Iron Oxide-based Superparamagnetic Polymeric Nanomaterials: Design, Preparation, and Biomedical Application

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Abstract

Superparamagnetic iron oxide nanoparticles (SIONPs) have great potential for various biomedical applications, including magnetic resonance imaging (MRI) contrast enhancement, targeted drug delivery, hyperthermia, catalysis, biological separation, biosensors, and diagnostic medical devices. For the development of SIONPs toward bio-related applications, control of the surface chemistry of SIONPs is required. Polymers with more than one group capable of binding to particle surfaces (multidentate ligands) can enhance the stability of SIONPs as well as their optical, magnetic, and electronic properties. Most synthetic and bio-based polymers are transparent in the visible range of electromagnetic spectrum, not interfering with biological process. Additionally, polymers provide mechanical and chemical stability to the nanomaterials. The present review summarizes the recent advances in design and biological applications of polymer-embedded SIONPs.

Outline

1. Introduction

Colloidal inorganic nanometer-sized particles (nanoparticles, NPs) or nanocrystals (NCs) have proved to be useful as building blocks for the development of nanomaterials and biomaterials in nanoscience and biotechnology. This is because of their unique structural and optical properties that are attributed to nanoscale phenomena.[1] Superparamagnetic iron oxide NPs (SIONPs) including Fe_3O_4 magnetite and Fe_2O_3 maghemite have great potential for various biomedical applications. They include magnetic resonance imaging (MRI) contrast enhancement, targeted drug delivery, hyperthermia, catalysis, biological separation, biosensors, and diagnostic medical devices.[2-8] Other magnetic NPs have also been developed, including iron-based FePt,[9-15] FePd,[16] Co-based CoPt,[17, 18] CoO,[19] and $CoFe_2O_4$,[20] as well as Mn-based MnPt,[21] Gd-based NPs,[22-26] and their inorganic-inorganic hybrid nanomaterials.[27-33]

For the development of SIONPs toward bio-related applications, control of the surface chemistry of SIONPs is required. Pristine SIONPs tend to aggregate into large clusters, because of their large surface-to-volume ratio and dipole-dipole interaction. The resulting large agglomerates reduce intrinsic superparamagnetic properties. The surface of SIONPs has been modified to not only prevent aggregation of the particles, leading to colloidal stability, but also render them with water-solubility, biocompatibility, and nonspecific adsorption to cells. In addition, control of surface chemistry can allow for the flexibility and functionality of SIONPs that enable efficient coupling of these probes to bioactive molecules capable of targeting and sensing biological processes. Several approaches to modification of the surface of SIONPs with small molecules including biomolecules have been investigated for the preparation of water-soluble SIONPs. The general approach is the post-addition of water-soluble ligands, including direct adsorption,[34-38] addition of second layer,[39-41] ligand exchange,[23, 42-45] functional silica coating,[46-50] and ionic interaction.[51] *In-situ* formation approach directly yields water-soluble SIONPs

in the presence of stabilizing ligands. Typical examples include Fe_3O_4 NPs coated with D-mannose,[52] 2-pyrrolidone,[53] and poly(ethylene glycol) diacids (HOOC-PEG-COOH),[54] as well as iron oxide nanoworms coated with dextran (Dex).[55]

Polymers with more than one group capable of binding to particle surfaces (multidentate ligands) can enhance colloidal stability of inorganic NPs including SIONPs as well as their optical, magnetic, and electronic properties.[56] Most synthetic and bio-based polymers are transparent in the visible range of electromagnetic spectrum, not interfering with biological process. Additionally, polymers provide mechanical and chemical stability to the nanomaterials. The present review will summarize the recent advances in design, preparation, and biological application of polymer-embedded SIONPs. The methods that have been developed to prepare unique polymer-SIONP hybrid nanomaterials include direct modification with polymers, surface-initiated controlled polymerization, inorganic silica/polymer hybridization, self-assembly, self-association, and various heterogeneous polymerization methods. These methods provide magnetic polymer composites that differ in morphologies.[57] Figure 1 illustrates the various morphologies, including magnetic core–polymer shell (a), magnetic multicores homogeneously dispersed in polymer matrix (b), magnetic NPs located on the surface of a polymer core ("raspberry" morphology, c), and brush (hair)-like morphology with polymer chains attached to a magnetic core (d).

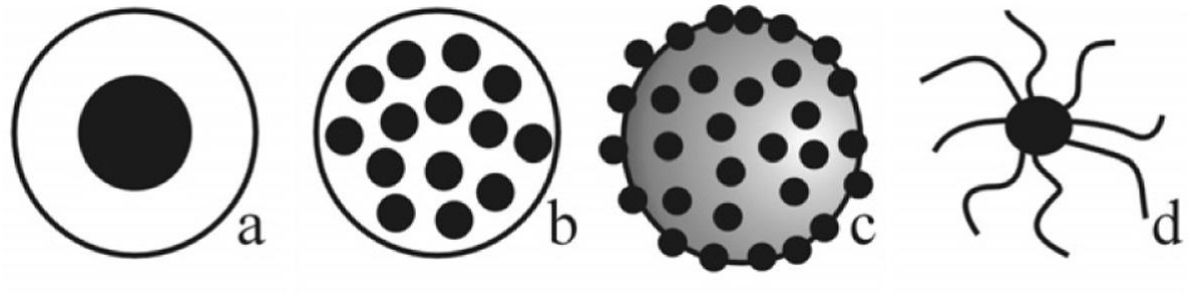

Figure 1. Different morphologies of composite magnetic polymer microspheres; single-core (a), multicore or embedded (b), raspberry-like or heterocoagulated (c), and brush-like morphology (d). Reprinted with permission from ref [57]. Copyright 2007 Wiley InterScience.

1.1. Synthesis of superparamagnetic iron oxide NPs (SIONPs)

Coprecipitation of Fe(II) and Fe(III) ions from an aqueous basic solution is a facile method for the preparation of SIONPs in water. Several parameters should be controlled to prepare SIONPs with narrow size distribution. They include pH, temperature, and mixing method, as well as nature and concentration of anions. In general, $FeCl_3$ and $FeCl_2$ solutions are mixed at a concentration ratio of Fe(III)/Fe(II) = 2/1 in an aqueous ammonia solution, yielding Fe_3O_4 SIONPs with d = 3 – 15 nm. Recently, a droplet-based microfluidic system has been designed to prepare SIONPs via coprecipitation of Fe(II) and Fe(III) solutions in an continuous oil phase (**Figure 2**). The microfluidic device was designed in such by injecting two aqueous Fe salt solutions through the outer channels, which were synchronously emulsified by central oil channel. This approach enabled fast (millisecond scale) preparation of SIONPs with d = 4 nm.[58]

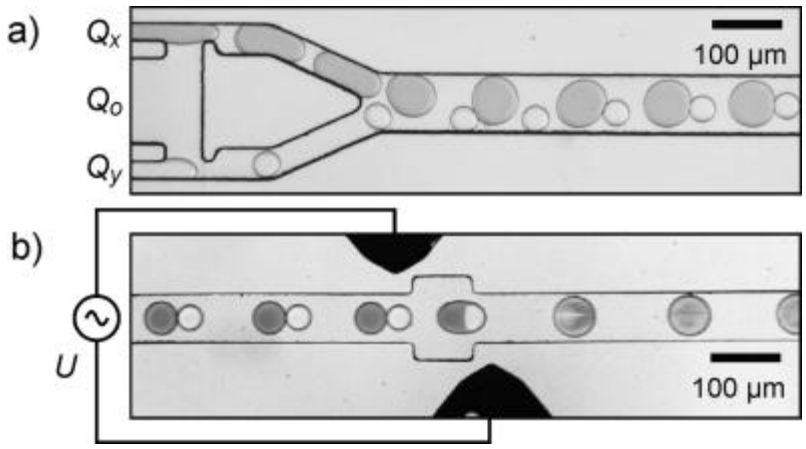

Figure 2. Design of droplet-based microfluidic system for the preparation of magnetic Fe_3O_4 nanocrystals via coprecipitation of aqueous Fe(II) and Fe(III) solutions in oil. Pairing module with Q_o for oil and Q_x and Q_y for two aqueous phases (a); fusion module where paired droplets are coalesced by applying an electric voltage U between two electrodes (b). Reprinted with permission from ref [58]. Copyright 2008 Wiley InterScience.

Organic solution-phase synthesis, also known as thermal decomposition of iron precursor in hot surfactant solutions, has been developed for the preparation of high-quality monodisperse SIONPs. Direct decomposition of $FeCup_3$[59] and $Fe(CO)_5$[60] followed by oxidation produced monodisperse Fe_2O_3 maghemite nanocrystals. High temperature reaction of Fe(III) acetylacetonate ($Fe(acac)_3$) in the presence of oleic acid and oleylamine as stabilizing ligands in phenyl ether at 265 °C yielded monodisperse Fe_3O_4 magnetite NPs with a diameter of 16 nm. The resulting magnetite NPs was oxidated to Fe_2O_3 maghemite NPs at 250 °C in the presence of oxygen for 2 h.[61] A mild condition of thermal decomposition of $Fe(CO)_5$ in oleic acid and octyl ether at 100 °C for 2 h and consecutive aeration was developed for the preparation of maghemite NPs with a diameter ranging from 5 to 19 nm and magnetite NPs with 19 nm diameter, as seen in TEM images (**Figure 3**).[62] Recently, thermal decomposition of iron oleate precursors in the presence of oleic acid salts was reported for the preparation of iron oxide nanocrystals with various shapes including spheres, cubes, and bipyrimids.[63] In addition, the thermal decomposition method combined with thermal oxidation was explored for the preparation of hollow Fe_3O_4 from Fe/Fe_3O_4 core/shell NPs.[64] To avoid the use of oleylamine, oleic acid,

or trioctylamine which may create environmental concerns, the thermal decomposition of $Fe(acac)_3$ in the presence of environmentally friendly benzyl alcohol at 200 °C for 2 days was conducted , producing Fe_3O_4 SIONPs with a diameter ranging from 12 to 25 nm.[65]

