Magnetic and hydrogel composite materials for hyperthermia applications

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Micron-sized magnetic particles (Fe_3O_4) were dispersed in a polyvinyl alcohol hydrogel to study their potential for hyperthermia applications. Heating characteristics of this ferrogel in an alternating magnetic field (375 kHz) were investigated. The results indicate that the amount of heat generated depends on the Fe_3O_4 content and magnetic field amplitude. A stable maximum temperature ranging from 43 to 47 °C was successfully achieved within 5–6 min. The maximum temperature was a function of Fe_3O_4 concentration. A specific absorption rate of up to 8.7 W/g Fe_3O_4 was achieved; this value was found to depend on the magnetic field strength. Hysteresis loss is the main contribution to the heating effect experienced by the sample.

Introduction

Hyperthermia is the heating of certain organs or tissues to temperatures between 41 and 46 °C for cancer therapy [1]. Depending upon heat delivery techniques, hyperthermia can be classified into three categories: whole body, regional and localized hyperthermia [2].

The three most essential challenges for the use of hyperthermia in clinical applications so far are (1) the generation of the temperature increase only within the target region (tumors) leaving all other regions unaffected, (2) the temperature control within as well as outside the target region and (3) the optimization of thermal homogeneity in the target volume [3].

For years many researchers have tried to come up with different solutions for these challenges. Self-regulating thermoseeds, that is, small metal pieces usually in needle shape that act as the heating agents, were fabricated to achieve better temperature control. The basic idea is to manipulate chemical composition (alloying) of magnetic materials such that their Curie points can be brought near the desired heating temperature range of 42–46 °C. Some examples include PdNi made by Wieringen [4], duplex stainless steel [5], amorphous metal flakes consisting of Fe–P–Cr–C [6], etc. The rationale behind this is to avoid overheating beyond the safe limit as all ferromagnetic materials become paramagnetic above their Curie points. At Curie temperature, the permeability of magnetic materials drops suddenly, both coercivity and remanance becomes zero and no magnetic hysteresis loss exists; thus, heating activity will be automatically terminated.

Recently, approaches to cancer therapy involve the attempt to combine hyperthermia with radiation and chemotherapy. Sato *et al*. [7] used a heating device made up of ferrite and a gold ring to treat malignant brain tumors. The ferrite serves as self-regulated hyperthermia whereas the gold ring enhances the effect of X-ray radiation. Another approach is to use microcapsules made up of ferromagnetic amorphous metal flakes that are additionally capable of releasing anticancer agents [8].

All the above-mentioned techniques are invasive and require varying degree of careful surgery. Our broader aim is to develop the hyperthermia technique in combination with drug delivery. The idea is to develop a magnetic and hydrogel composite material whereby the magnetic material will be responsible for heating up the tumor and the hydrogel will release the anti-cancer drugs. Eventually, it is hoped that this composite can be introduced into the body and guided to the target area by external magnetic field.

The feasibility of this idea was explored by using polyvinyl alcohol (PVA)−Fe_3O_4 ferrogel system. PVA and Fe_3O_4 were chosen because of their well-established bicompatibilty and history of clinical usage. Iron oxide is chemically stable, non-toxic and non-carcinogenic. The other alternative magnetic materials such as cobalt and nickel still face some issues on toxicity and biocompatibility. On the other hand, iron raises the concern of possible overheating as its capability to convert the energy (from alternating magnetic field) to heat is probably too high that it may cross the safety limit of hyperthermia. Further investigation, however, is required to prove this prediction. Therefore, the mild magnetic properties as well its biocompatibility made iron oxide as the most reasonable choice for magnetic hyperthermia agent.

The heating characteristics of (PVA + Fe_3O_4) composite when an oscillating magnetic field is applied are investigated in this paper. Calculation of the SAR is presented. The optimum concentration of Fe_3O_4 has been experimentally determined; these results will be discussed.

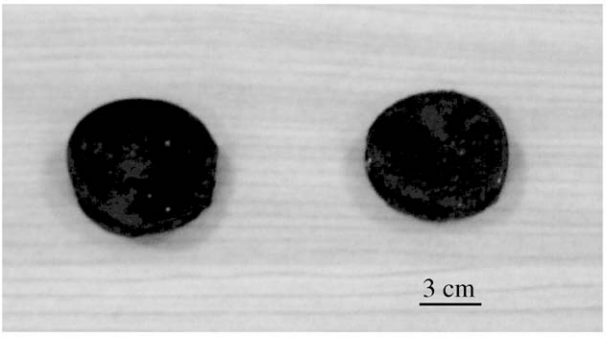

Figure 1 (PVA + Fe_3O_4) ferrogel sample for hyperthermia.

