On Demand Degradable h-BN–Fe_3O_4 Nanocomposite Powders for BNCT Delivery Agents (Focused Mini-Review)

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Abstract: This mini-review is focused on the nanopowder composite material h-BN–Fe_3O_4 (hexagonal boron nitride–magnetite) developed by the author's research group in recent years. Effective methods of their synthesis, structural and morphological characteristics, and physical properties are briefly described. They show that h-BN–Fe_3O_4 composite nanoparticles can serve as boron isotope ^{10}B delivery agents in BNCT (Boron-Neutron-Capture-Therapy) having high medical efficacy with controlled delivery, low toxicity and on-demand degradability.

Keywords: Boron nitride, Magnetite, Nanopowder composite, Therapeutic agents controlled delivery, Boron-Neutron-Capture-Therapy.

INTRODUCTION

Boron-rich compounds and composites are of interest for the BNCT (Boron-Neutron-Capture-Therapy), which from last decade has been actively utilized for treatment of some types of aggressive cancers, where standard chemo- and more obvious radiation therapies reveal lowered efficacy (see *e.g*. [1-4]). Recent review [5] considering the BNCT in connection with next-generation boron drugs shows that this is a therapy with high LET (Linear Energy Transfer) facilitating the delivery of radiation targeted to tumor and almost sparing healthy cells by targeting ^{10}B-containing species to cancer ones. Then, elaboration of new ease delivery agents with high payloads and selectivity is the field of intensive investigations.

Usually, the delivery of neutron-absorbing centers, *i.e*., ^{10}B isotopes, to cancer cells is done using the boron-containing macromolecules characterized by a predominant accumulation in the tumor. But, the low content of boron in such carriers leads to its insufficient concentration in the target tumor tissue as well. In current clinical practice of BNCT, only two types of boron-containing drugs with moderate selectivity have been frequently utilized. These are: BSH (sodium borocaptate) and BPA (boronophenylalanine).

Then, their replacing by tumor-targeted boron compounds or composites having heightened *in vivo* and/or *in vitro* efficacies are required. To be useful for BNCT, they also should meet the following conditions: (i) critical tumor concentration (at least ~30 μg^{10}B/g); (ii) high tumor- and low normal-tissues uptakes; (iii) rapid normal-tissue clearance, but persistence in tumor-tissue during the treatment procedure; and (iv) lowered toxicity.

There are available several reports on attempts to overcome this problem by developing boron-containing nanosystems (for delivering at least 20 ppm of B to the tumor cell). From their analysis choice was done [1] for hexagonal boron nitride h-BN (and boron carbide B_4C as well) based drug delivery nanocarriers for its: (i) high boron content; (ii) good tumor-to-nontumor boron accumulation ratio; (iii) good biocompatibility; (iv) low toxicity and almost negligible side-effects related to high chemical/oxidative stability; (v) overcoming the cancer multidrug resistance mechanisms; and (vi) possibility of rapid on-demand degradation under physiological conditions.

To the best of our knowledge, for the first time boron nitride nanotubes as ^{10}B-carriers were used in [6] to enhance the BNCT selective targeting and ablative efficacy for tumors. Following BN nanotubes dispersion in aqueous solution by noncovalent coating with biocompatible PLL (Poly-L-Lysine) solutions, they were

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[1] Makatsaria Sh, Chkhartishvili L, Chedia R, Tsagareishvili O. Boron carbide and nitride nanoparticles as ^{10}B-isotope delivering agents in boron-neutron-capture-therapy. In: Chkhartishvili L, Chikhradze M, editors. Abstracts of the 6th International Conference "Nanotechnology" (GTU nano 2021). Tbilisi, Georgia 4 – 7 October 2021. Georgian Technical University 2021: p. 80.

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functionalized with a fluorescent probe (in form of quantum dots to enable their tracking) and folic acid as selective tumor targeting ligand. *In vitro* studies confirmed substantive and selective uptake by glioblastoma multiforme cells. Again BN nanotubes were functionalized [7] under relatively mild conditions using a difunctional amine, *e.g.*, glycine, with targeting ligand folic acid (antibody against nerve growth factor). The BN nanotubes were loaded with a fluorescent probe for convenient imaging of treated glioblastoma multiforme cells. They demonstrated an increased efficiency of internalization in glioblastoma multiforme cells compared to non-modified ones.

