Magnetoresponsive iron oxide nanoparticles for biomedical use

Report on research from 2011-08-01 to 2016-07-31
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In the last years, the research of Aqueous Colloids Research Group focused on the preparation of well-characterized, hemocompatible magnetoresposive nanosystems in such a way that synthesis of single and multicore magnetic nanoparticles and their tailor-made surface modification for biomedical application, as well as the colloidal stability optimization of water based magnetic fluids were improved taking into account the newer and newer expectations of this rapidly developing field. These researches were conducted with financial support of the OTKA project 84014 over the past 5 years.

The objectives of this project were to increase our potential in preparing water based magnetic fluids (MF) containing magnetoresponsive iron oxide nanoparticles (IONs) for biomedical use, namely: 1) to synthetize magnetic nanoparticles below the superparamagnetic (SP) size limit (~20 nm for magnetite) as well as to prepare clustered IONs in order to optimize the response and efficiency in application; 2) to modify the SPIONs' surface with either indifferent biocompatible protective layer (PEGylated coat providing high stability under physiological conditions together with low cytotoxicity and low nonspecific phagocytosis) or the layer of intermediary molecules bound to the particle surface chemically as stable complexes leaving reactive groups in contact with water, which can be modified towards aqueous phase (e.g. suitable for binding antibody); 3) to improve and characterize the colloidal stability of MFs under physiological conditions, especially their pH and electrolyte tolerance and interactions with proteins, cell membranes to prevent particle aggregation; 4) to get an insight into the possible biomedical use of our products, nanotoxicity (MTT assay), MRI contrast enhancement and magnetic hyperthermia.

We accomplished these objectives; our results were presented at 2 scientific meetings, 5 workshops, and on 10 foreign and 1 national conferences. The total number of presentations was 26 among them 1 plenary, 1 keynote, 3 invited and several lectures. Our most important findings were summarized in 21 scientific papers and have published (except 4 of those under review) in highly ranked scientific journals (8 papers among them already have citations above 10 up to 41 at Google Scholar). In addition, we are working together with our international partners on two interesting papers about the role of magnetic cores (single-, multicores and clusters) and coatings (providing chemical and colloidal stability, preventing degradation of optimized cores and particle aggregation) in hyperthermia efficiency.

We recall briefly below some interesting facts from our published materials.

Synthesis: The magnetic response of small superparamagnetic iron oxide nanoparticles is not enough strong. The quality of crystalline phase, mainly magnetite and maghemite is the best in toxicity point view, so only the fine tuning of crystallite size and/or shape is the possible way to improve SPIONs' magnetic response. We tried to **increase the size of magnetite** nanoparticles. First we introduced a hydrothermal ageing process of naked SPIONs from co-precipitation after its purification [Tóth I. Thesis, 2013]. This treatment was successful, since the average TEM size of SPIONs increased from ~6 to ~10 nm, while the polydispersity of samples decreased. The increase in size was significant and approaches that of hyperthermia optimum (~12 nm). We tried to prepare larger magnetite nanoparticles in a green rust precipitation-oxidation process. Fe(II)-salt was hydrolyzed and the formed $Fe(OH)_2$ precipitate (green rust), which was gently oxidized in the presence of poly(acrylic acid). Nice

~50 and ~60 nm spherical and ~75 nm tetrahedral (TEM) particles formed; however, their stabilization was not possible, because their sizes were above the superparamagnetic size limit. We should mentioned that the point of zero charge (PZC) of synthetized magnetite nanoparticles measured by a self-developed method [Szekeres, Tombácz, 2012] shows significant size dependence, i.e., pH_{PZC}~7,8 and ~6,8 for 10 and 75 nm particles, respectively, in good agreement with the isoelectric points of particles. This is a noteworthy result for aqueous nanoparticulate materials in surface charging point of view.

