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Controlled post-synthesis grafting of thermoresponsive poly(N-isopropylacrylamide) on mesoporous silica nanoparticles

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Short title: Controlled post-synthesis grafting of PNIPAM on MSNs

Abstract

Ordered mesoporous silica nanoparticles with pore diameter of 5 nm were synthesized by modification of the sol-gel synthesis method. Post-synthesis two-step grafting of thermoresponsive poly(N-isopropylacrylamide) inside the mesopores of the nanoparticles was carried out by distillation precipitation polymerization of the methacryloxy-functionalized mesoporous nanoparticles with N-isopropylacrylamide monomer. A precise control on the quantity of the grafted polymer was achieved by changing the ratio of monomer to methacryloxy–functionalized nanoparticles. The polymer-grafted hybrid nanoparticles obtained were fully characterized by infrared spectroscopy, X-ray diffraction, dynamic light scattering, transmission electron microscopy, thermal and gas-volumetric analyses, which clearly showed presence and thermoresponsive behavior of the polymer inside the mesopores with the preservation of the characteristic mesoporous structure of the nanoparticles.

Keywords: Mesoporous silica nanoparticles; Sol-gel synthesis; Thermoresponsive polymer; Distillation precipitation polymerization; Poly(N-isopropylacrylamide)
1. Introduction

Mesoporous silica nanoparticles (MSNs) are at the forefront of research in a number of demanding technological fields requiring highly ordered porous structures with dimensions in the nanoscale. For example MSNs have already been proposed as catalyst supports, drug delivery vehicles for various drug molecules and proteins, as functionalized porous reservoirs in water purification and as nanocomposite fillers.[1-5] Biocompatibility, non-toxicity and ease of surface modification make MSNs a suitable and versatile material in the applications mentioned above.[6] Both in-situ and post-synthesis grafting of various groups and polymers on silica materials was reported and each method has its advantages and disadvantages.[7,8] The choice of the grafting of organic groups or polymers on the surface of MSNs depends on their stability in the grafting reaction conditions and applications under study. Standard sol-gel procedures for the preparation of mesoporous silica involve drastic conditions such as use of strong acid or base and the removal of the templating agents through calcination, hence in-situ grafting of sensitive organic and polymeric groups is impossible.[9] For this purpose the post-synthesis grafting provides an advantage, that is grafting of groups which are unstable in the experimental conditions used for the synthesis of MSNs is possible. Attempts are made to graft various compounds, drug molecules, biomolecules and polymers on such nanoparticles where reactivity of the hydroxyl groups present on the silica surface is used to react them with the complementary group on the incoming molecules.[10]

Poly(N-isopropylacrylamide) (PNIPAM) is a thermoresponsive polymer well-known for its specific coil-to-globule transition at its lower critical solution temperature (LCST), which is around 32 °C.[11-15] Being nontoxic and water soluble this polymer is used as drug delivery agent,[16] for cell attachments and as haemostatic agent.[17,18] Grafting of such polymer on various nanoparticles has shown applicability of the resulting hybrid thermoresponsive nanomaterials in diagnosis for protein identifications,[19] as controlled molecular transport agents[20] and in cellular imaging.[21] In the case of mesoporous materials the typical coil-to-globule transition of the polymer inside the pores of the nanoparticles applies a pore opening and closing mechanism to the PNIPAM-grafted nanoparticles, thus controlling the traffic of molecules, ions and various other substances entering and exiting from the pores. The length of polymer chains and more importantly the quantity of the polymer grafted on and inside the mesopores should be strictly controlled as the grafted organic or polymerizable groups and polymer reduce
the free volume inside the pores.\textsuperscript{[22]} Hence the attempt of grafting thermo-responsive polymers such as PNIPAM should be done in a controlled way to not occupy all the volume inside the mesopores. In this regard, previous studies on grafting of PNIPAM on MSNs reveal some limitations as the chemisorption of the polymer on nanoparticle surface is not fully convincing and the quantity of polymer grafted is extremely low to apply a pore opening and closing mechanism. Furthermore, most of those attempts used crosslinking agents for ensuring and increasing the grafting, which may considerably alter the properties of the polymer.\textsuperscript{[23]}

In the present study we report a post-synthesis two step controlled grafting procedure of PNIPAM on ordered MSNs with 5 nm pore size by first functionalization of the mesopores with polymerizable methacryloxy groups and their subsequent polymerization by distillation precipitation polymerization (DPP) with N-isopropylacrylamide, using azobisisobutyronitrile (AIBN) as initiator and without use of any crosslinking agent. Bare and polymer-grafted nanoparticles were fully characterized as for their composition, size, structure and thermo-responsive behavior.

