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Acta Biomaterialia 4 (2008) 11–16
Acta BIOMATERIALIA
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Hydrogel nanocomposites as remote-controlled biomaterials

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Received 28 April 2007; received in revised form 21 June 2007; accepted 19 July 2007
Available online 3 August 2007

Abstract

Nanocomposite hydrogels are a new class of intelligent materials which have recently attracted interest as biomaterials. In this study, magnetic nanocomposites of temperature-sensitive hydrogels have been developed and demonstrated to be responsive to alternating magnetic fields. Nanocomposites were synthesized by incorporation of superparamagnetic Fe_3O_4 particles in negative temperature-sensitive poly(*N*-isopropylacrylamide) hydrogels. The systems were characterized for temperature-responsive swelling, remote heating on application of an alternating magnetic field and remote-controlled drug delivery applications. The rise in temperature in external alternating magnetic field depends on the Fe_3O_4 particle loading of the system. Preliminary studies on remote-controlled drug release showed reduced release in the presence of an alternating magnetic field.

Keywords: Hydrogel; Nanocomposite; Remote control; Drug delivery; Magnetic

1. Introduction

Hydrogels are cross-linked hydrophilic polymers that can absorb water or biological fluids and swell several times of their dry volume. Due to the high level of water in their composition and their elastic structure, hydrogels are considered as excellent biocompatible materials [1]. There are numerous applications of hydrogels in the medical and pharmaceutical sectors, such as contact lenses, membranes for biosensors, sutures, drug delivery devices, and matrices for the repair and regeneration of tissues and organs [2–4].

Hydrogels can show swelling behavior depending on changes in the external environment. Some of the factors that can affect the swelling of responsive hydrogels include pH, ionic strength and temperature [5]. Hydrogels can also be made to respond to diverse external stimuli, such as light, electric current, ultrasound, and the presence of a magnetic field or a particular molecule. The unique property of responsiveness has resulted in their applications in sensors [6,7], self-regulated and externally actuated intelligent drug delivery systems [8–11] and microfluidic devices [12,13].

Hydrogel nanocomposites have recently attracted considerable attention due to their accelerated response and capability of action at a distance. The properties of the nanocomposites can be easily tailored by manipulating the properties of the hydrogel and the composite material. Hydrogel nanocomposites with magnetic particles have been demonstrated as potential candidates for pulsatile drug delivery and soft actuator applications. Zrinyi and co-workers reported that magnetic composites of poly (vinyl alcohol) undergo quick, controllable changes in response to an applied magnetic field and thus can be used in soft actuator-type applications [14,15]. Further studies on magnetic composites of *N*-isopropylacrylamide (NIPAAm) have shown that magnetic particles do not affect the temperature sensitivity of the hydrogel network, including the lower critical transition temperature (LCST) [16].

One of the first approaches to achieve an externally controlled drug delivery system using biomaterials was by Langer and co-workers [17–20]. They embedded macroscale magnetic beads (~1 mm diameter) in ethylene vinyl acetate along with various macromolecular drugs like insulin. Both in vivo and in vitro studies have shown that application of

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1742-7061/$ - see front matter
doi:10.1016/j.actbio.2007.07.009

an oscillating magnetic field leads to increased release rates. The release rates could be modulated by altering the geometry of the implant – the position, orientation and magnetic strength of the embedded materials – as well as changing the amplitude and frequency of the magnetic field. Recently, Liu et al. demonstrated gelatin and poly(vinyl alcohol) hydrogels with Fe_3O_4 nanoparticles as "on" and "off" drug delivery devices [21,22]. When a direct current magnetic field was applied there was reduced release, and when the field was switched off the drug was released rapidly. The release rate depends on the strength of the magnetic field, the particle size and the duration of the switching time.