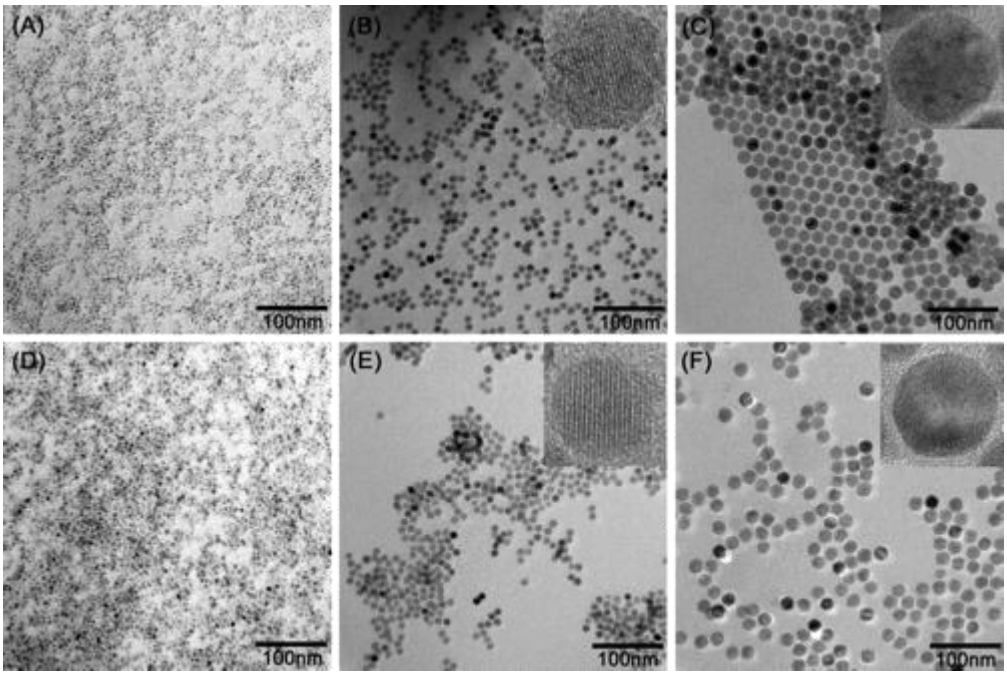

Figure 3. TEM images of respective intermediate and aerated iron oxide NPs: 5 nm (A) and (D), 11 nm (B) and (E), and 19 nm (C) and (F); insets are High resolution (HR) TEM images. Reprinted with permission from ref [62]. Copyright 2004 American Chemical Society.

Solvothermal reaction by reduction of $FeCl_3$ in hot organic solvents such as ethylene glycol has been explored for the preparation of water-dispersible Fe_3O_4 ferrite microspheres,[66-68] microclusters,[69] and nanorings[70] with a diameter of 30 – 800 nm. In addition, hetero-structured nanocrystals (or heterogeneous inorganic-inorganic hybrid NPs) containing iron oxides have been explored to integrate multiple nanocrystal components into a single nanosystem. Examples include Fe_2O_3/ZnS[71] and Fe_3O_4/Au[72, 73] core/shell, FePt/Fe_2O_3 yolk-shell,[74] as well as Fe_3O_4/CdSe[75, 76] heterodimers, and Fe_3O_4 core/layered double hydroxide.[77] Mn-doped iron oxide nanoparticles were prepared to enhance

MRI contrast and hyperthermic effects.[78-81] In addition, the preparation of various silica-coated Fe_2O_3 or Fe_3O_4 NPs,[82-85] silica/Fe_3O_4 core/shell,[86] Fe_2O_3/SiO_2 Janus,[87] and silica-satellite Fe_3O_4 NPs[88] has been reported.

2. Direct modification with polymers

Various approaches to modify SIONPs with multidentate polymers (possessing multiple anchoring groups in polymer backbones) have been explored to prepare water-soluble/water-dispersible polymer-stabilized SIONPs. The typical approaches include physical adsorption, addition of second layer, functional silica coating, and ionic interaction. For the approaches, novel polymers including synthetic polymers and biopolymers are designed, prepared, modified by various methods.

The physical adsorption can be achieved by addition of stabilizing copolymers either during or after the preparation of SIONPs. This approach includes the design and preparation of functional copolymers with two different blocks. An anchoring block contains particularly carboxylic acids that enable the adhesion to the surface of SIONPs; another water-soluble block contains water-soluble groups, particularly poly(ethylene oxide) (PEO), that render SIONPs water-soluble and biocompatible. Control radical polymerization (CRP)[89] methods have been utilized to prepare well-controlled block copolymers with predetermined molecular weight and narrow molecular weight distribution (M_w/M_n < 1.3). Atom transfer radical polymerization (ATRP) has allowed for the preparation of well-controlled poly(oligo(ethylene oxide) monomethyl ether methacrylate)-b-poly(t-butyl acrylate) (POEOMA-b-PtBA) block copolymer. The resulting POEOMA-b-PtBA was then hydrolyzed in acidic conditions, yielding POEOMA-b-poly(methacrylic acid) (POEOMA-b-PMAA). PMAA block is anchored to SIONP surface and POEOMA block renders water-soluble and biocompatible. In the presence of water-soluble POEOMA-b-PMAA, SIONPs were prepared by coprecipitation of Fe(II) and Fe(III), yielding Fe_3O_4 SIONPs stabilized with POEOMA-b-PMAA block copolymers (**Figure 4**). Their diameters were

tuned in the range of 10 – 25 nm by varying the initial copolymer concentration. The resulting polymer-stabilized SIONPs with long-term colloidal stability could be useful as MRI contrast agents.[90] The combination of ATRP of solketal acrylate (SA), functionalization with folate, and hydrolysis of PSA allowed for the preparation of well-controlled folate-functionalized poly(glycol monoacrylate) (Folate-PGA). Hydroxyl groups enabled PGA to be absorbed on SIONPs, yielding folate-conjugated PGA-coated SIONPs.[91]

Reversible addition-fragmentation chain transfer (RAFT) polymerization has also been utilized. Well-defined poly(acrylic acid) (PAA) homopolymer was prepared in dimethylformamide (DMF). A subsequent RAFT polymerization yielded well-defined triblock copolymer consisting of PAA, poly(N-isopropylacrylamide) (PNIPAM), and POEOMA blocks. The resulting PAA-b-PNIPAM-b-POEOMA block copolymer was post-added to Fe_3O_4 NPs. The resulting Fe_3O_4 NPs stabilized with triblock copolymers exhibited volume change in response to external stimuli such as temperature and pH. For example, the diameter of Fe_3O_4 NPs stabilized with PAA_{41}-b-$PNIPAM_{150}$-b-$POEOMA_{90}$ triblock copolymer decreased from 70 to 45 nm in response to temperature change from 39 to 25 °C. This quality is highly applicable towards hypothermia.[92] Well-controlled poly(2-acetoacetoxyethyl methacrylate) (PAAEM-b-POEOMA) was prepared by the RAFT polymerization. Coprecipitation of Fe(II) and Fe(III) in the presence of PAAEM-b-POEOMA block copolymer yielded SIONPs stabilized with diblock copolymer, in which pendent acetoacetoxy groups anchored to the surfaces of SIONPs.[93]

In addition to CRP, other polymerization methods have been explored for preparation of well-controlled block polymers that can stabilize SIONPs. These polymers consist of pendent COOH or epoxy groups as anchoring blocks, yielding polymer-encapsulated SIONP dispersions. Examples include anionic polymerization and sequential photo-crosslinking for poly(isoprene)-b-poly(2-cinnamoylethyl methacrylate)-b-PAA,[94] polycondensation for PEO-b-poly(COOH-containing urethane)-b-PEO,[95] ring-opening polymerization and subsequent hydrolysis for PEO-b-poly(aspartic

acid),[96] and ring-opening metathesis polymerization (ROMP) for diblock copolymer of bicycle[2,2,1]hept-5-ene-2-carboxylic acid oxiranylmethyl ester.[97]

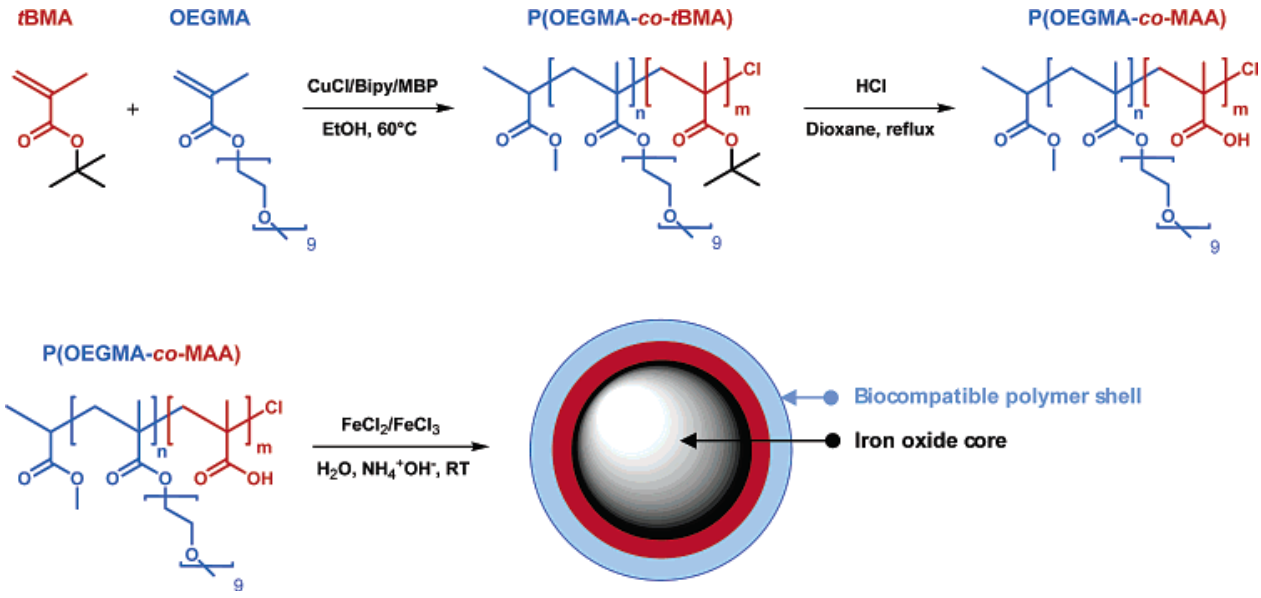

Figure 4. Schematic illustration for preparation of well-controlled POEOMA-b-PMAA copolymer and polymer-coated SIONPs. Reprinted with permission from ref [90]. Copyright 2006 American Chemical Society.

