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Chapter

Polymer Functionalization of Mesoporous Silica Nanoparticles Using Controlled Radical Polymerization Techniques

Leena Nebhani, Smrutirekha Mishra and Tina Joshi

Abstract

Mesoporous silica nanoparticles (MSNs) are widely studied and are an interesting material due to its application in wide range of areas, for example, in drug delivery, catalysis, in sensors, and in adsorption and separation. Specifically, MSNs contain high surface area and large pore volume, providing high drug loading capacity, tunable pore size, surface chemistry for accommodation of a variety of guest molecules, and versatile functionalization on the external and internal surface for a broad spectrum of applications. Many new strategies have been developed for the synthesis and functionalization of mesoporous silica-based materials. The functionalization of MSNs is highly important as it leads to the development of new chemical and physical properties. Thus, preparation of these organic/inorganic hybrid structures requires facile and controlled techniques to generate enhanced properties. The grafting of polymers using controlled radical polymerization (CRP) techniques has turned out to be the best suited method to synthesize these well-defined organic-inorganic hybrid MSNs. Most common polymerization techniques are atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT) polymerization, and nitroxide mediated polymerization (NMP). This chapter will be highlighting the state-of-the-art techniques for the synthesis of variety of MSNs, its functionalization using CRP techniques, and application of polymer functionalized MSNs.

Keywords: mesoporous silica nanoparticles, controlled radical polymerization, atom transfer radical polymerization, reversible addition-fragmentation chain transfer polymerization, nitroxide mediated polymerization

1. Introduction

Early innovation of mesoporous silica-based materials by Kresge and co-workers [1] in 1992 forged a strong desire in researchers to explore and demonstrate more about mesoporous silica and its novel applicability to bring tremendous changes in the field of porous materials. Porous silica network materials are broad classification [2] of inorganic materials having controllable pore size and surface area. IUPAC has classified porous materials into three categories according to its pore diameters; microporous (<2 nm), mesoporous (2–50 nm), and macroporous (>50 nm). Kresge

and co-workers acknowledged a new pathway for the preparation of ordered porous MS41 family [1] by utilizing sol-gel chemistry [3] and liquid crystal micellar templating route [4]. Further utilizing this concept, different porous structures were prepared such as MCM-41 (hexagonal) [5] and MCM-48 (cubic) [6]. Since then, mesoporous silica has been explored by different groups such as SBA [7] series from University of California Santa Barbara by Stucky group, KIT [8] series by Korean researchers, and FDU [9] series from Fudan University China by Prof. Zhao's group. Despite many synthesis strategies, mesoporous silica cannot be used in certain applications due to its amorphous pore wall structure [10]. Hence, it is enormously required to find new pathways to modify amorphous surface of mesoporous silica with variety of organic groups or polymers, in order to find its suitability for diverse applications.

The main motivation of this chapter is to highlight different strategies for construction of MSNs and essential techniques for the characterization of MSNs. The functionalization of MSNs by polymer grafting using controlled radical polymerization (CRP) [11] techniques and its implementation in distinct domains has been discussed in detail.

1.1 Origination of different types of MSNs

Prior discovery of mesoporous materials in 1970s did not make any tremendous change in the Materials Research until 1992, when Mobil Researchers (Kresge and co-workers) reported mesoporous molecular sieves using liquid crystalline template. These materials were designated as Mobil Composition of Matter (MCM) or Mobil Crystalline Materials. Generally, these MCM materials are synthesized utilizing different cationic surfactant-based templating agents. MCM are classified into different types such as; MCM-41 [12], MCM-48 [13], and MCM-50 [13]. Out of all, MCM-41 is one of the most investigated materials from Mobil crystalline materials family for various applications. MCM-41 contains a regular pore geometry of 2.5–6 nm with hexagonal type of ordered porous structure. These pore diameters can be tuned by varying the surfactants used. Other MCM materials are synthesized by varying the surfactant and its loading leading to cubic arrangement for MCM-48 and lamella-type arrangement for MCM-50 as shown in **Figure 1** [14].

Other than cationic surfactants, nonionic copolymer-based surfactants are also used in the synthesis of Santa Barbara Amorphous (SBA) type of MSNs. Copolymers of poly(ethylene oxide) and poly(propylene oxide) are commonly used as templating agents for synthesis of SBA. Once again in case of SBA materials, based on the type of copolymers used, it can be synthesized into different ordered patterns such as cubic structured for SBA-11, 3-D hexagonal structured for SBA-12,

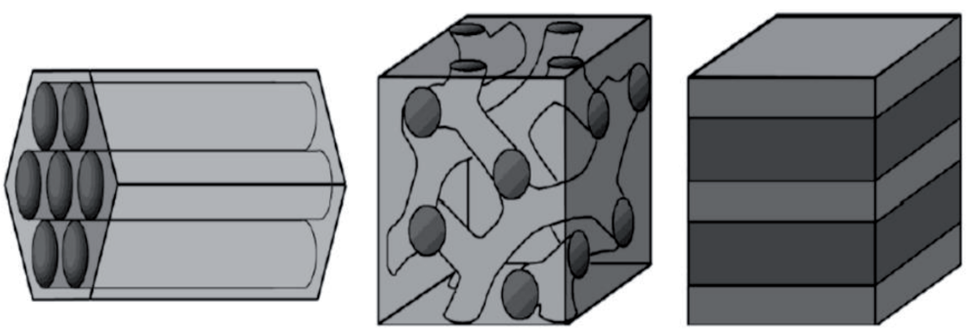

Figure 1.
Different types of pore geometry structure for MCM family (left side for MCM-41 with hexagonal structure, center for MCM-48 with cubic structure, and right for MCM-50 with lamella structure). Reproduced with permission from Ref. [14]).

hexagonal for SBA-15 [15], and 3-D cubic cage-structured for SBA-16 [16]. By altering the ratio of propylene oxide to ethylene oxide in the copolymer, different ordered structures can be obtained for this SBA. Mostly, highly ordered porous network of SBA-15 has been commonly used for different biomedical applications. These materials are broadly different than MCM due to its thicker amorphous wall and larger pore diameter of 4.5–30 nm.

Another interesting MSNs family material was discovered by Japanese researchers named as FSM-16 [17] (folded sheets of mesoporous materials) synthesized by an ion-exchange process between cations of layered structured sodium silicate and surfactant followed by hydrothermal treatment. Based on these investigations, numerous MSNs were then synthesized and designated such as Technical Delft University (TUD-1) [18], Korean Institute of Technology (KIT) [8], Hiroshima Mesoporous Material (HMM-33) [19], Indian Institute of Technology Madras (IITM), and Centrum voor Oppervlaktechemie en Katalyse/Centre for Research Chemistry and Catalysis (COK-12), [20] according to its pore size and symmetry. The detailed pore symmetry and pore size for different types of MSNs has been discussed in **Table 1**.

