

New Chemical Methods for Synthesis of Magnetic Nanoparticles for Biomedical Applications

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Abstract. An update is presented on some recent development in the synthesis of magnetic nanoparticles for potential use in biomedical applications. Particular attention is paid to (i) the preparation of magnetic nanoparticles that are readily dispersed in aqueous solution (ii) the synthesis of alloy magnetic nanoparticles and (iii) novel synthesis methods used control the physical properties of the nanoparticles.

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INTRODUCTION

Nanotechnology can be described as the development of materials at the atomic and molecular level in order to instill them with special physical and chemical properties¹. Nanoparticles (NPs) represent an area within nanotechnology, which deals with particles typically between 1 and 100 nm in size. These NPs can be divided into different types according to their physical and chemical properties. For example, semiconductor NPs fabricated from materials such as CdSe, CdS and ZnS, which exhibit atom-like energy states due to confinement effects, can be described as quantum dots². The electronic properties of these particles allows them to be used as active materials in single electron transistors³. Furthermore, the atom-like energy states also play a role in the special optical properties observed in these materials, such as particle-size dependent wavelength of fluorescence¹. Metallic NPs represent another class of nanomaterial that have been studied since the mid-1800s. For instance, gold NPs have been used in the past for medical applications⁴ and the optical properties of these particles have been found to differ greatly from the bulk material⁵. Metallic NPs of particular interest are the magnetic NPs that can consist of metals such as iron^{6,7}, cobalt⁸ and nickel⁹, alloys such as CoPt^{10,11} and FeCo¹² as well as iron oxides.

Interest in magnetic NPs has grown rapidly in recent years due to their diverse applications in biomedicines¹³, novel materials for engineering¹⁴ and devices¹⁴, which arise from the unique combination of small size, exotic properties and processability of these materials. Magnetic NPs can be extremely useful due to their potential biomedical applications in areas such as magnetic resonance imaging (MRI)¹⁵, targeted drug delivery¹⁶, hyperthermia treatment of solid tumors¹³ and cell separation¹³.

The physical properties can be attributed to the size and surface effect of the NPs as well as inter-particle interactions and unusual electron transport properties¹. These include a large surface area to volume ratio and ubiquitous tissue accessibility making the particles very suitable for use in *in vitro* diagnostic applications¹³. The magnetic properties of the NPs is particularly important for *in vivo* applications where superparamagnetic particles are preferred as these do not retain any magnetism upon the removal of a magnetic field as opposed to ferromagnetic material that aggregate after exposure to a similar field^{17, 18}.

As mentioned above, the physical properties of these nanostructures (optical, electrical, chemical, magnetic, etc) are dependent upon their size, composition and crystal structural ordering. Therefore, the fabrication of tailored NPs reliably and predictably is highly desirable. One of the ways to produce well defined NPs is to tailor the surface properties of the particles, often by coating or encapsulating them in a shell of a particular material¹⁹. This coating and encapsulation can also protect the core from extraneous chemical and physical changes^{6, 14, 20}. Various substances have been used to form the protective shell of NPs e.g. silica⁷, polymer²¹, peptide^{22, 23} and noble metals^{24, 25}, however achieving long term stability of the particles still remains a problem.

Modification of the surface properties is particularly important when considering *in vivo* applications to ensure that particles are biocompatible, non-toxic and stable to the reticulo-endothelial system: the body's major defense mechanism¹³. Particles possessing a hydrophobic surface are readily coated with plasma components in the blood stream and are therefore easily removed from the circulation, while more hydrophilic particles can resist coating and are cleared much more slowly²⁶. Many common hydrophilic coatings used on NPs include derivatives of dextran, polyethylene glycol, polyethylene oxide, poloxamers and polyoxamines²⁷. The dense brushes of polymers can inhibit the opsonisation (the process that causes foreign bodies to be recognized by the body's reticulo-endothelial system) of the particles, thereby increasing their circulation time.

Peptides

Peptides were used as capping ligands for the first time by Thanh et al²³ in the *in situ* synthesis of water-soluble cobalt NP with the aim to use these particles for biological applications. The peptide TLVNN (threonine-leucine-valine-asparagine-asparagine) afforded some degrees of stability upon the NPs. The ability to tune the properties of peptides (by varying the length, and sequence of amino acids) makes them a unique class of ligands for combinatorial nanomaterial synthesis. In addition to the 20 amino acids that occur naturally in proteins, over 100 unnatural amino acids are

available for peptide synthesis, which provide access to a huge chemical combinatorial space.

