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Study of interparticle interaction in conjugates of magnetic nanoparticles injected into mice

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Abstract In this work the first fast stage of the biodegradation *in vivo* of magnetic ferrofluid was investigated. The appearance of a paramagnetic doublet was observed in Mössbauer spectra of mouse liver within 2 h after intravenous injection of the ferrofluid. It was shown that nanosized superparamagnetic particles were combined into groups in the initial magnetic beads of the ferrofluid and were connected inside each group by magnetic dipole interaction. It was found that the appearance of a paramagnetic doublet in the spectrum of mouse liver is caused by the decrease of the magneto-dipole interaction between the superparamagnetic nanoparticles.

Keywords Mössbauer spectroscopy · Magnetic nanoparticles · Biodegradation · Interparticle interaction

1 Introduction

Magnetic particles based on iron oxide magnetite Fe_3O_4 and maghemite γ-Fe_2O_3 are considered to be the most promising materials for targeted drug delivery. Their popularity is due to an assumption of their good bio-compatibility. Human organs contain a lot of endogenous iron, for example, in liver ferritin or in gem-containing proteins, such as blood hemoglobin. On the other hand, nanoparticles may have greater toxicity than iron in a molecular form. Therefore, a study of mechanisms of their natural degradation and removal is vital for the implementation of the method into clinical practice.

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Mössbauer spectroscopy is one of the methods for the investigation of the metabolism of superparamagnetic particles *in vivo* [1, 2]. This method is insensitive to the majority of organic atoms (carbon, hydrogen, oxygen, nitrogen, etc.) and provides a means of segregation of spectral contributions from exogenous iron contained in particles and endogenous iron contained in ferritin or hemoglobin. Furthermore, Mössbauer spectroscopy regards a set of nanoparticles as a system of interacting single domain magnetic clusters and gives information about magnetic interactions between particles [3].

It was shown using the Mössbauer spectroscopy of mouse's organs [1, 2] that after the injection of magnetite nanoparticles in the form of ferrofluid into the tail vein of mice that they are accumulated mainly in their liver and spleen. The control measurements of mouse's organs without injection did not show a significant concentration of iron. In addition, the shape of the Mössbauer spectrum of the mouse liver after injection differs significantly from the original spectrum of the injected nanoparticles. In particular, along with the magnetically split component of the liver's spectrum, corresponding to the injected particles, an additional paramagnetic doublet was observed which is typical for non-magnetic forms of iron. It indicates a degradation processes of the injected particles in the mice body. The measurements showed that qualitative changing of the spectra occurs within a few hours after injection. Such rapid transformation cannot only be explained by the slow biodegradation processes only.

In [3] we observed a similar behavior of Mössbauer spectra of hematite nanoparticles. In that work samples of superparamagnetic particles were prepared by precipitation of a suspension of the powder in ethanol with small addition of ethanol-soluble glue. Samples demonstrated classical superparamagnetic behavior with temperature. But the blocking temperature of the superparamagnetic transition proved to be different for samples with different amounts of glue. This transformation was caused by changing of the magnetic interparticle interaction.

Similar processes can take place in a live body due to interaction of magnetic nanoparticles with the biochemical environment. This hypothesis can be tested in in vitro experiments on the destruction of intrinsic magnetic beads chemically or by heat and the dissolution of the resulting nanoparticles in analogy with [3].

2 Experiment

We used commercially available magnetite nanoparticles enclosed in magnetic beads and conjugated with a polysaccharide matrix in form of ferrofluid ARA250 produced by Chemicell GmbH (Germany) [4].

