TOPICAL REVIEW

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IOP PUBLISHING JOURNAL OF PHYSICS D: APPLIED PHYSICS

J. Phys. D: Appl. Phys. **42** (2009) 224002 (11pp) doi:10.1088/0022-3727/42/22/224002

TOPICAL REVIEW

Progress in the preparation of magnetic nanoparticles for applications in biomedicine

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Received 9 March 2009
Published 6 November 2009
Online at stacks.iop.org/JPhysD/42/224002

Abstract

This review summarizes recent advances in synthesis routes for quickly and reliably making and functionalizing magnetic nanoparticles for applications in biomedicine. We put special emphasis on describing synthetic strategies that result in the production of nanosized materials with well-defined physical and crystallochemical characteristics as well as colloidal and magnetic properties. Rather than grouping the information according to the synthetic route, we have described methods to prepare water-dispersible equiaxial magnetic nanoparticles with sizes below about 10 nm, sizes between 10 and 30 nm and sizes around the monodomain–multidomain magnetic transition. We have also described some recent examples reporting the preparation of anisometric nanoparticles as well as methods to prepare magnetic nanosized materials other than iron oxide ferrites, for example Co and Mn ferrite, FePt and manganites. Finally, we have described examples of the preparation of multicomponent systems with purely inorganic or organic–inorganic characteristics.

1. Introduction

The last five years have witnessed an exponential growth in activities associated with the potential use of magnetic nanoparticles in biomedical applications [1–18]. In our previous review published in 2003, we described state-of-the-art synthetic routes for the preparation of magnetic nanoparticles for biomedical applications and the importance of having well-defined synthetic routes to produce materials not only with similar physical features but also with similar crystallochemical characteristics [2]. Following the same principles, this short review intends to summarize some of the progress achieved in the development of synthetic strategies for the controlled production of magnetic nanoparticles during the period 2003–2008.

The first section of this review describes synthetic routes to produce ferrites with different sizes and shapes, which are the most suitable materials for biomedical applications. It is well known that size and composition influence the bio-application of magnetic nanoparticles [19]. Thus, for applications in angiography and tumour permeability, ultra-small superparamagnetic iron oxide particles (USPIO) are preferred (figure 1). However, for liver imaging superparamagnetic particles (SPIO) with intense macrophage uptake are preferred. For hyperthermia treatment, particles with sizes around the monodomain–multidomain transition, i.e. particles below 50 nm in diameter, have been found to produce the maximum specific absorption rate (SAR) [15, 20–22]. It has been reported that the SAR of 35 nm magnetite particles is twice that of 10 nm particles [23]. The first section of this review describes synthetic routes producing equiaxial magnetic iron oxide particles below 10 nm (USPIO) which exhibit superparamagnetism combined with surface effects; those between 10 and 30 nm (SPIO) which exhibit superparamagnetic effects and some blocking; above 30 nm which are at the monodomain–multidomain boundary and also methods that produce anisometric nanoparticles. It should

also be noted that due to high crystallinity and low size dispersion many of the examples described for the production of the iron oxide ferrites make use of high boiling point organic solvents [24–26]. For these materials further surface modification is required to yield hydrophilic particles. Some of the strategies followed to achieve this are described and are summarized in table 1.

In the second section of this review we describe synthetic methods dealing with cobalt ferrite [27], manganese ferrite [28], metals and alloys such as Fe [29] and FePt [30], and manganites [31] which are alternative magnetic nanoparticles proposed for biomedical applications. Finally, the future of magnetic nanoparticles in biomedicine lies in their combination with other materials that can impart multifunctionality to the system [32]. Thus, the final section of this review deals with multicomponent colloidal systems.

2. Synthesis of magnetite/maghemite nanoparticles with different size

Differences in iron oxide particle size and shape are reflected by significant differences in the ratio of relaxation constants. These factors affect their heat-generating capacity, plasma half-life and biodistribution, which determines the application [19, 33]. These are the reasons for classifying synthetic methods as a function of the particle size (very small, medium and large particles) and shape (spherical and anisometric).

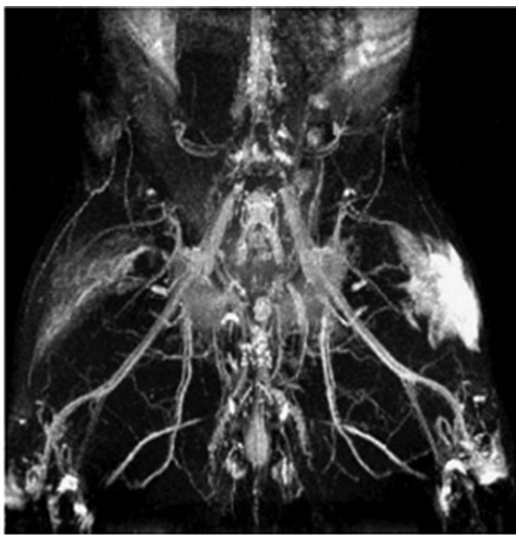

Figure 1. Angio-MR in rabbit after the injection of a USPIO contrast agent (Ferumoxtran-10). Due to the blood pool effect, even small arteries and veins are visible. Reprinted with permission from [19] copyright 2006 Elsevier.

