene carriers.[11] In recent years, a variety of responsive drug delivery systems, such as temperature-pH sensitive hydrogels and membranes, has been investigated.[9,12–14] Polymers that have a lower critical solution temperature (LCST) in aqueous solution can be used for such responsive delivery systems by utilizing their swelling and de-swelling properties. The poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel is a typical thermosensitive material, and it exhibits a phase transition temperature or LCST at approximately 33 °C.[15,16] Below the phase transition temperature, PNIPAAm is soluble in water; however, it exhibits a severe volume decrease (phase transition) when the temperature is increased above its LCST. This temperature-dependent phase transition has motivated much research into the use of this substance for the controlled release of drugs. Generally, the drug molecules are physically loaded into the hydrogels, and the drug release is controlled by external temperature changes because of the temperature-responsive behaviors of PNIPAAm hydrogels. Functional nanohybrids based on silica-PNIPAAm have also attracted considerable attention for control of molecular transport, including drug release, because it makes possible the self-regulated delivery of a drug when it is needed.[17] The design of a temperature-dependent loading and release method based on stimuli-responsive PNIPAAm hybrids with nanoparticles has also been reported.[18–20]

There are two popular methods for physically loading drug molecules into hydrogels.[21] In the first method, a previously prepared hydrogel is placed in a drug solution until it swells to equilibrium, thus allowing the drug to diffuse into the hydrogel.[6,22–24] The second method involves mixing hydrogel monomers with the drug and initiator, with or without a crosslinker, followed by polymerization, which consequently traps the drug within the hydrogel.[8,21,25] The drug-loaded hydrogels are then washed several times to remove unreacted monomers and initiators. Then, through spectrophotometric analysis, the actual composition of the hydrogels (monomer/water ratio, drug content) is calculated. To the best of our knowledge, most of the previous studies reported loading of the drug using either of the two aforementioned methods. Improper washing of the hydrogel may result in unreacted chemicals being present inside the hydrogel, which may cause undesirable effects for medical and biological applications. In addition, these methods are complicated

[1]Department of Applied Chemistry and Biochemistry, Kumamoto University, Kumamoto, Japan; [2]Department of Applied Chemistry and Chemical Engineering, Noakhali Science and Technology University, Noakhali, Bangladesh; [3]Department of New Frontier Science, Kumamoto University, Kumamoto, Japan and [4]Kumamoto Institute for PhotoElectro Organics (Phoenics), Kumamoto, Japan
Correspondence: Dr M Takafuji, Department of Applied Chemistry and Biochemistry, Kumamoto University, 2-39-1 Kurokami, Kumamoto 860-8555, Japan
or Professor H Ihara, Department of New Frontier Science, Kumamoto University, 2-39-1 Kurokami, Kumamoto 860-8555, Japan.
E-mail: takafuji@kumamoto-u.ac.jp or ihara@kumamoto-u.ac.jp
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multistep approaches through which control of drug loading is quite difficult.

We have recently reported a new type of hybrid hydrogel with high tunability obtained by chemical crosslinking using silica nanoparticles (SiP) as multifunctional crosslinking agents.[26,27] As these SiP-crosslinked hybrid hydrogels (*p*NS-SiP) can be prepared by mixing the purified copolymer solution and SiP suspension, there is no possibility of unreacted monomer or initiators remaining in the hydrogels, and their properties can be adjusted very easily by modulating the properties of the copolymer and nanoparticles.[26] We reported that these hybrid hydrogels have a well-formed porous network structure, which results in high swelling ratios, enhanced de-swelling rate behavior and a remarkable improvement in mechanical strength.[27] All of these improved properties make this hybrid hydrogel potentially useful in a wide range of industrial applications, including drug-release systems, enzyme supports, etc.

Herein, the application of SiP-crosslinked thermosensitive hybrid hydrogels in the construction of a controlled drug-release system is demonstrated. Poly[*N*-isopropylacrylamide-co-(3-methacryloxypropyltrimethoxysilane)] (*p*NS) copolymer was used as the backbone, and commercially available SiP were used as the crosslinkers of the hybrid network to evaluate the basic thermo-responsive release behavior of the model drug, caffeine, from the hybrid hydrogels. Drug molecules were loaded into the hybrid hydrogel by adding them into the SiP suspension before mixing with the reactive copolymer solution at 25 °C to prepare the hybrid hydrogel (Scheme 1). The drug-loaded hydrogels were then allowed to release the drug through swelling and shrinking by placing them into deionized water (and buffer solution) at 20 °C (below the LCST) and at 37 °C (above the LCST), respectively.

