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Binary Polymer Brushes on Silica@Polymer Hybrid Nanospheres and Hollow Polymer Nanospheres by Combined Alkyne−Azide and Thiol−Ene Surface Click Reactions

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ABSTRACT: Silica@polymer core−shell hybrid nanospheres and air@polymer hollow nanospheres with surface-grafted binary polymer brushes were synthesized by a combination of sol−gel reaction, distillation−precipitation polymerization, and dual "click" reactions (alkyne−azide and thiol−ene "click" chemistry). Initially, 179 nm silica@poly(methacrylic acid-*co*-propargyl methacrylate-*co*-divinylbenzene) (SiO_2@P(MAA-*co*-PMA-*co*-DVB)) core−shell hybrid nanospheres were prepared by distillation−precipitation copolymerization of MAA, PMA, and DVB in acetonitrile, using the 151 nm silica nanospheres from sol−gel reaction as templates. The propargyl groups from PMA and residual C═C double bonds from DVB on the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell hybrid nanospheres provided dual clickable functionalities for the respective alkyne−azide and thiol−ene reactions with the azido-terminated hydrophobic polystyrene (PS-N_3, $M_n = 2550$ g/mol) and thiol-terminated hydrophilic poly(ethylene glycol) (PEG-SH, $M_n = 5000$ g/mol). Finally, hairy hollow nanospheres with a hollow core, cross-linked copolymer shell, and binary polymer brushes on the shell surface were prepared by selective removal of the inorganic silica core from the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres in HF solution.

Introduction

Combined inorganic, organic, and polymer syntheses have provided new opportunities for the preparation of novel molecular materials and nanostructures.[1−3] The emergence of "click" chemistry, in particular the Huisgen 1,3-dipolar cycloaddition of alkyne to azide, has had an important impact on materials science and engineering.[4−9] Following Sharpless's concept on several idealized reactions involving a click process, the thiol−ene chemistry has recently been established as a reaction with all of the desirable feactures of a click reaction, such as high efficiency and mild reaction conditions.[10−14] The emergency of "click" chemistry has greatly facilitated the synthesis of complex macromolecular structures, such as dendrimers[15,16] and macrocyclic polymers[17−19] Combination of "click" chemistry with controlled/"living" radical polymerization techniques, such as atom transfer radical polymerization (ATRP)[20,21] and reversible addition−fragmentation chain transfer (RAFT) polymerization,[22] have been reported recently in the synthesis of functional copolymer brushes.

Inorganic−polymer hybrid core−shell and polymer hollow micro- and nanospheres with well-defined morphology will have important applications in drug delivery systems.[23] Covalent grafting of polymer brushes or biopharmaceuticals on the surface of red blood cells (RBCs) has been reported to be an effective and biocompatible approach to render them suitable for biomedical applications.[24] Combination of alkyne−azide and thiol−ene click chemistry with conventional synthetic techniques, such as sol−gel reaction and precipitation polymerization, holds great promise for the design and preparation of unique hybrid functional structures.

Benefiting from recent works on the synthesis of molecular brushes by combination of ATRP and click reactions,[20,21] the present work demonstrates the unique synthesis of binary polymer brushes by dual click reactions, utilizing combined alkyne−azide and thiol−ene click chemistry, from a surface having dual clickable functionalities. We first describe the covalent grafting of binary polymer brushes to the surface of silica core−copolymer shell (SiO_2@copolymer) hybrid nanospheres with dual clickable functionalities on the surface, prepared a priori by sol−gel reaction and distillation−precipitation polymerization. Hydrophobic polystyrene with terminal azide groups (PS-N_3) and hydrophilic poly(ethylene glycol) with terminal thiol group (PEG-SH) were grafted consecutively on the hybrid nanosphere surface via the corresponding alkyne−azide and thiol−ene surface click reactions. Subsequent removal of the silica core produced the hairy hollow nanospheres with binary polymer brushes on the surface.

Experimental Section

Materials. Methacrylic acid (MAA, Sigma-Aldrich, 99%) was purified by vacuum distillation. Divinylbenzene (DVB80, Fluka, containing 80% divinylbenzene isomers) was washed with 5% aqueous sodium hydroxide and water and then dried over anhydrous magnesium sulfate. Styrene (St, Sigma-Aldrich, 99%) and propargyl methacrylate (PMA, Alfa Aesar, 98%) were passed through a inhibitor removing column prior to being stored under an argon atmosphere at −10 °C. 2,2′-Azobis-(isobutyronitrile) (AIBN, Kanto, 97%) was recrystallized from methanol. Tetraethyl orthosilicate (TEOS, Sigma-Aldrich, 98%), 3-(trimethoxysilyl)propyl methacrylate (MPS, Sigma-Aldrich, 98%), *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA, Sigma-Aldrich, 99%), *O*-[2-(3-mercaptopropionylamino)ethyl]-*O′*-methylpoly(ethylene glycol) 5000 (PEG-SH, Sigma-Aldrich, M_n = 5000 g/mol), hydrofluoric acid (HF, Riedel-de Häen,

