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Monodisperse Thermoresponsive Microgels with Tunable Volume-Phase Transition Kinetics**

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A facile method to control the volume-phase transition kinetics of thermo-sensitive poly(*N*-isopropylacrylamide) (PNIPAM) microgels is presented. Monodisperse PNIPAM microgels with spherical voids are prepared using a microfluidic device. The swelling and shrinking responses of these microgels with spherical voids to changes in temperature are compared with those of voidless microgels of the same size and chemical composition prepared using the same microfluidic device. It is shown that the PNIPAM microgels with voids respond faster to changes in temperature as compared with their voidless counterparts. Also, the induced void structure does not have a detrimental effect on the equilibrium volume change of the microgels. Thus, the volume phase transition kinetics of the microgels can be finely tuned by controlling the number and size of the voids. The flexibility, control, and simplicity in fabrication rendered by this approach make these microgels appealing for applications that range from drug delivery systems and chemical separations to chemical/biosensing and actuators.

1. Introduction

Stimuli-sensitive hydrogel microspheres or microgels are polymeric particles that consist of cross-linked three-dimensional networks. They shrink or swell significantly by expelling or absorbing large amounts of water in response to external stimuli, such as changes in temperature, pH, electric or magnetic fields. The chemical composition of the microgel determines the stimulus that can trigger this volume-phase transition. The dramatic response and stimuli-specific behavior makes these materials extremely valuable for numerous applications,[1–5] including drug delivery,[6–11] chemical separations,[12,13] sensors,[14–16] catalysis,[17] enzyme immobilization,[18] and color-tunable crystals.[19]

Several potential applications of these microgels, such as 'smart' actuators, on–off switches, and pulse-release, require a short response time. Currently, numerous strategies are employed to speed up the response kinetics of typical thermo-responsive hydrogel microspheres such as poly(*N*-isopropylacrylamide) (PNIPAM) microgels.[1–5,7,20–29] One simple strategy is to use small sized microgel particles. Since the characteristic time of gel swelling is proportional to the square of the linear dimension of the hydrogels,[30] this results in a significant decrease in the response time. However, for certain applications, like actuators in a tube of fixed diameter, the size of the microgel cannot be used as a control variable. Another well-known method is to chemically graft linear side chains of the same stimuli-sensitive polymer onto the cross-linked polymer network.[31–35] The linear side chains, with one free end each, respond to stimulus faster than the cross-linked network, and this leads to a shorter response time for the entire hydrogel as compared with a hydrogel with ungrafted polymer networks. However, the process of chemically grafting linear side chains onto a polymer network is complicated, which limits the widespread use of this technique. Another alternative is to fabricate hydrogels with heterogeneous internal microstructures[36–40] instead of a homogeneous net-like microstructure. The microgel-like particle clusters with numerous free ends inside the heterogeneous hydrogels can flex without any restrictions,[40] which results in a faster response to stimuli as compared to microgels with a homogeneous microstructure. However, the heterogeneity of the microstructure may also cause some unwanted side effects; for example, the temperature-dependent equilibrium volume-deswelling ratio of PNIPAM hydrogels with a heterogeneous microstructure is much smaller than that of PNIPAM hydrogels with a homogeneous microstructure.[40]

In this study, we report a new method to control the volume-phase transition kinetics of thermo-sensitive PNIPAM microgels. Our method does not involve any chemical manipulation of PNIPAM networks, nor does it require any change in the size of the microgel particles. The response rate is controlled simply by changing the size and number of spherical voids in-

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side the microgel. In addition, it is shown that this change in the internal structure has no adverse effect on the equilibrium volume change of the PNIPAM microgels.

