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Comparative Study on the Collapse Transition of Poly(N-isopropylacrylamide) Gels and Magnetic Nanoparticles Loaded Poly(N-isopropylacrylamide) Gels

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Summary: A novel polymer gel exhibiting simultaneous temperature and magnetic field sensitivity has been prepared and studied. Poly(N-isopropylacrylamide) (PNIPA) and magnetic nanoparticles (magnetite, Fe_3O_4) loaded PNIPA gel beads with mm size and monolith gels with cm size were prepared. The dependence of swelling degree on the temperature has been studied. The effects of cross-linking density and the presence of magnetic nanoparticles on the equilibrium swelling degree as well as on the collapse transition have been investigated. Swelling kinetic measurements were also made. By comparing the equilibrium swelling properties of PNIPA and magnetite loaded PNIPA gels it was found that the built in magnetic nanoparticles do not modify the temperature sensitivity of these gels. Within the experimental accuracy the temperature of the collapse transition was not sensitive to the presence of magnetic particles. We have compared the swelling behaviour of mm size gel beads to the cm size monolith gels in order to study the influence of surface skin layer on the swelling equilibrium. It was established that the extent of surface skin formation was decreased by the presence of magnetic particles.

Keywords: gels; kinetics; magnetic particles; swelling behaviour; thermal properties

Introduction

Response to stimuli is a basic process of in living systems. Based on the lessons from nature, scientists have been designing smart materials that respond to external stimuli such as temperature, pH, light, magnetic and electric field, chemicals and ionic strength.[1–3] Applications of stimuli responsive, or 'smart', polymers in therapeutics, tissue engineering, bioseparation, sensors or actuators have been studied extensively and numerous papers and patents evidences of the rapid progress in this area.[1–6] Understanding the structure – property relationship is essential for the further development and design of new functional smart materials.

Recent advances in the design of stimuli responsive gels have created opportunities for novel biomedical applications. Latest reviews have summarized research progress in biomimetic actuators, immobilized biocatalysts, drug delivery, bioseparation and bioconjugates.[4,5]

Among the synthetic responsive polymer gels the best known and studied are those which have hydrophobic side chains like poly(N-isopropylacrylamide) (abbreviated as PNIPA) gels.[6,7] The main characteristic property of fully or partially hydrophobic network chains is that at lower temperature they are more hydrated and more expanded than at higher temperature. Hence, they can convert thermal energy directly into mechanical work by swelling

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or collapsing. The temperature range in which this conversion abruptly occurs can be adjusted by the chemical composition of the network backbone. These gels exhibit a remarkable volume change in response to temperature changes. The lowest temperature above which the network chains are still in the collapsed state is called lower critical solution temperature, LCST. For PNIPA gels swollen in water, LCST has been found to be 34 °C. There are several other gels showing reversible swelling and shrinking transition with different LCST. These gels are often used to immobilise enzymes and as carriers of certain functional groups important for biochemical or biomedical applications.[6]

Since polymer gels contain substantial amount of liquid as swelling agent, it is possible to fabricate magnetic field sensitive gels with ferrofluid as swelling agent[8–13]. A ferrofluid or a magnetic fluid is a colloidal dispersion of monodomain magnetic particles with a typical size of below 10 nm. In the ferrogel, the finely distributed ferromagnetic particles are attached to the flexible network chain by adhesive forces, which result in a unique magnetoelastic behaviour. In uniform magnetic field, a ferrogel experiences no net force. When a ferrogel is placed in a gradient of an external magnetic field, forces act on the filler particles and the magnetic interaction is enhanced. The magnetic field attracts particles together with the polymer network. Depending on the geometrical arrangement, elongation, contraction, bending and rotation can be achieved. Since a ferrogel moves with a smooth, lifelike quality and can create a wide range of motions, operating quickly and with precise controllability; these magnetocontrolled soft and wet gels seem to be promising materials in the growing family of stimuli-responsive gels and actuators.[9]

The collapse transition of the PNIPA gel is extensively studied. Several papers and review articles summarize valuable information about its mechanical and swelling behaviours.[3,7,14–29] Magnetic field sensitive PNIPA gels have not been systematically investigated, yet.[30–38]

The main purpose of the present work is to study the temperature dependence of PNIPA and magnetic field sensitive PNIPA gels. The influence of magnetic nanoparticles on the temperature of the collapse transition as well as the swelling and shrinking kinetics was also the subject of this investigation. Gel beads of mm size as well as monolith gels of cm size were prepared from both pure PNIPA and magnetite loaded PNIPA gels. Swelling and shrinking behaviour was studied and compared in order to establish the influence of magnetic nanoparticles on the equilibrium and kinetic behaviour of PNIPA gels. Temperature responsive PNIPA gel beads loaded with magnetic nanoparticles may be good candidate for developing smart drug delivery systems with magnetic targeting possibilities.

