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Diamond nanoparticles as a contrast agent for MRI

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The efficiency of detonation nanodiamonds with a surface modified with manganese (ND-Mn) and gadolinium (ND-Gd) ions in application as contrast agents for magnetic resonance imaging is studied. The use of polyvinylpyrrolidone as a stabilizing agent prevents the agglomeration of particles in saline solution. According to the method of nuclear magnetic resonance, the ND-Mn and ND-Gd particles in saline hydrosols increase the rates of spin-lattice and spin-spin relaxation of protons in the hydrosol.

Keywords: magnetic resonance imaging, nuclear magnetic resonance, detonation nanodiamonds, gadolinium, manganese.

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Introduction

The improvement of the image contrast is one of the urgent tasks of magnetic resonance imaging (MRI). A common way to solve this problem is to use contrast agents, which are chelated complexes of paramagnetic ions, shortening the spin-lattice (T_1) and spin-spin (T_2) relaxation times of protons (^{1}H) of water, and thereby contrast-enhancing magnetic resonance images [1–9]. Compounds based on gadolinium ions (Gd^{3+}, magnetic moment $7.9\,\mu_B$, μ_B — Bohr magneton) such as „Dotarem©", „Gadovist©", „Magnevist©" are one of the most popular contrast agents in MRI diagnostics now.

Nanometer-sized diamond particles — nanodiamonds (ND) are getting an increasingly prominent place in the search for new contrast agents [10–12]. Interest in the use of ND as a basis for the synthesis of contrast agents is determined by the biocompatibility, low toxicity and chemical inertness of diamond. Several reviews and publications have been devoted to biomedical studies of ND [13–18]. Some papers describe the potential hazards and the effect of the surface functionalization of the ND obtained by different synthesis methods [19,20]. Data on the toxicity of ND are ambiguous and depend on the method of obtaining diamond nanoparticles, its purity, functional composition, particle sizes, etc. [15,21]. The agglomeration of ND particles is a serious problem for medical applications. In particular, the main cause of cytotoxicity of 4–5 nm ND is its high tendency to form agglomerates in cellular media [20]. Therefore, it is crucial to promote the stability of colloidal solutions of nanodiamonds.

In essence, it has been necessary to perform two main tasks for creating such a „diamond contrast agent" to modify diamond nanoparticles with paramagnetic ions and obtain a hydrosol ND stable in a saline solution suitable for medical use. However, agglomeration of ND in aqueous salt solutions, including saline, has long been an obstacle for the use of ND in medical studies.

The principal possibility of using diamond nanoparticles doped with iron ions in MRI has been demonstrated in publications [22,23]. It has been shown that such particles with average size of 100 nm increase the contrast of T_2-weighted images, the stability of the hydrosol over time has not been studied.

Another approach to obtaining of the „diamond contrast agent", based on the binding of the chelate complex Gd^{3+} with the surface groups of a diamond nanoparticle (ND-Gd), has been proposed in the papers [24,25]. A contrast agent derivative containing Gd^{3+} has been used as a chelate complex of Gd^{3+}. Measurements of the magnetic relaxation of water protons with the addition of ND-Gd have demonstrated a significant decrease of the value of T_1 protons. There are also known studies in which Gd^{3+} ions have been attached to a chelate compound bound to the surface of ND. Diethylenetriamine pentacetic acid (DTPA) [26,27], tenoyltrifluoroacetone (TTA) [28], polyglycerin (PG) [29–31] and gadoteric acid (DOTA) have been used as chelating compounds [32]. In all cases, the ND-Gd synthesized using the Gd(III) chelates demonstrate a significant increase in contrast of T_1-weighted images. Clinical studies conducted on laboratory mice [25,28] have showed that ND particles bound with Gd chelate complexes are biocompatible.

The presence of carboxyl groups on the surface of a diamond nanoparticle makes it possible to modify the surface with gadolinium ions through the ion exchange reaction between protons of carboxyl groups on the surface of ND and gadolinium ions as shown in Ref. [33,34]. A significant decrease in both T_1 and T_2 protons [35] was demonstrated in the case of such modification of the ND surface, which improved the contrast of the obtained MR images.

