Journal of Magnetism and Magnetic Materials 413 (2016) 65–75

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Synthesis of aqueous suspensions of magnetic nanoparticles with the co-precipitation of iron ions in the presence of aspartic acid

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
4 April 2016
Accepted 14 April 2016
Available online 15 April 2016

Keywords:
Nanoparticle synthesis
Colloidal stability
Iron-oxide nanoparticles
Amino acid
Aspartic acid

ABSTRACT

There is increasing demand for the production of large quantities of aqueous suspensions of magnetic iron-oxide nanoparticles. Amino acids are one possible type of inexpensive, nontoxic, and biocompatible molecules that can be used as the surfactants for the preparation of stable suspensions. This preparation can be conducted in a simple, one-step process based on the co-precipitation of Fe^{3+}/Fe^{2+} ions in the presence of the amino acid. However, the presence of this amino acid changes the mechanism of the magnetic nanoparticles' formation. In this investigation we analyzed the influence of aspartic amino acid (Asp) on the formation of magnetic iron-oxide nanoparticles during the co-precipitation. The process of the nanoparticles' formation was followed using a combination of TEM, x-ray diffractometry, magnetic measurements, in-situ FT-IR spectroscopy, and chemical analysis, and compared with the formation of nanoparticles without the Asp. The Asp forms a coordination complex with the Fe^{3+} ions, which impedes the formation of the intermediate iron oxyhydroxide phase and suppresses the growth of the final magnetic iron-oxide nanoparticles. Slower reaction kinetics can lead to the formation of nonmagnetic secondary phases. The aspartic-acid-absorbed nanoparticles can be dispersed to form relatively concentrated aqueous suspensions displaying a good colloidal stability at an increased pH.

1. Introduction

Magnetic nanoparticles prepared in the form of colloidally stable aqueous suspensions, i.e., aqueous ferrofluids, are becoming increasingly important materials in biomedicine and other technologies. For some *in vivo* medical applications, for example, diagnosis (e.g., contrast agents for magnetic resonance imaging (MRI)) [1] and therapy (e.g., in magnetic-nanoparticles-mediated hyperthermia) [2] magnetic nanoparticles have already been successfully introduced into clinical practice, while a large number of other nanoparticle-based strategies for diagnosis and therapy are still under development. New methods for applying magnetic nanoparticles are being developed for the detection, separation and sorting of biomolecules and cells, in immunoassays, in lab-on-chip devices, for magnetic gene transfection, magnetic particle imaging, magnetic drug delivery, etc. [3]. Even today, ferrofluids based on non-polar liquids have many applications [4] and the development of new technologies also requires aqueous suspensions of magnetic nanoparticles in large quantities. Typical technologies may range from water remediation (e.g., the magnetic separation of heavy metals and organic pollutants from water) [5] to the separation of microorganisms from beverages in the food industry [6]. Aqueous suspensions of nanoparticles are also often used as the starting materials in the synthesis of nanocomposite materials [7].

The two magnetic iron oxides with a spinel structure, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are by far the most studied magnetic materials to be applied in the form of nanoparticles. They are considered to be nontoxic and were also approved by the US Food and Drug Administration (FDA) for in-vivo applications [3]. Of special advantage in the broad application of nanoparticles in technology are their low price and relatively good chemical stability, especially when compared to the magnetically superior metallic (Fe, Ni, Co) nanoparticles, which are prone to oxidation.

Different methods can be applied for the synthesis of magnetic iron-oxide nanoparticles, e.g., co-precipitation [8–10], thermal decomposition [8,11], precipitation in micro-emulsions [8,12], hydrothermal synthesis [13], and microwave synthesis [14]. By far the most common method for the synthesis of magnetic nanoparticles remains the co-precipitation of Fe^{2+} and Fe^{3+} ions from an aqueous solution using the appropriate base, as it is an

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http://dx.doi.org/10.1016/j.jmmm.2016.04.032
0304-8853/

inexpensive process as well as being appropriate for mass production. The nanoparticles form with the rapid, homogeneous nucleation of the solid product after the rapid addition of the base to the aqueous solution of iron ions. Depending on the experimental conditions (the presence of counter ions, the temperature, the reactant concentrations, etc.) the final magnetic iron oxide can form through different chemical reactions and transformations [15]. The Fe^{3+} precipitates already at a low pH of 2.8 to form Fe oxyhydroxide lepidocrocite (γ-FeOOH). At a higher pH above 6 the Fe^{2+} also precipitates and reacts with the FeOOH to form a magnetic spinel ferrite magnetite (Fe_3O_4). In the ambient air the magnetite nanoparticles usually oxidize to maghemite (γ-Fe_2O3) [15].

Whether we are talking about specially designed nanoparticles for high-tech biomedical applications or aqueous ferrofluids for mass production in different technologies, the requirements are similar. First of all, the suspensions have to display a good colloidal stability. Usually, organic molecules are covalently bonded or adsorbed onto the nanoparticles' surfaces to provide compatibility with the aqueous medium and electrostatic or electrosteric repulsive forces between the nanoparticles preventing the agglomeration. At the same time, a layer of organic molecules defines the surface properties of the nanoparticles, such us the surface charge or the availability of the specific functional groups needed for the further bonding/conjugation of the specific molecules required in a certain application. The surface shell of the nanoparticles also significantly determines the interactions of the nanoparticles with living systems. It influences the adsorption of the plasma proteins onto the nanoparticles, the interactions with cells, e.g., the amount of nanoparticles internalized in the cells, a blood-circulation time, and the fate of the nanoparticles after intravenous administration [16].

