Ph.D. thesis

Synthesis of variable sized magnetite nanoparticles and their surface modification by polianionic coatings

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2013

1. Introduction and aims

The iron is a widespread element in the nature, its Fe^{2+} and Fe^{3+} oxidation forms create 16 well-known iron oxides / iron hydroxides / iron oxide-hydroxides, for example the ferrimagnetic magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3). The magnetic properties of materials depend on the size of particles in the colloidal range (1 – 1000 nm). The bulk magnetite is ferromagnetic with a multi domain structure, and its remanent magnetization reaches the highest value at the border of the single domain and the multi domain structure (~120 nm). The nanoparticles have superparamagnetic properties below the superparamagnetic limit (~20 nm for magnetite), namely the magnetic moments of the particles align themselves only in the presence of external magnetic field, so their remanent magnetization is zero.

There are several well-known procedures for magnetite synthesis, e.g. sol-gel method, preparation in microemulsion, hydrothermal synthesis, decomposition at high temperature, precipitation techniques. The precipitation synthesis is the most popular method, because large quantities of magnetite can be produced in aqueous media easily, its variation are the co-, the oxidation- and the reduction-precipitation.

The superparamagnetic iron oxide (magnetite, maghemite) nanoparticles can be used to prepare magnetic fluids (MFs), which are popular in scientific research nowadays. The MFs can be manipulated by an external magnetic field. The organic-based MFs are widely used in industrial applications (e.g. sealings, loudspeakers). The water-based MFs are planned to be used in biomedical applications, such as contrast agent for MRI (magnetic resonance imaging), targeted drug delivery, hyperthermia, magnetic cell separation.

Most of the biomedical applications require the nanoparticles in MFs to be well dispersed under physiological conditions (e.g. in blood pH ~7,2 - 7,4; 0,15 mol/dm^3 NaCl). Since the naked magnetite nanoparticles (MNPs) do not meet this criteria, their surface has to be modified to reach the necessary colloidal stability. There are several possibilities to enhance the stability of MFs. One of them is to increase the electrostatic repulsion between the particles, for example citric acid is attached to the surface of MNPs. The other opportunity is the sterical hindrance of the aggregation by adsorption of macromolecules (e.g. dextran) on the magnetite. These two possibilities can be combined, too, for example by the adsorption of macromolecules containing carboxylic groups (e.g. polyacrylic acid) to form a combined electrosteric shell on nanoparticles. The colloidal stability of MNPs can be characterized by coagulation kinetics measurements. The other requirement for biomedical applications is the

non-toxicity of MFs, which can be studied by acute and chronic toxicity tests, e.g. by MTT-assay.

The main aim of my work was to synthesize variable sized magnetic iron oxide nanoparticles and to prepare water-based magnetic fluids from core/shell structured polyelectrolyte (PE) coated superparamagnetic magnetite nanoparticles (MNPs) exhibiting enhanced colloidal stability under physiological conditions. I planned to use three different surface modification agents, two of them are synthetic polyelectrolytes containing carboxyl(ate) groups (polyacrylic acid (PAA; M_w ~1800 Da) and poly(acrylic acid-co-maleic acid) (PAM; M_w ~3000 Da)), the third one is a polysaccharide of natural origin (chondroitin-sulfate-A (CSA)) with carboxyl(ate) and sulfate groups.

I set the following aims in the course of my work:

- to synthesize and to characterize variable sized magnetic iron oxide (magnetite, partly maghemite) nanoparticles prepared by co-precipitation and oxidation-precipitation;
- to determine the effects of the systematically changed parameters during oxidation-precipitation synthesis on the quality, size and morphology of the prepared iron oxide particles;
- to describe the pH- and ionic strength-dependent charging of polyelectrolytes;
- to characterize the adsorption of polyelectrolytes on magnetite nanoparticles at pH ~6,3 and 0,01 mol/dm^3 NaCl by adsorption isotherms quantitatively and to identify the quality of the chemical bonds between the MNPs and the polyelectrolytes by ATR-FTIR spectroscopy;
- to study the pH-dependent surface charging and the aggregation of the polyelectrolyte-coated magnetite nanoparticles (PE/MNP);
- to test the prepared magnetic fluids for biomedical applications (examination of their salt tolerance through determining the critical coagulation concentration (CCC) by coagulation kinetics studies, measuring the dissolved iron-content of the magnetic fluids by ICP atomic spectroscopy, characterisation of toxicity by MTT-assays and determining their compatibility with blood by erythrocyte sedimentation rate experiments).

