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FOCUS REVIEW

Design of nano- and micro-structured molecule-responsive hydrogels

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Stimuli-responsive hydrogels have attracted considerable attention for use as smart materials, such as in molecular sensors and drug delivery systems. With a focus on their crosslinking density, we have prepared various molecule-responsive hydrogels that undergo volume changes in response to target molecules based on the association/dissociation of molecular complexes that act as crosslinkers. Recent developments in polymerization techniques enabled us to design various types of polymer nanomaterials. This focus review provides a short overview of our recent studies on the nano- and micro-structured molecule-responsive hydrogels prepared using various polymerization techniques, such as photopolymerization, surface-initiated atom transfer radical polymerization and soap-free emulsion polymerization. The nano- and micro-structured molecule-responsive hydrogels showed not only rapid swelling/shrinkage in response to a target molecule owing to their large surface area but also smart functions, such as autonomous molecule-responsive microchannel flow regulation and highly sensitive detection of a target molecule. The smart functions of nano- and micro-structured molecule-responsive hydrogels can provide tools for constructing, for example, sensors, microdevices and smart biomaterials.
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INTRODUCTION

Hydrogels are soft materials composed of hydrophilic organic polymer components crosslinked into networks by either covalent or non-covalent interactions in aqueous media.[1] Since hydrogels absorb and retain large amounts of water, they exhibit various fascinating properties, such as swelling, permeation, storage and immobilization capabilities, optical properties, and biocompatibility. Such properties of hydrogels enable their application as, for example, superabsorbent materials, chromatographic media, drug carriers for drug delivery systems (DDSs), contact lenses and cell culturing scaffolds for regenerative medicine. Since the volume phase transition of hydrogels was discovered by Tanaka, stimuli-responsive hydrogels that undergo abrupt changes in volume in response to external stimuli, such as temperature,[2–4] pH,[5] electric fields[6,7] and light,[8] have been extensively studied. Such stimuli-responsive hydrogels have attracted considerable attention as smart materials because their volumetric changes induce changes in other properties, such as the refractive index, permeability, elastic modulus, interfacial tension and adhesion. The stimuli-responsive behavior of hydrogels reported previously was based on drastic changes in the affinity of the polymer network to water or in the osmotic pressure induced by the charged groups of the polymer network. Because the swelling/shrinkage behavior of hydrogels is strongly influenced by the number of crosslinks, we have proposed a novel strategy for the preparation of biomolecule-responsive hydrogels with biomolecular recognition abilities by using biomolecular complexes that act as dynamic crosslinks in the network.[9–12] The biomolecule-responsive hydrogel exhibits volume changes in response to a target molecule because the crosslinking density changes with the association and dissociation of molecular complexes that act as dynamic crosslinks (Figure 1). The biomolecule-responsive hydrogel has potential for application in self-regulated DDSs and biomolecular sensors.[13] However, the swelling of the molecule-responsive hydrogels that we previously reported took a comparable amount of time to reach equilibrium. In general, the kinetics of the swelling/shrinkage of hydrogels are governed by the diffusion-limited transport of the polymer chains in water. Therefore, rapid swelling/shrinkage responses of hydrogels can be achieved by decreasing the size of the stimuli-responsive hydrogel, as this leads to an increase in the surface area.[14] The present paper provides an overview of our studies on the nano- and micro-structured molecule-responsive hydrogels prepared by utilizing various polymerization techniques, such as photopolymerization,[15] surface-initiated atom transfer radical polymerization (SI-ATRP)[16–19] and soap-free emulsion polymerization.[20] The nano- and micro-structured molecule-responsive hydrogel provides not only rapid responsiveness but also highly selective and sensitive detection of target molecules when combined with sensing devices.[16–18]

MICRON-SIZED MOLECULE-RESPONSIVE HYDROGELS

Photopolymerization is of substantial scientific and industrial interest because of its wide range of applications, including its use in photoresists, inks, coatings and adhesives. Photopolymerization is also

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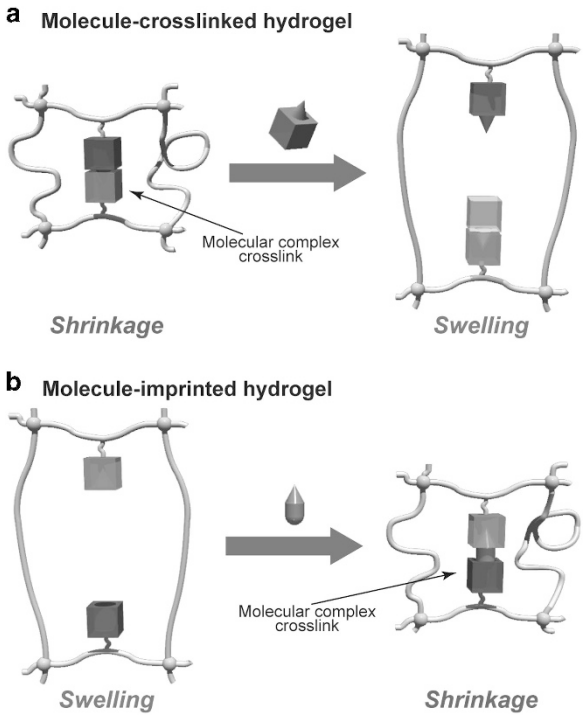

