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Magnetic hyperthermia with hard-magnetic nanoparticles

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ABSTRACT

Recent clinical trials of magnetic hyperthermia have proved, and even hardened, the Ankinson-Brezovich restriction as upon magnetic field conditions applicable to any site of human body. Subject to this restriction, which is harshly violated in numerous laboratory and small animal studies, magnetic hyperthermia can relay on rather moderate heat source, so that optimization of the whole hyperthermia system remains, after all, the basic problem predetermining its clinical perspectives. We present short account of our complex (theoretical, laboratory and small animal) studies to demonstrate that such perspectives should be related with the hyperthermia system based on hard-magnetic (Stoner–Wohlfarth type) nanoparticles and strong low-frequency fields rather than with superparamagnetic (Brownian or Neél) nanoparticles and weak high-frequency fields. This conclusion is backed by an analytical evaluation of the maximum absorption rates possible under the field restriction in the ideal hard-magnetic (Stoner–Wohlarth) and the ideal superparamagnetic (single relaxation time) systems, by theoretical and experimental studies of the dynamic magnetic hysteresis in suspensions of movable hard-magnetic particles, by producing nanoparticles with adjusted coercivity and suspensions of such particles capable of effective energy absorption and intratumoral penetration, and finally, by successful treatment of a mice model tumor under field conditions acceptable for whole human body.

1. Introduction

Last two decades witness exponentially growing interest in magnetic hyperthermia of cancers. The underlying idea, that was proposed many years ago [1], is simple – to destroy tumor thermally by its local heating above the physiological temperature with the use of small magnetic particles delivered inside malignant area and absorbing there the energy of externally applied AC magnetic field. However, practical implementation of this idea appeared not so simple, especially by comparing modest practical achievements with enormous amount of published papers. The main body of performed studies are with stable colloidal suspensions of ultrasmall single-domain magnetic nanoparticles, the approach, originated [2,3] as "magnetic fluid hyperthermia" (MFH). It should be mentioned here that particulate systems of magnetic fluids are soft-magnetic not only in liquid but also in frozen state, which is characteristic of superparamagnetic (SPM) particles with thermally unstable magnetic moment orientation. Both internal (Neél) and external (Brownian) thermofluctuation mechanisms of magnetization relaxation can be involved in MFH.

Preclinical examination of the method feasibility includes laboratory studies of the AC field energy absorption and small animal studies of the antitumor effects of local magnetic hyperthermia. The inventors of MFH were the first to thus demonstrate its feasibility [2–6], to develop a magnetic field applicator for medical use in any part of human body [7], and to perform clinical experiments with tumors of different location [8–12]. These achievements are widely referred to support the importance of ongoing laboratory and small animal studies, but hardly ever to learn a lesson about conceptual restrictions of magnetic hyperthermia in whole, and MFH particularly. The basic is the restriction on the magnetic field conditions that can be safely applied to any site of human body without the side effect of intolerable non-specific heating of conductive human body by eddy currents. Besides, seemingly advantageous stability of magnetic colloids is found inappropriate for localized hyperthermia because colloidal particles gradually leave the intended area. A gel-forming coating is employed to trap the particles [12]. This implys that laboratory data on the energy absorption, mostly obtained in liquid systems, may be misleading as for practical application. Moreover, this questions the idea [13] of enhancing the energy

Abbreviations: MFH, magnetic fluid hyperthermia; SPM, superparamagnetic; HM, hard-magnetic; SAR, specific absorption rate

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absorption by choosing Brownian, not Neél magnetic nanoparticles. As a matter of fact, subject to the magnetic field limitation, magnetic hyperthermia can relay on rather moderate heat source, so that optimization of the whole hyperthermia system remains, after all, the basic problem predetermining its clinical perspectives.

Over some years, we have been studying the alternative hyperthermia system based on the use of intrinsically athermal hard-magnetic (HM) nanoparticles with pronounced stationary magnetic hysteresis. Here we summarize our previous and novel findings and came to conclusion that namely HM nanoparticles, rather than SPM nanoparticles, provide reliable basis for practical magnetic hyperthermia.

