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Communication

Magnetic-Responsive Microparticles that Switch Shape at 37 °C

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Abstract: Shape-memory polymers have seen tremendous research efforts driven by the need for better drug carries and biomedical devices. In contrast to these advancements, fabrication of shape-memory particles which actuate at body temperature remains scarce. We developed a shape-memory microparticle system with dynamically tunable shapes under physiological temperature. Temperature-responsive poly(ε-caprolactone) (PCL) microparticles were successfully prepared by an in situ oil-in-water (o/w) emulsion polymerization technique using linear telechelic and tetra-branched PCL macromonomers. By optimizing the mixing ratios of branched PCL macromonomers, the crystal-amorphous transition temperature was adjusted to the biological relevant temperature. The particles with a disk-like temporal shape were achieved by compression. The shape recovery from the disk to spherical shape was also realized at 37 °C. We also incorporated magnetic nanoparticles within the PCL microparticles, which can be remote-controllable by a magnet, in such a way that they can be actuated and manipulated in a controlled way.

Keywords: shape-memory particles; poly(ε-caprolactone); magnetic-responsive

1. Introduction

Polymeric micro/nano particles have enjoyed growing interest over the past several decades in drug delivery [1], optical bio-sensors [2], and bio-imaging [3]. In many of these applications, the ability to change chemical or physical properties in response to an external stimulus is greatly desired. Smart or stimuli-responsive polymers are one of the most common materials for these purposes [4]. Among them, thermally responsive, crystalline polymers are known to exhibit shape memorizing abilities. The shape memory effect usually requires two components at the molecular level: cross-links, which determine the permanent shape and switching segments, which are used to maintain the temporary shape. Although the shape memory effect in an uncrosslinked crystalline polymer has been also reported [5], it was shown to have relatively low values of shape memory performance compared to that of the crosslinked one. Most of the SMPs reported so far use heat as a stimulus. The glass transition temperature (T_g) or the melting temperature (T_m) are commonly used as the reference point for thermo-mechanical deformation and recovery [6,7]. More recently, continuous efforts have been devoted into modifying existing SMPs and developing new ones for tailored properties and special functions such as photo-responsive or chemo-responsive SMPs [8–13]. Despite the advancements of various SMPs, however, fabrication of shape-memory particles remains

scarce. One of the major reasons is the difficulty of chemical crosslinking process to obtain stable and high-performance shape-memory particles. Furthermore, almost all existing SMPs possess their shape switching temperature in a relatively higher temperature range than a biologically relevant temperature range. For example, poly(ε-caprolactone) (PCL), which has been approved by the US Food and Drug Administration (FDA), has the T_m around 60 °C [14]. Each of these issues limits the potential of shape-memory particles for biological applications.

From these perspectives, we have been developing PCL-based SMPs with the shape switching temperature near biologically relevant temperature [15,16]. In general, one of the easiest ways to control the shape switching temperature is to copolymerize or blend with other components to decrease the T_m [17]. These approaches, however, demonstrated the difficulty in developing SMPs that actuate sharply in a narrow temperature range because incorporation of other components also hinder crystallization of PCL. Therefore, we have developed the alternative approach to modulate the T_m of PCL by controlling the nanoarchitectures such as branched arm numbers and molecular weight. Specifically, we prepared linear telechelic (2b) and tetra-branched (4b) PCL macromonomers and mixed them at different ratios followed by crosslinking. The crosslinked samples demonstrated that increasing 4b/2b-PCL ratio led to a linear increase in T_m. Especially, the 50/50 wt % sample had the T_m below 37 °C. These results suggest that the unit length of the PCL macromonomers and netpoint density within the crosslinked PCL structure are the predominant contributors in controlling thermal and mechanical properties.

