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Nan N. Liu,[1] Alexander P. Pyatakov,[1] Mikhail N. Zharkov,[2] Nikolay A. Pyataev,[2] Gleb B. Sukhorukov,[3,4] Yulia A. Alekhina,[1] Nikolai S. Perov,[1] Yurii K. Gun'ko,[5,a)] and Alexander M. Tishin[1,6,a)]

AFFILIATIONS

[1]M.V. Lomonosov Moscow State University, Leninskie gory 1-2, 119991 Moscow, Russia
[2]National Research Ogarev Mordovia State University, Bolshevistskaya str. 68, 430005 Saransk, Russia
[3]School of Engineering and Materials Science, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom
[4]Skolkovo Institute of Science and Technology, Bolshoy Boulevard 30, bld. 1, 143025 Moscow, Russia
[5]Trinity College, The University of Dublin, Dublin 2, Ireland
[6]AMT&C Group, Promyshlenaya street 4, 108840 Troitsk, Russia

[a)]Authors to whom correspondence should be addressed: igounko@tcd.ie and tishin@amtc.org

ABSTRACT

Magnetothermal applications of nanoparticles in biomedicine are currently limited by low thermal responses to oscillating magnetic fields on one side and by detrimental physiological effects of electromagnetic radiation on the other side. In this paper, using Zn–Mn ferrite nanoparticles, we demonstrate that an appropriate choice of size and chemical composition of magnetic nanoparticles results in the superquadratic (upto 5th power) dependence of the Specific Absorption Rate (SAR) on a magnetic field (SAR proportional to H^5). This gives an opportunity to obtain SAR values above 10 W/g in an oscillating magnetic field, while maintaining the field-frequency product at a level close to the physiological Brezovich's limit $\sim 10^9$ A/(m s).

Magnetic nanoparticles (MNPs) have found a range of important biomedical applications. For example, MNPs can be targeted in the human body and activated by an alternating current (AC) magnetic field that is used in magnetic hyperthermia, magnetically controlled drug delivery, magnetothermal neurostimulation, etc.[1] The clinically approved magnetic fluid hyperthermia is based on the conversion of electromagnetic energy to heat, which may be characterized by the Specific Absorption Rate (SAR), the power of heat production divided by mass. The SAR is related to the size, size distribution of MNPs, and the frequency (f) and amplitude (H) of the applied AC magnetic field.[2,3] The increase in frequency, as a rule, leads to the proportional increase in the SAR value due to the increase in remagnetization cycles per second. The conventional dependence SAR(H) is quadratic, typical for superparamagnetic MNPs. However, to minimize physiological side effect, the product of the $H \times f$ should remain below the so-called Brezovich's limit.[4,5] Furthermore, to reduce the mass-dimensional characteristics of the magnetic field source (the energy of magnetic field in a coil is proportional to H^2), it is very important from a practical point of view to have superquadratic dependence of SAR as it is also highly desirable to maintain the values of H and f at the minimum level.

These competing requirements can be successfully balanced in the case of superquadratic SAR(H) dependence: As the amplitude increases, the power dissipated into heat may grow much faster than the power of electromagnetic energy entering into the system. Basically, the conversion efficiency[6] is defined as the ratio of the absorbed power to the power of the magnetic part of electromagnetic wave SAR/H^2 and increases with amplitude.

Previously it was demonstrated that the conversion efficiency SAR/H^2 may either increase or decrease, tending to a constant value at sufficiently small fields ("linear regime" of magnetic response) and that the cobalt ferrite MNPs become more efficient above a critical field, close to the transition from the linear to the nonlinear regime.[6] However, cobalt-based particles are toxic and their SAR value is rather small (less than 0.05 W/g) in the AC magnetic field within the Brezovich's limit (H = 10–20 Oe at f = 0.5 MHz). This is why the search for efficient and biocompatible MNPs at conditions complying with the Brezovich's criterion is very important.