2. Allowable fields and achievable energy absorption

In order to allow the local heating by magnetic particles, the non-specific heating of the electrically conductive body by the AC magnetic field should be avoided. Naturally, the pattern of temperature increment will depend on the distribution of tissue electric conductivity and the heat transfer peculiarities. However, the concept of the AC field limitation is easily understood [14] from the simple model of a homogeneous cylindrical body affected by uniform AC field. At a cylindrical layer of tissue with the radius r under the AC magnetic field with the frequency f and the amplitude H_0 the eddy currents produce heat with local power density $w \sim (rH_0 f)^2$, which gives, in the field-affected cylindrical volume with the length equal to the radius R, the total absorption power $W \sim R^5 (H_0 f)^2$. This simple estimation indicates that magnetic field conditions are represented by the amplitude–frequency product $H_0 f$, and the heating power increases with the increase of the dimension of the affected region. Purposeful studies of the tolerable AC magnetic fields were performed as far as in 1984 [14] in connection with the idea of local hyperthermia with metallic inclusions. In this work the concept of the whole-body restriction was introduced that indicates the field conditions tolerable in prolonged application to any part oh human body. In experiments with volunteers, a single-turn electric coil around the thorax, the prolonged application of AC magnetic was found tolerable if its frequency–amplitude product did not exceed the value of 4.85×10^8 A/(ms). More relevant to practical magnetic hyperthermia data can be found in clinical experiments [10] with magnetic field applicator [7] that represents a huge electromagnet with a ferrite magnetic circuit, the patient body between its flat poles. The applicator was design to produce magnetic field with the frequency of 100 kHz, and the amplitude of up to 18 kA/m. The tolerated by patients field amplitudes were reported in the range 3–5 kA/m in pelvic region, up to 8.5 kA/m in the upper thorax, and 3.8–13.5 kA/m (median: 8.5 kA/m) in the head. That is, the tolerable frequency–amplitude product for different patients and different body regions was in the range of $(3–13.5) \times 10^8$ A/(ms), the lower level smaller than that established in experiments with single-turn electric coil [14]. In our opinion, at the research stage, it is not appropriate to reduce requirements to magnetic hyperthermia systems by considering small parts of human body and small exposure times. We accept $H_0 f = A \equiv 4 \times 10^8$ A/(ms) to be the reference value for appraisal of magnetic field–particle systems considered at the research stage for magnetic hyperthermia. This limitation is harshly violated in all publications that report high energy absorption, as it is illustrated in Fig. 1 which plots reported [7,15–25] specific energy absorption rate (SAR) vs. the violation degree of the magnetic conditions limitation. Note, that in case of MFH system developed for clinical use, the SAR at the boundary of acceptable magnetic fields is only about 4 W/g [7]. This small SAR strongly reduces the range of possible magnetic

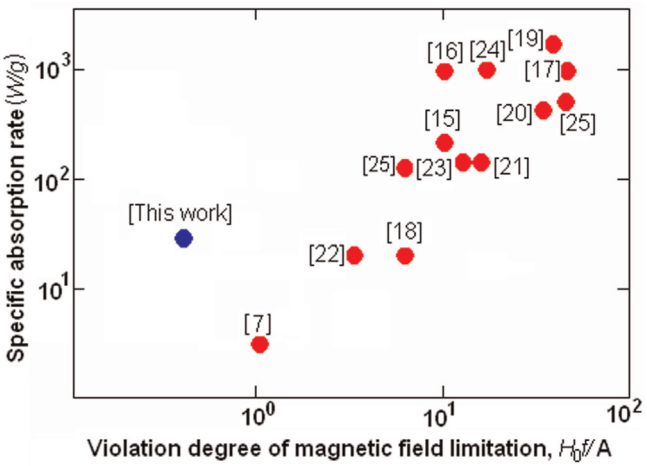

Fig. 1. Reported SAR vs. the used magnetic field conditions. Dots are marked by the numbers of corresponding references. Dot [this work] presents the data of this study (see below).

hyperthermia targets and sharpens the methodological question, so far practically avoided, to what extent the efficiency can be increased of the energy absorption by magnetic particles under restricted magnetic fields. To obtain simple and reliable estimation, in the perplexed world of magnetic nanoparticles, we can count on two marginal cases corresponding to the idealized (Stoner–Wohlfarth) system of athermal single-domain uniaxial HM particles and the idealized monodisperse system of SPM particles with single magnetic relaxation time. In the first case, the absorption is maximum if the particles are oriented along the field polarization axis and magnetic reversal proceeds by abrupt magnetic jumps between opposite directions of the anisotropy axis. The hysteresis loop is the perfect rectangle with the area $4c\mu_0 I_b H_c$ (μ_0 is the vacuum magnetic permeability, c is the particle volume concentration, I_b is the particle magnetization, and H_c, the coercive force), and SAR achieves its maximum value ($I_b' = I_b/\rho$, the particle specific magnetization).

$$\mathrm{SAR}^*_{HM} = 4\mu_0 A I_b' \tag{1}$$

at the field amplitude $H_0 = H_c$ and the maximum allowable frequency $f = A/H_c$. It is worth to notice that SAR in Eq. (1) does not depend on the coercive force. Only the particle specific magnetization and the squareness of hysteresis loop is important.