The use of SMPs has found growing interest in biologically and environmentally friendly technologies. The first mention of SMPs is in a United States patent where they developed dental restoration materials with elastic memory property, which are thermoplastic synthetic resins made of methacrylic acid ester [18,19]. Since then, many efforts to design and develop SMPs have started. Especially, the 1980s was considered as a time period when SMP research was at its first peak. These works were mainly in industrial fields. Significant research efforts started again in the early 2000s after Lendlein and Langer demonstrated the concept of biodegradable SMP sutures [20,21]. The unique property of SMPs provides enormous opportunities for the design of next-generation less invasive, smart medical implants, dynamic tissue scaffold, and medical devices. Among them, SMPs with particle shape have been attracting much attention as carriers for drug delivery and other biomedical applications. It has a strong advantage to be able to change the particle shape on the carrier performances, since particle shape has been recognized as an important parameter. SMPs with particle shape have been already reported [22–25]; however, there are still only few reports which achieved the sharp shape memory actuation within totally biological temperature range. In this study, we apply linear telechelic/tetra-branched PCL system to prepare shape-memory microparticles. The spherical microparticles were prepared by an oil-in-water (o/w) emulsion technique using a mixture of linear telechelic/tetra-branched PCL macromonomers, and poloxamer surfactant. The macromonomers were simultaneously polymerized by heating in the presence of an initiator. This process introduces covalent netpoints into microparticles. The particles with a disk-like temporal shape were achieved by pressing with flat substrate and subsequent cooling to 4 °C. The shape recovery from the disk to spherical shape was also realized at 37 °C. We also incorporated magnetic nanoparticles (MNPs) within the PCL microparticles. The MNP-loaded PCL microparticles were remote-controllable by a magnet, thus it allows us to employ magnetophoresis ability to shape memory microparticles for future biomedical applications, such as biomolecule enrichment, cell separation, and targeted drug delivery.

2. Materials and Methods

ε-Caprolactone was purchased from Tokyo Kasei (Tokyo, Japan), and purified by distillation over calcium hydride under reduced pressure. Pentaerythritol, 1,4-butanediol, and acryloyl chloride were also purchased from Tokyo Kasei and used as received. Triethylamine was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), and dehydrated by distillation over potassium hydroxide for overnight. Tin octanoate and other chemicals were also purchased from Wako Pure Chemical

Industries, Ltd. (Osaka, Japan), and used as received. Pluronic® F-127 and benzoyl peroxide (BPO) was purchased from Sigma (St. Louis, MO, USA) and used as received. Magnetic nanoparticles (EMG1300, Fe_3O_4) were purchased from Ferrotec and used as received.

Linear telechelic and tetra-branched PCLs were synthesized by ring-opening polymerization from 1,4-butanediol and pentaerythritol, respectively (Figure S1). The average degrees of polymerization of each branch in two-branched and four-branched PCLs were 20 and 10, respectively. Then, acryloyl chloride was reacted to the hydroxyl end group of the branched chains. Microparticles were prepared by an in situ oil-in-water (o/w) emulsion polymerization using xylene solutions containing PCL macromonomers having acrylate end groups and BPO as an initiator with or without magnetic nanoparticles as oil phase and emulsifying 1390 μL of this solution in 20 mL of an aqueous stabilizer solution containing 5 wt/v % Pluronic® F-127. Here, the equimolar amounts of linear telechelic and tetra-branched PCL macromonomers in the presence or absence of MNPs were dissolved at 50 wt % in xylene containing two-fold molar excess benzoyl peroxide (BPO) to the end-group of macromonomers. The mixed solution was vigorously stirring for 5 min and then increased solution temperature to 80 °C with oil bath and reacted for overnight to allow for in situ polymerization. The reacted microparticles were washed with a large amount of distilled water, acetone, and methanol, and collected by centrifugation after each washing. Each washing process repeated three times, and finally the purified particles were dispersed in distilled water (Figure 1a). To program temporary particle shape, the purified particles were casted on a solid substrate and compressed (compressive stress of 1 MPa) by heating at 40 °C for 10 min. The thermal treatment of samples and measurement temperature was controlled using hotplate (Microwarm plate, KM-3, Kitazato, Shizuoka, Japan) or thermos chamber (Chromato chamber M-600FN, TAITEC, Saitama, Japan). The compressive stress was then released at 4 °C after 15 min of cooling. Samples had a temporary shape that could be triggered to transition to permanent sphere shape by heat at 37 °C for a period of 15 min.

