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Microfluidic Synthesis and Properties of Thermoresponsive Hydrogel Core–Shell Particles

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Abstract: An approach is demonstrated for the generation of swellable core–shell particles in the sub-millimeter range using a one-step microfluidic method. Particles are made of an agarose gel core and a shell consisting of hydrogel based on crosslinked poly-(N-isopropylacrylamide) (PNIPAM). Solidification of the core was achieved by cooling below the sol–gel temperature, while the shell was cured by photoinitiated co-polymerization. The shell of the particles is reversibly thermoresponsive; it contracts upon heating, releasing water, and becomes hydrophobic. The transition temperature as well as the stability of the particles are mainly affected by the shell monomer composition, while they are less affected by the type of the core material. Such composite particles remain swellable after drying.

Keywords: hydrogel; core–shell particles; microfluidics; one-step preparation; thermo-response

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1. Introduction

Core–shell microparticles are of interest for analytical as well as therapeutic or theranostic applications, for example, drug targeting [1–4]. The design of the shell material allows for specific interaction of the particle with its targets [5] as well as for control of the release of drugs or other agents stored in the core [6–8]. In general, the kinetics of uptake and release of substances by the whole particle are mainly determined by the shell. For triggered dispersion and transport properties, it is required to change permeability and/or solvation behavior. The core–shell particles of suitable shell material would open the possibility to selectively switch the properties of the shell while keeping those of the core constant. Switching by temperature changes could be a very convenient strategy, if thermoresponsive materials are utilized. Hydrogels of crosslinked PNIPAM are suitable materials for such a temperature-controlled switching [9]. Above the critical temperature, the material shrinks and its hydrophilic character gets gradually lost, thereby shifting into a more hydrophobic state [10,11]. This paper shows a sol–gel transition at moderately enhanced temperature.

Thermoresponsive particles based on PNIPAM are usually produced by thermal free-radical polymerization of the related monomers. Typically, the formation of particles occurs from an emulsion [12], by precipitation polymerization from a solvent [13], or by growth on preformed nanoparticle seeds [14,15]. The seed-based method can also be used for generating core–multishell particles, which mostly have an inorganic core in the nanometer range [15]. The resulting particles by either of these methods generally have diameters well below 1 µm or slightly above. On the other hand, particles with sizes between a few micrometers and one millimeter can be generated with high homogeneity by using microfluidic techniques [16], which are applicable for producing core–shell particles too. Polymer and gel particles that are swellable in aqueous environments are well-suited for the storage and release of drugs and other chemicals. Microfluidic methods are advantageous because they allow for the efficient use of the chemicals employed, are easy to conduct, and

usually have a short time of fabrication. To the best of our knowledge, the microfluidic generation of particles composed of two or more different hydrogel materials has hardly been addressed up to now [17]. Here, we report on the investigation of the generation of composed hydrogel microparticles and on how an existing microfluidic method [18] has been advanced to produce such particles consisting of a thermoresponsive PNIPAM shell around the core of a second hydrogel material in one step.

2. Materials and Methods

2.1. Materials

All commercially available chemicals were reagent grade and were used without further purification. Monomers—N-isopropylacrylamide (NIPAM, Sigma-Aldrich, St. Louis, MO, USA), acrylamide (AA, Merck, Darmstadt, Germany), N,N′-methylenebisacrylamide (MBBA, Merck, Darmstadt, Germany), 1,4-butanediol diacrylate (BDDA, Merck, Darmstadt, Germany), tripropylene glycol diacrylate (TPGDA, abcr, Karlsruhe, Germany), and ethylene glycol dimethacrylate (EGDM, Merck, Darmstadt, Germany). Solvents—tert-amyl alcohol (Merck, Darmstadt, Germany), tert-butanol (Merck, Darmstadt, Germany), n-butanol (TCI, Eschborn, Germany), n-hexanol (Merck, Darmstadt, Germany), cyclohexanol, and cyclohexanone. Silicone oil 500 cSt (Carl Roth, Karlsruhe, Germany), gelatin G9391 (Sigma-Aldrich, St. Louis, MO, USA), agarose Sigma-Aldrich, St. Louis, MO, USA), and trehalose (Fisher Scientific, Schwerte, Germany) were used. Photoinitiators—irgacure 819 (Merck, Darmstadt, Germany). Lithium 2,4,6-trimethylbenzoyl-phenylphosphinate (Li-TPO)—was synthesized as described in [19]. In-house bi-distilled water was used, with a conductivity of 1–2 μS/cm and a pH of 5.5–6.5.

