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Collective magnetic behavior of biocompatible systems of maghemite particles coated with functional polymer shells

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ABSTRACT

Three series of core–shell maghemite nanoparticles were prepared by a template synthesis using surface active oligoperoxides and further surface initiated grafting functional polymers, forming shell suitable for biomedical applications. Because the polymer shells prevent exchange coupling between maghemite particles, the overall magnetic properties of the samples studied are dominated by dipolar interparticle interactions. Only the sample with the highest polymer fraction displays superparamagnetic relaxation phenomena close to the room temperature. On cooling, the magnetostatic interactions lead to a disordered collective magnetic state that should be described in terms of a spin-glass phenomenology. This collective freezing cannot however be considered as a generic spin-glass phase transition at a well-defined temperature but rather as freezing to a metastable glass-like state of locally correlated structural domains (clusters) without a long-range order. A quasi static spin ordering is only achieved at temperatures much below the freezing temperature.

1. Introduction

Iron oxide nanoparticles are interesting objects in various biomedical and bioanalytical applications including magnetic resonance imaging (MRI), magnetic microsensors, magnetically guided drug delivery, cell-, DNA-, protein-separation, in vivo magnetic hyperthermia and radiotherapy [1–5]. Such an extensive use of maghemite and/or magnetite particles originates from their biocompatibility, nontoxicity, biodegradability, large surface area, low particle dimensions and suitable magnetic properties. Many synthesis methods can be applied to produce iron oxide nanoparticle. These methods include electrochemical, sol–gel, polyol, aerosol/vapor, co-precipitation, thermal decomposition, sonoanalysis and hydrothermal synthesis (see e.g. [6–9] and references therein). Among them, the co-precipitation has been proven to be the most promising method as this procedure is relatively simple allowing the particles with a controlled size to be obtained. Nanoparticles are likely to aggregate because of a large surface-to-volume ratio and associated tendency for reduction of their surface energy, long-range magnetostatic interparticle interactions and van der Waals attraction. In a biological medium (blood plasma) they will adsorb proteins (biopolymers) on their surfaces, which additionally results in formation of agglomerates and prevents from achieving the target (affected) organ [10–12]. Thus a key issue in medical applications is the surface modification of iron oxide particles by creating a very thin layer of biocompatible organic (polymer), inorganic (noble metals) or oxide (e.g. silica) materials that, on the one hand, prevent spontaneous aggregation of particles and unwanted surface opsonization of the mineral cores and, on the other, enable further functionalization with bioactive molecules [3–6]. The presence of reactive fragments in the shell enables to perform a controlled modification and creation of vectors (e.g. antibodies) which will ensure effective targeted delivery of the magnetic nanoparticles to the cells of affected organ. Localization of magnetic particles in the target organ will enable application of e.g. a magnetic hyperthermia in order to destroy the pathologic cells.

Well isolated, non-interacting, single domain particles exhibit a superparamagnetic (SPM) behavior at elevated enough temperatures and a collective blocking of their magnetic moment on cooling below the blocking temperature T_b (see e.g. [13] and references therein). At finite interparticle distances the dipole–dipole interactions between particles appear and have pronounced effect on the magnetic properties of a nanoparticle system ([14–17] and references therein). In an assembly of randomly oriented single domain particles the sufficiently strong interparticle dipolar

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interactions cause frustration effects and lead to a spin-glass (SG) (or super-spin-glass SSG) behavior below a certain glass transition temperature T_g (see e.g. [15–18] and references therein). While the properties of SPM single phase particles are relatively well described, the more complex systems such as particles with core–shell morphology and/or interaction effects are far from being well understood especially considering that the surface and interaction effects are often superimposed. These effects have been the subject of a number of studies for free standing iron oxide nanoparticles, surface coated particles and particles embedded in polymer matrices [19–22].

In this work magnetic properties of γ-Fe_2O_3 nanoparticle systems with a core–shell structure are investigated. Surface-active polyfunctional oligoperoxides were used as the nanoreactors (soft-templates) for the controlled formation and modification of γ-Fe_2O_3 particle shells that is a promising and effective method to elaborate magnetic nanocomposites for further medical applications. The novelty of this method consists in application of polyfunctional oligoperoxide surfactant, which acts simultaneously as a regulator of particle size and as a surface modifier [23,24]. Irreversible localization of oligoperoxide macromolecules on the nanoparticle surfaces allows us to construct core–shell nanocomposites via graft polymerization method for which the creation of stable coatings has been proved by a range of physico-chemical methods. We have already tested this type of nanoparticles for biomedical applications to study e.g. the phagocytic activity of macrophages [23] and for bioanalysis to label stem cells [24]. Experiments with rat mesenchymal stem cells (rMSCs) confirmed that coated γ-Fe_2O_3 nanoparticles were not cytotoxic and that the average efficiency of stem cell labeling was good and comparable to that obtained with commercial agents. Thin oligoperoxide copolymer coating enables high density of the nanoparticle assembly and eliminates the direct exchange coupling between particles that would dominate their magnetic properties. From the point of view of basic research important aspects of the nanoparticle systems studied are: (1) the preservation of the same magnetic cores (crystalline interiors as well as their surfaces) in all samples and (2) the modification of the polymer shell thickness from one sample to another. This allows the detailed studies of the magnetic behavior of concentrated nanoparticle systems and, due to elimination of the surface phenomena from the comparative analysis, the elucidation of the effects related to interparticle interactions. For potential medical applications of the particles for e.g. anticancer magnetic hyperthermia, understanding and control of these interactions is clinically relevant as the dipolar interactions are known to affect the nanoparticle heating efficiency [25].