Using the CVD (Chemical-Vapor-Deposition), the BNNPs (Boron-Nitride-NanoParticles) of nearly spherical form (100–150 nm in diameter) with smooth or peculiar petal-like surfaces were first fabricated [8] and then loaded with DOX (DOXorubicin) with efficacy about 0.095 mg/mg. BN–DOX nanoparticles were relatively stable at neutral pH, whereas DOX was effectively released at acidic pH. Using confocal microscopy, the uptake of BN–DOX nanoparticles by various cells, was studied. After intracellular delivery, most of them were found in the endosomes or lysosomes. BNNPs are especially promising due to their high B-content and good biocompatibility as they can undergo rapid degradation under physiological conditions.

To design an on-demand degradable boron carrier, BNNPs were coated [9] by a PTL (Phase-Transitioned-Lysozyme) that protects them from hydrolysis during blood circulation and can be readily removed by vitamin C after BNCT. The coated BNNPs exhibited high tumor B-accumulation, while maintaining a good tumor-to-nontumor ratio. Compared with the control group, animals treated with BNCT showed suppression of tumor growth, while almost negligible side-effect was observed. Strategy of on-demand degradation of BNNPs avoids the toxicity caused by their long-term accumulation.

For h-BN nanopowders (as well as some isostructural carbon nanomaterials), it was developed [2] several versions of chemical synthesis methods from liquid charge.

It should be also mentioned that h-BN nanosheets and nanotubes possess properties which enable them to be promising in the manipulations, including their functionalization with various organic molecules and biospecies [10], some of biomolecules reveal affinity to and selectivity for h-BN [11]; and solid-state thermal neutrons detector based on ^{10}B-enriched h-BN epitaxial layer demonstrated its high detection efficiency [12].

A novel approach (see conference presentations in Paris [3] and Frascati [4], and also review [13]) lies in the basic idea of responding to the above challenge of medical physics by creating h-BN magnetic nanopowders that can be transported to tumor cells with exposure to an external magnetic field.

In this mini-review, we are focused on the nanopowder composite material h-BN–Fe_3O_4 (hexagonal boron nitride–magnetite) developed in recent years. Some methods of its synthesis, structural and morphological characteristics, and physical properties are briefly described. The conclusion is done that h-BN–Fe_3O_4 composite nanoparticles can serve as boron isotope ^{10}B delivery agents having high medical efficacy in combination with controlled delivery, low toxicity and on demand degradability.

OBTAINING METHODS

In the literature, there are available some reports on formation different h-BN based magnetic nanomaterials. Boron nitride with a few layers is structurally similar to graphene. It is why they frequently act as similar chemical reagents. This is clearly seen in intercalation ability with different species [14, 15]. Growth mechanism of nanocomposites BN–Fe can be based on this analogy [16].

One of the methods of obtaining h-BN–Fe or h-BN–Fe_3O_4 compositions can be the iron compounds reduction in the presence of boron nitride [17]. That technique involves reduction of Fe(II) to Fe(O) followed by aerial oxidation and then application in the

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[3] Makatsaria Sh, Chkhartishvili L, Mirzayev M, Barbakadze N, Tsagareishvili O, Jinikashvili I, *et al*. Nanopowder h-BN:Fe(Fe_3O_4) as ^{10}B delivery agent in BNCT. In: Abstracts of the 21st International Symposium on Boron, Borides and Related Materials. Paris, France 5 – 9 September 2022. Sorbonne University 2022: p. 33.

[4] Makatsaria Sh, Chkhartishvili L, Chedia R, Barbakadze N, Tsagareishvili O, Kekutia Sh, *et al*. Coating and intercalation of h-BN nanoparticles with Fe and Fe_3O_4. In: Abstracts of the Conference "Nanoscience and Nanotechnologies – 2023". Frascati, Italy 29 May – 1 June 2023. National Institute for Nuclear Physics – Frascati National Laboratory 2023: p. 122.

multicomponent reactions. The nano zero-valence iron formed during the reduction of iron(II) sulphate $FeSO_4$ intercalates in the h-BN matrix, which further oxidizes to Fe_3O_4 forming the h-BN–Fe_3O_4 composite. A composite material in form of magnetite nanoparticles supported by h-BN, was also prepared via mussel-inspired chemistry of dopamine by hydrothermal synthesis [18]. Obtained h-BN decorated with Fe_3O_4 nanoparticles exhibits a remarkable superiority in enhancing the anticorrosion performance of epoxy coatings as lamellar structural h-BN and nano-Fe_3O_4 provide a significant synergistic effect.