2.2. Photopolymerization

A 120 W mercury short-arc lamp HXP 120 V (Leistungselektronik Jena, Jena, Germany) was used as the light source. The light was fed by a 5 mm diameter glass fiber cable, and light intensity was adjusted to 2/3 of the maximum value. Irradiation was carried out perpendicular to the flow direction of the particles in the microfluidic experiments. For bulk polymerization, as was necessary for testing the solvents and for producing adequate amounts of polymer, all required components (monomers, solvents, and photoinitiators) were mixed in a 10 mL beaker to make about 2 mL of mixture, which was then irradiated for 10–20 s.

2.3. Particle Separation Post Treatment

After irradiation, the cured particles were collected. The carrier (silicone oil) was removed by suction over a frit, and the particles were washed with tert-butanol and finally filled in a vial with bi-distilled water. During storage in water, residual organic solvents (tert-amyl alcohol and tert-butanol) from the particle shell are exchanged with water. Core particles with trehalose was a main constituent, storage was performed with an adequate trehalose solution rather than with mere water.

2.4. Measuring Swellability

An aliquot of the polymer gel was weighed and then immersed in bi-distilled water. After a period of 2–3 h, the water was replaced by fresh water and stored for about 24 h. The sample was then taken from the water, dried with filter paper, and weighed again. Thereafter, the sample was examined for thermosensitivity by adding it back into the water and heating. Thermosensitivity was observed when it became opaque and shrunk when heated.

2.5. Measuring Thermosensitivity via Microscopy

In order to follow-up the thermal behavior of the composite particles quantitatively, a Keyence VHX-5000 microscope (Keyence Deutschland GmbH, Neu-Isenburg, Germany) with a VH-Z00R objective was employed. On the microscope stage, a 40 × 35 mm heating

element (DBK David + Baader GmbH, Kandel, Germany) was mounted, and its temperature was adjusted by a thermo-controller UR3274 (Wachendorff GmbH, Geisenheim, Germany). On the heating element, a glass slide with indentation was placed, where 100 µL of diluted particle suspension was pipetted in. The temperature was increased in intervals of 2 °C, and a photograph was taken at each step. The particle size was measured by using the standard graphic software ImageJ, version 1.53m and later. To investigate the construction of the particles in more detail, a Zeiss Axioplan 2 microscope (Zeiss, Göttingen, Germany) was used, which allows for transmitted light and bright and dark field observations. By using polarization filters, the agarose core could be clearly defined from the rest of the particle. Photographs were taken using a Sony SLT-A37 digital camera (Sony, Minato, Tokyo, Japan).

3. Results and Discussion

3.1. Microfluidic Arrangement

Co-flow devices are widely used in the preparation of particles in higher micrometer ranges and have been well described [16]. The specific apparatus employed in this study is depicted schematically in Figure 1.

