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ORIGINAL CONTRIBUTION

The influence of PEG macromonomers on the size and properties of thermosensitive aqueous microgels

Andrij Pich · Sebastian Berger · Olga Ornatsky · Vladimir Baranov · Mitchell A. Winnik

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Abstract We describe the preparation and thermal response of aqueous microgels based on poly(*N*-vinyl caprolactam) containing grafted poly(ethylene glycol) (PEG) chains. These microgels were synthesized by free radical copolymerization of vinyl caprolactam and acetoacetoxyethyl methacrylate in the presence of methoxy-capped poly(ethylene glycol)methacrylate macromonomers. We show that variation of the amount of PEG macromonomer or the length of the PEG chain provides effective control of the microgel diameter in the range 60–220 nm. The presence of the grafted PEG chains improves the colloidal stability of the microgels. The incorporation of the PEG macromonomers into microgel structure decreases the swelling degree and induces a shift of the volume phase transition to higher temperatures.

Keywords Microgel · PEG macromonomer · Temperature sensitive

Introduction

In this paper, we describe the influence of poly(ethylene glycol) (PEG) macromonomers on the size and thermoresponsive properties of poly(*N*-vinyl caprolactam) (PVCL)-based aqueous microgels. Recently, there has been considerable progress in understanding the behavior of macromonomers in copolymerization reactions with conventional monomers for the preparation of well-defined polymer structures. The polymerization of PEG macromonomers in water often involves micelles. Micellar polymerization of PEG macromonomers in water has been studied extensively both for homopolymerization and for copolymerization [1–4] processes. There are also studies of copolymerization of these macromonomers with conventional monomers in heterophase polymerization [5–9].

PEG macromonomers are widely used as reactive stabilizers in emulsion polymerization. For example, they have been used in the preparation of monodisperse poly (butyl methacrylate) [5, 6], poly(methyl methacrylate) [7], and poly(styrene) [8, 9] microspheres. In these cases, the PEG macromonomers remain grafted on the particle surface, providing effective colloidal stabilization. In these reactions, the size of the particles obtained could be varied by variation of the macromonomer concentration in the reaction mixture.

Recent reports describe the use of PEG macromonomers for the synthesis of microgel particles to achieve effective stabilization of colloidal systems [10–12], to incorporate reactive groups into a microgel structure [13], or to enhance the biocompatibility of the microgel for the application as drug carriers [14]. Armes and coworkers reported the synthesis of pH-sensitive poly[2-(diethylamino)ethyl methacrylate) microgels by using monomethoxy-capped poly (ethylene glycol)methacrylate macromonomer with M_n= 2,000 g/mol [10]. Steric stabilization of the microgels by grafting of the macromonomer provided better colloidal stability than charge stabilization or surfactant stabilization. Similar macromonomers have been used along with cationic surfactants for the preparation of sterically stabi-

This paper is dedicated to Professor Haruma Kawaguchi in honor of his many contributions to the field of polymer particle synthesis and applications.

A. Pich (✉) · S. Berger
Department of Macromolecular Chemistry,
Technische Universität Dresden,
01069 Dresden, Germany
e-mail: pich@dwi.rwth-aachen.de

O. Ornatsky · V. Baranov · M. A. Winnik
Department of Chemistry, University of Toronto,
M5S 3H6 Toronto, Canada

lized poly(2-vinylpyridine) microgels [11]. The variation of the macromonomer and surfactant concentration allowed the mean microgel diameter to be controlled over a wide range (from 370 to 970 nm). Poly(ethylene glycol) methyl ether methacrylate has been used for the preparation of pH-responsive ampholyte microgels based on the copolymer of methacrylic acid and 2-(diethylamino)ethyl methacrylate [12]. Due to the presence of the macromonomer in the microgel structure, no coagulation or phase separation occurred at the isoelectric point of the microgel. Hydroxy-capped poly(ethylene glycol)methacrylate has been used for the preparation of poly(*N*-isopropylacrylamide) (PNIPAAm) microgels [7]. In this way, temperature-sensitive microgels functionalized with OH-groups have been prepared.