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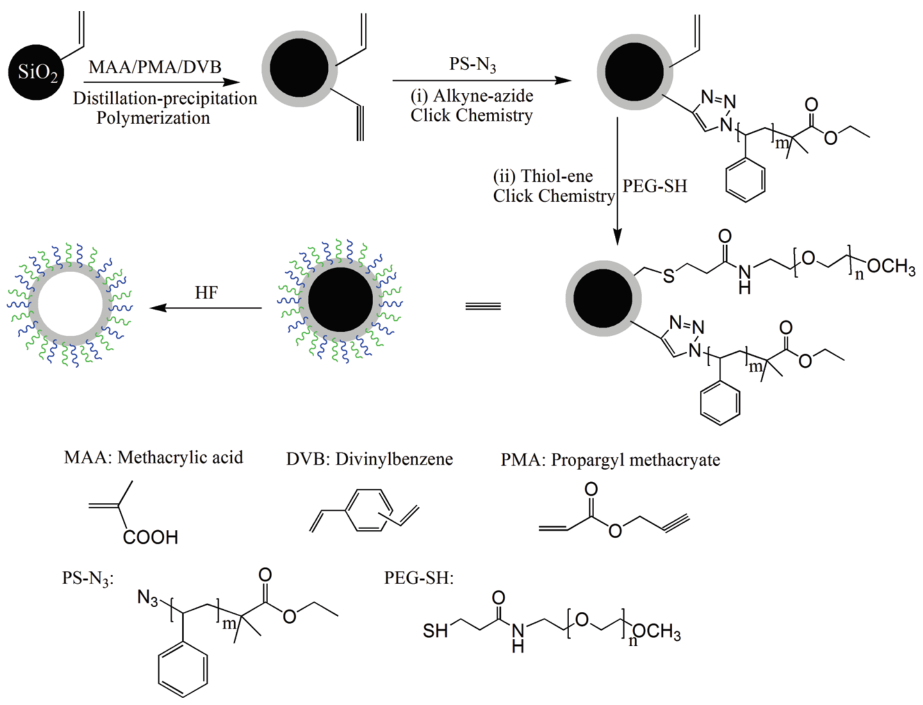
Scheme 1. Illustration of the Synthesis of Binary Polymer Brushes on the Silica@Copolymer Core−Shell Hybrid Nanosphere Surface via the Alkyne−Azide and Thiol−Ene Dual Click Reactions



48%), ammonia solution ($NH_3 \cdot H_2O$, Merck, 25 wt %), sodium azide (NaN_3, Merck, extra pure), acetonitrile (Merck, HLPC grade), dimethylformamide (DMF, Merck, HPLC grade), and tetrahydrofuran (THF, Fisher Scientific, AR) were used as received without further purification.

Synthesis of the Silica Template Nanospheres via Sol−Gel Reaction. Silica template nanospheres were prepared via sol−gel reaction according to the modified Stöber method.[25,26] In an actual reaction, about 9 mL (0.040 mol) of tetraethyl orthosilicate (TEOS) was added dropwise to a mixture of ethanol (150 mL), deionized water (15 mL), and 25 wt % mmonia solution (3 mL). The reaction mixture was stirred for 6 h at room temperature. Then, 2 mL (8.4 mmol) of 3-(trimethoxysilyl)propyl methacrylate (MPS) was introduced into the silica sol, and the reaction was allowed to proceed for another 18 h. After the reaction, the resulting silica nanospheres with C=C double bonds on the surface were purified by three centrifugation/redispersion cycles in acetone, ethanol, and deionized water. The silica template nanospheres were finally dried in a vacuum oven at room temperature overnight. About 3.3 g of silica template nanospheres with an average diameter of 151 nm was finally obtained.

Synthesis of the SiO_2@P(MAA-co-PMA-co-DVB) Core−Shell Nanospheres by Distillation−Precipitation Copolymerization. The SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres were prepared by distillation−precipitation copolymerization of methacrylic acid (MAA), propargyl methacrylate (PMA), and divinylbenzene (DVB) in acetonitrile.[27] Briefly, about 0.20 g of the SiO_2 template nanospheres was first dispersed in 40 mL of acetonitrile with the aid of sonication for 0.5 h in a 100 mL two-neck round-bottom flask, equipped with a reflux condenser. A mixture of MAA (0.30 mL, 3.5 mmol), PMA (0.15 mL, 1.2 mmol), DVB (0.15 mL, 1.1 mmol), and 2,2-azobis(isobutyronitrile) (AIBN, 10 mg, 0.061 mmol) was then introduced into the flask. The polymerization temperature was increased from room temperature (25 °C) to the reflux temperature of the reaction mixture (~83 °C) over a period of 25 min. The copolymerization reaction was then allowed to proceed for 4 h under reflux conditions. The synthesized SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell hybrid nanospheres were collected by centrifugation and cleaned with 50 mL each of tetrahydrofuran (THF), acetone, and ethanol, in that order, to remove the unreacted monomers and oligomers. The SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres were finally dried in a vacuum oven at 50 °C until a constant weight was obtained. The core−shell nanospheres had an average diameter of 179 nm.

Synthesis of the SiO_2@P(MAA-co-PMA-co-DVB) Nanospheres with Surface-Clicked Polystyrene Chains via the Alkyne−Azide Click Reaction. The azido-terminated polystyrene (PS-N_3) chains were prepared a priori via atom transfer radical polymerization (ATRP) of styrene, followed by substitution reaction of terminal bromide with sodium azide in dimethylformamide (DMF).[28,29] A mixture of styrene (10 mL, 87 mmol), CuBr (0.32 g, 2.2 mmol), ethyl 2-bromoisobutyrate (EBIB, 0.31 mL, 2.2 mmol), and diphenyl ether (1.1 mL) in a 50 mL two-neck round-bottom flask was degassed by three freeze−evacuate−thaw cycles. Then, *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA, 0.46 mL, 2.2 mmol) was introduced, and the reaction mixture was stirred at 90 °C for 6 h. The reaction mixture was diluted with THF and passed through a neutral Al_2O_3 column to remove the copper catalyst. The resulting solution of polystyrene with an alkyl bromide chain end (PS-Br) was concentrated by rotary evaporation, followed by precipitation in methanol and drying under reduced pressure. For the preparation of PS-N_3 chains, about 2.0 g of the PS-Br and NaN_3 (0.13 g, 2.0 mmol) were dissolved in 20 mL of dimethylformamide (DMF). The reaction mixture was stirred at room temperature for 24 h. The azido-terminated polystyrene (PS-N_3) chains were obtained by precipitation of the reaction mixture into 100 mL of the methanol/water (1/1, v/v) mixture, followed by drying under reduced pressure. Gel permeation chromatography (GPC) measurement indicated that the PS-N_3 chains had a number-average molecular weight (M_n) of 2550 g/mol and a narrow polydispersity (PDI) of 1.15.