Consider the ideal SPM system with the particle volume V, the particle number concentration n, and the magnetic relaxation time τ. The amplitude of the field remains within the linear region of the system static magnetization, which implies small Langevin parameter, $\xi_0 = \mu_0 I_b V H_0 / kT < 1$ (k is the Boltzmann constant, and T the temperature). In such a case, the absorption power density w is given by the well-known relations [13]:

$$w = \pi\mu_0 \chi'' f H_0^2, \quad \chi'' = \chi_0 \frac{2\pi f\tau}{1 + (2\pi f\tau)^2}, \quad \chi_0 = \frac{\mu_0 n I_b^2 V^2}{3kT}. \tag{2}$$

Here, χ_0 is the steady magnetic susceptibility, and χ'' is the imaginary part of the dynamic magnetic susceptibility. The absorption power in Eq. (2) can be easily rewritten in the following form:

$$w = \frac{1}{3}\pi\mu_0 A c I_b \xi_0 \frac{2\pi f\tau}{1 + (2\pi f\tau)^2}.$$

As it follows from the extremum condition $dw/df = 0$, the absorption power reaches the maximum value $w = (1/6)\pi\mu_0 A c I_b \xi_0$ at

the frequency $f = 1/(2\pi\tau)$, the corresponding maximum SAR.

$$\mathrm{SAR}^{*}_{SPM} = \frac{1}{6}\pi\mu_0 I_b' A\xi_0. \tag{3}$$

Eqs. (1) and (3) indicate that subject to the field limitation the ideal HM particles are much better energy absorbers as against the ideal SPM particles ($\mathrm{SAR}^{*}_{SPM}/\mathrm{SAR}^{*}_{HM} = \pi\xi_0/24$). Eq. (1) represents the absolute maximum of SAR theoretically possible in magnetic hyperthermia applicable to any part of human body. Say, if magnetite nanoparticles ($I_b' = 92$ A m^2/kg) had a square hysteresis loop, they would provide $\mathrm{SAR}^{*}_{HM} = 185$ W g^{-1}.

3. Feasibility of magnetic hyperthermia in limited magnetic field conditions

Unlike ultrasmall SPM particles, their both spatial and orientational motion dominated by thermal diffusion, the behavior of HM nanoparticles is dominated by the regular magnetic interactions as far as the magnetic anisotropy energy, the Zeeman energy, and the energy of the interparticle dipole–dipole interactions overpower thermal energy. The possible use of HM nanoparticles for hyperthermia arouses a number of questions related with physical chemistry (producing appropriate nanoparticles), colloidal chemistry (stabilization of magnetic suspensions and their intratumoral penetration), and physics (dynamic magnetic hysteresis in HM systems with mechanically movable particles). Importance of understanding the role of the interconnected processes of the internal orientational dynamics (orientational behavior of the particle magnetic moment inside the crystal matrix) and the external orientational dynamics (mechanical rotation of particles in viscous liquid under electrodynamic torque) is seen from the Stoner–Wohlfarth theory of magnetic reversal in uniaxial particles: when aligned in the AC field direction, such particles absorb four times more energy as against randomly oriented, and transversely oriented particles do not absorb energy at all. Mechanical orientation of the movable HM particle in the AC magnetic field should be considered an independent variable, additional to the magnetic moment orientation. Our studies based upon the generalized Stoner–Wohlfarth model of magnetic reversal in movable particles [26] have brought an important conclusions: depending on the field–liquid–particle system parameters, the magnetization dynamics proceeds by either mechanical rotation of particles or internal Stoner–Wohlfarth jumps of their magnetic moments, the latter regime appearing in the AC field with the amplitude above the particle coercivity and with the frequency above the critical value $f^{*} \approx 5\times10^{-4}\mu_0 I_b H_c/\alpha\eta$ (η, the liquid viscosity and α, the particle hydrodynamic form-factor). It was shown that in this regime the particles are steadily orientated along the field polarization direction, the dynamic hysteresis loop is rectangular, and the energy absorption takes on the maximum possible value (1). Hence, to achieve maximum absorption in suspension of HM particles one have to ensure conditions $H_0 > H_c$, and $f > f^{*}$. Finally, to avoid any essential influence of thermal fluctuations of the particle magnetic moment upon magnetic reversal, the energy of the particle magnetic anisotropy should be large as against the thermal energy kT. Taking into account the results of many studies of magnetic reversal in single-domain uniaxial particles with the finite anisotropy energy (for example [27]), we write this condition as $\sigma = \mu_0 I_b H_c V/kT > 400$, the particle volume V to be in the single-domain range. Conditions $f > f^{*}$ and $\sigma > 400$ imply that the particle coercive force should be limited from both below and above, namely,

$$H_c < 10^2(\alpha\eta A/5\mu_0 I_b)^{1/2}, \quad H_c > 400\, kT/\mu_0 I_b V. \tag{4}$$

