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Magnetic nanoparticles: synthesis, functionalization, and applications in bioimaging and magnetic energy storage

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Abstract

This *tutorial review* summarizes the recent advances in the chemical synthesis and potential applications of monodisperse magnetic nanoparticles. After a brief introduction to nanomagnetism, the review focuses on recent developments in solution phase syntheses of monodisperse MFe_2O_4 , Co, Fe, CoFe, FePt and SmCo_5 nanoparticles. The review further outlines the surface, structural, and magnetic properties of these nanoparticles for biomedicine and magnetic energy storage applications.

Introduction to nanomagnetism

Nanoparticles (NPs) are of intense current interest for a variety of applications, not only for the general miniaturization of devices, but because their physical properties vary dramatically from their bulk counterparts. The case of magnetic NPs is especially interesting as the NP size is comparable to the size of a magnetic domain. This results in two important types of magnetic behavior in NPs, namely single domain ferromagnetic (FM) NPs and superparamagnetic (SPM) NPs.

Like bulk ferromagnets, an array of single domain magnetic NPs can exhibit hysteresis in the magnetization *versus* field dependence. A traditional bulk ferromagnet experiences an increase in magnetization with increase in field as the domains grow *via* domain wall movement to result in a net magnetization. However, in an array of single domain particles, the moment of each particle interacts with its neighbors and the field to align in the field direction. The magnetization at which all the moments are aligned in both instances is referred to as the saturation magnetization (M_s). The decrease of the external field to zero in both cases results in the sample retaining a measurable amount of magnetization. The magnetization present after saturation and the subsequent removal of the field is referred to as the remnant magnetization (M_r). The reversal of the field (in the direction opposite to the remnant magnetization) causes the magnetic moments to randomize again, and the field required to bring the net magnetization back to zero is called the coercivity, H_c .¹ The key difference between the magnetic behavior of a bulk magnetic material and a collection of single domain FM NPs arises from the mechanism by which the magnetization is cycled through the hysteresis loop. In a bulk material, the magnetization increases in response to the field *via* domain wall nucleation and rotation as well as the rotation of the magnetization vector away from the easy axis of magnetization. In a single domain nanoparticle, domain wall movement is not possible and only coherent magnetization rotation can be used to overcome the effective anisotropy (K) of the particle.² Thus the maximum coercivity of a given material as a function of particle diameter actually falls in the single domain range.

The critical diameter for a magnetic particle to reach the single domain limit is equal to

$$R_{\text{sd}} = \frac{36 \sqrt{AK}}{\mu_0 M_s^2}$$

where A is the exchange constant, K is the effective anisotropy constant and M_s is the saturation magnetization.³ For most magnetic materials, this diameter is in the range 10–100 nm, though for some high-anisotropy materials the single domain limit can be several hundred nanometres.³

For a single domain particle, the amount of energy required to reverse the magnetization over the energy barrier from one stable magnetic configuration to the other is proportional to $KV/k_B T$ where V is the particle volume, k_B is Boltzmann's constant and T is temperature.⁴ If the thermal energy is large enough to overcome the anisotropy energy, the magnetization is no longer stable and the particle is said to be superparamagnetic (SPM). That is, an array of NPs each with its own moment can be easily saturated in the presence of a field, but the magnetization returns to zero upon removal of the field as a result of thermal fluctuations (*i.e.* both M_r and H_c are zero). This behavior is analogous to conventional paramagnets, only instead of individual electronic spins displaying this fluctuating response, it is the collective moment of the entire particle, hence the term “superparamagnetism”.⁵ The temperature at which the thermal energy can overcome the anisotropy energy of a NP is referred to as the blocking temperature, T_B .⁴ For an array of NPs with a distribution in volume, T_B represents an average characteristic temperature and can be affected by inter-particle interactions as well as the timescale over which the measurement is performed due to the magnetic relaxation of the particles.⁶ Keeping these caveats in mind, T_B as the general transition from ferromagnetism to superparamagnetism is one of the most important quantities that define the magnetic behavior of an assembly of particles. Fig. 1 shows a schematic illustrating the difference in the magnetization *versus* field behavior of an array of single domain magnetic NPs in the blocked state (Fig. 1a) and an array of SPM NPs (Fig. 1b).

The magnetic instability of small, SPM NPs has proven to be a challenge in the current design of magnetic data storage.⁷ “Beating the superparamagnetic limit” by developing synthesis routes for NPs with high anisotropy constants is one way to try to compensate for thermal fluctuations that become dominant at small particle volumes.⁸ It has also been found that the ability to synthesize small NPs with high coercivity and anisotropy could lead to significant improvements for the next generation of permanent magnets.⁹

On the other hand, the properties that characterize SPM NPs—namely high saturation magnetization accompanied by a low saturation field and no remnant magnetization—have proven to be ideal for biomedical applications. The lack of prominent inter-particle interactions, which normally lead to aggregations of particles, enable the synthesis of NP dispersions (ferrofluids) which can be injected into biological systems and manipulated by external field gradients. Such dispersions are currently finding applications in site specific treatments such as targeted drug delivery, localized heating of cancerous cells (hyperthermia), and magnetic resonance imaging (MRI) contrast enhancement.¹⁰

In this review, we discuss the general chemistry used to obtain monodisperse magnetic NPs and to functionalize these NPs for biomedical applications with special emphasis on bioimaging. We also introduce how two different NP species can be independently synthesized and combined to fabricate exchange-spring nanocomposite magnets for energy storage applications.