The addition of second layer approach involves the use of amphiphilic block copolymers consisting of a hydrophobic portion that intercalates the hydrophobic stabilizing ligands such as oleic acid on magnetic NPs and a hydrophilic portion that ensures water solubility of magnetic NPs. As illustrated in **Figure 5**, oleic acid-stabilized Fe_3O_4 NPs was first prepared by thermal decomposition of iron oleate ($Fe(oleate)_3$) in dioctyl ether. The resulting organic solution was added into an aqueous solution of Pluronic F127, an amphiphilic PEO-b-poly(propylene oxide) (PPO)-b-PEO block copolymer. The obtained oil-in-water microemulsion was dried, yielding a fine powder of F127-stabilized Fe_3O_4 NPs. They were then redispersed in water, resulting in the formation of water-soluble magnetic NPs.[98] Amine-end-functionalized PNIPAM (PNIPAM-NH_2) was prepared by free radical polymerization in DMF, and then reacted with poly(maleic anhydride-alt-octadecene). Magnetic NPs stabilized with the

resulting PNIPAM-based amphiphilic block copolymer exhibited volume change in response to temperature change.[99]

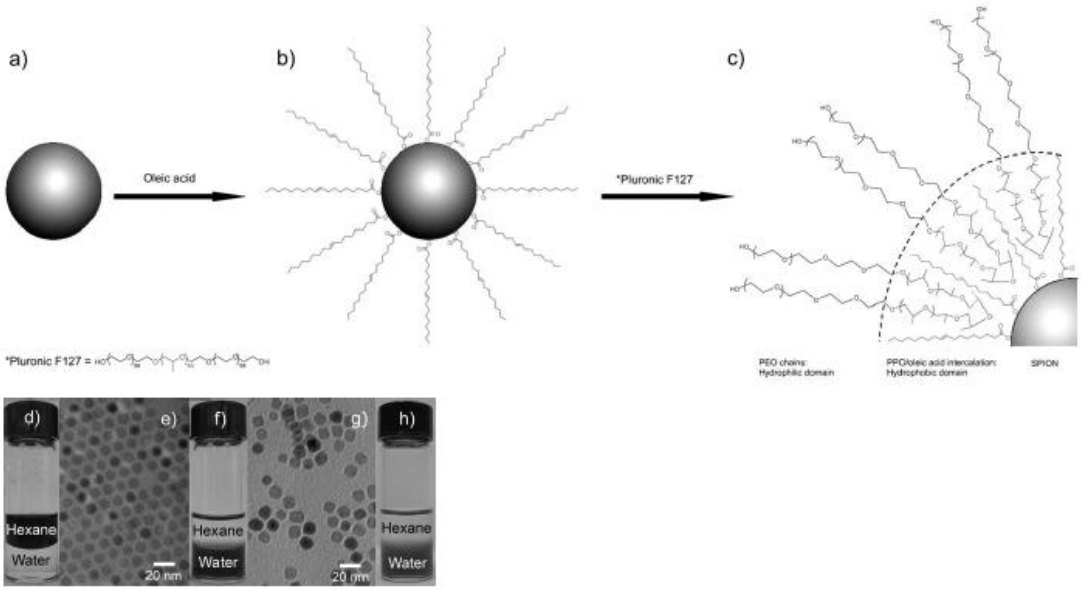

Figure 5. Schematic illustration for preparation of water-soluble magnetic NPs by addition of second layer approach, in which F127 PEO-b-PPO-PEO amphiphilic block copolymer is added into to oleic acid-stabilized magnetic NPs (a-c). Digital pictures show the distribution of magnetic NPs before (d) and after (f) phase transfer and F127-stabilzied magnetic NPs in water showing colloidal stability after four months (h). TEM images of magnetic NPs in hexane (e) and water (g). Reprinted with permission from ref [98]. Copyright 2007 Wiley InterScience.

For the functional silica coating approach, copolymers bearing trimethoxysilyl groups capable of crosslinking reactions on SIONPs have been prepared. Examples include copolymers consisting of poly(3-trimethoxysilyl)propyl methacrylate (PEPMA) and poly(N-acryloxysuccinimide) (PNAS).[100] PNAS block was further functionalized with Cy5.5 fluorescent dye for *in vivo* tumor detection by dual magnetic resonance and fluorescence imaging.[101] Ionic interaction between negatively charged SIONPs and positively charged poly(L-lysine) has been utilized for stem cell labeling.[102] In addition, dopamine-conjugated hyaluronic acid (HA),[103] polypeptide with a sequence of GGGGYSAYPDSVPMMSK (a targeting ligand for ovarian cancer cells),[20] virus,[104] Dex,[105] Dex-

derivative modified with TAT-derived peptide,[106] dopamine-plus-human serum albumin,[107] and dendrimer[108] has been utilized to modify SIONPs for MR cancer imaging.

3. Surface-initiated controlled polymerization: "grafting from" method

The general approach for "grafting from" method involves the utilization of surface-initiated CRP methods. ATRP method has been extensively utilized for modification of single SIONP with well-controlled polymers because of facile functionalization of SIONPs with ATRP initiating species (halides) for surface-initiated controlled polymerization. Two routes for immobilization of halide-initiating species have been proposed. The first route involves physical absorption of acid-functionalized halides on SIONPs. They include 3-chloropropionic acid,[109, 110] 2-bormo-2-methyl propionic acid,[111] and 10-carboxydecanyl-2-bromo-2-methyl-thiopropanoate,[112] which initiate the ATRP of styrene (St) and OEOMA in bulk or in organic solvents, yielding single SIONP coated with hydrophobic PSt or water-soluble POEOMA. In addition, SIONPs were functionalized with 2-bormo-2-methyl propionic acid, which initiated ATRP of 2-methoxyethyl methacrylate (MEMA). The resultant PMEMA-coated SIONPs exhibited quick temperature responsiveness at upper critical solution temperature (UCST) in MeOH. As seen in **Figure 6**, PMEMA-coated magnetic NPs were precipitated at below UCST; however at above UCST, they were redispersed to form a stable dispersion that shows collective response to a permanent magnet.[113] The other route for the functionalization of SIONPs with ATRP initiating halides involves the covalent attachment via silanization. Examples include the immobilization of 2-(4-chlorosulfonylphenyl)ethyltrichlorosilane for poly(methyl methacrylate),[114] [11-(2-bromo-2-methyl)-propionyloxy]undecyltrichlorosilane for PSt,[115] and [4-(chloromethyl)phenyl]trichlorosilane for POEOMA.[116]

The RAFT polymerization method has also been explored to modify single SIONP with well-controlled polymers. An example includes the treatment of SIONPs with ozone to create hydrogen

peroxides, free radical initiating species. RAFT polymerization of St or acrylic acid (AA) in the presence of 1-phenylethyl dithiobenzoate (PDB) in DMF was then carried out, yielding PSt or PAA-grafted magnetic NPs. They were characterized with X-ray photoelectron spectroscopy (XPS), FT-IR spectroscopy, and gel permeation chromatography (GPC).[117] Another example include the ligand exchange oleic acid on Fe_3O_4 with S-1-dodecyl-S'-(α,α'-dimethyl-α"-acetic acid)trithiocarbonate (DDMAT), a RAFT agent, followed by RAFT polymerization of NIPAM. The resulting PNIPAM-coated SIONPs exhibited thermoresponsiveness.[118]

In addition to the "grafting from" method, the "grafting onto" method has also been utilized for the preparation of SIONPs coated with single layer of polymers. For the method, polymers are designed to be monodentates that possess a terminal anchoring group at the end of polymer, or made of hyperbranched architectures with functionalities introduced in the focal points. Examples include thiol-terminated PSt[119] and phosphonate-functionalized PEO.[120]

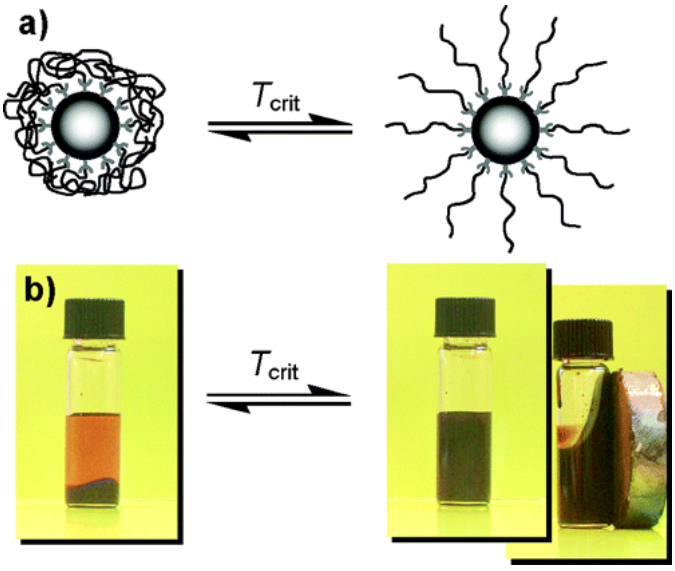

Figure 6**.** Schematic illustration (a) and photographs (b) of thermoresponsive PMEMA-coated magnetic NPs. The particles precipitate at below UCST; at above UCST, they are redispersed that reacts collectively under the influence of a permanent magnet. Reprinted with permission from ref[113]. Copyright 2006 American Chemical Society.

4. Inorganic silica/polymer hybridization

SIONPs prepared by either coprecipitation or thermal decomposition are encapsulated with a silica shell through a sol-gel process of tetraethyl orthosilicate (TEOS). The resulting silica-coated SIONPs were further functionalized and encapsulated with polymers, yielding multifunctional hybrid nanomaterials. The preparation of hairy hybrid nanomaterials consisting of magnetic core, fluorescent silica shell, and functional polymer brushes is illustrated in **Figure 7**. This approach began with the sol-gel reaction in the presence of Fe_3O_4 NPs including fluorescein isothiocyanate (FITC), a fluorescent dye, producing Fe_3O_4 core-fluorescent silica shell, in which FITC is covalently incorporated. The resultant silica shell was functionalized with methacrylates by reacting with 3-methacryloxypropyltrimethosysilane (MPS) and then chlorines via radical crosslinking polymerization of ethylene glycol dimethacrylate (EGDMA) and vinyl benzyl chloride. The chlorine groups served as initiators for ATRP of OEOMA, yielding hybrid nanomaterials with biocompatible POEOMA brushes.[121] Silica-coated Fe_3O_4 SIONPs prepared by the sol-gel reaction of TEOS were encapsulated with crosslinked polyphosphazene, yielding pomegranate-like core/shell structured nanomaterials.[122] In addition, sol-gel reaction of TEOS in the presence of Fe_3O_4 NPs and cetyltrimethylamonium bromide (CTAB), functionalization with MPS, and then removal of CTAB yielded methacrylate-functionalized, Fe_3O_4-embedded silica nanomaterials with channels. They were coated with thermoresponsive polymeric shells consisting of PNIPAM copolymers for drug delivery applications.[123]

