Thermo-magnetic stability of magnetic Fe₃O₄ nanoparticles for hyperthermia

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Monodispersed Fe₃O₄ magnetic particles adsorbed by amylase (such as citric acid (CA), carboxymethyl chitosan (CMCH) and β -cyclodextrin (CD)) were prepared by means of co-precipitation method. The absorption character of the samples was investigated by FT-IR, TG and VSM. It was found that the carboxyl (COOH groups) of amylase reacted with the hydroxyl (OH groups) on the surface of Fe₃O₄ particles, resulting in the formation of iron carboxylate that was adsorbed onto Fe₃O₄. The induction heating properties of the magnetic Fe₃O₄ nanoparticles in an alternating current magnetic field were also investigated and the thermo-magnetic stability in induction heating was discussed.

Keywords: Fe₃O₄; adsorption; thermo-magnetic stability; carboxylic; hyperthermia

1. Introduction

Magnetic nanoparticles (MNPs) have increasingly been used in the fields of bioscience and medicine with the rapid development of nanostructured materials and nanotechnology in the recent years [1–7]. These nanosystems, a novel modern medical technology, can be applied in tumor therapy. Acting as hyperthermia agents or chemotherapy and radiotherapy enhancement agents, they can deliver some amount of thermal energy to specified toxic tumors after heating up. This method of adequate heating could lead to more effective cell destruction [8, 9]. Magnetic fluids hyperthermia is another kind of medical technology which can be used in cancer therapy. Its treatment principle is to kill the cancer cells by raising the cell temperature above 43 °C and then dissipate the heat energy through the magnetic nanoparticles exposed to an alternating current magnetic field [10–13].

One approach for the preparation of aqueous-based magnetic fluids is to coat the magnetite nanoparticles with surfactant bilayers. Citric acid (CA) is an organic compound with three carboxyl groups. CA is not only able to react with Fe³⁺ on the surface of magnetic particles Fe₃O₄, but also has a good stability connected with the drugs having amino groups [14–16]. Carboxymethyl chitosan (CMCH) is also capable of binding medicine because it has two groups (amino and carboxyl) which can serve as chelation sites [17, 18]. Therefore, another novel magnetic nano-adsorbent for the efficient carrier of medicine, β -cyclodextrin (CD) came out due to the binding between the magnetic CMCH and the medicine [19]. In other words, these connected complexes result from weak interactions, such as hydrophobic effects, van der Waals interactions and hydrogen bonds [20].

Herein, we used the CA, CMCH and CD-bound magnetic nanoparticles as a heat medium, when preparing the samples by two-step co-precipitation methods. Depending on the physicochemical properties of these magnetic systems, it is necessary

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to study their properties in the application of hyperthermia. The structure, stability and magnetic properties of the covered magnetite nanoparticles have been investigated by Fourier transform infrared (FT-IR) spectroscopy, thermo-gravimetric (TG) analysis and magnetization curve measurement. Moreover, the induction heating properties of magnetic Fe₃O₄ nanoparticles in an alternating magnetic field were studied. In addition, the magnetic core used in thermotherapy was also discussed.

2. Experiments

2.1. Reagents

The inorganic reagents used in the study included: ferric chloride, ferrous chloride 4-hydrate (FeCl₂·4H₂O), 6-hydrate (FeCl₃·6H₂O) and 25 wt.% ammonia (NH₃·H₂O), which were purchased from Guangzhou Chemical Company, China. The organic reagents comprised: CMCH (Mw ≈ 20 kDa, Qingdao Hepe Biotechnology Company, China), citric acid CA (Shandong Lemon Biochemical Company, China) and β-cyclodextrin CD (Shandong Binzhou Zhiyuan Biotechnology Company, China). In the experiment distilled water was used. All the raw reagents were used without further purification.