At that time when the proposal was submitted, the **clustering of superparamagnetic nanoparticles** (SPIONs) seemed to give a good solution of this weak response problem of small particles. Meanwhile this assumption was disproved, although the r2 relaxivity of SPION clusters, which is in close relation with the power of local magnetic field, was higher than that of individual nanoparticles. We have prepared SPION clusters in two ways. On the one hand the carboxylated nanomagnets were bound via Ca-bridges as planned in our proposal then stabilized by alternating layers of anionic and cationic polyelectrolytes (layer by layer - LbL method). Unfortunately we did not manage to produce a colloidally stable composition. On the other hand we managed to produce stable SPION clusters from carboxylated nanomagnets via PEI linkers in electrostatic and chemical ways. The results of the electrostatic method based on the particle-particle interaction, heterocoagulation of the oppositely charged interacting partners at optimized pH, i.e., negatively charged carboxylated cores and positively charged PEI polycations. The results have been published [Nesztor et al. 2015]. The covalent bond formation between –COOH and $–NH_2$ groups on the coated magnetic cores and in the PEI, respectively, was also successful by using carbodiimide linker. The reaction has been implemented by Dr. L. Novák (University of Debrecen). The colloidal stability of clusters linked by PEI is good in the wide region of solution conditions, their polydispersities are low. The MRI and hyperthermia efficiency of cluster samples, however, seems to be weaker than that expected on the basis of newer literature. We compared the clusters prepared by physical and chemical ways in a paper [Tóth et al. 2016]. Its main message is that the covalently bound clusters result in better MRI and hyperthermia efficiency.

By now, researchers prefer the shape variation and they tend to force the **multicore formation** from superparamagnetic cores, since the latter have remarkable hyperthermia efficiency according to the latest literature as we analyzed in a review [Tombácz et al. 2015]. We have proved that the most predominant method, i.e., the co-precipitation magnetite synthesis results in the mixture of single and multicore SPIONs within the superparamagnetic size limit, which can be effectively fractionated in a magnetic separation device under appropriate colloidal stability condition. It was clarified that the colloidal and chemical stability of freshly precipitated particles and their concentration as well are the main factors influencing multicore formation during hydrothermal ageing of co-precipitation products. We worked out the appropriate colloidal stability conditions for magnetic separation based on the magnetophoretic forces. The latter is important, since the magnetic properties of the cores are fundamental besides their size limitation in the hyperthermia application point of view according to the latest literature.

Surface modification and characterization: If we are serious about the biomedical application of SPIONs, their coatings at least as important as the magnetic core themselves. In a paper written on request of Prof. Nguyễn T. K. Thanh recently [Tombácz et al. 2016] we have stated that coatings largely influence not only the colloidal stability, but also the functionality and biological fate of SPIONs. We summarized several **distinguished functions of coating**, namely i) colloidal stabilization under physiological conditions (protecting against

aggregation at biological pHs and salty medium), ii) inhibiting corrosion and oxidation of magnetic core (passivation reducing the iron leakage), iii) hindering non-specific protein adsorption in biological milieu, iv) providing reactive groups for grafting drugs and targeting molecules, and v) control nano-biointerfacial interactions (bio/hemocompatibility, reticuloendothelial system (RES) uptake, blood circulation time, IONP's internalization efficiency, toxicity, targeting efficiency, *in vivo* fate, etc.) as discussed in the comprehensive literature in detail.

