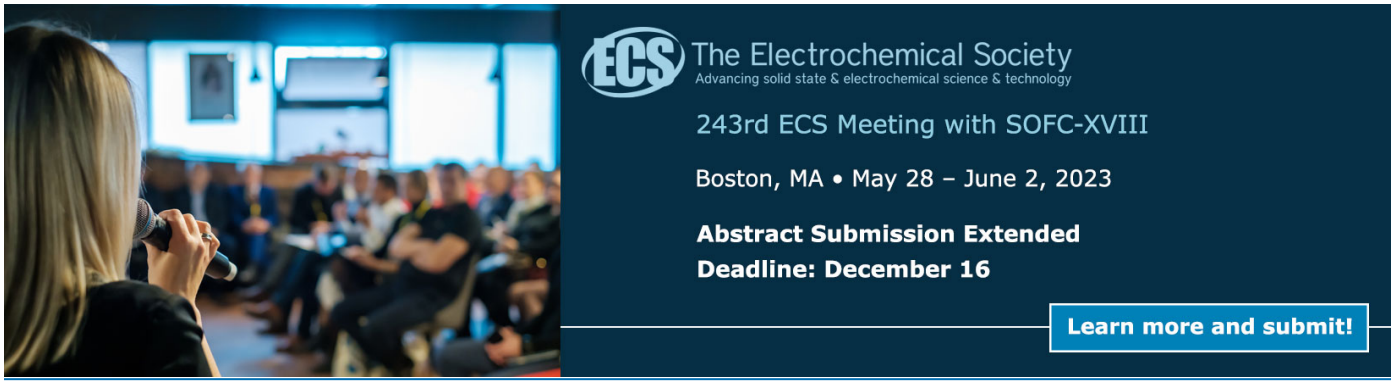
$Gd_xFe_{3-x}O_4$ nanoparticles with silane shell as potential theranostic agent for cancer treatment



$Gd_xFe_{3-x}O_4$ nanoparticles with silane shell as potential theranostic agent for cancer treatment.

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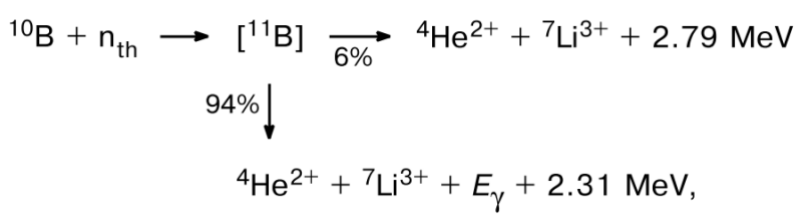
Abstract. In this study of $Gd_xFe_{3-x}O_4$ compound core silane shell nanoparticles method is represented. Samples were analyzed with SEM, EDA and FTIR spectroscopy. Further attaching of carborane compounds is discussed. Products can be used in biomedical applications for MRI imaging and drug delivery for NCT, so can be considered as potential theranostic agents for cancer treatment.

1. Introduction

Since cancer disease is the second leading reason of death worldwide according to WHO, it's treatment remains an actual problem [1]. Traditional methods, for example surgery or chemotherapy might be invasive and cause negative consequences [2,3]. On the other hand, new approaches are appearing, such as radiotherapy, cancer hyperthermia, gene therapy etc. [4–6]. Even though radiotherapy is effective and used in almost 50% cases of cancer treatment, there is a type of radioresistant tumors, which demand special approach [7,8].

One of these promising approaches is neutron capture therapy (NCT): some isotopes are being delivered to the cancer tissues and irradiated by epithermal neutron flux. Resulting products of neutron capture reaction are bombarding cell's DNA, damaging it and causing apoptosis process to start. If the pathlength of particles are small enough, healthy tissues, surrounding the tumor, would not be injured. Consequently, ^{10}B isotope might be used in this therapy due to its large neutron-capture cross section. Scheme of neutron capture reaction is represented at scheme 1.



Scheme 1. ^{10}B neutron capture reaction.