Chemical synthesis of magnetic nanoparticles

A variety of chemical methods have been developed for preparing monodisperse magnetic nanoparticles (NPs).¹¹ Here we briefly review recent advances in organic solution phase syntheses of monodisperse magnetic NPs from thermal decomposition of organometallic precursors and metal salt reduction.

Nanoparticle synthesis in general

A commonly used route to synthesize monodisperse NPs in the solution phase is to separate nucleation and growth steps during the synthesis. In the theory developed by LaMer,¹² a burst nucleation occurs when the monomers quickly increase over critical supersaturation without further formation of nuclei afterwards.¹³ The produced nuclei then grow at the same rate, giving monodisperse particles. The process is illustrated in Fig. 2a. However, small NPs have an extremely high surface area to volume ratio and agglomerate easily to minimize their surface energy. To prevent this agglomeration from occurring, surfactant molecules have to be used to coat the particle surface. The repulsive forces introduced by the surfactant molecules around any two NPs offer the much-needed long-term NP stabilization.

Fig. 2b illustrates a schematic lab set-up utilizing the frequently applied “hot-injection” procedure to achieve the burst nucleation by rapid introduction of reagents into the reaction vessel. Alternatively, a so-called “heating-up” strategy is also widely applied¹⁴ which heats up a pre-mixed solution of precursors, surfactants, and solvent to a certain temperature to initiate the particle clustering and growth. Recent synthetic advances have indicated that both hot-injection and heating-up procedures are capable of yielding highly monodisperse NPs (standard deviation in diameter $\sigma < 10\%$) *via* fine control of the reaction parameters.^{11,13,14}

Synthesis of magnetic nanoparticles *via* thermal decomposition reaction

One of the simplest and most important methods for preparing magnetic NPs is *via* the decomposition of metal precursors, most often of the organometallic complexes. Due to their metastable nature, such organometallic complexes can readily undergo decomposition by mild agitation, such as heat, light, or even sound.¹¹

Metal carbonyls and their related derivatives are one representative class of organometallic complexes and are usually applied to the synthesis of metallic NPs. These reactive carbonyls have a strong tendency to dissociate the carbonyl groups when heated, leaving the zero-valent metal centers to nucleate and grow into NPs.¹⁵ Iron(0) pentacarbonyl, $\text{Fe}(\text{CO})_5$, has been used to produce monodisperse magnetic iron and iron oxide NPs in the presence of surfactants. For example, Fe NPs with various sizes ranging from 5 nm to 19 nm were synthesized by thermal decomposition of $\text{Fe}(\text{CO})_5$ in dioctyl ether solvent and oleic acid (OA) and oleylamine (OAm) as surfactants.¹⁵ Monodisperse face centered cubic Co (fcc-Co) NPs with multi-twinned structures were fabricated by thermolysis of dicobalt octacarbonyl, $\text{Co}_2(\text{CO})_8$, in diphenyl ether with OA and tributylphosphines.¹⁶ ϵ -Co NPs were produced by thermolysis of $\text{Co}_2(\text{CO})_8$ using trialkylphosphine oxides as surfactant.^{16,17} CoFe alloy particles were made by simultaneous decomposition of $\text{Fe}(\text{CO})_5$ and $\text{Co}_2(\text{CO})_8$ in 1,2-dichlorobenzene.¹⁸

However, the metallic NPs described above are extremely reactive and subject to fast oxidation. To stabilize these active NPs, an efficient surface coating is needed to prevent oxygen from penetrating through the coating layer. The authors recently reported a simple one-pot synthesis of monodisperse Fe NPs ($\sigma < 7\%$) by thermal decomposition of $\text{Fe}(\text{CO})_5$ in 1-octadecene (ODE) with OAm.¹⁹ Fig. 3 shows TEM images of the Fe NPs prepared with this method. The as-synthesized Fe NPs were unstable and were readily oxidized during treatment in ambient conditions, producing an amorphous Fe_3O_4 layer around the metallic Fe core (Fig. 3a).

However, when trimethylamine *N*-oxide, Me₃NO, was added to the Fe NP dispersion before its exposure to air, a well-crystallized Fe₃O₄ shell was formed, giving core-shell Fe/Fe₃O₄ NPs (Fig. 3b). The core-shell NPs were SPM at room temperature with a saturation magnetization of 103 emu g⁻¹ and were stable against deep oxidation upon their further exposure to air. In contrast, the as-synthesized Fe NPs without Me₃NO treatment were subject to fast oxidation and rapid agglomeration in the dispersion.

Synthesis of magnetic nanoparticles *via* metal reduction

Magnetic NPs have also been frequently synthesized by the reduction of metal salts using reducing agents in the presence of surfactant molecules. Compared to the thermal decomposition approaches, where unstable organometallic precursors are involved, metal reduction methods offer a larger variety of stable metal precursors, such as oxides, nitrates, chlorides, acetates, and acetylacetonates.¹⁵ Conventionally, hydride-based reducing agents, such as sodium borohydride and lithium superhydride, are used for metal salt reduction. More recently, organic reducing agents have been employed for such reduction. These reducing agents include polyols, hydrazine and dihydrogen gas.²⁰