It was demonstrated [19] the tailoring of a magnetic nanocomposite through h-BN templates hybridization with magnetic nanomaterial such as well-dispersed Fe_3O_4 superparamagnetic nanoparticles. These magnetic nanoscrolls derivatives may be suitable for high-performance nanocomposite materials useful, in particular, in medical devices.

Patterned growth of magnetic boron nitride nanostructures in forms of hexagonal nanosheets and bamboo-like nanotubes was achieved [20] by thermal CVD technique at 1150°C from amorphous boron and ammonia NH_3 as reagent gas using iron compounds mixture FeS–Fe_2O_3 catalyst. Experimental and theoretical insights in catalytic properties of Fe_3O_4/BN, Fe_3O_4(Pt)/BN, and FePt/BN heterogeneous nanomaterials in CO_2 hydrogenation reaction were done in [21] based on their microstructure.

The h-BN nanosheets functionalized with Fe_3O_4 serve [22] for arsenic adsorbents to remove them from wastewater. Similarly, boron nitride nanosheets functionalized with Fe_3O_4 and $CoFe_2O_4$ magnetic nanoparticles are found [23] to be useful for nanofiltration applications.

Some of previously known obtaining methods for boron nitride (in addition to that of isostructural carbon) nanomaterials doped with ferromagnetic clusters were presented in [24]. For effective synthesizing the nanopowder composite h-BN–Fe_3O_4, it was specially modified a chemical approach using liquid-charges, which initially was developed [25] for advanced boron carbide matrix nanocomposites.

In detail they are described in papers [26-28] and proceedings of the Paris, Tbilisi and Kyiv conferences together with obtained materials structure and some physical properties:

▪ Makatsaria Sh, Chkhartishvili L, Barbakadze N, Tsagareishvili O, Kekutia Sh, Markhulia J, *et al*. Magnetite-doped nanopowder boron nitride for ^{10}B delivery agent in BNCT. Solid State Sci 2024 – *to be published*.

▪ Makatsaria Sh, Chkhartishvili L, Tsagareishvili O, Chedia R, Gabunia V, Kekutia Sh, *et al*. Hexagonal 2D-materials intercalation by magnetic clusters. In: Tatrishvili T, Abadie MJM, editors. Advanced Topics in Polymer Chemistry and Materials Science. Current Strategies and Future Prospects of Nanomedicine. Palm Bay: Apple Academic Press 2025; Part 5, Ch. 24 – *accepted for publication*.

▪ Chkhartishvili L, Makatsaria Sh, Barbakadze N, Tsagareishvili O, Batsikadze T, Kekutia Sh, *et al*. Synthesis of 2D-material(G,GO,rGO,h-BN)–magnetic(Fe,Fe_3O_4) nanocomposites. Nano Hybr Compos. 2024 – *accepted for publication*.

Here we consider three most recently prepared [5] and characterized [6] series of h-BN based magnetic nanocomposite samples.

Sample 1 is of composition h-BN–Fe_3O_4. It synthesized in the presence of boron nitride by co-precipitation from compounds of iron(II) and iron(III). This route uses the reaction: $FeSO_4 + 2\ FeCl_3 + 8\ NH_4OH \rightarrow Fe_3O_4 + (NH_4)_2SO_4 + 6\ NH_4Cl + 4\ H_2O$. 10 g of h-BN, 2.8 g of $FeSO_4{\cdot}7H_2O$, and 5.4 g of $FeCl_3{\cdot}6H_2O$ are placed in a 250 ml flask with thermometer, dropping funnel and gas tube. Flask filled with Ar is added with 100 ml of 50°C distilled water. After 30 min, 13 ml of 25% solution of ammonia is added drop-by-drop. The obtained suspension of black color at 75°C is stirred for 3 h. Then it is cooled down (to room temperature). Obtained precipitate of black color is washed in water and ethanol. Then precipitate is filtered in Ar flow and again washed in anhydrous ethanol. Wet mass obtained in this way for 6 h at temperature 120°C is dried in vacuum. The obtained black mass of h-BN–Fe_3O_4 composite is stored under Ar atmosphere (as it changes color and turns brown in humidity).