2. Experimental

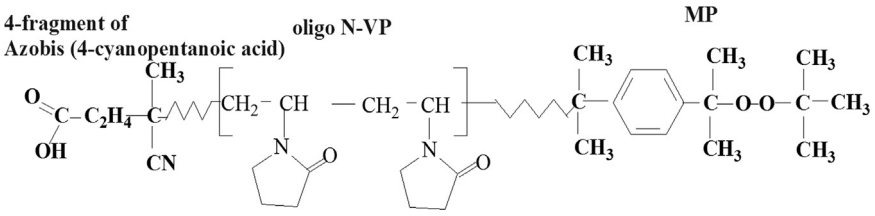
2.1. Preparation of core–shell magnetic nanoparticle systems

The nanoparticle systems were produced by nucleation from the solution of corresponding salts in the presence of the oligoperoxide surfactant as a soft-template. Irreversible attachment of oligoperoxide macromolecules to γ-Fe_2O_3 particle surfaces allows to construct an organic shell via graft polymerization method. This resulted in nanoparticles with a magnetic core and polymer shell of specified nature, with high-density packing of the polymer chains and with a controlled set of functional groups, which can be used to attach a variety of biological vectors (antibodies, lectins, etc.). Three sets of nanocomposites were prepared.

(1) *Sample **A** – γ-Fe_2O_3 nanoparticles with COOH-poly(NVP)-MP shell*. The maghemite particles were obtained in the presence of oligoperoxide modifier as a soft-template. This modifier is a heterofunctional telechelic oligoperoxide on the basis of oligo (N-vinyl pyrrolidone NVP), containing terminal functional groups of 4-cyanopentanoic acid (CPA) (carboxyl group) and 1-isopropyl-3 (4)-[1-(tert-butyl peroxy)-1-methylethyl]benzene (MP) (peroxide group) with the structure shown in Scheme 1. $M_n \approx 17{,}000$ g/mol, [MP-fragments]=1.5 mol%, [COOH]=0.27 mol%. Preparation of oligoperoxide modifier has already been described in [23]. Maghemite particles (γ-Fe_2O_3) were synthesized via mixing of solutions of Fe^{2+} and Fe^{3+} salts in the presence of ammonium hydroxide, according to the following reaction [26]: $2FeCl_3 \cdot 6H_2O + 2FeCl_2 \cdot 4H_2O + 10NH_4OH + H_2O_2 \rightarrow 2Fe_2O_3 + 10NH_4Cl + 26 \cdot H_2O$. Molar ratio of reagents was Fe^{3+}:Fe^{2+}=2:3 (taking into account Fe^{2+} oxidation during solution preparation under aerobic conditions). An amount of ammonium hydroxide, greater than the stoichiometric one, was applied in order to maintain solution pH > 11 [27]. Water solution of oligoperoxide modifier (concentration of oligoperoxide ~1% in the aqueous phase) was charged into the flask with iron salts and then the solution of ammonia was added. The process was carried out in a three-necked flask, equipped with a paddle stirrer and a backflow condenser at 363 K for 1.5 h. Then, 1 M solution of HCl was added to the reaction medium to lower pH of solution to neutral whereas the synthesized Fe_3O_4 particles were oxidized into γ-Fe_2O_3 using 10% H_2O_2 solution, and then washed with distilled water until the filtrate conductivity remained constant. The maghemite particles obtained were coated with COOH-polyNVP-MP shell and kept in a form of a water suspension.

(2) *Sample **B** – γ-Fe_2O_3 nanoparticles with a mixed type COOH-poly(NVP)-MP and Tween80 shell*. Maghemite particles were prepared as in sample **A** but the surfactant Tween80 (polyethylene glycol sorbitan, monooleate, manufactured by Aldrich) was used for the additional modification of γ-Fe_2O_3 nanoparticles with a chemisorbed oligoperoxide shell (Scheme 2). Tween 80 was dissolved in a water and the obtained solution was added to the aqueous dispersion of γ-Fe_2O_3 nanoparticles and stirred for 20 min. Ratio Tween 80:maghemite=10:90%, concentration of nanoparticles in the dispersion – 10%. After modification the product was purified by repeated washing (five times) with water (20 mL) using magnetic separation.

(3) *Sample **C** – γ-Fe_2O_3 nanoparticles with COOH-poly(NVP)-MP-graft-poly(NVP-co-GMA) shell* (Scheme 3). Maghemite particles with heterofunctional telechelic oligoperoxide were prepared as in sample **A** but in order to obtain the polymer shell of required functionality a surface-initiated polymerization of NVP and Glycidyl methacrylate (GMA) monomer mixture was carried out. Polymerization was performed in an airtight sectional flask, equipped with a stirrer. Water suspension of maghemite particles



Scheme 1. The general structure of heterotelechelic poly(N-vinylpyrrolidone) based surfactant with end carboxyl and ditertbutylarylperoxide groups.