

THE CONCENTRATION EFFECT OF MAGNETIC IRON OXIDE NANOPARTICLES ON TEMPERATURE CHANGE FOR HYPERTHERMIC DRUG RELEASE APPLICATIONS VIA AC MAGNETIC FIELD

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ABSTRACT:

Magnetic Nanoparticles (MNP) can be used as nano-sized heat sources that are capable of dissipating uniformly distributed heat at the target tissue when they are placed in an AC magnetic field. They can be integrated along with anti-cancer medications inside thermo-sensitive gel type micro-carriers where they can be used as hyperthermic drug release agents and trigger release upon change in their temperature. In this work we tested the rate of change of temperature versus time for three concentration groups of 10, 25 and 50 mg Fe/ml magnetic fluid nanoparticles. Promising results demonstrated a linearly increasing trend between concentration of MNP and temperature change.

KEY WORDS: Hyperthermia, Magnetic Nanoparticles, MNP, AC field

INTRODUCTION

Hyperthermia is an artificial increase of body temperature to damage cancer cells. Magnetic Nanoparticles (MNP) could be thought of nano-sized heat sources that are capable of dissipating uniformly distributed heat at the target tissue once they are placed in an AC magnetic field. MNP can be integrated with therapeutic agents in polymeric micro-carriers that are capable of transiting through the smallest capillaries. These micro-carriers are to be navigated towards a target such as a tumor using a method similar to the one described in [1] where a 1.5 mm ferromagnetic bead was navigated in the carotid artery of a living swine. In this process, MNP are used as drug carries either directly attached to the particles or indirectly suspended in biocompatible temperature sensitive gels such as hydrogels. These gels are able to shrink in response to temperature change caused by heat dissipation from the MNP imbedded within them and hence releasing desired medication at the target area allowing maximum drug efficiency with minimum dosage [2]. In the latter application, due to lack of space inside the polymeric capsule containing MNP plus anti-cancer medication, MNP concentration becomes an important factor.

MATERIALS AND METHOD

Theory

The heat generated by MNP via AC magnetic field may be due to three major mechanisms which depend greatly on the particle size and their magnetic properties. Large multi-domain ferro- or ferrimagnetic materials contain several sub-domains each having their own specific magnetization direction. When these materials are exposed to the AC magnetic field, the sub-domain with magnetization direction along the magnetic field axis elongates and the other ones shrink. This leads to “domain wall displacements”. Since the magnetization curves for increasing and decreasing magnetic field amplitudes do not coincide, the material demonstrates “hysteresis behavior” and produces heat. In smaller particles such as superparamagnetic nanoparticles, there is no domain wall and therefore hysteresis losses cannot occur. However the external AC magnetic field energy helps magnetic moments to rotate and overcome the anisotropy energy barrier [3]. This energy is then dissipated as heat when the particle relaxes to its equilibrium orientation. This mechanism is called Néel relaxation. There is also a third mechanism called Brownian relaxation that causes both multi-domain and single domain particles to heat up. In this process energy barrier for reorientation of a particle is given by rotational friction due to the rotation of the entire magnetic particle caused by the AC field torque force on the magnetic moment of the particle. The power for which the magnetic material is heated per gram of that material is given by specific absorption rate (SAR) or specific loss power (SLP).

Experimental Procedure and Setup

Superparamagnetic iron oxide (Fe_3O_4) nanoparticles coated with dextran (Product number: 79-00-201, micromod, Germany) suspended uniformly in water were purchased. These particles are also used as MRI contrast agents for imaging purposes. TEM (Jeol JEM-2100F) measurements confirmed the crystal structure and it revealed their mean size diameter to be about 7 nm (Figure 1). Hydrodynamic mean diameter was measured to be 58.77 nm by analysis of Photon Intensity Spectroscopic Analyzer. This difference in diameter may be explained by agglomeration of the particles as seen in Figure 2 and also high concentration of dextran coating provided in the solution. Lack of hysteresis curve measured by VSM (EV5, Magnetics) verified superparamagnetic nature of the MNP shown in Figure 3. In this experiment MNP were concentrated into three pairs of 10, 25, and 50 mg Fe/ml by means of distillation from the initial 10 mg Fe/ml iron oxide such that each sample contained 1 ml MNP fluid.

