CHAPTER 17

Organic Layered Magnetic Nanoparticles

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CONTENTS

1. INTRODUCTION

Nanoparticles have a wide range of uses in various applications and their research has been accelerating with the development of nanoscience and nanotechnology in recent decades [1]. Above all, magnetic nanoparticles are important nanomaterials for industrial, environmental, biological, and medical fields. In the medical field, magnetic nanoparticles have been investigated mainly with respect to magnetic separation, drug carrier, magnetic resonance imaging, and magnetic hyperthermia [2–5]. Magnetic nanoparticles require different shapes and sizes depending on their applications. For example, nanoparticles several tens of nanometers in diameter are required for magnetic hyperthermia (cancer therapy by heating of organs and tissues) because the heating rate of magnetic particles with alternating magnetic fields is dependent on their diameter. For magnetic separation, too, small particles less than 10 nm are not convenient because of the difficulty of collecting them by magnetic field. The surface properties of the magnetic nanoparticles are also important for their proper application; therefore many surface modification techniques for organic and inorganic materials have been developed. The surface covering materials influence the dispersion state in a medium and interface with external environments. Furthermore, functional groups on the surface can be utilized to load a substance such as a drug and to perform additional modification of biomolecules such as protein. Surface modifications then definitely characterize the magnetic nanoparticles and are important techniques for increasing their applications.

The purpose of this paper is to provide a broad review of surface-modified magnetic nanoparticles with organic components. In this review, organic-layered magnetic nanoparticles are classified into six categories (Fig. 1): surfactant coating (including ferrofluid), magnetosome (magnetoliposome), polymer coating, polymer composite, molecular grafting, and polymer grafting. Each method has advantages and disadvantages in its process of preparation and utilization, therefore the method and the material for surface modification should be adapted to the purpose of application. Silica [6–9] or other inorganic material [10–12] coated magnetic nanoparticles are also important, but they are not described in this review.

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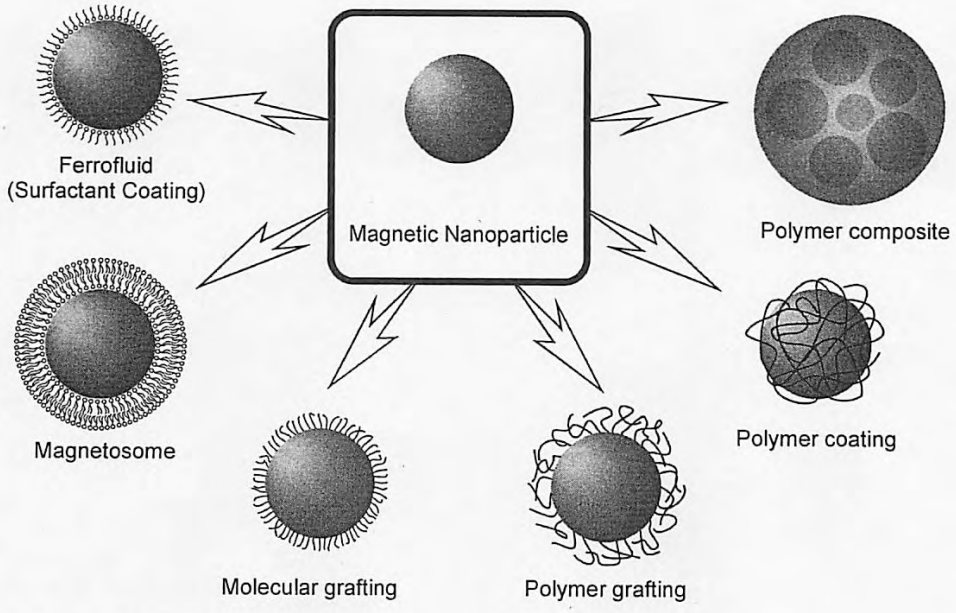


Figure 1. Classification of organic-layered magnetic nanoparticles.

2. APPLICATIONS

Magnetic powders have been used for magnetic recording media such as VCR tapes and floppy disks. However, these media are recently being replaced with optical memory storage because of their limited capacity. More recently, the use of the periodic arrays of magnetic nanoparticles for the development of high-density memory storage has been investigated. Monodispersion with narrow size distribution is required for these nanoparticles and their self-assembling phenomenon is used to make the arrays [13]. A ferrofluid, which consists of surfactant-coated magnetic nanoparticles in aqueous or organic solvents, is useful for seals, bearings, and speakers [14, 15]. The magnetic ferrofluid [16] forms stable colloidal suspension with black or dark brown color and is sensitive to external magnetic fields. Once magnetic field is applied to the ferrofluid, the particles array along the magnetic field, but relax again after the magnetic field is removed. Ferrofluids are used in biomedical applications through additional surface modifications with various biologically active molecules such as antibodies and lectins [17]. Biomolecule-modified magnetic nanoparticles will be described later.

Magnetic particles have been widely used in medical applications which can be categorized into *in vivo* and *in vitro* as shown in Figure 2. *In vivo* applications include hyperthermia, drug delivery, and magnetic resonance imaging, and *in vitro* applications include magnetic separation and magnetic marker for immunoassay.

Hyperthermia [18, 19] is treatment for cancer by heating of organs and tissues to the temperature 42–43°C. The recent focus of clinical research in thermotherapy systems is optimization of temperature and targeting of tumor volume. Magnetic hyperthermia is one of the most promising modern clinical techniques because only targeted cancer cells are heated by localized magnetic nanoparticles with external magnetic fields. The heating of metal oxide magnetic nanoparticles occurs under external alternating magnetic fields and is based on loss processes during the reorientation of the magnetization [20]. A drug delivery system is used to carry the medicines or antibodies to specific sites (drug targeting) and releases a proper dose for the diseased part (controlled release) [21, 22]. The first successes of magnetic drug targeting were demonstrated by Widder et al. in the 1970s [23]. Magnetic microspheres containing anticancer drugs were localized and accumulated by external magnetic field. Magnetic resonance imaging (MRI) [24] is a powerful diagnostic tool. It is well-known that gadolinium ions and superparamagnetic iron oxide (SPIO) are contrast agents

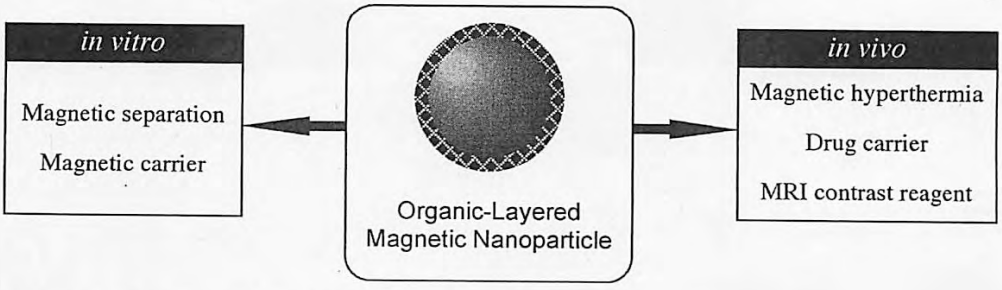


Figure 2. Medical application filed of organic-layered magnetic nanoparticles.

because they are effective for the T_1 and T_2 relaxation time of ^1H, respectively. Water is present in almost all tissues and organs and the relaxation time depends on the surrounding environment of water. High contrast images will be observed where there are high concentrations of contrast agents.

Separation and purification are very important in medical and biochemical fields [25–28]. Precise and quick methods for this have been developed by many researchers. Magnetic separation techniques for purification and fractionation of biological molecules are already established and are widely used in clinical and experimental fields. Many kinds of surface-modified magnetic particles are commercially available, in which specific ligand molecules are bound onto the surface of magnetic particles. Cell separations have been realized by using specific attachment of magnetizable particles. An automatic microscopic analysis for counting of labeled and unlabeled cells was investigated by Winoto-Morbach and Tchikov [29]. Detailed applications of magnetic nanoparticles have been reviewed in several articles [2–5, 14, 15, 30].

3. ORGANIC LAYERED MAGNETIC NANOPARTICLES

3.1. Surfactant-Covered Magnetic Nanoparticles (Including Ferrofluid)

Ferrofluids (magnetic fluid) were invented in the 1960s [31] and their unique magnetic and fluidic properties have been investigated [32]. Magnetic fluids are colloidal solutions of magnetic nanoparticles in either polar (aqueous) or nonpolar (organic) liquids as a carrier medium. In organic solvents, the nanoparticles with about 10 nm in diameter are stabilized with a surfactant such as oleic acid [33, 34] to prevent coagulation. On the other hand, magnetic nanoparticles in water can be stabilized with a surfactant [35, 36], aspartic and glutamic acid [37], citrate [38], and peptides [39], Magnetic fluids with many solvents are commercially available and are used in industrial, environmental, and medical fields. The first example of a ferrofluid was prepared by grinding micrometer-sized magnetic particles in a ball mill for several weeks, then transferring nanometer-sized particles into kerosene, and subsequently stabilizing them with oleic acid [31]. In the last 2 decades, many other preparation procedures have been developed. The controlling of particle size and stability in media are key technologies for preparation of magnetic fluids. The most successful method is the coprecipitation of ferrous/ferric ions in reversed micelle, which is formed in water-in-oil microemulsions. This method provides narrow size distribution with spherical particle shape and stability against agglomerate nature of magnetic nanoparticles.

Sun et al. reported [40] the synthesis of highly crystalline and monodisperse Fe_3O_4 nanoparticles without any size-selection process. Figure 3 shows a typical TEM image of magnetic nanoparticles with 16 nm in diameter. These uniform magnetite nanoparticles were obtained by high-temperature (265°C) reaction of iron(III) acetylacetonate in phenyl ether in the presence of alcohol, oleic acid, and oleylamine. High-resolution TEM (HRTEM) and X-ray diffraction (XRD) were used to determine the crystalline structure. It is well-known that Fe_3O_4 is oxidized to γ-Fe_2O_3 and α-Fe_2O_3 by heating under O_2 [41]. The obtained Fe_3O_4 nanoparticles can be oxidized to γ-Fe_2O_3 at 250°C under O_2 atmosphere and further transformation into

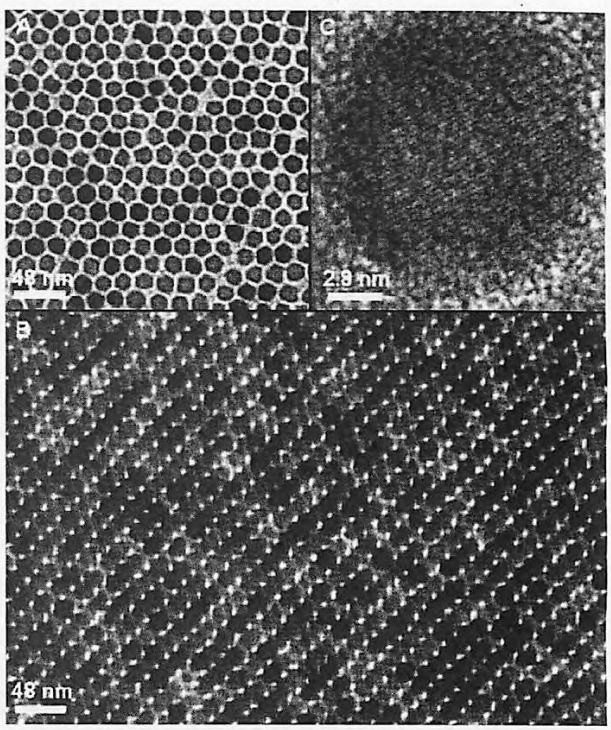


Figure 3. TEM bright field image of 16-nm Fe_3O_4 nanoparticles deposited from their dodecane dispersion on amorphous carbon surface and dried at 60°C for 30 min: (A) a monolayer assembly; (B) a multilayer assembly; (C) high-resolution TEM image of a single Fe_3O_4 nanoparticle. The images were acquired from a Philips EM 430 at 300 kV. Reprinted with permission from [40], S. Sun and H. Zeng, *J. Am. Chem. Soc.* 124, 8204 (2002). © 2002, American Chemical Society.

