8-4-2014

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Proposal submitted for the 2014—2015 Faculty Research Fellowship
August 04, 2014

A. SPECIFIC AIMS

In recent years, the application of magnetic nanoparticles (MNPs) in magnetic fluid hyperthermia (MFH) has emerged as a viable alternative to radiotherapy, chemotherapy, and surgery for the treatment of a wide variety of cancerous tumors. The MFH procedure, which requires raising the temperature of the tumor to 42 – 45^{o} C, has become more prevalent in Europe and Asia as compared to the rest of the world. Despite a number of ongoing phase III trials to use MHF clinically, it still remains a mostly experimental method in the United States due to the possibility of necrosis of normal tissue due to overheating. Therefore the search is on for a smart MNP system with the ability to maintain a temperature in the desired range without the possibility of overheating.

The concept of MFH is based on the high heat-sensitivity of malignant neoplastic tissue when compared to that of normal human cells. For local magnetic fluid hyperthermia, MNPs in a carrier fluid are delivered to the tumor site via direct injection or targeted to the site through the use of tumor specific antibodies. Once inside the tumor, the nanoparticles are exposed to an alternating magnetic field which causes heating of the MNPs due to magnetic relaxation (both Néel and Brownian mechanisms) as well as hysteretic losses. Such a rise in temperature is enough to kill cancer cells while leaving healthy tissue unharmed.

Much research into MFH has centered on iron-oxide-based based materials due to their ferrimagnetic nature and biocompatibility; however, one desirable property which these materials lack is the ability to "self-control" the thermal characteristics of the hyperthermia treatment. During treatment, heat conduction and energy absorption are extremely difficult to monitor *in vivo* which may cause overheating that can damage normal human tissue. In some complex magnetic oxides the "turn-off" temperature for the ferrimagnetic behavior (referred to as the Curie temperature) can be suppressed to coincide with the desired maximum MFH temperature. These smart materials, such as **$La_{1-x}Sr_xMnO_3$**, are the subject of our proposed investigation.

Specific Aim #1: Synthesis of $La_{1-x}Sr_xMnO_3$ for use in MFH studies. We will prepare a series of samples by varying x between 0.1 and 0.8 in $La_{1-x}Sr_xMnO_3$ to obtain materials with different Curie temperatures in the range of 40˚C – 50˚C. This will provide MNPs to regulate the maximum temperature reached during MFH treatments.

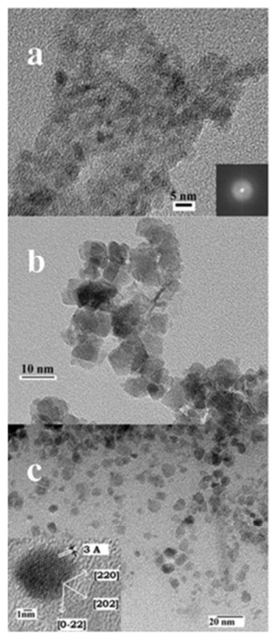
Specific Aim #2: Investigation of the structural characteristics of the synthesized samples. The $La_{1-x}Sr_xMnO_3$ MNPs will be characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) for phase identification as well as the determination of particle morphology.

Specific Aim #3: Investigation of the magnetic properties of the proposed nanoparticles through the use of dc- and ac-magnetometry. In order to determine the Curie temperature and magnetodynamics of the $La_{1-x}Sr_xMnO_3$ MNPs we will perform temperature-dependent magnetic experiments using the magnetometer at Wayne State University.

Specific Aim #4: Investigation of the magnetic heating of an aqueous suspension of the nanoparticles under an alternating magnetic field. These studies must be performed for a number of reasons which include the determination of the temperature dependent specific absorption rate (SAR) of the aqueous $La_{1-x}Sr_xMnO_3$ MNP solution as well as the "shut-off" characteristics of the smart MNPs as they near their Curie temperature.

B. BACKGROUND AND SIGNIFICANCE

Magnetic hyperthermia has been widely considered as a possible non-invasive treatment for cancerous solid tumors since its introduction in 1957 when Gilchrist *et al* [1] used 20—100 nm particles of γ-Fe_2O_3 in conjunction with an alternation magnetic field in the MHz range to heat various tissue samples. In broad terms, MFH involves the dispersion of magnetic nanoparticles throughout a tumor site and the exposure of these nanoparticles to a small (~mT) time-varying magnetic field in the RF range. The relaxation of the magnetic nanoparticles into the field causes dispersion of heat due to various methods of energy loss (Néel relaxation, Brownian relaxation, hysteretic losses, etc.). This heat is conducted to the nearby cancerous tissue whereby, if the temperature can be maintained above a threshold of 42˚C – 46˚C for a time of not less than 30 minutes, the cancer will be destroyed via necrosis, coagulation and carbonization. The most commonly used materials for this treatment are mono-metallic oxides such as γ-Fe_2O_3 and Fe_3O_4 (Figure 1) because of their abundance and biocompatibility.