The aim of the present work was to prepare aqueous microgels with grafted PEG chains exhibiting temperature-sensitive properties. We are interested in the preparation of microgel architectures that undergo non-specific endocytosis by a variety of different living cells. For this particular application, the microgel size and surface functionalization play an important role. We use *N*-vinyl caprolactam (VCL) for the microgel synthesis due to following reasons. In contrast to PNIPAAm, PVCL exhibits poorer structuring properties in aqueous solutions. Additionally, unlike PNIPAM, it does not produce small amide derivatives upon hydrolysis [15]. The application of PEG macromonomers can offer following benefits: (a) effective control of the microgel size (the desired size range is 50–150 nm to achieve effective uptake of the microgels into the cell interior); (b) functionalization of the microgel surface with PEG chains that minimize non-specific adsorption of proteins (for example, from serum-containing media), and (c) superior colloidal stability. In this paper, we explore the influence of concentration and chain length of monomethoxy-capped poly(ethylene glycol)methacrylate macromonomers on the synthesis and physico-chemical properties of PVCL-based microgels.

Experimental section

Materials

VCL was purified by distillation under vacuum. Acetoacetoxyethyl methacrylate (AAEM) and poly(ethylene glycol) methyl ether methacrylate macromonomers (PEGMEMA) with variable PEG length and average molecular weights 475 g/mol, 1,100 g/mol, and 2,080 g/mol have been obtained from Aldrich and used as received. Initiator 2,2′-azobis(2-methylpropyonamidine) dihydrochloride (AMPA) and cross-linker *N,N*′-methylenebisacrylamide (BIS; Aldrich) were used as received.

Microgel preparation

The synthesis of VCL/AAEM microgels has been reported elsewhere [16]. The copolymerization of VCL and AAEM in the aqueous phase leads to the formation of the microgels with narrow particle size distribution. In this study, we used similar batch polymerization procedure but PEG macromonomers were introduced into the reaction mixture. The polymerization procedure can be described as follows. Appropriate amounts of AAEM (0.336 g), VCL (1.877 g), PEGMEMA (amounts were varied from 0.024 to 0.52 g or 0.17 to 1.63 mol%) and cross-linker (0.05 g, 3 mol-%) were dissolved in 147 ml deionizer water. A double-wall glass reactor equipped with stirrer was purged with nitrogen. A solution of the monomers was placed into the reactor and stirred for 1 h at 70 °C under continuous purging with nitrogen. After that, 0.06 g of initiator dissolved in 3 ml water was added under continuous stirring. Reaction was carried out for 8 h. Microgel dispersions were purified by dialysis with a Millipore Dialysis System (poly(ether sulfone) membrane, MWCO 50,000).

Microgel characterization

Dynamic light-scattering measurements were performed using a Malvern Zetasizer Nano-ZS instrument. The experiments were carried out at a fixed scattering angle $\theta = 173°$.

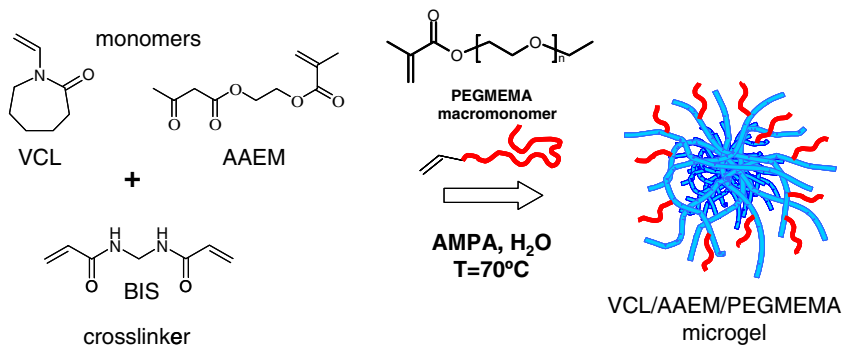
The sedimentation measurements of microgel dispersions were performed with separation analyzer LUMiFuge 114 (LUM GmbH, Germany). Measurements were made in glass tubes at acceleration velocity 3,000 rpm. The slopes of the sedimentation curves were used to calculate the sedimentation velocity and to get information about stability of the samples.

