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Original Research Paper

Preparation of hydrogel capsules with thermoresponsive interpenetrating polymer network using concentric two-fluid nozzles

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ABSTRACT

Hydrogel capsules in which shell was composed of thermoresponsive interpenetrating polymer network (IPN) of crosslinked poly(*N*-isopropylacrylamide) (PNIAPM) and calcium alginate, were prepared using concentric two-fluid nozzles. To introduce different amount of PNIPAM into the capsule shell, the concentrations of the NIPAM monomer and the polymerization initiator were changed in a wide range and the characteristics of the resulting capsules were evaluated. Spherical and uniformly sized capsules were obtained under all conditions. Elemental analyses showed that the PNIPAM/alginate weight ratio increased with the increase of initial concentrations of NIPAM monomer and polymerization initiator and was proportional to the initial rate of polymerization. In addition, the thermoresponsive properties of IPN hydrogel capsule were measured at temperatures from 10 °C to 50 °C and the thermoresponsive volume change ratio was expressed as a function of the PNIPAM/alginate weight ratio raised to a power. From these results, the relationship between the experimental conditions and the amount of PNIPAM in the capsule shell was clarified, and it indicated the magnitude of volume change of IPN hydrogel capsules can be controlled by introducing the desired amount of PNIPAM in the capsules.

1. Introduction

Recently, there has been increasing interest in the development of stimuli–responsive hydrogels, which can change their swelling behavior or other properties in response to environmental stimuli, such as temperature, pH, light, and specific ions [1–3]. Many researchers have reported the potential of stimuli–responsive hydrogels for use in biomedical applications, including drug delivery, bioseparations, and biosensors [4,5]. Among various stimuli–responsive systems, thermoresponsive polymer-based materials have been extensively studied because of their controllability and the lack of involvement of chemical reactions [6].

Poly (*N*-isopropylacrylamide) (PNIPAM) hydrogel is well known as a thermoresponsive hydrogel that exhibits a sharp volume phase transition at approximately 33 °C in aqueous solution [7–10]. Below the volume phase transition temperature (VPTT), the hydrogel swells, whereas above the VPTT, the hydrogel shrinks because it dehydrates to a collapsed state due to the breakdown of the delicate hydrophilic/hydrophobic balance in the network structure. However, while PNIPAM hydrogels do have special properties, they also exhibit poor mechanical properties, such as low strength, particularly in the highly swollen state, which causes difficulties in practical applications [11].

To overcome this problem, chemically independent interpenetrating polymer network (IPN) comprising the PNIPAM network and another polymer network has been proposed [6,12]; the formation of such complementary structures have enhanced the mechanical strength of hydrogels. Park and Choi demonstrated the preparation of monodisperse spherical IPN hydrogel beads comprising PNIPAM and calcium alginate [13]. This was an application of a dripping method with a single nozzle which was developed to produce calcium alginate hydrogel beads. In the experiment, droplets of viscous solution containing sodium alginate (SA), NIPAM monomer, and a crosslinking agent were dripped into a receiving solution containing Ca^{2+} and a polymerization initiator. IPN hydrogel beads were obtained via the free radical polymerization of PNIPAM within the calcium alginate hydrogel beads that were immediately formed in the receiving solution. This method is very simple for the preparation of IPN hydrogel beads in one step. Lima et al. also reported the development of a new preparation method for thermoresponsive dextran-MA/PNIPAM particles using superhydrophobic surfaces [14]. Although the preparation process required two steps, nearly 100% of PNIPAM could be incorporated into the gel beads. In such studies, polysaccharide and PNIPAM were used as constituent materials and the generated polymer networks were of IPN or semi-IPN structure, however, their shapes were bead or particle in most of the case.

On the other hand, Shah et al. reported the preparation of monodisperse stimuli–responsive colloidosomes via the

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self-assembly of PNIPAM microgels using a microfluidic device [15]. In this case, the stimuli–responsive colloidosome had a capsule-like core–shell structure and was considered to be an attractive candidate for use in the targeted, pulsed-release of materials. However, the capsule consisted of only pure PNIPAM.

Therefore, in this study, we developed a new method for the preparation of thermoresponsive IPN hydrogel capsules with a core–shell structure, in which the shell comprises crosslinked PNIPAM and calcium alginate and the core comprises a buffer solution. The preparation of IPN hydrogel capsules was conducted in a very simple, single-step process using concentric two-fluid nozzles [16]. With concentric two-fluid nozzles, it is possible to independently prepare and introduce the core and shell solutions through the inner and outer nozzles. On the other hand, in the case of IPN hydrogel beads, to encapsulate a desired material, it is necessary to mix the material into a highly viscous solution that contains the polysaccharide and NIPAM monomer or introduce the material after bead formation, both of which are difficult. In addition, using concentric two-fluid nozzles, various core solutions can be utilized, which increases the potential applications for the hydrogel capsules.

