Synthesis of superparamagnetic magnetite nanoparticles for thermoresponsive drug delivery

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ABSTRACT

Superparamagnetic magnetite nanoparticles (MNPs), Fe_3O_4, were synthesized via the modified coprecipitation method. The morphology of these MNPs is polyhedral. The particle size of MNPs ranged from 20 to 100 nm. For combined hyperthermia and thermoresponsive drug delivery applications, the heating element, MNPs, in the core of drug carriers should increase the temperature of the target up to 43 °C under AC magnetic field. Therefore, the heating effect of these MNPs under AC magnetic field produced by a high frequency induction heater was examined. From the results, one can see that as the weight of these MNPs increased, the higher the increase in temperature was observed. Besides, the temperature increase has reached 8.7 °C in 15 min, when 20 mg MNPs were added to 2 ml water. The preliminary temperature rise suggests that it is applicable for hyperthermia and thermoresponsive drug delivery.

Keywords: hyperthermia, drug delivery, magnetic nanoparticles, magnetite, nanoparticles

1 INTRODUCTION

Magnetic nanoparticles have been proposed for many applications, including audio devices, magnetic information recording, sensors [1,2], and some biomedical applications [3,4]. In biomedical applications, magnetite has been widely researched due to its biocompatibility [5] and easy synthesis. Furthermore, to be applicable to the biomedical field, such as hyperthermia and drug delivery, these magnetite particles should be nanosized and have ability to increase the temperature of the target above 43°C. In this report, MNPs were synthesized and analyzed. The possibility of coating thermoresponsive polymer for drug delivery application is also discussed.

2 EXPERIMENTAL

2.1 Materials

Fe(III) chloride hexahydrate (99%) was purchased from Acros and used as received. Sodium hydroxide (99%) and sodium sulfite (99%) were purchased from Riedel-de Haën. Poly(2-ethyl-2-oxazoline) (MW~5,000) was purchased from Alfa Aesar. Other chemicals were of analytical grade and used without further purification. Distilled and deionized water was used throughout the work.

2.2 Synthesis of Fe_3O_4 nanoparticles

MNPs were first synthesized via the modified coprecipiatation according to literature [6]. In this process, 50 ml of 1.0 M $FeCl_3$ in 2.0 M HCl aqueous solution and 25 ml of 2.0 M Na_2SO_3 aqueous solution were added in 100 ml of 10.0 M NaOH aqueous solution with vigorous stirring at 70 °C under N_2. After precipitation, these MNPs were purified by centrifugation, and the supernatant was discarded with the assistance of a magnet; this procedure was repeated several times. Finally, these MNPs were lyophilized.

2.3 Morphology of Fe_3O_4 nanoparticles

The morphology of MNPs was determined using a JOEL JEM-1230 transmission electron microscope (TEM). Samples for TEM measurement were prepared by dispersing the particles in water and then depositing on carbon-coated 200–300 mesh copper grids and dried.

2.4 X-ray diffraction analysis

X-ray diffraction measurements with monochromatic Cu $K\alpha$ radiation were done to investigate the crystal structure of the magnetite particles.

2.5 Measurement of particle size distribution

The size distribution of MNPs was measured at 25 °C with a dynamic laser scattering analyzer (Malvern Zeta Sizer 3000H). Before the measurements, these particles were dispersed in water and pretreated by ultrasonication for 5 min.

2.6 SQUID analysis

The magnetization curves of the MNPs were measured at 25 °C with a superconducting quantum interface device (SQUID) magnetometer (Quantum Design MPMS7). The applied magnetic field was ranged between ±10,000 gauss.

2.7 Hyperthermia test

The heating effect of these MNPs under AC magnetic field produced by a medium-high frequency induction heater (New HP-Cube 15 kw) was examined. The strength and frequency of the applied magnetic field were 88.24 kA/m and 69.44 kHz, respectively. Different weights of magnetite particles were added into 2.0 ml water in a test tube situated in the middle of the heating coil of the induction heater. The time courses of temperature increase (ΔT) were recorded with a Pt thermocouple (Thermo Recoder TR-81).

2.8 Turbidity Measurements

The optical transmittance of aqueous poly(2-ethyl-2-oxazoline) polymer solution was monitored at 500 nm by means of a UV/vis spectrophotometer (V-570, Jasco) [7]. The samples (1.0 wt %) were placed in Teflon-stopped quartz cuvettes. The transmittance of the copolymer solution at room temperature was set at 100% and the temperature range employed was 50-95 °C. At least 5 min was allowed for the sample to reach thermal equilibrium. The phase transition temperature is defined as the temperature at which 50% of the maximum transmittance change of the polymer solution has attained.

