Optimization of MRI Contrast Agents for Magnetic Fluid Hyperthermia Considering the Human Safety Limits

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Introduction

Over the last decade, magnetic particle hyperthermia has been improved by the advent of "magnetic fluid hyperthermia" [1], where colloidal dispersions of superparamagnetic iron oxide nanoparticles (magnetic fluids) exhibit an extraordinary specific absorption rate (SAR [W/*g*]) under the AC magnetic field. Moreover, these superparamagnetic particles provide contrast under MRI and their quantitative distribution can be obtained during an MRI scan. Much work has been done to find the optimum [1-2]magnetic fluid parameters (particle size, frequency, magnetic field strength, etc.) for hyperthermia, but none of these investigations has considered the human safety limits at the same time. In this work, we obtained the optimal hyperthermia parameters by considering human safety limits (nerve stimulation and tissue eddy current heating). The heating potential of the MRI contrast medium, Endorem™, was evaluated both theoretically and experimentally as a hyperthermia mediator

Methods

The physical principles regarding the heating of superparamagnetic particles in AC magnetic fields have been reviewed by Rosensweig [3]. Basically, the power dissipation density(W/m^f) for a monodispersion is given by:

$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} W/m^3$$

where H_0 is the magnetic field intensity, f is the frequency of the magnetic field, χ_0 is the actual susceptibility, which is also a function of volume fraction of solids, domain magnetization of the suspended particle, and magnetic particle radius. τ is the effective relaxation time based on the Brownian and Néel relaxations, which is the function of the viscosity coefficient of the matrix fluid, the hydrodynamic volume of the magnetic particle, and the anisotropy constant., It is known that log normal particle distribution provides a reasonably good fit to the ferrofluid distribution and power dissipation density (P) is modified for the lognormal distribution as below:

$$\overline{P} = \int_0^\infty P g(R) dR$$

where g(R) is the log normal particle size distribution and R is the particle radius. Finally, the corresponding SAR(W/kg) value is found by: $SAR = \overline{P}/\rho$ where ρ (kg/m^3)is the density of the ferrofluid. For the verification of theoretical calculations, an in vitro hyperthermia experiment is made. A well-known MRI contrast agent, Endorem™, based on magnetite, was used as a hyperthermia mediator, which has a mean particle radius of 6nm and a lognormal size distribution with standard deviation of 3nm[2]. The experimental setup of the hyperthermia applicator system can be seen in Figure1. We applied an H_0 of 3.1kA/m at various frequencies, ranging from 15 to 35kHz. SAR measurements were made with the rate of temperature rise method, such that the initial slope of the temperature versus time graph was multiplied with the specific heat capacity of Endorem™ according to the formula, SAR=c*($\Delta T/\Delta t$). Both theoretical and experimental results are plotted in Figure2. With the in vivo hyperthermia studies, a safety limit for the magnitude and frequency of the applied AC magnetic field was obtained. According to Reilly estimates [4], H_0 should satisfy the inequality (1) so that no nerve stimulation would occur. In addition, for a tolerable eddy current heating of body tissues, inequality(2) should be satisfied[5].

$$H_0 \le \frac{1}{\mu_0}\left(\frac{13.5}{f} + 7.45\times10^{-3}\right)(A/m) \quad (1)$$

$$H_0 \le \frac{4.85\times10^{-3}}{f}(A/m) \quad (2)$$

Both safety limits are plotted together in Figure 3 to obtain an overall safety limit for the applied magnetic fields. To satisfy both safety conditions, region under the two graphs should be taken. To find the optimum parameters that yield the highest SAR value, we have calculated the SAR with respect to frequency and particle radius while staying below the overall safety limit. Figure 4 shows the resulting graph. The ferrofluid used in this calculation has the same physical properties as Endorem™ (for example: magnetite volume fraction, density, domain magnetization, etc.)

