Multifunctional Magnetic Hydrogels with Polyethylene Glycol-Derivative Colloidal Nanospheres for Drug Delivery and Hyperthermia Applications

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ABSTRACT

A novel magneto-active gel based nanomaterial system is presented to provide precise control of temperature to a localized area in response to externally controlled magnetic stimuli. Integration of ferromagnetic nanoparticles (Fe_3O_4) in the polyethylene glycol (PEG) based thermo-responsive polymer provides the swelling and de-swelling behavior of magnetic stimuli controlled system by generating the heat due to the hysteresis loss of Fe_3O_4 under exposure in an alternating magnetic field. The shrinkage and heating capability of the nanomaterial system are investigated. Magnetic nanoparticle dependent shrinkage rate, actuation efficiency and temperature generation are ideal for various applications like magnetic particle/fluid based hyperthermia, magnetically controllable micro/nano pump drug delivery devices. Detail characterization of the magnetic hydrogel in terms of shrinkage and heating efficiency are in progress.

Keywords- ferromagnetic nanoparticles, magneto-active hydrogels, microfluidics, thermoresponsive.

1 INTRODUCTION

In the last ten years, there has been an explosion of advances in the fields of structured and intelligent materials science and based on tunable nanomaterial properties, micro/nano devices and magnetically controllable biomedical applications have been constantly amended so as to make them more comprehensive. The ability to actively manipulate fluid-flow patterns through microfluidic devices or target specific heat generation inside the body are increasingly becoming more and more important to many current applications and vital to the development of more complex systems/delivery mechanisms in the future. The small volume of sample and fast response are the primary features of microfluidics and nano-scale drug delivery system. The working principle of a typical actively controlled valve to date relies on its mechanical or electromagnetic properties. However, the issues of biocompatibility, packaging and mechanical/electrical integration, actuation and multifunctionality lead to the search for smarter valve materials with enhanced actuation efficiency and better performance level. Magnetic responsive hydrogels has become an interesting subject of study as they offer several potential advantages over other material systems for the controlled release of drugs, local heating of the target region leaving all other regions unaffected and the temperature control within as well as outside the target region due to their response to the magnetic stimuli. Because of the hysterisis loss from the magnetic nano particles, temperature of the system goes up, and once the temperature crosses the lower critical solution temperature (LCST), the thermoresponsive gel goes under large contraction. In this present work, the goal is to design a magneto active nanomaterial system, which can be externally tuned to change its shape or size and has the potential of generating local heat at the targeted area. The idea is to develop a magnetic and hydrogel nanocomposite material whereby the magnetic material will be responsible for heating up the system and the de-swelled hydrogel will release the drugs and/or control the fluid flow through the microfluidic channel, simultaneously. The heat was generated inside the gel due to the hysteresis loss of Magnetite (Fe_3O_4) under exposure in an alternating magnetic field. Magnetic nanopartcles were primarily being used as contrast agents in magnetic resonance imaging and for magnetic cell sorting and magnetic immunoasseys [1-2]. However, recently researchers have engineered their chemical and physical properties to apply them as intelligent carriers in controlled drug delivery systems [3]. Development of magnetic particle/fluid hyperthermia treatment for cancerous tumors and the controlled and direct transport of phermaceuticals and theraptic genes have met with more limited success [4-7]. Magneto-active hydrogels have also been used in the development of a nanomaterial system for controlled conformal changes under an alternating magnetic field for soft robotic applications or for cell targeting in drug delivery [8-9]. Magnetite provides the most attractive magnetic material of common use due to its strong magnetic property and low toxicity [10]. The integration of magnetic nanoparticles in hydrogel therefore provides a new generation of material system for magnetic force based immunoassay. Hydrogels based on poly(N-isopropylacrylamide) (PNIPAM) or PEG are well known thermoresponsive polymers that undergoes a volume phase transition across the low critical solution (LCST) [11-12]. Their excellent biocompatibility suggests the use in the applications of microfluidic systems and drug delivery applications. Therefore, the inherent temperature-sensitive swelling properties of the polymers offer the potential to control gel performance with an alternating electromagnetic field. Use of magnetism as a stimulus is particularly attractive as it is easily directed to specific locations within a channel network, possibly allowing further control. A cost effective, simple yet highly efficient magnetically drivable system can be designed as thermal and magnetic response can be tuned varying the size and concentration of the embedded nanoparticles and magnitude as well as frequency of the magnetic field, making them easy to operate with simple magnetic excitation These systems can be effective for many purposes, like magnetic drug delivery device, magnetic fluid based hyperthermia applications, magnetic nano valve, soft robotic applications and magnetic resonance imaging.

The shrinkage rates of the nanomaterial systems at the bulk and micro/nano scale are investigated. Both PNIPAM and PEG based systems have been synthesized and magnetic heating properties have been investigated. Polymer and magnetic nanoparticle concentration is selected to provide optimum rigidity and physical motion of the embedded magnetic nanoparticles and therefore, the extent of the deformation.