Monodisperse ε-Co NPs have been prepared *via* the reduction of cobalt chloride using lithium triethylborohydride (LiBEt₃H, superhydride) in dioctyl ether with the presence of OA and trialkylphosphine surfactants.¹⁶ The trialkylphosphine surfactants with shorter alkyl chains allowed faster growth, thus favored the production of larger particles, and *vice versa*. The synthesis of FeCo particles was achieved by simultaneous co-reduction of ferrous sulfate and cobalt chloride salts using sodium borohydride, while hollow FeCo was prepared similarly using potassium borohydride.²¹ The reduction of FeCl₂ and Pt(acac)₂ in diphenyl ether by LiBEt₃H in the presence of OA-OAm gave 4 nm FePt particles.²²

Metal reduction using polyols, especially the ones with adjacent hydroxyl groups and long hydrocarbon chains, has become much more popular recently due to their versatility as solvent, reducing agent and surfactant during the reaction. Frequently used poly-ethylene glycols (poly-EG) have been applied to fabricate various magnetic metal and alloy NPs.¹¹ Moreover, the polyol process has been extended to the synthesis of rare-earth hard magnets. SmCo₅ particles were prepared by heating a tetraethyleneglycol (TEG) solution of SmCl₃ and Co(acac)₃ in the presence of polyvinyl pyrrolidone (PVP) at 300 °C.²³ The particles had a room temperature H_c of 1100 Oe. Very recently, *via* co-reduction of Sm and Co nitrates in TEG with the presence of PVP, air-stable 10 × 100 nm blade-like SmCo nanorods were made.²³ Their H_c and M_s were 6.1 kOe and 40 emu g⁻¹ at room temperature, and 8.5 kOe and 44 emu g⁻¹ at 10 K.

1,2-Alkanediols represent another group of polyols. Monodisperse Fe₃O₄ NPs (4 nm–18 nm) were prepared by reduction of Fe(acac)₃ with 1,2-hexadecanediol in benzyl ether in the presence of OA-OAm. Excess diol further reduced Fe₃O₄ into Fe NPs.²⁴ This procedure has been extended to the syntheses of other ferrites (MFe₂O₄, M = Co, Mn, *etc.*). The 16 nm Fe₃O₄ NPs were SPM at room temperature (M_s = 83 emu g⁻¹), and became ferromagnetic at 10 K (H_c = 450 Oe). In comparison, the 16 nm CoFe₂O₄ NPs had a room temperature H_c of 400 Oe and a much larger H_c of 20 kOe at 10 K. Recently, FeCo alloy NPs were synthesized *via* 1,2-hexadecanediol reduction of Fe(acac)₃ and Co(acac)₂ in OA-OAM under an Ar + 7% H₂ atmosphere.²⁴ The resulting 20 nm FeCo NPs had an M_s of 207 emu g⁻¹. The M_s reached 230 emu g⁻¹ upon thermal annealing under which a robust carbon coating was formed around the CoFe NPs.

Alkyl amines and acids have also been proven to have reducing abilities at elevated temperatures. Using this chemistry, nanocubes and hollow-frames have been synthesized.²⁵ The process utilized high temperature (380 °C) decomposition of OA to give reductive species, such as C, CO, and H₂, and to reduce Fe(*n*)-stearate into metallic Fe particles. The addition of

extra sodium oleate led to the formation of Fe nanocubes, and further heating gave hollow nanoframes. The formation of the hollow structure was due to the severe molten salt corrosion. Hollow Co particles were made by simultaneous fast out-diffusion of CoO and surface reduction of the oxides by OAm.²⁵ FeO NPs and nanocubes have also been made by reduction of Fe(acac)₃ in an OA-OAm mixture at 300 °C.²⁶

Solid state processes utilizing high temperature reduction with alkaline metals have been used to reduce rare earth metal salts. SmCo₅ nanocrystalline hard magnets were prepared by reductive annealing of core-shell structured Co/Sm₂O₃ particles²⁷ with metallic Ca at 900 °C to reduce Sm₂O₃ and to promote interfacial diffusion between Sm and Co. KCl was used as the dispersion medium to facilitate reduction and to prevent NPs from growing into large single crystals. The coercivity of the magnets reached 24 kOe at 100 K and 8 kOe at room temperature with remnant magnetization values of 40–50 emu g⁻¹.

The combination of thermal decomposition and metal salt reduction are often applied to make alloy NPs, particularly FePt NPs. For example, simultaneous thermolysis of Fe(CO)₅ and reduction of Pt(acac)₂ in the presence of 1,2-hexadecanediol was a common route to monodisperse FePt NPs.⁸ The composition and the size of the resulting FePt NPs were controlled by tuning the Fe(CO)₅ : Pt(acac)₂ ratio and/or precursor : surfactant ratio. 7 nm FePt cube-like NPs were synthesized under similar conditions but without 1,2-hexadecanediol.⁸ More recently, FePt nanowires or nanorods from 20 to 200 nm were made by thermal decomposition of Fe(CO)₅ and reduction of Pt(acac)₂ in a mixture of OAm and ODE at 160 °C and the aspect ratio of the rods was controlled by the volume ratio of OAm : ODE.⁸ Polyol reduction of Sm(acac)₃ was combined with thermolysis of Co₂(CO)₈ to synthesize small (<10 nm) SmCo₅ particles with a coercivity of 2.2 kOe at 5 K and a calculated anisotropy (*K*) of about 2.1 × 10³ erg cm⁻³ which is about 1% of bulk SmCo₅.²⁸

