Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2015, Article ID 350596, 12 pages
http://dx.doi.org/10.1155/2015/350596

Review Article

Applications of Thermoresponsive Magnetic Nanoparticles

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Received 2 June 2015; Accepted 15 October 2015

Academic Editor: Nguyen V. Long

In recent years, magnetic nanoparticles carrying thermoresponsive polymeric coatings have gained increasing attention in material sciences due to the fact that resultant platforms offer controllable modalities such as imaging, drug delivery, and magnetic separation. As a result, novel materials including biosensors, therapeutic platforms, imaging agents, and magnetic separators have been realized. Since the number of publications reporting the applications of thermoresponsive magnetic nanoparticle has increased steadily over the years, a comprehensive review will be beneficial. In this paper, we aim to review publications studying applications of thermoresponsive nanoparticles in biomedical sciences as well as in environmental and chemical sciences. The paper also briefly discusses chemical formulations, characterizations, and properties of the thermoresponsive magnetic particles and then provides future outlooks.

1. Introduction

Thermoresponsive polymers have the ability to change their conformational states based on a variable temperature input in solution, and this phenomenon has been utilized to design a variety of smart materials in various fields [1–9]. Most of the thermoresponsive polymers display a phase transition from an extended/hydrophilic coil to a globular/hydrophobic state upon heating above a certain temperature known as lower critical solution temperature (LCST) [10]. Polymers of this type exhibit a soluble state in water below their LCST as a result of considerable hydrogen bonding with surrounding water molecules. By contrast above their LCST inter- and intramolecular hydrogen bonding dominates between polymer chains. Besides, intramolecular hydrophobic interactions also become prominent above their LCST; therefore a globular/shrunken, less water soluble state is produced. In fact, it is this feature that makes LCST-type polymers attractive as smart tools in material and biomedical sciences. Based on a variable temperature input, shrinking/swelling or aggregation/dispersion of polymer units leads to controllable microscopic or macroscopic changes [11]. Poly(N-isopropylacrylamide) (PNIPAAm) is a well-studied thermoresponsive polymer since its LCST is close to the physiological temperature and was utilized mostly in biomedical applications [12]. Another interesting aspect of PNIPAM is that its LCST can be modified using hydrophilic or hydrophilic comonomers, and copolymers displaying higher or lower LCST could be synthesized [13]. In addition to PNIPAAm, there are a number of other polymers showing LCST-type behaviors such as poly(N-vinylcaprolactam) (PNVCL), poly(oligo(ethylene glycol)-methacrylate) (POEGMA), and poly(N-dimethylacrylamide) (PDMAAm), and readers may be referred to the comprehensive reviews for the detailed lists of (co)polymers and their properties [11, 14, 15]. Alternatively, a different type of thermoresponsive polymers, albeit not as common as the LCST-type, is known as upper critical solution temperature (UCST) polymers, and they display a reversible phase change from less soluble to more soluble state upon heating above their UCST [16].

Controlled/living radical polymerization (CLRP) techniques such as reversible-addition fragmentation chain transfer (RAFT) polymerization [17], atom transfer radical polymerization (ATRP) [18], and nitroxide-mediated polymerization (NMP) [19] had an immense impact on the generation of novel thermoresponsive polymers. Due to the fact that LCST of polymers depends mostly on polymer structure, composition, and end functionality, these techniques have paved ways to the generation of thermoresponsive polymers that

have tunable LCSTs and properties. Furthermore, the development of novel orthogonal chemistries [20] to functionalize polymers with other molecules, drugs, imaging moieties, and targeting groups, or to functionalize nanoparticles with polymers has brought about new designs and formulations of composite nanomaterials having multistimuli responsive behaviors and multimodal features [2].

In this review, we surveyed publications focusing on the design and construction of hybrid composite materials composed of thermoresponsive polymeric shells and magnetic core particles. However, the emphasis was given to the application-based studies. For the detailed synthetic procedures and characterizations, readers may be referred to the publications focusing exclusively on material design and engineering rather than applications [21–27]. Although most of the publications inherently tend to align with biomedical applications [28], new studies have started to appear in environmental and chemical sciences such as water treatment [29] and catalysis [30]. In 2009 Liu et al. have published a review article with the biomedical emphasis in this field [31]. Similarly, Medeiros et al. have published a review article in 2010 covering all types of stimuli responsive magnetic particles in biomedical sciences with little emphasis on thermoresponsive magnetic particles [32]. Therefore, we envisaged that a comprehensive recent review on the applications of thermoresponsive magnetic nanoparticles in material and biomedical sciences will be beneficial to researchers having interests in this field.

2. Thermoresponsive Magnetic Nanoparticles

Magnetic nanoparticles (MNPs), in particular Fe_3O_4 and γ-Fe_2O_3, are heavily utilized platforms in various research areas, especially in biomedical sciences, due to their apparent biocompatibility and unique size-dependent properties [33]. MNPs were widely employed as drug carriers [34], Magnetic Resonance Imaging (MRI) contrast agents [35], hypothermic therapeutics [36], and magnetic separators for cells [37] and biomolecules [38]. Integration of MNPs and thermoresponsive polymers into a composite/hybrid core-shell system results in multistimuli responsive platforms. Therefore, manipulation of two external stimuli, namely, the temperature and the magnetic field, may lead to the design of smart devices capable of being turned "ON" or "OFF" at convenience. In the following subsections, specific applications of the hybrid MNPs/thermoresponsive polymers will be covered.