Sample 2 is composite h-BN–Fe obtained by iron deposition on boron nitride using iron(O)

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pentacarbonyl. As iron carbonyl is known as a strong poisonous substance, process is conducted in a fume cupboard. In teflon flask, 3 g of h-BN is added with 2.5 ml iron(O) pentacarbonyl. This mixture is stirred on a magnetic stirrer for 1 h at room temperature under argon atmosphere. Then the test tube is placed in 0.5 l autoclave (high pressure reactor) with teflon-covered inner surface under argon atmosphere, heated at 50°C/min and retained for 2 h at 200°C. Autoclave is vacuumed for 2 h at temperature of 120–140°C using the connected vacuum system. Obtained black powder showing magnetic properties is stored in a desiccator. Note that impregnation of iron in h-BN is also possible carried out at 150–200°C by flowing $Fe(CO)_5$ vapor (under argon atmosphere, 120 min).

Sample 3 is h-BN–Fe_3O_4 composite prepared by using iron(O) pentacarbonyl. In teflon flask, 3 g of h-BN is added with 2.5 ml of iron(O) pentacarbonyl and then for 2 h is stirred magnetically at room temperature under Ar. Reaction mixture added with 2 ml of water is placed in a 0.5 l autoclave (high pressure reactor) with teflon-covered inner surface under argon atmosphere. Process is conducted in following conditions: holding temperature and time are 200°C and 2 h, respectively. Then the autoclave is vacuumed at 120–140°C for 2 h by connected vacuum system. Obtained black magnetic powder is stored in a desiccator.

STRUCTURE AND PROPERTIES

Figures **1**-**3** present the SEM (Scanning-Electron-Microscopy) images of above described three samples. It's possible to see the presence of Fe_3O_4 on the surface of h-BN.

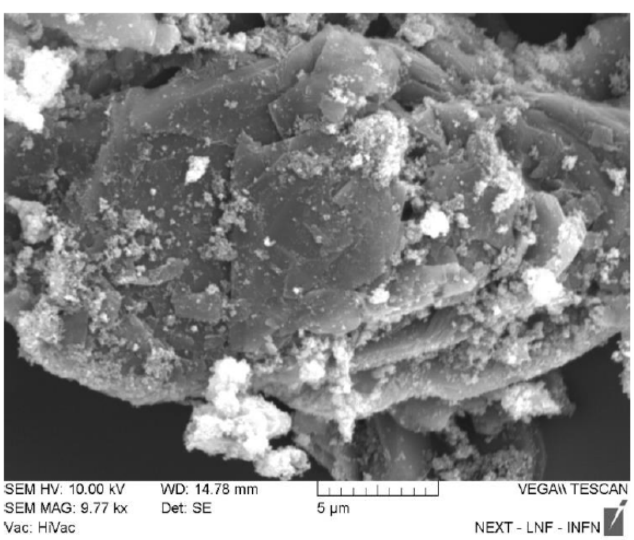

Figure 1: SEM image of h-BN–Fe_3O_4 composite obtained by co-precipitation of iron(II) and iron(III) compounds in presence of h-BN.

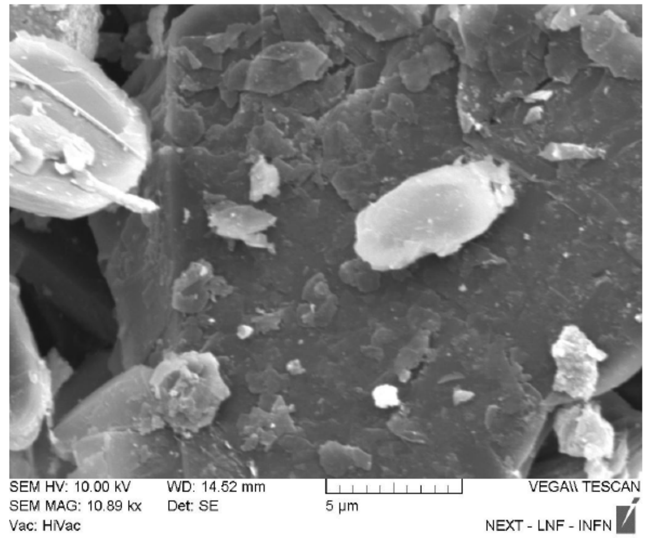

Figure 2: SEM image of h-BN–Fe composite obtained by iron deposition on boron nitride using iron(O) pentacarbonyl.

