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# NANODIAMONDS AND CARBON NANOTUBES AS PERSPECTIVE CARRIERS OF BISMUTH ISOTOPES FOR NUCLEAR MEDICINE

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***Abstract.*** *Currently, a wide range of nanomaterials, including carbon nanomaterials (CNMs), are being investigated as possible carriers of radionuclides for nuclear medicine as a part of radiopharmaceuticals (RPs). The present work considers the possibility of using nanodiamonds (ND) and multi-walled carbon nanotubes and their derivatives to act as a potential basis for RPs containing bismuth which have radioisotopes $^{212,213}$Bi for targeted alpha-therapy. To study this, the kinetics of Bi(III) sorption onto selected CNMs in aqueous media with different pH, as well as Bi(III) desorption from these samples by a solution of fetal bovine serum at 37 °C were investigated. The optimal conditions for the sorption of Bi(III) onto the studied CNMs were found; it was shown that oxidized ND was the most promising carrier for bismuth isotopes: sorption at pH 3 to 7 for this sample was close to quantitative, and desorption in 120 min does not exceed 5 %. The cytotoxicity of CNMs was investigated in the standard MTT test, it was shown that $LC_{50}$ for all studied samples was > 200 μg/mL.*

***Keywords:*** *Carbon nanomaterials; bismuth radioisotopes; sorption and desorption; nanodiamonds; multi-walled carbon nanotubes; carriers for nuclear medicine; targeted alpha-therapy*

## 1. INTRODUCTION

Nowadays, nanomaterials in general and carbon nanomaterials (CNMs) in particular are promising substances for use in a huge number of fields of technology and science and attract the attention of an increasing number of researchers due to the unique physicochemical properties [1–4]. Uniqueness is primarily associated with the high surface area of such materials, as well as with the possibility of its directed functionalization by various groups or substances [5, 6].

The variety of possibilities for modifying the surface of the CNMs allows to design materials with the properties for different tasks solutions [7–9]. Thus, the ability to bind metal cations, their complexes, and various organic molecules to the surface of the CNMs makes it possible for the CNMs to be considered as a basis for RPs [10, 11]. Different CNMs includes ND [12, 13], graphene and its oxide [14–19], carbon nanotubes [20–26] – are considered as promising carriers of various radioactive isotopes and drugs for nuclear medicine for the diagnosis and treatment of cancer.

One of the most effective methods of killing cancerous tumors is targeted alpha-therapy [27–30]. In this method, an alpha-emitting radionuclide is delivered to tumors and selectively binds to tumor cells using specially chosen molecule vectors or carriers; and after these alpha particles destroy the tumor without damaging the surrounding healthy tissues due to a short emitting range. Various nanoparticles can act as such carriers, however, information on the use of CNMs as carriers of radionuclides for targeted alpha-therapy is limited [31–34].

Among the radionuclides used in targeted alpha-therapy, there are two promising bismuth isotopes $^{212}$Bi (36% α, 64% $\beta^-$, $T_{1/2}$ = 60.6 min) and $^{213}$Bi (complex α and $\beta^-$ decays chain, $T_{1/2}$ = 45.6 min) [35]. The preparation of both isotopes is well studied: $^{212}$Bi is isolated from $^{212}$Pb/$^{212}$Bi generators [36], and $^{213}$Bi – is from $^{225}$Ac/$^{213}$Bi generators, where $^{225}$Ac undergoes four fast alpha decays [37]; the use of both generators *in vivo* is also being studied [35, 38]. The half-lives of both isotopes are slightly less than optimal for alpha-therapy, but nevertheless they allow $^{212}$Bi and $^{213}$Bi to be used in the case of rapid delivery of RPs with those isotopes to tumors [39]. Usually, $^{212}$Bi and $^{213}$Bi are chelated by DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) derivatives and bind to antibodies, while studies of ever new methods of their use in targeted alpha-therapy have been conducted over the past decades [40].

In our recent work, the ability of CNMs to sorb bismuth was demonstrated [34]. The aim of the present research is a detailed study of the dependence of sorption and desorption of Bi(III) onto the most promising CNMs (ND and multi-walled carbon nanotubes (MWCNT)) in various media to search for optimal conditions for the synthesis of bismuth based RPs for further possible use in targeted alpha-therapy.

