UDC 620.3(063)+ 621.318.1 DOI: 10.25808/08697698.2018.202.6S.055

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Cationic hybrid nanoparticles for cancer visualization and therapy

Radiotherapy is widely used for oncological diseases. Reducing the X-ray photons energy allows to increase the efficiency of cancer therapy. Synthesis of various hybrid nanoparticles based on metal oxides was carried out to impart to them magnetic and radiomodifying properties. They also possess X-ray and NMR-contrast properties. Such nanoparticles carry a positive charge on the surface and can be held for a long time by the tissue at the injection site. Their application makes it possible to mark the postoperative field for further visualization and focused radiotherapy.

Key words: cationic nanoparticles, X-ray and NMR contrast, magnetic properties

Radiotherapy of oncological diseases is a powerful and effective method. But the inseparability of external, even focused, irradiation leads to severe side effects. In addition, high-energy gamma quanta are rapidly deactivated and cannot penetrate deeply into tissues. One way to improve the effectiveness of radiotherapy can be reduction of the energy of photons when interacting with large-diameter nuclei, such as tantalum [2]. Targeted delivery of drugs to the therapy area can be carried out using nanoparticles bearing a surface positive charge [1, 4]. In addition, the use of an external magnetic field can be used to accumulate magnetic nanoparticles in a certain region [3].

The purpose of our study was to obtain hybrid nanoparticles (NPs) based on magnetic ferroxide as a core and a radiomodifying shell layer of tantalum oxide, which carry a surface positive charge.

NPs were synthesized in a multi-stage method. At the first stage, a Fe_3O_4 core was prepared by coprecipitation from ferrous sulfate (1 mol) and ferric chloride (2 mol) in the presence of citric acid (0-10 mol) as a stabilizer and excess aqueous ammonia at room temperature and vigorous stirring. After boiling for half an hour, the reaction mixture was subjected to hydrothermolysis at 180 °C for a minimum of 12 hours. All the preparations obtained were washed from unincorporated compounds with distilled water and finally dried by lyophilization.

To prepare the hybrid core/shell NPs a solution of tantalum-hydrofluoric acid (0.2-1 mol), kindly presented by Professor M.A. Medkov (IC FEB RAS) was added to the suspension of ferroxide NPs in excess of aqueous ammonia and presence of citric acid (1-8 mol). After the hydrothermolysis NPs was purified and dried similarly as described above. The hybrid NPs obtained were characterized by dynamic light scattering, atomic force microscopy (AFM), and X-ray phase analysis. According to the results of elemental analysis, the final composition (core/shell ratio) of NPs is completely determined by the amounts introduced into the synthesis.

For the synthesis of cationic NPs, the surface modification of the nanoparticles was used

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The work was supported by grants of the FEB RAS «Far East» project No 18-3-042

3-aminopropyl-triethoxysilane (APTES) in an alkaline medium. To obtain NPs with different charge density, a different amount of reagent was introduced into the reaction (Table 1).

Table 1.

Size and Z-potential of cationic nanoparticles

NPs (ratio in moles)	Dimension, nm (%)	Zeta potential, mV
Fe/Ta/APTES (1/1/0,02)	107 (93,0)	13,9
Fe/Ta/APTES (1/1/0,04)	107(100,0)	17,8
Fe/Ta/APTES (1/1/0,08)	125 (91,9)	21,8
Fe/Ta/APTES (1/1/0,16)	120 (79,5)	27,5
Fe/Ta/ polyethyleneimine (1/1/0,09)	388 (100,0)	6,4
Fe/Ta/ hexamethylenediamine (1/1/0,09)	204 (100,0)	4,4

In addition, surface modification with polyethyleneimine and hexamethylenediamine was carried out by activation of the carboxyl groups of anionic NPs by using of a carbodiimide method and binding with the amine groups to form an amide bond. As can be seen from the Table, the the positive charge density of NPs can be varied by the concentration of APTES introduced into the synthesis. The use of polyamines leads to NPs with a much lower potential, but NPs with high molecular weight and high-branched polyethyleneimine (25 kDa) should interact with the cell surface preferably.

The X-ray analysis of NPs synthesized by coprecipitation at room temperature showed the absence of magnetite and the presence of amorphous oxides and hydroxides. The hydrothermal treatment method was used to recrystallize them. NPs obtained have excellent magnetic properties; its purification was greatly simplified. The cationic hybrid NPs possess good X-ray and NMR contrast properties as previously obtained anionic hybrid nanoparticles.

To study acute and chronic toxicity NPs were introduced to CD-1 mice at different doses by intraperitoneal injection. The spontaneous deaths were not noted after 30 days. Morphological changes in brain, liver, kidneys, spleen and lungs were not observed according to the histological analysis. Thus, it is established that NPs obtained are not toxic at a dose of 200 mg/mouse and below.

To study the diffusion of nanoparticles from the zone of intramuscular injection in the absence of a magnetic field, the anionic NPs (1 mg/mouse) showed the disappearance of the drug on the second day according to X-ray tomography. The magnetic NPs were detected for 24 days after using an external magnetic field.

Thus, a technology has been developed for the production of cationic hybrid nanoparticles based on iron and tantalum oxides, which carry a positive charge of different density on their surfaces. The use of such NPs is very promise for local radiotherapy and visualization of the resection zone of the neoplasm in humans.

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