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Thermosensitive nanospheres of low-density core – An approach to hollow nanoparticles

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Abstract

A novel strategy for the preparation of hollow core–shell nano- and microparticle is reported. Nanoparticle cores were created from poly(*N*-isopropylacrylamide) (PNIPAM) by controlled heating above the LCST of this polymer in the presence of a small amount of sodium dodecyl sulfate. Shells were formed by radical copolymerization of 2-hydroxyethyl methacrylate (HEMA) and poly(ethylene glycol) dimethacrylate (PEG-DMA) as cross-linking agent. The PNIPAM particles were acting as nucleating agents so that core–shell colloidal particles of PNIPAM covered with cross-linked PHEMA resulted. Subsequent release of a part of the PNIPAM chains from the interior of the particles was obtained by dialysis. The sizes and the temperature behavior of obtained particles were measured by DLS, TEM and SEM. The semi-hollow particles showed reversible volume response to cyclic temperature changes.

Keywords: Nanocontainer; Thermosensitive template; HEMA shell

1. Introduction

Polymeric hollow nano- and microcontainer has a variety of applications such as in medical therapy, materials science, and the paint industry [1,2]. The structure of the nanocapsules consists of a hollow interior surrounded by a thin wall. The size of the hollow interior as well as the wall thickness can be controlled. Compared to the polymer nano- and microsphere, the polymer nanocontainers or capsules with a hollow-sphere structure can encapsulate large quantities of guest molecules or large-sized guests within the empty core domain.

In recent years, considerable progress has been made in the development of synthetic methods for the preparation of hollow nano- and microparticle. Various methods such as the self-assembly of block copolymers in a selective solvent [3–5], layer-by-layer deposition of polyelectrolytes on a sacrificial core [6,7] and miniemulsion polymerization [8–10] have been developed to fabricate hollow polymeric spheres. The method most frequently used to prepare hollow particles is to coat a sacrificial core particle with a shell and then to destroy the core. Most of the proposed applications of the hollow nanospheres are concentrated in the biomedical area; the majority of the polymeric capsules described up to now is not well-suited for this type of applications. They load and release guest molecules from their interior only by diffusion. It is therefore rather difficult to control either the loading or the release process. In addition, there are only a limited number of reports which address the diffusion of chemical agents across the shells of the hollow particles [11]. The final goal has been always focused on the preparation of pure well defined and monodispersed in size nano- and microcapsule whereas the problems with loading and release were practically always ignored [12]. The drawback of the current methods of loading is the inability to encapsulate large compounds, such as proteins and DNA molecules. This drawback can be overcome by loading such large molecules while the hollow particles are being synthesized provided the conditions are sufficiently mild for the molecules to retain their biological activity. The

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development of suitable methods for overcoming these problems will open the door to considerably more diverse application opportunities than that are available at present.

Lately Lyon et al. [13,14] and Richtering et al. [15,16] have reported the synthesis of microgel particles with core–shell morphologies. The core template in their studies was composed of cross-linked poly(*N*-isopropylacrylamide) (PNIPAM). The shell was obtained by radical polymerization and simultaneously cross-linking of acrylic acid or *N*-isopropylmethacrylamide.

In our work we explore the formation of nanoparticles by phase separation of linear PNIPAM aqueous solutions upon heating [17]. PNIPAM is the most studied water soluble thermosensitive polymer which precipitates out of water when the solution is heated above its lower critical solution temperature (LCST) of about 33 °C [18]. The almost ambient temperature of the LCST of PNIPAM makes it an attractive candidate for studying transitions of molecular structures from hydrophilic to hydrophobic nature. Moreover the transitions were found to be rather abrupt [19]. Under some conditions it was observed that when the dilute aqueous solutions of PNIPAM were heated above its LCST, the colloidal spherical particles – mesoglobules of the sizes between 60 nm and 300 nm in diameter, were created [20,21]. Also in the presence of a small amount of sodium dodecyl sulfate (SDS) and at temperatures above the precipitation temperature the PNIPAM macromolecules collapse to form small colloidal particles [22,23].

Our objective is to develop a novel strategy (Scheme 1) for the preparation of hollow nano- and microparticle through a combination of PNIPAM phase transition followed by shell formation through seeded radical copolymerization and the subsequent release of PNIPAM by dialysis. This will open a pathway for the preparation of mechanically stable polymeric capsules with a wide range of size and shape. The method has the advantages that the PNIPAM template may easily be removed from the matrix under very mild conditions. Nano- and microcapsule of a different size would be readily obtained by adjusting the size of the template particle. A wide range of thermoresponsive polymers and copolymers can be used as the initial core constituents or templates. The major advantage of this method is that it will allow the loading of biologically active substances (enzymes, proteins, RNA or DNA) to occur already during the first stage of the process through the formation of initial core nanoparticles consisting of PNIPAM and PNIPAM block copolymers, which are able to carry biomacromolecules [24,25].