3 RESULTS AND DISSCUSSIONS

According to Fig. 1, the magnetic particles obtained have six diffraction peaks at $2\theta = 30.2°$, 35.6°, 43.2°, 53.5°, 57.5° and 62.8°, which belongs to those of standard Fe_3O_4 crystal. Comparing to the work of Qu *et al.* [6], our magnetite particles were synthesized under nitrogen purge, and with the above-mentioned treatment, the degree of crystallization of the particles can be enhanced. Besides, the magnetic property also can be affected by this treatment (see Fig. 2). The saturated magnetization and susceptibility were both enhanced after nitrogen purge.

According to the TEM result, as shown in Fig. 3, the shape of magnetite particles synthesized is polyhedral and their sized ranged from 20 to 100 nm. Moreover, these nanoparticles tend to aggregate, which is probably due to free from the surface modification or under the influence of a magnetic field caused by the electron beam. The result of dynamic laser scattering (Fig. 4) shows that the particle size distribution is quite narrow and is consistent with the TEM result (Fig. 3).

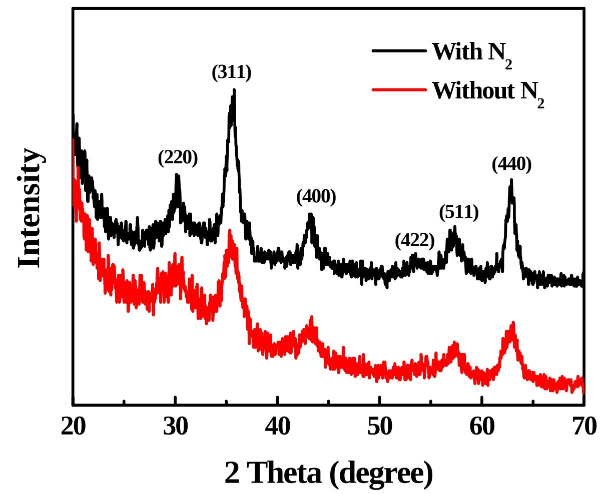

Fig. 1 XRD analysis of Fe_3O_4 nanoparticles.

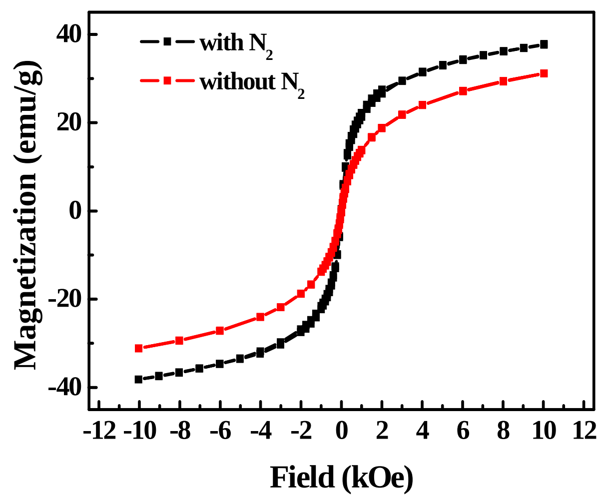

Fig. 2 Magnetization curve of pure magnetite particles at 298 K.

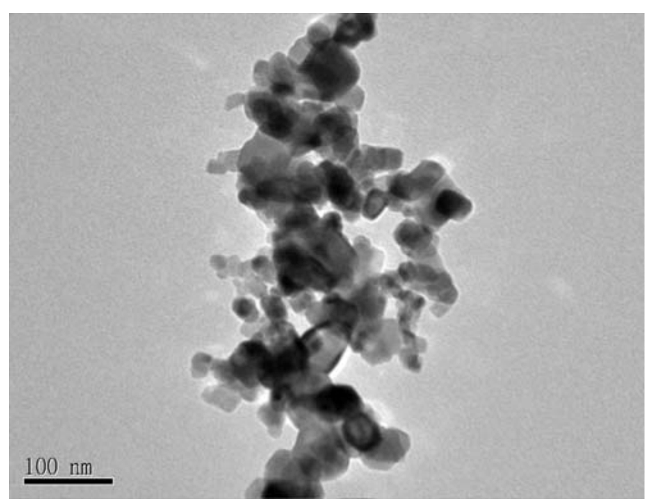

Fig. 3 TEM photograph of the magnetite nanoparticles.

