Effect of direct-current magnetic field on the specific absorption rate of metamagnetic CoMnSi: A potential approach to switchable hyperthermia therapy

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Effect of direct-current magnetic field on the specific absorption rate of metamagnetic CoMnSi: A potential approach to switchable hyperthermia therapy

K. C. Ugochukwu, M. M. Sadiq, E. S. Biegel, L. Meagher, M. R. Hill, K. G. Sandeman, A. Haydon, and K. Suzuki

ABSTRACT

Materials with 1st order antiferromagnetic (AFM) to high-magnetization (MM) phase transition known for their inverse magnetocaloric effect, abrupt rise in magnetization and magnetoelastic coupling, are promising for application in combined simultaneous diagnosis and targeted cancer therapy. A therapy that combines alternating-current (ac) and direct-current (dc) magnetic fields for simultaneous magnetic hyperthermia therapy (MHT) and magnetic resonance imaging (MRI), using same magnetic particles for heating and as contrast agents. We report a proof-of-concept study on the induction heating ability of 1st order metamagnetic material with moderate specific absorption rates (SAR) and no tendency for agglomeration, for potential MHT and MRI cancer therapy. CoMnSi, a metamagnetic antiferromagnet (MM) was used in this study because of its desirable ability to rapidly switch from a low to high magnetization state in an applied dc bias field condition without particle agglomeration on field removal. The results showed that the magnetization switched from $<20\,\text{Am}^2\text{kg}^{-1}$ at 0.75 T to about $53.31\,\text{Am}^2\text{kg}^{-1}$ at 1.0 T applied dc field, a field large enough for magnetic resonance imaging. An SAR value of $10.7\,\text{Wg}^{-1}$ was obtained under an ac field of $31.0\,\text{kAm}^{-1}$ at $212.0\,\text{kHz}$. When combined with a dc bias field of 1.0 T, SAR values of $9.83\,\text{Wg}^{-1}$ and $6.65\,\text{Wg}^{-1}$ were obtained in the directions 45$^\circ$ and 90$^\circ$ away from the dc bias field direction respectively. These SAR values obtained from CoMnSi particles in the presence of simultaneous ac and dc magnetic field bias are in comparison, at least 25 times greater than those obtained from 2nd order magnetic phase transition Fe$_3$O$_4$ suspension. It is observed that Fe$_3$O$_4$ particles showed large suppression of SAR, and agglomeration under the same experimental conditions. This study shows the great potential of 1st order phase transition metamagnets for simultaneous MHT and MRI cancer therapy using MRI equipment.

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I. INTRODUCTION

There is a growing interest in finding biomedical materials with multifunctional properties, such as magnetic materials, for application in consolidated diagnosis, targeted treatment and real-time monitoring of cancer treatment, also known as cancer theranostics.\textsuperscript{1–8} Magnetic particles (MP) are promising candidates as cancer theranostics agents\textsuperscript{9–12} due to their ease of manipulation by non-invasive external magnetic field stimuli.\textsuperscript{13} Also, magnetic particles are easily rendered biocompatible by coating with biopolymers or biofunctionalization methods.\textsuperscript{14,15} MPs are used as contrast agents for magnetic resonance imaging (MRI),\textsuperscript{14,16,17} in magnetic particle imaging (MPI)\textsuperscript{1,6,9,10} and in magnetic hyperthermia therapy (MHT).\textsuperscript{14,17} MHT is a medical modality that uses the heat released by magnetic particles in the presence of an alternating-current (ac) magnetic field, at a frequency within 100 kHz – 1.0 MHz to induce temperature rise of 42 – 47 °C within the body part of interest, thereby selectively killing cancerous cells through apoptosis.\textsuperscript{14,18,19}

Current magnetic materials used for cancer therapy and diagnosis are materials with second order magnetic phase transition and are classified as superparamagnetic (SPM), ferro- (FM) or ferrimagnetic (FiM) materials.\textsuperscript{19–24} SPM materials have an intrinsic low response to ac magnetic field and give low power dissipation rate, that is low specific absorption rate (SAR) values in hyperthermia applications.\textsuperscript{25} FM and FiM materials on the other hand, though possessing high SAR values, have the tendency to agglomerate into large particles which could potentially lead to occlusion of blood vessels or cause nonuniform local heating due to large variations in agglomerate sizes.\textsuperscript{26}

