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A comparative measurement technique of nanoparticle heating for magnetic hyperthermia applications

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Abstract

We describe a method for the determination of the heating power of magnetic nanoparticle colloids which have potential for application in the remedial treatment of malignant and non-malignant tumours. The method is based upon a comparison between the heating power observed when the colloid is exposed to a radio frequency magnetic field and that which is observed using a resistive electrical heater. A new design of measurement cell has been made which has the advantages of reducing or eliminating the effects of convection, ensuring the measurement is made in a magnetic field of known uniformity and that the heat losses in the system are constant and minimized under both magnetic and Joule heating.

Keywords: hyperthermia; magnetite; nanoparticles; heating

Introduction

The subject of magnetic hyperthermia in colloids of magnetic nanoparticles is of high interest at the present time. This is because the heating of aqueous solutions of nanoparticles has potential to be used as a remedial treatment for malignant and non-malignant tumours in the human body [1]. At the time of writing human trials are underway [2] and animal trials have also been undertaken [3,4]. There have been a number of factors which have inhibited more rapid advancement in the medical use of this technique, the most important of which was associated with a clear lack of understanding of the process(es) that give rise to the heating effect. In recent works [5,6] we have shown that the heating mechanisms that give rise to nanoparticle heating have three distinct origins with hysteresis losses being dominant. Despite the comprehensive nature of our description of the mechanisms of nanoparticle heating the agreement between theoretical calculations and experimental values was in some cases poor. In seeking reasons for these disagreements we now direct our attention towards the commonly used measurement methods for the determination of nanoparticle heating.

The measurement of the thermodynamic properties of any material is always difficult. Generally the measurement of thermal properties of materials is undertaken in thermal equilibrium but by its very nature such an approach cannot be used to determine the heating power of magnetic nanoparticles. A good review of the different measurement techniques used for hyperthermia experiments can be found in [7]. For instance, Natividad et al. [8] explored the difference in taking measurements of the heat produced by magnetic nanoparticles under adiabatic and non-adiabatic conditions. The main conclusion reached was that taking measurements non-adiabatically raised some potentially appreciable errors that are difficult to control. It was argued that using an adiabatic setup would lead to an easier comparison between results from different experiments. However, Terán et al. [9] showed that similar temperature variations could be achieved by a given field strength under non-adiabatic conditions. This suggests that using a calorimetry approach can lead to accurate results of heat transfer from the magnetic nanoparticles. More recently, Coïsson et al. [10] proposed an alternative method whereby measuring the equilibrium temperature at a stationary state can remove the need for a calorimetry based procedure. However, this approach has the disadvantage of being more complicated.

In terms of the experimental setups several designs can be found in the literature most of which are based on a resonant circuit. Lacroix et al. [11] proposed a system based on a simple electromagnet, described by an inductor/capacitor model, and a purpose built amplifier. The system did not require cooling the magnet as the coil was made using Litz wire and a homemade resonant transformer. As a result low power was required to produce an alternating magnetic field. A similar setup was proposed by Cano et al. [12]. The Cano system works on a similar principle but uses a resonant inverter. This has the added benefit of being specifically designed to perform in-vitro measurements However, the system did not offer the possibility of changing the frequency of measurement. Garaio et al. [13] used an AC susceptometer consisting of an air coil connected to a resonant circuit, run by a power amplifier, to measure the heat produced by a sample of magnetic nanoparticles. Skumiel et al. [14] compared the difference in field magnitude and homogeneity achieved using different magnetic circuits. While the amplitude of the field generated using a double layer solenoid was greater, field uniformity was improved by using a Helmholtz coil. However, none of these setups account for the three issues that we have identified which need addressing in order to obtain meaningful results.

The first of these issues relates to heat losses to the environment during the course of the measurement. Given that the temperature is changing during the measurement the heat losses also change, making it almost impossible to take account of the losses directly. The power lost through the container and to the environment (P_l) is given by

$$P_l = \kappa \frac{T_2 - T_1}{l} \tag{1}$$

where κ is the thermal conductivity of the container material, $(T_2-T_1)/l$ is the temperature gradient across it and l is the thickness of the wall. A second problem occurs due to the fact that the particles are suspended in a liquid. Hence it may well be the case that the measured temperature is not representative of the sample as a whole due to convection. The issue of convection also influences the sample shape that should be used. Convection effects are greater in long, thin samples which should not be used. The sample shape also influences the heat losses as the material close to the container wall will lose more heat than that in the centre. The third problem with measurements of nanoparticle heating is that in general, short coils are used so that an RF oscillator can provide sufficient current to generate a magnetic field of adequate amplitude. In typical laboratory systems the coil has dimensions with a radius of about 25mm and a length of about 60 to 80mm. To limit the inductance of the coil they are generally made from copper tubing so that cooling water can be flowed through and have between 10 and 20 turns. A coil of these dimensions will not generate a uniform field and hence design of the apparatus requires careful consideration of the field uniformity. In this work we have attempted to address these three critical issues.