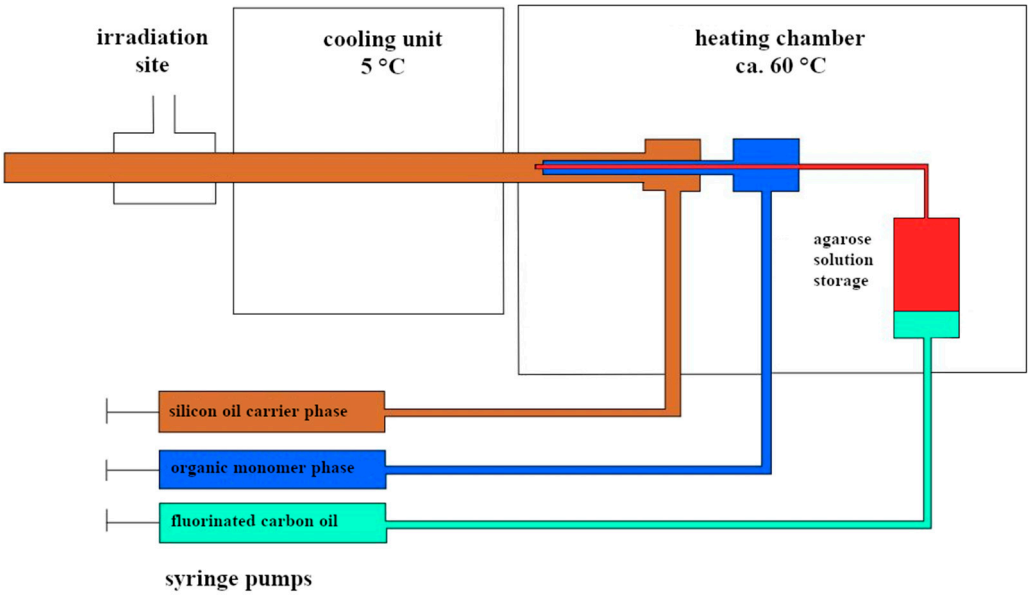


Figure 1. Sketch of the microfluidic device.

The co-flow arrangement was placed inside a heating chamber. The silicone oil carrier fluid flowed through a glass tube of 1.5 mm inner width where, in the center, the outer capillary was placed, which piped the monomer solution for building the particle shell. It consisted of a metal having an inner diameter of 600 µm. Again, in its center, a fused silica capillary of 250 µm width was placed to inject the agarose solution into the particle core. The chamber temperature was set to 60 °C, which is well above the sol–gel temperature of the agarose, ensuring that the agarose sol is of low viscosity during droplet generation. Since the pumping equipment was placed outside the heating chamber, fluorinated carbon oil was used as a mediator between the pump and the warm agarose sol. Silicone oil 500 cSt was chosen as the carrier liquid based on earlier studies [18]. It is well suited for water-based droplets due to immiscibility with water and its similar density, which prevents the droplets from going up or down after leaving the capillary. A moderate viscosity works best with the dimensions of the device parts used.

Flow rates were chosen in a way that the monomer solution leaving the outer capillary comes along with the inner agarose droplet, building a layer around it, before the whole

droplet tears off of the capillary due to the pull effect of the carrier fluid. Figure 2 shows an image of the geometry of the capillaries and the droplets formed.

Figure 2. Detailed view of the capillary geometry and droplet formation.

Droplets were connected from the heating chamber to an aluminum block kept at a temperature of 5 °C. Thus, the particle core turned solid (sol–gel transition), while the shell still remained liquid. In the subsequent irradiation unit, the particle shell was cured by polymerization and it solidified eventually, which is below the transition temperature of the thermoresponsive polymer. The microgel composite particles formed left the apparatus and were collected.

3.2. Core and Shell Materials

Both the core and shell of the particles should be hydrophilic and swellable. Thus, the materials have to be chosen carefully in order to ensure that they do not mix and dissolve during particle synthesis.

It is important that the material used for the core turns into the gel state at rather low temperatures and then builds up high strength. All tested agarose types have melting temperatures above 90 °C. Finally, agarose 0169 (1–2% in water) was favored and used for most of the studies. On cooling, the sol keeps the low viscosity down to around 45 °C. This wide temperature hysteresis until re-solidification ensures reliable and safe processing and handling. At room temperature, the gel has sufficient strength. In addition, agarose A4018 was also used.