In another approach, amino-functionalized silica-coated Fe_3O_4 SIONPs were prepared by the reaction of silica-coated Fe_3O_4 with 3-aminoporpyltirethyoxysilane (APS). They were mixed with acid-functionalized core/shell microgels consisting of P(St-co-NIPAM) core and crosslinked PNIPAM shell. The removal of core P(St-co-NIPAM) by dissolving in tetrahydrofuran (THF) yielded crosslinked PNIPAM capsules surface-anchored with silica-coated Fe_3O_4 SIONPs (**Figure 8**).[124]

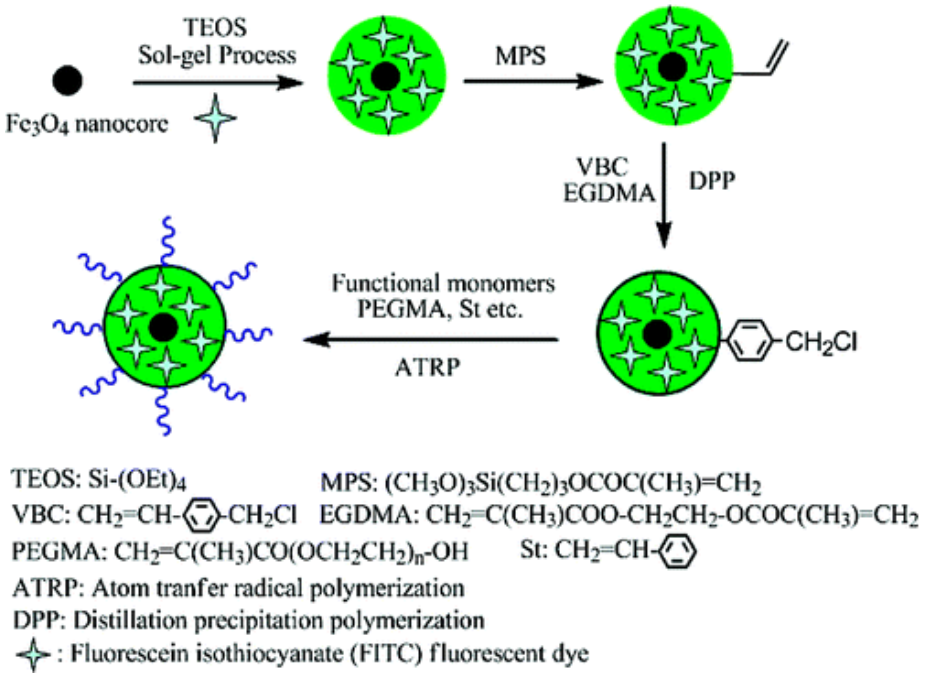

Figure 7. Synthesis of hairy hybrid nanomaterials with a magnetic core, fluorescent silica shell, and functional polymer brushes. Reprinted with permission from ref [121]. Copyright 2009 American Chemical Society.

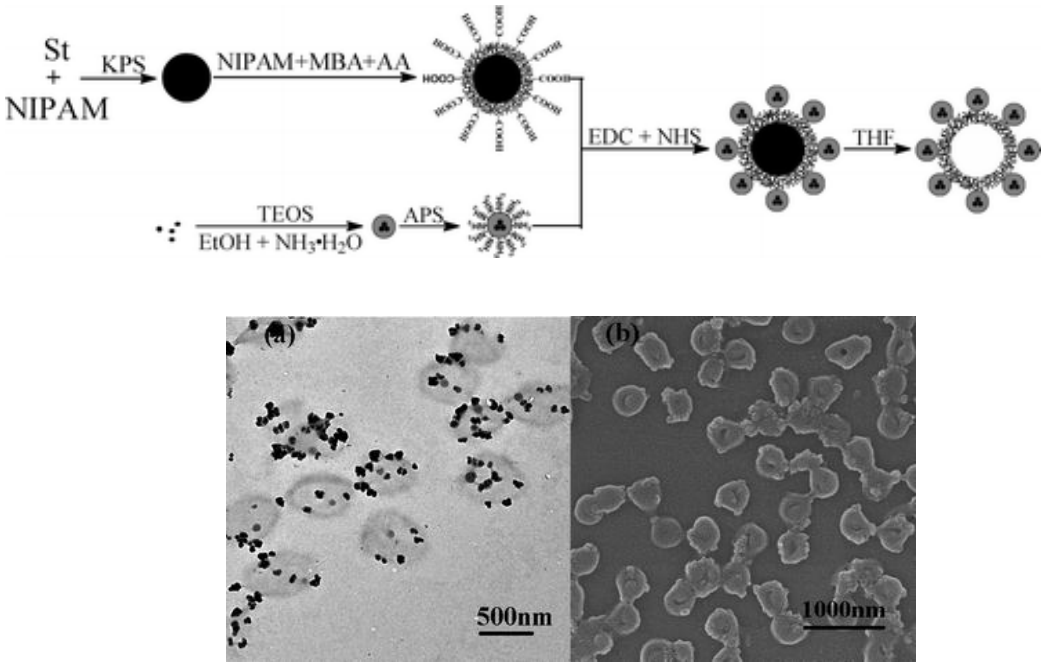

Figure 8. Preparation (upper) and TEM (a) and SEM (b) images of crosslinked PNIPAM capsules surface-anchored with silica-coated Fe_3O_4 NPs (lower). Reprinted with permission from ref [124]. Copyright 2009 American Chemical Society.

5. Self-assembly and self-association

Self-assembly method involves the design and preparation of amphiphilic block copolymers that enable self-assembly in water, forming stable core/shell micellar NPs wherein the hydrophobic core serves as a carrier for SIONPs and anticancer drugs and the hydrophilic shell allows particle stabilization in aqueous solution. Hydrophobic SIONPs stabilized with oleic acid are physically embedded in micellar particles through self-assembly. Further targeting ligands are attached to the surface of self-assembled NPs embedded with SIONPs and anticancer drugs for multifunctional nanomedicine platform. Polyester-based amphiphilic block copolymers were generally prepared by ring opening polymerization (ROP) of D,L-lactide (LA) and ε-caprolactone (CL). Well-defined COOH-terminated PEO-b-PLA amphiphilic block copolymer self-assembled in the presence of hydrophobic SIONPs and doxorubicin (Dox). The resulting core/shell NPs embedded with SIONPs and Dox were then functionalized with therapeutic antibodies (targeting species to tumor) for an ultrasensitive MRI probe. It was reported that Mn-doped Fe_3O_4 ($MnFe_3O_4$) is more efficient of T_2 relaxivity for MRI than Fe_3O_4 NPs.[125] Well-controlled PLA-b-POEOMA amphiphilic block copolymer was prepared by a combination of ROP and ATRP from 2-hydroxyethyl-2'-methyl-2'-bromo-propionate, a double-headed initiator. The copolymer self-assembled in the presence of hydrophobic Fe_3O_4 NPs, and further functionalized with folates for cancer cell targeting (**Figure 9**).[126] Maleimide-terminated PEO-b- PLA and methoxy-terminated PEO-b-PLA self-assembled in the presence of Dox and SIONPs through mixed micellization. The resulting maleimide-functionalized polymeric NPs reacted with RGD tripeptide that can target integrin $\alpha_v\beta_3$ on tumor endothelial cells.[127] In addition, the preparation and self-assembly of folate-encoded PEO-b-PCL amphiphilic block polymers,[128] PEO-modified PSt,[129, 130] and PEG-phospholipid[131] amphiphilic block copolymers have been explored.

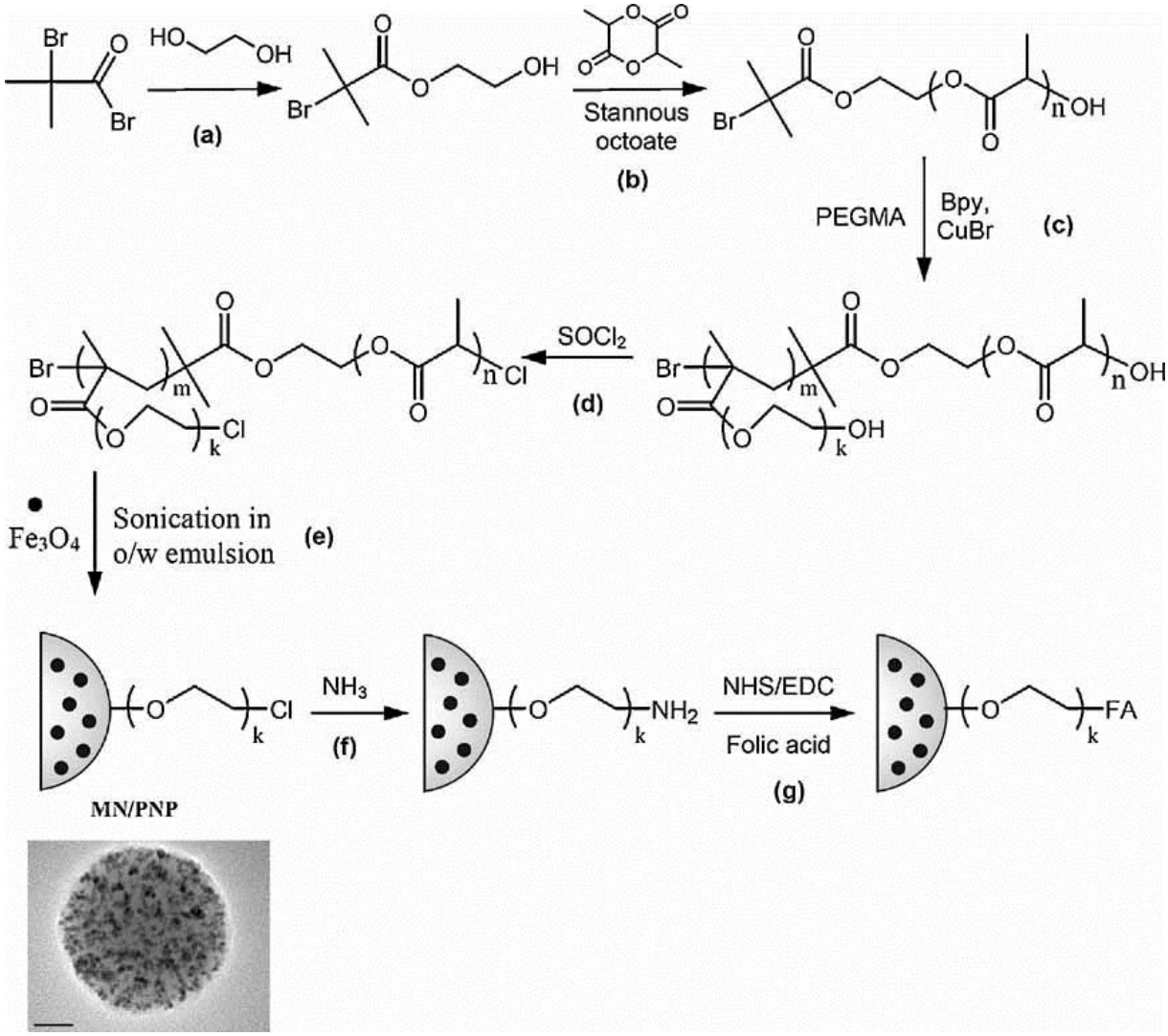

Figure 9. Schematic illustration to prepare folate-functionalized micellar NPs embedded with SIONPs from well-controlled PLA-b-POEOMA amphiphilic block copolymer by a combination of ROP and ATRP. Reprinted with permission from ref [126]. Copyright 2009 Wiley InterScience.

