Triggered Decomposition of Polymeric Nanoparticles

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Received August 3, 2007

ABSTRACT: Acid-catalyzed hydrolysis of 2,5-dimethyl-2,5-hexanediol dimethacrylate (DHDMA)-containing nanoparticles has been carried out to bring about topological reorganization from spherical macromolecular cross-linked particles to linear polymer. The reactive cross-linked poly(methyl methacrylate)-based (x-PMMA) nanoparticles have been prepared via aqueous emulsion techniques where the size of the particles depends upon the type of emulsion polymerization employed, surfactant-free or surfactant-based. Potassium persulfate has been employed as the water-soluble initiator and sodium dodecyl sulfate as the surfactant. Because of the acid-sensitive nature of the tertiary ester groups of the 2,5-dimethyl-2,5-hexanediol dimethacrylate within the cross-linked nanoparticles, they can be easily cleaved into their linear polymer chain composition under acidic conditions. The particles were degraded by heating in dioxane in the presence of *p*-toluenesulfonic acid at 100 °C for 12 h. The cleavage of the cross-linked nanoparticles was observed by the correlation and size distribution plots obtained using dynamic light scattering. The particles and the acid cleaved, linear polymer residue were characterized using scanning electron microscopy (SEM), solubility tests, and gel permeation chromatography.

Introduction

The ability to fabricate reactive macromolecular architectures at the nanometer scale while controlling chemical functionality is of great scientific and technological interest.[1,2] The ability to synthesize and decompose polymeric nanostructures upon exposure to external stimuli has great potential in a number of nanotechnology-related fields including lithography, optics, sensors, ordered colloids, drug delivery systems, cell biology, and biotechnology. Macromolecular design enabling well-controlled and selective decomposition of networks can be applied to more complex multifunctional systems. While there are numerous reports on polymeric nanoparticles (NPs) prepared by micellar assembly of amphiphilic block copolymers or stabilized colloids by emulsion polymerization, a need exists for routes toward stable NPs that can maintain their structural integrity in a variety of environments including polar and nonpolar solvents and under shear conditions. Such particles would enable processing routes that are not currently available to most micellular systems. One approach has been to incorporate cross-links into NPs via surfactant-free emulsion polymerization techniques, enabling the NPs to maintain structural integrity under a variety of conditions.[3,4] For example, cross-linked NPs, unlike micelles, are stable in various solvents and in the dry state, giving the opportunity to characterize and use them for further applications. Jhaveri observed that by adding a small amount of a functionalized methacrylate comonomer containing a dormant atom transfer radical polymerization (ATRP) living free radical initiator group to the solution during the polymerization results in functionalized NPs with ATRP initiator groups available at the particle surface. Subsequent controlled polymerization of the initiator-functionalized particles with various methacrylate and styrene-based monomers yielded nanostructured polymeric particles with core−shell architectures.[4] However, in many applications, it would be desirable to have a method for triggering the decomposition of this cross-linked architecture using external stimuli.

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In this paper we report the synthesis of acid-sensitive cross-linked poly(methyl methacrylate) (x-PMMA) nanoparticles (NPs) prepared via emulsion polymerization and the triggered decomposition of these spherical nanoparticles under acidic conditions to give linear polymer chains. This ability to synthesize monodisperse cross-linked NPs using water-based emulsion polymerization and controllably decompose the cross-linked component within the network using external stimuli represents a significant advance in polymeric NP chemistry.

Methacrylate-based cross-linked polymeric systems have included various acid-labile chemical moieties, such as anhydrides,[5] acetals,[6] and esters.[7] Among the various functionalities, the *tert*-butyl ester group has received significant attention as an effective protecting group due to the labile ester−alkyl bond.[8] Deprotection of the *tert*-butyl group contained in linear polymers has been demonstrated to occur via acid-catalyzed processes, in the presence[9] or absence of water.[10] Tertiary esters present in divinyl cross-linked networks have also been shown to undergo facile cleavage reactions. For example, 2,5-dimethyl-2,5-hexanediol dimethacrylate (DHDMA), an acid labile cross-linking reagent, has been effectively used by researchers to synthesize acid-cleavable polymer networks[7] and cleavable cores for star polymers.[11,12] Poly(2,5-dimethyl-2,5-hexanediol dimethacrylate) (PDHDMA) networks have also attracted attention as positive photoresists in microlithography[13,14] because of the highly acid-labile nature of DHDMA.

