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Heating Effect in Biocompatible Magnetic Fluid[1]

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This work is devoted to the study of heating of a biocompatible magnetic fluid due to time-varying magnetic induction. The adsorption of dextran on magnetite particles was confirmed by IR spectroscopy. A considerable thickness of the surfactant layer (oleate sodium + dextran) of about 4.3 nm prevents the formation of clusters made of nanomagnetic particles as evidenced by the fact that no maxima of the ultrasound wave absorption coefficient corresponding to cluster formation have been detected. The results show that the observed heating effect may be applied in hyperthermia treatments especially in the preferable region of 500 – 800 kHz. An "H^2– law" observed for the dependence of the SAR on the square of the amplitude of the magnetic field demonstrates the presence of superparamagnetic particles in the ferrofluid.

KEY WORDS: biocompatible magnetic fluid; hyperthermia; nanomagnetic particles; specific absorption rate.

1. INTRODUCTION

Water-based magnetic fluids have been used for diagnostics and therapy in medical applications. In order to be used for biomedical purposes, magnetic particles must be coated with a substance that ensures their stability and biocompatibility. Application of magnetic materials for hyperthermia

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of biological tissue with the goal of tumor therapy has been known, in principle, for more than four decades [1]. A number of studies have demonstrated the therapeutic efficacy of this form of treatment in animal models [2]. To date, however, there have been no reports of the successful application of this technology to the treatment of a human patient. The challenge lies in being able to deliver an adequate quantity of the magnetic particles to generate enough heat in the target using ac magnetic field conditions that are clinically acceptable.

The heating of oxide magnetic materials with low electrical conductivity in an external alternating magnetic field is due to loss processes during the reorientation of the magnetization. If the thermal energy $k_B T$ is too low to facilitate reorientation, hysteresis losses dominate which depend on the type of remagnetization process (wall displacement or several types of rotational processes). With decreasing particle size, thermal activation of reorientation processes leads to superparamagnetic behavior of the particle ensemble and the occurrence of the so-called Neel-losses [3]. In the case of ferrofluids, losses related to the rotational Brownian motion of magnetic particles [4] may arise, too.

In the present article the physical properties of a biocompatible magnetic fluid in which magnetite particles are coated by a double layer (oleate sodium + dextran) are investigated with respect to their applicability for hyperthermia.

2. EXPERIMENTAL

The magnetic fluid used in this work was obtained by co-precipitation of ferric and ferrous salts. The biocompatible magnetic fluid magnetite particles (Fe_3O_4) were coated with sodium oleate and polysaccharide dextran. During the first step, the magnetite particles were dispersed in water and stabilized by sodium oleate. During the second step, the water solution of polysaccharide dextran ($(C_6H_{10}O_5)_n$, $M_r \sim 60\ 000\,g{\cdot}mol^{-1}$) was added to the prepared magnetic fluid, and after mixing and centrifugation, we obtained biocompatible magnetic fluids with a saturation magnetization of 65×10^{-4} T and a concentration of magnetic particles of $60\,mg{\cdot}ml^{-1}$. The adsorption of dextran to magnetite nanoparticles was confirmed by infrared (IR) spectroscopy by the KBr pellet method. In this method, the solid sample is finely pulverized with pure, dry KBr, the mixture is pressed in a hydraulic press to form a transparent pellet, and the spectrum of the pellet is measured. The changes of the ultrasonic wave attenuation were measured by the pulse method based on measurement of the intensity of the ultrasonic pulse passed through or reflected by the magnetic fluid studied [5]. In ferrofluids, heating effects can be achieved

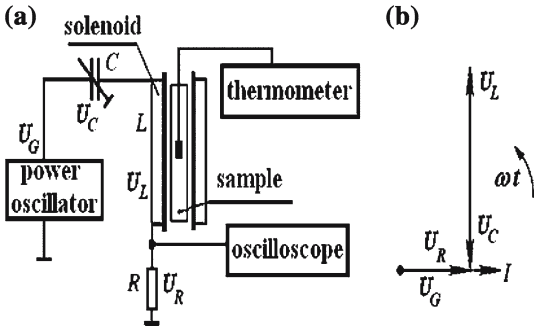

Fig. 1. (a) Experimental setup for determination of hyperthermia heating of the ferrofluid in an alternating magnetic field and (b) the vectors of voltage and current at the conditions of series resonance.

in ac magnetic fields by remagnetization losses (Néel losses) or energy dissipation during particle rotation in the liquid (Brown losses) [10]. The Specific absorption rate (SAR) values were determined from the time-dependent calorimetric measurements. The experimental setup is shown in Fig. 1. This figure presents the experimental setup used for recording temperature changes in the ferrofluid that is subjected to the alternating magnetic field. The ferrofluid sample placed in a glass vial is mounted inside the solenoid and represents an element of the *RLC* series circuit. The circuit is supplied by the sinusoidal signal generator with a signal of frequency f and voltage U_G.

