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Simultaneous immobilization of gadolinium ions and di(*o*-carborano-1,2-dimethyl)borate on Fe₃O₄ nanoparticles

Neutron capture therapy is a promising method for cancer treatment based on targeted delivery of specific isotopes into cancer cells and subsequent irradiation with epithermal neutrons. As a result, a large amount of energy is released at a distance comparable to the size of the cell, destroying it from the inside. For the targeted delivery of isotopes, magnetic iron oxide nanoparticles can be used. In this article, iron oxide nanoparticles (Fe₃O₄) were modified with silanes and polyelectrolyte complexes for simultaneous immobilization of gadolinium ions and carborane compounds through ionic interaction for potential application in targeted delivery into cancer cells for neutron capture therapy. Structure, size and element composition was elucidated by Fourier-transform infrared spectroscopy (FTIR), Energy-dispersive X-ray spectroscopy (EDA), dynamic light scattering (DLS) and X-ray diffraction (XRD) analysis. It was found that according EDA, resulting nanoparticles consist of 15.4 % boron and 1.5 % gadolinium, with average hydrodynamical size of 386 nm measured by DLS. An in vitro cytotoxicity test using HepG2 (a cancer cell line) and human skin fibroblasts (a normal cell line) showed minor cytotoxicity in concentration range from 0.05 to 1 mg/mL.

Keywords: Fe₃O₄ nanoparticles, silane, surface modification, targeted delivery of payload, BNCT, carborane, cytotoxicity.

Introduction

Due to the development of medicine a significant progress in cancer treatment was reached during past two decades. But still, cancer remains a problem. For example, there were 2.7 million of new cases and 1.3 million of lethal cases in 2020. Such approach as radiotherapy has shown its effectiveness, 40 % of cancer types can be treated using it alone or combined with other methods [1]. However, there is a type of tumor considered to be radioresistant [2], and it can't be treated with traditional radiotherapeutic approaches. The neutron capture therapy (NCT) could be one of the ways to solve this problem [3].

To treat cancer with this method, a drug labeled with specific isotopes (usually ¹⁰B and ¹⁵⁷Gd) is delivered to the tumor. After that, it is irradiated with epithermal neutron flux. As the result, we have a neutron capture reaction localized in tumor. In case of B, the safety of nearby tissues can be achieved due to the pathlength of the resulting α -particles (4–9 μ m) and its high cellular response efficiency [4]. Other studies indicate that the simultaneous use of Gd and B increases the efficiency of NCT by 80 % [5]. Currently, only clinical trials have been conducted with BPA (*p*-borophenylalanine) and BSH (disodium mercaptoundecahydrododecaborate), and they have shown no selectivity. On the other hand, selectivity can be improved by using nanocarriers as a drug delivery system. Nanoparticles possess unique physical properties, such as a high surface-to-volume ratio, the ability to penetrate through vascular architecture and cellular membranes, and, in some cases, low cytotoxicity [6, 7].

In this study we present a method for the simultaneous immobilization of Gd ions and di(*o*-carborano-1,2-dimethyl)borate to the core-shell Fe₃O₄ nanoparticles covered with polyacrylic acid/polyallylamine (PAA/PALAM) polyelectrolyte. This approach has the following goals: the presence of Gd can not only increase the efficiency of NCT, but also be used as a diagnostic agent for MRI, so after the injection of nanocarriers it is possible to determine the drug distribution in body area [8, 9]. On the other hand, the magnetic core makes it possible to manipulate nanoparticles using an external magnetic field. In addition, alt-

though di(*o*-carborano-1,2-dimethyl)borate has a large number of boron atoms in its structure, it is insoluble in water. Therefore, simple injection it into the blood could be problematic. This problem can be avoided if it is immobilized on the nanocarriers surface. In contrast to our previous study [10], di(*o*-carborano-1,2-dimethyl)borate is bonded to PAA/PALAm trough NH_3^+ groups via ionic bond, which may provide better drug release.

Experimental

Reagents and materials

Iron chloride (II) tetrahydrate, iron chloride (III) hexahydrate, acrylic acid (AA), polyallylamine hydrochloride (PALAm), aluminum oxide, 3-(trimethoxysilyl)propyl methacrylate (TMSPM), 2,2'-azobis(2-methylpropionamide) dihydrochloride (AAPH), gadolinium (III) nitrate hexahydrate were purchased at Sigma-Aldrich (Germany). Ethanol, methanol, benzene, *o*-xylol, diethyl ether, hydrochloric acid, ammonium hydroxide aqueous solution, NaOH, and ethyl acetate were analytical grade (Russia).