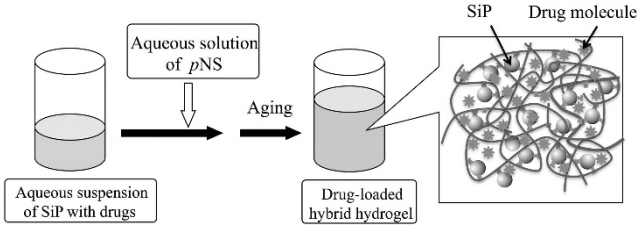
## EXPERIMENTAL PROCEDURE

### Materials

*N*-Isopropylacrylamide (NIPAAm; Kohjin Film & Chemicals Co., Ltd, Tokyo, Japan) was purified by recrystallization from hexane/benzene (50/50, v/v) to remove the inhibitor before use. The initiator, 2,2-azobisisobutyronitrile, was purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan) and was recrystallized from methanol. Colloidal SiP (mean diameter of 14.3 nm) suspensions were purchased from Nissan Chemical Industries Ltd (Tokyo, Japan). *N,N′*-Methylene-bis-acrylamide, ammonium peroxodisulfate, caffeine, 3-methacryloxypropyltrimethoxysilane and *N,N,N′,N′*- tetramethylethylenediamine were of analytical grade and were used as received.

### Synthesis and analysis of copolymer (*p*NS)

*p*NS was synthesized via the free radical copolymerization of NIPAAm and 3-methacryloxypropyltrimethoxysilane in methanol at 60 °C, as reported previously.[27] PNIPAAm homopolymers were synthesized and used as a reference. FTIR spectra of PNIPAAm and *p*NS were obtained using a FT-IR 4100 spectrometer (JASCO, Tokyo, Japan). Powder samples were prepared by dispersing the polymers in KBr and compressing the mixture to form disks. $^1$H Nuclear magnetic resonance spectra of the dried polymers were obtained using a JNM-LA400 (JEOL, Ltd, Tokyo, Japan) instrument at 400 MHz with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. The number-average and weight-average molecular weights ($M_n$ and $M_w$) and polydispersity indices of the prepared polymers were determined by size exclusion chromatography with a Shodex Asahipak GF-7M HQ column (Showa Denko K. K., Tokyo, Japan) using dimethylformamide containing 0.01 M lithium chloride (LiCl) as the eluent. Polystyrene standards were used as calibration standards.




**Scheme 1** Facile preparation of drug-loaded thermosensitive hybrid hydrogel. *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle. A full color version of this figure is available at *Polymer Journal* online.

### Synthesis of organic-inorganic hybrid hydrogels

Hybrid hydrogels were prepared by mixing the aqueous solution of copolymer (*p*NS) with a certain amount of the SiP suspensions at room temperature (25 °C) in small cylindrical Teflon tubes with bottom-end sealing. After 24 h, the hydrogels were pushed out of the tubes and used. Conventional NIPAAm hydrogel was also prepared as a standard using MBAAm as an organic crosslinking agent, following a procedure from the literature[28] by maintaining the NIPAAm concentration equal (at 5 wt%) to that of our hybrid hydrogels (Supplementary Information).

### Equilibrium/swelling ratios of hybrid hydrogels

The gravimetric method was employed to measure the equilibrium/swelling ratios of different hydrogels at different temperatures. The as-prepared hybrid hydrogels were immersed in distilled water at a predetermined temperature ranging from 20 to 50 °C for at least 48 h to reach equilibrium. Then, the hydrogels were removed from the water and weighed (wet weight of the hydrogel, $W_w$, after removing the excess water on the hydrogel surface). After measuring the weight at one temperature, the hybrid hydrogels were re-equilibrated at another predetermined temperature for subsequent measurements. The equilibrium/swelling ratio, $S_{eq}$, at different temperatures was calculated using the following equation:

$$S_{eq} = (W_w - W_d)/W_d$$

where $W_w$ is the wet weight of the hybrid hydrogel and $W_d$ is the theoretical dry wet of the corresponding hydrogel.

### Drug loading and release behavior of the hybrid hydrogels

*Standard absorbance curve.* A standard calibration curve of the absorbance as a function of the caffeine concentration was obtained at 272 nm using a ultraviolet spectrophotometer from a series of caffeine solutions with standard concentrations.

### Drug loading and release studies

The caffeine-loaded hybrid hydrogels were prepared as follows. The aqueous copolymer solution and SiP suspensions were added to separate tubes. The desired amount of caffeine was added to the aqueous SiP suspension and dissolved by ultra-sonication. Then, the drug-loaded hydrogel was prepared by mixing the copolymer solution and drug-loaded SiP suspension in a 1:1 (v/v) ratio in a cylindrical Teflon tube with the bottom end sealed. After 24 h, the drug-loaded hydrogels were used for the release study in deionized water at 20 and 37 °C. Each drug-loaded hydrogel was immersed into a glass bottle containing 150 ml of deionized water while the temperature was maintained at 20 or 37 °C using an incubator at a shaking speed of 100 r.p.m. Samples of 3 ml aliquots were withdrawn at predetermined time intervals, and the same volume of medium was replaced to maintain the liquid volume. The withdrawn aliquots were analyzed for their drug contents using a ultraviolet spectrophotometer at 272 nm. The amount of drug present in the samples was calculated using the calibration curve constructed from a series of caffeine solutions with standard concentrations. The drug release at specified time periods was plotted as a percentage released versus time curve. The release of caffeine at 37 °C (above the LCST) was also investigated in acid buffer (pH 1.7) and in phosphate buffer (pH 6.8). Standard buffer solutions with pH 1.7 and pH 6.8 were prepared using 0.2 M potassium chloride (KCl) and 0.1 M monobasic potassium phosphate ($KH_2PO_4$). Hydrochloric acid (0.2 M) and