SEM images were taken with a Gemini microscope (Zeiss, Germany). Samples were prepared in the following manner. Microgel dispersions were diluted with deionized water, dropped onto cleaned glass support and dried at room temperature. Samples were coated with thin Au/Pd layer to increase the contrast and quality of the images. Pictures were taken at voltage of 4 kV.

Results and discussion

In the present system, VCL (the main monomer) was copolymerized with acetoacetoxyethyl methacrylate (AAEM) and different PEGMEMA macromonomers by a simple batch polymerization procedure in an aqueous medium leading to the formation of colloidally stable microgels (Scheme 1).

Scheme 1 Synthesis of VCL/AAEM/PEGMEMA microgels described in this study



In this reaction, microgel particle formation occurs by a homogenous nucleation process. In the first stage, a water-soluble cationic radical initiates polymerization of monomers. The polymer chains grow in the aqueous phase until they reach a critical chain length, when they become insoluble and precipitate forming a colloidally unstable precursor particle. The precursor particles follow one of two competing processes. Either they act as independent nucleation centers and continue to grow, or they aggregate with other precursor particles until they form a particle sufficiently large to be colloidally stable. The precursor particles grow by further polymerization of monomers and finally become polymeric particles. The number of the nucleation centers as well as final polymer particle number and size in such systems is strongly influenced by the presence of species able to act as stabilizers. The PEG macromonomers are able not only to participate in the polymerization process due to the presence of active double bonds, but at the same time, provide steric stabilization for the nuclei. According to the discussion above, the incorporation of PEG macromonomer should lead to the formation of a larger number of nucleation centers, and, therefore, smaller microgel particles should be formed.

The validity of this prediction is confirmed by the data presented in Fig. 1, where we plot the experimentally determined hydrodynamic radii of microgel particles as a function of PEGMEMA content. The general trend that can be observed in Fig. 1a is a decrease of the microgel size with increase of PEGMEMA content. The reduction of the microgel size becomes more pronounced for macromonomers with increasing chain length. This result is related to the increase of stabilizing efficiency with the increase of PEG-chain length.

The incorporation of PEG macromonomers into microgels improves their colloidal stability. As shown in Fig. 1b, the sedimentation velocity decreases with the increase of PEGMEMA content, and the stabilizing efficiency increases with the increase of the macromonomer molecular weight. The experimental results presented in Fig. 1a,b indicate that PEGMEMA macromonomers of higher molecular weight influence strongly the size of the microgels and their colloidal stability and in the case of the PEGMEMA 475 such effects can be not observed.

The variation of the particle size distribution with PEGMEMA content can be followed in Fig. 2, which presents CONTIN plots from DLS measurements of the distribution curves for microgels prepared with three different macromonomers. The data in Fig. 2 indicate that microgel particles have a narrow size distribution. A shift of the peak to lower R_h values with an increase of macromonomer concentration easily can be distinguished (especially for systems with

