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Review

Magnetic iron oxide nanoparticles: Recent trends in design and synthesis of magnetoresponsive nanosystems

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ABSTRACT

Recent developments in nanotechnology and application of magnetic nanoparticles, in particular in magnetic iron oxide nanosystems, offer exciting possibilities for nanomedicine. Facile and precise synthesis procedures, high magnetic response, tunable morphologies and multiple bio-functionalities of single- and multi-core magnetic particles designed for nanomedicine applications are thoroughly appraised. This review focuses on the structural and magnetic characterization of the cores, the synthesis of single- and multicore iron oxide NPs, especially the design of the latter, as well as their protection, stabilization and functionalization by desired coating in order to protect against the corrosion of core, to prevent non-specific protein adsorption and particle aggregation in biological media, and to provide binding sites for targeting and therapeutic agents.

1. Introduction

Superparamagnetic iron oxide – magnetite and maghemite-nanoparticles are the most used constituents of magnetoresponsive nanosystems in the rapidly expanding researches and applications in nanomedicine and biology, including magnetic resonance imaging, magnetic particle imaging, magnetic drug delivery systems, magnetic fluid hyperthermia and magnetic labeling and separation of cells [1–10]. Patient safety is an important motivation for a proper choice of magnetic particulate systems designed for both diagnosis and therapy (theranostics). To exemplify, iodine or gadolinium tracers are hazardous for patients with chronic kidney disease, therefore their use as contrast agents is a public health safety concern and requires a safer replacement, such as iron oxide nanoparticles (IONPs) [11]. Complex nanosystems of coated and multiple functionalized superparamagnetic iron oxide nanoparticles started to become the most important tools of nanomedicine [7,9,12,13], as they represent the best compromise between good magnetic properties and very reduced toxicity, evidenced by extensive in vitro and in vivo tests [14] and by quantitative evaluation of biodistribution and local therapeutic effects [12,15]. Other magnetic nanoparticles, like Co or FePt [16,17], have higher saturation magnetization and better magnetic response, but are toxic, which impedes their use in most of biomedical applications. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the medical use of only a few iron oxide nanoparticle formulations, most probably due to the lack of commonly accepted physicochemical practice of particle design and manufacturing, as well as of qualifying criteria. The nanoparticle systems involve the magnetic iron oxide core and the sterically and/or electrostatically repulsive shell(s) around the core to ensure colloidal stability and salt tolerance in the biological environment [18], usually a biocompatible polymer and additionally molecules fulfilling the roles of anchors, spacers and various functionalities [19]. The surface engineered iron oxide nanoparticles for biomedical applications should be highly water dispersible, i.e. the resulted IONP systems should be colloidally stable water based ferrofluids [10,19].

The synthesis procedures, physicochemical properties, toxicity and biocompatibility, as well as vectorization methods of iron oxide nanoparticle systems for biomedical applications were thoroughly reviewed along the years in several comprehensive works [1,3,5,6,8–10,20]. The basic physical properties of magnetic nanoparticles, the size and surface effects on their magnetic behavior (spin canting) and the specific composition, structure and functional coatings for biomedical applications, are summarized in Refs. [4,10,21].

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The actual composition of magnetic nanoparticles in ferrofluids used in biomedical applications involves single core and multicore iron oxide particles [22–25]. The multicore particle ferrofluids have the advantage of improved magnetic response of particles, while keeping the superparamagnetic behavior and satisfactory colloidal stability in spite of greater hydrodynamic size of dispersed particles, actually iron oxide nanoparticle clusters. Therefore the use of multicore products in magnetic targeting and hyperthermia treatment is of great importance. These multicore ferrofluids have to be distinguished from single core (``true'') ferrofluids [26], both of great interest for nanomedicine.

Polymer based magnetic microspheres encapsulating magnetite nanoparticles were proposed already in 1978 by Senyei et al. [27] for magnetic drug delivery and targeting. The actual high interest for water dispersible surface functionalized multi-core magnetic particles is related to the development of more facile and precise synthesis procedures, high magnetic response, tunable morphologies and multiple bio-functionalities of particles designed for nanomedicine applications. The terms ``single core'' and ``multicore'' were used more frequently in the last few years; however, they cannot be found for example in the excellent book on magnetic nanomaterials [28] or even in some recent reviews [3,29], but a review on single versus multi-core iron oxide nanoparticles has just appeared [30].

The present minireview will focus on recent results on the synthesis and properties of surface coated single core and multicore iron oxide nanoparticle systems designed for applications in nanomedicine.

