TOPICAL REVIEW — Magnetism, magnetic materials, and interdisciplinary research

Surface modification of magnetic nanoparticles in biomedicine*

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Progress in surface modification of magnetic nanoparticles (MNPs) is summarized with regard to organic molecules, macromolecules and inorganic materials. Many researchers are now devoted to synthesizing new types of multi-functional MNPs, which show great application potential in both diagnosis and treatment of disease. By employing an ever-greater variety of surface modification techniques, MNPs can satisfy more and more of the demands of medical practice in areas like magnetic resonance imaging (MRI), fluorescent marking, cell targeting, and drug delivery.

Keywords: magnetic nanoparticles, surface modification, functionalization, magnetic resonance imaging

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1. Introduction

Magnetic nanoparticles (MNPs) have shown enormous potential in disease diagnosis and therapy. Due to their superior magnetic properties and high specific surface, MNPs are perceived as promising materials for magnetic resonance imaging (MRI) agents, biomedical drug carriers, magnetic hyperthermia, etc.[1–3] Based on the interaction between protons and surrounding molecules of tissues, MRI is already a key tool for medical imaging diagnosis of cancer and is considered one of the most efficient imaging techniques in medical practice. Colloidally stable MNPs, which display strong magnetization, now attract much attention for their great potential in MRI. In particular, they can be used as contrast agents in MRI, inducing hypo-intensities on T_1/T_2 and T_1/T_2^*-weighted MRI maps. Drug delivery is another medical application for MNPs. Magnetic drug delivery is a method to target drugs to the diseased area in the body. The drug is attached to an MNP and injected into the blood flow. A magnetic field located close to the diseased area is used to capture the MNPs in the target area. Under the influence of the magnetic field, the MNPs move irregularly in the target area which accelerates the release of drugs. Apart from pharmaceutical therapy, MNPs are also widely used in magnetic hyperthermia therapy. On account of excellent magnetic properties, metal carbide nanoparticles especially ferromagnetic NPs, can induce strong attractive forces between the dipoles of neighboring NPs, and aggregate under a static magnetic field.

While the efforts to develop new engineered MNPs and constructs continue to grow, with new chemistry and synthesis approaches every year, the importance of specific functionalization designs has been increasingly recognized. Because the surface of MNPs is the interface of nanomaterials and patients' bodies, surface biocompatibility is a prerequisite to the medical application of nanomaterials.[4] As a convenient and quick approach to adjust the properties of MNPs, surface modifications have become a vital component of a great many medical applications of MNPs, due to various requirements to add non-magnetic surfactants.

Cell phagocytosis of MNPs has expanded the applications of contrast enhanced MRI beyond vascular and tissue morphology imaging, and enabled many novel applications of MNPs for MRI diagnosis of liver diseases, cancer metastasis to lymph nodes, and *in vivo* MRI tracking of implanted cells and grafts.[5] The magnitude of contrast effects also needs to be improved for higher sensitivity to minimal changes in a disease and for biomarker-specific detection. Therefore, surface modifications of MNPs are developed to meet the increasing interests in non-invasive *in vivo* imaging of the molecular and cellular activities that characterize a disease. Surface modifications can inhibit MNPs' reactions and agglomeration in aqueous phase, which is a precondition for medical applications and endows MNPs with multifunctional properties such as fluorescent marking, cell targeting, drug loading and so on.[6–8] Furthermore, the addition of non-magnetic surfactants can influence the magnetic performance of MNPs.

Surface modifications are accomplished mainly via two approaches, ligand exchange and ligand adsorption. In this case, ligand exchange means changing a hydrophobic ligand into a hydrophilic one. Generally, these ligands consist of hydrophilic groups and linking groups. The linking groups can combine with the surface of the MNPs, whereupon the hydrophilic groups are exposed to the surrounding environment and make the MNPs disperse in the aqueous solution. The key

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to designing a successful ligand exchange is to select linking groups that have the strongest combination with the surface of the MNPs.