2. Results and Discussion

2.1. Fabrication Strategy

The kinetics of swelling and de-swelling of stimuli-responsive polymeric hydrogels are typically governed by the diffusion-limited transport of water in and out of the polymeric networks.[30,41–43] Hence, if a facile way to control this transport of water is devised, the volume-phase transition kinetics of the microgels can be precisely tuned. In this study, this is accomplished by introducing different void structures inside the microgels. An internal structure with voids offers less resistance to the transport of water compared to a voidless core. Thus, by varying the size and number of voids inside a microgel, its swelling and shrinking dynamics can be effectively controlled.

Microgels with spherical voids have been prepared using a two-step method. First, monodisperse microgels with different number/sizes of solid polystyrene microspheres are synthesized in a microfluidic device. Second, the embedded microspheres are chemically dissolved to form spherical voids inside the microgels. The microfluidic device used to synthesize the microgels consists of cylindrical glass capillary tubes nested within square glass capillary tubes, as shown in Figure 1. It features a coaxial co-flow geometry ensured by matching the outside diameters of the cylindrical tubes to the inner dimensions of the square tubes. An aqueous suspension that contains the monomer, *N*-isopropylacrylamide (NIPAM), a crosslinker, *N*,*N*′-methylenebisacryamide (BIS), an initiator, ammonium persulfate (APS), and polystyrene microspheres, is pumped into the left end of the left square tube. The continuous phase, kerosene that contains a surfactant, polyglycerol polyricinoleate (PGPR 90), is pumped through the outer coaxial region between the left square tube and a tapered round microcapillary tube. The aqueous phase breaks into droplets at the entrance orifice of the tapered tube, to form monodisperse emulsion drops in the tube. The accelerator, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), dissolved in the continuous phase, is pumped through the outer coaxial region between the right square tube and the right end of the tapered round tube. When the accelerator meets the initiator, it starts a redox reaction that polymerizes the monomers, thus forming monodisperse microgels with embedded polystyrene microspheres. The addition of the reaction accelerator downstream of the other chemicals delays the polymerization process long enough to allow the formation of monodisperse emulsion drops of these chemicals in the continuous phase and eliminates the possibility of the entrance orifice of the round tube becoming clogged by untimely polymerization of the monomers. Once the polymerization process is completed, the PNIPAM microgels are washed with isopropyl alcohol and subsequently immersed in xylene for a fixed period of time to dissolve the polystyrene beads and leave behind holes in the microgels. The microgels with spherical voids thus formed are again rinsed with isopropyl alcohol and are finally dispersed in water. Specific comparisons are made between the thermo-sensitive behavior of the voidless microgels, without any voids, and those with hollow void structures, which have either one large void of 75 μm diameter or different numbers of smaller voids.