2.2. Preparation of magnetic CA, CMCH and CD nanoparticles

Magnetite nanoparticles coated with CA, CMCH and CD were synthesized by a two-step process [21, 22]. According to the quantity of ammonia, the molar ratio of FeCl₂:FeCl₃:NH₃·H₂O was 1:2:16. The mixture was heated at 90 °C with stirring at 1200 rpm for 10 min, and then at 625 rpm for 2.5 hours. In order to obtain stable magnetic fluids, it was necessary to remove the excess of electrolytes from the solution. The particles were magnetically separated and washed with distilled water until the conductivity of the supernate was less than 50 μS/cm. The fluids with magnetic particles and aqueous mixture of different mass of CA, MCH and CD magnetite were mixed with an appropriate quantity of ammonia. The mixture was then heated

to 90 °C with stirring at 400 rpm for 2.5 hours. In order to remove the excess of CA, CMCH, CD and electrolytes from the stable magnetic fluid solution, the particles were magnetically separated and then washed with distilled water until the conductivity of the supernates as low as 50 μS/cm was achieved. Finally, the liquid magnetic particles were ultrasonically centrifuged at 2000 rpm for one hour, dried in vacuum at 90 °C for 24 hours, and then stored in a refrigerator at 4 °C. The magnetic fluids (15 ml each) which were put into 25 ml vials with a 3.6 cm diameter were heated in the high-frequency magnetic induction heater machine with a two-loop induction coil with a 4 cm diameter at 50 kHz and 450 A output current [23]. The increasing temperature of the magnetic fluids was recorded, and the magnetic properties of the fluids before and after heating were analyzed.

2.3. Characterization of magnetic CA, CMCH and CD nanoparticles

The FT-IR spectra of nanoparticles coated with CA, CMCH and CD were recorded by Bio-Rad FTS 3000 Fourier transform infrared spectrometer. Magnetite nanoparticles coated with CA, CMCH and CD were dried and mixed with KBr powder, and then compressed into pellets. The weight percentage of CA, CMCH and CD bound to Fe₃O₄ nanoparticles was estimated by thermogravimetric (TG) analysis with Netzsch TG 209 instrument, at a heating rate of 10 °C/min from room temperature to 700 °C in the atmosphere of N₂. The magnetization curve of magnetic fluids at 25 °C was measured at a Lakeshore 7404 vibration sample magnetometer. The heating curves of magnetic fluids were recorded by heating in the SP15 high frequency induction heating equipment (Shuangping Instrument Technology, Co., Ltd., Shenzhen, China), and alcohol thermometer was applied for the temperature measurement. After the exposure time started, the samples needed 10 min to achieve the desired temperature. Magnetic liquid properties at different concentrations were tested with the use of an AC magnetic field generator [24–26]. The frequency applied in the current work was 50 kHz, which is within the scope of biomedical applications [27].

The experimental magnetic induction heating setup is shown schematically in Fig. 1 [28].

Fig. 1. Experimental setup for measurement of heating performance of magnetic fluids.

3. Results and discussion

To confirm the binding of CA, CMCH and CD on the surfaces of the magnetic nanoparticles, FT-IR spectra of the magnetic nanoparticles were investigated. Fig. 2 shows the FT-IR spectra of naked magnetic nanoparticles (MNP) (a mean size about 8 nm) [29], CA-MNP (a mean size about 30 nm with 11 nanoscale coatings) [30], CMCH-MNP (a mean size about 24.5 nm with 8 nanoscale coatings) [31] and CD-MNP (a mean size about 50 nm with 21 nanoscale coatings) [32] in the 300 cm⁻¹ to 2000 cm⁻¹ wave number range. By comparing the FT-IR spectra of the Fe₃O₄ powders, we can see the band of Fe–O in tetrahedral structure, whose characteristic absorption is 585 cm⁻¹. As shown in Fig. 2, the two main characteristic peaks of the bands of COOM (M represents metal ions) appear at 1625 cm⁻¹ (CA), 1621 cm⁻¹ (CMCH), 1633 cm⁻¹ (CD), 1396 cm⁻¹ (CA), 1401 cm⁻¹ (CD), 1407 cm⁻¹ (CD). This indicates that the COOH groups of CA, CMCH and CD react with the OH bonds on the surface of Fe₃O₄ particles to form iron carboxylate [33, 34]. Although CD does not have the COOH groups, the carboxyl group COOM on the surface of Fe₃O₄ magnetic particle can be regarded as the result of oxidation of aldehyde group and alcohol hydroxyl group in CD by Fe³⁺ in acid