2.1. Synthesis of small particles (USPIO) (<10 nm)

Water compatible magnetite–maghemite particles have been obtained by precipitation of iron salts in aqueous media for more than a decade [34, 35]. Recent reports describe only slight modifications to the synthesis protocols (figure 2). Iron oxide nanoparticles synthesized by these methods need to be coated with polymers [36–38], dendrimers [39], organic acids [40–42], fluorescent compounds [43], sugars [44, 45], etc to ensure their colloidal stability under physiological conditions and enhanced functionality. This is undertaken either during or after synthesis.

The Massart method to produce ionically stabilized colloids has been modified by changing the temperature leading to particle sizes smaller than 5 nm [46] or by controlling the reaction time, obtaining particles between 4 and 10 nm [47]. Lu *et al* also used Massart's method, grinding the precursors and adding water afterwards [48], leading to 2.7 nm particles with a narrow size distribution (∼1–5 nm) (figure 2(*a*)). These nanoparticles are well crystallized and display good superparamagnetic properties. The abundant surface hydroxyl groups allow the nanoparticles to be dispersed to form highly concentrated ferrofluids in water and also permit further biochemical functionalization.

Probably, the most widespread strategy to obtain very small particles is the 'arrested precipitation method' where a molecule is added to the salt mixture. This molecule works as a growth inhibitor coating the particle surface after the nucleation process and preventing the growth and agglomeration steps. Frequently, these molecules protect the particle surface from unwanted reactions such as oxidation and supply different active groups, which provide a number of options for further conjugation reactions. For instance, uniform 4 nm nanoparticles doubly functionalized with carboxylate and thiol groups can be obtained by a shot injection of iron precursors into a refluxing aqueous solution of a polymer ligand [43] (figure 2(*b*)). If the molecular size

Table 1. Routes for transferring to water hydrophobic magnetic nanoparticles prepared by thermal decomposition of organic precursors.

Coating	Method	Examples
Bifunctional molecules	Ligand exchange	DMSA [60, 61], Citric acid [62], Phosphonates [63], MAOH [65].
	Oleic acid oxidation	O_3 [66], $KMnO_4$ [68]
Polymers	Intercalation	Pluronic F-127 [74, 75], Cyclodextrines [76]
	Ligand exchange	PAA-PAH [69] , PNIPAAm-b-PNIPPAAm [71], HOOC-PEG- COOH [70]
	Polymerization on the particles	2-bromopropionylester [72]
Silica	Sol/gel	TEOS [84]
	Ligand exchange	APS [80]
	Reverse micelles	Silsesquioxane [81]
		Triton X-100/Hexanol [82]
Gold	Heterogeneous nucleation	Au on Fe_3O_4: Au $(acet)_2$ [85–87]
	Bifunctional bridge molecule	Fe_3O_4 on Au: $Fe(CO)_5$ [88]

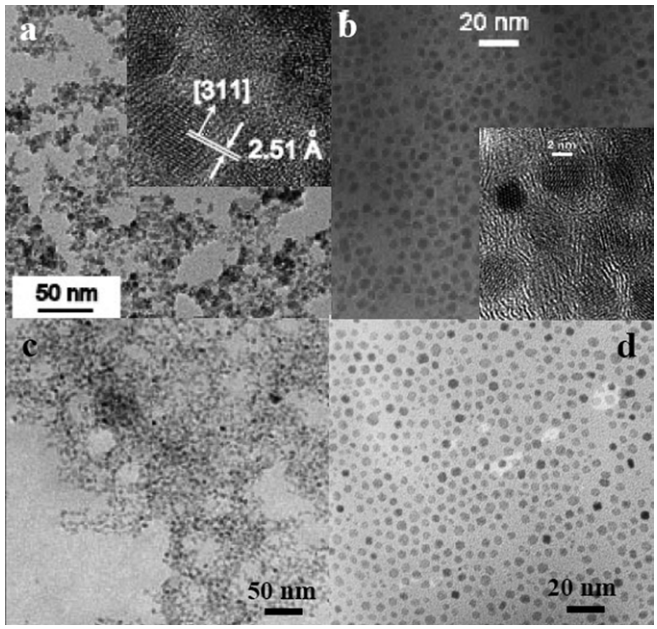

Figure 2. Small magnetite–maghemite nanoparticles prepared by (*a*) coprecipitation, (*b*) in the presence of a polymer, (*c*) microemulsions and (*d*) thermal decomposition of iron acetylacetonate in benzyl ether (synthesized following protocol by Sun *et al* [27]). Reprinted with permission: (*a*) from [48] copyright 2006 IOP Publishing; (*b*, *c*) from [43, 50] copyright 2008, 2005 Wiley-VCH; (*d*) from [27] copyright American Chemical Society.)

of the growth inhibitor is large, e.g. a polymer, it can also provide protection against aggregation by steric hindrance. Particles between 4 and 9 nm can also be obtained by electro-precipitation in ethanol, where Fe_3O_4 precipitates close to the electrode when an electric current passes through an iron nitrate ethanol solution [49].

Precipitation in reverse microemulsions is a well-established technique for preparing magnetic particles with diameters smaller than 10 nm. The particles can have a narrow particle size distribution by varying the relative concentration of the iron salts, surfactant and solvent [50] (figure 2(*c*)). Reverse microemulsions are formed of nanodroplets of an aqueous phase dispersed in an oil continuous phase. The drawback of low yield has been overcome by the use of bicontinuous microemulsions while preserving the properties of the magnetic nanoparticles [51, 52]. Yields from 0.1–0.4 g of product per 100 g of total mixture can increase up to 1.16 g in bicontinuous microemulsions. This type of microemulsion is formed of interconnected aqueous channels, with diameters usually smaller than 10 nm which are immersed in a continuous oil phase.

