ОСОБЕННОСТИ ПЕРСПЕКТИВНЫХ В БИОМЕДИЦИНЕ МАГНИТНЫХ НАНОЧАСТИЦ

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FEATURES OF THE ADVANCED BIOMEDICAL MAGNETIC NANOPARTICLES

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Для магнитно-контролируемой термохимиотерапии были подготовлены водные суспензии и декстран-ферритовые растворы наночастиц магнетита Fe_3O_4, маггемита γ-Fe_2O_3, Gd-замещенных ферритов $Fe[Gd_xFe_{2-x}]O_4$. Получены момент и температура Кюри магнитных наночастиц. Обсуждаются модели магнитной структуры наночастиц

The water-based magnetite Fe_3O_4, maghemite γ-Fe_2O_3, Gd-substituted ferrites $Fe[Gd_xFe_{2-x}]O_4$ particles suspensions and dextran-ferrite (DF) solutions were prepared for the magnetically controlled thermochemotherapy (MCT). The moment and Curie temperature of magnetic nanoparticles are obtained. The corresponding models of magnetic structure for nanoparticles.

The authors succeeded in finding a mechanism of the robust size effect in the magnetic moment, Curie temperature, and the blocking temperature of magnetite and maghemite nanoparticles. Discussions on magnetic properties focus on the core-shell Weizsäcker model ($\Delta M(N) \sim N^{-1/3}$) extended to a ferrimagnetic nanoparticle. Here the magnetic moment of the inner fraction ("core") of the nanoparticle interacts with the magnetic moment of the outer layer ("shell") adjacent to the interface with a passivating "coat". Via this interface the type and kind of the "coat" affect the total magnetic response. This phenomenological approach gives a deeper insight to the complex behavior of the magnetic characteristics and better agreement of the calculated curves with the experimental data in contrast to Langevin model. Theoretical part takes advantages of the core-shell model, where the atoms in the core and in the shell are different, and classical Heisenberg model. Monte Carlo calculations include a parameter (s) that accounts for the ratio of their magnetic moments relatively to the bulk value. Calculated magnetic moment of the individual nanoparticle showing a predicted $\sim N^{-1/3}$ size dependence was found considerably sensitive to the s value. Moreover, the Curie temperature revealed a considerable decline for the particles sized below 1000 formula units. The coating was found to have a significant impact on T_C for these

smaller particles.

The samples are well characterized and the Monte Carlo analysis is well performed.

This tezis treats monodispersed nanoparticles of ferrimagnetic (FM) spinel ferrites (4 to 22 nm) covered with passivation coating (dextran, glass, polymers). The materials, the iron oxides magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are the most prospective to date because of their appropriate magnetic properties and biological compatibility. Particle sizes of ~10 nm are generally considered suitable to enable effective delivery to the site of the cancer, either via encapsulation in a larger moiety or suspension in a "carrier fluid". A therapeutic effect is achieving due to local hyperthermia via magnetically induced heating. Usually the amount of heat generated per unit volume was associated with the area of the hysteresis loop. The most serious problem was that substantial hysteresis heating could be obtained using strongly anisotropic magnets (high coercivity), whereas fully saturated loops cannot be used due to constraints on the high amplitudes of the magnetic field. Partial loops would give rise to heating at greatly reduced levels. Furthermore, in realistic ensemble of randomly aligned FM particles the most effect that one can hope for is about 75% below that. A recent progress in the field of magnetic particle hyperthermia is associated with the 'magnetic fluid hyperthermia', where the superparamagnetic (SPM) ensemble of nanoparticles is suspended in a hydrocarbon fluid transforming it into a 'magnetic fluid'. Magnetically induced heating arises due to physical rotation of the particles within the fluid (Brownian rotation, τ_B) and rotation of the atomic magnetic moments within each particle (Neel relaxation, τ_N). Magnetic moment, Curie temperature (T_C), depending differently on the particle size as well as surface coating type become the key characteristics of relaxation processes τ_N and τ_B relating to the thermal energy.