α-Fe_2O_3 can be achieved at a higher temperature (500°C) [42]. Monodispersed MFe_2O_4 (M = Co, Mn) is obtained by a similar synthetic procedure [42]. Aqueous ferrofluids can be synthesized by the chemical coprecipitation of Fe(II) and Fe(III) salts in the presence of fatty acids. In aqueous media, the fatty acids form bilayer structures on the surface of nanoparticles and stabilize aqueous ferrofluids [36]. Various dispersants and dispersion media are described in patents and many types of ferrofluids are commercially available. These magnetic ferrofluids are widely used in engineering fields [43] such as seals, bearing, and speakers.

3.2. Magnetosome

Various organisms living on the earth are able to synthesize magnetic nanoparticles. Magnetotactic bacteria [44], which were discovered in 1975, form a heterogeneous group of Gram-negative prokaryotes which have an ability to synthesize fine intracellular membrane-bound ferromagnetic crystalline particles under ambient conditions. Until now, various types of magnetic bacteria have been discovered from sediment in diverse environments. The bacterial magnetic nanoparticles are usually called "magnetosome" because the magnetic nanoparticles are encapsulated into liposome (vesicle) [45, 46]. A large amount of iron must be accumulated in the cell for production of magnetic nanoparticles. Matsunaga et al. reported on the magnetic bacterium *Magnetospirillum* sp. AMB-1 [47], in which approximately 170-fold of iron was accumulated as compared with the

enterobe *Escherichia coli* DH5α. The thickness of the organic layer, constructed of bilayer membranes, was observed by TEM to be 2–4 nm. Phospholipids comprised 58% of the total lipid, and phosphatidyl ethanolamine accounted for 50% of the total phospholipids present. Figure 4 shows a typical TEM image of bacterial magnetosomes isolated from *M. gryphiswaldense*. The magnetite crystals are 40 nm in diameter and are surrounded by bilayer membranes [48]. Many magnetotactic bacteria with various morphologies have been discovered in aquatic environments [49]. This is a sort of biomineralization and the particles were made up of magnetite (Fe_3O_4) or greigite (Fe_3S_4) and covered with intercellular phospholipid membranes. Figure 5 shows a typical TEM image of magnetosome dimyristoylphosphatidylglycerol (DMPG)-coated magnetites [50] which are prepared by incubation and dialysis of lauric acid-coated aqueous magnetic fluid with preformed vesicles from DMPG.

3.3. Polymer Coating

In the early 1980s, Molday described the preparation of colloidal size ferromagnetic iron oxide coated with dextran [51, 52], which is a water-soluble polysaccharide. In this case, magnetic nanoparticles are obtained by the chemical coprecipitation of Fe(III) and Fe(II) ions in alkaline medium, following surface coating with dextran. The dextran is apparently adsorbed to the surface of the iron oxide to provide a steric stabilizing layer. The typical preparation method is as follows [51, 53–56]: A solution of a mixture of Fe(III) and Fe(II) ions in an equal molar ratio (0.5:0.5 M) is prepared from $FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot 4H_2O$ in deaerated distilled water. An equal volume of a solution of 20% (w/v) dextran (40 kDa) in distilled water is then mixed with the iron mixture solution and kept at a constant temperature of 60°C for 15 min. An approximately equal volume of 1 M aqueous ammonia solution is then added dropwise to the iron–polymer mixture, which is heated at 60°C for a further 15 min, with vigorous stirring. The suspension is finally dialyzed against distilled water to approximately pH 6.5 and centrifuged to remove the solid material. The clear supernatant of each preparation is then collected.

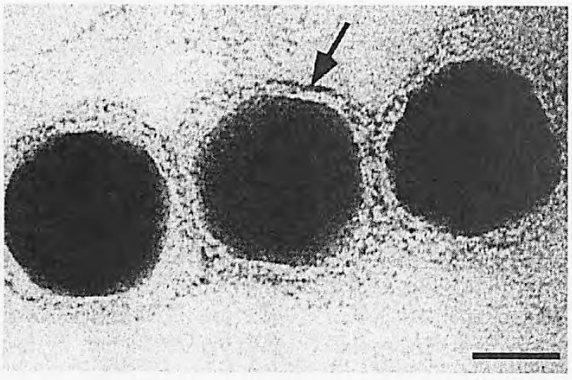


Figure 4. Magnetosome particles isolated from *M. gryphiswal*-dense. The magnetite crystals are typically 42 nm in diameter and are surrounded by the magnetosome membrane (arrow) (bar equivalent to 25 nm). Reprinted with permission from [48], D. Schüler and R. B. Frankel, *Appl. Microbiol. Biotechnol.* 52, 464 (1999). © 1999, Springer Verlag.

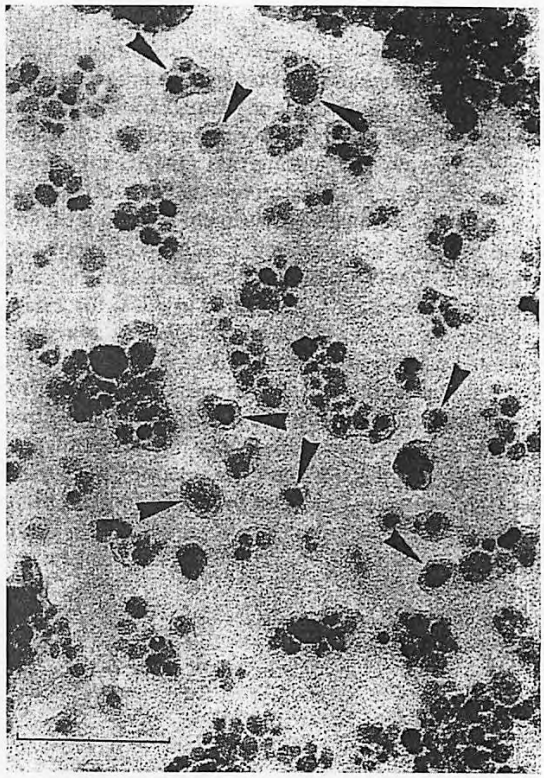


Figure 5. TEM image of a representative sample of Fe_3O_4-DMPG (dimyristoylphosphatidylglycerol) colloids, negatively stained with 2% solution of phosphotungstate. The arrows clearly indicate the typical phospholipid bilayer architecture. Scale bar: 100 nm. Reprinted with permission from [50], M. de Cuyper and M. Joniau, *Eur. Biophys. J.* 15, 311 (1988). © 1988, Springer Verlag.

Surface modification of magnetic nanoparticles using poly(vinyl alcohol) [53], poly(vinyl chloride), [57] poly(methyl methacrylate) [58], poly(methyl acrylate) [59], and poly(ethylene oxide) [60] as a synthetic polymer and starch [61, 62] and carboxymethyldextran [63] as a natural polymer has been reported. Preparation method of these polymer-coated magnetic nanoparticles can be classified into

(a) mixing of magnetic nanoparticles and polymer,
(b) coprecipitation of metal oxide in the presence of polymer, and
(c) polymerization of monomers in the presence of magnetic nanoparticles.

Many functional groups such as –OH, –COOH, $-NH_2$, and $-PO_3H_2$ can be introduced by copolymerization with functional monomers [58, 60] or additional modification of the polymer side chain. [59]. Figure 6 shows TEM images of dextran-coated and poly(vinyl alcohol)-coated magnetic nanoparticles [53]. Electron diffraction patterns from the samples indicated the presence of magnetite (Fe_3O_4) and/or maghemite (γ-Fe_2O_3). Gas phase reaction was reported to produce polymer-coated nanoparticles. The monomer condenses on the surface of the magnetic nanoparticles and polymerizes under the influence of the heat and UV radiation emitted by plasma [64].

Since a polymer was physisorbed on the surface of magnetic nanoparticles, it is detachable with environmental changes

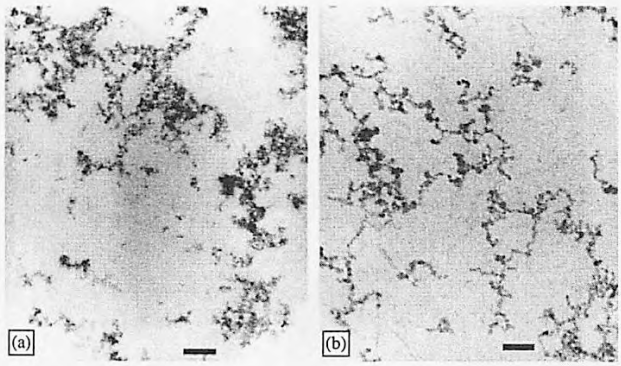


Figure 6. TEM images of (a) dextran-coated Fe_3O_4 and (b) poly(vinyl alcohol)-coated Fe_3O_4. Scale bar = 50 nm. Reprinted with permission from [53], H. Pardoe et al., *J. Magn. Magn. Mater.* 225, 41 (2001). © 2001, Elsevier B. V.

such as pH and temperature. In the adsorption system, the adsorption behavior of polymers is dominated by competitive interactions among the polymers, the magnetic particles, and the solvents. Carbonyl groups help to avoid polymer detachment from the surface because they can form complexes with iron on the surface of iron oxide. The block copolymers are useful to prepare water dispersible magnetic nanoparticles [65]. The block copolymer with branched poly(ethylene imine) (PEI) and poly(ethylene oxide)-*b*-poly(glutamic acid) (PEO-PGA) was prepared for stabilization with two layer-by-layer decomposition steps. The PEI was used for the first layer and the PEO-PGA was used for second layer. Obtained polymer-coated magnetic nanoparticles were dispersed in aqueous solution.