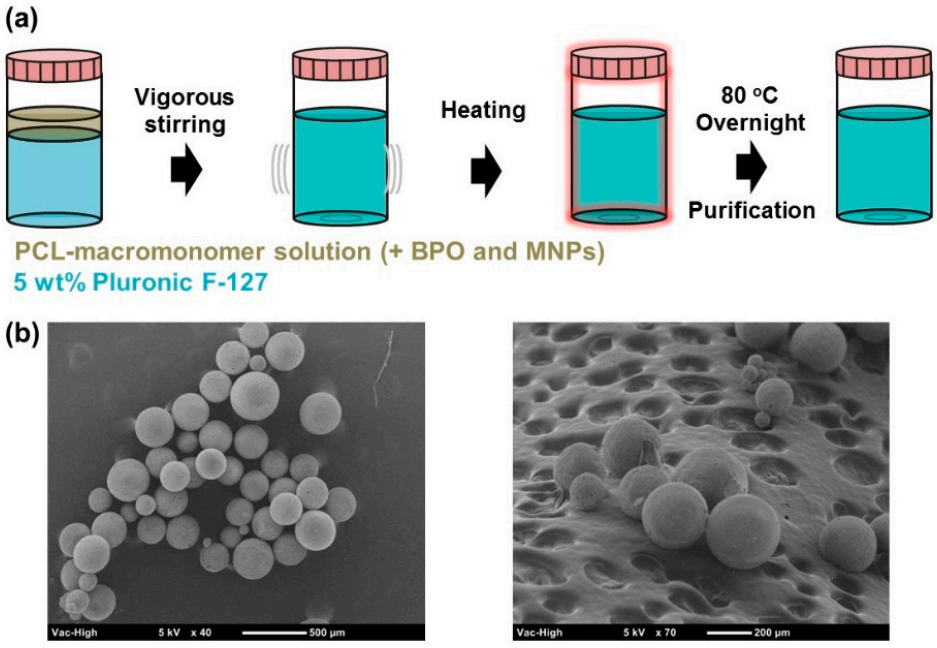

Figure 1. (**a**) Schematic illustration of preparation procedure of shape-memory PCL microparticles by in-situ oil-in-water (o/w) emulsion polymerization technique; (**b**) Top view (Left) and tilt view (Right) SEM images of prepared shape-memory PCL microparticles with acceleration voltage of 5 kV. Scale bars, 500 μm (Left) and 200 μm (Right).

Particle shape was observed by using a scanning electron microscope (SEM, JCM-5000, JEOL, Tokyo, Japan). The actual content of magnetic nanoparticles in the microparticles were evaluated

by thermogravimetric analysis (EXSTAR6000 TG/DTA, SII Nanotechnology, Northridge, CA, USA). The melting temperature as well as endothermic enthalpy change (ΔH) were determined by differential scanning calorimetry (DSC 6100, SEIKO Instruments, Chiba, Japan). To examine the magnetic attractivity of the microparticles hybridized with magnetic nanoparticles, the transmittance of the dispersed solutions at wavelength of 500 nm were measured by a UV–vis spectrometer (V-650, JASCO, Tokyo, Japan).

3. Results

3.1. Preparation of Shape-Memory Microparticles

The endothermic peaks correspond to the T_m of the samples. This analysis was performed because the T_m and crystallinity of the PCLs play an important role in affecting the shape-memory ability. Interestingly, PCL microparticle shows an extremely sharp transition over the T_m around 33 °C which is almost the same temperature as the one for PCL film. The ΔH associated with T_m for the particle is also similar to the one for film even though the PCL microparticles contain MNPs. This implies that microparticles composed of 2b/4b-PCL still possess a sharp transition around 33 °C. The successful encapsulation of the MNPs in the PCL microparticles was confirmed by TGA. Figure 2b shows the weight loss of the PCL particles when heated to above 500 °C. The MNP-loaded PCL microparticles exhibited a weight loss between 250 and 400 °C. By comparing the weight losses between bare MNPs and MNP-loaded PCL, the MNP content was calculated to be 4.49 wt % which corresponds well to the feed concentration (5 wt %).

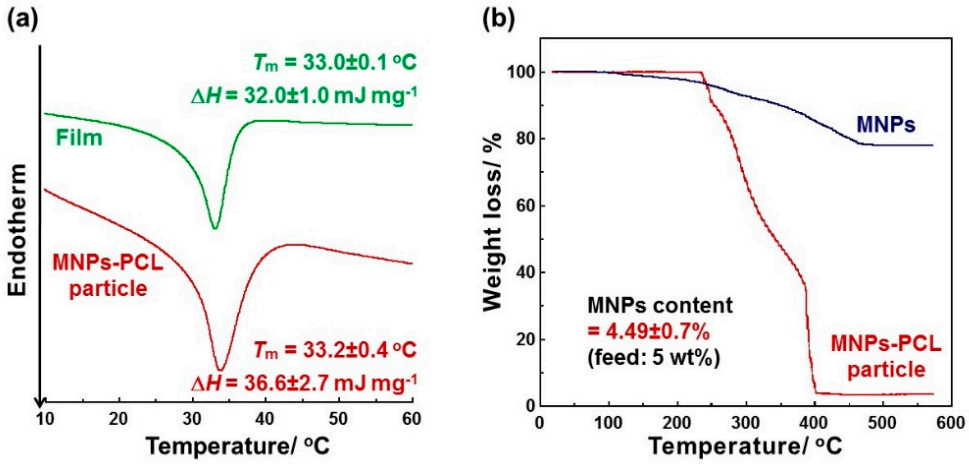

Figure 2. (**a**) DSC curves of shape-memory PCL microparticles containing MNPs and crosslinked PCL film as a control. The T_m and ΔH were estimated from peak top and area of endothermic peak, respectively; (**b**) Thermogravimetric analysis for MNPs as a control and shape-memory PCL microparticles containing MNPs.