Here we report the results from a series of preliminary experiments to fabricate semi-hollow nanoparticles. Microspheres with low-density core were obtained via template radical copolymerization of 2-hydroxyethyl methacrylate (HEMA) and poly(ethylene glycol) dimethacrylate (PEG-DMA) onto the surfactant/PNIPAM colloidal particles' surface and subsequent partial dissolution of the core.

2. Experimental

2.1. Materials

The following chemicals (all purchased from Sigma–Aldrich with exception of 2-hydroxyethyl methacrylate (HEMA) (Fluka) and acetone (POCH)) were used in this study: poly(*N*-isopropylacrylamide) (PNIPAM) $M_n = 20\,000$ g/mol (Aldrich) (according to our SEC-MALLS measurements in DMF – $M_n = 84\,000$ g/mol), poly(ethylene glycol) dimethacrylate (PEG-DMA) $M_n = 330$ g/mol, sodium dodecyl sulfate (SDS) 99+%, 2-hydroxyethyl methacrylate (HEMA), potassium persulfate (KPS) 99.99%. HEMA was distilled under vacuum and kept in a refrigerator before use. The other commercial chemicals were of reagent grade and used as-received without further purification. Water for the polymerizations was filtered through 200 nm PTFE filter and 20 nm cellulose filter. In the dialysis procedure deionized water was used.

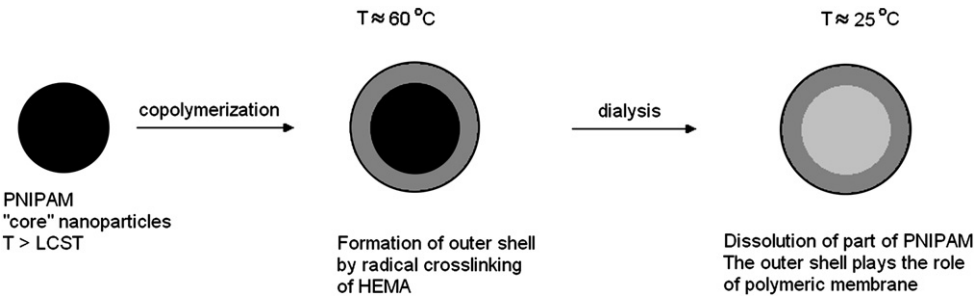
2.2. Synthesis of the nanoparticles

2.2.1. Preparation of the core template

The procedure was followed as described by Lee and Cabane [22]. Mesoglobules of PNIPAM were obtained in the presence of a small amount of surfactant, sodium dodecyl sulfate. PNIPAM (1 g/L) and SDS (0.05–0.55 g/L) were separately dissolved in water at room temperature, then the aqueous solutions were combined, stirred and immersed into oil bath heated beforehand to 70 °C. The solution was stirred for 1 h. The size of the particles was estimated by DLS. Once formed, the core template solution was kept at 70 °C until the start of shell formation. Different cores obtained are described as C_1, C_2 and C_3.

2.2.2. Preparation of core–shell particles

Aqueous solutions of HEMA (1.0–4.0 g/L) and PEG-DMA (0.2 g/L or 0.4 g/L) were added into the flask containing the



Scheme 1.

bluish colloidal template solution under nitrogen. After 20 min of extensive nitrogen purging, aqueous solution of KPS (0.5 g/L) was added. The flask was purged again with nitrogen, closed and left for polymerization at 70 °C.

The particles are stable in aqueous medium at temperatures higher than the phase transition temperature of PNIPAM. It was shown that their sizes almost did not change in an interval of 2 months.

Table 1 presents the preparation conditions of the core–shell particles. The names of the samples are abbreviated as follows C_xP_y, where C_x is the core used and P is related to different polymerization conditions in the shell forming process.

2.2.3. Preparation of PHEMA capsules

The core–shell particles were extracted by dialysis (Spectra/Pore MWCO:50000 dialysis membrane with cut-off of 50 000 Da) against deionized water at 5 °C for 1 month. The water was changed 2 times per day.

2.3. Characterization

2.3.1. Size exclusion chromatography (SEC)

SEC measurements of PNIPAM were carried out on the following column system: guard (Polymer Laboratories) + GRAM 100 Å (Polymer Standards Service) + 2 × Mixed-C (Polymer Laboratories) with refractive index detector Δn-2010 RI WGE Dr. Bures and a multiangle light scattering detector DAWN HELEOS of Wyatt Technologies ($\lambda = 658$ nm). Measurements were performed at 45 °C in DMF with a nominal flow rate of 1 mL/min.

dn/dc value for PNIPAM in DMF was 0.075 mL/g (independent measurements). SEC results were collected and evaluated by ASTRA IV software from Wyatt Technologies.