3.4. Polymer Composite

Polymer–magnetic nanoparticle composite is a hybrid of polymers and magnetic nanoparticles and differs from polymer coating in which the surrounding polymer forms molecular level thin layers and the particles are independent of each other. Two types of polymer–magnetic nanoparticle composites have been reported: (a) magnetic nanoparticle-incorporated polymer particle and (b) magnetic particle-surrounded polymer particle. The magnetite–polystyrene nanoparticles with a high magnetite content were obtained by miniemulsion processes [66]. The average diameter of magnetite–polystyrene composites was 60 nm and up to 40% magnetite could be encapsulated in the polymer particles (Fig. 7). Kondo et al. reported thermosensitive magnetite–polymer composites. [67, 68]. The thermosensitivity of magnetic incorporated poly(styrene/*N*-isopropylacrylamide/methyl acrylic acid) copolymer particles was evaluated by minimum NaCl concentration for flocculation concentration of these composites (critical flocculation concentration, CFC) [67]. These polymer composite particles are useful for purification and immunoassay because they can be easily collected by external magnetic fields after flocculation. Poly(methyl methacrylate) composites [85] and poly(styrene/divinylbenzene/methyl acrylic acid) composites [70] can be prepared by the emulsion polymerization method. Poly(styrene/2-hydroxyethyl methacrylate) composites [71] and poly(*N*-isopropylacrylamide) (poly(NIPAM)) composites were prepared by dispersion polymerization method.

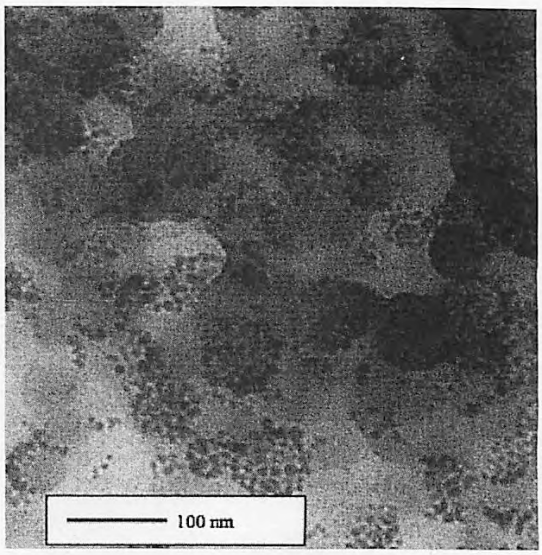


Figure 7. TEM image of magnetite polystyrene particles. Reprinted with permission from [66], L. P. Ramirez and K. Landfester, *Macromol. Chem. Phys.* 204, 22 (2003). © 2003, John Wiley & Sons, Inc.

Chitosan composites [72] and poly(L-lactic acid) composites [73] were prepared by adding magnetic nanoparticles to the polymer suspension in the preparation of microspheres. Alginate composite can be obtained by oxidation of ferrous chloride tetrahydrate in the alginate matrices [74]. Sauzedde et al. reported on ionic iron oxide adsorbed on cationic polymer latexes such as poly(NIPAM) [75]. The encapsulation of magnetic particles on the polymer particle is carried out by seed precipitation polymerization [76]. Xulu et al. reported that magnetic particle composed poly(NIPAM) gel beads with 0.5–4 mm diameter form a straight chainlike structure in a uniform magnetic field, whereas in a nonhomogeneous field the beads aggregate due to the magnetophoretic force directed to the highest field intensity [77]. Polymer composite magnetic particles covered with a polyglycidyl methacrylate (GMA) surface were prepared by a two-step polymerization procedure [78]. The magnetic nanoparticles were coated with a surfactant to make hydrophobic, which were dispersed in an oil-based, mixed solution of styrene monomer, and GMA monomer. The oil-based monomer solution was poured into an aqueous solution containing as initiator and polymerized at 70°C. The obtained magnetic nanoparticles containing-polymer composites were coated with poly-GMA by seeded polymerization method. The poly-GMA has epoxy groups, onto which bioactive molecules such as protein can be fixed. Kim et al. used amphiphilic block copolymer to prepare polymer composites [79]. The poly(styrene$_{250}$-*block*-acrylic acid$_{13}$) was synthesized via atom-transfer radical polymerization for this purpose. The block copolymer was first dissolved in DMF, a good solvent for both the hydrophobic (polystyrene) and hydrophilic (poly(acrylic acid)) blocks. A solution of surfactant-coated nanoparticles in THF was then combined with the DMF solution of copolymer in a defined ratio, and water was added gradually to this mixture to desolvate both the particles and the hydrophobic polymer block simultaneously. The poly(acrylic acid) block which exists on the surface of particles was fixed permanently with 2,2′-(ethylenedioxy)bis(ethylamine) cross-linker and

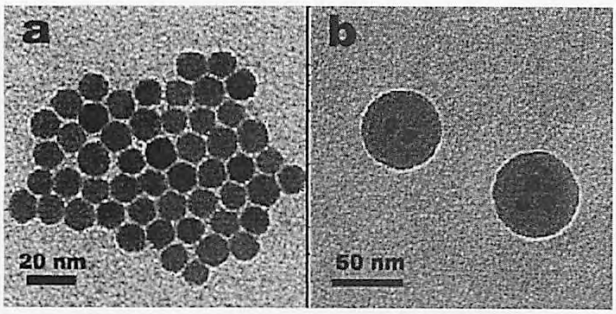


Figure 8. TEM images of 10.9-nm γ-Fe_2O_3 nanoparticles (a) before and (b) after encapsulation within PS_{250}-*b*-PAA_{13}. Reprinted with permission from [79], B.-S. Kim et al., *Nano Lett.* 5, 1987 (2005). © 2005, American Chemical Society.

N-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide methiodide activator. Typical TEM images of γ-Fe_2O_3 nanoparticles before and after encapsulation within block copolymer are shown in Figure 8.

3.5. Small Molecule Grafting

Silane coupling agents (in Fig. 9) are useful to modify the surface of magnetic nanoparticles of metal oxides. The silanation method was first developed by Whitehead et al. in 1985 [80]. After that, several reports have described the advantages of direct silanation [81–87] for the modification of the particle surfaces because of the high density of surface functional groups and simple operation. Xu et al. reported the direct silanation of γ-Fe_2O_3 with 3-aminopropyltriethoxysilane [81]. Detailed studies by using XPS, diffuse reflectance FT-IR, and ζ-potential measurements revealed that the ethoxysilyl groups condensed each other and also with OH groups on the surface of iron oxide. Figure 10 shows a TEM image of amino-silane modified superparamagnetic silica particles by Liu et al. [85].

It was reported that thiol derivatives can be used for self-assembly coatings on the amorphous iron oxide [88–91] and FePt [92] magnetic nanoparticles. Numerous reports on the synthesis and characterization of self-assembly monolayer (SAM) coatings of flat surfaces of metal and metal oxide have been published [93, 13] in the last decade.

Small biocompatible organic molecules were tested as coating reagents [94]. Functional groups, phosphonates, phosphates, sulfonates, and carboxylic acids were chosen because all groups were known to have adsorption properties on metallic surfaces. Among the tested molecules, the macroscopic stability (flocculates) at a neutral pH follows this order: diphosphonic esters ≈ sulfonates ≈ phosphates carboxylates < diphosphates ≈ diphosphonates < disulfonates ≈ bisphosphonates. A simple but highly effective 2,3-dimercaptosuccinic acid (DMSA) was used to modify the surface of magnetic nanoparticles to hydrophilic (as shown in Fig. 11) [95, 96]. The DMSA first forms a stable coating through its carboxylic chelate bonding and further stabilization of the ligand shells is attained through intermolecular disulfide cross-linkages between the ligands under ambient conditions. The remaining free thiol groups of the DMSA ligand are used for the attachment of target-specific antibodies. The Herceptin was immobilized on the DMSA-grafted magnetic nanoparticles for *in vivo* magnetic resonance detection of cancer cells [96].

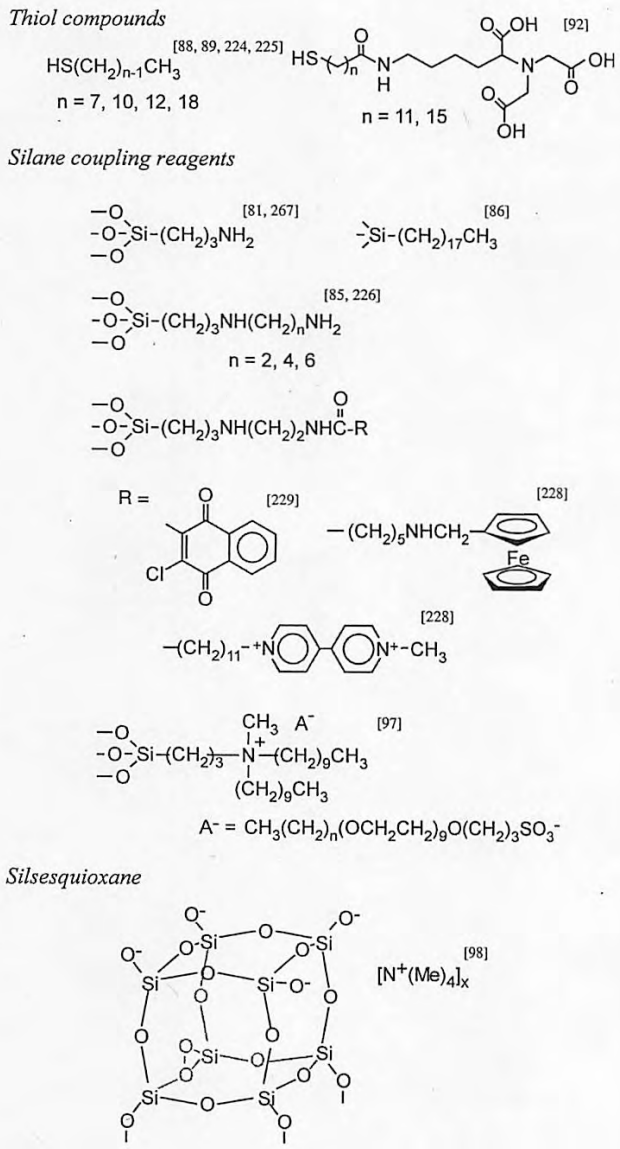


Figure 9. Chemical structures of small molecular for surface coating of magnetic nanoparticles.