2 EXPERIMENTAL

2.1 Magnetic Field Generator

An efficient magnetic field generator is designed and constructed to test the de-swelling rate of the magnetic hydrogel. This device consists of an AC signal generator, a power amplifier, and two Helmholtz coils. A commercial function generator, LEADER LFG-1300S, generates AC signal. The power amplifier is a classic op-amp-plus-power-transistor design with multiple power transistors parallel to increase the output current. During testing, the magnetic hydrogel sample is placed between the two Helmholtz coils. The frequency and magnetic field strength can be adjusted conveniently from the function generator and measured by a Hall effect sensor.

2.2 Transmission Electron Microscopy

Transmission Electron Micrographs show the size and distribution of iron oxide nanoparticles inside the gel nanospheres. A TECNAI High Resolution Transmission Electron Microscope (HRTEM) was used to observe the morphology of the iron oxide nanocrystals. HRTEM images were obtained under an accelerating voltage of 200 kV. In the HRTEM image (Fig.1), a near homogeneous particle distribution was observed. Some degree of localized coagulation is noticed, which comes from nanoparticle magnetic property; but overall, uniform distribution for heat generation purpose has been achieved.

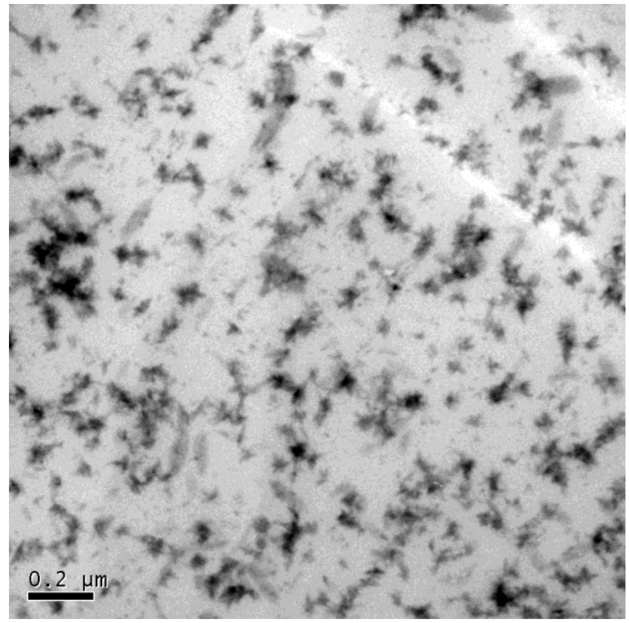

Figure 1: High Resolution Transmission Electron Microscope image showing the magnetic- nanoparticle distribution inside the hydrogel nanosphere.

2.3 Optical Microscopy and Thermal Response Measurement

A high resolution Zeiss Axiovert 200M optical microscope was used to observe the shape of the magnetic gel (bulk and micro-scale) before and after placing in the AC magnetic field. The imaging was performed with an attached Spot camera with 6.45micrometer pixel size. For micro fluidic channel temperature regulation, a 25 mm diameter thermal chamber was placed under the microscope and the channel was kept inside the isolated chamber. Temperature of the chamber was regulated (Fenwal Inc., Ashland, Mass.; model 551) from 22°C to 70°C within three minutes. 2 frames per second were captured during the experiment.

3 RESULTS AND DISCUSSION

Magnetic and thermal actuation of the gel have been confirmed. In both cases, the nanocomposite material collapses once the temperature crosses LCST. Volumetric changes of the magnetic PEG nano-spheres were compared against widely used PNIPAM nano-spheres in the range of 20-40°C by dynamic light scattering measurements and electron microscopy. Specific absorption rate for the magnetic hydrogel nanospheres (PNIPAM and PEG) have been measured. Both de-swelling and LCST were not affected due to nanoparticle incorporation. Moreover, as PEG is anti-immunogenic and FDA-approved, this innovative application has led to a fast-responsive, magnetic hydrogel system consisting of all FDA-approved bio-materials. For microfluidics application, valve opening time for the microfluidic channel was compared against the bulk scale for similar shrinkage. Detailed studies of the de-swelling response and temperature generation against polymer concentration (gel stiffness) and nanoparticle density are in progress.

4 CONCLUSION

As the heat generation is controlled by tuning the magnetic field and frequency, this ability can allow one to design a series of valve or actuators in a microfluidic chamber or other type of microfluidic devices, which could be activated by changing the magnetic field (using magnetic cores) or particle size and concentration. Differential control could be achieved either by using multiple materials sensitive to different magnetic fields or by using one material subjected to varying field, or a combination of these approaches. Additionally, the LCST of the magnetic gel system could be tailored by altering the copolymer concentration. By raising the LCST, the system can be operated at higher temperatures. The smaller size of the nanoparticles and low concentration facilitated the gel to maintain its swelling and de-swelling property unaffected, yet the actuation was possible under very small magnetic field, thus bringing down the power consumption, toxicity and enhancing gel performance. Nanoshells are particularly attractive for such a system. Also, the temperature can precisely be controlled inside the body within a very small area, which has the potential to achieve the target specific cellular heating for hyperthermia applications at the nano-scale. Magnetic particles hold the added advantage of being the contrast enhancer, thus can play an important role in detection and imaging. Thermoresponsive behavior of the hydrogel system holds the key for controlled release of drugs and can be tuned externally. The enhanced shrinkage rate and actuation efficiency is ideal for various applications like magnetic micro/nano pump, magnetic field controlled drug delivery devices and magnetic switch applications by allowing one to incorporate many independently controlled components within a single device.

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