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Topic: Magnetic Nanoparticles for Biomedicine: Synthesis, Characterization and Application

Relevance of the topic: Currently, magnetic nanoparticles (MNPs) are used as contrast agents for MRI, magnetic hyperthermia (MHT), and separation of cells and molecules, as promising objects for magnetomechanical control of enzyme activity and cell viability. MNPs consist of metals such as Fe, Co, Ni, as well as their simple and complex oxides. MNPs formed by pure metals are extremely easily oxidized and their use is limited. In addition, among the above metals, iron is the most accessible and least toxic. All this makes MNPs formed by simple and complex iron oxides the most promising for use in biomedicine.

Objective: To establish the relationship between the shape, size, composition, and related physicochemical properties of MNPs with the potential for biomedical application as MR contrast agents, drug delivery systems, and as drugs for magnetic hyperthermia. Design and development of methods for synthesizing MNPs based on complex oxides for tumor therapy and diagnostics.

Research objectives:

• 1) To develop chemical methods for synthesizing MNPs based on complex iron oxides and obtaining nanoparticles of a given shape (spheres, cubes, rods, clusters), size (5-40) nm, and composition;

• 2) To study the morphology, structure, and magnetic properties (static and dynamic) of the synthesized MNPs;

• 3) To develop methods for functionalizing the MNP surface with biocompatible coatings, allowing to obtain stable aqueous colloidal solutions;

• 4) To study the effect of the size and shape of MNPs on toxicity in in vitro experiments;

• 5) To study the effect of the size and shape of MNPs on the efficiency of tumor visualization using MRI;

• 6) To study the possibility of using MNPs to deliver antitumor drugs of various natures (doxorubicin, bacteriochlorin A) for tumor therapy;

• 7) To study the possibility of using cobalt ferrite MNPs for tumor therapy using magnetic hyperthermia;

Scientific novelty of the work

or the first time, a systematic study was conducted on the relationship between the physicochemical and magnetic properties of MNPs with the potential for biomedical application as MR contrast agents, drug delivery vehicles, and as drugs for magnetic hyperthermia.

Preparative methods for obtaining MNPs were developed. Thus, it was found that the method of thermal decomposition of iron (III) acetylacetonate in benzyl alcohol allows obtaining highly crystalline, monodisperse, hydrophilic MNPs of spherical morphology. For the first time, it was found that the introduction of oleic acid and its derivatives into the reaction mixture leads to obtaining MNPs of cubic morphology, cyclic aliphatic and aromatic carboxylic acids - cluster morphology, and polyethyleneimine and dopamine - rod-shaped morphology. It is shown that by replacing iron (III) acetylacetonate with cobalt (II) acetylacetonate in a stoichiometric ratio, cobalt ferrite MNPs of cubic morphology can be obtained.

For the first time, an exponential increase in saturation magnetization for cubic MNPs with an increase in the crystallite size has been experimentally demonstrated, whereas for cluster MNPs, the increase in saturation magnetization is determined by the size of the entire cluster, and not its individual crystallite. It is shown that the dependence of the T2 relaxivity and SAR parameters on the MNP size has a nonlinear character with local maxima in the MNP size range of 10-20 nm.

It has been established that MNPs functionalized with biocompatible polymers containing polyethylene glycol do not exhibit a cytotoxic effect on cell cultures, regardless of their shape. It has been shown that MNPs functionalized with biocompatible polymers allow the delivery of therapeutic drugs to tumor cell cultures *in vitro*.

It was found that a biocompatible coating based on serum albumin and polyethylene glycol ensures the highest accumulation of MNPs in tumors. It was shown that the morphology of MNPs determines their distribution after intravenous administration. Thus, among anisotropic MNPs, cubic MNPs have the greatest potential as a contrast agent for tumor diagnostics using MRI.

It was found that conjugation of MNPs coated with serum albumin functionalized with polyethylene glycol and loaded with doxorubicin and with antibodies to vascular endothelial growth factor can increase the efficiency of MNP delivery to the tumor and increase the median survival of animals with 4T1 mammary adenocarcinoma.

It has been shown that intravenous administration of MNPs coated with serum albumin functionalized with polyethylene glycol and loaded with a bacteriochlorin series photosensitizer allows determining the time of maximum accumulation of the photosensitizer in the tumor by MRI, which allows for maximum inhibition of tumor growth after photodynamic therapy.

Among the variety of MNPs studied, only cobalt ferrite nanoparticles of spherical morphology with a size of 12±4 nm show efficiency in magnetic hyperthermia of tumors. Thus, using the example of the CT26 tumor, it has been shown that magnetic hyperthermia leads to a cure of animals in 100% of cases.

Theoretical and practical significance of the work

The parameters of chemical synthesis of magnetic nanoparticles have been determined, allowing to control their shape, size and composition. The obtained dependences of the properties of magnetic nanoparticles on their shape, size and composition allow to determine the optimal type of MNPs for use as contrast agents for MRI, drug delivery and tumor therapy by magnetic hyperthermia. A contrast agent for MRI based on spherical magnetite nanoparticles stabilized by serum albumin and polyethyleneglycol has been developed, its efficiency and safety in tumor diagnostics have been demonstrated. The obtained nanoparticles allow to conduct non-invasive monitoring of drug accumulation in a tumor after intravenous administration by MRI. MNPs based on cobalt ferrite have been developed, their efficiency and safety as agents for magnetic hyperthermia have been demonstrated.

Provisions submitted for defense

1) The morphology of magnetic nanoparticles is determined by the physicochemical properties of surfactants, solvents and metal-containing precursors, their ratios, as well as the heating rate and the final temperature of the reaction mixture;

2) The static and dynamic properties of magnetic nanoparticles are determined by the size and shape of the magnetic core;

3) The shape of magnetic nanoparticles determines the parameters of their pharmacokinetics after intravenous administration;

4) Modification of the surface of magnetic nanoparticles with biocompatible coatings containing polyethylene glycol allows obtaining stable aqueous colloidal solutions of nanoparticles that do not exhibit toxicity in the target concentration range in experiments both on cell culture and upon intravenous administration;

5) Conjugation of magnetic nanoparticles carrying antitumor drugs with vector ligands allows increasing the efficiency of their delivery to the target organ and enhancing the therapeutic effect;

6) Immobilization of photosensitizers on the surface of magnetic nanoparticles allows monitoring of photosensitizer accumulation in the tumor lesion using MRI, as well as determining the most favorable time for photodynamic therapy;

7) The use of cobalt ferrite as a magnetic phase increases the heat-generating capacity of particles, which allows controlled heating of tumor tissue after intratumoral administration during magnetic hyperthermia of tumors;