For the alkyne−azide surface click reaction on the nanospheres, about 0.25 g of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres, 0.15 g (0.38 mmol) of PS-N_3, and 14 mg (0.10 mmol) of CuBr were first dispersed in 16 mL of DMF. The reaction mixture was degassed with argon for 30 min. Then, 18 μL (0.09 mmol) of the PMDETA was quickly introduced into

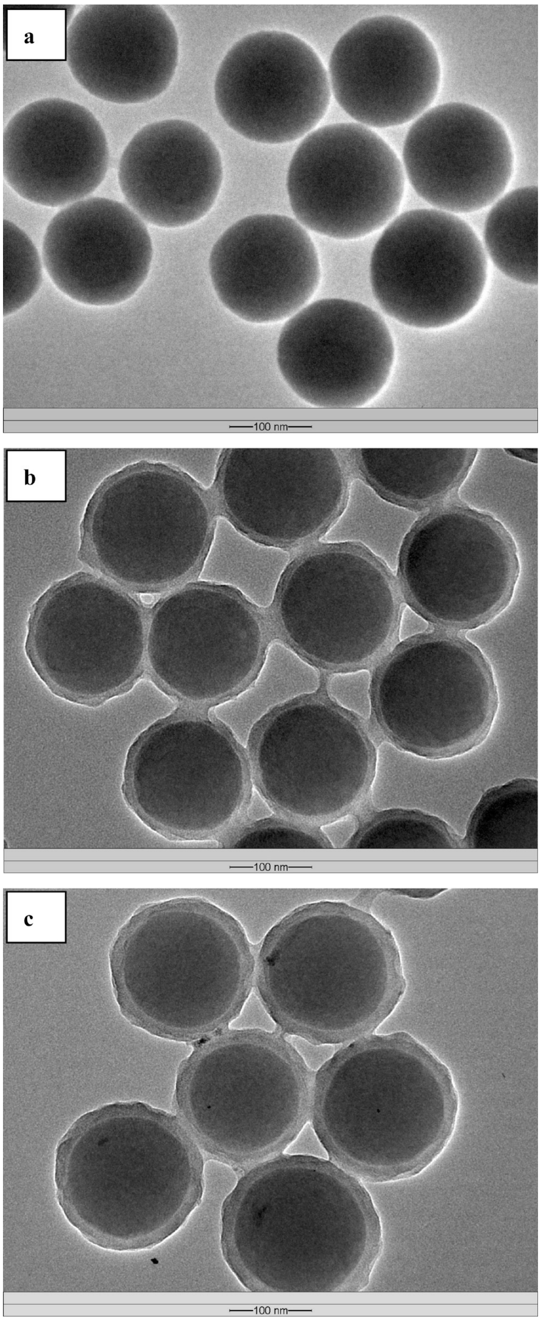


Figure 1. Transmission electron microscopy (TEM) micrographs of the (a) SiO_2, (b) SiO_2@P(MAA-*co*-PMA-*co*-DVB), and (c) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, and DVB = divinylbenzene). The scale bars for (a)−(c) are 100 nm.

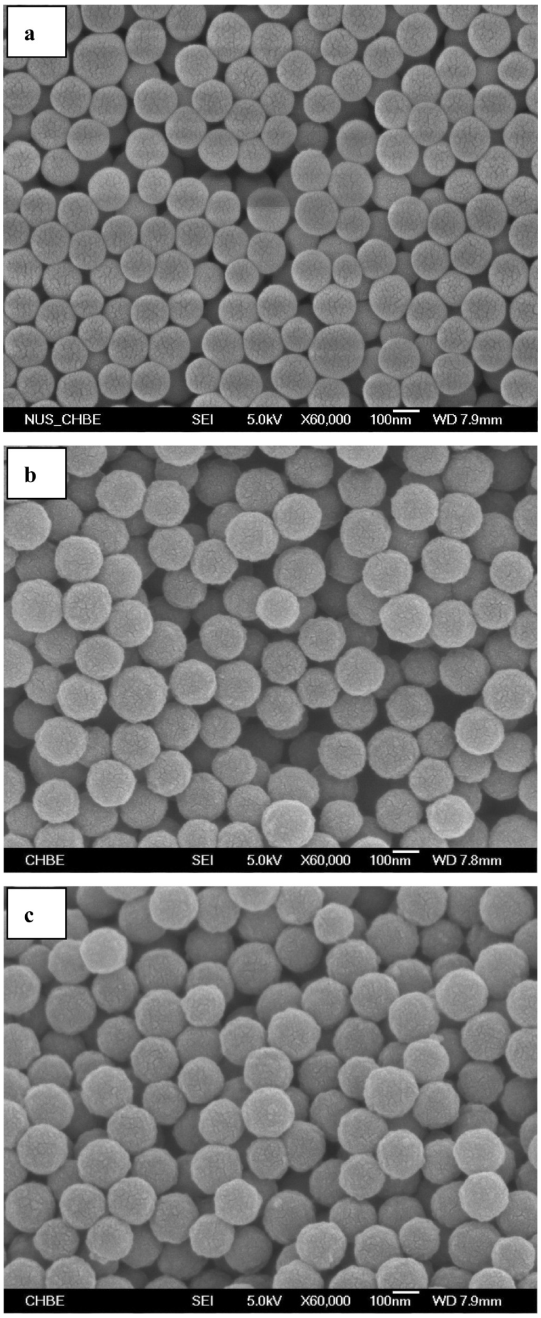


Figure 2. Field-effect scanning electron microscopy (FESEM) micrographs of the (a) SiO_2, (b) SiO_2@P(MAA-*co*-PMA-*co*-DVB), and (c) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, and DVB = divinylbenzene). The scale bars for (a)−(c) are 100 nm.

