New magnetic implant material for interstitial hyperthermia

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Abstract

Magnetic properties and heat generation characteristics of a bio-compatible ceramic Mg$_{1+x}$Fe$_{2-x}$Ti$_x$O$_4$ system have been investigated as an implant material for the magnetic induction hyperthermia. Curie temperature ($T_c$) of the ceramic decreases with increasing x, and become $T_c \approx 350$ K at $x = 0.35$ and $-315$ K at $x = 0.38$, which is suitable Curie temperature for implant material. The temperature of ceramic as a function of time under the high frequency alternating magnetic field is self-controlled at $T_c$. The surface temperature of a powder injection sphere cancer model, which was a mixture of the agar phantom and the ceramic powder implant, and the temperature distribution around the sphere set in the pure agar phantom matrix have been measured. The result is in good agreement with calculation using a finite element method (FEM). It was found that the temperature distribution inside of the sphere and the minimum quantity of Mg$_{1+x}$Fe$_{2-x}$Ti$_x$O$_4$ necessary for hyperthermia could be estimated by the FEM calculation.

Keywords: Hyperthermia; Implant heating system; Powder implant material; Low Curie temperature; Mg$_{1+x}$Fe$_{2-x}$Ti$_x$O$_4$; Biocompatible; Spinel structure; Ferrite

1. Introduction

Hyperthermia is the cure harnessing the nature that a cancer tissue has less heat-resistant than normal one. In the hyperthermia, it is important that the cancer tissue is selectively heated without damaging the normal tissue. The interstitial hyperthermia using magnetic material is known as Magnetic Induction Hyperthermia [1,2], Soft Heating [3] or Implant Heating System (IHS) [4] is an excellent system to perform the purpose. In the system, the ferromagnetic material (implant) is implanted in the cancer tissue at first, and it is heated by utilizing the eddy current or the magnetic hysteresis loss under the high frequency alternating magnetic field (HFMF). Then, the temperature of the cancer tissue is raised and regulated at a Curie temperature ($T_c$) of the implant material. We previously reported on the mechanism of heat generation by the eddy current [5], which depends on the magnetic field, the frequency of HFMF, the permeability, the resistivity and the size of the implant. Moreover, in order to gain the maximum heat generation, it is necessary that the direction of HFMF is parallel to the long axis of the implant. Fe–Pt alloy needles [6], which were developed based on this concept, were used for treatments of brain tumors [7] and oral malignant tumors [8]. On the other hand, the hysteresis loss is hardly dependent of the direction of HFMF and of the size of the implant. Therefore, the materials heated by the magnetic hysteresis loss can also be used for hyperthermia in a fine powdered form. Furthermore, the powder implant is more advantageous than the bulk implant, since the powder can be molded in various forms, or can be injected into the tumor tissue through a blood vessel. In the case of magnetic material like ceramics with large electrical resistivity, the eddy current is restrained and the hysteresis loss mainly causes the generation of heat. Iron oxide such as ferrite [9] has been so far proposed as the powder implant. But, the heat generation ability of such ferrites was considered to be insufficient for hyperthermia of human body because of the small saturation magnetization, that is, the small hysteresis loss. Recently, there were reports of interesting investigations using Fe$_3$O$_4$ as powder implant [10,11], where Fe$_3$O$_4$ powder coated by dextran was injected into a mouse cancer [10], or a needle like Fe$_3$O$_4$ molded by the adhesive was used for the cancer of a rat. However, $T_c$ of Fe$_3$O$_4$ 858 K is much higher than the suitable Curie temperature (315 $\sim$ 350 K) as the implant material. Namely, new implant materials having low $T_c$ have to be developed.

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Besides the problem of Curie temperature, we have to solve the following problems for implant materials. First, considering the burden to patients, it is necessary to lessen the quantity of the implant for hyperthermia. So that, the material with large heat generation ability must be developed. Second, the implant material should be biocompatible. It is necessary for the implant to be composed by biocompatible elements such as C, O, N, Na, Mg, Si, K, Ca, Ti, and Fe. From the above viewpoints, we prepared the magnetic materials, such as (Mg,K)Fe2O4, Mg12CaTiO4, Mg(Fe,Si)2O4 and the magnetic properties and the heat generation characteristics were investigated. It was found that Mg12Fe2Ti4O12 ceramic fulfills the all conditions as implant mentioned above.

In this paper, we report the ferrimagnetic properties and the characteristics of the heat generation for the powder Mg12+xFe2−xTi4O12. In order to investigate fundamentals for clinical application of hyperthermia, the temperature distribution around a powder injection sphere cancer model, which is a mixture of the agar phantom and the ceramic powder implant, has been measured in the pure agar phantom matrix and the calculation using a finite element method (FEM) has been investigated.