Despite the use of gadolinium ion chelate complexes in MRI diagnostics, there remains a potential hazard of its release in the body, therefore, new contrast agents with less toxic ions are being developed and manganese ions (Mn^{2+}, magnetic moment $5.92\,\mu_B$) can be considered as a component of such contrast agents. Mn^{2+} is less toxic, as it is a part of living cells, and is a valuable agent for both T_1- and T_2-visualization [2,36–39].

Studies of „diamond contrast agents" containing manganese ions are conducted by three scientific groups [40–44] that have demonstrated a decrease of T_1 and T_2 ^1H and increased contrast of T_1- and T_2-weighted images.

Thus, in publication [40], the authors have demonstrated the doping of ND (average particle size 100 nm) with manganese ions by ion implantation and, after mixing with bovine albumin, obtained a hydrosol stable in saline solution [41]. Manganese ions were bound to the surface of a diamond particle (ND-Mn) in Ref. [42] using ethylenediaminetetraacetic acid (EDTA) and DOTA as chelating agents. It has been found that the formation of such chelate complexes in an aqueous medium leads to agglomeration of particles up to 60−80 nm, which requires further study of the behavior of such particles in saline solution. It should be noted here that particle agglomeration in an aqueous medium is not observed in case of modification of ND surface with Mn^{2+} by the ion exchange [43,44].

The use of Gd-containing contrast agents in MRI could lead to a partly accumulation of the substance in the body for a long time that causes a large number of side effects. The developed „diamond contrast agents" ND-Mn and ND-Gd stabilized with polyvinylpyrrolidone (PVP) in saline solution allow the injection of a lower concentration of paramagnetic ions in comparison with commercial contrast agents.

The objective of the study the results of which are presented in this paper is to examine the effect of paramagnetic ions (Mn^{2+}, Gd^{3+}) on the magnetic relaxation of protons in aqueous salt solutions of diamond nanoparticles with a surface modified with gadolinium ions (ND-Gd) and manganese ions (ND-Mn).

1. Experimental part

1.1. Materials

A sample of a disaggregated nanodiamond was prepared from a commercial detonation ND produced by SKTB „Technolog" (St. Petersburg, Russia) by chemical purification followed by disaggregation [45]. A hydrosol of highly purified disaggregated particles with an average size of 4−5 nm was used as the starting material.

Chemical reagents $Gd(NO_3)_3 \cdot 6H_2O$ (LLC „Rare Metals Plant", Koltsovo, Russia) and $MnSO_4 \cdot 5H_2O$ (LLC „JSC REAKHIM", Moscow, Russia) qualified as „chem. pure.", were obtained by an industrial method and used without additional purification. Aqueous 0.01 M solutions of metal salts were obtained by dissolving the hydrates in demineralized water.

PVP powder K-17 was purchased from „Yuking Water Soluble Materials Tech Co. Ltd." (Shanghai, China) and was used for the preparation of aqueous solutions.

Aqueous salt solutions were prepared by dissolving NaCl („high purity") produced by LLC „JSC REAKHIM" (Moscow, Russia) in demineralized water.

Demineralized water was obtained using the laboratory equipment „arium®advance" produced by „Sartorius Lab Instruments GmbH & Co. KG" (Göttingen), Germany).

1.2. Production of ND particles with surface modified with paramagnetic ions

1.2.1. Hydrosol

The ND surface was modified with manganese ions (ND-Mn) and gadolinium ions (ND-Gd) by mixing a hydrosol ND with a solution of salt $MnSO_4$ and $Gd(NO_3)_3$, respectively [33,43]. The obtained solution was subjected to ultrasonic treatment followed by centrifugation and decantation for removal of unreacted metal ions. The hydrosols were stepwise diluted for obtaining a series of samples of ND-Mn and ND-Gd.

1.2.2. Aqueous salt solutions

It was first necessary to create a PVP shell around the particles of ND-Mn and ND-Gd for obtaining stable aqueous-salt solutions. The method of obtaining such complexes is described in Ref. [34,36]. PVP solution was added to serially diluted ND-Mn and ND-Gd hydrosols. It is assumed that PVP is bound to the ND particle by forming a hydrogen bond between the PVP carbonyl groups and carboxyl groups on the surface of the ND particles. Then a NaCl solution was added to the resulting hydrosols containing ND-Mn or ND-Gd and PVP.