Results:

As can be seen from Figure 2, the experimental data closely matched the theoretical calculations, which demonstrated that theoretical heating calculations based on the work of Rosensweig[3] are suitable for actual predictions. Note also that Figure2 shows that Endorem™ is far from being used as a hyperthermia mediator. Heat deposition of 100mW/ml of tissue is necessary for a successful hyperthermia application. Again, looking at Figure2 , to obtain a heating power of 100mW/ml by using Endorem™ at nearly 25kHz(where SAR ≈ 5mW/g), 20g of Endorem™ would be required for 1ml of tissue, which is physically impossible,. Figure 4 demonstrates that SAR results in a sharp peak at the particle radius of 7.25 nm and the frequency of 80kHz;

i.e., magnetic fluid, which has the same physical properties of Endorem™ (with the same volume fraction of magnetite, the same anisotropy constant, the same viscosity coefficient, and the same density, etc.) provides the maximum SAR for a monodisperse particle size of 7.25nm while staying within the safety limits. With this magnetic fluid, to obtain heat deposition of 100mW/ml of tissue, nearly 0.171g (of ferrofluid) could be enough for 1 ml of tissue, which demonstrates that, even with a very dilute magnetic fluid such as Endorem™ (where the magnetite volume fraction is 0.0035), the necessary heating rates can be achieved using very small portions of Endorem™, provided that optimum conditions are satisfied.

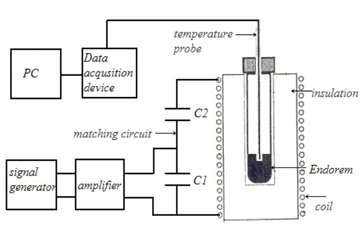

Figure1:Hyperthermia applicator System.

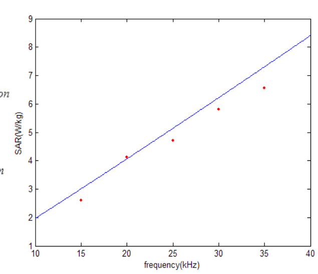

Figure2:Endorem™ heating versus frequency; dotted graph shows the experimental results. Solid line is the result of theoretical calculations.

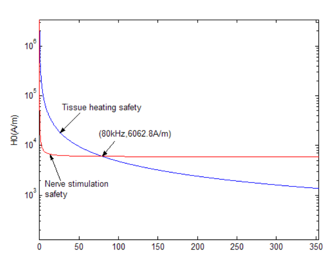

Figure3: Nerve stimulation and tissue eddy current heating safety graphs.

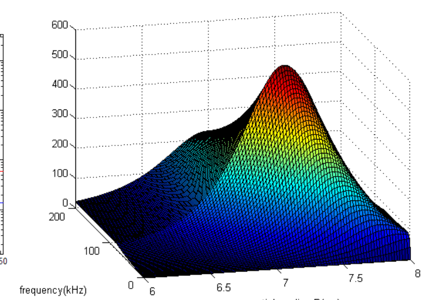

Figure4: SAR(W/kg) of Endorem-like substance, as a function of particle radius and frequency. Peak(584.6W/kg) occurs at the radius of 7.25nm.

Discussion and Conclusion: Considering human safety limits, optimal hyperthermia parameters(H_0 , f, R) are obtained for a magnetite-based ferrofluid with the physical properties of Endorem™. With the optimal parameters, very small amounts of magnetic fluids, even with a low magnetite volume fraction (such as Endorem™) can be used successfully as a hyperthermia mediator. Future work should focus on obtaining vary narrow magnetic particle size distributions to approach the optimal particle diameter dictated by the safety limits.

References: [1] 1993 *Int. J. Hyperthermia* **9** 51–68 [2] 1998 *IEEE Trans. Magn.* **34** 3745–54 [3]2002 *J. Magn. Magn. Mater.* **252** 370–4 [4] J.Magn.Reson.Imaging 2000;12:20–29.[5]1984 seeds *IEEE Trans.Biomed. Eng.* **31** 70–5. **Acknowledgments:** This work was supported by NIH grants RO1RR15396, R01HL61672 and R01HL57483. We would like to thank Mr. Tarik Reyhan for his ideas on the construction of the experimental setup and Ms. Mary McAllister for her editorial support.