2. Experimental methods

The magnetic nanoparticles (magnetite, partly maghemite) were synthesized at air atmosphere by co-precipitation and oxidation-precipitation. In the case of co-precipitation the iron oxide was prepared from the mixture of concentrated $FeCl_2$ and $FeCl_3$ solutions by

adding NaOH, and after the purification of the product it was hydrothermally aged combined with ultrasonication (US) at pH ~3. Using the oxidation-precipitation method I studied the effects of the systematically changed synthesis parameters (quantity of oxidation reagent, temperature, type of Fe^{2+} salt, reaction time and finally the added PAA's molecular weight, amount and the point of dosage) on the quality, size, morphology and the coalescence of the prepared particles.

The quality of the iron oxide and the particle size of the superparamagnetic magnetite nanoparticles were determined by X-ray diffraction (XRD, Bruker D8 Advance). The primary size and the morphology of MNPs were characterized by transmission electron microscopy (TEM, Philips CM-10). The magnetic properties of magnetite particles were measured by vibrating sample magnetometer (VSM, VSM 880, DMS/ADE Technologia).

The pH- and ionic strength-dependent charging of magnetite nanoparticles and different polyelectrolytes was determined by potentiometric acid-base titrations (GIMET1 automatic home-made titrator system). The adsorption isotherms of polyelectrolytes on magnetite nanoparticles were measured at pH ~6,3 and 0,01 mol/dm^3 NaCl by the batch method. The equilibrium concentration was determined by UV spectroscopy (USB-ISS-UV-VIS and USB4000, Ocean Optics) and by density measurements (DMA58, Anton Paar). The amount of polyelectrolytes is expressed in the summarized number of moles of carboxyl and carboxylate groups. The chemical bonds between the MNPs and the polyelectrolytes were identified by ATR-FTIR spectroscopy (FTS-65A/896 FTIR, Harrick's Meridian Split Pea ATR accessory) at pH ~6,3 and 0,01 mol/dm^3 NaCl. The zeta potential of naked MNPs and PE/MNP systems was determined by laser Doppler electrophoresis (Zetasizer NanoZS, (Malvern). The aggregation of particles was followed by dynamic light scattering (DLS, Zetasizer NanoZS). The critical coagulation concentration (CCC) of PE/MNP systems was determined by coagulation kinetic measurements (DLS). The iron-content dissolved by PE in the magnetic fluids was measured by ICP atomic spectroscopy (Agilent 7700x, ICP-MS spectrometer).

The toxicity of prepared magnetic fluids was studied by MTT (3-(4,5-dimetil thiazol-2-yl)-2,5-difenil tetrazolium bromide) assay, and their compatibility with blood was tested by erythrocyte sedimentation rate experiments (Sedi-15, BD Inc).

3. Summary of novel scientific results

T1. Synthesis and characterization of variable sized magnetite nanoparticles

T1.1. Optimization of the synthesis of variable sized MNPs

I observed that the polydispersity of magnetite decreased and the size of MNPs increased from 6,7 ± 1,7 nm to 9,4 ± 0,8 nm (TEM) in parallel when hydrothermal ageing combined with ultrasonication was performed at 80 °C during co-precipitation synthesis. This rise in particle size will probably influence the effect of MNPs in hyperthermia auspiciously.

Since air atmosphere was used instead of inert atmosphere (typically reported in the publications), it was necessary to optimize the conditions of oxidation-precipitation synthesis of magnetite nanoparticles. Based on the results I can state that the formation of magnetite is preferred to the formation of goethite in case of preparation from $FeCl_2$ in fast reaction, by using the oxidation reagent in the stoichiometric amount and applying high temperature.