Thermal decomposition of organometallic compounds has gained much attention recently [16, 24]. These methods have several advantages over conventional procedures including precise control of size and shape, high crystallinity and narrow particle size distribution [25, 53, 54]. However, the use of non-polar solvents and different non-biocompatible surfactants has led the medical community to doubt the suitability of these methods for biological applications. Iron acetylacetonate has been proposed as an excellent iron precursor for the one-step synthesis of magnetite particles with improved size control [55]. The formation of an intermediate Fe–oleate complex is a critical step in determining the final particle size [56, 57]. Reducing the precursor concentration and the Fe/oleic acid ratio to 1 : 1 [58] and using low boiling temperature solvents such as phenyl ether or benzyl ether [27] together with surfactants such as oleic acid and tri-*n*-octylphosphine oxide (TOPO) with high coordination capacity [59], particles between 4 and 6 nm in size can be obtained (figure 2(*d*)).

Strategies described in the literature for replacing the surfactant include ligand exchange, surface silanization and polymer or micelle coating (table 1). The ligand exchange reaction of oleic acid has been carried out with small molecules with two or more functional groups, one with high coordination capacity (carboxylic, phosphate) to be bonded to the nanoparticle and the other to stabilize the particles in aqueous media, normally by electrostatic repulsion. Examples of these molecules are dimercaptosuccinic acid [60, 61], citric acid [62], phosphonates [63], mercapto-11-undecanoic acid [64] and tetramethylammonium hydroxide [65] (see table 1). The resulting particles are never isolated but form stable aqueous suspensions of aggregates around 100 nm in diameter. Recently, oleic acid has been modified by oxidation of the double bond, by ozonolysis [66] or $KMnO_4$ [67, 68], leading to carboxylic groups freed into the suspension responsible for water stability. In this way the nanoparticle surface is never exposed and the size of the aggregates is significantly reduced to around 30 nm [68].

Oleic acid has also been exchanged for polymers with functional groups with affinity for the nanoparticle surface. This exchange must be carried out in extreme conditions due to the high molecular weight of the polymers [69–71]. Bonding molecules to the magnetic particles that are able to initiate polymerization via free radicals species like 2-bromopropionylester [72, 73] is another strategy that has been tested. Without removing the surfactant, amphiphilic polymers having a hydrophobic and a hydrophilic end like Pluronics [74, 75], cyclodextrines [76] or block polymers [77, 78] have been intercalated between the oleic acid chains. Magnetic nanoparticles coated with oleic acid have been also encapsulated inside micelles forming magnetic colloids of a few hundred nanometres [79]. Although this route is expensive, it results in particles with long *in vivo* blood lifetimes in spite of their hydrodynamic size. This is due to their low recognition by the immune system.

Surface silanization has also been carried out by ligand exchange of oleic acid with 3-amino-propyltriethoxysilane (APS) [80] leaving amine groups free in the solution (or a silsesquioxane (TMA-POSS) [81]). However, the most promising silica coating method is via reverse micelles, hydrolyzing TEOS inside the droplets containing the particles [82–84]. Finally, oleic acid coated particles have been coated with gold to make then hydrophilic by heterogeneous nucleation [85–87] and by using bifunctional bridge molecules [88] (table 1).

Direct synthesis in polar organic solvents in the presence of hydrophilic polymers or molecules has been proposed as a method to produce hydrophilic magnetic nanoparticles

directly. These particles would be ready as prepared for biomedical uses. Magnetite particles of 5 nm were synthesized using $Fe(acac)_3$ as a precursor and 2-pyrrolidone both as coating and solvent [89]. However, this coating is inadequate to screen dipolar interactions requiring the use of mono and dicarboxylic-terminated polyethylenglycol (PEG) [90, 91]. The same precursor in triethylenglycol with $FeCl_3$, polyacrilic acid (PAA) and NaOH as a catalyst was employed to obtain particles of 8 nm which were stable in water [92]. Despite the variety of protocols used to obtain hydrophilic iron oxide nanoparticles by thermal decomposition, the size distribution and the long-term stability in water must be improved. This task currently represents the main challenge associated with this method.

Laser and spray pyrolysis of vapours and aerosols have been reported for the single step preparation of very small magnetic iron oxide particles. In the last five years a significant effort has been devoted to the surface modification of these particles. This modification has been undertaken directly by pyrolysis of hybrid (organo-inorganic) aerosols [93] or in a second step to stabilize them at pH 7 and physiological salinity [94, 95].

2.2. Medium size particles (SPIO) (10–30 nm)

High temperature decomposition of organic precursors allows the production of nanoparticles in a wide size range depending on the precursors, surfactants and solvents. The higher concentration of the iron precursor, higher Fe/oleic acid ratio and the use of high boiling point solvents such as octyl ether or trioctylamine leads to particles with sizes over 10 nm. For example, particles of up to 22 nm are produced by increasing the boiling point of the solvent from 1-hexadecane (b.p. 274 °C) to trioctylamine (b.p. 365 °C) [96].