3.2. Shape-Memory Behavior

Next, the direct deformation and shape recovery of microparticles was performed. A typical shape memory cycle consists of two primary stages: programming a deformed (temporary) shape and recovering the original (permanent) shape. Specifically, PCL microparticles displays rubbery-like behavior above the T_m and were easily deformed during the programming process at 40 °C. After removal of the compressive stress below the crystallization temperature T_c, the temporary shape was fixed at 4 °C. SEM images show that, following this procedure, deformed particles are successfully programmed to hold highly strained temporary shapes (Figure 3, left). The particles exhibited flattened programmed shapes. When these deformed particles are annealed at 37 °C for a period of 15 min, they exhibit significant recoveries of their permanent shapes (Figure 3, right).

3.3. Magnetic-Responsive Capture/Release of Microparticles

Figure 4a shows SEM images of the MNP-loaded PCL microparticles after removing the large size of particles by sedimentation technique. The average diameter after purification was approximately 4.1 (±2.4) μm. Both morphology and size before the separation by sedimentation were similar to the sample without MNPs. This implies that incorporation of MNPs does not affect particle formation and crosslinking. To investigate the response of the MNP-loaded particles to a magnetic field, a neodymium magnet was kept near a vial in which particles were dispersed in water. Figure 4b shows the photographs of the capture/release experiment. The particles were quickly attracted by the magnet within 60 s. When the applied field was removed, on the other hand, the captured particles were released back into the solution within 10 s by simple stirring or pipetting. Transmittance change was observed to assess the magnetophoretic mobility of the particles. Initially, the transmittance of the solution was zero, meaning that the solution was turbid. The optical transmittance for the particles without applying the magnetic field hardly changed during 10 min, suggesting that the particles have high dispersivity. When the magnetic field was applied, on the other hand, the transmittance sharply increased as shown in Figure 4c. Repeated on and off cycles of magnetic field was also conducted (Figure 4d). The particles were first captured on the wall (on), and then released (off). This magnetic-responsive behavior enables remote manipulation of particles under a controlled magnetic field.