condition. By the hydrolysis reaction of hydroxyl CD with the carboxyl group, CD can be adsorbed on the surface of magnetic nanoparticles [20]. The peak at 1030 cm⁻¹ corresponds to the antisymmetric glycosidic $\nu_a(\text{C–O–C})$ vibrations and coupled $\nu(\text{C–C/C–O})$ stretching vibrations [20].

Fig. 2. The FT-IR spectra of magnetic particles modified by (a) naked, (b) CA, (c) CMCH, (d) CD.

The results showed that the organic molecules were adsorbed on the surface of Fe₃O₄ magnetic particles, with two oxygens of the deprotonated carboxylic acid bound to Fe³⁺. Thus, the chemical adsorption mode can be expressed as shown in Fig. 2, which means, a single layer of CA, CMCH and CD molecules have been adsorbed on the surface of the nanoparticles. The chemisorbed quantities can be estimated from the intensity ratio of characteristic peaks of COOM band. According to this, it was found that the adsorption quantity of CA-MNP was higher than that of the other two kinds of MNPs.

The amount of CA-MNP, CMCH-MNP and CD-MNP adsorbed on the surface of MNP can be estimated by thermogravimetric analysis of the coated magnetic nanoparticles. Fig. 3 shows typical TG curves of Fe₃O₄ nanoparticles covering CA-MNP, CMCH-MNP, and CD-MNP. The TG curves of CA-MNP, CMCH-MNP and CD-MNP show two steps of weight loss, one at 140 °C due to evaporation of residual water and the other for CA, CMCH and CD losses in the range of 140 °C to 500 °C.

From RT to 140 °C, massive weight loss resulting from significant heat absorption can be observed, which is due to the evaporation of water in the samples [34]. In addition, as shown in Fig. 3, the huge weight loss between 140 °C and 500 °C is due to the desorption and preliminary degradation of CA-MNP, CMCH-MNP and CD-MNP, and then, at about 266 °C, the weak heat absorption is due to the further degradation of CA, CMCH and CD. It has been found that in the samples (CMCH) containing about 87.7 wt.% of Fe_3O_4 and 8.79 (96.49 – 87.7) wt.% of CMCH, the mass ratio of CMCH to Fe_3O_4 was about 0.1. On account of small molecular weight, the mass ratio of CA to Fe_3O_4 was about 0.061. Because of similar average molecular weight, the mass ratio of CD to Fe_3O_4 was about 0.089. This result also indicated that CA, CMCH and CD molecules have successfully grafted onto the magnetic surface [35].

Fig. 3. Typical TG curves for the CA (b), CMCH (c) and CD (d) bound Fe_3O_4 nanoparticles.

From Fig. 4 we can conclude that the temperature of the magnetic fluids with different saturation magnetization increases with time under an alternating magnetic field with a frequency of 50 kHz, alternating current 450 A and a field strength of 10 kA/m. The temperature of the samples with high saturation magnetization (1.8835 emu/g) rises to 63 °C from room temperature RT in 900 s, whereas the temperature of the samples with lower saturation magnetization rises to lower temperature (35 °C to 45 °C) from RT. The results indicate that the

saturation magnetization of the magnetic fluids has a great influence on the final temperature.

Temperature of the magnetic fluids increases as the intensity of saturation magnetization of the fluids increases. However, when the temperature reaches saturation, it does not increase any longer. In general, the heating effect in the material depends on various factors, such as size, structure, magnetic properties, bilayer surfactant [36] and so on. The heat generated by the magnetic fluid is equal to the heat released to the environment, so the temperature does not rise with time.