Figure 1 Schematic illustration of the responsive swelling/shrinkage behaviors of the molecule-responsive hydrogels: (**a**) molecule-crosslinked hydrogel and (**b**) molecule-imprinted hydrogel. A full colour version of this figure is available online from the *Polymer Journal*.

utilized for the preparation of various kinds of hydrogels because, by controlling the photoirradiation time, position and area, it provides a hydrogel with a specified size and shape. For example, miniaturization of hydrogels can be achieved by photopolymerization with a decreased photoirradiation area. By utilizing photopolymerization, micron-sized molecule-imprinted hydrogels with a minute number of crosslinkers were prepared.[15] Differing from standard molecular imprinting, which uses a large number of crosslinkers to attach functional groups at a strictly defined, optimal position within the molecular recognition site, molecule-imprinted hydrogels were successfully prepared by using a minute amount of crosslinker.[12,21] The molecule-imprinted hydrogels were able to selectively recognize a target molecule, and the hydrogels shrank with an increase in the concentration of the target molecule because the gel networks formed by molecular imprinting memorized the target molecule and formed dynamic crosslinks composed of molecular complexes. For example, a bisphenol A (BPA)-imprinted hydrogel was prepared by using β-cyclodextrin (CD) as a ligand for BPA.[21] The BPA-imprinted hydrogel was prepared as follows: CD containing a polymerizable acryloyl group (acryloyl-CD) and BPA were mixed to form CD–BPA–CD complexes. The resulting CD–BPA–CD complexes were copolymerized with acrylamide (AAm) and *N,N′*-methylenebisacrylamide (MBAA), followed by removal of the template BPA from the gel network by immersion in an acetone solution. The BPA-imprinted hydrogels gradually shrank in response to BPA because the CD units as ligands formed sandwich-like CD–BPA–CD complexes, and their crosslinking density increased. In addition, the BPA-imprinted hydrogel showed greater shrinkage in response to BPA than a non-imprinted hydrogel prepared without