The influence of the type of surfactant has been shown for particles synthesized from $Fe(CO)_5$ in *o*-dichlorobenzene. The size increases from 6 to 12 nm when using trioctylphosphine oxide (TOP) or dodecylamine as a surfactant instead of oleic acid [59].

The Fe/surfactant ratio also affects the final nanoparticle size. It has been observed that the particle size increases from 7 to 28 nm when increasing the Fe:oleic acid ratio from 1:3 to 1:8 [97]. The opposite trend was observed when a polymer was used instead of oleic acid indicating the important role of the formation of the Fe–oleic acid complex [90]. Also the growth of iron oxide nanoparticles can be controlled in one nanometre steps by 'seeding up' [58].

The particle shape can be modified by changing the nature and concentration of precursors or by the addition of impurities during the synthesis in organic media (figures 3(*a*)–(*c*)). High precursor concentrations lead to the growth of particles kinetically controlled and therefore the particle shape becomes cubic or tetrahedral [98, 99] (figure 3(*c*)). The use of squalene as a solvent and the presence of sodium oleate also induce the formation of cubic particles [100]. However, the presence of dodecylamine in octyl ether when $Fe(CO)_5$ is added produces a mixture of triangular, spherical and diamond shaped particles [59]. A 10-fold increase of dodecylamine in the reaction results in particles with a hexagonal shape. When the precursor is changed to FeO(OH) or $Fe(acac)_3$, the increase of the surfactant:iron ratio produces cubic particles [97]. The formation of hollow structures, like spheres, cubes or frames using molten salts like sodium oleate to produce empty cavities, has also been reported [101] (figure 3(*b*)). Strategies for replacing the surfactant in these systems are the same as those described in the previous section for small particles.

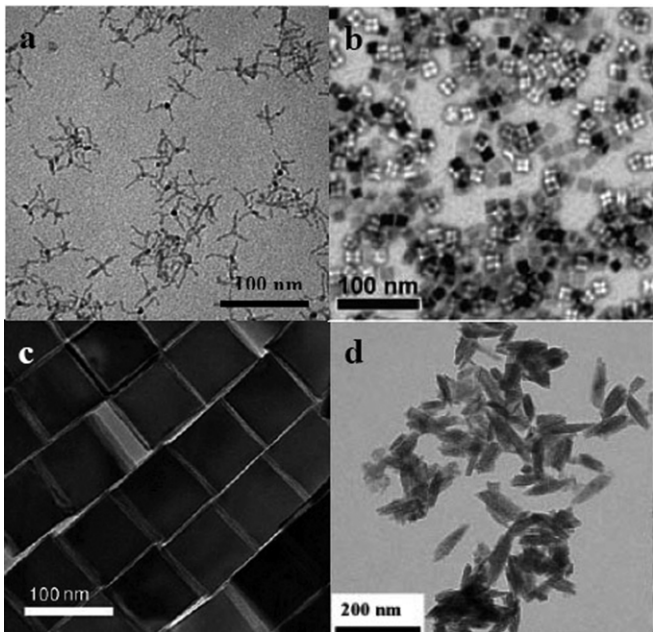

Figure 3. Magnetic iron oxide nanoparticles with different shapes (*a*) tetrapod-shaped magnetic nanocrystals, (*b*) hollow cubes, (*c*) cubes and (*d*) iron oxide nanorods/nanorices [113]. Reprinted with permission: (*a*, *b*, *c*) from [98, 101, 99] copyright 2006, 2007, 2009 American Chemical Society; (*d*) from [113] copyright 2008 Wiley-VCH.

2.3. Large particles (>30 nm)

Particles around the monodomain–multidomain size exhibit larger SAR values in the allowed frequency range of 10^5–10^6 Hz, which makes them useful for hyperthermia treatment [20, 23] (figure 4). This is also the ideal size range for tomography imaging using the non-linear response of the magnetic particles. This technique, called MPI from 'magnetic particle imaging', has shown important advantages in resolution time and sensitivity [102, 103].

By controlling the ratio of ferrous and ferric salts with hexanediamine, the classical coprecipitation method can produce particles from 9 to 40 nm [104]. A more precise particle size control can be achieved by oxidation of an iron (II) salt by a mild oxidant such as KNO_3 in a mixture of water/ethanol [22, 105]. Particles from 25 nm up to 300 nm can be obtained by this method (figure 4(*a*)). After sonification at pH 7, stable colloidal dispersions are produced probably due to the presence of sulfate groups on the particle's surface, which can be further functionalized. Particles around 30 nm can also be obtained using H_2O_2 as an oxidant [106]. These nanoparticles are synthesized in neutral pH conditions, which

