Information on the synthesis and biomedical applications of magnetic oxide nanoparticles.

**Introduction**

Magnetic oxide nanomaterials, including iron oxide (Fe$_3$O$_4$ and γ-Fe$_2$O$_3$), spinel ferrites (MFeO$_4$; M=Mn, Zn, Cr, Ni, or Co) and hexagonal ferrite (MFe$_{12}$O$_{19}$, M=Ba and Sr) are attracting much attention due to their wide application potentials in advanced magnets, electronic devices, information storage, magnetic resonance imaging (MRI), and drug-delivery technology [1-6]. Hence, the synthesis and applications of nanostructured magnetic ferrite has become a particularly important research field. In this mini-review, we will first focus on the recent research progress of the synthesis of magnetic oxide nanoparticles. Afterwards, the biomedical applications, particularly the hyperthermia, drug delivery and contrast agents in magnetic resonance imaging (MRI), will be reviewed.

**Synthesis of magnetic oxide nanoparticles**

In the last decades, tons of efforts have been devoted to the synthesis of shape-controlled; highly stable and monodisperse magnetic oxide nanoparticles. Here, we will introduce the methods, including co-precipitation, hydrothermal, microwave, sol-gel and combustion, to produce high quality magnetic oxide nanoparticles.

**Co-precipitation method**

Co-precipitation is a facile and convenient way to synthesize metal oxides and ferrites from aqueous salt solutions [7-9]. The advantages of this method include low reaction temperature, high product yield, environmental-friendly solvent, i.e. water, and relatively narrow size distribution. Iron oxide nanomaterials, e.g., magnetite (Fe$_3$O$_4$) and hematite (γ-Fe$_2$O$_3$), and various ferrites, including spinel and hexagonal structured, have been synthesized in an aqueous medium by the addition of a base under inert or nonoxidation atmosphere at room temperature or elevated temperatures. The size, shape and composition of the magnetic iron oxide or ferrites are largely dependent on the type of used salts, such as chlorides, sulfates and nitrates, the Fe³⁺/M²⁺ ratio (M = Fe, Co, Ni, Cu, Mg, Ba, Sr, etc.), the reaction temperature, the pH value and ionic strength of the media. With this synthesis, once the synthetic conditions are fixed, the quality of the iron oxide or ferrites nanoparticles can be fully reproducible. However, the shape of nanoparticles produced by co-precipitation is not well controllable, thus more efforts need to be done. Our previous study reported the fabrication and
morphism control of strontium ferrite (SrFe\(_{12}\)O\(_{19}\)) ultrafine particles by co-precipitation in an aqueous solution with cetyltrimethyl ammonium bromide (CTAB) as a surfactant [10].

**Thermal decomposition technique**

Inspired by the preparation of high-quality semiconductor nanocrystals and oxides in non-aqueous media by thermal decomposition, researchers have developed similar methods to synthesize size and shape controllable magnetic oxide nanoparticles. Monodisperse magnetic ferrites with smaller size have been synthesized through the thermal decomposition of organo metallic precursor in high-boiling organic solvents containing stabilizing surfactants. The metal acetylacetonates, \([M(acac)n]\) \((M=Fe, Mn, Co, Ni, Cr; n=2\) or \(3, acac=a\)cetylacetona\(c)te\), metal cupferronates, \([MxCu(\text{N})\text{p}]\) \((M=-metal\text{ ion}; \text{Cu(p)}=\text{N(N-}}\text{itrosophenyl hyd}oxy\text{ylamine, C}_6\text{H}_5\text{N(NO)}\text{O})\text{H})\] \([11]\), and carbonyls \([12]\) are typically used as organo metallic precursor. The surfactants used in the method include fatty acids, oleic acid \([13]\), and hexadecylamine \([14]\). In general, the ratios of the starting reagents including organo metallic compounds, surfactant, and solvent are the decisive factors for the control of the size and morphology of magnetic nanoparticles.

**Hydrothermal approach**

Hydrothermal technique, performed in an aqueous media in reactors or autoclaves where the pressure can be higher than 2000 psi and temperatures higher than 200 °C, has been extensively reported recently to fabricate a broad range of nanostructured materials. Wang et al. [15] synthesized Fe\(_3\)O\(_4\) nanoscale powder under hydrothermal condition at 140 °C for 6h, possessing a saturation magnetization of 85.8emu/g, which is only a little lower than that of the corresponding bulk Fe\(_3\)O\(_4\) (92emu/g). Chitosan-modified magnetic Mn ferrite nanoparticles have been synthesized by one step microwave-assisted hydrothermal method in our prior work [16]. The prepared nanoparticles have a cubic shape with a mean diameter of ~100nm.

