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Opponent report on Ph.D. thesis of M.Sc. Ilona S. Smolkova entitled

"Iron Oxide Nanoparticles and Polymer Composites on thereof for Magnetic Hyperthermia"

The aim of the Ph.D. study of Ilona S. Smolkova was to obtain a new composite material for effective cancer treatment by magnetic hyperthermia. This defines the practical and scientific importance of the research. For the improvement of efficiency of magnetic hyperthermia a non-toxic and inexpensive polymer magnetic material based on iron oxide nanoparticles was developed.

On the first working stage the magnetic iron oxide nanoparticles with certain magneto-structural properties were synthesized. To this end the well known method of coprecipitation of ferrous and ferric salts was utilized; however the method was improved by the author to obtain nanoparticles having a narrow size distribution and optimum crystal structure. Comprehensive analysis of the mechanism of coprecipitation processes allowed to find a nontrivial approach, i.e. to carry out the reaction in a narrow range of pH, $9 < pH < 11$, where the magnetic phase is formed almost immediately, and the reaction proceeds through the steps of rapid nucleation followed by slow growth of particles. The new approach to the synthesis yielded magnetic nanoparticles (of 13 nm) with a narrow size distribution, which differ from the particles obtained in conventional coprecipitation method, whose dimensions vary over a wide range. The study of the reaction products at different stages of the synthesis revealed that during the entire process only magnetic iron oxide nanoparticles, magnetite and small amount of maghemite are formed. The obtained particles are of a high crystallinity, uniform in size and shape which is very important for their application in magnetic hyperthermia.

The second work stage comprises the detailed investigation of as-prepared nanoparticles and particles subjected to post treatment by annealing to achieve stability of properties over time. It was carried out by different methods including TEM, HRTEM, XRD, Mössbauer spectroscopy, static and dynamic magnetic measurements etc. The results obtained convincingly demonstrate that magnetic nanoparticles produced using the developed synthesis protocol significantly differs from that synthesized by the standard coprecipitation method. The novelty of nanoparticles obtained is that in spite of the fact that the size of individual particles correspond to the superparamagnetic state, they demonstrate ferromagnetic properties, which is evidence from non-zero coercivity. It is explained by exchange interaction between spins of neighboring superparamagnetic particles leading to the enhancement of anisotropy energy which must be overcame during magnetization reversal.

Further investigation comprised the study of Specific Loss Power of the prepared iron oxide nanoparticles in alternating magnetic fields and obtaining of a polymer composite filled with nanoparticles, which provides uniform distribution of particles and their delivery to the tumors by introducing into the artery supplying blood to the tumor. The author has shown that the obtained material causes a rapid (10 – 40 sec) heating of the environment to temperatures of 42 – 45 °C using acceptable (not dangerous to humans) frequency and amplitude of the alternating magnetic field, whereas the material obtained by conventional coprecipitation practically does not heat under these conditions. The use of a silicone matrix with tailored kinetic of viscosity increase has allowed the author to combine the therapeutic effect of hyperthermia with the tumor embolization. Therefore the developed iron oxide based silicone composite fulfills two functions: the thermal destruction of the tumor and the blocking of the blood vessels that feed the tumor.

It should be pointed out that over a short period of Ph.D. study a lot of important work was done towards the final result, namely starting from the synthesis of the magnetic nanoparticles and explanation of the mechanism of iron salts coprecipitation leading to the formation of uniform, highly crystalline particles with high heating rate, and development of a polymer magnetic composite with a set of required magnetic and rheological properties. The author fulfilled the strict rules imposed on the non-toxicity and the scope of amplitudes and frequencies of the alternating magnetic field established in magnetic hyperthermia. That is why the material obtained is ready for *in-vitro* and *in-vivo* studies. Moreover the obtained results on correlation between magneto-structural properties of nanoparticles and coprecipitation reaction course are of particular importance for other applications of magnetic iron oxides in medicine.

The work deserves high praise and the author to award the degree

"Doctor of Philosophy".

In course of reading the following questions arouse which can initiate the discussion during and after the defense:

1. The obtained material contains a small fraction of maghemite in addition to magnetite. Maghemite arises already at the initial stages of the synthesis. Its appearance does not match the stoichiometry of the reaction. Could the author explain this fact?
2. It is demonstrated that the nanoparticles have a uniform crystal structure. Does it mean that maghemite forms separate nanoparticles.

The questions relate only to elucidation of the synthesis mechanism. The opponent confirms that the presence of maghemite may not negatively affect the uniformity of the produced magnetic material as after the synthesis the entire magnetite is transferred to maghemite by thermal oxidation in air.

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