FOCUS REVIEW

Polymeric hydrogel microspheres: design, synthesis, characterization, assembly and applications

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Hydrogel microspheres (microgels), which consist of crosslinked hydrophilic or amphiphilic polymer chains, are components of stable colloidal dispersions. Their typical size is below ~ 10 µm, and they exhibit fascinating properties in aqueous solution. Owing to their attractive properties, they have been used for a variety of applications (for example, as templates, sensors, catalysts, and coatings) and have promising prospects for advanced chemical technologies such as drug carriers. In this context, we have been conducting research on microgels, including their synthesis, characterization, assembly, and application. In this focus review, we summarize recent results of microgel research conducted mainly by our group as well as work by our collaborators.

INTRODUCTION

In contrast to bulk or macroscopic materials, small materials (sizes: <10 µm) show unique colloidal behavior. Polymeric hydrogel microspheres (microgels) are a good example for such materials. Microgels are water-swellable colloidal particles consisting of cross-linked polymeric networks. Consequently, microgels are soft and deformable, albeit that such phenomena are in general difficult to observe with the naked eye or by optical microscopy. Considering that research on microgels has been ongoing for more than 30 years, and that interest has been steadily growing during this period, it is hardly surprising that the body of relevant scientific literature reported is vast.[1–13] Especially the biomedical applications of microgels[12,13] have received much attention in recent years, owing to the tunability of their size, surface charge, softness and stimuli-responsiveness, as well as on account of their biocompatibility. In this focus review, we summarize recent results mainly from our research group and from those of our collaborators, whereby particular emphasis is put on how to control the spatiotemporal structures of polymeric microgels.

NANOCOMPOSITE MICROGELS: SYNTHESIS AND PROPERTIES

The design and control of the chemical composition and morphology of microgels are important to realize various applications for microgels. Since Pelton and Chibante first reported the synthesis of uniform poly(*N*-isopropyl acrylamide; pNIPAm) microgels by precipitation polymerization,[14] various types of functional microgels, such as core-shell microgels[15] and hollow microgels[16] have been reported. Suzuki and Kawaguchi reported a different approach to control the size and spatial distribution of metal nanoparticles using pNIPAm-based microgels as templates.[17–20] As the metal nanoparticles are

formed within the microgels, and are thus covered with a hydrated gel layer, the nanocomposite microgels exhibit high colloidal stability in aqueous solution. Moreover, such hybrid microgels exhibit color changes on account of their thermosensitive properties, for example, the surface plasmon resonance adsorption of Au, Au@Ag, and Au@Ag@Au nanoparticles can be changed by controlling interparticle interactions between these nanoparticles within the microgels. Such hybrid microgels are thus expected to serve as functional sensors.

More recently, our group has focused on the hydrogel-solid polymer nanocomposite microgels synthesized by seeded 'dispersion' or 'emulsion' polymerization (SEP) in the presence of functional microgels (Figure 1).[21–25] In contrast to the functionalized or core-shell microgels prepared by (seeded) precipitation polymerization with water-soluble monomers, the morphology of our nanocomposite microgels is non-spherical, and they also assume the functions of the seed microgels, for example, response to external stimuli and high colloidal stability. Additionally, the relationship between the local environment in microgels, i.e., the polarity and hydrophobicity, and the hydrophobic monomer used for the polymerization can be investigated by evaluating the spatial distribution of solid spheres formed in the resulting nanocomposite microgels using electron microscopy (Figure 1).