sodium hydroxide (0.1 M) solutions were used to adjust the ionic strengths of the solutions. The experimental procedures and calculations for caffeine release are similar to those described for caffeine release in deionized water. Caffeine-loaded conventional PNIPAAm hydrogel with a 5 wt% PNIPAAm (*p*N5) content was also prepared as explained previously by adding caffeine to the initial mixture.

## RESULTS AND DISCUSSION

Figure 1 shows the chemical structure of the synthesized copolymer. The preparation conditions, molecular weights and polydispersity indices of the prepared copolymer (*p*NS) and PNIPAAm homopolymer are listed in Table 1. The characterization of the copolymer was performed using $^1$H nuclear magnetic resonance, Fourier-transform infrared and size exclusion chromatography. Both the $^1$H nuclear magnetic resonance and Fourier-transform infrared results (Supplementary Figures 1 and 2, Supplementary Information) confirmed the copolymerization of NIPAAm and 3-methacryloxypropyltrimethoxysilane.

### Preparation of hybrid polymer hydrogels

To investigate the effects of different hydrogel structures on the properties of the thermosensitive hybrid hydrogels, a series of *p*NS-SiP hydrogels with different SiP contents were prepared and investigated. Comparatively homogeneous polymer networks were confirmed by the transparency of the hybrid gels, even at high concentrations of SiPs. As the hydrogels were prepared from a previously prepared and purified copolymer solution, this method does not require any further processing of the hydrogels to purify them from unreacted monomers and initiators.[28,29] This significant advantage of this novel method motivated us to further investigate the drug loading and release behaviors of these hydrogels with different network structures. Desired amounts of drug molecules can be added to the aqueous SiP suspension before mixing with the copolymer solution while preparing the hydrogel. The tuning of the drug loading is only a matter of changing the amount of drug before adding it to the SiP suspension. All of the hydrogels in our experiment contained a fixed concentration (5 wt%) of copolymer (*p*NS) solution, which was mixed with different concentrations of SiP. For example, the hydrogel compositions *p*NS5-SiP5, *p*NS5-SiP10 and *p*NS5-SiP15 contained 5 wt% *p*NS and 5, 10 and 15 wt% SiP, respectively.

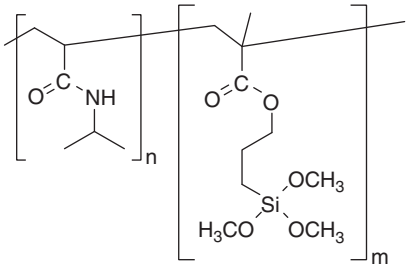



**Figure 1** Chemical structure of synthesized copolymer (poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)] (*p*NS)).

### Effect of temperature on the equilibrium-swelling ratio

The equilibrium-swelling behaviors of the hydrogels are considered to be important factors that influence the drug-release rate and the cumulative release.[8] The well-formed porous network structure of SiP-crosslinked hybrid hydrogels results in high swelling ratios[27] compared with conventional hydrogels crosslinked with organic chemicals.[30,31] The higher swelling ratios and their fine controllability are advantageous for loading and releasing high volumes of target materials, such as drug molecules. Figure 2 illustrates the effect of temperature on the equilibrium-swelling ratios of hybrid hydrogels that contain a fixed copolymer concentration of 5 wt% and different concentrations of SiP compared with the conventional PNIPAAm hydrogel with the same polymer concentration. As shown, at any temperature below the LCST, the equilibrium-swelling ratios of all the hybrid hydrogels decreased as the SiP content in the corresponding hydrogel increased. For example, *p*NS5-SiP5 had the highest equilibrium-swelling ratio (42 g/g) at 20 °C, whereas those of *p*NS5-SiP10 and *p*NS5-SiP15 were 33 and 27 g/g, respectively. Again, the equilibrium-swelling ratios of the hybrid hydrogels decreased gradually as the temperature increased, and the changes in the equilibrium-swelling ratios were pronounced at approximately