3. RESULTS AND DISCUSSION

With the aim to confirm immobilization of dextran to the magnetic particles, infrared spectra of pure dextran, magnetite, and composite particles were obtained. Figure 2 shows the infrared spectra of the pure dextran and magnetic nanoparticles coated by dextran. As observed, the spectrum of the composite particles is very similar to that of pure dextran. The presence of characteristic bands of dextran in infrared spectra of the magnetite-dextran complex confirmed successful adsorption of the dextran to magnetite nanoparticles.

As follows from an ultrasound study of the MF-Dextran ferrofluid, the applied magnetic field has a small effect on the ultrasound wave absorption coefficient. Figure 3 shows changes in the ultrasound wave absorption coefficient $\Delta\alpha$ as a function of the magnetic field intensity at different temperatures. The immobilization of dextran results in a greater

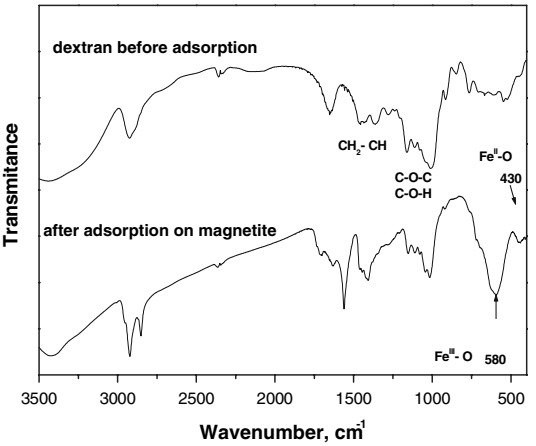

Fig. 2. Infrared spectra of magnetite, pure dextran, and magnetite/dextran composite particles. The spectra are shifted vertically for clarity.

stability of the ferrofluid structure; changes in the absorption coefficient are many times smaller than in a water-based magnetic fluid stabilized only by sodium oleate [6]. On the basis of magnetic experiments, an average radius $r_m = 5.6\,\text{nm}$ of the magnetic cores of composite particles was determined. The standard deviation of a magnetic core size was $\sigma = 1\,\text{nm}$. From calorimetric experiments it follows that the mean hydrodynamical radius of composite particles is $\langle R_H \rangle = 9.9\,\text{nm}$. The thickness of the surfactant layer was determined from the difference between the hydrodynamical radius and the magnetic core radius. The considerable thickness of the surfactant layer (oleate sodium + dextran) of about 4.3 nm prevents the formation of clusters made of nanomagnetic particles as evidenced by the fact that no maxima of $\Delta\alpha$ corresponding to cluster formation have been detected. This property is of particular importance in medical applications in which a magnetic fluid is injected intravenously, and then blood circulation is used to transport the magnetic particles to the region of treatment. In such applications it is required that the particles do not aggregate and block their own spreading [7].

Calorimetric measurements were performed as a function of the ac-field amplitude over a range of frequencies from 250 kHz up to 2.94 MHz. Figure 4a shows the time evolution of the temperature inside the ferrofluid sample for various magnetic field amplitude values at $f = 1\,\text{MHz}$. A linear dependence between the experimental data for $\Delta T/\Delta t$ and H^2 is shown in Fig. 4b. For superparamagnetic ferrofluids, an "H^2– law" is observed for the SAR dependence on the amplitude of the magnetic field [8].

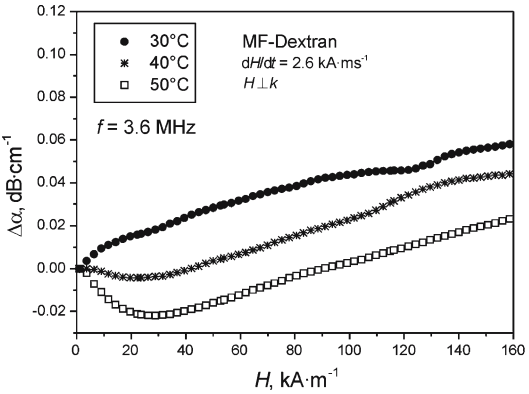

Fig. 3. Changes of the ultrasonic wave absorption coefficient as a function of the magnetic field at different temperatures.