The resulting α-particle's pathlength is ~ 4μm - 9μm, which is less then cell's diameter, that's why isotopes should be delivered precisely to tumor [9]. Also using ^{157}Gd isotopes with ^{10}B has synergetic effect which causes the decreasing the survival of cancer cells by 80-90% [10]. That shows requirement in new method for simultaneous delivery of ^{10}B and ^{157}Gd isotopes. The resulting α-particle's pathlength is ~ 4μm -9μm, which is less then cell's diameter. Another benefit of adding Gd is that is Gd considered to be well known enhancer for MRI. MRI can be provided before the irradiation by neutrons for diagnostic purposes and estimating the area where drugs have been delivered [11].

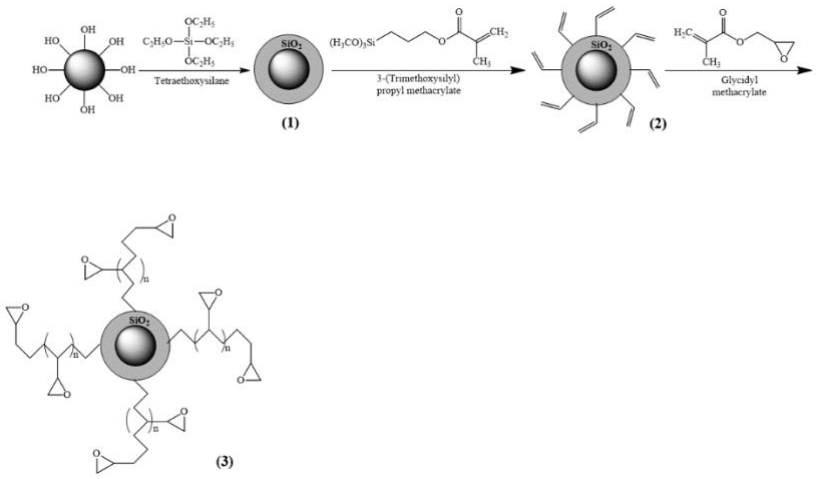
Drug delivery via nanoparticles can achieve better efficiency of cancer treatment including NCT due to the possibility to encapsulate drug, which will protect it from degradation, ability of nanoparticles to penetrate through vascular architecture, large surface-to-volume ratio, possibility to immobilize drugs to the surface via chemical modification [12,13].

In this study we represent the method of synthesis $Gd_xFe_{3-x}O_4$ nanoparticles covered with silane shell and functionalized with epoxy groups for the further carborane immobilization.

2. Experimental part

2.1. Synthesis of $Gd_xFe_{3-x}O_4$ nanoparticles

$Gd_xFe_{3-x}O_4$ nanoparticles were synthesized by chemical precipitation method [14]. In brief, 1.418 g of $FeCl_3 \cdot 6H_2O$ and 3g of $Gd(NO_3)_3 \cdot 6H_2O$ were dissolved in 100 ml of deionized water. The reaction was kept under vigorous stirring and argon flux. The temperature was adjusted to 90℃. Then ammonium hydroxide was dropwise added until pH was adjusted to 9. Reaction was kept for 5 h. Then the precipitate was separated, washed with deionized water until pH became normal. Then nanoparticles were modified according to Scheme 2.



Scheme 2. Steps by step functionalization of $Gd_xFe_{3-x}O_4$ nanoparticles.

2.2 Covering the nanoparticles with tetraethoxysilane (TEOS)

1g of $Gd_xFe_{3-x}O_4$ nanoparticles was dispersed in 200 ml of EtOH by ultrasonication. Reaction was kept under argon flux and vigorous stirring. Then 6 ml of TEOS and 10 ml of ammonium hydroxide was added. Reaction lasted for 5h at 50℃. Then the particles were separated, washed with ethanol and diethyl ether.

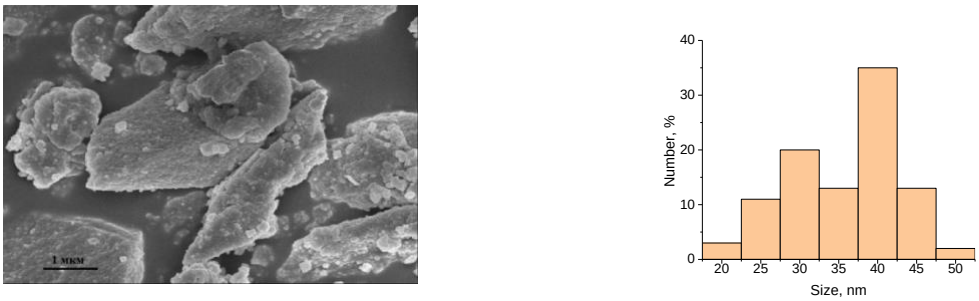
2.3 Functionalizing the surface by C=C double bonds

1 g of nanoparticles was dispersed in 100 ml of *o*-xylol. Reaction was kept under neutron flux and vigorous stirring at 70℃. Then 10 ml of Trimethoxysislylpropyl methacrylate was added. Reaction was lasting for 5 h.