The degradation of polymeric nanoparticles for drug, protein, and DNA delivery systems has been an active research area. For example, Frechet et al. have employed the degradation of protein-loaded polymer particles, functionalized with acid-cleavable acetal linkages, as antigen-based vaccines.[15] The same team also demonstrated the release of encapsulated antigens from acid-degradable cationic NPs encapsulating a model antigen (i.e., ovalbumin) which were prepared using acid-cleavable acetal cross-linkers.[16] Ulbrich et al. have studied the degradation of poly(ethylene oxide)-coated polyamide NPs, cross-linked via disulfide linkages, by glutathione.[17] Controlled release from degradable NPs based on functionalized hydroxy-

10.1021/ma071750x CCC: $37.00
Published on Web 10/09/2007

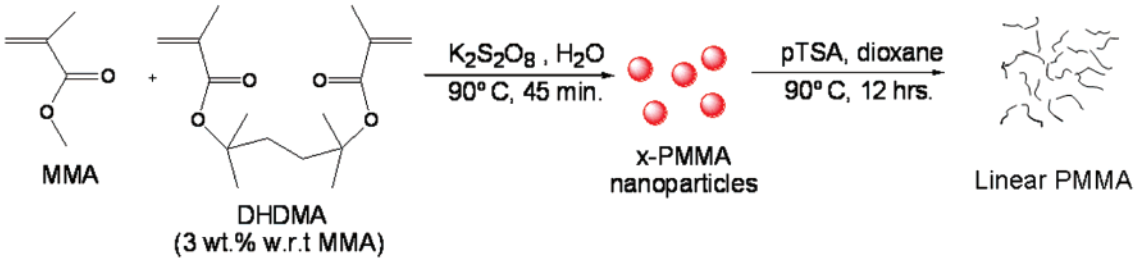

Figure 1. Synthetic strategy of x-PMMA NPs using emulsion polymerization and subsequent cleavage under acidic conditions.

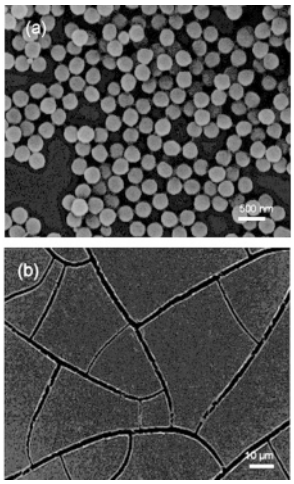

Figure 2. SEM images of (a) NP1 (R_{SEM} = 140 nm) prepared using surfactant-free emulsion polymerization of MMA and (b) soluble, linear PMMA (M_n = 75 300, PDI = 2.92) obtained after acid-catalyzed degradation of NP1.

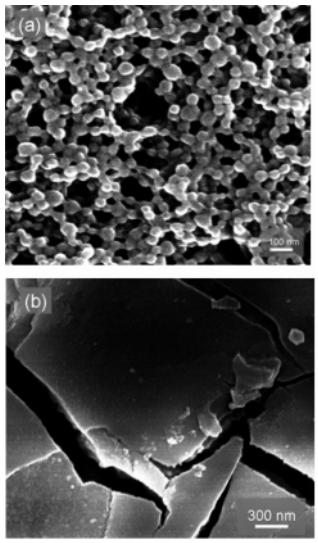

Figure 3. SEM images of (a) NP2 (R_{SEM} = 25 nm) prepared using SDS−hexadecane surfactants and (b) linear PMMA (M_n = 82 500, PDI = 2.72) obtained after degradation of NP2.

propylcellulose with change in pH have been shown by Cai et al.[18]

We have utilized DHDMA to in-situ cross-link colloid nanoparticles during emulsion polymerization to produce cross-linked polymeric NPs. In this report two different types of emulsion polymerization techniques were employed for the synthesis of the nanoparticles: surfactant-free emulsion polymerization and surfactant-assisted emulsion polymerization. Surfactant-free emulsion polymerization of MMA is known to produce uniform micelles, roughly between sizes 250 and 800 nm. The synthesis of smaller particles, specifically in the sub-100 nm range, generally requires the addition of surfactants to form smaller micelles during the polymerization.