For our current studies with magnetic nanocomposites, NIPAAm was used due to its temperature responsiveness, while superparamagnetic iron oxide (Fe_3O_4) nanoparticles (20–30 nm diameter) were used as they have been widely considered for remote heating in the case of hyperthermia [23–25]. The application of an alternating high-frequency magnetic field to the nanocomposite should lead to heat generation, which could drive the swelling transition of the hydrogel. This is the first demonstration utilizing an alternating magnetic field for the remote control of drug release from nanocomposite hydrogels, and we expect these systems to find application in implantable biomedical devices. Although this paper only demonstrates remote control for short release durations, the release profiles can be easily modulated by altering the nanocomposite hydrogel composition (e.g. physical size, cross-linking percentage, molecular weight between cross-links, etc.). Currently, additional studies are under way to look into systems that can demonstrate control over extended periods of time. In addition, on/off control of the release is possible, and is being studied. Fig. 1 includes a schematic of the nanocomposite systems for remote-controlled drug delivery in the case of negative and positive temperature-sensitive systems.

The synthesis and swelling behavior of NIPAAm-based magnetic nanocomposites has been described earlier with special emphasis on the effect of the type of cross-linker [26]. In this work, we report the characterization of the magnetic nanocomposites, which includes the effect of the degree of cross-linking on swelling behavior, the remote heating response on the application of an alternating magnetic field and the preliminary results of remote-controlled (RC) drug delivery.

2. Materials and methods

2.1. Hydrogel synthesis

Hydrogel nanocomposites were synthesized by ultraviolet (UV) photopolymerization with various cross-linking densities and magnetic nanoparticle loadings. The hydrogel systems were based on *N*-isopropylacrylamide (Sigma–Aldrich) as the monomer with poly(ethylene glycol) 400 dimethacrylate (Polysciences, Inc) as the cross-linker. 2,2-Dimethoxy-2-phenylacetophenone (Sigma–Aldrich) was

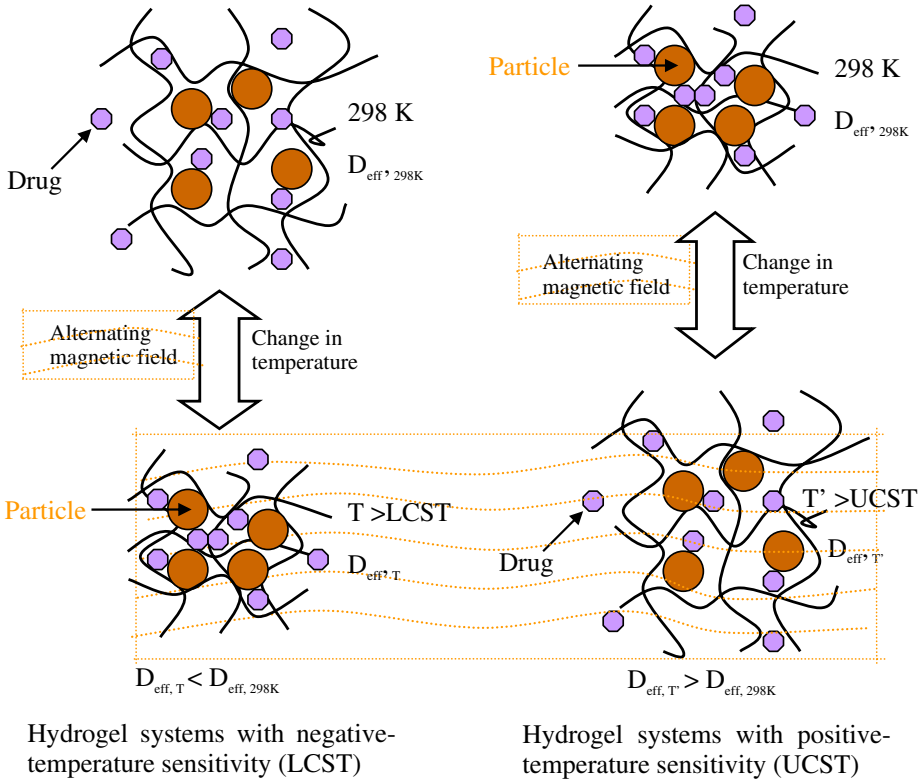

Fig. 1. Schematic of the proposed remote-controlled drug delivery system for negative and positive temperature-sensitive systems.

used as the photosensitive initiator for UV photopolymerization. Iron oxide nanoparticles (Fe_3O_4, Nanostructured and Amorphous Materials Inc.) used for magnetic nanocomposite synthesis were spherical, with a mean size of 20–30 nm.