2.1. Drug Delivery and Imaging. Thermoresponsive polymers in drug delivery applications provide controlled release of therapeutics with the temperature stimulus. Drug loaded polymers exhibit decreases in their volumes above their LCST as a result of a phase change from extended coil to globular form which causes the diffusion of entrapped drug molecules from polymer particles into the surrounding environment [11]. Incorporation of MNPs into these constructs, in essence, might provide additional benefits: (i) Magnetic core component could be used as an internal heat source as a result of magnetically induced heating, and this could trigger shrinking of polymer shell [31]; (ii) preferential accumulation of the polymers into the targeted locations could be achieved by utilizing magnetic force, and this process is known as Magnetic Drug Targeting (MDT) [53]; (iii) MRI could be benefitted for imaging and diagnostic applications [54].

In this regard, Purushotham et al. have reported formulation of a thermoresponsive drug delivery system based on γ-Fe_2O_3 MNPs [55]. PNIPAAm has been coated on the surface of MNPs by means of dispersion free-radical polymerization of NIPAM monomers. Common therapeutics, doxorubicin, was loaded into the polymeric shell (Figure 1). The drug release profile of resultant system was tested *in vitro* under magnetically induced heating conditions, and therapeutically significant amount of drug release was observed. However, thermally induced drug delivery process has proven to be inefficient. Furthermore, *in vivo* MDT was studied using buffalo rat model which was implanted with hepatocellular carcinoma cells in liver. After the implantation and the growth of the tumor, drug loaded particles were injected through the main hepatic artery of the rat model followed by placement of a permanent magnet over the liver for some period. MRI and histology studies have shown efficient localization of the particles in the tumoral region and the liver.

In another study, Kim et al. have prepared a magnetic platform composed of poly(N-isopropylacrylamide-co-acrylamide)-block-poly(ε-caprolactone) (P(NIPAAm-co-AAm)-b-PCL) and superparamagnetic iron oxide nanoparticles particles (SPIONs) [56]. Amphiphilic nature of the copolymer favored formation of polymeric micellar structures in aqueous solution, and it was found that doxorubicin molecules were encapsulated efficiently by micelles. *In vitro* drug release profile has been tested through alternating the temperature between physiological temperature and LCST (43°C) of the polymer, and it was shown that the rate of drug release was significant at and above LCST. Interestingly, amount of the released drugs was significantly higher at LCST with magnetically induced heating. This phenomenon was attributed to the efficient heat transfer to the polymeric shell from nearby SPIONs while thermal heating of the polymer shell required multistep heat transfer from the surrounding matrix. To assess the applicability of the construct in *in vitro* cell studies, magnetic micelles were functionalized with an integrin β4 antibody which is specific to A9 antigen overexpressed in the squamous cell carcinoma of the head and neck. The experiments revealed that magnetic micelles were localized on the surface of the squamous cells, whereas magnetic micelles without the antibody did not interact with the cells. However, no further studies were reported in terms of thermally or magnetically induced drug delivery.

Hoare et al. have formulated a membrane-based drug delivery platform composed of ethyl cellulose membrane matrix, SPIONs, and a thermoresponsive nanogel which was produced by copolymerization of NIPAM, N-isopropylmethacrylamide (NIPMAAm), acrylamide (AAm), and N,N-methylenebisacrylamide cross-linker [57] (Figure 2). LCST of the copolymer was controlled by varying the monomer ratios. With the adjustment of LCST,

