How to Cite: Korolkov, I.V., Zibert, A.V., Lisovskaya, L.I., Ludzik K., Anisovich, M., Vasilyeva, M., Shumskaya, A., Usseinov, A., Yeszhanov, A.B., & Zdorovets, M.V. (2022) Simultaneous Immobilization of Gadolinium Ions and Di(o-carborano-1,2-dimethyl) borate on Fe_3O_4 Nanoparticles. *Bulletin of the University of Karaganda – Chemistry, 106(2), 87-94.* https://doi.org/10.31489/2022Ch2/2-22-3

INORGANIC CHEMISTRY

Article Received: 14 January 2022 | Revised: 25 March 2022 | Accepted: 8 April 2022 | Published online: 12 April 2022

UDC 544.77, 547.1, 546.05 https://doi.org/10.31489/2022Ch2/2-22-3

I.V. Korolkov[1,2*], A.V. Zibert[2], L.I. Lisovskaya[1,2], K. Ludzik[3,4], M.V. Anisovich[5], M.M. Vasilyeva[5], A.E. Shumskaya[6], A. Usseinov[2], A.B. Yeszhanov[1,2], M.V. Zdorovets[1,2]

[1]*Institute of Nuclear Physic of the Republic of Kazakhstan, Almaty, Kazakhstan;*
[2]*L.N. Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan;*
[3]*University of Lodz, Poland;*
[4]*Frank Laboratory of Neutron Physics, Joint Institute for Nuclear Research, Dubna, Russia;*
[5]*Republican Unitary Enterprise, Scientific-Practical Centre of Hygiene, Minsk, Belarus;*
[6]*Institute of Chemistry of New Materials, National Academy of Sciences of Belarus, Minsk, Belarus*
*(*Corresponding author's e-mail: i.korolkov@inp.kz)*

Simultaneous Immobilization of Gadolinium Ions and Di(*o*-carborano-1,2-dimethyl)borate on Fe_3O_4 Nanoparticles

Neutron capture therapy is a promising method for cancer treatment based on the 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. Magnetic iron oxide nanoparticles can be used for the targeted delivery of isotopes. In this article, iron oxide nanoparticles (Fe_3O_4) 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 the 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 to 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: Fe_3O_4 nanoparticles, silane, surface modification, targeted delivery of payload, BNCT, carborane, cytotoxicity.

Introduction

The development of medicine has led to significant progress in cancer treatment during the past two decades. Nevertheless, cancer remains a problem; for example, there were 2.7 million new cases and 1.3 million lethal cases in 2020. Such an 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 cannot be treated with traditional radiotherapeutic approaches. 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 ^{10}B and ^{157}Gd) is delivered to the tumor. After that, it is irradiated with epithermal neutron flux. As a result, we have a neutron capture reaction localized in tumor. In the case of B, the safety of nearby tissues can be achieved due to the pathlength of the resulting α-particles (4–9 μm) 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 Fe_3O_4 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, although 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 of 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 through 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-methylpropionamidine) 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 previous work [10]. Fe_3O_4 nanoparticles were modified according to the scheme presented in Figure 1.

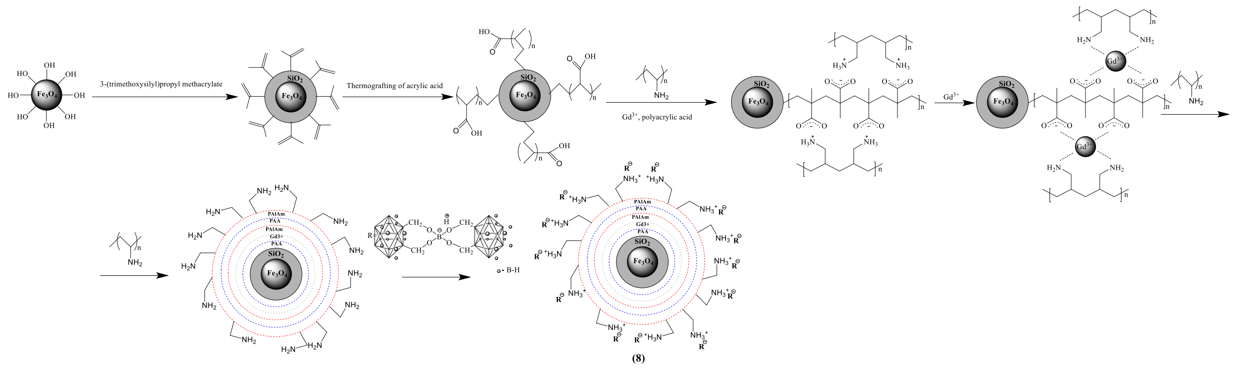

Figure 1. Schematic representation of iron oxide NPs modification,
and gadolinium and carborane immobilization via ionic interaction