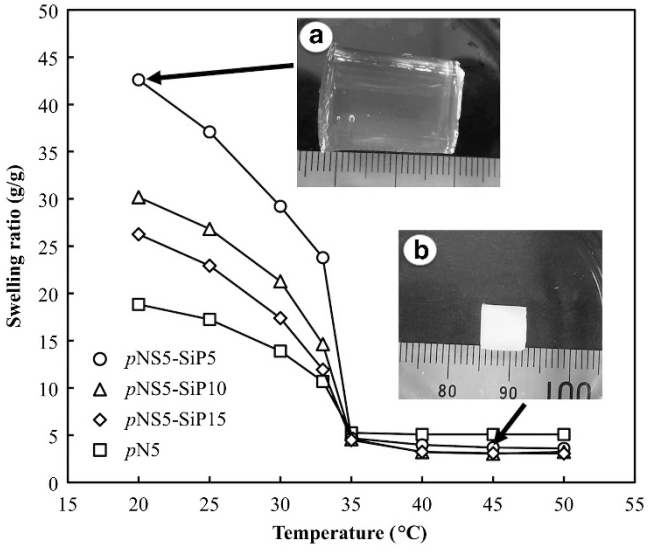



**Figure 2** Equilibrium-swelling ratios as a function of temperature for the hybrid hydrogels and conventional poly(*N*-isopropylacrylamide) hydrogel (*p*N5). Inset photographs: *p*NS5-SiP5 hydrogel after swelling at 20 °C (a) and after heating at 45 °C (b) for 48 h. *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle. A full color version of this figure is available at *Polymer Journal* online.

**Table 1 Preparation conditions, molecular weights and PDIs of the prepared polymers**

| *Sample* | *NIPAAm g* | *MAPTS g* | *AIBN mg* | *MeOH ml* | *Yield %* | $M_W(\times 10^5)$ | *PDI* | *n/m in pNS (observed)* |
|---|---|---|---|---|---|---|---|---|
| *p*NS | 11.32 (100 mmol) | 0.25 (1 mmol) | 56.7 | 80 | 88 | 2.37 | 2.48 | 106 |
| PNIPAAm | 11.32 (100 mmol) | — | 56.7 | 80 | 86 | 2.15 | 2.86 | — |

Abbreviations: AIBN, 2,2-azobisisobutyronitrile; MAPTS, methacryloxypropyltrimethoxysilane; PDI, polydispersity index; PNIPAAm, poly(*N*-isopropylacrylamide); *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)].

33 °C, which was considered to be their LCST. The inset pictures show the hydrogel states after reaching equilibrium-swelling at 20 °C (Figure 2a) and de-swelling at 37 °C (Figure 2b). As the external temperature changed, the hydrophilic and hydrophobic balance within the hybrid network changed, and the interactions among the hydrophobic groups dominated; thus, phase separation occurred. The equilibrium-swelling ratios of the hybrid hydrogels were also observed to be considerably greater than that of the conventional PNIPAAm hydrogel. For example, the equilibrium-swelling ratio of the conventional PNIPAAm hydrogel at 20 °C was 18 g/g, whereas it was 26, 33 and 42 g/g for hybrid hydrogels with 15, 10 and 5 wt% SiP, respectively. We hypothesize that the incorporation of SiP provided more hydrophilic sites and pores in the networks, which improved the swelling ratios of these hybrid hydrogels.

The network structure and its hydrophilicity affected the thermosensitivity of the hybrid hydrogels. As the temperature increased, the reductions in the equilibrium-swelling ratios of the hydrogels were different. The *p*NS5-SiP5 hydrogel had a sharper decrease in the curve than the *p*NS5-SiP10 and *p*NS5-SiP15 hydrogels near the LCST. This result indicates that the temperature sensitivity of the hydrogels was greater with a lower SiP content because of the lower hydrophilicity and loose network structure of the *p*NS5-SiP5 hydrogel with a lower crosslinker (SiP) content. Consequently, the hydrogen bonding interactions became weaker, which led to a stronger hydrophobic aggregation force for de-swelling compared with the other hydrogels (*p*NS5-SiP10 and *p*NS5-SiP15).

**Loading of caffeine**

Caffeine was loaded into the hydrogels using a unique and efficient strategy, which involved adding a desired amount of caffeine into the SiP suspension before mixing with the copolymer solution. After incubating for 24 h, the as-prepared drug-loaded hydrogels were used to investigate the drug-release pattern. Therefore, the amount of drug loaded was identical to the amount of drug added during mixing. Moreover, the drug loading can be easily controlled by only changing the mixing quantity while adding to the SiP suspension in comparison with the other methods.[32,33]

**Effect of temperature on drug (caffeine) release from hybrid hydrogels**

Drug release from a gel is generally controlled by two factors: (1) the diffusivity of the drug and (2) the swelling of the polymer.[24,34] In addition, various interactions between drug molecules, hydrogel networks, and water molecules also have an important role in the drug-release behaviors.[35,36] To investigate the effect of temperature on the caffeine-release behaviors of different hybrid hydrogels, the release experiments were performed at 20 °C (below the LCST) and at 37 °C (above the LCST) in deionized water (pH 6.8), and the release as a function of time was determined from the ultraviolet–visible spectra of the solutions. The amount of drug released was estimated from the standard calibration curve (Supplementary Figure 3, Supplementary Information). The results are shown in Figure 3, which indicate that higher temperatures led to a rapid release of caffeine from all three of the hydrogels. However, the final cumulative release was similar for all of the hydrogels at both temperatures. For instance, the equilibrium release of caffeine reached approximately 93% at both temperatures from the *p*NS5-SiP5 hydrogel (Figure 3a) after 10 h, although the release rate is comparatively low at 20 °C (temperature below the LCST). Similarly, the cumulative release reached approximately 92% from the *p*NS5-SiP10 hydrogel after the same time period (Figure 3b). The same trend was observed for the *p*NS5-SiP15 hydrogel, as shown in Figure 3c. The caffeine-release behaviors in this hybrid system can be explained under the following two headings: (1) release at different rates and (2) similar cumulative release.