Among the different types of MNPs, $Zn_xMn_{1-x}Fe_2O_4$ has one of the highest heating efficiencies in an AC magnetic field.[7] Thus, in this work, zinc manganese ferrite MNPs with the advanced magnetothermal performance have been selected to demonstrate the possibility of a significant increase in the conversion efficiency. As the conversion efficiency is related to the volume of MNP, we have investigated the impact of chemical content and sizes of MNPs on the character of the dependence of SAR value on the amplitude of AC magnetic fields. As a result of our detailed studies, we have demonstrated that the SAR(*H*) dependence can be superquadratic and close to the fifth power (i.e., rather nontrivial), which is highly important for further development of MNPs and devices necessary for clinical applications of magnetic hyperthermia.

Nanoparticles have been prepared by the previously reported chemical coprecipitation method.[8] Zinc manganese ferrite particles were produced by co-precipitation of Fe^{3+} and Me^{2+} ($Me^{2+} = Mn^{2+}$, Zn^{2+}) salts (in a molar ratio of 2:1, respectively) in an alkaline sodium hydroxide medium[6] (see the supplementary material for the list of reagents and procedures).

X-ray diffraction phase analysis (XRD) of the samples and full profile analysis by the Rietveld method[9] were carried out using a PANalytical diffractometer ($CuK\alpha_{1+2}$) in the continuous mode in the range $2\theta = 10°–100°$. The results were processed using MAUD software.

Magnetic measurements were performed using a Lake Shore Model 7407 Vibrating Sample Magnetometer (VSM) with a maximum magnetic field of 1.5 T.

AC magnetic field-calorimetry facility manufactured by AMT&C Group (Moscow, Russia) has been used to measure the magnetothermal properties of the MNPs. The experimental setup included a magnetic module with an inductive coil, connected in series with the AC generator and the reconfigurable capacitor system enabling switching of the frequency range. The setup also had a water cooling system to prevent parasitic heating due to Eddy currents and PC based data acquisition system comprising the micro-voltmeter Agilent 34410A connected to thermocouple with one end in the test tube and another one in the reference temperature thermostat.

The SAR values were calculated based on the time derivative of temperature,[10–13]

$$SAR = C(dT/dt)\,(M/m), \tag{1}$$

where *C* is the heat capacity of a liquid, *dT*/*dt* is the heating rate that can be obtained either by a corrected slope method (the sum of the modulus of the slopes for heating and cooling curves at a fixed temperature[14]), and *M*/*m* is the ratio of the mass of water to the mass of MNPs.

Zinc manganese ferrite particles have been prepared by co-precipitation techniques and characterized by XRD, magnetization measurements, and transmission electron microscopy (TEM).

According to x-ray diffraction analysis (XRD), each prepared powder sample contains the phase with cubic F d-3 m space group (see Fig. S1 in the supplementary material). Broadened reflection lines are observed in the diffraction patterns, which indicate the small size of the coherent scattering regions (CSRs). The analysis showed that the CSR size of $x = 0.2$ and $x = 0.3$ is, respectively, 30–35 nm and 20–25 nm; the lattice parameter of $x = 0.2$ and $x = 0.3$ is, respectively, 8.449(2) Å and 8.438(2) Å.

The measured VSM hysteresis loops of zinc manganese ferrite particles are shown in Fig. 1(a). The dependence of the residual magnetization on the Zn content is nonmonotonic, reaching a maximum at the $x = 0.1$, similarly to earlier reported results,[10] that can be explained by the distribution of replacement cations on the *A* and *B* sublattices. The coercivity [Fig. 1(b)] decreases monotonously with the increase in zinc content similar to the previous reports.[7,15]