The toxicological safety of nanoparticles is currently under increased supervision. The toxicity is dependent on many factors including dosage, chemical composition of the particle surface, size and the shape of their distributions. After nanoparticles appear in the bloodstream they could be transported and accumulated in vital organs. In connection with this the initial assessment of in-vitro biocompatibility of the obtained nanoparticles was carried out, in particular, their cytotoxicity was examined. Five different particles were taken for the study: oxides of W, Cu, Zn, Fe1 and Fe2. The initial particle concentration in solution was 1 mg/ml. The particles were agitated, diluted and added to the cell cultures at a concentration in the range from 0.3 mg/ml to 1.6 μg/ml. For the determination of cytotoxicity there were selected the human tumor cell lines: PLC / PRF / 5 - human hepatocarcinoma, MT4 - human Tlymphocytes (lymphoma) and diploid cells - human fibroblasts – the line MRC-5. The diploid cells were also used in the transformation and cytogenetic analysis tests. The cells were seeded in 96-well plates then placed in a CO_2 incubator and cultured at 37 ° C. The cell cultures were examined on the growth medium DMEM with 10% cow fetal serum (CFS) and by adding nanopreparation the medium was changed to the one supported by DMEM with 2% CFS. The concentration of the cells in determination of the cytotoxicity was:

for the line MT4 - 100,000 cells per mL, for the line MRC-5 - 100,000 cells per cm^2 of the monolayer, and for the line PLC / PRF / 5 - 150,000 cells per cm^2 of the monolayer. Note the standard MTT test is not easily applicable for low cytotoxic drugs. In our study, the differentiation and counting of live and dead cells were performed by using a vital dye as trypan blue (0.2%). The cells with NPs were incubated at 37 ° C for 20 min or more and then the vitality.

Acute toxicity of initial magnetite particles was studied in normal 30 male mice C57Bl/6j, 30 BDF_1 female mice, 30 BALB/c female mice in two modes of administration: intravenous and intraperitoneally. Properties of the $Fe[Gd_{0.1}Fe_{1.9}]O_4$ solutions and Ni-Cu alloy suspensions were compared with those of the Fe_3O_4, and γ-Fe_2O_3 solutions. At the histological analysis liver tissues samples were collected, stored in formaldehyde and submitted for histological processing and microscopic evaluation. Dextran-ferrite # 361 acute toxicity was studied in normal 36 male mice C57Bl/6j, 30 BDF_1 female mice, 30 BALB/c female mice in two modes of administration: intravenous and intraperitonealy. At the histological analysis liver tissues samples were collected, stored in formaldehyde and submitted for histological processing and microscopic evaluation.

Applying the methods of magnetic separation and centrifugation allowed dividing nanoparticles into fractions with different sizes in the range from 4 to 22 nm (Figure 1).

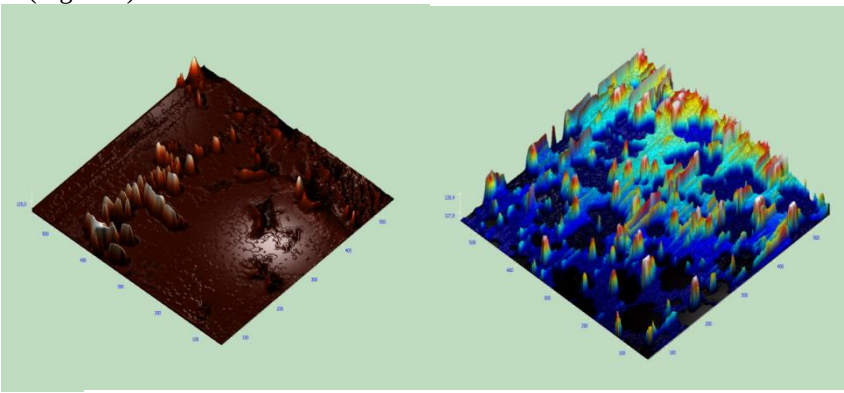

Fig. 1. The results of atomic force microscopy study of magnetite nanoparticles of the two fractions with different average sizes of the nanoparticles.