Thus, a series of samples of aqueous (ND-Mn; ND-Gd) and aqueous-salt (ND-Mn-PVP; ND-Gd-PVP) colloidal solutions was obtained by serial dilution. The range of hydrosol concentrations in the ND-Mn and ND-Mn-PVP series was 0.370−1.20 wt%, 0.1−0.39 wt% in the series ND-Gd and ND-Gd-PVP.

1.3. Research methods

1.3.1. Measurements of electrical conductivity and electrophoretic mobility of ND particles by titration

Measurements of electrical conductivity and electrophoretic mobility were carried out on the Zetasizer Nano ZS analyzer (Malvern Panalytical, UK) by laser Doppler electrophoresis. The values of the electrokinetic potential (ξ-potential) were calculated using the Smolukhovsky equation. The molecular weight of one ND particle was taken to be 96000 g/mol for calculating the content of metal atoms per ND particle.

1.3.2. Particle size measurement

Particle size was measured by Zetasizer Nano ZS analyzer (Malvern Panalytical, UK) using dynamic light scattering (DLS).

1.3.3. Energy dispersive X-ray analysis

The elemental composition of the powders was analyzed using TESCAN VEGA 3 SBH scanning electron microscope (TESCANBRNO, Czech Republic) with energy dispersion analyzer Advanced Aztec Energy (Oxford Instruments, England).

1.3.4. Nuclear magnetic resonance (NMR) method

The nuclear spin-lattice (T_1) and spin-spin (T_2) relaxation of protons (^{1}H) was measured at temperatures of 295 and 310 K using a solid-state pulsed NMR spectrometer (Tecmag Inc., Houston, TX) with a superconducting magnet (Oxford Instruments) in a magnetic field of $B_0 = 8.0$ T.

As is known, the relaxivities (r_1 and r_2) are the main characteristics of contrast agents and determine the intensity of the dipole-dipole interaction between protons and paramagnetic ions, while the contrast of MRI images increases with values of r_1 and r_2 [4].

The values of the relaxivities (r_1) and (r_2) were determined graphically from the slope of the straight lines on the dependences of the relaxation rates ($1/T_1$, $1/T_2$) on the concentration of paramagnetic ions. The relaxation times T_1 and T_2 were determined according to the methods in Ref. [33,35,44].

2. Results and discussion

2.1. Measurements of electrical conductivity and electrophoretic mobility of ND particles by titration

At the first stage of synthesis, the amount of metal ions bound to the surface of the ND was estimated using conductometric titration and measurement of electrophoretic mobility. The basic principle of the method is to measure the electrical conductivity and determine ξ-potential of the analyzed solution (ND) during gradual adding of a salt solution ($MnSO_4$, $Gd(NO_3)_3$) (Fig. 1).

The dependence of the specific electrical conductivity of the hydrosol on the volume of the added salt solution is plotted using the obtained data. The addition of a salt solution to the hydrosol leads to an increase in the electrical conductivity of the colloidal solution. This is associated with the release of H^+ into the reaction mixture as a result of the ion exchange reaction with metal ions, as can be seen in the potentiometric titration curves shown in Fig. 2. The rate of increase of electrical conductivity significantly drops at the end of the reaction, since only ions of the added solution contribute to the electrical conductivity. The equivalence point (EP) has been determined at the intersection point of the linear sections of the conductometric titration curve.

The stability of the hydrosol is determined by the formation of a double electric layer surrounding each ND particle, and is characterized by an absolute value of ξ-potential. Double electric layer is caused by surface carboxyl groups dissociation, which leads to a negative charge of the ND surface due to the formation of carboxylate ions.

As can be seen in the curves, the addition of cations neutralizes the negative charge of the ND particle as a result of interaction with carboxyl groups on the surface of the diamond particle. An isoelectric point ($\xi = 0$ mV) is observed in case of the addition of the Gd^{3+} ion, i.e. all carboxyl groups are completely neutralized at a certain volume of the gadolinium nitrate solution added. Only the critical value of the ξ-potential is observed in the case of the Mn^{2+}ion [47].