My observations show that the coalescence of magnetite nanoparticles during the synthesis can be prevented by sonochemical method (ultrasonication treatment) and also by adding polyacrylic acid. I observed that *(i)* the shorter time of ultrasonication (~2 minutes) leads to individual, octahedral particles with slightly reduced size; *(ii)* the presence of PAA higher molecular weight PAA or addition of larger amounts shifts the formation of iron oxide from magnetite to maghemite; *(iii)* the prepared particles are individual, spherical and reduced in size independently of the point of PAA dosage compared with the particles synthesised at the same condition without PAA; *(iv)* the adsorbed polyacrylic acid can be removed from the surface of MNPs by hydrogen peroxide treatment.

T1.2. The physicochemical and colloidal characterization of variable sized MNP

I proved that the nanoparticles prepared by co-precipitation are superparamagnetic (VSM), ~10 nm and spherical (TEM) magnetite (XRD) particles, simultaneously the products synthesised by oxidation-precipitation method using PAA and ultrasonication treatment are ferromagnetic (VSM) ~50 and ~60 nm spherical or ~75 nm octahedral (TEM) magnetite (XRD) nanoparticles.

I observed that pH values of the point of zero charge (PZC) determined by potentiometric acid-base titration are different for MNPs prepared by co-precipitation ($pH_{10\ nm}$ ~7,8) and oxidation-precipitation ($pH_{75\ nm}$ ~6,8), and they agree with the pH values of their isoelectric points (IEP) obtained from zeta potential measurements. Hence I can state that the value of PZC depends on the size of synthetic magnetite nanoparticles.

T2. The surface modification of superparamagnetic magnetite nanoparticles by biocompatible polyelectrolytes

I defined the reactions taking place during the adsorption of biocompatible polyelectrolytes on magnetite by using *(i)* the adsorption isotherms; *(ii)* the bonds between the MNP's ≡Fe–OH and the PE's functional groups identified by ATR-FTIR spectroscopy; *(iii)* the real quantity of charges on the adsorbed PE at the isoelectric point (IEP) (zeta potential measurement, adsorption isotherm, potentiometric acid-base titration); *(iv)* the amount of the surface charge (~0,05 mmol/g) of MNP at pH ~6,3 and 0,01 mol/dm^3 NaCl.

T2.1. The surface modification of MNPs by polyacrylic acid

I found that adsorption isotherm of PAA on MNPs is not of high affinity type, it reaches a plateau value at ~0,6 mmol/g, it has an inflection at ~0,4 mmol/g adsorbed amount, and higher equilibrium concentrations of PAA is necessary to a get stable MF. I identified H-bonds between MNP and PAA from the ATR-FTIR spectra, because the C=O vibration (–COOH) shifted from 1697 cm^{-1} to 1713 cm^{-1}, but the symmetric and asymmetric C–O vibrations (COO$^-$) remained unchanged at 1404 cm^{-1} and 1564 cm^{-1}. I observed that the IEP is at ~0,13 mmol/g added amount of PAA and this corresponds to ~0,05 mmol/g of negative charge effectively, which equals in absolute value with the positive charge typical for MNPs (~0,05 mmol/g) at this pH. Thus it can be stated that the oppositely charged species form H-bonds during the adsorption of PAA on MNP, but the reaction between the neutral species is also possible:

$\equiv Fe–OH_2^+ + {}^-OOC– \rightarrow \equiv Fe–OH\cdots O(HO)C–$ and $\equiv Fe–OH + HOOC– \rightarrow \equiv Fe–OH\cdots O(HO)C–$.

T2.2. The surface modification of MNPs by poly(acrylic acid-co-maleic acid)

I discovered that adsorption isotherm of PAM on MNPs is of high affinity type, it reaches a plateau value at ~0,9 mmol/g adsorbed amount and in comparison with PAA it is not necessary to have high equilibrium concentration of PAM to get a stable MF. I also identified H-bonds and inner sphere metal-carboxylate complexes between MNPs and PAM from the ATR-FTIR spectra, because the C=O vibration (–COOH) shifted from 1690 cm^{-1} to 1717 cm^{-1}, and the symmetric and asymmetric C–O vibrations (COO$^-$) shifted from 1400 cm^{-1} and 1568 cm^{-1} to 1404 cm^{-1} and 1574 cm^{-1} in parallel. I observed that the IEP is located at ~0,17 mmol/g added amount of PAM and this corresponds to ~0,10 mmol/g of negative charge effectively, which is larger in absolute value than the positive charge typical for MNPs (~0,05 mmol/g). Therefore I can state that the oppositely charged species form H-bonds

during the adsorption of PAM on MNP, but it can also take place between the neutral species. Simultaneously the neutral charged surface groups are involved in the formation of the inner sphere metal-carboxylate complexes, but the reaction on the positively charged surface groups is also possible:

$\equiv Fe–OH_2^+ + {}^-OOC– \rightarrow \equiv Fe–OH\cdots O(HO)C–$ and $\equiv Fe–OH + HOOC– \rightarrow \equiv Fe–OH\cdots O(HO)C–$, $\equiv Fe–OH + {}^-OOC– \rightarrow \equiv Fe–OOC– + OH^-$ and $\equiv Fe–OH_2^+ + {}^-OOC– \rightarrow \equiv Fe–OOC– + H_2O$. My observations show that the PAM can bind to the MNP's surface with high affinity, because the PAM can form inner sphere metal-carboxylate complexes due to the carboxyl(ate) groups on the adjacent/neighboring carbon atoms, which makes the PE's geometry suitable to the MNP's ≡Fe–OH groups.

T2.3. The surface modification of MNPs by chondroitin-sulfate-A

I experienced that adsorption isotherm of CSA on MNPs is of high affinity type, it reaches a plateau value at ~0,1 mmol/g, and like PAM lower equilibrium concentration of CSA is enough to get a stable MF if special pretreatments are applied during preparation because of the base and cetylpyridinium chloride contamination of the polysaccharide. I identified inner sphere metal-carboxylate complexes between MNP and CSA from the ATR-FTIR spectra, because the C=O vibration (–COOH) did not appear, the symmetric and asymmetric C–O vibrations (COO^-) shifted from 1375 cm^{-1} and 1612 cm^{-1} to 1379 cm^{-1} and 1630 cm^{-1}, and the C–O–S and S=O vibrations ($–O–SO_3^-$) remained unchanged at 856 cm^{-1} and 1260 cm^{-1} at the same time. Simultaneously the vibrations of the alcohol groups and pyranose rings remained unchanged at 1055 cm^{-1}, 1035 cm^{-1} and 925 cm^{-1}, but their relative ratio somewhat changed. I observed that the IEP can be found at ~0,035 mmol/g added amount of CSA and this corresponds to ~0,07 mmol/g of negative charge effectively, which is slightly higher in absolute value than the positive charge typical for MNPs (~0,05 mmol/g) at these circumstances. Hence I can state that the neutral charged and positively charged surface groups are also involved in the formation of the inner sphere metal-carboxylate complexes:

$\equiv Fe–OH_2^+ + {}^-OOC– \rightarrow \equiv Fe–OOC– + H_2O$ and $\equiv Fe–OH + {}^-OOC– \rightarrow \equiv Fe–OOC– + OH^-$. My observations show that the CSA can bind to the MNP's surface with high affinity, because the CSA is also able to form inner sphere metal-carboxylate complexes due to the coordination of the alcohol groups to the nanoparticle.

T3. The pH-dependent charging and colloidal stability of magnetite nanoparticles coated with biocompatible polyelectrolytes

I proved that the PAA/MNP, PAM/MNP and CSA/MNP systems have the following very similar properties at various amounts of added biocompatible polyelectrolytes:

(i) the IEPs of the PE/MNP particles shift from pH ~7,9 to the lower pH values with increasing amounts of added PE;

(ii) the shape of the pH-dependent zeta potential curves at trace amounts of added PE (PAA and PAM: 0,1 mmol/g, CSA: 0,05 mmol/g) are very similar to the naked magnetite, i.e. the zeta potentials decrease monotonically from +40 mV to -40 mV, simultaneously the particles aggregate at the whole pH-range studied due to the patch-wise adsorption of the negatively charged PE on the originally positively charged MNP;

(iii) the surface of the particles are totally covered at sufficiently high added amounts of PE (PAA: 1,15 mmol/g, PAM: 1,30 mmol/g, CSA: 0,2 mmol/g), in this case the zeta potentials of PE/MNP are negative at the whole pH-range studied, the particles are overcharged and colloidally stable at pH >4.