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## 2. MATERIALS AND METHODS

### *2.1. CNMs preparation and characterization*

In our work we used commercial samples of ND (SKTB Tekhnolog, Russia, trademark UDA-TAN) and MWCNT (NanoTekhTsentr Ltd, Russia) and also oxidized ND (*namely, oxND*) and hydrogenated MWCNT (*namely, hydMWCNT*), prepared in our experiments. To obtain oxND and hydMWCNT, following reactions (1) and (2) were carried out. All chemical reagents used in the work had purity not lower than "chemically pure".

$$\mathrm{ND} \xrightarrow{\mathrm{H_2SO_4/HNO_3\ (3:1),\ (120\ ^\circ C,\ 24\ h)}} \mathrm{oxND} \qquad (1)$$

$$\mathrm{MWCNT} \xrightarrow{\mathrm{10\ \%\ H_2 + 90\ \%\ Ar\ (800\ ^\circ C,\ 5h)}} \mathrm{hydMWCNT} \qquad (2)$$

Earlier we made a characterization of commercial and modified CNMs samples used in present research [34, 41, 42]. Table 1 summarizes the main characteristics of the CNMs used, and Fig. 1 shows the SEM images of ND and MWCNT.

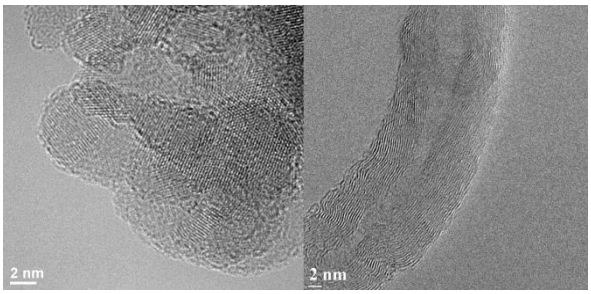


Figure 1. SEM images of ND (left) and MWCNT (right) which are similar to oxND and hydMWCNT, respectively [34].

The cytotoxicity of the studied CNMs was investigated in a standard MTT test, for which CNMs were suspended in phosphate buffered saline (PBS) with a nanoparticles content of 1, 5, 10, 50, 100, 200 μg/mL. The MTT test was performed on mononuclear cells of healthy donors as well as on B-lymphoblastic leukemia cells; in each case cells from three different donors were taken.

### *2.2. Detection of Bi(III)*

To determine sorption behavior of Bi(III), gamma-emitting isotope $^{207}$Bi ($T_{1/2}$ = 31.55 y) was used in all experiments which were conducted in a glove box.

No-carrier-added $^{207}$Bi(III) in 1 M HCl solution was obtained from Cyclotron Co. Ltd. (Obninsk, Russia) with volume activity 2.37 MBq/mL, radionuclidic purity more than 99.7 % and content of inactive metal impurities no more than $1\times10^{-6}$ μg per 1 Bq of $^{207}$Bi.

The $^{207}$Bi content in all studied solutions was determined by gamma-ray spectrometry using the 569.7 keV line on a spectrometer with a high-purity germanium detector GC 1020 (Canberra Ind, Meriden, CT, USA).

Table 1. Characterization of commercial and modified CNMs

| Characteristics | ND | oxND | MWCNT | hydMWCNT |
|---|---|---|---|---|
| Particle size of the original samples (nm) | 3 – 10 | 3 – 10 | Length > $2\cdot10^4$ Diameter – 30 Wall thickness 5 – 10 | Length > $2\cdot10^4$ Diameter – 30 Wall thickness 5 – 10 |
| The total content of impurities according to ICP-MS, mg/g | 1.4 | n/d | 14.0 | n/d |
| The main impurities (more than 0.1 mg/g) and their content, mg/g | Fe – 0.538 Ti – 0.459 K – 0.156 | n/d | Mo – 6.880 Co – 5.830 Al – 0.635 Ni – 0.156 | n/d |
| Specific surface area, $m^2/g$ | 240 | 250 | 160 | 155 |
| Elemental composition of the surface according to XPS, % | C ($sp^3$) – 92.3 O – 7.7 | C($sp^3$) – 90.1 O – 9.9 | C ($sp^2$) – 99.0 O – 1.0 | C ($sp^2$) – 99.4 O – 0.6 |
| The size of particles and their aggregates in hydrosols, nm | 100 | 95 | n/d[1] | 150 and 650 |
| Amount of -COOH according to titration, μmol/g | 330 | 990 | n/d | n/d |

[1]*impossible to determine by DLS if at least one of the linear particle sizes exceeds 1000 nm*

### *2.3. Sorption and desorption experiments*

Initial $^{207}$Bi radioactivity and concentration in each sample was 800 Bq and $1.9 \times 10^{-9}$ M.

Each experiment with $^{207}$Bi sorption or desorption was repeated at least three times until converging values.