"Ligand adsorption" in this case mainly means to adsorb amphiphilic molecules, which have a hydrophilic portion on one side and hydrophobic part on another side. By means of hydrophobic forces, the hydrophobic portion can combine firmly with a hydrophobic surfactant on the MNPs and the hydrophilic portion is exposed so that the MNPs disperse in aqueous phase. In addition, chemical reaction is a third approach to surface modification. In these three strategies, organic molecules, macromolecules and inorganic materials are usually used. In this review article, we will summarize the progress in surface modification of MNPs by considering the principal types of surface materials one by one.

2. Surface modification with organic molecules

For organic molecular agents, only a single approach (ligand exchange or ligand adsorption) can be chosen for a given application because of the simple structure. In ligand exchange, monodentate ligand is the simplest ligand. Due to ease of preparation, simple structure and other advantages, monodentate ligands are widely used in ligand exchanges. Since there is only one ligand, the binding force between monodentate ligands and MNPs is weak and the combination process is reversible. To deal with this problem, researchers need to screen the ligands for strong coordination ability. Carboxyl,[9,10] sulfydryl,[11] silane,[12] and some inorganic ions[13–15] are most commonly used in monodentate ligand exchange. Murray *et al.* used nitrosonium tetrafluoroborate ($NOBF_4$) to replace the organic ligands attached to nanocrystals' (NCs) surface (Fig. 1).[16] The replacement by inorganic BF_4^- anions enabled NCs to be fully dispersible in polar, hydrophilic solvents without changing the particle size and shape. After surface modification, the NCs were readily further functionalized by various capping molecules that greatly enrich the surface function of NCs.

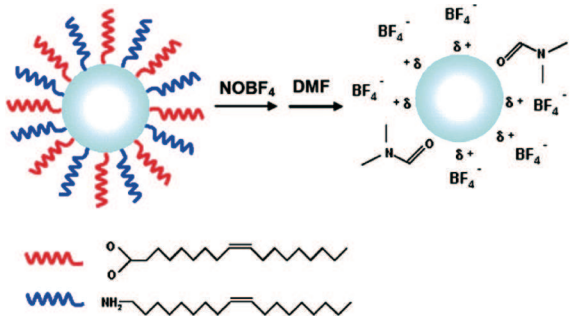


Fig. 1. Schematic illustration of surface modification of MNPs via the ligand exchange process with $NOBF_4$.[16] Reproduced with permission from Ref. [16]. Copyright 2011 American Chemical Society.

Although monodentate ligands have simple structure and react fast with an MNP surface, the resulting MNPs are not stable in aqueous phase, due to the reversibility of the coordination process. This problem is preferably solved by the application of polydentate ligands. Polydentate ligands have a plurality of coordinating groups that significantly enhances the force of binding with the MNPs. Therefore, these surface-modified MNPs have high stability constant and exhibit favorable aqueous solubility. The polydentate ligands are diphenols,[17–19] polyacids,[20] polyols and their derivatives.[21–23] For all of those, catechol and its derivatives are most commonly used. With its benzene ring structure as electron-donor, catechol and its derivatives can be intensely coupled with metal ions.[18] Hou *et al.* invented a rapid ligand-exchange method to make hydrophobic Fe_3O_4 NPs water-soluble, employing dihydroxybenzoic acid as a ligand (Fig. 2).[24] Another common polydentate ligand is dimercaptosuccinic acid (DMSA). A small molecule, DMSA has notably superior hydrophilicity, biocompatibility and coordination ability due its double sulfhydryl and double carboxyl structure.[25–27]

Recently, a new class of dual-modality imaging agents were reported, based on the conjugation of radiolabeled bisphosphonates (BP) directly to the surface of superparamagnetic iron oxide (SPIO) nanoparticles.[28] By linking ^{99m}Tc-dipicolylamine(DPA)-alendronate with SPIO, the dual-modality imaging agents exhibit good performance in single photon emission computed tomography (SPECT) imaging and magnetic resonance imaging (MRI).