We developed a **self-coating** method based on complex bond formation between carboxylates and ≡Fe-OH sites on SPIONs' surface under mild conditions to build a stabilizing layer on SPIONs' cores. We used a series of **carboxylated small** (oleic - OA, citric - CA and gallic - GA - acids) **and macromolecules** without (poly(acrylic acid) - PAA, poly(gallic acid) - PGA, poly(acrylic-*co*-maleic acid) – PAM and chondroitin-sulfate-A – CS-A) or **with PEG moieties** (PEGylated oleic acid double layer, synthetized poly(poly(ethylene glycol) methyl ether methacrylate) (PEGMA) and comb-like poly(PEGMA-co-acrylic acid)). The adsorption of different polycarboxylates, the pH-dependent stability of systems with various loadings and their salt tolerance were analyzed in a comprehensive paper [Tombácz et al. 2013], while the colloidal stability issues of these systems in relation to biomedical application was evaluated a bit later [Tombácz et al. 2014]. In the special issue „Magnetic Nanoparticles 2013", we wrote a paper by the request of Editor Prof. Jon Dobson. We explained the chemical and colloidal stability of different carboxylated core–shell magnetite nanoparticles designed for biomedical applications [Szekeres et al. 2013], in which several examples are shown for citrated SPIONs failed in our characterization protocol due to the chemical degradation of IO core and poor colloidal stability in saline condition (particle aggregation is expected *in vivo*). The characterization of pH-dependent surface charge formation and the analysis of sensitivity against electrolytes similar to the biological systems triggered the greatest interest in professional circles. We suggested testing SPION products according to this physical chemistry and colloidal protocol prior to their expensive *in vitro* tests. In RADIOMAG (COST action TD1402), I have recommended these tests for **unified characterization** of magnetic nanoparticles (MNP). Preparation and characterization of PAA and PAM coated SPIONs were published in high ranked journals [Hajdú et al. 2012; Tóth et al. 2012]. The PGA coating formed *in situ* on the SPION cores in the polymerization of gallic acid under mild conditions [mechanism analyzed in Tóth et al. 2014] provides excellent hydrophilic protective layers on magnetic cores. Besides the outstanding colloidal stability of these core-shell products, the PGA coating has a unique antioxidant effect [Szekeres et al. 2015]. The remarkable results of chondroitin-sulfate-A-coated SPIONs were published [Tóth et al. 2015a] together with the paper on the magnetic hyaluronate (HyA) hydrogels [Tóth et al. 2015b], in which the CSA coated SPIONs were dispersed perfectly. These HyA-based magnetic hydrogels may cover an interesting biomedical application as magnetic intra-articular fluid in the treatment of osteoarthritis. The oleate double layers are frequently used stabilizing method to prepare stable magnetic fluids (surfacted MFs). Better biocompatibility of these products is expected by adding polyethylene glycol (PEG). This PEGylation procedure is empirical, neither the quality nor the quantity of PEG has been clarified. We tested two ways of preparation by adding PEG with different molecular weights during co-precipitation synthesis (*in situ* method) and after purification of surfacted MF (post-synthesis method). It has been proved that PEG molecules are bound to carboxylated surface by ester bonds and the hydrophilicity of PEGylated products is remarkable. The r2 relaxivity of one type of sample was extraordinary due to the cluster structure formed *in situ* during preparation [Illés et al. 2014]. These procedures cannot result in biocompatible PEGylated products because of the excess surfactant and PEG content. This disadvantage was solved in an elegant

way with the help of the outstanding polymer chemists. Carboxylated copolymers with comb-like polyethylene oxide (PEO) chains were synthetized by the research group of Prof. B. Iván. This fruitful cooperation was initiated by Dr. E. Illés postdoctor. The self-coating of SPIONs by PEO-poly-carboxylates (poly(poly(ethylene glycol) methyl ether methacrylate) - P(PEGMA) and poly(PEGMA-co-acrylic acid)) provides excellent hydrophilic protective layers on magnetic cores. Besides their outstanding colloidal stability in bio-relevant media, the PEO-poly-carboxylate coating is super-hydrophilic and so noteworthy protein repellency can be expected. The hemocompatibility and also the theranostic potential of these products are remarkable (see below). The results of the novel carboxylated PEG-coated SPION products have been published in part [Illés et al. 2015]. We believe that our surface modification concept, i.e., the self-coating of purified SPION by designed macromolecules resulted in superb products in bio-nano-interactions point of view. We wrote two comprehensive manuscripts on self-coated SPION products with super-hydrophilic coatings (the novel synthetized comb-like PEO-poly-carboxylates and the natural chondroitin-sulfate-A were used), which probably cannot or hardly interact with cell membranes and proteins, were submitted to Nanoscale (RSC) and ACS Nano, respectively. Unfortunately both were rejected, the Editor of RSC journal suggested submitting it to another RSC journal with a bit lower IF (J. Mat. Chem. B), it is under revision now [Illés et al 2016]. I have to mention that this novel PEO-poly-carboxylate coated SPION product besides its good hemocompatibility, has outstanding r2 relaxivities, which suggests a high-contrast enhancement effect in MRI.