1.2 Synthesis and characterization of MSNs

The synthesis of MSNs is commonly conducted in the presence of a templating agent, also called as structure-directing agent. The two important types of templating agents commonly used are soft templates, for example, cationic, anionic and nonionic surfactants, block co-polymers, etc. The other type of templating agent used is, for example, preformed mesoporous silica or carbon. The commonly used precursor for silica formation is tetraethoxysilane (TEOS); however, other inorganic salts can also be used. The synthesis of MSNs can be performed using bases, for example, sodium hydroxide, potassium hydroxide, and ammonium hydroxide, as well as under acidic conditions. Finally, the mesoporous structure is achieved by the extraction of templates via various methods, for example, calcination and solvent extraction. The mechanism of the formation of mesoporous silica has been studied using combination of several techniques, for example, X-ray diffraction (XRD) [21], small angle X-ray scattering (SAXS) [22], solid state NMR [23], electron microscopy, thermal analysis,

Type of MSNs	Pore symmetry	Pore diameter (nm)	Type of surfactant
MCM-41	Hexagonal	1–8	Cationic (CTAB)
MCM-48	Cubic	2–5	Cationic (CTAB)
MCM-50	Lamellar	2–5	Cationic (CTAB)
SBA-11	Cubic	2–5	Non-ionic co-polymer (Igepal CO630)
SBA-12	Hexagonal	3–5	Non-ionic co-polymer (Brij-76)
SBA-15	Hexagonal	6–15	Non-ionic co-polymer (Pluronic P123)
SBA-16	Cubic	5–15	Non-ionic co-polymer (Pluronic F127)
KIT-5	Cubic	4–10	Non-ionic co-polymer (Pluronic F127)
COK-12	Hexagonal	4–15	Non-ionic co-polymer (Pluronic P123)
FSM-16	Sheet	2–5	Cationic (CTAB)
TUD-1	Foam	2–25	Cationic (CTAB)

Table 1.
Detailed inherent characteristics of different types of MSNs.

and sorption analysis [24]. For the preparation of MCM41/Mobil, scientists proposed that it is a liquid-crystal template mechanism because liquid crystals of surfactants work as templates to generate mesopores. The mesopores that are created after extraction have a long range order which can be analyzed by X-ray diffraction (XRD) at low 2θ (small angle XRD, 2θ = 2–10). The wide angle XRD is commonly used to study inorganic amorphous pore walls, which are formed by the condensation of TEOS (wide peak from 2θ =20–25). The diffraction peaks obtained by performing XRD on MSNs can be used to identify a known mesostructure. In the case of MCM-41, four different diffraction peaks have 1/d value in the ratio of $1:\sqrt{3}:\sqrt{4}:\sqrt{7}$, which corresponds to 2D hexagonal pore structure and space group of P6mm symmetry.

In order to monitor the kinetics and growth mechanism of MSNs, SAXS [25] has been utilized. SAXS is an important and nondestructive technique for the structural characterization of MSNs in solution which is not possible with other techniques like transmission electron microscopy (TEM). Using SAXS, MSNs can be utilized for studying their morphology and dispersion in any form such as in colloids, nanopowder, nanocomposite, and microemulsions. Other than predicting the structure and morphology of the MSNs, one can understand the growth mechanism during synthesis of MSNs by synchrotron time-resolved small angle X-ray scattering. Yi et al. [26] revealed a better understanding for the growth mechanism of MSNs by predicting the scattering proportions of the incident X-ray beam via synchrotron time-resolved small angle X-ray scattering measurements. This technique was modeled at the micellar level upon addition of CTAB to predict the shape and size of micelles at the interface. It was concluded that the micellar size changes from ellipsoid to spherical upon addition of TEOS due to its solubilization in the medium. Hence, it was efficiently demonstrated that utilizing SAXS, a good understanding of growth kinetics of MSNs can be obtained.

Electron microscopy [24, 27], mainly high resolution TEM, can be utilized for the structural characterization of MSNs. An electron microscopy technique uses an electron beam accelerated at a high voltage as the source of radiation. The back-scattered and secondary electron provides structural characterization, while X-ray generated provides chemical composition. As shown in **Figure 2**, mesoporous structure can be directly observed under TEM. The white area represents the pores and black area represents amorphous silica framework.

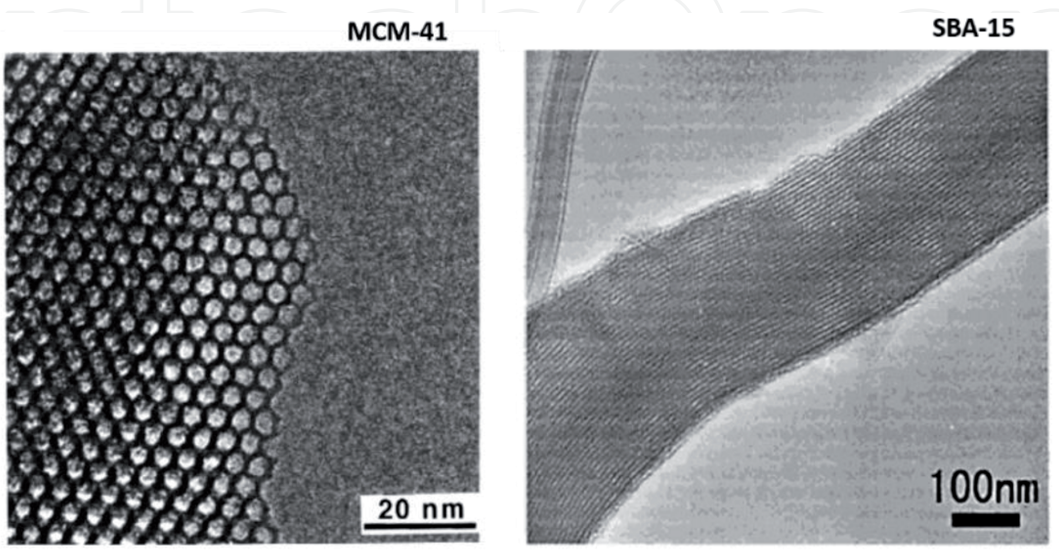

Figure 2.
TEM micrographs for (a) MCM-41 (reproduced with permission from Ref. [24]) and (b) SBA-15 (reproduced with permission from Ref. [27]).

MSNs are commonly characterized for surface area, pore volume, pore size, and pore size distribution using physical adsorption of an inert gas, for example, nitrogen. As the pore size in the mesoporous materials is greater than 2 nm and less than 50 nm, commonly type IV and V isotherms are obtained. The surface area is calculated using Brunauer-Emmett-Teller (BET) equation. Many methods are available for calculation of pore size and pore size distribution, for example, Barrett, Joyner, and Halenda (BJH) method, non-local density functional theory (NLDFT), etc.

2. Polymer functionalization of MSNs

The grafting of polymers from the surface of MSNs is one of the efficient techniques for the surface functionalization of MSNs. The growth of polymeric chains from MSNs is highly important in the area of Materials Science, as it provides MSNs with the properties which are desired in several applications [28].

The commonly preferred grafting techniques are based on different surface initiated polymerization methods such as reversible addition-fragmentation chain transfer polymerization (RAFT), atom transfer radical polymerization (ATRP), and nitroxide-mediated radical polymerization (NMP). The polymer functionalized MSNs can be easily used in the field of drug delivery, catalysis, and sensors to name a few. As shown in the **Figure 3**, the polymer chains can be physically adsorbed on MSNs (physisorption) or can be covalently attached (chemisorption). Generally, the physisorption method is not an appropriate technique since it is noncovalent in nature and