*Release at different rates.* For all three of the hybrid hydrogels, differences can be observed in the caffeine-release rates. For example, the release of caffeine from the *p*NS5-SiP5 hydrogel after 60 min reached approximately 75% and 44% when the temperature was fixed at 37 °C and 20 °C, respectively. Similar release rate behaviors were also observed for the other hydrogels. The reason for this release rate behavior might be due to the sharp decrease in the effective density of the drug-loaded hydrogel network via the precipitation of thermosensitive polymer chains at 37 °C (above the LCST). Consequently, the size of the porous channel increased, which would accelerate the release of caffeine from the severely collapsed hydrogels. In addition, the hydrogen bonding interactions between the hydrophilic sites of caffeine and the polymer hydrogels[8] weakened at high temperatures. All of these factors contributed to the rapid release of caffeine at the higher temperature (37 °C). Similar results concerning the effect of temperature on the release rate have also been reported in other drug-release systems.[6,8,37] For instance, Deng *et al.* reported that the cumulative release of a drug is significantly increased because of the increase in the pore sizes of the channels at temperatures above the LCST.[6] Bao-Lin Gua and Qing-Yu Gao also observed similar drug-release behaviors from semi-IPN hydrogels based on PNIPAAm.[38] In another study, Zhang *et al.* reported that rapid drug release is due to the collapse of the thermosensitive hydrogel networks at temperatures greater than the LCST.[8]

*Similar cumulative release.* Notably, very high and similar cumulative releases (greater than 90%) at both temperatures were observed (Figures 3a–c). For example, the cumulative release from the *p*NS5-SiP5 hydrogel after 10 h was approximately 93.6% and 93.8% when the temperature was 20 and 37 °C, respectively (Figure 3a). The case for the *p*NS5-SiP10 hydrogels was similar, with a cumulative release of approximately 92% within the same time frame (Figure 3b). There was a slight deviation in the case of the *p*NS5-SiP15 hydrogels; the percent cumulative releases were approximately 82% and 87% after 10 h at 20 and 37 °C, respectively. The reason for the higher cumulative releases at the higher temperature was explained in the previous paragraph. The following discussion explains the factors that caused the high cumulative release at the low temperature (20 °C). It has been reported that SiP-crosslinked hybrid hydrogels possess a well-formed porous network structure, which provides numerous channels for macromolecular agents to be squeezed out of the hydrogel network.[27] At the lower temperature, when the drug-loaded hydrogel was placed in water, the polymer chains were solvated with water molecules and distributed randomly. The solvent begins diffusing into the hydrogels; therefore, relaxation of the polymer chains could not immediately occur.[39] As the experiment proceeded, the hybrid hydrogels began to slowly swell because of polymer chain relaxation, which created paths for caffeine to be released from the hydrogels. The chain relaxation and molecular diffusion might occur at similar rates, resulting in the slow release rate behavior at this temperature. However, the swelling of the hydrogel continued to a high degree, causing the network pores to increase in size, which allowed the majority of the drugs to diffuse out of the hydrogels as time passed. Hence, a high cumulative release was also observed at this temperature.

However, the cumulative release of caffeine from all of the hydrogels was unable to reach 100% for either temperature. To

