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The effects of particle size and surface coating on the cytotoxicity of nickel ferrite

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Abstract

The safety and toxicity of nanoparticles are of growing concern despite their significant scientific interests and promising potentials in many applications. The properties of nanoparticles depend not only on the size but also the structure, microstructure and surface coating. These in turn are controlled by the synthesis and processing conditions. The dependence of cytotoxicity on particle size and on the presence of oleic acid as surfactant on nickel ferrite particles were investigated in vitro using the Neuro-2A cell line as a model. For nickel ferrite particles without oleic acid prepared by ball milling, cytotoxicity was independent of particle size within the given mass concentrations and surface areas accessible to the cells. For nickel ferrite particles coated with oleic acid prepared by the polyol method, the cytotoxicity significantly increased when one or two layers of oleic acid were deposited. Large particles (150 ± 50 nm diameter) showed a higher cytotoxicity than smaller particles (10 ± 3 nm diameter).

Keywords: Cytotoxicity; Surface treatment; Particle size; Magnetic nanoparticles

1. Introduction

With emerging biomedical applications (e.g. cell labeling [1,2], drug targeting [3–5], gene delivery [6,7], hyperthermia therapy [8] and biosensors [9]), nanoparticles attract increasing fundamental and technological interests. Major advances have been made in developing methods for tailor-designing the properties of nanostructures for improved performances. Recent highlights [10–12] on potential environmental and health impacts of nanoparticles, however, have raised concerns of toxicity being a critical factor on evaluating their applications (especially for in-vivo biomedical applications).

It is well known that the reduction of particle size from macroscopic to nanometer length-scale, the chemical and physical properties may change due to the size and surface effects. In bulk materials, the ratio of surface atoms to that of interior atoms is small and the surface effect is insignificant. This ratio noticeably increases with decreasing particle size and, the surface effect may predominate the material properties. Meanwhile, surface coating of nanoparticles also affects the material properties. For example, manganese ferrite ($MnFe_2O_4$) nanoparticles were surface-modified by benzoic acid and substituted benzene ligands to enhance biocompatibility. Coating with the liagands decreased coercivity and increased saturation magnetization for particle size of 4, 12 and 25 nm [13]. Changes in optical properties were reported in gold nanoparticles with

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different surface coatings for improving stability and water solubility [14,15].

Presently it is unclear to what extent that particle size and surface coating have influence on the toxicological properties. Few reported works have addressed this issue [16–18]. Further complications in comparative toxicity studies arise when the surface coatings for the ''same'' material (with similar range in particle size) may depend on the type of synthesis and/or processing chosen. One should therefore not assume that coated and uncoated nanoparticles would have the same degree of biosafety. Often cytotoxicity studies on nanoparticles did not include sufficient data on their surface properties. Commercialized products have also been used [19].

Ferrite nanoparticles have been considered for magnetic resonance imaging, magnetic extraction and targeted drug delivery due to good chemical stability and magnetic property [20,21]. Though the toxicity of nickel is known, the biocompatibility of nickel ferrite has not been well studied. Oleic acid has been widely used as a surfactant in the synthesis of monodispersed nanoparticles [22,23]. It contains a carboxyl functional group. The carboxyl group has been used in bioapplications, for example, to immobilize oligonucleotides [24], proteins [25] and anti-cancer drug on particle surfaces [26]. The cytotoxicity of the nanoparticles coated with oleic acid is not well understood. In this work it is therefore of interest to investigate the effects of particle size and surface coating of oleic acid on the cytotoxicity of nickel ferrite particles.

2. Materials and methods

2.1. Particle preparation

Nickel ferrite particles without oleic acid and with limited coating of oleic acid (hydrophobic surface) were prepared using ball milling and polyol method, respectively [27–29]. The nickel ferrite particles with two layers of oleic acid coverage (hydrophilic) were prepared by redispersing the particles that were previously coated with limited oleic acid in excess oleic acid solution and mixing them using ultrasonic bath. The coverage of oleic acid was confirmed by the zeta-potential measurements. Two different particle diameters of nickel ferrite were used in this study, i.e. large particles (150 ± 50 nm) and small particles (10 ± 3 nm). The average particle size was averaged by measuring at least 50 particles (using transmission electron microscopy TEM).

2.2. Characterization of nickel ferrite particles

It has been reported that nickel ferrite nanoparticles prepared by ball milling method was a single-phase [27]. This observation is also supported by our X-ray diffraction (XRD) measurements (Cu K_α radiation, $\lambda = 1.5418$ Å) (data not shown here). The XRD patterns of polyol-synthesized particles (large and small) with limited oleic acid coatings are shown in Fig. 1. It indicates that as-prepared particles were nickel ferrite with no other detectable phases. Fig. 2 shows the TEM micrographs of uncoated nickel ferrite particles and those coated with limited oleic acid. Large and small particles without oleic acid prepared by ball milling are shown in Fig. 2(a) and (c), whereas that prepared by the polyol method but coated with limited oleic acid shown in Fig. 2(b) and d. In Fig. 2(b), the oleic acid layer is marked with arrows. The fully extended length of one oleic acid molecule is about 2.5 nm. However, the observed thickness was not uniform and generally larger than 2.5 nm. This may be due to the focusing conditions of microscopy. The zeta potential measurements (to be discussed later) confirmed that the particle surface was coated with one layer of oleic acid. In Fig. 2(d) the oleic acid layer was not clear because of the small particle size. The TEM micrographs of particles coated with two layers of oleic acid (data not shown here) do not show noticeable differences from those coated with one layer.

Table 1 summarizes the properties of as-synthesized nickel ferrites particles. The surface atomic composition determined by X-ray photoelectron spectroscopy (ESCA LAB 220i-XL spectrometer) and the bulk atomic composition measured by energy-dispersive X-ray spectrometer are compared. The bulk compositions appeared to depend on the synthetic methods and the particle sizes. The surface composition was very similar to the bulk composition, indicating that there was no composition segregation at the surface. The surface areas of individual particles were calculated using the average particle size based on a hard sphere model and the results are also listed in Table 1. Considering a

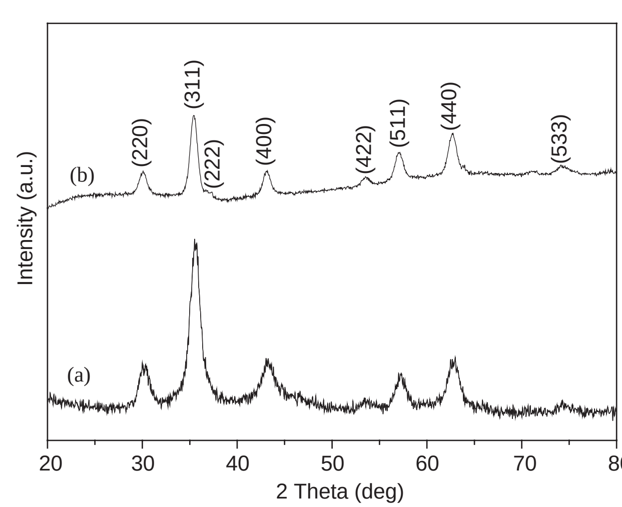

Fig. 1. XRD patterns of as-synthesized nickel ferrite particles prepared by polyol method. (a) small particles (10 ± 3 nm), (b) large particles (150 ± 50 nm).