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 to 50 % ethanol (90 ml) for fine desperation 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-methylpropionamidine) dihydrochloride (AAPH) were added to the solution. The reaction was heated to 80 °C and kept at this temperature for 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 desperation 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(oxymethyl)-*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 ^{1}H (DMSO-d6, δ, ppm): 0.3–3.7 (m., 20H, B–H); 4.02 (s., 8H, CH_2).

NMR ^{11}B (DMSO-d6, 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 Fe_3O_4

1 g of NPs was dispersed in a 0.5 % solution of di(*o*-carborano-1,2-dimethyl)borate in $CH_3COOC_2H_5$ for 1 h and then it was additionally shacked for 1 h. The samples were washed several times in ethyl acetate and aceton, 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 TM3030 (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 BrukerAXSDIFFRAC.EVAv.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 toluidine blue.

Cytotoxicity Assay

Cytotoxicity was evaluated using HepG2 cancer cell line and human skin fibroblasts as normal cells. Cells were grown in a CO_2 incubator (Herra Cell) at 37 °C, 5 % CO_2, 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 Fe_3O_4 nanoparticles was functionalized according to the scheme presented in Figure 1 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 CH_3O- from alkoxysilane and attaching it to the OH group of Fe_3O_4 nanoparticles. The reaction temperature of 80 ^{0}C makes it possible to remove effectively 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. Considering 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]. Table 1 demonstrates the results. 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 PAlAm 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 NH_3^+, 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 their 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} (NO_3^-) with low intensity. 2.9 % gadolinium has also been found in the EDA.

Table 1

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

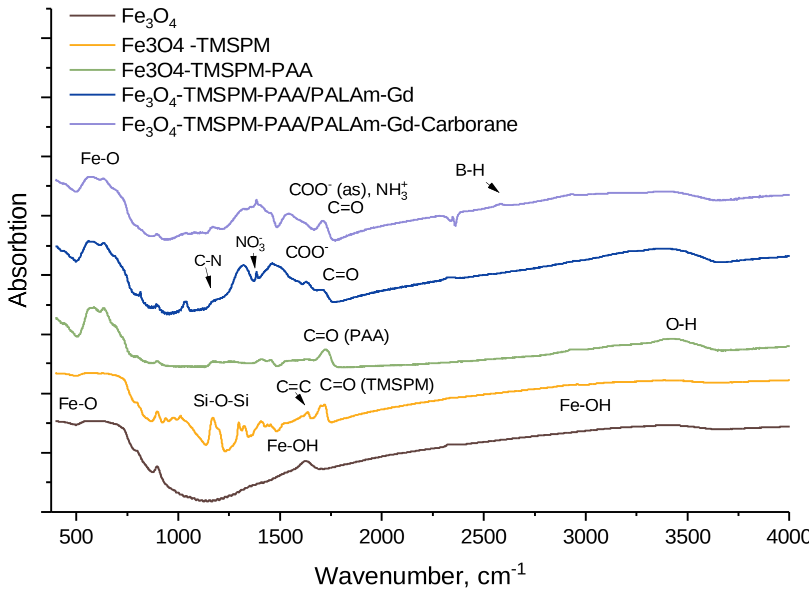

Figure 2. FTIR spectra of Fe_3O_4 at different stages of modification and carborane immobilization

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. Figure 3 represents the results. 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). Figure 3b provides the results of zeta potential measurements at different pH. 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.

