Preparation of MgFe₂O₄ microsphere using spray dryer for embolization therapy application

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MgFe₂O₄ microspheres having a 20–32 μm diameter range were prepared by a spray dryer using bead-milled nano-sized particles. A commercial powder having a several μm particle size was bead-milled to an approximate 6.2 nm crystallite size. The microspheres were obtained using the spray dryer when the air pressure was low (0.03 MPa). The yield of the MgFe₂O₄ 20–32 μm microspheres was improved by combination of a low air pressure and high ferrite concentration in the slurry. The heat generation ability in an AC magnetic field (370 kHz, 1.77 kA/m) was improved by the bead milling.

Key-words : MgFe₂O₄, Microsphere, Embolization therapy, Spray dryer, Thermal coagulation therapy

1. Introduction

Thermal coagulation therapy using magnetic materials in an AC magnetic field has been expected as a new treatment of cancerous tissues. A drug delivery system (DDS) using nano-sized magnetic particles encapsulated in a liposome (<100 nm) is applicable for the deep type of cancer therapy. Up to now, Fe₃O₄ (magnetite) nanoparticles, prepared by a chemical method, have been mainly investigated as the candidate material for this type of therapy. We have developed new magnetic materials having a higher heat generation ability compared to that of the Fe₃O₄. We found that MgFe₂O₄ has the highest heating ability of commercial ferrite powders (particle size: several μm) of MgFe₂O₄ (M = Mg, Mn, Fe, Co, Ni, Cu, and Sr). Furthermore, we reported that the Mg₀.₇Fe₂.₃O₄ system synthesized by the reverse coprecipitation method has a higher heat generation compared to the X = 0 (MgFe₂O₄) material. The heat generation in an AC magnetic field of these ferrite materials depended on the hysteresis loss value of the B–H magnetic property. On the other hand, the needle-type magnetic materials for surface cancer obtained by the sintering of the MgFe₂O₄ powder were studied for breast cancer therapy. In addition, the heat generation ability of a Ti tube with ferrite powder was also studied for this same purpose.

As another type of magnetic material, a microsphere for the embolization of blood vessels, can be considered for this therapy. The embolization method has already been utilized to block the bloodstream (nourishment) of a cancer tumor. Yttrium-90 microspheres using Therasphere® and SIR-Sphere® have already been used for the radioembolization of liver tumors. In the case of thermal coagulation therapy, magnetic materials containing glass ceramics have been studied for the embolization method. Kawashita et al. reported the synthesis of FeFe₂O₄ microspheres with a 20–30 μm diameter range prepared by melting the powder in a high frequency induction thermal plasma and by precipitation from an aqueous solution.

The preparation of microspheres by spray drying has been specifically reported for organic materials such as a chitosan for colon drug delivery. Up to now, microspheres made by spray drying have not been reported for the embolization method. We considered that microspheres with a 20–32 μm diameter range could be obtained by spray drying using a water-based slurry of MgFe₂O₄ nanoparticles. Liquid fog of the slurry from the nozzle of a spray dryer will then isotropically dry to form microspheres. In addition, utilization of nanosized particles using the bead-milling technique will be very effective for obtaining microspheres.

In this study, we investigated the preparation of MgFe₂O₄ microspheres with a 20–32 μm diameter range in high yield using the spray drying of bead-milled nanosized particles.

2. Experimental

2.1 Preparation of samples

The nanosized ferrite powder was prepared using a bead-mill (DMS65, Ashizawa Finetech, Ltd.). The apparatus consisted of a zirconia (0.14 L) vessel and beads. A commercial MgFe₂O₄ (99.9%, Kojyundo Chemical Lab.) powder was used as the milling samples. Ethanol was used as the solvent during the milling. The bead size and milling time were 0.1 mmφ for 8 h after milling using the 0.3 mmφ beads for 2 h. After the bead milling, the solvent was evaporated at 100°C.

For preparation of the slurries, the mixture of the bead-milled MgFe₂O₄ (4.0 g) and purified water (45 mL) was mixed by ultrasonication for 3 min. The amount of purified water (11.3, 22.5, 45 mL) with 4.0 g MgFe₂O₄ was changed in order to study the effect of the ferrite concentration in slurry on the yield. The slurries of ferrite with water were atomized using a spray drier (ADL311S, Yamato Co.) with a 0.46-mm diameter orifice nozzle atomizer, a 52-cm high chamber with a 13-cm inside diameter.