2. Results

2.1 Coil parameters

Figure 1 shows the precise dimensions of the coil used in this study. This is the bigger of two coils available in our measurement setup, a Nanotherics Magnetherm system [15]. As can be seen from the figure a 17 turn coil of these dimensions would not be expected to generate a uniform magnetic field across a significant length or radius within the coil. To examine the field uniformity we have placed the coil in series with a 1Ω resistor and powered the system from a 15A DC magnet power supply. Measurements of the field both radially and axially have been made using a Hall probe and are shown in Figures 2(a) and (b), respectively.

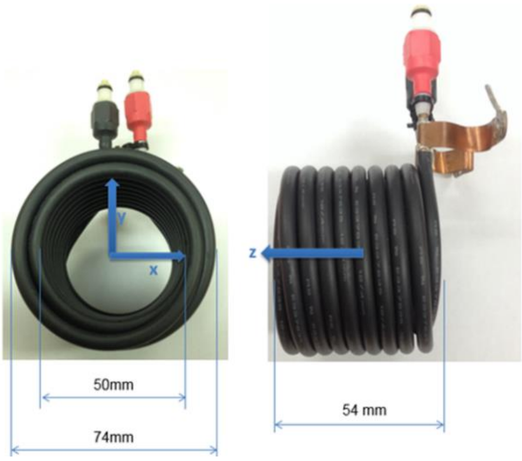

Figure 1. The heating coil studied.

From the data in figure 2, the field profile is non-uniform but there is a significant area of uniformity towards the centre of the coil. We have set a requirement for field uniformity that it should vary by no more than 10% across the sample in either the axial or radial direction. These limits are indicated in figure 2(a) and (b) by the vertical and horizontal black lines, respectively. Based on this analysis it is clear that this required field uniformity can be achieved by constructing a measurement cell of diameter 20mm which then allows for a similar field uniformity in the vertical direction over a distance of 10mm. Conveniently such a cell allows for a sample volume for measurement of almost exactly 3cc.

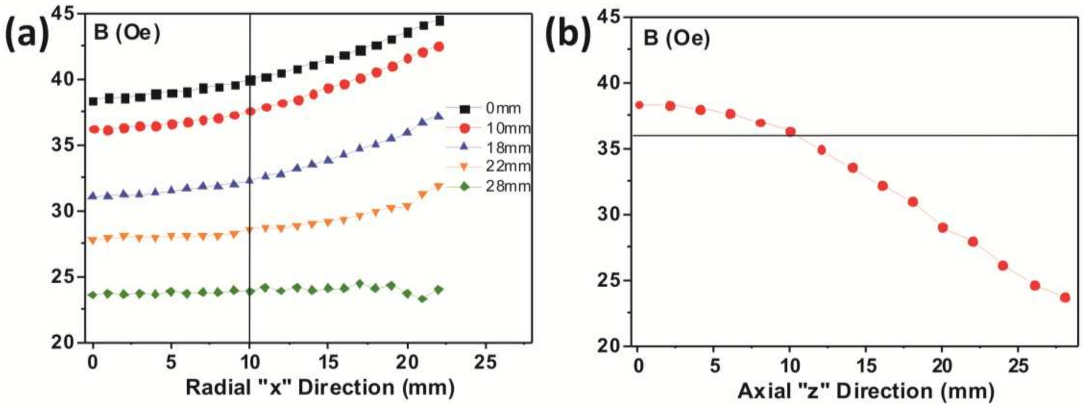

Figure 2. Field profile of the coil: (a) the radial direction for different off axis positions of the Hall probe where 0 mm is the centre (b) the axial direction where again 0 mm corresponds to the centre of the solenoid.