Also, a suitable polymer system for the particle shell had to be selected and optimized. For thermosensitivity, N-isopropylacrylamide (NIPAM) was chosen as a base monomer and combined with a crosslinker. It is well known that a non-crosslinked polymer (PNIPAM) above its LCST (lowest critical solution temperature) of ca. 33 °C precipitates from an aqueous solution [20]. Crosslinked PNIPAM, on the other hand, is not soluble in water but absorbs a significant amount of water, thereby forming a clear gel, which behaves similarly. When it is heated above the VPTT (volume phase transition temperature), it collapses and becomes hydrophobic.

Water in its pure form cannot be used as a solvent for the monomers because it instantly merges with the agarose core. In fact, the solvent has to have a limited solubility in water so that it can be washed out of the particles later on in the process and replaced by water. This is necessary since the thermoresponsive effect takes place only in water. Furthermore, it must not interfere with the polymerization (e.g., chain transfer reactions) process and must form a stable gel with the polymer. To meet these requirements, a series of relevant fluids were examined in bulk polymerization tests (Table 1), where tert-amyl

alcohol turned out to be best-suited. However, pure tert-amyl alcohol was not suitable for microfluidic droplet generation due to low interface tension between the monomer solution and silicone oil carrier. Instead of definite droplets only a thin thread was formed. This behavior was overcome by adding a share of water to the monomer mixture. A mixture of 80% tert-amyl alcohol and 20% water (*v*:*v*) showed optimum results. As a result, the photoinitiator could be changed to a water soluble one (Li-TPO).

Table 1. Performance of solvents in polymerization experiments: monomer 0.99 M N-isopropylacrylamide, crosslinker 0.036 M N,N′-methylenebisacrylamide, and photoinitiator 0.013 M irgacure 819.

Solvent	Solubility in Water (g/L) [1]	Result of Polymerization
n-butanol	77	sticky gel
tert-amyl alcohol	118	firm gel
n-hexanol	5.9	soft gel
cyclohexanol	40	viscous solution
cyclohexanone	103	liquid unchanged

[1] Data from ref. [21].

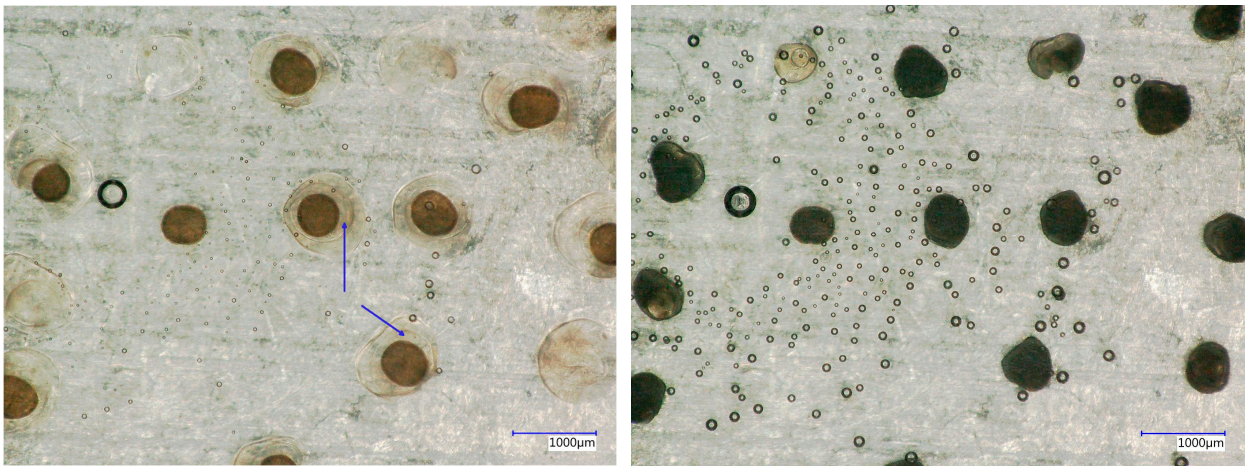
Monomer composition governs the swelling behavior of the polymer network and its mechanical and thermoresponsive properties. In analogy to the solvent tests, the impact of crosslinker type and concentration on polymer properties were studied in bulk polymerization experiments. In Table 2, these data are summarized, showing good results in experiments 2, 4, 6, and 8, which produced only a slight extra swelling (1.3–1.8), when the organic solvent was replaced by water. This keeps the hydrogel mechanically stable. As expected, the gels formed are firmer when crosslinker concentrations are higher. Butanedioldiacrylate (BDDA), compared to MBBA, has a stronger effect in this respect. At the same time, it lowers the transition temperature. For subsequent studies, we concentrated on compositions related to number 8.

