Review Article

Biocompatible SiO$_2$ in the Fabrication of Stimuli-Responsive Hybrid Composites and Their Application Potential

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Organic/inorganic hybrid composite materials have been extensively studied as they combine the properties of inorganic material and organic polymer. Among the inorganic material biocompatible silica (SiO$_2$) is an interesting candidate for application in biotechnology because such material is wide spread in nature as well as in medicine. During the last few decades, stimuli-responsive polymers are drawing much attention from the researchers for application versatility such as target-specific delivery of drug and corrosion inhibitors. Considering the biocompatibility and many such important properties as high cargo loading capacity, long blood circulation lifetime, enhanced permeability and retention, mechanical strength, and easy processability, combination of SiO$_2$ particles with stimuli-responsive polymers is gaining attention over the last decade. This review article will report the progress made towards the development and application of stimuli-responsive hybrid composites based on SiO$_2$.

1. Introduction

Hybrid composites comprising inorganic and organic materials are attracting rapidly expanding interest from material scientists as they offer advantages due to the combination of unique physical properties of inorganic materials with the processability and flexibility of organic polymer [1–11]. A huge variety of inorganic particles have been incorporated into hybrid materials with silica (SiO$_2$) being the most widely used because colloidal SiO$_2$ spheres uniform in size, shape, and composition are widespread in nature and in electronics as well as in medicine [12–16]. Additionally mesoporous SiO$_2$ particles have been recognized as one of the most promising biomedical platforms for therapeutic, diagnostic, prognostic, and combinatorial applications [17–20]. Because of their stable mesoporous structures, large surface area, tunable pore size, easy surface functionalization, chemical inertness, and good biocompatibility, mesoporous SiO$_2$ particles can be used for accommodating multiple cargo molecules such as therapeutic drugs, proteins, genes, corrosion healing, and imaging agents either alone or in combination and be engineered to facilitate the on-demand release of cargo molecules [21–23]. However, it has been observed that before surface

modification a simple mixture of mesoporous SiO$_2$ particles and cargo molecules cannot be used particularly for diagnostic applications because such practice induces interactions between the silane groups on the surface of SiO$_2$ particles and biological molecules, thus making them less promising.

Recently delivery systems based on stimuli-responsive polymers are gaining attention because of their ability to release cargo on the targeted site like cells, organs, or metal surface [24–27]. Of the stimuli-responsive polymers, pH- and temperature-responsive polymers are the mostly used triggers especially to release drug molecules as they are both important environmental factors in biomedical and physiological systems. As such to design controlled targeted release systems based on porous/mesoporous/rigid SiO$_2$ particles many reports are available on the functionalization of SiO$_2$ particles with pH- and temperature-responsive polymers. The most common pH-responsive and thermoresponsive SiO$_2$ based hybrid composites are derived from polymers bearing poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(N-isopropylacrylamide) (PNIPAM), and poly(2-dimethylaminoethyl methacrylate) (PDM) residues due to their aqueous solubility, polyelectrolyte character, and ability to conjugate biologically active molecules. In addition

to pH- and temperature-responsive hybrid composites, few researches are also available on other stimuli such as enzyme, light, and redox.

In the last ten to fifteen years, much research has been done on the modification of inorganic biocompatible SiO_2 particles with stimuli-responsive polymers using various approaches. Depending on the fabrication method, morphological structure, size and size distribution, and chemical composition, the modified SiO_2 particles are considered to have different properties and application potential. To exploit the full benefits of SiO_2-stimuli-responsive composite microspheres it is necessary to understand the simplicity of the synthesis process with good reproducibility and desired properties. For better understanding, this review on SiO_2-stimuli-responsive hybrid composites is differentiated on the nature of stimuli-responsive properties and morphological structure of SiO_2.

2. Porous/Mesoporous SiO_2 Particles

As already mentioned porous/mesoporous SiO_2 particles had received particular interest in biotechnology due to their tailorable mesoporous structure. Moreover, the fabrication of porous structure is simple, scalable, cost-effective, and controllable. The porous/mesoporous SiO_2 particles have been used to design numerous stimuli-responsive drug carriers which are outlined here.

2.1. pH-Responsive Carriers. The construction of stimuli-responsive "gatekeepers" of the mesopores can efficiently reduce the immature leakage problem, whilst achieving site-specific release of drug and nanomedicine [28–31]. Biomacromolecule-gated mesoporous SiO_2 nanoparticles (MSNPs) are highly desirable for practical applications in disease-related environments. pH-responsive delivery system is considered to be useful for cancer therapies because most cancer tissues have lower extracellular pH values (pH = 5.7–7.8) than normal tissues and the bloodstream, and pH values drop further inside cells, especially inside endosomal (pH = 5.5–6.0) and lysosomal (pH = 4.5–5.0) compartments [32, 33]. To date, some research articles on pH-responsive release of molecules from pore voids of mesoporous SiO_2 materials have mainly been reported using pH-sensitive linkers and polyelectrolytes.

The polyelectrolyte pair comprising sodium poly(styrene sulfonate) (PSS) and poly(allylamine hydrochloride) (PAN) has been widely investigated for designing hollow microcapsules and confirmed the controlled encapsulation and release of several kinds of molecules such as dyes, enzymes, and DNA from the capsules in response to the change in pH or ionic strength of the release medium [34–38]. Zhu and his group designed novel pH-responsive controlled drug release system by using the polycation PAN/PSS multilayers to cap the mesopore openings of drug-loaded mesoporous SiO_2 particles (MSP) [39]. The drug storage capacity of the system reportedly increased three times relative to conventional MSP and the system exhibited stimuli-responsive controlled release into stomach instead of intestine. The drug release rate

was also well controlled with changing pH value from the PAN/PSS multilayers coatings on MSP loaded with ibuprofen. In another research, Feng et al. constructed a pH-responsive carrier system by coating the MSNPs with polyelectrolyte multilayers (PEMs) composed of PAN and PSS via layer-by-layer technique and anticancer drug doxorubicin hydrochloride (DOX) was loaded into the prepared PEM-MSNP [40]. The biocompatibility and efficiency, influence of the layer number on the release profiles, cytotoxicity, and hemocompatibility were extensively studied. The cellular uptake of DOX-loaded PEM-MSN particles in HeLa cells was remarkably larger than that in L929 cells and hence resulted in a desirable growth-inhibiting effect on cancer cells. DOX-loaded PEM-MSN particles exhibited a slower and prolonged DOX accumulation in the nucleus than free DOX. In vivo biodistribution indicated that they induced a sustained drug concentration in blood plasma but lower drug accumulation in the major organs, especially in the heart, compared to free DOX. The histological results also revealed that DOX-loaded PEM-MSNPs had lower systemic toxicity than free DOX. The same researchers fabricated pH-responsive drug delivery nanocarriers by the same layer-by-layer assembly of biocompatible PEMs of alginate/chitosan on MSNPs with improved biosafety features [41]. The functionalized MSN particles showed improved biocompatibility compared to reference SiO_2 nanoparticles in terms of low haemolytic and cytotoxic activity against human red blood cells. The anticancer drug DOX with fluorescent properties was loaded into nanocarriers and measured their use for the pH-responsive drug release both in vitro and in vivo. The DOX released from nanocarriers was pH dependent, and the release rate was much faster at lower pH than that of at higher pH. The in vitro evaluation on HeLa cells showed similar behavior as observed for the previously fabricated PEM-MSN particles. In addition, the pharmacokinetic and biodistribution studies in healthy rats showed that DOX-loaded nanocarriers had longer systemic circulation time and slower plasma elimination rate than free DOX.

The pH- and competitor-driven nanovalves of cucurbit[7]uril (CB[7]) pseudorotaxanes based on MSP (MCM-41) were investigated by Liu and Du [42]. The chemistry of the controlled release driven by this dual stimuli was pretty complex. MCM-41 particles generally exhibit relatively narrow pore size distribution in the range of 2–4 nm in diameter were first modified with 1,4-butanediamine. Calcein, an anionic dye, was loaded within the modified MPS particle and the protonated 1,4-butanediamine was then encircled with CB[7] which blocked the pore entrances. The entrapped calcein was successfully released into bulk solution by opening of pores at higher pH value due to the dissociation of the CB[7]-1,4-butanediamine supramolecular complexes. The nanovalve closing and opening were followed from the change in fluorescence intensity of calcein. The amount of released calcein increased with increasing pH. Besides this routinely used method, the pores were also activated by binding of simple cationic competitors such as cetyltrimethylammonium bromide (CTAB) and 1,6-hexanediamine. Another research group designed acid and base dual-responsive MSNPs and studied the release of gemcitabine, a

powerful anticancer drug against different malignancies [43]. The drug was loaded inside the MSNPs and CB[7] macrocycles attached to the protonated hexylammonium sites were used to block the pore orifices at neutral pH. The release of cargo molecules either under acidic or alkaline conditions based on the pH controlled binding affinities of CB[7] with secondary dialkylammonium and ferrocenecarboxylic acid (FcCOOH) immobilized on the surface of MSNPs was investigated.

The pH-responsive nano-multidrug delivery systems (drugs@-micelles@MSNs or DOX@CTAB@MSNs) prepared by in situ co-self-assembly among water-insoluble anticancer drug DOX, surfactant micelles CTAB as chemosensitive, and silicon species showed the antileaking of loaded drug in normal tissues at pH 7.2–7.5 but released the drug in a sustained way within cancer cells at a relatively lower pH value through the ion exchanging interaction between H^+/H_3O^+ and positively charged drugs@micelles [44]. The released drug exhibited high drug efficiencies against drug-resistant MCF-7/ADR cells as well as drug-sensitive MCF-7 cells.

