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Research of NMR relaxation efficiency of composite magnetic nanoparticles for biomedical diagnostics

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Abstract –Results of proton NMR relaxation measurements in aqueous solutions of iron oxide composite magnetic nanoparticles are discussed. It is shown that their r_2 relaxation efficiency coefficient is much higher than r_1 relaxation efficiency coefficient and depends on the composition, method of MNPs synthesis. It allows to use this parameter to assess the stability of MNPs in aqueous solutions and estimate their aggregation behavior.

Key words – NMR relaxation, magnetic nanoparticles (MNPs), magnetic resonance.

I. INTRODUCTION

Magnetic nanoparticles (MNPs) is currently finding increasingly wide application in medicine and biology for diagnostics, magnetic separation, hyperthermia, drug delivery, etc. [1]. Particular interest is aroused by use of MNPs in magnetic resonance (MR) diagnostics as in vivo [2] and in vitro [3]. The magnetic nanoparticles should have certain magnetic characteristics, to be stable (have low aggregation capacity), biocompatible, non-toxic, have the ability of functionalization to interact or bind with specific biological objects. Composite MNPs and functional systems based on them are promise materials for the MR-diagnostics. One of the most common methods for the synthesis of iron oxide MNPs is the co-precipitation method. Due to the high sensitivity to different parameters (nature of the precipitant, concentration of reagents, temperature of synthesis, pH of the reaction medium, etc.), it allows to widely vary the size and properties of the resulting nanoparticles.

The aim of this paper is research the NMR relaxation properties of protons in aqueous solutions of composite nanoparticles based on solid solutions of zinc ferrites, magnesium and iron (magnetite).

II. EXPERIMENTAL METHODS

Composite MNPs substituted with zinc and/or magnesium magnetite were obtained by co-precipitation method from solutions of the corresponding salts using different precipitants – NaOH and Na_2CO_3 . The solution taken in stoichiometric ratio of initial reagents at room temperature was introduced into the solution of precipitator, taken with some excess, and stood for 1 h with intensive mixing until the completion of

crystallization processes. The pH of the system during the reaction was maintained at ~ 11 , due to which it is managed to achieve full deprotonation of aqua complexes ions of all metals, but to prevent the formation of water-soluble hydroxocomplexes. In the event carbonate co-precipitation, the reaction mixture was rapidly heated to a temperature of 90°C , after that heating was stopped. To obtain colloidal solutions of nanoparticles the ultrasonic bath (Sapfir, Russia) and submersible ultrasonic disperser (USG-13-0,1/22, Russia) have been used. Magnetic nanoparticles were functionalized by polyelectrolyte shell (polydiallyldimethylammonium chloride-PDDA).

X-ray patterns of powdered samples were recorded on a diffractometer DRON-2.0 (Co $K\alpha$ -radiation) in the range $2\theta = 20-90^\circ$. The size and morphology of particles were examined using scanning and transmission electron microscopy by LEO 906E, JOEL EM100 CX and LEO 1420 microscopes. Measurements of magnetic characteristics of MNPs were performed using Cryogen Free Measurement System by Cryogenic Ltd. ($T = (7 - 300) \text{ K}$, $B_{\text{max}} = 18 \text{ T}$).

The NMR measurements were made using NMR relaxometer (Spin Track, Russia) with the magnitude of the magnetic field of 0.33 T. The resonance frequency for protons - 14 MHz. To measure T_1 spin-lattice relaxation time the "inversion-recovery" 180° - τ - 90° pulse sequence was used (the duration of 90° pulse - 2.6 μs ; the duration of the 180° pulse - 5.2 μs). To measure T_2 spin-spin relaxation time the Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence was used (the duration of the 90° pulse - 2.6 μs ; the duration of the 180° pulse - 5.2 μs).

III. RESULTS AND DISCUSSION

The results of x-ray phase analysis (XRA) confirm the formation of single-phase crystalline compounds with a spinel structure when alkaline or carbonate co-precipitation methods were used. According to electron microscopy data, the average size of the nanoparticles is $\sim 10 \text{ nm}$ for hydroxide precipitant, and $\sim 20 \text{ nm}$ for sodium carbonate precipitant. All investigated composite MNPs show superparamagnetic behavior with no coercivity and no remanent magnetization at room temperature.

An aqueous suspensions of unmodified nanoparticles are characterized by multimodal size distribution with a high polydispersity index ($PDI > 0.4$) and sediment instability. A stable suspensions with a narrow size distribution ($PDI < 0.250$) were obtained by powders dispersing of ferrites solid solutions with PDDA. The size of particles covered with a layer of PDDA in distilled water practically does not change within 45 days.

According to the results of NMR relaxation measurements dependencies of longitudinal R_1 and transverse R_2 nuclear magnetic relaxation rates of water protons on the concentration of composite MNPs were obtained. For the most of samples the concentration dependencies of the relaxation rates correspond to a linear dependence of the general form

$R_i = r_i \cdot C + A$, where C is the concentration of MNPs, expressed in mmol, A is a constant determined by the relaxation rate of water protons in the absence of MNPs, r_i is the relaxivity (relaxation efficiency coefficient). The analysis of concentration dependencies allows to determine the relaxation efficiency coefficient r_i as the derivative of $R_i = f(C)$ function at this point and in the case of linear dependence to calculate the angular coefficient as the ratio: $r_i = (1/C \cdot \Delta R_i)$ (mmol \cdot s/l) $^{-1}$. The analysis of relaxation efficiency of the studied samples shows that:

- r_1 and r_2 relaxation efficiency coefficients for the MNP samples, obtained by co-precipitation with carbonate, higher than the relaxation efficiency coefficients for MNP samples, obtained by co-precipitation with alkali (without heating);
- r_2 relaxation efficiency coefficient is much higher than the r_1 relaxation efficiency coefficient for all MNP samples, regardless of synthesis, which confirms the fact that the investigated MNPs are negative contrast agents in MRI [2] ;
- r_2 relaxation efficiency coefficient for the samples obtained by co-precipitation with carbonate is lower for the composite MNPs with Zn in the structure.

Concentration dependencies of the R_2 transverse nuclear magnetic relaxation rates of water protons for some MNP samples have been nonlinear. The analysis of these dependencies shows a decrease in the relaxation efficiency by increasing the MNP concentration in the solution. It indicates instability of these MNPs in aqueous solutions and their aggregation ability to form clusters when the concentration of MNPs in the solution increases. This effect of MNP clustering was observed in these samples visually and increased with increasing residence time of the sample in the magnetic field of the NMR relaxometer. Similar results were obtained earlier in the NMR relaxation study of protons in aqueous solutions of Fe_3O_4/SiO_2 nanoparticles [4].

IV. CONCLUSIONS

The research of the protons NMR relaxation in aqueous solutions of iron oxide composite MNPs show that their r_2 relaxation efficiency is much higher than r_1 relaxation efficiency and depends on the composition, method of MNP synthesis. It allows to use this parameter to assess the stability of MNPs in aqueous solutions and estimate their aggregation behavior.

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