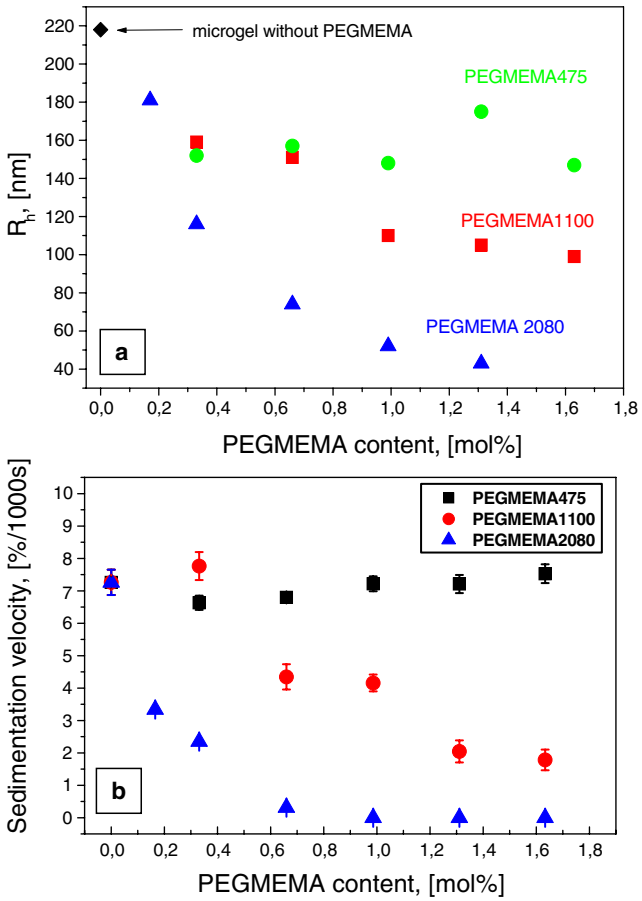


Fig. 1 Hydrodynamic radii (R_h) (**a**) and sedimentation velocity (**b**) of microgel particles as a function of PEGMEMA content (T=20 °C)