Using a different technology, Tang et al. synthesized pH-responsive nanocarriers comprising chitosan-PMAA shells and MSN cores via a simple in situ polymerization approach [45]. MSNPs, chitosan, and MAA were ultrasonicated in water and polymerized at 80°C for 2 h using potassium persulfate (KPS) as initiator. Afterwards, the reaction temperature was reduced to 50°C and glutaraldehyde was added as crosslinker for chitosan. The composite microspheres had both high loading capacity (22.3%) and encapsulation efficiency (95.7%) for anticancer drug DOX. The cumulative release of DOX@MSN/chitosan-PMAA showed a low leakage at pH 7.4 with only 18% amount was released after 24 h while being significantly enhanced to 70% at pH 5.5. The cytotoxicity test by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay showed that the blank carrier MSN/chitosan-PMAA microspheres are suitable as drug carriers. The cellular uptake of composite microspheres investigated by confocal laser scanning microscopy (CLSM) indicated that microspheres could deliver the drugs into human cervical carcinoma (HeLa) cell. Based on pH-responsive chitosan, a research group proposed a straightforward synthesis of chitosan-capped MSNPs to accommodate guest molecules [46]. The amino groups in chitosan can be protonated within a certain pH range and therefore can be responsive to external pH-stimulus. (3-Glycidyloxypropyl) trimethoxysilane (GPTMS) was grafted onto the surface of the MSNPs in an acidic EtOH medium, in which GPTMS reacted with the silanol groups through the formation of Si-O-Si bonds. Subsequently, a solution of chitosan was added into the reaction solution and a connection between chitosan and GPTMS on the surface of the MSNPs was accomplished through an acid-catalyzed amino-oxirane addition reaction. The synthesis of the chitosan capped MSNPs is shown in Figure 1.

The degree of release for anticancer drug DOX from chitosan capped MSNPs increased correspondingly as the pH of the media decreased. The capping of SiO_2 particles with chitosan lowered the cytotoxicity as observed also in the

previous work by Tang. The in vitro killing potency of drug-loaded SiO_2 increased with time as well as with concentration of drug carriers. In a similar work another group prepared pH-responsive chitosan coated MSNPs via surface functionalization with amino groups followed by grafting of chitosan [47]. The anticancer drug DOX was loaded into the cavities of chitosan-coated MSNPs and demonstrated pH-dependent release without showing the activity of the released anticancer drug. Compared to this in a relatively early work, Popat et al. described the covalent binding of positively charged polymer chitosan onto phosphonate functionalized MSNPs based on the well-known phosphoramidate chemistry [48]. Phosphonate functionalized MSNPs were activated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, followed by covalent bonding between the primary amine of chitosan and the phosphonate groups. A pH-responsive release of ibuprofen was achieved by varying the shell structure of positively charged chitosan in the designed pH 4.0–7.4 solution. Under basic conditions, chitosan formed a gel-like structure which was insoluble and prevented release of ibuprofen at pH 7.4. When the pH was reduced to below 6.3, the drug was released due to protonation of the amino group on chitosan.

There are some anticancer drugs which do not form coordination bonds with metals and remained a significant challenge for the development of pH-responsive drug delivery. For noncoordination drugs, a simple and effective strategy for pH-responsive delivery of these drugs is trapping drugs in the pores by physical adsorption and subsequently capping the pores by coating such coordination polymers (CPs) on the MSNP surface that can be broken by a reduction in external pH. Xing and his group reported the fabrication of a novel CP-coated MSNPs for pH-responsive drug delivery [49]. The amino group surface functionalized MSNPs (MSN-NH$_2$) were first used to encapsulate the topotecan (TPT), a typical noncoordination anticancer drug, within the pores. The TPT-loaded MSN-NH$_2$ (MSN-NH$_2$-TPT) was then capped by the CPs of zinc and 1,4-bis(imidazol-1-ylmethyl) benzene (BIX) grown on the MSNP surfaces, giving rise to MSN-NH$_2$-TPT@BIX-Zn architecture. The TPT loading of MSN-NH$_2$-TPT was about 0.151 mmol g^{-1} (~57.8 mg g^{-1}) and the drug release was triggered by H$^+$ cleavage of the coordination bond between BIX and Zn of the CP nanolayer [50] and the CP-coated MSNPs showed a remarkably enhanced efficiency in killing cancer cells.

Wu et al. prepared Concanavalin A- (Con A-) gated mannose functionalized MSN delivery systems for the controlled release of drugs utilizing the principle of carbohydrate-protein interaction [51]. The Cona A tetramers bound to the mannose epitopes in the presence of Mn^{2+} and Ca^{2+} ions encapsulated the Rhodamine 6G, selected as a model drug, within the pores. On reducing the pH to the acidic conditions the protein nanogates opened and released the cargo because Ca^{2+} and Mn^{2+} ions were dialyzed out of protein binding pockets. Additionally Con A tetramer can also be fragmented as dimers and/or monomers below pH 5.5 as illustrated in Figure 2.

Zhao et al. reported a novel multifunctional pH-responsive nanocomposite composed of a magnetite nanocrystal
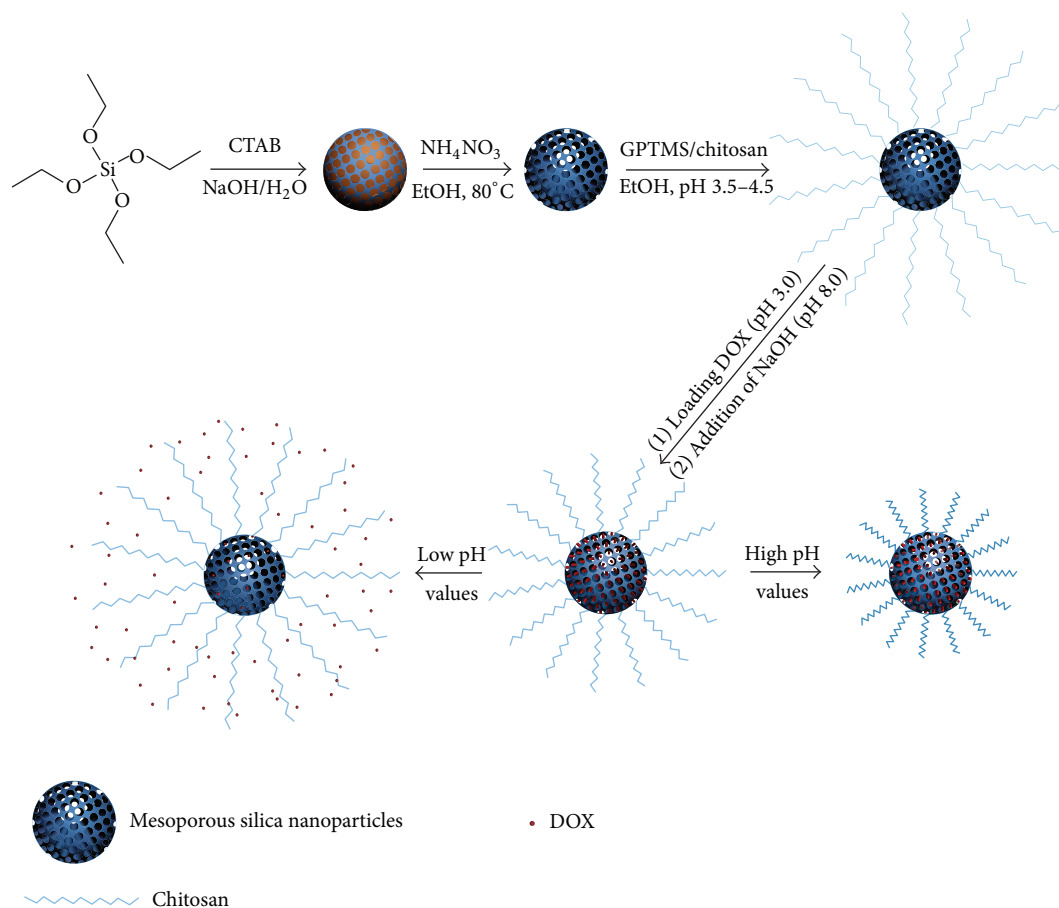
FIGURE 1: Schematic representation of the formation of chitosan-capped MSNPs and the loading and release of the drug doxorubicin hydrochloride (DOX) by changing the pH value (reproduced from [46], with permission from Wiley-VCH Verlag GmbH & Co. KGaA).

core and a mesoporous silica shell ($Fe_3O_4@SiO_2$), end-capped with pH-stimuli-responsive hydroxyapatite (HAp) nanovalves [52]. Here microemulsion method was used to prepare Fe_3O_4 core and MSNPs and the coating of the natural nontoxic component HAp was achieved through a biomimetic mineralization process. The $Fe_3O_4@SiO_2@HAp$ nanoparticles possessed pH-responsive drug-release for model drug ibuprofen. The dissolution of HAp in an acidic environment triggered the release of the loaded drugs from $Fe_3O_4@SiO_2@HAp$ nanoparticles.

2.2. Temperature-Responsive Carriers. Fu and his team prepared thermosensitive SiO_2/PNIPAM membranes and particles with ordered porosity using a simple low-temperature process [53]. The random copolymer of NIPAM and 3-methacryloxypropyltrimethoxysilane (MPS) prepared by free radical copolymerization was added to a mixture of TEOS, ethanol, water, and acid in which ethoxy groups in MPS and TEOS were hydrolyzed to form a stock sol. Surfactant molecular assemblies acted as template to produce an ordered porous network with well-defined pore size. Permeation experiments with crystal violet and poly(ethylene glycol) suggested that SiO_2/PNIPAM hybrid membranes could function as a switchable molecular actuator with high stability.

Temperature-dependent uptake and release of small molecules within porous SiO_2 nanoparticles were achieved by treatment of preformed, thiol-functionalized micro-to-MSNPs with pyridyl disulfide-terminated PNIPAM (PNIPAM-S-S-Py) [54]. The temperature-responsive polymer, PNIPAM, containing a pyridyl disulfide end group was prepared via reversible addition fragmentation chain transfer (RAFT) polymerization. The trithiocarbonate-terminated PNIPAM was treated with hexylamine to yield thiol-terminated PNIPAM (PNIPAM-SH) which was later treated with 2,2'-dipyridyl disulfide in glacial acetic acid-methanol solution to obtain PNIPAM-S-S-Py. Thiol functionalized micro-to-MSNPs synthesized by a method as reported elsewhere [55] was finally reacted with PNIPAM-S-S-Py to prepare MSN-PNIPAM composites shown in Figure 3. The chemistry of this preparation technique is rather complex and requires technical hand in industrial production. The MSN-PNIPAM composites had low level of leakage of small molecules encapsulated within pores at 38°C (above lower critical solution temperature, LCST, <2% after 2 h) as the pores were blocked by the collapsed PNIPAM chains while the release of entrapped molecules occurred at temperature below the LCST.