T4. The salt tolerance of magnetite nanoparticles coated with biocompatible polyelectrolytes at pH ~6,3

Based on the critical coagulation concentration (CCC) values I can conclude the following characteristics for the salt tolerance of PE/MNP systems:

(i) the added amounts of PE close to the plateau value are high enough to protect the PE/MNP against the aggregation under physiological conditions (~150 mmol/dm^3) for PAM and CSA with high affinity type adsorption isotherm ($CCC_{PAM\ 0,9\ mmol/g}$ ~270 mmol/dm^3; $CCC_{CSA\ 0,2\ mmol/g}$ ~150 mmol/dm^3), in contrary this added amount of PAA does not guarantee the required colloidal stability ($CCC_{PAA\ 0,6\ mmol/g}$ ~80 mmol/dm^3) of PAA/MNP;

(ii) the added amounts of PE well above the plateau values of adsorption isotherms increase the salt tolerance further ($CCC_{PAA\ 1,1\ mmol/g}$ ~ $CCC_{PAM\ 1,2\ mmol/g}$ ~ $CCC_{CSA\ 1,0\ mmol/g}$ ~ ~500 mmol/dm^3) suggesting the rearrangement of PE chains in the adsorbed layers.

T5. The chemical stability of core/shell magnetite nanoparticles coated by biocompatible polyelectrolytes

I revealed that the chemical stability of magnetite products for biomedical applications is very important, because they are used under extreme pH and in presence of strong complex forming agents (e.g. citrate like anticoagulant), so the redox transformation of magnetite to maghemite and the increased amount of iron dissolved by the complex forming agents can hurt the living systems through oxidative stress.

The chemical stability of PE/MNP systems can be characterised by the amount of the dissolved iron content, so using these data I proved that:

(i) the PAA, PAM and CSA protect the surface of magnetite and hinder the corrosion of MNP much better than citric acid, because the dissolved iron content is very low for these PE/MNP magnetic fluids in contrary to the values measured in citric acid coated MNP systems;

(*ii)* for PAM and CSA coatings the concentration of dissolved iron remained unchanged even at high equilibrium concentration of PE, nevertheless the high equilibrium concentration of PAA slightly increased the iron dissolution;

(iii) the best chemical stability can be guaranteed by polyelectrolytes that adsorb on magnetite with high affinity.

T6. The *in vitro* tests of core/shell magnetite nanoparticles coated by biocompatible polyelectrolytes

From the toxicity data measured by the MTT-assay I determined that for PAA/MNP, PAM/MNP and CSA/MNP prepared under special conditions:

(i) all of the magnetic fluids have been found to be nontoxic; the viability of cells is below the significant toxicity level in the presence of MNPs;

(ii) the averaged inhibition values of PAA/MNP product are systematically higher than the values of PAM/MNP and CSA/MNP, this can be caused by the difference between the used human cells: the MCF7 breast cancer cell line is more virulent (PAM/MNP and CSA/MNP) than the MRC5 normal lung tissue cell line (PAA/MNP).

I proved by using the erythrocyte sedimentation rate experiments that the presence of the PE/MNP has no effect on the aggregation of red blood cells, so the prepared magnetic fluids in all probability can also be used in biomedical applications by directly injecting them into blood.

Possible practical application

The ferrimagnetic, variable sized (~75 nm, ~60 nm, ~50 nm) iron oxide nanoparticles synthesized by oxidation-precipitation method can be used in preparation of magnetorheological fluids.

The superparamagnetic (~10 nm) magnetite nanoparticles were stabilized with different biocompatible polyelectrolytes containing carboxyl(ate) groups. The prepared magnetic fluids are stable under physiological conditions and their biocompatibility was confirmed in biological tests. These products may be suitable in clinical diagnosis and also in therapeutic applications.

It should be noted that in case of stable PAA/MNP magnetic fluids the equilibrium concentration of PE is pretty high and this can be unfavourable for later biomedical applications according to the MTT-assays and chemical stability experiments.

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