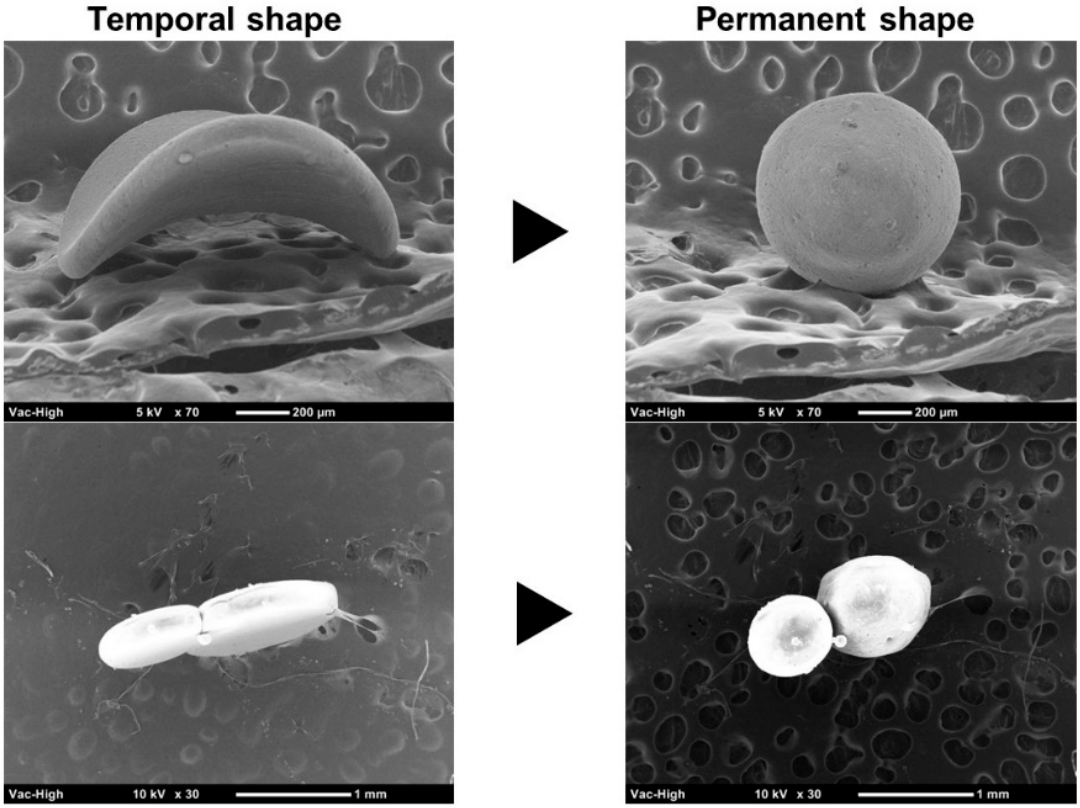

Figure 3. SEM images of thermally-induced shape recovery of shape-memory PCL microparticles with acceleration voltage of 5 kV (**top**) and 10 kV (**bottom**). Highly strained temporary shape (**left**) was returned to original permanent shape (**right**) by heating at 37 °C for 15 min. Images shows the shape recovery of particles for two different sets (**top** and **bottom**). Scale bars, 200 μm (**top**) and 1 mm (**bottom**).

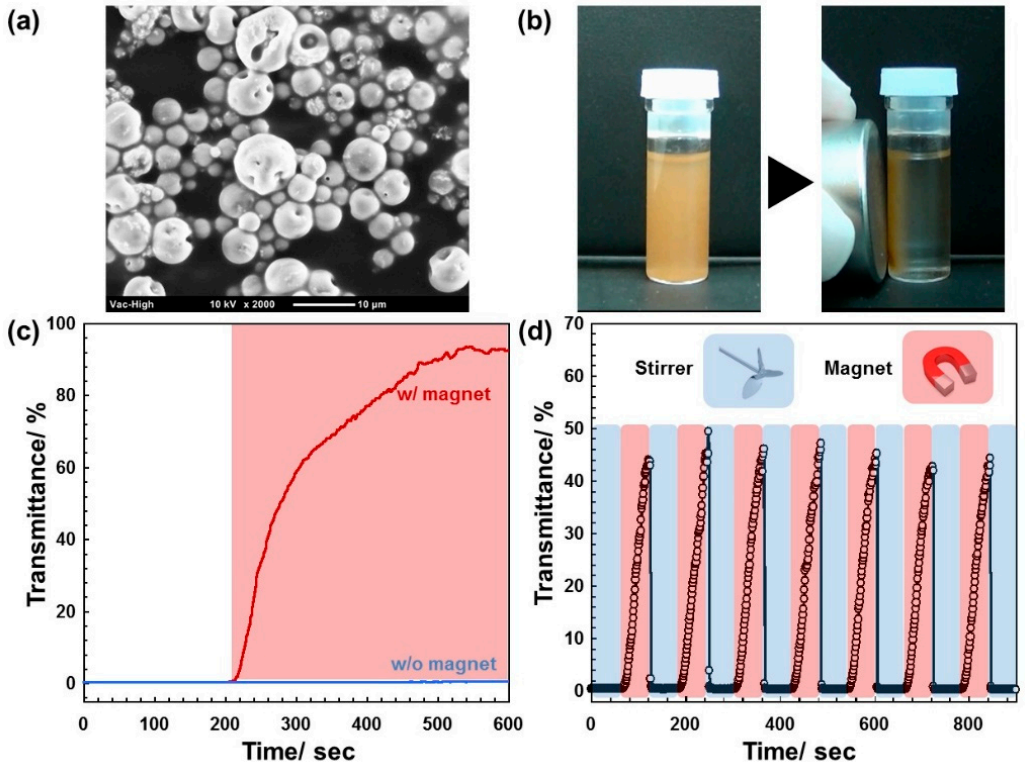

Figure 4. (**a**) Top view SEM image of shape-memory PCL microparticles containing MNPs after size separation by sedimentation technique; (**b**) Photographs of dispersion of purified shape-memory PCL microparticles containing MNPs before and after applying an external magnetic field; (**c**) Time course of magnetophoretic mobility for purified shape-memory PCL microparticles containing MNPs with or without external magnetic field. The measurement was conducted in distilled water; (**d**) Repeatability of magnetophoretic mobility and dispersion of shape-memory PCL microparticles containing MNPs. Stirring (blue) and applying with externa magnetic field (red) were repeated alternately every 60 s for 15 min. (**c**,**d**) Magnetophoretic mobility was estimated by measuring the optical transmittance at 500 nm.