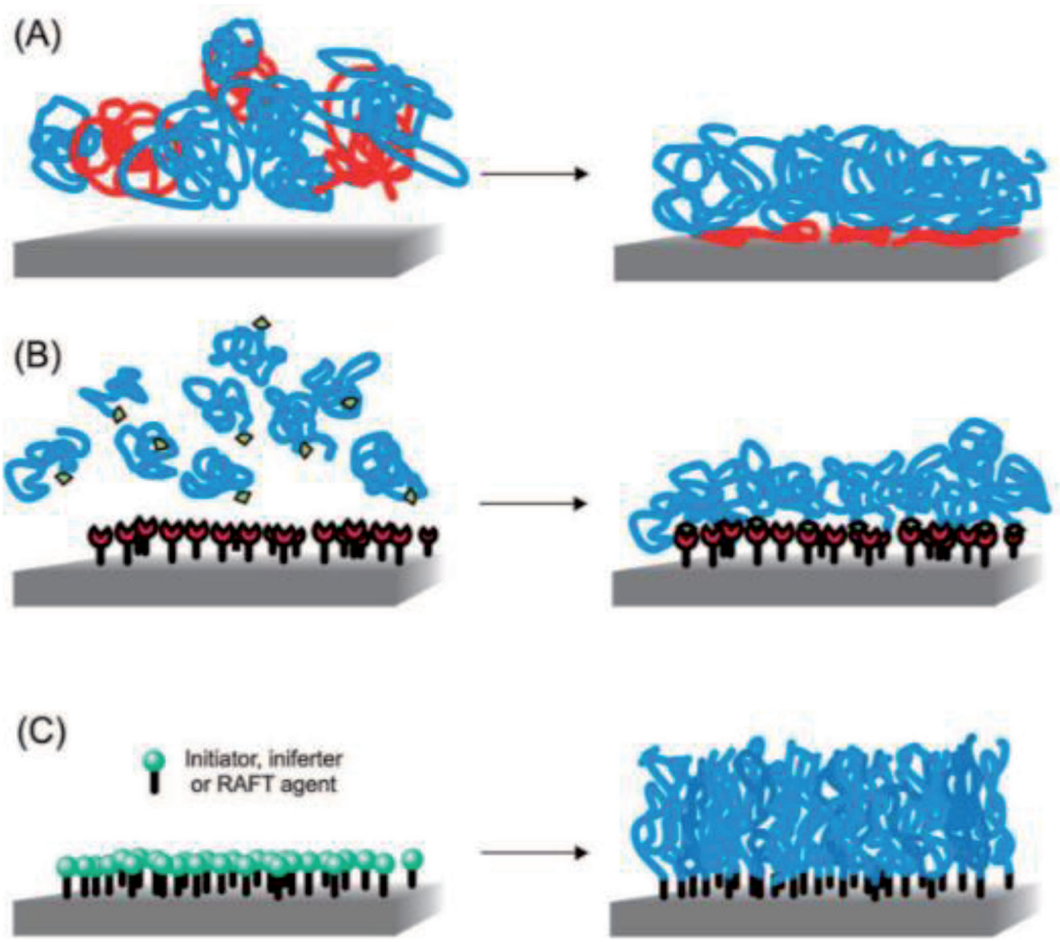

Figure 3.
Approaches for grafting of polymer chains from solid substrate. (A) Physical adsorption, (B) Grafting-to approach, and (C) Grafting-from approach (reproduced with permission from Ref. [28]).

is reversible. The chemical grafting via covalent bonding is a favored method due to its irreversible compatibility in the midst of organic and inorganic group. The chemical grafting can be carried out by two means such as "grafting-to" and "grafting-from." The grafting-to utilizes covalent bonding by reacting pre-synthesized macromolecules carrying specific group with specific group attached on the inorganic surface, while grafting-from involves modifying the surface of MSNs with an initiator followed by surface initiated polymerization. The growth of polymer chain can be achieved by controlled radical polymerization techniques, for example, RAFT, ATRP or NMP.

2.1 RAFT polymerization

In the year 1998, RAFT polymerization was first reported by Rizzardo et al. [29], involving an array of addition-fragmentation equilibria mechanism as shown in the **Figure 4**. The polymerization is started by activation of the initiator generating radical. This radical then drives toward the thiocarbonylthio group of the RAFT agent which then forms a carbon-centered intermediate by reacting with the propagating radicals. Once again the intermediate undergoes a β scission generating radicals in order to reinitiate propagation. The process will continue by adding reversibly to the chain transfer agent. Finally, equilibria point is generated between the dormant and propagating species.

This polymerization demands a convenient transfer agent having high transfer constant in the radical polymerization for any monomer under the required polymerization conditions. RAFT polymerization is a highly effective technique than ATRP and NMP, since it can be easily carried out in different reaction conditions and is suitable for wide range of monomers. Since the polymer chains in this method carries a thiocarbonyl group, the synthesis of any block copolymer using a second monomer is also convenient using RAFT polymerization. Thus by utilizing this technique, different inorganic surfaces can be functionalized with the polymeric chains. Ma et al. [30] reported grafting of copolymers of positively charged quaternary amines and polyethylene glycol (PEG) via RAFT polymerization using grafting-from technique from the surface of MSNs. The schematic representation for this synthesis is detailed in **Figure 5**. Initially, MSNs are synthesized, which are later on modified with amine functionalities via post-modification. Then, trithiocarbonate-based RAFT agent was synthesized from the surface of amine functionalized MSNs. Subsequently, these RAFT functionalized MSNs are utilized for RAFT polymerization for grafting of poly(ethylene glycol) and 2-(dimethylamino) ethyl acrylate. The successfully synthesized co-polymer-grafted MSNs were later on reacted with methyl iodide (MeI) in order to generate quaternary amines from tertiary amines. The aim of introducing quaternary amines was to maintain the positive charges on the surface of MSNs even in different pH conditions and enable the dispersity of the particles due to its positive charge leading to electrostatic repulsion. Finally, these co-polymer-grafted MSNs were applied for in-vivo studies in drug-delivery application.

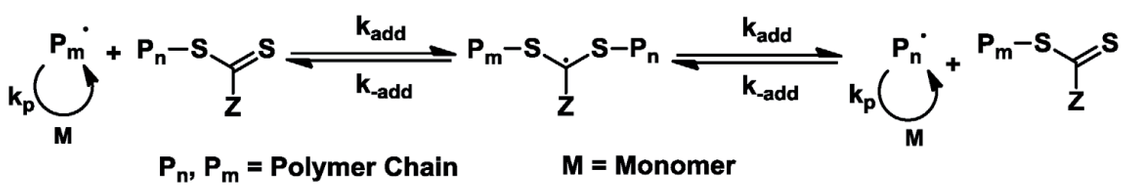

Figure 4.
Addition-fragmentation equilibria during RAFT polymerization.

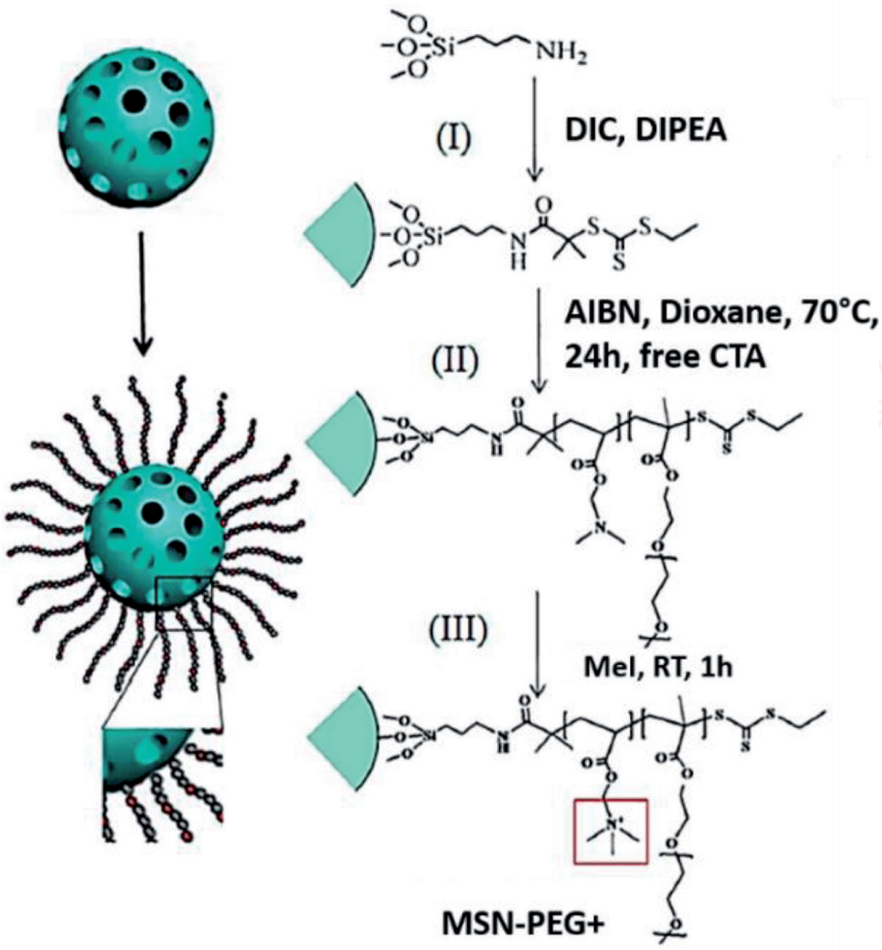

Figure 5.
Schematic representation for synthesis of MSNs grafted with copolymer of positively charged quaternary amines and PEG via RAFT as reported by Ma et al. (reproduced with permission from Ref. [30]).