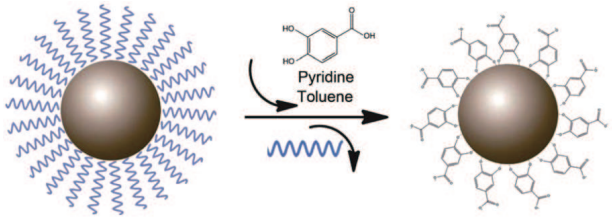


Fig. 2. Ligand exchange process with dihydroxybenzoic acid.[24] Reproduced with permission from Ref. [24]. Copyright 2013 Royal Society of Chemistry.

Some organic molecules are amphipathic. Their structures combine a hydrophilic portion with a hydrophobic portion that is able to attach to the surface of hydrophobic MNPs. The hydrophilic portion is usually long chains hydrocarbons, but the hydrophobic portion has different structures. In addition to enhancing the dispersibility of MNPs in aqueous solutions, optical dyes, targeting agents and therapeutic agents, amphipathic compounds are useful in the ligand adsorption process that helps endow some MNPs with multifunctionality.[29] In combination with organic dyes, some MNPs have a dual-mode imaging property that contributes to disease diagnosis (Fig. 3).[30–32] Among the organic dyes, near-infrared fluorescent (NIRF) dyes may be the best choice, due to their low interference and excellent deep penetration of issues.[33] Likewise, surface modification with a targeting

agent or therapeutic agent can strengthen the diagnostic capacity of an MNP.[34] Manuel *et al.* synthesized biocompatible, multimodal, theranostic functional iron oxide nanoparticles that exhibit excellent properties for targeted cancer therapy and both optical and magnetic resonance imaging.[35] Using a novel water-based method, they finished the encapsulation of both near-infrared dyes and anticancer drugs and realized successful theranostics.[36] In recent research, a novel method to synthesize Gd-NPs was reported wherein a Gd-based MR contrast agent self-assembled into gadolinium NPs under the action of furin proteins. These NPs can be used to locate the right position for treatment.[37]

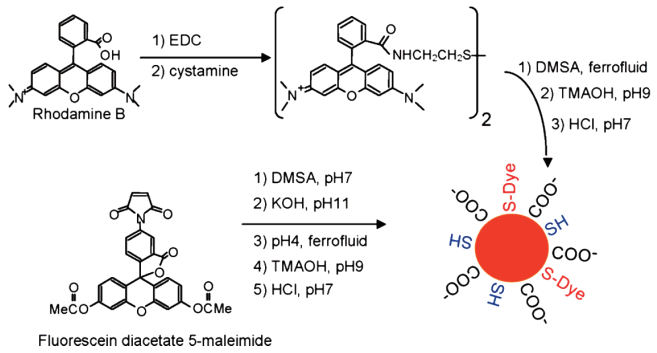


Fig. 3. Schematic of surface modification of MNPs via the ligand absorption process with DMSA and fluorescent dye.[30] DMSA is coupled to the particle and the fluorescent dye is coupled to DMSA. The coupling between DMSA and the fluorescent dye can be made before or simultaneously with the one between DMSA and the magnetic particles. Reproduced with permission from Ref. [30]. Copyright 2006 American Chemical Society.

3. Coating modification with macromolecules

3.1. Polymer coating

For macromolecular agents, due to their complex structure with numerous functional groups, the two approaches, ligand exchange and ligand adsorption are usually applied together to form a more stable structure. By ligand exchange or ligand adsorption, polymers with multiple functional groups can be expediently combined with MNPs. Because of the same reaction process, polymer coating usually needs the help of active terminal groups. Various monomeric species, such as bisphosphonates, DMSA and alkoxysilanes, have been evaluated to facilitate attachment of polymer coatings on MNPs.[19,38] In polymer coatings, polymers form a barrier among MNPs to avoid agglomeration and provide varieties of surface properties. Most biocompatible MNPs developed for *in vivo* applications need to be stabilized and functionalized with coating materials. The coating moieties can affect the relaxation of water molecules in various forms, such as diffusion, hydration and hydrogen binding.[5] In the research, these coatings also serve to link MNPs with biomolecules or to change the surface charge or chemical environment. Moreover, polymer coatings improve the colloidal stability of NPs.[39] Due to the complex structures of polymers, there are many aspects that affect the surface performance of MNPs (for example, the molecular weight, the properties of terminal groups and the conformation of the polymers).