Magnetic nanoparticles for biomedical applications

Magnetic NPs, especially superparamagnetic (SPM) NPs, are attractive magnetic probes for biological imaging and therapeutic applications.²⁹ At a core diameter of less than 20 nm and overall hydrodynamic diameter of less than 50 nm, these NPs are of a size that is comparable to the nuclear pore size (~50 nm) and are much smaller than a cell (normally 10–100 nm). Once coupled with a target agent, they can serve as a nano-vector and interact specifically with biomolecules of interest through well-established biological interactions, providing controllable means of magnetically tagging a bio-entity. Under the normal range of magnetic field strengths used in magnetic resonance imaging (MRI) scanners (usually higher than 1 tesla), these SPM NPs in the targeted area can be magnetically saturated, establishing a substantial locally perturbing dipolar field that leads to a marked shortening of proton relaxation (*T*₂ relaxation) in the MRI process and giving a “darker” image of the targeted area over the biological background. Furthermore, under an alternating (AC) magnetic field with controlled field amplitude and field reversal frequency, magnetization of the SPM NPs attached to the bio-entity can be switched back and forth. This magnetization re-orientation creates friction between the NP and its surrounding liquid medium, or between the magnetic easy axis of the particle and the atomic lattice within the NP structure. In both cases, the energy originating from this friction is converted to thermal energy, and these SPM NPs function as a heater to heat the area they target to. This magnetic field induced NP heating is known as magnetic fluid hyperthermia and has been studied extensively for future cancer therapy.

Surface functionalization of magnetic nanoparticles

Due to the monodispersity in size, shape and composition, high moment SPM NPs prepared in organic phase syntheses are ideal for biomedical applications. However, these SPM NPs are normally stabilized by surfactants like oleic acid and/or oleylamine and are hydrophobic. To

make these NP hydrophilic for biological applications, their surfaces are often functionalized via surfactant addition or surfactant exchange, as illustrated in Fig. 4. Surfactant addition is achieved through the adsorption of amphiphilic molecules that contain both a hydrophobic segment and a hydrophilic component. The hydrophobic segment forms a double layer structure with the original hydrocarbon chain, while hydrophilic groups are exposed to the outside of the NPs, rendering them water-soluble. Surfactant exchange is the direct replacement of the original surfactant with a new bifunctional surfactant. This bifunctional surfactant has one functional group capable of binding to the NP surface tightly *via* a strong chemical bond and the second functional group at the other end has polar character so that the NPs can be dispersed in water or be further functionalized.

The surfactant addition strategy was first developed for making water-soluble quantum dots and was then successfully demonstrated for dispersing magnetic NPs into aqueous media. The amphiphilic ligands possess a lipophilic structure (*i.e.* hydrocarbon chain) and hydrophilic polar functional groups (either ionic or uncharged), such as poly(maleic anhydride-*alt*-1-octadecene)-PEG block copolymer, or amphiphilic PEG-phospholipids.³⁰ The introduction of amphiphilic ligands to as-synthesized nanoparticles results in the formation of a robust double layer around the particles. Recently, Dai's group developed a PEG-modified phospholipid micelle coating for functionalization of high moment SPM FeCo NPs (Fig. 5).³¹ The hydrocarbon chains of the phospholipid are bound to the graphitic shells of FeCo NPs *via* hydrophobic interactions to form stable double layers while the PEG chains are exposed to aqueous media, leading to high water solubility. Very recently, Shin *et al.* used the same strategy to encapsulate hollow manganese oxide nanoparticles into a PEG-phospholipid shell to provide them with good biocompatibility.³²

Similarly, various amphiphilic polymers, such as polystyrene-poly acrylic acid block copolymer (PS-PAA), tetradecylphosphonate and polyethylene glycol-2-tetradecyl ether, have been successfully used for transferring hydrophobic NPs from organic solvents to aqueous solution.³³ Various commercially available amphiphilic polymers provide different functional groups, including carboxylic acid, thiol, amine, carbonyl, and biotin, for immobilization of various biological moieties, such as peptides, proteins, oligonucleotides.

In comparison to the amphiphilic micelle coating, the bifunctional ligand exchange strategy provides in principle better colloidal stability of the magnetic NPs in physiological conditions due to strong interactions between the bidentate or multidentate functional groups and the iron oxide surface. Xu *et al.* reported that bidentate ligand, dopamine, can coordinate to the surface of iron oxide as a result of improved orbital overlap of the five-membered ring and a reduced steric effect on the iron complex (Fig. 6a).³⁴ The resulting NPs showed excellent stability in physiological conditions. The utilization of a mixture of PEG ligands (dopamine-PEG and thiol terminated PEG) not only enhances colloidal stability of FePt alloy NPs in aqueous media but also provides an easy way to immobilize biomolecules onto magnetic NPs.³⁵ Carboxyl acid terminated dopamine-PEG successfully transferred the Fe/Fe₃O₄ core-shell magnetic nanoparticles from an organic solvent to aqueous media with relatively high stability (Fig. 6b).¹⁹ Very recently, Wang *et al.* have synthesized Fe₃O₄ NPs coated with an amine-terminated PEG ligand, which is readily attached to various molecules, for example chromone, for drug delivery.³⁶

The ligand exchange strategy was also developed to replace hydrophobic ligands on magnetic NPs with organosilanes possessing various functional groups.³⁷ The alkoxy moieties of organosilanes associate with the metal oxide by forming a covalent bond with surface hydroxyl groups *via* dehydration or esterification. It was found that amino-, carboxylic acid- and polyethylene glycol-terminated silanes not only make the magnetic NPs highly stable and water-soluble, but also render them with diverse functionalities for subsequent bioconjugation.