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Figure 1 shows the spray dryer used for the preparation of the microspheres. The temperature and flow rate of the heated dry air were at 200°C and 0.4 m³/min, respectively. The air pressure for atomization was between 0.03 and 0.08 MPa. The slurry feed rate was 4.0 ml/min.

The spray-dried powder was washed using purified water on a 32-μm sieve to screen out the larger particles. The sifted slurry containing the particles under 32-μm and purified water, was then thoroughly washed on a 20-μm sieve to remove any smaller particles. The powder on the 20-μm sieve, which contained 20–32 μm particles, was then dried at 100°C.

2.2 Characterization

The crystallite size of the MgFe₂O₄ was estimated by the FWHM (full-width at half maximum) of the X-ray diffraction peaks (XRD, Model Rint 2000, Rigaku Co., using Cu-Kα radiation). The specific surface area was measured by the one-point BET method (Flowsorb II 2300, Shimadzu Co.) and then the particle diameter was calculated by assuming a spherical particle size. The elemental analysis for the bead milled samples was confirmed using a fluorescence X-ray analysis (RIX2100, Rigaku Co.). For measurement of the heat generation ability of the ferrite powder, the powder sample (1.0 g) was placed in a glass case (Pyrex: 20 mmφ, 45 mm), and an AC magnetic field (370 kHz, 1.77 kA/m) was applied to the sample using an external coil. The coil consisted of eight loops of copper pipe (6φ) wound around a polypropylene (PP) bobbin (48 mmφ x 40 mm). The copper pipe was cooled by flowing water to maintain its temperature and impedance. The coil was connected to a power supply (T162-5712B, Thamway Co., Ltd.) through an impedance tuner. The temperature of the sample was measured using a radiation thermometer (505s, Minolta Co., Ltd.). The temperature measurement was started after keeping the sample at room temperature (25°C) in ambient air for several hours.

The hysteresis loss and the magnetic permeability in the AC magnetic field (370 kHz, 500 A/m) were obtained using a B-H analyzer (Iwatsu Electric Co., Ltd., SY-8258). For this measurement, ring-type samples (about a 20-mm outside diameter, about 13-mm inside diameter, about a 5-mm height) were prepared using a mixture of the ferrite powder and epoxy resin adhesive (4:1 weight ratio).

3. Results and discussion

Figure 2 shows the XRD results for the MgFe₂O₄ powders of a commercial sample, bead-milled sample, and spray-dried sample after the bead milling. Sharp peaks were obtained for the commercial powder (no milling time) because of its large crystallite size. The XRD peaks of the bead-milled powder were very broad due to the fact that the crystallite diameter had been significantly reduced by this physical milling method. The estimated crystallite diameter using the Scherrer equation from the XRD peak at 2θ = 62° (440) was 6.2 nm. The estimated particle diameter was 18.6 nm using the surface area from the BET method. The particle size was 3 times greater than the crystalline size. Figure 3 shows TEM photo for bead-milled sample. The crystalline size from the TEM observation was ca. 10 nm or smaller. This means that aggregation of the small crystals would result in larger particle size from the BET method. The broad XRD peaks were not influenced by utilization of the spray dryer after the bead milling. No contamination from the zirconia vessel and beads by the bead milling and the spray drying was detected by XRD and a fluorescence X-ray analysis. Figure 4 shows typical SEM photos (low and high magnification) of the spray dried particles before sifting. The micro-
spheres having a variety of particle sizes were obtained using the spray drying. The nano-particles were aggregated to form these microsphere particles by the spray drying process. The maximum particle size distribution of the collected powder was less than 20 μm for all the examined samples. Figure 5 shows SEM observations of the 20–32 μm sifted particles. The air pressure was changed in order to study the optimized conditions to form the MgFe₂O₄ microspheres. At high pressure, the spherical particle shape was deformed. MgFe₂O₄ microspheres were obtained at the low pressure of 0.03 MPa. The high air pressure would deform the liquid fog of the microspheres. However, the dried powder was not obtained at lower than 0.02 MPa, because the liquid fogs could not spray out from the orifice nozzle. Table 1 lists the yield of the 20–32 μm particles in the spray dried powder using 4.0 g of MgFe₂O₄ in the slurry. The total weight of the powder in the collection container decreased with a decrease in the pressure. The weight loss in the collection container was due to the powder remaining on the wall and the bottom of the chamber. The dried powder could not move quickly to the container and remained in the chamber at the lower pressure. However, the sifted powder weight of the 20–32 μm particles in the collection container increased with a decrease in the pressure. The low air pressure would be effective for obtaining a large liquid fog size in the chamber in order to form large microspheres. The maximum yields of the 20–32 μm particles were obtained when the air pressure was 0.03 MPa, which were 3.9 and 11.4 wt% versus the starting 4.0 g and collected powder in the container, respectively. Based on these results, an increase in the MgFe₂O₄ concentration for the slurry seemed to be one of the methods to obtain a high yield of large microsphere particles. Table 2 shows the effect of the ferrite concentration in the slurry. The total powder weight in the