Mishra et al. [31, 32] described grafting of poly(*N*-isopropyl acrylamide) (PNIPAM) onto MSNs via surface-initiated RAFT polymerization. In this work, initially two different R group containing organoalkoxysilane-based RAFT agent were synthesized. Then, these organoalkoxysilane-based RAFT agents were functionalized onto MSNs via co-condensation resulting in-built RAFT agent containing MSNs. Subsequently, NIPAM was polymerized further from these in-built RAFT agent containing MSNs via surface-initiated RAFT polymerization as shown in **Figure 6**. Further to understand about the thermoresponsiveness behavior of MSNs grafted with PNIPAM so that it can be utilized in drug delivery application, in-vitro studies of fluorescein dye and doxorubicin drug was investigated at different temperatures. Hong et al. [33] studied post-modification of the surface of MSNs by a trithiocarbonate-based RAFT agent. MSNs were synthesized without CTAB extraction and then it was post-modified by 5,6-epoxyhexyltriethoxysilane (EHTES) on the outer surface of MSNs as shown in **Figure 7**.

Further, EHTES functionalized MSNs were refluxed in methanol/hydrochloric solution in order to extract CTAB, as well as epoxyhexyl group were converted to 5,6-dihydroxyhexyl units. Then, trithiocarbonate-based RAFT agent was functionalized to MSNs via esterification. Thus, adopting such mechanism, polymers such as polystyrene, poly(acrylic acid), and PNIPAM were grafted from the surface of MSNs via surface-initiated RAFT polymerization. Gonçalves et al. [34] reported a pH-responsive polymer coated on surface of MSNs via RAFT polymerization. Nanocontainers based on fluorescent core

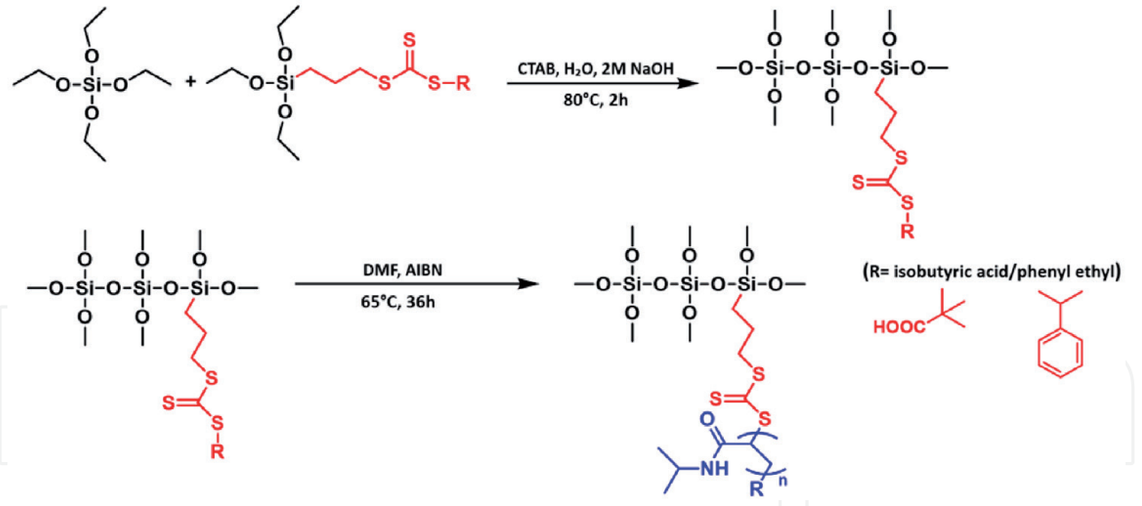

Figure 6.
Schematic representation for MSNs functionalized with different R group containing organoalkoxysilane RAFT agent via co-condensation and further grafting with PNIPAM via surface-initiated RAFT polymerization as reported by Mishra et al. (reproduced with permission from Ref. [31]).

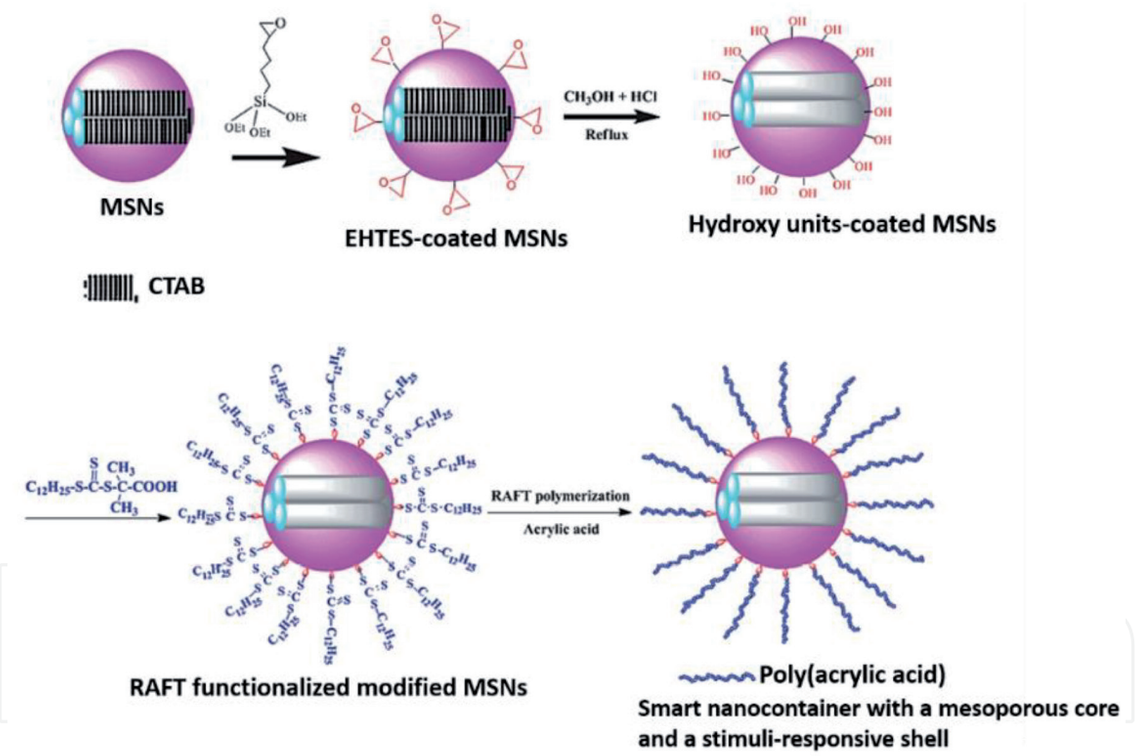

Figure 7.
Schematic representation for grafting of poly(acrylic acid) on the exterior surface of MSNs via RAFT polymerization as reported by Hong et al. (reproduced with permission from Ref. [33]).

MSNs were prepared, which were coated with a shell of pH-responsive polymer poly(2-(diisopropylamino)ethyl methacrylate). The synthesis was carried out by incorporation of a fluorescent dye in the silica network and by functionalization of a RAFT agent on the outer surface of MSNs. Further utilizing this RAFT polymerization, the pH-responsive polymer was coated only outside the surface of MSNs in order to keep the pores free to encapsulate drug into it. The pH-responsive polymer-grafted MSNs displayed an outstanding drug release from the pores at low pH due to electrostatic interaction of the cargo with the charged silica and due to the pH-responsive polymer.