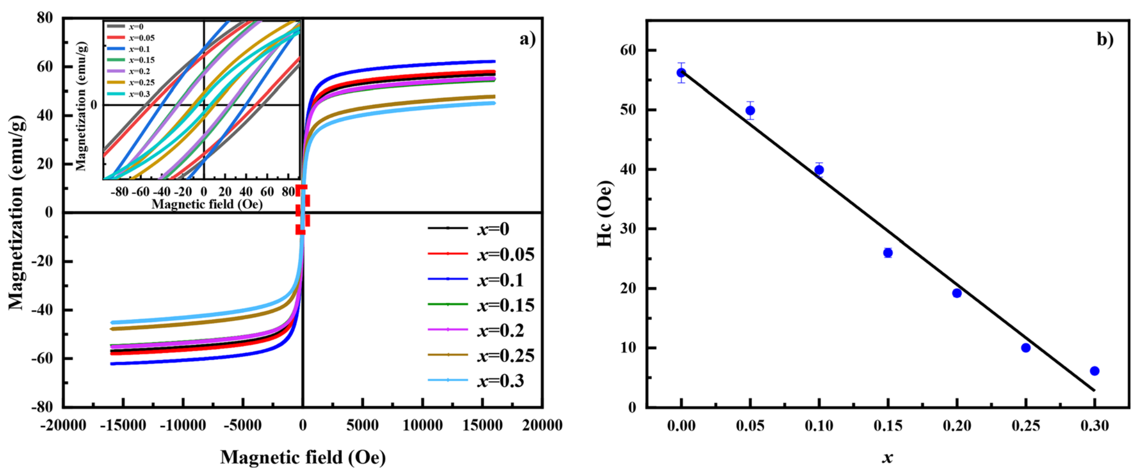

FIG. 1. Magnetic properties of the $Zn_xMn_{1-x}Fe_2O_4$ MNPs: (a) hysteresis loops of MNPs, inset shows the amplified hysteresis loop; (b) the dependence of coercive force on Zn-content *x*. The points represent the experimental data, and the solid line is a linear fit by a least squares method.

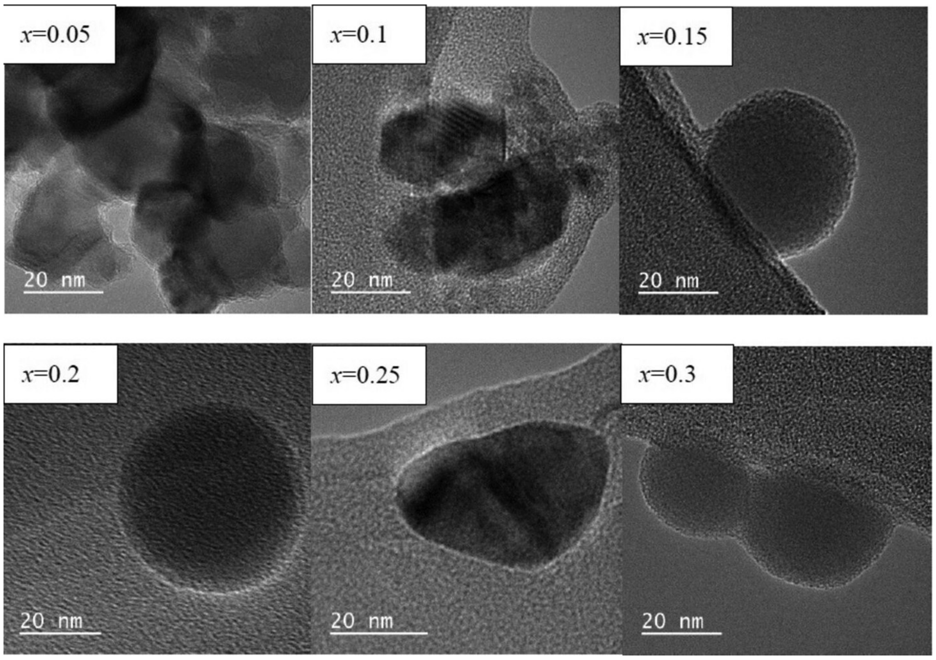

FIG. 2. TEM images of $Zn_xMn_{1-x}Fe_2O_4$ ($x = 0.05$; 0.1; 0.15; 0.2; 0.25; 0.3).

Figure 2 shows TEM images of zinc manganese ferrite particles. The shape of the particles is spherical. The results show that as the Zn content increases, the size of the nanoparticles decreases. Possible mechanisms leading to the smaller size of particles with the increasing Zn concentration include changes in the parameters of unit cells, the length of interatomic bonds, and the distribution of cations over octahedral and tetrahedral crystallographic positions in the cubic crystal structure.