Many small bifunctional molecules, such as cystamine and 2,3-dimercaptosuccinic acid (DMSA), have also been used for replacement of hydrophobic layers *via* either the formation of metal–S bonds or chelate bonding of the carboxylate groups to the magnetic NPs.³⁷ Unlike PEGylated or other polymer-based NPs, the hydrodynamic particle size remains sufficiently small after ligand exchange coating.

In situ coating becomes popular as it requires no subsequent surfactant exchange. Magnetic NPs have been made in the presence of a variety of carboxylates (*i.e.* citric acid), phosphates, phosphonates, or other multidentate ligands for obtaining biocompatible and thermodynamically stable dispersions of NPs in aqueous media.³⁸ Xie *et al.* developed a new strategy to synthesize ultrasmall, water-soluble NPs by combining the *in situ* coating with post-synthesis functionalization.³⁹ A small ligand 4-methylcatechol (4-MC) was used as the surfactant to stabilize ultrasmall iron oxide NPs during the synthesis. Like dopamine, 4-MC forms a strong chelate bond with the surface of iron oxide. A cyclic RGD peptide (c(RGDyK)) was directly conjugated to 4-MC functionalized NPs *via* the Mannich reaction between the aromatic ring of 4-MC and amine groups of c(RGDyK). The NPs showed the desired biocompatibility and specificity to target $\alpha_v\beta_3$ -rich tumor cells.

Superparamagnetic nanoparticles as contrast agents in MRI

MRI is one of the most powerful non-invasive imaging modalities utilized in clinical medicine. It is based on the principle that protons align and precess along an applied magnetic field. Upon applying a transverse radiofrequency pulse, these precessed protons are perturbed from the magnetic field direction. The subsequent process, through which the pulsing field is turned off to allow protons to return to their original state, is referred to as relaxation. Two independent relaxation processes, longitudinal relaxation (T_1 -recovery) and transverse relaxation (T_2 -decay), are utilized to generate a bright and a dark MR image, respectively. Local variations in relaxation, corresponding to image contrast, arise from proton density as well as the chemical and physical nature of the tissues within the specimen. Upon accumulation in tissues, SPM NPs act typically as T_2 contrast agents to provide a dark image and the contrast enhancement is proportional to the magnetization magnitude.

As the magnetization value of a SPM NP at a certain magnetic field is dependent on the size and magnetocrystalline anisotropy of the NP, SPM NPs with different sizes and structures have been compared for their contrast effects in MRI.³⁷ In a recent comprehensive study on ferrite NPs for MRI application,³⁸ 12 nm MnFe_2O_4 NPs were shown to have the highest mass magnetization value of 110 (emu per mass of magnetic atoms). This value is reduced to 101, 99 and 85 (emu per mass of magnetic atoms) for Fe_3O_4 , CoFe_2O_4 and NiFe_2O_4 , respectively. The spin–spin relaxation time (T_2)-weighted MR images for each sample at 1.5 tesla (T) are consistent with the magnetization results, with MnFe_2O_4 NPs showing the strongest MR contrast effect with a relaxivity value reaching $358 \text{ mM}^{-1} \text{ s}^{-1}$, much larger than 218, 172 and $152 \text{ mM}^{-1} \text{ s}^{-1}$ for Fe_3O_4 , CoFe_2O_4 and NiFe_2O_4 NPs, respectively. This size and structure dependent relaxivity of MnFe_2O_4 NPs can be seen in Fig. 7, from which one can conclude that larger NPs have a large contrast effect, but at the same size, MnFe_2O_4 NPs have the largest contrast enhancement due to the small magnetocrystalline anisotropy and easy magnetization reversal in the MnFe_2O_4 structure.

The cancer detection sensitivity of these ferrite NPs have been further evaluated. In a recent test, the MnFe_2O_4 NPs were coupled with the cancer-targeting Herceptin, an antibody specifically binding to the HER2/neu marker over-expressed on the surface of breast and ovarian cancers.³⁷ Fig. 8 shows the color coded MRI of a mouse implanted with the cancer cell line NIH3T6.7 and treated with 50 mg of NP–Herceptin. It can be seen that the tumor treated with the MnFe_2O_4 –Herceptin NPs shows color changes from red to blue in the color-coded MR images (Fig. 8a–c). In contrast, those treated with the Fe_3O_4 –Herceptin NPs at the same

dosage have no apparent change in the color-coded MR images (Fig. 8d–f). These indicate that the high MR sensitivity of MnFe_2O_4 –Herceptin conjugates enables the MR detection of tumors.³⁸ An even higher MRI sensitivity can be achieved by using high moment SPM NPs. In a recent demonstration, SPM CoFe NPs were made biocompatible and exhibited an r_2 relaxivity of $644 \text{ mM}^{-1} \text{ s}^{-1}$.³¹