2.3.2. ^1H NMR

The ^{1}H NMR spectra were recorded at 25 °C on a Varian Unity-Inova spectrometer operating at 300 MHz by using $CDCl_3$ as a solvent.

2.3.3. Dynamic light scattering (DLS)

DLS measurements were performed on a Brookhaven BI-200 goniometer with vertically polarized incident light of wavelength $\lambda = 632.8$ nm supplied by a He–Ne laser operating at 75 mW and a Brookhaven BI-9000 AT digital auto-correlator. The samples were kept for 1 h at particular temperature (60 °C or 25 °C) in the measuring cell before data collecting. The scattered light was detected at 90° with an integration time of 120 s. The autocorrelation functions were analyzed by BIC DLS software v3.36 using the constrained regularized algorithm CONTIN [26]. The hydrodynamic apparent radius R_h^{90} was obtained.

The dispersity of particles sizes was given as $\mu^2/\overline{T}^2$ where $\overline{T}$ is the average value of relaxation rates (gamma) and μ^2 is their second moment.

Table 1
Synthetic recipes for the preparation of PNIPAM/PHEMA core–shell particles in water at 70 °C

Particle code	Core		Shell			Water [mL]	Polym. time [h]
	PNIPAM [g]	SDS [g]	HEMA [g]	PEG-DMA [g]	KPS [g]		
C_1P_1	0.07	0.014	0.07	0.014	0.035	70	24
C_1P_2	0.07	0.014	0.07	0.014	0.035	70	48
C_2P_1	0.03	0.006	0.03	0.006	0.015	30	24
C_2P_2	0.03	0.006	0.12	0.006	0.015	30	24
C_3P_1	0.03	0.006	0.03	0.012	0.015	30	18
C_3P_2	0.03	0.006	0.06	0.012	0.015	30	18
C_3P_3	0.03	0.006	0.09	0.012	0.015	30	18

2.3.4. Scanning electron microscopy (SEM)

SEM was used to characterize the particles' morphology and was performed with a JEOL JSM-5510 scanning electron microscope operating at 10 kV. A drop of water solution of core–shell nanoparticles before and after dialysis was deposited on a glass substrate, dried and coated with gold for 60 s.

2.3.5. High-resolution field emission scanning electron microscopy (FESEM)

FESEM images ware performed with an Ultra-high-Resolution Field Emission Scanning Electron Microscope S-4800 Hitachi model, equipped with TEM detector. Scanning electron microscopic images were recorded with an accelerating voltage of 30 kV.

3. Results and discussion

3.1. Stable colloidal dispersions of PNIPAM

At first our goal was to establish a protocol for the preparation of stable PNIPAM particles of a controlled size.

PNIPAM used was measured by SEC in DMF/LiBr using MALLS detector. The SEC indicates $M_n = 84\,000$ g/mol (dn/d$c = 0.075$) and $M_w/M_n = 1.72$, which is different from the nominal value indicated by the supplier. This may be due to the formation of aggregates, as reported in Refs. [27,28].

Gorelov et al. [21] obtained stable colloidal particles from pure PNIPAM and called these particles mesoglobules thus indicating that each particle consists of many collapsed polymer chains. Aseyev et al. prepared mesoglobules from PNIPAM and showed that the PNIPAM particles formed have quite regular spherical shape [20]. Once formed, the mesoglobules are very stable with time at temperatures higher than the LCST.

For the formation of PNIPAM mesoglobules above the LCST we used the method described in Refs. [17,22]. The polymer solution contains added different amounts of charged surfactant (SDS). This method leads to smaller particles than those obtained without surfactant addition.

Experiments performed allowed us to carefully control the size and the size distribution of the PNIPAM particles formed by immersing aqueous solutions of PNIPAM and SDS into oil bath heated beforehand to 70 °C. This temperature is much higher than the phase transition temperature, however, it is quite convenient for carrying out radical polymerization to coat the particle surface. The colloidal PNIPAM particles are stabilized

by the charged surfactant. Solutions of varying SDS concentrations were prepared at ambient temperature. Then SDS solution was mixed with the solution of PNIPAM. The resulting PNIPAM concentration was 1 g/L, which is less than the overlapping concentration c^*. Therefore the solutions can be considered dilute with respect to the polymer [29]. The concentration of SDS varied between 0.05 g/L and 0.55 g/L whereas the critical micelle concentration of SDS in water is 2.3 g/L [30].

Without the surfactant additive our PNIPAM solutions were macroscopically phase separated at 70 °C: a white solid of PNIPAM was observed. As seen in Fig. 1 at SDS concentration in the range 0.05–0.55 g/L the PNIPAM macromolecules collapse to form colloidal particles.