The heating tests of the samples of the magnetite nanoparticles were carried out with different surfactant bilayers. As shown in Fig. 4, with an increase in concentration of the unmodified (naked) magnetic liquids, the temperature of the magnetic fluids increases rapidly. The maximum heating temperature can reach 45 °C in the unmodified (naked) magnetic liquids (0.89375 emu/g). When the magnetite nanoparticles were modified by different surfactant bilayers, the final temperature can be as high as 43 °C in the modified magnetic liquids (0.8000 emu/g or so). However, in the process of heating, the rising temperatures in the magnetic fluids with similar saturation magnetization and different surfactant bilayers do not differ very much. The high-frequency induction heating rate and maximum rising temperature are directly related to the saturation magnetization of magnetic fluids [36]. The heating rate of similar CA, CMCH and CD-modified magnetic fluids is lower than that of unmodified (naked) magnetic fluids, which is caused by the heat capacity of the magnetic particles and the heat dissipation process of magnetic fluids modified by CA, CMCH and CD.

In the process of high-frequency induction heating, there are many factors that affect the thermomagnetic properties of the samples, such as the heating temperature, the structure and composition of the materials [37, 38]. It can be seen from Fig. 5 that the saturation magnetization of the magnetic fluids after increasing temperature under an alternating magnetic field is lower than that before heating. The curves of samples 3 and 2 in Fig. 5 are similar due to the similar saturation magnetization. Some magnetic particles in the magnetic fluids are

Fig. 4. Temperature increase in magnetic fluids for the CA (a), CMCH (b) and CD (c) - bound Fe_3O_4 nanoparticles under AC magnetic field.

heating elements and the temperature of the particles is higher than the fluids temperature [39]. These magnetic particles may be oxidized after heating in the alternating magnetic field and lose

Fig. 5. Magnetic hysteresis of magnetic fluids for the CA (a), CMCH (b) and CD (c)-bound Fe_3O_4 nanoparticles under AC magnetic field.

their magnetism, causing the decrease of the saturation magnetization.

Magnetic change in CA, CMCH and CD modified magnetic fluids is slightly lower than that in unmodified (naked) magnetic fluid with the similar saturation magnetization, which is attributed to the lower rise of temperature in the modified fluids and the encapsulation of CA, CMCH and CD hindering the reaction of oxygen with divalent iron. The results show that the number of magnetic oxidized Fe_3O_4 particles was reduced in the heating process. But for the sample 1 including three kinds of modified magnetic fluids, the saturation magnetization after temperature increasing is slightly larger than that during temperature rise. This is mainly because the maximum temperature is relatively low and the magnetic particles are less oxidized. Furthermore, the ratio of magnetic particles in the magnetic fluids has also increased because of water evaporation. Therefore, the total saturation magnetization has increased. Magnetic fluids must be heated from 41 °C to 46 °C in practical medical hyperthermia applications [40]. As the magnetic properties of the magnetic fluids are only slightly weakened after the temperature increase, the magnetic fluids have a certain application value in the medical field.

4. Conclusion

High-quality monodispersed MNPs modified by CA, CMCH and CD were synthesized by chemical co-precipitation method. The thermal-magnetic properties of the magnetic fluids before and after high-frequency induction heating were investigated. The results showed that the stronger the intensity of magnetic fluid, the higher rising rate and maximum temperature of the magnetic fluids. Saturation magnetization of magnetic fluids can be reduced after heating. For the magnetic fluids with a low saturation magnetization, saturation magnetization changes little before and after heating. For the magnetic fluids with high saturation magnetization, thermal-magnetic properties have also only slightly changed after temperature rising. The excellent stability of CA, CMCH and CD modified magnetic fluids indicates their potential application in magnetic fluid hyperthermia.

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