Ultra-small Fe_3O_4 NPs (<10 nm in hydrodynamic diameter) are also attractive for tumor-specific detection. In a recent demonstration, Fe_3O_4 NPs with a 4.5 nm core size were synthesized and conjugated with c(RGDyK) peptide.³⁹ The targeting ability of the c(RGDyK)– Fe_3O_4 NPs to integrin $\alpha_v\beta_3$ *in vivo* was evaluated by T_2 -weighted fast spin-echo MR imaging with mice bearing U87MG tumors. The r_2 relaxivity of the c(RGDyK)– Fe_3O_4 NPs was measured to be $165 \text{ mM}^{-1} \text{ s}^{-1}$, which is larger than that of the commercial Feridex NPs ($104 \text{ mM}^{-1} \text{ s}^{-1}$) with similar core size. The tumor MR signal intensity decreases significantly after injection of c(RGDyK)– Fe_3O_4 NPs (Fig. 9a and b). Such signal reduction is significantly inhibited in the presence of a blocking dose of c(RGDyK) peptide (10 mg kg^{-1}) (Fig. 9c), proving the specificity of the particle targeting. To chemically characterize the preferred Fe_3O_4 NP uptake, Prussian blue staining is employed to visualize the disposition of the c(RGDyK)– Fe_3O_4 NPs in the tissue samples obtained after the MR scan at the 4 h time point. Prominent blue spots on the U87MG tumor slices are observed (Fig. 9d) and the blue spots are significantly reduced in the presence of free c(RGDyK) (Fig. 9e), further confirming that the accumulation of c(RGDyK)– Fe_3O_4 NPs is specifically mediated by integrin $\alpha_v\beta_3$ binding.

Nanoparticles for magnetic energy storage applications

An ideal permanent magnetic material emanates a large enough magnetic field such that after it is magnetized it maintains a robust magnetic moment. On the hysteresis loop, this corresponds to a high remnant magnetization (M_r). However, for long-term stability it must also not be easily demagnetized. This corresponds to a large coercivity (H_c). Unfortunately, materials with high remnant magnetization all tend to be magnetically “soft” (coercivity less than $\sim 1000 \text{ Oe}$) and materials that are magnetically “hard” (coercivity greater than $\sim 1000 \text{ Oe}$) tend to have low remnant magnetization. Until recently, finding the ideal permanent magnetic material has involved a trade-off of these two characteristics and the need to strike a balance between high magnetic moment and high coercivity.

A figure of merit for evaluating the quality of a permanent magnet takes these factors into consideration and is referred to as the maximum energy product, or $(BH)_{\text{max}}$. The $(BH)_{\text{max}}$ for a material can be found first by converting the heretofore discussed M – H curve into a B – H curve *via* the relation $B = \mu_0 M + H$. Since permanent magnetism is assessed with respect to the magnetostatic energy stored within the magnetic material, it is only the magnetized state (second quadrant of the B – H curve) that is of interest. By plotting the energy product (BH) from the second quadrant *versus* either B or H , one can identify $(BH)_{\text{max}}$ as the maximum. Conceptually, $(BH)_{\text{max}}$ corresponds to the area of the largest rectangle that can fit inside the second quadrant of the hysteresis loop.

While it would seem that the coexistence of the two main criteria for useful permanent magnets (M_r and H_c) are naturally incompatible, hard–soft magnetic composite materials are a viable and oft-used route for permanent magnet applications. Hard–soft magnetic composites are materials composed of two phases: the hard magnetic phase (high coercivity) and the soft magnetic phase (high remnant magnetization). When the two phases are properly coupled *via* exchange interactions across the interface, the result is a smooth hysteresis curve which exhibits the desirable properties of both phases. This type of coupled structure, termed an “exchange-spring”, was first proposed by Kneller and Hawig in 1991⁴⁰ though the actual behavior was observed earlier by Coehoorn *et al.*⁴¹ in the melt-spun and annealed $\text{Nd}_2\text{Fe}_{14}\text{B}$ –

Fe₃B–Fe composite system. Later, Skomski and Coey⁴² theorized that the optimal exchange-spring system could yield a $(BH)_{\text{max}}$ of up to 120 MG Oe, more than three times that of commercially available permanent magnets. In the years that followed, groups have made exchange-spring thin film multilayers and composites by a variety of methods including magnetron sputtering, melt-spinning, mechanical alloying, and hydrogen-assisted processes.⁴³

There are several compelling reasons to use chemical synthesis to produce NPs of the hard and soft phases necessary for exchange-spring permanent magnets. Most importantly, exchange coupling of the hard and soft magnetic phases is optimized on the nanoscale. A robust coupling between the phases is necessary to achieve coherent magnetic switching throughout the structure. The dimensions of the soft phase dominate the nucleation characteristics of the composite, and it has been shown that when the dimensions of the soft phase are kept smaller than twice the width of the domain wall $\delta_h = \pi\sqrt{(A_h/K_h)}$ of the hard phase, the soft phase can be thoroughly pinned by the hard phase and no inhomogeneous switching should occur.⁴³ For the most commonly used hard phases, the domain wall width falls in the range of 3–15 nm,³ which corresponds well to the NP size following common chemical synthesis procedures.

Secondly, chemical synthesis of NPs affords fine control over chemical phase. Currently, many of the conventional approaches to hard magnetic materials fabrication result in the presence of impurity phases, most commonly α -Fe. The synthesis methods described throughout this review have been found to yield high-purity materials while avoiding unwanted secondary phases.