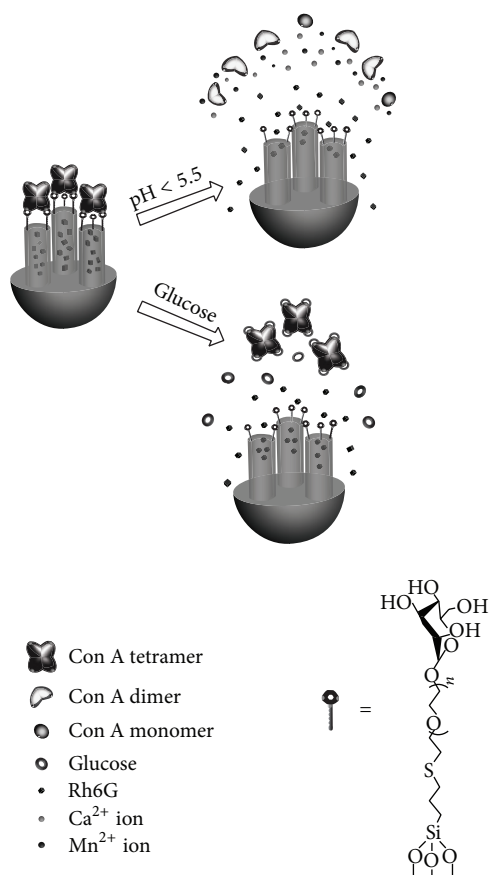Singh and his group had used relatively simple technique to prepare temperature-sensitive MSNPs for triggered drug

Figure 2: Illustration of the controlled release of cargo from Con A-gated mannose-functionalized mesoporous SiO_2 nanocontainers in response to changes in pH value and glucose concentration (reproduced from [51], with permission from Wiley-VCH Verlag GmbH & Co. KGaA).
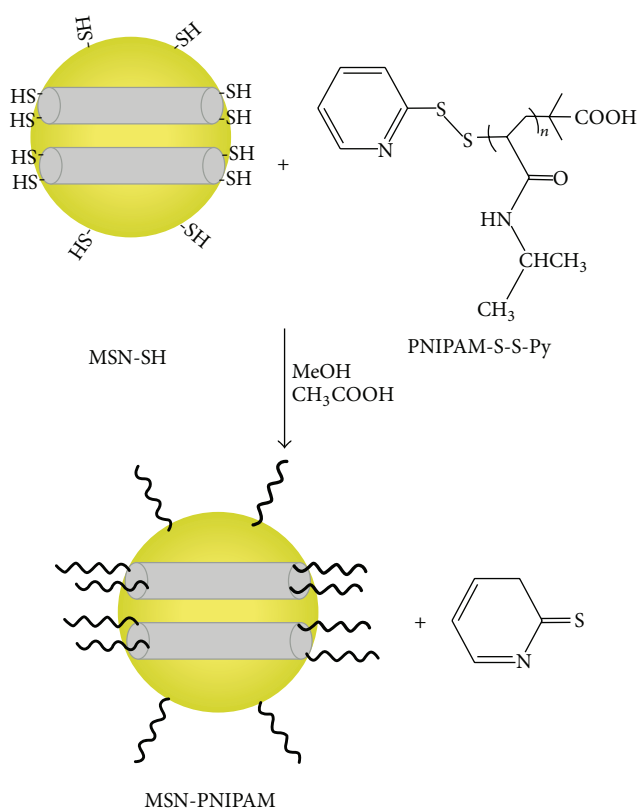

Figure 3: Reaction of MSN particles- (MSN-) SH with PNIPAM-S-S-Py to form MSN-PNIPAM (reproduced from [54], with permission from American Chemical Society).

release [56]. The anionic surface of MSNPs was functionalized with bifunctional N-(3-aminopropyl) methacrylamide hydrochloride and the acrylamide group was subsequently copolymerized at room temperature by radical copolymerization of NIPAM and poly(ethylene glycol) diacrylate. The loading of DOX in polymer-coated MSNPs was only slightly lower (~50% of total DOX added) compared with the uncoated MSNPs (~60% of total DOX added) as polymer coating partially hindered the loading inside the pores. At temperatures greater than the LCST (37°C), more than 50% DOX was released within the first 2 h of incubation, compared with the same formulation maintained at room temperature. In contrast, uncoated MSNPs released the same quantity of DOX at either temperature.

2.3. pH- and Temperature-Responsive Carriers. The inclusion of multiple stimuli-responsive properties into microstructures has broadened their properties and application [57–59]. The design of the structured hybrid microspheres, combining the multistimuli-responsive polymer as the shell and the functional inorganic nanoparticles as the core, had promising potential applications in biomedical fields [60–63].

Not much research is carried out with pH- and temperature-sensitive carriers based on MSPs. Chang et al. prepared a kind of core-shell composite microsphere based on P(NIPAM-co-MAA) coated magnetic MSNPs via precipitation polymerization using different NIPAM/MAA feed mole ratios [64]. The magnetic MSNPs prepared by a modified sol-gel method [65, 66] were subsequently functionalized with MPS coupling agent. The thermosensitive volume phase transition was dependent on molar ratios of MAA to NIPAM and the concentration of NaCl. An increase in the pH value led to a significant increase in volume phase transition temperature, which can be adjusted as desired close to human body temperature (37°C). The drug (DOX) loading behavior of the composite microsphere was pH dependent, and the composite microsphere had a maximal embedded drug efficiency of about 91.3% at pH 10. The cumulative in vitro release (37°C, 0.15 M NaCl) showed a low leakage of only 7.2% at pH 7.4 in 24 h but was significantly enhanced to 80.2% at pH 5.0. The drug release rate increased above the volume phase transition temperature than below the volume phase transition temperature. In in vitro cell assays, the blank carrier showed no cytotoxicity to normal 293 cells at low concentrations (#10 mg mL^{-1}). However, significant growth inhibition of HeLa cells was observed when the cells were treated with DOX-loaded composite microspheres or the free DOX.
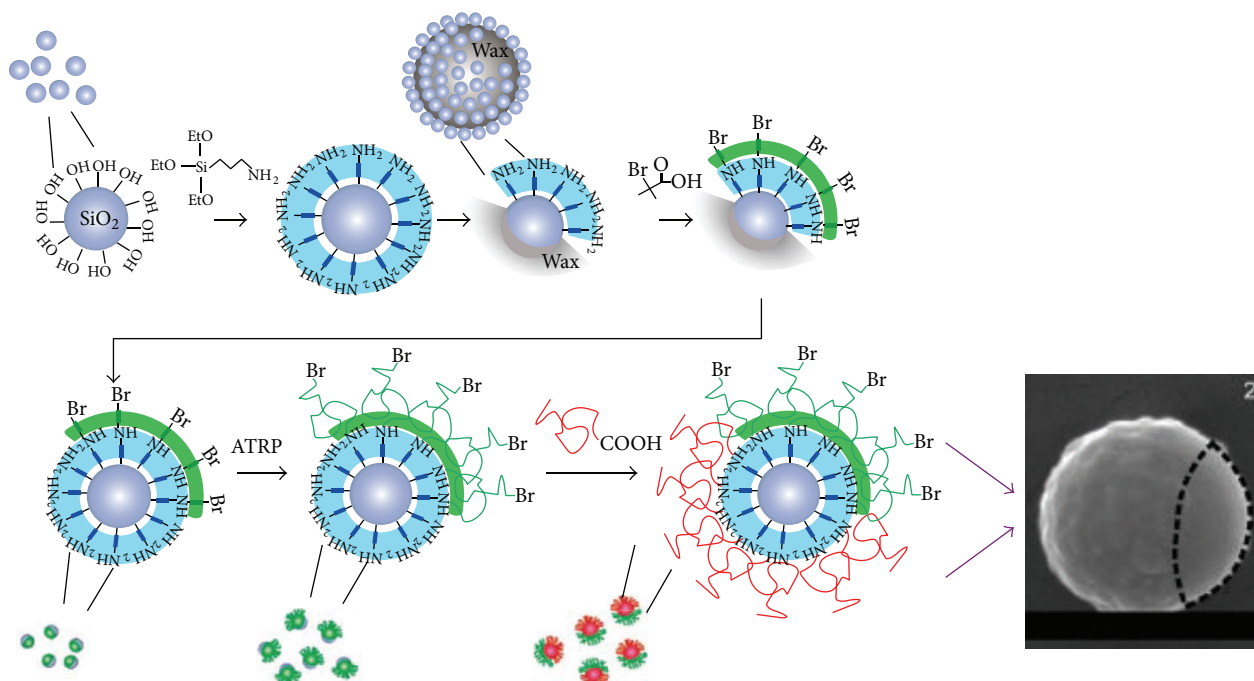
FIGURE 4: Synthesis of biocomponent Janus particles by "grafting from" and "grafting to" approaches (reproduced from [72], with permission from American Chemical Society).

3. SiO$_2$ Particles

3.1. pH-Responsive Carriers. The preparation of polymer nanocomposites by surface modification of nanoparticles is attracting much interest due to their potential applications in optics, electronics, and bioapplications [65–68]. Numerous literatures are available on the fabrication of pH-responsive carriers without much elaboration on application except for a few applied for stabilization of oil in water emulsions. The formation of mixed poly(*tert*-butyl acrylate) (P*t*BA)/polystyrene (PS) brushes from SiO$_2$ particles by nitroxide-mediated radical polymerization (NMRP) technique and subsequent hydrolysis of P*t*BA with iodotrimethylsilane to produce amphiphilic mixed PAA/PS brushes has been reported [69]. Tyndall scattering experiments and ^{1}H NMR study showed that the mixed PAA/PS particles can be dispersed and form a stable suspension in CHCl$_3$, a selective solvent for PS, and also in CH$_3$OH, a selective solvent for PAA, demonstrating the capability of these hairy nanoparticles to undergo chain reorganization in response to environmental changes.