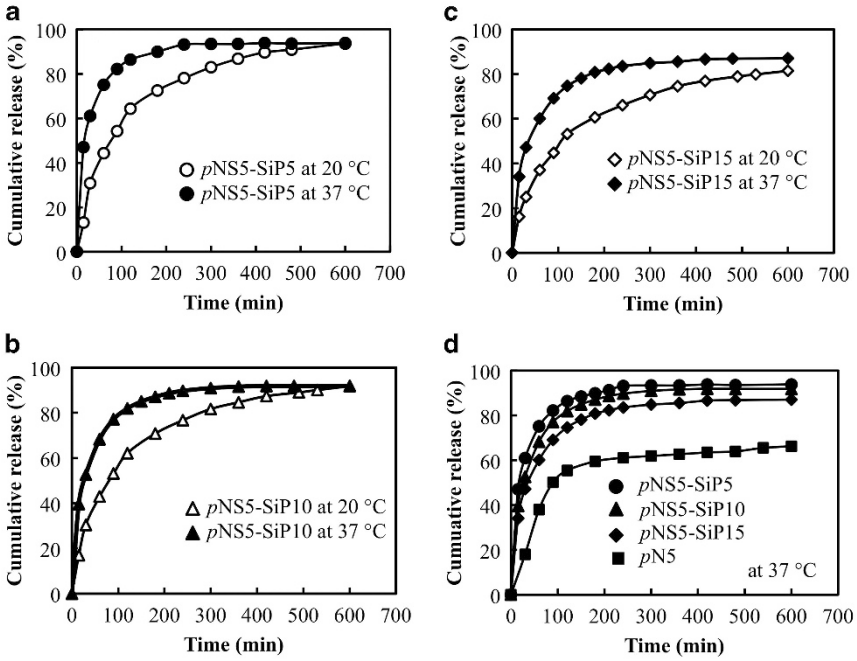



**Figure 3** Cumulative release of caffeine from hybrid hydrogels at different temperatures in deionized water (pH 6.8): (**a**) *p*NS5-SiP5, (**b**) *p*NS5-SiP10 and (**c**) *p*NS5-SiP15; and (**d**) cumulative release of caffeine from hybrid hydrogels with different SiP contents and from conventional poly(*N*-isopropylacrylamide) hydrogels (*p*N5) in deionized water (pH 6.8) at 37 °C. *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle.

determine the maximum release for all of the hydrogels (equilibrium % cumulative release), we continued the release experiments at both temperatures for up to 15 h. We observed that the equilibrium cumulative release was increased by approximately only 1% for all of the hydrogels at 20 °C, whereas it had already reached equilibrium within 10 h at 37 °C (that is, no increase in the % cumulative release up to 15 h). As discussed previously, caffeine interacts with the hydrophilic sites of the hydrogel networks. The diffusion of caffeine molecules might be affected at lower temperatures. We hypothesize that the hydrogen bonding interactions were not sufficiently disturbed at the lower temperature (20 °C). Consequently, some caffeine remained inside the hydrogel network. On the other hand, although the hydrogen bonding interactions were destabilized at the higher temperature (37 °C), the severely collapsed hydrogel network entrapped a small amount of caffeine inside the network. Therefore, at temperatures below the LCST, the release of caffeine was primarily caused by the swelling phenomenon, whereas it was mainly caused by diffusion through the severely collapsed temperature-sensitive porous network at temperatures above the LCST.

**Effect of crosslinker (SiP) concentration on caffeine release**

Figure 3 also shows the effect of the SiP (crosslinker) content on the caffeine-release behavior in deionized water at 37 °C (Figure 3d). The release of caffeine from the conventional PNIPAAm hydrogel (*p*N5) at 37 °C is also shown in the same figure for comparison. In comparison to the *p*N5 hydrogel, the hybrid hydrogels exhibit faster and higher cumulative release. For instance, the cumulative release after 2 h was approximately 86% and 55% for the *p*NS5-SiP5 and *p*N5 hydrogels, respectively. The maximum cumulative release reached approximately 96% for *p*NS5-SiP5, whereas it is approximately 65% for the *p*N5 hydrogel. This result arises because, for the *p*N5 hydrogel, the release of caffeine at 37 °C was considerably affected by the formation of a thick, dense skin layer, which is an inherent property of conventional PNIPAAm hydrogels.[40] It is well known that a thick skin layer forms on the surface of conventional PNIPAAm hydrogels when heating at a temperature above the LCST.[28,29,41,42] This skin layer affects the permeability of the hydrogel and prevents the water or drug molecules from being squeezed out of the hydrogel.[29,43,44] Therefore, bubbles appear on the surface of the PNIPAAm hydrogel during the shrinking process.[41,43] In this study, we also observed many bubbles on the surface of the *p*N5 hydrogel during the release process at 37 °C, whereas no bubbles were observed on the surface of the SiP-crosslinked hybrid hydrogels. The use of hydrophilic SiP as a crosslinker in this hybrid system could inhibit the formation of the skin layer and improve the permeability of the hydrogels. Moreover, the porous network structures of the hybrid hydrogels might have allowed the caffeine to be easily released at a faster rate. Therefore, the release rate and the cumulative release are higher for the hybrid hydrogels than for the *p*N5 hydrogel.

A comparison of the caffeine-release properties of the prepared hybrid hydrogels indicates that the cumulative release decreased as the crosslinker content in the hybrid hydrogels increased. For example, the cumulative release after 2 h reached approximately 86% and 74% for the *p*NS5-SiP5 and *p*NS5-SiP15 hydrogels, respectively. The reason for this result is clear from the structural perspective of hybrid hydrogels. With higher SiP contents, the hybrid hydrogel networks become significantly tighter and denser.[27] Therefore, caffeine molecules encountered comparatively more hindrances during the release process, and a greater proportion of the caffeine molecules became entrapped within the dense collapsed network, which resulted in a lower cumulative release. However, the differences in the release curves are marginal, although the crosslinker concentrations are notable. The marginal differences in the cumulative release of different hydrogels might be due to the larger pores of the polymer network with all hydrogel compositions. The smallest pore sizes in the highest density hydrogel network in this study might be large enough