However there is also a requirement to determine the exact amplitude of the AC field generated by the RF oscillator. Often the value of the field is not measured directly but is inferred from a calculation which often assumes a coil of infinite length. Clearly this is unsatisfactory. To overcome this difficulty we have produced a small search coil consisting of 10 turns wound on a bobbin 4.75mm in diameter and 3.50mm long. The search coil was calibrated by energising the field coil with a 50Hz current driven from a mains source through a 1 Ω resistor. At this low frequency the response of a calibrated Hall probe is equivalent to its DC response due to the nature of the Hall effect. Hence the form factor for the coil has been obtained by direct calibration back to the Hall probe. The search coil was then used along the axis of the coil to determine the actual field generated.

Given the strong linearity between current and field independent of frequency, this gave a peak field at the centre of the coil of 180 Oe.

2.2. Design of the measurement cell

Knowledge of the field uniformity to ± 10% has allowed the design of a measurement cell 20mm in diameter containing a sample which is 10mm deep. In addition to providing a uniform field across the sample, this shape inhibits convection current effects which would be of greater significance in a long thin sample. However convection effects will inevitably occur in any liquid that is being heated. To overcome the effects of convection and sample cooling near the container walls which can cause significant errors in the measure of temperature, it is essential that the sample be stirred during measurement.

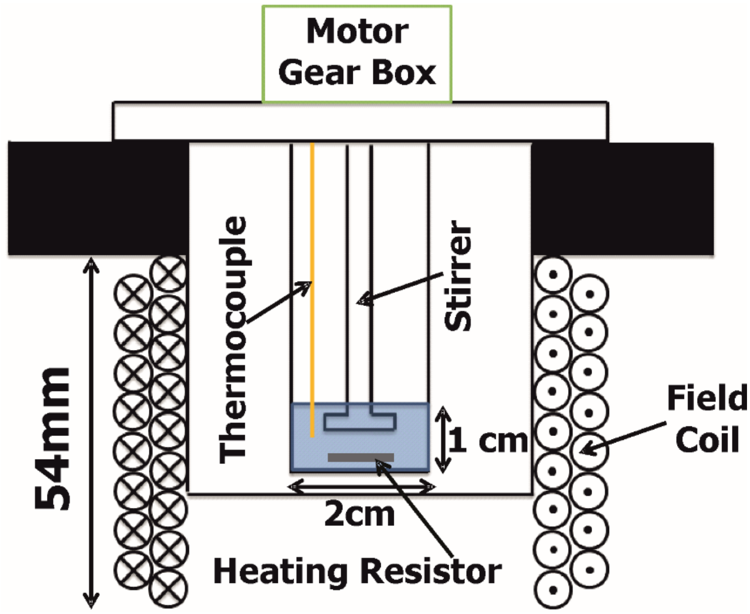

Figure 3. Schematic diagram of the measurement cell placed inside the solenoid.

Figure 3 shows a schematic of the measurement cell that we constructed. The cell was fabricated out of an engineering plastic (PEPT) which is a hard fluorinated based polymer and is easy to machine and clean. A simple electric motor and gear-box was mounted on top of the cell allowing for stirring of the liquid during measurements. Typical stirring rates used were 40rpm. Temperature changes were monitored using a type T thermocouple data logged via an RS232 interface giving a measurement temperature accuracy of ±0.1 K. Also incorporated in the measurement cell was an on-board non-inductive electrical resistor rated at 1W.

The most important issue with the design of the cell is that of heat losses. As discussed previously it is not possible to calculate the loss of heat which will vary with both the heating rate and in particular the temperature difference between one point and another. Furthermore the temperature will be non-uniform through the walls of the cell making any attempt to calculate heat losses impossible. The principle of our measurement technique is that the heating rate generated by a water based colloid of magnetic nanoparticles will be compared to the heating rate generated by the flow of current through the resistor in a sample of water containing no nanoparticles. This requires calibration of the cell by the careful measurement of the heating rate of a sample under Joule heating which can then be compared with the heating rate generated by the magnetic field. In this way the heating rate from the nanoparticles can be determined via a simple comparison.

Figure 4. Components of the measurement cell including on-board resistors and stirring paddle.