Lastly, the chemical synthesis of both hard and soft magnetic NPs allows for the optimization of physical properties including magnetic response, composite density, and even grain size. It is well-documented that the manipulation of synthesis parameters such as polarity and amounts of solvents and surfactants can lead to vast differences in particle morphology resulting in spheres, cubes, rods, and other shapes. Controlling particle aspect ratio can lead to higher magnetic anisotropy in nanoparticles due to the added shape anisotropy contribution, and changing particle shape from spherical to orthorhombic can increase the particle packing density leading to a higher $(BH)_{\text{max}}$. Grain size can be manipulated *via* the controlled assembly of the hard and soft phases.⁴⁴ While similar morphologies for hard and soft particles lead to a more thorough mixing of the two phases, and thus smaller grain sizes, differences in phase size and shape can lead to limited phase segregation and ultimately larger grain sizes. In this section, we describe progress being made towards the use of magnetic NPs for exchange-spring composite permanent magnets.

Binary assembly of magnetic nanoparticles and exchange-spring composite magnets

While the use of small NPs for both the hard and soft phases of an exchange-spring composite is attractive for the reasons described in the previous section, there has been relatively little progress made in composite systems where both phases were chemically synthesized NPs. This is mainly due to the difficulty in chemically synthesizing high-anisotropy NPs, specifically rare-earth–transition metal alloys such as SmCo₅ and Nd₂Fe₁₄B. Attempts have mainly focused on embedding soft magnetic NPs into a hard magnetic matrix, usually either a thin film or a ribbon.⁴⁵ The first demonstration of an exchange-coupled composite formed where both phases originated as NPs was the FePt–Fe₃Pt system.⁴⁴ First, self-assembled 3-D binary arrays of FePt and Fe₃O₄ magnetic NPs were made by evaporation of a mixture of particle dispersions with controlled volume, concentration, and sizes. The FePt NPs were made following the combination thermal decomposition and metal reduction procedure while the Fe₃O₄ particles were synthesized *via* reduction of Fe(acac)₃.²⁰ It was found the 4 nm/4 nm FePt/Fe₃O₄ arrays gave rise to a high-quality hexagonal lattice with random occupation of the two kinds of particles (Fig. 10a), while this binary assembly depended on the size ratio of FePt

and Fe₃O₄ NPs (Fig. 10b). Various binary assembled arrays were then reductively annealed (Ar + 5% H₂, 650 °C, 1 h) to desorb the organic surfactants, transform as-assembled fcc-FePt into hard phase fct-FePt, reduce the Fe₃O₄ into metallic Fe, and to promote partial interdiffusion between Fe and FePt giving a new soft phase of Fe₃Pt.

The FePt/Fe₃Pt nanocomposite resulted from the annealing of a randomly-occupied 4 nm/4 nm FePt/Fe₃O₄ array (mass ratio of 10 : 1). Magnetic measurements (Fig. 10c) showed a smooth hysteresis loop, implying coherent switching and thus efficient coupling of the hard and soft phases. In comparison, the annealed composite from a phase-segregated 4 nm/12 nm FePt/Fe₃O₄ assembly gave a kinked loop (Fig. 10d), indicating an uncoupled structure due to the existence of a soft Fe phase (larger Fe₃O₄ particles inhibited Fe–Pt diffusion) with grain size over twice the domain wall width of the hard FePt phase. HRTEM revealed the Fe₃Pt phase with dimensions below 10 nm uniformly dispersed into the sintered FePt matrix (Fig. 10e). The optimized exchange-coupled nanocomposite yielded both high coercivity and remnant magnetization, with an enhanced energy product $(BH)_{\max}$ of 20.1 MG Oe (Fig. 10f), which exceeded the theoretical limit of 13 MG Oe for non-exchange-coupled isotropic FePt by over 50%.

However, such binary self-assembly approaches require precise control over the mass and size ratios between the two types of NPs, and subtle management of the assembly conditions as well. A more convenient alternative was developed utilizing single modal bi-magnetic core-shell particles.⁴⁶ Pre-made 4 nm Fe₅₈Pt₄₂ NPs were coated with a layer of Fe₃O₄ with tunable thicknesses of 0.5 nm–3 nm *via* a seed-mediated polyol process. In the resulting core-shell particles, the dimensions of the hard and soft phases were controlled by the shell thickness, and strong exchange coupling was ensured by the direct contact between the core and shell. These FePt/Fe₃O₄ NPs were further used as building blocks to form exchange-coupled hard magnetic nanocomposites. For instance, upon reductive annealing (Ar + 5% H₂, 650 °C, 1 h), the 4 nm/1 nm FePt/Fe₃O₄ array was transformed into a composite with greatly enhanced hard magnetic properties ($H_c = 13.5$ kOe and $M_s = 1040$ emu cc⁻¹) at room temperature. The annealed nanocomposite exhibited an energy product $(BH)_{\max}$ of 18 MG Oe.

The ability to use exchange coupling to increase the coercivity often over-shadows the pressing need to increase the remnant magnetization in permanent magnetic materials. The rare-earth based compound SmCo₅ has the largest known anisotropy among all materials though it often shows low remnant magnetization.³ Recently, soft phase metallic Fe was employed to fabricate exchange-coupled SmCo₅/Fe_x composite nanomagnets.⁴⁷ Water-soluble Fe₃O₄ NPs were co-precipitated with SmCl₃ and CoCl₂ in aqueous solutions, followed by baking at 120 °C to give Fe₃O₄ embedded in a Sm-Co-oxide matrix. Reductive annealing was carried out in the presence of metallic Ca at 900 °C, and using KCl as a dispersion medium to facilitate the reduction as well as to prevent sintering and alloying of the SmCo₅ and Fe grains. The final SmCo₅/Fe_x ($x = 0$ –2.9) nanocomposites contained hcp-SmCo₅ with an average grain size of 29 nm and metallic Fe of 8 nm. The SmCo₅/Fe_{1.5} showed an enhanced remnant magnetization of 56 emu g⁻¹ (25% larger than that of SmCo₅), while the SmCo₅/Fe_{0.23} exhibited the largest coercivity of 11.6 kOe.