Each sample was placed in custom made isolation foam fitted inside an 8 turn copper tube 15 mm in diameter induction coil. The 1.5 kW induction machine (Norax Induction, Quebec) provided a magnetic field close to 80 kA/m (~1000 Oe) at a frequency of 150 kHz inside the coil. Temperature changes were monitored and recorded every 15 seconds for a period of 800 seconds by two thermocouples (T-Type, Omega HH506R); one measuring the temperature of the sample and another

measuring that of the isolation foam as shown in Figure 3. A control sample, 1ml of D-Ionized water, was placed inside the coil prior to any other test to measure effect of the field on thermocouples. There on each MNP sample was tested twice in the same field to minimize experimental errors.

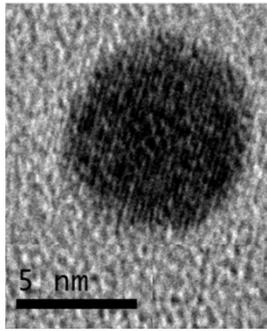


Figure 1: TEM image of a single MNP

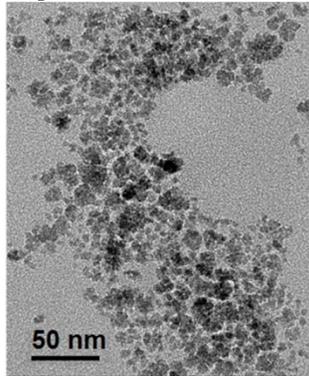


Figure 2: Agglomeration of MNP

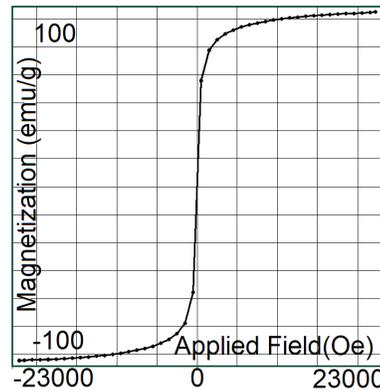


Figure 3: Hysteresis curve of MNP obtained by VSM measurements

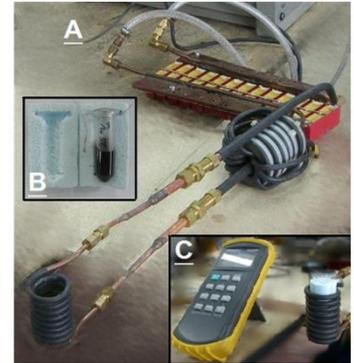


Figure 4: Induction Machine (A), MNP Sample in isolation foam (B), Thermocouples (C).

Experimental Results

As can be seen in Figure 5, the higher the concentration of MNP, the higher raise in temperature. There was no major temperature change in isolation foam or in the control sample (DI-H₂O) while applying the AC field. The experimental SAR value from graph was determined to be 1.156 W/g[Fe] which was close to the theoretical value of 1.295 W/g[Fe] obtained from calculation shown in [4]. Although the SAR value was low, the final temperature reached was higher than expected.

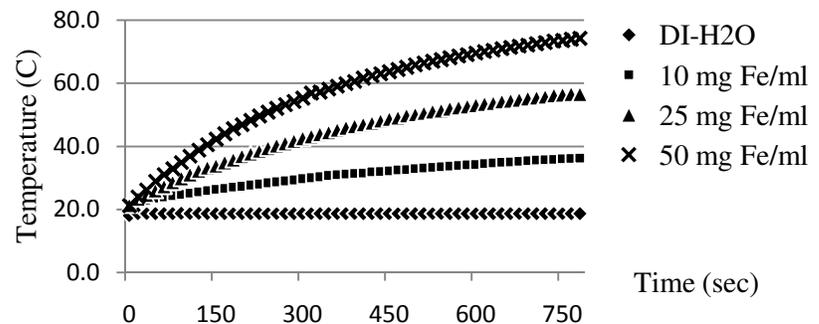


Figure 5: Temperature vs. Time plot obtained for 3 different MNP concentrations and DI-H₂O as control sample

CONCLUSION

Proposed micro-carriers can rely on an agglomeration of MNP (Figure 2) used for propulsion through an induction of magnetic gradients generated by a clinical MRI system. Contrast agent property of MNP allows for tracking of the micro-carriers as local distortion of the magnetic field inside the MRI. Due to some biocompatibility uncertainties to MNP as well as lack of space in micro-carriers there are limitations to concentration of MNP. However via experiments such as this, for given target temperature to trigger drug release integrated in micro-carriers, one can predict what concentration of MNP is needed and the time required for that temperature to be reached.

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