Quite a few natural and synthetic polymers have been demonstrated in polymer coating of MNPs.[2,23,40,41] The glycans such as dextran or chitosan are widely used in polymer coatings.[42,43] Chitosan, a biodegradable natural polymer, is derived by deacetylation of chitin obtained from the shells of crustaceans. It has many biological applications because of its biological activities, biocompatibility, high charge density, low toxicity toward mammalian cells and ability to improve dissolution. Weissleder and his group research dextran coated iron oxide nanoparticles and derivative magnetic nanoparticles. Their work on monocrystalline iron oxide nanoparticles (MION)[44] and cross-linked iron oxide (CLIO) nanoparticles[45] found that dextran-coated superparamagnetic iron oxide nanoparticles were a very suitable platform for the synthesis of multifunctional imaging agents.[46] Hyeon *et al.* developed chitosan oligosaccharide-stabilized ferrimagnetic iron oxide nanocubes (Chito-FIONs) as an effective heat nanomediator for cancer hyperthermia.[47] The Chito-FIONs' magnetic heating ability is superior to that of commercial superparamagnetic iron oxide nanoparticles, enabling eradication of cancer cells through caspase-mediated apoptosis.

Another frequently-used polymer is polyethylene glycol (PEG).[48–50] PEG is a flexible water-soluble polymer. The high hydrophilicity of PEG chains can render the MNP core soluble and stabilized in aqueous media. PEG has been demonstrated to reduce uptake by macrophages[31] sharply, so as to increase the blood circulation time *in vivo*. By changing the molecular weight of PEG, the thickness of the coating can be controlled.[49,51] PEG-derivative modified MNPs were prepared by post-synthesis coating. With increasing molecular weight, the number of branched chains and functionalities, higher stability and better dispersion can be attained. Sun *et al.* synthesized heterobifunctional PEG ligands using 3-(3,4-dihydroxyphenyl) propanoic acid and PEG as reactants (Fig. 4).[52] They successfully modified porous hollow NPs (PHNPs) of Fe_3O_4 via this ligand and achieved targeted delivery and controlled release of the cancer chemotherapeutic drug cisplatin. However, a PEG shell is unfavorable for uptake of MNPs by most cells. To solve this problem, these MNPs can be modified by hyaluronic acid (HA), a targeting moiety, for uptake by stem cells.[53] A recent study reported that different terminal groups partly affected the MRI images of MNPs.[54]

Other polymers such as cellulose, poly (ethylene oxide) (PEO), poly (vinyl alcohol) (PVA), poly(acrylic acid) (PAA) and poly (lactide-co-glycolide) (PLGA) are also used for polymer coatings of MNPs. PLGA and cellulose are Food and Drug Administration (FDA) approved for a variety of uses in

humans and commonly employed for drug delivery and oral formulations. Xu *et al*. used a single emulsion method to obtain oleic acid-stabilized iron oxide NPs (10 nm core size) encapsulated in PLGA.[55] The PLGA coating gave the NPs a much higher $r_2$relaxivity than normal SPIO nanoparticles. Hong *et al.* synthesized novel polymeric nanoparticles (YCC-DOX) composed of poly (ethylene oxide)-trimellitic anhydride chloride-folate (PEO-TMA-FA), doxorubicin (DOX) and superparamagnetic iron oxide.[56] These NPs show unusually high MRI sensitivity, comparable to a conventional MRI contrast agent, despite their lower iron content. Lin *et al.* prepared PAA modified $GdVO_4$ NPs by filling PAA hydrogel into $GdVO_4$ hollow spheres. The PAA@ $GdVO_4$ NPs can act as a dual mode agent for MRI and up-conversion imaging and be applied for pH-dependent drug release due to their hollow structure.[57]

