Synthesis of Magnetic Oxide Nanoparticles for Biomedical Applications

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Abstract

Magnetic oxide nanoparticles have been intensively studied both for the intrinsic physical properties and for wide potential applications. In this mini-review, we focus on the synthesis methods and biomedical applications of these magnetic oxide nanoparticles. We first introduce several synthesis methods, including co-precipitation, hydrothermal, microwave, sol-gel and combustion, to produce high quality magnetic oxide nanoparticles. Then, particular attention is paid to the biomedical applications, such as hyperthermia, drug delivery and magnetic resonance imaging (MRI) contrast agents. We genuinely hope that this review will attract the readers’ attention into this emerging field.

Keywords: Magnetic oxide nanoparticles; Co-precipitation; Hydrothermal; Microwave; Sol-gel; Combustion; Biomedical applications; Hyperthermia; Drug delivery; Magnetic resonance imaging

Abbreviations: MRI: Magnetic Resonance Imaging; CTAB: Cetyltrimethyl Ammonium Bromide; PAA: Polyacrylic Acid

Introduction

Magnetic oxide nanomaterials, including iron oxide (Fe₃O₄ and γ-Fe₂O₃), spinel ferrites (MFe₂O₄; M=Mn, Zn, Cr, Ni, or Co) and hexagonal ferrite (MFe₁₂O₁₉, 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 mono disperse 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 (Fe₃O₄) and hematite (γ-Fe₂O₃), 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
morphology control of strontium ferrite (SrFe12O19) 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 acetylacetanates, [M(acac)n] (M=Fe, Mn, Co, Ni, Cr; n=2 or 3, acac =acetylacetone), metal cupferronates, [MxCupx] (M=metal ion; Cup=N-nitrosophenyl hydroxylamine, C6H5N(NO)O-)[11], and carbonyls [12] are typically used as organo metallic precursor. The surfactants used in this 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 medium 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 Fe3O4 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 Fe3O4 (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 MFeO4 (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 NiFe2O4 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 (BaFe12O19) 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 nanoparticltes. 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 FeO (92emu/g), converting them to final cobalt ferrite. They illustrated that the porosity and friability of the product was increased by the extensive emission of CO2. Besides, only for carbon concentrations exceeding 12 wt.% can lead to a complete conversion to ferrite CoFe2O4 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, can date back to the late of 1970s by the work of employing magnetically responsive micropsheres 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