It was found by titrimetric analysis methods that the number of Mn^{2+} and Gd^{3+} ions bound with the maximum possible number of carboxyl groups on the surface of the ND particle is $\sim 6-7$ manganese ions and $\sim 7-8$ gadolinium ions, respectively. Modification of the surface of ND with a smaller number of metal ions makes it possible to obtain stable hydrosols with ξ-potential absolute value of ≥ 30 mV. The addition of an amount of metal ions exceeding the value of EP leads to agglomeration of particles and subsequent sedimentation in hydrosol.

Therefore, the following initial ratio of components in the solution was chosen for obtaining stable colloidal solutions: $Gd^{3+} : ND = 6$, $Mn^{2+}: ND = 3$.

2.2. Energy dispersive X-ray analysis

ND-Mn and ND-Gd hydrosols were dried in a rotary evaporator under vacuum for obtaining powders. The elemental composition of ND-Mn and ND-Gd powders is provided in Table. 1 and in Fig. 3.

2.3. Particle size measurement

The hydrosols provided in Table 2 were selected for DLS measurements in each series of samples.

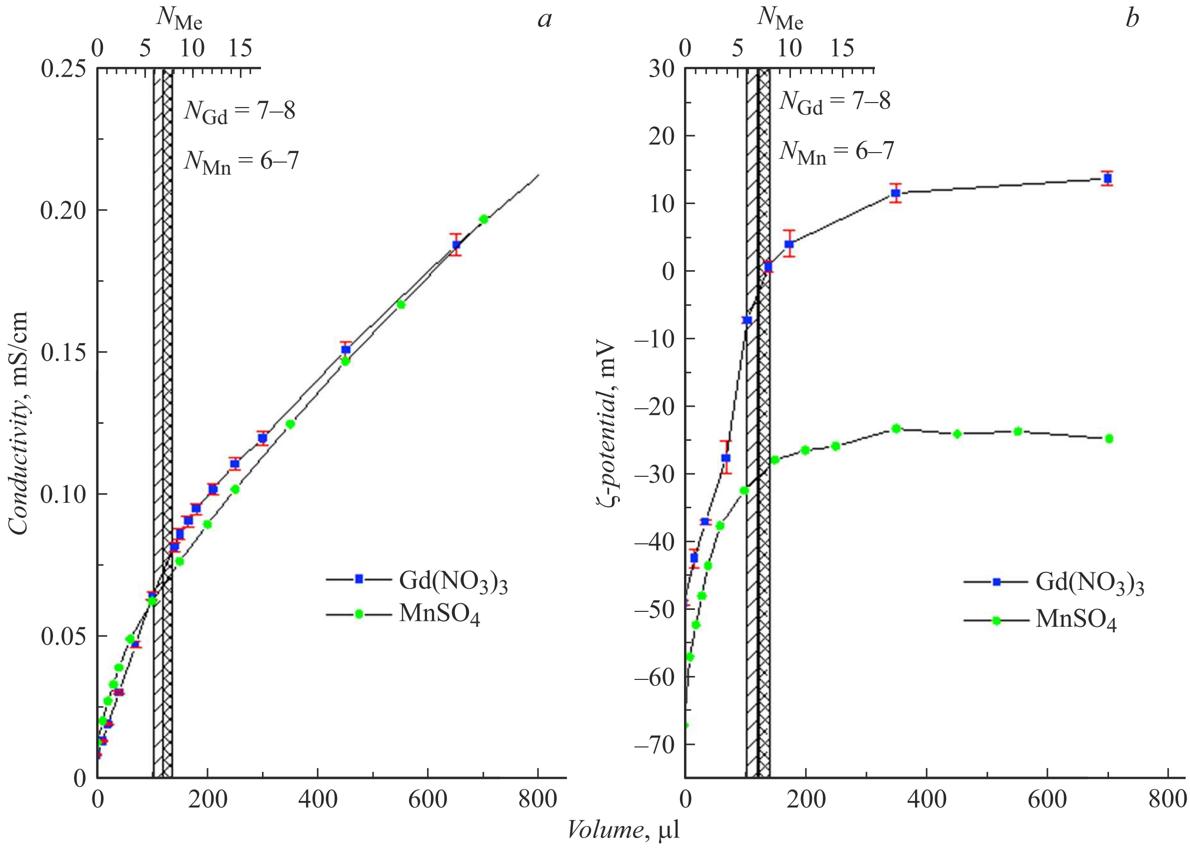

Figure 1. Conductometric titration curve (*a*) of hydrosols ND with aqueous solutions of metal salts and dependence of ξ-potential on volume of metal salt solution (*b*).