Results and Discussion

The synthetic strategy employed in the synthesis of x-PMMA NPs using surfactant-free emulsion polymerization and the subsequent cleavage of the particles under acidic conditions is shown in Figure 1. The polymerization of MMA with the cross-linker DHDMA was carried out in water, using potassium persulfate ($K_2S_2O_8$) as the initiator, yielding nanoparticles, NP1. In order to obtain lightly cross-linked particles the DHDMA content was held at 3 wt % with respect to MMA. The SEM images of NP1 revealed monodisperse spherical particles with a radius R_{SEM} = 145 nm (Figure 2a). The hydrodynamic radius for NP1 obtained using dynamic light scattering was measured to be R_h = 151 nm. While NP1 could be suspended in organic solvents such as THF and dioxane, they did not form stable dispersions, although they formed cloudy dispersions in $CHCl_3$. Decomposition of the nanoparticles was triggered by treatment with *p*-toluenesulfonic acid (*p*-TSA) at 100 °C in dioxane and yielded linear free polymer which was fully soluble in THF, dioxane, and chloroform. The SEM image of the resulting polymer showed no presence of particles and hydrodynamic radius of the polymer obtained using dynamic light scattering dropped to 3 nm, clearly indicating the cleavage of the particles into small linear polymer chains (Figure 2b). The M_n of the cleaved polymer obtained using GPC was observed to be 75 300 g/mol with a PDI = 2.92, which was consistent with the free radical polymerization technique employed. SEM images were taken of the particles NP1 before decomposition and of the cleaved linear polymer after acid-triggered decomposition.

A surfactant-based miniemulsion polymerization of MMA was developed to prepare smaller NPs and our approach was inspired by the reported procedure for preparation of polystyrene micelles. Landfester et al.[19] reported the synthesis of polystyrene micelles in a size range of 30−180 nm by polymerization in miniemulsions where the particle size responds to the amount of the surfactant sodium dodecyl sulfate (SDS) added, between 0.5 and 50 wt % with respect to monomer, and the use of hydrophobes (such as hexadecane) which were critical for the long-term stability of the miniemulsions.[20]

In our miniemulsion preparation of nanoparticles NP2, MMA, and DHDMA were used as the monomers and SDS was used as a surfactant with hexadecane as a cosurfactant/hydrophobe. In these reactions the DHDMA content was held at 5 wt % with respect to MMA. Potassium persulfate was used as the initiator and water as the solvent for the miniemulsion polymerization. The resulting nanoparticles, NP2, were washed several times with water and methanol and centrifuged in order to remove SDS from the polymer particles. The SEM images of NP2 revealed spherical NPs with a radius R_{SEM} = 28 nm (Figure 3a). The hydrodynamic radius for NP2 obtained using dynamic light scattering was observed to be R_h = 30 nm. The size distribution plots for the particles are shown in Figure 4. The

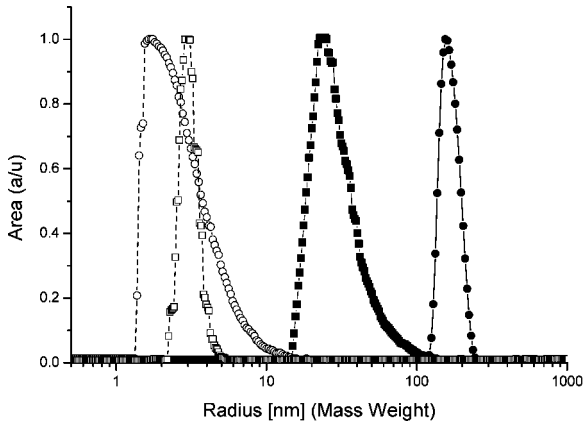

Figure 4. Hydrodynamic radius (R_h) plots obtained using DLS for particles NP1 (R_h = 151 nm) and NP2 (R_h = 30 nm), before (■, ●) and after (□, ○) acid treatment.

smaller particles, NP2, formed very stable, translucent dispersions in various organic solvents (THF, $CHCl_3$, MeOH) as well as water. Like the NP1 samples, treatment of NP2 with *p*-TSA at 100 °C in dioxane yielded linear free polymer which was precipitated by pouring the solution into methanol. The linear polymer obtained was soluble in organic solvents THF, dioxane, and chloroform. Figure 3b shows the SEM images of the cleaved linear polymer obtained after acid treatment on NP2. The SEM image of the resulting polymer showed no presence of particles, and the hydrodynamic radius obtained using dynamic light scattering was 3 nm, clearly indicating the cleavage of the particles (Figure 3). The M_n of the cleaved polymer obtained using GPC was observed to be 82 500 g/mol with a PDI = 2.72.