Multi-layered composite microgels were obtained using glycidyl methacrylate (GMA; solubility in water: 120 mM) as a monomer,[22] while raspberry-shaped composite microgels were obtained using styrene (solubility in water: 2.9 mM).[23–25] For example, when pure (non-functionalized) pNIPAm microgels were used as cores for the SEP of styrene, raspberry-shaped composite microgels, which contain polystyrene particles of different size attached to the core of microgels, were obtained (Figure 2a). These particles developed irregular surfaces

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($D = 137$ nm, CV = 16%) with increasing polymerization time on account of the fusion of neighboring polystyrene nanoparticles.[23] Moreover, when the anionic surfactant SDS was added during the polymerization, polystyrene nanoparticles ($D = 46$ nm, CV = 13%) were formed on the surface and also within the core microgels (Figure 2b), indicating the formation of aggregates of SDS within the microgels during the SEP, where they work as polymerization fields for hydrophobic polystyrene.[25] These results indicate that the monomer styrene can be dissolved and polymerized in deswollen pNIPAm microgels, and that SDS aggregates are formed within the pNIPAm microgels.[23] Interestingly, when poly(NIPAm-co-methacrylic acid) microgels, whose charge groups are localized at the center of the microgels,[26] were used as cores, polystyrene nanoparticles were localized on the surface of the microgels (Figure 2c).[24] In contrast, Watanabe et al., found that when poly(NIPAm-co-fumaric acid) microgels, whose charge groups are localized on the surface, were

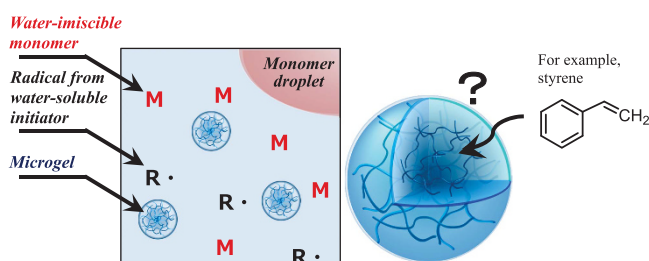used as cores, the core microgels were covered almost entirely with polystyrene (Figure 2d). The thus obtained composite microgels exhibited high colloidal stability, as they are covered with a thin hydrogel layer.[25] It should be noted that cryo-TEM measurements are very important for the structural analysis of swollen composite microgels. These results indicate that monomeric styrene can penetrate the polyelectrolyte hydrogel layers. However, the resulting polystyrene nanoparticles do not readily combine with polyelectrolyte hydrogels.[25] To control the morphology of microgels, including the size distribution of the hydrophobic particles ($\sim$ CV = 5%), the structural anisotropy and the hierarchy of gel-solid layers, as well as the effects of microgel properties on the polymerization behavior of hydrophobic monomers needs to be investigated in more detail. The details of such studies should provide key factors for the design of the morphology of nanocomposite microgels, and thus further the understanding of the properties of such microgels. We believe that this conclusion should be a key factor for the design of the morphology of nanocomposite microgels, and we will continue to develop nanocomposite microgels with unique structures and functions.

CHARACTERIZATION OF THE MORPHOLOGY, MICROSTRUCTURE AND FUNCTION OF SWOLLEN MICROGELS

As microgels are colloidal in nature, they can be characterized by their size, polydispersity, shape, and the state of dispersion/flocculation. In addition, microgels possess gel properties, and therefore, the degree of swelling and the network structure are equally important features. The size and size distribution of microgels are usually visualized by optical microscopy. Microgels with diameters approximating or largely