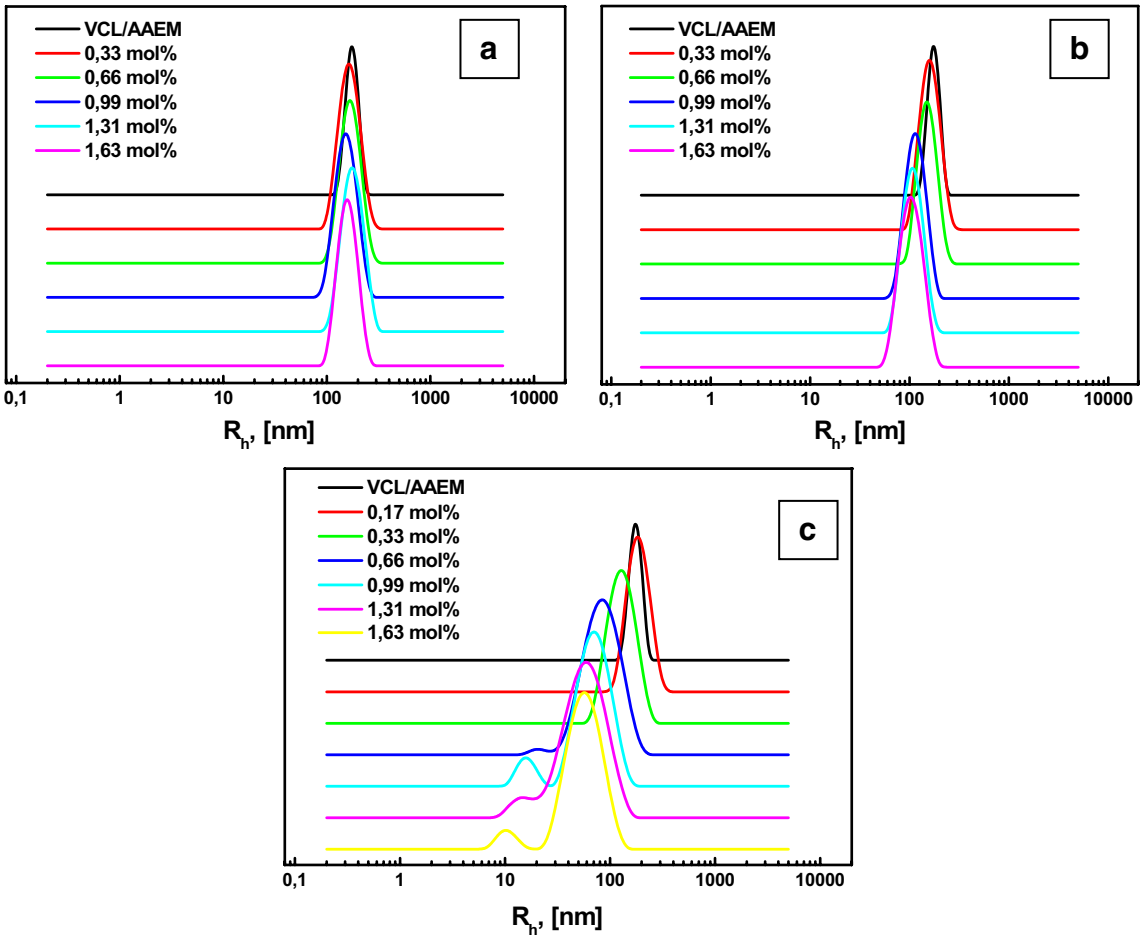


Fig. 2 Size distribution curves for microgels prepared with different PEGMEMA macromonomers: **a** PEGMEMA475; **b** PEGMEMA1100; **c** PEGMEMA2080

PEGMEMA1100 and PEGMEMA2080). For the microgel particles prepared with PEGMEMA475 and PEGMEMA1100, no strong change in particle size distribution was detected with the increase of the macromonomer concentration.

In contrast, microgels prepared with PEGMEMA2080 exhibit broadening of the size distribution with the increase of macromonomer content and even show a bimodal distribution starting from 0.99 mol% PEGMEMA2080 (Fig. 2c). Here, there is likely an excess of macromonomer in the reaction mixture, leading to the formation of secondary particles.

Figure 3 shows SEM images of microgel particles prepared with different macromonomers. The decrease of the microgel size with increase of macromonomer concentration is obvious in the case of PEGMEMA1100 and PEGMEMA2080 systems. Microgel particles with regular spherical morphology were obtained. However, the results in Fig. 3 indicate that PEGMEMA1100- and PEGMEMA2080-modified microgels became irregularly shaped above a critical macromonomer concentration. In the case of PEGMEMA2080 macromonomer, the appearance of 10-nm-large secondary particles is clearly visible in Fig. 3. This result correlates with the light-scattering results presented in Fig. 2c. It is important to recall that small particles scatter much less light than large particles. The SEM image provides a much better representation of the size distribution than the CONTIN plots of the DLS data.

VCL/AAEM microgels are thermosensitive and undergo a volume phase transition when the temperature of their solutions is increased. The phase transition temperature (T_{tr}) of VCL segments occurs at approximately 28 °C, a value somewhat lower than the lower critical solution temperature (LCST) for linear PVCL (ca. 32 °C) [17]. The driving force for the collapse transition is due to the different solvation of VCL segments by water molecules at temperatures below and above the phase transition temperature. Below 28 °C, the PVCL chains are swollen by water molecules, and above 28 °C, the chain become dehydrated. It is believed that the volume phase transition in the microgel occurs as a result of reduced hydrogen bonding between water molecules and the polymer, accompanied by hydrophobic

