Magnetic fluid based on Fe$_3$O$_4$ nanoparticles: Preparation and hyperthermia application

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Abstract. The paper presents results of research on preparing the magnetic fluid based on Fe$_3$O$_4$ nanoparticles and its potential hyperthermia application. Magnetic fluids were manufactured by dissolving superparamagnetic nanoparticles coated by suitable biocompatible starch layer during the co-precipitation processing. The coated particle size changes in range of 15÷17 nm were characterized by FESEM images. At room temperature, the samples exhibit super-paramagnetic behaviour with a saturation moment of 65 emu/g. The concentration of magnetic nanoparticles contained in carried liquid reach to 15 mg/ml. The magnetic fluid was used as a mediator for heating by an AC magnetic field with the frequency of 184 kHz and field strength of 12 kA/m. The dependence of heating on nanoparticle concentration was observed and it implied that the magnetic fluid is a suitable mediator for cancer treatment by hyperthermia application with appropriate controlling the heating temperature ranges from 45 to 50°C.

Keywords: Nanotechnology, Fe$_3$O$_4$ nanoparticles, hyperthermia application.

1. Introduction

In recent years, the magnetic fluids have attracted great interest in research due to their offer of many possibilities for numerous in-vivo applications such as separation cells [1], magnetic resonance imaging as contrast agents [2], magnetic drug targeting and delivery [3], and especially they can generate heat in an alternating magnetic field and become promising material for tumor hyperthermia. Magnetic Hyperthermia is a method of cancer treatment using magnetic nanoparticles. In the process, magnetic particles were injected locally into cancer tissues that can be heated up to the required temperature of about 45°C with the help of an external alternating magnetic field. The method was first introduced by Gilchrist et al. since 50 years ago [4]. By now, several works devoted to this subject were reported [5, 6, 7]. It was found that magnetic fluid based on superparamagnetic Fe$_3$O$_4$ nanoparticles coated by biocompatible layer is suitable for hyperthermia because the particles have a high magnetic moment, strong magnetic specific loss power (SLP) and non-toxicity. The Food and Drug Administration approved that superparamagnetic Fe$_3$O$_4$ nanoparticles is biocompatible with human body [8]. In addition, for superparamagnetic nanoparticles where the magnetic hysteresis is vanished, the Néel and the Brownian losses are dominant so the specific loss power of magnetic fluid strongly depends on the alternating magnetic field and the nature and structure of the particles such as particle size and size distribution, anisotropy constant, saturation magnetization and surface
modification [9, 10, 11]. However, the challenging of work is the development of heating mediator with high specific loss power, which allows reduction of ferrofluid doses in-vivo. In the aim of improving SLP of Fe₃O₄ nanoparticle, several methods were established [12, 13]. The highest value of SLP of 960 W/g at the field of 410 kHz and 10 kA/m was found for magnetosomes produced by magnetotactic bacteria [14]. Besides, it is important in hyperthermia to control saturation temperature in the range of 42÷47°C to destroy the cancerous cells within minimal damage to healthy tissue and limit negative side effects.

The purpose of this research was preparing magnetic fluid based on Fe₃O₄ nanoparticles that have high saturation magnetization to enhance the SLP value and focus on investigating the dependent of heating on the concentration of magnetic particles at alternating magnetic field. We are also able to control the heating temperature in the range of 42 to 47°C with low concentration of nanoparticles.

2. Experimental

1.1. Synthesis of Fe₃O₄ nanoparticles

Fe₃O₄ nanoparticles were prepared by the chemical co-precipitation method. Aqueous solution of FeCl₃, FeCl₂ salt were mixed and kept at 40°C while maintaining a molar ratio of Fe²⁺/Fe³⁺ = 1/2. The mixed solution was added by solution of NaOH under vigorous mechanical stirring for 30 minutes. The precipitation and formation of nanoferrites took place by a conversion of the metal salts into hydroxides and that, in turn, immediately transformed into ferrites. During the reactions, magnetic-stirring speed was kept at 1000 round/min.

1.2. Coating particles

Starch was dissolved in water with a concentration of 0.1 g/ml at 80°C. After the starch was thoroughly dissolved, the solution was immediately placed in a 60°C water bath and dropped into the obtained aqueous of dispersed Fe₃O₄ particles after a co-precipitation reaction at 80°C in 2 h. Around 50 wt.% of water was evaporated during the boiling. The remaining suspension was then cooled to 0°C within 12 h. The formed gels were washed with deionized water until the pH of the solution was lowered to less than 8.5. Excess salts and ions were then removed by washing. To cleave glycosides bond and reduce the polymer chain to an average molecular weigh, starch-coated iron oxide particles were oxidized by H₂O₂ solution.

1.3. Characterization

The structure and the morphological investigation of the studied sample were taken by X-ray diffraction (XRD) and field-emission scanning electron microscopy (FESEM), respectively. The magnetic properties were carried out by using vibrating sample magnetometer (VSM) and physical property measurement system (PPMS).

