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Biodegradation of magnetic nanoparticles evaluated from Mössbauer and magnetization measurements

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Abstract In order to extract a quantitative information about characteristics of the magnetic nanoparticles injected into a living organism it is necessary to define a model of the magnetic dynamics for fitting self-consistently the whole set of the experimental data, specifically, the evolution of Mössbauer spectral shape with temperature and external magnetic field as well as the magnetization curves. We have developed such a model and performed such an analysis of the temperature- and magnetic field-dependent spectra and magnetization curves of nanoparticles injected into mice. This allowed us to reliably evaluate changes in the characteristics of the residual particles and their chemical transformation to paramagnetic ferritin-like forms in different mouse organs as a function of time. Actually, the approach makes it possible to quantitatively characterize biodegradation and biotransformation of magnetic nanoparticles delivered in a body.

Keywords Magnetic nanoparticles · Magnetic dynamics · Biodegradation

1 Introduction

Among number of techniques used for characterizing structural, magnetic and thermodynamic properties of magnetic nanoparticles (NP) the Mössbauer spectroscopy is one of the most informative. Diversity of the temperature- and field-dependent Mössbauer absorption spectra of NP supplies the researcher with a large amount of information about physical characteristics inherent to NP [1]. At the same time the ^{57}Fe Mössbauer spectroscopy is widely used to study spin states, electronic and

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dynamical properties of iron-containing proteins (hemoglobin, myoglobin, ferritin, etc.) of animals and humans [2].

The serious difficulty in analysis the Mössbauer spectra of iron-containing NP introduced into a living organism is to decompose them surely into partial subspectra of exogenous iron in NP and endogenous iron in proteins [3]. The temperature evolution of the spectral shape for initial NP agrees qualitatively with the conventional behavior of the spectra of an ensemble of single-domain particles with magnetic anisotropy [4]. For the spectra of the mouse spleen after NP injection both a noticeable increase in the linewidths and an effective doublet of lines in their central parts are observed, the doublet parameters are typical for iron in ferritin-like proteins. The well known foundation for analysis the temperature-dependent Mössbauer spectra of NP is the multi-level relaxation model accounting their magnetic anisotropy and diffusion of uniform magnetization [4]. This model was successfully used to describe the temperature series of spectra of magnetic NP, including those delivered in a living organism [3]. Its natural generalization taking into account quadrupolar hyperfine interaction [5] makes accessible to analysis a new wide range of nanomaterials.

Another powerful extension of the standard multi-level relaxation model for describing magnetization measurements and Mössbauer spectra of NP in a weak static magnetic field was completely finished in recent work [6]. These results allowed us to offer a technique for diagnostics magnetic fine particles in different environments on the base of self-consistent treatment of a minimal set of experimental data, in the simplest realization including three Mössbauer spectra measured at different temperatures and in a magnetic field as well as the magnetization curve. This approach is enough to reveal the most important sample characteristics, such as NP size distribution and iron concentrations for all observed chemical phases. The advantages of the pointed scheme will be demonstrated in this paper by the example of biodegradation and biotransformation of magnetic fine particles into mice organism.

2 Samples and experiment

We have used ferrofluid "fluidMAG-ARA-250" (Chemicell Gmbh, Germany). The suspension of the magnetic nanoparticles was injected into mice. On the expiry of fixed intervals of time the mice were killed, their organs removed and lyophilized. The dried initial ferrofluid and lyophilized mouse organs were then triturated and the powder samples were prepared for Mössbauer studies. The ^{57}Fe gamma-resonant absorption spectra of the samples were measured at liquid nitrogen and room temperatures as well as in the magnetic field of the intensity 3.4 kOe. Magnetization curves for the samples were taken in a field up to 5 kOe. The Mössbauer spectra and magnetization curves for initial nanoparticles as well as mouse liver two days after NP injection are shown in Fig. 1.