Self-association is generally achieved through ionic interaction between SIONPs and anionic-or cationic polymers. Examples include ionic interactions of positively-charged SIONPs/negatively-charged PAMAM dendrimers,[132] negatively-charged SIONPs (with PAA)/poly(trimethylammonium ethyl acrylate methylsulfate)-b-PAAm,[133] and vesicle aggregates crosslinked by positively-charged SIONPs.[134] Interestingly, positively-charged poly(L-lysine) (PLK) mixed with negatively-charged SIONPs modified with citrate ions resulted in self-complex coacervates, which were then post-

crosslinked with glutaraldehyde (GA) crosslinkers to obtain PLK-MIONP hybrid microspheres.[135, 136] In addition, self-complexation through hydrophobic interactions has been explored. An example includes inclusion interactions of β-cyclodextrins with oleic acid-stabilized SIONPs.[137]

Emulsification/solvent evaporation technique has also been explored for the preparation of polymeric NPs based on PLA homopolymers embedded with hydrophobic SIONPs. For the approach, hydrophobic PLA dissolved in volatile organic solvents were mixed with aqueous surfactant solution, forming oil-in-water emulsion. Solvents were then evaporated, yielding stable PLA-based NPs embedded with SIONPs in water with an aid of surfactants.[138-140]

6. Heterogeneous polymerization

Various heterogeneous polymerization reactions of hydrophilic or water-soluble monomers have been explored to prepare well-defined SIONP-embedded magnetic spheres as well as crosslinked microgels/nanogels and hydrogels for biomedical applications. These reactions include inverse (mini)emulsion polymerization, dispersion polymerization, and precipitation polymerization. In addition, heterogeneous polymerization of hydrophobic monomers such as styrene in the presence of hydrophobic SIONPs in conventional emulsion, miniemulsion, and suspension has produced magnetic hydrophobic particles.[141-149] This review concentrates on the preparation of hydrophilic magnetic particles for biomedical applications.

6.1. Inverse (mini)emulsion polymerization

Inverse (mini)emulsion polymerization is a water-in-oil (W/O) polymerization process that contains aqueous droplets consisting of water-soluble monomers stably dispersed with the aid of oil-soluble surfactants in a continuous organic medium. Stable dispersions are formed by mechanical stirring for inverse emulsion process and by sonification for inverse miniemulsion polymerization. When radical

initiators are added, polymerization occurs within the aqueous droplets producing colloidal particles.[150] An introduction of multifunctional crosslinkers allows for preparation of crosslinked microgel particles.[151] When the size of microgels is in submicron-sized, it is defined as nanogels. Several reports have demonstrated the use of inverse (mini)emulsion polymerization for the preparation of hydrophilic or water-soluble polymeric particles [152-154] and crosslinked microgels/nanogels.[155-160] Recently, a unique method utilizing controlled ATRP in inverse miniemulsion has been developed for the preparation, functionalization, and application of well-defined biodegradable nanogels for targeted drug delivery.[161-168] The details are reported elsewhere.[169]

Inverse miniemulsion polymerization has been explored to prepare well-defined hybrid magnetic polymer particles. This method requires the preparation of hydrophilic or water-soluble SIONPs.[170] An example includes the preparation of magnetic PAAm-based microgels with a diameter of 60 – 160 nm. An aqueous homogeneous solution of AAm, N,N'-methylenebisacrylamide (MBAm), and MAA-stabilized magnetic fluid in a dilute aqueous ammonia was mixed with an organic solution of Span 80 (sorbitol monooleate) in cyclohexane under stirring. The resulting bi-phase was sonicated and polymerized upon the addition of free-radical initiator, producing stable miniemulsion of magnetic PAAm-microgels with a diameter of 100 nm. The magnetite content in the particles was determined to be 13 wt %, which was consistent with the concentration of magnetite NPs in the feed.[171]

Inverse emulsion/microemulsion polymerization has also produced well-defined magnetic polymer particles. Aqueous droplets of MAA, 2-hydroxyethyl methacrylate (2-HEMA), and SIONPs were dispersed in a solution of sodium dioctylsulfosuccinate in toluene. Copolymerization of the monomers yielded hydrophilic polymer beads physically loaded with magnetic NPs, yielding composite magnetic particles of hydrophilic polymers. However, they were relatively polydisperse and only contained 3.3 wt% magnetic NPs.[172] Several approaches have been proposed to increase loading level of SIONPs into polymeric particles. One approach involves stabilization of SIONPs with double-hydrophilic block

copolymer, PEO-*b*-PMAA. A water soluble monomer mixture containing SIONPs stabilized with PEO-b-PMAA, 2-HEMA, and MAA was mixed with organic solution of poly(ethene-co-butene)-b-PEO in decane. The addition of an organic initiator yielded magnetic microspheres with a diameter of 50–250 nm and a loading level of SIONPs up to 18 wt%.[173] Another approach involves albeit the size uniformity. The magnetic loading further increased to 23%. Submicrometer-sized magnetic hydrophilic polymer particles were prepared by inverse microemulsion polymerization of AAm, MBAm, and suspension of trisodiumcitrate-stabilized SIONPs dispersed in a solution of sodium bis(2-ethylhexyl) sulfosuccinate in toluene. The resulting magnetic PAAm microgels had their particle size ranging from 80 to 180 nm in diameter, which can be controlled by the concentration of MBAm crosslinker and surfactant/water ratio. The magnetite content in polymer particles was determined to be 5–23 wt %.[174]

6.2. Dispersion polymerization

Dispersion polymerization is advantageous because micrometer-size polymer microspheres with a narrow size distribution can be obtained in a single step. Of utmost importance for the technique is the appropriate selection of the reaction medium, in which monomers are soluble, while the resulting polymer and magnetic material are insoluble. By heating the polymerization mixture, initiator is decomposed to form oligomer radicals. The oligomeric chains do not remain dissolved in the medium, but precipitate when reaching the critical chain length. The chains associate forming nuclei, which aggregate and at the same time adsorb the stabilizer forming primary mature particles containing magnetic cores. Under conditions where no new nuclei are formed, the primary particles grow and reach the uniform size.[175-177]

Dispersion polymerization was conducted with 2-HEMA in the presence of iron oxide needles or cubes (ca. 100~500 nm) in a mixture of toluene/2-methylpropan-1-ol, yielding magnetic microspheres with a diameter of 1–2 μm stabilized with acetate butyrate cellulose. Ethylene glycol dimethacrylate

(EGDMA) was added to prepare crosslinked microspheres.[178] Similar process was applied to prepare magnetic microspheres of PGMA[179-181] and PAAm[182] stabilized with poly(vinyl pyrrolidone) (PVP). In addition, magnetic microspheres of P(St-co-GMA) with 72 wt% of magnetic content measured by thermal analysis methods were prepared.[183]

Thermoresponsive polymeric microgels loaded with SIONPs and anti-cancer drugs are of interest for multi-functional cancer therapies. This is because such nanoparticles can be used for magnetic drug targeting followed by simultaneous hyperthermia and drug release. γ-Fe_2O_3 SIONPs with diameter of 14, 19, and 43 nm were synthesized by high temperature decomposition. Composite magnetic nanoparticles of PNIPAM were prepared by aqueous dispersion polymerization of NIPAM in the presence of SIONPs. As seen in Figure 10, thermo-responsiveness of PNIPAM exhibited facile loading and release of drugs at temperatures below and above the lower critical solution temperature (34◦C). The particles showed Fickian diffusion release kinetics; the maximum Dox release at 42◦C after 101 h was 41%. *In vitro* simultaneous hyperthermia and drug release of therapeutically relevant quantities of Dox was achieved. For example, 14.7% of loaded Dox was released in 47 min at hyperthermia temperatures.[184]

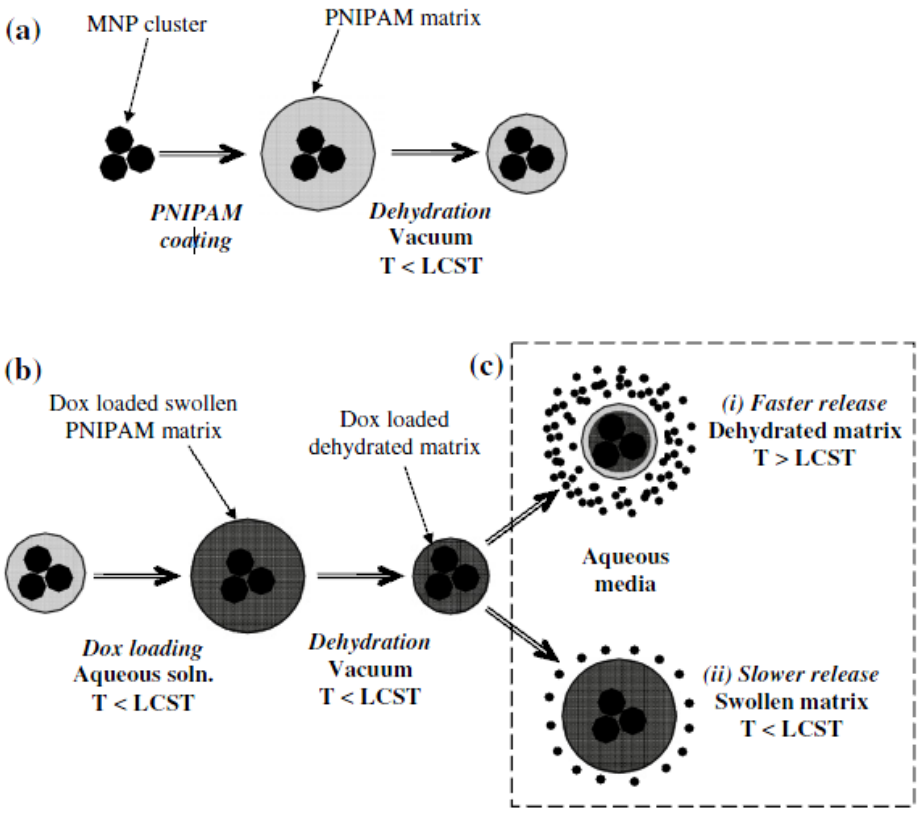

Figure 10. Schematic overview of composite magnetic microsphere preparation(a), drug loading(b), and drug release processes(c). Reprinted with permission from ref [184]. Copyright 2009 IOP.