2.2 ATRP and NMP polymerization

Among other methods of controlled radical polymerization, surface-initiated atom transfer radical polymerization (ATRP) is gaining importance for the synthesis of polymer on the mesoporous surface of inorganic moieties. ATRP is an another technique through which growth of polymeric chains of controlled molecular weight can be performed on the surface of MSNs [1]. The general mechanism of ATRP as shown in **Figure 8** comprises of an alkyl halide initiator, R–X, or a latent polymer chain, P_n–X, (where X is a halogen), which is activated by a metal/ligand catalytic complex in a lower oxidation state, for example, [Cu(I)/L], resulting in the formation of a propagating radical and the catalytic complex in a higher oxidation state [X–Cu(II)/L]. Then, monomer units add to the growing radical and polymerization occurs.

Since MSNs provide high specific area and thermal stability, they have been further modified so as to achieve enhancement in the performance which is required in most of the applications. In field of biomedicine, Huang et al. [35] discussed the applications of visible light-induced surface-initiated ATRP for drug delivery using mesoporous silica polymer nanocomposites. They synthesized a nanocomposite named MSNs-NH_2-poly(IA-co-PEGMA) using itaconic acid (IA) and poly(ethylene glycol)methyl acrylate (PEGMA), which were grafted on MSNs. Importantly, they have loaded an anticancer drug cisplatin effectively onto these nanohybrid structures and thus performed studies based on controlled drug release in response to a change in pH. The light-induced surface-initiated ATRP proved promising compared to traditional ATRP, as the prior could avoid the use of metallic catalyst and other organic ligands as well as the reaction can be performed at much lower temperature and with increased rate of polymerization. **Figure 9** shows the preparation of the nanohybrid along with the control released studies performed for cisplatin.

In recent times, ATRP with activators regenerated by electron transfer (ARGET) is popular among researchers. It provides major improvements in usage as it can be performed easily using closed vial and involves low concentration of copper catalyst. In ARGET ATRP, a reducing agent (tin(II) 2-ethylhexanoate, or vitamin C) is added to convert Cu(II) to Cu(I) and to remove the oxygen. ARGET ATRP has been successfully utilized for growing polymer brushes on flat surfaces as well as on nanoparticles. Cao and Kruk [9] demonstrated ARGET-ATRP for modification of SBA-15 with different polymers, for example, polystyrene and poly(methyl methacrylate) of low polydispersity index. The technique of ARGET ATRP was demonstrated to be useful for the synthesis of high surface area silica-polymer composites. The work concluded the simplicity of the technique for synthesizing well-defined polymer brushes in porous architecture of silica. **Figure 10** illustrates the synthesis route of grafting polymer in nanopores of MSNs.

Mesostructure cellular foam materials (MCFs) have large pore of 15–40 nm and can easily host large molecules. Zhou et al. [36] reported the synthesis and design engineering of drug system based on thermoresponsive polymer (PNIPAM) inside

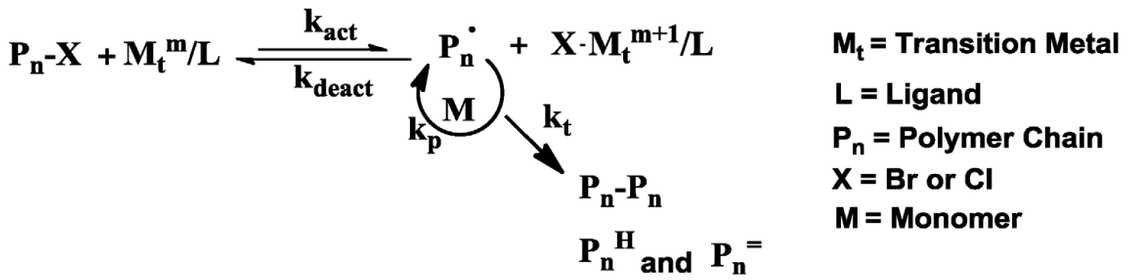

Figure 8.
Activation-deactivation during ATRP.

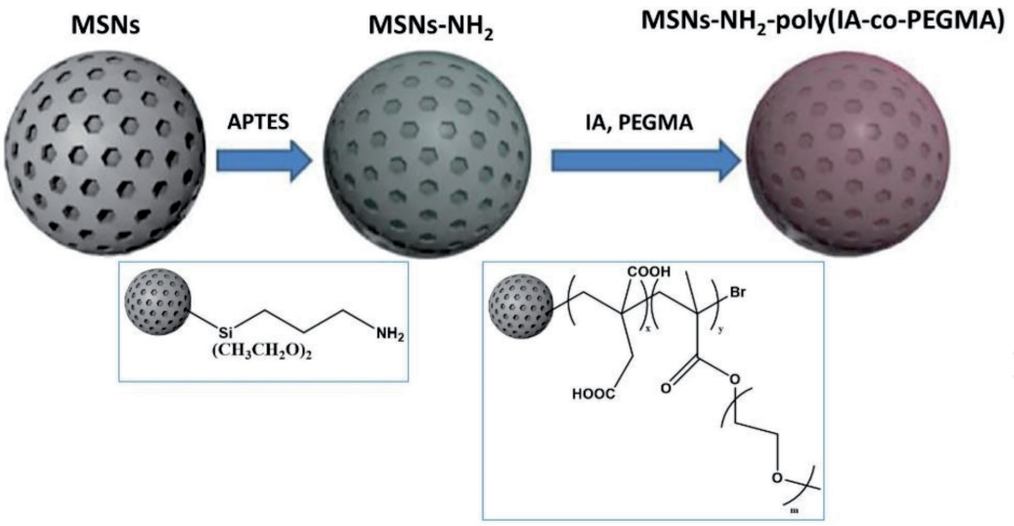

Figure 9.
Synthesis route of MSNs-NH_2-poly(IA-co-PEGMA) via a catalyst free ATRP (reproduced with permission from Ref. [35]).

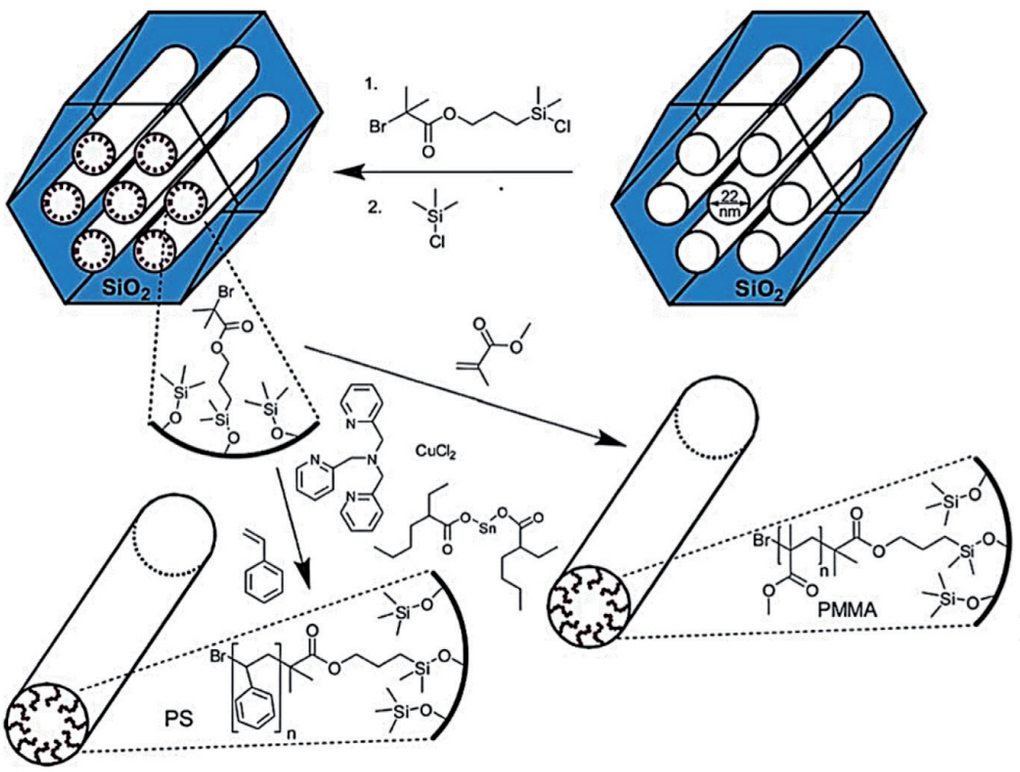

Figure 10.
Grafting poly(methyl methacrylate) and polystyrene in the cylindrical mesopores of SBA-15 silica using ATRP (reproduced with permission from Ref. [9]).