1. Gupta AK, Gupta M (2005) Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials 26(18): 3995-4021.
2. Chen D, Liu Z, Zeng D (2016) Synthesis, structure, morphology evolution and magnetic properties of single domain strontium hexaferrite particles. Mater Res Express 3(4): 045002.
3. Mornet S, Vasseur S, Grasset F, Veverka P, Goglio G, et al. (2006) Magnetic nanoparticle design for medical applications. Prog Solid State Chem 34(2-4): 237-247.
4. Chen D, Meng Y, Gandha KH, Zeng D, Yu H, et al. (2017) Morphology control of hexagonal strontium ferrite micro/nano-crystals. AIP Adv 7(5): 056214.
5. Hyeon T, Lee SS, Park J, Chung Y, Na HB (2001) Synthesis of highly crystalline and monodisperse maghemite nanocrystallites without a size-selection process. J Am Chem Soc 123(51): 12798-12801.
6. Pullar RC (2012) Hexagonal ferrites: A review of the synthesis, properties and applications of hexaferrite ceramics. Prog Mater Sci 57(7): 1191-1334.
7. Doh SG, Kim EB, Lee BH, Oh JH (2004) Characteristics and synthesis of Cu-Ni ferrite nanopowders by coprecipitation method with ultrasound irradiation. J Magn Magn Mater 276(3): 2238-2240.
8. Meng YY, Liu ZW, Dai HC, Yu HY, Zeng DC, et al. (2012) Structure and magnetic properties of Mn(Zn)Fe$_2$O$_4$ ferrite nanopowders synthesized by co-precipitation and refluxing method. Powder Technol 229: 270-275.
9. Li Z, Tan B, Allix M, Cooper AI, Rosseinsky MJ (2008) Direct coprecipitation route to monodisperse dual-functionalized magnetic iron oxide nanocrystals without size selection. Small 4(2): 231-239.
10. Chen DY, Meng YY, Zeng DC, Liu ZW, Yu HY, et al. (2012) CTAB-assisted low temperature synthesis of SrFe$_2$O$_4$ ultrathin hexagonal platelets and its formation mechanism. Mater Lett 76: 84-86.
11. Rockenberger J, Scher EC, Alivisatos AP (1999) A new nonhydrolytic single precursor approach to surfactant-capped nanocrystals of transition metal oxides. J Am Chem Soc 121(49): 11595-11596.
12. Farrell D, Majetich SA, Wilcoxen J P (2003) Preparation and characterization of monodisperse Fe nanoparticles. J Phys Chem B 107(40): 11022-11030.
13. Samia AC, Hyzer K, Schluter JA, Qin GJ, Jiang JS, et al. (2005) Ligand Effect on the Growth and the Digestion of Co Nanocrystals. J Am Chem Soc 127(12): 4126-4127.
14. Li YA, Afsal M, O’Brien P (2006) The synthesis of amine-capped magnetic (Fe, Mn, Co, Ni) oxide nanocrystals and their surface modification for aqueous dispersibility. J Mater Chem 16(22): 2175-2180.
15. Wang J, Sun J, Sun Q, Chen QW (2003) One-step hydrothermal process to prepare highly crystalline Fe$_3$O$_4$ nanoparticles with improved magnetic properties. Mater Res Bull 38(7): 1113-1118.
16. Meng YY, Chen DY, Sun YT, Jiao DL, Zeng DC, et al. (2015) Absorption of Cu$	ext{II}$ ions using chitosan-modified magnetic Mn ferrite nanoparticles synthesized by microwave-assisted hydrothermal method. Appl Surf Sci 324: 745-750.
17. Komarneni S (2003) Nanophase materials by hydrothermal, microwave hydrothermal and microwave-solvothermal methods. Curr Sci 85(12): 1730-1734.
18. Wang WW (2008) Microwave-induced polyol-process synthesis of Mn$_{1-x}$Fe$_x$O$_{3-y}$ (M=Mn, Co) nanoparticles and magnetic property. Mater Chem Phys 108(2-3): 227-231.
19. Chen DH, He XR (2001) Synthesis of nickel ferrite nanoparticles by sol-gel method. Mater Res Bull 36(7-8): 1369-1377.
20. Meng YY, He MH, Zeng Q, Jiao DL, Shukla S, et al. (2014) Synthesis of barium ferrite ultraline powders by a sol-gel combustion method using glycine gels. J Alloys Compd 503: 220-225.
21. Martirosyan KS, Chang L, Rantschler J, Khizroev S, Luss D, et al. (2007) Carbon Combustion Synthesis and Magnetic Properties of Cobalt Ferrite Nanoparticles. IEEE T Magn 43(6): 3118-3120.
22. Martirosyan KS, Luss D (2007) Carbon Combustion Synthesis of Ferrites: Synthesis and Characterization. Ind Eng Chem Res 46(5): 1492-1499.

23. Arruebo M, Fernández PR, Ibarra R, Santamaría J (2007) Magnetic nanoparticles for drug delivery. Nano Today 2(3): 22-32.

24. Shin J, Anisur RM, Ko MK, Im GH, Lee JH, et al. (2009) Hollow Manganese Oxide Nanoparticles as Multifunctional Agents for Magnetic Resonance Imaging and Drug Delivery. Angew Chem Int Edit 48(2): 321-324.

25. Sharifi I, Shokrollahi H, Amiri S (2012) Ferrite-based magnetic nanofluids used in hyperthermia applications. J Magn Magn Mater 324(6): 903-915.

26. Kumar CS, Mohammad F (2011) Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Adv Drug Delivery Rev 63(9): 789-808.

27. Tartaj P, Morales M, Veintemillas VS, González CT, Serna CJ (2003) The preparation of magnetic nanoparticles for applications in biomedicine. J Phys D36: R182-R197.

28. Thiesen B, Jordan A (2008) Clinical applications of magnetic nanoparticles for hyperthermia. Int J Hyperthermia 24(6): 467-474.

29. Pankhurst QA, Connolly J, Jones SK, Dobson J (2003) Applications of magnetic nanoparticles in biomedicine. J Phys D Appl Phys 36: R167-R181.

30. Bain MSC, Yiu HHP, Dobson J (2008) Magnetic nanoparticles for gene and drug delivery. Int J Nanomedicine 3(2): 169-180.

31. Laurent S, Forge D, Port M, Roch A, Robic C, et al. (2008) Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications. Chem Rev 108(6): 2064-2064.

32. Liu Z, Lammers T, Ehling J, Liua Z, Lammersa T, et al. (2011) Iron Oxide Nanoparticle-Containing Microbubble Composites as Contract Agents for MR and Ultrasound Dual-Modality Imaging. Biomaterials 32(26): 6155-6163.