In a rather different type of work Fujii et al. discussed the synthesis of highly cross-linked poly(4-vinylpyridine)/SiO$_2$ (P4VP/SiO$_2$) nanocomposite microgels and applied the microgels as pH-responsive particulate emulsifiers for three different oils, dodecane, methyl myristate, and 1-undecanol [70]. Ethylene glycol dimethacrylate (EGDMA) was employed as a crosslinker to prevent dissolution of nanocomposite particles at low pH. At low pH value, 4VP residues became protonated and nanocomposite particles acquired cationic microgel character, leading to efficient deemulsification of oil in water emulsions. Followed by this work the same

group reported the stabilization of methyl myristate-in-water emulsions with lightly cross-linked P4VP/SiO$_2$ nanocomposite microgel particles as a function of pH and salt (NaCl) concentration [71]. With the similar objectives, Berger and his associates proposed a new concept for designing stimuli-responsive bicomponent Janus particles decorated with oppositely charged polyelectrolytes comprising PAA and poly(2-vinyl pyridine) P2VP immobilized to the opposite sides of micrometer-sized SiO$_2$ particles [72]. The first polymer was grafted on one side of SiO$_2$ particles using the surface-initiated ATRP, "grafting from" method, and the second polymer was immobilized using the "grafting to" procedure in melt by reaction of reactive terminating carboxylic group and functional groups on the other side of the particle surface. The preparation scheme is illustrated in Figure 4. The authors expected that switchable Janus particles decorated with two sorts of responsive polymers can be used for controlled stabilization of emulsions and regulation of the molecular transport at interface between immiscible liquids.

The pH-sensitive hollow poly(N,N′-methylenebisacrylamide-co-MAA) (P(MBAAm-co-MAA)) microspheres with movable Fe$_3$O$_4$/SiO$_2$ cores were prepared by the selective removal of PMAA layer in ethanol/water from the corresponding Fe$_3$O$_4$/SiO$_2$/PMAA/P(MBAAm-co-MAA) tetralayer microspheres, which were synthesized by the distillation precipitation copolymerization of MBAAm and MAA in the presence of Fe$_3$O$_4$/SiO$_2$/PMAA trilayer microspheres as seeds in acetonitrile with 2,2′-azobisisobutyronitrile (AIBN) as the initiator [73]. The detailed preparation scheme is outlined in Figure 5. The thickness of PMAA layer was controlled in the range between 17 and 57 nm by varying the MAA monomer feed during the
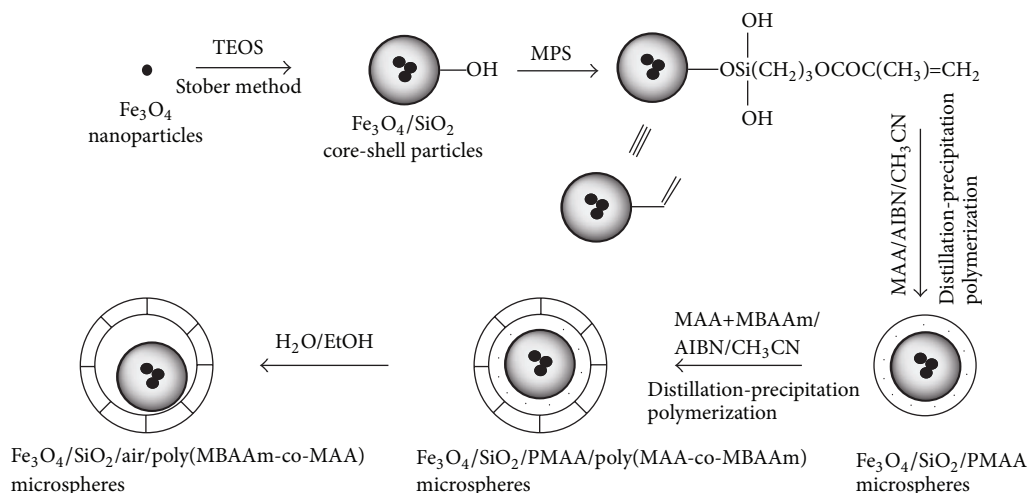
Figure 5: Preparation of pH-sensitive hollow P(MBAAm-co-MAA) microspheres with movable magnetic Fe_3O_4/SiO_2 cores (reproduced from [73], with permission from Elsevier).

second-stage distillation precipitation polymerization. The thickness of hollow P(MBAAm-co-MAA) microspheres was afforded ranging from 35 to 159 nm via changing the MAA monomer loading and MBAAm crosslinking degree for the third-stage polymerization. The hydrodynamic diameters of pH-sensitive hollow P(MBAAm-co-MAA) microspheres with movable magnetic Fe_3O_4/SiO_2 cores increased with the increase of pH in the environment.

Cash et al. prepared functional SiO_2 nanoparticles bearing various densities of -COOH residues to expand the scope of engineered surface-modified nanoparticles for bioapplications and reported the postmodifications of these polymers [74]. First, a monolayer of carboxylic acid residues was attached to the nanoparticles by treating amino-modified particles with succinic anhydride. Furthermore, the addition of a small amount of an amine reactive fluorescent dye followed by excess succinic anhydride yielded bifunctional nanoparticles. Second, surface-initiated reversible addition fragmentation chain transfer (RAFT) polymerization of *tert*-butyl methacrylate (*t*BuMA) from the surface of the SiO_2 nanoparticles was conducted to yield grafted polymers with controlled molecular weights and narrow polydispersities. Postmodifications of the surface grafted polymer were successfully performed to convert the thiocarbonylthio into a stable end group followed by removal of the *tert*-butyl ester to yield PMAA grafted SiO_2 nanoparticles. In a similar work, Wang and Benicewicz demonstrated two methods for the preparation of dye-labeled PMAA grafted SiO_2 nanoparticles [75]. In one method, dye-labeled CPDB coated SiO_2 nanoparticles were prepared by treating amino functionalized nanoparticles with activated dyes and followed by activated CPDB. Then surface-initiated RAFT polymerization of *t*BuMA was conducted followed by sequential removal of thiocarbonylthio end groups and *tert*-butyl groups to generate dye-labeled PMAA grafted SiO_2 nanoparticles. In the second method, as a more straightforward strategy, direct

polymerization of MAA on SiO_2 nanoparticles with a diameter size as small as 15 nm was conducted via the RAFT polymerization technique.

3.2. Temperature-Responsive Carriers. Numerous techniques were used to prepare temperature-responsive carriers based on SiO_2 particles without much discussion or work on application potential; however, some sort of speculation has been drawn on their usefulness in drug delivery system. In a novel approach thermosensitive, polymer magnetic microspheres based on PNIPAM with core-shell structure were prepared by colloid template polymerization [76]. First trisodium citrate stabilized Fe_3O_4 nanoparticles with an average size of 10 nm were synthesized by conventional method and then the negatively charged Fe_3O_4 were coated with thin SiO_2 layer from the hydrolysis of TEOS in methanol-water mixture. MPS was used to insert vinyl group on the surface of SiO_2 coated Fe_3O_4 particles and finally seeded precipitation copolymerization of NIPAM and MBAAm was carried out in the presence of SiO_2 coated Fe_3O_4 nanoparticles. Reversible swelling-deswelling transition upon changing the environmental temperature was studied.

Guo et al. reported the preparation of luminescent/ magnetic microspheres with cross-linked PNIPAM shell [77]. The microspheres were aimed to contain specific molecules for molecular recognition, targeting compounds designed for homing in on sites, imaging agents to image biological process, and a release mechanism induced by exterior stimuli. To address this SiO_2 spheres dotted with Fe_3O_4 nanoparticles were coated by multicolor CdTe nanocrystals via metal ion-driven deposition, which was further protected by formation of the outer SiO_2 shell. Then these luminescent/magnetic SiO_2 particles were used as seeds to grow a temperature-responsive PNIPAM polymer shell. The PNIPAM-covered luminescent/magnetic microspheres were able to be taken up
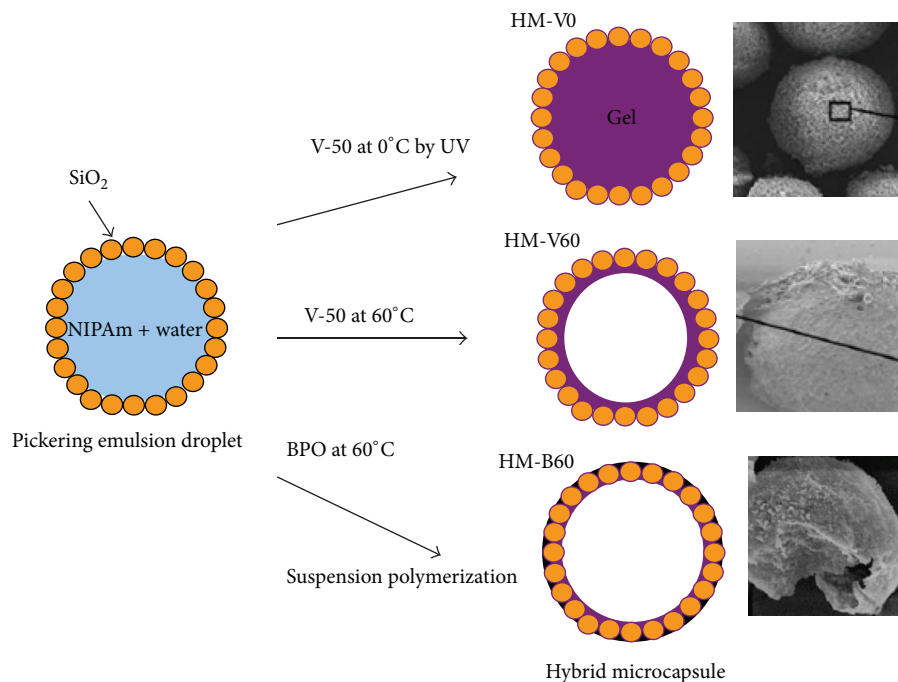
FIGURE 6: Schematic illustration of the fabrication of hybrid microcapsules at different polymerization conditions (reproduced from [81], with permission from Elsevier).

by Chinese hamster ovary (CHO) cells without inducement of any specific ligands.