Studies so far on the theranostic application of FM and FiM materials revealed that, the SAR of these 2\textsuperscript{nd} order magnetic materials with finite magnetization vis-à-vis their heating properties are drastically suppressed or canceled in the presence of an applied direct-current (dc) magnetic field bias.\textsuperscript{16,17} Thus, limiting their usage in simultaneous MHT and MRI cancer therapy. MRI requires a dc magnetic field bias, due to the presence of large particles which could potentially lead to occlusion of blood vessels or cause nonuniform local heating due to large variations in agglomerate sizes.\textsuperscript{26}

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III. RESULTS AND DISCUSSION

A. Microstructural and magnetic properties

In order to evaluate the potential of using 1st order MM particles for magnetic hyperthermia cancer therapy, the structural properties, particle size distribution and magnetic properties studies of the CoMnSi particles were investigated and results obtained are discussed as follows:

Figure 1(a) displays the particle size distribution of the crushed CoMnSi particles of mean size $\approx 75.42 \pm 58.53 \mu m$ as calculated from SEM images (see inset). The XRD pattern of Figure 1(b) confirms that the CoMnSi sample has polycrystalline orthorhombic phase, while Rietveld refinement with DIFFRAC.SUITE TOPAS Rietveld Analysis Software gave a TiNiSi structure with all the peaks indexed to the space group $Pnma$ crystal structure.\(^\text{36,37}\)

The refinement gave lattice parameters values $a = 5.8574(4) \text{ Å}$, $b = 3.6906(3) \text{ Å}$, $c = 6.8604(4) \text{ Å}$ and crystallite size of 467.5(32.5) nm with an internal stress of 0.0949(70), similar to data by previous investigators.\(^\text{36,38,39}\) This result agrees with the generally acceptable microstructural properties of CoMnSi as a highly strained magnetoelastic alloy.\(^\text{40}\)

In order to investigate room temperature magnetic properties of the CoMnSi sample and compare them with those of the conventional 2nd order transition Fe$_3$O$_4$, field dependent magnetization measurements were made on the samples and are shown in Figure 1(c) and (d) respectively.

The CoMnSi M-H curve of Figure 1(c) shows a clear 1st order transition from AFM ground state to a high magnetization MM state with increasing magnetic field ($\mu_0 H$) in accordance with earlier studies.\(^\text{39,41}\) At low fields, the magnetization ($M$) remains low, with $M < 20.0 \text{ Am}^2\text{kg}^{-1}$ until a critical field ($\mu_0 H_{\text{crit}}$) = 0.75 T above which the magnetization dramatically jumps up, reaching $M = 53.3 \text{ Am}^2\text{kg}^{-1}$ at about $\mu_0 H = 1.0T$. At $\mu_0 H = 1.5 \text{ T}$ the magnetization reaches $M = 79.6 \text{ Am}^2\text{kg}^{-1}$, which represents a magnetization change ($\Delta M$) = 59.7 Am$^2$kg$^{-1}$, for a magnetic field change ($\mu_0 \Delta H$) = 0.75 T. The drastic magnetization change $\Delta M$ around $\mu_0 H_{\text{crit}}$ is attributed to the field-induced AFM-MM 1st order magnetic phase transition due to the inherent magnetoelastic coupling present in CoMnSi alloys.\(^\text{34,38,42,43}\)

From Figure 1(d), it can be seen that the Fe$_3$O$_4$ sample with 2nd order magnetic phase transition shows a higher remanent magnetization ($M_r$) = 9.0 Am$^2$kg$^{-1}$ and a smaller coercivity value ($\mu_0 H_c$) = 6.56 mT. In comparison with the 1st order MM CoMnSi sample a very small

![FIG. 1](image-url) (a) Particle size distribution of the crushed CoMnSi alloy (inset is a representative SEM image), (b) Refined XRD pattern acquired from the CoMnSi sample, and room temperature M-H loops for (c) CoMnSi and (d) Fe$_3$O$_4$. Insets show the remanent magnetization of the samples.
$M_r = 0.86 \text{Am}^2\text{kg}^{-1}$ and a moderate $\mu_0H_c = 33.2 \text{mT}$ can be observed. The $M_r$ of the CoMnSi is at least 10 times smaller than that of the Fe$_3$O$_4$, indicating lesser dipolar interactions amongst the CoMnSi particles than the Fe$_3$O$_4$ particles in the absence of an applied dc magnetic field.