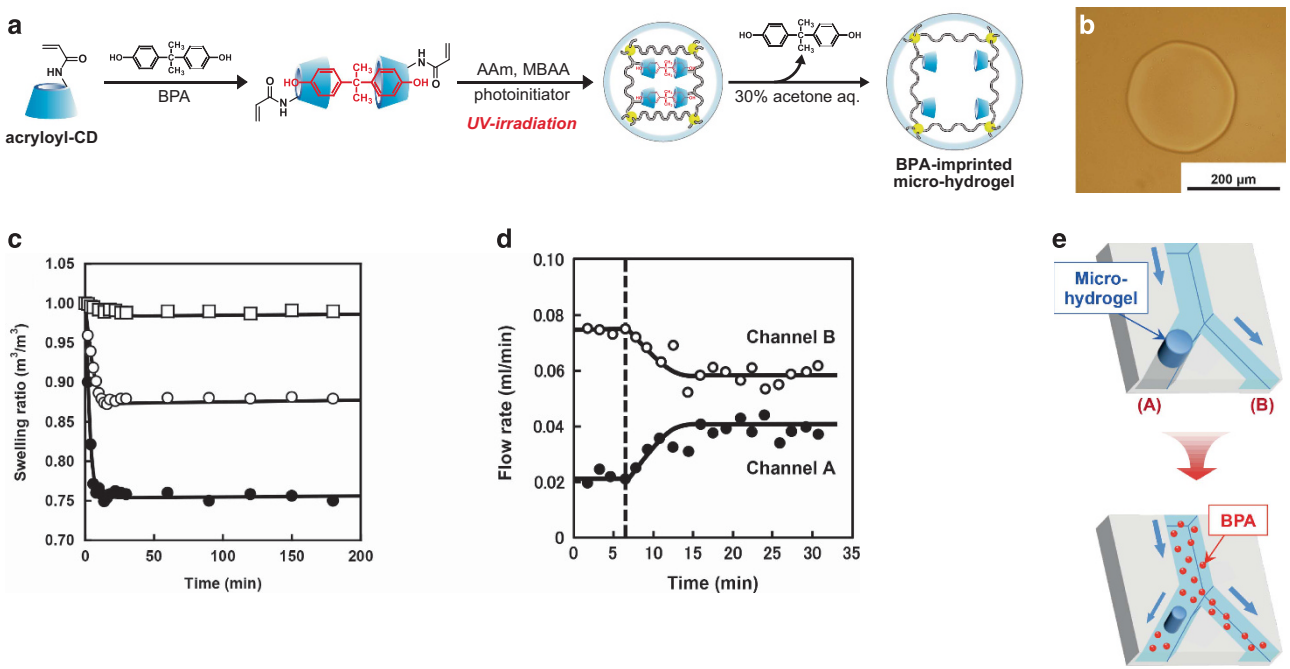

Figure 2 (**a**) Synthetic scheme for the BPA-imprinted micro-hydrogel. (**b**) Phase contrast microscope image of the BPA-imprinted micro-hydrogel. (**c**) Changes in the swelling ratio of the BPA-imprinted (●), non-imprinted (○) and PAAm micro-hydrogels (□) as a function of time after immersion in an aqueous BPA solution (0.12 mg ml^{-1}). (**d**) Flow rate changes in channel A with a BPA-imprinted micro-hydrogel and channel B without micro-hydrogel as a function of time when deionized water and aqueous BPA solution were flowed through the microchannel at a rate of 0.1 ml min^{-1}. (**e**) Schematic illustration of the flow change induced by the responsive shrinkage of the BPA-imprinted micro-hydrogel in the Y-shaped microchannel.

using the BPA template; this is because the CD ligands within the imprinted network were arranged at suitable positions for the formation of the 2:1 CD:BPA complexes via molecular imprinting. Although the BPA-imprinted hydrogel exhibited BPA-responsive shrinkage, the swelling took a long time to reach equilibrium after immersion in an aqueous BPA solution. Therefore, BPA-imprinted micro-hydrogels exhibiting rapid volume changes were prepared on a glass substrate via photopolymerization using a standard fluorescence microscope.[15]

A cylinder-shaped, BPA-responsive micro-hydrogel with a diameter of 200 μm was successfully prepared on a glass substrate by photopolymerization of the acryloyl-CD involved in the CD–BPA–CD complexes with AAm and MBAA using a fluorescence microscope, followed by extracting the BPA template from the resulting network by immersion in an acetone solution (Figure 2a and b). A non-imprinted micro-hydrogel was prepared by a similar method but without using the BPA template. The resulting BPA-imprinted and non-imprinted micro-hydrogels shrank rapidly in the presence of BPA. In addition, the BPA-imprinted micro-hydrogel exhibited greater shrinkage than the non-imprinted micro-hydrogel (Figure 2c). The BPA-responsive shrinkage is attributed to an increase in the apparent crosslinking density induced by the formation of CD–BPA–CD complexes that act as dynamic crosslinks. Furthermore, molecular imprinting organized the CD ligands at optimal positions, which facilitated CD–BPA–CD complex formation. Therefore, the BPA-imprinted micro-hydrogel showed a larger BPA-responsive shrinkage than the non-imprinted micro-hydrogel. Because the BPA-imprinted micro-hydrogel can be prepared at an arbitrary position and exhibits ultrafast shrinkage in response to the target BPA, we used it to develop a self-regulated microvalve for controlling the flow in a microchannel. The BPA-imprinted micro-hydrogel was prepared in one channel, A, of a Y-shaped microchannel. When deionized water flowed through the system, the flow rate was much lower in channel A than in channel B because the swollen micro-hydrogel inhibited water flow (Figure 2d and e). On the other hand, soon after the water was switched with an aqueous BPA solution, the flow rate of channel A increased, whereas that in channel B decreased because the BPA-imprinted micro-hydrogel spontaneously shrank in response to BPA, thus opening channel A. Therefore, the BPA-imprinted micro-hydrogel acted as a valve that could autonomously regulate the microchannel flow in response to BPA. These results indicate that the molecule-responsive micro-hydrogel provides promising self-regulated microvalves for microchannel flow control, facilitating the simplification and miniaturization of micro total analysis systems.

MOLECULE-RESPONSIVE THIN HYDROGEL LAYERS

The recent development of controlled radical polymerization methods, such as nitroxide mediated radical polymerization, atom transfer radical polymerization (ATRP) and reversible addition fragmentation chain transfer polymerization, opened the door for the preparation of various types of polymeric nanomaterials, such as micelles, vesicles and brushes, because the methods enabled the facile synthesis of well-defined block and graft copolymers under mild conditions.[22] In particular, polymer brushes on a solid substrate have attracted considerable attention because they change the substrate's surface properties, such as the wettability, tribology, adhesion and biocompatibility.[23] Polymer brushes are generally prepared via SI-ATRP, which allows for accurate control of the brush thickness, composition and architecture. Utilizing SI-ATRP, molecule-responsive hydrogel layers were prepared on the surface of a surface plasmon resonance (SPR) sensor chip.[16–18] The SPR sensor is most commonly used for measuring biological macromolecules, such as proteins, DNAs, RNAs and polysaccharides because it provides a highly sensitive quantitative analysis. SPR sensors detect a permittivity change near the