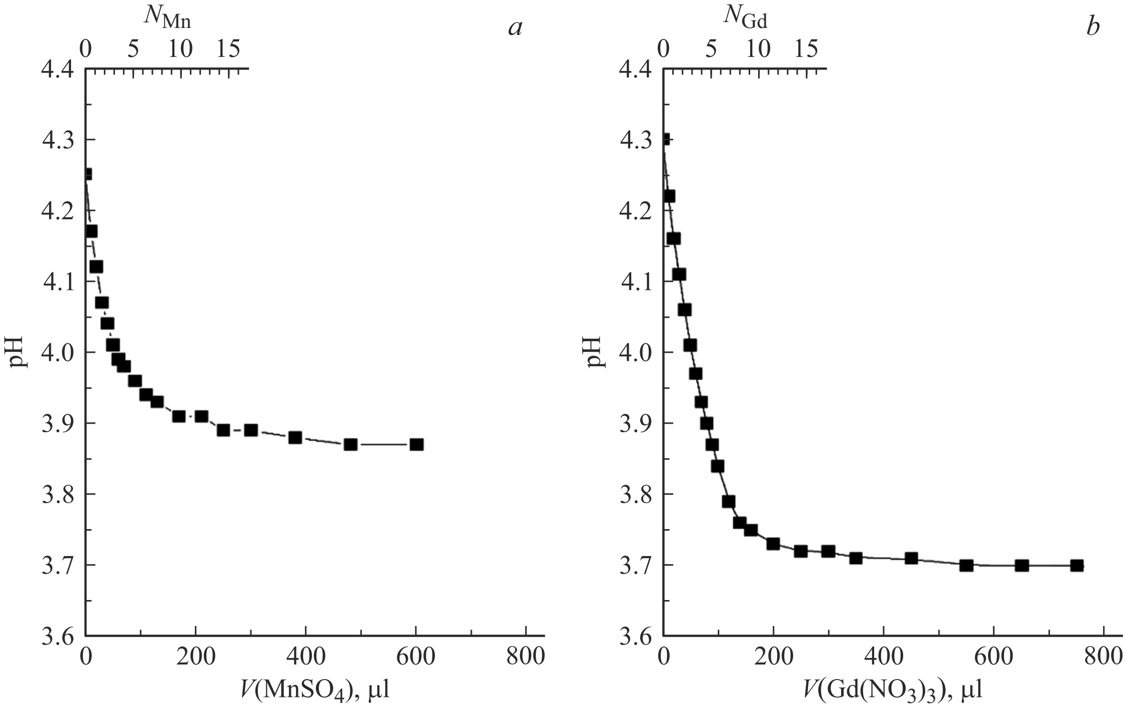

Figure 2. Potentiometric titration curve of a hydrosol ND with an aqueous solution of manganese sulfate (*a*) and gadolinium nitrate (*b*).

Table 1. Elemental composition of ND-Mn and ND-Gd powders

Sample	Mn content, wt%	Gd content, wt%	Quantity of metal ions per ND particle
ND-Mn	0.03 ± 0.01	–	1
ND-Gd	–	0.63 ± 0.1	4