Karg et al. presented a simple way to prepare thermosensitive SiO_2/PNIPAM core-shell microgels via surface functionalization with MPS followed by emulsion polymerization of NIPAM [78]. The particles obtained exhibited swelling properties similar to those known from pure PNIPAM microgels. They had applied this approach to Au@SiO_2 particles. These particles were modified with MPS and the simple emulsion polymerization was carried out to obtain Au@SiO_2/PNIPAM particles. Following this work, the same group in another article compared the volume phase transition in heavy water for SiO_2/PNIPAM core-shell microgels measured by DLS and small angle neutron scattering (SANS) [79]. Both methods provided a transition temperature between 33.0°C and 34.0°C, which was slightly higher than the one in H_2O. The SiO_2 core had no significant influence on the behaviour of the NIPAM shell. In a similar type of work, another group discussed the preparation of SiO_2/PNIPAM core-shell microgel with various internal crosslinking densities, where MPS modified SiO_2 cores were encapsulated by free radical emulsion polymerization of NIPAM [80]. Polymer shell thickness and degree of internal cross-linking influenced the interfacial behaviors. A thicker polymer shell and reduced internal cross-linking density favored the stabilization and packing of the particles at oil-water (o/w) interfaces. Temperature-responsiveness measured by DLS indicated that heating rate affected the LCST. Upon increasing the heating rate, the LCST increased from 32°C to 38°C (at 8°C min^{-1}) and goes down again to 37°C at even higher heating rates.

Gao et al. developed a polymerization using pickering emulsion droplets as reaction vessels to become a powerful tool for fabrication of hybrid polymer particles with supracolloidal structures [81]. In this paper, two kinds of thermosensitive hybrid PNIPAM microcapsules with supracolloidal structures were prepared from suspension polymerization stabilized by SiO_2 nanoparticles based on inverse pickering emulsion droplets. NIPAM monomers dissolving in suspended aqueous droplets were subsequently polymerized at different temperatures. The hollow microcapsules with SiO_2/PNIPAM nanocomposite shells were obtained when the reaction temperature was above the LCST of PNIPAM, while the core-shell microcapsules with SiO_2 nanoparticles' shells and PNIPAM gel cores were produced when the polymerization was conducted at the temperature lower than LCST using UV light radiation. The schematic representation of the formation of such structure is illustrated in Figure 6. Two polymerization temperatures, 60°C and 0°C, and two initiators, water-soluble 2,2-azobis(2-methylpropionamidine) dihydrochloride (V-50) and oil-soluble benzoyl peroxide (BPO), were considered in the experiment. The hybrid microcapsules demonstrated reversible deswelling and swelling during the drying/wetting cycle and thermosensitivity due to the presence of PNIPAM. In another paper, stable PNIPAM/SiO_2 composite microspheres were successfully synthesized via the same inverse pickering suspension polymerization using SiO_2 particles with variable diameters of 53, 301, 500, and 962 nm as stabilizers [82]. The obtained composite microspheres exhibited enough stability, confirmed in centrifugation, washing, and redispersion processes. The methylene blue (MB) was used as a model dye to perform encapsulation/release experiment. The release experiments showed that release rate of the microspheres increased with increasing SiO_2 size and the temperature, indicating that the releasing
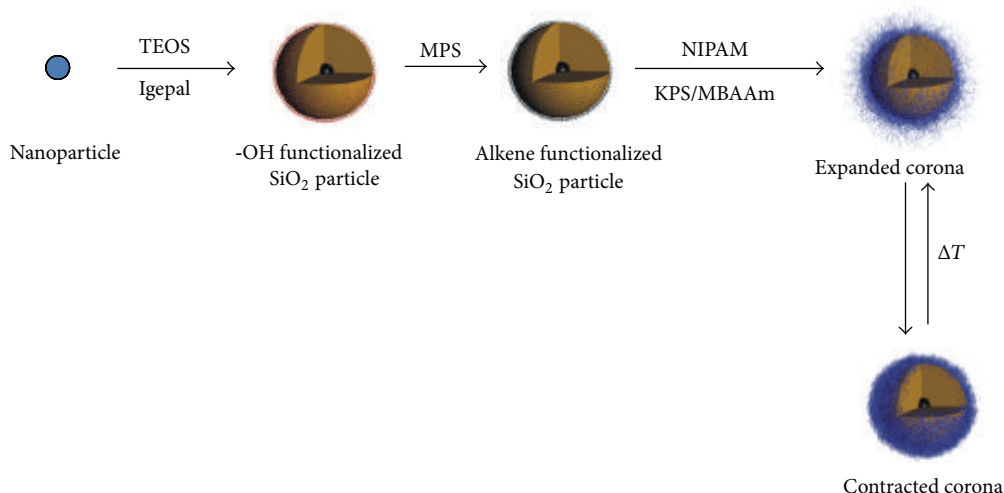
FIGURE 7: Synthesis of NP/SiO$_2$/PNIPAM core-shell-corona hybrid nanogels (reproduced from [86], with permission from Elsevier).

property can be either controlled by the particle size of SiO$_2$ or the temperature.

Monodisperse organic/inorganic composite microspheres with well-defined structure were prepared through the encapsulation of SiO$_2$ coated superparamagnetic magnetite colloidal nanoparticle clusters (CNCs) with crosslinked PNIPAM shell [83]. The surface of Fe$_3$O$_4$/SiO$_2$ microspheres was functionalized with the traditional MPS and finally Fe$_3$O$_4$/SiO$_2$/PNIPAM composite microspheres were prepared by precipitation polymerization. The size of superparamagnetic Fe$_3$O$_4$ core was easily controlled from ~90 to ~260 nm by simple change of the reaction time, and the thickness of SiO$_2$ shell was controlled from ~10 to ~83.5 nm in a straightforward fashion of feeding amount of TEOS. The application potential in biotechnology was expected but not investigated.

Wang and his group synthesized SiO$_2$-PNIPAM nanocomposite by combining the free radical polymerization of vinyl monomers and the hydrolysis/condensation of siloxanes through a one-pot approach by introducing all raw materials such as NIPAM, vinyltriethoxysilane (VTEO), TEOS, initiator AIBN, crosslinker MBAAm, and hydrolysis agent (acetic acid) into one autoclave using supercritical carbon dioxide (scCO$_2$) as green solvent [84]. The effects of initiator, crosslinker, and reaction process parameters on the morphologies and properties of the composite particles were comprehensively investigated. The composite microgels exhibited higher LCSTs than the corresponding PNIPAM microgels. The in vitro release simulation of the particles in situ impregnated with ibuprofen indicated that inclusion of SiO$_2$ improved the drug releasing effect of the microgels.

Composite microcapsules with improved chemical stability and mechanic integrity comprising a thermoresponsive hydrogel PNIPAM and coated by SiO$_2$ nanoparticles were synthesized by the inverse pickering emulsion polymerization method [85]. The polymer crosslinking ratio was varied from 0.6% to 9%. The composite PNIPAM/SiO$_2$ microcapsules exhibited reversible shrinking-swelling behavior

independence of temperature changes consistent with pure PNIPAM polymer, which demonstrated that hybrid microcapsules retained the thermoresponsive ability and the shell formed by SiO$_2$ nanoparticles did not affect this feature.

An efficient and reproducible method for the synthesis of monodisperse core-shell-corona hybrid nanomaterials with a γ-Fe$_2$O$_3$/SiO$_2$, CdSe(ZnS)/SiO$_2$ and γ-Fe$_2$O$_3$/CdSe(ZnS)/SiO$_2$ core-shell structure and a thermosensitive PNIPAM corona was proposed by Ruhland and his group [86]. First, the different nanoparticles (NPs) were entrapped into a SiO$_2$ shell using a microemulsion process where TEOS was used for the formation of SiO$_2$ shell. In a second step, a polymer coating of PNIPAM was attached onto the surface of the multifunctional core-shell particles via free radical precipitation polymerization with reactive double bonds via modification with MPS, furnishing multifunctional core-shell-corona hybrid nanogels as shown in Figure 7. The author demonstrated that NP/SiO$_2$/PNIPAM core-shell-corona hybrid nanomaterials possessed a high magnetization and/or bright luminescence as well as uniform temperature sensitivity and enhanced chemical protection of the functional core. Additionally, they observed drastically increased chemical stability due to the barrier properties of the intermediate SiO$_2$ layer that protects and shields the inner functional nanocrystals and the responsive character of the smart PNIPAM shell.

3.3. pH- and Temperature-Responsive Carriers. Fe$_3$O$_4$/SiO$_2$/P(NIPAM-co-DM) multiresponsive composite microspheres with core-shell structure were synthesized by template precipitation polymerization [87]. The MPS modified Fe$_3$O$_4$/SiO$_2$ particles of about 100 nm were prepared and subsequent seeded precipitation copolymerization of NIPAM and DM was carried out containing 4 wt.% comonomer and 5 wt.% MBAAm. The magnetite nanoparticles imparted superparamagnetic property for the composite microspheres. The effect of the second monomer on the formation of polymer shell

layer was investigated and also illustrated that more DM was dissolved in aqueous dispersion initially. The formation of the thinner polymer shell was effected by higher hydrophilic character of the copolymer. The composite microspheres with core-shell structure had both pH-sensitive and thermoresponsive volume phase transition behavior. The volume phase transition temperature increased with increasing DM content and the transition broadened with increasing DM content.

Rahman et al. examined rather simple one step seeded copolymerization process for the encapsulation of submicron-sized SiO_2 particles by stimuli-responsive copolymer shell layer comprising NIPAM, DM, and crosslinker EGDM to produce SiO_2/P(DM-NIPAM-EGDMA) composite polymer particles [88]. Prior to the seeded copolymerization, the author did not functionalize the SiO_2 particles with silane coupling agent. The phase transition temperature remained almost same and was close to the LCST of PNIPAM aqueous solution (~32°C). The magnitude of adsorption irrespective of the nature of biomolecules was higher at temperature above the LCST compared to that at temperature below the LCST. The activity of the adsorbed trypsin measured against the hydrolysis of lysine methyl ester hydrochloride suggested only limited conformational change.