For magnetothermal measurements, 20 mg of MNPs was suspended in 100 μl of de-ionized water. The heating/cooling curves of a series of $Zn_xMn_{1-x}Fe_2O_4$ suspensions under an AC magnetic field with root mean square (RMS) value $H = 100$ Oe and a frequency of 0.1 MHz are presented in Fig. 3, while Fig. 4 shows the SAR value of zinc manganese ferrite MNPs with different Zn content at $f = 0.1$ MHz and at $H = 100$ Oe (the maximum $f \times H$ product that remains within Brezovich's limit). The dependence of SAR values on the diameter of $Zn_xMn_{1-x}Fe_2O_4$ nanoparticles with different Zn content at $f = 0.1$ MHz and $H = 60$ Oe is shown in Fig. 5. It may be concluded that the dependence of SAR(x) from Zn content, x, has a clear nonmonotonic character, which demonstrates better heat response of application of the AC magnetic field for MNPs at $x = 0.2$. Thus, the

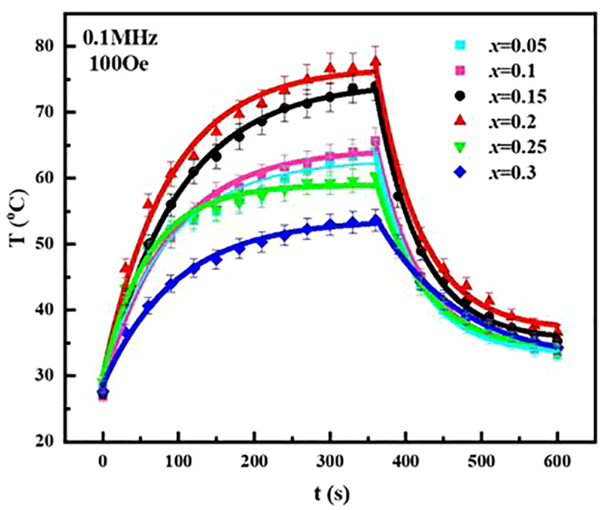

FIG. 3. The heating/cooling curve of a series of $Zn_xMn_{1-x}Fe_2O_4$ suspensions under an AC magnetic field with a frequency of 0.1 MHz and RMS value 100 Oe.

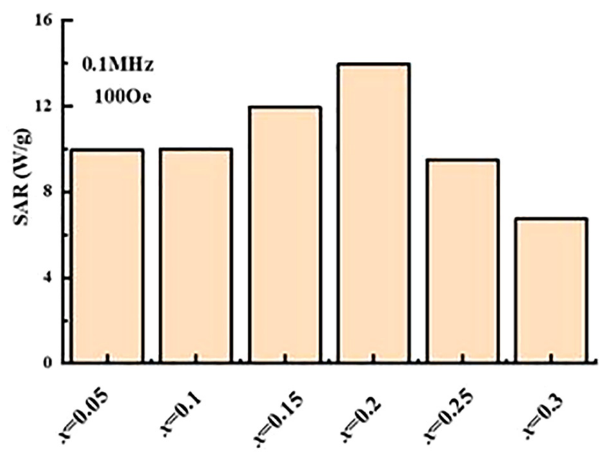

FIG. 4. The SAR value of a series of $Zn_xMn_{1-x}Fe_2O_4$ ($x = 0.05$; 0.1; 0.15; 0.2; 0.25; 0.3) suspensions at $f = 0.1$ MHz and RMS field $H = 100$ Oe.