MCFs using ATRP. The controlled release of the drug inside MCFs was investigated via thermoresponsive nature of the polymer used under environmental temperature. The occurrence of polymerization was restricted to the surface of MCFs. They have investigated the high storage capacity of 58 wt.% for ibuprofen (IBU/silica) which was comparatively much higher than that reported for functional SBA-15 (37 wt.%). Zhou et al. [37] demonstrated the synthesis of PGMA (poly(glycidyl methacrylate)) MSNs based nanocarriers capable of drug delivery applications using disulfide bonds as redox-responsive cross-linkers. The successful grafting of PGMA on the surface of MSNs was performed using SI-ATRP as shown in **Figure 11**. The epoxy ring opening

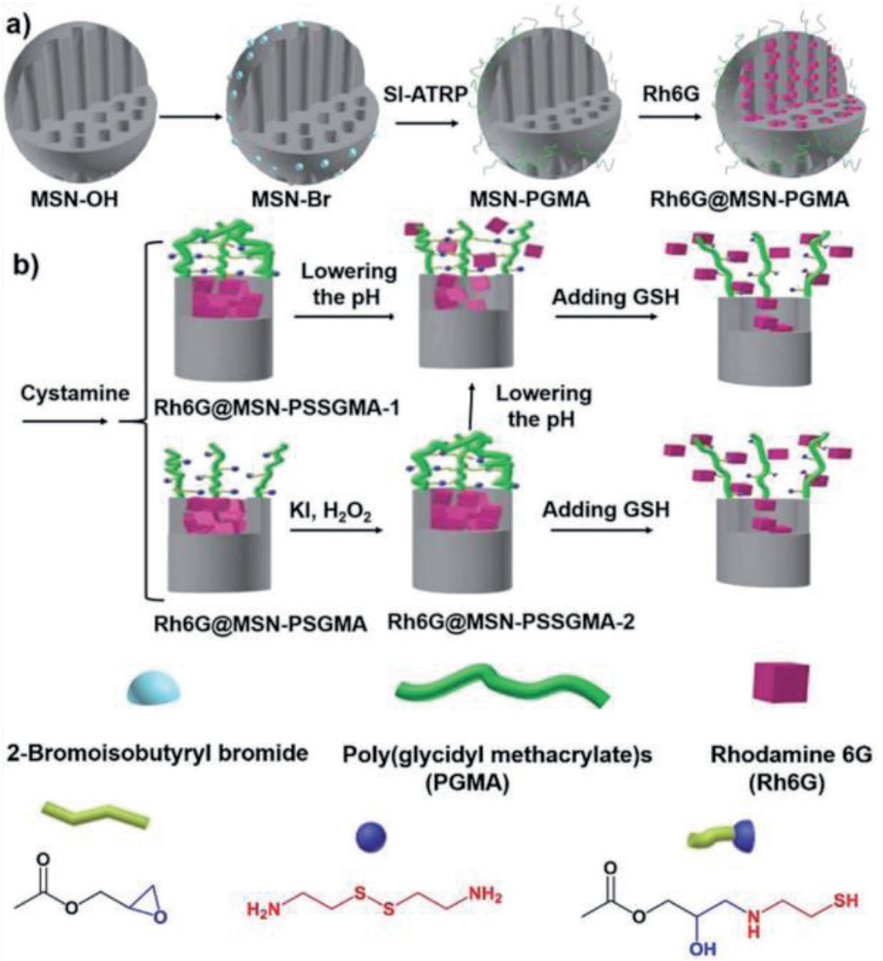

Figure 11.
Schematic illustration of (a) the synthetic route of MSN–PGMA and Rh6G (Rhodamine 6G)-loading process; (b) cystamine cross-linked PGMA network on MSNs and its Rh6G release in response to pH and GSH (reproduced with permission from Ref. [37]).

reactions of PGMAs was performed using cystamine dihydrochloride and a facile mechanism for building disulfide-containing cross-linked structures. The dual external stimuli responsive system based on pH and GSH (glutathione) in cancer cells. These biocompatible materials having degradable S–S bonds can find application in biomedical area. Hence, ATRP is a powerful approach and can be effectively used for grafting of polymers or polymer brushes from mesoporous surfaces. ATRP allows to achieve grafting of polymer chains of controlled molecular weight and low polydispersity index while maintaining the pore accessibility and moderate to high surface area.

Nitroxide-mediated polymerization (NMP) is an another easy way of controlled radical polymerization, which gives well-defined, functional macromolecular structures. IUPAC has endorsed the term "nitroxide" to "aminoxide" and thus recommended aminoxyl-mediated radical polymerization (AMRP). NMP involves the process of activation/deactivation having a reversible combination of propagating radicals with free nitroxide radicals as shown in **Figure 12**.

A variety of nitroxide and nitroxide-based alkoxyamines have been reported in the literature in order to conduct polymerization of different monomers. Adequate surface-active initiators required for the development of grafting on the inorganic surface via NMP is much less explored. The nitroxide radical combines with carbon-centered radicals and gives alkoxyamines. Due to thermal activation requirement, NMP is considered as a simple and effective method for polymerization. In NMP, no further purifications are required except a precipitation to remove unreacted monomer. The materials prepared using NMP

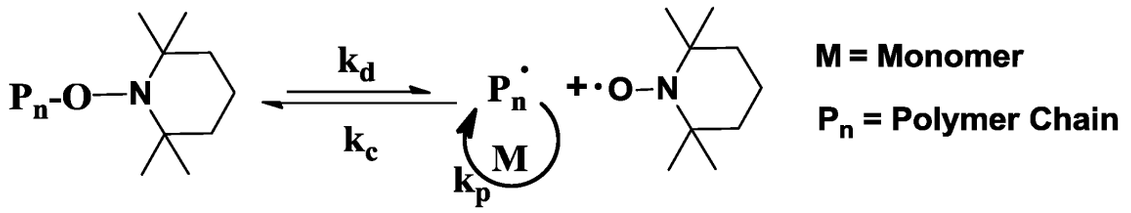

Figure 12.
Activation-deactivation during NMP.

can find applications in various fields such as optoelectronics, nanoporous, nanostructured materials, and surfactants/dispersants, etc. [38]. Charleux [39] reported the polymerization of styrene using NMP on the surface of various types of ordered mesoporous silica (OMS). NMP, being a reversible termination technique, can provide surface-initiated polymerization mechanisms for mesoporous substrates. This was able to successfully determine that there is no effect of the OMS particle structure on the polymerization kinetics. The important conclusions drawn from the experiments are that pore size of 5 nm is adequate for diffusion reactions while 2 nm are too small for the same. In addition, large pore size (≥5 nm) is important for the pore connectivity. Barthalome et al. [40] reported the two-step synthesis of nitroxide-mediated radical polymerization of styrene onto the silica nanoparticles. Using this technique, it was manifested that polymer graft densities of around 110 chains per particle were obtained. The alkoxyamine-functionalized silica nanoparticles were prepared, followed by growth of polystyrene chains having narrow polydispersity and targeted molecular weights. By varying styrene-to-initiator molar ratios, an insight of the growth mechanism was obtained by comparison of molecular weights and polydispersity index of the grafted and free polymeric chains. The novelty of the approach was found in using triethoxysilyl-functionalized alkoxyamine initiator. Using this approach, the well-defined structures of polystyrene-coated MSNs were obtained, which can find good potential as nanocomposite in the field of materials science.