2. Experimental

2.1 Materials
Tetraethoxysilane (TEOS), cetyltrimethylammoniumbromide (CTAB), 1,3,5-trimethylbenzene (TMB), N-isopropyl acrylamide (NIPAM), 3-(methacryloxypropyl) trimethoxysilane (MPS), azobisisobutyronitrile (AIBN) were purchased from Sigma-Aldrich, Italy. All the solvents used for the synthesis were of high purity and used as received.

2.2 Instruments and methods
Powder X-ray diffraction (XRD) patterns were collected on an X'Pert Pro Bragg Brentano diffractometer (Philips) using Cu Kα radiation (40 mA and 45 kV), with a scan speed of 0.01 °C/min.

Gas-volumetric analysis, specific surface area (SSA), pore volume and size were measured by N\textsubscript{2} adsorption–desorption isotherms at 77 K using an ASAP 2020 (Micromeritics) gas-volumetric analyzer. SSA was calculated using the Brunauer–Emmett–Teller (BET) method, average pore size and volume were calculated on the adsorption branch of the isotherms according to the Barrett–Joyner–Halenda (BJH)
method (Kruk–Jaroniec–Sayari equations). Prior to analyses, samples were outgassed at RT overnight.

Fourier Transform Infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum 100 instrument in the attenuated total reflectance (ATR) mode with a diamond crystal, using 32 scans per spectrum and a resolution of 4 cm\(^{-1}\) and a spectral range of 4000-600 cm\(^{-1}\).

Thermogravimetric analyses (TGA) were carried out on a TA Q500 model from TA Instruments by heating samples contained in alumina pans at a rate of 10 °C/min from 25 to 600 °C in a nitrogen flow and from 600 to 800 °C in air. Change of the gas at 600 °C was used to remove completely the carbonaceous residues from pyrolysis reactions and measure the exact organic residue amount.

A differential scanning calorimeter (DSC Q200, TA Instruments) was used to collect DSC thermograms. DSC measurements were performed with closed aluminium pans under nitrogen atmosphere and with a 10 °C/min heating rate, from 20°C up to 60°C.

Size exclusion chromatography (SEC) was performed with a Viscotek modular instrument equipped with a VE 1122 pump, a VE 7510 degasser, manual injection valve, VE 3580 refractive index detector, column oven and two PLgel 10µm MIXED-B columns (Polymer Laboratories, UK). N,N-Dimethylformamide (DMF) (1.0 mL/min) was used as eluent and analyses were performed setting the column oven at 70 °C. DMF solutions of the samples (3 mg/mL) were filtered through 0.45 μm PTFE membrane filters. Calibration was obtained with poly(methyl metacrylate) (PMMA) molecular weight standards.

High resolution Transmission Electron Microscopy (HRTEM) images were obtained with a JEOL 2010 instrument (300 kV) equipped with a LaB\(_6\) filament. For specimen preparation powdery samples were supported onto holed carbon coated copper grids by dry deposition.

Dynamic Light Scattering (DLS) measurements were carried out by using a Malvern ZS 90 Zetasizer instrument. 0.1 % suspensions of nanoparticles were prepared in deionized water and these suspensions were sonicated for 20 minutes before the analysis.

2.3 Synthesis of mesoporous silica nanoparticles (MSNs)

The synthesis of MCM-41-like MSNs was carried out by slight modifications of the already reported methods.\(^{[24]}\) CTAB was used as cationic micelle forming templating agent, while TMB was used as the micelle core swelling agent, thus providing larger
pore size (i.e. 5 nm) than conventional MCM-41.\textsuperscript{[25]} In a typical reaction CTAB (1 g) was dissolved in water (480 mL) then NaOH (3.5 mL, 2 M) was added and the solution was heated at 80 °C. After stabilization of the temperature, a proper amount of TMB was added to the system. The mixture was stirred for 30 minutes for the formation of a stable white emulsion. TEOS (5 mL) was added drop wise. The mixture was then stirred for two hours at 80 °C. After cooling to room temperature, the powder product was isolated by filtration, washed with distilled water and methanol and air-dried for 24 h. The as-synthesized material was then calcinated at 550 °C for seven hours in air (2°C/min from room temperature to 550°C in Nitrogen and then isotherm at 550°C in air).