2.4 Graft polymerization with glycidyl methacrylate (GMA)
0.5 g of as prepared nanoparticles was dispersed in 50 ml of *o*-xylol. Reaction was kept under argon flux and at vigorous stirring. Then 4 ml of GMA and 0.05g of benzoyl peroxide were added to the reaction. The temperature was adjusted to 75℃ and kept for 24 h. Then the precipitate was separated and washed with acetone and water.

3. Results and discussion

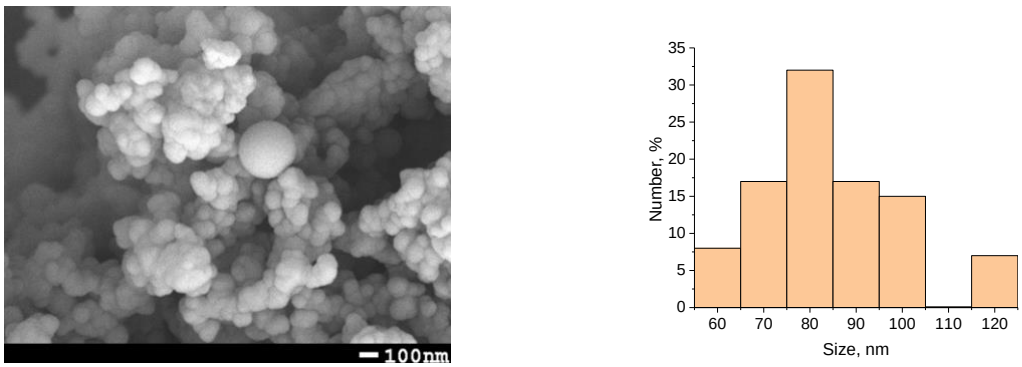
The synthesis of $Gd_xFe_{3-x}O_4$ nanoparticles is familiar with the synthesis of magnetite nanoparticles, but due to the presence of gadolinium salt, gadolinium ions are doping the lattice. SEM scans and size distribution of particles are shown at Figure 1.



A B

Figure 1. A. SEM scans of $Gd_xFe_{3-x}O_4$ nanoparticles B. Size distribution.

Due to this distribution the average size of this particles is 33 nm and ranges from 7 to 75 nm. After that nanoparticles were covered by TEOS shell via the polycondensation reaction to the hydroxy groups at the surface of the $Gd_xFe_{3-x}O_4$ nanoparticles. Since particles are covered by TEOS they are less subjected to degradation in human body, also it might reduce toxic properties of gadolinium. SEM scans of this steps are shown at Figure 2.

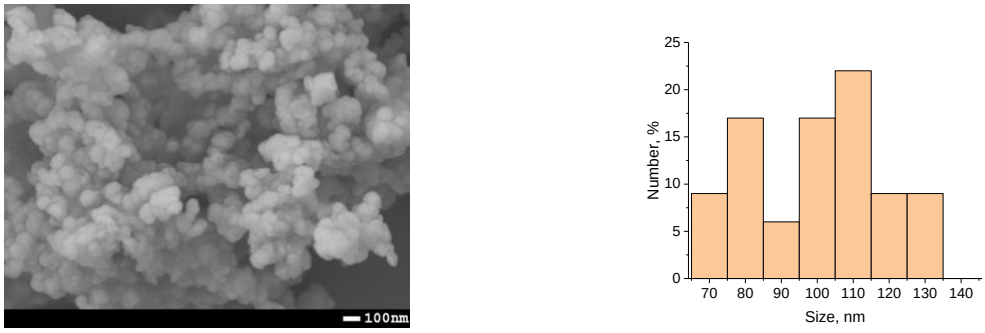


A B

Figure 2. A. SEM scans of $Gd_xFe_{3-x}O_4$-TEOS nanoparticles B. Size distribution.

As we can se from given size distribution average size was increased by 50 nm and became 83 nm. Also, we can observe that particles are more conglomerated, probably because of change of zeta potential.