This paper is organized as follows. First, preparation of monolith PNIPA and magnetite loaded PNIPA gels are described. It is followed by the synthesis of gel beads. In the next part, the equilibrium swelling degree measurements are discussed. Thereafter, the influence of magnetic nanoparticles on the equilibrium and kinetic behaviour of PNIPA gels is emphasized.

Experimental part

Materials

Chemically cross-linked temperature sensitive poly(N-isopropylacrylamide) (PNIPA) gels were prepared from N-isopropylacrylamide (NIPA), N,N′-methylenebisacrylamide (BA), ammonium-persulfate (APS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) from Aldrich Chemicals. These chemicals were used without further purification.

Preparation of Magnetite Containing Ferrofluids

Ferrofluid, which contains magnetite (Fe_3O_4) nanoparticles, was formed by a conventional co-precipitation method. Identical volumes

of aqueous $FeCl_3$ (1.2 M) and $FeCl_2$ (0.7 M) solution were mixed together. Magnetite particles were flocculated with concentrated NaOH solution (pH = 11). After removing supernatant liquid, the resulting magnetite slurry was washed with water, adjusting the pH to 5.5. The sediment was dispersed with 1M HCl, which induced peptization. Then the purified and stabilized magnetite sol, having a concentration of 17.2 wt%, was used for further preparative work. More detailed description of the preparation procedure can be found in our earlier papers.[10,17]

We have determined the average size and size distribution of the magnetite particles by small angle X-ray scattering (SAXS). The radius of the magnetite nanoparticles was found to be 2 nm.

Preparation of Monolith PNIPA Gel Discs

Poly(N-isopropylacrylamide) gel was prepared by free radical polymerization from 7.5 ml of 1 M NIPA (monomer) solution, 0.49 ml of 0.1 M BA (cross-linker) solution, 10 μl TEMED (accelerator) and 8 ml distilled water. In order to change the cross-linking density, the amount of 0.1 M BA solution was varied from 0.19 to 1.5 ml. Nitrogen gas was bubbled through the solution for 30 min prior to polymerization to remove the absorbed oxygen. Finally, 50 μl APS (10 wt%) was added to the mixture as initiator. The reaction mixture was poured into a mould and covered by a glass sheet. The gelation process took two hours. Uniform discs were punched out of the slab using a cork borer and the samples were washed several times in pure water in order to remove the unreacted monomers. The gels were kept in distilled water for 1 week to reach the equilibrium swelling degree.

Preparation of Monolith Magnetic PNIPA Gel Discs

1.96 ml ferrofluid of 17.2 wt% was added to the aforementioned mixture of the monomer, the cross-linker and the accelerator, and then 50 μl APS (10 wt%) was added to induce the polymerization. The reaction mixture was poured into a mould and covered by a glass sheet. The gelation took two hours. After the gelation was completed the gel slab was removed from the mould. Uniform discs were punched out of the slab using a cork borer and the samples were washed several times in distilled water to remove the unreacted monomers. The gels were kept in distilled water for 1 week to reach the equilibrium swelling degree.

Preparation of PNIPA and Magnetic PNIPA Gel Beads with the Diameter of mm

Gel beads of mm size were prepared according to the method developed by Park and Choi.[14] An interpenetrated network (IPN) was prepared by the gelation of Ca-alginate (Aldrich) to form spherical beads and the simultaneous free radical polymerization of the NIPA and cross-linker within the beads. Alginate dissolved in 8.33 ml of 0.01 M Tris buffer (1.75 w/v%) was degassed and then mixed with 0.64 g NIPA monomer, 0.027 g BA. This solution was injected into 300 ml of 0.01 M Tris buffer solution, containing 3 w/v% $CaCl_2$ and 0.1 w/v% APS. The gel beads were kept for 30 min under nitrogen atmosphere. At the end of the polymerization, which took 24 hours, beads were washed three times with distilled water to remove the unreacted monomers. Afterwards, the beads were treated with a 0.1 M EDTA (Reanal) solution at pH = 7 for three hours in order to form a chelate complex of calcium ions and extract the alginate from the IPN beads.