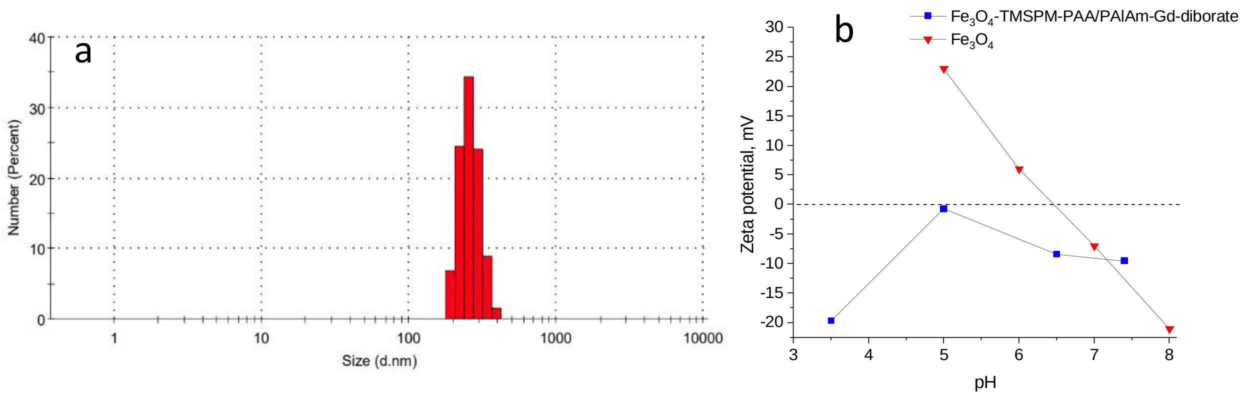

Figure 3. Size distribution (*a*) and zeta-potential as function of pH (*b*) of Fe_3O_4-TMSPM-PAA/PALAm-Gd-diborate

Figure 4 illustrates the results of XRD analysis of the initial Fe_3O_4 and after diborate immobilization. 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. Fe_3O_4 NPs are characterized by a large number of disordered regions [13, 17].

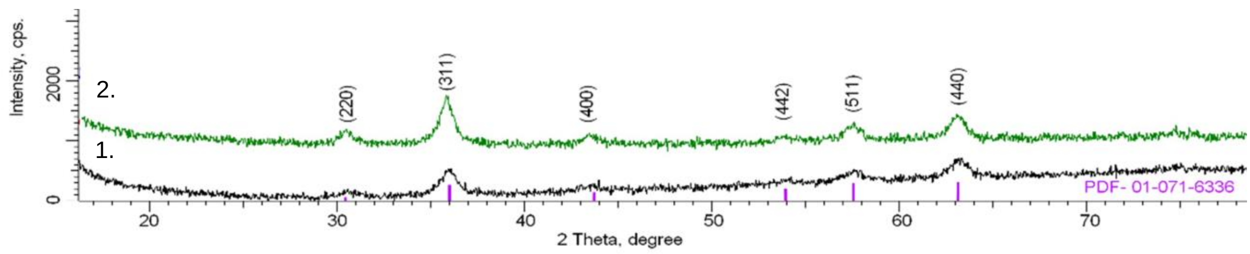

Figure 4. XRD patterns of: 1) initial Fe_3O_4; 2) Fe_3O_4-TMSPM-PAA/PAlAm-Gd-diborate

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 $Fe_{2.88}O_4$ stoichiometry, and the final NPs have $Fe_{2.78}O_4$ 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	$Fe_{2.88}O_4$
Fe_3O_4-TMSPM-PAA/ PALAm-Gd-diborate	*a* = 8.30408	21.5	59.7	$Fe_{2.78}O_4$

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. Figure 5 presents the results.

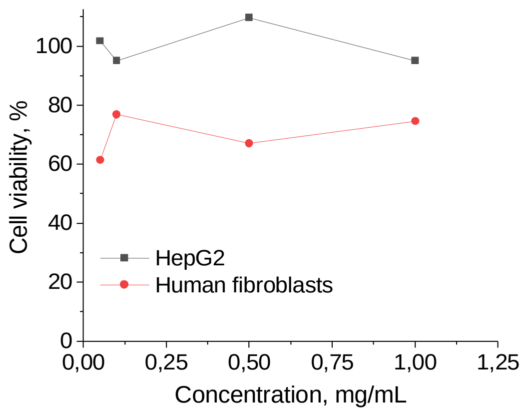

Figure 5. Cell viability after incubation depends of NPs concentrations for HepG2 and human fibroblast cell lines

The cytotoxicity of Fe_3O_4/TMSPM/PAA/PALAm/Gd-diborate towards HepG2 and human fibroblasts is low even at the heist concentration of 1 mg/mL, so, it is not possible to determinate 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.