![Fig. 4. SEM photos of the prepared powder (before sifting) by spray drying (Pressure: 0.03 MPa, Powder concentration: 26.2%).](image)

![Fig. 5. SEM photos of the prepared powder (after sifting the 20–32 μm particle size) using a spray drying at various air pressures (0.03–0.08 MPa).](image)

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<th>Table 1. Effect of air pressure on the yield of the 20–32 μm particles in a spray dried powder using 4.0 g of MgFe₂O₄ in a slurry. The concentration of the ferrite was 8.2 wt% in the slurry (4.0 g MgFe₂O₄ and 45 ml purified water)</th>
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<td>Total powder weight in collection container (g)</td>
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<td>Yield of 20–32 μm particles from 4.0 g of starting powder (%)</td>
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collection container decreased with an increase in the powder concentration. However, the yield of the 20–32 μm particles in the collection container was significantly improved by the increased ferrite concentration. The maximum yields of 20–32 μm particles were 10.4 and 40.5 wt % versus the starting 4.0 g and collected powder in the container, respectively. The high ferrite concentration would be an effective way to obtain large microspheres. However, the increase in the particle size with the ferrite concentration acted to increase the remaining powder in the chamber. The nozzle of the spray dryer was clogged when the ferrite powder concentration was greater than 26.2%. We confirmed the sifted particle size of 20–32 μm using the SEM for the three concentrations shown in Table 2. Similar microsphere particles shown in Fig. 5 (0.3 MPa) were obtained for all the examined ferrite concentrations. Figure 6 shows the temperature enhancement in the AC magnetic field (370 kHz, 1.77 kA/m) for the commercial, bead-milled, and spray-dried MgFe2O4 powders. The temperature of these samples significantly increased with time in the AC magnetic field. The temperature enhancement of the sample after 20 min reached a saturated value in the AC magnetic field. The heat ability and the cooling rate in ambient air were equilibrated at the elevated temperature. The temperature enhancement (ΔT) after 20 min was 26°C for the commercial sample (non-milled sample). However, the milled sample showed a ΔT = 34°C temperature enhancement. The heat generation ability was improved by this milling. The hysteresis value for the commercial sample and bead-milled sample were 9.8 and 14.8 mW/g, respectively. One of the reasons for the improvement in the heat generation is the increase in the hysteresis loss. In addition, the Néel relaxation and Brownian relaxation were also investigated for the heat generation mechanism of the magnetite nanoparticles. In this case, the Brownian relaxation can be ignored due to the dry particles. The microsphere powder consisting of 20–32 μm particles showed a heat generation ability (ΔT = 33°C) similar to the bead-milled sample.

4. Conclusions

We obtained MgFe2O4 microspheres with a 20–32 μm diameter range using a spray dryer from the bead-milled nano-sized particles. The heat generation ability in an AC magnetic field (370 kHz, 1.77 kA/m) was improved by the bead milling. The yield of microspheres can be improved by changing the spray drying conditions, such as the air pressure and the ferrite concentration. Up to now, microspheres have been prepared using magnetic materials containing glass ceramics, melting the powder in a high frequency induction thermal plasma, and precipitation from an aqueous solution. This simple method is expected for use in the embolization method for thermal coagulation therapy.

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References