3. Applications of polymer functionalized MSNs

Mesoporous silica nanoparticles find versatile potential in the developing field of catalysis [41], coating, sensing, and as drug carriers [42]. Due to its high surface area, bio-compatibility, chemical stability, and tunable porous architecture, MSNs are capable of various modifications which can be easily anchored on its surface [43]. Accordingly, modification/functionalization methods, e.g., co-condensation method, encapsulation process, and post-synthesis like grafting-to and grafting-from techniques are recently captivating immense attentions. Due to its low toxicity and high drug loading capacity, MSNs are now extensively investigated as smart system which can be used for controlled and targeted drug-delivery systems. Targeting ligands toward the selective diseased area have proven to be a difficult task. The concept of a stimuli-responsive drug release system takes into account of control and targeted release of the required dosage of drug [44]. Internal as well as external stimuli such as pH, temperature, light, magnetic fields, electric fields, ultrasounds, and redox potential can be used in many cases. Paris et al. [45] demonstrated a new approach to stimuli-responsive system by making use of hybrid MSNs. These hybrid-MSNs are mesoporous silica as carriers coated with dual temperature and ultrasound-responsive copolymer having lower

critical solution temperature (LCST) below 37°C which act as nanogates sensitive to ultrasound stimulations. On providing ultrasound, copolymer changes its physical state at the respective temperature leading to release of loaded molecules from carriers. Doxorubicin-loaded hybrid MSNs were incubated with LNCaP (androgen-sensitive human prostate adenocarcinoma) cells to show their capacity to induce cell death only when this hybrid system was exposed to ultrasound as shown in **Figure 13**.

Stimuli-responsive polymers such as poly(methacrylic acid) (PMAA) and poly(*N*-isopropyl acrylamide) (PNIPAM) have been widely investigated. Zheng et al. [46] has reported thermo- and pH dual-responsive nanocarrier silica acting as core and block copolymer as shell. Surface-initiated-RAFT (SI-RAFT) polymerization of methacrylic acid (MAA) and *N*-isopropyl acrylamide (NIPAM) was performed on the silica surface. The polymer-grafted MSNs showed higher loading efficiency of drug doxorubicin (DOX) and these dual-responsive nanoparticles were used as a drug carrier. The rate of drug release depends upon both temperature and pH of the surrounding media. The agglomeration was observed under acidic and elevated temperature conditions, whereas particles were dispersed in an aqueous media at high pH and low temperatures. The features of resulting SiO_2-PMAA-b-PNIPAM show potential for therapeutic applications as revealed by a cellular uptake study. These systems were able to deliver DOX successfully into the nuclei of HeLa cells (cervical cancer cells from Henrietta Lacks). In addition, cytotoxicity study revealed that DOX-loaded nanoparticles were more active and effective with HeLa cells than free equivalent dosage of DOX. Liu et al. [47] reported dual-responsive smart polymer coated on MSNs for laryngeal carcinoma therapy. Thermo/pH dual-responsive polymer poly[(*N*-isopropyl acrylamide)-co-(methacrylic acid)] was grafted onto mesoporous silica to act as a "valve" to restrain the diffusion of the incorporated drugs in and out of the pore channels. They reported "on-off" drug release pattern at higher temperature and lower pH value. The folic acid molecules were further attached to the polymer-modified MSNs in order to target Hep2 cells. The synthesis of polymer-grafted MSNs and control delivery of drugs is depicted in **Figure 14**.

The organic/inorganic nanocomposites possess combined advantages as inorganic materials are thermally stable and give rigidity, whereas organic materials are much more flexible and can be easily processed. Also, the size of fillers gives increased interfacial area than ordinary composites. Silica is considered as suitable

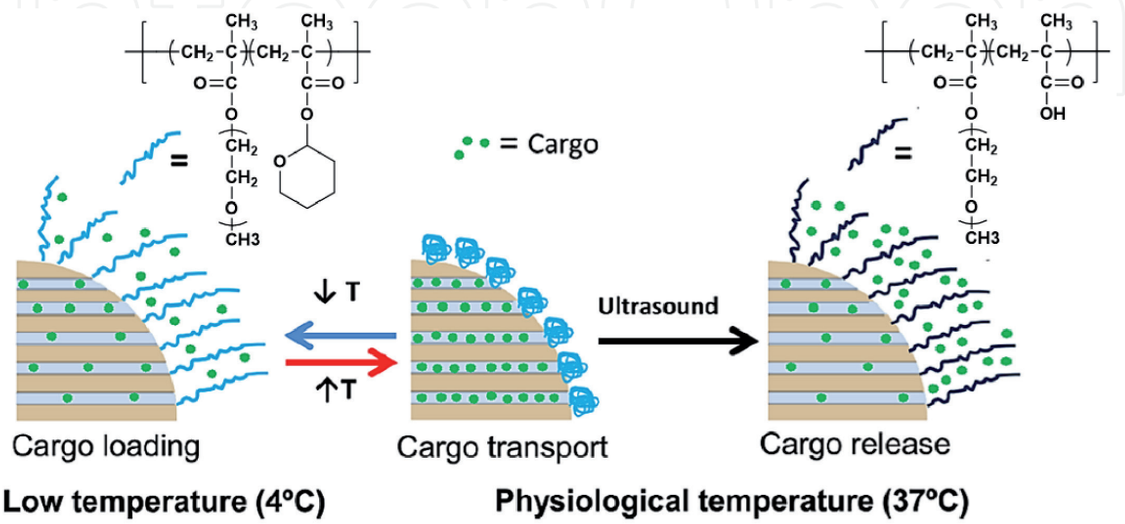

Figure 13.
Illustration of the behavior of dual-responsive system in aqueous medium (reproduced with permission from Ref. [45]).

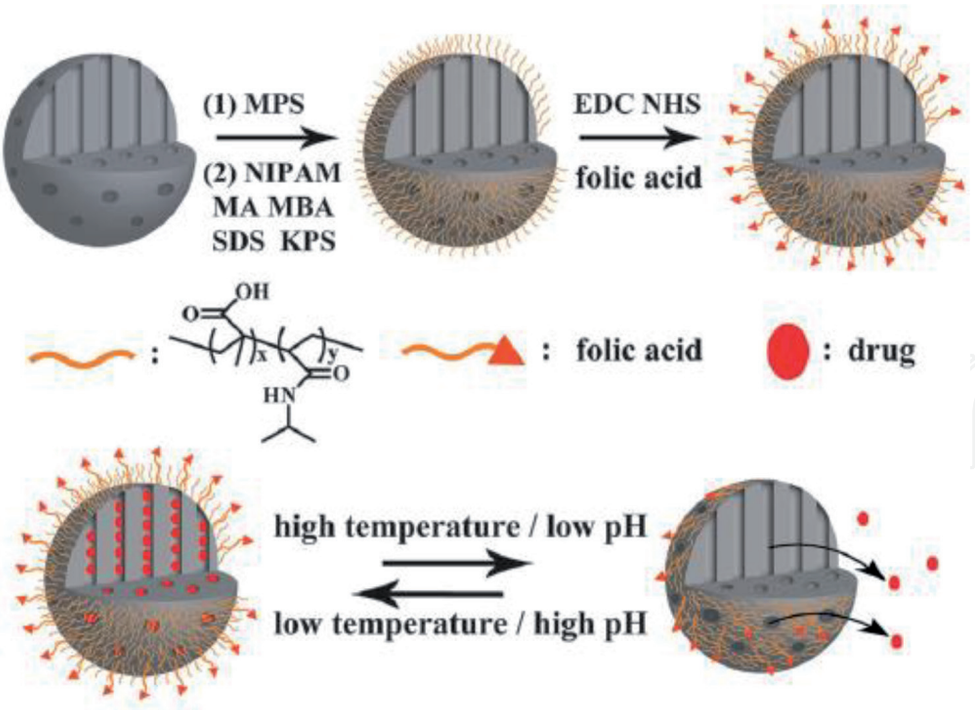

Figure 14.
Illustration of synthesis of dual-responsive drug delivery system (reproduced with permission from Ref. [47]).