4. SiO_2 Wafer/Substrate

4.1. pH-Responsive Carriers. ATRP, a controlled/"living," is a useful technique to control brush thickness over the solid substrate and to prepare block copolymers through reinitiation of the dormant chain ends and subsequent regrowth of the polymer chains. However, ATRP has limitation for functional monomers, for example, MAA which contains acid groups poisons the ATRP catalyst [89]. Treat and his group proposed ATRP for controlled PAA brushes from a planar SiO_2 surface utilizing a chemical free deprotection strategy of P*t*BA [90]. The acid hydrolysis approach for the conversion of *t*BA to AA is problematic for polymer brushes because the anchoring moiety often contains an ester functional group that can also be cleaved, leading to the loss of the polymer brush from the surface. They had used the pyrolysis reaction of *tert*-butyl esters to produce a carboxylic acid and isobutylene as a side product. The responsive nature of these PAA brushes to pH and electrolyte concentration was confirmed. Ayres and his group also discussed the synthesis of controlled PAA polymer brushes from SiO_2 substrate using the same chemical free deprotection strategy of P*t*BA [91]. Here P*t*BA chains were converted to PAA via simply heating the samples in an oven set to ~190–200°C for 30 min. The surface of the SiO_2 substrate responded to pH stimuli and salt concentration. Additionally they had used PAA polymer brushes for the synthesis of metallic nanoparticles. They had also reported the synthesis of AB diblock polyampholyte polymer brushes and its response to electrolyte. In a similar work Wu and coworkers described experiments pertaining to the formation of surface-anchored PAA brushes with a gradual variation of the PAA grafting densities on flat surfaces and provided detailed analysis of their properties [92].

4.2. Temperature-Responsive Carriers. Modification of SiO_2 wafer/substrate by temperature-responsive polymer is scarcely available. In a research well-defined PNIPAM was grown from SiO_2 wafer by surface-initiated ATRP [93]. Kinetic study revealed that the thickness of the surface-graft polymerized brush increased with polymerization time. A comparative cell attachment and detachment experiments were carried out at temperature above and below the LCST to study the suitability for application as a stimuli-responsive modifier for cell adhesion in biomedical microdevices. The incorporation of small amount of poly(ethylene glycol) monomethacrylate polymer was proved to be effective to increase the rate of cell detachment at temperature below the LCST of PNIPAM. Park et al. deposited star polymer comprising temperature-responsive photo-cross-linkable poly[oligo(ethylene oxide) monomethyl ether methacrylate] on SiO_2 wafer by spin coating [94]. The deposited polymer film showed LCST at ~27°C and exhibited temperature-responsive behavior.

5. SiO_2 Particles as Template for Hollow Stimuli-Responsive Carriers

Polymer capsules with shells made of environmentally sensitive materials have attracted a lot of interest as a novel carrier or microreactor in recent years as they exhibit unique properties such as small size, large inner volume, and tunable permeability [95–98]. They are considered to be useful for encapsulation of drugs, enzymes, DNA, and other active macromolecules.

Guo and his group presented the fabrication of thermoresponsive polymer microcapsules with mobile magnetic cores showing a volume phase transition with changing temperature and can be collected under an external magnetic field [99]. They prepared organic/inorganic composite microspheres composed of a cross-linked PNIPAM shell and SiO_2 cores dotted centrally by Fe_3O_4 nanoparticles. The SiO_2 layer sandwiched between the magnetic core and the PNIPAM shell was quantitatively removed to generate PNIPAM microcapsules with mobile magnetic cores by treatment with aqueous NaOH solution. For development of the desired multifunctional microcapsules the unetched SiO_2 surface interiors were modified by treatment with a silane coupling agent containing functional groups that can easily be bonded to catalysts, enzymes, or labeling molecules. Herein, fluorescein isothiocyanate (FITC), a common organic dye, was attached to the insides of the mobile magnetic cores to give PNIPAM microcapsules with FITC-labeled magnetic cores. These microcapsules exhibited a reversible swelling-deswelling transition upon changing the external temperature that could allow the loading of drugs, biomacromolecules, or chemical compounds and a temperature induced release via the permeable PNIPAM shells. The FITC molecules bonded to the cores can be traced easily by fluorescence spectroscopy, which may help to provide information about the distribution, enrichment, and transfer of microcapsules during the release process.
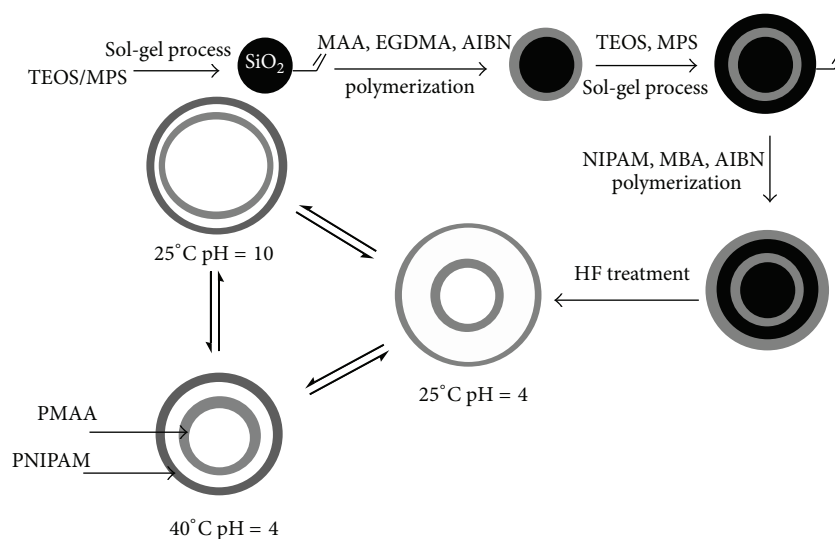
FIGURE 8: Preparation of polymer/SiO$_2$ multilayer hybrid microspheres and double-walled concentric hollow polymeric microspheres with independent sensitivity to pH and temperature (reproduced from [101], with permission from American Chemical Society).

Li et al. reported a simple route to prepare nearly monodispersed pH-responsive hollow polymeric microspheres with flexible (deformable) shells and concentric hollow SiO$_2$ microspheres with rigid shells from the SiO$_2$-polymer core-shell microsphere precursors [100]. MPS modified SiO$_2$ templates were prepared and the SiO$_2$-PMAA core-shell microspheres were prepared by distillation precipitation polymerization of MAA in acetonitrile using EGDM as a crosslinker. SiO$_2$-PMAA-SiO$_2$ trilayer hybrid microspheres were then prepared by coating a SiO$_2$ outer layer on SiO$_2$-PMAA core-shell microspheres in a sol-gel process. The pH-responsive PMAA hollow microspheres were prepared by removal of the SiO$_2$ core from the SiO$_2$-PMAA core-shell hybrid microspheres, whereas the concentric hollow SiO$_2$ microspheres were obtained by selective removal of the PMAA interlayer off the SiO$_2$-PMAA-SiO$_2$ trilayer hybrid microspheres during calcination at 700°C for 3 h. The hybrid composite microspheres, pH-sensitive hollow microspheres, and concentric hollow SiO$_2$ microspheres were confirmed by field emission-SEM, TEM, FTIR, XPS, and energy-dispersive X-ray (EDX) analysis. The hydrodynamic diameter of the hollow PMAA microspheres increased significantly from 340 to 520 nm as the pH of medium was increased from 4 to 8. This same group prepared SiO$_2$/PMAA/SiO$_2$ trilayer and SiO$_2$/PMAA/SiO$_2$/PNIPAM tetra-layer hybrids from the SiO$_2$/PMAA core-shell microspheres by alternating the sol-gel and distillation precipitation polymerization processes [101]. Finally, nearly monodispersed double-walled concentric hollow PMAA-PNIPAM microspheres were obtained by selective removal of the inorganic SiO$_2$ core and interlayer by hydrogen fluoride (HF) treatment for 48 h. The whole process is illustrated in Figure 8. The DOX-loaded PMAA-PNIAPM hollow microspheres exhibited temperature and pH-controlled release of anticancer drug.

Nanocontainers with controlled release properties are also believed to be useful in a new family of self-healing coatings. If the environment of the coating changes, smart nanocontainers quickly respond and release the healing agent onto the metal surfaces to stop corrosion [102–105]. Hollow tubes which allow encapsulation of active molecules' are of great interest in nanotechnology, drug delivery, and energy storage [106]. The development of SiO$_2$/polymer double-walled hybrid nanotubes consisted of a hollow cavity, a porous SiO$_2$ inner wall, and a stimuli-responsive (pH, temperature, and redox) polymeric outer wall, as a novel nanocontainer system for application in self-healing coatings was reported by Li and his group [107]. Here pH-responsive SiO$_2$/PMAA, temperature-responsive SiO$_2$/PNIPAM, and redox-responsive SiO$_2$/polypoly(ethylene glycol) methacrylate (PPEGMA) hybrid nanotubes were prepared by surface graft precipitation polymerization in the presence of double-bond modified nickel-hydrazine/SiO$_2$ core-shell rod templates in acetonitrile followed by selective etching of the nickel-hydrazine core. The length, diameter, wall thickness, and aspect ratio of the hybrid nanotubes were precisely controlled in the range of 48–506 nm, 41–68 nm, 3–24 nm, and 1.2–7.6, respectively. The anticorrosion agent benzotriazole encapsulated in the hybrid nanotubes was released in controlled fashion in the absence and presence of external stimuli. The SiO$_2$/PMAA hybrid nanotubes revealed pH-dependent release of the benzotriazole because of the carboxylic acid groups from the PMAA outer wall. The SiO$_2$/PNIPAM hybrid nanotubes exhibited a temperature-dependent release because of the grafted PNIPAM polymers and the SiO$_2$/PPEGMA hybrid nanotubes showed a redox-dependent release because of the existence of disulfide bonds in the PPEGMA polymer networks.