2. Experimental and calculation methods

The powder samples, Mg12+xFe2−xTi4O12 (x = 0 ~ 0.5), were prepared using MgO, Fe2O3, and TiO2 with the purity of 4N using the sintering method. The above mixture was pre-sintered in air at 1003 K for 22 h, and then pelletized into a disk (18 mm diameter) under a pressure of 600 MPa at room temperature. The pellet was sintered at 1473 K for 6 h and then it was finally ground into the fine powder in a mortar. The observed average particle size and the standard deviation of the powder sample were 8 μm and ±4 μm, respectively. The size is small enough to pass a hypodermic injection needle (0.14 mm in inside diameter, Gauge 30). The nominal sample composition was used in this paper.

The X-ray diffraction measurement revealed that all powder samples had no extra phase besides a spinel type structured phase. The magnetization as a function of temperature and the hysteresis loop at room temperature were measured by means of the vibrating sample magnetometer (VSM, Toei Kogyo Co., Ltd). \( T_c \) was determined as a point where the square of magnetization vs. temperature curve crosses the temperature axis. The magnetic hysteresis loss \( W_h \) is expressed by the equation,

\[
W_h = \int f M \, dH
\]

where \( f \), \( M \) and \( H \) are the frequency of the magnetic field, the magnetization, and external magnetic field, respectively. Accordingly, \( W_h \) was estimated by multiplying \( f \) and the area surrounded by the hysteresis loop measured in the static magnetic field. It should be noted that the value of \( W_h \) decreases with decreasing the saturation magnetization \( M_s \).

The quantity of heat generation \( Q \) of an implant was derived from the gradient of the temperature vs. time curve at \( t = 0 \) by a following equation,

\[
Q = \frac{w}{M} C_p \left( \frac{dT}{dt} \right)_{t=0}
\]

where \( w \), \( M \) and \( C_p \) are the weight of sample, the molecular weight and the specific heat of the sample, respectively. The temperature was measured as a function of time using the planimeter thermocouple [12] under HFMF, which is generated by a transistor inverter (2.5 kW, 230 kHz) with field coils (\( \phi 120 \times 5 \) turns for 100 Oe and \( \phi 90 \times 7 \) turns for 200 Oe). The powdered sample was stuffed into a Teflon tube (\( \phi 1.5 \times 15 \) mm), and the tube was put in the coil. A thermocouple was directly put in the powder sample.

In order to investigate the temperature distribution in the cancer and normal tissues, we prepared a pure agar phantom matrix and a powder injection sphere cancer model, which was a mixture of the agar phantom and the ceramic powder sample. The agar phantom was made of a solution of agar (4%), salt (0.24%), sodium azide (0.1%) and water (95.66%). The powder injection sphere cancer model was prepared by the casting a mixture of powder sample and the agar phantom solution (0.092 g/cc in fraction of powder) into a sphere mold of 10 mm in radius. The sphere cancer model was positioned in the pure agar phantom matrix as shown in Fig. 1. The pure agar phantom matrix (about 350 cc) was regarded as the normal tissue. The temperature was measured using the thermocouples, which were set at...
positions shown in Fig. 1(b), as functions of time and distance from a center of the sphere.

The FEM based on Galerkin method, which is a kind of the weighted residual method, was used to calculate the temperature distribution around the implant in the agar phantom. The heat conduction equation,

\[ \rho C_p \frac{\partial T}{\partial t} = \frac{\partial}{\partial x} \left( \kappa \frac{\partial T}{\partial x} \right) + \frac{\partial}{\partial y} \left( \kappa \frac{\partial T}{\partial y} \right) + \frac{\partial}{\partial z} \left( \kappa \frac{\partial T}{\partial z} \right) + Q, \quad (3) \]

was used for the governing equation. In above equation, \( \rho \), \( C_p \), \( k \) and \( Q \) are the density, the specific heat, the thermal conductivity and the heat generation of the sample, respectively. The region of 30 mm from a center of the sphere was taken as the calculation area, and 1800 triangular elements were adopted in the \( x-y \) plane. It was supposed that the length along the \( z \)-axis of each element is proportional to the distance from the center of sphere. A heat flow to the \( z \)-direction can be disregarded by the symmetric property of a sphere.