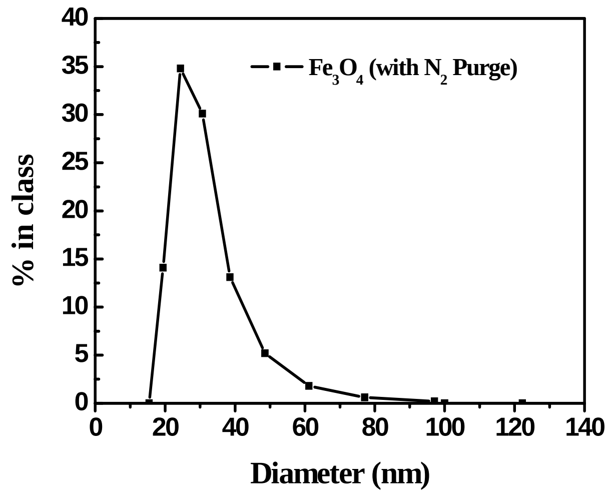

Fig. 4 Particle size distribution of the ferrofluid.

For the hyperthermia application, the heating element, MNPs, should increase the temperature of the target up to 43 °C under AC magnetic field. From the results of hyperthermia tests (Fig. 5), one can see that as the weight of these magnetite particles increased, the higher the increase in temperature was noticed. Besides, the temperature increase reached 8.7 °C in 15 min, when 20 mg MNPs were added into 2 ml water, which is applicable for hyperthermia. However, the heating ability of the MNPs without nitrogen purge (data not shown) is worse than that of the MNPs with nitrogen purge.

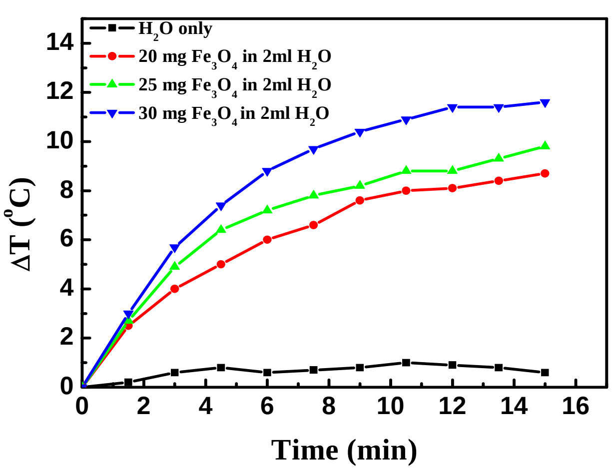

Fig. 5 The heating effect for different amounts of magnetite particles under AC magnetic field (88.24 kA/m, 69.44 kHz).

For drug delivery application, we chose poly(2-ethyl-2-oxazoline, a highly hydrophilic polymer, as a thermoresponsive drug delivery carrier. Its lower critical solution temperature (LCST) is about 82.5 °C (see Fig. 6), which is too high to be used for thermoresponsive drug delivery. Therefore, this polymer has been copolymerized with some more hydrophobic polymer, such as polylactide, to reduce its LCST to about 43 °C [8]. After that, this copolymer can be used as a carrier to entrap the magnetite nanoparticles and cancer drugs. The latter experiments are still under investigation.

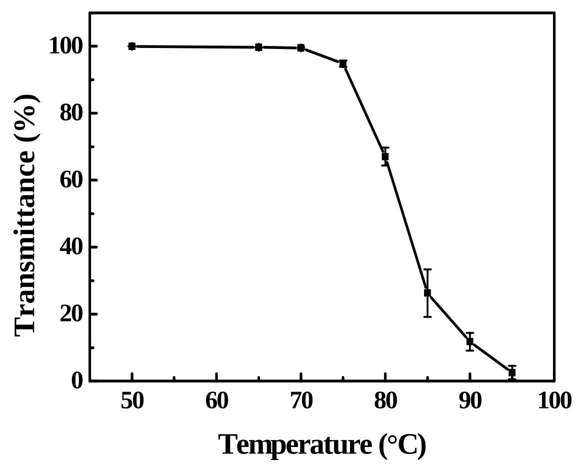

Fig. 6 Transmittance changes at 500 nm of 1.0 wt % poly(2-ethyl-2-oxazoline) solutions

4 CONCLUSION

MNPs were synthesized and their physical properties were examined. These NMPs were nanosized and superparamagnetic. Furthermore, these nanoparticles are able to heat water with an increment of 8.7 °C in 15 min, which can be used for hyperthermia. Moreover, if these naniparticles can be entrapped in some thermosensitive polymers or copolymers, they can be used as a heating element for thermoresponsive drug delivery.

5 ACKNOWLEDGEMENT

his work was sponsored by the National Research Council of Taiwan, The Republic of China, under grants NSC 94-2218-E-006-031 and NSC 95-2221-E-002-307.

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