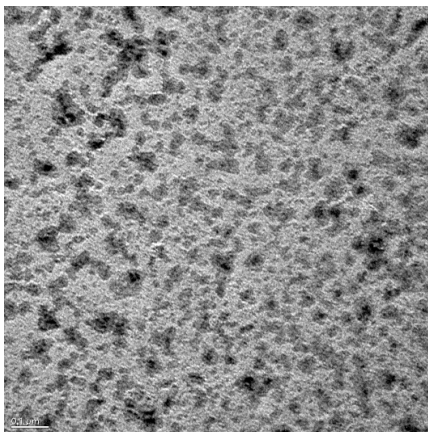


FIGURE 1. TEM images of Co NP synthesized in the presence of peptide and DMF after a few minutes dispersed in water. Scale bar, 100 nm

Thermoresponsive polymers

Using a similar single step method it was possible to synthesize monodisperse water-soluble Co and γ -Fe₂O₃ NPs that were coated with a thermo-responsive polymer, based on poly-N-isopropylacrylamide, with tert-butylacrylamide as a co monomer²⁸. The polymer can undergo a conformational change in response to changes in temperature that allow the synthesis of monodisperse particles at high temperature, but facilitate the transfer of the synthesized particles into the aqueous phase at room temperature (Figure 2). Furthermore, the fabricated NPs can exhibit ‘smart’ behavior such as a non-linear response to an external change, e.g., temperature or pH, which can be used to control drug delivery together with hyperthermia cancer treatment¹⁹.

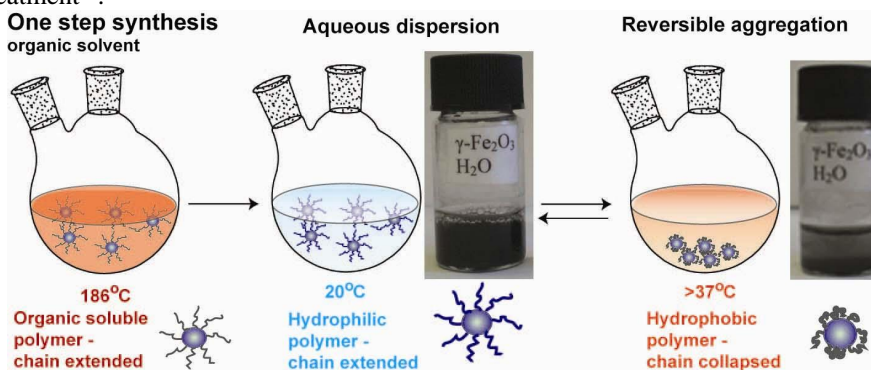


FIGURE 2. Polymers used as stabilizing ligands can retain their physical properties.

Thermo-responsive polymers can also be used in a two-step synthesis method involving, initially the thermal decomposition of the respective organometallic complexes in the presence of oleic acid to produce hydrophobic Co and γ -Fe₂O₃ NPs²⁹. Then, using a ligand-exchange process with the thermo-responsive polymer, the NPs can be dispersed in aqueous solution. Among different thermo-responsive polymers investigated, it was found that the polymer based on poly(N-isopropylacrylamide) with a co-monomer component of acrylic acid and acrylamide can be used in the ligand-exchange to coat Co and γ -Fe₂O₃ NPs, respectively. The NPs are found to be water-soluble at temperatures below coil-to-globule phase transition of the coating polymer (Figure 3).