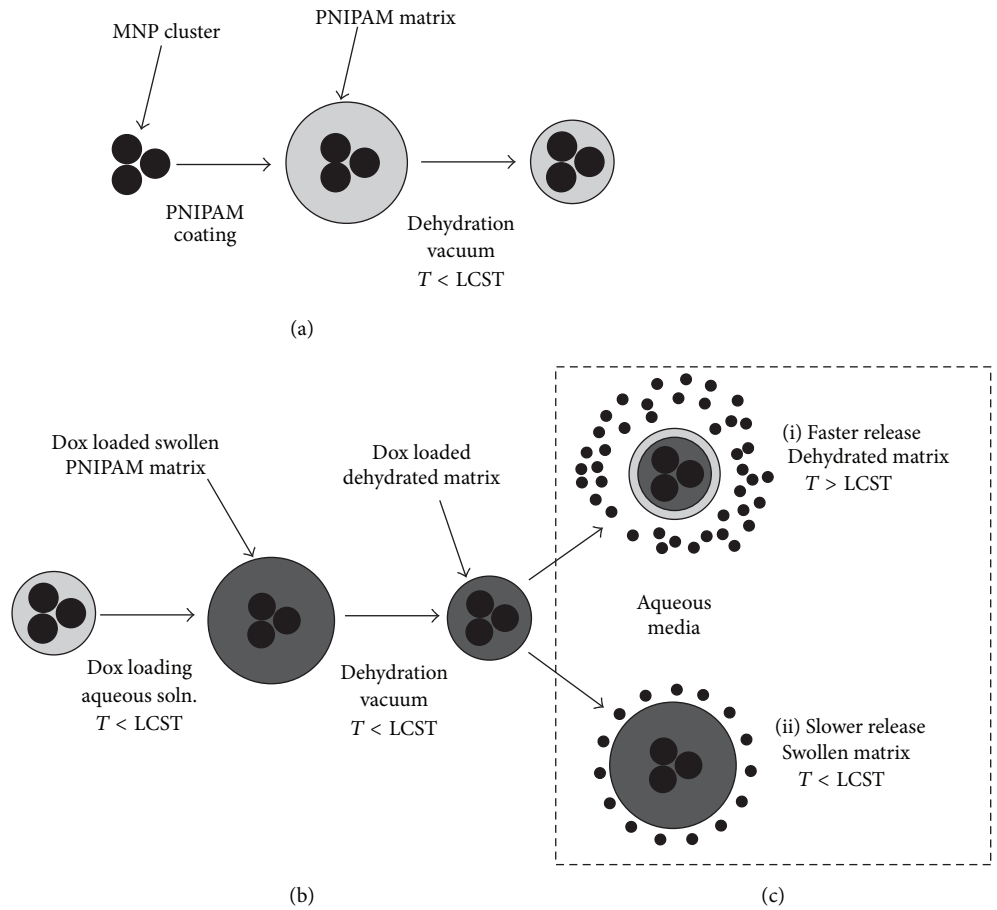

Figure 1: Formulation of thermoresponsive MNP for drug delivery applications. (a) NIPAM monomers together with a cross-linker monomer were polymerized around clusters of γ-Fe_2O_3 MNPs to generate thermoresponsive MNPs. Dehydration of the particles below LCST under vacuum led to shrinking of the composite system. (b) Loading of a cancer chemotherapeutics, doxorubicin, in aqueous solution, is governed through hydrophobic interaction of drug molecules with the polymeric shell. (c) *In vitro* drug release could be achieved setting the temperature above LCST and accompanying phase change from coil to globule causes expulsion of drug molecules into the surrounding medium (reprinted with the permission of publisher, IOP Publishing Ltd., copyright 2009, from [55]).

membrane thickness, and gel loading, it was demonstrated that the flux of a model drug from a reservoir across the membrane could be increased manifold upon application of an external magnetic field. It was shown that the flux could be turned ON and OFF by switching on and off the magnetic field, and a range of drugs with molecular weight from 500 Da to 40 kDa could be transported across the membrane. Although the system was thoroughly characterized and tested and it produced very promising results on a model system, its *in vivo* applicability and biocompatibility need to be tested and engineered for potential biomedical applications.

Hiraiwa et al. have investigated the feasibility of employing commercially available thermoresponsive MNPs as MRI contrast agents to map sentinel lymph node (SLN) by subcutaneous injection of these particles into the thoracic wall of model rats [58]. They have tested magnetic particles having different PNIPAAm loadings such as Therma-Max 36 with the LCST of 36°C, Therma-Max 42 with the LCST of 42°C, Therma-Max 55 with the LCST of 55°C, and a control Ferridex without thermoresponsive polymer coating. They hypothesized that formulations with proper LCSTs will be able to enter the lymphatic vessels after injection, and due to physiological temperature these particles will aggregate and will be retained in SLN. Post-MRI and histological studies showed that Therma-Max 36 aggregated just after injection and was not able to enter SLN, whereas Therma-Max 42, Therma-Max 55, and Ferridex were able to enter into SLN. Furthermore, Therma-Max 42 aggregated in SLN; however Therma-Max 55 and Ferridex were carried to distant lymph nodes (DLN). These results clearly indicated that thermoresponsive MNPs have great potentials as being superior MRI contrast agents.

Wadajkar et al. have developed a magnetic platform with a thermoresponsive polymeric surface for MRI applications [59]. A silica shell was grown on the commercially available iron oxide nanoparticles followed by the attachment of vinyl groups. Poly(N-isopropylacrylamide-co-acrylamide-co-allylamine) (P(NIPAAm-co-AAm-co-AH)) was grafted on the surface of particles through polymerization of the vinyl groups with the corresponding monomers. The polymeric