the mixture prior to sealing the flask under an argon atmosphere. The reaction mixture was stirred in a 60 °C water bath for 24 h. The reaction mixture was cooled, and the core−shell nanospheres were collected by centrifugation. The nanospheres were washed with DMF three times to remove the unreacted PS-N_3 chains. After the final centrifugation, the particles were rinsed with a solution of the sodium salt of EDTA and a water/ethanol (1/1, v/v) mixture (to remove the copper catalyst) to finally obtain the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS nanospheres.

Click-Grafting of Poly(ethylene glycol) Chains on the SiO_2@P(MAA-co-PMA-co-DVB)-click-PS Nanospheres via the Thiol−Ene Click Reaction. About 0.12 g of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS nanospheres and 0.25 g (0.05 mmol) of *O*-[2-(3-mercaptopropionylamino)ethyl]-*O*′-methylpoly(ethylene glycol) (PEG-SH, M_n = 5000 g/mol, Sigma-Aldrich) were introduced into 10 mL of acetonitrile in a reaction flask under vigorous stirring. The reaction mixture was degassed with argon for 15 min. Then, 0.020 g (0.12 mmol) of AIBN initiator was added into the reaction mixture. The flask was sealed under an argon atmosphere, and the reaction was allowed to proceed at 70 °C for 24 h. The resultant SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres were washed three times with ethanol and acetone to remove the unreacted PEG-SH chains. The hairy nanospheres had an average diameter of 184 nm.

Synthesis of the Hairy Hollow Air@P(MAA-co-PMA-co-DVB)-click-PS/PEG Nanospheres. The hollow polymer nanospheres with surface-grafted binary brushes, or air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres, were prepared by HF etching of the inorganic silica core in the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres. Briefly, 0.1 g of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres was stirred in 10 mL of 20% HF at room temperature for 24 h to dissolve the silica core. (*Caution*: HF is hazardous and very corrosive. Goggles and gloves must be worn during the operation.) The excess HF and SiF_4 were removed from hairy hollow nanospheres by dialysis in deionized water for 1 week. Finally, the hairy hollow air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres were freeze-dried.

Characterization. Field-emission scanning electron microscopy (FESEM) images were obtained on a JEOL JSM-6700 SEM. Transmission electron microscopy (TEM) images were obtained on a JEOL JEM-2010 TEM. X-ray photoelectron spectroscopy (XPS) measurements were carried out on a Kratos AXIS Ultra HSA spectrometer equipped with a monochromatized Al Kα X-ray source (1468.6 eV photons). Fourier-transform infrared (FT-IR) spectroscopy analysis was carried out on a Shimadzu 8400 FT-IR spectrophotometer. Dynamic laser scattering (DLS) measurements were performed on a Brookhaven 90 plus laser light scattering spectrometer at a scattering angle of $\theta = 90°$. The hydrodynamic diameter of the nanospheres was obtained by averaging the values from five measurements. The molecular weight and molecular weight distribution of PS-N_3 chains prepared by ATRP were characterized by gel permeation chromatography (GPC). GPC measurements were performed on Waters GPC system, equipped with a Waters 1515 isocratic HPLC pump, a Waters 717 plus Autosampler injector, a Waters 2414 refractive index detector, and a series of three linear Jordi columns (Jordi Gel DVB 1000A, 300 × 7.8 mm, Cat. No. 10512, Serial No. 15072-17, packed with 5 μm PDVB particles), using THF as the eluent at a flow rate of 1.0 mL min^{-1}. The calibration curve was generated using polystyrene standards. Thermogravimetric analysis (TGA) was carried out on a thermogravimetric analyzer (TA Instrument, Model 2050) at a heating rate of 10 °C/min in nitrogen. The polydispersity index, or the size distribution, of the nanoparticles was determined from the following statistical formula:[30]

$$\mathrm{PDI} = D_{\mathrm{w}}/D_{\mathrm{n}}, \quad D_{\mathrm{n}} = \sum_{i=1}^{k} n_i D_i \Big/ \sum_{i=1}^{k} n_i,$$

$$D_{\mathrm{w}} = \sum_{i=1}^{k} n_i D_i^4 \Big/ \sum_{i=1}^{k} n_i D_i^3$$

PDI is the polydispersity index, D_n is the number-average diameter, D_w is the weight-average diameter, and D_i is the particle diameter. The calculation was based on the cumulative diameters of 50−100 nanospheres in an FESEM image. The coefficient of variation (CV = δ/D_n), defined as the ratio of the standard deviation to the mean, was used to estimate the error in nanosphere size of D_n.

The grafting density in number of chain per unit surface area (D_s, chains/nm^2) was calculated, based on a unit weight of the nanospheres, according to the equation of $D_s = WN_a/M_nS$ (W, N_a, M_n, and S are the graft amount, Avogadro's number, molecular weight, and surface area, respectively). The graft amount, W, was obtained from weight loss variations among the SiO_2 nanospheres, the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres, and the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-polymer nanospheres in TGA measurements. The surface area, S, was calculated from the average size and number of nanospheres per unit weight. The latter in turn was estimated from the density of the core−shell nanosphers (taken to be the average density of the silica core and the polymer shell, or 1.7 g cm^{-3}) and the average size of the core−shell nanospheres.