Surface functionalized magnetic nanoparticles with unique small molecules have been reported. Magnetic nanoparticles were modified by condensation of $(CH_3O)_3 \cdot Si(CH_2)_3N^+(CH_3)(C_{10}H_{21})_2Cl^-$ with surface hydroxyl groups. The chloride counterions present can be readily exchanged with other anions, the sulfonate anion $R(OCH_2CH_2)_7O(CH_2)_3SO_3^-$ (R = alkyl chain) to obtain the corresponding nanosalts [97]. While the chloride nanosalt is a solid and does not melt up to 150 °C, the sulfonate analog is a viscous liquid at room temperature and flows easily at 40°C. The cubic silsesquioxane-grafted magnetic nanoparticles have been reported by Frankamp et al. [98]. First, iron oxide nanoparticles were prepared by thermal decomposition of the iron cupferron precursor in the presence of octylamine and trioctylamine [99]. The obtained nanoparticles were soluble in organic solvents such as toluene and hexane. The organic solution was stirred with an aqueous anionic octa(tetramethylammonium)-polyhedral oligometic

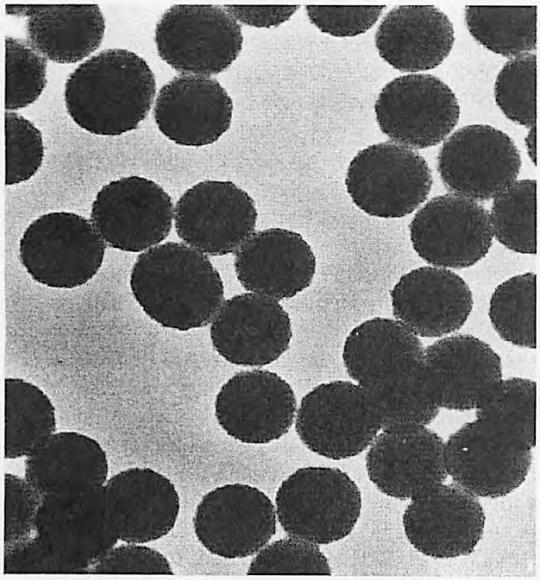


Figure 10. TEM image of *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEAPS)-treated magnetic silica nanospheres. Reprinted with permission from [85], X. Liu et al., *J. Magn. Magn. Mater.* 270, 1 (2004). © 2004, Elsevier B. V.

silsesquioxane (TMA-POSS) solution to generate water-soluble magnetic nanoparticles. The TMA-POSS treated magnetic nanoparticles transferred completely to the aqueous phase from the organic phase. The aqueous dispersions showed excellent stability in biologically relevant pH ranges and salt concentrations.

3.6. Polymer Grafting (Graft-to and Graft-from)

Polymer-grafted magnetic nanoparticles, in which the polymer is covalently bonded on the particle surface, have advantages compared with polymer-coated particles and/or polymer composites. First, the particle size shows little effect on polymer immobilization. Polymer chain immobilized on magnetic particles remains flexible. Also, polymer-grafted magnetic particles can be used in good solvents. Finally, the method is applicable to many kinds of polymers. Preparations for polymer grafting can be divided into two methods, the so-called

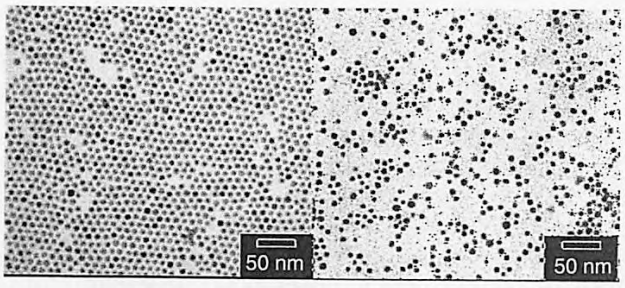


Figure 11. TEM images of 9-nm iron oxide nanocrystals. (left) As-synthesized nanocrystals, (right) 2,3-dimercaptosuccinic acid (DMSA) coated nanocrystals. Reprinted with permission from [96], Y.-M. Huh et al., *J. Am. Chem. Soc.* 127, 12387 (2005). © 2005, American Chemical Society.

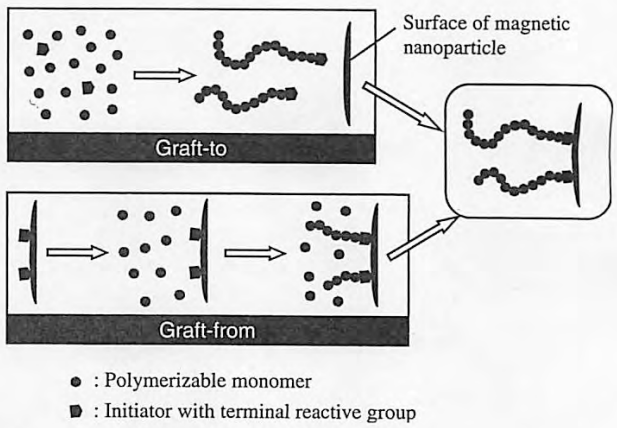


Figure 12. Schematic illustration of graft-to and graft-from methods.

"graft-from" and "graft-to" methods (schematically illustrated in Fig. 12). In the "graft-from" method, initiator groups for polymerization were bound on the surface of magnetic nanoparticles and the polymerizable monomers were then polymerized from the surface of particles [100–103]. Shimomura et al. reported that 3-mercaptopropyltrimethoxysilane-grafted nanoparticles can be used for redox polymerization initiated with ceric ion [104]. Matsuo et al. reported on poly(styrene) [105] and poly(3-vinylpyridine)-grafted [106] magnetite nanoparticles by nitroxide-mediated polymerization method. However, the nitroxide-mediated polymerization method is limited for several polymers and co-polymers [107, 108]. Living polymerization has also been used as a surface initiated "graft-from" method which allows dense polymer-layered substrate to be prepared successfully. Vestal et al. reported atom transfer radical polymerization (ATRP) of styrene initiated with CuCl and 4,4′-dinonyl-2,2′-dipyridyl [109]. Marutani et al. reported copper-mediated atomic

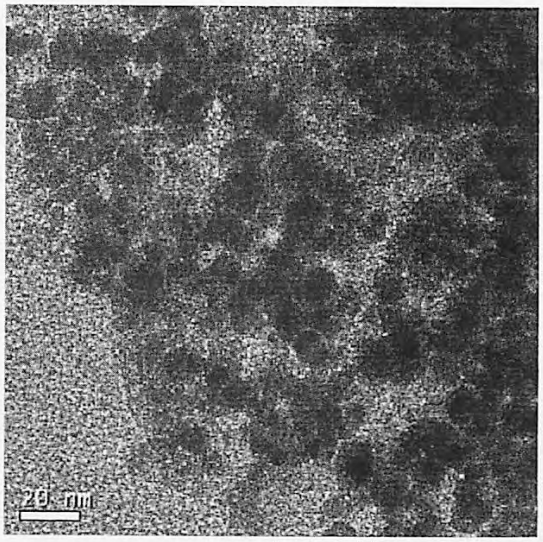
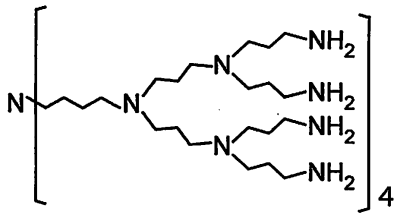
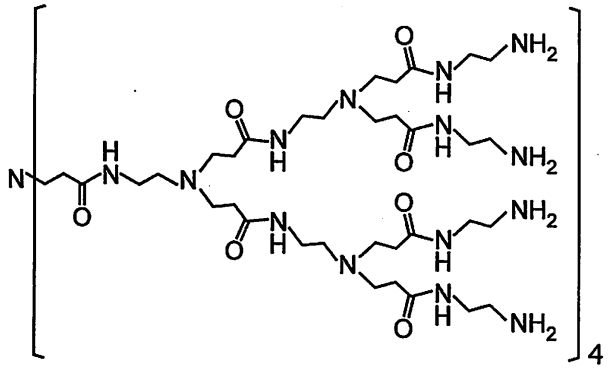


Figure 13. TEM image of Fe_3O_4/poly(ε-caprolactone) core–shell particles cast from $CHCl_3$ dispersion. Reprinted with permission from [112], A. M. Schmidt, *Macromol. Rapid Commun.* 26, 93 (2005). © 2005, John Wiley & Sons, Inc.

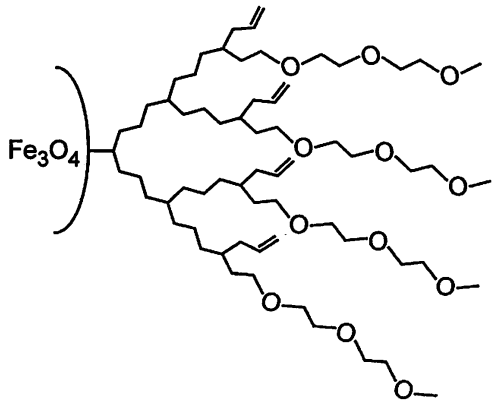
transfer radical polymerization (ATRP) of methyl methacrylate with 2-(4-chlorosulfonylphenyl) ethyltrichlorosilane-grafted magnetite nanoparticles [110]. Poly(poly(ethylene glycol) monomethacrylate), P(PEGMA)-grafted magnetic nanoparticles, was obtained by similar surface-initiated atom transfer radical polymerization [111]. The responses of macrophage cells to pristine and P(PEGMA)-immobilized nanoparticles were compared. The results showed that the macrophage cells are very effective in cleaning up the pristine magnetic nanoparticles. With the P(PEGMA)-immobilized nanoparticles, the amount of nanoparticles internalized into the cells in greatly reduced. Surface-initiated ring-opening polymerization of ε-caprolactone was demonstrated by Schmidt [112]. The



DAB-Am dendrimer[123]



PAMAM dendrimer[124]



Poly(ethylene glycol)-terminated dendron[231]

Figure 14. Chemical structures of dendrimers for surface coating of magnetic nanoparticles.

magnetic nanoparticles which were prepared by common precipitation method were surface-functionalized *in situ* by the addition of glycolic acid and the application of sonication. After removing free glycolic acid by NH_4OH aqueous solution, the particle suspension was added to distilled ε-caprolactone. Tin(II) 2-ethylhexanoate was then added as a catalyst and the reaction mixture was stirred at 130°C for 5 h to obtain poly(ε-caprolactone)-grafted magnetic nanoparticles. The magnetic core–shell structure was observed by TEM (Fig. 13).

Takafuji et al. reported on poly(vinylimidazole) [113] and poly(4-vinylpyridine)–grafted [114] magnetic nanoparticles by the "graft-to" method. A polymer with a terminal reactive group was obtained by the telomerization method of polymerizable monomers with 3-mercaptopropyletrimethoxysilane. The surface charge of poly(4-vinylpyridine) can be controlled by the quaternization of pyridinium groups with methyl iodide. The telomerization method using thiol groups initiated with radical initiator is applicable for most vinyl and acryl monomers [115–117]. Trimethoxysilane-poly(ethylene glycole) (PEG) [118–121] was prepared for cell targeting and cell uptake studies. Terminal reactive PEG can be obtained by coupling reaction of carboxyl-PEG with amino alkoxysilane [120, 121] or purchased from Shearwater (Ala, USA). The chitosan-grafted [122] magnetic nanoparticles were also prepared by modified "graft-to" methods. Dendrimer is known as a carrier for small guest molecules such as oligonucleotides and drugs. The dendrimer (shown in Fig. 14) was grafted onto the surface-aminated magnetic nanoparticles to move the complex of guest molecule and dendrimer [123, 124]. The radionuclide separation for europium and americium was realized by chelator molecule-bound starburst dendrimers (DAB-Am) [123]. The PAMAM dendrimer-grafted magnetic nanoparticles with amino surface groups were investigated for binding to bovine serum albumin protein (BSA). Both the binding constant and the binding stoichiometry of dendrimer-grafted magnetic nanoparticles to BSA strongly depend on their surface groups and pH value.