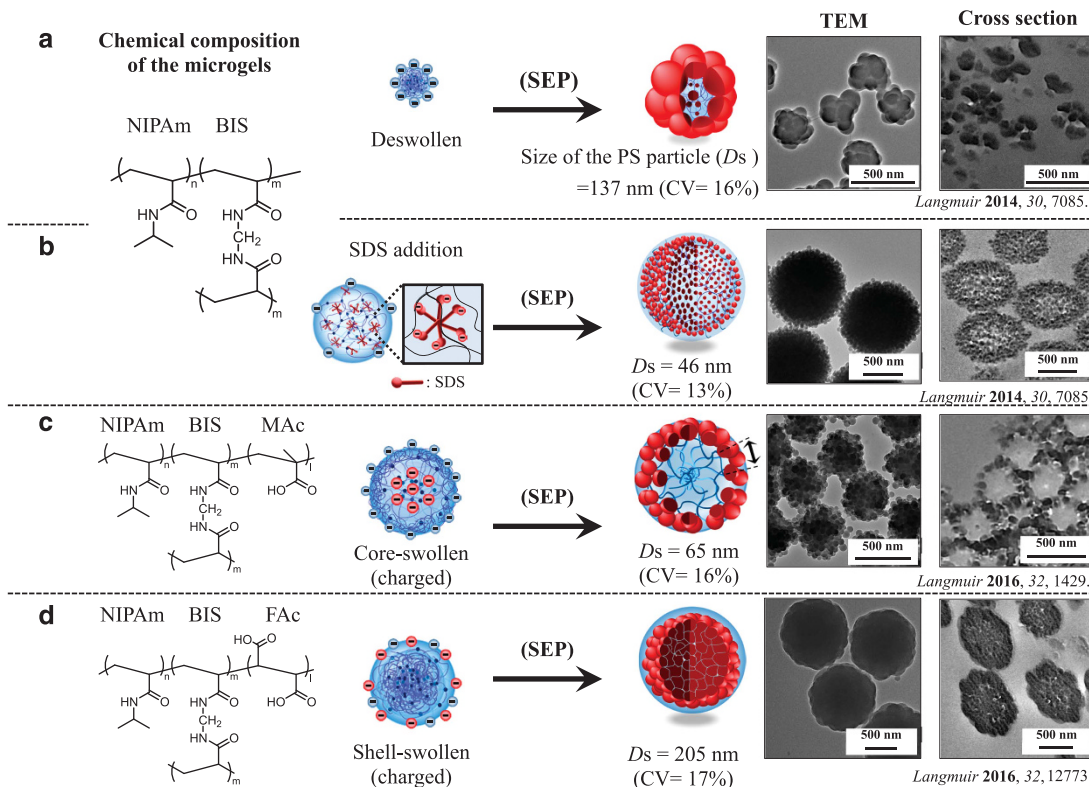**Figure 1** Schematic representation of seeded emulsion polymerization (SEP) in the presence of microgels.

Figure 2 Summary of nanocomposite microgels prepared by seeded emulsion polymerization (SEP). Reproduced with permission from [23–25] Copyright (2014 and 2016) American Chemical Society.
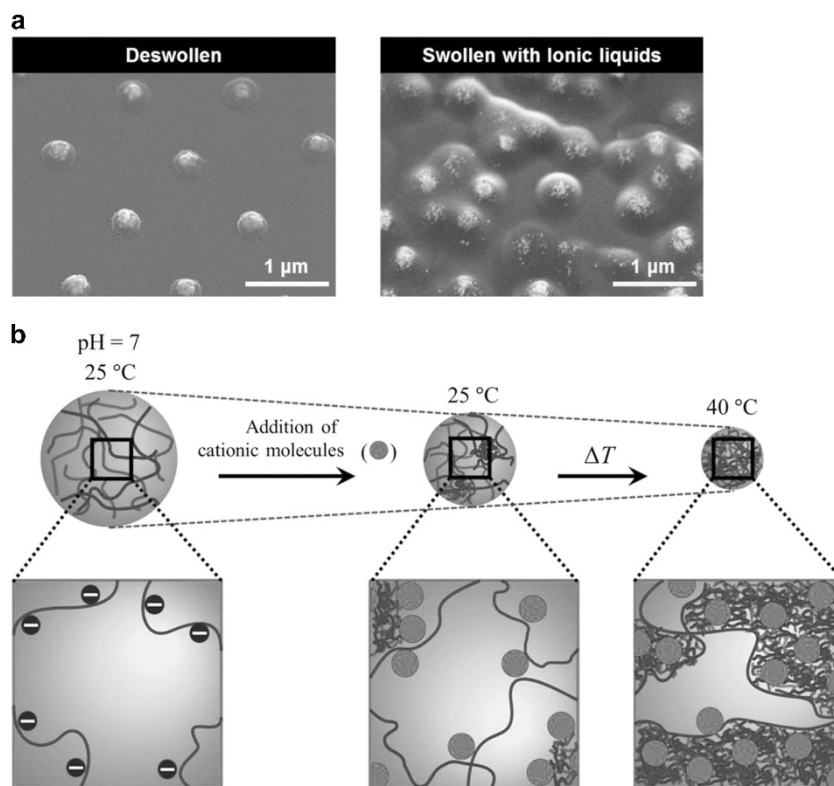
Figure 3 (**a**) SEM images of hybrid microgels containing metal nanoparticles. Pt/Pd sputtering was performed prior to the measurement (left). The microgels were swollen using 0.5 µl of [dema][OTf] (diethylmethylamine trifluorosulfonate) (right). Reprinted with permission from[29] Copyright (2016) Nature Publishing Group. (**b**) Schematic diagram of the microscopic structural changes in poly(NIPAm-*co*-acrylic acid) microgels in the presence of cationic organic dyes. Reprinted with permission from[33] Copyright (2016) American Chemical Society. A full color version of this figure is available at *Polymer Journal* online.