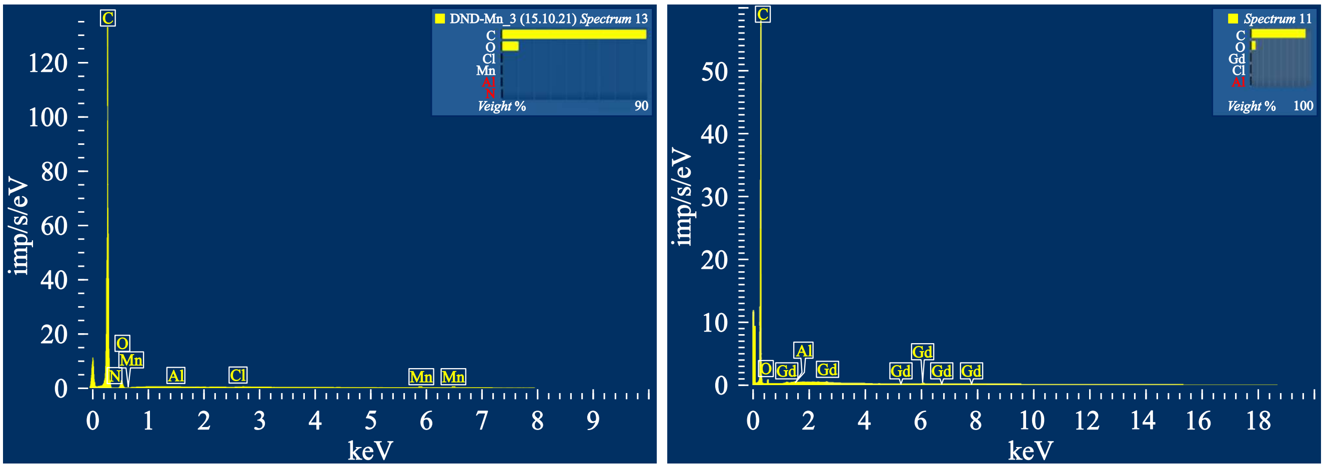

Figure 3. The initial EDX spectrum of the ND-Mn (left) and ND-Gd (right) samples.

Table 2. Concentration of components in hydrosols for DLS measurements

№	Sample	Concentration				
		ND (wt%)	Mn (wt%/mM)	Gd (wt%/mM)	PVP (wt%)	NaCl (wt%)
1	ND	0.30	0	–	0	0
2	ND-Mn	0.37	0.00011/0.020	–	0	0
3	ND-Mn-PVP	0.37	0.00011/0.020	–	0.569	0.90
4	ND-Gd	0.29	–	0.00188/0.120	0	0
5	ND-Gd-PVP	0.29	–	0.00188/0.119	1.42	0.90

The results of DLS measurements of the size of ND-Mn and ND-Gd particles are shown in Fig. 4.

The average particle size of ND-Mn (Fig. 4, *a*) and ND-Gd (Fig. 4, *b*) in hydrosol does not exceed ∼ 10 nm. The formation of agglomerates of ND-Mn-PVP and ND-Gd-PVP particles with an average size of 40–50 and 60–70 nm, respectively, is observed in aqueous-salt solutions.

No significant changes in the particle size distribution have been observed for at least a month.

It should be noted that the same parameters of hydrosol stability and particle size distribution in an aqueous salt medium were obtained as a result of several complex chemical reactions using the chelate complex Gd^{3+} [25,29]. Modification of the surface of a diamond nanoparticle with metal ions as a result of an ion exchange reaction and stabilization of a hydrosol in a physiological solution with polyvinylpyrrolidone make it possible to obtain particles with a smaller size and prevent agglomeration.

2.4. NMR method

The values of the spin-lattice (r_1) and spin-spin (r_2) relaxivities of protons in a hydrosole are presented in Table 3 and in Fig. 5.

Not only the ND particles whose surface is modified by metals, but also the ND particles are able to inherently reduce the relaxation times of water protons, especially T_2 in all the studied series as can be seen from the figure.

It is found that the addition of paramagnetic ions (Mn^{2+}; Gd^{3+}) to the surface of a diamond particle results in at least a tenfold increase of r_1 and r_2. The values of r_1, r_2 in ND-Gd-PVP and r_1 in ND-Mn-PVP samples are slightly lower than for ND-Gd and ND-Mn particles. This may be explained by the fact that the PVP layer bound to the