3 Relaxation models for describing the experimental data

The multi-level relaxation model is based on the quantum-mechanical description of NP with the total spin S and its $2S+1$ possible projections on to the easy

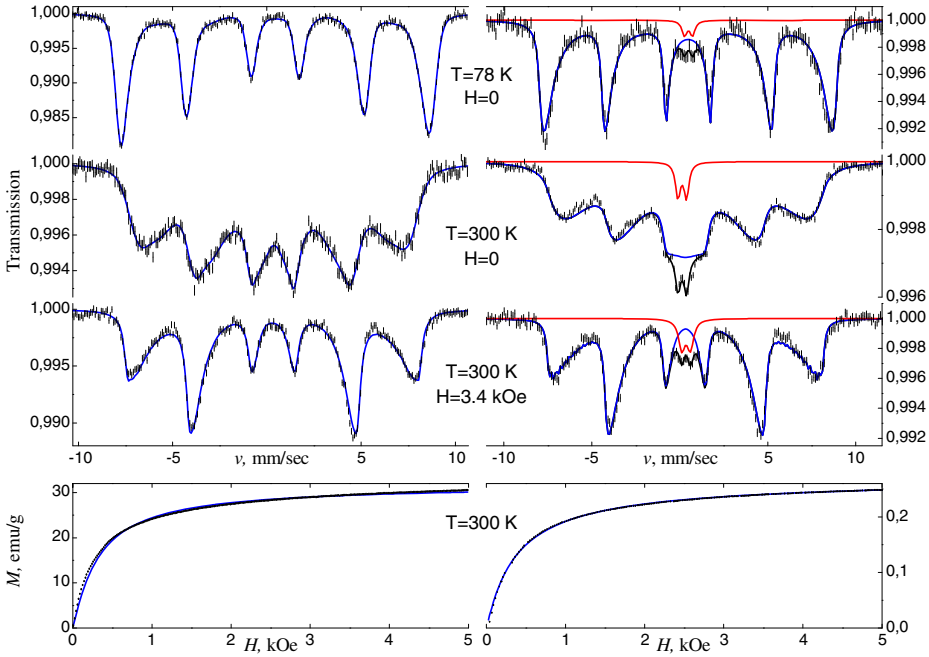

Fig. 1 ^{57}Fe Mössbauer spectra and magnetization curves for initial nanoparticles (*left panel*) and a mouse liver 2 days after nanoparticles injection (*right panel*). The results of simultaneous treating are represented by *solid lines*. These are partial spectra of nanoparticles (*blue*), ferritin-like contribution (*red*) as well as the resulting spectra and magnetization curves

magnetization axis. The intensity of random transitions between these energy levels is specified by phenomenological diffusion constant D [4]. Calculations of the Mössbauer spectra within the model can be performed in terms of the stochastic approach which leads to the following expression for the absorption spectrum [1, 4]:

$$\sigma(\omega) \propto -\mathrm{Im} \sum_{\alpha} |C_{\alpha}|^2 \langle W| \widehat{A}_{\alpha}^{-1}(\omega) |1\rangle.$$

Here $\alpha = (m_{\mathrm{e}}, m_{\mathrm{g}})$ specifies hyperfine transition with the nuclear spin projections m_{e} and m_{g} onto the $\mathbf{H}_{\mathrm{hf}}$ direction, C_{α} is the intensity of α-th transition, $\langle W|$ is the row vector of the equilibrium occupation probabilities of the stochastic states, $|1\rangle$ is a column vector with all components equal to unity. The operator $\widehat{A}_{\alpha}(\omega)$ is defined by the diagonal matrix of hyperfine interaction and the tree-diagonal relaxation matrix.

The Mössbauer spectra of nanoparticles in the presence of quadrupolar interaction can be described within a similar stochastic approach with operators of more general type [5]:

$$\sigma(\omega) \propto -\mathrm{Im} \int \sin\Theta d\Theta \sum_{\eta} \mathrm{Sp}\left(\widehat{V}_{\eta} \left\langle \widehat{\mathbf{W}} \right| \widehat{\mathbf{A}}^{-1}(\omega, \Theta) \left| \widehat{\mathbf{1}} \right\rangle \widehat{V}_{\eta}^{+}\right).$$

Here Θ is the angle between the principal direction of electric field gradient and the particle's easy axis, $\left\langle \widehat{\mathbf{W}} \right| = \langle W| \otimes \widehat{\mathbf{1}}_n$, $\left| \widehat{\mathbf{1}} \right\rangle = |1\rangle \otimes \widehat{\mathbf{1}}_n$, where $\widehat{\mathbf{1}}_n$ is the identity operator in the space of nuclear variables $(m_{\mathrm{e}}, m_{\mathrm{g}})$, $\widehat{V}_{\eta}$ is the operator for the interaction of the