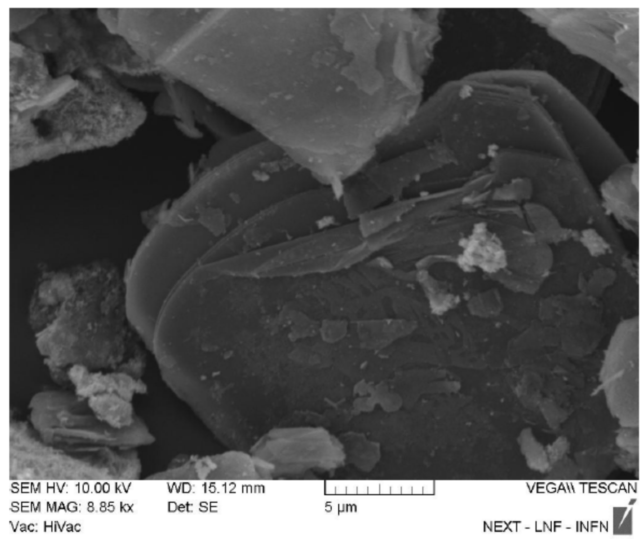

Figure 3: SEM image of h-BN–Fe_3O_4 composite obtained by using iron(O) pentacarbonyl.

Tables **1**-**3** show the results of EDX (Energy-Dispersive-X-ray) analysis of elements content in same three samples.

Their Raman spectra (Figure **4**) can be interpreted based on data [19] available on rolled up boron nitride hexagonal nanosheets tailored with Fe_3O_4 superparamagnetic nanoparticles: (i) a blu shift of 1346 cm^{-1} peak (*Sample 1*) to 1364 and 1361 cm^{-1} (*Samples 2* and *3*, respectively) is noticed; (ii) despite the predominant presence of the peak at 1360 cm^{-1}, other peaks of weak intensity can be seen at around 200, 270, 390 and 660 cm^{-1}; (iii) the peak at 660 cm^{-1} of *Sample 3* shows a red shift of 7 cm^{-1} compared to *Sample 2*; (iv) the blue shift of the E_{2g} phonon mode indicates a slightly shorter B–N bond, probably caused

Table 1: Content of Elements in Composition h-BN–Fe_3O_4 Synthesized from h-BN Using Co-precipitation of Compounds of Iron(II) and Iron(III) (wt.%)

Statistics	B	C	N	O	Mg	S	Fe
Maximal	29.96	13.85	38.01	26.63	0.22	0.13	15.92
Minimal	21.17	8.62	22.98	17.52	0.08	0.05	5.63
Average	24.65	12.28	29.41	21.38	0.17	0.10	12.02
Deviation	3.85	2.48	6.51	3.83	0.06	0.04	4.67

Table 2: Content of Elements in h-BN–Fe Composite Obtained by Iron Deposition on Boron Nitride Using Iron(O) Pentacarbonyl (wt.%)

Statistics	B	C	N	O	Fe
Maximal	22.88	21.52	39.13	8.82	7.65
Minimal	22.88	21.52	39.13	8.82	7.65
Average	22.88	21.52	39.13	8.82	7.65
Deviation	0.00	0.00	0.00	0.00	0.00

Table 3: Content of Elements in h-BN–Fe_3O_4 Composite Obtained by Using Iron(O) Pentacarbonyl (wt.%)

Statistics	B	C	N	O	Mg	Al	Fe
Maximal	27.46	17.40	38.29	51.96	7.06	12.48	15.54
Minimal	13.41	5.79	7.27	11.58	0.23	12.48	2.03
Average	19.61	10.81	24.42	32.66	–	–	7.56
Deviation	5.90	4.86	14.17	17.04	–	–	5.76

by isolated monolayers or compressive stresses compared with h-BN.