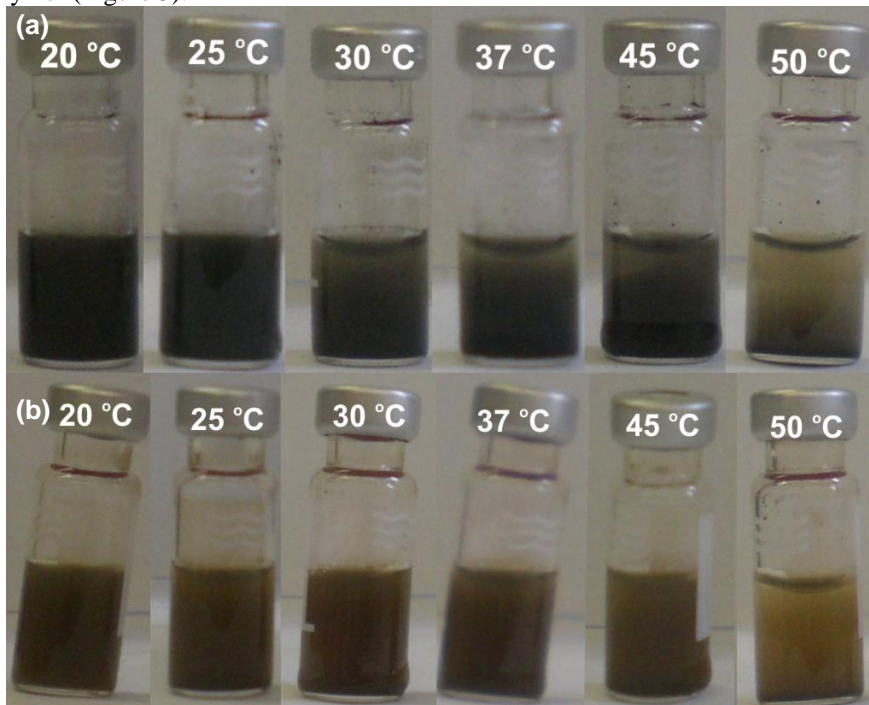


FIGURE 3. The effect of temperature upon the stability in water of the polymer coated Co (a) and iron oxide (b) NPs.

Synthesis in aqueous solution

An alternative method used to synthesize monodisperse water-soluble magnetic Co NPs used the facile reduction of CoCl₂ in aqueous media in the presence of alkyl thioether end-functionalized poly(methacrylic acid) (PMAA-DDT) ligands³⁰. The size and shape of the NPs are both tunable by varying synthesis conditions. The size of the spherical NPs can be tuned between 2–7.5 nm by changing the concentration of the polymer (Figure 4). This synthesis approach also provided a route for producing much larger spherical NPs of 80 nm as well as anisotropic nanorods of 15 x 36 nm. The spherical NPs were superparamagnetic at room temperature and were stable in water

for up to eight weeks when 0.12 mM PMAA-DDT with molecular weight of 13500 g mol⁻¹ is used as ligand.

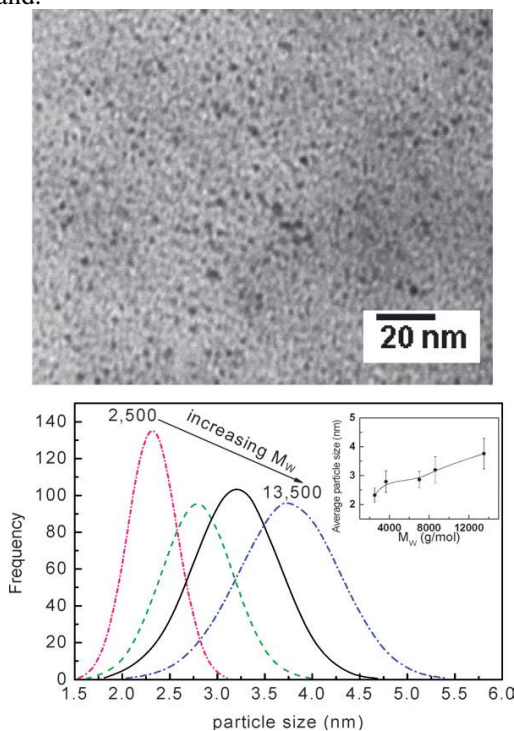


FIGURE 4. TEM image of the Co NPs synthesized in the presence of the PMAA-DDT polymer (molecular weight $MW = 8\,610\text{ g mol}^{-1}$) (upper panel); size distribution histograms of the Co NPs synthesized in the presence of PMAA-DDT polymers with different molecular weights at a concentration of 0.12 mM (bottom panel); the inset shows the average particle size as a function of the polymer molecular weight.

Other material such as CoPt hollow nanostructures have also been produced using this simple reduction method³¹. The NPs were prepared in aqueous solution in the presence of poly(methacrylic acid) pentaerythritol tetrakis (3-mercaptopropionate) (PMAA-PTMP) polymer or a mixture of O-[2-(3-mercaptopropionyl-amino)ethyl]-O'-methylpolyethylene glycol (PEG-SH) polymer and cysteine-cysteine-alanine-leucine-asparagine-asparagine (CCALNN) peptide ligands. The presence of the multi-thiol functional group of the ligands was found to be essential for the formation of the hollow nanostructures (Figure 5) and their perimeter size could be tuned within the range of 7–54 nm by changing peptide concentration or length of polymer. These hollow nanostructures were water-soluble and superparamagnetic at room temperature. They were stable in a wide range of pH from 1 to 10, high electrolyte concentration up to 2 M NaCl, and in cell culture medium giving them great potential to be utilized in biomedical applications.