Preparation procedure of magnetite loaded – magnetic – PNIPA gel beads (abbreviated as mPNIPA) is similar to previously described method. Alginate dissolved in 25 ml of 0.01 M Tris buffer (1.75 w/v%) was degassed and then mixed with 1.92 g NIPA monomer, 0.09 g BA, 0.125 ml TEMED and 0.89 ml ferrofluid. The gel beads (magnetic and non magnetic) were washed and kept in distilled water for 1 week to remove the unreacted chemicals and reach the equilibrium state.

Experimental Methods

SAXS Measurement

Small angle X-ray scattering was used to determine the average size and the size distribution of the magnetite particles in the ferrofluid as well as in the PNIPA gels, the measurements were carried out in JUSIFA center (DESY, Hamburg). The energy of the X-ray was 85200 eV. The size distribution can be seen in Figure 1.

Based on Figure 1 it can be appointed that the size of the magnetite particles in the ferrofluid and in the gels is the same within the experimental accuracy. This result evidences that during the preparation process no significant aggregation of the particles occurred.

Quantitative Characterizing of the Volume Phase Transition

For gel beads, the relative swelling degree (q_r) was used to characterize the volume phase transition:

$$q_r = \frac{r_T}{r_{10^\circ C}} \quad (1)$$

where $r_{10\,^\circ C}$ means the radius of the gel bead at 10 °C and r_T represents the radius of the gel bead at T arbitrary temperature.

In order to characterize the phase transition behaviour of monolith PNIPA and mPNIPA gel, the mass swelling degree (q_m) was used:

$$q_m = \frac{m_T}{m_0} \quad (2)$$

where m_T is the mass of the gel at certain temperature, m_0 is the mass of the dry network.

Image Analyses

In order to determine the temperature dependence of the swelling degree, volume change of the beads were monitored by a digital video system. A CCD camera with a 1/3″ video chip has been connected to a PC through a real time video digitising card. Change of the diameter, d of PNIPA and mPNIPA gel beads was followed in magnified pictures taken by a software developed at our laboratory. By this method very small change in the diameter can be monitored and measured on the real time video image. The error of the measurement depends on the magnification, however in our cases it was within 0.01 mm. The gel beads were dispersed in water and the temperature was controlled by a thermostat (Haake P2-C30P). The temperature of the system was increased stepwise from 10 °C to 50 °C. The increment of temperature was 2 °C and the waiting time was 20 minutes at each temperature.

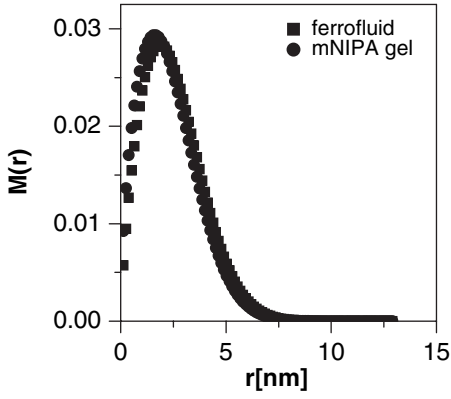

Figure 1.
Size distribution of magnetite nanoparticles in the ferrofluid and in magnetite loaded PNIPA gel.

Results

It is know that the bulk PNIPA gel has a phase transition temperature at 34 °C.[7,22–25] In this study we focus on how the preparation procedure as well as the presence magnetic nanoparticles make their influence felt on the swelling behaviour of PNIPA gels.

Temperature Sensitivity of PNIPA and Magnetic PNIPA Gel Beads

Figure 2 shows the dependence of relative swelling degree on the temperature for pure PNIPA and magnetite loaded PNIPA gel beads. Both kinds of gels have the same polymer concentration and cross-linking ratio. The only difference is due to the

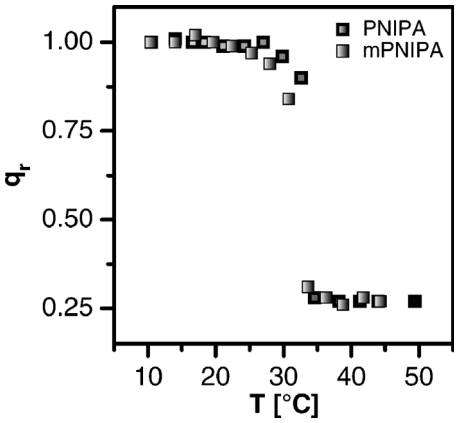

Figure 2.
Temperature dependence of the relative swelling degree of PNIPA and mPNIPA gel beads. Molar ratio between monomer and cross-linker molecules: [NIPA]/[BA] = 50. The magnetite content of mPNIPA gel was 2.1 wt%.