Acknowledgments

This study was funded by the Ministry of Education and Science of the Republic of Kazakhstan (grant No. AP08051954) and grant #M20MC-024 of The Belarusian Republican Foundation for Fundamental Research.

References

1 Grilo, A.M., Santos, B., Baptista, I., & Monsanto, F. (2021). Exploring the cancer patients' experiences during external radiotherapy: A systematic review and thematic synthesis of qualitative and quantitative evidence. *European Journal of Oncology Nursing*, *52*, 101965. https://doi.org/10.1016/j.ejon.2021.101965

2 Cohen-Jonathan-Moyal, Vendrely, V., Motte, L., Balosso, J., & Thariat, J. (2020). Radioresistant tumours: From identification to targeting. *Cancer/Radiotherapie*, *24* (6–7), 699–705. https://doi.org/10.1016/j.canrad.2020.05.005

3 Vares, G., Jallet, V., Matsumoto, Y., Rentier, C., Takayama, K., Sasaki, T., Hayashi, Y., Kumada, H., & Sugawara, H. (2020). Functionalized mesoporous silica nanoparticles for innovative boron-neutron capture therapy of resistant cancers. *Nanomedicine: Nanotechnology, Biology, and Medicine*, *27*, 102195. https://doi.org/10.1101/471128

4 Issa, F., Ioppolo, J.A., & Rendina, L.M. (2013). Boron and Gadolinium Neutron Capture Therapy. *Comprehensive Inorganic Chemistry II (Second Edition): From Elements to Applications*, *3*(9), 877–900. https://10.1016/C2009-0-63454-1

5 Yoshida, F., Yamamoto, T., Nakai, K., Zaboronok, A., & Matsumura, A. (2015). Additive effect of BPA and Gd-DTPA for application in accelerator-based neutron source. *Applied Radiation and Isotopes*, *106*, 247–250. https://doi.org/10.1016/j.apradiso.2015.07.030

6 Huang, S., Li, C., Cheng, Z., Fan, Y., Yang, P., Zhang, C., Yang, K., & Lin, J. (2012). Magnetic Fe_3O_4@mesoporous silica composites for drug delivery and bioadsorption. *Journal of Colloid And Interface Science*, *376*(1), 312–321. https://doi.org/10.1016/j.jcis.2012.02.031

7 García-Fernández, A., Sancenón, F., & Martínez-Máñez, R. (2021). Mesoporous silica nanoparticles for pulmonary drug delivery. *Advanced Drug Delivery Reviews*, *177*, 113953. https://doi.org/10.1016/j.addr.2021.113953

8 Farhood, B., Samadian, H., Ghorbani, M., Zakariaee, S.S., & Knaup, C. (2018). Physical, dosimetric and clinical aspects and delivery systems in neutron capture therapy. *Reports of Practical Oncology and Radiotherapy*, *23*(5), 462–473. https://doi.org/10.1016/j.rpor.2018.07.002

9 Lee, W., Jung, K.H., Park, J.A., Kim, J.Y., Lee, Y.J., Chang, Y., & Yoo, J. (2021). In vivo evaluation of PEGylated-liposome encapsulating gadolinium complexes for gadolinium neutron capture therapy. *Biochemical and Biophysical Research Communications*, *568*, 23–29. https://doi.org/10.1016/j.bbrc.2021.06.045

10 Korolkov, I.V., Zibert, A.V., Lissovskaya, L.I., Ludzik, K., Anisovich, M., Kozlovskiy, A.L., Shumskaya, A.E., Vasilyeva, M., Shlimas, D.I., Jażdżewska, M., Marciniak, B., Kontek, R., Chudoba, D., & Zdorovets, M.V. (2021). Boron and gadolinium loaded Fe_3O_4 nanocarriers for potential application in neutron cancer therapy. *International Journal of Molecular Sciences*, *22*(16), 8687. https://doi.org/10.3390/ijms22168687