exceeding 1 µm are generally considered suitable for observation by optical microscopy.[27] If higher resolution is required, microscopy techniques based on radiation of much smaller wavelength are required. Thus far, dried microgels have frequently been characterized by electron microscopy, such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM).[28] However, it is difficult to observe the swollen microgels on the submicron or decanano scale using these techniques. Although swollen microgels exhibit unique properties, for electron microscopy, samples must be dried, and sample chambers in electron microscopes are normally maintained under high vacuum. To overcome these limitations, Horigome *et al.*[29] have proposed the swelling of microgels with ionic liquids, as these are nonvolatile even under high-vacuum conditions. Indeed, the aforementioned hybrid microgels could be visualized using conventional SEM techniques (Figure 3a). Particularly, the degree of dispersion of the embedded metal nanoparticles in the microgels could be evaluated on account of the swelling caused by the ionic liquids.

However, the microscopic structural parameters of these microgels (for example, mesh size) cannot be easily characterized by these techniques, although the characterization of the microscopic structures is important for the understanding of the microgel properties.[30] Therefore, our group collaborated with that of Sato, who had already established techniques for the structural analyses of microgels and other colloids using small- and wide-angle X-ray scattering (SWAXS).[31] Indeed, Sato *et al.* discovered for the first time two interference peaks in the high-q regime of SWAXS profiles that allowed the calculation of a characteristic distance (d^*) for pNIPAm

microgels. The characteristic distance d^* is related to the hydrodynamic diameter as a function of temperature.