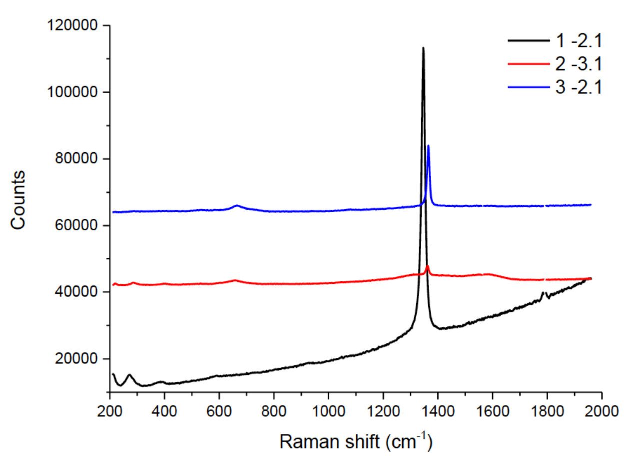

Figure 4: Raman spectra of: (1) composite h-BN–Fe_3O_4 synthesized in presence of h-BN by co-precipitation of iron(II) and iron(III) compounds; (2) h-BN–Fe composite obtained by iron deposition on boron nitride using iron(O) pentacarbonyl; and (3) h-BN–Fe_3O_4 composite obtained by using iron(O) pentacarbonyl.

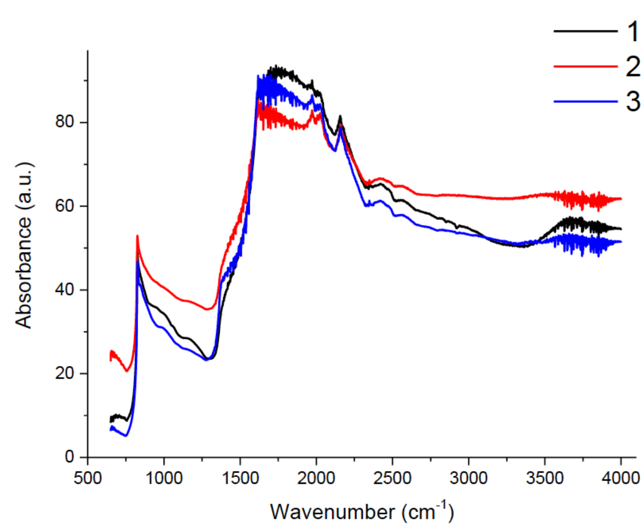

Figure 5: FTIR spectra of: (1) composite h-BN–Fe_3O_4 obtained in presence of h-BN by co-precipitation of iron(II) and iron(III) compounds; (2) h-BN–Fe composite obtained by iron deposition on boron nitride using iron(O) pentacarbonyl; and (3) h-BN–Fe_3O_4 composite obtained by using iron(O) pentacarbonyl.

FTIR (Fourier Transform InfraRed) spectra (Figure **5**) of these three samples were analyzed on the basis of information [18] detected for h-BN samples decorated with Fe_3O_4 nanoparticles: (i) the three samples show almost the same patterns; (ii) apparently, the peak at 3500 cm^{-1} is due to the presence of residual alcohol used to clean the instrument; and (iii) the peaks at 800 and 1390 cm^{-1} could be related, respectively, to B–N bending and stretching.

FTIR spectra of h-BN–Fe composites samples prepared earlier showed main peaks characteristic of h-BN at 762 and 1356 and 758 and 1349 cm^{-1} related, respectively, to bending B–N–B and tension B–N vibrations. However maghemite Fe_2O_3 fingerprint peak was not detected, which indicates that interaction between iron oxide and hydrogen reduces iron. Such reduction depends on reaction routes and conditions, nanoparticles size, and some other factors [21]. In the spectra of h-BN–Fe_3O_4 composites, the peaks characteristic of h-BN were observed, respectively, at 794 and 1366 and 766 and 1349 cm^{-1}. In addition, they revealed peaks characteristic of the Fe–O bond [22]: 560 and 562 cm^{-1}. This indicates that the tested samples indeed contained magnetite Fe_3O_4 phase in addition to h-BN. It should be emphasized that intensities and positions of these peaks are determined by both components, h-BN and Fe_3O_4, and then vary with the magnetite dopants concentration. Peaks at 3420–3250 cm^{-1} can be related [23] to stretching vibrations of boron–hydroxyl group B–OH due to absorbed water molecules.

Some of magnetic properties, in particular, the room temperature magnetization curves and hysteresis loops parameters were previously determined [29] for different five series of h-BN based magnetic composite samples: *Sample I* – BN–Fe obtained from $FeSO_4$ with $NaBH_4$; *Sample II* – BN–Fe obtained from BN–Fe_2O_3 with hydrogen H_2; *Sample III* – BN–Fe_3O_4 obtained by co-precipitation of Fe(II) and Fe(III) compounds; *Sample IV* – BN–Fe obtained by decomposition of Fe(O) pentacarbonyl; and *Sample V* – BN–Fe_3O_4 obtained in presence of water H_2O by Fe(O) pentacarbonyl decomposition.