A fit of the $\Delta T/\Delta t$ dependence on the square of the magnetic field amplitude is shown in Fig. 5. It follows that for the frequency range of 500 – 706 kHz at a definite intensity H_{AC} value, the heating process is the most effective.

The SAR values can be calculated from [9]

$$\text{SAR} = \frac{C}{m_{\text{Fe}}}\frac{\Delta T}{\Delta t}, \tag{1}$$

where C is the sample specific heat capacity which is calculated as a mass weighted mean value of magnetite and water m_{Fe}. ΔT is the change of temperature during time Δt. In order to reduce errors due to heat conduction from the ferrofluid to the sample environment, the initial slope of the time-dependent temperature curve $(\Delta T/\Delta t)$ is used. The appropriately chosen SAR functions for some frequencies are shown in Fig. 6.

The rate of temperature changes obtained at a constant magnetic field amplitude ($H_{AC} = 1500 \text{A} \cdot \text{m}^{-1}$) shows (Fig. 7) that for $f_o = 681.7$ kHz the losses of thermal energy attain a maximum. According to Eq. (2), we can assume there are relaxation processes in this frequency range.

According to Rosensweig [10], the density of the thermal energy released in the ferrofluid per unit of time is

$$P = f\,\Delta U = \pi\,\mu_o \chi_o f H_0^2 \frac{2\pi f \tau}{1 + (2\pi f \tau)^2}, \tag{2}$$

where f is the frequency of the alternating magnetic field in the sample, ΔU is the thermal energy released during one period, χ_o is the magnetic

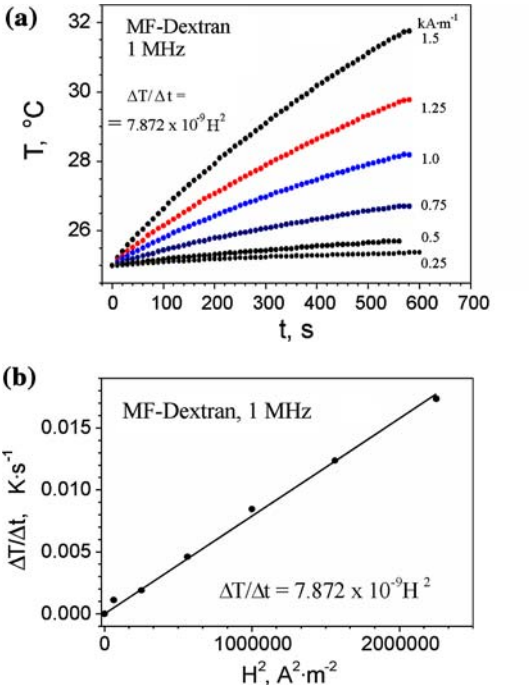

Fig. 4. (a) Time change of the ferrofluid sample temperature, for the sample subjected to an alternating magnetic field of different intensities H_{AC} and frequency $f =$ 1 MHz and (b) experimental data of $\Delta T/\Delta t$ as a function of the square of the magnetic field amplitude for a ferrofluid sample and the fitted curve.

susceptibility at a constant magnetic field, τ is the relaxation time, H_o is the applied magnetic field, and μ_o is the permeability of vacuum.

This loss of thermal energy causes an increase in the ferrofluid temperature by ΔT in the time Δt:

$$\Delta T = \frac{P\,\Delta t}{C_V}, \tag{3}$$

where $C_V \cong 4.9 \times 10^6 \mathrm{J \cdot m^{-3} \cdot K^{-1}}$ is the ferrofluid specific heat (per unit volume).

From the Néel relaxation time estimation ($r_m \cong 5.6\,\mathrm{nm}$, $\tau_N = 61\,\mathrm{ns}$), on the basis of magnetic tests results, the energy absorption maximum of the magnetic fluid should appear at a frequency $f_N \approx 2.7\,\mathrm{MHz}$. It is fourfold larger than the value obtained in our experiment. Therefore, Brown's

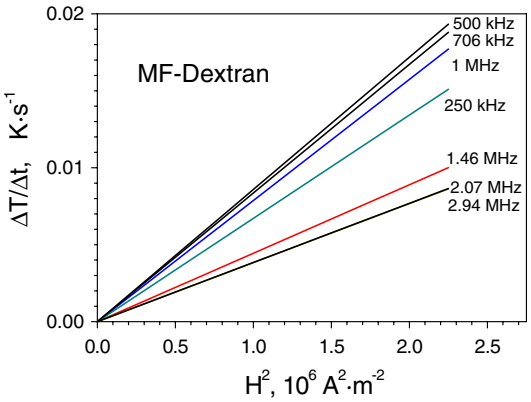

Fig. 5. Fits of $\Delta T/\Delta t$ dependence on the square of the magnetic field amplitude for a ferrofluid sample at different frequency values.

