Synthesis conditions of nano-sized magnetite powder using reverse coprecipitation method for thermal coagulation therapy

Hiromichi AONO, Taiga NAGAMACHI, Takashi NAOHARA, Yoshiteru ITAGAKI, Tsunehiro MAEHARA and Hideyuki HIRAZAWA*

Graduate School of Science and Engineering, Ehime University, Matsuyama 790–8577, Japan
*Department of Environmental Materials Engineering, Niihama National College of Technology, Niihama 792–8580, Japan

The synthesis conditions of a nano-sized magnetite powder using a reverse coprecipitation method were studied in order to control the particle size and the heat generation ability in an AC magnetic field for thermal coagulation therapy. A low temperature reaction and high concentration of the mixed iron ions as the starting materials in solution increased the particle size of the magnetite powder. The particle size decreased with an increase in the concentration of the coexisting Na⁺ and Cl⁻ ions. The particle size was enhanced with an increase in the $R = \frac{Fe^{2+}/(Fe^{2+} + Fe^{3+})}{Fe^{3+}/(Fe^{2+} + Fe^{3+})}$ molar ratio of the divalent iron, and the maximum heat generation ability was obtained at the $R = 0.33$ molar ratio. The maximum heat generation ability of 0.25–0.28 W·g⁻¹ in the AC magnetic field (370 kHz, 1.77 kA·m⁻²) was obtained for the magnetite having an ca. 13–14 nm particle size.

Key-words : Magnetite, Nano sized powder, Chemical synthesis, Thermal coagulation therapy, AC magnetic field

1. Introduction

One of the most important treatments for cancer tissues is thermal coagulation therapy such as microwave coagulation therapy and radio-frequency ablation therapy. The thermal effects are also expected during application of an alternating magnetic field from external coils to the tumors with a magnetic material. The magnetic materials, such as the needle-type and powder-type materials, have been reported for this type of therapy. For the powder-type material, a drug delivery system (DDS) using nano-sized magnetic particles encapsulated in a liposome (≤100 nm) can be used for this therapy. Heat generation from the magnetic particles in the AC magnetic field locally damages the cancer tumor, then it can be expected that the immune system begins to act for a spontaneous cure.

The nano-sized magnetite ($Fe_3O_4$) particles prepared by the chemical synthesis method have been investigated as the candidate magnetic material, since a nano-sized magnetite powder having a heat generation property in an AC magnetic field can be easily prepared by a coprecipitation method. We have investigated many types of ferrites having a higher heat generation ability compared to that of magnetite. However, the preparation of nano-sized ferrite particles is very difficult using the chemical method except for the magnetite. We have obtained nano-sized ferrite materials by physical bead milling. In the case of the magnetite, nano-sized particle directly form using a reverse coprecipitation method even below 100°C in an alkaline aqueous solution.

$$FeCl_2 + 2FeCl_3 + 8NaOH \rightarrow Fe_3O_4 + 8NaCl + 4H_2O$$ (1)

In the case of the normal coprecipitation method, the pH value gradually increases by dropping an alkali solution into the mixed metal solution. Teraoka et al. reported that a reverse coprecipitation method is very effective for synthesizing a homogeneous fine powder for the preparation of poly-metallic oxides, because the mixed metal solution was directly dropped into an alkaline solution. The magnetic properties of the nano-sized magnetite strongly depended on the synthesis route. The study of the synthesis conditions is very important for the nano-sized super-paramagnetic magnetite, because the main heating mechanism of the Néel relaxation in the AC magnetic field is strongly influenced by the particle size. In the case of magnetite, the $R = \frac{Fe^{2+}/(Fe^{2+} + Fe^{3+})}{Fe^{3+}/(Fe^{2+} + Fe^{3+})}$ value was fixed at 0.33 for the preparation. The preparation of the magnetic iron oxides, such as FeO (Wüstite, $R = 0$) and γ-Fe$_2$O$_3$ (Maghemite, $R = 1.0$), is also expected to provide a heat generation ability.

In this study, we optimized the synthesis conditions of the nano-sized magnetite powder using the reverse coprecipitation method for a high heat generation ability. In addition, the $R$ value was varied in order to study the formation of the iron oxides and their heat generation ability.