11 Ho, A., Ho, K., Thiele, T., & Schedler, U. (2012). Scope and Limitations of Surface Functional Group Quanti Fi Cation Methods: Exploratory Study with Poly(Acrylic Acid)-Grafted Micro- and Nanoparticles. *Journal of American Chemical Society*, *134* (19), 8268–8276. https://doi.org/10.1021/ja302649g

12 Shahbazi, M., Bahari, A., & Ghasemi, S. (2016). Studying saturation mobility, threshold voltage, and stability of PMMA-SiO_2-TMSPM nano-hybrid as OFET gate dielectric. *Synthetic Metals*, *32*, 100–108. https://doi.org/10.1088/1361-6528/aa87fa

13 Korolkov, I.V., Ludzik, K., Lisovskaya, L.I., Zibert, A.V., Yeszhanov, A.B., & Zdorovets, M.V. (2021). Modification of magnetic Fe_3O_4 nanoparticles for targeted delivery of payloads. *Bulletin of the University of Karaganda – Chemistry*, *101*(1), 99–108. https://doi.org/10.31489/2021Ch1/99-108

14 Purwar, R., Rajput, P., & Srivastava, C.M. (2014). Composite Wound Dressing for Drug Release. *Fibers and Polymers, 15*(7), 1422–1428. https://doi.org/10.1007/s12221-014-1422-2

15 Yue, J., Li, Y., Zhao, Y., Xiang, D., & Dai, Y. (2016). Thermal degradation behavior of carborane-containing phenylethynyl terminated imide systems. *Polymer Degradation and Stability*, *129*, 286–295. https://doi.org/10.1016/j.polymdegradstab.2016.05.006

16 Eaton, P., Quaresma, P., Soares, C., Neves, C., de Almeida, M.P., Pereira, E., & West, P. (2017). A direct comparison of experimental methods to measure dimensions of synthetic nanoparticles. *Ultramicroscopy*, *182*, 179–190. https://doi.org/10.1016/j.ultramic.2017.07.001

17 Kozlovskiy, A.L., Ermekova, A.E., Korolkov, I.V., Chudoba, D., Jazdzewska, M., Ludzik, K., Nazarova, A., Marciniak, B., Kontek, R., Shumskaya, A.E., & Zdorovets, M.V. (2019). Study of phase transformations, structural, corrosion properties and cytotoxicity of magnetite-based nanoparticles. *Vacuum*, *163*, 236–247. https://doi.org/10.1016/j.vacuum.2019.02.029

18 Bondarenko, L.S., Kovel, E.S., Kydralieva, K.A., Dzhardimalieva, G.I., Illés, E., Tombácz, E., Kicheeva, A.G., & Kudryasheva, N.S. (2020). Effects of modified magnetite nanoparticles on bacterial cells and enzyme reactions. *Nanomaterials, 10*(8), 1499. https://doi.org/10.3390/nano10081499

И.В. Корольков, А.В. Зиберт, Л.И. Лисовская, К. Луджик, М.В. Анисович,
М.М. Васильева, А.Е. Шумская, А. Усеинов, А.Б. Есжанов, М.В. Здоровец

Fe_3O_4 нанобөлшектеріне ди(*о*-карборан-1,2-диметил)борат және гадолиний иондарды қатар иммобилизациялау

Нейтрондыбасып алу терапиясы — рак клеткаларына арнайы изотоптарды мақсатты түрде жеткізуге және эпитермиялық 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. Мақалада темір оксиді нанобөлшектері (Fe_3O_4) нейтрондыбасып алу 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, энергодисперсиялық рентген спектроскопиясы, жарықтың динамикалық шашырауы және рентгендік фазалық талдаудың көмегімен зерттелді. Алынған нанобөлшектерде 15,4% бор және 1,5% гадолиний бар (EDA мәліметтері бойынша) және олардың орташа гидродинамикалық мөлшері 386 нм құрайды (DLS мәліметтері бойынша). HepG2 (қатерлі ісік жасушаларының желісі) және адам терісінің фибробласттары (қалыпты жасуша сызығы) қолданылған *in vitro* зерттеулер 0,05–1 мг/мл концентрация диапазонында төмен цитоуыттылықты көрсетеді.

Кілт сөздер: Fe_3O_4 нанобөлшектері, силан, беттік модификациялау, пайдалы жүктемені мақсатты жеткізу, БНҰТ, карборан, цитоуыттылық.