17 mg of ferrofluid was injected intravenously into a mouse. The mouse was sacrificed in 2 h after the injection of nanoparticles. The mouse liver was extracted and lyophilized. The Mössbauer spectrum of the mouse liver was measured on a conventional gamma-resonance spectrometer with a ^{57}Co (Rh) source at a temperature of 300 K (Fig. 1d). Another sample of ferrofluid was dried and 12 mg of dry powder was dissolved in ethanol with the addition of the binding polymer (ethanol dissolvable phenol-formaldehyde resin and polyvinyl butyral). In another experiment the polysaccharide has been removed by heating the sample to high temperature (400°C). Mössbauer spectra of the initial nanobeads, the nanobeads dissolved in

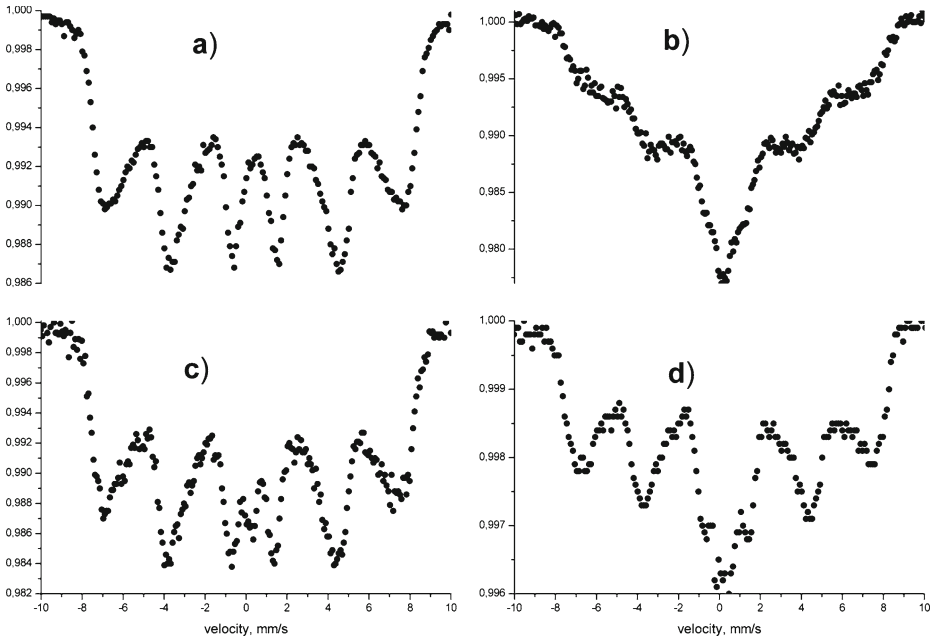

Fig. 1 Mössbauer spectra of ^{57}Fe nuclei in magnetite nanoparticles ARA250 in **a** initial bead, **b** the bead after its partial destruction in vitro in alcohol with addition of a the binding polymer, **c** the bead after its partial destruction by heating and **d** mice liver in 2 h after injection *in vivo* of the nanoparticles

ethanol with the polymer addition and the nanobeads after heat destruction were measured at temperature 300 K (Fig. 1a, b, and c).

3 Results and discussions

The Mössbauer spectrum of initial nanobeads (Fig. 1a) does not contain any sign of the paramagnetic doublet. In accordance with our assumption the superparamagnetic particles in the magnetic bead are divided into groups and connected inside each group by magnetic dipole interaction. After heating the sample of initial nanobeads at 400°C the polysaccharide matrix was destroyed and part of the particles left their magneto-coupled groups and have acquired superparamagnetic properties (Fig. 1c). After dissolving in ethanol the superparamagnetic particles separate as consequence of polysaccharide shell partial dissolution. In this case, the binding polymer prevents aggregation of the particles increasing the effective distance between them. In this case, the interaction between separated particles disappears also and the Mössbauer spectrum demonstrates a paramagnetic doublet (Fig. 1b).

In the case of biodegradation *in vivo*, magnetic beads demonstrate similar behavior: in a live body the polysaccharide shell of beads was destroyed, the superparamagnetic particles were separated and the interaction between them disappeared.

As a consequence, the generation of a paramagnetic doublet in the spectrum of the mouse liver was observed (Fig. 1d).

All these procedures give rise to the generation of the same paramagnetic doublet in the spectra. Hence, our assumption was proven experimentally.

Thus, the appearance of the paramagnetic doublet in the spectrum of mouse liver is a consequence of decreasing of magneto-dipole interaction.

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