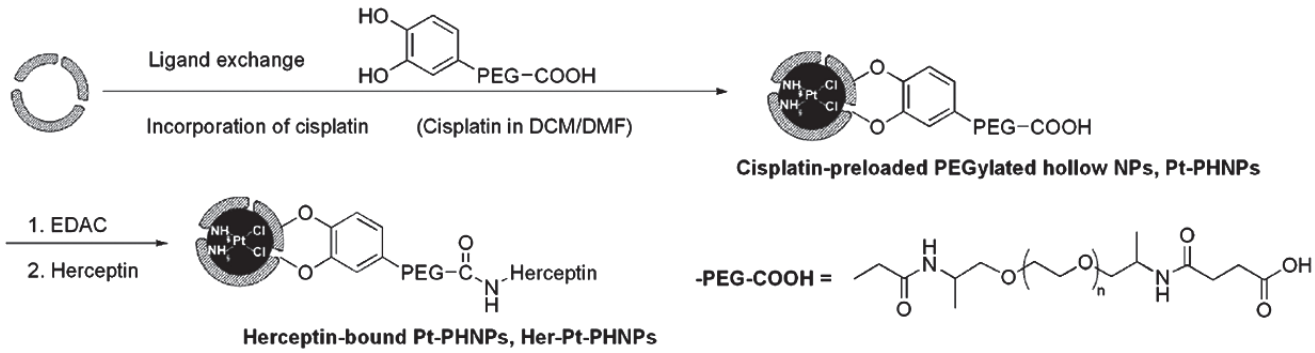


Fig. 4. Schematic of surface modification of hollow NPs with heterobifunctional PEG ligands.[52] Reproduced with permission from Ref. [52]. Copyright 2009 American Chemical Society.

To gain specificity and reduce side effects and toxicity, biomarker targeted functional proteins or peptide fragments, such as RGD targeting $\alpha_v\beta_3$ integrin, HER2/neu antibodies, urokinase type plasminogen activator (uPA) amino-terminal fragments (ATF), and single chain anti-epidermal growth factor receptor (EGFR) antibodies, have been conjugated on the surface of MNPs, so that the nanoprobes would be recognized and internalized by tumor cells expressing a specific receptor.

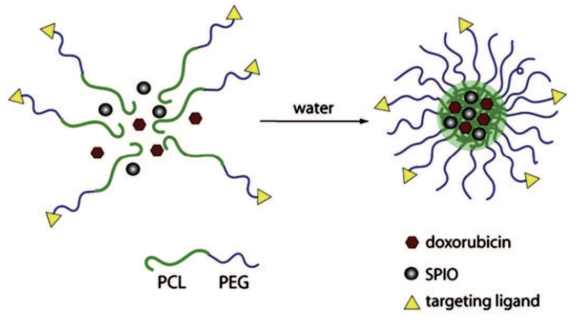


Fig. 5. Schematic illustration of the encapsulation process for DOX-SPIO.[50] Reproduced with permission from Ref. [50]. Copyright 2008 Elsevier Ltd.

Other applications in polymer coatings are also beneficial. To simplify the coating procedures, researchers have developed "one-pot" methods, a series of copolymers can now be used to accomplish *in situ* coating of MNPs.[58] Nevertheless, the growth of nanocrystals can be influenced as a result of the presence of polymers, leading to abnormal structures and surfaces of MNPs (Fig. 5).[59] Polymers or macromolecules such as peptides or PEG have the conformation to form a monolayer by self-assembly;[60] consequently polymer coatings can be formed by self-assembly on the surface of MNPs.[59,61–64] Polymer coatings' effects on NP magnetic properties is also a research field.[43,65,66] Gao *et al.* reported novel multifunctional polymeric micelles composed of a chemotherapeutic agent doxorubicin (DOXO) and a cRGD ligand.[65] They demonstrated that each micelle loaded a cluster of superparamagnetic iron oxide (SPIO) nanoparticles inside, allowing the micelles to be tracked by ultrasensitive MRI detection of the MNPs.