Synthesis of iron oxide nanoparticles and its modification

Fe_3O_4 nanoparticles (NPs) were synthesized by the precipitation method described in our previously published work [10]. Fe_3O_4 nanoparticles were modified according to the scheme presented in Figure 1.

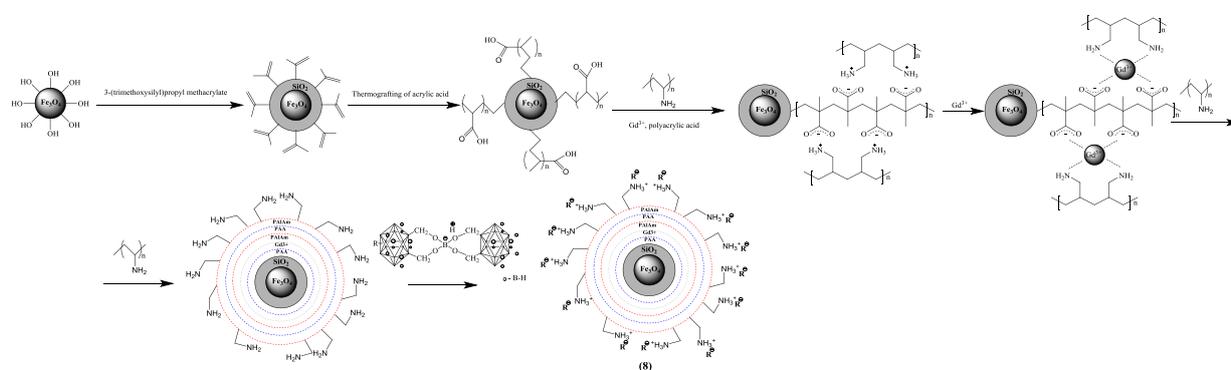


Figure 1. Schematic representation of iron oxide NPs modification, and gadolinium and carborane immobilization via ionic interaction

To form methacrylate groups on iron oxide nanoparticles, 1 g of Fe_3O_4 NPs was added to a solution of 100 ml *o*-xylol, then it was ultrasonicated for 2 hrs, and bubbled with argon. After that, 3 ml of 3-(trimethoxysilyl)propyl methacrylate was dropped under vigorous stirring, then the reaction was heated to 80 °C and continued for 5 h. The precipitate was magnetically separated and washed with *o*-xylol and diethyl ether.

Then, for acrylic acid grafting, 1g of Fe_3O_4 NPs with methacrylate groups was ultrasonicated in 50 % ethanol (90 ml) for fine desparation and degassing, moreover, argon was bubbled during 15–20 min to remove oxygen. 10 ml of purified AA and 0.05 g of thermal initiator 2,2'-azobis(2-methylpropionamide) dihydrochloride (AAPH) were added to the solution. Reaction was heated to 80 °C and kept at this temperature during 24 h. After that, obtained precipitate was magnetically separated and washed with water several times.

To form a polyelectrolyte complex on modified nanoparticles, 1 g of grafted NPs was ultrasonicated in a 0.012 g/ml of polyallylamine solution for desparation for 2 h and then shaken using tube shaker for 24 h.

Then, Gd ions formed complexes from 0.016 g/ml of gadolinium (III) nitrate solution in ethanol and were shaken for 48 hrs. Samples were washed several times in ethanol and water, and magnetically separated from the solution.

Synthesis of di(*o*-carborano-1,2-dimethyl)borate

0.62 g (0.01 M) of an aqueous solution of boric acid was added to 4.08 g (0.02 M) of a dioxane solution of 1,2-bis(oxyethyl)-*o*-carborane, and the reaction was stirred for 2 h. The precipitate was filtered. The extract was dried over Na_2SO_4 and evaporated. The yield was 3.58 g (86 %), m.p. > 400 °C.

FTIR (ν , cm^{-1}): 3000 (CH), 2625, 2596, 2568 (BH), 1350 (B–O).