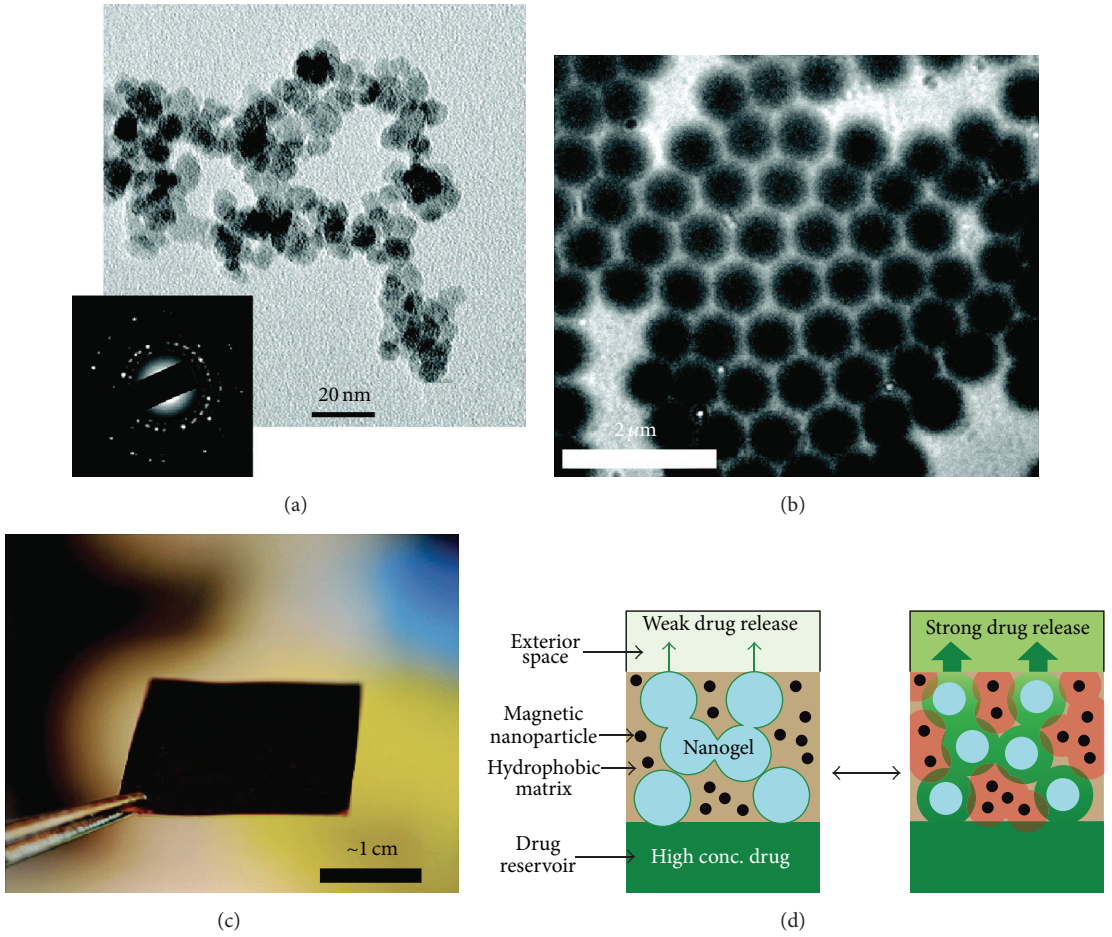

Figure 2: Fabrication of a drug delivery membrane based on nanocomposite materials composed of SPIONs and thermoresponsive hydrogel. (a) TEM micrograph and diffraction pattern of SPIONs synthesized from alkaline hydrolysis of iron salts. (b) TEM micrograph of hydrogel synthesized via copolymerization of NIPAAm, NIPMAAm, and AAm. (c) Photograph of the composite membrane prepared through dissolving SPIONs, ethyl cellulose, and hydrogel in ethanol followed by evaporation to form a thin film. (d) Membrane flux assay was performed by placing membrane film between two glass flow chambers filled with saline. A fluorescent model drug was placed in one of the chambers and upon the temperature or magnetic field stimuli drug molecules were transported into the other chamber across the membrane due to increased permeability of the membrane as a result of shrinking of hydrogel (reprinted with the permission of publisher, American Chemical Society, copyright 2011, from [57]).

surface was chemically modified with the prostate cancer specific R11 peptides. *In vitro* cell culture studies using prostate cancer cell lines showed the localization of particles inside the cells. *In vivo* animal studies have revealed that systemically injected formulation containing R11 targeting peptide has accumulated more in the tumor as compared to the control animals injected with the same formulation without R11 peptide. Besides, the accumulation of the targeted formulation in the tumor has led to a significant T2 signal intensity decrease, whereas the decrease with the nontargeted formulation was negligible. Therefore, this platform has potentials in the diagnosis of the prostate cancer using MRI technique. Although no studies regarding the thermoresponsive behaviour of the polymer coating was mentioned, possible drug delivery and hypothermia studies deserve to be explored in future studies.

Thermoresponsive MNPs could be exploited more in the future studies as both contrast agents and targeted drug delivery vehicles using MDT technique. To this end, more studies are needed to design and engineer formulations that are biocompatible, safe, and easy to manufacture. In Table 1, a variety of drug delivery systems and MRI contrast agents based on MNPs and thermoresponsive polymers have been summarized [39–45].

2.2. Magnetic Separation. Purification and isolation of peptides, cells, and biomolecules including proteins, nucleic acids, enzymes, and antibodies rely on the chromatographic and electrophoretic techniques which, in general, require lengthy time of procedures and involve multiple steps [60–62]. Most of these techniques invoke interaction of an affinity ligand, antibodies, peptides, and synthetic molecules,

Table 1: Thermoresponsive polymer-magnetic nanoparticle composites for drug delivery and imaging application.

Magnetic core-size (diameter-TEM)	Polymer	LCST	Application	Reference
$Mn_{1-x}Zn_xFe_2O_4$-50 nm	Poly(N,N′-isopropylacrylamide-co-N-hydroxymethylacrylamide) (P(NIPAAm-co-HMAAm))	40°C	*In vitro* hyperthermia	[39]
Fe_3O_4-Au-115 nm	PNIPAAm	32°C	Surface plasmon resonance (SPR) based heating	[40]
Fe_3O_4-8 nm	Dextran grafted poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide) [dextran-g-poly(NIPAAm-co-DMAAm)]	38°C	Not reported	[41]
Fe_3O_4-12 nm	PNIPAAm	40°C	*In vitro* drug delivery, magnetic heating	[42]
γ-Fe_2O_3-7.5 nm	Poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) (PVOH-b-PNVCL)	41°C	*In vitro* drug delivery, magnetic heating	[43]
Fe_3O_4-13 nm	Poly(N,N′-isopropylacrylamide-co-styrene) (P(NIPAAm-co-St))	27–35°C	*In vivo* MRI	[44]
Fe_3O_4-SiO_2-80 nm	Poly(N,N′-isopropylacrylamide)-block-polystyrene (PNIPAAm-b-PSt)	32°C	*In vitro* MRI	[45]