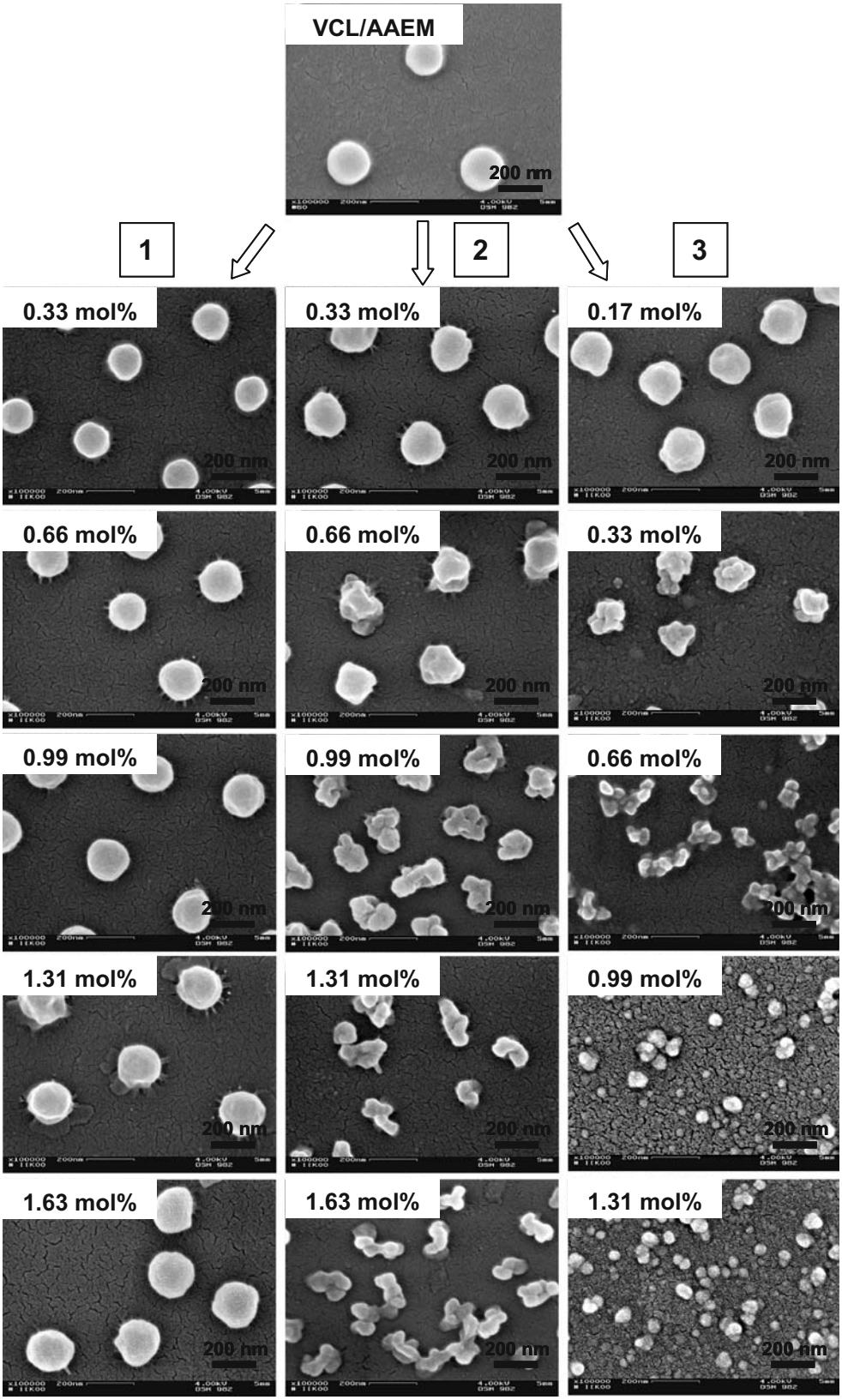


Fig. 3 SEM images of VCL/AAEM/PEGMEMA microgels: (*1*) PEGMEMA475; (*2*) PEGMEMA1100; (*3*) PEGMEMA2080

aggregation of the polymer that leads to the collapse of the microgel.

The presence of PEGMEMA macromonomers in the microgel structure has several important consequences on the microgel behavior at different temperatures. The influence of the macromonomer incorporation on the thermosensitive behavior of microgel particles is demonstrated in Fig. 4.