NMR ^1H (DMSO- d_6 , δ , ppm): 0.3–3.7 (m., 20H, B–H); 4.02 (s., 8H, CH_2).

NMR ^{11}B (DMSO- d_6 , δ , ppm): 4.47 (s., 1B, B–O); 4.66 (s., 6B, B–H); 11,29 (s., 14B, B–H).

Complexation of di(o-carborano-1,2-dimethyl)borate on modified Fe₃O₄

1 g of NPs was dispersed in 0.5 % solution of di(o-carborano-1,2-dimethyl)borate in CH₃COOC₂H₅ for 1 h and then it was additionally shaken for 1 h. The samples were washed several times in ethyl acetate and acetone, magnetically separated from the solution, and dried.

Methods of characterization

InfraLum FT-08 FTIR (Russia) was used to record FTIR spectra in KBr pellets. The scanning range was 4000–400 cm⁻¹, the resolution was 2 cm⁻¹, and the number of scans was 25.

Hitachi TM 3030 (Japan) was used for EDA. Samples were magnetron sputtered with gold before the analysis.

D8 ADVANCE ECO diffractometer (Germany) was used for X-ray diffraction analysis. To identify the phases and study the crystal structure, the software Bruker AXSDIFFRAC.EVA v.4.2 and the international database ICDD PDF-2 were used.

ZetaSizer Nano-ZS (United Kingdom) was used for evaluation of average hydrodynamical size and zeta potential at different pH.

To determine the concentration of carboxyl groups, a colorimetric assay was applied [11]. The concentration of carboxyl groups was determined using the toluidine blue.

Cytotoxicity Assay

Cytotoxicity was evaluated using HepG2 cancer cell line and human skin fibroblasts as normal cells. Cells were grown in a CO₂ incubator (Hera Cell) at 37 °C, 5 % CO₂, 80 % relative humidity on 96-well plates (50–70 thousand cells/ml was the seed concentration). Samples of NPs dissolved in Fetal Bovine Serum were added to wells with adherent cells (second day of cultivation). After 24-hours of sample exposure, total cell mitochondrial dehydrogenase activity in each well was measured photometrically in the methyltetrazolium test (MTT).

Results and Discussion

The surface of Fe₃O₄ nanoparticles was functionalized according to the scheme presented in Figure 1, in order to immobilize gadolinium ions and carborane compounds. At the first stage, iron oxide nanoparticles were covered with silane shell using 3-(trimethoxysilyl)propyl methacrylate (TMSPM) by reaction of hydrolysis and condensation. This reaction is based on the removal of CH₃O- from alkoxy silane and attaching it to the OH group of Fe₃O₄ nanoparticles. The reaction temperature of 80 °C makes it possible to effectively remove the reaction product (methanol), forming an azeotropic mixture with xylene. The FTIR spectra presented in Figure 2 confirm the formation of Si-O-Si and C=C bonds at 1175, 1015 cm⁻¹ and 1640 cm⁻¹. Also Si-OH bond was detected at 935 cm⁻¹, it points to incompleteness of polycondensation reaction [12, 13]. EDA detected silicon in elemental composition.

At the second stage, thermoinitiated graft polymerization of acrylic acid (AA) was performed on silanized iron oxide nanoparticles. The effect of reaction time, temperature, concentration of initiator and monomer on the efficiency of graft polymerization was studied. Taking into account the solubility of monomer and initiator, and the good dispersion of NPs, 50 % ethanol is the optimal solvent.