2.3. Calibration curve: Joule heating

Six 1 Ω resistors were mounted in parallel to avoid loops in the system. Due to the limited space available inside the cup and the delicate nature of the experimental setup, a mount was 3D printed and attached to the measurement cup. This ensured reproducibility between measurements as all components were always placed in the same position. The mount and the six resistors are shown in

Figure 4. Figure 5 shows a set of curves for the rise in temperature as a function of time for different levels of power supplied to the heater. For all values of power to the heating resistor, the variation of temperature with time is non-linear. This arises because of the wall thickness of the measurement cell and the fact that a significant temperature gradient will exist across the wall. This is in contrast to previous measurements using the same system where the sample was contained in a polycarbonate bottle with a relatively thin wall so that presumably there would be no significant temperature gradient across the wall. In this case a linear increase in temperature with time was observed [5].

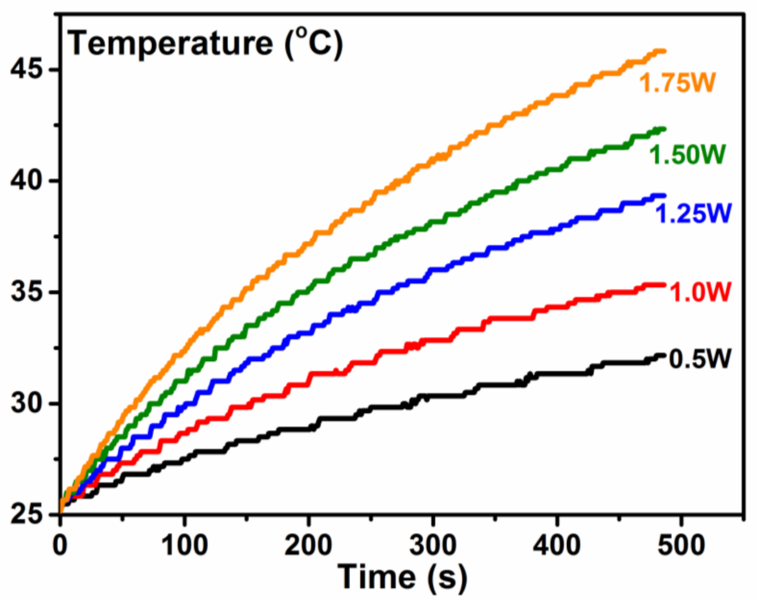

Figure 5. Heating measurements from the use of Joule heating from a resistor.

This new technique requires a number of curves at different heating powers to be measured. However in the initial stages of heating, say the first 100 seconds or so, the rise in temperature is relatively modest and generally less than 5 K. Under these conditions the temperature gradient across the walls of the cell will similarly be significantly lower than if measurements are extended to higher temperatures. This is shown by equation 1. If a curve is fitted to the measured data it is possible to obtain the value of dT/dt as the temperature difference $\Delta T(=T_2-T_1)$ tends to zero. From equation 1, as $\Delta T \rightarrow 0$ the heat losses also tend to zero. The concept of measurement as $\Delta T \rightarrow 0$ also requires that the sample and the cell are in thermal equilibrium prior to the measurement commencing.

We have measured the gradient $(dT/dt)_{\Delta T\rightarrow 0}$ as a function of the power supplied to the resistor. As can be seen in Figure 6 in this regime a highly linear variation of $(dT/dt)_{\Delta T\rightarrow 0}$ with power is observed with a linearity correlation of R^2=0.99. This then allows for the initial heating rate of the colloid exposed to the magnetic field to be converted directly to the effective heating power generated by a sample of magnetic nanoparticles. From the data in figure 6 and from a detailed analysis of our results in terms of reproducibility, we conclude that this measurement of the heating power of the resistor is accurate to better than ± 2%. This measurement technique and methodology is therefore significantly superior to previous published techniques both in terms of accuracy, simplicity and the validity of the measurement.