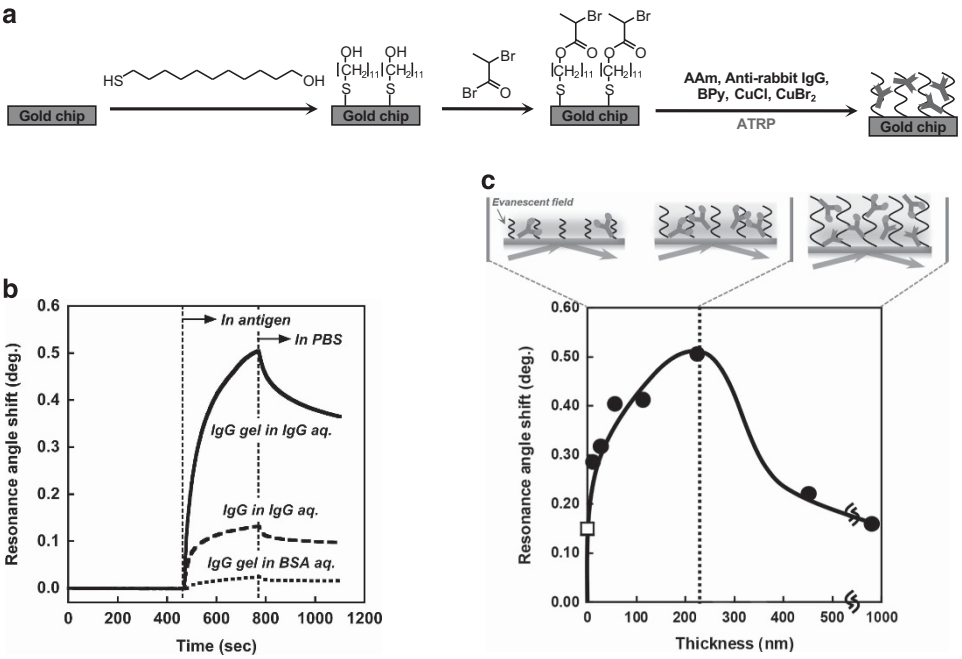

Figure 3 (**a**) Schematic illustration of the preparation of the 3D antibody-immobilized hydrogel layer chip via SI-ATRP. (**b**) Resonance angle shift of the antibody-immobilized hydrogel layer chip (solid line) and the chip with directly immobilized antibodies (dashed line) in phosphate buffer solution (PBS) containing the IgG target or BSA (dotted line) as an antigen. (**c**) Relationship between the hydrogel layer thickness and the maximum resonance angle shift of the antigen-immobilized hydrogel layer chip in a buffer solution containing IgG as a target antigen. The figure is reproduced from Kuriu *et al.*[16] from the Chemical Society of Japan. A full color version of this figure is available online from the *Polymer Journal*.

gold sensor chip surface, which is caused by complex formation or dissociation between target molecules and ligands immobilized on the surface of the gold sensor chip as the resonance angle shifts.[24] The sensitivity of SPR sensors can be improved by increasing the quantity of ligands immobilized on the sensor chip. Therefore, a three-dimensional (3D) anti-immunoglobulin G (anti-IgG) antibody-immobilized hydrogel layer was prepared via SI-ATRP on a gold SPR sensor chip. Self-assembled monolayers of 11-mercapto-1-undecanol were fabricated on the surface of a gold SPR sensor chip. Then, the gold SPR sensor chip with 11-mercapto-1-undecanol on the surface was treated with 2-bromopropionylbromide to introduce alkyl bromide as an ATRP initiator. The 3D antibody-immobilized hydrogel layer was prepared by SI-ATRP of AAm and anti-IgG containing polymerizable acryloyl groups under an argon atmosphere (Figure 3a).[16] The thickness of the 3D antibody-immobilized hydrogel layer was controlled by the polymerization time of the SI-ATRP. The resonance angle shift of the resulting sensor chip with the 3D antibody-immobilized hydrogel layer in response to the target antigen (immunoglobulin G: IgG) was much larger than that of the sensor chip with directly immobilized antibodies prepared by a conventional amino coupling method (Figure 3b). Furthermore, the resonance angle shift of the 3D antibody-immobilized hydrogel layer chip did not change in the presence of bovine serum albumin. The lack of a resonance angle shift in the presence of bovine serum albumin indicates that the 3D antibody-immobilized hydrogel layer chip not only selectively recognizes the target IgG but also prevents the non-specific adsorption of bovine serum albumin via the hydrated hydrogel layer. In addition, the resonance angle shift increased with an increase in the hydrogel layer thickness up to approximately 225 nm (Figure 3c). The increase in the hydrogel layer thickness led to an increase in the amount of immobilized antibody within the hydrogel layer. Therefore, the 3D antibody-immobilized hydrogel layer chip showed a large resonance angle shift in response to the target IgG. The crosslinking density of the hydrogel layer was low enough for penetration by the IgG analyte, even after the formation of antigen-antibody complex crosslinks. Therefore, the IgG analyte could penetrate the outermost layer of the hydrogel and approach the anti-IgG ligand of the inner hydrogel layer, resulting in an increase in the resonance angle shift. However, when the hydrogel layer thickness increased above 225 nm, the resonance angle shift of the 3D antibody-immobilized hydrogel layer chip decreased to a small value, similar to that of the sensor chip with directly immobilized antibodies. The SPR sensor could detect a permittivity change within 300 nm from the top surface of the gold SPR sensor chip.[25] The change in permittivity near the gold surface with an overly thick hydrogel layer was small because the approach of the analyte to the gold surface was inhibited by its lower diffusivity within the gel layer. These results revealed that the sensitivity of SPR sensor chips can be improved by the formation of a hydrogel layer with an optimal thickness.