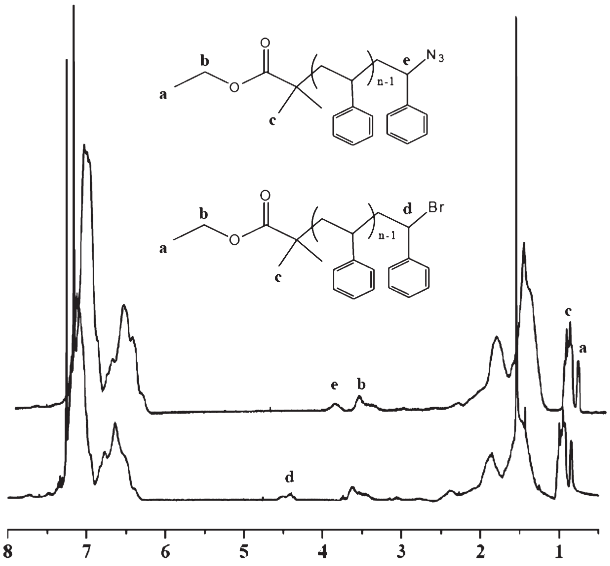


Figure 3. ^{1}H NMR spectra of polystyrene (PS) prepared from atom transfer radical polymerization before and after end-group transformation: (bottom) alkyl halide-terminated PS-Br and (top) azido-terminiated PS-N_3 chains.

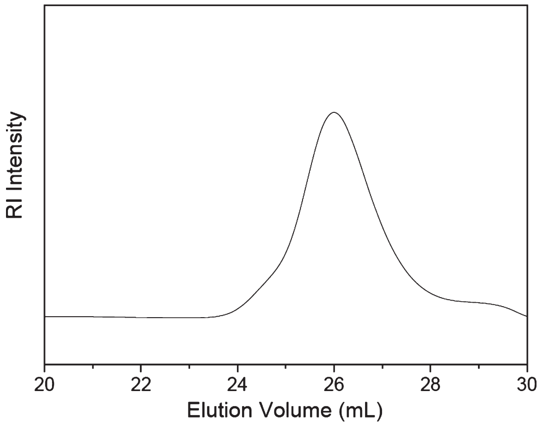


Figure 4. Gel permeation chromatography (GPC) elution curve of azido-terminiated polystyrene (PS-N_3) chains in tetrahydrofuran (THF) at an elution rate of 1.0 mL min^{-1}.

Results and Discussion

Procedures for the covalent attachment of polystyrene/poly(ethylene glycol) (PS/PEG) binary polymer brushes on the

Table 1. Size, Size Distribution, and Shell Thickness of the SiO_2@Polymer Nanospheres

sample[a]	D_n[b] (nm)	D_h[b] (nm)	PDI[b]	shell thickness[c] (nm)	CV[d] (%)
SiO_2	151	165	1.18		9
SiO_2@P(MAA-*co*-PMA-*co*-DVB)	179	204	1.10	15/19	7
SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG	184	212	1.06	17/24	6

[a] MAA = methacrylic acid, PMA = propargyl methacrylate, DVB = divinylbenzene, PS = polystyrene, and PEG = poly(ethylene glycol). [b] D_n is the number-average diameter from field-effect scanning electron microscopy (FESEM) images, D_h is the hydrodynamic diameter in dimethylformamide (DMF) from dynamic light scattering (DLS), and PDI is the polydispersity index. [c] The shell thickness of the SiO_2@polymer nanospheres was measured from the transmission electron microscopy (TEM) images/DLS results. For DLS analysis, a suspension of the nanospheres in DMF at a concentration of 0.5 mg/mL was used. [d] CV is the coefficient of variation or the ratio of the standard deviation to the mean of particle size (CV = δ/D_n).