Fu et al. developed an intelligent anticorrosion coating, based on the mechanized hollow MSNPs as smart nanocontainers implanted into the self-assembled nanophase particles (SNAP) coating [108]. The smart nanocontainers released the caffeine molecules encapsulated at neutral pH molecules
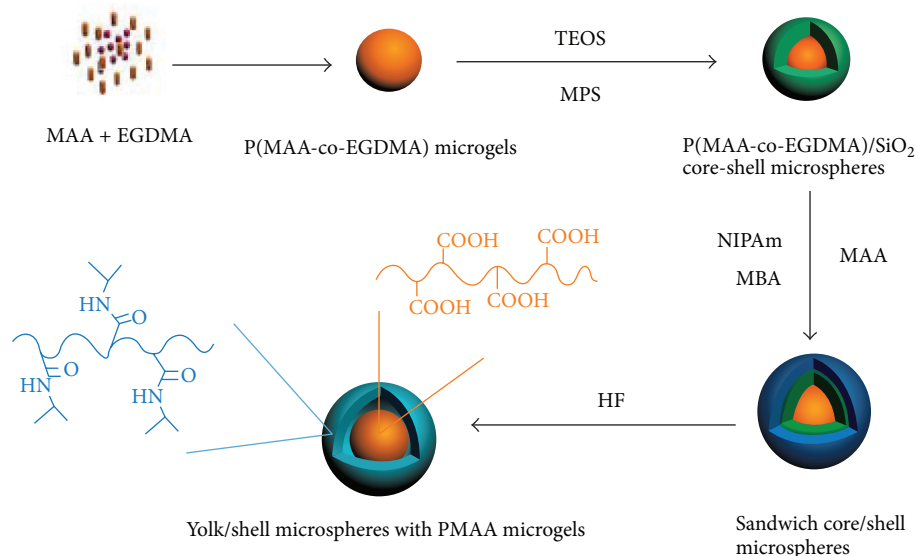
FIGURE 9: Schematic illustration of the fabrication process of the multifunctional yolk/shell microspheres for controlled microspheres for controlled release of drug from the sandwich core/shell microspheres with sacrificial SiO$_2$ interlayer (reproduced from [109], with permission from American Chemical Society).

either under acidic or alkaline conditions. The intelligent anticorrosion coating was deposited on the surface of aluminium alloy AA2024 and investigated by electrochemical impedance spectroscopy and scanning vibrating electrode technique. Compared with the pure SNAP coating, the well-dispersed smart nanocontainers delayed the penetration rate of corrosive species and also repaired damaged aluminium oxide layer to maintain the long-term anticorrosion behavior.

Du and Liu developed an effective strategy to fabricate the novel dually thermo- and pH-responsive yolk/shell polymer microspheres as a drug delivery system for the controlled release of anticancer drugs via two-stage distillation precipitation polymerization and seed precipitation polymerization according to the scheme shown in **Figure 9** [109]. The uniform microgel cores responded independently to medium pH, and the cross-linked P(NIPAM-co-MAA) shell exhibited pH-induced thermosensitivity toward the pH changes of the surrounding medium. Their pH-induced thermally responsive polymer shells acted as a smart "valve" to adjust the diffusion of the loaded drugs in/out of the polymer containers according to the body environments, while the movable P(MAA-co-EGDMA) cores enhanced the drug loading capacity for the anticancer drug DOX. The yolk/shell polymer microspheres had a low leakage at high pH values but significantly enhanced release at lower pH values equivalent to the tumor body fluid environments at human body temperature. Meanwhile, the yolk/shell microspheres expressed very low in vitro cytotoxicity on HepG2 cells.

6. SiO$_2$ Based Nontraditional Stimuli-Responsive Carriers

For more sophisticated drug delivery applications, the ability to functionalize nanoparticles with nanovalves and

other controlled-release mechanisms has become an area of widespread interest. As the solid support of molecular or supramolecular nanovalves, MSNPs are recognized as smart nanocontainers for the bioapplications of drug delivery, imaging, and tumor therapy. To better control the loaded therapeutic compounds, many materials have been crafted on the surface of MSNPs including organic molecules [50, 110, 111], inorganic nanoparticles [112, 113], and molecular machines [114–116]. Significantly, a series of external non-traditional stimuli have been employed to operate the nanovalves for the entrapment and release of cargos from the pores of MSNPs, such as enzyme, light, and redox.

Mal et al. showed that the uptake, storage, and release of organic molecules in MCM-41 can be regulated through the photocontrolled and reversible intermolecular dimerization of coumarin derivatives attached to the pore outlets [117]. Irradiation of sample with UV light at wavelengths longer than 310 nm induced photodimerization, and the adsorption had almost disappeared after 50 min. In contrast, irradiation with UV light of wavelength around 250 nm regenerated the coumarin absorption band within 2-3 min due to photocleavage of the coumarin dimers. Controlled-release experiments were conducted with the steroid cholestane as its molecular size allowed it to be stored in the pores of MCM-41. Agostini and his group also designed light driven gated system based on MCM-41, mesoporous SiO$_2$ particles using bulky molecule containing two bulky *tert*-butyl moieties with photo-cleavable o-methoxybenzylamine [110].

Patel et al. designed enzyme-responsive snap-top covered SiO$_2$ nanocontainers [115]. The mesoporous SiO$_2$ was treated with aminopropyltriethoxysilane to achieve an amine-modified surface which was then alkylated with a tri(ethylene glycol) monoazide monotosylate unit to give an azide-terminated surface. Cargo molecules were loaded into the nanopores by diffusion, and the loaded, azide-modified

particles were then incubated with α-cyclodextrin (α-CD) at 5°C for 24 h. The α-CD tori thread onto the tri(ethylene glycol) chains at low temperature effectively blocked the nanopores, while the azide function served as a handle to attach a stoppering group. A system activated by porcine liver esterase (PLE) was designed to test the viability of an enzyme-responsive snap-top motif [116]. To prepare PLE-responsive snap-top covered SiO_2 nanocontainers, a precursor loaded with luminescent cargo molecules (rhodamine B) was capped with the ester-linked adamantyl stopper. In this snap-top system, PLE catalyzed the hydrolysis of the adamantyl ester stopper, resulted in dethreading of the α-CD, and released the cargo molecules from the pores. Bernardos and his group described the gate-like functional hybrid systems consisted of nanoscopic MCM-41-based materials functionalized on the pore outlets with different "saccharide" derivatives and a dye $[Ru(bipy)_3]^{2+}$ contained in the mesopores [118]. The saccharide derivatives used were Glucidex 47, Glucidex 39, and Glucidex 29. Additionally, for comparative purposes another system containing lactose was prepared. Enzyme hydrolyzed the saccharide network which resulted in an uncapping of the pores and delivery of the entrapped dye molecule. Another research group headed by Mondragón et al. discussed the synthesis and characterization of enzyme-responsive intracellular controlled release using MSNPs (MCM-41) capped with ε-poly-L-lysine [119]. Two different anchoring strategies were employed for the capping of polymer on MSNP. In both cases, nanoparticles were loaded with model dye $[Ru(bipy)_3]^{2+}$ molecule. Both nanoparticles showed a nearly zero cargo release in water due to the coverage of the nanoparticle surface by polymer ε-poly-L-lysine. In contrast, a remarkable release was observed in the presence of proteases due to the hydrolysis of the polymer's amide bonds.

Yan et al. reported novel MSNPs functionalized with [2]rotaxanes in which the α-CD ring was threaded with a linear photothermal-responsive azobenzene axle containing a preattached stopper at one end (Figure 10) [120]. The back and forth movements of the α-CD ring along the azobenzene axle upon exposure to visible light or heating resulted in the closing and opening of nanopores and thereby allowed for both drug storage and remote-controlled release. Rhodamine B and curcumin were used as cargos to investigate the photothermal-induced release of MSNP. MSNP has been successfully used for in vivo release of curcumin into five-day-old zebrafish embryos.

Sun and his associates produced two types of biocompatible nanovalves based on MSNPs (MSN-C1 and MSN-C2) through the introduction of biocompatible stalks, containing choline derivatives and enzyme cleavage sites, onto the surface of mesostructured SiO_2, followed by cargo loading via diffusion and calix[4]arene capping via host-guest complexation [121]. These versatile systems were capable of entrapment and controlled release of cargo molecules in response to three different types of external stimuli, that is, enzyme, pH variation, and adding competitive binding agent.

7. Conclusions and Future Perspectives

There are a variety of approaches for the preparation of stimuli-responsive polymer particles based on SiO_2 particles

and much progress has only been made in the area during the last 5 to 10 years. The usefulness of SiO_2 particles in the preparation of stimuli-responsive polymers is mainly based on their biocompatibility, nontoxicity, simple preparation technique, low cost, high surface area, easy functionalization, porosity, and pore volume. SiO_2 particles with two different morphologies such as mesoporous and solid sphere have been used mostly for the fabrication of stimuli-responsive hybrid microspheres. Of these two types of SiO_2 particles the potential of mesoporous SiO_2 particles can be considered to be high as large volume of work is available in the area. The importance of such particles lies on their ability to function as a drug storage, high drug loading capacity, and possibility of functionalizing them with molecular/supramolecular ensembles onto their external surface to develop gated drug delivery system. Different types of gated materials responding to light, enzyme, pH, and temperature have been extensively studied along with fabrication, gate opening, and loading and release of model drugs both in vivo and in vitro as well as toxicity. Table 1 summarizes the work done based on mesoporous SiO_2 particles. The gated materials to be used are preferentially to be nontoxic and biocompatible and should release drugs in controlled fashion in vivo without the release of pore-blocking units to avoid side effects. It is also desirable that enzymatic hydrolysis of gated materials does not produce degradation products with harmful side effects. Considering this gated materials attached to mesoporous SiO_2 surface with pH, temperature, and light-responsive property are expected to be more promising as in most cases they do not produce any degradation products. In order to design enzyme-responsive gated mesoporous SiO_2 systems, biodegradable molecules like ε-poly-L-lysine and saccharides are considered to be useful. Although much effort has been made so far for the development of mesoporous SiO_2 with different gate-like scaffoldings, the preparation of real systems suitable for application in living cells remained a challenge. For example, some systems reportedly displayed gating features in nonaqueous media, often require large and complicated synthetic route, and sometimes used external stimuli that are difficult to apply in certain delivery applications. Not all the gated materials have been applied for drug delivery system as depicted in Table 1.