### 3. Results and discussion

Fig. 2 shows \( T_c \) of \( \text{Mg}_{1-x}\text{Fe}_{2-2x}\text{Ti}_x\text{O}_4 \) \((x = 0 \sim 0.5)\) plotted against the atomic composition \((x)\). The temperature range \((315 \sim 350 \text{ K})\) indicated by the shaded area is the suitable Curie temperature range for the implant material \([8,13]\). Because \( T_c \) is a maximum self-controlled temperature at the center of powder particle, but the surface temperature and the temperature of the cancer tissue are much lower than \( T_c \) because of the heat losses of the system. \( T_c \) decreases with increasing \( x \) linearly, and it is about 350 K at \( x = 0.35 \) and 315 K near \( x = 0.38 \) as shown in Fig. 2. The X-ray diffraction measurement showed that \( \text{Mg}_{1+\delta}\text{Fe}_{2-2\delta}\text{Ti}_\delta\text{O}_4 \) \((x = 0 \sim 0.5)\) had a mixture of the normal and inverse spinal structure which has two sub-lattices, A and B sites. The saturation magnetization is depending on the difference between numbers of Fe atoms at A and B sites. In the present material, the Ti atoms mainly substituted Fe atoms at B-site and Mg atoms substituted Fe atoms at A-site \([14]\). Since the decrease in Fe atoms at B-site is larger than those at A-site, the saturation magnetization decreases with increasing \( x \). Furthermore, \( T_c \) decreases with increasing \( x \) because \( T_c \) is mainly depending on the number of Fe atoms at A-site \([15,16]\). Accordingly the saturation magnetization and \( T_c \) decreased with increasing \( x \).

The temperature as a function of time for \( x = 0.35 \) is shown for various magnetic field \((H = 20 \sim 100 \text{ Oe})\) in Fig. 3. The temperature is rapidly elevated after applying the magnetic fields, and reaches the constant value. It is noted that the constant value increases with increasing the field and approaches \( T_c \) asymptotically. This behavior means that the temperature of sample in the low field reaches an equilibrium value determined by the balance of heat generation and the heat losses in the system. On the other hand, in the high field region higher than 100 Oe, the temperature become well controlled around \( T_c \); even when the sample is exposed to HFMF more than 200 Oe, where the heat generation become enough to overcome...
the all heat losses in the system. Namely, it is noted that the
temperature is safely controllable around $T_c$ without the
temperature measurement by the thermodouple.

The hysteresis loss ($W_h$) is shown as a function of $x$ by
open circles in Fig. 4. It increases with increasing the
magnetic field, and it decreases with an increase of $x$. The
decrease of $W_h$ is explained by the decrease of saturation
magnetization with increasing $x$ as mentioned above. The
heat generation ($Q$) of Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ ($x = 0 \sim 0.5$)
is also shown by closed circles in Fig. 4, where the values of
$Q$ are in good agreement with those of $W_h$. This fact
reveals that the heat generation ($Q$) of Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$
($x = 0 \sim 0.5$) is generated by the hysteresis loss ($W_h$). It can
be therefore used with the fine powder as the implant,
because the hysteresis loss is hardly dependent on the size of
the powder implant.

Fig. 5 shows the time dependence of the temperature at
the center of the sphere cancer model in the pure matrix
agar phantom as shown in Fig. 1, where the powder
Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ ($x = 0.35$) of 0.092 g/cc is uniformly
distributed in the sphere cancer model. The solid line in
Fig. 5 indicates the result calculated by FEM, using
$\rho = 1.0$, $C_p = 4.08 \times 10^3$ J/kg/K, $k = 0.78$ W/m/K for the material
constants of a agar phantom [17] in Eq. (3).

Fig. 6 shows the temperature distribution after 30
minutes in HFMF, together with the result by FEM
calculation. It is seen that the temperature in the range of
10 mm from the center of the sphere is over the temperature
(315 K) needed for hyperthermia. The calculated values are
in good agreement with the experimental data when $Q$
is 3.0 W/g, which is 1.2 W in terms of the heat generation
of the sphere. The value (3.0 W/g or 1.2 W) coincides
approximately with the value (2.8 W/g or 1.1 W) calculated
by the Eq. (2) for $x = 0.35$. This means that the temperature
in the cancer tissue, where the powder implant material is
distributed uniformly, can be predicted and the required
quantity of the powder implant material can be estimated by
the FEM calculation.

4. Conclusion

The magnetic properties and the characteristics of the
heat generation for Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ ($x = 0 \sim 0.5$) cer-
amic were investigated. It was found that the ceramic ($x = 0.35$)
was most suitable for the powder implant material.
The results are summarized below.

(1) Curie temperature ($T_c$) of Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ ($x = 0 \sim 0.5$) decreases with increasing $x$ linearly, and it is about
350 K at $x = 0.35$ and 315 K near $x = 0.38$. These are
suitable Curie temperatures for implant material, since
$T_c$ is a maximum self-controlled temperature at the
center of powder particle, but the surface temperature
and the temperature of the cancer tissue are much
lower than $T_c$ because of the heat losses of the system.

(2) The heat generation ($Q$) of Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ ($x = 0 \sim 0.5$) is induced by the hysteresis loss, and its
temperature is regulated around in HFMF more than
200 Oe at 230 kHz.

(3) The temperature distribution in a cancer tissue and
the quantity of Mg$_{1+x}$Fe$_{2-2x}$Ti$_x$O$_4$ needed to raise the
temperature for hyperthermia can be predicted by the
FEM calculation.

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