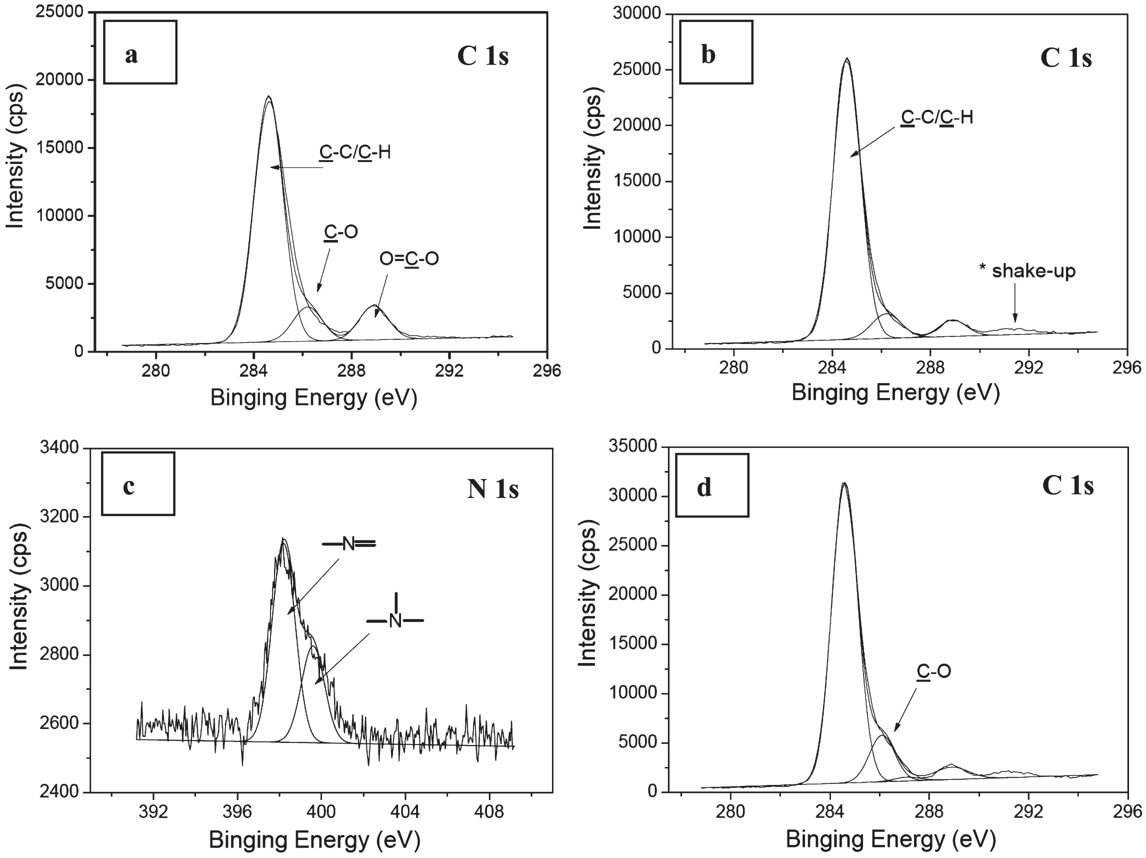


Figure 5. X-ray photoelectron spectroscopy (XPS) analysis of the (a) SiO_2@P(MAA-*co*-PMA-*co*-DVB), (b, c) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS, and (d) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, DVB = divinylbenzene, PS = polystyrene, and PEG = poly(ethylene glycol)).

SiO_2@polymer nanospheres are illustrated in Scheme 1. The SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell hybrid nanospheres with an average diameter of 179 nm were first synthesized using the 151 nm silica nanosphere templates with C=C double bonds on the surface from sol–gel reaction[25,26] of tetraethyl orthosilicate (TEOS) and 3-(trimethoxysilyl)propyl methacrylate (MPS), followed by distillation–precipitation copolymerization of methacrylic acid (MAA), propargyl methacrylate (PMA), and divinylbenzene (DVB) in acetonitrile.[31–33] The as-synthesized SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell nanospheres have functional alkyne groups and residual double bonds on the polymer outer shell, thus providing dual "clickable" functionalities for the respective alkyne–azide and thiol–ene click chemistry.

Figure 1a,b shows the respective TEM images of the silica template core and SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell nanospheres. The TEM image of Figure 1b reveals a polymer shell encapsulating a dense silica core, giving rise to a distinctive core–shell hybrid nanostructure. The corresponding FESEM images are shown in Figure 2a,b. The surface morphology of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell nanospheres in the FESEM image of Figure 2b suggests that the narrowly dispersed nanoparticles with dual clickable surface functionalities retain a well-defined spherical shape after surface-initiated copolymerization from the silica templates. The increase in size of the SiO_2@copolymer core–shell nanospheres from that of the silica nanospheres is readily discernible from the TEM and FESEM images under the same magnification (Figure 1a,b and Figure 2a,b).

Surface modification of substrates with hydrophobic/hydrophilic polymer brushes can be carried out via the "grafting from" or "gafting to" approach.[34–36] Azido-terminated polystyrene ($PS-N_3$) and thiol-termniated poly(ethylene glycol) (PEG-SH) were selected for the respective alkyne–azide and thiol–ene click reactions on the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell nanosphere with dual clickable surface functionalities. The $PS-N_3$ chains were prepared via atom transfer radical polymer (ATRP) of styrene (PS-Br), followed by substitution reaction of terminal bromide with sodium azide in DMF.[28] The resultant azido-terminated PS ($PS-N_3$) chains were characterized by ^1H NMR spectroscopy and gel permeation chromatography (GPC). The conversion of PS-Br chains to $PS-N_3$ chains was confirmed by ^1H NMR spectroscopy in Figure 3. Before the substitution reaction, the chemical shift for the proton next to the terminal bromide atom (d) was at 4.4 ppm. After transformation of the PS-Br to $PS-N_3$ chains, the chemical shift at 4.4 ppm has disappeared. The new chemical shift at 3.8 ppm (e) corresponds to the proton next to the azido groups, suggesting that the $PS-N_3$ chains have been prepared.[29] The GPC analysis results of $PS-N_3$ is shown in Figure 4. The $PS-N_3$ chains have a number-average molecular weight (M_n) of 2550 g/mol and a narrow polydispersity or PDI of 1.15. The PEG-SH polymer chains (M_n = 5000 g/mol) were characterized by FT-IR spectroscopy and X-ray photoelectron spectroscopy, or XPS (Supporting Information, Figures S1 and S2, respectively). The functional –SH groups located at the end of the polymer chains were used for the subsequent thiol–ene click reaction at the surface.