In conventional SPR sensor systems, biomolecules such as lectin, antibodies and DNA are usually utilized as ligands for the target biomolecules, such as saccharides, proteins and DNAs. On the other hand, molecular imprinting has attracted considerable attention as a useful technique for creating synthetic hosts containing molecular recognition sites.[26,27] Lai *et al.* reported pioneering work on SPR sensor chips with molecularly imprinted layers prepared using theophylline, caffeine and xanthine as template molecules.[28] The SPR sensor chips with molecularly imprinted layers showed the highly selective detection of the target molecules. Other research groups also reported the highly selective and sensitive detection of various low molecular weight biomolecules, such as sialic acid[29] and amino acid derivatives,[30] by using SPR sensor chips with a molecularly imprinted polymer layer. On the other hand, not only low molecular weight BPA but also α-fetoprotein, which is a tumor-specific marker glycoprotein with a high molecular weight, could be imprinted in the hydrogel.[12] The α-fetoprotein-imprinted hydrogel selectively recognized the target α-fetoprotein and gradually shrank in its presence. By combining such biomolecule-imprinted hydrogels with SPR sensors, the biomolecular recognition of the hydrogel can be converted into a resonance angle shift. The lectin concanavalin A (ConA)-imprinted hydrogel layer was prepared on the surface of an SPR sensor chip via SI-ATRP combined with molecular imprinting.[17] After the complexation of 2-glucosyloxyethyl methacrylate (GEMA) with ConA, the GEMA–ConA complexes were copolymerized with AAm and MBAA via SI-ATRP on an SPR sensor chip modified with alkyl bromide as an ATRP initiator. The ConA template was removed from the resulting hydrogel network by immersion in an aqueous glucose solution. In the SPR measurements, the resonance angle shift of the ConA-imprinted hydrogel layer chip in response to the target ConA was much higher than that of the non-imprinted hydrogel layer chip prepared without using the ConA template (Figure 4). In addition, the affinity constant of ConA for the ConA-imprinted hydrogel layer chip was higher than that for the non-imprinted hydrogel layer chip by approximately two orders of magnitude. The larger resonance angle shift and higher affinity constant of the ConA-imprinted hydrogel layer chip to ConA were attributed to the molecular imprinting with a minute quantity of crosslinkers creating ConA recognition sites with optimally arranged GEMA ligands. A similar strategy enabled the preparation of an

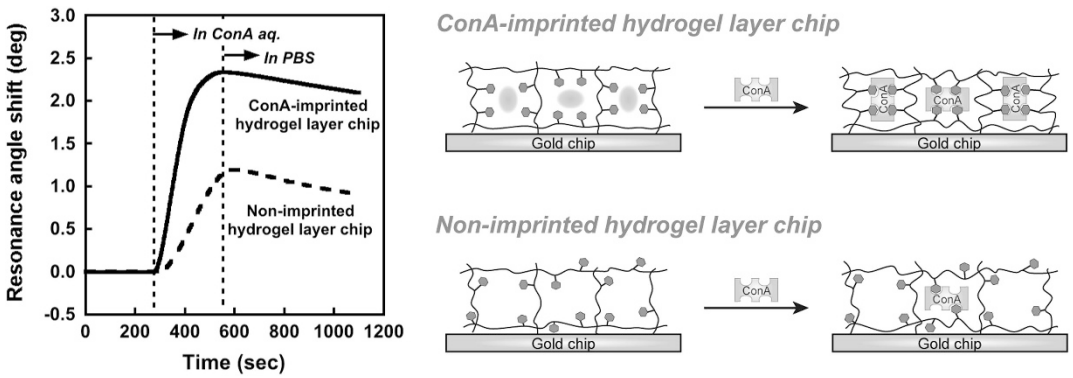

Figure 4 Resonance angle shift for the ConA-imprinted (solid line) and non-imprinted hydrogel layer chips (dashed line) in PBS containing ConA as an analyte. The figure is reproduced from Kuriu *et al.*[17] from the Chemical Society of Japan. A full color version of this figure is available online from the *Polymer Journal*.