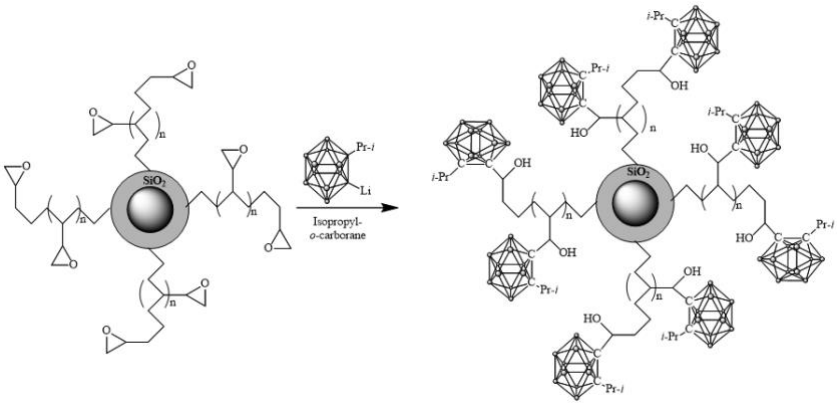
The next step is treating nanoparticles with TMSPM in order to functionalize their surface with double bonds. In this case methoxy groups are being removed from TMSPM and bounded with OH groups of TEOS (Figure 3)



A B

Figure 3. A. SEM scans of $Gd_xFe_{3-x}O_4$-TEOS-TMSPM nanoparticles B. Size distribution.

After treating with TMSPM Size was increased by 12% up to 95 nm. The next step is thermoinitiated graft polymerization of GMA. GMA can be bounded to C=C double bonds by its methacrylic bonds. Then, it is possible to immobilize boron containing carborane compounds via epoxy groups of GMA (Scheme 3) [15].



Scheme 3. Immobilization of carboranes.

EDA analysis also confirms the formation of shells (Table 1).

Table 1. Data of EDA analysis

Sample	Atomic content, %				
	Fe	O	Gd	Si	C
$Gd_xFe_{3-x}O_4$	20,55	40,23	9,82	-	-
$Gd_xFe_{3-x}O_4$–ТЭОС	4,35	47,20	2,02	36,34	6,53
$Gd_xFe_{3-x}O_4$–ТЭОС- ТМПМА	1,88	56,01	1,15	20,93	18,73

We can observe that after treating with silanes elemental content is being altered. After treating with TEOS and TMSPM content of Si and C was increased up to 20,93 and 18,73 at. % respectively.

Samples were examined by FTIR spectroscopy (Figure 4).

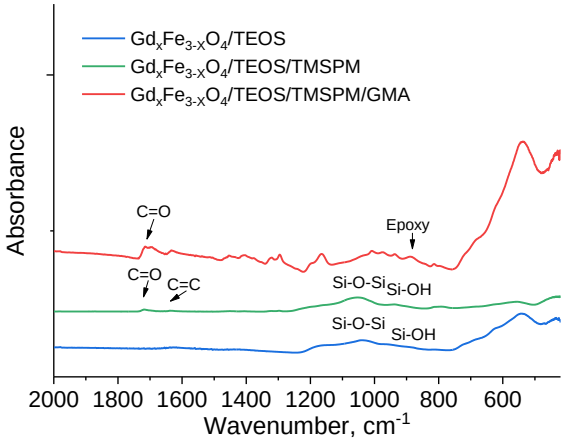


Figure 4. FTIR analysis of prepared samples.

The coating of nanoparticles with TEOS led to the appearance of peaks at 1041 and 1150 cm^{-1} (Si-O-Si) and 913 cm^{-1} (Si-OH). This indicates the incompleteness of the reaction. Further modification by TMSPM led to appearance of C=O peak at 1728 cm^{-1} and C=C at 1640 cm^{-1}. FTIR analysis also confirms grafting of GMA through detection of new peaks at 890 cm-1 (epoxy ring stretching). Thus, FTIR analysis support chemical reactions presented in Scheme 2.

4. Conclusion

Average size of particles is 95 nm. Shell formation and its modification was confirmed by SEM, EDA and FTIR spectroscopy. After carborane immobilization these nanoparticles might be used as potential agents in NCT and for MRI, so can be considered as theranostic agents.

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