which is generally immobilized on a solid matrix, with the biomolecule of interest [63]. Magnetic separation utilizing MNPs functionalized with the affinity ligands have emerged as a complementary/alternative technique to the chromatography techniques [38]. In magnetic separation, biomolecules in complex mixtures could be separated and isolated in a single step and in a relatively short period of time. An ideal magnetic separation platform should have a high magnetophoretic mobility; that is to say, it should respond to external magnetic field fast, and this property depends on the size and magnetic susceptibility of the materials [64]. Both commercial and home-made micrometer size magnetic particles were extensively used in the separation of the biomolecules due to the fast magnetic responses [65]. Although small size MNPs tend to respond poorly to low magnetic field gradients, they offer a variety of inherent advantages as compared to micron size counterparts such as high binding capacity and faster binding kinetics [66]. So as to harness the potentials of the small size MNPs as effective magnetic separators, several strategies have been developed to increase magnetic response including aggregating particles, confining particles within polymers, and encapsulating particles in silica matrix [67]. However, these strategies result in loss of high surface to volume ratio. Recently, there have been efforts to develop strategies to induce reversible aggregation/dispersion of small MNPs so that higher magnetic responses could be maintained without sacrificing high surface to volume ratio [68, 69]. To this end, surface modification of MNPs with thermoresponsive polymers is one of the most promising alternatives. In principle, below LCST of the polymers, MNPs modified with affinity ligands could bind to the biomolecules and then above LCST magnetic separation could be performed more effectively.

In this regard, Nash et al. have developed a novel system to separate a model protein, streptavidin, from human plasma using PNIPAAm, and PNIPAAm functionalized Au and Fe_3O_4 nanoparticles [70] (Figure 3). Negatively charged Au nanoparticles were modified with positively charged PNIPAAm carrying an affinity ligand, biotin, against streptavidin using electrostatic charge interaction, whereas Fe_3O_4 nanoparticles were directly prepared in the presence of PNIPAAm as a stabilizer ligand. In this setup, incubation of PNIPAAm, Au-PNIPAAm-biotin, and Fe_3O_4-PNIPAAm with streptavidin spiked plasma at 45°C (above LCST) caused aggregation of particles together with streptavidin. By means of magnetic separation and redispersion, Au-PNIPAAm-biotin bound streptavidin was concentrated manifolds into a smaller volume and was quantified without any further treatment with a lateral flow immunochromatography test.

Lai et al. have designed a microfluidic separation system based on PNIPAAm having hydrophobic alkyl chain at one terminus and polar carboxylic acid at the other terminus [71]. PNIPAAm was used as a micellar template and surfactant to synthesize γ-Fe_2O_3 MNPs. The surface carboxylic acid moieties were chemically modified with biotin ligands. With the manipulation of both the magnetic field and the temperature, it was shown that streptavidin bound MNPs could be accumulated on the walls of a microfluidic channel. In this way, a target biomolecule could be captured in a heterogeneous mixture below LCST and then could be selectively accumulated in the microfluidic device by both raising the temperature above LCST and applying magnetic field. By either decreasing the temperature below LCST or turning off the magnetic field, MNPs bound with proteins could be recovered.

Hoshino et al. have designed a novel method to separate neutrophils, short lived immune cells against microorganisms, from macrophages by utilizing commercial thermoresponsive MNPs modified with streptavidin (Therma-Max LSA Streptavidin, Magnabeat Incorporated, Chiba, Japan) [72]. The magnetic construct has shown an average diameter of 167.6 nm at 10°C (below LCST) and aggregated to a bigger size at 40°C (above LCST) according to DLS measurements.