2.4 Synthesis of MPS-functionalized MSNs by post-synthesis surface modification

280 mg of MSNs synthetized according to the procedure described in paragraph 2.3 were taken in a single neck round bottom flask and 10 mL of toluene were added. Then 25 μL of MPS were added. The resulting suspension was sonicated for 15 minutes to allow MPS molecules to diffuse inside the pores. The flask was then equipped with a condenser and the suspension was refluxed for app. 16 hours at 125-130 °C in nitrogen atmosphere. At the end of the reaction the particles were separated by centrifugation. The nanoparticles were washed two times with app. 3 mL of fresh toluene and then with 5 mL of ethanol to remove excess and physically adsorbed MPS. The particles were then dried in air and characterized.

2.5 Grafting of PNIPAM on MPS-functionalized MSNs by distillation precipitation polymerization

50 mg of MPS-functionalized MSNs were taken in a 25 mL capacity single neck round bottom flask, to it weighed quantity of NIPAM monomer, 20 mL of acetonitrile and 4 mg of AIBN initiator were added. The suspension was sonicated for 10 minutes and then heated to 80-90 °C until boiling of acetonitrile. This takes app. 10-15 minutes. Then half of the acetonitrile (10 mL) was distilled off from the flask. The suspension turns milky, heating of the suspension in flask at this stage was continued for another 15 minutes. The whole process of polymerization takes approximately 50 minutes since the first heating of the suspension. The obtained suspension was cooled and centrifuged to get the polymer grafted particles. For purification, particles were washed once with 3 mL fresh acetonitrile and twice with 3 mL ethanol by keeping them under stirring for 10 minutes each time and then dried in air and characterized. Five samples as listed in Table 1 were synthetized by changing the ratio in weight of NIPAM monomer to MPS-
3. Results and discussion

3.1 Grafting of the polymer

The grafting of thermoresponsive poly(N-isopropylacrylamide) on MCM-41-like nanoparticles was carried out in two steps according to an approach where first polymerizable groups are grafted on the surface of nanoparticles and later they are polymerized with desired monomers,[26-28] as illustrated in Figure 1. In the first step polymerizable methacryloxy groups were grafted on and inside the mesopores of the nanoparticles by reacting 3-(methacryloxypropyl) trimethoxysilane (MPS) with hydroxyl groups. This takes into account the reactivity of the hydroxyl groups present on the surface of silica nanoparticles. However it is important to graft a reasonable amount of polymerizable groups which will remain reactive in the subsequent polymerization reactions. In the second step distillation precipitation polymerization (DPP) of MPS-functionalized nanoparticles is carried out with N-isopropylacrylamide (NIPAM) in acetonitrile solvent with AIBN as radical initiator. Acetonitrile is the preferred solvent for DPP as it is non-oxygenated and its lower boiling point makes it easy to distil off from the reaction mixture to concentrate the suspension.[29-33] It is worth mentioning that no crosslinking agent is used. Crosslinking agents such as di-acrylates are used to increase the possibility of grafting of the polymer on the surface of nanoparticles. Crosslinking agents if used get added in the polymer structure and may alter considerably the original properties such as LCST of the polymer (PNIPAM). Different samples were prepared by changing the weight ratio of NIPAM monomer to the MPS-functionalized nanoparticles, while keeping constant the initiator to NIPAM molar ratio.