Theranostic potential: During biomedical applicability tests of SPION products, toxicity and biocompatibility studies have to be essential issues besides the specific ones, to which the application in diagnosis and treatment is directed. The *in vitro* tests were implemented in cooperation: cyto**toxicity** (MTT method, Dr. I. Zupkó), **hemocompatibility** and blood cell viability measurements (K. Farkas, Dr. I. Földesi), antioxidant effect of PGA coated SPIONs (Prof. C. Alexiou, Dr. C. Janko). The toxicity tests of all our products were done, the MTT assays performed on healthy and tumor cell lines in the presence of naked and coated iron oxide nanoparticles indicated that our samples have no detectable toxicity as published in papers belonging to the given SPION products [Hajdú et al. 2012, Tóth et al. 2012 and 2015a, Szekeres et al. 2013 and 2015, Tombácz et al. 2014, Illés et al. 2014 and 2015]. Hemocompatibility testing developed successfully by Dr. E. Illés K. Farkas and supported fully by Dr. I. Földesi has been recognized internationally. The red blood cell sedimentation, the peripheral blood smear tests showed that no aggregation occurs in the tested healthy human blood samples, and the white blood cell viability tests proved that well-stabilized SPIONs do not disturb the viability of cells; the effect of magnetic fluids was the same as that of pure water, which causes a small osmotic stress. These tests of nanoparticulate products are essential especially, if they are intended to be administered intravenously like in case of MRI contrast agents as we emphasized many times [Tóth et al. 2012, Szekeres et al. 2015, Tombácz et al. 2016].

Regarding the theranostic potential of our SPION products, we focused on the **MRI contrast enhancement** and **hyperthermia activity** studies. First we investigated the magnetic field dependent MRI contrast enhancement of three SPION products in a clinical apparatus (under the direction of Dr. M. Babos, Euromedic Diagnostics Szeged Ltd.) and two NMR devices (under the direction of Dr. I. Bányai, University of Debrecen). Our products showed significant effect and a definite maximum at 1,5 T, where the most of clinical MRI apparatus works [Jedlovszky-Hajdú et al. 2012]. Our SPION products have high r2 relaxivities [Illés et al. 2014, Tóth et al. 2016] measured only at 1.5 T (Diagnoscan Szeged Ltd. with the help of I. Kaszás) in general, some of them very high such as the PGA and PEO-poly-carboxylate

coated SPIONs, which have outstanding r2 relaxivities [Szekeres et al. 2015 and Illés et al. 2015, 2016, respectively] suggesting a high-contrast enhancement effect in MRI.

Besides the MRI contrast efficiency, we studied the heat evolving ability of our SPION products by means of MagneTherm apparatus using the improved thermometer device developed in Veszprém by Prof. I. Szalai. Several samples were tested in parallel in cooperation with Prof. Patricia de la Presa (Instituto de Magnetismo Aplicado, Madrid). The effect of magnetic cores (single and multicore fractions), the influence of coating and clustering (the same magnetic core with different coating shells and clustered samples) on heat evolving ability were investigated systematically. The advanced magnetic characterization of liquid samples was done by SQUID magnetometer (magnetization and ZFC-FC curves, hysteresis loops at 10 and 250 K) in Madrid, while the dynamic behavior in AC field was measured by means of a DynoMag AC susceptometer in Sweden (Acreo Swedish ICT). The evaluation of results and their comparison to qualify our novel magnetoresponsive nanoparticles have not finished yet. The calorimetric characterization of magnetic hyperthermia efficiency suffers from several methodological pitfalls. Therefore the MC members of RADIOMAG TD1402 COST action decided to standardize measurements. Our laboratory is one of dedicated measuring sites. We have measured 2 double blind samples from 6. The measurements and evaluations are in progress.