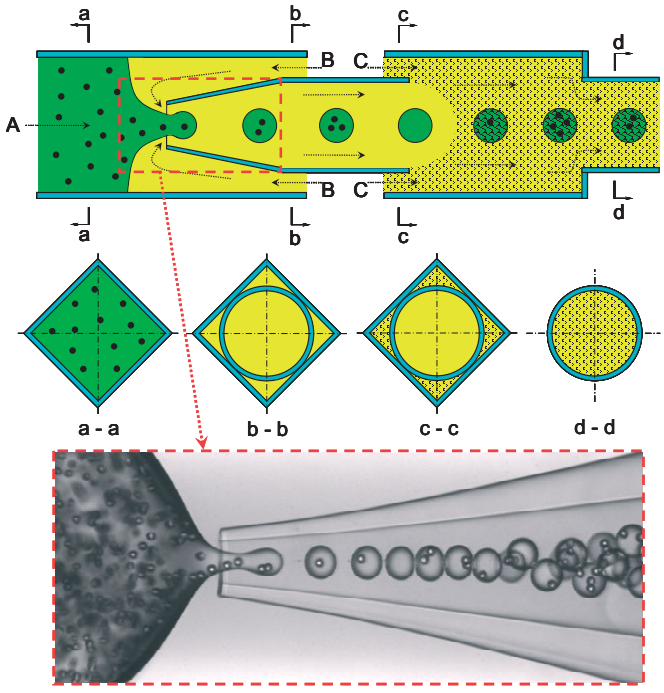

Figure 1. Microfluidic device for preparing monodisperse microgels with embedded solid particles. Fluid A is an aqueous suspension that contains the monomer, initiator, crosslinker, and solid polystyrene particles. Fluid B is an oil that contains a surfactant. Fluid C is a mixture of an oil and a reaction accelerator. Illustrations a-a, b-b, c-c and d-d are cross-section images of the capillary microfluidic device in relevant positions, which clearly show how the square capillary tubes and cylindrical tubes are assembled in the device.

2.2. Morphological Analyses and Temperature-Dependent Equilibrium Volume Change of Microgels

Microgels that contain different numbers of 25 μm diameter polystyrene beads, and the microgels with spherical voids formed by dissolving these beads from similar microgels, are shown in Figure 2. The optical micrographs suggest that the size and number of spherical voids in a microgel depend on the size and number of the encapsulated polystyrene beads. The precise circular periphery of the voids and unchanged size of the microgels also suggest that the chemical dissolution of the beads does not affect the structural integrity of the surrounding microgel structure. The equilibrium diameter of the microgel with four voids is compared with that of the microgel with no voids at various temperatures between 20 and 47 °C in Figure 3. The samples were equilibrated for 30 min at each temperature before the measurements were made. It appears that the induced void structure has no effect on the equilibrium size

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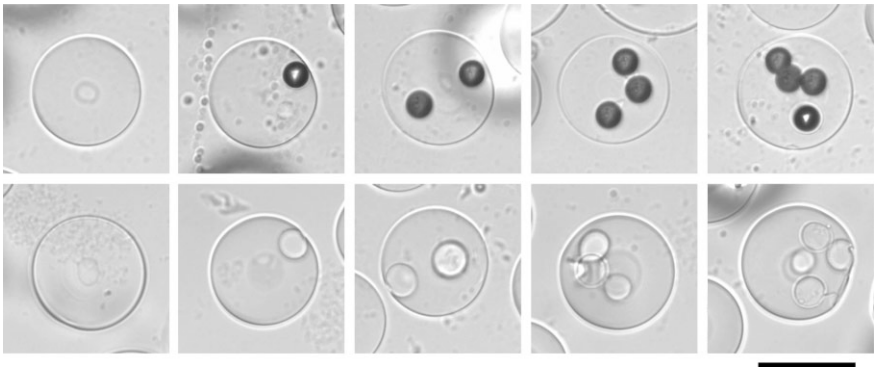

Figure 2. Microgels with different numbers of embedded polystyrene beads (top). Microgels with spherical voids formed by dissolving the embedded beads from such microgels (bottom). Scale bar = 100 μm.

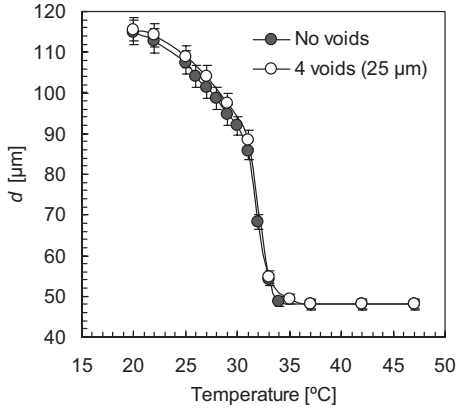

Figure 3. Equilibrium diameters of the voidless microgel and the microgel with four voids (25 μm diameter each) plotted as a function of temperature. The samples were held for 30 min at each temperature before measuring their diameters.

change of the microgels. For microgels of the same size, the equilibrium volume change is a function of the homogeneity of the internal microstructure.[40] Since NIPAM is polymerized under identical conditions in both cases, the two microgels should have the same homogenous microstructures. The overlap of the two curves confirms that the presence of polystyrene microspheres during the NIPAM polymerization process does not affect the homogeneous net-like microstructure of the microgel.