N-Isopropylacrylamide (NIPAAm) and poly(ethylene glycol) 400 dimethacrylate (PEG400DMA) mixtures were prepared in molar compositions of 90:10, 80:20 and 70:30, and dissolved in an equal weight of ethanol as the solvent. The nanocomposites were synthesized for a 90:10 molar ratio with the Fe_3O_4 nanoparticles added to the monomer mixtures prior to polymerization. The nanoparticle loadings were varied as 0%, 1%, 2.5% and 5% of the combined weight of the monomer and cross-linker. The uniform dispersion of particles was ensured in monomer mixtures by probe sonication (Fisher Scientific Sonic Dismembrator Model 500) for 10 min followed by ultrasonic bath for 10 min. Initiator was added to 1% by weight of the monomer and cross-linker together, and manual shaking was continued until complete dissolution. The mixtures were then pipetted into two $15 \times 15\ cm^2$ clamped glass plates separated by a 500 μm Teflon spacer. The glass plate assembly was then transferred to a UV source (LESCO) preset at 365 nm wavelength and adjusted to give an intensity of $17.5\ mW\ cm^{-2}$. Photopolymerization was carried out for 5 min and the gel was carefully removed and placed in deionized water. For hydrogel nanocomposites, uniform UV light exposure of both sides of the gel was ensured during polymerization. The hydrogel films were washed daily with deionized water. UV analysis of the wash water samples was performed with deionized water as the baseline. Washing was continued until no significant peaks were observed (Cary 50 UV Spectrophotometer). The gels were then taken out of the water, cut into 15 mm diameter discs and dried in air. The discs were stored in a vacuum oven for at least 24 h to ensure complete drying.

2.2. Swelling studies

The swelling studies were carried out for pure hydrogel discs and 5 wt.% particle loaded 90:10 molar discs at 15–45 °C and the volume swelling ratio Q was calculated by methods described previously [26].

2.3. Remote heating on the application of an alternating magnetic field

The heating response of the nanocomposites to an electromagnetic field was characterized using a Taylor Winfield induction power supply model MMF-3-135/400-2 (solenoid of 15 mm diameter and five turns). Dry hydrogel discs with NIPAAm:PEG400DMA at a molar composition of 90:10 and various particle loadings were placed in a Petri dish on top of the solenoid and subjected to an alternating magnetic field of strength $2.98\ kA\ m^{-1}$ and frequency 297 kHz. An infrared (IR) camera (AGEMA Thermovision 470) was used to acquire thermal images and record the resulting increase in surface temperature. The heating was continued for 5 min and the results were averaged over three samples.

2.4. Demonstration of RC drug delivery

Pyrocatechol violet dye was used as a model drug for the release studies. The hydrogel discs with 0 and 5 wt.% particles and a molar composition of 90:10 NIPAAm:PEG400DMA were loaded with the dye by imbibition in a $1\ mg\ ml^{-1}$ dye solution at room temperature (22 °C) for 48 h. To observe the effect of an alternating magnetic field on dye release, a release study was carried out with one set of discs placed in an alternating magnetic field at the center of the solenoid ($5.3\ kA\ m^{-1}$, 297 kHz), while another was set outside the field. The set inside the field was subjected to a 10 min ON/5 min OFF cycle. The infinite dilution method was used for release studies for the first hour by changing the supernatant solution every 15 min. The final supernatant was collected at 24 h and the cumulative release was quantified as M_{inf}. The supernatant was quantified by UV spectrophotometry for a peak at 443 nm.