**Microwave synthesis**

The microwave-assisted solution method, introducing microwaves during the chemical reaction route, has become widely reported due to its advantages such as its rapid volumetric heating, higher reaction rate and more products yield compared to conventional synthesis methods [17]. The extremely rapid kinetic for crystallization under microwave condition can be attributed to the localized superheating of the solutions. Wang et al. prepared the spinel nanostructured MFe\(_{2}\)O\(_{4}\) \((M=Co, Mn)\) particles with diameters less than 10 nm by a fast and simple microwave-assisted polyol procedure [18]. The ultrafine particle probably resulted from the fast and homogeneous reactions occurring during the microwave process. Additionally, they found that the volume ratio of distilled water to EG under microwave heating can adjust the reaction temperature and crystal quality.

**Sol-gel process**

The sol-gel method is a useful and attractive technique for the preparation of nanoparticles due to its advantages including good stoichiometric control and the production of ultrafine particles with a narrow size distribution in a relatively short processing time at lower temperatures. In aqueous sol-gel synthesis, an aqueous solution of metal salts is co-precipitated by a base, followed by treated to form a colloidal sol, inorganic or metallo-organic precursor, which can then be concentrated to a gel and subsequently fired to give the fine grained polycrystalline ferrites. Recently, pure spinel nickel ferrite nanoparticles were prepared by the sol-gel method using polyacrylic acid (PAA) as a chelating agent. The size, specific surface area, and crystallinity of NiFe\(_2\)O\(_4\) nanoparticles could be controlled by varying the molar ratios of PAA to total metal ions and calcination temperature [19]. In our group, ultrafine barium ferrite (BaFe\(_{12}\)O\(_{19}\)) nanoparticles, with size from 55 to 110nm, were fabricated via a modified sol-gel combustion method using glycine gels prepared from metal nitrates and glycine solutions [20].

**Combustion synthesis**

Combustion synthesis has been applied for the preparation of ceramic nanoparticles. Martirosyan et al. [21] produced crystalline cobalt ferrite nanopowders with particle size in the range of 50-100nm by using the carbon combustion synthesis of oxides (CCSO). In the combustion synthesis process, the exothermic oxidation of carbons generate a thermal reaction wave that propagates through the solid reactants mixture of CoO and Fe\(_3\)O\(_4\), converting them to final cobalt ferrite. They illustrated that the porosity and friability of the product was increased by the extensive emission of CO\(_2\). Besides, only for carbon concentrations exceeding 12 wt.% can lead to a complete conversion to ferrite CoFe\(_2\)O\(_4\) structure. Solid state interactions between the precursors, including CoO and FeO, with the growth of the crystalline cobalt ferrite particles started in the early period of the combustion and continued into the post combustion zone. In addition, Mn-Zn and Ni-Zn ferrites submicrometer powders were also prepared through this CCSO method by the same group [22]. The self-propagating temperature front can reach up to 1300 °C. Meanwhile, the particle size and the corresponding magnetic properties of the product depend on the carbon content in the reactants mixture and oxygen concentrations.

**Biomedical applications**

Nowadays, magnetic oxides nanoparticles are extensively investigated in the field of clinical diagnostic and therapeutic techniques, such as drug delivery, magnetic resonance imaging (MRI) contrast enhancement and hyperthermia treatments [23-25]. In the following section, we will present the progress of these biomedical applications. Hyperthermia is a therapeutic procedure used to employ treatment based on the heat generation at the affected body region by malignancy or the
tumor sites [26,27]. Due to the hysteretic properties, magnetic oxide nanoparticles can give rise to magnetically induced heating when exposed to a time varying magnetic field, which conducts into the surrounding diseased tissue immediately.

If the producing temperature can be maintained above the therapeutic threshold of 42 °C for 30 min or more, the cancer will be killed. The magnetic hyperthermia can provide a safe approach for the treatment of cancer, because it only treats the intended target tumor area without heating or destroying the healthy tissue [28,29]. In addition, magnetic oxide nanoparticles are widely used in drug delivery, where magnetic nanomaterials attached with drugs can directly go to the pathological site with assistance of external magnetic field gradient, it can date back to the late of 1970s by the work of employing magnetically responsive micropheres to deliver anti-tumor drugs [30]. Since then, tremendous investigations have been conducted and significant progress has been made. The magnetic targeted drug delivery can specifically treat the cytopathic cancer or tumor cell and avoid the side effect of attacking normal or healthy cells, comparing with conventional chemotherapy. Besides, in the field of magnetic resonance imaging (MRI) applications, magnetic oxide nanoparticles are used as MRI contrast agents to enhance the contrast to identify the difference between the normal and abnormal tissues [31,32].

Conclusion

In this mini-review, the synthesis of magnetic oxide nanoparticles and their biomedical applications have been summarized. Although a great progress has been made in the last decade in this field, controllable nanoparticle size and shape, uniform size distribution, good dispersion of magnetic oxide nanoparticles are highly desirable for the hyperthermia, drug delivery and contrast agents in magnetic resonance imaging (MRI) applications. We genuinely hope this mini-review will attract the readers’ attention into this emerging field.

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References