6.3. Other heterogeneous polymerization methods

Precipitation polymerization of hydrophilic or water-soluble monomers in the presence of crosslinkers in water produces microgel particles. Typical examples are thermoresponsive PNIPAM-based microgels. Carboxylic acid-functionalized P(NIPAM-HEA-AA) microgels were prepared, and used as reactors for *in-situ* formation of inorganic NPs including Fe_3O_4 NPs.[185] After being immersed in aqueous solution of Fe(II) and Fe(III), microgels of poly(acetoacetoxyethyl methacrylate-co-N-vinylcarprolactam) (P(AAEM-VCL)) became temperature-sensitive hybrid microgels with magnetic properties.[186] Thermally-responsive magnetic microgels of poly(di(ethylene glycol) methyl ether methacrylate) ($PMe(EO)_2MA$) crosslinked with disulfides were prepared by ATRP under emulsion conditions. They

were then mixed with oleic acid-stabilized SIONPs, magnetic microgels, followed by physical loading of Rhodamine B. Upon addition of reducing agents, the microgels degraded to release the hydrophilic drugs.[187] In addition, the preparation of magnetic polyvinylamine NPs by in situ precipitation polymerization was reported.[188]

7. Bulk physical and chemical crosslinking - magnetic hydrogel preparation

Magnetic hydrogels containing magnetic NPs, called ferrogels, have been prepared by both physical and chemical crosslinking reactions in the presence SIONPs. For physical crosslinking, poly(vinyl alcohol) (PVOH) with degree of hydrolyzation of >97% was mixed with dimethylsulfoxide (DMSO) at 80 ℃ under stirring and then SIONPs under ultrasonification. The resulting mixture was subjected to five freeze-thaw cycles at -20 ℃ for 16 h and 25 ℃ for 5 h. The resulting physically-crosslinked PVOH-based hydrogels exhibited controlled release of drugs upon external application of magnetic field due to a precise control of opening and closure of pore configuration.[189, 190] Collagen molecules self-assembled into higher-order structure when pH of collagen solution increased to 7.4 at 37 ℃. An addition of SIONP solution at pH = 4 resulted in the formation of physically-crosslinked collagen gels. The gels were further stabilized by a carbodiimide coupling reaction in the presence of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide (EDAC). Rhodamine-labeled Dex was incorporated into magnetic collagen gels for controlled release of Dex, a model drug, in external magnetic field.[191]

For chemical crosslinking, free-radical crosslinking polymerization in water has been utilized. Thermosensitive hydrogels of alginate-PNIPAM semi-interpenetrating networks (IPN) embedded with SIONPs were prepared by simultaneous free-radical crosslinking polymerization of NIPAM with MBAm and physical crosslinking of Alg with Ca^{2+} ions. The alginate-PNIPAM IPN gels had larger pores than PNIPAM gels, exhibiting fast response to temperature, and thus leading to high rate of

swelling/deswelling. The resulting cylindrically shaped gels of 20 mm were immersed in an aqueous basic solution of Fe(II) and Fe(III), yielding magnetic hydrogels for hyperthermia applications.[192, 193]

8. Bio-applications of SIONP-polymer hybrids

This section discusses bio-related applications of hybrid magnetic polymer particles embedded with SIONPs. They include MR imaging (or dual imaging with optical imaging based on fluorescence), targeted drug delivery, hypothermia, protein immobilization, and biosensors.

8.1. MR imaging

MR imaging is one of the most powerful non-invasive imaging methods utilized in clinical medicine, which is based on the relaxation of protons in tissues. Upon accumulation in tissues, SIONPs enhance proton relaxation of specific tissues when compared with the surrounding tissues, serving as a MR contrast agent. For *in vivo* MR imaging applications, SIONPs should have longer half-life time in the blood circulation for the improved efficiencies of detection, diagnosis, and therapeutic management of solid tumors. Because opsonin plasma proteins are capable for interacting with plasma cell receptors on monocytes and macrophages, opsonin-absorbed SIONPs will be quickly cleaned by circulating monocytes or fixed macrophages through phagocytosis, leading to elimination of SIONPs from blood circulation. The smaller the particle and the more neutral and hydrophilic its surface, the longer is its plasma half-life. Therefore, the surface of SIONPs has been modified with hydrophilic polymers to prevent absorption of the circulating plasma proteins.

POEOMA-coated SIONPs were incubated with RAW 264.7 microphage cells and the extent of their cellular uptake was compared with pristine SIONPs. As seen in Figure 11, iron concentration in RAW264.7 cells incubated with POEOMA-coated SIONPs is much smaller than that with pristine SIONPs, indicating the importance of surface properties of SIONPs for *in vitro* and *in vivo* MR imaging applications.[116] SIONPs coated with POEOMA-b-PMAA block copolymer were injected into a rat.

Figure 12 shows the *in vivo* MR images of liver section of the live rat over time after injection. The liver was observed to be significantly darker after 2 h, which is much longer than 5 min for Resovist®, a larger commercial SIONP. The results suggest that ultra small SIONPs coated with POEOMA (diameter = 10 nm) have a longer half-life time in the bloodstream than standard commercial contrast agent.[90]

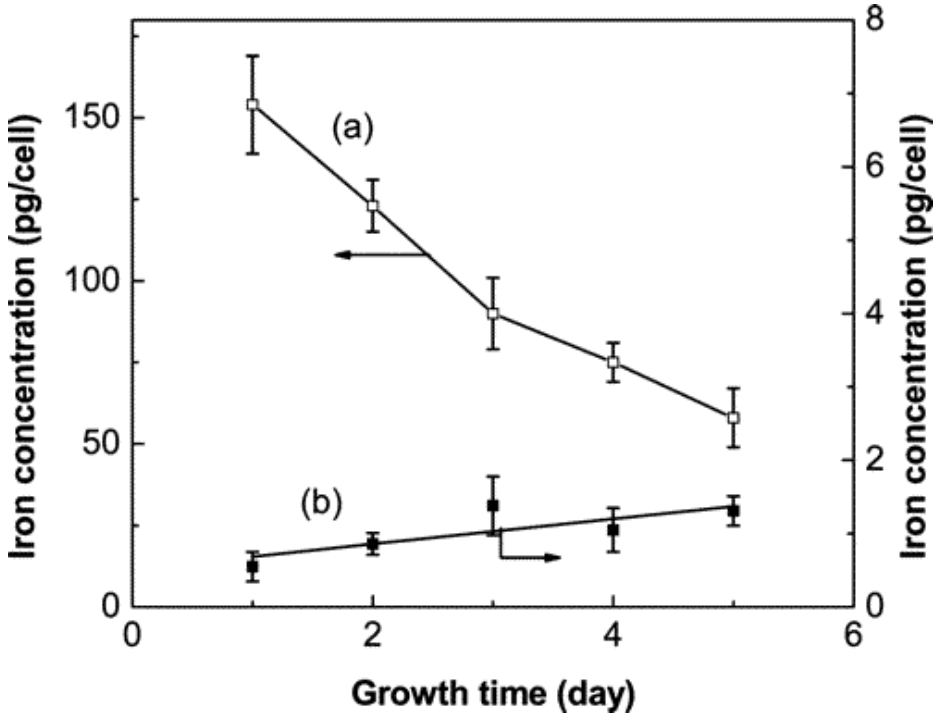

Figure 11. Iron concentration in RAW 264.7 cells cultured in medium containing pristine (a) and POEOMA-coated SIONPs (b). Reprinted with permission from ref [116]. Copyright 2006 American Chemical Society.

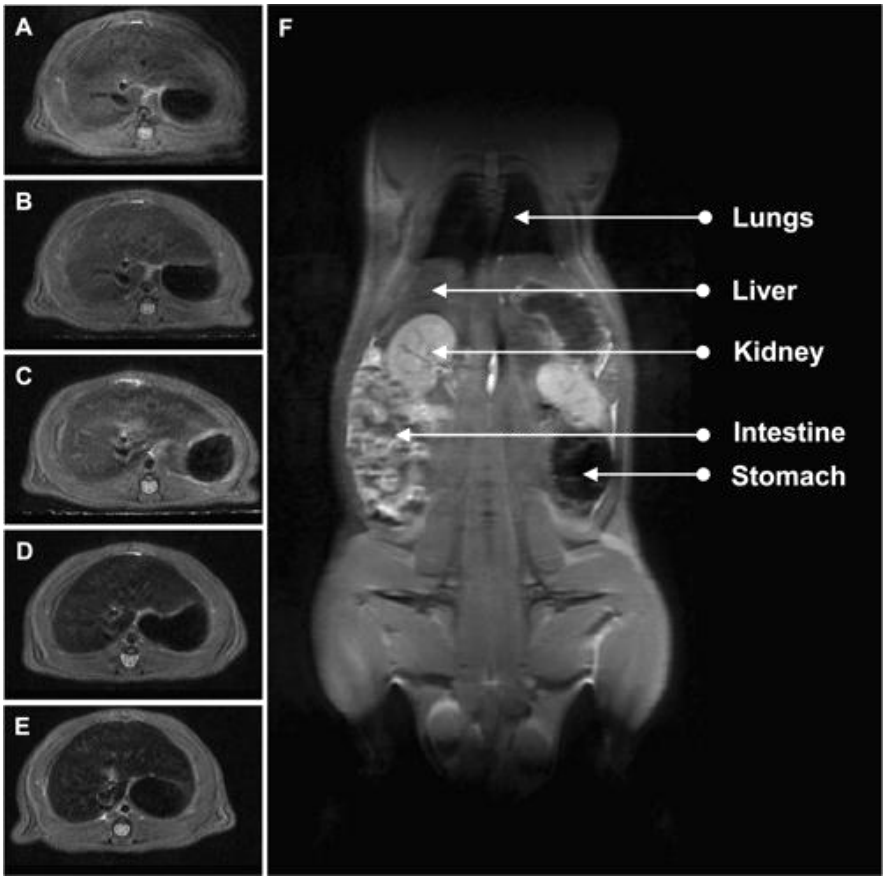

Figure 12. MR Images of a live rat after injection of 500 µL of a solution containing SIONPs coated with POEOMA-b-PMAA (d = 10 nm). Images on the left show liver selections measured at 0 min (a), 15 min (b), 1 h (c), 2 h (d), 6 h (e). Right image shows a coronal section measured after 70 min. Reprinted with permission from ref [90]. Copyright 2006 American Chemical Society.