2.3. Time-Dependent Volume Change of Monodisperse Microgels with Different Internal Structures

The dynamics of shrinking and swelling of the microgels were studied by heating them together with water from 23 to 47 °C and subsequently cooling them back to 23 °C in a transparent sample holder placed on a microscope-mounted thermal stage. The same sample holder and volume of water were used for microgels with different internal structures.

Although the equilibrium volume change of the microgels is unaffected by the internal structure, their shrinking and swelling kinetics are affected by the induced void structure. When the temperature is increased from 23 to 47 °C, the microgel with multiple voids and the one with a hollow shell structure (one large void) shrink faster than the voidless microgel, as shown in Figure 4a. For example, at t = 49 s, the diameter of the voidless microgel is the largest, while that of the one with multiple voids is the smallest. Similar behavior is observed when the microgels are cooled back to 23 °C: The microgel with multiple voids and the one with a hollow shell structure swell faster than the voidless microgel (Fig. 4b). A quantitative comparison of the temporal evolution of sizes of the three microgels during heating and cooling is presented in Figure 5 where the instantaneous diameters of the microgels as a function of time have been plotted. The temperature of the microgels is shown in the lower panel, and t = 0 refers to when the temperature change is initiated. The different behavior for each sample is evidenced by the separation between the curves. The inset in Figure 5b reveals that the inception of swelling in the microgel with multi-voids, indicated by a sudden change in its diameter, precedes that in the voidless microgel by as much as 10 s. The swelling of the microgels is perceptible only after a significant amount of water is transferred into the microgel. Thus, the result suggests that the transport of water in the microgels with voids occurs much before the voidless microgel.

The response rate of the PNIPAM microgels to changes in temperature is governed by diffusion-limited transport of water in and out of the polymeric networks. Voids within a microgel offer much less resistance to the transport of water compared with the three-dimensional PNIPAM network; hence, the microgels with voids respond faster to changes in temperature than the voidless one. Furthermore, in the microgel with multi-voids, the voids can form continuous channels from the core to the surface of the microgel, which further expedites transport of water in and out of the microgel. This is presumably why the microgel with multi-voids responds faster to temperature changes than even the microgel with the hollow shell structure.

To evaluate the effects of a progressive increase in the number of voids inside the microgels on their response kinetics, monodisperse PNIPAM microgels with one, two, three, and four voids of 25 μm diameter each, were prepared. The dynamics of shrinking and swelling of these microgels are compared with that of a same sized voidless microgel in Figure 6. When the temperature is increased from 23 to 47 °C, the microgels with four voids shrink faster than all other samples, whereas, the voidless microgel is the slowest to respond. The differences are more distinct during swelling. The inset in Figure 6b clearly reveals a systematic decrease in the time required for the inception of swelling with an increase in the number of voids. This suggests that the volume-phase transition kinetics of microgels can be tuned simply by varying the number of voids in them. To gain such a precise control it is neces-