In order to understand the agglomeration behavior of CoMnSi particles with 1$^{\text{st}}$ order magnetic phase transition in comparison with Fe$_3$O$_4$ particles with 2$^{\text{nd}}$ order magnetic phase transition, the samples were subjected to a dc magnetic field. To achieve this, an inplane horizontal dc magnetic field $\mu_0H_c = 1.0 \text{T}$ was applied to some randomly dispersed Fe$_3$O$_4$ and CoMnSi particles on glass slides for 2 minutes and then removed. Figure 2 is a side by side comparison of optical images of the Fe$_3$O$_4$ and CoMnSi samples respectively; (a) and (d) are the Fe$_3$O$_4$ and CoMnSi samples before dc field application, (b) and (e) with 1.0 T dc field in place, (c) and (f) after the removal of the dc field followed by 30 s sample vibration in the horizontal plane using an electrical sample vibrator.

The images of Figure 2(a) and (d) indicate that prior to dc field application, Fe$_3$O$_4$ and CoMnSi particles were randomly dispersed on the glass slides, but on the application of $\mu_0H = 1.0 \text{T}$ the particles became magnetized and aligned along the applied field direction as can be seen in Figures 2(b) and (e). This observation agrees with the VSM M-H curve measurements of Figure 1, that both samples possessed high magnetization. But, as the field was switched off, then followed by 30 s vibration of the sample glass slides on an electrically vibrated horizontal surface, the Fe$_3$O$_4$ and CoMnSi particles behaved differently as shown in Figure 2(c) and (f). In a material with substantial $M_r$, dipole-dipole interaction among the particles hinders easy randomization of magnetic particles after magnetic field removal, leading to particle aggregation and agglomeration among aggregates as shown in (c). But for a material without substantial $M_r$ in the absence of an applied magnetic field, such as AFM CoMnSi, a little horizontal vibration of the sample will result in the randomization of the particles. This is clearly shown by the CoMnSi image in Figure 2(f) and this result indicates the absence of agglomeration in the CoMnSi in the absence of dc magnetic field.

B. Time dependent heat generation properties under an applied ac magnetic field

Heat generation by magnetic particles in an ac magnetic field can occur as a result of hysteresis losses or Neel-Brownian relaxation losses. The mechanism that dominates heat generation in a particular system depends on its particle size, but for multidomain size particles, hysteresis loss is the dominant heating mechanism in an ac field at room temperature. This heat generation mechanism has been widely reported by several authors.

Recall that the heating ability of a magnetic particle is given in terms of the specific absorption rate; which is defined as power delivered per unit mass of magnetic material. This can be determined using calorimetric method in an adiabatic condition. Hence, the SAR of a magnetic particle sample in an ac magnetic field is as given in Eq. (1)\textsuperscript{15,16,24,45}

$$\text{SAR} = \frac{P}{m_{mp}} = c_r \left( \frac{m_r}{m_{mp}} \right) \times \left( \frac{dT(t)}{dt} \right)_{t \to 0}$$

where $m_r$ and $c_r$ are the mass and specific heat capacity of the solvent bearing the particles, water in this case, $m_{mp}$ is the mass of the magnetic particle and $T(t)$ is the time dependent temperature of the sample in the applied ac field. This $T(t)$ is the solution to the differential equation describing the power balance between the sample and its environment.\textsuperscript{15,16,24}