The condition for this range to exist reads:

$$\left(\frac{\alpha\eta A\mu_0 I_b}{5}\right)^{1/2}\frac{V}{4kT} > 1. \tag{5}$$

It involves the particle shape, volume and magnetization. In case of spherical particles with magnetization of magnetite ($I_b = 480$ kA/m) in water ($\eta = 0.001$ Pa s) Eq. (5) demands the particles with diameter above 53 nm. For 53 nm particles, the range of proper coercivity shrinks to the point $H_c = 440$ Oe.

The above presented evaluation based on the minimalist Stoner–Wohlfarth model gives a helpful notion as about the proper hyperthermia system with HM nanoparticles. The adequate experimental method to examine such systems, at both research and development stages, is measuring the loops of dynamic magnetic hysteresis. The loops not only quantify the power of energy absorption (equal to the product of the field frequency and the loop area) but also shed light upon the physics of the underlying orientational processes in the heat producing systems of HM nanoparticles, which is the basic advantage over the commonly used calorimetry. The dynamic hysteresis technique was first developed to study the dilute systems of needle maghemite particles (1000 nm long, 100 nm in diameter) in very viscous liquid [28]. Experiments in the field with the frequency of 430 Hz and the amplitude of up to 1.1 kOe had confirmed predicted noticeable increment of the squareness of the dynamic hysteresis loops, and hence the increment of the energy absorption, in the liquid dispersion as against the disordered solid dispersion (Fig. 2).

The needle maghemite particles proved rather efficient energy absorbers with specific heat production $q_1 = 8\,J/\mathrm{kg}$ in each field variation period at the field amplitude $H_0 = 56$ kA/m [28]. At the allowable frequency $f = A/H_0 = 7.15$ kHz this gives $\mathrm{SAR} = q_1 f = 57.2\,W/g$, more than tenfold higher as against SAR obtained [7] in the clinical MHF system. Their drawback, from our experience, is poor penetration about tumor. An optimistic suggestion was that needle shape and big size of particles may be the cause. Needles could be easily trapped by the tissue and could initiate, due to the strong interparticle magnetic interactions, the formation of solid plugs. Our hope for smaller quasispherical HM nanoparticles came true. Using a fairly simple method of producing spherical high-coercivity particles, which consist of ferric oxides with some amount of cobalt (introduced for increasing the particle coercivity) we were able to produce HM nanoparticles of around 60 nm in diameter with the coercive force and the specific energy absorption close to those of the above considered needle maghemite [29,30]. The only requirement to ensure relative stability of the suspension of these hydrophobic particles in physiological saline solution and their intratumoral penetration is intensive dispersing of the dry powder with appropriate biocompatible admixture. Let us illustrate this statement by the following sampling studies. The biocompatible polymer, polyvinylpyrrolidone (M.w 12,600 $\pm$ 2700), was employed as the suspension stabilizer to reduce the hydrophobic aggregation of particles. The magnetic suspension homogenization was effected by the mechanical disperser KIA 10 basic.

The rat model tumor (see [30]) served for the penetration studies. The particle distribution upon injection was visualized by a clinical X-ray device. The structure of magnetic particles in prepared suspension was visualized with optical microscope in thin layers formed by manual compressing the suspension droplet between glass plates. Our main finding is that the stabilised suspension of quasi-spherical hydrophobic magnetic nanoparticles is capable of spreading homogeneously enough about tumor upon