SIONPs coated with hydrophilic polymers, typically POEOMA and poly(L-lysine) have also been utilized for *in vitro* and *in vivo* labeling cancer and stem cells. They were accumulated in tissues by enhance permeability and retention (EPR) effect for MR imaging of specific cells.[100, 136] Fe_2O_3 maghemite NPs coated with poly(N,N-dimethylacrylamide) (PDMAAm) were prepared by solution radical polymerization of DMAAm in the presence of aqueous solution of maghemite NPs, which were prepared by the coprecipitation method. *In vitro* cellular uptake results indicate that PDMAAm-coated

Fe_2O_3 maghemite NPs exhibited higher efficiency in labeling rat and human bone marrow mesenchymal stem cells than pristine Fe_2O_3 NPs and even Dex-modified NPs (Endorem® , a commercial MRI contrast enhancement agent)[194, 195] In addition, Cy5.5, a fluorescent-dye, was incorporated into polymer/SIONPs for dual MR and fluorescence imaging. The resulting Cy5.5-conjugated polymer/SIONPs were injected intravenously into the rat through its tail vain. They were accumulated in tumor by EPR effect, as seen *in vivo* MR and fluorescence images of tumor after injection (Figure 13).[101]

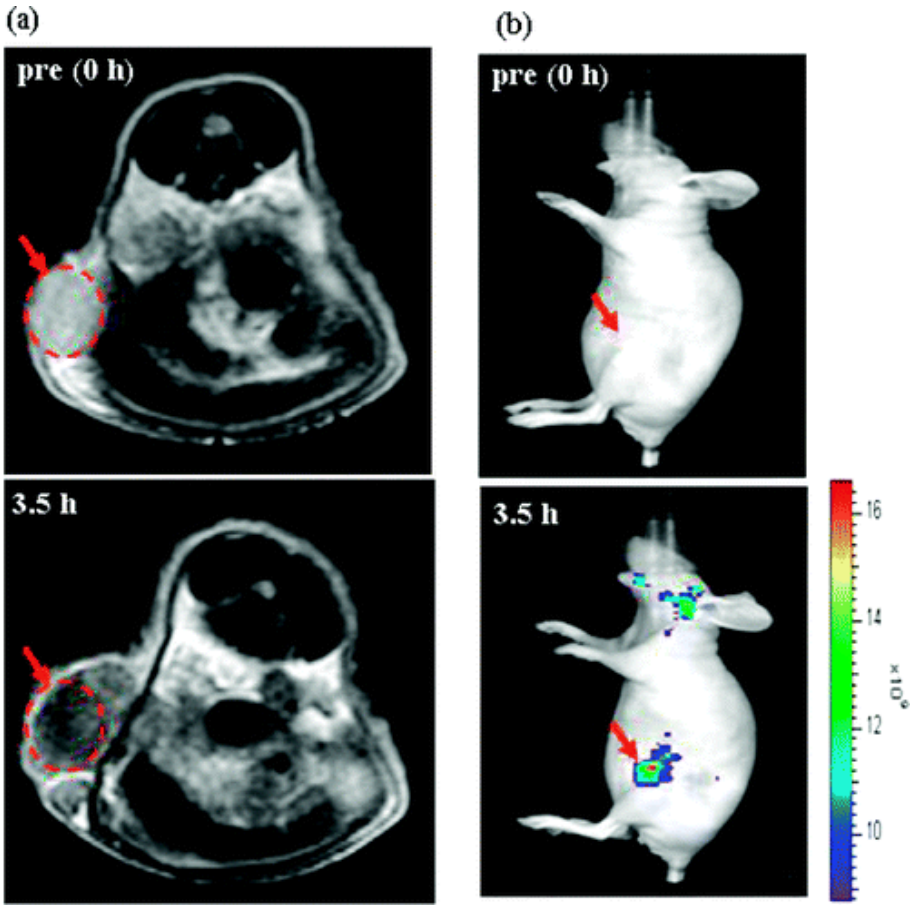

Figure 13. T_2-weighted fast spin-echo images taken at 0 and 3.5 h post-injection of 14.7 mg of Cy5.5-conjugated SIONPs coated with POEOMA at the level of tumor (320 mm3) on the flak above the upper left thigh of a nude mouse (a) and optical fluorescence images of the same mouse taken at 0 and 3.5 h (b). The red arrows indicate the position of the allograft tumor. Reprinted with permission from ref [101]. Copyright 2007 American Chemical Society.

Active targeting or specific targeting is a promising approach toward increasing the local accumulation of SIONPs in diseased tissue.[8, 196] This approach requires the design and preparation of SIONPs coated with functional polymers, which are further conjugated with targeting biomolecules to specific cells. The effective targeting biomolecules include folic acid and its analogues, peptides, proteins, and antibodies, utilizing specific interactions such as receptor-ligand or antigen-antibody interactions. Folate,[91, 126] Tat peptide,[106] and a polypeptide with a sequence of GGGGYSAYPDSVPMMSK[20] have been conjugated to SIONPs through functional polymers for *in vitro* and *in vivo* targeting cancer cells. Dopamine-functionalized hyaluronic acid (HA) was conjugated with SIONPs in water, yielding stable HA-SPIONPs with a diameter of 15 nm on mica surface by atomic force microscopy (AFM). They were cultured with CD44+ cells (HCT116, human colon carcinoma cell line) and CD44- fibroblast cells (NIH3T3, mouse fibroblast). As seen in Figure 14, the MR imaging revealed that the cellular uptake of HA-SIONPs was greatly enhanced in HCT116 by specific CD44-HA receptor-ligand interactions.[103]

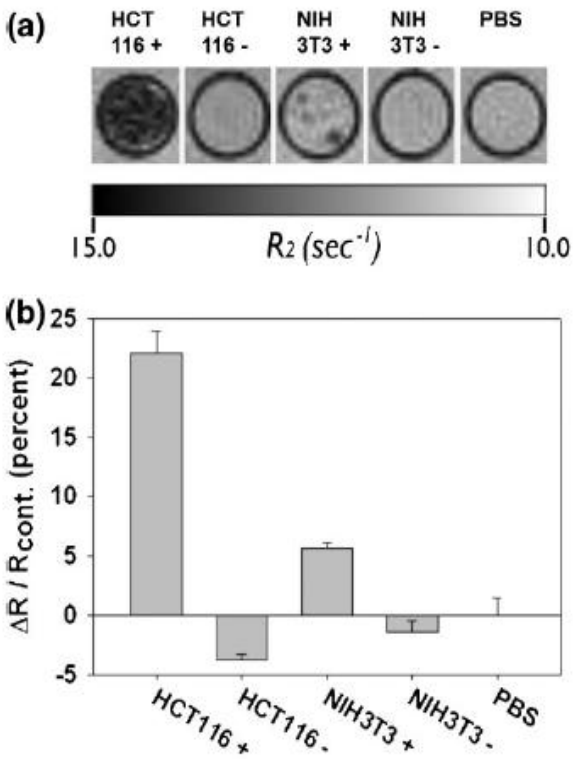

Figure 14. T_2-weighted MR images and their color map for HCT116 and NIH3T3 cells (a) and relative relaxation rates ($R_2 = \Delta R_2/R_{2cont}$; $R_2 = T_2^{-1}$) (b). Notation: HCT116+: HA-SIONPs treated cells, HCT116-: control HCT116 cells, NIH3T3+: HA-SIONPs treated cells, and NIH3T3-: control NIH3T3 cells. Reprinted with permission from ref [103]. Copyright 2008 Wiley InterScience.

8.2. Drug delivery

Polymer-based drug delivery systems (Polymer-DDSs) have gained an increasing attention in polymer science, pharmaceutics, nanobiomedicine, and biomaterials science. In particular, polymer DDS conjugated with cell-targeting ligand biomolecules that can recognize specific cell receptors may enhance non-specificity of chemotherapeutic agents as well as reduce their side effects. Several types of polymer-DDS have been exploited, including polymer pro-drugs,[197] micelles and vesicles based on amphiphilic and double block copolymers,[198, 199] dendrimers,[200] hydrophobic polyester-based nanoparticulates,[201] and microgels/nanogels.[151, 202-204] For *in vivo* drug delivery applications, several criteria are required for the design and development of effective polymer -DDS. Primary requirements

include non-toxicity to cells, stability for prolonged circulation in blood stream, high loading efficiency, and controllable release of therapeutics. Additional requirements include biodegradability, novel functionality for further bioconjugation with cell-targeting biomolecules, and dimensional control.[205]

A recent advance in SIONP/polymer system is the development of SIONP-loaded polymer-DDS with cancer-cell targeting capability for controlled drug release and efficient MR imaging contrast characteristics. These systems can allow for real-time tumor-tracking by MR imaging upon controlled release of anticancer drugs in cancer cells. Self-assembled nanoparticles of amphiphilic block copolymers loaded with SIONPs and anticancer drugs such as Dox are typical examples for simultaneous drug delivery and MR imaging. Cell-targeting ligands such as folate,[128] RGD tripeptide,[127] and antibody[125] were attached to nanoparticles for intercellular delivery of anticancer drugs. They were then released upon collapse of micellar aggregates in cells after internalization into cells (**Figure 15**). PEG-based phospholipid self-assembled micelles consisting of SIONPs, quantum dots, and Dox were prepared for simultaneous magnetofluorecent imaging and drug delivery.[131]