Experimental methods

The (PVA + Fe_3O_4) ferrogel was prepared by using a conventional freezing/thawing method. PVA powder (99% hydrolyzed supplied by Aldrich Chemicals Inc.) was dissolved in water with weight composition of 23 : 100. The solution was stirred and heated to 70–90 °C to increase the solubility of PVA in water. Depending on the weight ratio, Fe_3O_4 powder (supplied by Aldrich Chemicals Inc.) of size $\sim 5\,\mu m$ was added to the solution and mixed homogenously. The sample was then frozen and thawed repeatedly until complete gelation was achieved. Examples of ferrogels prepared can be seen in Fig. 1.

The sample was then placed on a thermally insulating surface within the excitation coil at room temperature for induction heating testing. An alternating magnetic field in the range of 1.7–2.5 kA/m and frequency 375 kHz was applied. Increase in the sample's surface temperature was recorded as a function of time. Magnetic properties were measured using a Lakeshore model 7300 Vibrating Sample Magnetometer (VSM).

Results and discussions

Fig. 2 shows the *B–H* curve of the iron oxide (Fe_3O_4) particles obtained before they were embedded in the PVA gel. Since the particle size was in the range of 3–5 μm, there is only a small amount of hysteresis loss associated with every cycle.

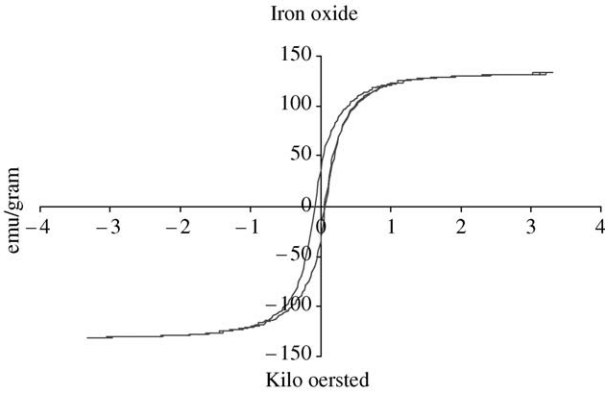

Figure 2 Hysteresis curve of Fe_3O_4 powder (diameter = 5 μm).

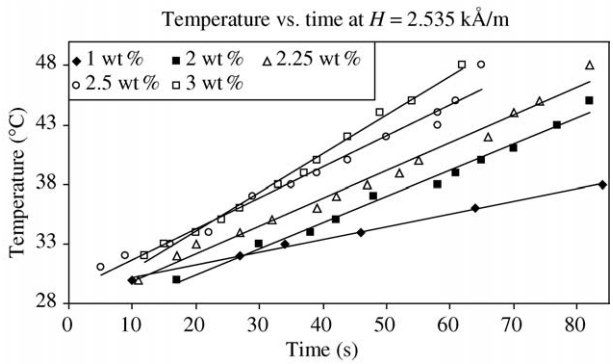

Figure 3 Temperature vs. time at $H = 2.5$ kA/m.

Temperature vs time as a function of iron oxide concentration

Fig. 3 shows the plot of the temperature of the composite as a function of time for different values of iron oxide content. It is constructed for a constant magnetic field strength of $H = 2.5$ kA/m. The heating effect is a result of absorbing energy from the alternating magnetic field and transforming it into heat by means of three mechanisms: (1) eddy current losses, a minor effect since Fe_3O_4 has very low-electrical conductivity; (2) hysteresis loss during reversal of magnetization (Fig. 2); and (3) rotational losses due to the rotation of the magnetic material relative to its surroundings, described by Neel and Brownian effects [3]. Fig. 3 shows that the temperature increase is roughly linear as a function of heating time for small heating times.

As the iron oxide concentration increases the rate of temperature increase (dT/dt) also increases, meaning the sample gets heated faster by the magnetic field. The initial slope (dT/dt) of the curve is very useful in calculating the specific absorption rate (SAR) of the sample, shown in the later sections.

Temperature vs time as a function of magnetic field strength *H*

Fig. 4 is constructed for iron oxide content of 2 wt %. It shows that the magnetic field amplitude H has a very strong effect on the maximum temperature the (PVA + iron oxide) system can reach as well as the rate of temperature increase.