4. BIOACTIVE MOLECULE-MODIFIED MAGNETIC NANOPARTICLES

Immobilization of enzymes, antibodies, oligonucleotides, and other biologically active molecules is a very important technique for bioscience and biotechnology applications. Biologically active molecule-immobilized magnetic nanoparticles can be removed/recovered from the system by using an external magnetic field. Also, external magnetic fields can move magnetic nonoparticles to the desired place and keep them on the target. In this chapter, some biologically active molecule-grafted magnetic nanoparticles are introduced. In many cases, the biologically active molecules are immobilized on the surface through an intermediate organic layer as described above. The immobilized compounds can be used to express their activities or as affinity ligands, enabling the capture or modification of target molecules or cells.

Magnetic nanoparticles obtained from magnetotactic bacteria have been used for the immobilization of various enzymes such as glucose oxidase and uricase [125], antibodies [126–128], and oligonucleotides [129, 130]. Aqueous suspensions of superparamagnetic nanoparticles composed of maghemite and forming an ionic ferrofluid have been coupled with lectins,

Table 1. Summary of organic-layered magnetic nanoparticles.

Class[a]	Magnetic particle	Organic layer[b]	Size[c]	Characterization[d]	Ref.
SC	γ-Fe_2O_3	Oleic acid, pyrene derivative (–COOH, –OH, COOEt)	12 nm* (TEM)	HRTEM, UV-vis, FS	[157]
SC	Co	Poly(St-block-4-vinylpyridine)	3–5, 10–21 nm* (TEM)	TEM, XRF, FT-IR, EA, FMR	[158]
SC	γ-Fe_2O_3	Sodium citrate	7–12 nm* (TEM)	TEM, VSM	[159]
SC	γ-Fe_2O_3	16-mercaptohexadecanoic acid		TEM, XPS, FT-IR, Film flotation	[160]
SC	Co	Oleic acid	5–10 nm, 1 μm* (TEM)	TEM, TEM-EDX, FT-IR, SQUID, VSM	[161]
SC	Co	Trioctylphosphine	5.8 nm* (TEM)	TEM, SQUID	[162]
SC	Fe_3O_4	Decanoic acid, n-alkanoic acid (C9-C13)	9.3 ± 2.6 nm* (TEM)	TEM, SQUID, TGA, DSC	[36]
SC	Fe_3O_4	Oleic acid, oleyl amine	4, 8, 12, 16 nm* (TEM)	XRD, TEM	[40]
SC	γ-Fe_2O_3	Oleic acid	4–16 nm* (TEM)	HRTEM, TEM, XRD, UV-vis, FT-IR, ED, SQUID	[33]
SC	γ-Fe_2O_3 $CoFe_2O_4$	Oleic acid, aromatic surfactant			[163]
SC	Fe_3O_4	Tetramethylammnonium 11-aminoundecanoate	6 nm* (TEM)	FT-IR, TEM	[42]
SC	Fe_2O_3	Oleic acid	5.2 × 16.8, 6.8 × 24.3, 8.1 × 25.9 nm* (TEM)	XRD, SEM, FT-IR, TEM, HRTEM, MS	[164]
SC	Fe_3O_4	Decanoic acid, n-alkanoic acid (C9-C13)	9.4 nm* (TEM)	TEM, SQUID, TGA, DSC, SANS	[37]
SC	Iron oxide	Dodecyl amine n-alkyl acid (C9-C18)		Saturation magnetization	[165]
SC	Iron oxide	Sodium dodecyl sulphate oleic acid			[166]
SC	Fe_3O_4	Oleic acid undec-10-enoic acid ricinpleic acid	10–30 nm* (TEM)		[167]
SC	γ-Fe_2O_3	Dextran	2–18 nm* (TEM)	TEM, UV-vis, VSM	[168]
SC	Co	Oleic acid	6, 9 nm* (TEM)	PAES, TEM, XRD, SQUID	[169]
SC	FePt	Oleic acid, oleyl amine	3–10 nm* (TEM)	TEM, HRSEM, XRD, SQUID	[170]
SC	Co	Oleic acid, trioctylphosphine oxide	8–16, 4 × 25–75 nm* (TEM)	TEM, XRD	[171]
SC	Fe	Poly(vinylpyrrolidone) oleic acid	3–8 nm* (TEM) 8 nm* (TEM)	TEM, ED, SQUID	[34]
SC	Amorphous Fe	Trioctylphosphine oxide	2 nm* (TEM)	TEM, ED, SQUID	[172]
	α-Fe	Trioctylphosphine, DDAB	2 × 11, 22, 27 nm* (TEM)		
SC	Fe_3O_4 $CoFe_2O_4$	Oleic acid	2, 6 nm* (TEM)	TEM, XRD, XPS, RMCD, SQUID	[173]
SC	FePt	Oleic acid, oleyl amine	3–4 nm*	FT-IR	[256]
SC	Fe_3O_4	Lauric acid, decanoic acid	4–16 nm* (TEM)	TEM, SQUID, TGA	[257]
SC	Fe_3O_4, γ-Fe_2O_3 Metal ferrites (Co, Mn, Ni, Zn)	NaDBS	3–9 nm* (TEM) 4–8 nm* (TEM)	TEM, XRD, SQUID, ICP-AES, XMCD	[258]
MS	Iron oxide	PC, PE	89.4–142.3 nm (DLS)	TEM, DLS	[139]
MS	Fe_3O_4	DMPG, DMPE-PEG_{2000}	40 nm (TEM)	TEM, Variable-field T1-T2 relaxometer	[148]
MS	Iron oxide	HDBS, CTAB	1.91–2.66 nm* (TEM)	Cryogenic-TEM, XRD, Force balance	[174]
MS	Fe_3O_4	DMPG, DMPC	43–105 nm (PCS)	PCS	[138]
MS	Fe_3O_4	DMPG	14 nm* (TEM)	TEM, Gas-liquid chromatography, AAS	[50]
MS	γ-Fe_2O_3	DDAB	0.1–5 μm (TEM)	OM, TEM, Magnetization curve	[175]
MS	Fe	Cholesterol, lecithin	10–50 nm*	UV-vis	[176]
MS	Fe_3O_4	DPPC	1.03 μm	Laser particle size analyzer, UV-vis	[177]
MS	Iron oxide	DMPE, DMPC	550 nm (QLS)	TEM, QLS	[178]
		DPPS, DMPC			
		Cardiolipin, DMPC	180–220 nm (QLS)		

Table 1. Continued.

Class[a]	Magnetic particle	Organic layer[b]	Size[c]	Characterization[d]	Ref.
MS	Iron oxide	DMPC, cholesterol, DHP	<25 nm*(TEM)	TEM, XRD, FS, SQUID	[179]
MS	Fe_3O_4	TMAG, DLPC, DOPE	10 nm*		[180]
MS	Fe_3O_4	TMAG, DLPC, DOPE	35 nm*		[181]
MS	Fe_3O_4	PC, cholesterol, mPEG-PE, PDP-PEG-PE	445 ± 25 nm (DLS)	TEM, DLS	[38]
PC	γ-Fe_2O_3	Poly(MMA) Poly(MMA-co-HEMA) Poly(MMA-co-AA) Poly(MMA-co-Phosmer)	400 nm* (BET)	VSM	[58]
PC		Poly(isobutylcyanioacrylate)	220 nm*	Laser light scattering	[182]
PC	Iron oxide	Dextran, γ-glycidoxypropyltrimethoxysilane	100 nm*		[183]
PC	γ-Fe_2O_3	Poly(MA)	15 nm (TEM)	TEM, MS	[64]
PC	Fe_3O_4	Dextran	9.4 nm*		[55]
PC	Co-γ-Fe_2O_3, γ-Fe_2O_3	PVC-SO_4		AC susceptibility, TGA	[57]
PC		Starch	100 nm		[61]
PC	Iron oxide	Carboxymethyldextran	12–34 nm* (TEM)	TEM, PCS, VSM	[63]
PC	Iron oxide	Dextran	4.11 nm* (TEM)	AAS, TEM, ^{57}Fe-MS, SQUID	[53]
		Poly(vinyl alcohol)	5.78 nm* (TEM)		
PC	Fe_3O_4	PEO-COOH-PEO	8.8 ± 2.7 nm* (TEM)	TEM, FEGTEM, EA, ICP, XRD, SAED, HRTEM, VSM	[60]
PC	Fe_3O_4	Dextran	105.4–768.1 nm (DLS)	SEM, AFM, DLS, DC magnetometer	[56]
PC	Fe_3O_4	Starch having ion-exchange groups	50, 100 nm* (DLS)		[62]
PC	γ-Fe_2O_3	Dextran	28–57 nm* (TEM)	TXRF, TEM, PCS, TGA, TQMS, FT-IR	[259]
PC	Fe_3O_4	Poly(SSA-co-VSA-co-AA)	70 nm* (TEM)	DLS, TEM, VSM, ZP	[184]
PC	Fe_3O_4	Poly(MA-co-HEMA)	290, 340, 400 nm (DLS)	DLS, VSM, XRD, FT-IR, MS	[185]
PC	Fe_3O_4	Poly(MA-co-HEMA)	18.5 ± 3.2 nm (TEM)	TEM, DLS, sequential XRF, FT-IR, VSM, UV-vis	[186]
PC	Fe	Poly(St)	15–20 nm* (TEM)	TEM, Field-dependent magnetization, Dynamic transverse susceptibity	[187]
PC	Fe_3O_4	Dextran	30–40 nm (SEM)	TEM, SEM	[51]
PC		Chitosan			[188]
PC		Chitosan			[189]
PC	Magnetic powder	Chitosan	10.2 μm* (TEM)	TEM, SEM, Specific surface area, VSM, FT-IR	[190]
PC	Hydrous iron(III)oxide	Poly(acrylamide)		FT-IR	[191]
PC	Fe_2O_3	Dextran	100 nm		[192]
PC	γ-Fe_2O_3	Dextran	10–20 nm* (TEM)	TEM, MS	[193]
PC	γ-Fe_2O_3	PEI, poly(ethylene oxide-b-glutamic acid)	25–110 nm (DLS)	DLS, ZP, XRD, MS, Raman	[65]
PC	Fe_3O_4	Chitosan	13.5 nm (TEM)	TEM, ZP, XRD	[260]
PC	γ-$Al_nFe_{2-n}O_3$	Cellulose	5–30 nm* (TEM)	TEM, ED, MS, XRD, VSM	[261]
PCm	Fe_3O_4	Carbon	50 nm, 2–5 μm (TEM)	TEM, SEM, XRD, Magnetic balace	[194]
PCm	Fe_3O_4	Human serum albumin	1 μm		[23]
PCm	Fe_3O_4	Poly(St), polyelectrolytes (PDADMAC, PAH)	640–765 nm (TEM)	ZP, TEM	[195]
PCm	Iron oxides	Alginate		XRD, Susceptibility, MS	[74]
PCm	γ-Fe_2O_3	Poly(acrylamide)	6–14 nm* (TEM)	TEM, EA, FT-IR, Foner magnetometor, RB	[196]
PCm	Fe_3O_4	Poly(MMA-co-GMA)	400–800 nm (SEM)	TEM, SEM, TGA, EXAFS, SQUID, XANES	[197]
PCm	Magnetite powder	Poly(HEMA-co-MA)			[198]

Table 1. Continued.