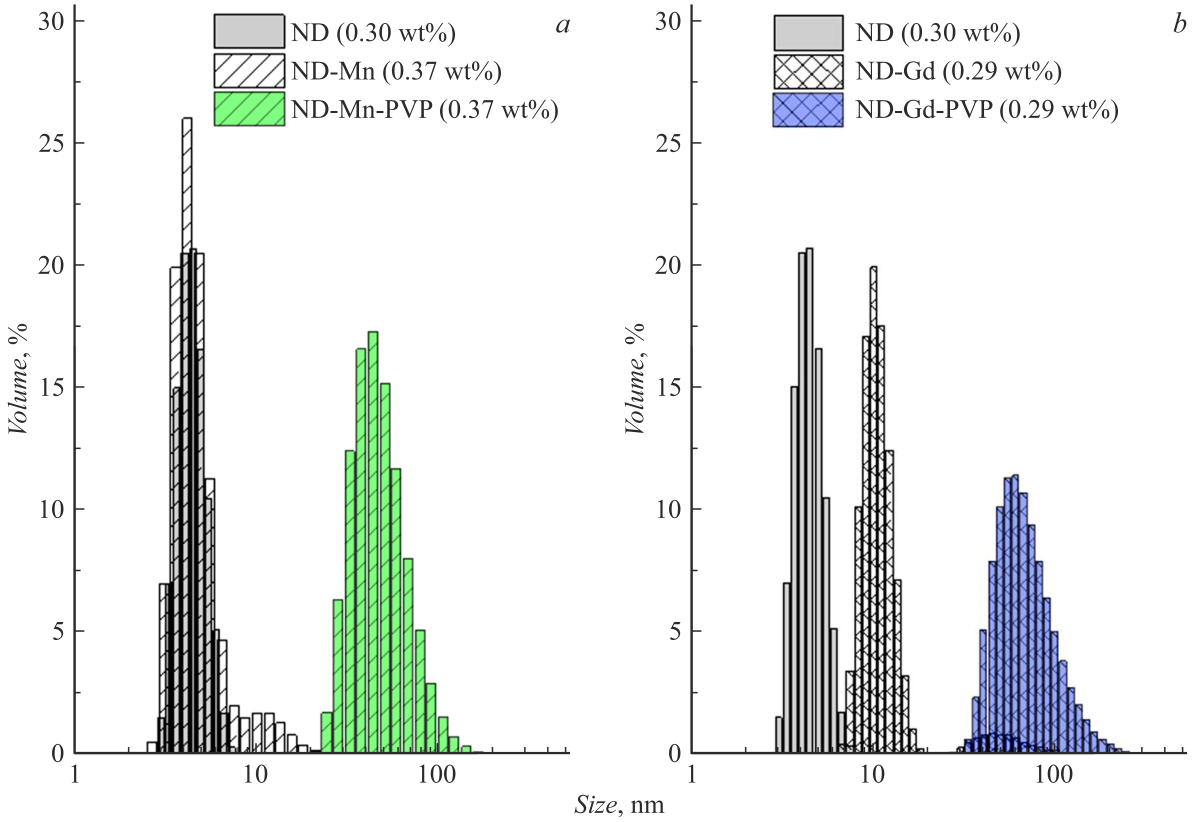

Figure 4. The particle size distribution of ND-Mn (a) and ND-Gd (b) determined by the dynamic light scattering method.

Table 3. Values of r_1 and r_2 in aqueous and aqueous-salt hydrosols at 310.1 K

Sample	Metal concentration, mM	r_1, $\mathrm{mM^{-1}s^{-1}}$	r_2, $\mathrm{mM^{-1}s^{-1}}$	r_1/r_2	r_2/r_1
Dotarem©	500	3.56	4.75	0.75	1.33
ND	0	2.1±0.3	15.8 ± 1.0	0.13	7.52
ND-Mn	0.020−0.066	24.0 ± 2.6	164 ± 11	0.15	6.83
ND-Mn-PVP	0.0200−066	22.0 ± 0.1	288 ± 44	0.08	13.09
ND-Gd	0.040−0.160	33.4 ± 0.6	332 ± 13	0.10	9.94
ND-Gd-PVP	0.040−0.160	15.9 ± 0.8	262 ± 15	0.06	16.48

surface of the particle somewhat hinders the access of water molecules to paramagnetic ions [33,34].

The concentration of paramagnetic ion in diamond nanoparticles modified with gadolinium or manganese ions is four orders of magnitude lower compared with a commercial product, and the values of r_1 and r_2 are higher by ~ 8 times. Therefore, this may allow a lower dose of the drug to be administered during MRI contrast.

Conclusion

The surface of diamond nanoparticles containing carboxyl groups has been modified with paramagnetic ions Mn^{2+} and Gd^{3+}. Modification of the surface of nanodiamonds by metal ions occurs as a result of the ion exchange reaction between protons of carboxylic groups ND and metal ions. The hydrosols have remained stable not only in an aqueous medium, but also in an aqueous-salt medium when the surface is stabilized with polyvinylpyrrolidone.