![Figure 1. The experimental set up for SLP values measurements.](image-url)
induction coil with a 4.5 cm diameter and a 6.3 cm length. During the heating experiment, the temperature of the sample was observed by using a Copper-Constantan thermocouple. The magnetic heating experimental setup is shown in figure 1.

3. Result and discussion

Figures 2 and 3 present the FESEM image of the uncoated powder particles and the coated particles of the magnetic fluid sample, respectively. The magnetic nanoparticles have a mean size about 15÷17 nm with a narrow distribution. For the coated samples, there is good dispersion of nanoparticles in matrix polymers (starch) and particles were capsulated by the polymer layer. The FESEM images of uncoated and coated particles also show that the coating layer is probably very thin because the coated particles size is not much larger than that of uncoated particles. A typical XRD pattern of the nanoparticles is presented in figure 4. It indicates that the samples are single phase with the inversed cubic spinel structure of Fe₃O₄. This success in fabricating high quality Fe₃O₄ nanoparticles is essential for further research work.

![Figure 2. FESEM image of uncoated particles.](image1)

![Figure 3. FESEM image of coated particles.](image2)

![Figure 4. XRD pattern of Fe₃O₄ nanoparticles of magnetic fluid.](image3)

The magnetic hysteresis loop of the magnetic fluid measured at room temperature was shown in figure 5. At the field strength of 1.2 kOe, the saturation magnetization of magnetic liquid is measured about 65 emu/g and the coercive field closed to zero. It means that the sample exhibited superparamagnetic behaviour and has high magnetization that determines the heating power in magnetic heating experiments [15].

Figure 6 presents the time-dependence of heating temperature of the magnetic fluid samples with particles concentration varying from 3 to 15 mg/ml exposing an alternating magnetic field having a frequency of 184 kHz and its field strength of 12 kA/m. After about 15÷20 minutes of heating, the temperature of the samples comes to saturation when the energy loss to the surrounding medium
equals to the energy generated by the alternating magnetic field. It is clear from this figure that the saturation temperature and rising temperature rate strongly depend on the concentration of particles in the liquid. The more concentrated samples have higher rising temperature rates and saturation temperatures (as shown in table 1). These dependences are almost linear as can be seen in figure 7.

Figure 5. The hysteresis loop at 300 K of the magnetic fluid.

Figure 6. The heating curves of the magnetic fluid with various particles concentration.

Figure 7. The dependence of the initial heating rate and saturation temperature on particles concentration.

The specific loss power (SLP) can be calculated by using the following formula [16]:

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SLP = \left( C \cdot m_s \cdot \frac{dT}{dt} \right) / m_i,
\]

where C is the specific heat capacity of magnetic liquid, which was accepted equal to that of water, because of the mass mi of iron oxide in the liquid is much smaller than water contained in it, m_s is the total mass of magnetic liquid, dT/dt is the initial temperature rising rate, which was defined at the moment of a few seconds after starting the heat. The SLP value was estimated for the magnetic liquid with various concentrations, presented in table 1.

Table 1. The initial heating rate, SLP and saturation temperature values of different particles concentration of magnetic fluid.

| Concentration of particles (mg/ml) | dT/dt (°C/s) | Saturation temperature (°C) | SLP values (W/g) |
|-----------------------------------|-------------|----------------------------|-----------------|
| 3                                 | 0.092       | 45                         | 129             |
| 6                                 | 0.141       | 53                         | 97              |
| 7                                 | 0.159       | 62                         | 94              |
| 12                                | 0.240       | 73                         | 83              |
| 15                                | 0.310       | 80                         | 86              |

The highest SLP value is approximately 129 W/g, estimated for the liquid with the smallest concentration (3 mg/ml) and decreasing with increasing concentration of particles in liquid. As is
known the response of magnetic nanoparticles is mainly derived by Néel and Brownian relaxation [15]. It is implied that the increasing concentration of magnetic particles would decrease distance between adjacent magnetic particles, and the interparticle interaction might affect the relaxation behaviour, that leads to reducing the SLP value. According to a previous report, magnetic particles with mean size of 15 nm and their SLP value of 100 W/g were effectively used in the tumour heating therapy [17]. Our results are particularly of interest for applications in the heating therapy because of the high SLP value at the examined magnetic field parameter (of 129 W/g) while allowing to achieve the saturation temperature of 45°C, which is ideally desired for cancer treatment application, with a minimal iron oxide dose.

4. Conclusion
The Fe₃O₄ nanoparticles and their starch-coated biocompatible ferrofluid have been successfully prepared by co-precipitation methods. The material exhibited the superparamagnetic behaviour with the magnetization is 65 emu/g and coated particles size are smaller than 20 nm. The heating ability investigation of the ferrofluid was performed under an alternating magnetic field of 184 kHz and field strength of 12 kA/m. The SLP of magnetic liquid linearly depends on nanoparticle concentration and achieve a high of 129 W/g at the low concentration of iron oxide. Ability of controlling the heating temperature of the magnetic liquid confirms its possibilities in hyperthermia applications

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