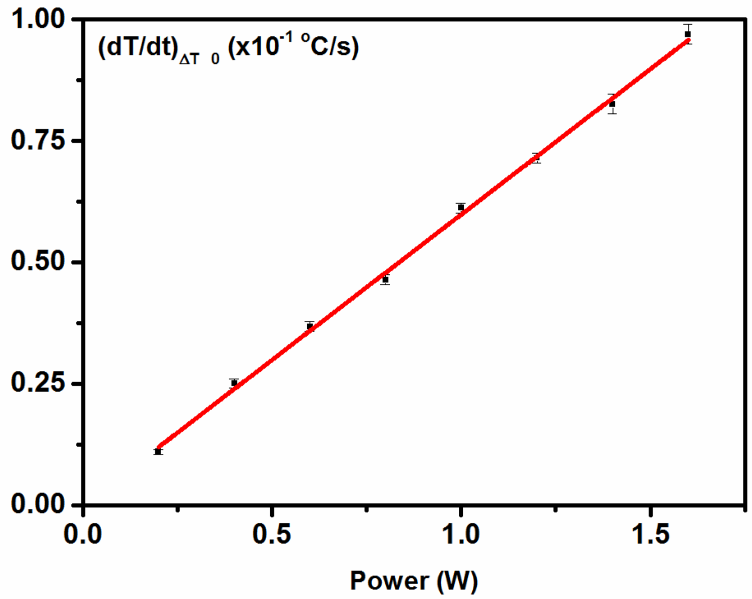

Figure 6. $(dT/dt)_{\Delta T\rightarrow 0}$ for different heating powers.

We have also measured the contribution to the total heating arising from inductive effects in the thermocouple and the resistor. This was done by monitoring the rise in temperature when 3cc of water were placed in an AC field of 180 Oe cycled at 111.5 kHz. These parameters were chosen as they are typical values used in magnetic hyperthermia experiments. The experiment was carried out with both the resistor and the thermocouple submerged in water and also with just the thermocouple submerged. This allowed us to quantify the contribution from each component. The rate of temperature rise due to both components was (8.0±0.4)x10^{-3} K/s with the thermocouple being responsible for 90% of this effect. In the case of the colloids studied in this work the overall heating rate varied in the range 3.3-6.0x10^{-2} K/s. Note that changes due to the temperature dependence of the physical properties, eg. resistivity, of the thermocouple and the resistors were negligible over the temperature range of our measurements.

Table 1. Characteristics for samples studied in this work.

Sample	Size (nm)	dT/dt (x10^{-2}Ks^{-1})	Power (mW)	Power/gram(W/g_{Fe})	SAR (W/g_{Fe})
HyperMAG A	10.3	3.33±0.06	435±9	29.0±0.6	21.8±0.4
HyperMAG B	11.7	4.31±0.06	596±10	39.7±0.8	30.0±0.4
HyperMAG C	15.2	6.0±0.1	885±20	59.0±1.0	44.5±0.7

2.4. Heating power of magnetic nanoparticles

Table 1 shows the result of the measurement of the heating power for three samples of iron oxide nanoparticles dispersed in water produced by Liquids Research Ltd and currently available on the market with the trade name HyperMAG® A, B and C. Table 1 also shows the particle size distribution parameters for these three samples. For more detailed information on these samples see reference [5]. Also shown in the table are the values of the specific absorption rate (SAR) calculated from the rise in temperature without making use of the calibration curve shown in figure 6. The SAR is conventionally defined as

$$SAR = \frac{C\rho}{\phi}\frac{dT}{dt} \qquad (2)$$

where C is the specific heat of the colloid, ϕ is the concentration of Fe per ml of solution and ρ is the density of the colloid. In our case C = 4184 J$kg^{-1}K^{-1}$, ρ = 1.0 g/cc and ϕ = 5 mg_{Fe}/ml. From the data in Table 1 it is clear that there are significant advantages to our current technique in providing a direct measurement of the heating power of the nanoparticles themselves either in absolute terms for a given concentration, or in terms of the power per unit weight of Fe generated by the particles which can be compared directly to the measurement of SAR. Note that to estimate the power dissipated by the nanoparticles, the contributions from the thermocouple and the resistor to the initial heating rate were taken into account. It is clear that in our system heat losses account for ~25% of the total heat resulting in conventional SAR measurements being an underestimate of the true heating properties of the nanoparticles.

3. Conclusions

We have described an improved technique for the measurement of nanoparticle heating in colloidal dispersions of nanoparticles for magnetic hyperthermia applications. The new technique is a simple comparison method but in the design of the apparatus which is relatively simple, steps have been taken to remove the effects of convection and to improve the magnetic field uniformity. Most importantly the comparative measurement technique allows for the determination of the heating rate effectively with zero temperature difference between the sample and its container. This removes the effect of heat losses so that an accurate measurement of the heating power can be obtained. Knowledge of the concentration of nanoparticles within the colloid then allows for the determination of the SAR parameter commonly used to characterise such systems.

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