Table 2. Polymer properties in dependence of monomer composition: solvent tert-amyl alcohol/water 4:1 (*v*:*v*), monomer N-isopropylacrylamide (NIPAM), crosslinker methylenebisacrylamide (MBBA), tripropylene glycol diacrylate (TPGDA), 1,4-butanediol diacrylate (BDDA), ethylene glycol dimethacrylate (EGDM), and photoinitiator 0.015 M Li-TPO.

	Monomer Composition				Polymer Properties		
ID	NIPAM (mol/L)	Cross-Linker	mol/L	Molar Ratio	Mass Increase after Swelling	Water/Polymer Ratio in Swollen State	Thermo-Responsive y/n (VPTT)
1	1.96	MBBA	0.050	0.025	3.36	11.9	y (33 °C)
2	1.71	MBBA	0.076	0.045	1.79	12.2	y (34 °C)
3	1.72	MBBA	0.038	0.022	6.17	42.7	y (33 °C)
4	1.96	MBBA	0.149	0.076	1.72	5.6	y
5	1.73	TPGDA	0.040	0.023	3.17	22.4	y
6	1.74	TPGDA	0.059	0.034	1.57	10.6	y
7	1.73	EGDM	0.061	0.035	8.91	64.6	y
8	1.73	BDDA	0.061	0.035	1.29	8.5	y (<26 °C)
9	1.72	BDDA	0.046	0.027	0.95	6.0	y

3.3. Generation and Properties of Particles

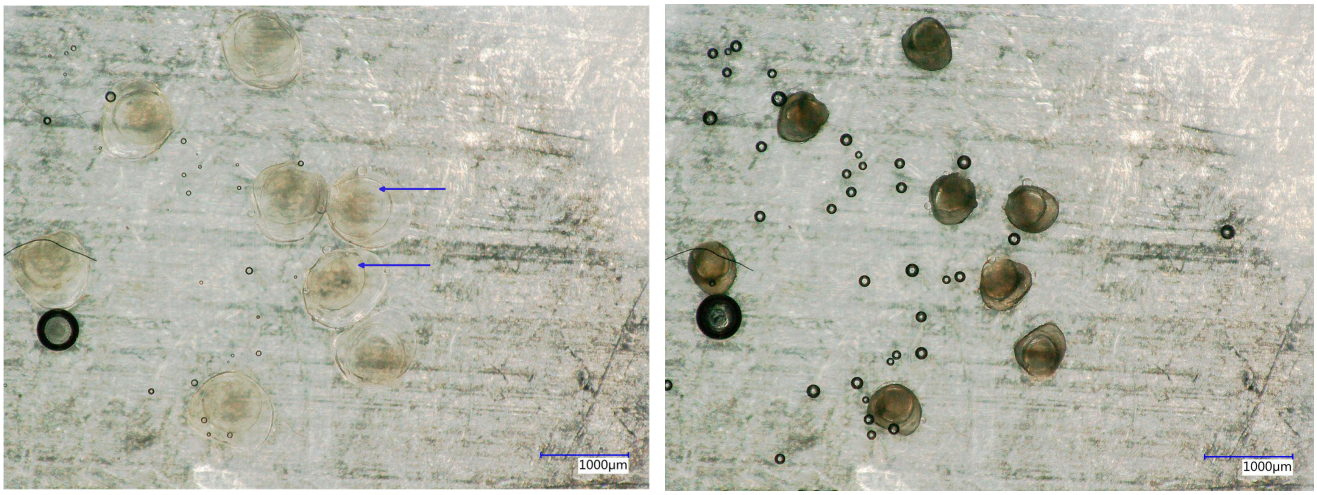
By using the microfluidic arrangement and the core and shell materials as described above, flow rates were optimized for particle production. The core phase favors particle generation. It easily forms compact droplets due to its higher surface tension, with the shell phase enclosing them when it emanates from the outer capillary simultaneously. In this way, optimized flow rates of 200/20/5 µL/min (carrier/shell/core) were obtained, and composite particles of various shell compositions were produced. These particles show thermoresponsive behaviors. When heated, the particle shell shrinks, releasing water to the environment, as shown in Figure 3.