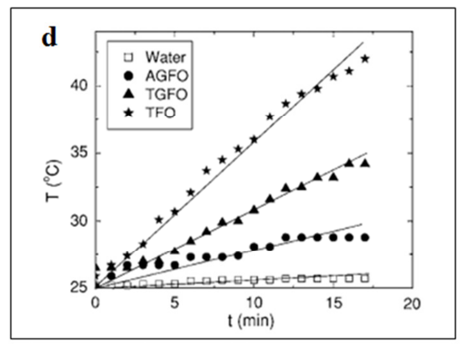


Figure 1. EM images of (a) g-Fe2O3 nanoparticles embedded in a larger alginate nanoparticle (AGFO), (b) g-Fe2O3 nanoparticles with a tetramethyl ammonium hydroxide coating (TGFO), and (c) Fe3O4 nanoparticles with a TMAH coating (TFO). In addition, a plot of the heating characteristics of the AGFO, TGFO, and TFO particles heated using a 250 Oe ac magnetic field driven at 125 kHz. The heating curve for de-ionized water is also provided as a reference. The solid lines drawn through the data are intended as guides to the eye. Figures taken from Vaishnava *et al*, *J. Appl. Phys.* **102**, 063914.

In general, heat production via magnetic materials in alternating magnetic fields arises due to two general classes of materials: multi-domain ferro(ferri-)magnetic systems and single-domain superparamagnetic systems. In the former, heat production originates primarily through hysteretic power losses. For superparamagnetic nanoparticles, heating is accomplished through losses as the particles' superspins align with the external field through the Néel mechanism (rotation of the magnetic moment within a fixed particle) and Brownian motion (physical rotation of the particle with a fixed moment), the latter of which can contribute to the dissipation of energy by means of friction [2]. Typically, MFH is accomplished using superparamagnetic iron oxide nanoparticles (Fe_3O_4 and γ-Fe_2O_3) [3-7]. However, these materials lack the ability to self-control the maximum temperature reached by MFH due to their high Curie temperatures. Perovskite manganites have been proposed as possible materials in which the Curie temperature can be suppressed into the range between 42—38˚C by doping with non-magnetic cations. These materials, of the form $La_{1-x}Sr_xMnO_3$ and $La_{1-x}Ag_xMnO_3$ [8-9], have been shown to have Curie temperatures in this desired range (achieved through the replacement of lanthanum by strontium or silver ions in the perovskite A sites). We wish to study these materials in order to confirm the optimized doping needed in order to achieve a Curie temperature near 46˚C.

C. SUMMARY OF EXPERIMENTAL DESIGN AND METHODS

Synthesis of perovskite manganite nanoparticles. The synthesis of $La_{1-x}Sr_xMnO_3$ nanoparticles will be accomplished via solid state reaction of La_2O_3, $SrCO_3$ and MnO_3 powders mixed in appropriate stoichiometric quantities, pressed into pellets and heated to high temperatures (up to 1500˚C). The resulting powders will be milled until we have achieved the desired particle size (20—100 nm diameters). A variety of different stoichiometric samples will be made in order to compare the physical properties of each sample (we will vary the amount of strontium in the samples).

Structural and morphological characterization. Samples synthesized via the method above will be analyzed through x-ray diffraction in order to confirm the perovskite nature of the materials in addition to confirmation of particle size. In addition, scanning and transmission electron microscopy will be used to further investigate the phase and morphology of the samples.

Magnetic characterization. Using a Quantum Design Model 6000 Physical Properties Measurement system (at Wayne State University), we will investigate the ac- and dc- magnetic properties of the synthesized samples. We will specifically look at the temperature-dependent properties in order to determine the Curie temperature of the samples.

Analysis of the heating characteristics. The heating characteristics of each sample will be measured using Kettering University's Ambrell EASYHEAT system. Specifically, we are interested in determining two main points: The specific absorption rate (SAR) of the sample as it heats from room temperature, and the samples ability to hold a constant temperature in the range of 42—46˚C while constantly being driven by the ac magnetic field. The SAR is defined to be the power dissipated by a magnetic material subjected to an alternating magnetic field. For MFH, the SAR is related to the specific heat of the solvent in which the magnetic nanoparticles are suspended, the weight fraction of the magnetic element, and the slope of the temperature vs. time curve.

D. POTENTIAL SOURCES OF EXTERNAL FUNDING

The preliminary data obtained from this project presents itself well to solicitation of funds from both the National Institutes of Health (NIH) and the National Science Foundation (NSF). For example, the Biomaterials program (BMAT) within the NSF's Division of Materials Research (DMR) which supports fundamental research related to (1) biological materials, (2) biometric, bioinspired, and bioenabled materials, (3) synthetic materials intended for applications in contact with biological systems, and (4) the processes through which nature produces biological materials (taken from www.nsf.gov) would be ideal sources of future external funding for this research.

E. BUDGET

We anticipate the following expenses for this project

Budgeted Item	Amount
Undergraduate Research Assistantships	$3,000.00
Planetary Ball Mill (cost-share with startup funds – IGA 350134)	$1,500.00
Materials and Lab Supplies	$1,000.00
Publication Charges	$500.00
TOTAL	$6,000.00

F. REFERENCES (Co-PIs Underlined and in Bold)

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