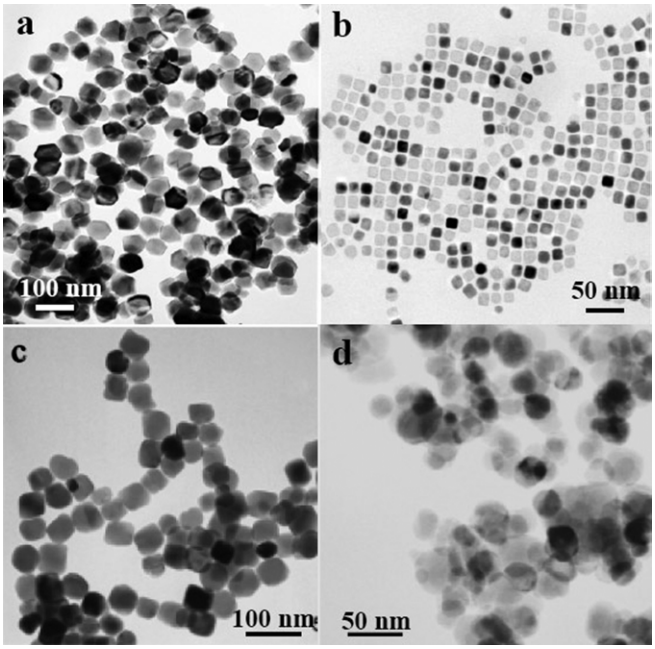

Figure 4. Large magnetite nanoparticles prepared by (*a*) precipitation of Fe(II) salts (70 nm), (*b*) thermal decomposition of oleate precursors in octadecene, (*c*) in the presence of a protein and (*d*) electro-oxidation. Reprinted with permission: (*a*) from [22] copyright 2008 IOP Publishing; (*c*, *d*) from [107, 109] copyright 2007, 2008 Elsevier.

is desirable when a simultaneous coating is required. Partial oxidation of ferrous hydroxide has also been carried out in the presence of a recombinant protein Mms6 *(Magnetospirillum magneticum)* obtaining uniform magnetite nanocrystals of 20–30 nm [107, 108] (figure 4(*c*)). The protein acts as a template for the nucleation and/or acts as a growth regulator by adhering to one crystal face.

Magnetite nanoparticles with sizes between 20 and 30 nm have been obtained by Fe electro-oxidation in the presence of an amine surfactant, which acts both as supporting electrolyte and coating agent [109] (figure 4(*d*)). Their surface can be easily modified by exchange reactions with biomolecules of interest or coated with polymers. Experimental conditions such as current density and oxidation potential determine the particle size distribution.

Finally, by thermal decomposition of organic precursors in organic media, magnetite particles up to 50 nm in diameter can be obtained by decreasing the solvent coordination capacity [57] (figure 4(*b*)).

2.4. Anisotropic particles

While substantial research exists in the field of isometric iron oxide nanoparticles, little effort has been put into the preparation of anisometric materials. Anisometric particles when compared with isometric nanoparticles are likely to behave quite differently both magnetically and when interacting with biological entities and this is expected to influence the relaxation times of neighbouring protons in MRI. In hyperthermia treatment of malignancy, we anticipate substantial changes in relaxation times. In drug/gene delivery/targeting, given that genes are also anisometric, magnetic vectorization is likely to be favoured by shape anisotropy. Also magnetophoresis is favoured in anisometric particles. Regarding the interaction with biological entities the influence of shape has been well established in other materials during recent years. For example, cellular uptake has been found to be dependent on the axial ratio of gold nanoparticles [110]. Nanocylinders have been found to deliver drugs more effectively than nanospheres because they align with the blood flow and persist in circulation considerably longer than spherical particles [111]. On the other hand, experiments with human blood plasma show that blood clotting above rectangular patches only occurred when the ratio of the lengths of the rectangle's sides met a particular criterion [112].

Recently, iron oxide nanorods/nanorices [113] (figure 3(*d*)) and iron oxide nanocapsules with rod-like morphology have been shown to have potential for biomedical applications [114]. Superparamagnetic iron oxide nanorods have been prepared by a modified carbonate route combined with an electrostatically induced self-assembly method, which gives uniformity especially at short axial lengths (below 200 nm) along with a good production rate. The electrostatically induced self-assembly method produces homogeneous coatings with different spatial arrangements. Iron oxide nanocapsules with rod-like morphology have been produced by a thermal/reduction heating process of akaganeite (β-FeOOH) precursors obtained from the forced hydrolysis of $FeCl_3$ precursors. Akaganite precursors obtained by a new ternary water-in-oil/water liquid solvo-thermal method allow a better control of size and shape [115]. These materials have also been used for the production of water-stable porous magnetic nanorods.

3. Other nanoparticulate materials

Other materials have been proposed for biomedical applications such as cobalt and manganese ferrites, or perovskite manganites with Curie temperatures below 60 °C. Metals and metal alloys such as Fe and FePt have also been prepared and protected against oxidation. Most of these materials are toxic but this toxicity is significantly reduced when coated or encapsulated with an appropriate material.

Significant progress has been made in the synthesis of materials such as Co, Ni or Mn ferrites. Monodispersed $CoFe_2O_4$ nanocrystals have been synthesized using normal and reverse micelle microemulsion methods and by combining a non-hydrolytic process and seed-mediated growth [116]. A more general method has been developed for the preparation of monodispersed MFe_2O_4 (M = Fe, Co, Mn) nanoparticles with tunable sizes ranging from 3 to 20 nm through the reaction of metal acetylacetonate and 1,2-hexadecanediol [27, 28, 117]. Water-stable ferrites ($Co_xNi_yFe_{3-x-y}O_4$, $x = 0.6, 0.3, 0.2, 0$; $y = 0, 0.6, 0.7, 0.8$) monodispersed nanoparticles have been prepared by heating mixtures of inorganic salts and sodium dodecylbenzenesulfonate (SDBS) in n-octanol [118]. The size and composition of these materials can be controlled by adjusting the reaction time and the molar ratio of inorganic salts in the initial mixture. Water-dispersible nanoparticles have been obtained by simply washing the as-prepared nanoparticles