The particles have a relatively narrow, monomodal size distribution. The size of the particles diminishes by increasing the SDS concentration. Since the experiments were performed at a constant PNIPAM concentration of 1 g/L, the concentration of SDS is equal to the surfactant/polymer ratio (*S*/*P*, g/g). At concentrations higher than 0.55 the R_h^{90} of the particles decreases to 10 nm, which is in agreement with reported SANS studies on the role of the SDS additive in the formation of PNIPAM colloidal solutions [22]. At higher SDS concentrations the colloidal particles dissolve and turn into a solution of ''necklaces'', what leads to stretching of PNIPAM chains.

Obviously, by applying an appropriate solution composition and *S*/*P* ratio we were able to control effectively the size of the PNIPAM template. By lowering the temperature to 25 °C, the particles of PNIPAM covered by SDS do not dissolve fully (Fig. 2) even after conditioning the samples at 11 °C for 2 weeks.

The second heating leads to the same abrupt collapse of the PNIPAM chains. As a result a reversible formation of small colloidal nanoparticles of the same size was observed.

3.2. Formation of cross-linked hydrophilic shell

Recently the use of various polymerization methods, which allow the growth of polymer chains on the surface of nano- or

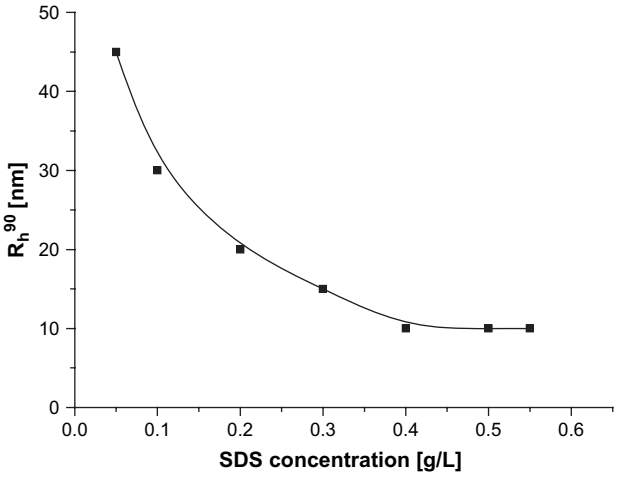


Fig. 1. Hydrodynamic radius R_h^{90} of PNIPAM/SDS mesoglobules as a function of the surfactant concentration at 60 °C. $C_{PNIPAM} = 1$ g/L.

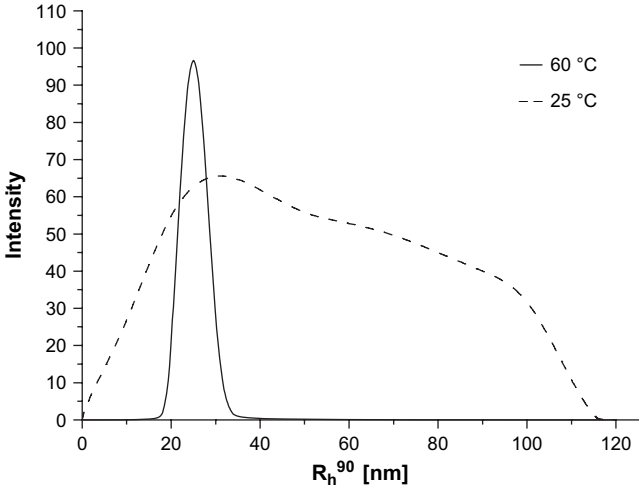


Fig. 2. Hydrodynamic radius R_h^{90} distribution of the PNIPAM/SDS mesoglobules (sample C_3) at 60 °C and 25 °C. $C_{PNIPAM} = 1$ g/L; $S/P = 0.2$.

microparticle has been intensively studied [12,14,31–33]. One obvious prerequisite for the formation of a layer onto the particles is the presence of a large number of primary particles in the solution so that the final particles will be small enough to be colloidally stable (generally on the order of <1 μm). In many cases SDS has been proven to be effective for further stabilization of the resulting particles.

The radical surface copolymerization of HEMA and PEG-DMA as cross-linker was used to produce the outer hydrophilic shell of the PNIPAM nanoparticles. PHEMA was chosen because $-OCH_2CH_2OH$ prevents flocculation of the particles. On the other hand PHEMA has good biocompatibility and has been widely used in biomedical applications. The polymerization was initiated by the hydrophilic KPS radical initiator. The polymerization was expected to take place at the periphery of the PNIPAM mesoglobules but the KPS radicals are too hydrophilic to adsorb on the PNIPAM surface. In this case the polymerization will proceed in the aqueous phase resulting in HEMA oligomers with increasing hydrophobicity since it is well known that water is a poor solvent for linear PHEMA. Once the oligomers are hydrophobic enough, they can adsorb and collapse on the nanoparticle surface as PHEMA is insoluble but swellable in water. The first PHEMA layer formed will further trap the monomer and the cross-linker away from the aqueous phase so that the polymerization will continue and the shell will grow. The resulting properties of the particles are summarized in Table 2.