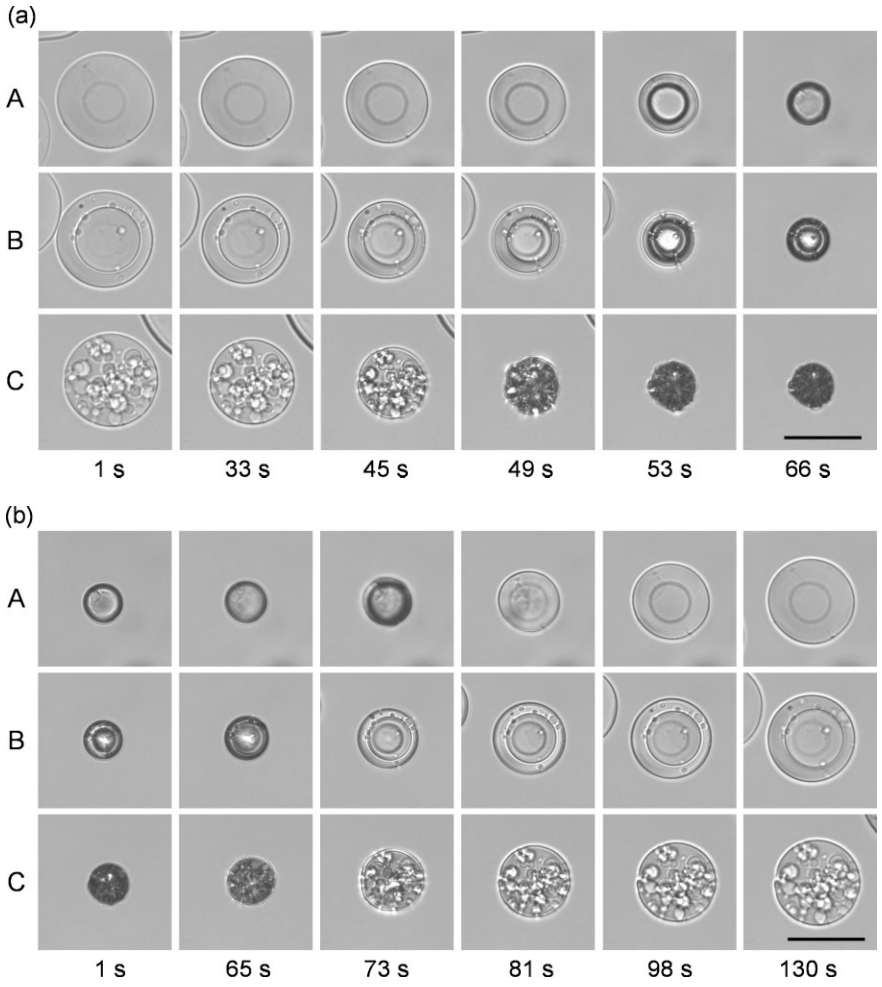

Figure 4. Effect of internal structure on the dynamic volume-shrinking and swelling behavior of microgels upon a) heating from 23 to 47 °C, and b) cooling from 47 to 23 °C. A: Voidless microgel; B: microgel with hollow shell structure; and C: microgel with multiple voids. Scale bar = 100 μm.

sary that all microgels in a given sample should not only be monodisperse, as shown above, but also contain the exact same number of voids. New microfluidic techniques that will allow us to do so are currently under development.[44]

3. Conclusion

A novel and convenient method to control the volume-phase transition kinetics of thermo-sensitive PNIPAM microgels has been presented. The method does not involve any alteration of the PNIPAM networks nor does it require any change in the size of the microgels. The response rate can be varied by fabricating different void structures inside the monodisperse microgel particles synthesized using a microfluidic technique. The more voids the microgel has, the faster is its response to changes in temperature. Furthermore, the induced void structure has no adverse effect on the equilibrium volume change of these microgels. The flexibility and control over the response kinetics offered by this method should make these microgels more useful for a wide range of applications in pharmaceutics and cosmetics, and as sensors and actuators.

4. Experimental

Materials: The monomer, NIPAM (99%), initiator, APS, and accelerator, TEMED (99%) were purchased from Acros Organics. The cross-linker, BIS, kerosene, deuterium oxide, and xylene were purchased from Sigma–Aldrich. The surfactant, polyglycerol polyricinoleate (PGPR 90), and polystyrene microspheres (Polybead), were obtained from Danisco USA, Inc. and Polysciences, Inc., respectively. All chemicals were used as received.