In this process, however, the amount of the PNIPAM incorporated in the IPN hydrogel capsule becomes less than that of input NIPAM since certain portions of NIPAM monomer and oligomer leak into the receiving solution during polymerization. This leakage is an issue because the stimuli–responsive properties of PNIPAM hydrogels are determined by the amount of incorporated PNIPAM. Therefore, it is absolutely necessary to determine the fabrication conditions that enable control of the incorporation of PNIPAM. Thus, in this study, both the relationship between the preparation conditions and the amount of incorporated PNIPAM in IPN hydrogel capsules as well as the relationship between the incorporated amount and the thermoresponsive properties of the capsules were examined.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAM) was kindly supplied by Kohjin Co., Ltd. *N*,*N*′-methylenebisacrylamide (MBAA), SA, and calcium chloride ($CaCl_2$) were purchased from Kanto Chemical Co., Inc. Ammonium persulfate (APS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were purchased from Wako Pure Chemical Industries, Ltd. Tris–HCl buffer (pH 8.6) was used as the solvent in all experiments.

2.2. Preparation of IPN hydrogel capsules

IPN hydrogel capsules were prepared using concentric two-fluid nozzles (outer nozzle; O.D. = 1.26 mm, I.D. = 0.90 mm; inner nozzle; O.D. = 0.55 mm, I.D. = 0.30 mm). The experimental apparatus is shown in Fig. 1. NIPAM (4.8–14.4 wt%) was dissolved in a buffer solution and degassed for 30 min using N_2. MBAA (0.2–0.6 wt%) as a crosslinker and SA (2.0 wt%) as a structural support polymer were added to the above solution and used as the shell solution. The same buffer solution was simply used as the core solution. To form droplets with a double-layered structure, the shell and core solutions were simultaneously pumped from the outer nozzle (15 mL/h) and inner nozzle (3 mL/h), respectively, using syringe pumps. The droplets were fallen into receiving solution which contains APS (0.5–2.0 wt%) as a polymerization initiator, TEMED (0.25–1.0 vol%) as an accelerator and $CaCl_2$ (1.1 wt%) as a gelator of the alginate. After 90 min of polymerization at room temperature (approximately 22 °C), the resulting capsules were recovered from the receiving solution and washed with water several times. Subsequently, the capsules were shrunk and swollen three times at 50 °C and 10 °C for 2 h each in the $CaCl_2$ solution to harden the shell via the formation of calcium alginate and then stored at 10 °C until used. The experimental conditions are summarized in Table 1. The sample name indicates the input concentration of NIPAM in the shell solution and APS in the receiving solution. For example, N4.8A0.5 indicates that the NIPAM concentration was 4.8 wt% and the APS concentration was 0.5 wt%. In addition, to visualize the core–shell structure of the capsules, IPN hydrogel capsules encapsulating a cocoa particle suspension were prepared. In these experiments, a cocoa particle solution was used as the core solution instead of the buffer solution; the other conditions were exactly the same as described before.

2.3. Characterization

IPN hydrogel capsules were observed under a stereomicroscope, and the outer diameter was measured using image analysis software (Azokun, Asahi Kasei Engineering).

Fourier transform infrared (FTIR) spectroscopy (IRPrestige-21, Shimadzu) confirmed the structure of IPN hydrogel capsules. The FTIR measurement was taken using the KBr tablet method.

Elemental analyses were performed to determine the PNIPAM content in IPN hydrogel capsules using a CHN elemental analyzer (EA1110, CE Instruments). The PNIPAM/alginate weight ratio was calculated on the basis of the obtained N/C ratio by assuming that the NIPAM and MBAA were polymerized at the input ratio. It should be noted that alginate does not contain N.

2.4. Measurement of the thermoresponsive volume change

The thermoresponsive volume changes of IPN hydrogel capsules were measured in the temperature range 10–50 °C. The capsules were maintained in a 0.1 M $CaCl_2$ solution at each temperature for 10 h before stereomicroscope observation. The volumes of the entire capsules were determined on the basis of the outer diameter as determined from the image analysis. The thermoresponsive properties of the capsules were evaluated on the basis of the relative volume V_T/V_{10}, where V_T and V_{10} are the entire volume of IPN hydrogel capsules at temperature T (°C) and 10 °C, respectively.

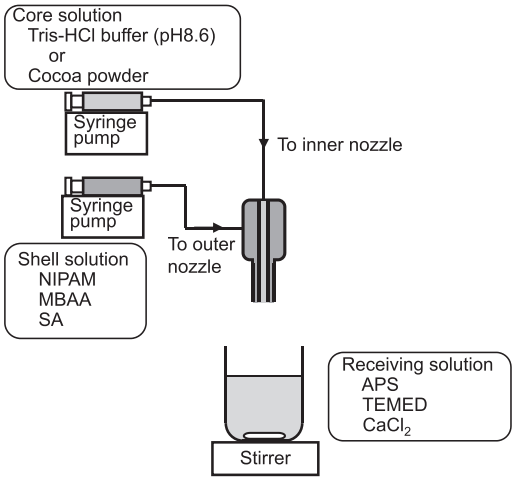

Fig. 1. Experimental apparatus for the preparation of IPN hydrogel capsules.