Binary PS/PEG brushes were clicked on the shell surface of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core–shell nanospheres via consecutive alkyne–azide and thiol–ene surface click reactions. The morphology of the resultant SiO_2@polymer hybrid nanospheres with binary polymer brushes (the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres) is revealed by TEM and FESEM images of Figures 1c and 2c, respectively. Nanospheres of well-defined spherical shape are retained after the consecutive alkyne−azide and thiol−ene click reactions of the PS and PEG brushes on the surface of SiO_2@P(MAA-*co*-PMA-*co*-DVB) hybrid core−shell nanospheres. The covalent grafting of PS and PEG chains on the core−shell nanospheres produces a hairy surface, as suggested by the increase in shell thickness and surface roughness of the nanospheres in the TEM image (Figure 1c). The average diameter of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres, as determined from the FESEM and TEM images, increases from 179 nm of that of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres to about 184 nm. The hydrodynamic diameter (D_h) of the as-synthesized hairy core−shell hybrid nanospheres is further determined by dynamic light scattering (DLS), as shown in Table 1. The D_h of the core−shell nanospheres dispersed in DMF increases from 204 to 212 nm upon click grafting of the PS/PEG binary brushes on the surfaces.

XPS was used to identify the changes in chemical composition of the nanospheres with surface-grafted binary polymer brushes. Figure 5 shows the XPS C 1s core-level spectra of the nanospheres before and after surface click grafting of the binary PS/PEG brushes. The C 1s core-level spectrum of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) core−shell nanospheres in Figure 5a can be curve-fitted with three peak components having binding energies (BEs) at about 284.6, 286.2, and 288.9 eV, attributable to the C−C/C−H, C−O, and C═O−O species, respectively.[37] The respective C−O and C═O−O species are associated with the ester groups of PMA and carboxylic acid groups of MAA. The alkyne−azide click reaction of PS-N_3 brushes on the shell surface has caused an increase in the intensity of the C−C/C−H signal in the XPS C 1s core-level spectrum of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS nanospheres (Figure 5b). The appearance of high BE signal at about 291 eV, associated with the $\pi-\pi^*$ shake-up satellite of aromatic rings, is consistent with the presence of surface-grafted PS brushes.[37] The formation of 1,2,3-triazole groups after 1,3-dipolar cycloaddition of PS-N_3 chains on the nanosphere surface is suggested by the XPS N 1s core-level spectrum of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS nanospheres in Figure 5c. The N 1s peak components of the nanospheres at the BE of 398.2 and 399.6 eV and with an area ratio (molar ratio) of 2:1 are associated respectively with the imine (−N=) and amine (−N−) species in the triazole ring.[38] The subsequent thiol−ene click grafting of PEG brushes on the nanosphere has caused an increase in intensity of the C−O signal in the C 1s core-level spectrum of the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres of Figure 5d.

Grafting densities of the respective PS and PEG brushes on the SiO_2@polymer nanospheres were determined from the corresponding weight losses of clicked PS and PEG chains in thermogravimetric analysis (TGA, Figure 6) to be 0.5 and 0.1 chains/nm^2.[39−43] The lower grafting density of PEG chains on the surfaces via the thiol−ene click reaction is probably due to the sterical hindrance from the initially grafted PS-N_3 chains on the nanosphere surface. The grafted PS brushes on the nanosphere surface hinder the subsequent access of PEG-SH chains to the surface reaction sites (residual carbon−carbon double bonds).

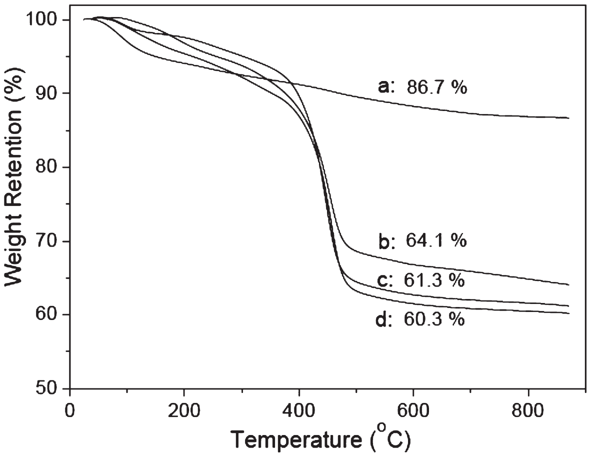


Figure 6. Thermogravimetric analysis (TGA) of the (a) SiO_2, (b) SiO_2@P(MAA-*co*-PMA-*co*-DVB), (c) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS, and (d) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, DVB = divinylbenzene, PS = polystyrene, and PEG = poly(ethylene glycol)).