Magnetization curves of *Samples I*, *II* and *V* exhibit hysteresis loops with similar shapes. The magnetization of these samples rises with the increasing magnetic field. At 14 kG, the applied magnetic field maximum, their magnetizations M_{Hmax} were, respectively, 26.5, 18.0 and 6.75 emu/g. Note that the magnetization of *Sample I* was not saturated at H_{max}. As for the *Sample II*, the M_{Hmax} value was very close to the saturated magnetization M_S. And for *Sample V*, the M_{Hmax} value coincided with M_S. For these three samples remnant magnetization M_R and coercive force H_C equal, respectively, 1.85, 3.80, 1.76 emu/g and 114, 456, 164 G. All of them exhibit soft magnetic materials characteristic behavior. And *Sample I* is mostly similar to superparamagnetic materials.

The room temperature magnetization curves of rest *Samples III* and *IV* display so-called S-shaped hysteresis loops, which are too thin because of no remnant magnetization and almost negligible coercivity. The *Sample III* actually with no coercivity (M_{Hmax} = 16 emu/g) and, therefore, this nanocomposite exhibited the superparamagnetic behavior. Coercivity of *Sample IV* is small (H_C = 63 G and M_{Hmax} = 24.5 emu/g) and it reveals something similar behavior with the *Sample I*.

INTRODUCTION OF CURRICULUM IN EDUCATION

Let mention that BNCT-related nanotechnology is considered as one of the important topics for introduction of curriculum in medical education. [7]

In the Georgian Technical University (Tbilisi, Georgia), in this direction it has been prepared one PhD dissertation:

▪ Makatsaria Sh. Boron ^{10}B Isotope Delivery Nanoagents in Cancer Neutron Capture Therapy. Tbilisi: Georgian Technical University 2023.

and six MSc dissertations:

▪ Gigilashvili A. Possibilities of Utilization of Boron-Containing Nanostructures in Neutron-Capture-Therapy. Tbilisi: Georgian Technical University 2017.

▪ Svanidze L. Estimation of Boron Nitride Nanoparticles' Toxicity in Dependence of Their Sizes. Tbilisi: Georgian Technical University 2017.

▪ Arutinovi D. Actual Problems of Boron-Neutron-Capture-Therapy and Prospects for Its Implementation in Georgia. Tbilisi: Georgian Technical University 2018 [30].

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▪ Lezhava P. Possibilities for Attenuating Gamma-Irradiation Accompanying Neutron Cancer Therapy. Tbilisi: Georgian Technical University 2020.

▪ Gurgenidze D. Sources and Dosimetry of Boron Neutron Capture Therapy (BNCT). Tbilisi: Georgian Technical University 2020.

▪ Shanidze G. Dosimetric Monitoring of Radiation Safety of Medical Personnel in Case of Center for Radiation and Nuclear Medicine (Tbilisi, Georgia). Tbilisi: Georgian Technical University 2022. [31]

Two of them are published in form of full-text papers [30, 31].

CONCLUSION

In summary, note that iron valence states characteristic of free iron Fe and iron oxides such as magnetite Fe_3O_4 and maghemite Fe_2O_3, respectively, are: Fe(O), $Fe(II)Fe(III)_2O_4$ and $Fe(III)_2O_3$. They lead to ferro-, ferri- and antiferromagnetic properties of these materials. At glance, h-BN doped with Fe is expected to be the best magnetic among investigated composites. However, utilization of h-BN–Fe in BNCT will be problematic due to fast oxidation of free iron in media mainly consisted of water. As for the h-BN–Fe_2O_3, it is not a magnetic material. Thus, the magnetite-doped hexagonal boron nitride h-BN–Fe_3O_4 should be considered for an optimal choice.

Proposed novel liquid-charge chemical synthesis routes have allowed the effective obtaining of hexagonal boron nitride nanopowders doped both with iron and magnetite nanoclusters. Studying their magnetization curves has confirmed potential of these composites to be effectively applied in BNCT as agents of external magnetic field controlled delivery of boron ^{10}B isotopes to tumor tissues.

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