(**a**) (**b**)

Figure 3. Microscopic images of composite particles with shells of PNIPAM crosslinked with MBBA (**a**) at 26 °C and (**b**) 38 °C, respectively. NIPAM 0.93 M, MBBA 0.076 M, and dark agarose cores; arrows indicate the voids between the core and shell.

With this basic NIPAM-MBBA system, however, the mechanical strength of the shell and adhesion to the core are rather poor. During production (immersion and swelling in water), a water-filled void develops between the core and shell that may subsequently even cause the core to fall out of the shell. An improvement was achieved with the partial replacement of NIPAM by acrylamide. Acrylamide is known to produce firm gels, which are widely used in bio sciences, e.g., for the preparation of electrophoresis gel plates. On the other hand, the crosslinked pure AA gels are not thermoresponsive. Thus, in our system, acrylamide improves gel strength but changes thermal transition as well. Replacing 1/3 weight of NIPAM by AA (i.e., 0.62 M NIPAM and 0.49 M AA) causes complete loss of thermosensitivity. By replacing 1/6 (0.78 M/0.25 M) and 1/12 (0.85 M/0.12 M), VPTT is increased to >56 °C and 38 °C, respectively. Using BDDA, instead of MBBA, as a crosslinker, the mechanical strength is further improved, while VPTT reduces to 33 °C, as shown in Figure 4. Nonetheless, despite all these measures, the voids still occurred.



(**a**) (**b**)

Figure 4. Microscopic images of composite particles with improved shells at (**a**) 26 °C and (**b**) 38 °C, respectively. NIPAM 0.85 M, AA 0.12 M, BDDA 0.076 M, and dark agarose cores; arrows indicate the voids between the core and shell.

In Figure 5, the relative changes in size with temperature for composite particles of varying shell composition are plotted. While MBBA crosslinked NIPAM, independently of monomer concentration, it shows a quite sharp size change at ca. 33 °C. This effect is mitigated upon the partial replacement of NIPAM by AA (Figure 5a,b).