2. Experimental

2.1 Preparation of magnetite powder and characterization

The magnetite ($Fe_3O_4$, Fe(III)Fe(II)O$_4$) was prepared by the reverse coprecipitation method (Fig. 1). In this case, the molar ratio of $R = \frac{Fe^{2+}/(Fe^{2+} + Fe^{3+})}{Fe^{3+}/(Fe^{2+} + Fe^{3+})}$ was 0.33 for the starting materials. As a standard method, FeCl$_2$·4H$_2$O (0.10 mol) and FeCl$_3$·6H$_2$O (0.20 mol) were dissolved in 200 mL of pure water. In this case, the concentration of the iron was ca. 1.3 M (mol·L⁻¹). This mixed iron solution was dropped into a NaOH (6 M, 140 mL) solution placed in a water bath at 80°C with stirring and then held at the same temperature for 1 h in ambient air. The synthesis conditions for controlling the particle size were changed for (1)
temperature of the reaction in solution, (2) concentration of mixed irons in solution, and (3) amount of coexisting NaCl in the solution. The powder was collected and washed by centrifugal separation. The supernatant liquid after the centrifugal separation was replaced several times using deionized water until the pH of the wash water dropped below 9. The powder was dried at 50°C for several days in ambient air and then heat-treated for 1 h at 200°C in an Ar atmosphere.

The X-ray diffraction (XRD) patterns using Cu-Kα radiation were recorded using a Rigaku Rint 2000 at the scanning rate of 2°/min, 40 kV and 20 mA. The specific surface area ($A_{BET}/m^2·g^{-1}$) was measured by the one-point BET method and then the particle size ($D/\bar{m}$) was calculated by assuming a spherical particle size using the following equation:

$$D = 6 \cdot (A_{BET} \cdot \rho)^{-1}$$

where $\rho$ is the density of the material (g·cm$^{-3}$).

The saturation magnetization value was obtained by a homemade VSM (Vibrating Sample Magnetometer) between $-600$ and $+600$ kA·m$^{-1}$ in the magnetic field.

### 2.2 Measurements of heat generation ability

**Figure 2** shows the setup for measuring the heat generation ability of the ferrite powder in the AC magnetic field. The sample was placed in a glass case (Pyrex: 20 mm, 45 mm) and the AC magnetic field (370 kHz, 1.77 kA·m$^{-1}$) was applied to the sample using an external coil. The temperature of the sample was measured using a radiation thermometer (TP-L0225EN, CHINO Co.). For the quantitative measurement, the sample powder (2.0 g) in 10 mL of water was utilized to study the heat generation ability (W·g$^{-1}$). Air was bubbled into the glass case for stirring the water. The measurement was started after stabilizing at 25°C in ambient air for several hours. The heat generation ability was calculated based on the temperature enhancement ratio ($dT/dt = K \cdot s^{-1}$) during the initial 5 min of the $\Delta T$ measurement using the following equation:

$$\text{Heat generation ability} = C \cdot (dT/dt) \cdot M^{-1}$$

where $M$ and $C$ are the sample weight (g), and the estimated total heat capacity (J·K$^{-1}$) of 10 mL of water and the glass case, respectively. The average value for the measurement of three samples or more was used for this calculation.

### 3. Results and discussion

#### 3.1 Effects of synthesis conditions on the magnetite preparation

**Figure 3** shows the XRD results for the products prepared by reverse coprecipitation at various temperatures. The XRD patterns showed that the cubic magnetite ($Fe_3O_4$) was formed at all the tested temperatures. The peaks for the magnetite

Fig. 1. Apparatus for preparation of the magnetite by the reverse coprecipitation method.

Fig. 2. Apparatus for measurement of the heat generation ability of the ferrite powder in an AC magnetic field.

Fig. 3. XRD results for products prepared by reverse coprecipitation at various temperatures.

Fig. 4. Heat generation ability in AC magnetic field (370 kHz, 1.77 kA·m$^{-1}$) and particle diameter for the magnetites prepared by the reverse coprecipitation method at various temperatures.
were very broad which means that the crystalline size of the magnetite is very small. Figure 4 plots the heat generation ability and the calculated particle diameter using the surface area from the BET analysis. The particle size decreased and the heat generation ability was enhanced with an increase in the synthesis temperature. The particle size would be enlarged by the slow particle growth at low temperature. This enhancement in the heat generation ability would be ascribed to the influence of the particle size.