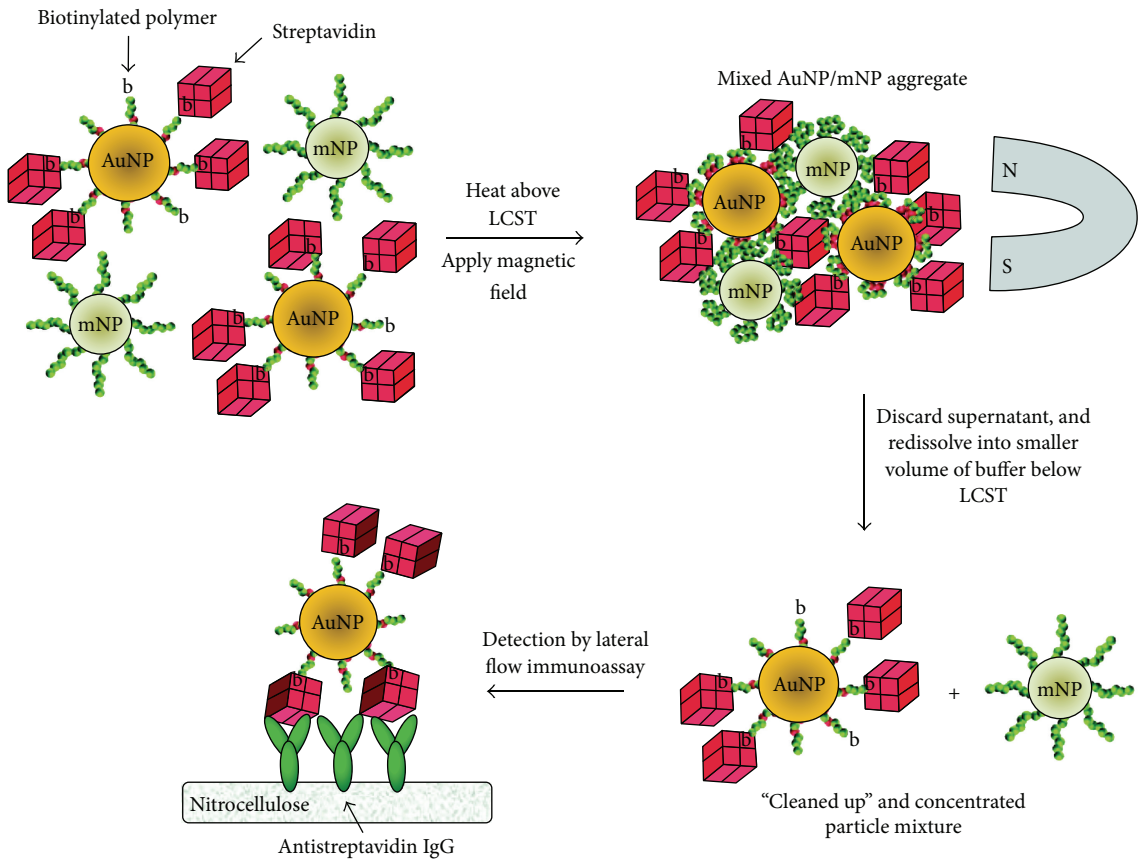

Figure 3: Separation and enrichment of a model protein using thermoresponsive MNPs and Au nanoparticles. Au nanoparticles functionalized with a thermoresponsive block polymer, PNIPAAm-b-P DMAEAm, were conjugated to biotin molecules to capture streptavidin from spiked human plasma. Capture of streptavidin was carried out by incubation of the plasma with PNIPAAm-b-PDMAEAm-Au, PNIPAAm-MNP, and free PNIPAAm followed by magnetic separation above LCST (45°C). After removing supernatant, the sample was dissolved in buffer below LCST which caused dispersion of assembly, and streptavidin was still bound to Au nanoparticles. The sample was directly applied to lateral flow assay which contained anti-streptavidin antibody for detection of streptavidin (reprinted with the permission of publisher, American Chemical Society, copyright 2010, from [70]).

A biotinylated macrophage-specific anti-F4/80 antibody has been functionalized on the surface of the MNPs through the streptavidin-biotin interaction. Incubation of the resultant MNPs with the Murine peritoneal fluid, containing neutrophils and macrophages, below LCST has led to the capture of macrophages. Aggregates consisting of MNPs bound with the macrophages were obtained above LCST and separated with a permanent magnet leaving behind peritoneal fluid containing mostly neutrophils. This was validated through fluorescence-activated cell sorting (FACS) study.

It is obvious that thermoresponsive MNPs will be studied in great detail for biomedical separation purposes in future, and it seems that there should be more emphasis on the isolation or recovery of biomolecules from MNPs. To this end, a number of strategies could be adapted from chromatographic separation techniques to elute biomolecules from MNPs. Table 2 summarizes a variety of magnetic separation platforms in biomedical field based on MNPs and thermoresponsive polymers [46–52].

2.3. Environmental Applications. Thermoresponsive MNPs have proved to be a promising tool in environmental sciences, especially in water treatment, and desalination applications. In this regard, Zhao et al. have designed a forward osmosis (FO) draw solution based on Fe_3O_4 nanoparticles encapsulated within a thermoresponsive copolymer, poly(sodium styrene-4-sulfonate-co-N-isopropylacrylamide) (P(SSS-co-NIPAAm)) through ligand exchange process [73]. In this design, they tested the ability of draw solution to draw the sea water through FO membrane, and the resulting osmotic pressure and the water fluxes were measured. The polyelectrolyte, PSSS, has provided the driving force for the flux which was caused by higher osmotic pressure of PSSS than the seawater. In a typical setup (Figure 4), water was drawn across the membrane towards the draw solution and then the draw solution was subjected to magnetic separation above LCST, and this process produced regenerated draw solute and fresh water.

Table 2: Thermoresponsive polymer-magnetic nanoparticle composites for magnetic separations of biomolecules and cells.

Magnetic core-size (diameter)	Polymer/analyte	LCST	Affinity ligand/application	Reference/note
Fe_3O_4 polystyrene-(Therma-Max) 100 nm	PINAAm/thyroid stimulating hormone (TSH)	22°C	β-antibody/TSH isolation and detection (Immunoassay)	[46]
Fe_3O_4-SiO_2-80 nm	Poly(2-(2-methoxyethoxy)ethyl methacrylate-co-methacrylic acid-co-N-(4-vinyl)-benzyl iminodiacetic acid) P(MEO_2MA-co-MAA-co-VBIDA)/Lysosome	15–25°C	Molecularly imprinted lysosome receptor/thermal capture and release of lysosome	[47]
γ-Fe_2O_3-SiO_2-5 μm	Poly(N-vinylcaprolactam) (PNVCL)/Bovine Serum Albumin (BSA)	33.4°C	Hydrophobic interaction/protein separation-purification	[48]/size measurement was based on SEM of whole assembly
Fe_3O_4-100 nm	Poly(polyethylene glycol-co-N-isopropylacrylamide) poly(PEG-co-PINAAm)/lysozyme	40°C	Hydrophobic interaction/protein separation-purification	[49]/size measurement based on TEM of aggregates due to inclusion complexes between cyclodextrin and PEG
PLGA-iron oxide MNPs-(Meliorum technologies, Rochester, NY) silica microparticles-50–100 μm	Poly(N-isopropylacrylamide-co-allylamine) poly(NIPAAm-co-AH)/stem cells	33°C	CD34 antibodies/isolation, enrichment, and detachment of endothelial progenitor cells (EPCs)	[50]/size measurement was based on SEM of whole assembly
Fe_3O_4-100 nm	Poly(N,N′-isopropylacrylamide-co-N-methacroyl-N′-biotinylpropylenediamine) (P(NIPAAm-co-MBPDA))/ZZ-displaying yeast cells	30°C	Anti-goat IgG (heavy and light chains) (rabbit IgG)/affinity selection and separation of target cells from model yeast cells	[51]/size measurement was based on DLS of whole assembly
Fe_3O_4–dextran-(Therma-Max) 70 nm	Poly(N-acryloyl glycinamide-co-N-(3-biotinamidepropyl)-methacrylamide) P(NAGAM-co-NBPMA)	18°C (UCST)	(i) CD4 antibody/capture and enrichment of *Arabidopsis* protoplasts (plant cells) (ii) Silkworm storage protein (SP2)/anti-SP2 antibody	[52]/size measurement was based on DLS of whole assembly

