

## “SMART” MEDIATORS FOR SELF-CONTROLLED INDUCTIVE HEATING

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**INTRODUCTION:** Hyperthermia is a rapidly developing technique in cancer therapy. It takes advantage of the higher sensitivity of tumor tissue to heat and typically involves heating of the affected organ to 43 – 45 °C. Magnetic fluid hyperthermia [1] attracts increasing attention, since it allows minimizing side effects by the localized heating of only desired parts of the organism, including tumors located deep inside the patient's body. The method involves introduction of ferromagnetic particles (mediators) into the desired part of the organism and heating them with an alternating electromagnetic field of radio-frequency range (*RF*). Magnetic fluids based on nanocrystalline Fe<sub>3</sub>O<sub>4</sub>, stabilized by biocompatible surfactants [2-6], are typically used as mediators. Unfortunately, it is impossible to control the local temperature near the mediator particles, possibly causing local overheating and necrosis of normal tissue. This problem could be solved with ferromagnetic particles of high *RF* absorption and a Curie temperature (*T<sub>c</sub>*) of ca. 42 - 45 °C. Thus, local temperature control can be ensured even with a nonuniform distribution of mediator particles throughout the tissue, variable *RF* intensity and uneven dissipation of the evolving heat. If *T<sub>c</sub>* of this material can be purposefully varied, mediators could be adapted to the particular medical application.

Similar approach is used in cancer thermal therapies, which utilize implantable “thermoseeds” with a particular Curie temperature [7,8]. These macroscopically sized solid units are surgically inserted in the affected organ and are heated by an external *RF*. The *T<sub>c</sub>* of the “thermoseed” determines the temperature of the heating. Significant limitations of these methods are the necessity of a stressful surgical intervention and a relatively small volume around each “thermoseed” which can be effectively heated. The reduction of size of the heat-producing elements so that they can be delivered as a suspension via catheter into the bloodstream of the tumor and

spread throughout its capillaries, is the obvious solution of these problems. Sato et al [9,10] reported using 50 μm flakes of an amorphous ferromagnetic metal alloy with *T<sub>c</sub>* of ca. 45 °C for intratissue hyperthermia in dogs. However, these relatively large electrically conducting particles are heated in an *RF* field by eddy currents even above *T<sub>c</sub>* and do not penetrate into small capillaries. Numerous studies [1-6,12,13] have shown that submicron-sized non-conducting particles are most effective for hyperthermia. The goal of this work was to produce biologically compatible, electrically non-conductive nanoparticles with *T<sub>c</sub>* in the range of 40-50°C.

Individual ferromagnetic substances with *T<sub>c</sub>* in this range do not exist, but by combining several elements and by varying the composition of the mixture it is possible to produce alloys, amorphous structures, ferrites and other multi-component systems consisting of metals and metalloids. We used several synthesis techniques to produce a variety of ultradisperse particles with suitable *T<sub>c</sub>* and tested their behavior in an *RF* field.

**MATERIALS AND METHODS:** In order to study their *RF* absorption rate, fine powders of ZnFe<sub>2</sub>O<sub>4</sub> (*T<sub>c</sub>* = 100 - 102°C), La<sub>0.8</sub>Sr<sub>0.2</sub>MnO<sub>3</sub> (*T<sub>c</sub>* = 48°C) and La<sub>0.75</sub>Sr<sub>0.25</sub>MnO<sub>3</sub> (*T<sub>c</sub>* = 56°C) have been prepared by the freeze-drying synthesis technique [11]. During absorption studies 0.5 g of each powder has been ultrasonically dispersed in 3 ml of water and placed in a glass test tube inside an air-cooled inductor (inner diameter 60 mm; length 200 mm) with a matching high-Q-resonator fed with *RF* power [12](Fig. 1). To avoid *RF* absorption by metal parts, the temperature of the fluid was monitored with an alcohol thermometer. A sample of magnetic fluid containing dextran-coated nanocrystalline Fe<sub>3</sub>O<sub>4</sub> [4,12] was used for comparison. Previous studies have confirmed the absence of *RF* absorption in this frequency range by water or by components of the measuring cell [12].