The concentration of the mixed irons of FeCl$_2$·4H$_2$O (0.10 mol) and FeCl$_3$·6H$_2$O (0.20 mol) in the solution was changed by the amount of added water. Figure 5 shows the XRD results for the products prepared at the various concentrations of the mixed irons in solution using the reverse coprecipitation method. The temperature of the reaction was fixed at 80°C. The cubic Fe$_3$O$_4$ magnetite was formed in all the examined samples. The peak intensity increased with the increase in the concentration of the irons. Figure 6 plots the heat generation ability and the particle diameter. The particle size increased with the increase in the concentration of the irons. The particle size would be reduced by the lack of iron in the solution at the low iron concentrations. The maximum heat generation ability was obtained for the 0.91 M sample having an ca. 15 nm particle size. The heat generation ability would also be influenced by the particle size along with the concentration of the irons.

The amount of coexisting NaCl in the solution was changed in order to control the particle growth. Figure 7 shows the XRD results for the products prepared using various amounts of mixed NaCl in the solution. The temperature and concentration of the irons for the reaction was fixed at 80°C and 1.3 M, respectively. Although the cubic Fe$_3$O$_4$ magnetite was formed in all the examined samples, the peak intensity decreased with the increase in the amount of the mixed NaCl in the solution. Figure 8 plots the heat generation ability and the particle diameter for the magnetites prepared with the various amounts of mixed NaCl in solution. The particle size decreased with the increase in the amount of the mixed NaCl. The Na$^+$ and Cl$^-$ ions would act as interference ions for the formation of the magnetite.

The heat generation ability was changed by the particle size with the synthesis conditions of the magnetite based on (1) temperature of the reaction, (2) the concentration of mixed irons.
in the solution, and (3) the amount of coexisting Na\(^+\) and Cl\(^-\) ions in the solution. The relationship between the particle size and the heat generation ability is plotted in Fig. 9. The heat generation ability was clearly influenced by the particle size. The maximum heat generation ability of 0.25–0.28 W·g\(^{-1}\) was obtained at around a 13–14 nm particle size.

### 3.2 Effect of Fe\(^{2+}/(Fe^{2+} + Fe^{3+})\) molar ratio

The R value was fixed at 0.33 for the preparation of the magnetite. However, there are many types of iron oxides such as FeO (Wüstite, \(R = Fe^{2+}/(Fe^{2+} + Fe^{3+}) = 1.0\)), Fe\(_2\)O\(_4\) (Magnetite, \(R = 0.33\)), α-Fe\(_2\)O\(_3\) (Hematite, \(R = 0\)), and γ-Fe\(_2\)O\(_3\) (Maghemite, \(R = 0\)). These iron oxides have magnetic properties except for the paramagnetic α-Fe\(_2\)O\(_3\). The R value was varied in order to study the formation of the iron oxides and their heat generation ability. Figure 10 shows the XRD powder diffraction patterns for the products prepared at various R values using the reverse coprecipitation method. The temperature and the concentration of irons for the reaction were fixed at 80°C and 1.3 M, respectively. The same pattern of cubic Fe\(_2\)O\(_4\) magnetite was detected in all the examined samples. The formation of FeO and α-Fe\(_2\)O\(_3\) was not confirmed in the XRD pattern. The peak intensity increased with the increase in the R value. In the R region lower than 0.33, the formation of the γ-Fe\(_2\)O\(_3\) phase could not be completely denied due to the low intensity of the XRD peaks, because the iron oxides of the magnetite and γ-Fe\(_2\)O\(_3\) have almost the same XRD pattern.

Figure 11 plots the heat generation ability and the particle diameter versus the R value. The particle size increased with an increase in the R value. In the R region lower than 0.33, the particle size would decrease by the lack of divalent iron needed for the formation of the magnetite (\(R = 0.33\)) in the solution. This behavior seems to be similar to the relationship between the particle size and the concentration of the irons in Fig. 6. In the case of the higher R region, the concentration of the irons for the magnetite also decreased with the increase in the R value due to the oxidation of the divalent iron in the solution from oxygen in the ambient air. The maximum heat generation ability was obtained for \(R = 0.33\) of the magnetite.