The progress of the polymerization reaction was followed visually. When the initial PNIPAM/SDS mesoglobules were formed at 70 °C (Fig. 3a) the colloidal aqueous solution turned bluish.

During the copolymerization of HEMA and PEG-DMA initiated by KPS the solution turned slightly cloudy and then became a white colloidal dispersion. DLS analyses provided the information on the hydrodynamic particle size. The monomodal distribution, low dispersity of the nanoparticle population and no evidence of the presence of huge particles in the investigated solution after the copolymerization (Fig. 3b) indicate

Table 2
Parameters describing the size and the volume change of the core–shell nanoparticles

Sample	T_{DLS}[a] [°C]	R_h^{90} [nm]	$V_{particle} \times 10^4$ [μm^3]	Dispersity	Swelling ratio[b] V_{25}/V_{60}
C_1	60	55	6.96	0.031	
C_1P_1	60	61	9.50	0.045	1.26
C_1P_1	25	66	12.03	0.060	
C_1P_2	60	62	9.97	0.047	1.63
C_1P_2	25	73	16.28	0.064	
C_2	60	40	2.68	0.033	
C_2P_1	60	43	3.32	0.050	1.22
C_2P_1	25	46	4.07	0.061	
C_2P_2	60	50	5.23	0.064	87.62
C_2P_2	25	222	458.29	0.121	
C_3	60	24	0.58	0.042	
C_3P_1	60	34	1.64	0.046	1.39
C_3P_1	25	38	2.29	0.065	
C_3P_2	60	44	3.56	0.044	13.20
C_3P_2	25	104	47.09	0.081	
C_3P_3	60	48	4.63	0.044	52.76
C_3P_3	25	180	244.29	0.092	

[a] Temperature of measurements (DLS).
[b] Particle volume at 25 °C (V_{25}) and 60 °C (V_{60}).

that the polymer formed at the second stage grows preferentially around the existing PNIPAM particles, which act as nuclei for further polymerization [13]. For the particles C_1P_1 TEM image is shown in Fig. 4.

Since PNIPAM is a thermosensitive polymer, an increase in the particle size at ambient temperature is expected. Indeed, the DLS measurements reveal that the lower temperature leads to an increase in the hydrodynamic radius of the particles. At 25 °C the PNIPAM core swells and expands in volume (Fig. 2) while PHEMA alone has no thermoresponsive properties. The swelling ratio of most dense cross-linked shells at 25 °C and 60 °C (V_{25}/V_{60}) rises up to 1.6 only and differs significantly from the swelling ratio of cross-linked PNIPAM microgels (3–7) [15]. Obviously, when the PNIPAM particles are covered by PHEMA shell, the expanding core pushes the shell outward. This expansion, however, is limited by a mechanical stress in the shell. Therefore the swelling ratio of the pure parent PNIPAM is not reached. The balance between the core expansion and the mechanical stress in the shell is affected by

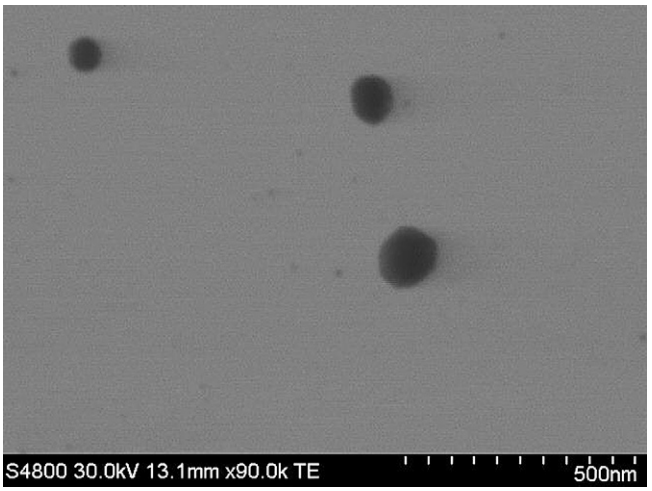


Fig. 4. TEM image of the sample C_1P_1.

the shell thickness. Thus, the swelling behavior of the core–shell nanoparticles can be controlled by the amount and the cross-link density of the PHEMA shell. It could be expected that a reduced shell thickness will lead to a higher swelling ratio of the entire particle and that the swelling ratio will increase at a lower cross-link density of the shell.