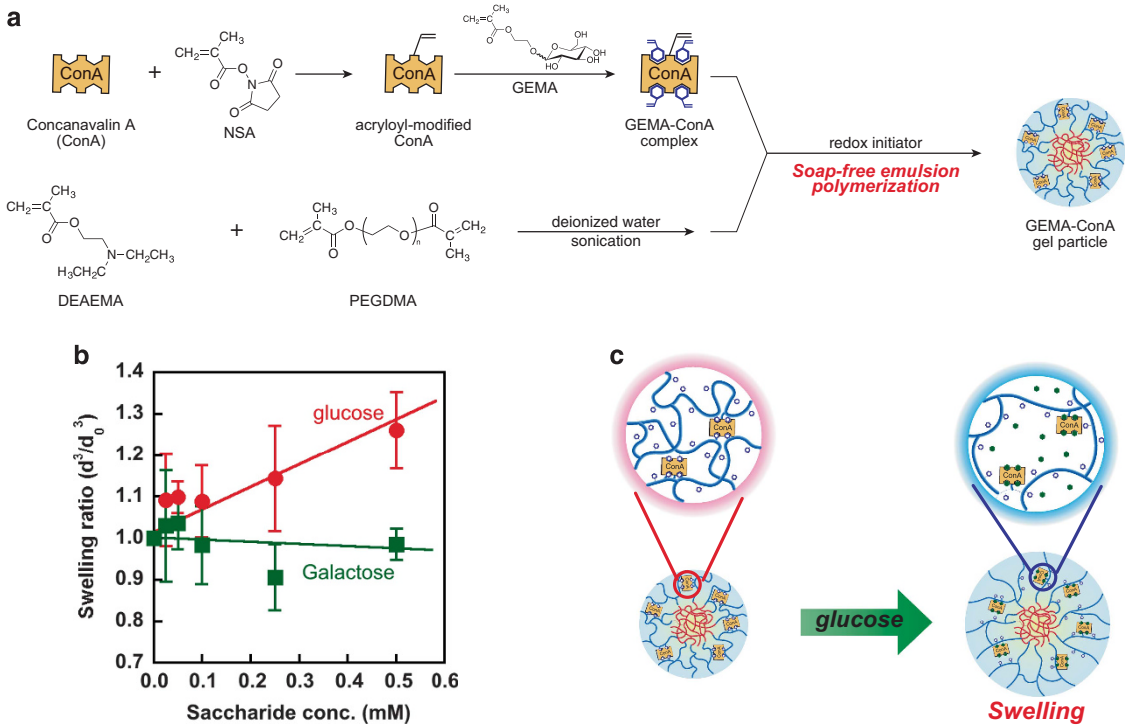

Figure 5 (**a**) Schematic illustration of the preparation of GEMA–ConA gel particles by soap-free emulsion polymerization. (**b**) Effect of the saccharide concentration on the swelling ratio of the GEMA–ConA gel particles (●: glucose; ■: galactose). (**c**) Schematic of the glucose-responsive behavior of the GEMA–ConA gel particles. The figure is reproduced from Kawamura *et al.*[20] from Elsevier.

IgG-imprinted thin hydrogel layer on the surface of an SPR sensor chip using anti-IgG and ConA as ligands for IgG.[18] The ConA template binds to the *N*-acetylglucosamine group of IgG, and anti-IgG participates in antigen-antibody binding with IgG. The IgG-imprinted hydrogel layer chip showed a higher affinity constant than a polymer brush layer chip for the IgG target because of the IgG recognition sites formed through molecular imprinting. These SPR sensor chips with biomolecule-responsive hydrogel layers are likely to be used as a fundamental system for the highly sensitive and accurate detection of target biomolecules.