As shown in Fig. 4 the phase transition region becomes broader when macromonomer content in the microgel structure is increased. At the highest macromonomer content, the microgels show a continuous decrease of size upon heating. At the same time, the temperature-induced swelling degree of the microgel particles decreases with the increase of the macromonomer content.

This is illustrated in Fig. 5, where we plot the ratio $\left(R_h^M/R_h^{SW}\right)^3$, where R_h^M is the measured hydrodynamic radius and R_h^{SW} is the hydrodynamic radius at maximum swelling (T=10 °C), against macromonomer content in the microgel. The results in Fig. 5 indicate that the temperature-induced swelling decreases after incorporation of macromonomers. We interpret this result to mean that the hydrophilic PEG chains prevent complete particle collapse. One can also see in these plots that macromonomers with higher molecular weight reduce the extent of the temperature-induced swelling compared to lower molecular weight analogues.

Figure 5 indicates additionally that the volume phase transition temperature is shifted toward higher temperatures after incorporation of macromonomers. The maxima of the first derivative curves of the swelling ratio vs. T curves were used to determine the volume phase transition temperature. Figure 6 shows a summary of data obtained for the microgels prepared with different macromonomers.

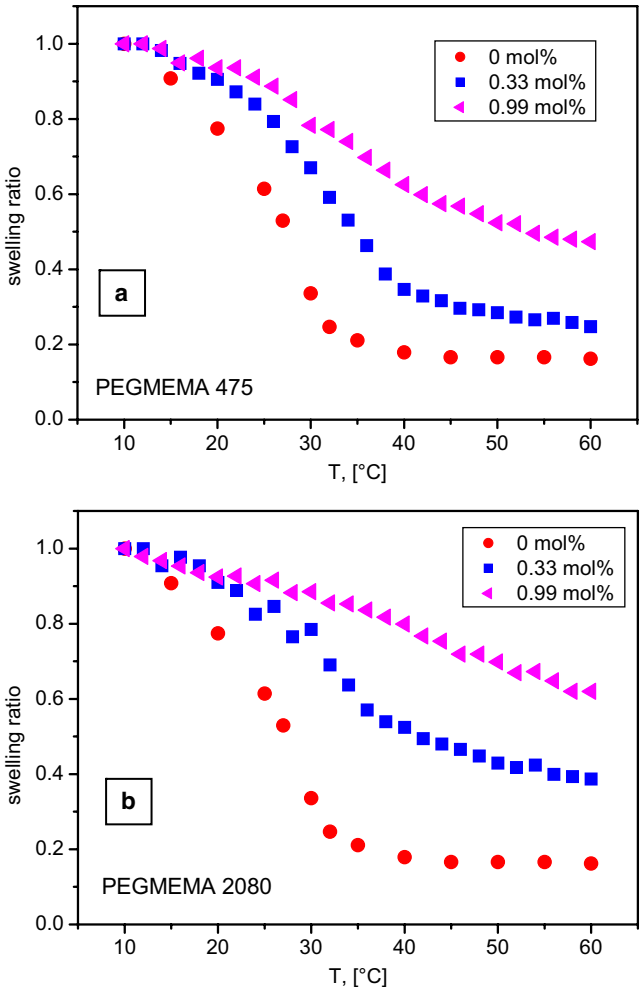


Fig. 5 The microgel swelling ratio $\left(R_h^M/R_h^{SW}\right)^3$ as a function of the temperature: **a** microgels prepared with PEGMEMA 475; **b** microgels prepared with PEGMEMA 2080