To obtain samples for sorption, aliquots of initial $^{207}$Bi solution in 1 M HCl were diluted by double distilled water (to obtain solutions with pH 1, 2 and 3) or were evaporated to dryness in a glass beaker and then residues were diluted by solutions of HCl or $NH_3$ to obtain solutions with pH 5 or 7; pH was always controlled by pH-meter "Expert" (Econix-Expert Ltd, Moscow, Russia). Aliquots of $^{207}$Bi solutions with established pH and aliquots of suspension of CNMs were successively added to the Eppendorf tube, with a total volume of 1 mL containing 100 μg of CNMs (this amount was previously determined as sufficient for maximum sorption of Bi(III) [34]). The experiments were carried out at 25 (sorption) and 37 °C (desorption);

the temperature was controlled by a thermal shaker attachment (TS-100, Biosan, Latvia); rate of shaking was 1100 rpm. After sorption, the phases were separated by centrifugation for 15 min at 15,000 g (in preliminary experiments, it was shown that these conditions are sufficient for quantitative phase separation), 800 μL of the supernatant were taken and the gamma spectrum was registered, comparing with the initial activity of the solutions before sorption.

The stability of the obtained $^{207}$Bi@CNMs conjugates was evaluated by studying desorption of $^{207}$Bi in fetal bovine serum (FBS) which is a model blood plasma medium. For this, sorption was carried out for 15 min at pH 3 for ND and oxND, at pH 5 for MWCNT and hydMWCNT, and then samples were centrifuged. After it, the supernatant was removed, FBS was added to the sediment of CNMs, and the solution was agitated, placed on a shaker, then centrifuged again and the supernatant was again separated for further gamma-ray measurement.

## 3. Results and discussion

We studied the sorption of $^{207}$Bi onto ND, oxND, MWCNT, and hydMWCNT from aqueous solutions with pH 1, 2, 3, 5 and 7, as well as the desorption of $^{207}$Bi from all studied CNMs samples by FBS.

### *3.1. Sorption of $^{207}$Bi onto CMNs*

It is well-known that $Bi^{3+}$ in aqueous solutions has a high tendency to hydrolysis (solubility constant for $Bi(OH)_3$ is $3.2 \cdot 10^{-32}$), which determines the existence of polynuclear oxo- and hydroxocomplexes of various structure even in acidic solutions. The study of the dependence of Bi(III) sorption onto CNMs on the pH of the solution was an interesting and important task, since different compounds of Bi(III) exists in different solutions, which can affect sorption.

Studying the sorption of $^{207}$Bi from aqueous solutions, it was found that the absence of sorption was observed onto all studied CNMs samples for 60 min at pH 1. The results of studying sorption at pH 2 to 7 are shown in Fig. 2a-d. It was determined that with increasing pH, the sorption value increases for all studied CNMs. Thus, at pH 2, sorption onto ND and oxND is 40 and 60%; with an increase in pH to 3, sorption onto these CNMs becomes more than 80%, Fig. 2a,b. MWCNT and hydMWCNT do not sorb Bi(III) at pH 2; sorption at pH 3 is about 60-70% (Fig. 2c,d). Finally, at pH 5 to 7, the maximum sorption of $^{207}$Bi is observed for all four CNMs and is 80 to >95 %. It is also noticeable that the sorption of $^{207}$Bi(III) onto all samples is characterized by fast kinetics - equilibrium occurs in 5-15 minutes.

### *3.2. Desorption of $^{207}$Bi by FBS*

To study the desorption of $^{207}$Bi from CNMs, the FBS medium was chosen; the results are shown in Fig. 3. Data in Fig. 3 shows that the strongest binding of $^{207}$Bi is observed for ND and oxND, for which desorption in 120 min was 19 and 7 %, respectively.