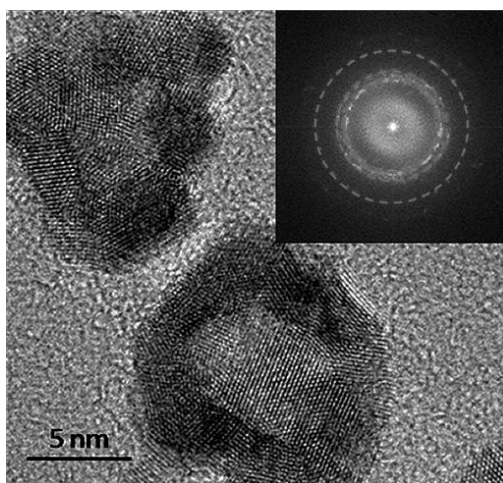


FIGURE 5. HRTEM image of the CoPt hollow nanostructures synthesized in the presence of 0.12 mM CCALNN and 0.24 mM PEG-SH ($M_w = 5,000 \text{ g mol}^{-1}$). The inset shows the corresponding Fast Fourier Transform (FFT) image which shows 3 strongest rings with d-spacings of 2.213, 1.954 and 1.362 Å.

Magnetic alloy nanoparticles

Magnetic alloy NPs are a particularly interesting class of nanomaterial because of their magnetic properties and chemical stability. Ung *et al*³² reported the controlled syntheses of Fe–Pt, Fe–Pd and Fe–Pt–Pd NPs having different isolated shapes including sphere, cube, octopod-cube, star, rod, bilobe, tetrahedron, or multipod with size of 5–50 nm (Figure 6). The formation of such a rich variety of shapes was made possible by controlling the synthetic conditions (e.g. nature and concentration of the precursors, reaction time, temperature and atmosphere) of a thermal decomposition and reduction of precursors in the presence of surfactants. The results of the investigation gave insight to the possible connection between formation of different shapes and the symmetry of the nuclei as well as the divergent kinetics of particle growth.

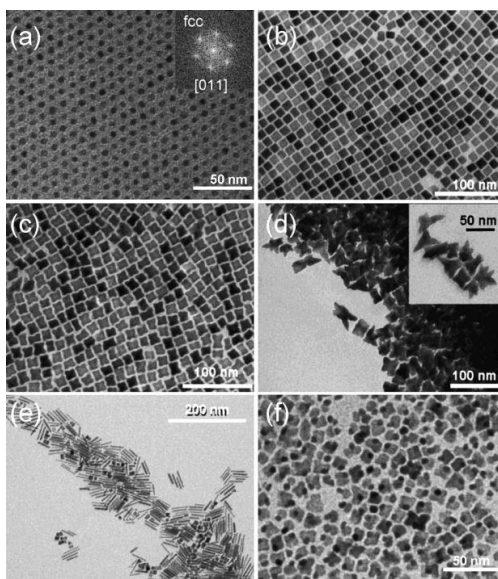


FIGURE 6. Formation of spherical (a), cubic (b), octopod-cubic (c), star (d), rod (e) and bilobar (f) Fe–Pt NPs. The image of the Fast Fourier Transform (FFT) of self-assembled NPs in the inset of (a) indicate that they were in a fcc structure. The inset of (d) shows zoom-in view on a few nanostars.

It can sometimes be difficult to control the composition of magnetic alloy NPs when they are produced from two or more precursors. This could be overcome by using a single precursor of bimetallic carbonyl cluster in a thermal decomposition process. This novel synthesis method has been used to produce FeCo_3 , FeNi_4 , FePt , and Fe_4Pt alloy magnetic NPs, with average diameters of 7.0, 4.4, 2.6, and 3.2 nm³³ (Figure 7). The chemical composition of the synthesized NPs reflected that of the bimetallic carbonyl cluster used for their synthesis. Different reaction conditions, such as ligand concentration, ligand type, and reaction temperature had very little effect upon the chemical and physical properties of the synthesized NPs. Due to the great diversity of carbonyl cluster chemistry, this versatile method for the synthesis of magnetic alloy NPs and can be applied to a wide variety of other nanomaterials.