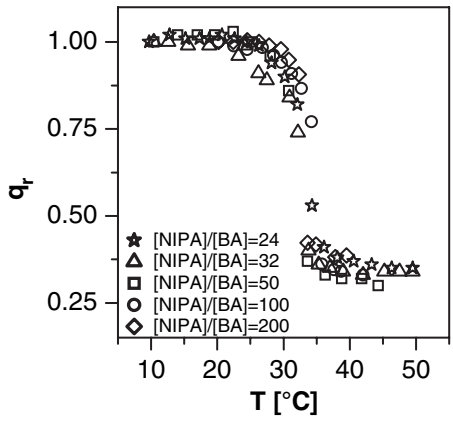

Figure 3.
Effect of the cross-linking density on the temperature dependent relative swelling degree of PNIPA beads. The cross-linking ratio is indicated on the figure. The initial diameter of the PNIPA gel beads were 1 mm.

presence of magnetite. The initial diameter of the gel beads were 1 mm.

One can see on the Figure 2 that for both gel systems the temperature dependent volume change is not continuous, an abrupt change occurs in the relative swelling degree when the temperature exceeds 30 °C. It is also seen that within the experimental accuracy no difference has been observed between the pure PNIPA and magnetite loaded PNIPA gel beads. The presence of magnetic nanoparticles does influence neither the measure of volume change nor the collapse transition temperature (abbreviated as T_C). This can be identified as the temperature belonging to the inflexion point of $q_r - T$ curves. A careful analysis of the $q_r - T$ curves has shown that for both kinds of PNIPA beads T_C was found to be around 32 °C.

We have also studied the effect of cross-linking density on the volume phase transition. Figure 3 shows these results. It can be concluded that the cross-linking density does not affect the temperature dependence of the relative swelling degree. Within the experimental accuracy T_C was to be found 32 °C for all the gel homologues. The same effect was found for magnetite loaded PNIPA gels, too.

Phase Transition of Monolith PNIPA and mPNIPA Gels

In order to characterize the effect of the magnetic nanoparticles, the mass swelling degree of both the unloaded and loaded PNIPA gels was determined. For the experiments, gel discs with 1 cm diameter and 0.2 cm height were used. The results are shown in Figure 4.

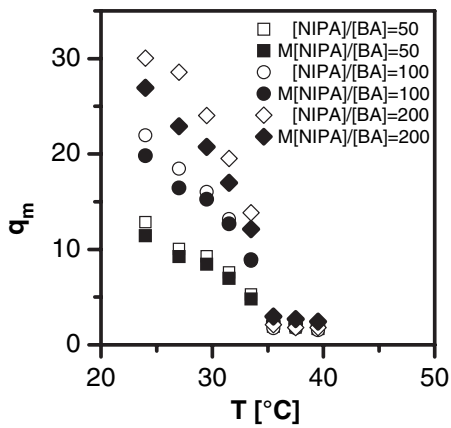

Figure 4.
Influence of cross-linking density as well as the presence of magnetic particles on the mass swelling degree. The cross-linking ratio is indicated on the figure. The magnetite content of mPNIPA gel is 2.1 wt%.

One can see on the figure that the magnetic nanoparticles do not have significant effect on the character of volume phase transition. T_C was found 34 °C in every case. Below the T_C the mass swelling degree decreases by increasing the cross-linking density (decreasing [NIPA]/[BA] ratio) as it is expected on the basis of thermodynamics of swelling.[7,22–25] The presence of the magnetite particles slightly decreases the mass swelling degree. If the temperature exceeds T_C neither the magnetite particles nor the cross-linking ratio influence the swelling behaviour.