Microfluidic Device: The microfluidic device was fabricated by assembling borosilicate glass capillary tubes on glass slides. The cylindrical capillaries (World Precision Instruments, Inc.) had an inner diameter of 580 μm and an outer diameter of 1.0 mm, the same as the inner dimension of the square tubes (Vitrocom). A transparent epoxy resin was used to seal the tubes where required. The device was mounted on a microscope stage (Leica, DMIRBE) and solutions were supplied to it through polyethylene tubing (Scientific Commodities) attached to syringes (Hamilton Gastight) operated by syringe pumps (Harvard Apparatus, PHD 2000 series). The emulsification process was imaged with a high-speed camera (Vision Research) attached to the microscope.

Polymerization and Characterization of Thermo-sensitive Microgels: An aqueous suspension that contained NIPAM, APS, BIS, and polystyrene beads was pumped into the left end of the left square tube as shown in Figure 1. To prevent gravitational sedimentation of polystyrene microspheres in the aqueous phase, the density of the aqueous phase was increased to 1.05 $g\,cm^{-3}$, the same as the density of the microspheres, by mixing it with a measured quantity of deuterium oxide (density 1.12 $g\,cm^{-3}$). Concentrations of NIPAM, APS, and BIS in the aqueous phase were fixed at 9.4, 0.7, and 0.64% (w/v), respectively, whereas, the size and concentration of the polystyrene beads were varied to prepare microgels with different void structures. The continuous phase, kerosene that contained 8% (w/v) PGPR 90, was pumped into the gap between the right end of the left square tube and the round capillary. Fluid C, kerosene that contained 10% (v/v) TEMED and 8% (w/v) PGPR 90, was added downstream in the flowing emulsion as shown in Figure 1. TEMED is both oil- and water-soluble. Hence, it was able to diffuse from kerosene into the emulsified aqueous phase and start a redox reaction that polymerized the monomers.

After polymerization, the microgels were separated from the oil phase and collected in a glass vial. Adsorbed kerosene was then removed from the surface of the microgels by washing them five times with isopropyl alcohol using a centrifuge (IEC Centra, CL2; 1500 rpm, 3 min per wash). Polystyrene beads embedded in the microgels were dissolved by immersing the microgels in xylene for 3 h followed by four washes with fresh xylene using the centrifuge (1500 rpm, 3 min per wash). The microgels were washed again several times with isopropyl alcohol to dissolve the adsorbed xylene and were finally stored under water. Water was frequently changed over the course of seven days to ensure complete removal of isopropyl alcohol from the system before studying the thermo-sensitive behavior of the samples.

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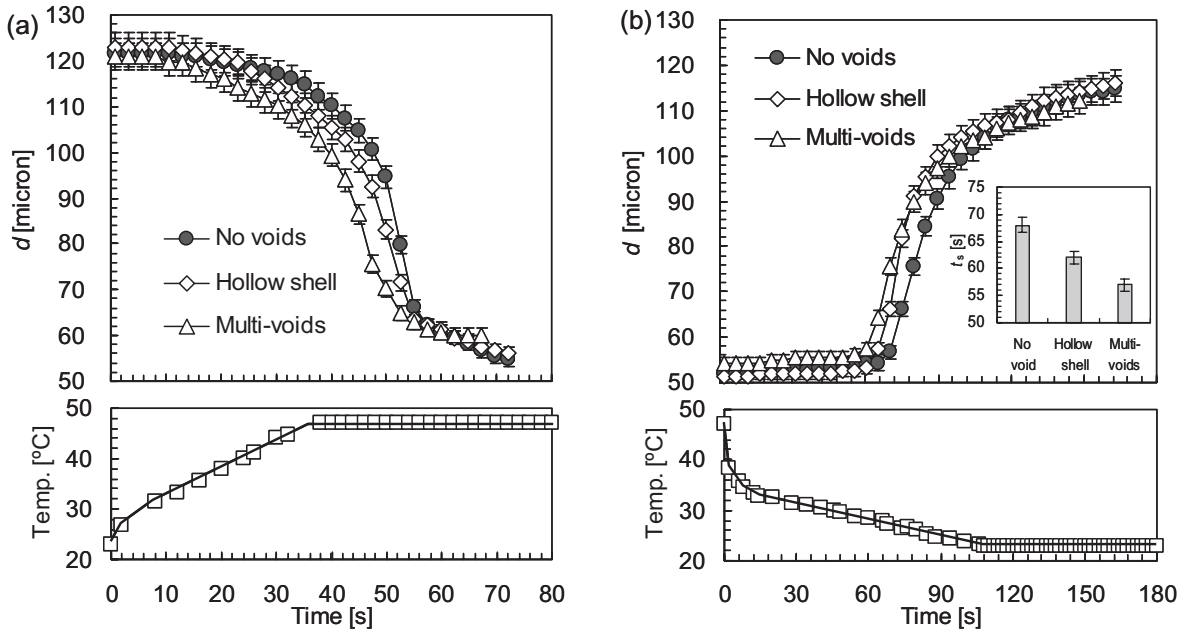