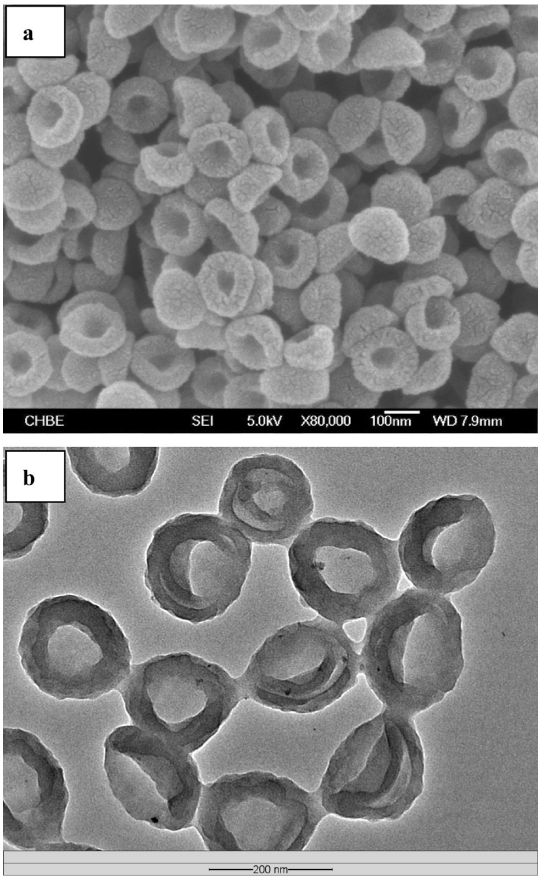
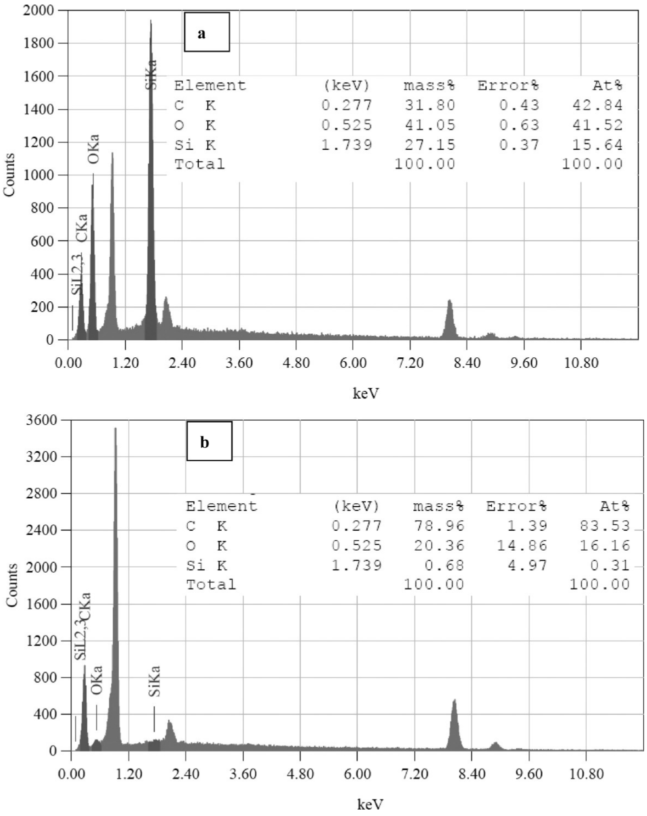


Figure 7. (a) Field-effect scanning electron microscopy (FESEM) and (b) TEM micrographs of the air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy hollow nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, DVB = divinylbenzene, PS = polystyrene, and PEG = poly(ethylene glycol)). The scale bars for (a) and (b) are 100 and 200 nm, respectively.

HF etching of the so-obtained SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy core−shell hybrid nanospheres removes the silica template core and gives rise to the air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy hollow nanospheres with hydrophobic/hydrophilic binary brushes on the shell surfaces. The FESEM and TEM images of the air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy hollow nanospheres are shown in parts a and b of Figure 7, respectively. The biconcave shape of the hollow nanospheres is similar to that of the red blood cells (RBCs) in human beings.[44−46] The TEM image of air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres in Figure 7b suggests that the silica core has been removed, giving rise to the unique hairy hollow structure. The successful removal of the silica core from the SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres is further ascertained by energy-dispersive X-ray (EDX) analysis. In comparison with the EDX



a

Element	(keV)	mass%	Error%	At%
C K	0.277	31.80	0.43	42.84
O K	0.525	41.05	0.63	41.52
Si K	1.739	27.15	0.37	15.64
Total		100.00		100.00

b

Element	(keV)	mass%	Error%	At%
C K	0.277	78.96	1.39	83.53
O K	0.525	20.36	14.86	16.16
Si K	1.739	0.68	4.97	0.31
Total		100.00		100.00

Figure 8. Energy-dispersive X-ray (EDX) analysis spectra of the (a) SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres and (b) air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hollow nanospheres (MAA = methacrylic acid, PMA = propargyl methacrylate, DVB = divinylbenzene, PS = polystyrene, and PEG = poly(ethylene glycol)).

spectrum of the starting SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG nanospheres in Figure 8a, the Si signal in the EDX spectrum of the air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy hollow nanospheres in Figure 8b is barely discernible. Thus, a unique nanostructure of hollow nanospheres with binary brushes on the surfaces have been prepared by combining the conventional sol−gel reaction and distillation−precipitation polymerization with the alkyne−azide and thiol−ene "click" reactions. The unique nanostructure consists of a hollow cavity for drug encapsulation and hydrophilic polymer brushes (PEG chains) on the surface for protein antifouling resistance in drug delivery systems. In addition, the alkyne−azide and thiol−ene click grafting of PS/PEG binary polymer brushes on the particle surface are the "grafting to" approach, in which the nature, such as chain length and functionality, of end-functionalized polymer chains can be precisely controlled prior to the covalent attachment.[34]

Conclusions

Well-defined silica@polymer core−shell hybrid nanospheres and air@polymer hairy hollow nanospheres with surface-grafted binary polymer brushes were prepared from consecutive alkyne−azide and thiol−ene "click" reactions of PS-N_3 and PEG-SH chains on the shell surface of the SiO_2@P(MAA-*co*-PMA-*co*-DVB) hybrid core−shell nanospheres, prepared a priori by conventional sol−gel reaction of TEOS in the presence of MPS and distillation−precipitation copolymerization of MAA, PMA, and DVB. The SiO_2@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG core−shell and air@P(MAA-*co*-PMA-*co*-DVB)-*click*-PS/PEG hairy hollow nanospheres with binary polymer brushes on the surface exhibited unique morphology and functions. The use of dual click reactions to construct solid, hybrid, and hollow nanostructures with multifunctional surface is expected to allow the mimicking of more complex molecules and macromolecular structures in life science as well as for applications in multifunctional and stimuli-responsive delivery systems.

Supporting Information Available: Fourier-transform infrared (FT-IR) spectroscopy and X-ray photoelectron spectroscopy (XPS) analysis of the thiol-terminated poly(ethylene glycol) (PEG-SH). This material is available free of charge via the Internet at http://pubs.acs.org.

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