In recent years, stimuli-responsive polymer nano/microcapsules with shells made of environmentally sensitive materials have attracted a lot of interest as a novel type of carrier or microreactor. Such capsules have wide applicability in encapsulation of drugs, enzymes, DNA, and other active macromolecules as they exhibit unique properties such as small size, large inner volume, and tunable permeability. However, the success of these hollow capsules depends on the complete transfer and controlled release of object at the right moment in the right place and at an adequate concentration guided by exterior stimuli. To satisfy these requirements a number of research group discussed the preparation and characterization of multifunctional hollow nano/microcapsules possessing magnetic-, pH-, temperature-, light-, enzyme-, and redox-responsive properties. The multifunctional nano/microcapsules can provide several advantages
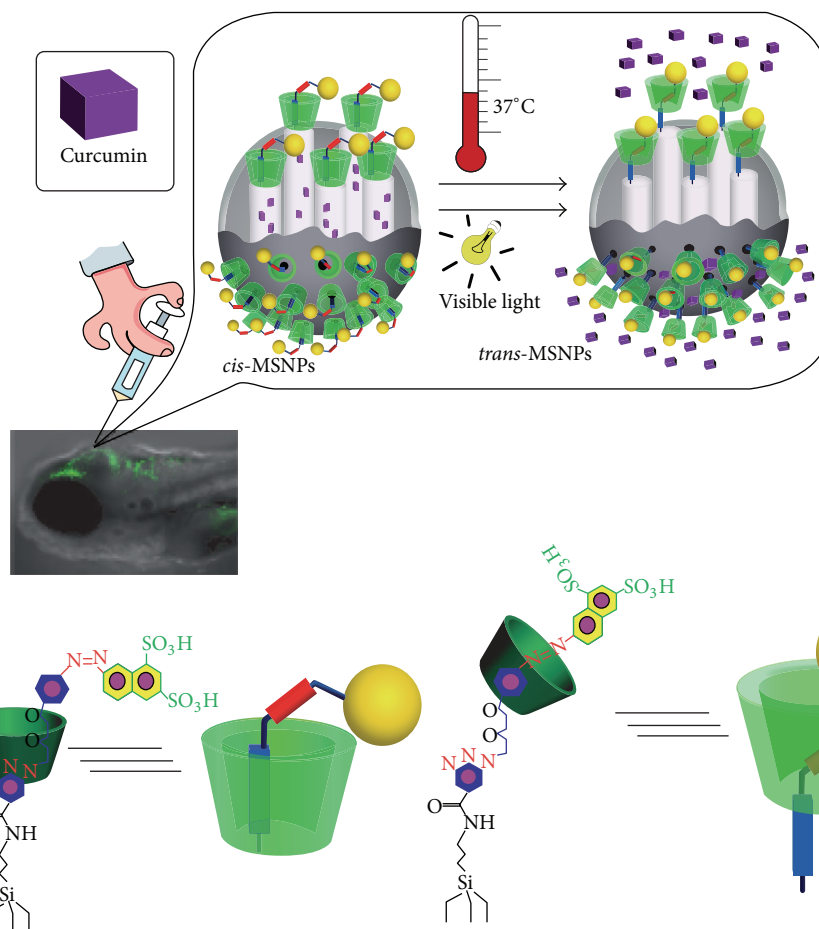
FIGURE 10: A graphical representation of the injection of drug-loaded MSNPs into zebrafish larvae for in vivo drug delivery triggered by either heating or visible light irradiation. MSNPs were functionalized with photothermal-responsive [2]rotaxanes on the surface. The chemical structure of the [2]rotaxane containing the α-CD ring and azobenzene unit is shown (reproduced from [120], with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

as follows: they can undergo fast change of the stimuli-responsive shells and can controllably release the loaded molecules from hollow cages and the magnetic property can allow the manipulation of the microcapsules by an external magnetic field. The performance of such stimuli-responsive capsule was evaluated for controlled release of anticancer drugs. Additionally the efficiency of nanocapsules with controlled stimuli-responsive release properties for controlled release of healing/anticorrosion agent for stopping corrosion on the metal surface was also evaluated. These nano/microcapsules were preferentially prepared by selective extraction of solid SiO_2 core/layer from inorganic/organic core-shell stimuli-responsive polymer microspheres.

Much effort has also been made for the surface modification of solid SiO_2 spheres with either pH- or thermoresponsive polymer or both for the preparation of pH-, temperature-, and multiesponsive microspheres. The designing of pH-responsive core-shell microspheres containing surface carboxyl groups via surface-initiated ATRP is not that straightforward as the carboxylic monomers normally reduce the initiation efficiency. In this case surface-initiated ATRP has been mostly carried out with acrylate monomers followed

by hydrolysis into carboxyl group. The same methodology has also been used to modify SiO_2 wafer/substrate with pH-responsive carboxylic monomers. However, the introduction of silane coupling agent followed by radical polymerization with carboxylic monomer is rather simple to fabricate pH-responsive polymer. Direct polymerization of monomers via immobilizing RAFT agent on the SiO_2 support is also possible for the encapsulation of SiO_2 particles but this method sometimes needs complex synthesis of RAFT agent. Most of these reported literatures did not put emphasis on the application of stimuli-responsive microspheres except for the fabrication and characterization. This part still needs much attention from the researchers. Considering the cargo loading capacity mesoporous/hollow SiO_2 particles should be advantageous compared to solid SiO_2 sphere/wafer.

Few reports are available as well on the usefulness of nanosized SiO_2 particles as pickering emulsifier for the preparation of either pH- or temperature-responsive microspheres. In this case SiO_2 particles constitute the shell in the core-shell morphology. The objective of these researches was mostly centred on designing pH- or temperature-responsive particulate emulsifier for different oils.

TABLE 1: Stimuli-responsive materials based on mesoporous SiO_2 particles (MSP) in nano/microsize range.

References	Materials	Stimuli-	Applications studied
Zhu et al. [39]	MSP/PAN/PSS multilayers	pH-	Drug release behavior
Feng et al. [40]	MSP/PAN/PSS multilayers	pH-	Drug release profiles, growth inhibiting effect of cancer cells
Feng et al. [41]	MSP/alginate/chitosan multilayers	pH-	Drug release profiles, growth inhibiting effect of cancer cells, and toxicity effect
Liu and Du [42]	MSP/CB[7]-1,4-butanediamine	pH- and competitor driven	Dye loading and release profile
Chen et al. [43]	MSP/CB[7]-1,4-butanediamine	pH-	Drug release profile
He et al. [44]	DOX@CTAB@MSP	pH-	Drug release profile and drug activity
Tang et al. [45]	MSP/chitosan-PMAA	pH-	Drug loading and release profile, and cytotoxicity
Hu et al. [46]	MSP/chitosan	pH-	Drug loading and release profile, cytotoxicity, drug efficiency, and so forth
Gulfam and Chung [47]	MSP/chitosan	pH-	pH-dependent drug release
Popat et al. [48]	MSP/chitosan (multistep synthesis)	pH-	pH-responsive drug release
Xing et al. [49]	MSP-NH$_2$-TPT@BIX-Zn	pH-	Drug (TPT) release profile
Xing et al. [50]	Con A-gated mannose-functionalized MSP	pH-	Loading and release of cargo molecules
Wu et al. [51]	Fe$_3$O$_4$@SiO$_2$@HAp	pH-	Release profile of drug
Fu et al. [53]	MSP/PNIPAM	Temperature-	Permeation of cargo molecules
You et al. [54]	MSP/PNIPAM-S-S-Py	Temperature-	Uptake and release of small molecules
Singh et al. [56]	MSP-PNIPAM	Temperature-	Uptake and release of drug
Chang et al. [64]	Magnetic MSP/P(NIPAM-MAA)	pH- and temperature-	Stimuli-dependent drug release, cytotoxicity
Agostini et al. [110]	MSP-tert-butyl-o-methoxybenzylamine	Light-	—
Patel et al. [115]	Azide-modified MSP	Enzyme-	Loading of cargo molecules
Mal et al. [117]	MSP-coumarin	Light-	Uptake, storage, and release of steroid
Bernardos et al. [118]	Saccharide modified MSP	Enzyme-	Delivery of entrapped dye molecule
Mondragón et al. [119]	ε-Poly-L-lysine caped MSP	Enzyme-	Release of dye molecule
Yan et al. [120]	MSP/[2]rotaxanes	Photothermal	Release of rhodamine B and curcumin
Sun et al. [121]	Calix[4]arene caped MSP	Enzyme, pH, and competitor driven	—

The volume of the work available on the preparation and characterization of SiO_2 based stimuli-responsive polymer microspheres is enormous but still much work is needed on the optimization and simplification of preparation technology. In some cases multisteps synthetic procedure is needed which may be discouraging to the pharmacist for designing drug delivery system. The idea of stimuli-responsive hollow capsules derived from mesoporous SiO_2 or solid SiO_2 sphere is found to be encouraging from the view point of delivery applications of drugs/anticorrosion healing agents. In ideal case such delivery systems need to have maximum drug loading capacity with 100% release while changing the environment and this has not been achieved yet.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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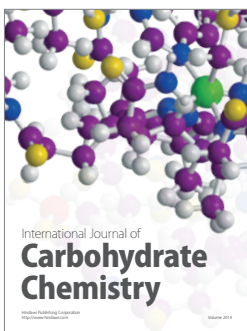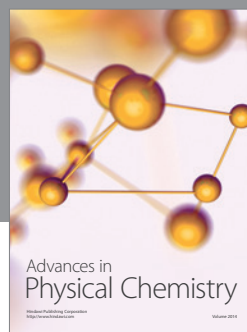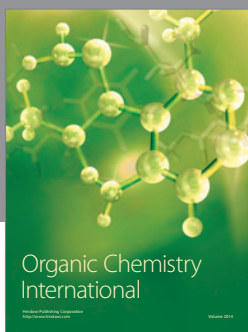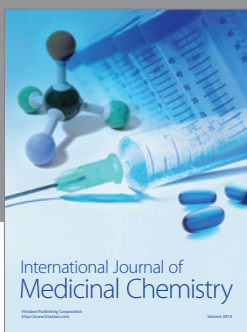
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