It is worth noting that the core–shell particles at 60 °C represent a combination of a hard hydrophobic PNIPAM spherical core and a swollen hydrophilic shell whereas at 25 °C the core swells and the volume of the PHEMA shell will not change significantly [34]. Core–shell particles with different PHEMA shell thicknesses were prepared (Table 2). The thickness of the PHEMA shell varied while the cross-linker content remained constant. Thus the cross-link density was gradually changed. The particle size increased with increased amount of PHEMA shell in both the collapsed and the swollen states.

In Table 2 the influence of the shell thickness and cross-link density on the thermal response is illustrated. It was shown that with increase of the monomer concentration the thickness of the shell increases (Samples C_3P_1, C_3P_2, C_3P_3). The comparison of the results given in Table 2 for differently cross-linked shells shows significant increase of swelling ratio with the decreasing cross-link density.

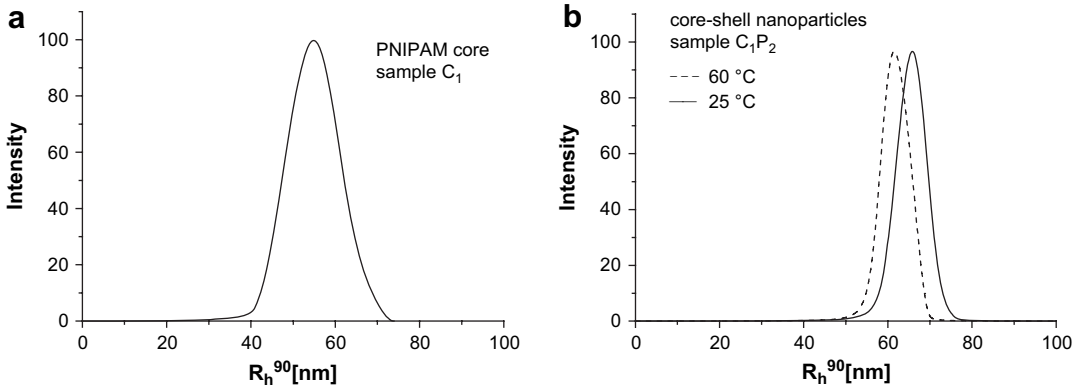


Fig. 3. Hydrodynamic radius distribution of (a) C_1 at 60 °C and (b) C_1P_2 at 25 °C and 60 °C.

Due to the constant concentration of the cross-linker and the increased amount of HEMA, the synthesized shells display a quite different cross-link density. Wide-meshed outer shells are more flexible which leads to loss of core compression. The less cross-linked PHEMA shell of C_2P_2 exhibit an unusually large particle swelling ratio of about 87, much higher than the ratio observed for PNIPAM microgels [15]. Obviously, in this case the expansion force of the swelling core prevails over the elastic mechanical stress of the shell.

When prepared nanoparticles are stored in water solution they tend to swell, which is shown in Fig. 5.

Fig. 5 presents the hydrodynamic radius of sample C_1P_1 just after polymerization and after 1 month of storage in water. After polymerization hydrodynamic radius of the nanoparticles measured by DLS was about 66 nm at 25 °C. When particles were kept in water for 1 month their hydrodynamic radius detected by DLS was 125 nm. SEM image of the latter particles is shown in Fig. 5. SEM clearly shows that these particles are quite uniform and have a rough surface. The core–shell particles are round in shape just like the PNIPAM template. Their size and low dispersity measured by DLS agree with the SEM results.

3.3. Formation of hollow nano- and microparticles

The formation mechanism of hollow spheres is proposed in Scheme 1, where the last step represents the subsequent removal of the PNIPAM chains from the particle core by means of dialysis. It is well known that the pure PNIPAM mesoglobules are commonly dissolved in an aqueous medium below LCST as shown by Aseyev et al. [20]. Most likely the release of the PNIPAM core from the shell membrane strongly depends on the molar mass and the mass distribution of the polymer, on the permeability of the shell structure to allow the core material to penetrate, on the temperature and the additives in the aqueous environment.

The formation of the PHEMA gel hinders the diffusion of PNIPAM. The shell plays the role of a membrane where the shell thickness or density will specify and mark the molar mass range of the core polymer to be released.

In order to prepare hollow spheres the core–shell nanoparticles (C_1P_1 and C_1P_2) were dialysed for 1 month in water at 5 °C. The high PNIPAM concentration in the interior compared to that in the surrounding solution increases the osmotic pressure and thus leads to the permeation of water into the core domain, which results in swelling and expansion of the core.

The presence of PNIPAM in the water out of membrane was confirmed by ^{1}H NMR spectrum of the product extracted from water. According to the elemental analysis (nitrogen content before and after analysis) only about 42% of PNIPAM was removed in both samples independent of their different swelling behavior shown in Table 2.