$$T(t) = T_o + \Delta T_{\text{max}} \left[ 1 - e^{-\frac{t}{\tau}} \right]$$

Hence, for all experimental calorimetric measurements in this study, the initial slope $\frac{dT(t)}{dt} \bigg|_{t = 0}$ of the $T(t)$ vs $t$ measurement was obtained by approximating $\frac{dT(t)}{dt} \bigg|_{t = 0} \approx \frac{\Delta T_{\text{max}}}{\tau}$, where $T_o$ is the initial temperature of the sample, $T_{\text{max}}$ is the maximum temperature, $\Delta T_{\text{max}}$ is the temperature rise $T_{\text{max}} - T_o$, and $\tau$ is the time constant, that is the time to reach $T = T_o + 0.63aT_{\text{max}}$.

Experimentally, the SAR was calculated from the time dependent temperature profile of the CoMnSi particle suspension, with concentration 15 mg/ml dispersed in 0.8% (w/v) agar-agar gel, acquired with EasyHeat induction heating system (Ambrell EASY-HEAT 0224 by Cheltenham Induction Heating Ltd, England) under an adiabatic condition, using an applied ac magnetic field of amplitude 31.0 kAm$^{-1}$ and frequency 212 kHz.

For the dc bias field measurement, in the first case, the bias field $\mu_0H_{dc} = 1.0 \text{T}$ was applied horizontally such that it made an angle of 45° with the CoMnSi suspension axis (see Figure 3(a)) and the ac field was applied along the axis of the suspension. Figure 3(b)
FIG. 3. (a) Schematic of experimental setup for the calorimetric determination of dc magnetic field bias dependent SAR for CoMnSi particles suspension, (b) Time dependent temperature profile for CoMnSi in the absence of an applied dc bias field $\mu_0H_{dc} = 0.0$ T (black) and in the presence of dc bias field $\mu_0H_{dc} = 1.0$ T (red), (c) Time dependent temperature profile of Fe$_3$O$_4$ in the absence of an applied dc bias field $\mu_0H_{dc} = 0.0$ T (black) and in the presence of dc bias field $\mu_0H_{dc} = 1.0$ T (red).

compares the temperature profile of the CoMnSi suspension in zero dc bias field $\mu_0H_{dc} = 0.0$ T with that of dc bias field $\mu_0H_{dc} = 1.0$ T. The profiles show that without dc bias present, the CoMnSi suspension temperature increased rapidly with time, from $T \sim 22.20$ °C to $T \sim 42.2$ °C in less than 14 minutes, that is a $\Delta T = 20$ °C. But, in a dc bias field $\mu_0H_{dc} = 1.0$ T, a slower rate of rise was obtained. However, the temperature rose from $T \sim 22.20$ to $T \sim 36.7$ °C within 14 minutes time interval. This is a $\Delta T = 14.5$ °C. The heating profile of the conventional 2nd order Fe$_3$O$_4$ shown in Figure 3(c) shows a more rapid temperature rise in zero applied dc field. The temperature rose from $T \sim 22.20$ to $T \sim 42.3$ °C in 3.33 minutes. This represents a $\Delta T = 20.0$ °C. However, performing the same measurement under a dc bias field $\mu_0H_{dc} = 1.0$ T applied at an angle of 45° to the suspension axis, resulted in no significant temperature change in the Fe$_3$O$_4$ suspension sample after 7 minutes of measurement. The Fe$_3$O$_4$ suspension was further exposed to the combined ac and dc magnetic field for another 23 minutes, resulting in a final temperature $T \sim 23.7$ °C. This represents a $\Delta T = 1.4$ °C from suspension initial temperature $T_0 \sim 22.0$ °C. From this result, it can be inferred that a dc bias field $\mu_0H_{dc} = 1.0$ T was enough to cancel the heating ability of the 2nd order Fe$_3$O$_4$ particles. Our result is in agreement with previously reported work on the effect of combined ac and dc field on the heating ability of conventional 2nd order SPM/FiM/FM materials with finite magnetization, an unfavorable outcome on achieving MHT and MRI theranostic cancer therapy using conventional 2nd order SPM/FiM/FM materials. This is because the heating ability of conventional 2nd order magnetic materials are either significantly suppressed or totally canceled in the presence of dc bias field, depending on the dc bias field amplitude. The dc field induces fast magnetization saturation of the 2nd order FM/FiM suspension particles along the dc field direction. It should be recalled that the amplitude of ac fields employed in magnetic hyperthermia therapy are always small and not able to realign the saturated magnetic moments from the dc field direction to its own direction. However, CoMnSi is a 1st order AFM metamagnet which undergoes MM transformation at a critical dc field through nucleation-and-growth of the MM state within the AFM matrix. Thus, its magnetization is not easily saturated even at a relatively high dc field up to 1.5 T in comparison with its conventional 2nd order magnetic material as seen in Figure 1(c). This explains the temperature change $\Delta T = 14.5$ °C obtained from the CoMnSi sample in the dc bias field of 1.0 T in comparison with the negligible 1.4 °C temperature...
change obtained from the conventional 2nd order magnetic Fe$_3$O$_4$ material.