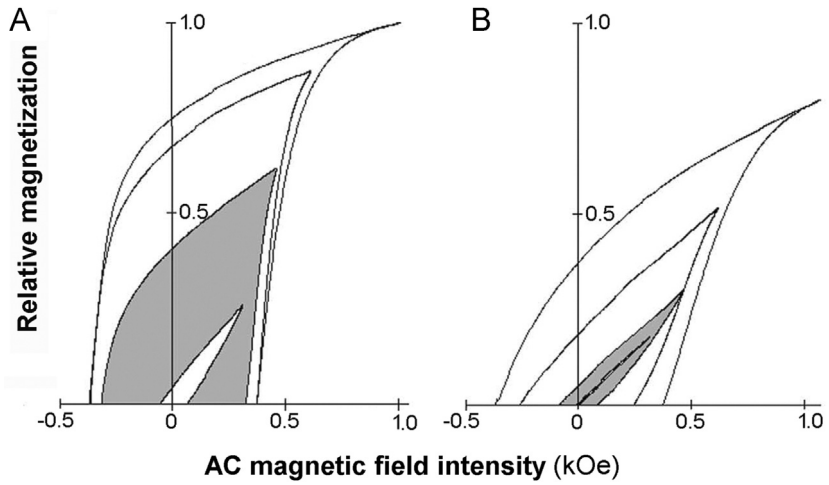

Fig. 2. Dynamic hysteresis loops in liquid (A) and solid (B) dispersions of needle maghemite particles with volume content of 0.001(with permission from Ref. [28]).

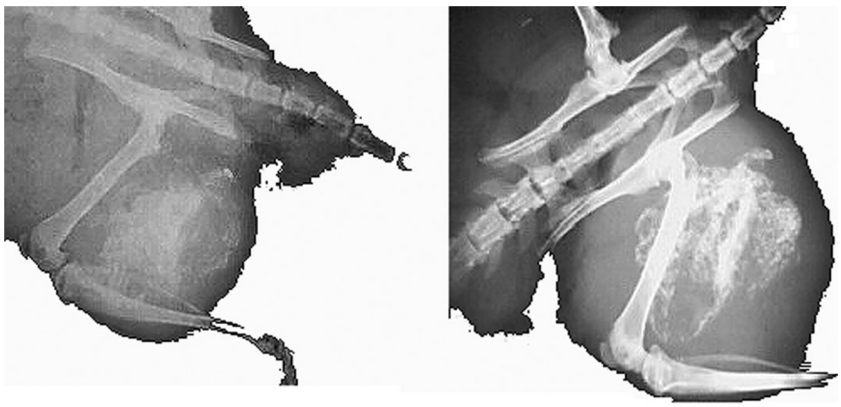

Fig. 3. X-ray pictures of the quasispherical FM nanoparticles inside a tumor (in rat), taken just after introduction (left) and two weeks later (right) demonstrate that the particles remain at the site of injection in growing tumor.

slow injection with a siring, and the injected particles do not move from the site of injection (Fig. 3).

Visualization of the structure of magnetic particles (Fig. 4) highlights the role of the stabilizer. Without stabilizer, the hydrophobic interactions lead to formation of huge aggregates. Upon smashing between glasses, these aggregates form thick rods (Fig. 4, left) that characterize the size of aggregates, too large for intratumoral penetration. The stabilizer (Fig. 4, right) reduces hydrophobic interactions, and the structure is dominated by the magnetic dipole interactions, these interactions producing small aggregates with presumably compensated magnetic moments, the aggregates entrapped in a fragile particulate mesh network capable of preventing the suspension from gravitational segregation.

One more question we reckon among prerequisites of ferromagnetic hyperthermia is the influence of the inevitable in real conditions magnetic aggregation as upon the energy absorption. Experiments with different-viscosity liquid carriers and different concentrations of particles did not show significant differences of

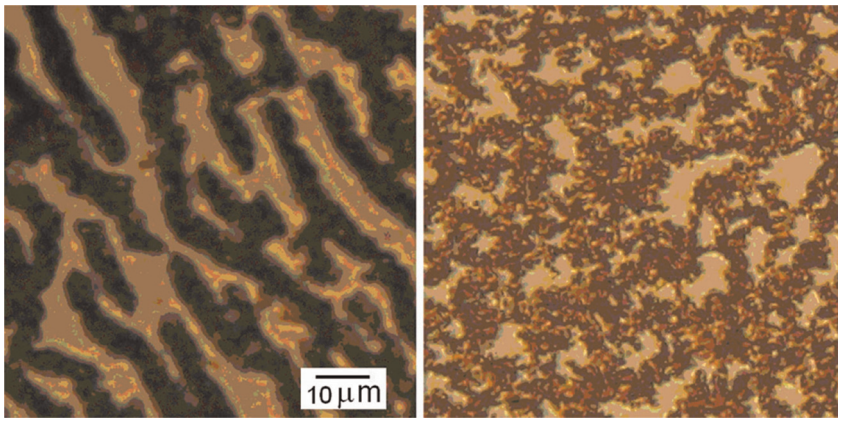

Fig. 4. Structure of a magnetic suspension in thin layer without (left) and with stabilizer (right).