Class[a]	Magnetic particle	Organic layer[b]	Size[c]	Characterization[d]	Ref.
PCm	Fe_3O_4	Poly(St)	4 nm	TEM, SEM, Laser particle size analyzer	[199]
PCm	γ-Fe_2O_3	Poly(styrene sulfonate)	30–150 μm	SEDXD, MS, TEM, XRD, EA, DC susceptibility, Optical absorption	[200]
PCm	Iron oxides	Poly(NIPAM)	230–490 nm (DLS)	TEM, SEM, XRD, DLS, VSM	[201]
PCm	Fe_3O_4	Poly(St)	210–280 nm (TEM)	TEM, SEM, XRD, DSC, TG, VSM, ZP	[202]
PCm	Fe_3O_4	Poly(St) having ion exchange groups		SEM, XRD, Susceptibility	[203]
PCm	Iron oxides	Poly(pyrrole)	50, 100, 150 nm (TEM)	TEM, DCP, VSM	[204]
PCm	Fe_3O_4	Chitosan	100–250 μm (OM)	SEM, OM, VSM, FT-IR	[72]
PCm	Fe_3O_4	Poly(St-co-NIPAM)	7.20–67.15 μm (SEM)	SEM, LDSA, AAS	[205]
PCm	Fe_3O_4	Poly(St-co-NIPAM), Poly(NIPAM)	30–38 μm (LDSA)	SEM, LDSA	[206]
PCm	Fe_3O_4/γ-Fe_2O_3	Poly(Iron(III)allyacetylacetonate)	10 nm* (TEM)	TEM, XRD, XPS, SAED	[207]
PCm	γ-Fe_2O_3	Poly(ethylene)	50–500 nm (TEM)	OM, TEM, AFM, SQUID, DSC	[208]
PCm	γ-Fe_2O_3	Human serium albumin	0.1–1 μm (SEM)	SEM, AFM	[209]
PCm	Iron oxide	Poly(St/NIPAM-co-AEM), Poly(NIPAM-co-IA)	330 nm (TEM)		[210]
PCm	Iron oxide	Poly(St-co-AEM), Poly(NIPAM-co-IA)	329–346 nm (TEM)	TEM, SEM, QELS, Electrophoretic mobility	[76]
		Poly(St/NIPAM-co-AEM), Poly(NIPAM-co-IA)	341–721 nm (TEM)		
PCm	Iron oxide	Poly(St-co-AEM)	145–473 nm (TEM)	TEM, Electrophoretic mobility	[75]
		Poly(St/NIPAM-co-AEM)	288–543 nm (TEM)		
		Poly(NIPAM-co-AEM)	149 nm (TEM)		
PCm	Iron oxide	Poly(acrylamide-co-MA)	0.34 μm (TEM)	TEM, TG-DTA, SQUID	[211]
PCm	Iron oxide	Poly(St)	60 nm (TEM)	TEM, TGA, VSM, GPC	[66]
PCm	γ-Fe_2O_3	Poly(pyrrole-N-propylsulfonate)		EA, FT-IR, XRD, VSM	[212]
PCm	Fe_3O_4	Poly(MMA-co-HEMA-co-MA)	40 nm (SEM)	SEM	[213]
PCm	Fe_3O_4	Poly(St)	100–600 nm (TEM)	TEM, TG-DTA	[214]
		Poly(MMA)	60 nm (TEM)		
PCm	Fe_3O_4	Poly(St), Poly(NIPAM-co-MA)	110–270 nm (DLS)	SEM, TEM, DLS, ZP, TGA	[67]
PCm	Iron oxide	Poly(St-co-MMA-co-SSS)	134 nm (TEM)	XRD, TEM, SQUID, EDXRF, ZP, AAS	[215]
PCm	Fe_3O_4	Poly(NIPAM-co-MA)	150–250 nm (DLS)	DLS	[68]
PCm	Iron oxide	Poly(HEMA-co-MA)	35-200 nm (TEM)	SEM, TEM, TGA, UV-vis, DLS	[216]
PCm	Fe_3O_4	Poly(St-co-HEMA)	52.5 μm (TEM)	TEM, IR	[71]
PCm	Fe_3O_4	Poly(St)	58–1240 nm (TEM)	TEM, TGA	[217]
PCm	Iron oxide	Poly(L-lactic acid)	52–557 μm (SEM)	TEM, VSM, SEM	[73]
PCm	Fe_3O_4	Poly(MMA)	101.5 nm (TEM)	TEM, FT-IR, VSM	[69]
PCm	Fe_3O_4	Poly(St-co-MA)	2.8 μm (OM)	FT-IR, TEM, OM, VSM, TGA	[70]
PCm	Fe_3O_4	Poly(MA)	390 nm (TEM)	TEM, FT-IR, VSM	[59]
PCm		Albumin	1 μm (SEM)	SEM	[218]
PCm	α-Fe_3O_3	Poly(Iron(III)allyacetylacetonate)	10–40 nm* (TEM)	UV-vis, TG-DTA, XRD, ED, TEM, VSM	[219]
PCm	Fe_3O_4/γ-Fe_3O_4	Poly(Iron(III)allyacetylacetonate)	10 nm* (TEM)	TG-DTA, XRD, XPS, TEM, ED, VSM	[220]
PCm	γ-Fe_2O_3	Poly(ethylene)	5–10 nm*	TEM, SQUID	[221]
PCm	Carbonyl-iron	Starch	50 μm		[222]
PCm	Fe	Carbon	1.2 nm (TEM)	SEM, TEM, XRD, Faraday balance, PCS	[223]
PCm	Iron oxide	Poly(St), poly(GMA)	180 ± 50 nm (TEM)	XRD, TEM, DLS, Saturation magnetization	[78]
PCm	Fe_2O_3	Poly(NIPAM)	2 nm	VSM	[77]
PCm	γ-Fe_2O_3	Poly(St-block-AA)	40–128 nm (TEM)	TEM, SAED, XRD, SQUID	[79]
PCm	α-Fe_2O_3	Poly(vinylpyridine)	7–10 nm* (TEM)	TEM, FT-IR, DSC, XRD, SQUID, ED, EA	[262]
	CoO		50 nm* (TEM)		
PCm	$CoFe_2O_4$	Poly(DL-lactic acid)	990 nm (SEM)	SEM, Susceptibility	[263]

Table 1. Continued.

Class[a]	Magnetic particle	Organic layer[b]	Size[c]	Characterization[d]	Ref.
PCm	Fe_3C, Fe	Carbon	10–50 nm (TEM)	HRTEM, XRD, EDX, VSM, Magnetic balance	[264]
PCm	Fe_3C, α-Fe	Graphite carbon	30–50 μm (TEM)	HRTEM, XRD, Magnetization curve	[265]
PCm	Ferrite powder $Sm_2(Co_{0.6}Fe_{0.4})_{17}$	Cellulose	50–2000 μm 20–350 μm	OM	[266]
MG	Amoluphous iron oxide	n-alkylthiol (C7, C12, C18)		FT-IR, EA, TGA	[224]
MG	FePt	Nitrilotriacetic acid	1 nm* (TEM)	TEM, XPS, TOF-SIMS, FT-IR	[92]
MG	Fe_3O_4	Silica, AEAPS	100–200 nm (TEM)	TEM, XRD, VSM	[85]
MG	γ-Fe_2O_3	APS	30 nm* (TEM)	TEM, XPS, DRIFTS, ZP, EA	[81]
MG	Iron oxide	Molecules having –COOH, $-SO_3H$, $-PO_3H_2$, $-PO_4H_2$	4.3 ± 0.6 nm* (TEM)	TEM, UV-vis, PCS	[94]
MG	Amoluphous Iron oxide	n-alkanethiol (C7, C10, C12)	60–80 nm* (TEM)	FT-IR, TGA, DSC, BET, VSM, SQUID, EA	[89]
MG	Fe	n-alkanethiol (C7, C10, C12)		DSC, TGA, Mass spectroscopy	[88]
MG	Fe	n-alkyl alchol (C8, C12, C13)		FT-IR, XPS, Floatability, VSM	[225]
MG	Fe	Octadecyltrichlorosilane sodium dodecyl sulfate		FT-IR, EA, Floatability, XANES	[86]
MG	Fe_3O_4	Amino-silane (APS, AEAPS, ABAPS, AHAPS)	10–15 nm* (TEM)	BET, TEM	[226]
MG	Iron oxide	APS, CMPO-TBP		XRD, SEM, FT-IR	[227]
MG	γ-Fe_2O_3	Amino acid (aspartic acid, glutamic acid)	10.5 nm*	XRD, DCA, Ramam, FT-IR	[37]
MG	Fe_3O_4	AEAPS having redox-active ligand (FAA, MDBP)	1 μm*	DPV	[228]
MG	Fe_3O_4	AEAPS, DNQ	1 μm*	CV	[229]
MG	Iron oxide FePt	TMA-POSS	3.5–10 nm* (TEM)	TEM, UV-vis, IR	[98]
MG	γ-Fe_2O_3	DMTSA with PEG-sulfonate anion	4 nm* (TEM)	TEM, XRD, TGA, Ionic conductivity	[97]
MG	Fe_3O_4	DMSA	9 nm* (TEM)	TEM, DLS	[96]
MG	Fe_3O_4	APS	10 ± 2 nm* (TEM)	TEM, UV-vis, FT-IR, VSM	[267]
MG	γ-Fe_2O_3	Caprylic acid	30–80 nm* (TEM)	TEM, FT-IR, XRD, ESR, MS	[268]
PG	Fe_3O_4	Chitosan	10 nm* (TEM)	TEM, DLS	[122]
PG	Iron oxide	Poly(AA)		FT-IR, EA	[105]
PG	Iron oxide	PEG		FT-IR	[119]
PG	Iron oxide	TFEE-terminal PEG	5 nm* (TEM)	TEM, FT-IR	[121]
PG	Fe_3O_4	PEG	44.1 ± 1.0 nm* (AFM)	AFM, FT-IR, XPS	[120]
PG	γ-Fe_2O_3	Poly(1-vinylimidazole)	28 nm* (BET)	TEM, DRIFTS, EA, ZP, Susceptibility	[114]
PG	Fe_3O_4	PEG	50 nm (PCS)	PCS, Electrophoretic mobility, TGA, BET	[118]
PG	Fe_3O_4	Poly(MMA)	60 nm*	GPC, FT-IR	[113]
PG	Fe_3O_4	Poly(3-vinylpyridine) Poly(St)	<50 nm* (TEM)	GPC, TEM, TGA, DLS, UV-vis	[107]
PG	Iron oxide	Silica, DAB-Am-n dendrimer (n: 16, 32, 64)			[123]
PG	Iron oxide	Poly(amidoamine) dendrimer	54 nm (TEM)	TEM, ZP	[124]
PG	γ-Fe_2O_3	Poly(4-vinylpyridine)	28 nm* (BET)	TEM, DRIFTS, EA, ZP	[115]
PG	$MnFe_2O_4$	Poly(St)	12.7 ± 2.3 nm (TEM)	TEM, FT-IR, SQUID	[121]
PG	Fe_3O_4	Poly(St)	<50 nm* (TEM)	GPC, TEM, TGA, UV-vis	[230]
PG	Fe_3O_4	PEGn-HA		FT-IR, TEM, UV-vis, SAED	[231]
PG	Fe_3O_4	Poly(PEGMA)	26 ± 5 nm (DLS)	FT-IR, TEM, XPS, TGA, VSM, DLS, GPC	[111]
PG	Fe_3O_4	Poly(ε-caprolactone)	5–15 nm* (TEM)	FT-IR, TEM, XRD, TGA, VSM, GPC	[112]

[a]SC: surfactant covered magnetic nanoparticle (including ferrofluid); MS: magnetosome; PC: polymer coating; PCm: polymer composite; MG: small molecule grafting; PG: polymer grafting.