Author of the cells was analyzed. For the accuracy the testing was conducted in a Goryaev counting chamber. Neither during the experiment, nor during the subsequent cultivation the transformation centers did not identified. The total amount of the cell passages of MRC-5 treated by NPs and of the control cells was similar. The experiment showed very low cytotoxicity of the NPs. When the concentration of NPs was 0.3 mg/mL the cytopathic changes were not identified. Only the zinc preparation at concentration of 0.05 mg/mL or more induced the cell death in all cultures. The observation period for the determination of the cytotoxicity was 7 days. The observation period for the determination of the cyto-

transforming effects was 14 days. Thus, the low cytotoxicity was observed and the cytogenetic and transforming effects of the examined NPs were not identified in our study.

There is a great difference between magnetic properties of maghemite in the form of nanoparticles and bulk material. The relationship between temperature and magnetization is virtually linear and descending; extrapolation yields a Curie temperature of 545 K [1], which is considerably lower than the value for bulk samples, 918 K. This effect is due to the competition between superexchange interaction of Fe^{3+} ions in the tetrahedral and octahedral crystallographic positions under conditions of supersmall sizes of around several atomic layers, as was confirmed by calculations performed using the Monte Carlo method [2].

Magnetic parameters of $Fe[Gd_xFe_{2-x}]O_4$.nanoparticles

x	T_C, K	J_S, emu/g	$N=M_S/\mu_{Fe3O4}$
0.1	738	29,1	$7,657*10^{20}$
0.16		27,1	$7,124*10^{20}$
0.71		19,0	$4,998*10^{20}$
0.97		15,1	$3,211*10^{20}$
1	724	14,68	$3,862*10^{20}$
1.12		12,94	$3,404*10^{20}$
1.9	626	1,36	$3,590*10^{19}$

The prospective field of the cancer therapy is the magnetically controlled thermochemotherapy (MCT). The heterogeneous results with MCT reflect the problem of the homogeneity of intratumoral magnetic nanoparticles (MN) distribution. Regions of MN- underdosage may become the source of thermal underdosage when AC magnetic fields are applied. The Curie temperature of all the samples proved to be too high for the auto-regulation of temperature in the desirable range. Figure 2 shows in vitro analysis time/temperature curves for 0.3 ml Fe_3O_4, γ-Fe_2O_3, $Fe[Gd_{0.1}Fe_{1.9}]O_4$ nanoparticles 30% solutions and 3 ml Ni-Cu alloy 30% suspension.

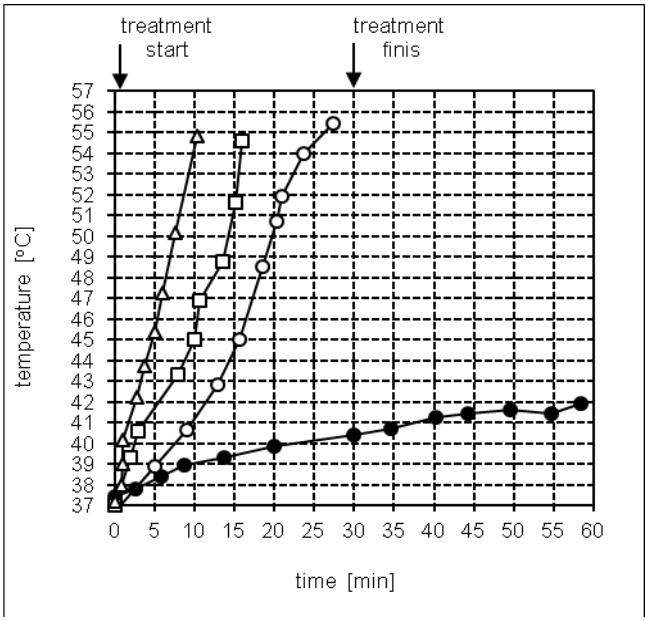

Fig. 2. The temperature elevation for Fe_3O_4 (Δ); γ-Fe_2O_3 (□); $Fe[Gd_{0.1}Fe_{1.9}]O_4$ (○); Ni-Cu (●).

Self-regulating magnetically controlled thermochemotherapy can be achieved by synthetic magnetic targeted carriers with: desired Curie temperature, high elevation speed of temperature in AC magnetic field and low toxicity.

References

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