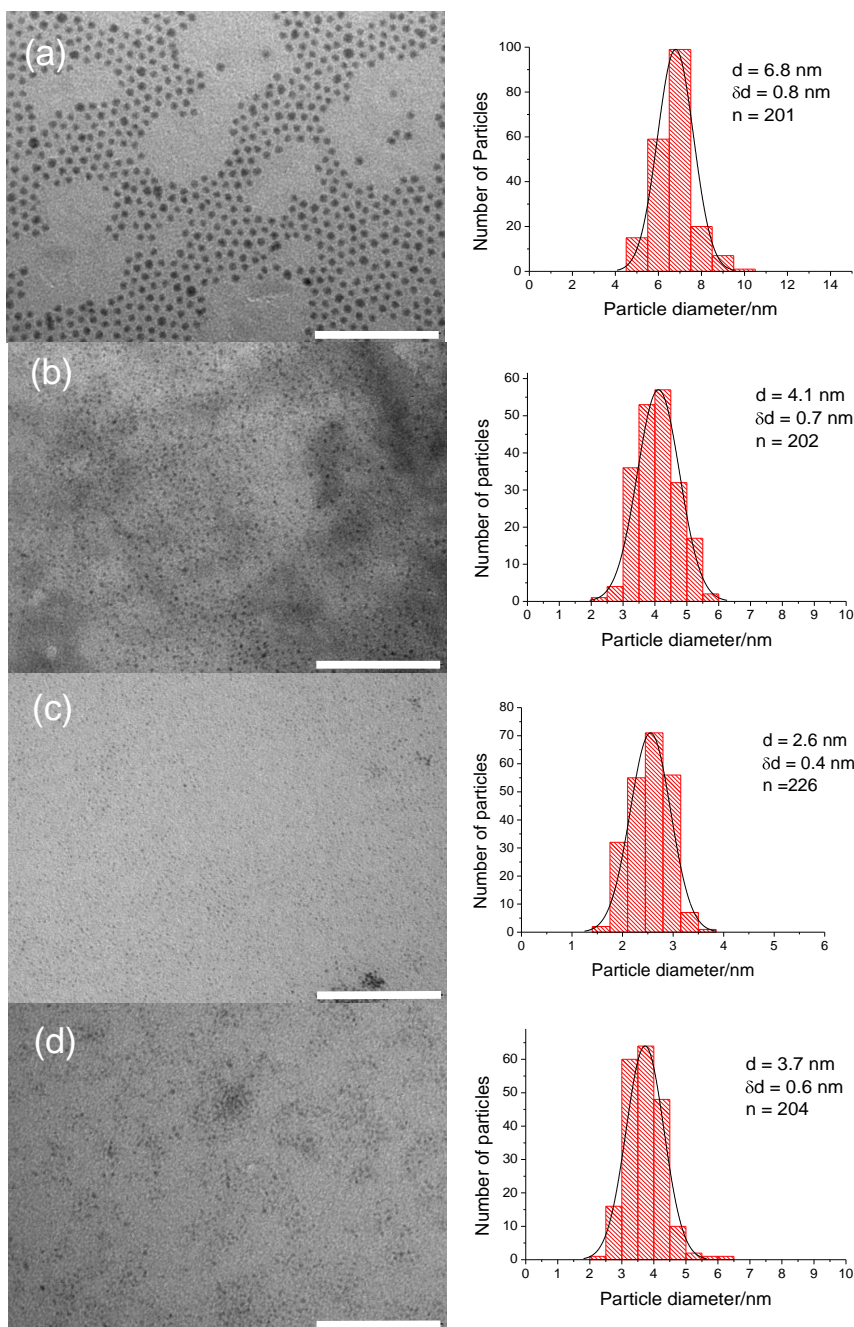


FIGURE 7. TEM images and size distributions of (a) FeCo₃ (b) FeNi₄ (c) FePt and (d) Fe₄Pt NPs synthesized by the thermal decomposition of [NEt₄][FeCo₃(CO)₁₂], [NMe₄]₂[FeNi₅(CO)₁₃], [NMe₃CH₂Ph]₂[Fe₃Pt₃(CO)₁₅] and [NMe₃CH₂Ph]₂[Fe₄Pt(CO)₁₆] and coated with OA and TOPO. Scale bar, 100nm.

Pulsed laser irradiation

As mentioned above, NPs have a wide variety of potential applications and each application requires NPs that have tailored properties for that application e.g. size. Interest in producing magnetic NPs with controllable sizes has led to the development of new synthesis methods. For example, Robison *et al*³⁵ synthesized sub 4 nm cobalt NPs by using pulsed laser irradiation to decompose cobalt carbonyl in a solution of stabilizing ligands. Using this synthesis method it was possible to control the size of the NPs by varying the reaction conditions such as the ligand concentration and the wavelength of light used. The formation mechanism of the NPs was also investigated by changing these conditions. It is possible that this technique could be applied to the synthesis of a variety of nanomaterials with potential applications such as biomedicine, catalysis, and water purification.

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