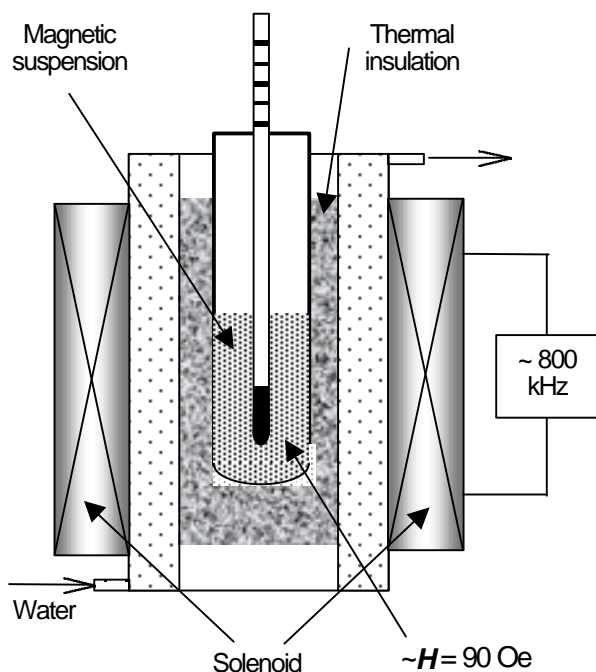


Fig.1: Scheme of the experimental setup.

**RESULTS AND DISCUSSION:** Experimental heating curves are presented in Fig.2.  $\text{Fe}_3\text{O}_4$  - based magnetic fluid demonstrates a fast, almost linear heating rate, close to that shown in [13], without any significant decrease in the tested experimental conditions. **RF** irradiation of the  $\text{ZnFe}_2\text{O}_4$  suspension leads to significant, but less intense heating with no obvious temperature limit over the time of the experiment. This curve, taking into account the lower absorption rate of  $\text{ZnFe}_2\text{O}_4$ , is also similar to those of typical magnetic ferrofluids [13]. Both samples of La-Sr manganite powders demonstrate intense heating during the initial stages of the process, followed by temperature stabilization at  $46.3^\circ\text{C}$  and  $37.8^\circ\text{C}$ , respectively. These temperatures correspond rather well with the  $T_c$  of the samples. The observed difference between  $T_c$  and the temperatures of **RF** absorption termination can be attributed to the sharp decrease of saturation magnetization  $M$  - usual for ferromagnetics in the vicinity of  $T_c$  and predicted by ferromagnetic exchange theory - and to the heat exchange balance. These results create many prospective applications of magnetic particles with predetermined  $T_c$  for heating of biological tissues and other objects to the optimum temperature using the demonstrated parametric feedback.

Absorption of **RF** by ferromagnetic particles of various diameters is known to involve several physical mechanisms, including different types of remagnetization processes [5]. Usually **RF** absorption strongly depends on the crystallite size. Absorption rates of superparamagnetic nanoparticles are usually much higher than those of multi-domain crystallites, mostly due to Neel's losses. Powders produced by freeze-drying, are usually substantially agglomerated [14]. Intense milling of  $\text{La}_{0.75}\text{Sr}_{0.25}\text{MnO}_3$  powders in a high-energy planetary ball mill resulted in a decrease of average aggregate size from 2 to 0.15-0.2 microns, as measured by light scattering. This is close to the average crystallite size observed by SEM (0.1-0.2 microns, Fig. 3). Meanwhile, this treatment did not affect the **RF** absorption rate of this powder, with the heating curve being practically the same as that of the initial sample (data not shown). Since the observed size of crystallites even after milling is still much larger than the typical size of superparamagnetic particles, the most probable dominating absorption mechanism for these powders is scattering by displacement of magnetic domain walls. However, **RF**