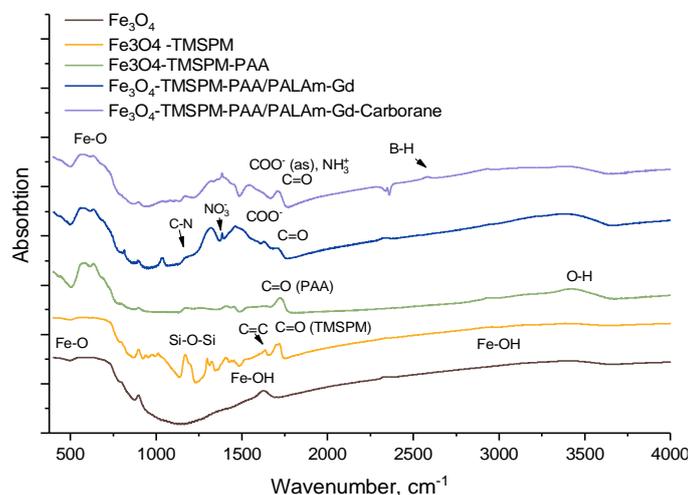
The main peaks in the FTIR spectra, which can be seen after graft polymerization on iron oxide NPs, appear at 2950 cm⁻¹ (C-H), and at 1725 cm⁻¹ (C=O of carboxyl group). The amount of grafted polymeric chains can be evaluated using ratio of intensities or area under the peak at 575 cm⁻¹ (Fe-O) and 1725 cm⁻¹ (C=O of PAA) [14]. The results are presented in Table 1. The amount of grafted polymer chain continuously increased with time and decreased with the increase in the concentration of monomer due to homopolymerization but not grafting. Additionally, colorimetric assay was used to evaluate concentration of carboxylic group on modified nanoparticles. Concentration of COOH groups was 174.61 μM/g (at 0.03125 % AAPH, 10 % AA and 24 hour reaction time). This additionally confirms the grafting of PAA on the surface of nanoparticles.

Then, the samples were soaked in PAIAm solution to form polyelectrolyte layer on the surface of NPs. In the FTIR spectra, the peaks were detected at around 1500–1600 cm⁻¹, which may be related to COO⁻ and NH₃⁺, 3340 cm⁻¹ (O-H/N-H), 1635 cm⁻¹ (N-H stretching), 1452 cm⁻¹ (C-H stretching) and 1178 cm⁻¹ (C-N stretching) [12].

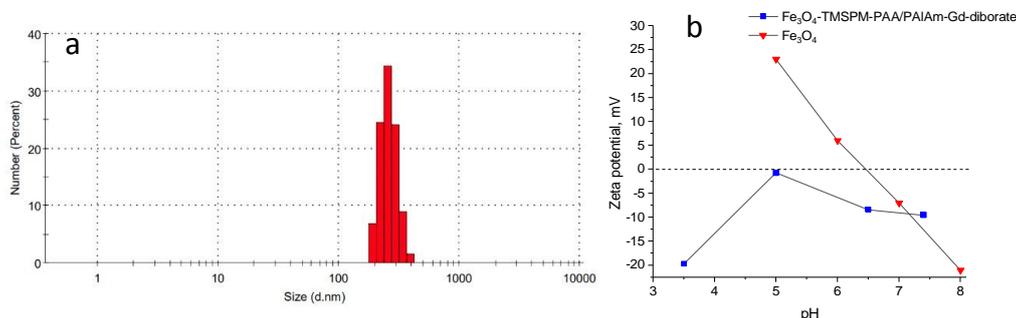
After the formation of polyelectrolyte complexes, the immobilization of Gd ions from its nitrate salt was performed. After the complexation of Gd ions and the formation of chelates, as presented in Figure 1, the FTIR spectra show a shift of the peak of the COO⁻ group from 1319 to 1399 cm⁻¹. A peak was in addition recorded at 1386 cm⁻¹ (NO₃⁻) with low intensity. 2.9 % gadolinium has also been found in the EDA.

Effect of different parameters on efficiency of PAA grafting

	Concentration of AAPH, %			Concentration of AA, %			Time, h		
	0.0125	0.03125	0.05	10	20	30	2	6	24
I_{1725}/I_{575}	0.15	0.184	0.181	0.184	0.181	0.103	0.162	0.181	0.184

Figure 2. FTIR spectra of Fe_3O_4 at different stages of modification and carborane immobilization

After that, a second layer of polyelectrolyte was formed for attaching the di(*o*-carborano-1,2-dimethyl)borate through ionic interaction, while in our recent article [10], attaching of carborane diborate was performed by covalent bonding. A new peak at around 2600 cm^{-1} (B–H stretching) of diborate [15] was detected in the FTIR spectra. Moreover, B was found in EDA in the amount of 15.4 at.%. This sample was also characterized by DLS analyses to evaluate hydrodynamic diameters and zeta potential at different pH. Results are presented in Figure 3. It was found out that the average hydrodynamic diameter of the Fe_3O_4 -TMSPMS-PAA/PALAm-Gd-diborate sample is 386 nm. DLS analyzes the solvated state of the sample, in which H_2O molecules associate with nanoparticle [16], it should also be noted that the obtained sample is unstable and tends to agglomerate, so it is necessary to find a method for suspension stabilization (for instance, surfactants can be used for this purpose). The results of zeta potential measurements at different pH are presented in Figure 3b. It is clearly seen that the modified samples are negatively charged at pH range of 3.5–7.5 due to an excess of negatively charged carboxylic groups of the grafted polyacrylic acid.