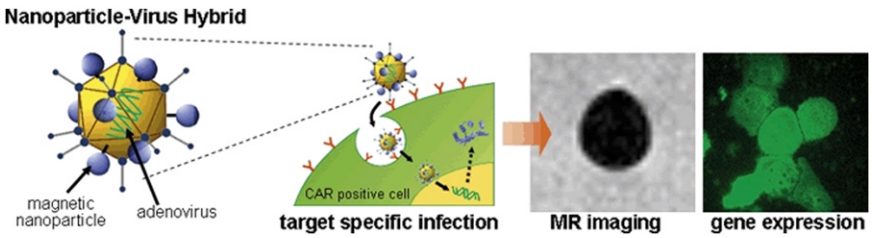

Figure 5. Multicomponent system with multifunctional capabilities. Reprinted with permission from [32] copyright 2007 Wiley-VCH. (This figure is in colour only in the electronic version)

with acetic acid. Recently, the potential of manganese ferrite nanoparticles as high performance nanoprobes for selective imaging has been demonstrated. The particles were synthesized by thermal decomposition of organic precursors and transferred into water using three different approaches: ligand exchange, with amphiphilic tri-block copolymers and the particles embedded into micelles [79]. This material when used as NMR contrast agent, displays stronger contrast than magnetite [70, 119].

Manganese perovskite ($La_{1-x}Sr_xMnO_3$) nanoparticles of crystalline size 20–200 nm have been prepared by annealing a citrate gel precursor in the temperature range 570–900 °C [31, 120]. The smaller particle sizes lead to a gradual decrease in the magnetization and Curie temperature, until the ferromagnetic particles become paramagnetic. Dissipation of an alternating magnetic field causes heating of their aqueous suspensions up to the Curie temperature without external temperature control. Thus, manganites could work as smart mediators for self-controlled heating of tumours where the heat source is switched off when the local temperature of the tumour reaches the desired value.

FePt nanomaterials have also been considered for biomedical applications [30, 121]. The potential toxicity of these materials could be highly valuable for cancer treatments. In fact, Pt compounds have been widely used for chemotherapy for a long time. In addition FePt particles are a promising material due to their magnetic properties. These effects could be further improved by transforming the as-prepared cubic phase into the high anisotropy tetragonal phase. These properties make this material suitable for hyperthermia treatment of tumours [122]. FePt nanoparticles, nanorods and nanowires have been synthesized by thermal decomposition of Pt acetylacetonate and Fe carbonyl in the presence of solvents/surfactants by simply controlling the sequence of addition of the surfactants [123–127].

Passivated iron nanoparticles (10–30 nm) have been synthesized by laser pyrolysis of a mixture of iron pentacarbonyl and ethylene vapours followed by controlled oxidation. The nanoparticles show a well-constructed iron–iron oxide core–shell structure [29]. Pharmaceutical grade magnetic colloidal dispersions prepared from these iron composite particles with dextran showed a contrast improvement of 60% in NMR images from the liver with respect to commercial samples [95]. Nanoparticles of nickel from 5 to 50 nm with lower oxidation tendency, have also been prepared by laser-driven decomposition of $Ni(CO)_x$ [128].

4. Synthesis of multicomponent nanoparticles

Magnetic nanoparticles have been combined with other materials resulting in systems with multifunctional capabilities for sensing, biocatalysis, targeted infection, magnetic resonance imaging, drug delivery, etc [13, 17, 32] (figure 5).

Polymeric matrixes that enhance stability and biocompatibility are frequently used to disperse magnetic nanoparticles [17]. Many of these systems have been developed as magnetic carriers in separation processes including proteins, DNA, cells and bacteria. Coating with linear dextrans was the earliest attempt to stabilize particles in solution with ligand molecules forming hydrophylic brushes around the particle surface [129]. Another successful approach was to create a steric surface barrier of sufficient density with non-ionic copolymers such as poloxamers and poloxamines, or PEG and their derivates [70]. Surface modification with PEG was performed by adsorption, incorporation during the production of nanoparticles, or by covalent attachment to the surface of the particles [130].

Smart polymers are well known for their responsive properties to changing environments. The fabrication of polymer-magnetic hybrid systems with a combination of thermosensitive and magnetic properties has received significant interest for instant dispensability, thermoreversible formation of magnetic fluids and novel magnetoresponsive properties [131]. The energy dissipated when the system cannot follow the oscillating magnetic field causes an increase in temperature in the medium surrounding the thermosensitive polymer. Liposomes, polyelectrolyte multilayer microcapsules or micelles are typical examples of organic matrixes that can be used for encapsulation of magnetic nanoparticles [132–136] (figure 6(*a*)). Their ability to encapsulate water-soluble materials makes them attractive nanodevices for transporting a whole spectrum of molecules, including drugs. The majority of the liposomes are based on phospholipids but also fatty acids and their salts. Derivatives of polymers such as polyoxyethylene and polyglycerol and recently palmitic acid together with cholesterol have been used in the preparation of liposomes with high stability and pH sensitivity [137].