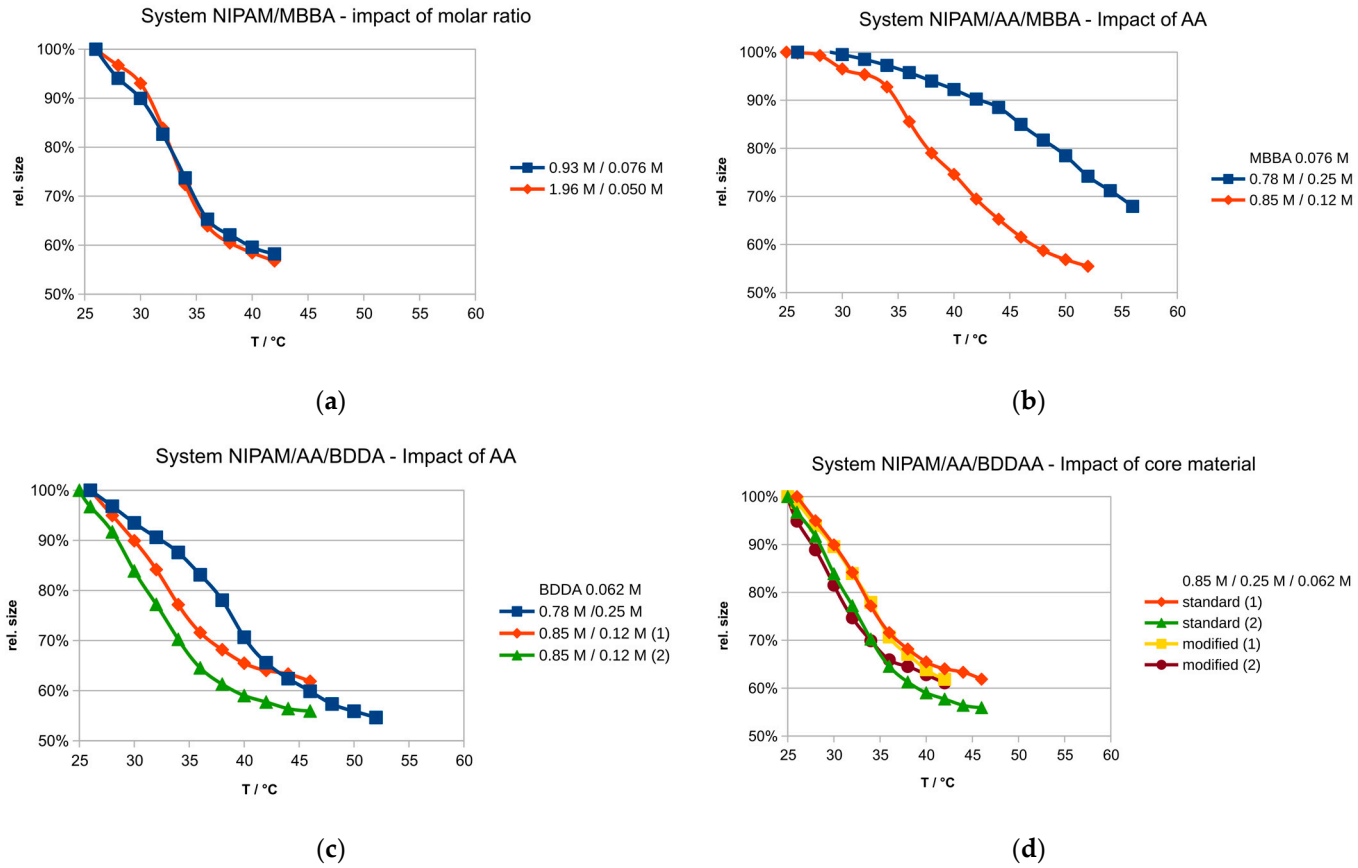
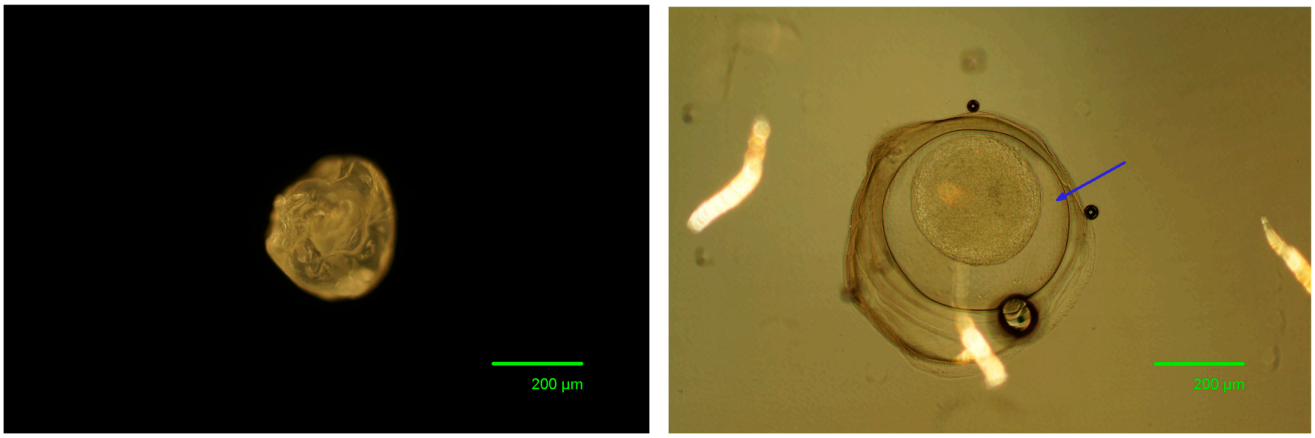