3. Results and discussion

3.1. Characterization of swelling behavior

The swelling behavior of the gels was analyzed at different temperatures to characterize the effect of cross-linking density and particle loading on the swelling transition temperature. The swelling studies on the NIPAAm based system with various cross-linker densities of PEG400DMA at temperatures of 15–45 °C show that, for a given system, the equilibrium volume swelling ratio Q decreases with increasing temperature (Fig. 2). This trend is expected since NIPAAm is a negative temperature-sensitive hydrogel with an LCST of about 34 °C in its pure form [27]. As temperature increases, the hydrogen bonds of the network break, resulting in a decrease in hydrophilicity. This forces water

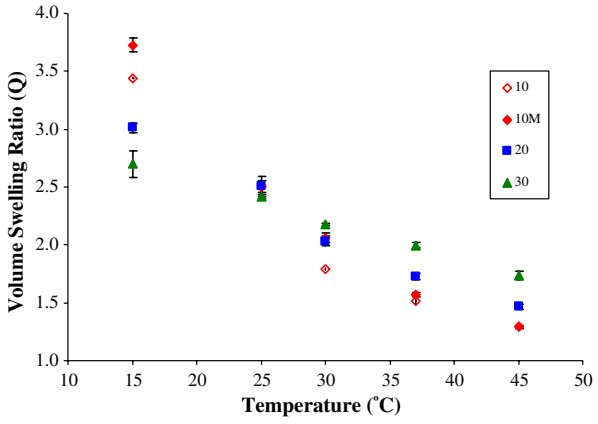

Fig. 2. Effect of temperature on equilibrium swelling of hydrogels. 10, 20, and 30 represent mol.% PEG400DMA in the NIPAAm–PEG400DMA system. *M* represents magnetic nanocomposite. $N = 3$, ±SD.

out of the hydrogel network and results in decreased swelling. Thus, at 15 °C, the gel is in a swollen state and hence the equilibrium volume swelling ratio observed is greater than that at 45 °C, where it is in a collapsed state.

Confirming prior research, we observed that the swelling transition is broadened due to the effect of PEG400DMA cross-linking [26]. At temperatures below the critical transition range, the higher degree of cross-linking (less NIPAAm content) leads to smaller Q values (less equilibrium swelling) due to the smaller mesh size. There is a larger reduction in equilibrium swelling with increasing temperature for systems with a lower degree of cross-linking (higher NIPAAm content). As a result, Q values above the critical transition temperature range are higher for systems with a higher degree of cross-linking. The comparison between swelling ratios of gels with and without nanoparticles shows that 5 wt.% magnetic particles do not have a significant effect on swelling behavior. Similar observations were reported in prior research incorporating lower amounts of particle loadings in NIPAAm systems [26].

3.2. Remote heating on the application of an alternating magnetic field

Dry NIPAAm:PEG400DMA hydrogel nanocomposite discs with 5 wt.% Fe_3O_4 particles were subjected to an alternating magnetic field of strength 2.98 kA m^{-1} and frequency 297 kHz. IR camera images (Fig. 3a and b) show that the surface temperature at the centre of the disc rises from an initial temperature of 22 °C to about 55 °C within the first minute. When an alternating magnetic field is applied, superparamagnetic Fe_3O_4 particles heat due to Neel and Brownian relaxations and high temperatures are generated at the nanoscale [28]. This leads to an increase in the temperature of the hydrogel matrix. The field intensity of the solenoid varies, with the maximum strength at the centre, leading to a temperature distribution in the heated disc.