For hyperthermia therapy, a fever condition is induced in the desired part of the body in order to increase its temperature to within 42 – 46 °C. This is a 5 – 9 °C temperature rise above the 37 °C physiology body temperature. It is clear that the CoMnSi sample achieved this required temperature increase, both in the absence and presence of applied dc field, indicating that it has a better heating ability in static field than conventional 2nd order SPM/FIM/FM materials.

In the second case, the dc bias field experiment was repeated with the CoMnSi and Fe$_3$O$_4$ suspension axes transverse to the applied dc bias field (i.e. ac and dc fields were at 90°). Table I summarizes the SAR values calculated from the measured $T \sim t$ curves using Eq. (2). The moderate SAR value 10.67 Wg$^{-1}$ of the CoMnSi in the absence of dc bias and the relatively small decrease in SAR value to 9.85 and 6.63 Wg$^{-1}$ in the absence of dc bias field 1.0 T applied at 45° and 90° respectively to the ac magnetic field stands out when compared with the Fe$_3$O$_4$ SAR values of 22.61 Wg$^{-1}$ in zero dc bias, 0.21 and 0.25 Wg$^{-1}$ in the presence of the dc field bias applied at 45° and 90° respectively. The decrease in the SAR values observed in the presence of $\mu_0 H_d = 1.0$ T dc field for the CoMnSi is relatively small compared to the difference in SAR values obtained from the Fe$_3$O$_4$ suspension in the absence and presence of an applied dc field bias. This observation is very important for theranostic use of MRI technique for real-time monitoring of cancer treatment progress and responses in hyperthermia cancer therapy, using the same magnetic particles as heating and contrast agents.

### IV. CONCLUSION

In this study, we have demonstrated the use of CoMnSi particles with 1st order metamagnetic phase transition for heat generation by magnetic field induction. We observed that the heat generation was not significantly suppressed or cancelled in the presence of an applied moderately high dc magnetic field. Our study suggests that 1st order metamagnetic antiferromagnets can yield higher SAR than conventional 2nd order superpara-, ferro- or ferrimagnetic materials in the presence of an applied dc field bias. This proof-of-concept study concludes that heating effects in 1st order antiferromagnetic metamagnetic materials can be explored for theranostic combination of magnetic hyperthermia therapy and MRI imaging. While we note that this study was performed using particles of size bigger than those presently used in actual practice, we are currently investigating particle size effects on the heating properties and SAR of ball milled CoMnSi particles in the size range 30 nm – 1 μm for practical MHT and MRI applications.

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### TABLE I

| Material | $\text{SAR}_{H_d=0.0 \, \text{T}}$ (Wg$^{-1}$) | $\text{SAR}_{H_d=1.0 \, \text{T}}$ (Wg$^{-1}$) | $\text{SAR}_{H_d=1.0 \, \text{T}}$ (Wg$^{-1}$) |
|----------|-------------------------------|-------------------------------|-------------------------------|
| CoMnSi   | 10.6 ± 1.2                    | 9.83 ± 0.67                   | 6.65 ± 0.73                   |
| Fe$_3$O$_4$ | 22.6 ± 1.2                    | 0.21 ± 0.56                   | 0.25 ± 0.06                   |
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