Generally speaking, it is very difficult to prepare stable suspensions of larger magnetic particles because they tend to strongly agglomerate because of the magnetic dipole–dipole interactions. However, this magnetic agglomeration is not a problem when the nanoparticles are small enough to be in the superparamagnetic state as the magnetic moments of the superparamagnetic nanoparticles thermally relax. The superparamagnetic limit at room temperature is at approximately 15 nm for soft-magnetic materials such as magnetite or maghemite [17]. However, with a decrease in the nanoparticles' size the proportion of magnetically distorted surface atoms increases and, as a consequence, their saturation magnetization (M_S) decreases [18]. For that reason, aqueous suspensions of magnetic nanoparticles with sizes just below the superparamagnetic limit are usually required.

One possible type of nontoxic and biocompatible molecules that can be used for the engineering of the nanoparticles' surface properties and for stabilization of their aqueous suspensions is amino acids (AAs). The large number of different AAs provides an opportunity to change the properties, e.g., the surface charge and the availability of different surface functional groups, across a broad range. They are inexpensive and therefore appropriate surfactants for use in mass production. It is widely accepted that the AAs adsorb onto the iron-oxide surface by forming a chemical bond of the chelate type involving Fe(III) surface ions and the carboxylate group [19–23]. It was even proposed that the adsorbed AAs can be used for the functionalization of nanoparticles, providing specific functional groups at the nanoparticles' surfaces for the subsequent bonding of different molecules [19–21]. As the AAs play a very important role in the body, their adsorption onto the magnetic nanoparticles was proposed for their targeted delivery [24].

The synthesis of an aqueous suspension of amino-acid-adsorbed magnetic iron-oxide nanoparticles can be conducted in a two-step process with the synthesis of the nanoparticles in the first step and the adsorption of the AA onto the nanoparticles in the second step [19,20], or in a one-step process with the co-precipitation of Fe^{3+}/Fe^{2+} ions in the presence of the AA [22,24–27]. In the one-step process, the AA can change the mechanism of the nanoparticle formation during the co-precipitation [26,28]. The mineralization of iron oxides in the presence of polypeptides and individual AAs has been intensively studied [28–33]. The polypeptides and AAs can be used in biomimetic syntheses to stabilize otherwise unstable crystal phases [31]. Lenders et al. [32] used random co-polypeptides having different AA compositions as control agents in the bioinspired co-precipitation of magnetite through a ferrihydrite/Fe(II) precursor in a mildly alkaline aqueous medium. They demonstrated that the polypeptides containing acidic AAs (aspartic acid, glutamic acid) stabilize the precursor and thus they can regulate the crystal size by delaying nucleation and reducing growth. Baumgartner et al. [33] showed that negatively charged proteins also inhibit the magnetite formation as they likely inhibit nucleation by the stabilization of an amorphous structure through the coordination of iron. Mantion et al. [28] studied the influence of different single AAs on the precipitation of Fe^{2+} from an aqueous solution in air. They clearly showed that the AAs have a strong influence on the selection of the iron oxide crystal phase formed. They explained the effects of the AAs with their adsorption onto growing particles. In addition, the AAs can also change the course of the synthesis process by the strong complexation of iron ions in a solution before the precipitation [25,26]. Culita et al. [26] studied the synthesis of magnetite nanoparticles using the in-situ decomposition of the precursors – coordination compounds containing the AAs histidine and tyrosine as ligands. In the Fe^{3+}/Fe^{2+} solution containing a high concentration of the AA ($2Fe^{3+}$: Fe^{2+}: 8AA) the coordination compound formed at low pH ($pH \leq 4$), which can influence the subsequent formation of the nanoparticles.

In this work we analyze the differences in the process of the formation of magnetic iron-oxide nanoparticles during the co-precipitation of Fe^{3+} and Fe^{2+} ions from an aqueous solution with and without the presence of Asp. Asp is an α-AA with one amino group and two carboxyl groups (HOOC–CH_2–CH–(NH_2)COOH). Due to the presence of the two carboxyl groups a strong interaction between the AA and the iron ions in the solution before precipitation and with the surfaces of the precipitating particles can be expected. In contrast to the general literature [28,32,33], which ascribes the influence of the AA on the co-precipitation process of the iron ions to the adsorption of the AA onto the intermediate phases, we suggest that the main influence of the Asp on the nanoparticles' formation is related to a strong interaction between the iron ions and the Asp in the solution already before the precipitation with a base addition.

2. Experimental section

2.1. Synthesis

The magnetic nanoparticles of iron oxide with a spinel structure (spinel ferrite) were synthesized using the co-precipitation of Fe^{3+} and Fe^{2+} ions from an aqueous solution with aqueous ammonia in the presence of, or without Asp. In our basic procedure, the Asp solution (L-aspartic acid, Sigma Aldrich) was added to a solution of Fe^{2+}($FeSO_4 \cdot 7H_2O$, Alfa Aesar) and Fe^{3+}($Fe_2(SO_4)_3 \cdot 7H_2O$, Alfa Aesar) ions and mixed for 30 min. Then, the iron ions were co-precipitated by the rapid addition of concentrated ammonia (aq, Fluka, p.a., 25%) to the solution (500 mL, 27 mmol Fe^{2+}/L, 23 mmol Fe^{3+}/L) to reach a final pH value of ~11 and aged for 30 min. The molar ratio of the aspartic acid/Fe^{3+}(Asp/Fe^{3+}) was 0, 1.5, and 12. For the Asp/Fe of 1.5, the content of Asp in