[b]MMA: methylmethacrylate; HEMA: hydroxyethylmethacrylate; AA: acrylic acid; Phosmer: 2-acidphosphoxyethylmrthacrylate; MA: methacrylic acid; PVC: poly(vinyl chloride); PEO: poly(ethylene oxide) monomethyl ether oligomer; DDAB: didodecyldimethylammoniumbromide; SSA: styrenesulfonic acid; VSA: vinylsulfonic acid; APS: 3-aminopropyltriethoxysilane; AEAPS: *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane; ABAPS: *N*-(4-aminobutyl)-3-aminopropyltrimethoxysilane; AHAPS: *N*-(6-aminohexyl)-3-aminopropyltrimethoxysilane; FAA: *N*-(ferrocenylmethyl)aminohexanoic acid; MDBP: *N*-methyl-*N'*-(dodecanoic acid)-4,4'-bipyridinium; DNQ: 2,3-dichloro-1,4-naphthoquinone; TFEE: trifluoroethylester; DAB-Am-16: polypropyrene imine hexadecaamine; DAB-Am-16: polypropyrene imine hexadecaamine;

Table 1. Continued.

DAB-Am-32: polypropyrene imine dotriacontaamine; DAB-Am-64: polypropyrene imine tetrahexacontaamine; PEGn-HA: PEG-terminated dendrons with a hydrozamic acid group; PDADMAC: poly(dimethylammonium chloride); PAH: poly(allylamine hydrochloride); GMA: glycidyl methacrylate; DVB: divinylbenzene; NIPAM: *N*-isopropylacrylamide; IA: itaconic acid; AEM: aminoethyl methacrylate hydrochloride; St: stylene; SSS: sodium styrene sulfonate; PC: phosphatidylcholine; PE: phosphatidylethanolamine; DMPG: dimyristoylphosphatidylglycerol; DMPE-PEG_{2000}: dimyristoylphosphatidylethanolamine-*N*-(ethylene glycol)$_{2000}$; HDBS: dodecylbenzenesulfonic acid; CTAB: cetyltrimethylammonium bromide; DMPC: dimyristoylphosphatidylcholine; PEG: poly(ethyleneglycol); DPPC: dipaimitorylphosphatidylcholine; DMPE: dimyristoyphosphatidylethanolamine; DPPS: dipaimitorylphosphatidylserine; DHP: dihexadecylphosphate; TMAG: *N*-(α-Trimethylammonioacetyl)didodecyl-D-glutamate chloride; DLPC: dilauroylphosphatidylcholine; DOPE: dioleoylphosphatidyiethanolamine; mPEG-PE: methoxy poly(ethylene glycol); PDP-PEG: 3-(2-pyridyldithio)-propionoyl poly(ethylene glycol); CMPO: octyl(phenyl)-*N*,*N*-diisobutylcarbamoylmethylphosphine oxide; TBP: tri-n-butylphosphate; PEGMA: poly(ethylene glycol)monomethacrylate; PEI: poly(ethylene imine); TMA-POSS: anionic octa(tetramethylammonium)-polyhedral oligomeric silsesquioxane; DMTSA: *N*,*N*-didecyl-*N*-methyl-*N*-(3-trimethoxysilylpropyl)ammonium chloride; DMSA: 2,3-dimercaptosuccinic acid; NaDBS: sodium dodecylbenzenesulfonate.

[c,e] diameter of core magnetic particles.

[d] VSM: vibration sample magnetometer; TGA: thermogravimetric analysis; PCS: photon correlation spectroscopy; AAS: atomic absorption spectrometry; TEM: transmission electron microscopy; MS: Mössbauer spectroscopy; SQUID: superconducting quantum interference device magnetometry; FEGTEM: field emission gun transmission electron microscopy; EA: elemental analysis; ICP: inductively coupled plasma spectrometry; XRD: X-ray diffraction; SAED: selected area electron diffraction; HRTEM: high-resolution transmission electron microscopy; SEM: scanning electron microscopy; AFM: atomic force microscopy; TXRF: total reflection X-ray fluorescence spectroscopy; TQMS: thermostar quadrupole mass spetrometry; FT-IR: Fourier transform infrared spectroscopy; DLS: dynamic light scattering; ZP: zeta-potential; XRF: X-ray fluorescence spectroscopy; UV-vis: Ultraviolet-visible absorption spectroscopy; FS: fluorescence spectroscopy; EDX: energy dispersive X-ray; ED: electron diffraction; DSC: differential scanning calorimetry; SANS: neutron scattering; PAES: plasma-atomic emission spectroscopy; HRSEM: high-resolution scanning electron microscopy; XPS: X-ray photoelectron spectroscopy; RMCD: reflectance magnetic circular dichroism; TOF-SIMS: time-of-flight second ion mass spectroscopy; DRIFTS: diffuse-reflectance Fourier transform infrared spectroscopy; BET: Brunauer-Emmett-Teller (a method of measuring surface area); XANES: X-ray absorption near-edge structure; DCA: dichromatometric chemical analysis; DPV: Differencial pulse voltammetry; CV: cyclic voltammetry; EXAFS: X-ray absorption fine structure analysis; SEDXD: synchrotron energy-dispersive X-ray powder diffraction; DCP: disc centrifuge photosedimentometry; QELS: quasielastic light scattering; TG-DTA: thermogravimetry-differential thermal analysis; EDXRF: energy dispersive X-ray fluorescene spectrometry; QLS: Quasi-elastic laser light scatering; FMR: Ferromagnetic resornance; LDSA: Laser diffraction size analysis; OM: optical microscopy; RB: relaxation of birefringence.

enzymes, or antibodies by a specific thiol group [131, 132]. 3-Aminopropyltrimethoxysilane-grafted magnetic nanoparticles have been used for the immobilization of various enzymes, antibodies, and protein A after the glutaraldehyde treatment [83, 133].

PEG–enzyme conjugates can be conjugated to magnetic nanoparticles. Alternatively, PEG-coated magnetic nanoparticles are prepared first and then conjugated to the target enzyme. Magnetically modified enzymes can be dispersed stably in both organic solvents and water. Magnetically modified lipase catalyzes ester synthesis in organic solvents and can be easily recovered by magnetic force without loss of enzyme activity [134, 135]. Other enzymes such as L-asparaginase [135] and urokinase [136] have also been modified by conjugation with PEG-coated magnetic nanoparticles. Kobayashi et al. reported the magnetite-labeled antibody with the use of poly(ethylene glycol) derivatives. Poly(ethylene glycol) (PEG)-magnetite consisting of magnetite (Fe_3O_4) and PEG with terminal carboxyl or amino groups was prepared and then monoclonal antibody was immobilized covalently onto the PEG-magnetite. Magnetite-labeled antibodies are expected to be applicable clinically as therapeutic agents for the induction of hyperthermia [137].

Magnetosomes containing magnetic nanoparticles entrapped within the cavity have been used for the immobilization of membrane-bound enzymes [138] or antibodies [139]. de Cuyper et al. reported the effects of surface charge density of the phospholipids of magnetosomes on the catalytic activity of beef heart cytochrome *c* oxidase. The highest reactivation was found in the lower negative charge range. Preincubation of the charged colloidal biocatalytic particles with cytochrome *c* induced aggregation and reduced overall enzymatic activity [138]. Magnetosomes for hyperthermia treatment of cancer were prepared by coating phospholipid coated-magnetic nanoparticles with hydrazide pullulan [139]. The hydrazide pullulan stabilized the phospholipid capsules and provided an anchor for the immobilization of antibodies.

In order to elucidate the molecular and genetic mechanism of magnetite biomineralization, a magnetic bacterium *Magnetospirillum sp.* AMB-1, for which gene transfer and transposon mutagenesis techniques have been developed, has been used as a model organism. Several findings on the bacterial magnetic particle formation process have been obtained within this decade by means of studies with this and related model organisms. Biomineralization mechanism and potential availability in biotechnology of bacterial magnets have been elucidated through molecular and genetic approaches [49]. Matsunaga et al. reported the fully automated sandwich immunoassay for the determination of human insulin using antibody-protein A-bacterial magnetic particle complexes and an alkaline phosphatase-conjugated secondary antibody. Bacterial magnetic particles bearing protein A-MagA inserted on the *Magnetospirillum sp.* AMB-1 transconjugant for a protein A-MagA fusion gene. MagA protein was used as an anchor to attach protein A onto the membrane. Protein A-bacterial magnetic particle complexes harvested from transconjugant AMB-1 were subsequently complexed with anti-human insulin antibodies by specific binding between the Z domain of protein A and the Fc component of IgG to form the antibody-protein A-bacterial magnetic particle complexes. The complexes were monodisperse after the binding of the antibody [140]. Bacterial magnetic nanoparticles containing protein A [141], luciferase [142], and acetate kinase [142] have already been constructed.

Magnetic carriers for drug delivery of chemotherapeutic agents have been investigated since the 1970s. Widder et al. [143] and Morimoto et al. [144] developed albumin microspheres encasing anticancer drugs. The magnetic particles injected into an animal were retained at the magnet site depending on the magnetic field strength. It has also been shown that magnetic particles can be retained in other parts of the body depending on the placement of the external magnet [23]. The chemotherapeutic agent adriamycin was encapsulated in the albumin-magnetite microsphere. In their research, Widder et al. first demonstrated in animals the potential therapeutic benefit of magnetically directing micropheres containing adsorbed drugs into the capillary beds of tumors [23].

Shinkai et al. have developed the magnetic particles conjugated to the Fab' fragments of human MN antigen-specific antibody and their hyperthermia effects were demonstrated

Table 2. Examples of biomolecule-modified magnetic nanoparticles.