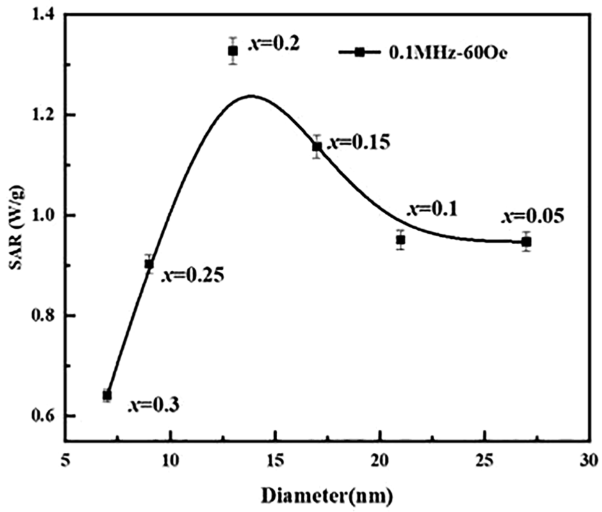

FIG. 5. Dependence of SAR on the diameter of $Zn_xMn_{1-x}Fe_2O_4$ ($x = 0.05$; 0.1; 0.15; 0.2; 0.25; 0.3) at a $f = 0.1$ MHz and RMS field $H = 60$ Oe).

magnetic properties of nanoparticles depend on the size and composition and can influence SAR values.

The SAR value varies with the Zn content, being the largest for medium-sized particles $x = 0.2$ with the SAR value at $f = 0.1$ MHz at both RMS values of magnetic field 60 and 100 Oe.

Figure 6 presents the dependencies of SAR on the magnetic field root mean square value: The character of SAR(H) dependence changes with Zn content (and as a consequence, the MNPs average size). For smaller particles ($x = 0.25$, $x = 0.3$), the dependence tends to the conventional quadratic law, while for larger particles ($x = 0.1$, 0.15, 0.2), it is superquadratic dependence. The superquadratic dependences (SAR proportional to H^5) for larger particles can be explained by the nonlinear magnetic response of MNPs,[16,17] due to the increased contribution

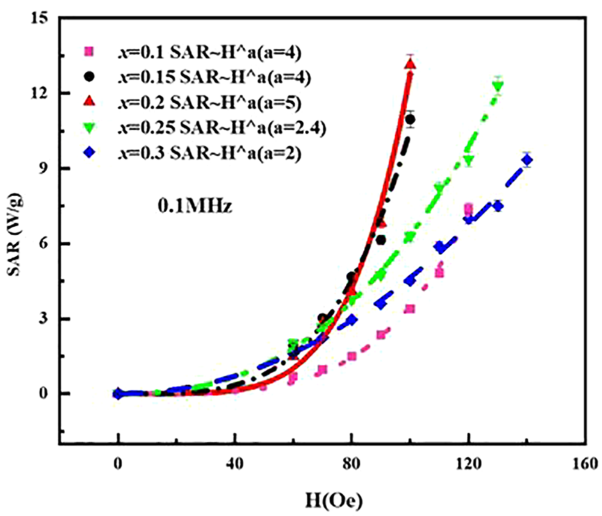

FIG. 6. SAR(H) dependence of the $Zn_xMn_{1-x}Fe_2O_4$ ($x = 0.1$; 0.15; 0.2; 0.25; 0.3) MNPs on the magnetic field at $f = 0.1$ MHz.

of hysteresis losses. (The hysteresis loop and coercivity are more pronounced for $x = 0$–0.2 ZnMn ferrite MNPs in Fig. 1.) At the same time for small particles ($x = 0.25$, $x = 0.3$), with low coercive field, the conventional mechanisms of magnetothermal heating due to Neel and Brown magnetic relaxation,[1,10] typical for superparamagnetic MNPs, are dominant.

Therefore, it has been established that the SAR dependence on the amplitude of an AC magnetic field may be nontrivial even in a range of the product of $H \times f$ within the Brezovich's physiological limit.[4] This is very important finding, since the potential side effects on healthy tissues increase with the square of the amplitude,[4] the SAR of MNPs increases more rapidly that ensures the selectivity of heating of MNPs containing tissues.

In conclusion, we have shown that the compositions and sizes of MNPs may provide a significant increase in conversion efficiency of electromagnetic energy to provide the heat at the minimum value of the frequency of the AC magnetic field. It has been demonstrated that by adopting the size and chemical content of ZnMn ferrite MNPs, we can reach a much higher value of MNPs heat response to the AC magnetic field at 0.1 MHz and 60–100 Oe while maintaining the magnitude of the product of the amplitude and the field frequency at a level close to the physiological Brezovich's limit $\sim 10^9$ A/(m s). We demonstrated the nontrivial, higher than 3^d power, superquadratic dependence of the at low Zn content in $Zn_{0.2}Mn_{0.8}Fe_2O_4$ nanoparticles that may be explained by additional contribution of hysteresis losses due to the need for additional work to remagnetize MNP.