Figure 5. Relative change in particle diameter with temperature depending on shell and core composition. (**a**) Shell system NIPAM/MBBA—variation in NIPAM/MBBA molar ratio, (**b**) shell system NIPAM/AA/MBBA—variation in NIPAM/AA molar ratio at constant [MBBA], (**c**) shell system NIPAM/AA/BDDA—variation in NIPAM/AA molar ratio at constant [BDDA], and (**d**) shell system NIPAM/AA/BDDA—variation in core composition. Standard core (**a**–**d**) 1% agarose 0169 and modified core (**d**) 2% agarose 4018 + 5% gelatin G9391 + 3% trehalose.

When BDDA is used as a crosslinker, the addition of AA has the same effect but is less pronounced (Figure 5c). In Figure 5d, the effect of using a modified agarose core (2% agarose 4018 + 5% gelatin G9391 + 3% trehalose) are shown in comparison to the standard (1% agarose 0169). A higher percentage of solids in the core was chosen to enhance the stability after drying and re-swelling. Compared to the standard core, there is no significant impact in terms of thermal behavior. Figure 6 shows a composite particle with an even higher modified core in the dried and re-swollen states.

The re-swollen particles remained in good shape. They looked very much the same like prior to desiccation. The void space between the core and shell is clearly visible when viewed under polarized light.



(**a**) (**b**)

Figure 6. Microscopic images of a composite particle (**a**) in the dried state (3 d drying above silica-gel; dark field image) and (**b**) 80 min after subsequent immersion in water (transmitted light with polarization filter; arrow indicates the void between the core and shell). Core—2% agarose 4018 + 1% gelatin G9391 + 27% trehalose; shell—NIPAM 0.85 M + AA 0.12 M + BDDA 0.062 M.

4. Conclusions

Utilizing carefully selected materials makes it possible to produce composite particles in one step, which consist of hydrogels both in the core and the shell. Shells constructed using thermoresponsive materials allow for switching the particles' hydrophilic and hydrophobic properties on the outside by heating. Such particles have the potential for the controlled uptake of water-soluble materials, such as biomolecules, to their shell from the environment and subsequent release to the core for further treatments like analytical reactions. Moreover, the switching from hydrophilic to hydrophobic stage may facilitate phase transition of the particles from an aqueous to an organic environment. The presented method in principle is not restricted to agarose/NIPAM, i.e., thermoresponsive materials. Other material combinations can also be potentially used. The key ideas for particle construction can be summarized as follows:

- Liquid solutions for core and shell materials must have poor or no miscibility with each other and with the carrier fluid;
- The carrier should be chosen for best particle geometry; i.e., viscosity, density, and interfacial tension have to be selected or adjusted;
- Core and shell materials must allow for fast solidification (during temperature change, irradiation, etc.);
- Solvents should be easily removable, if required (by diffusion, evaporation, etc.).

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Conflicts of Interest: Author Thomas Ellinger was employed by the company BLINK AG. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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