In a similar fashion, Razmjou et al. have designed a FO system based on a draw solution composed of γ-Fe_2O_3 nanoparticle and poly(sodium acrylate-co-N-isopropylacrylamide) (P(SA-co-NIPAAm)) hydrogel [74]. The polymer was synthesized in the presence of MNPs, and this process yielded MNPs physically trapped within the polymeric units. They have studied the swelling behavior of the draw solution, the water flux through FO membrane, and water recovery was assessed through both thermal heating and magnetic heating. It was found that the recovery of water was higher with magnetically induced heating as compared to thermal heating, and it was attributed to the efficient local heating of hydrogels through magnetic particles which resulted in an efficient phase change of the polymers.

Oil harvesting from industrial wastewater and spill accident sites is another potential application for thermoresponsive MNPs. Chen et al. have developed an oil harvesting platform consisting of Fe_3O_4–SiO_2 microsphere core and PNIPAAm polymer shell [75]. Polymeric layer was grown using ATRP technique. The amphiphilic PNIPAAm shell interacted with the oil droplets in water through hydrophobic interactions, and as a result bigger oily emulsions could be separated from water with an external magnet. Upon setting the temperature above LCST, oil could be released from the particles as a result of destabilization of the emulsion caused by phase transition of the polymer.

Thermoresponsive MNPs showed very promising results in desalination of seawater. In the future, there will be a growing demand to produce fresh water from the seawater. To this end, more studies are needed to integrate thermoresponsive MNPs into the current membrane technologies.

2.4. Chemical/Biological Catalysis. Over the last decade, MNPs have been incorporated into various platforms in order to carry out chemical and biological transformations either as reactants or as catalysts [30]. Inclusion of thermoresponsive polymers into these types of constructs, in essence, could provide a couple of benefits. Recovery of the catalyst bound to magnetic platform could be achieved through magnetic separation with the modulation of aggregation/dispersion of the thermoresponsive unit with a variable temperature input. Besides, kinetics of the catalytic reactions could be controlled

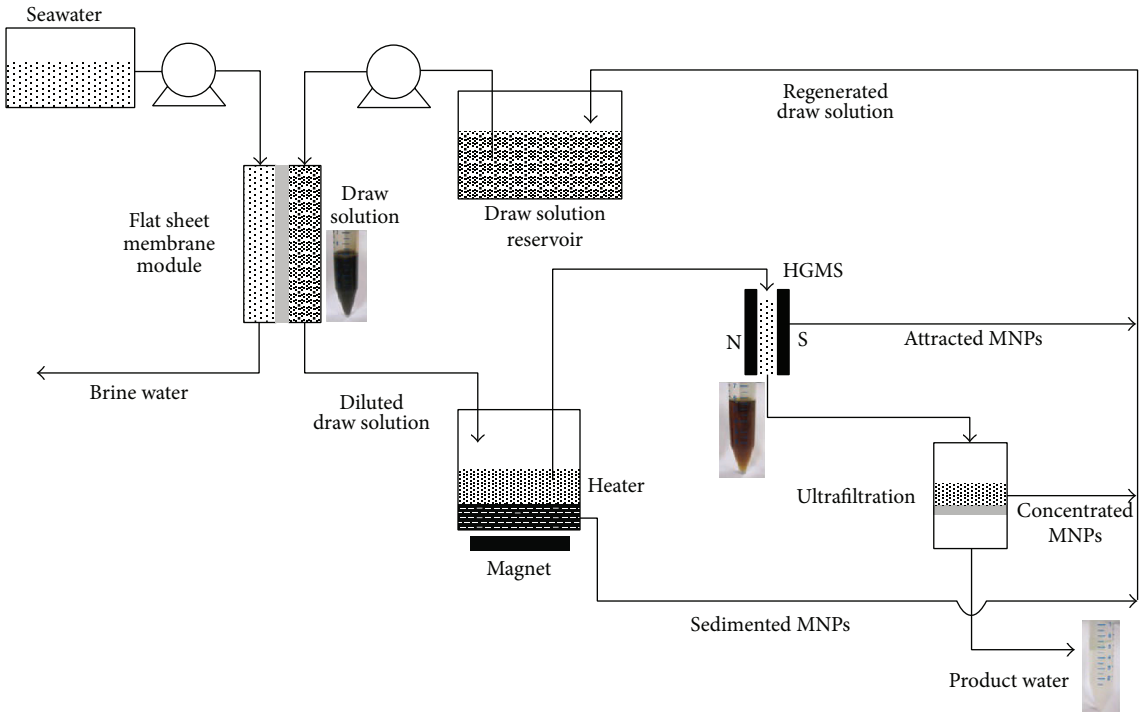

Figure 4: Application of thermoresponsive MNPs as FO draw solute in water desalination. The polyelectrolyte present in the thermoresponsive polymer creates an osmotic pressure which leads to the flux of water from seawater through the membrane towards the draw solution. Setting temperature above LCST leads to shrinking of the polymer and dehydration of the draw solute, and thermoresponsive MNPs could be separated and regenerated with the application of magnetic field (reproduced with permission of publisher, American Chemical Society, copyright 2013, from [73]).

via control of the size of MNPs with aggregation/dispersion process. Furthermore, surfaces of the MNPs could provide a nanoreactor/container for the catalytic transformations.