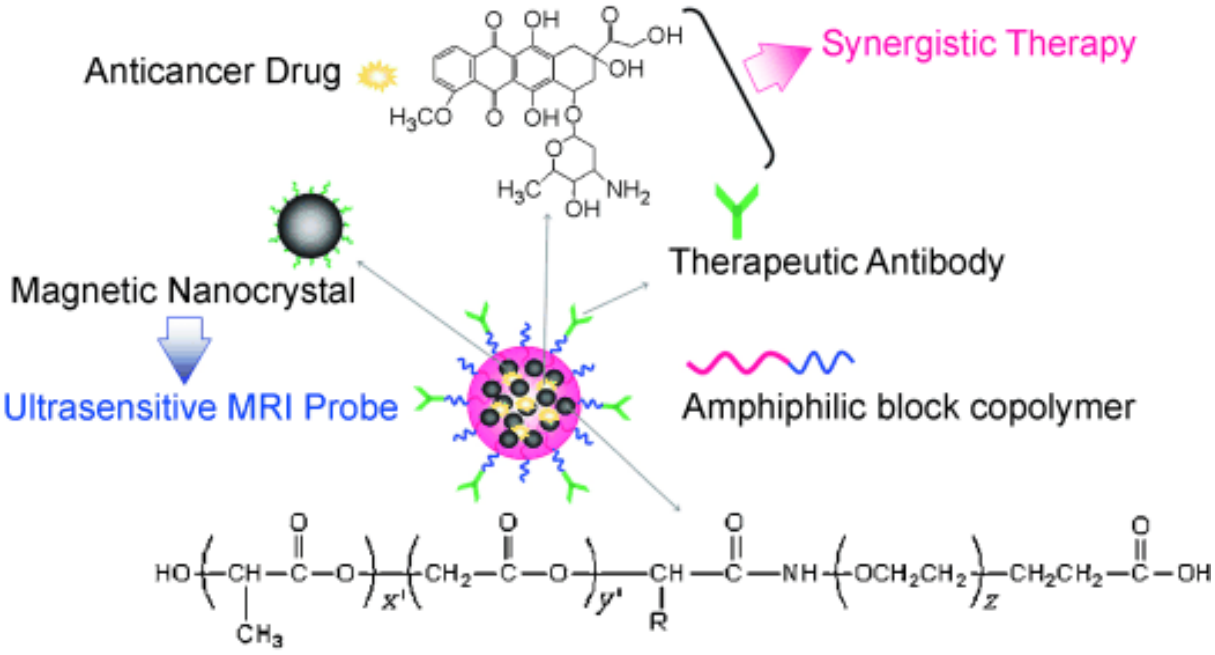

Figure 15. Schematic illustration for the fabrication of ultrasensitive MRI probe from core/shell micellar NPs consisting of hydrophobic PLA core embedded with SIONPs and Dox and hydrophilic PEO shell functionalized with targeting therapeutic antibodies to tumor. Reprinted with permission from ref [125]. Copyright 2007 Wiley InterScience.

Crosslinked microgels/nanogels/hydrogels embedded with SIONPs (ferrogels) have been designed for controllable release of drugs. In particular, ferrogels based on thermally-responsive polymers are attractive because temperature change is generated by applying an external magnetic field onto SIONPs.[206] When magnetic field is on, temperature increased. At temperatures above lower critical solution temperature (LCST), thermoresponsive polymeric ferrogels are shrunken, enhancing release of drugs from ferrogels. When the magnetic field is absent and the temperature is below the LCST, they become swollen, reducing drug release. Therefore, a magnetically remote-controlled drug release can be achieved without additional stimuli. Ferrogels based on poly(vinyl alcohol)[190] and Fluronic PF127 triblock copolymer consisting of PEO and poly(propylene glycol) (PPO) were prepared by thermally-induced sol-gel process.[189, 207] PF127 block copolymer formed micellar nanoparticles consisting of PPO core and PEO corona in water. In the presence of SIONPs and indomethacin (IMC), a hydrophobic

drug, thermal gelation of the micelles occurred at elevated temperature, yielding ferrogels embedded with IMC which is mainly located in micelle cores. As seen **Figure 16**, the half-time ($t_{1/2}$) of drug release was reduced to 1500 min when magnetic field is on, compared to the 3195 min when magnetic field is off, indicating that the drug release is enhanced upon applying magnetic field.[207] In addition, microgels/nanogels of water-soluble POEOMA, in which SIONPs are physically or covalently embedded, were prepared for drug delivery applications.[208, 209]

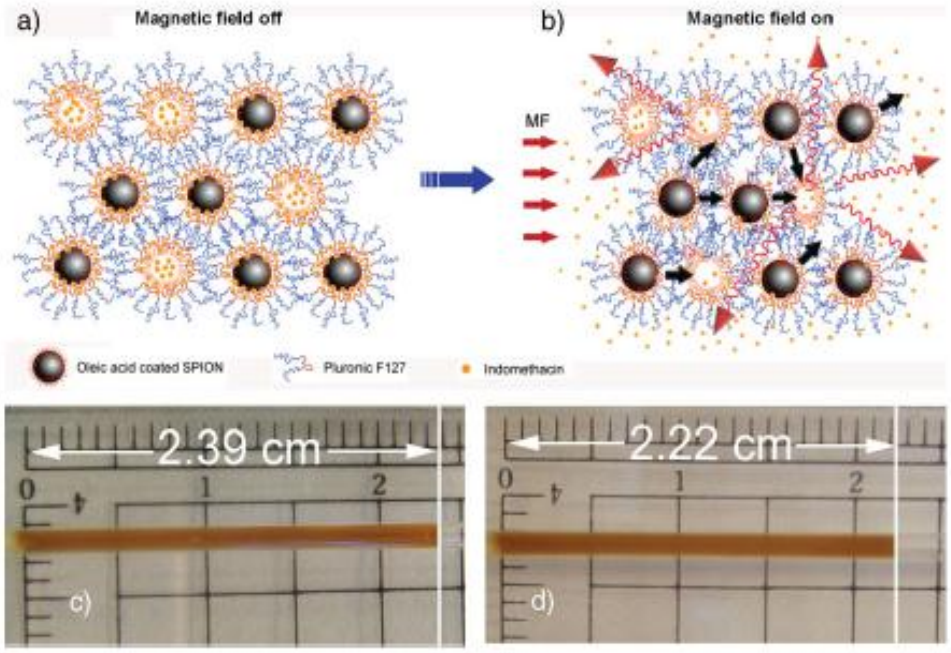

Figure 16. Schematic illustration of ordered microstructure of thermally-induced ferrogels based on Fluronic PF124 block copolymers: before applying magnetic field, IMG hydrophobic drug molecules are encapsulated in the hydrophobic core of micelles (a) and when magnetic field is on, SPONPs orient and approach each other, squeezing the micelles and leading to enhancement of IMC release (b). Reprinted with permission from ref [207]. Copyright 2009 Wiley InterScience.

8.3. Other applications including hyperthermia, protein immobilization, and catalysts

Hyperthermia therapy with SIONPs involves a local increase in temperature (up to 45 ℃) when external magnetic field is applied on SIONPs. Such a temperature increase enables to kill temperature-sensitive cells, such as cancer cells. Recent studies using calorimetry shows that the heating rate

depends on the particle size of SIONPs, in good agreement with theoretical prediction. This result suggests that the SIONPs should be designed to have optimal particle size with narrow size distribution for enhanced hyperthermia therapy.[210] Several papers reported novel SIONP-polymer nanocomposites for hyperthermia. They include SIONPs coated with temperature-responsive PNIPAM-based copolymer[92, 184] and chitosan[211] as well as SIONPs embedded in hydrogels,[130, 212, 213] solidified gels,[214] and silica microparticles.[215] In addition, well-designed polymer/SIONPs nanohybrids have been utilized for microfluidic separation,[105] immobilization of proteins such as bovin serum albumin,[216] and peroxidase-like catalyst.[105]

9. Conclusion

SIONPs have great potential for various biomedical applications, including MRI contrast enhancement, targeted drug delivery, hyperthermia, catalysis, biological separation, biosensors, and diagnostic medical devices. Polymers as multidentate ligands enhance the stability of SIONPs in solution as well as their optical, magnetic, and electronic properties. Various methods have been developed to yield unique polymer-SIONP hybrid nanomaterials. They include direct modification with polymers, surface-initiated controlled polymerization, inorganic silica/polymer hybridization, self-assembly and self-association, and various heterogeneous polymerization methods. The resulting hybrid magnetic polymer composites exhibit various morphologies such as magnetic core–polymer shell, magnetic multicores homogeneously dispersed in polymer matrix, raspberry morphology, and hair-like morphology. Direct modification with polymers requires the design, preparation, and modification of novel polymers including synthetic polymers and biopolymers. The general approaches include physical adsorption of well-controlled polymers, addition of second layer consisting of amphiphilic block copolymers, functional silica coating, and the ionic interaction approaches, yielding water-soluble/water-dispersible polymer-stabilized SIONPs. The surface-initiated CRP methods including ATRP and RAFT methods

have been utilized for modification of single SIONP with well-controlled polymers. Inorganic silica/polymer hybridization involves the encapsulation of SIONPs with a silica shell through a sol-gel process of tetraethyl orthosilicate (TEOS). The silica-coated SIONPs are further functionalized and encapsulated with polymers, yielding multifunctional hybrid nanomaterials. Self-assembly method involves the assembly of amphiphilic block copolymers in water, forming stable core/shell micellar particles. The hydrophobic core serves as a carrier for SIONPs and anticancer drugs and the hydrophilic shell allows particle stabilization in aqueous solution. The amphiphilic block copolymers include biodegradable polyester-based amphiphilic block copolymers of PLA and PCL. Self-association method involves the physical association between SIONPs and anionic-or cationic polymers. The associations are typically achieved through ionic interaction, stereo-complexation, and sol-gel process with thermoresponsiveness. In addition, various heterogeneous polymerization methods of hydrophilic or water-soluble monomers have been extensively explored to prepare well-defined SIONP-embedded magnetic polymer spheres as well as crosslinked microgels/nanogels and hydrogels for biomedical applications. They include inverse (mini)emulsion polymerization, dispersion polymerization, precipitation polymerization, and bulk physical and chemical crosslinking. These methods have allowed for the preparation of noble hybrid magnetic polymer nanomaterials embedded with SIONPs for bio-related applications such as MR imaging (or dual imaging with optical imaging based on fluorescence), targeted drug delivery, hypothermia, protein immobilization, and biosensors.

Future design and development of effective magnetic polymer nanocomposites for biomedical applications require a higher degree of control over their key characteristics. Proper particle diameters in usually sub-micron size range can offer high surface areas for immobilization of biomolecules. Narrow size distribution can allow a uniform response to an external magnetic field. Appropriate surface functionalities enable selective adsorption or binding with biomolecules. Homogeneous distribution and proper encapsulation ensure high degree of non-toxicity and biocompatibility by avoiding direct contact

of magnetic materials with some sensitive molecules and biomolecules (e.g. enzymes). Biodegradability and stimuli-responsiveness allow for controlled loading and release of encapsulated anticancer drugs and SIONPs. In addition, good colloidal stability in aqueous medium and high iron oxide content for rapid separation in the magnetic field are necessary.

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