Kureha *et al.*[32] have investigated the relationship between the uptake/release of organic dyes and revealed microscopic structures for pNIPAm microgels. In the case of non-functionalized pNIPAm microgels that are slightly negatively charged by initiator residues, hydrophobic interactions occur between the association of hydrophobic isopropyl groups in the pNIPAm microgels and rhodamine 6 G or erythrosine, which represent cationic and anionic organic dyes, respectively. Thus, an increasing uptake of dye with growing hydrophobic domains in the pNIPAm microgels was observed. More recently, the uptake/release behavior of anionic poly(NIPAm-*co*-acrylic acid) microgels, which are the most extensively studied microgels on account of their responsiveness to pH and temperature changes, have been investigated by relating microscopic structural information on the anionically charged microgel to the quantity of incorporated cationic molecules.[33] At pH = 7, where the acrylic acid groups are deprotonated, highly swollen microgels were observed and their volume transition, originating from pNIPAm segments in the microgels, was suppressed by the presence of charged carboxyl groups. Conversely, at 25 °C in the presence of cationic dyes, the electrostatic interactions between the charged groups and the cationic dyes dominate the uptake behavior and the changes in the microscopic structure of the microgels and result in a contraction of the microgels. When the temperature was increased above the lower critical solution temperature of pure pNIPAm (~33 °C), the charge of the carboxyl groups was screened by cationic dyes in the first step, followed by a growth of hydrophobic domains, which was accompanied by a coil-to-
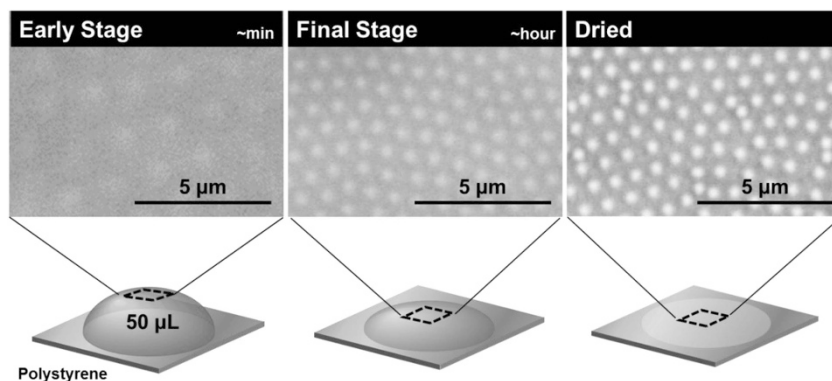
Figure 4 Schematic images of the drying mechanism of pNIPAm microgels in dilute dispersion. Reprinted with permission from[43] Copyright (2012) American Chemical Society. A full color version of this figure is available at *Polymer Journal* online.
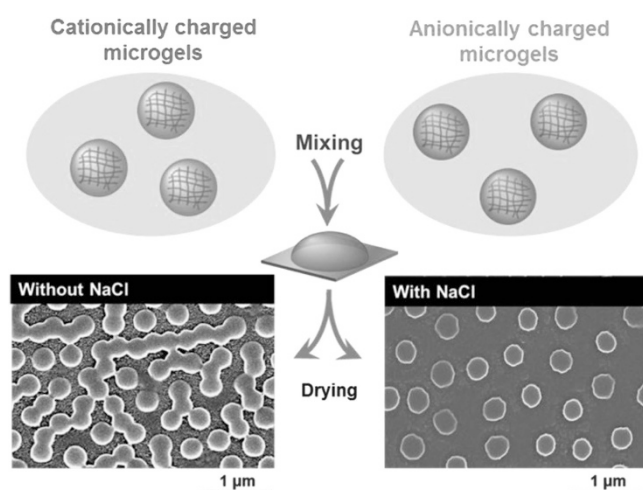

Figure 5 SEM images of binary mixtures of cationically and anionically charged microgels deposited on polystyrene substrates and dried at 25 °C. It should be noted that the SEM sample (right image) was prepared by drying the mixture in the presence of 1 mM NaCl; after drying, the NaCl was gently removed by repeated washing with deionized water. Reprinted with permission from[44] Copyright (2011) American Chemical Society. A full color version of this figure is available at *Polymer Journal* online.

globule transition of the pNIPAm chains, resulting in an increased uptake (Figure 3b). Accordingly, the combination of hydrophobic and electrostatic partitioning of the cationic dyes by the negatively charged microgels affects the separation and volume transition behavior of the microgel. Such studies are ongoing in our group in order to improve the design of microgels as separation carriers to achieve a selective separation, high recyclability, and suppression of structural changes in the presence of target molecules.

MICROGEL ASSEMBLY IN BULK SOLUTIONS, PASTES AND AT INTERFACES

Assemblies of microgels exhibit unique properties that cannot be achieved by individually dispersed microgels in a liquid. Regularly arranged microgels diffract specific visible light, and as a result, exhibit structural colors.[34,35] In 2006, Suzuki joined the Lyon group at Georgia Institute of Technology, and fabricated thermosensitive colloidal crystals of the aforementioned nanocomposite microgels, wherein gold nanoparticles are localized in the first shell of the core/shell/shell microgels synthesized by seeded precipitation

polymerization.[36] Several years later, Okubo and Suzuki *et al.* found that pNIPAm microgels form such photonic materials at ultralow concentrations in the microgels (~0.04 wt.%) after careful purification with resins.[37,38] These results indicate that soft microgels, whose interfaces are vague, may afford unique regularly arranged structures that can diffract visible light, that is, high concentrations of microgels (pastes) due to steric stabilization from highly hydrated superficial polymer chains[35,36] in combination with low concentrations of microgels due to electric double layers formed on the vague interface.[37,38]