Table 1 Characteristics of the initial NP and the samples of the mice liver for 2 hours (2h), 2 days (2d), 2 weeks (2w) and 2 months (2m) after NP injection: the mean particle diameter $\overline{d}$, Gaussian width of particle's size distribution $\sigma_d/\overline{d}$, the ^{57}Fe concentration for NP n_{NP} and iron-contain proteins n_{pr} (in brackets we point errors in the least significant digit)

	NP	2h	2d	2w	2m
$\overline{d}$, nm	10.9 (4)	7.0 (4)	6.8 (5)	6.8 (4)	6.3 (6)
$\sigma_d/\overline{d}$	0.21 (3)	0.8 (1)	0.7 (1)	0.7 (1)	0.9 (1)
n_{NP}, 10^{18} cm^{-3}	6.3 (4)	5.8 (5)	4.7 (4)	2.1 (3)	1.6 (4)
n_{pr}, 10^{18} cm^{-3}		0.07 (2)	0.08 (1)	0.14 (2)	0.63 (4)

gamma-quantum with a given polarization η and $\widehat{\mathbf{A}}(\omega, \Theta)$ is a superoperator defined by the Liouville operators of hyperfine interaction for each stochastic state and the relaxation matrix.

The description of the magnetization curves can be performed by solving the eigenvalue problem for Hamiltonian of NP with magnetic anisotropy in the external magnetic field, and the spectrum in this situation may be calculated by the last formulae, where Θ for this case is the angle between the direction of the field and easy axis, and $\widehat{\mathbf{A}}(\omega, \Theta)$ depends explicitly from solution of the eigenvalue problem [6].

4 Results

Using the formalism described above we have managed a least-squares fitting procedure for consistent treating the set of experimental spectra and magnetization curve for the initial NP as well as the samples of mouse liver at different stages of biodegradation (Fig. 1 represents examples of the analysis). This allows us to numerically characterize the metabolic processes in the living organism by the estimates of particles sizes as well as iron content for both exogenous and endogenous chemical phases as a function of time. The last characteristics were calculated from the partial spectral areas and recoilless fractions evaluated within the Debye model. The results of this analysis are shown in Table 1.

This Table allows the researcher to trace changes in NP characteristics during their stay in the living organism. First of all, an essential decrease in mean value of NP diameters even two hours after injection strikes the eye. With that it is necessary to notice very significant increase in the relative width of the particles distribution over diameters. It means, that NP with different sizes up to the size of NP in the initial ferrofluid appear after transformation in the living tissues. Parameters of the distribution depend on time only slightly, but total number of the fine particles is reduced continuously, what is obvious from change in the resonance isotope concentration relating to iron in NP. At the same time the ^{57}Fe concentration in the ferritin grows steadily, what points to long-term metabolic processes, agreed upon the embedding of exogenous iron in the organism and lasts for at least two months. The comparison of iron amounts in extrinsic and intrinsic chemical phases shows that there are two stages in NP biodegradation: the first, relatively short one from the injection instant to approximately two weeks after it, when exclusion from the body the foreign impurities prevails over their conversion to animal proteins, and the next one, when iron decrease in NP is the same as its increase in ferritin, so there

is no noticeable removal of particles stuff out of the organism. Thus, essential part of foreign iron accumulates in the mouse liver and transforms gradually to the form of iron-contain proteins in times comparable with the animal lifetime.

5 Conclusions

Thus, several generalizations of multilevel relaxation model were developed. They underlie the analytical technique for diagnostics magnetic nanomaterials in different environments realized on the basis of self-consistent treatment of a large set of experimental data. We demonstrated that only three Mössbauer spectra taken at different temperatures and in a magnetic field combined with the magnetization curve are enough to extract the most important information about metabolism of magnetic NP in a living organism.

The further improvement of the stated approach for precise diagnostics of nanomagnets requires development of the models specific for materials of various magnetic nature (ferro-, antiferro- and ferrimagnets). Though Mössbauer spectral shapes for particles of different magnetic types often are similar the mechanisms of their formation are essentially different and the exact spectrum calculation needs its own scheme for each sort of magnetic structure. The first steps in implementation of this program were published in [7]. The work is in progress.

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