3.2 Chemical and molecular characterization: ATR-FTIR, Thermal and SEC analyses

The chemical grafting of MPS on the MSNs and its subsequent polymerization with NIPAM was confirmed by ATR-FTIR analysis. The ATR-FTIR spectra of MPS-functionalized nanoparticles (Figure 2 spectra A) show the absorption peaks for the polymerizable C=C and acryl C=O groups at 1635 and 1703 cm\(^{-1}\) respectively,[26] while all the ATR-FTIR spectra of PNIPAM grafted nanoparticles (Figure 2 spectra B-E) show the characteristic peaks of the polymer at 1633, 1533 and 1455 cm\(^{-1}\) due to C=O, C-N and C-H stretching respectively. Bands at 1363 and 1381 cm\(^{-1}\) are attributed to C-H
deformation and bending.\[34\] Increased intensities of typical PNIPAM peaks with increase in the quantity of polymer grafted was clearly evident in the ATR-FTIR spectra indicating that a good control over the quantity of the polymer grafted can be achieved by changing the silica to monomer ratio. The amount of polymer grafted was found to increase with increasing the ratio of monomer (NIPAM) to MPS-functionalized nanoparticles, and was determined by thermogravimetric analysis as illustrated in Figure 3. Curve B shows 10 % of weight loss for the MPS-functionalized nanoparticles with respect to the starting MSNs which was only 1 %, while curves C-F show increasing order of weight loss due to the degradation of the polymeric component confirming the controlled grafting. The grafting obtained in percentage weight, as determined from TGA analysis, is reported in Table 1. As explained earlier the quantity of PNIPAM grafted in case of MSNs is of importance as excess quantity, approximately more than 20 wt. %, may lead to block all the pores and hence sufficient pore volume will not be available for loading such hybrid nanoparticles with molecules of interest. The exact quantity needed to block all the pores depends upon the pore diameter and also upon the surface coverage with the polymer chains. In order to estimate the average molecular weight of PNIPAM grafted on MSNs, a separate sample of polymer was prepared using the same monomer to initiator ratio and polymerization reaction conditions, and assuming that the molecular dimension of this untethered polymer was the same as for the polymer chains grafted on MSNs. The number average and weight average molecular weight of the polymer, as determined by size exclusion chromatography, were $M_n = 138000$ Da and $M_w = 1080000$ Da respectively. Although the molecular weight distribution is relatively large, these values indicate that reasonably the size of PNIPAM chains grafted on MSNs is large enough to close the silica mesopores when the grafted chains are in their coil conformation. In order to determine the exact LCST of the thermoresponsive polymer a concentrated solution of the homopolymer was subjected to DSC analysis. The thermoresponsive behaviour of the polymer at its LCST is due to two essential factors: hydrogen bond interaction and hydrophobic effect. Programmed heating-cooling cycles of the samples under nitrogen have clearly showed such endothermic transition due to polymer dehydration around 31 °C which is well in accordance with the LCST of PNIPAM (see Supplementary Information). At this point the extended and hydrated polymer chains expel water molecules.\[35\] The thermoresponsive behaviour of the polymer on the surface of the nanoparticles was further confirmed by DLS analysis.
3.3 Structural characterization: XRD, BET, TEM analyses

The XRD spectra of the synthesized nanoparticles show the (100) peak (overlapped to a steep instrumental baseline) and also the well-separated (110) and (200) reflections proving that the samples have pores in a hexagonal setting and with a high degree of structural order, as typical of the MCM-41-like structure. Importantly, upon MPS functionalization and subsequent polymer grafting such order is preserved indicating stability of the starting material in the process (see Supplementary Information). Nitrogen adsorption desorption isotherms for the bare and PNIPAM grafted nanoparticles (Figure 4) featured narrow steps of capillary condensation in primary mesopores indicating high pore size uniformity. Specific area calculated by BET method for bare nanoparticles was 1017 m²/g. Cumulative pore volume was 2.42 m²/g and pore diameter was approximately 49 Å. Upon polymer grafting the specific surface area was 876 m²/g and as expected the pore volume decreased to 1.60 m²/g as the polymer grafted occupies certain volume inside the pores. It is worth mentioning that all of the volume available inside the mesopores is not occupied by the grafted polymer and reasonable pore volume is available for inclusion of other compounds inside the pores. The pore diameter decreases from 49 to 46 Å indicating a very thin layer of polymer grafted on the pore walls. High resolution transmission electron microscopy images of MSNs are shown in Figure 5A and 5B. The ordered hexagonal mesoporous structure can be easily seen in the images further supporting the information obtained by XRD and BET analyses. The average particle size obtained was in the range of 80-100 nanometers. The porous structure was found to be intact upon polymer grafting as seen in Figure 5C and 5D.