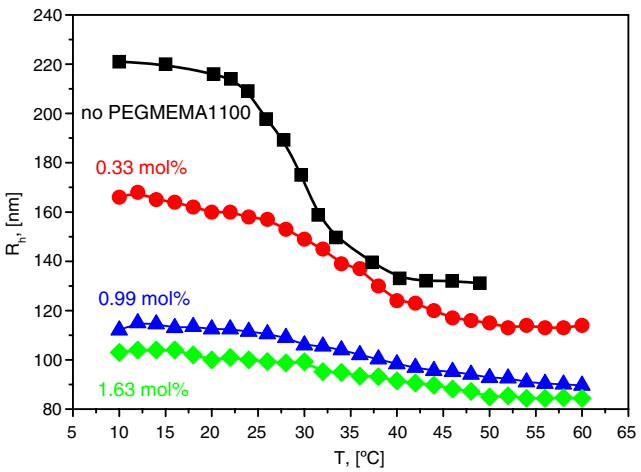


Fig. 4 The variation of the hydrodynamic radii (R_h) with temperature for microgel particles prepared with PEGMEMA1100

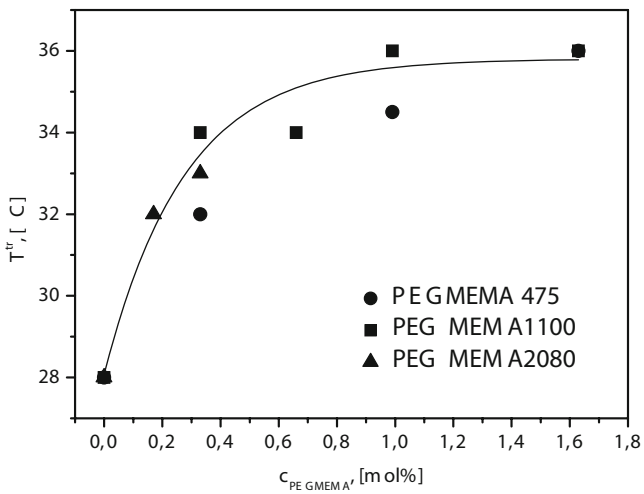


Fig. 6 Volume phase transition temperature as a function of PEGMEMA content in the microgel

Figure 6 indicates a systematic increase of the volume phase transition temperature of the microgels with the increase of macromonomer concentration. These results indicate that macromonomers influence the hydrophilic/hydrophobic balance within the microgels. The hydrophilic PEGMEMA chains integrated into the microgel network prevent collapse of the PVCL segments, and therefore higher temperature is needed that hydrophobic interaction within microgel start to dominate.

The experimental results presented above indicate that microgel properties such as size, morphology, colloidal stability, and temperature-sensitive properties can be tuned by incorporation of the hydrophilic macromonomers. The microgels obtained in this way are less sensitive to pH changes and electrolyte concentration in the aqueous medium. Our preliminary results indicate the superior efficiency of PEG-modified microgels during their endocytosis by living cells [18]. These results will be presented elsewhere. Microgel modification with PEG macromonomers eliminates undesired protein adsorption and recognition by the immune system by application in the direct contact with body fluids. This ensures efficient application of microgels as long-circulating smart devices for diagnostic and therapeutic needs.

Conclusions

In the present paper, we describe the preparation of aqueous microgels containing grafted PEG chains. These microgels were synthesized by free radical polymerization in the presence of methoxy-capped poly(ethylene glycol)methacrylate macromonomers. The dynamic light-scattering data show that variation of the amount of PEG macromonomer or the length of the PEG chain provides effective control of the microgel diameter in the range 60–220 nm. The increase of the PEG macromonomer concentration in the reaction mixture and increase of the PEG-chain length reduce the microgel size. For the microgel particles prepared with PEGMEMA475 and PEGMEMA1100, no strong change in particle size distribution was detected with the increase of the macromonomer concentration. In contrast, microgels prepared with PEGMEMA2080 exhibit broadening of the size distribution with the increase of macromonomer content and even show a bimodal distribution starting from 0.99 mol% PEGMEMA2080. The presence of the grafted PEG chains improves the colloidal stability of the microgels. Obtained microgels are temperature-sensitive. The incorporation of the PEG macromonomers into microgel structure decreases the swelling degree and induces a shift of the volume phase transition to higher temperatures.

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