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BIOCOMPATIBILITY OF MAGNETIC NANOPARTICLES BASED ON ZINC AND MAGNESIUM FERRITES

The development of drugs based on magnetic nanoparticles (MNPs) attracts great attention in such branches of medicine as diagnostics (contrast in magnetic resonance imaging), therapy (magnetic hyperthermia of tumors), targeted drug delivery, magnetic separation of biomolecules, etc. [1]. The most common applications are based on magnetic iron oxides with a spinel-type structure, i.e. magnetite and maghemite, as well as ferrites with the general formula $MeFe_2O_4$ (Me = Zn, Ni, Co, Mn, Mg). The main requirements for MNPs suitable for biomedical use include low cytotoxicity, colloidal and aggregative stability, sizes less than 40 nm and high values of specific magnetization [2, 3]. Substitution of some Fe^{2+} ions in magnetite for ions of other metals can increase the specific magnetization of the material. Some papers describe the effect of increasing the specific magnetization of zinc-doped magnetite nanoparticles in the $ZnxFe_{3-x}O_4$ system at low (x = 0.4) degrees of substitution [4].

In this work, changes in the magnetic properties and biocompatibility of zinc ferrite-based nanoparticles with partial substitution of zinc ions with magnesium ions were evaluated.

MNPs $ZnFe_2O_4$ and $Mg_{0.7}Zn_{0.3}Fe_2O_4$ were obtained by co-precipitation with a 10 % excess of NaOH from solutions of metal nitrates taken in a stoichiometric ratio. For a comparative assessment of the cytotoxicity of doping ions, commercial samples of ZnO and MgO (chemically pure) were also used.

The size and morphology of nanoparticles were studied using scanning and transmission electron microscopy using LEO 906E and LEO 1420 microscopes. The magnetic characteristics of the powders were measured using Cryogen Free Measurement System Cryogenic Ltd (T = 7 –300 K, H_{max} = 18 T).

The MTT test was used to study the cytotoxic properties of the studied compounds. Tumor cell lines MCF-7 (human breast adenocarcinoma), HepG2 (human liver carcinoma) were placed in a 96-hole tablet at a concentration of $5 \cdot 10^3$ cells/hole and incubated for 24 hours. The next day, test substances were added at concentrations of 0.4 –

4000 μM. The preparations were diluted to final concentrations sequentially with the incubation medium. After 72 h of culturing cells with test preparations under standard conditions (37 °C, 5 % CO_2, 92 % humidity), 20 μl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) at a concentration of 5 mg/ml was added to each hole of a 96-hole plate. After 4 h exposure at 37 °C and 5 % CO_2, cells were reduced from yellow MTT to dark purple formazan granules. Formazan granules were dissolved in 200 μl of DMSO, the amount of reduced product was measured photometrically at a wavelength of 570 nm on an AIF-M/340 plate analyzer.

According to electron microscopy data, ferrite nanoparticles have a spherical shape, narrow size distribution and an average diameter not exceeding 10 nm. This makes it possible to predict superparamagnetic properties for these powders, ensuring their aggregative stability, as well as effective interaction with cells [2].

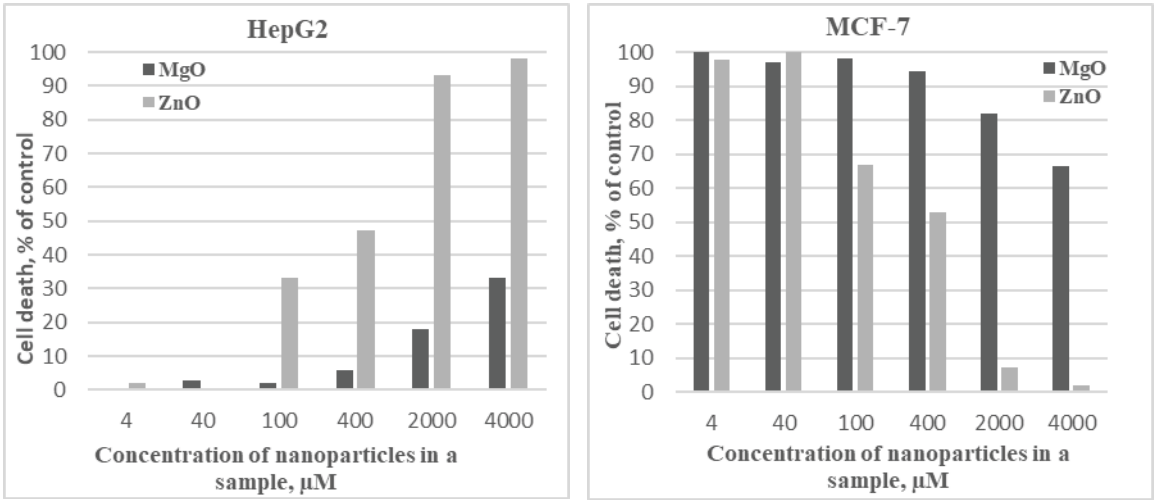
The values of the specific magnetization M_s and coercivity H_c of magnetic powders obtained at room temperature at H = 5 T are given in Table 1. Low values of coercivity (60 – 70 Oe) and specific magnetization are observed for the samples. This indicates the superparamagnetic state of the samples and is in good agreement with the particle size data obtained by transmission electron microscopy.