3.4 Dynamic light scattering (DLS) and thermoresponsive behavior

DLS measurements were carried out on very dilute suspensions of bare and PNIPAM-grafted MSNs (sample 1 from Table 1). The results obtained are shown in Figure 6. The temperature dependence of the dimensions of PNIPAM-grafted MSNs is quite evident. The average hydrodynamic diameter (H_D) of the bare silica nanoparticles which was 122 nm increases in case of PNIPAM-grafted nanoparticles to 250 nm at room temperature. At this temperature the polymer chains are present in their full extended hydrated coil form thus increasing the overall H_D of the particles. The extension of the adsorbed polymer layer decreases as the temperature increases. The shrinkage of the polymer chains occur due to the hydrophobic attraction between the isopropyl moieties attached to the polymer backbone and also due to hydrogen bond formation. On the
contrary, by increasing temperature the hydrogen bonding with water molecules is disrupted, the attraction between polymer segments is increased and the extended chains of the polymer shrink in the globular form and fall on the particles. The $H_D$ of the polymer grafted nanoparticles gets reduced to 142 nm upon heating the sample and overcoming the LCST of the polymer. These results confirm the typical thermoresponsive behavior of PNIPAM on the particles as reported for the homopolymer and also for PNIPAM grafted on various nanoparticles.\cite{36-39}

4. Conclusions

Ordered MSNs with pore diameters of 5 nm were synthesized by suitable modification of the standard synthesis by using 1,3,5-trimethylbenzene as micelle core swelling agent to increase the diameter of the pores. Two step post-synthesis grafting of thermoresponsive poly(N-isopropylacrylamide) on the nanoparticles was successfully carried out. It was shown that the quantity of the polymer grafted can be controlled by changing the ratio of methacryloxy-functionalized MSNs with the NIPAM monomer. Importantly the characteristic ordered mesoporous structure remained intact in all subsequent polymerization steps as indicated by TEM, XRD and BET analysis. DLS analysis confirmed the presence and thermoresponsive behavior of the polymer grafted on the nanoparticles. This strategy can be easily adopted and modulated for grafting of desired quantities of such thermoresponsive polymer and its copolymers on various other silica, metal oxide and hybrid nanoparticles.

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References


Table 1. Synthesis conditions and amount of PNIPAM grafted on MSNs (wt %).

<table>
<thead>
<tr>
<th>Sample</th>
<th>NIPAM/MPS-MSNs Weight ratio</th>
<th>Grafted PNIPAM wt%</th>
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<tbody>
<tr>
<td>1</td>
<td>3.2 : 1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>1.6 : 1</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>1 : 1</td>
<td>7</td>
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<tr>
<td>4</td>
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<td>5</td>
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Figure captions

Figure 1. Scheme of the grafting of PNIPAM on MPS-functionalized MSNs.

Figure 2. ATR-FTIR spectra of MPS-functionalized nanoparticles (A), PNIPAM-grafted nanoparticles with increasing content of PNIPAM (B to E) and untethered PNIPAM (F).

Figure 3. TGA curves of MSNs (A), MPS-functionalized MSNs (B), and MSNs grafted with increasing amount of polymer (C to F).

Figure 4. Nitrogen adsorption-desorption isotherms and the corresponding pore size distribution of as synthesized MSNs (diamonds) and polymer-grafted MSNs (squares).

Figure 5. TEM images of as synthesized (5A, 5B) and PNIPAM-grafted (5C, 5D) MSNs.

Figure 6. Hydrodynamic diameters of MSNs (solid line), PNIPAM-grafted MSNs at 25 °C (long dashed line) and at 40 °C (short dashed line).
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5
Figure 6
Supplementary Information

Controlled post-synthesis grafting of thermo-responsive poly(N-isopropylacrylamide) on mesoporous silica nanoparticles

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Figure S1. DSC curves of two successive heating cycles showing lower critical solution temperature (LCST) of the PNIPAM polymer synthesized.
Figure S2. XRD pattern of as synthesized MSNs (solid line) and polymer-grafted MSNs (dashed line).