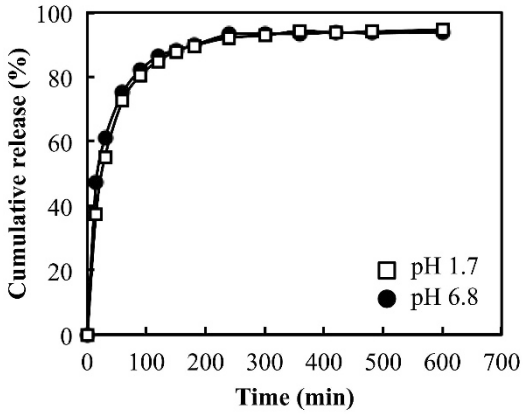



**Figure 4** Cumulative release of caffeine from *p*NS5-SiP5 hydrogels in different pH buffer media at 37 °C. *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle.

for caffeine molecules to be squeezed out. Therefore, the crosslinker concentrations (SiP contents) of these hybrid hydrogels are not sufficiently effective for causing sharp differences in the release behavior.

### Effect of pH on caffeine release

The drug-release behaviors of various hybrid hydrogels in buffer solutions at different pH conditions (pH 1.7 and 6.8) were investigated. Figure 4 presents the cumulative release profile from the *p*NS5-SiP5 hydrogel at 37 °C. The results indicate that pH has no effect on the release of caffeine from the hydrogel. A similar and almost identical cumulative release was observed throughout the release experiment for the hydrogel. The cumulative release after 60 min was approximately 75% and 73% when the release experiments were conducted at pH values of 6.8 and 1.7, respectively. The release reached equilibrium (93% release) within 4 h at both pH conditions.

From a chemical structural perspective of the hybrid hydrogels, it is evident that there are no pH-sensitive groups in the structure that can cause changes in the network structure in response to pH variations. Similar results were also observed for other hydrogels (figures not shown) with different SiP contents, which indicate that there was no effect of pH on the release behavior of this SiP-crosslinked hybrid hydrogel (*p*NS-SiP) system.

From the above results, it is revealed that the SiP-crosslinked hybrid hydrogels show a positive controlled release pattern, that is, rapid drug release at increased temperature and slow drug release at decreased temperature. It also shows that temperature and the compositions and morphologies of hydrogel materials are important factors in drug delivery from this type of hybrid system. Figure 5 shows different states of the typical *p*NS5-SiP5 hydrogel before and after the release of caffeine at 20 and 37 °C.

### Study of caffeine-release mechanism

The mechanism of caffeine release can be explained using the empirical power equation proposed by Peppas *et al.*,[45,46] as follows:

$$M_t/M_\infty = kt^n$$

where $M_t$ and $M_\infty$ are the absolute cumulative amount of drug released at time $t$ and at infinite time, respectively, $k$ is the rate constant and $n$ is the release exponent. The value of $n$ is used to characterize different release mechanisms. For cylindrical-shaped matrices, $0.45 \leqslant n$ corresponds to a Fickian diffusion mechanism (indicating diffusion-controlled drug release), $0.45 < n < 0.89$

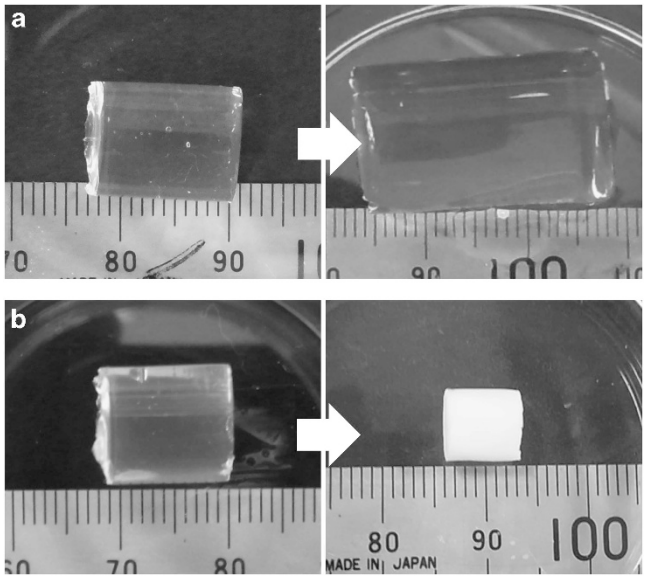



**Figure 5** Photographs showing the different states of the *p*NS5-SiP5 hybrid hydrogel: (**a**) drug-loaded hydrogel before and after release at 20 °C, (**b**) drug-loaded hydrogel before and after release at 37 °C. *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle. A full color version of this figure is available at *Polymer Journal* online.