Magnetic support particle	Biomolecule	Target	Application field	Ref.
Fe_3O_4	APS/poly(MMA-co-MA)/human IgG APS/PEG/human IgG	Staphylococcal protein A	Magnetic separation	[221]
Iron oxide	Dextran/glutaraldehyde/*staphylococcus aureus* protein A dextran/glutaraldehyde/goat antirabbit Ig Ab dextran/glutaraldehyde/wheat germ agglutinin	RBC	Magnetic separation	[222]
Fe_3O_4	Poly(acrylamide)/glutaraldehyde/rat GBM	Anti-GBMAb	Enzyme immunoassay	[223]
γ-Fe_2O_3, Mn-Zn ferrite	α-chymotrypsin/glutaraldehyde			[224]
Fe_3O_4	Dispase, chymotrypsine, streptokinase, BSA			[225]
Fe_3O_4	HSA-^{125}I-BSA/adriamycin HCl (drug)	Liver, spleen, kidney, lug, heart	DDS	[132]
Fe_3O_4	PEKY/anti-CEA MoAb	CEA	MRI	[226]
Fe_3O_4	PEG/MoAb G-22	HGCSA	MRI	[136]
Fe_3O_4/γ-Fe_2O_3	Trypsin			[227]
BMPs	Protein A/anti-human IgG Ab	Human IgG	CLEIA	[130]
BMPs	Luciferase	Luciferin	Enzyme activity	[131]
BMPs	Glutaraldehyde/streptavidin/oligonucleotides	Cyanobacterial DNA	DNA detection	[228]
Fe_3O_4	Collagen	Fibroblast	Calcium flux	[229]
Fe_3O_4	BSA, GOD, streptokinase, chymotrypsin, dispase			[230]
Iron oxide	Dextran/epichlorohydrin/SPDP/HIV-tat peptide	Lymphocyte, NK cell, HeLa cell	Cell labeling	[231]
Fe_3O_4	APS/glutaraldehyde/protein A	Mouse IgG	Magnetic separation	[232]
Fe_3O_4	Dicarboxy-PEG/lipase	Olive oil	Enzyme activity	[123]
Fe_3O_4	APS/glutaraldehyde/β-gulcosidase	PNPG	Enzyme activity	[79]
Fe_3O_4	APS/glutaraldehyde/anti-mouse IgG Ab APS/glutaraldehyde/protain A	Mouse IgG	ELISA	[141]
Iron oxide	BSA, alkaline phospatase			[233]
Iron oxide	Dextran/SPDP/Tat peptide	D34 + Cells	Cell labeling	[234]
BMPs	APS/glutaraldehyde/glucose oxidase APS/glutaraldehyde/uricase			[114]
BMPs	SPDP/FITC-IgE Ab	Allergen	Fluoroimmunoassay	[117]
BMPs	Sulfo-LC-SPDP/sulfo-SMCC/anti-IgG Ab	Mouse IgG	CLEIA	[115]
BMPs	SPDP/FITC-anti-*E. Coli* Ab	*E. Coli*	Cell detection	[116]
BMPs	SPDP/oligo(dT)$_{30}$, SPDP/bGH oligonucleotide	bGH mRNA	RNA recovery	[119]
BMPs	Plasmid DNA	Marine cyanobacterium	Ballistic transformation synechococcus	[235]
BMPs	FITC-anti-IgG Ab	IgG	Fluoroimmunoassay	[236]
γ-Fe_2O_3	DMSA/SPDP/MoAb DMSA/SPDP/lectin	Lymphiod cells Endothelial cells	Cell targeting	[120]
Fe_3O_4	DCPEG/HIS/lipase DCPEG/HIS/L-asparagine	Olive oil L-asparaginase	Enzyme activity	[124]
Fe_3O_4	DCPEG/urokinase	Fibrin clot	Enzyme activity, TTE	[125]
Fe_3O_4	PEG derivatives/mouse IgG	HCC cell line BM314	Cell targeting, hyperthermia	[126]
MPs	Lipid (egg-yolk PC)/6-carboxy-fluorescein (drug)		DDS	[237]
BMPs	Protein A/anti-human insulin Ab	Human insulin	CLIA	[129]
BMPs	Luciferase			[131]
MPs	Lipid (PC, PE, EMC-DPPE)/antibody fragments	Tumor, liver, spleen, kidney, lug, heart	Hyperthermia	[238]
Iron oxide	Arabinogalactan	Liver	MRI	[239]
Iron oxide	Starch/mitoxantrone (anticancer agent)	Squamous cell carcinoma in rabbit	Drug targeting, DDS	[240]
γ-Fe_2O_3	DMSA/BSA	Macrophage, HeLa cell	Cell labeling, MRI	[241]
MPs	Lc-SPDP/SATA/neutravidin	Bi-biotinylated peptide	Protease assay	[242]
Iron oxide	Dextran/dopamine, dextran/serotonin	Peroxidase	Enzyme activity, MRI	[243]
Fe_3O_4	VP-PVP/AGA/Ab	Antigen	Immunoassay	[244]
Fe_3O_4	Vancomycin	Gram-positive bacteria	Magnetic separation	[269]
Fe_3O_4	APS/glutaraldehyde/glucose oxidase	Glucose	Enzyme activity	[270]

Table 2. Continued.

Magnetic support particle	Biomolecule	Target	Application field	Ref.
Fe_2O_3/Au	Anti-AFP	α-1-fetoprotein antigen	ECIA	[271]
$MgFe_2O_4/SiO_2$	APS/glutaraldehyde/tyrosinase	Phenol	Biosenser	[272]
Fe_3O_4	Chitosan/epirubicin (drug)		DDS	[273]
Iron oxide	Carboxymethyl dextran/ ON-19 oligonucleotide	MCF-7 cells	Cell targeting	[274]

Ab: antibody; MMA: methylmethacrylate; MA: methacrylate; PEKY: poly(glutamic acid-co-lysine-co-tyrosine); MPs: magnetic particles; PEG: poly(ethyleneglycol); BSA: Bovine Serum Albumin; DCPEG: ω-dicarboxymethylpoly(ethyleneglycol); DMSA: *meso*-2,3-dimercaptosuccinic acid; VP-PVP: vinylphenylene-terminated poly(*N*-vinylpyrrolidone); AGA: *N*-acryloyl-L-glutamic acid; RBC: red blood cell; anti-GBM ab: anti-glomerular basement membrane antibody; GBM: glomerular basement membrane; HSA: human serum albumin; CEA: Carcinoembryonic antigen; HGCSA: Human glioma cell-surface antigen; MoAb: Monoclonal antibody; GOD: glucose oxidase; APS: 3-aminopropyltriethoxysilane; PNPG: *p*-nitrophenyl-β-D-glucopyranoside; FITC: fluorescein isothiocyanate; sulfo-LC-SPDP: sulfosuccinimidyl 6-[3′-(2-pyridyldithio)propionamido]hexanoate; sulfo-SMCC: sulfosuccinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate; PC: phosphatidylcholine; PE: phosphatidylethanolamine; EMC-DPPE: *N*-(6-maleimidocaproyloxy)-dipalmitoyl phosphatidylethanolamine; NK: natural killer; bGH: bonito growth hormone; HIS: N-hydroxysuccinimide; SATA: *N*-succinimidyl *S*-acetylthioacetate; Lc-SPDP: *N*-succinimidyl 6-[3′-(2-pyridyldithio)propionamido]hexanoate; anti-AFP: α-1-fetoprotein antibody.

CLIA: chemiluminescence immunoassay; CLEIA: chemiluminescence enzyme immunoassay; ELISA: enzyme-linked immunosorbent assay; MRI: magnetic resonance imaging; DDS: drug delivery system; TTE: therapy for thrombosis, embolism.

using a mouse renal cell carcinoma model. During recent years, there has been increasing interest in the use of paramagnetic contrast agents like dextran magnetite in magnetic resonance imaging (MRI) [145, 146]. Commercially available superparamagnetic iron oxide particles (SPIO) are useful for enhancing contrast of the lymph nodes or liver. The specific distribution of these agents by active targeting have been reported by several researchers. Suzuki et al. [147] reported that monoclonal antibody-conjugated poly(ethylene glycol)-grafted magnetite nanoparticles can work as a target-directed magnetic resonance contrast agent for human glioma cell surface antigen. Polyethylene glycol-modified magnetoliposomes with a diameter of 40 nm and containing one to six superparamagnetic iron oxide crystals per vesicle have been found to have excellent properties as bone marrow-seeking MR contrast agents [148].

Separation of specific molecules is an important tool for bioscience and biomedical fields. Magnetic nanoparticles with specific ligands are powerful tools for separation, isolation, removal, and recovery of biomolecules. Isolation of eukaryotic poly(A)$^+$ mRNA can be performed using oligo(dT)-immobilized magnetic nanoparticles [149]. Alternatively, oligonucleotides-immobilized bacterial magnetic particles can be used for the same purpose [131]. Alcohol dehydrogenase and lactate dehydrogenase have been isolated using 5′-AMP-sepharose 4B-modified magnetic nanoparticles as affinity adsorbents, whereas 2′,5′-ADP-sepharose 4B-modified nanoparticles were used to isolate glucose-6-phosphate dehydrogenase and 6-phosphate dehydrogenase. IgG and anti-human serum albumin antibodies have been isolated using protein A sepharose-modified and human serum albumin sepharose-modified magnetic nanoparticles, respectively [150, 151].

Antimouse IgG antibody or protein A-immobilized magnetic nanoparticles have been applied to enzyme-linked immnosorbent assay (ELISA) of mouse IgG. The assay time could be shortened substantially in comparison with the conventional method [152]. Very sensitive superconducting quantum interference device (SQUID) magnetometers have been utilized to measure the antigen-antibody interactions. In this system, antibodies are labeled with magnetic nanoparticles, and the antibody–antigen reaction is measured by detecting the magnetic field from the magnetic nanoparticles present in the complex. At present, 4×10^6 magnetic markers (diameter = 50 nm), corresponding to 520 pg of magnetic material, can be detected [153–155].

5. SUMMARY

Nanoparticle-based materials are very important in nanoscience and nanotechnology. Various surface modification techniques of nanoparticles have been enthusiastically developed because of their wide applicability in various fields. Organic-layered magnetic nanoparticles are powerful tools for engineering applications such as seals and magnetic storage media, and for medical and biotechnological applications such as hyperthermia and MRI contrast reagent. Various organic-layered magnetic nanoparticles prepared by different methods are summarized in Table 1 and are used for the above-described applications with and without additional treatments.

Bioactive molecule-modified magnetic nanoparticles immobilized through organic layers on the magnetic nanoparticles have been investigated widely for biomedical applications. Some examples of bioactive molecule-modified magnetic nanoparticles are listed in Table 2. A detailed review for the isolation and purification of proteins and peptide by using magnetic particles with bioactive surface was published by Safarik et al. [156]. Novel technologies and materials for organic-layered magnetic nanoparticles will open new avenues in a wide range of application fields.

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