Figure 3. Size distribution (a) and zeta-potential as function of pH (b) of Fe_3O_4 -TMSPM-PAA/PALAm-Gd-diborate

The results of XRD analysis of the initial Fe_3O_4 and after diborate immobilization are presented in Figure 4. The diffraction patterns are characteristic for polycrystalline-like nanopowders, moreover there are disordered regions that are typical for oxide nanoparticles synthesized by wet chemistry. Full-profile analysis shows that the presented peaks are attributed to cubic phase of magnetite with broadened reflections, in addition, the presence of altered positions of the interplanar distances indicates the disordering of the structure.

Modification is accompanied by partial ordering and an increase in the intensity of diffraction reflections due to changes in the stoichiometry and defect structures. It is well known that Fe_3O_4 NPs are characterized by a large number of disordered regions [13, 17].

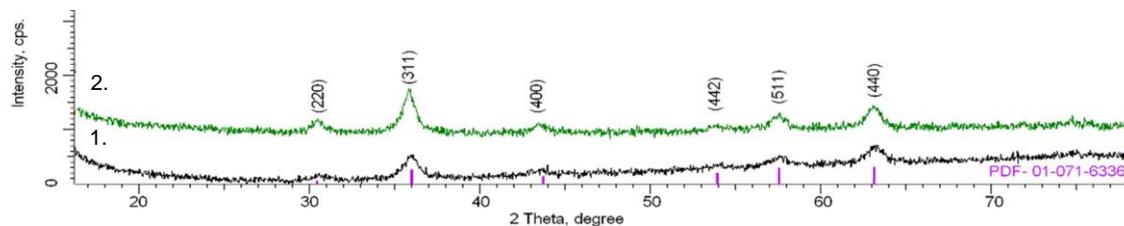


Figure 4. XRD patterns of: 1) initial Fe_3O_4 ; 2) Fe_3O_4 -TMSPM-PAA/PALAm-Gd-diborate

Table 3 shows the results of XRD analysis; the stoichiometry was calculated according to method presented in [18]. It is seen that Fe (II) oxidizes after modification and diborate immobilization. Thus, the initial NPs have the $\text{Fe}_{2.88}\text{O}_4$ stoichiometry, and the final NPs have $\text{Fe}_{2.78}\text{O}_4$ stoichiometry.

Table 3

Data of XRD analysis

Sample	Lattice parameter, Å	Crystalline size, nm	Degree of structural ordering, %	Stoichiometry
Fe_3O_4	$a = 8.29402$	10.5	53.6	$\text{Fe}_{2.88}\text{O}_4$
Fe_3O_4 -TMSPM-PAA/ PALAm-Gd-diborate	$a = 8.30408$	21.5	59.7	$\text{Fe}_{2.78}\text{O}_4$

The cytotoxicity of Fe_3O_4 -TMSPM-PAA/PALAm-Gd-diborate nanoparticles was elucidated by cell vitality by the example of HepG2 and human fibroblasts cell lines. Results are presented in Figure 5.

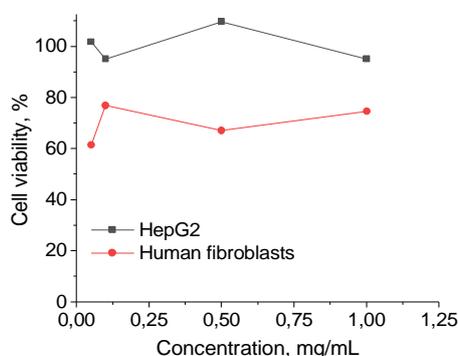


Figure 5. Cell viability after incubation depends of NPs concentrations for HepG2 and human fibroblast cell lines

The cytotoxicity of Fe_3O_4 /TMSPM/PAA/PALAm/Gd-diborate towards HepG2 and human fibroblasts is low even at the highest concentration of 1 mg/mL, so, it is not possible to determine the IC_{50} for the considered cell lines. Thus, the obtained nanoparticles can be further studied for targeted delivery of di(*o*-carborano-1,2-dimethyl) borate for BNCT.