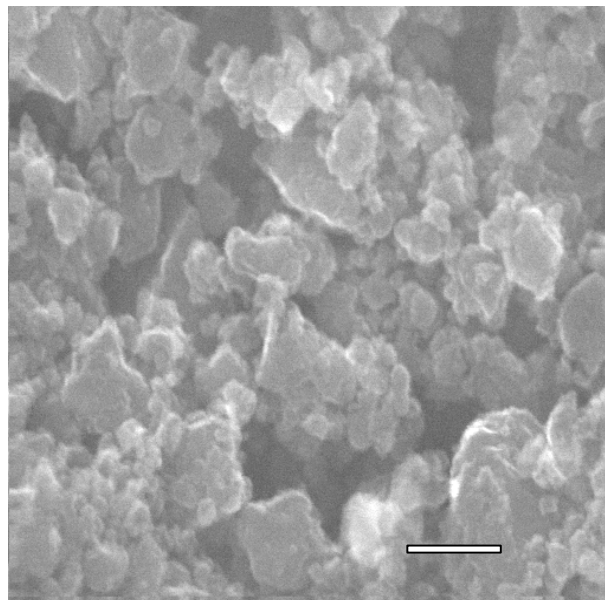


Fig.3: SEM micrograph of  $\text{La}_{0.75}\text{Sr}_{0.25}\text{MnO}_3$  powder after milling. The bar is 500 nm.

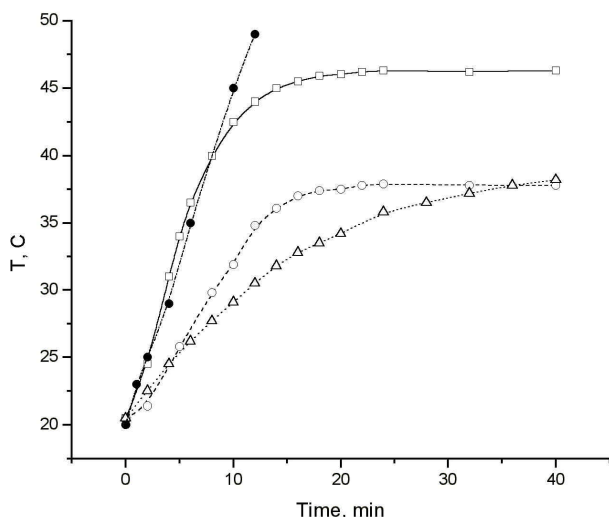


Fig. 2: Time course of the temperature inside the measuring cell during **RF** (800 kHz) heating using the following mediators: • Dextran-coated  $\text{Fe}_3\text{O}_4$  (commercially available); □  $\text{La}_{0.75}\text{Sr}_{0.25}\text{MnO}_3$ ; ○  $\text{La}_{0.8}\text{Sr}_{0.2}\text{MnO}_3$ ; △  $\text{ZnFe}_2\text{O}_4$ .

absorption rates of polycrystalline manganites are anomalously high compared to those of  $\text{Fe}_3\text{O}_4$  polycrystals.

From our results we can conclude, that powders of La-Sr manganites make it possible to heat a sample by **RF** to the necessary temperature without exceeding it. Further heating will be automatically switched off at  $T_{\text{lim}}$ , which is closely related to  $T_c$ .  $T_c$  of La-Sr manganites strongly depends on the content of Me in  $\text{La}_{1-x}\text{Me}_x\text{MnO}_3$  (where Me = Sr, Ba, Pb, Ag, Na). By varying the composition of the manganite it is possible to create materials with  $T_c$  ranging from 20 to  $90^\circ\text{C}$  [15]. Thus, **RF** heating to any desired temperature in this range without overheating can be achieved without any external temperature control. Application of  $\text{ZnFe}_2\text{O}_4$  for these purposes is less attractive due to severe dependence of  $T_c$  on the metastable, poorly reproducible cation distribution between sub-lattices of the spinel structure, and a lower absorption rate, while no advantages over existing  $\text{Fe}_3\text{O}_4$ -based ferrofluids were observed. The prospects of a direct manganites application in **RF** hyperthermia of tumors will depend on the results of the ongoing medical compatibility studies.

We have proven that the freeze-drying synthesis technique permits the production of ultradisperse particles with the predetermined composition and  $T_c$ . The particles have a high absorption rate at lower temperature and abruptly stop absorbing **RF** energy at a particular temperature, preventing further heating of the sample. We continue searching for more biologically compatible nanoparticles for self-regulating hyperthermia.

The proposed **RF** heating with parametric feedback can be useful not only in medicine, but also in solving technological problems, e.g., for precise localized temperature control in chemical and biochemical reactors. Coating of finely dispersed magnetic particles with a catalyst (including enzymes) combined with **RF** heating could ensure constant temperature at the reaction zone even in intense mass flows and strongly varying heat supply.

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