POLYMER PARTICLES HAVING MOLECULE-RESPONSIVE HYDROGEL

Polymer particles are of significant interest as functional materials because they have fascinating features, such as a large specific area, high colloidal stability and size effects.[31] In particular, polymer particles made from stimuli-responsive hydrogels, also referred to as stimuli-responsive gel particles, show rapid swelling/shrinkage behavior in response to external stimuli, such as pH and temperature. Therefore, such stimuli-responsive gel particles have attracted considerable attention as smart nanomaterials, such as sensors,[32] adsorbents[33] and DDSs.[34] Whereas most stimuli-responsive gel particles previously reported exhibit a change in size in response to physical stimuli, molecule-responsive gel particles that respond to target molecules have been minimally studied. Therefore, glucose-responsive gel particles with saccharide-lectin complexes as dynamic crosslinks were prepared.[20] In general, stimuli-responsive gel particles were prepared by emulsion polymerization using surfactants for stabilization of the monomer emulsions and the resulting particles in water. However, the complete removal of residual surfactants from the surface of the resulting particles is extremely difficult because the surfactants are strongly adsorbed on the particle. Residual surfactants on the surface of gel particles affect the stimuli-responsive behavior.[35] In addition, surfactants often lower the protein functions by causing a loss of their tertiary structures. On the other hand, soap-free emulsion polymerization enables the preparation of gel particles without using surfactants. Therefore, glucose-responsive gel particles with saccharide-lectin complexes as dynamic crosslinks were prepared by utilizing a soap-free emulsion polymerization method. After complexation between GEMA and ConA modified with polymerizable acryloyl groups, the complexes were copolymerized with *N,N*-diethylaminoethyl methacrylate and poly(ethylene glycol) dimethacrylate via soap-free emulsion polymerization to obtain submicron-sized GEMA–ConA gel particles (Figure 5a). The resulting gel particles were colloidally stable in a phosphate buffer solution. X-ray photoelectron spectroscopy and Fourier transform infrared spectroscopy measurements suggested that the GEMA–ConA gel particles had an inhomogeneous structure. The hydrophobic *N,N*-diethylaminoethyl methacrylate units were concentrated in the core of the gel particles. In contrast, the hydrophilic GEMA, poly(ethylene glycol) dimethacrylate and GEMA–ConA complexes were concentrated on the surface of the gel particles. The GEMA–ConA gel particles rapidly swelled in response to free glucose in a phosphate buffer solution and reached equilibrium swelling within 2 h. In addition, the swelling of the GEMA–ConA gel particles strongly depended on the glucose concentration (Figure 5b). However, the swelling ratio of the GEMA–ConA gel particles did not change in the presence of galactose. The glucose-responsive swelling of GEMA–ConA gel particles can be explained by the tentative model illustrated in Figure 5c. In the presence of free glucose, the GEMA–ConA complexes acting as dynamic crosslinks dissociate due to exchange between GEMA and free glucose, which occurs because ConA prefers to form complexes with free glucose

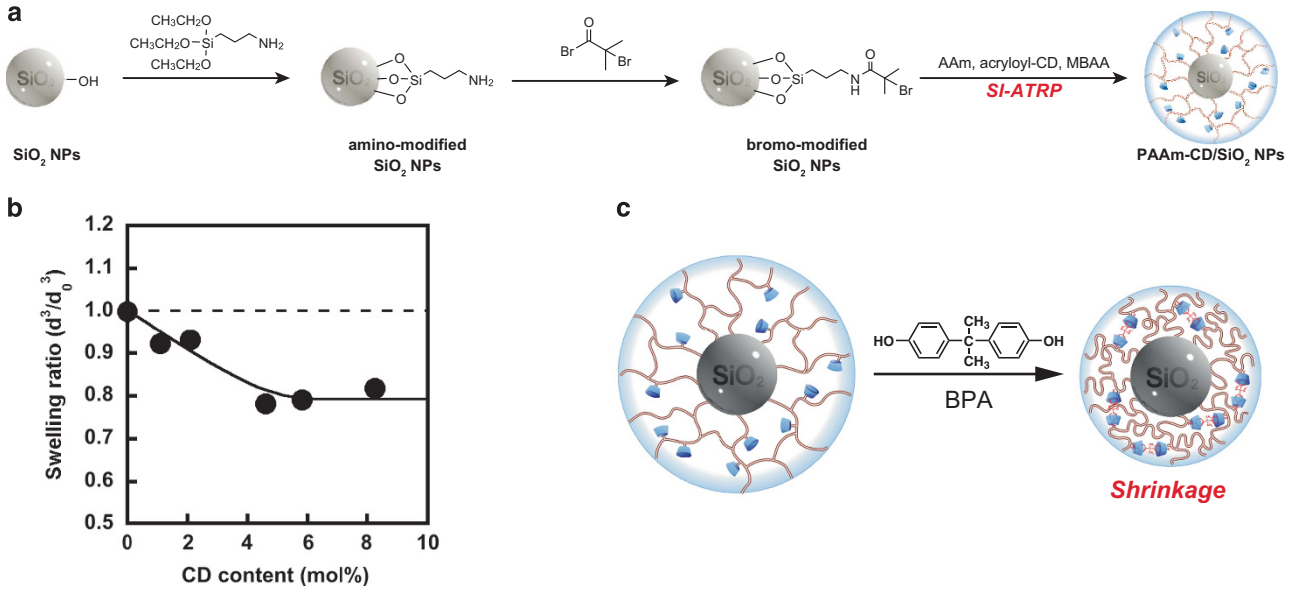

Figure 6 (**a**) Synthetic scheme for the preparation of the PAAm-CD/SiO_2 NPs. (**b**) Relationship between the CD content and swelling ratio of the CD-PAAm/SiO_2 NPs in the presence of BPA. (**c**) Schematic of the BPA-responsive behavior of the CD-PAAm/SiO_2 NPs. The figure is reproduced from Kawamura *et al.*[19] from the Society of Polymer Science, Japan.

rather than with the pendant glucose of GEMA. As a result, the GEMA–ConA gel particles rapidly swell in response to glucose owing to the decrease in the crosslinking density. The glucose-responsive functions of the GEMA–ConA gel particles can provide tools for constructing self-regulated DDSs in which a drug can be released in response to changes in the biological conditions.