Fig. 4 shows the results of detailed magnetic field effect on dry hydrogel nanocomposite discs of NIPAAm:PEG400DMA systems with varying particle loadings. Hydrogel nanocomposites with no particles showed minimal resistive heating, while an increase in the particle loading increased the maximum temperature achieved in the field. Higher temperatures are expected with increased particle loading since heat generation is proportional to the amount of nanoparticles present. It should be noted that the disc was open to air, and hence the temperature rise also depends on heat transfer to the air by convection. The initial temperature rise is fast, and is followed by a slow continuous increase in temperature.

3.3. Demonstration of RC drug delivery

Release studies were conducted for the system with a molar composition of NIPAAm:PEG400DMA of 90:10 (0 and 5 wt.% magnetic particles) using Pyrocatechol Violet dye as the model drug. One set of discs was placed in an alternating magnetic field of strength 5.3 kA m^{-1} and frequency 297 kHz, while another was set outside the field. Cumulative drug release was plotted vs. time showing that

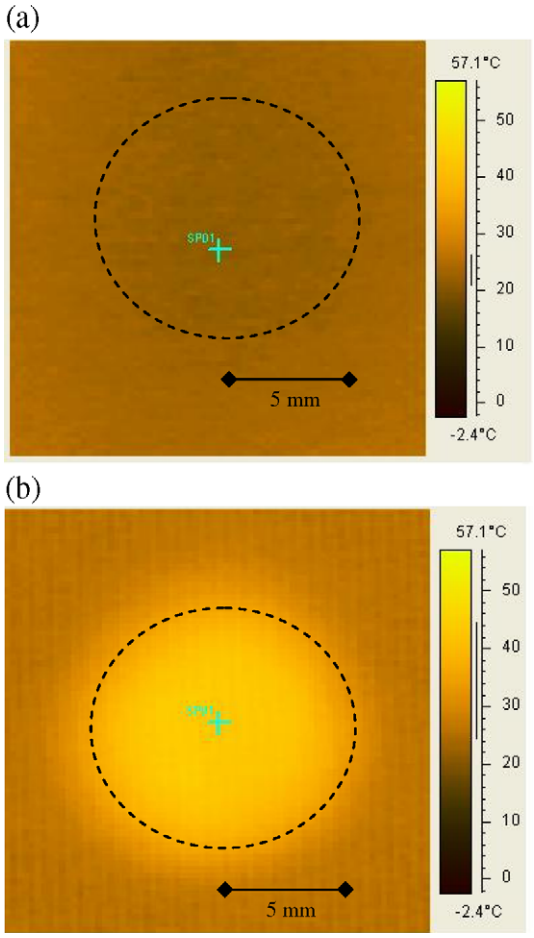

Fig. 3. Heating effect of nanocomposites in electromagnetic field. (a) IR image of 5 wt.% particle disc at 0 s; (b) IR image of 5 wt.% particle disc at 60 s. The dotted circle shows the disc area.

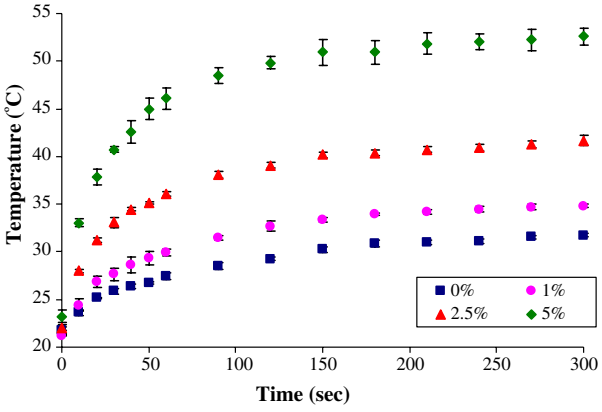

Fig. 4. Temperature increase of nanocomposites with varying particle loadings subjected to an electromagnetic field. % represents the particle loading by weight in the NIPAAm–PEG400DMA nanocomposite. $N = 3$, ±SD.

most of the drug was released in 1 h (Fig. 5). A faster release rate is expected when the composite is swollen (the mesh size of the systems is large), resulting in faster diffusion. Results of the set placed outside the field show that magnetic nanoparticles only slightly reduce the drug release rate.