The maximum temperature that can be achieved by the ferrogel at 1.7 kA/m was only 40 °C. This is insufficient for hyperthermia use. By increasing the magnetic field

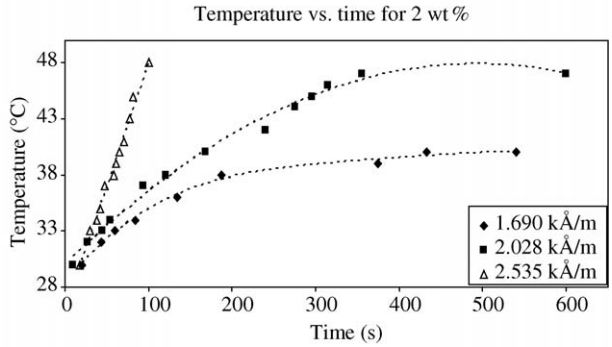

Figure 4 Temperature vs. time at iron oxide content of 2 wt %.

amplitude to 2 kA/m, the maximum temperature was raised to 47 °C. After reaching the maximum value, temperature then stabilized for a long time. This shows a good control of temperature and heat flux, requirement for hyperthermia application. If the temperature rises out of control (≥ 48 °C), the healthy tissues surrounding the tumor will be burnt and damaged. At an even higher field H, the temperature rose very fast, beyond 48 °C.

The magnetic field amplitude employed in this experiment (1.7–2.5 kA/m, 375 kHz) is comparable, if not smaller, than the field used by other researchers. For similar magnetic materials (Fe_3O_4, diameter 40 μm), Mitsumori *et al*. [9] applied a magnetic field strength of 21.6 kA/m at 100 kHz. Park *et al*. [5] employed duplex stainless steel as magnetic seeds and field of 1.35 kA/m at 114 kHz, while a higher field (7 kA/m, 185 kHz) was used by Sato *et al*. [1].

Specific absorption rate

The SAR is defined as the amount of heat released by a unit weight of the material per unit time. It can be calculated using the formula:

$$\mathrm{SAR} = c(\Delta T/\Delta t) \tag{1}$$

where c is sample-specific heat capacity, calculated as a mass weighted mean value of magnetic carriers and equivalent medium and $\Delta T/\Delta t$ is the temperature increase per time, that is, the initial slope of the temperature vs time curve.

For our composite, there are three main components: PVA, water and iron oxide powder. Therefore, heat capacity of the system is calculated as follow;

$$c = \frac{(\text{mass } Fe_3O_4 * c Fe_3O_4) + (\text{mass PVA} * c\text{PVA}) + (\text{mass water} * c\text{water})}{(\text{mass } Fe_3O_4 + \text{mass PVA} + \text{mass water})} \tag{2}$$

SAR dependence on the magnetic powder content and magnetic field strength was found as follows.

SAR as a function of magnetic powder content

The effect of magnetic powder content on SAR is illustrated in Table I. Two blocks of samples are presented. Each block contains samples exposed to the same heating condition (constant H and f) but varying iron oxide concentrations.

At block 1, two samples with different iron oxide loadings were subjected to magnetic field strength of 1.7 kA/m. The SAR values were very close to each other and averaged to 4.0 W/g.

Similarly, at block 2, five samples with different magnetic powder content were subjected to another set of heating condition ($H = 2.5$ kA/m, $f = 375$ kHz). Again, the SAR values did not change much although the iron oxide content was varied.

These findings imply that SAR is not very sensitive to the iron oxide content.

TABLE I SAR of samples with different H and wt %

Block	Magnetic field H (kA/m)	wt %	SAR (W/g)	Average SAR
Block 1	1.7	2.0	4.1	4.0
		2.5	3.8	
Block 2	2.5	1.0	11.0	8.7
		2.0	8.4	
		2.3	8.3	
		2.5	7.0	
		3.0	8.7	

TABLE II SAR as a function of magnetic field strength H

wt %	H (kA/m)	H^2 (kA/m)^2	SAR (W/g)	SAR/H^2
2	1.69	2.86	4.06	1.42
	2.03	4.11	5.82	1.41
	2.54	6.43	8.44	1.31

SAR as a function of magnetic field strength H

To investigate the dependence of SAR on magnetic field strength, three samples with 2 wt % Fe_3O_4 loadings were prepared. Subsequently, these samples were subjected to different magnetic field strength while other variables such as oscillation frequency were kept constant. The result is tabulated in Table II and plotted in Fig. 5. The SAR was found to increase linearly with the square of magnetic field strength. The good linear curve fitting ($R^2 = 0.9825$) indicates that this result matches well with the established relationship [2, 3]:

$$\mathrm{SAR} \cong k \times f^n \times H^2 \tag{3}$$

where k is a constant that depends on several factors (particle permeability, conductivity, size and shape, etc.), f is frequency of alternating magnetic field, n is an exponent (varies from 1 to 2) and H is the magnetic field strength.