Conclusion

In this review, we have discussed the importance of magnetic nanoparticles and their unique magnetic properties for technological advances. We have outlined the common chemistry applied for the synthesis of various magnetic nanoparticles with control over NP size, shape, and composition. We have described ways in which superparamagnetic nanoparticles are stabilized and functionalized for biomedical applications such as MRI contrast enhancement. Lastly, we have discussed ways in which self-assembly of magnetic nanoparticles leads to

nanocomposite magnets with magnetic properties superior to their individual components, resulting in an enhanced energy product. These illustrated examples further demonstrate that magnetic nanoparticles made from chemical synthesis with controlled size, surface chemistry and magnetic properties are indeed promising for further ultra-high density information storage, highly sensitive medical diagnostics and highly efficient therapeutic applications.

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Biographies

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Sheng Peng was born September 1982, in Hubei, China. He attended the Department of Chemistry, University of Science and Technology of China, and obtained a BSc in Chemistry in 2004. He was admitted by the Department of Chemistry at Brown University in September 2004. He held positions as research and teaching assistant, and has received the Metcalf Fellowship for excellence in academic performance. Since January 2005, he has been focusing on the chemical synthesis of monodisperse nanoparticles. He was recently awarded the Chinese Government Award (2008) for Outstanding Self-Financed Students Abroad. He received his PhD in Chemistry in May 2009.

Kai Cheng received his PhD in Chemistry from University of Vermont in 2007, under the supervision of Prof. Christopher C. Landry. He joined the group of Professor Shouheng Sun at Brown University as a postdoctoral researcher. His current research interests particularly focus on the development of targeted drug delivery systems for cancer therapies.

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Fig. 1. Schematic illustration of (a) a typical hysteresis loop of an array of single domain ferromagnetic nanoparticles and (b) a typical curve for a superparamagnetic material.

Fig. 2.

(a) Schematic illustration of the LaMer model: separate nucleation and growth for the synthesis of monodisperse nanoparticles; (b) a typical "hot-injection" set-up to achieve the burst nucleation in (a). Reprinted from ^{ref. 13} with permission from Annual Reviews.

Fig. 3. TEM images of (a) the as-synthesized 8 nm/2.5 nm Fe/Fe₃O₄ NPs (inset: HRTEM) and (b) the 5 nm/5 nm Fe/Fe₃O₄ NPs prepared by controlled oxidation of Fe NPs. Reproduced from ^{ref. 19} with permission from the American Chemical Society.

Fig. 4. Schematic illustration of NP surface functionalization *via* (a) surfactant addition and (b) surfactant exchange.

Fig. 5. (a) Schematic representation of the amphiphilic micelle coating of the CoFe NPs; (b) high-resolution TEM image of a single CoFe NP. Adapted from ^{ref. 31} with permission from Nature Publishing Group.

Fig. 6.

Magnetic Fe_3O_4 NPs with bifunctional ligands. (a) Surface coating of iron oxide with a dopamine-termination. (b) Water-soluble $\text{Fe}/\text{Fe}_3\text{O}_4$ core-shell nanoparticles coated with bifunctional PEG ligands.

Fig. 7. Size-dependent MR contrast effect of MnFe₂O₄ and Fe₃O₄ NPs. (a) TEM images of MnFe₂O₄ NPs (scale bar, 50 nm), (b) T₂-weighted MR images, (c) color maps of 6, 9 and 12 nm MnFe₂O₄ NPs, and (d) a plot of NP size *versus* R₂ relaxivity. Reproduced from ^{ref. 37} with permission from Nature Publishing Group.

Fig. 8. Color maps of T_2 -weighted MR images of a mouse implanted with the cancer cell line NIH3T6.7 at different time points after injection of MnFe_2O_4 -Herceptin (a-c) and Fe_3O_4 -Herceptin (d-f) conjugates. Adapted from ^{ref. 37} with permission from Nature Publishing Group.

Fig. 9.

MRI of the cross section of the U87MG tumors implanted in a mouse: (a) without NPs, (b) with the injection of 300 µg of c(RGDyK)-Fe₃O₄ NPs, and (c) with the injection of a blocking dose of c(RGDyK) then c(RGDyK)-Fe₃O₄ NPs; and Prussian blue staining of U87MG tumors in the presence of (d) c(RGDyK)-Fe₃O₄ NPs and (e) a blocking dose of c(RGDyK) and then c(RGDyK)-Fe₃O₄ NPs. Reproduced with permission from ^{ref. 39}.

Fig. 10.

TEM images of (a) randomly occupied 4 nm/4 nm FePt/Fe₃O₄ array and (b) phase segregated 4 nm/12 nm FePt/Fe₃O₄. Corresponding hysteresis loops (c) and (d) from the binary arrays of (a) and (b) after annealing. TEM image (e) of the annealed composite from (a). Second-quadrant B - H curves of (e) (dot) and annealed 4 nm FePt array (triangle). Reproduced from ref. 44 with permission from Nature Publishing Group.