On the application of the alternating magnetic field, the hydrogel nanocomposite gives about 25% reduction in dye release in 1 h. On the other hand, the hydrogel with no particles is unaffected by the field. We speculate that this suppression in release is a result of the collapse of the hydrogel network with heating. As observed in dry heating (Fig. 4), the application of an alternating magnetic field leads to high temperatures. If the temperatures generated are above the LCST, they can cause negative temperature-sensitive network of NIPAAm to collapse, shrinking the mesh size. Even when a field is not applied, there is a slight decrease in the release from the nanocomposite hydrogel system compared with that from hydrogel systems with no particles. This effect could potentially be attributed to affinity between particles and drug, and is currently being studied further.

The analysis of diffusion aspects of dye release was done by early time release data using methods described elsewhere [29]. The calculated power law exponent and effective diffusivity values are presented in Table 1. The effective diffusivity in the case of the 5 wt.% nanocomposite with the field ON is less than the other cases by a factor of five. This suggests that the hydrogel network collapses as the temperature increases above the LCST. Thus, drug release can be remotely controlled by the application of an alternating magnetic field. Extensive analysis of the heating time and ON–OFF durations is in progress to gain further insight into the effects of the alternating magnetic field and the resultant heating on the drug release rate. Some of the factors that can be used to modulate the release rate are hydrogel composition, nanoparticles loading, field exposure time and field strength.

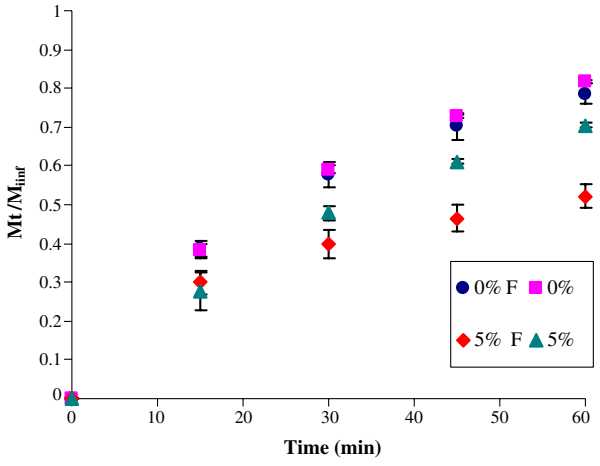

Fig. 5. Controlled drug release from nanocomposites in an electromagnetic field. % represents the particle loading by weight in the NIPAAm–PEG400DMA nanocomposite. F represents the application of a magnetic field. $N = 3$, ±SD.

Table 1.
Pyrocatechol Violet diffusion coefficients and power law exponents with varying particle loadings and electromagnetic field

Sample	Particles (%)	Field	Pyrocatechol Violet diffusion coefficient ($\times 10^8$ cm^2 s^{-1})	Power law exponent n
0%	0	OFF	3.064	0.59
0%F	0	ON	2.616	0.55
5%	5	OFF	2.870	0.73
5%F	5	ON	0.672	0.40

4. Conclusion

In conclusion, magnetic nanocomposites of NIPAAm show negative temperature sensitivity. The temperature sensitivity and swelling transition temperature can be controlled by the composition of NIPAAm in the hydrogel system. When exposed to an external alternating magnetic field, the heating of superparamagnetic Fe_3O_4 particles leads to a rise in the temperature of the nanocomposite system. This rise in temperature can be controlled by the particle loadings of the system. RC drug release was demonstrated from magnetic nanocomposites using an alternating magnetic field. The suppression of the release is speculated to be a result of the collapse of the hydrogel network with heating. This class of biomaterials holds promise for use in RC drug delivery systems for the pulsatile release of drug molecules on demand. Further analysis is underway to further understand the factors that control the drug delivery rate.

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