Figure 12 shows TEM observations for the particles of \(R = 0, 0.33, \) and 1.0. The tendency of the particle size agreed with those of Fig. 11. For \(R = 0\), the shape of the grains was not clear. Particle growth was observed for \(R = 1.0\) sample. Figure 13 shows the relationship between the R value and the saturation magnetization value from the VSM measurement. For \(R = 0\), the low saturation magnetization value suggests the formation of the paramagnetic α-Fe\(_2\)O\(_3\). The saturation magnetization value remained constant when the R value was greater than 0.33.

Figure 14 plots the relationship between the heat generation ability and the particle size for all the samples. Based on this figure, the data in Fig. 11 were added to the results of the magnetite in Fig. 9. The heat generation ability also clearly depended on the particle size. This means that changes in the R value would change the particle size of the magnetite. The maximum heat generation ability was obtained for the magnetite having an ca. 13–14 nm particle size.
4. Conclusions

The particle size for the magnetite was strongly influenced by the synthesis conditions, such as the temperature, concentration of the iron or coexisting ions, and the Fe\textsuperscript{2+}/(Fe\textsuperscript{2+} + Fe\textsuperscript{3+}) molar ratio in the solution. The maximum heat generation ability was obtained for the magnetite having a ca. 13–14 nm particle size. This means that the heat generation ability in an AC magnetic field for the magnetite can be easily controlled by the synthesis conditions.

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References
1) A. Jordan, P. Wust, H. Fähling, W. John, A. Hinz and R. Felix, *Int. J. Hyperthermia*, 9, 51–68 (1993).
2) M. Mitsumori, M. Hiraoka, T. Shibata, Y. Okuno, S. Masunaga, M. Koiwaka, K. Okajima, K. Naga, Y. Nishimura, M. Abe, K. Ohura, M. Hasegawa, H. Nagae and Y. Ebisawa, *Int. J. Hyperthermia*, 10, 785–793 (1994).
3) M. Shinkai, M. Yanase, H. Honda, T. Wakahayashi, J. Yoshida and T. Kobayashi, *Jpn. J. Cancer Res.*, 87, 1179–1183 (1996).
4) A. Jordan, R. Scholz, K. Maier-Hauff, M. Johannsen, P. Wust, J. Nadobny, H. Schirra, H. Schmidt, S. Deger, S. Loening, W. Lanksch and R. Felix, *J. Magn. Magn. Mater.*, 225, 118–126 (2001).
5) A. Jordan, R. Scholz, P. Wust, H. Fähling and R. Felix, *J. Magn. Magn. Mater.*, 201, 413–419 (1999).
6) P. Moroz, S. K. Jones and B. N. Gray, *Int. J. Hyperthermia*, 18, 267–268 (2002).
7) M. Johannsen, U. Gneveckow, B. Thiesen, K. Taymoorian, C. H. Cho, N. Waldöfner, R. Scholz, A. Jordan, S. A. Loening and P. Wust, *Eur. Urol.*, 52, 1653–1662 (2007).
8) A. Jordan, R. Scholz, K. Maier-Hauff, F. K. H. Landeghem, N. Waldöfner, U. Teichgraeber, J. Pinkermelle, H. Bruhn, F. Neumann, B. Thiesen, A. Deimling and R. Felix, *J. Neurooncol.*, 78, 7–14 (2006).
9) K. Maier-Hauff, R. Rothe, R. Scholz, U. Gneveckow, P. Wust, B. Thiesen, A. Feussner, A. Deimling, N. Waldöfner, R. Felix and A. Jordan, *J. Neurooncol.*, 81, 53–60 (2007).
10) M. Yoshida, Y. Watanabe, M. Aota, T. Maehara, H. Aono, T. Naohara, H. Hiraizawa, A. Horii, S. Yukumi, K. Sato, H. Nakagawa, Y. Yamamoto, H. Sugishita and K. Kawachi, *Int. J. Cancer*, 126, 1555–1565 (2010).
11) H. Aono, H. Hiraizawa, T. Naohara, M. Aota, Y. Watanabe, *J. Magn. Magn. Mater.*, 323, 88–93 (2011).
12) T. Naohara, H. Aono, K. Shirai, T. Maehara, H. Hiraizawa, S. Matsutomo and Y. Watanabe, *J. Magn. Magn. Mater.*, 331, 168–173 (2013).
13) M. Shinkai, M. Yanase, M. Suzuki, H. Honda, T. Wakahayashi, J. Yoshida and T. Kobayashi, *J. Magn. Magn. Mater.*, 194, 176–184 (1999).
14) A. Jordan, R. Scholz, P. Wust, H. Schirra, T. Schiestel, H. Schmidt and R. Felix, *J. Magn. Magn. Mater.*, 194, 185–196 (1999).
15) M. Ma, Y. Wu, J. Zhou, Y. Sun, Y. Zhang and N. Gu, *J. Magn.
16) H. Aono, K. Hiraoka, T. Naohara, T. Maehara, H. Kikkawa and Y. Watanabe, *Mater. Res. Bull.*, 40, 1126–1135 (2005).