Nanocomposite microcapsules with both gold and magnetite nanoparticles in the shell have been prepared by a layer-by-layer (LbL) procedure using biocompatible polyelectrolytes and nanoparticles [138]. The multifunctionality of microcapsules is demonstrated by their magnetic and optical

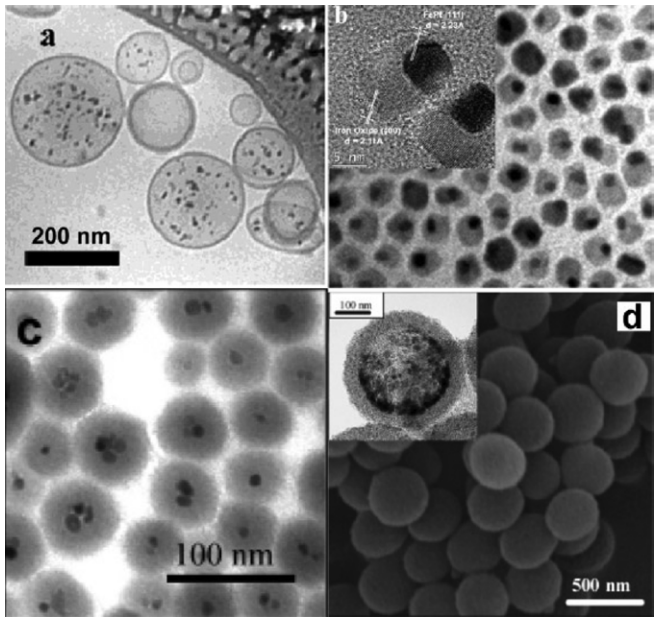

Figure 6. Multicomponent magnetic nanoparticles (*a*) magnetic liposomes, (*b*) dimmers FePt/iron oxide, (*c*) core/shell silica and (*d*) carbon capsules filled with magnetic nanoparticles. Reprinted with permission (*a*, *b*, *c*, *d*) from [136, 157, 149, 165] copyright 2003, 2008, 2008, 2007 American Chemical Society.

responses. Iron oxide nanoparticles embedded in microcapsule shells allow for the control over their positioning by external magnetic fields. Furthermore, the nanocomposite microcapsules can be opened by laser irradiation which is of interest for biomedical applications. The formation of magnetic colloidosomes by assembling Fe_3O_4 nanoparticles of different sizes at the interface of water-in-toluene droplets has also been reported [139]. By gelating the aqueous phase with agarose, robust magnetic NP colloidosomes 100 μm in diameter with controlled permeability have been obtained.

However, organic matrixes still face unsolved problems, such as their limited chemical and mechanic stability, swelling and susceptibility to microbiological contamination [140]. Inorganic coatings do not experience swelling or porosity changes with a change in pH and they are not vulnerable to microbial attacks. They also protect doped molecules (enzymes, drugs, etc) against denaturalization induced by extreme pH and temperature [17]. Of the inorganic matrixes available silica is the most suitable as it ensures the presence of easily functionalizable silanol groups. In addition, the silica surface confers high stability on suspensions of particles at high volume fractions, in a wide range of pH and at high electrolyte concentrations. In the case of metallic particles these coatings also prevent oxidation and degradation of the magnetic properties during and after synthesis [141]. Some commercial magnetic beads are based on silica spheres containing magnetic nanoparticles prepared either by precipitation of magnetite within long, narrow pores in silica nanoparticles [142] or by coating the magnetic particles with a silica layer through a modified aqueous sol–gel route [143] .

Silica coated iron oxide nanoparticles are commercially available as contrast agents for MRI (Lumirem®). The protocol to obtain silica coated nanoparticles involves the synthesis of the magnetic nanoparticles and a series of reactions to grow the coating layer based on the Stöber method [144]. Finally the functionalization of the coating is undertaken [91, 145]. Recently, silica shells have been produced by means of an enzyme [146] or using a mesoporous material (MCM-41) and a solvo-thermal procedure [147]. This shell can be porous to readily release active molecules for drug delivery applications [148].

Core–shell structures can also be synthesized by high temperature decomposition of organic compounds by a ligand exchange between the oleic acid and APS (amino propyltriethoxysilane) [80] or a silsesquioxane [81]. Other routes are also successful for silica coating, like microemulsions [82, 83, 149] (figure 6(*c*)), laser pyrolisis [150] and aerosol pyrolisis [151]. Magnetic mesoporous silica spheres have also been obtained by an aerosol assisted route involving the adsorption and release of several drugs [143]. Silica composites containing fluorescent and magnetic particles have been obtained by mixing particles previously synthesized with tetraethoxysilane. A silica shell trapped several iron oxide and CdTe particles yielding an average total diameter of 50 nm. Similarly embedded silver nanoparticles inside silica shells together with iron oxide nanoparticles and Raman reporter molecules, followed by a fluorophore attachment to the silica, have been demonstrated to constitute a magnetic plasmonic tracer for biological and environmental applications [152].