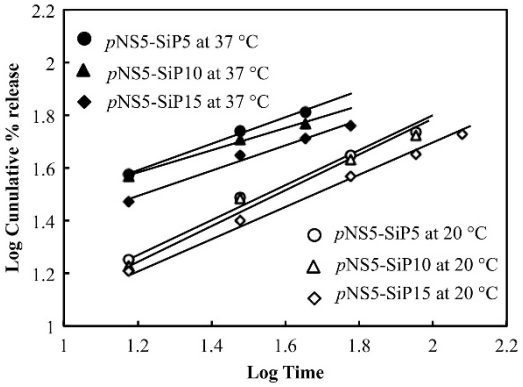



**Figure 6** Plots of log cumulative % release against log time for caffeine release from hybrid hydrogels with various silica nanoparticle (SiP) contents at 20 °C (below the lower critical solution temperature (LCST)) and at 37 °C (above the LCST).

corresponds to non-Fickian transport (anomalous transport) and $n = 0.89$ corresponds to case-II (relaxational) transport (indicating swelling-controlled drug release). In other words, Fickian diffusional release and case-II relaxational release are the limits of this model. Whereas Fickian diffusional release occurs through the usual molecular diffusion of the drug molecules because of the chemical potential gradient, the case-II transport mechanism is associated with stresses and state transitions in the case of hydrophilic polymers that can swell in water. When the value of $n$ is between 0.45 and 0.89, the drug-release behavior can be considered as the superposition of both phenomenon (that is, release occurs due to a coupling of Fickian diffusion and polymer relaxation), which is called anomalous transport. To determine the exponent $n$, only the region of the release curve in which $M_t/M_\infty < 0.6$ (first 60% drug release) should be used. We plotted the log cumulative percentage of caffeine release

**Table 2 Release components (*n*), rate constants (*k*) and correlation coefficients ($R^2$) for the hybrid hydrogels**

| | *At 20°C (below LCST)* | | | *At 37°C (above LCST)* | | |
|---|---|---|---|---|---|---|
| *Hydrogel* | *Log* k | n | $R^2$ | *Log* k | n | $R^2$ |
| *p*NS5-SiP5 | 0.55 | 0.62 | 0.99 | 0.99 | 0.50 | 0.99 |
| *p*NS5-SiP10 | 0.51 | 0.63 | 0.98 | 1.07 | 0.42 | 0.99 |
| *p*NS5-SiP15 | 0.55 | 0.57 | 0.99 | 0.92 | 0.48 | 0.99 |

Abbreviations: LCST, lower critical solution temperature; *p*NS, poly[*N*-isopropylacrylamide-*co*-(3-methacryloxypropyltrimethoxysilane)]; SiP, silica nanoparticle.

versus log time of the experimental data to study the release mechanism. Figure 6 shows a typical plot of caffeine release from different hydrogels at various SiP concentrations at 20 °C (below the LCST) and at 37 °C (above the LCST). The data exhibited good linearity, which indicates that Peppas's equation is applicable to the present system. The release component of *n*, rate constant of log *k* and the correlation coefficient of $R^2$ for the hydrogels at 20 and 37 °C were obtained from these plots (Figure 6) and are listed in Table 2. At 20 °C, the values of *n* for all three of the hydrogels (Table 2) were greater than 0.45 and considerably smaller than 0.89, indicating that the release of caffeine occurs through the anomalous transport mechanism at that temperature. On the other hand, the values of *n* were very close to 0.45 for the release curves at 37 °C, indicating that the release of caffeine occurs through the Fickian diffusion mechanism at this temperature. The differences in release mechanisms at these two temperatures suggest that the phase transition temperature has an influence on the caffeine-release behavior of these hybrid hydrogels. As shown in Table 2, the values of log *k* for all of the hydrogels were almost identical at the same temperature (20 or 37 °C), whereas the values of log *k* increased with increasing temperature. For example, the log *k* values of *p*NS5-SiP5 and *p*NS5-SiP10 at 20 °C are 0.5538 and 0.5148, respectively, whereas these values at 37 °C are 0.9859 and 1.0759, respectively. These observations suggest that the release rate of the hybrid hydrogels increased when the medium temperature was increased above the phase transition temperature.

## CONCLUSION

We developed a facile preparation route to obtain drug-loaded hybrid hydrogels based on *p*NS using a commercially available SiP suspension as a multifunctional crosslinking agent. The applicability of this hybrid system as a matrix for controlled drug release was investigated to determine the influence of temperature and crosslinker concentration on caffeine release. The results indicate that the *p*NS-SiP hybrid hydrogels have the potential to encapsulate macromolecules. The incorporation of hydrophilic SiP in the polymer network led to significant changes in the structural properties of the system without destroying the backbone structure of the polymer. Moreover, the thermosensitivity of the hybrid hydrogels was retained in the hybrid system, which had a LCST similar to that of pure PNIPAAm. This hybrid system provides an efficient loading strategy and a high cumulative release of drug with great tunability in the positive controlled release pattern. The response of this hybrid system as a drug delivery device is influenced by the volumetric changes of copolymer through swelling at temperatures below the LCST and through phase transitions at temperatures above the LCST. However, the release pattern reported here must be improved or optimized, and further studies are underway. This novel release system would have potential and promising applications in cases where positive controlled drug release is required.

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