Crassous et al. have formulated a platform composed of, respectively, γ-Fe_2O_3 magnetic core, a silica layer, and poly(N-isopropylmethacrylamide) (PNIPMAAm) shell [76]. The polymer layer was grafted using surfactant free seed precipitation polymerization. Small Au nanoparticles were synthesized inside the polymeric shell as the catalysis component. A different thermoresponsive polymer (PNIPAAm) layer was grown as the outermost polymeric shell. The second layer of thermoresponsive polymer, PNIPAAm, has grown so as to modulate the catalytic activity of Au particles and to provide better colloidal stability to overall composite material. The catalytic activity of the platform before and after the growth of second polymer shell was tested using reduction of 4-nitrophenol to 4-aminophenol by $NaBH_4$ and following with UV-Vis spectrophotometry. It was found that the rate of reaction without second shell is purely thermally controlled. However, for the composite system having the second polymer shell, the rate dependence is controlled by both thermal and the phase transition of PNIPAAm. It was also shown that the catalyst could be removed and recycled utilizing magnetic separation. Even though it proved that it is an efficient catalytic platform, the formulation of the system is complex and requires laborious work-ups.

Liu et al. have formulated a similar catalytic system composed of Fe_3O_4 magnetic core, poly(N-isopropylacrylamide-co-2-(dimethylamino)ethyl methacrylate) (P(NIPAAm-co-DMAEMA)) thermoresponsive shell, and Au nanoparticles [77]. Incorporation of the Au particles into final construct was driven by electrostatic interaction of the positively charged polymer and the negatively charged Au particles. The catalytic activity of system was measured using reduction of 4-nitrophenol and it was found that the rate of catalysis decreased as the temperature was increased above LCST. It was concluded that thermally activated phase change led to the aggregation of Au particles; thus less surface area was available for the catalytic reduction. Furthermore, the catalyst was separated with a magnet providing recycling option.

Biocatalysis utilizes enzymes to produce chemicals that are essential for both medical applications and industrial purposes [78]. It provides a number of advantages over the traditional wet-lab synthesis of the chemicals. Furthermore, the reuse of catalyst, especially expensive enzymes, bears utmost importance due to cost and availability factors. Employment of thermoresponsive MNPs in this field, in essence, could be an efficient solution to the reusability issues. Marten et al. have prepared a biocatalyst platform consisting of Fe_3O_4 core particles surrounded by thermoresponsive polymers synthesized through ATRP technique using monomers of oligo ethylene glycol based methacrylates

[79]. As the catalytic component, porcine pancreas trypsin was conjugated to the platform. The activity of immobilized catalyst was tested using benzoyl-Arg p-nitroanilide which hydrolyzes to p-nitroaniline and could be traced with UV-Vis spectroscopy. It was found that, above LCST of the polymer, the rate of reaction increased due to the shrinking of polymer layer which exposed the enzyme to the substrate to a considerable extent. Furthermore, it was shown that magnetically induced heating caused phase transition of the polymer faster than thermal heating.

Although the use of thermoresponsive MNPs has tremendous potentials in the biocatalysis field, the number of studies is limited. Potential future studies might focus on the development of conjugation protocols that yield the immobilization of enzymes on the surface of thermoresponsive MNPs in optimum quantity and without loss of catalytic activity.

2.5. Miscellaneous Applications. In addition to the previously described four categories, there are some studies related with thermoresponsive MNPs which cannot be placed in any category. Although they belong mostly to biomedical applications, it is worth mentioning some of these studies in a separate subheading. Thermoresponsive MNPs were used in the fabrication of 3D cell support matrices to grow stem cells [80], in cellular labeling and *in vivo* cellular tracking [81], in temperature sensing of living cells [82], and in sensing inorganic ions such as arsenic and cadmium [83].

3. Conclusion and Future Outlook

So far, it has been validated through extensive research that combining multiple materials into a single platform has potentials to generate multistimuli responsive smart devices that could be employed in many fields. Thermoresponsive MNPs may indeed find more application fields with the help of collaboration of chemical, material, and engineering sciences due to the interdisciplinary nature of applications. It is expected that these materials will be components of assays, imaging agents, therapeutics, sensors, and multifunctional devices, and it is not hard to visualize that they will be integral parts of many routine lab testing in medicine as well as nanoreactors in chemical sciences. Future studies might be directed to study alternative ways of linking thermoresponsive polymer with MNPs. Most of the reported protocols as outlined in the previous sections rely on the polymerization of corresponding monomers on the surface of MNPs. However, preformed polymeric architectures with reactive groups could be immobilized on the surface of MNPs using effective covalent chemistries. UCST polymers have been underutilized in the applications so far, and they might provide flexibility in designing new platforms especially in biomedical applications where temperature sensitive materials pose technical challenges with LCST polymers. In addition to magnetic and thermoresponsive stimuli, it is possible to include pH, redox, ion, and light responsive units in the material design, and thereby smart multimodular devices and platforms could be generated.

Abbreviations

LCST:	Lower critical solution temperature
PNIPAAm:	Poly(N-isopropylacrylamide)
UCST:	Upper critical solution temperature
MNPs:	Magnetic nanoparticles
MRI:	Magnetic Resonance Imaging
MDT:	Magnetic Drug Targeting
SPIONs:	Superparamagnetic iron oxide nanoparticles
DLS:	Dynamic light scattering
NIPMAAm:	N-Isopropylmethacrylamide
SLN:	Sentinel lymph node
FO:	Forward osmosis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by the UAE National Research Foundation's (NRF) grant, UIRCA 2013-24898, and Khalifa University Internal Research Fund (KUIRF), 210080.

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