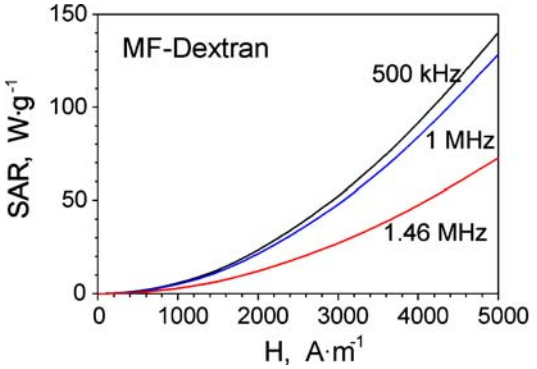

Fig. 6. SAR functions for frequencies $f = 500\,\text{kHz}$, 1 MHz, and 1.46 MHz.

mechanism was dominant. The standard deviation of the diameter size of particles provided by AFM method was $\sigma = 4.1\,\text{nm}$ (18%). Therefore, to a rough approximation, the ferrofluid can be treated as monodispersed, and then assuming that the main source of heat involves the rotations of magnetic grains suspended in the carrier liquid (Brown relaxation), we get the expression for the mean hydrodynamic radius $\langle R_H \rangle$:

$$\langle R_{\text{H}} \rangle = \sqrt[3]{\frac{3V_{\text{H}}}{4\pi}} = \sqrt[3]{\frac{k_{\text{B}}T}{8\pi}\frac{\mu_{\text{o}}\chi_{\text{o}}H_{\text{rez}}^2}{\eta C_V}\left\langle\frac{\Delta t}{\Delta T}\right\rangle}, \tag{4}$$

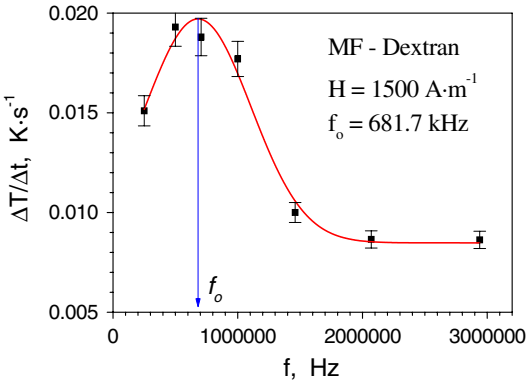

Fig. 7. $\Delta T/\Delta t$ dependence on frequencefrequency determined for $H = 1500\,\mathrm{A{\cdot}m^{-1}}$ ($\langle \Delta T/\Delta t \rangle = 0.01403$).

where k_B is the Boltzmann constant and η is the viscosity coefficient of the matrix fluid.

For the average experimental conditions ($\langle \Delta T/\Delta t \rangle = 0.01403\mathrm{K \cdot s^{-1}}$), at $H = 1500\mathrm{A \cdot m^{-1}}$, $\chi_o = 0.113$, $\eta \cong 0.807 \times 10^{-3}\mathrm{N \cdot s \cdot m^{-2}}$ (at $+30^\circ$C), we get

$$\langle R_H \rangle = \sqrt[3]{\frac{\left(1.38 \times 10^{-23}\right)\,(303)\,\left(4\pi \times 10^{-7}\right)\,(0.113)\,1500^2}{8\pi\,\left(0.807 \times 10^{-3}\right)\,\left(4.9 \times 10^{6}\right)}\,\frac{1}{0.01403}} = 9.9\,\mathrm{nm}.$$

The sample imaging by the AFM method provided the mean hydrodynamic diameter $< R_{AFM} > \cong 22.2$ nm. Good convergence between hydrodynamical radii values determined by calorimetric and AFM methods was obtained.

4. CONCLUSIONS

A biocompatible magnetic fluid with magnetite nanoparticles coated by an additional biocompatible layer of polysaccharide dextran subjected to a slow growing magnetic field shows a high stability of acoustic properties up to a field of $\mathrm{H = 70kA \cdot m^{-1}}$. Successful adsorption of dextran to magnetite particles was confirmed by IR spectroscopy. The reported experimental results show that the observed heating effect may be applied in hyperthermia treatments, especially in the preferable region of 500 – 800 kHz. An "H^2– law" observed for the dependence of the SAR on the square of the amplitude of the magnetic field demonstrates the presence of superparamagnetic particles in the ferrofluid. From magnetic ($r_m = 5.6$ nm) and calorimetric measurements, it follows that the surfactant layer $\delta = R_H - r_m = 4.3$ nm.

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