Because PNIPAM cannot be fully removed from the interior of the particles they exhibit the temperature sensitive behavior under the cyclic changes of the temperature.

Fig. 6 clearly shows the reversible contraction of dialysed C_1P_1 particles after repeated heating. It can be seen by DLS measurements that at 25 °C size of the nanoparticles increases to about 500 nm in diameter and the size distribution is broader than that at 60 °C. The hydrodynamic radius increased almost 2 times after cooling the particles from 60 °C to 25 °C.

The PHEMA shell acts as a hydrogel material, which is elastic and easily deformed and undergoes expansion as the core domain fills with water after the partial removal of the PNIPAM core. The extent of this expansion is significant, which suggests that the semi-hollow nanoparticles consist of soft and elastic gel shells of high porosity.

Fig. 7 presents the TEM image of dialysed particles C_1P_1 after fifth cooling–heating cycle.

The image clearly shows the difference between the shell and the particle interior. The radius of the particle shown in Fig. 7 is about 350 nm. The interior of the particles is brighter than that before dialysis (Fig. 4). The result confirms that the particles are partially empty.

The SEM of hollow particles in a dry state with a radius of approximately 300–750 nm displays the characteristic structure of collapsed hollow spheres (Fig. 8) instead of that of perfect spheres of primary core–shell particles (Fig. 5). The PHEMA shell tends to spread on the hydrophilic glass substrate leading to the large size difference. Obviously the resulting nanocapsules are not able to maintain their shape. The particles deform without coalescence after being dried

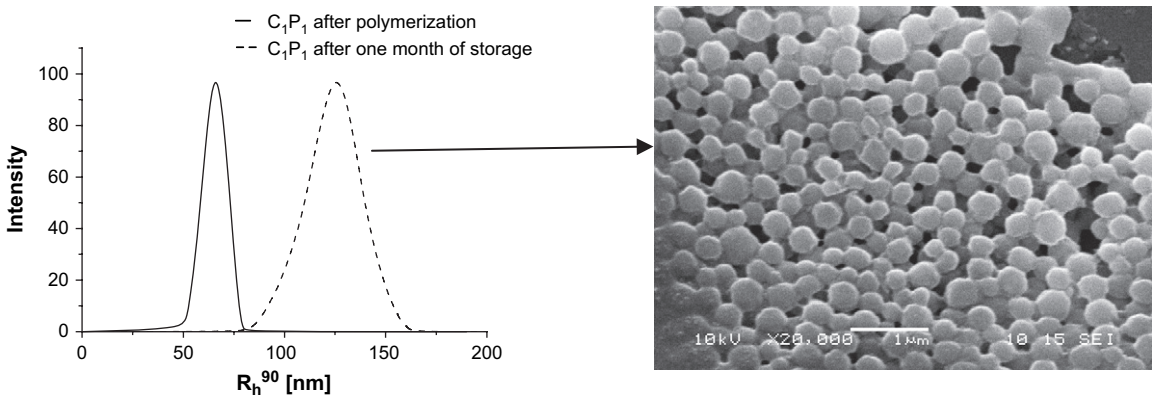


Fig. 5. Hydrodynamic radius of C_1P_1 (at 25 °C) after polymerization and after 1 month of storage in water, SEM micrograph of sample C_1P_1 after storage.

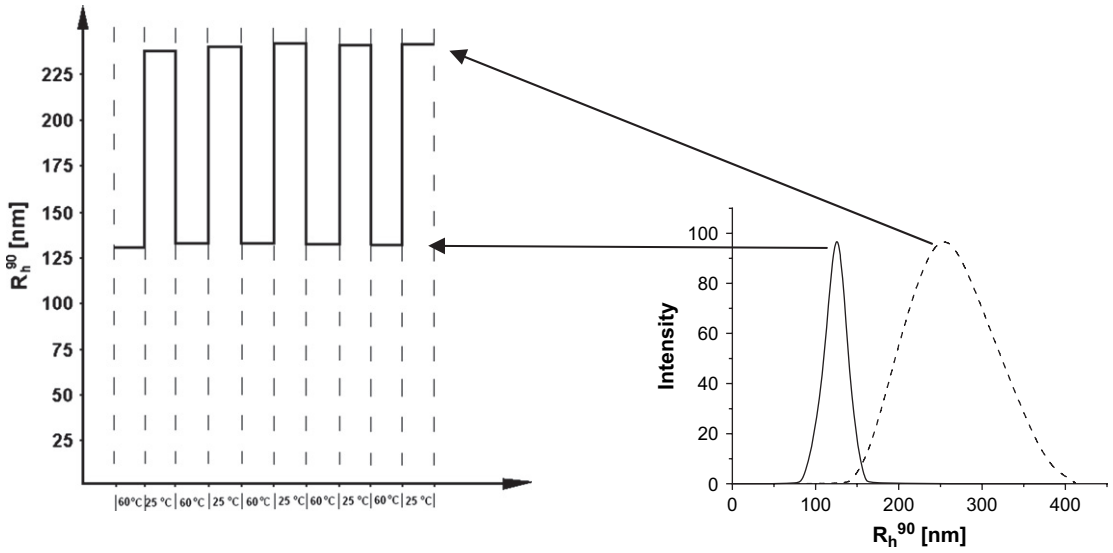


Fig. 6. Reversible volume response of the C_1P_1 particles by cyclic changes of temperature from 60 °C to 25 °C and intensity fraction distribution of particles in fifth cycle.