2. Structure and magnetic behavior

Magnetic iron oxides – magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) – are ferrimagnetic materials below their Curie temperatures (850 K and 986 K respectively [31]). Ferro- and ferrimagnets in bulk state present a multidomain magnetic structure, thus without a permanent magnetic moment. Reducing the volume of the material to the size range specific to magnetic nanoparticles, ferro- and ferri-magnetic particles can be single domain with a permanent magnetic moment due to collective spin correlation at the scale of the entire nanoparticle. The properties of usually subdomain size iron oxide nanoparticles are no longer similar to bulk materials and motivate the outstanding interest for their use in nanomedicine [3,10,13,21]. The size distribution and morphology are essential in defining the magnetic behavior of nanoparticles. The size and shape dependent magnetic properties of nanoparticles and nanoparticulate systems, such as magnetocrystalline and shape anisotropy, interparticle interactions and magnetic relaxation processes, investigated by static and dynamic magnetometry and Mossbauer spectroscopy, were thoroughly reviewed in Refs. [21,32].

Small spherical nanoparticles made of soft magnetic materials with diameter well below the domain size show negligible magnetic anisotropy which is why their magnetic moment is free to rotate relatively to the particle (Néel effect) and are thus superparamagnetic, i.e. paramagnetic below the Curie temperature [21]. The modulus of the permanent magnetic moment is given by the product of the volume of the monodomain nanoparticle and the domain magnetization, i.e. saturation magnetization of the material [33]. The direction of the permanent magnetic moment of the nanoparticle is set by the balance between thermal fluctuation and magnetic anisotropy that tend to fix it with respect to either crystalline structure (easy magnetization axis/axes) or particle morphology (shape anisotropy main axis/axes) [34]. The energy of the crystallographic and shape magnetic anisotropy is proportional to the particle volume, therefore the smaller the monodomain particle the wider the fluctuation of the magnetic moment around the direction of the anisotropy axis. Besides volume proportionality, the energy of the shape magnetic anisotropy is increasing with increasing nanoparticle morphological anisotropy, i.e. aspect ratio, so that spherical nanoparticles show zero shape anisotropy [34]. The volume is also relevant for the strength of the nanoparticle interaction with an external magnetic field (dipole–field interaction) as well as with the magnetic field generated by another nanoparticle (dipole–dipole interaction) [35].

The saturation magnetization of ferro- or ferrimagnetic materials is lower in nanoparticle than in bulk state due to either surface or core spin disorder [36]. The surface spin disorder breaks the homogeneity of the nanoparticle magnetic structure to a magnetic core surrounded by a ``dead'' magnetic layer of either canted or disordered spins, the thickness of this layer being dependent on the chemical reaction between the surfactant and iron oxide nanoparticle [37,38]. The core and surface spin disorder can originate from either amorphous or polycrystalline structure as a result of synthesis procedure and surface coating [39,40]. The surface spin canting is specific of small nanoparticles, while larger size nanoparticles show also volume spin canting. Low TEM size polydispersity of magnetic nanoparticles does not guarantee low polydispersity of the magnetic dipole moment. Crystal defects, such as twinning and dislocations, can have a highly detrimental effect on the strength and low polydispersity of the magnetic properties. Crystallite sizes from XRD, volume-averaged TEM and magnetogranulometry for iron oxide nanoparticles synthesized by aqueous coprecipitation [41,42] and thermal decomposition [43,44] processes show significant differences between geometric and magnetic sizes for ``twins'' and ``spheres'', while for the ``facets'', the ``precipitates'' and the 8 nm ``spheres'' TEM and magnetic measurements give a similar average size and polydispersity [39].

The interaction of a magnetic nanoparticle with an external magnetic field is twofold: (1) the orientation of the particle's magnetic moment such that it becomes parallel to the applied magnetic field in order to minimize the dipole–field interaction energy [10] and (2) the translation of the particle in the direction of the field gradient, i.e magnetophoresis [45].

The orientation of MNP's magnetic moment under the action of an external magnetic field occurs either by the movement of domain walls in multidomain particles or by the rotation in single domain particles. The rotation of the magnetic moment can occur either free with respect to the particle (Néel rotation) or together with the particle (Brown rotation) [21]. Except for particular situations, the orientation of MNP's magnetic moment in AC magnetic fields shows hysteresis. The phenomenon of AC magnetic hysteresis is the basis of magnetic particle hyperthermia [21,46] and susceptometric granulometry of single and multicore MNPs [47]. In DC magnetic fields, due to the permanent magnetic moment of subdomain MNPs, the magnetization of diluted single core particle dispersions follows the Langevin equation which gives the theoretical framework for the magnetogranulometry of single core particles [48]. Multicore particles have no permanent magnetic moment, provided that the constituent particles are small enough such that the magnetic dipole–dipole interaction is negligible. The induced (resultant) magnetic moment of multicore particles is parallel to the external magnetic field and follows the Langevin equation. If the constituent particles are large, i.e. the anisotropy energy overcomes the thermal energy, the multicore particles show magnetic coercivity and remanence due to dipole–dipole interactions. The induced magnetic moment of multicore particles at saturation is the sum of the constituent particles' magnetic moments [49]. Many applications of magnetic nanoparticles and nanocomposites rely on their ability to be