3.2. Liposome and micelle encapsulation

As one of the earliest tools for drug delivery in nanomedical practice, liposome techniques have been developing for a long time. Liposome are composed of a lamellar phase lipid bilayer, so they are usually biocompatible. Having a bilayer structure, amphipathic liposomes can encapsulate MNPs and can have diameters ranging from 100 nm to 5 μm. Thus, another advantage of liposome encapsulation is to gather a certain number of MNPs for collective delivery to the target. For these reasons, liposome complexes are an ideal platform for delivery of contrast agents in MRI.[67,68]

Polymeric micelles offer the advantage of multifunctional carriers that can serve as delivery vehicles carrying nanoparticles, hydrophobic chemotherapeutics and other functional materials and molecules. Stimuli-responsive polymers are especially attractive since their properties can be modulated in a controlled manner. Due to its large encapsulation range, molecules, proteins, DNA and MNPs can all be encapsulated

by liposome as one unit.[69]

4. Coating modification with inorganic materials

4.1. Silica coating

Coating MNPs with inorganic agents is generally accomplished by chemical reaction. Silica is most widely used for surface modification via an inorganic coating. Silica-coated MNPs always form core-shell structures. Silica has many advantages over organic coatings. Silica-coated NPs are robust, water-soluble, colloidally stable and photostable.[70,71] Serving as protective coatings, silica shells are easy to synthesize with controlled size. The general method to produce silica coating can be divided into two types: classical Stober method[72–74] (in aqueous phase) and sol-gel method[75–77] (in both aqueous and oleic phase).

The functionalization of silica shells is similar to ligand adsorption. This inevitably makes the diameter of the modified MNPs too large, which affects the biocompatibility, fluidity, stability and magnetic performance of the MNPs. To control the thickness of the silica shell, researchers have utilized tetraethoxysilane (TEOS) as the source of silica, controlled reaction conditions very carefully, and finally obtained diameters from 10 nm to 1 μm.[77–79] Zhang *et al.* studied the regulation of the controlled synthesis of Fe_3O_4@SiO_2 core-shell nanoparticles via a reverse microemulsion method.[80] They found that the thickness of the silica shell increased with the size of the aqueous domain. This result can guide us to avoid the formation of core-free silica particles (Fig. 6).

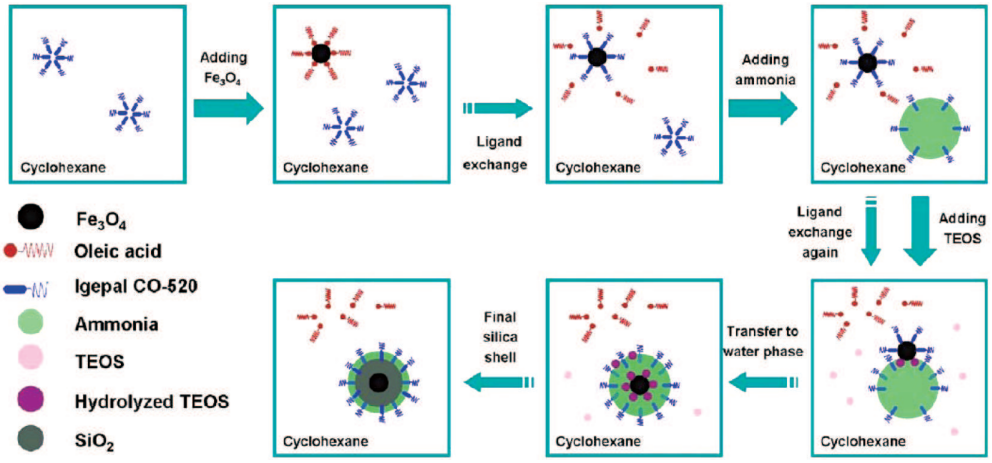


Fig. 6. The coating mechanism of SiO_2 on the surface of Fe_3O_4 NPs.[80] Reproduced with permission from Ref. [80]. Copyright 2012 American Chemical Society.