Recently, the Urayama group has studied the rheological behavior of microgel pastes,[39,40] and discovered that the yield strain of microgel pastes is virtually independent from the crosslink density, microgel diameter, and microgel concentration in a limited concentration range. Moreover, the yield strain remains almost constant in a wide range of equilibrium shear moduli that cover two orders of magnitude.[39]

In contrast to the microgel assemblies in bulk solutions or pastes, our group has been studying the assembly at the air/water and oil/water interfaces. Suzuki and Kawaguchi *et al.* have developed Janus microgels, whose physicochemical properties can be tuned by external stimuli. Such Janus microgels, whose back and front surfaces exhibit different chemical structures, were fabricated at the oil/water interface, and the portion of the microgels in the aqueous phase was chemically modified.[41,42] This strategy is currently applied in our group to the synthesis of unique anisotropic microgel assemblies that are able to mimic the functions of biological cells and will be reported in the near future.

Beyond that we found that dilute aqueous dispersions that contain pNIPAm-based microgels assemble at the air/water interface during the evaporation of water.[43] In general, when a droplet of a colloidal dispersion, such as conventional rigid polystyrene and silica particles, is dried on a solid substrate, ring-like, non-uniform films are obtained. However, in the case of our microgel, homogeneous thin films of a pNIPAm microgel monolayer were obtained on the solid substrate. Horigome and Suzuki have reported the formation mechanisms of the structures formed during the drying of dilute pNIPAm microgel dispersions (Figure 4).[43] When a dilute dispersion (~1 μm pNIPAm microgels; 50 μl) was dried at 25 ± 2 °C on a polystyrene substrate, the pNIPAm microgel was adsorbed at the air-water interface in an early stage (~3 min), and the microgels subsequently assembled at the interface. Finally, the assembled structure was transferred onto the solid substrate after all the water had been removed. We further extended this experiment by using oppositely charged microgels, that

is, cationic and anionic microgels.[44,45] These microgels were also assembled at the air/water interface upon mixing in solution (Figure 5).[44] The microgels were then assembled into linear and branched-chain structures at the air/water interface. We found that the total microgel concentration, the concentration ratio of cationic and anionic microgels, and the salt concentration were important factors to create the microgel chains.[45] Furthermore, the addition of a small amount of electrolyte to the binary mixtures prevented flocculation, resulting in non-close-packed structures on planar substrates in the dry state.[44] These findings should lead to new materials such as precisely controlled microgel coatings, and similar studies are currently pursued in our research group.

CONTROLLING THE TEMPORAL STRUCTURES OF MICROGELS

Living systems are usually based on periodic rhythms, such as the heartbeat or the assembling/disassembling of clock proteins. After graduating from Keio University in 2007, Suzuki joined Yoshida's group at the University of Tokyo, who has developed self-oscillating gels[46] that exhibit a swelling/deswelling in the absence of external stimuli, as a JSPS postdoctoral research fellow for two years. Learning from Yoshida's previous work, Suzuki accomplished the preparation of microgels with temporal structures of uniform size by copolymerizing the catalyst for the Belousov–Zhabotinsky (BZ) reaction[47] into pNIPAm-based microgels.[48] These autonomously oscillating microgels also show repeated swelling/deswelling, which is evident from UV-vis spectroscopy.[48–50] Moreover, Suzuki discovered that the microgels show dispersing/flocculating (or assembling/disassembling) oscillation near the volume-transition temperature of the pNIPAm-based microgels (Figures 6a and b).[48,51] Suzuki and Yoshida have also revealed that period, amplitude, and waveform of the swelling/deswelling and the dispersing/flocculating oscillation are controlled by the crosslinked network structures,[49] as well as by the initial substrate concentration of the BZ reaction.[50] Additionally, both the swelling/deswelling and the dispersing/flocculating oscillations of microgels can be detected as the changes in optical transmittance, and by the viscosity changes of the microgel dispersions (Figure 6c).[51,52] More recently, Matsui *et al.*[53] have discovered changes in the internal microscopic structure of autonomously oscillating microgels using SWAXS. Nevertheless, microgels with temporal structures still represent a novel phenomenon, and the intrinsic details remain to be determined. Therefore, we will continue to examine such complex nonequilibrium phenomena as a model system to better understand living systems.