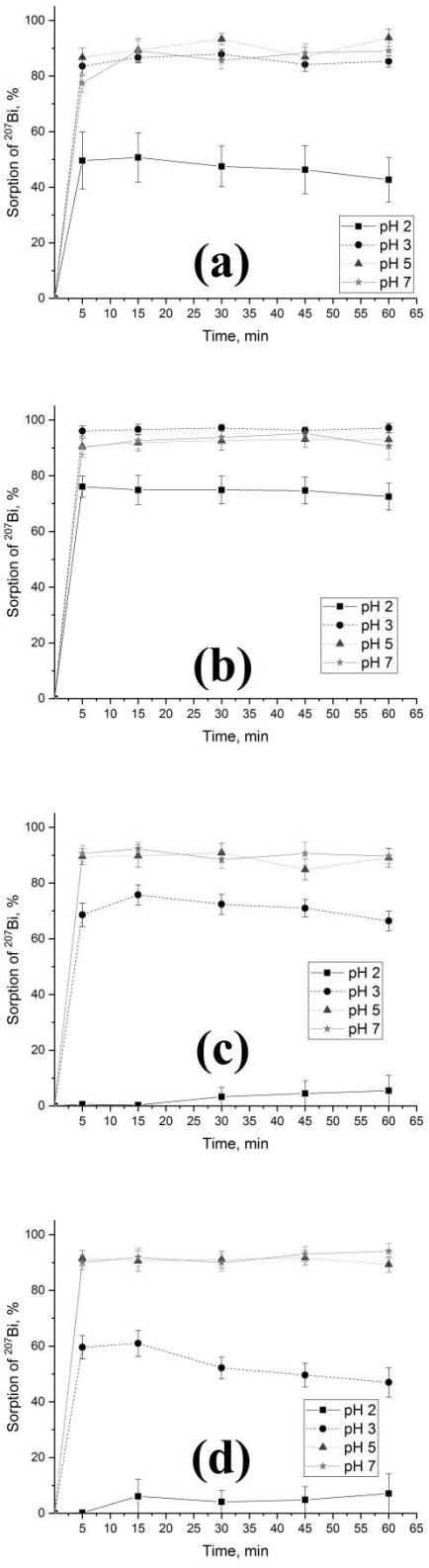


Figure 2. Sorption of $^{207}$Bi (III) onto (a) ND, (b) oxND, (c) MWCNT, and (d) hydMWCNT from aqueous solutions at 25 °C and 100 μg/mL of CNMs.

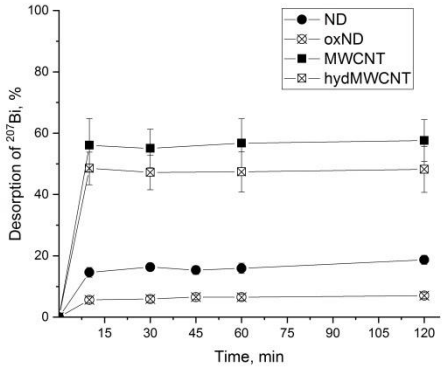


Figure 3. Desorption of $^{207}$Bi(III) from CNMs (100 μg/mL) in FBS medium at 37 °C.

MWCNT and hydMWCNT show less binding of $^{207}$Bi and desorb about 50% of the radionuclide for the same time.

The results of studying the desorption of $^{207}$Bi from ND and oxND in FBS show that oxidation of ND (that is, the formation of more carboxyl groups on the surface, see Table 1) promotes stronger retention of $^{207}$Bi on the surface. As for MWCNT and hydMWCNT, hydrogenation of MWCNT leads to a slight decrease in desorption of $^{207}$Bi; at the same time, the time-stable value of desorption on these samples probably indicates the existence of various mechanisms of interaction of $^{207}$Bi with them.

Thus, the oxND showed the highest resistance to desorption of $^{207}$Bi among the studied CNMs during $2T_{1/2}$ of $^{212}$Bi or $3T_{1/2}$ of $^{213}$Bi. In addition to the study of desorption in FBS in this work, we have previously shown the stability of the Bi(III)@oxND conjugate in 0.9% NaCl, PBS, and a solution of 40 g/L bovine serum albumin in PBS at 37 ° C [34].

### *3.3. Cytotoxicity of studied CNMs*

In the standard MTT test, the $LC_{50}$ values for ND, oxND, MWCNT and hydMWCNT were determined to be outside of the studied concentration range, i.e. > 200 μg/mL for both healthy and leukemic cells. The obtained values are consistent with the literature data on the cytotoxicity of ND [43] and MWCNT [44]. All these data together with sorption and desorption values make it possible to consider oxND as a promising carrier of these bismuth isotopes for further *in vivo* experiments and the creation of RPs.

## 4. Conclusion

In the present work, ND, MWCNT and their oxidized (oxND) and hydrogenated (hydMWCNT) derivatives were studied as sorbents for Bi(III) (using $^{207}$Bi isotope) as a part for further potential RPs. It was shown that ND and oxND sorb more than 80 % of $^{207}$Bi at pH 3 to 7, while the sorption onto oxND is 10 % higher (not less than 95 %), which indicates a positive effect of the amount of carboxyl groups on sorption. In addition, the desorption of $^{207}$Bi in the FBS medium for oxND is 5 % for 120 min, while for ND it is 15 % for the same time. MWCNT and hydMWCNT sorb more than 85 % of $^{207}$Bi at pH 5 to 7; however, the desorption from these CNMs reaches 50-60 % in 5 min. Thus, among the studied CNMs, oxND is promising for the creation of RPs based on it according to sorption and desorption values.

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