With controlled size, silica shells are appropriate for encapsulation of NPs and organic molecules like dyes or drugs. Salgueirino-Maceira *et al.* encapsulated Fe_3O_4 NPs and CdTe quantum dots within composite silica spheres.[81] These silica spheres can serve as both luminescent and magnetic nanomaterial. *Zhu et al.* accomplished the same function by embedding a dye molecule inside the silica shell.[82] Researchers also focus on the synthesis of various other core-shell structures. Deng *et al.* synthesized superparamagnetic microspheres with an Fe_3O_4@SiO_2 core and a perpendicularly aligned mesoporous SiO_2 shell (Fig. 7).[83] The microspheres possess very high magnetization, large surface area, large pore volume, and uniform, accessible mesopores. Wu *et al.* reported a silica nanoshuttle as a drug delivery system with a nanoscale PEGylated-phospholipid coating and a 13-(chlorodimethylsilylmethyl)heptacosane-derived mesoporous silica NP.[84] The therapeutic and imaging agents were trapped and ligand-assisted targeted delivery was achieved through surface functionalization of the phospholipids. Recently, silica shells with foamed or porous structures have received more attention do to the convenience of loading and releasing drugs.[85,86]

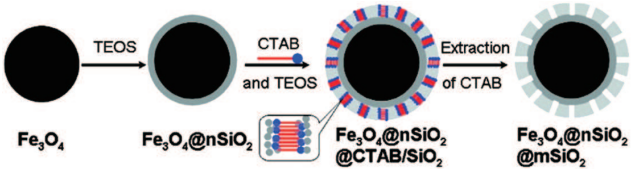


Fig. 7. Synthesis route of Fe_3O_4@nSiO_2@mSiO_2.[83] Reproduced with permission from Ref. [83]. Copyright 2008 American Chemical Society.

A robust core-shell structure, silica coated MNPs can be functionalized with various biomolecules. The silica shell tends to adsorb molecules, but silane coupling agents can significantly inhibit this process.[87,88] These agents always consist of siloxy (linking with silica shells) at one side and biocompatible groups like amino, sulfydryl and so on (linking with biomolecules) or even biomolecules themselves that al-

ready incorporate a silane group at another side. Biomolecules can easily be added to the outer shells by using alkoxysilanes with active groups, such as aminopropylsilane (APS) or mercaptopropylsilane (MPS).[89–92]

4.2. Metal element coating

The metallic elements used for surface modification are relatively inert in order to act as a protective layer. The coating metal and MNPs are tightly coupled through a chemical reaction process. The metal coating is more easily biofunctionalized than the bare surface of MNPs.

Gold is the major element among noble metal coatings. Due to strong conjugation with sulfur, gold offers remarkable advantages in sulfydryl-containing surface coatings.[93,94] Because of the chemical inertness of gold, forming gold shells is difficult, so gold coated MNPs are completely stable. Zhong *et al.* produced gold-coated iron oxide nanoparticles via a reduction of gold precursors on iron oxide nanoparticles of selected sizes as seeds.[94] Williams *et al.* synthesized gold-coated iron oxide NPs via iterative hydroxylamine seeding. The gold-coated particles exhibit a surface plasmon resonance peak that blue-shifts from 570 to 525 nm with increasing Au deposition and the magnetic properties of NPs are largely independent of Au addition. In addition to core-shell structures, Au-coated MNPs with heterostructures are widely used in medical practice (Fig. 8).[95,96] Gold also has a good photothermal property. Kim *et al.* fabricated a new gold nanorod (GNR) conjugated with MNP composite.[97] The GNR-MNP performed very efficiently as a photothermal agent for repeated cycles of photothermal ablation of bacteria.

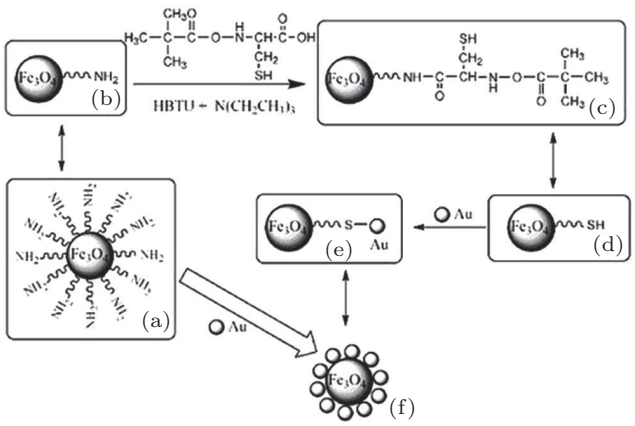


Fig. 8. Synthesis process of Au-Fe_3O_4 nanoparticles.[95] Gold nanoparticles are attached to the surface of Fe_3O_4 nanoparticles. Reproduced with permission from Ref. [95]. Copyright 2007 American Chemical Society.