17) T. Maehara, K. Konishi, T. Kamimori, H. Aono, T. Naohara, H. Kikkawa, Y. Watanabe and K. Kawachi, *Ipn. J. Appl. Phys.*, 41, 1620–1621 (2002).

18) T. Maehara, K. Konishi, T. Kamimori, H. Hirazawa, H. Aono, T. Naohara, S. Nomura, H. Kikkawa, Y. Watanabe and K. Kawachi, *J. Mater. Sci.*, 40, 135–138 (2005).

19) H. Hirazawa, S. Kusamoto, H. Aono, T. Naohara, K. Mori, Y. Hattori, T. Maehara and Y. Watanabe, *J. Alloys Compd.*, 461, 467–473 (2008).

20) H. Aono, K. Moritani, T. Naohara, T. Maehara, H. Hirazawa and Y. Watanabe, *Mater. Lett.*, 65, 1454–1456 (2011).

21) T. Nishimori, T. Naohara, T. Maehara, H. Hirazawa and H. Aono, *J. Iron Steel Res. Int.*, 19[Suppl. 1], 600–603 (2012).

22) H. Aono, T. Naohara, T. Maehara, H. Hirazawa and Y. Watanabe, *J. Ceram. Soc. Japan*, 118, 1207–1211 (2010).

23) H. Hirazawa, H. Aono, T. Naohara, T. Maehara, M. Sato and Y. Watanabe, *J. Magn. Magn. Mater.*, 323, 675–680 (2011).

24) H. Aono, Y. Watanabe, T. Naohara, T. Maehara, H. Hirazawa and Y. Watanabe, *Mater. Chem. Phys.*, 129, 1081–1088 (2011).

25) H. Aono, H. Ebara, R. Senba, T. Naohara, T. Maehara, H. Hirazawa and Y. Watanabe, *J. Am. Ceram. Soc.*, 94, 4116–4119 (2011).

26) H. Aono, H. Ebara, R. Senba, T. Naohara, T. Maehara, H. Hirazawa and Y. Watanabe, *J. Magn. Magn. Mater.*, 324, 1985–1991 (2012).

27) T. Nishimori, Y. Akiyama, T. Naohara, T. Maehara, H. Hirazawa and H. Aono, *J. Ceram. Soc. Japan*, 121, 13–16 (2013).

28) H. Aono, R. Senba, T. Nishimori and T. Naohara, *J. Am. Ceram. Soc.*, 96, 3483–3488 (2013).

29) T. Nishimori, Y. Akiyama, T. Naohara, T. Maehara, H. Hirazawa, Y. Itagaki and H. Aono, *J. Ceram. Soc. Japan*, 122, 35–39 (2014).

30) H. Aono, *J. Ceram. Soc. Japan*, 122, 237–243 (2014).

31) H. Aono, T. Nishimori, T. Naohara, Y. Itagaki, T. Maehara and H. Hirazawa, *Ceram. Int.*, 41, 8461–8467 (2015).

32) Y. Teraoka, S. Nannri, I. Moriguchi, S. Kagawa, K. Shimanoe and N. Yamazoe, *Chem. Lett.*, 2000, 1202–1203 (2000).

33) M. C. Mascaro, Y. Pei and T. A. Ring, *Materials (Basel)*, 6, 5549–5567 (2013).