The results of hemocompatibility, antioxidant effect and biomedical potential of PGA coated SPION product for theranostic use, namely as MRI contrast agent in diagnosis and magnetic heating agent in local hyperthermia have been published [Szekeres et al., 2015]. As a continuation of the collaboration with Prof. C. Alexiou (SEON, Erlangen, Germany), our PAM coated SPIONs were successfully decorated by a bioactive molecule. A joint paper about the tPA protein bound covalently to the free carboxylate groups of the PAM@MNP via the N-terminus using carbodiimide linker in comparison with that bound electrostatically has been published [Friedrich et al, 2016]. This work revealed the base of the **magnetically targeted delivery** of a tissue plasminogen activator.

In relation with the potential biomedical application, we studied the interactions of our SPION products with biological entities. We performed the light scattering study on the **interaction of human plasma** (HP) proteins with different SPION products in biorelevant media. The change in aggregation and zeta potential at various HP/SPION ratios was followed in time. Significant differences were observed at low plasma concentration. The naked and citrate coated SPIONs aggregated instantly while the hydrodynamic diameter of PAM and novel PEO-poly-carboxylates coated SPIONs increased only slightly at 1–3 v/v % HP concentrations, showing very low ability for protein corona formation on the top of these coated SPIONs [Szekeres et al. 2016]. The **interaction with membrane of HeLa cells** used in MTT assays was directly visualized by a common staining for iron (Prussian Blue formation, blue spots indicate the presence of iron), so we could reveal the fine and robust differences in the series of SPIONs with carboxylated and carboxylated/PEGylated coating. For example SPIONs with PAA coating dominantly penetrate into the cells, while the naked and CA, PAM, PGA coated particles were both on the surface and inside the cells, aggregation of CA coated NPs was also identified [Szekeres et al., 2013]. In turn, we could not indicate any blue spots on/in HeLa cells, when our novel PEO-poly-carboxylate coated SPIONs were tested, so we conclude that they were not able to interact with cell membrane [Illés et al. 2016].

Dissemination: Our important task is not only the implementation, but also the popularization of science. After invitation of Prof. M. Zrínyi academician, we wrote together an interesting

article about the special properties of magnetic nanoparticles, the research going on our research groups and the interesting applications as well in the journal of Magyar Tudomány [Zrínyi et al. 2014].

The **expected results** of project were to have chance attending international collaborative projects. This was achieved, since we attended 1 German project (BMBF 01DS13012, 2014-2015), 1 e-COST (TD 1402, RADIOMAG, 2014-2018), 2 H2020 proposals (MION4Med, ID 645950, SPIONs4CancerTherapy, ID 685592-1) and 5 M-Era-Net proposals (among them 2 are under review at present) with German, Roman, Slovak and Portugal partners mentioning only the direct collaborations. In addition, we expected that the new generation of young scientists, PhD and undergraduate students could get acquainted with the newest results and developments of the unique magnetoresponsive materials. During the project, we worked together students, 4 BSc, 2 MSc and 2 PhD dissertations (one of them has not completed yet) were successfully prepared. The global advantage of the planned teamwork according to our vision five years ago was to develop novel magnetorespective nanosystems fully biocompatible, which have fruitful prospective for biomedical use in future has been realized indeed.

Closing remarks: The promising research built systematically in the last decade has very good international response and is recognized in the European arena (e.g., RADIOMAG COST TD1402) by now; unfortunately, will be interrupted soon by absence of the local support. The project leader has retired meantime, so she will be no longer permitted to apply for research money and the lab equipped specially (magnetic separator - Frantz Co., NanoZS – Malvern, magneTherm™ apparatus - nanoTherics Ltd.) from grants (OMFB-01604/2006, NKTH-OTKA K-69109, NKFI-OTKA 84014) is planned to be closed even in front of a young colleague, who could have used successfully the facilities because of his promising plan to develop novel magnetoresponsive nanocomposites. The latter would be the combination of his favorite material (graphene oxide, graphene) with magnetic nanoparticles, novel therapeutic products showing extraordinary hyperthermia activity, based on the assumed synergistic effect arising from the coupling of the "magnetic heating" of the SPIONs and the inductive "electric" heating effect of the conductive graphene based support.

Publications

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