4. Discussion

We have been demonstrating the potential of SMPs in the area of tissue engineering, mechanobiology, and micro-electro-mechanical systems in the past decade [26,27]. We have recently reported shape-memory surfaces fabricated from PCL films with on-demand, tunable nano-grooves [28–31]. The key technology behind these studies is a rational method to control the shape switching temperature because PCL, for example, has a T_m around 60 which is very high for biological experiment. To achieve this purpose, we proposed a rational approach to modulate the T_m by mixing linear telechelic and four-branched PCLs in 2006 [15]. Other researchers also demonstrated successfully decreasing the T_m of PCL by a similar strategy based on regulation of molecular weight [20,32]. Despite the advancements of various SMPs; however, fabrication of shape-memory particles still remains scarce. In the current study, we demonstrated that PCL-based shape-memory microparticles exhibited shape recovery from a disk-like temporal shape to spherical shape at 37 °C. Incorporation of MNPs enabled the remote and reversible control of capture/release of the particles. It is noteworthy that incorporation of MNPs into the PCL microparticles did not affect the shape-memory ability, while incorporation of some impurities can affect polymer crystallinity in principle. We used chemical crosslinking (covalent bond) instead of physical crosslinking to introduce netpoints into PCL networks in this study, because chemically crosslinked polymer networks should provide a higher content of switching phase and high form stability. Those, in turn, allowed the system

to have sharp responsiveness and better shape memory performance [22]. Furthermore, they should also prevent erosion of loaded MNPs. Wischke and Lendlein have reported that 100% of shape recovery for chemically crosslinked shape-memory particles occurred within temperature change between 40 and 43 °C [22], while the shape recovery rate for physically crosslinked ones was still 90% at 90 °C [23]. In our previous study, crosslinked samples showed approximately 99% and 90% of the shape fixity and shape recovery rate, respectively [29]. When the magnetic field is applied, MNP-loaded particles were moved toward the magnet. The capture and release behavior reversibly occurred in response to an external magnetic field. This result indicates that magnetophoretic mobility can be controlled with the particle shape because the size and morphology are known to affect the diffusivity of MNPs [33]. Lai et al. reported that the diffusivity of individual MNPs decreases as the particle size becomes larger. In contrast, the magnetophoretic velocity of individual MNPs increases significantly as the particle size becomes larger [34]. Therefore, we can control the magnetic-responsive behavior of the particles with their shape.

Dynamic manipulation of particle properties has been attracting attention as it has great potential to precisely manipulate particle interactions with cells. In fact, Yoo and Mitragotri demonstrated the ability of shape-switchable particles in modulating interaction with cells, and the elliptical disk-shaped particles that are originally not phagocytosed by macrophages were made to internalize through shape switching [35]. They designed and prepared similar polyester particles as we designed in this study but it based on T_g for switching, meaning that it is difficult to keep the original particle shape once started incubation with cell. Our T_m-based shape-memory particles system would have sharper on–off controllability to induce shape change, and that in turn enables more controlled uptake of particles by macrophage. MNPs inside shape-memory particles also provide new particle functions, not only separation ability but also targeting to cells as well as remote-controllability to trigger shape change. Also, surface modification of the shape-memory particles with various biomolecule is possible. Such particles can potentially be used for bioseparation, and further study of drug delivery and immunoenginnering.

5. Conclusions

We have reported a novel strategy for the facile production of magnetic-responsive shape-memory microparticles. As it has been demonstrated, the MNPs can be easily incorporated into the PCL microparticles without disturbing the shape-memory ability. The particles with a disk-like temporal shape were achieved by compression and the shape recovery from the disk to spherical shape was also realized. Reversible and remote control of the particles was achieved by magnetic capture and subsequently detached by magnet removal. The whole procedure is carried out within few minutes. Thanks to the fact that the prepared PCL particles possess the shape-switching temperature near the body temperature, the proposed strategy is potentially compatible with biological applications.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3417/7/11/1203/s1, Figure S1: Synthesis scheme of linear telechelic and tetra-branched PCL macromonomers.

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Author Contributions: M. Ebara and K. Uto conceived and designed the experiments. K. Uto performed experiments, data collection, and data analysis. K. Uto and M. Ebara wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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