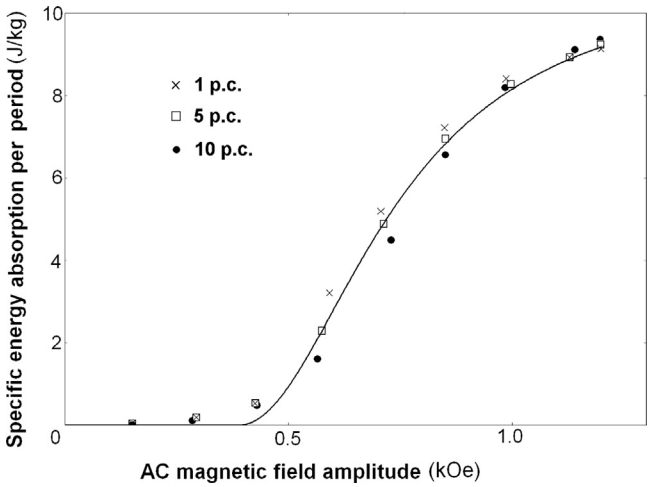

Fig. 5. Specific energy absorption in one period of field variation measured (dots) as function of the field amplitude in suspensions of HM nanoparticles with different concentrations (1, 5, and 10 vol%).

Fig. 6. The picture of recovered animals. Scars mark thermally destroyed tumors.

the specific energy absorption in fields of interest, that is, above the particle coercive force. An illustration of this statement is Fig. 5 that presents specific absorption per field variation period measured in different-concentration suspensions of the type used in hyperthermia experiments with small animals. Importance of this result consists in proving the possibility to use laboratory data to plan and analyze the hyperthermia procedures.

Finally let us present a short account of our in-vivo studies [31] of the antitumor activity of the ferromagnetic hyperthermia performed in physiologically acceptable fields ($f = 3700$ Hz, $H_0 \leq 56$ kA/m). The previously described [30] automated setup was capable of controlled maintenance of the tumor temperature at a given point that was chosen just under the lower tumor pole in healthy tissue. The field–particle system produced SAR=25 W/g with amplitude/frequency product well below the allowable one ($H_0 f \leq A/2$). Nevertheless, it ensured heating the edge of 0.5–1/5 cm^3 tumors to the prescribed 44 or 44.5 °C. The antitumor effect of hyperthermia itself and in combination with chemotherapy (cyclophosphamide, 50–200 mg/kg one week prior to the treatment) was studied at the mice-Erlich adenocarcinoma bearers. About 100 mice were treated. The main results are the following: the developed regime of controlled magnetic hyperthermia (44 °C under lower pole/20 min) is safe; the complete recovery after pure hyperthermia in different series amounts up to 25–50%; in combination with chemotherapy hyperthermia lead to complete recovery in up to 80% of cases. The picture of recovered animals is presented in Fig. 6.

4. Conclusion

Unambiguous conclusion from our theoretical, laboratory and small animal studies is that HM nanoparticles provide more reliable basis for practical magnetic hyperthermia as against SPM nanoparticles. Their basic advantage over SPM nanoparticles lays in much more effective specific energy absorption at any given magnetic field conditions that determine the background level of the unspecific tissue heating, and put limit upon the heat source achievable in magnetic hyperthermia. To get maximum SAR, the magnetic hyperthermia system with HM nanoparticles must be adjusted in terms of the particle volume and coercivity, and the field amplitude and frequency. In the adjusted system, HM nanoparticles are stationary aligned in the AC direction; the energy absorption is of pure solid-body nature and takes on its maximum possible level. If the hydrophobic interparticle interactions of the HM nanoparticles in the heat-producing suspension are sufficiently weakened by an appropriate dispersing agent, the magnetic aggregation of HM nanoparticles does not affect the AC field energy absorption, and does not prevent the penetration of particles about the tumor volume. The main characteristic that determines the effectiveness of the otherwise adjusted HM nanoparticles is the squareness of the magnetic hysreresis loop in the aligned particulate system. Improvement in the loop squareness is the main way to further improvement of the magnetic hyperthermia system with HM nanoparticles.