Silver is another element among noble metal coatings. Silver coating makes MNPs germicidal,[98] because silver has very strong sterilization ability. The study of silver coating is very similar to that of gold. Silver can also form both core-shell structures and heterostructures.[99,100] Chen *et al.* synthesized Fe_3O_4@C@Ag hybrid nanoparticles.[101] Owing to the carbon and silver on its surface, this nanoprobe, synergistically combining NIR-controlled drug release and the two imaging modes of MRI and two-photon fluorescence (TPF) imaging, could lead to a multifunctional system for medical diagnosis and therapy. Sometimes researchers utilize gold and silver together, looking for better biomedical properties.[102]

Some rare earth elements can be also be used in surface modification via the formation of core-shell structures. For example, an Fe_3O_4@$NaLuF_4$:Yb,Er/Tm core-shell nanostructure with multifunctional properties was developed by stepwise synthesis (Fig. 9).[103] Comprising an Fe_3O_4 core and a $NaLuF_4$shell, this class of nanoprobes combines the merits of three imaging modes, upconversion luminescence (UCL), MR and computed tomography (CT), and is suitable for various applications requiring different spatial resolutions and imaging depths.

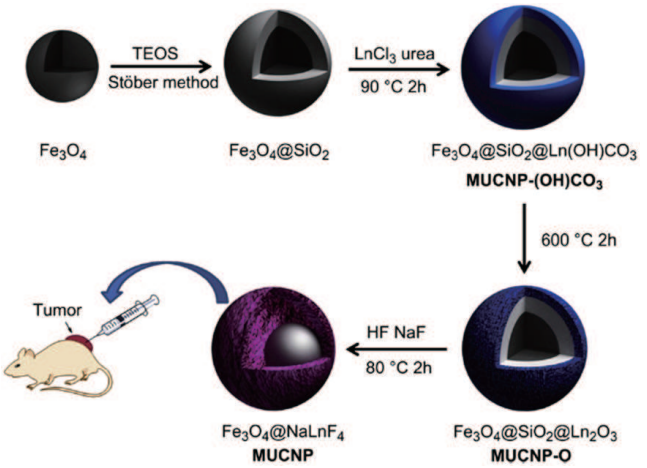


Fig. 9. Synthesis process of Fe_3O_4@$NaLuF_4$ nanoparticles.[103] Reproduced with permission from Ref. [103]. Copyright 2012 Elsevier Ltd.

5. Conclusions and outlook

This review presents the surface modification of MNPs by discussing separately three groups of surface modification agents and investigating the processes of applying them. With regard to ligand exchange and ligand absorption, two key modes of surface modification, an enormous variety of MNPs are discussed. Moreover, MNPs can be a multifunction platform for medical practice, in both diagnosis and therapy, after modifying the particles' surface with optical dyes, targeting agents, therapeutic drugs or other functional molecules.

Presently, the study of MNPs is developing rapidly. Researchers expect to attain MNPs that combine multiple functions that are much needed in clinical practice. It seems that functionality is the number on requirement for future MNPs. However, in research, we must think comprehensively of all the properties of MNPs, like stability, safety, economy and efficiency, rather than only multifunctionality, so that the MNPs can indeed be applied in medical practice. Accordingly, as-

pects such as biocompatibility, toxicity, *in vivo* and *in vitro* targeting efficiency, and long-term stability of the functionalized MNPs must receive more attention. Meanwhile, there is an immense requirement for surface-modification materials that are convenient, efficient, biocompatible and stabilized. In the future, further development of surface modification is expected to realize the union of diagnosis and therapy at nanoscale, and with ever-improving techniques of surface-modification engineering, research in multifunctional MNPs is sure to remain a frontier of biomedical science.

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