Measurements of the relaxation rate of protons in aqueous and aqueous-salt colloidal solutions have shown that ND-Mn and ND-Gd particles significantly increase the spin-lattice and spin-spin relaxivities of water protons.

A comparison of the results of measurements of r_1 and r_2 with similar parameters in the case of commercial contrast agent „Dotarem©" has demonstrated that metal-modified diamond nanoparticles ND-Mn and ND-Gd are more effective as T_1- and T_2- contrast agents for medical studies, ensuring an increase of the contrast of MRI images.

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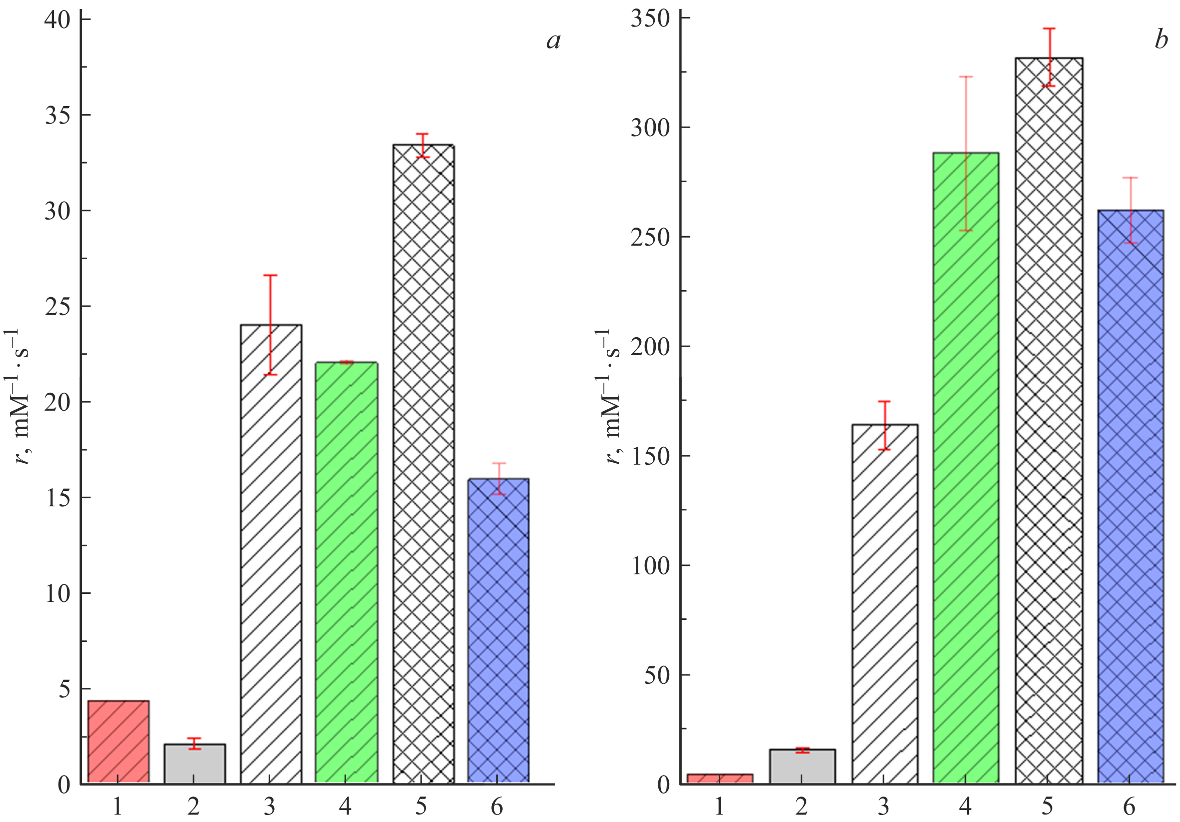

Figure 5. Spin-lattice (a) and spin-spin (b) relaxivities at 310.1 K. Along the horizontal axis: *1* — Dotarem©; *2* — ND, *3* — ND-Mn; *4* —ND-Mn-PVP; *5* —ND-Gd; *6* — ND-Gd-PVP.

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Conflict of interest

The authors declare that they have no conflict of interest.

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