Conclusions

This study presents the results of simultaneous immobilization of gadolinium ions and carborane compound on modified iron oxide nanoparticles through ionic interaction. Average hydrodynamic radius of the prepared nanoparticles was 386 nm, the boron content was 15.4 %, and the Gd content was 1.5 % according to EDA. An *in vitro* test using HepG2 (cancer cell) and human fibroblasts (normal cell line) showed minor cytotoxicity in concentration range from 0.05 to 1 mg/mL.

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Fe₃O₄ нанобөлшектеріне ди(о-карборан-1,2-диметил)борат және гадолиний иондарды қатар иммобилизациялау

Нейтронды басып алу терапиясы — рак клеткаларына арнайы изотоптарды мақсатты түрде жеткізуге және эпителиялық нейтрондармен кейіннен сәулелендіруге негізделген қатерлі ісік ауруын емдеудің перспективті әдісі. Нәтижесінде жасушаның өлшемімен салыстырылатын қашықтыққа үлкен мөлшерде энергия бөлініп, оны ішінен жояды. Изотоптарды мақсатты жеткізу үшін магниттік темір оксидінің нанобөлшектерін пайдалануға болады. Бұл мақалада темір оксиді (Fe₃O₄) нанобөлшектері нейтронды ұстау терапиясы қатерлі ісік жасушаларының мақсатты жеткізуде әлеуетті пайдалану үшін иондық өзара әрекеттесу арқылы гадолиний иондары мен карборан қосылыстарын бір уақытта иммобилизациялау үшін силандармен және полиэлектролиттік кешендермен модификацияланды. Құрылымы, өлшемі және элементтік құрамы инфрақызыл спектроскопия (ИК), энергетикалық дисперсиялық рентгендік спектроскопия (ЭДА), динамикалық жарық шашырауы және рентгендік фазалық талдау арқылы зерттелді. Алынған нанобөлшектердің құрамында 15,4 % бор және 1,5 % гадолиний бар (ЭДА мәліметтері бойынша), олардың орташа гидродинамикалық өлшемі 386 нм (DLS деректері бойынша). НерG2 (қатерлі ісік жасушаларының желісі) және адам терісінің фибробластары (қалыпты жасуша сызығы) қолданылған *in vitro* зерттеулер 0,05–1 мг/мл концентрация диапазонында төмен цитотоксикалықты көрсетеді.

Кілт сөздер: Fe₃O₄ нанобөлшектері, силан, беттік модификациялау, пайдалы жүктемені мақсатты жеткізу, БНҰТ, карборан, цитотоксикалық.

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Одновременная иммобилизация ионов гадолиния и ди(о-карборано-1,2-диметил)бората на наночастицы Fe₃O₄

Нейтронзахватная терапия — перспективный метод лечения рака, основанный на адресной доставке специфических изотопов в раковые клетки и последующем облучении эпителиальными нейтронами. В результате выделяется большое количество энергии на расстояние, сравнимое с размером клетки, разрушая ее изнутри. Для адресной доставки изотопов могут быть использованы магнитные наночастицы оксида железа. В данной статье наночастицы оксида железа (Fe₃O₄) были модифицированы силанами и полиэлектролитными комплексами для одновременной иммобилизации ионов гадолиния и карборановых соединений посредством ионного взаимодействия для потенциального применения в целевой доставке в раковые клетки для нейтронно-захватной терапии. Структура, размер и элементный состав были изучены с помощью инфракрасной спектроскопии (ИК), энергодисперсионной рентгеновской спектроскопии (ЭДА), динамического рассеяния света и рентгенофазового анализа. Полученные наночастицы содержат 15,4 % бора и 1,5 % гадолиния (по данным EDA), а их средний гидродинамический размер составляет 386 нм (по данным DLS). *In vitro* исследования с использованием НерG2 (линия раковых клеток) и фибробласты кожи человека (нормальная линия клеток) показывает низкую цитотоксичность в диапазоне концентраций 0,05–1 мг / мл.

Ключевые слова: Наночастицы Fe₃O₄, силан, модификация поверхности, адресная доставка полезного груза, БНЗТ, карборан, цитотоксичность.

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