Thermally Reversible Nanoparticle Aggregation: Modeling T2 Variation with Temperature

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Introduction: Magnetic nanoparticles (MNP) synthesized according to the formula $Mn_{0.5}Zn_{0.5}Gd_{0.02}Fe_{1.98}O_4$ have been previously used as both MRI contrast[1] agent (due to their magnetic moment) and hyperthermia[2] agent (due to their optimized Curie temperature 43°C). The overall aim is to develop (using multi-functional MNP) a non-invasive MRI-based thermal mapping technique for the heated tissue. The first step towards achieving this goal is the quantification and modeling of *T1* and *T2* relaxation times (enhanced by the same MNP used for hyperthermia) at different temperatures which we investigate in this work.

Materials & Methods: Agarose gel was doped with a range of MNP concentrations (0-0.17 mM/L Fe) and both relaxation rates were measured over temperature range 8 – 58°C using FSE sequence at 1.5T. Both uncoated and PEG-coated particles were used. Magnetization data was fitted to a Langevin function and the average magnetic moment per particle and the saturation magnetization were extracted. In order to fit the *R2* data we used the echo limited regime (ELR)[3] where the refocusing RF pulses are not effective as given by the equation $\{1/T2=1.8\, f\, x^{1/3}\,(1.52+f\,x)^{5/3}/\tau_D\}$, where f is the particles' volume fraction, $x=\omega_r\,\tau_{CP}$, ω_r is rms Larmor frequency at the surface of the particle, τ_{CP} is half echo time, $\tau_D=r^2/D$ is diffusion correlation time, r is particle radius, and D is diffusion coefficient of protons in 1.5% gel[4]. SEM- and magnetization-determined radii of the uncoated particles are 16.8 nm and 8.7 nm, respectively, while it is 31.5 nm for the coated ones. SQUID yields 66k A/m for the volume magnetization.

Results: The increase of transverse relaxivity r_2 with temperature is shown in Fig.1 with larger rate for the uncoated particles than the coated ones. Relaxivity (in s^{-1} mM^{-1}) for the uncoated and coated particles, respectively, increased as follows: from 2.5 to 3.2 and 0.4 to 0.7 for r_1; and from 162.3 to 253.7 and 59.7 to 82.2 for r_2 over the temperature range 8 to 58°C. The relaxation rate temperature coefficient (in s^{-1} °C^{-1}) increased from zero (pure gel) to maximum value at concentration 0.17 m*M*/L Fe as follows: 2.96×10^{-3} and 8.48×10^{-4} for *T1*; and 0.31 and 0.09 for *T2*. The ELR model is used to fit the *R2* data for the uncoated particles (Fig. 2). We have used a temperature-specific fitting parameter "packing factor α" that accounts for the agglomeration of particles and the non-magnetic part of the formed cluster[1,5] with $\alpha = (r_{REL}/r_{MAG})^3$. The ratio r_{REL}/r_{MAG} (Fig. 3) increases with temperature almost linearly from 4.4 at 8°C to 6.7 at 58°C for the uncoated particles, and 6.9 to 11.1 for the coated ones. In order to directly demonstrate the agglomeration effect we measured particle diameters for uncoated particles (suspended in water) using DLS. The average particle diameter is plotted as a function of temperature (Fig. 4, C = 10 μg/mL). It reached a peak diameter of 247 nm at 50°C. The reversibility of the particles size with temperature (up to 40°C) is also shown (C = 5 μg/mL).

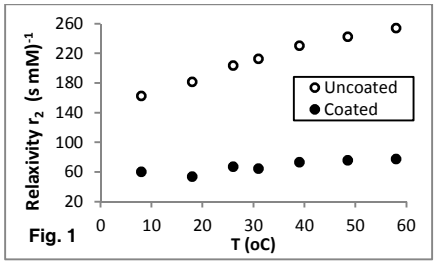

Fig. 1

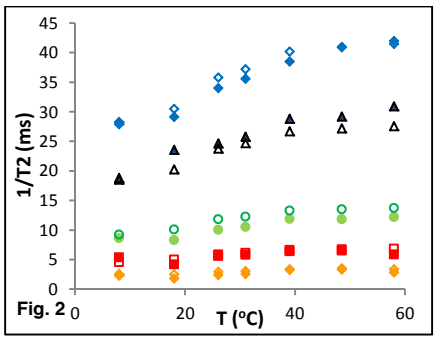

Fig. 2

Fig. 1 Transverse relaxivity increases more for the uncoated than the coated particles with temperature. Similar behavior exists for the longitudinal relaxivity but smaller increase (not shown).

Fig. 2 *R2* values are fitted successfully using the ELR model for all concentrations (mM/kg Fe: 0.014, 0.029, 0.058, 0.12, and 0.17) and temperatures.

Fig. 3 The ratio of cluster radius to particle radius increases with temperature due to inter-particle dipolar interactions, caused probably by thermally enhanced surface layer magnetization. This factor is pivotal to the *R2* model (Fig. 2).

Fig. 4 Dynamic light scattering (DLS) measurement of the particle diameter shows temperature dependence. Thermal reversibility is also exhibited for MNP suspended in water up to 45°C.

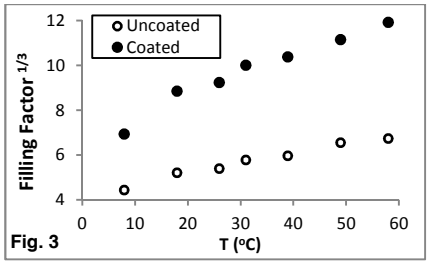

Fig. 3

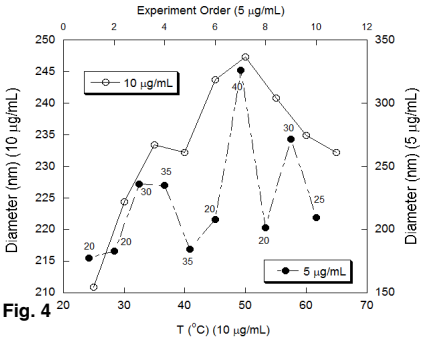

Fig. 4

Discussion: The *R2* data was successfully fitted by the use of a temperature dependent packing factor reflecting the clustering of particles which was found to increase linearly with temperature. This agglomeration is attributed to the dipolar coupling induced by easily and thermally agitated loose spins at the nanoparticles surface layer (it can also be enhanced by the uniform MRI fields as was used[6] to determine viscosity by MRI). The dipolar interaction energy E_d between moments μ separated by a distance d is on the order[7] of $E_d \approx (\mu_0/4\pi)\,\mu^2/d^3$. Ordering of the moments can ensue below a critical temperature T_0 given by $E_d \approx T_0\, k_B$. For our sample, the values of the ratio $E_d/T_0\, k_B$ varies from 14 and 40, suggesting that agglomeration is not excessive but is still possible. Cluster size appears to increase thermally up to 45°C.

Conclusion: We have demonstrated that these particles exhibit almost linear temperature dependent properties (e.g. *R2* and cluster size) that we aim to use for thermal mapping while using the same MNP for hyperthermia.

References: 1. Issa B et al JMRI 2011:34:1192. **2.** Haik Y et al Proceedings 16th ICMP 42, 2008. **3.** Laurent S et al Chem. Rev. 2008:108:2064. **4.** Sack I et al JMRI 2004:166:252 **5.** Noginova N et al JPCM 25:255301:2009. **6.** Hong R et al MRM 2008:59:515. **7.** Hansen MF et al JMMM 1998:184:262.

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