Magnetic and plasmonic particles are of increasing interest for biomedical applications [13]. Noble-metal nanostructures are beneficial not only because of their relative ease of biofunctionalization, but also for plasmonic biosensing [152, 153]. Unlike quantum dots, these particles do not show optical bistability or blinking, making them competitive with fluorophores for quantifying the number of cell surface markers. Gold seems to be an ideal coating owing to its low reactivity and its surface can be further functionalized with thiol groups. In fact, coating by biocompatible materials like gold seems to be a better way to reduce the cytotoxicity of magnetic nanoparticles such as FePt and manganese perovskites [152]. However, direct coating is very difficult because of the dissimilar nature of the two surfaces. Some progress has been achieved by a partial replacement reaction in a polar aprotic solvent and by a reverse microemulsion method leading to gold coated iron nanoparticles [154]. Sequential decomposition methods and reduction reactions have been used for the synthesis of core–shell heterostructured nanoparticles such as FePt/Au [155] and Co/Au [156] and dimmers FePt/iron oxide [157] (figure 6(*b*)). Au/Pt/iron oxide nanoparticles have also obtained by multistep colloidal chemical routes [158].

Iron oxide–carbon systems are becoming popular due to their high chemical stability. Mirkin's group described an original method for the large scale synthesis of core–shell iron–carbon nanoparticles with diameters smaller than 5 nm from the residues produced in the formation of carbon nanotubes [159]. Magnetic composites of Fe-based nanoparticles encapsulated in carbon/silica (C/SiO_2–Fe) or carbon (C–Fe) matrixes have been prepared by laser-induced pyrolysis of aerosols [150, 160]. Carbon nanocomposites were

formed by amorphous carbon nanoparticles of 50–100 nm diameter in which isolated iron based nanoparticles of 3–10 nm in size are located. The powders were dispersed in aqueous solutions at pH 7 resulting in biocompatible colloidal dispersions with potential high resistance to biodegradation. Structural and magnetic properties and the suitability of aqueous dispersions as contrast agents for MRI were analysed. The results of these characterizations and the NMR relaxivity data are very encouraging for applications of laser pyrolysis products in living tissues [160].

Iron nanoparticles coated with a carbon layer have also been prepared by a modification of the Kratschmere–Huffmann arc-discharge method [161]. The synthesis is performed at temperatures around 3000 °C at which the iron electrode and the silica powders are sublimed and then condensed in colder areas of the system. The particles consisting of a metallic iron core covered with carbon, show no toxic effects on dendritic cells and had no effect in their viability [162]. This suggests that loading dendritic cells with these magnetic nanoparticles properly functionalized could be a promising strategy for improved vectorization in cancer diagnosis and treatment.

Carbon nanotubes have been coated with magnetic nanoparticles by combining the polymer wrapping and the LbL assembly techniques [163]. The particle-coated multiwall carbon nanotubes, MWNTs, are superparamagnetic and can be aligned at room temperature on any substrate by deposition from an aqueous solution in an external field. Recently, carbon capsules have been filled with a significant amount of magnetic nanoparticles [164, 165] (figure 6(*d*)). The methodology involves the impregnation of carbon capsules with a solution of $Fe(NO_3)_3$ dissolved in ethanol, which is dried and exposed to propionic acid vapours. Finally, the composite is heated to develop superparamagnetic behaviour. A similar methodology has been used to prepare magnetic mesoporous hollow nanocomposites made of ferrite nanoparticles incorporated into the mesoporous shell of carbon capsules [166]. Though progress has been made in the last few years to implement functionality to carbon matrixes, it seems clear that the replacement of silica or gold by these matrixes requires significant advances. The addition of functionalizable polymers to the carbon matrixes, i.e. the formation of hybrid matrixes, is a reasonable route to give new functionalities to the carbon matrixes. For example, quaternized polycholoromethylstyrene with anion exchange sites has recently been inserted in the pores of monodispersed, spherical carbon superparamagnetic composites [167]. The presence of positively charged active surface sites allows for the adsorption of negatively charged biocompounds.

5. Final remarks

Following our previous review, the search for new and improved synthetic routes is in continuous development [2]. The objectives are to produce reliable magnetic nanoparticles with the correct characteristics of improved tissular diffusion, colloidal stability and biocompatibility. The future of magnetic nanoparticles in this field lies in the search for synthetic routes able to produce hybrid inorganic/organic systems with controlled composition. These systems can be synthesized by growing one material on top of another leading to core/shell systems or heterodimers. These particles have to be linked with biological molecules or packed in a container such as hollow capsules, liposomes or a virus [168]. Alternatively, the control of morphology and size could be achieved by using nanocasting techniques. Other routes that depart from the conventional are also being followed. For example, while substantial research exists in the synthesis of equiaxial magnetic nanoparticles for biomedical applications, little effort has been put into the preparation of anisometric particles. Substantial research is also being devoted to the synthesis of magnetic nanoparticles below the superparamagnetic limit at room temperature. However, little effort has been made in the preparation of particles around the monodomain–multidomain limit. These particles exhibit larger SAR values at the allowed frequency range which makes them useful for hyperthermia treatments. These particles are also in the ideal size range for tomography imaging using the non-linear response of magnetic particles with important advantages in resolution time and sensitivity [102]. Another route in which substantial research is expected to take place in the next five years is the replacement of iron oxide by other magnetic materials that could provide improved magnetic response for a particular application [169]. The major issues remain biocompatibility and functionalization. At this time progress is being made in clinical testing for future biomedical applications of magnetic nanoparticles.

Acknowledgments

The authors are grateful for the support of the Comunidad de Madrid under the NANOMAGNET S-0505/MAT/0194 project, the Spanish Ministerio de Ciencia e Innovación for MAT2008-01489 and MAT2008-03224 and to the EU for LSHB-CT-2006-037639.

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