The aforementioned oscillating microgels do not only exert a function as a single component, but they can also act as an assembly. For example, in a living muscle, hierarchical structures amplify and transform the microscopic movements of actin–myosin into macroscopic displacements. Using such living muscles as inspiration, our group introduced a hierarchical structure into an artificial muscle in order to amplify the swelling/deswelling oscillation. Autonomously oscillating soft actuators have been successfully obtained by simple methods, for example, by assembling pre-existing microgels (Figure 7a).[54] Such assemblies exhibit large displacements due to the
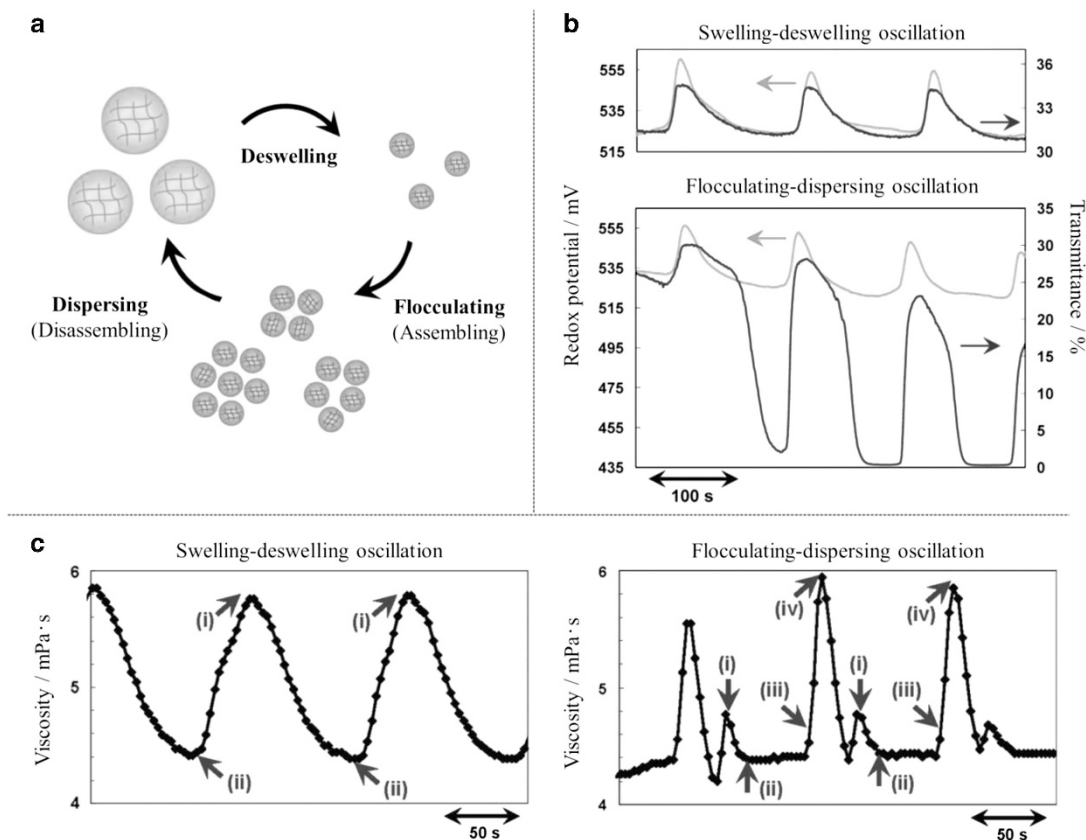