Effect of the Preparation Condition on the Swelling and Shrinking Kinetics

Shrinking kinetics of PNIPA and mPNIPA gels were investigated and compared. Figure 5 shows the shrinking kinetics of the monolith PNIPA and mPNIPA gel discs. In the Figure 5 the relative swelling degree (q_r) of PNIPA and mPNIPA gels at different cross-linking ratio are plotted against time, after a temperature jump from 20 to 40 °C. Significant difference in the kinetics of PNIPA and magnetite loaded PNIPA discs can be observed. This difference is due to the formation of surface skin layer on the pure PNIPA gels.[39]

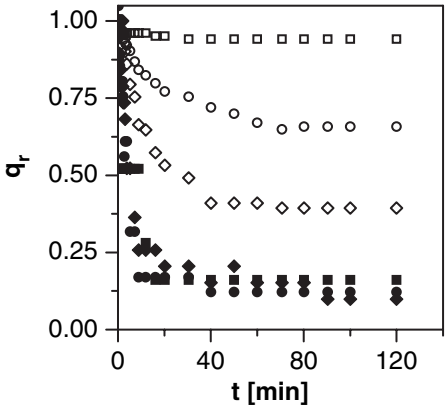

Figure 5.
Time dependence of the relative swelling degree of PNIPA and mPNIPA gel discs after a temperature jump from 20 to 40 °C. PNIPA and mPNIPA gel discs characterized by different cross-linking density. The initial diameter and thickness of the gel discs was 5 mm and 2 mm, respectively. Molar ratios between monomer and cross-linker molecules ([NIPA]/[BA]) for the PNIPA gels are 50 (□); 100 (○); 200 (◇) and for the mPNIPA gels are: 50 (■); 100 (●); 200 (◆).

This skin layer blocks the water molecules to leave the polymer matrix resulting bubbles on the surface. This phenomenon results in that PNIPA gel discs can not shrink to their equilibrium volume in this time scale, maybe an additional shrinking step follows this intermediate state.[40] The presence of the magnetite nanoparticles modifies the structure of the polymer network and the surface properties. This modified surface retards the formation of the surface skin layer and bubbles as shown in Figure 6.

In contradiction to the PNIPA gel discs, skin layer and bubbles formation were not observed on the surface of gel beads. The lack of skin layer and bubbles can be explained by the porous structure of the gel beads. In the first step of the preparation of the gel beads an interpenetration network was formed. This method results two polymer networks in each other. If one is removed from the other, a new polymer matrix with channels can be obtained. These channels guide the water molecules out of the gel beads during the phase transition and prevent the skin layer formation.

Conclusions

We have studied the effect of magnetic nanoparticles on the collapse transition of chemically cross-linked PNIPA gels. The cross-linking density was also varied. It was found that the incorporated magnetite particles slightly decrease the equilibrium swelling degree below the T_C but do not shift the collapse transition temperature. Below the phase transition temperature the mass swelling degree increased with decreasing the cross-linking density, above the phase transition temperature the cross-linking density does not alter significantly the swelling degree. Within the experimental accuracy the relative swelling

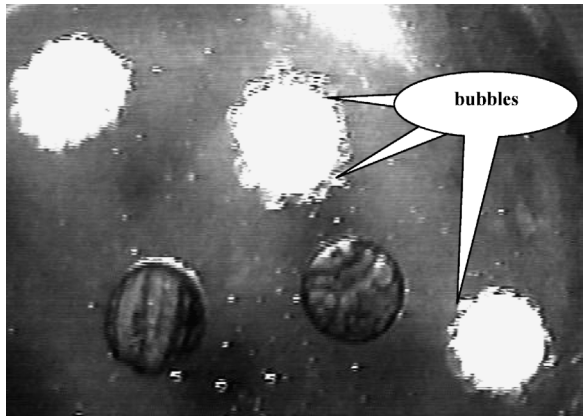

Figure 6.
The surface skin layer formed on PNIPA gel discs at 40 °C. The dark discs represent the magnetite loaded PNIPA gel discs.

degree was found to be dependent only on the temperature. In contrast to this behaviour the temperature dependence of the mass swelling degree is influenced by the cross-linking degree of PNIPA gels. Shrinking kinetics measurements were also performed in order to study the influence of the surface skin layer. The shrinking kinetics of PNIPA and mPNIPA gels is significantly different. Presence of the magnetic nanoparticles retards the formation of the surface skin layer and of the bubbles. It results in faster shrinking process.

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