These findings are very important and potentially enable to reduce the weight and size characteristics of modern clinical AC magnetic setups for magnetic hyperthermia. The observed superquadratic SAR $\sim H^5$ and SAR $\sim H^4$ dependences are also useful for potential applications in magnetically assisted drug delivery, magnetic stimulation of the brain and neuro-interfaces, and other biomedical applications.

See the supplementary material for detail of synthetic protocols, table with reagent ratios for the synthesis of various types of nanoparticles, XRD patterns of nanoparticles, dependence of saturation magnetization on Zn content in $Zn_xMn_{1-x}Fe_2O_4$, and power dependence approximations.

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AUTHOR DECLARATIONS

Conflict of Interest

We have no conflicts of interest to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available within the article and its supplementary material.

REFERENCES

[1] *Magnetic Materials and Technologies for Medical Applications*, 1st ed., edited by A. M. Tishin (Woodhead Publishing, 2021), p. 425.
[2] R. T. Salakhova, A. P. Pyatakov, V. I. Zverev, B. Pimentel, R. J. C. Vivas, L. A. Makarova, N. S. Perov, A. M. Tishin, A. A. Shtil, and M. S. Reis, J. Magn. Magn. Mater. **470**, 38 (2019).

[3]H. Etemadi and P. G. Plieger, Adv. Ther. **2000061**, 1 (2020).
[4]I. A. Brezovich, Med. Phys. Monogr. **16**, 11 (1988).
[5]M. R. Barati, C. Selomulya, K. G. Sandeman, and K. Suzuki, Appl. Phys. Lett. **105**(16), 162412 (2014).
[6]E. L. Verde, G. T. Landi, M. S. Carrião, A. L. Drummond, J. A. Gomes, E. D. Vieira, M. H. Sousa, and A. F. Bakuzis, AIP Adv. **2**, 032120 (2012).
[7]M. Jeun, S. J. Moon, H. Kobayashi, H. Y. Shin, A. Tomitaka, Y. J. Kim, Y. Takemura, S. H. Paek, K. H. Park, K.-W. Chung, and S. Bae, Appl. Phys. Lett. **96**(20), 202511 (2010).
[8]Y. B. Kannan, R. Saravanan, N. Srinivasan, K. Praveena, and K. Sadhana, J. Mater. Sci. **27**, 12000 (2016).
[9]H. M. Rietveld, J. Appl. Crystallogr. **2**, 65 (1969).
[10]E. A. Périgo, G. Hemery, O. Sandre, D. Ortega, and F. J. Teran, Appl. Phys. Rev. **2**(4), 041302 (2015).
[11]E. A. Périgo, F. A. Sampaio, and M. F. de Campos, Appl. Phys. Lett. **103**(26), 264107 (2013).
[12]F. J. Teran, C. Casado, N. Mikuszeit, G. Salas, A. Bollero, M. P. Morales, J. Camarero, and R. Miranda, Appl. Phys. Lett. **101**(6), 062413 (2012).
[13]D. Ketharnath, R. Pande, L. Xie, S. Srinivasan, B. Godin, and J. Wosik, Appl. Phys. Lett. **101**(8), 083118 (2012).
[14]R. R. Wildeboer, P. Southern, and Q. A. Pankhurst, J. Phys. D **47**, 495003 (2014).
[15]E. V. Gopalan, I. A. Al-Omari, K. A. Malini *et al.*, J. Magn. Magn. Mater. **321**, 1092 (2009).
[16]R. K. Gilchrist, R. Medal, W. D. Shorey *et al.*, Ann. Surg. **146**, 596 (1957).
[17]B. Pimentel, R. J. Caraballo-Vivas, N. R. Checca *et al.*, J. Solid State Chem. **260**, 34–38 (2018).