Figure 6 (**a**) Schematic illustration of the temporal structures of autonomously oscillating microgels synchronized with the BZ reaction. (**b**) Oscillation profiles of the optical transmittance and redox potential changes in the cell for the microgel dispersions measured under varying conditions. Reprinted with permission from[49] Copyright (2008) American Chemical Society. (**c**) Temperature-dependent oscillation profiles of the viscosity in the microgel dispersions. Reprinted with permission from[51] Copyright (2009) American Chemical Society. A full color version of this figure is available at *Polymer Journal* online.
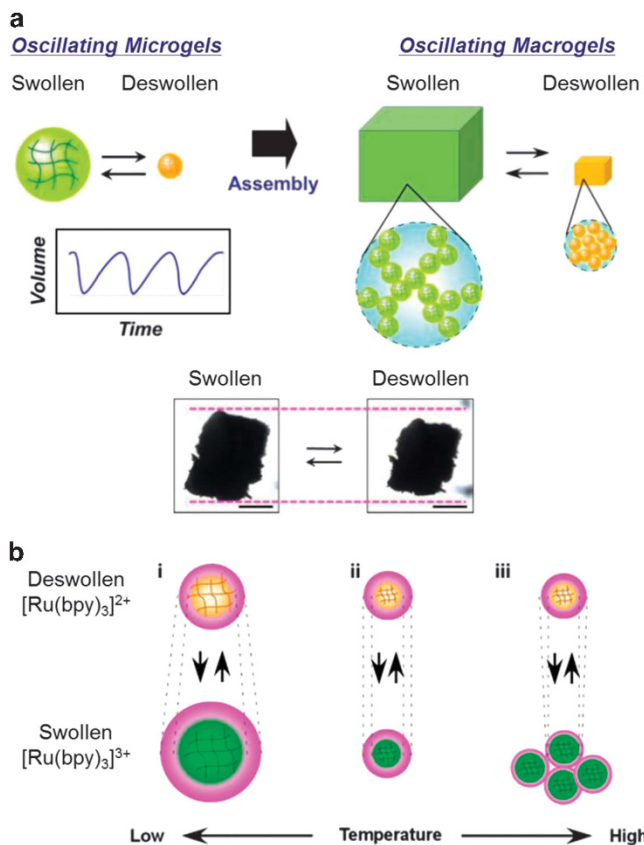
Figure 7 (**a**) Schematic illustration and optical microscopy images (scale bars: 0.5 mm) of an assembly of autonomously oscillating microgels. Reprinted with permission from[54] Copyright (2012) Royal Society of Chemistry. (**b**) Different oscillation modes for autonomously oscillating core/shell microgels. Reprinted with permission from[55] Copyright (2010) Nature Publishing Group.

cooperative dispersing/flocculating oscillation of the constituent microgels in the absence of external stimuli (on/off switch) under otherwise constant conditions. We expect that such autonomous soft materials could be used as micropumps that do not require an external device source. We will continue to develop microgels and microgel assemblies with temporal structures as model systems in order to better understand living systems, where small colloidal particles such as proteins show pre-programmed dynamic ordering to regulate vital functions. In order to progress in this research area, the design and construction of autonomously oscillating microgels with well-defined nanostructures, such as core/shell structures (Figure 7b)[55] should be of paramount importance.

CONCLUDING REMARKS
In this review, we have summarized recent advances of microgel research and technology of mainly our group and our collaborators. The results presented herein should contribute to further the development of microgel research. We hope that our microgel research will not only support the advancement of pre-existing applications, for example, in coatings and cosmetics, but also allow the development of unprecedented applications.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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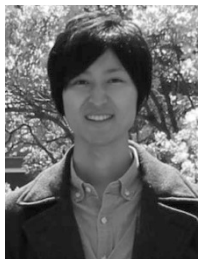
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