Organic–inorganic hybrid nanoparticles with molecule-responsive hydrogel layers were also successfully prepared by utilizing SI-ATPR on the surface of silica nanoparticles (SiO_2 NPs).[19] Organic–inorganic hybrid nanomaterials have attracted substantial attention because they have many applications, such as the reinforcement of polymer materials, coatings, optical devices, electronics, membranes and sensors. SiO_2 NPs are the most extensively studied material for the preparation of organic–inorganic hybrids because their surfaces can be easily modified with functional groups after treatment with a silane coupling agent. In particular, the synthesis of polymer brushes on the surface of SiO_2 NPs via SI-ATRP has been extensively studied for the preparation of organic–inorganic hybrid nanoparticles. However, few studies on the preparation of stimuli-responsive hydrogel layers on the surface of SiO_2 NPs via SI-ATRP have been reported. Therefore, organic–inorganic hybrid nanoparticles with molecule-responsive hydrogel layers were prepared via SI-ATRP. BPA-responsive hybrid nanoparticles were successfully prepared via SI-ATRP of AAm, acryloyl-CD and MBAA using an ATRP initiator on the surface of SiO_2 NPs (Figure 6a). The resulting CD-PAAm/SiO_2 NPs had an inorganic SiO_2 core and a CD-PAAm hydrogel layer with a CD ligand for binding BPA. The CD-PAAm/SiO_2 NPs had individual spherical shapes and were dispersed in an aqueous solution without interparticle aggregation. When the CD-PAAm/SiO_2 NPs were colloidally stable in an aqueous solution containing BPA, they immediately shrank and attained equilibrium without aggregation. The swelling ratio of the CD-PAAm/SiO_2 NPs in an aqueous BPA solution decreased with increasing CD content and remained constant above a CD content of 4.6 mol% (Figure 6b). However, the swelling ratio of the PAAm/SiO_2 NPs without CD ligands in the hydrogel layer did not change in the presence of BPA. The shrinkage behavior of the CD-PAAm/SiO_2 NPs can be explained by the tentative model schematically illustrated in Figure 6c. When the CD-PAAm/SiO_2 NPs are dispersed in an aqueous solution of BPA, BPA easily diffuses into the CD-PAAm hydrogel layer. The BPA associates with the CD ligands within the hydrogel layer to form sandwich-like CD–BPA–CD complexes that act as dynamic crosslinks. The CD–BPA–CD complex crosslink formation leads to an increase in the crosslinking density of the CD-PAAm hydrogel layer followed by BPA-responsive shrinkage. Furthermore, an increase in the CD content of the hydrogel layer results in an increase in the crosslinking density due to the sandwich-like CD–CPA–CD complex formation. However, the shrinkage of the CD-PAAm/SiO_2 NPs with a CD content of more than 4.6 mol% became constant because the quantity of CD–BPA–CD complex crosslinks was unchanged above the CD content of 4.6 mol% owing to an excess of CD ligands relative to BPA molecules in water. Such BPA-responsive CD-PAAm/SiO_2 NPs can provide a useful platform for designing rapidly responsive nanomaterials for use in molecular sensors and separation technologies.

CONCLUSIONS AND OUTLOOK

This paper summarized our recent studies on nano- and micro-structured molecule-responsive hydrogels with molecular complexes acting as dynamic crosslinks. Molecule-responsive micro-hydrogels, thin hydrogel layers, gel particles and organic–inorganic hybrid nanoparticles were successfully prepared by utilizing photopolymerization, SI-ATRP and soap-free emulsion polymerization methods. These nano- and micro-structured molecule-responsive hydrogels showed not only rapidly responsive swelling/shrinkage behavior but also smart functions, such as the ability to be used as microvalves for autonomous microchannnel flow regulation and as highly selective and sensitive sensors in SPR systems. Such nano- and micro-structured molecule-responsive hydrogels were prepared on various substrates. For example, molecule-responsive thin hydrogel layers were prepared not only on an SPR sensor gold chip but also on a quartz crystal microbalance gold chip sensor, and they provided highly selective and sensitive detection in both scenarios.[36] The knowledge gained from the successful design of nano- and micro-structured molecule-responsive hydrogels provides a basis for the development of

innovative smart materials in various fields, such as DDSs, sensors, absorbents and microdevices. Even though nano- and micro-structured molecule-responsive hydrogels still require further research, they are likely to become innovative and important smart materials in the future.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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