И.В. Корольков, А.В. Зиберт, Л.И. Лисовская, К. Луджик,
М.В. Анисович, М.М. Васильева, А.Е. Шумская, А. Усеинов, А.Б. Есжанов, М.В. Здоровец

Одновременная иммобилизация ионов гадолиния и ди(*о*-карборано-1,2-диметил)бората на наночастицы Fe_3O_4

Нейтронозахватная терапия — перспективный метод лечения рака, основанный на адресной доставке специфических изотопов в раковые клетки и последующем облучении эпитепловыми нейтронами. В результате выделено большое количество энергии на расстояние, сравнимое с размером клетки, разрушая ее изнутри. Для адресной доставки изотопов могут быть использованы магнитные наночастицы оксида железа. В статье наночастицы оксида железа (Fe_3O_4) 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, энергодисперсионной рентгеновской спектроскопии, 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 HepG2 (линия раковых клеток) и фибробласты кожи человека (нормальная линия клеток) показывают низкую цитотоксичность в диапазоне концентраций 0,05–1 мг / мл.

Ключевые слова: наночастицы Fe_3O_4, силан, модификация поверхности, адресная доставка полезного груза, БНЗТ, карборан, цитотоксичность.

Information about authors*

Korolkov, Ilya Vladimirovich (corresponding author) — PhD, Senior Researcher of the Institute of Nuclear Physics, Abylay khana 2/1, 010000, Nur-Sultan, Kazakhstan; e-mail: i.korolkov@inp.kz, https://orcid.org/0000-0002-0766-2803

Zibert, Aleksandr Vitalevich — Student of L.N. Gumilyov Eurasian National University, Satbayev str., 2, 010000, Nur-Sultan, Kazakhstan; e-mail: alexandr.zibert@bk.ru, https://orcid.org/0000-0003-0218-4790

Lisovskaya, Lana Igorevna — Engineer of the Institute of Nuclear Physics, Abylay khana 2/1, 010000, Nur-Sultan, Kazakhstan; e-mail: ms.defrance@mail.ru, https://orcid.org/0000-0002-3894-6366

Ludzik, Katarzyna — Researcher of Department of Physical Chemistry, University of Lodz, 90-137, ul. Uniwersytecka 3, 90-137 Łódź, Poland; e-mail: katarzynaludzik82@gmail.com, https://orcid.org/0000-0003-1749-808X.

Anisovich, Marina Vladimirovna — Senior Researcher of Republican Unitary Enterprise, Scientific-Practical Centre of Hygiene, 220012, 8 Akademicheskaya st., Minsk, Belarus, e-mail: m_anisovich@mail.ru, https://orcid.org/0000-0002-9179-7523

Vasilyeva, Marina Maksimovna — researcher of Republican Unitary Enterprise, Scientific-Practical Centre of Hygiene, 220012, 8 Akademicheskaya st., Minsk, Belarus, e-mail: m_vasilyeva@gmail.com, https://orcid.org/0000-0002-8548-1960

Shumskaya, Alena Evgenievna — Senior Researcher of the Institute of Chemistry of New Materials, National Academy of Sciences of Belarus, 220072 Minsk, Belarus, e-mail: lunka7@mail.ru, https://orcid.org/0000-0001-5429-820X

Usseinov, Abay — Senior Lecturer at L.N. Gumilyov Eurasian National University, 010008 Astana, 2 Satpayev str., Kazakhstan, e-mail: usseinov_ab@enu.kz, https://orcid.org/0000-0002-4066-8422

Yeszhanov, Arman Bachitzhanovich — Junior Researcher of the Institute of Nuclear Physics, Abylay khana 2/1, 010000, Nur-Sultan, Kazakhstan; e-mail: arman_e7@mail.ru, https://orcid.org/0000-0002-1328-8678

Zdorovets, Maxim Vladimirovich — Candidate of Physical and Mathematical Sciences, Director of the Astana Branch of the Institute of Nuclear Physics, Abylay khana 2/1, 010000, Nur-Sultan, Kazakhstan; e-mail: mzdorovets@inp.kz, https://orcid.org/0000-0003-2992-1375

*The author's name is presented in the order: *Last Name, First and Middle Names*