Figure 5. Time-dependent diameter of microgels with different internal structures upon a) heating from 23 to 47 °C and b) cooling from 47 to 23 °C; t_s is the time elapsed before the microgels begin to swell.

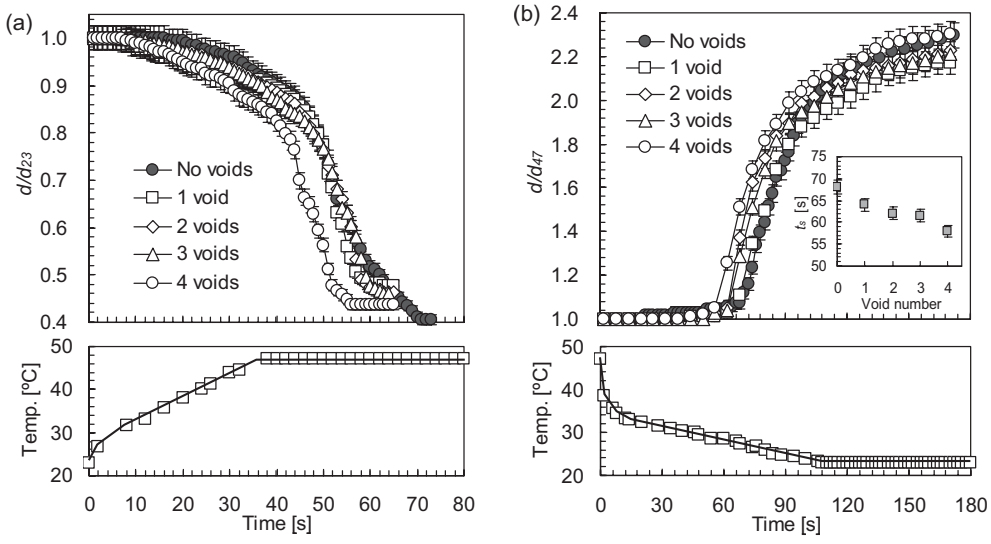

Figure 6. Effect of the number of spherical voids on the dynamic volume-shrinking and swelling behavior of microgels. The diameter of the spherical voids is 25 μm. The samples were a) heated from 23 to 47 °C and b) cooled from 47 to 23 °C; d_{23} and d_{47} are the microgel diameters at 23 and 47 °C, respectively, and t_s is the time elapsed before the microgels begin to swell.

The PNIPAM microgels together with pure water were put in a transparent holder on a glass slide, which was placed on a microscope-mounted heating and cooling stage (Physitemp Instruments, TS-4ER) to examine the thermo-sensitive behavior. Several microgels with the same structures were measured to obtain data with better statistics for the thermo-responsive characteristics. The temperature of the liquid inside the sample holder was confirmed using an infrared thermometer (VWR). The thermo-responsive behavior was recorded using a digital camera (Hamamatsu, C4742-95).

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