The linear trend observed in Fig. 5 was expected as the frequency employed was constant and the magnetic particles used in all samples were exactly the same. Thus constant (SAR/H^2) value, which is the slope of the curve, is obtained.

The SAR value obtained from this ferrogel system is comparable to that of other hyperthermia researchers. Mitsumori *et al*. [9] obtained a value of 1.2 W/g for Fe_3O_4 of 40 μm size using field parameters of 21.6 kA/m and 100 kHz. If the particle size was reduced to nanoscale (350 nm), as high as 75 W/gr was obtained

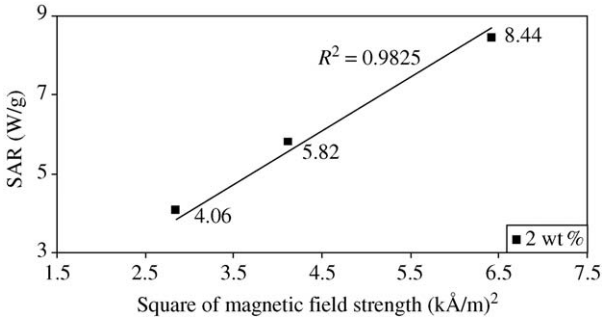

Figure 5 SAR vs. magnetic field strength H.

TABLE III Best combination of magnetic field H and iron oxide content for hyperthermia

Sample	wt %	Magnetic field (kA/m)	Max. temperature (°C)	Time to reach max. temperature (s)	SAR (W/g)
A	2	2.0	47	355	5.8
B	2.5	1.7	43	320	3.8

by Hergt *et al*. under conditions of 14 kA/m, 300 kHz. This tells us that a possible improvement to this work can be done by reducing the magnetic particle size.

Optimum concentration and magnetic field

After several tests varying the iron oxide content and magnetic field strength, as described in the earlier section, the best combination was found to be as shown in Table III.

This combination corresponds to 2.5 wt % iron oxide content and a magnetic field of 1.7 kA/m (sample B). With these conditions, a maximum temperature of 43 °C was achieved in 320 s. These values are superior to sample A (which has iron oxide content of 2 wt % and magnetic field of 2 kA/m) in terms of rise time and maximum temperature, as 43 °C is safer for surrounding healthy tissues compared to 47 °C. In addition, shorter rise time gives benefits of less sample weight loss and faster treatment. The weight loss of the sample detected after heating were suspected due to the evaporation of volatiles contained in PVA gel. Sample A, however, has higher SAR value due to stronger magnetic field.

Conclusions

A study of magnetic and hydrogel composite materials for hyperthermia applications was conducted. The following results were obtained:

1. Localized heating was achieved by subjecting $(\mathrm{PVA} + \mathrm{Fe_3O_4})$ ferrogel to alternating magnetic field.
2. Maximum temperature of 43 °C was obtained at 2.5 wt % Fe_3O_4 concentration. The time taken was ≈ 5 min under field amplitude of 1.7 kA/m and frequency of 375 kHz.
3. SAR was found to increase with magnetic field strength, but insensitive to Fe_3O_4 content. A value of 3.75 W/g was obtained for the optimum condition identified in Point 2.

The distinguished advantages of this composite over other alternative hyperthermia agents are; (1) maximum temperature can be easily adjusted by changing the Fe_3O_4 content and/or magnetic field strength so as to meet different requirements of various cancer or tumor cells; (2) temperature control can be obtained without setting the Curie point close to desired heating temperature through complicated alloying and chemical composition manipulation. Instead, the magnetic particles and PVA gels are equally capable of reaching the intended maximum temperature and stabilize afterwards; (3) combined hyperthermia and drug targeting as a new and more powerful approach to cancer treatment is made possible by this composite as described in Section 1; and (4) less invasive and less traumatic treatment is possible by employing an *in situ* gelation method.

Future works

The *in vivo* heating characteristics of this composite have not been investigated. The environment surrounding the device will certainly affect the heat transport efficiency from the device to the targeted cells. Some of the determining factors are the proximity of blood-vessels and blood flow rate, tissue conductivity, interface resistances, application of catheters or coatings, etc.

Nevertheless, the data obtained by Sato *et al*. [8] showed that the maximum *in vivo* temperature of ferromagnetic amorphous flakes in a dog kidney (44 °C) were relatively the same or slightly lower than that measured *in vitro* (45 °C). Unfortunately, the rise time is shifted to longer time, from 5 min *in vitro* to 25 min *in vivo*. However, for our system, the rise time and maximum temperature can be easily modified by changing the iron oxide concentration and/or magnetic field strength as discussed previously.

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