nanofillers for such nanocomposites and MSNs find its unique application in catalysis. Tang et al. [48] synthesized a series of nanocatalyst based on MSNs for polymerization of 1,3-butadiene and simultaneously immobilizing salicylaldimine cobalt complexes on MSNs surface. Combining MSNs with methylaluminoxane (MAO) gives excellent catalytic efficiency for the polymerization. The yield of the polymer and its molecular weight also depends on the size of the particles used for catalysis. Thus, this catalysis process provides an easy way to directly synthesize polymer/silica composites. Further, Tang et al. [49] demonstrated a novel synthesis route for in situ polymerization of isoprene wherein MSNs were used as catalyst to synthesize rare earth oxide-containing luminescent polymer/silica nanocomposites having core-shell architecture. In this case, MSNs functioned both as catalyst as well as inorganic core for nanocomposites and caused phase separation for more interfacial interactions. The mesoporous materials have shown its potentiality over microporous zeolites in the area of heterogeneous catalysis. Keeping note, Albuqerque et al. [50] reported new improved catalysts for trans-esterification of vegetable oils with methanol using MSNs such as SBA-15, MCM-41, and fumed silica. A linear model was reported and found to predict the conversion rate for the product formation. The reported process states that the most active catalyst consisted with a sample having 14 wt.% of CaO on SBA-15, achieving 95% of conversion with sunflower oil in 5 h and 65% with castor oil in 1 h. Similar studies were reported by Abdullah et al. [51] by using responsive surface methodology for trans-esterification of palm oil using mesoporous K/SBA-15. The type of alcohol and oil used with various reaction time and temperature, their molar concentration along with catalyst type all were the factors affecting the efficiency for production of biodiesel. Potassium (K) was introduced via conventional impregnation method to make SBA-15 act as basic catalyst sites. An effective mathematical method was developed which can be used to determine the product yield (biodiesel) with optimum reaction conditions with the accuracy. The relation between reaction time, temperature, and catalyst loading was successfully elucidated. It was reported that 87.3% was highest yield, which was obtained when the system conditions were 11.6 mol/mol for methanol to oil ratio

with 3.91 wt.% of catalyst with reaction time of 5 h at 70°C reaction temperature. Farjadian et al. [52] reported comparative studies of palladium as catalyst with phosphinite-ligands immobilized on silica and hexagonal mesoporous silica (HMS) having palladium nanoparticles as catalyst for Heck coupling reaction (HCR). Mono-, di-, tri-phosphinite ligands were functionalized on silica and hydroxyl functionalized HMS. Then, phosphinite functionalized silica/HMS-based palladium complexes were formed. The recycling ability of the catalyst was also determined and reported. Higher efficiency and stability were shown by Pd catalyst for HCR, whereas HMS-based catalyst show less efficiency and this was attributed to the time taking process of insertion of substrate into pores and thus renders onto its efficiency as catalyst. Chen et al. [53] reported new nucleophilic catalytic system based on dialkylaminopyridine functionalized mesoporous silica nanospheres (DMAP-MSNs). Initially, DMAP was functionalized with triethoxysilyl groups to produce 4-[*N*-[3-(triethoxysilyl)propyl]-*N*-methylamino]pyridine (DMAP-TES). DMAP-TES were then functionalized into MSNs via co-condensation to produce DMAP-MSNs. Finally, these DMAP-MSNs were utilized for Baylis-Hillman, acylation, and silylation catalytic reactions. It was observed that by this approach, the protonation of DMAP was avoided, which produced a heterogeneous catalyst with high reactivity and recyclability for Baylis-Hillman, acylation, and silylation reactions.

An upcoming research area of MSNs is to utilize it as an efficient material for the generation of clean energy, for example, hydrogen. It is a major challenge when it comes for hydrogen storage and release application. Different microporous materials particularly metal organic frameworks (MOFs) have made an impact on hydrogen storage and release applications. MSNs have created a significant interest to work on due to its large mesoporous channels that allow easy storage of chemical hydrides. Peru et al. [54] reported nanoconfinement of sodium borohydride ($NaBH_4$) into the mesoporous architecture of highly ordered SBA-15 and carbon-based materials (C-based CMK3) by using embedding approach such as wet chemical impregnation which is solvent (ammonia) free route. By such nanoconfinement process, there exists many advantages, for example, particle size of the activated phases can be precisely modulated, depending upon the nanoscale materials used; thus, alterations can be performed in the properties of nanoconfined particles. Also, major benefits of having nanoconfinement are not only reversibility observed for absorption/desorption cycle of hydrogen gas but also safe handling of the system. Thus, nanosizing leads to low temperature (below 120°C) desorption for $NaBH_4$ dispersed in mesoporous scaffolds of silica as well as carbon-based systems. Similarly, Lai et al. [55] reported the thermal behavior of ammonia borane (AB) embedded in mesoporous scaffolds of silica-based nanoparticles (SBA-15 and MCM-41). It was observed that dehydrogenation temperature for hydrogen release was lowered and the liberation of borazine and diborane as side products was minimized. The ammonia borane incorporated in MCM-41 showed favorable results than SBA-15. The was possibly due to pore size difference in MCM-41 and SBA-15. Smaller particles of AB molecules are more easily formed in MCM-41 having higher surface area and smaller pore size than SBA-15 leading to intensive contact of these particles onto the scaffolds of MCM-41 than SBA-15. The formation of coordination bond as O: → BH_3 occurs which reduces the H-bonding (intermolecular) in AB particles; thus, the release of hydrogen was lowered and simultaneously strong bonding of BH_3 with scaffolds remains intact and reduces diborane and borazine release. Deka et al. [56] reported confinement and fabrication of Ru nanoparticles in S1B-C10 (cubic MSNs modified via carboxylic acid functionality) using double chemical reduction approach. The 3D cage structure of mesoporous silica SBA-1 offers direct and effective growth of nanoparticles and also avoids agglomerations of these nanoparticles. The carboxylic acid functionality within the mesoporous silica ensures the great dispersion and size control of Ru

metal NPs and thus limits its escape from the recyclable system and also enhances the stability of the catalyst. The ordered porous structure of MSNs can be utilized for preparation of shear thickening fluids (STF). Such behavior of MSNs finds application in flexible protective gear. It has been demonstrated that when MSNs are dispersed in any polar solvent/fluid, its high surface area and rough surface would enhance the interfacial interaction between the MSNs and dispersing medium, resulting in shear thickening behavior, in which an increase in viscosity has been observed with an increase in the shear rate. He et al. [57] studied the shear thickening behavior of suspensions prepared using porous silica nanoparticles. It was observed that the suspension remarked STF behavior with 42.5 wt.% concentration of nanoparticles which is much lower than the STF of non-porous silica nanoparticles. The possible mechanism for such behavior due to interfacial interactions was studied and was successfully demonstrated that it can be used in engineering composite applications.

4. Conclusions

MSNs are an important substrate possessing several favorable characteristics, for example, tunable pore size, surface area, and possibility of functionalization using wide variety of strategies. These important features makes MSNs widely applicable in the biomedical area, as sensors and catalysts. The grafting of a stimuli-responsive polymer from MSNs makes then suitable for drug-delivery application. We have summarized in this chapter, various controlled radical polymerization techniques, for example, RAFT, ATRP, and NMP for grafting of polymer chains. There is still a lot of scope in the synthesis and characterization of MSNs via co-condensation approach. In addition, in-depth characterization and mechanism of synthesis of MSNs in the presence of organoalkoxysilane can help in understanding the preferential location of organoalkoxysilane moieties after co-condensation. The modified/functionalized MSNs can also find application as a source of clean energy and novel composites with application in the area of protective materials.

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