References

[1] R.K. Gilchrist, W.D. Shorey, R.C. Hanselman, J.C. Parrott, C.B. Taylor, R. Medal, Selective inductive heating of lymph nodes, Ann. Surg. 146 (1957) 596–606.
[2] A. Jordan, P. Wust, H. Fahling, W. Johns, A. Hinz, R. Felix, Inductive heating of ferrimagnetic particles and magnetic fluids: physical evaluation of their potential for hyperthermia, Int. J. Hyperth. 9 (1993) 51–68.
[3] A. Jordan, R. Scholz, P. Wust, H. Fähling, R. Felix, Magnetic fluid hyperthermia (MFH): cancer treatment with AC magnetic field induced excitation of biocompatible superparamagnetic nanoparticles, J. Magn. Magn. Mater. 201 (1999) 413–419.
[4] A. Jordan, R. Scholz, K. Maier-Hauff, F.K. van Landeghem, N. Waldoefner, U. Teichgraebe, J. Pinkernelle, H. Bruhn, F. Neumann, B. Thiesen, The effect of thermotherapy using magnetic nanoparticles on rat malignant glioma, J. Neurooncol. 78 (2006) 7–14.
[5] M. Johannsen, B. Thiesen, A. Jordan, K. Taymoorian, U. Gneveckow, N. Waldöfner, R. Scholz, M. Koch, M. Lein, K. Jung, Magnetic fluid hyperthermia (MFH) reduces prostate cancer growth in the orthotopic Dunning R3327 rat model, Prostate 64 (2005) 283–292.
[6] M. Johannsen, B. Thiesen, U. Gneveckow, K. Taymoorian, N. Waldöfner, R. Scholz, S. Deger, K. Jung, S. Loening, A. Jordan, Thermotherapy using magnetic nanoparticles combined with external radiation in an orthotopic Dunning rat model of prostate cancer, Prostate 66 (2006) 97–104.
[7] U. Gneveckow, A. Jordan, R. Scholz, V. Bruess, N. Waldöfner, J. Ricke, A. Feussner, B. Hildebrandt, B. Rau, P. Wust, Description and characterization of the novel hyperthermia- and thermoablation-system MFH 300 F for clinical magnetic fluid hyperthermia, Med. Phys. 31 (2004) 1444–1451.
[8] K. Maier-Hauff, R. Rothe, R. Scholz, U. Gneveckow, P. Wust, B. Thiesen, A. Feussner, A. von Deimling, N. Waldöfner, R. Felix R, A. Jordan, Intracranial thermotherapy using magnetic nanoparticles combined with external beam radiotherapy: results of a feasibility study on patients with glioblastoma multiforme, J. Neurooncol. 81 (2007) 53–60.
[9] M. Johannsen, U. Gneveckow, K. Taymoorian, B. Thiesen, N. Waldöfner, R. Scholz, K. Jung, A. Jordan, P. Wust, S.A. Loening, Morbidity and quality of life during thermotherapy using magnetic nanoparticles in locally recurrent prostate cancer: results of a prospective phase I trial, Int. J. Hyperth. 23 (2007) 315–323.
[10] B. Thiesen, A. Jordan, Clinical applications of magnetic nanoparticles for hyperthermia, Int. J. Hyperth. 24 (2008) 467–474.
[11] M. Johannsen, B. Thiesen, P. Wust, A. Jordan, Magnetic nanoparticle hyperthermia for prostate cancer, Int. J. Hyperth. 26 (2010) 790–795.
[12] K. Maier-Hauff, F. Ulrich, D. Nestler, H. Niehoff, P. Wust, B. Thiesen, H. Orawa, V. Budach, A. Jordan, Efficacy and safety of intratumoral thermotherapy using

magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme, J. Neurooncol. 103 (2011) 317–324.
[13] R.E. Rosensweig, Heating magnetic fluid with alternating magnetic field, J. Magn. Magn. Mater. 252 (2002) 370–374.
[14] W.J. Atkinson, I.A. Brezovich, D.P. Chakraborty, Usable frequencies in hyperthermia with thermal seeds, IEEE Trans. Biomed. Eng. 31 (1984) 70–75.
[15] I. Hilger, W. Andrä, R. Hergt, R. Hiergeist, H. Schubert, W.A. Kaiser, Electromagnetic heating of breast tumors in interventional radiology: in vitro and in vivo studies in human cadavers and mice, Radiology 218 (2001) 570–575.
[16] R. Hergt, R. Hiergeist, M. Zeisberger, D. Schulerb, U. Heyen, I. Hilger, W. A. Kaiser, Magnetic properties of bacterial magnetosomes as potential diagnostic and therapeutical tools, J. Magn. Magn. Mater. 293 (2005) 80–86.
[17] M. Levy, C. Wilhelm, J.-M. Siaugue, O. Horner, J.-C. Bacri, F. Gazeau, Magnetically induced hyperthermia: size-dependent heating power of γ-Fe2O3 nanoparticles, J. Phys.: Condens. Matter 20 (2008) 5 pp. (Art. no. 204133).
[18] B. Samanta, H. Yan, N.O. Fischer, J. Shi, D.J. Jerry, V.M. Rotello, Protein-passivated Fe_3O_4 nanoparticles: low toxicity and rapid heating for thermal therapy, J. Mater. Chem. 18 (2008) 1204–1208.
[19] B. Mehdaoui, A. Meffre, L.-M. Lacroix, J. Carrey, S. Lachaize, M. Respaud, M. Gougeon, B. Chaudret, Large specific absorption rates in the magnetic hyperthermia properties of metallic iron nanocubes, J. Magn. Magn. Mater. 322 (2010) L49–L52.
[20] D.-H. Kim, D.E. Nikles, C.S. Brazel, Synthesis and characterization of multifunctional chitosan-$MnFe_2O_4$ nanoparticles for magnetic hyperthermia and drug delivery, Materials 3 (2010) 4051–4065.
[21] A.P. Khandhar, R.M. Ferguson, K.M. Krishnan, Monodispersed magnetite nanoparticles optimized for magnetic fluid hyperthermia: implications in biological systems, J. Appl. Phys. 109 (2011) 07B310 (3 pp.).
[22] P.-E. Le Renard, R. Lortz, C. Senatore, J.-P. Rapin, F. Buchegger, A. Petri-Fink, H. Hofmann, E. Doelker, O. Jordan, Magnetic and in vitro heating properties of implants formed in situ from injectable formulations and containing superparamagnetic iron oxide nanoparticles (SPIONs) embedded in silica microparticles for magnetically induced local hyperthermia, J. Magn. Magn. Mater. 323 (2010) 1054–1063.
[23] A. Khandhar, R.M. Ferguson, J.A. Simon, K.M. Krishnan, Tailored magnetic nanoparticles for optimizing magnetic fluid hyperthermia, J. Biomed. Mater. Res. A 100 (2012) 728–737.
[24] P. Guardia, R. Di Corato, L. Lartigue, C. Wilhelm, A. Espinosa, M. Garcia-Hernandez, F. Gazeau, L. Manna, T. Pellegrino, Water-soluble iron oxide nanocubes with high values of specific absorption rate for cancer cell hyperthermia treatment, ACS Nano 6 (2012) 3080–3091.
[25] C. Martinez-Boubeta, K. Simeonidis, A. Makridis, M. Angelakeris, O. Iglesias, P. Guardia, A. Cabot, L. Yedra, S. Estrade, F. Peiro, Z. Saghi, P.A. Midgley, I. Conde-Lebora, D. Serantes, D. Baldomir, Learning from nature to improve the heat generation of iron-oxide nanoparticles for magnetic hyperthermia applications, Sci. Rep. 3 (2013) 1652 (8 pp.).
[26] B.E. Kashevskii, Orientational dynamics and energy dissipation in a liquid dispersion of single-domain ferroparticles on exposure to a linearly polarized field, J. Eng. Phys. Thermophys. 78 (2005) 293–303.
[27] N.A. Usov, Y.B. Grebenshchikov, Hysteresis loops of an assembly of superparamagnetic nanoparticles with uniaxial anisotropy, J. Appl. Phys. 106 (2009) 023917.
[28] B.E. Kashevsky, S.B. Kashevsky, I.V. Prokhorov, Dynamic magnetic hysteresis in a liquid suspension of acicular maghemite particles, Particuology 7 (2009) 451–458.
[29] K.A. Kekalo, B.E. Kashevsky, V.E. Agabekov, S.B. Kashevsky, I.V. Prokhorov, G.K. Zhavnerko, Influence of Co amount on the efficiency of energy absorption of Fe–Co ferrite nanoparticles, J. Magn. Magn. Mater. 321 (2009) 1514–1516.
[30] B.E. Kashevsky, YuP. Istomin, V.S. Ulashchik, S.B. Kashevsky, A.G. Pastushenko, I.V. Prokhorov, Low-frequency ferromagnetic hyperthermia is feasible, AIP Conf. Proc. 1311 (2010) 280–287.
[31] T.I. Terpinskaya, B.E. Kashevsky, S.B. Kashevsky, E.Yu Manina, V.S. Ulashchik, Antitumor effect of local ferromagnetic hyperthermia and cyclophosphamid at Erlich carcinom, Doclady NAN Belarusi (Reports of the NAS of Belarus), 57, 106–110 (in Russian).