Table 1 - Magnetic properties of zinc ferrite-based nanoparticles

Substance	M_s, emu/g	H_c, Oe
$ZnFe_2O_4$	12	65
$Mg_{0.7}Zn_{0.3}Fe_2O_4$	15	79

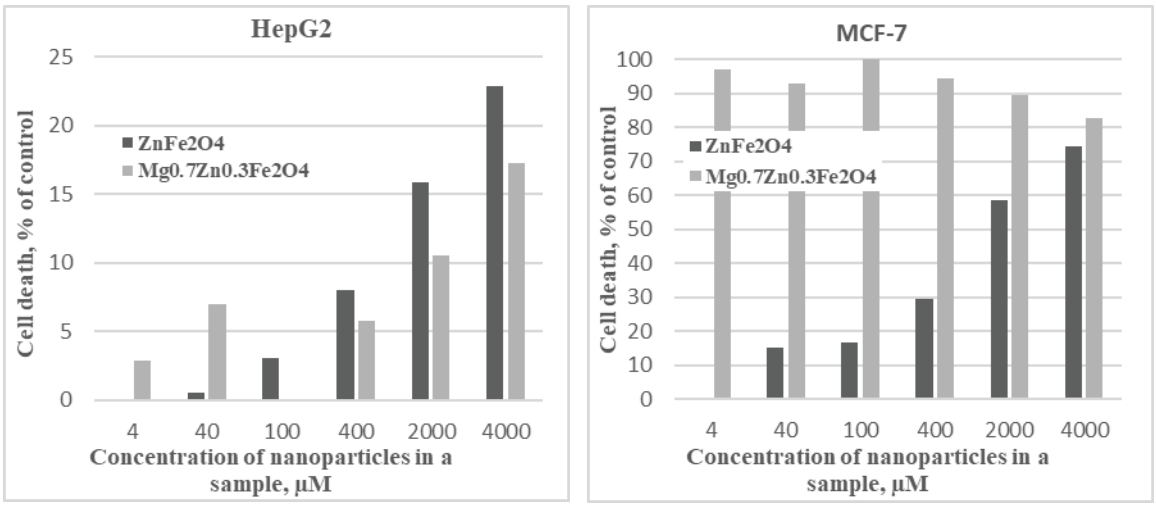
The addition of magnesium ions to the zinc ferrite crystal lattice makes it possible to increase the specific magnetization of the material from ~ 12 to 15 emu/g. It can be assumed that zinc and magnesium ions tend to occupy opposite positions in the ferrite crystal lattice (tetra- and octahedral positions, respectively). When replacing a part of zinc ions with magnesium, iron ions with magnetic moment are redistributed between tetra- and octa-sublattices in the structure, and the effective magnetic moment of mixed ferrite increases as compared to zinc ferrite.

In this work, it was suggested that the cytotoxic effect of nanoparticles was reduced when magnesium was added to zinc ferrite, due to the reduced toxicity of magnesium oxide compared with zinc oxide. To confirm this assumption, the viability of MCF-7 and HepG2 cells in the presence of zinc and magnesium oxides was studied (Fig 2).



a *b*

Figure 2 – Effect of powdered ZnO and MgO on specific cell death: *a* – HepG2 line, *b* – MCF-7 line



a *b*

Figure 3 – Effect of $ZnFe_2O_4$ and $Mg_{0.7}Zn_{0.3}Fe_2O_4$ nanoparticles on specific cell death: *a* – HepG2 line, *b* – MCF-7 line

At high oxide concentrations of more than 400 μM, MCF-7 cells were more sensitive to analytes than HepG2, while at low concentrations, the reverse pattern was observed. The increase in oxides concentration causes an increase in cell death. However, if for zinc oxide this value reaches 90 % already at concentrations of the order of 2000 μM, then for magnesium oxide at the maximum studied concentration of 4000 μM it does not exceed 40 and 60 % for HepG2 and MCF-7, respectively. Based on this, it can be assumed that the cytotoxicity of nanoparticles of magnesium-doped ferrite in similar experiments will also be lower than that of stoichiometric zinc ferrite.

The results of determination of cell viability depending on the concentrations of ferrite nanoparticles are shown in Fig 3. In the case of HepG2 cells, starting from a concentration of nanoparticles of 100 μM, a decrease in cell viability is observed in the presence of $ZnFe_2O_4$ compared to $Mg_{0.7}Zn_{0.3}Fe_2O_4$. For the MCF-7 cell line, a similar pattern is observed in the entire studied range of concentrations.

Conclusions. Superparamagnetic $ZnFe_2O_4$ and $Mg_{0.7}Zn_{0.3}Fe_2O_4$ nanoparticles with sizes less than 20 nm were obtained by coprecipitation. With partial replacement of zinc ions with magnesium, the specific magnetization of ferrite increases from 12 to 15 emu/g. Evaluation of the viability of MCF-7 and HepG2 cells in the presence of zinc and magnesium oxides demonstrated a significant increase in the viability of cells of both lines during the transition from zinc oxide to magnesium oxide. It was also shown that in the presence of $Mg_{0.7}Zn_{0.3}Fe_2O_4$ nanoparticles, compared with $ZnFe_2O_4$, the viability of cells of both lines also increases. This allows us to predict the potential applicability of nanoscale magnesium-zinc ferrites for biomedical purposes.

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