at ambient temperature, confirming our suggestion that their outer shell is soft and flexible. Due to the partial removal of PNIPAM chains from the core, these particles are in a collapsed state similar to a deflated balloon as described in Ref. [5]. The significant difference in morphology between the core–shell particles and the capsules could be attributed to a change in the shell properties after the partial core removal.

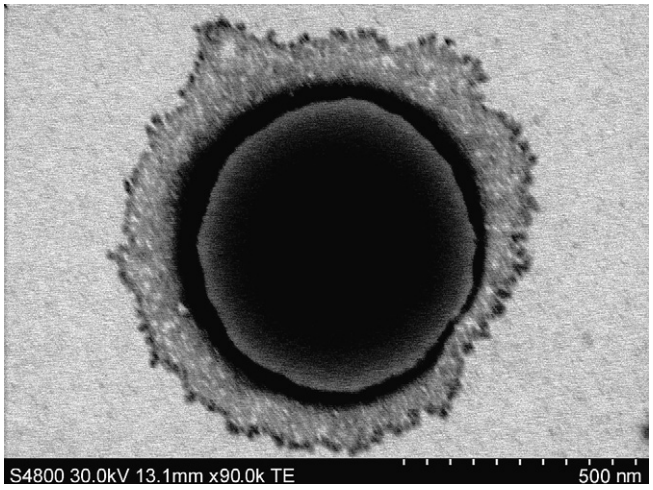


Fig. 7. TEM image of particles C_1P_1 after fifth cooling–heating cycle.

4. Conclusions

A new and simple approach to the synthesis of polymeric nano- and microcapsule in aqueous medium under very mild conditions was demonstrated. The method consists of two stages: (1) formation of PNIPAM/SDS core mesoglobules followed by seed precipitation copolymerization of HEMA and (2) release of the PNIPAM template by dialysis. Obviously, the molar mass of PNIPAM used and the cross-linking density of the PHEMA shell are important as the latter plays the role of a permeable polymer membrane. Since the first experiments of this study were performed with comparatively high molar mass PNIPAM, the release of the PNIPAM template was not fully accomplished. Thus, the produced final particles are semi-hollow with a low-density core. The method can be

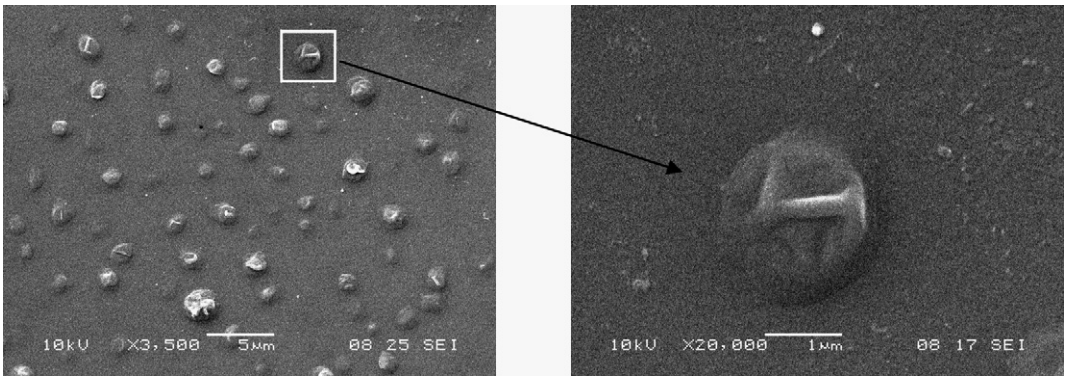


Fig. 8. Morphology of the semi-hollow capsules (sample C_1P_1 after dialysis) as revealed by SEM image.

easily employed to design a wide variety of polymeric shells surrounding a core of thermosensitive polymer while keeping control over the size of the nanostructures.

The application of this method could be extended by entrapping enzymes, proteins or DNA into the hollow particles, which could have a significant potential in the pharmaceutical and biotech industries. The method allows the loading of biologically active substances to proceed already at the first stage of the process – through formation of the initial core comprising PNIPAM and PNIPAM block copolymers which are able to carry biomacromolecules.

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