Conclusions

In conclusion, acid-sensitive cross-linking functionalities have been successfully incorporated within network polymeric NPs using emulsion polymerization processes. The size of the reactive NPs can be controlled by adjusting monomer and initiator concentrations and the addition of surfactants vs surfactant-free emulsion techniques. Facile degradation of the particles triggered by exposure to an organic acid was shown to produce linear polymer. This simple approach for macromolecular design and structure conversion has future potential in nanotechnology, lithography, optics, sensors, colloidal stability, drug delivery systems, cell biology, and biotechnology. Further studies are being conducted toward synthesizing other functionally reactive NP cores.

Experimental Section

Materials. Potassium persulfate, methyl methacrylate (MMA), and hexadecane (99%) were purchased from Sigma-Aldrich. Sodium dodecyl sulfate (electrophoresis grade) and 1,4-dioxane were purchased from Fisher Scientific. Synthesis of 2,5-dimethyl-2,5-hexanediol dimethacrylate, DHDMA, was performed in accordance with literature procedure.[14] Unless otherwise specified, all reagents were used without further purification.

Instruments. Dynamic light scattering experiments were performed at room temperature using an ALV unit equipped with an ALV/SP-125 precision goniometer (ALV-Laser Vertriebsgesellschaft m.b.h.), an Innova 70 argon laser (λ_0 = 514.5 nm, maximum power 3 W, Coherent Inc.) operated at 300 mW, and a photomultiplier detector (Thorn EMI Electron Tubes). Signal from the detector was processed by an ALV 5000 Multiple Tau Digital Correlator board and associated software. The samples for DLS were prepared by making a 2 mg/mL solution/dispersion of the particles in $CHCl_3$. Gel permeation chromatography (GPC) was performed in tetrahydrofuran (THF) at room temperature with 1.0 mL/min elution rate. A Waters R403 differential refractometer and three PLgel columns (105, 104, and 103 Å) calibrated with narrow molecular weight poly(methyl methacrylate) standards were used.

An FE-SEM JEOL 6320FXV was used to take the SEM images. Samples were dispersed in methanol and solution drop-cast onto a copper substrate. A thin layer of gold (~5 nm thick) was sputtered onto the sample to prevent charging of the polymer by the electron beam.

Synthesis of NP1 via Surfactant-Free Emulsion Polymerization. $K_2S_2O_8$ (50 mg, 0.185 mmol) was added to 25 mL of water in a 100 mL round-bottom flask equipped with a magnetic stir bar. The flask was charged with MMA (1.75 g, 17.48 mmol) and DHDMA (53 mg, 0.188 mmol, 3 wt % wrt MMA). The mixture was sparged with nitrogen for 10 min and then heated at 90 °C for 45 min with stirring under nitrogen. The resulting turbid solution was cooled and precipitated dropwise into 500 mL of methanol. 50 mL of brine was added to break the emulsion, and the particles were separated by filtration. The polymer particles were washed with water, methanol, and acetone and dried to obtain 1.68 mg (96%) of DHDMA cross-linked PMMA nanoparticles, NP1.

Synthesis of NP2 via Surfactant-Based Emulsion Polymerization. MMA (3 g, 29.97 mmol), DHDM (150 mg, 0.531 mmol, 5 wt % wrt MMA) and hexadecane (140 mg, 0.618 mmol) were mixed and added to a solution of SDS (45 mg, 0.156 mmol) in 12 mL of water in a 25 mL round-bottom flask equipped with a stir bar. The solution was sparged with nitrogen for 10 min and allowed to stir for 2 h. The miniemulsion was prepared by ultrasonicating the emulsion for 5 min. For polymerization, the reaction flask was put in an oil bath set at 75 °C, and after 2 min potassium persulfate (60 mg, 0.222 mmol) was added. The reaction was heated for 2 h under nitrogen and then cooled to room temperature. The reaction solution was added to methanol (100 mL) and centrifuged to separate the precipitate. The precipitate was washed and centrifuged three times with water to remove SDS. The viscous particulate solution was dried under vacuum to obtain DHDMA cross-linked PMMA nanoparticles, NP2 (2.98 g, 99%), as a white powder.

Degradation of NPs Using *p*-TSA. The particles (NP1) (75 mg) were dissolved/dispersed in dioxane (2 mL) in a test tube. *p*-TSA (15 mg, 0.087 mmol) was added, and the test tube was sealed under nitrogen. The solution was heated at 100 °C for 12 h. The solution was cooled, precipitated in methanol, and filtered to obtain linear PMMA (70 mg, 93%) as a white powder. NP2 particles were degraded under similar conditions as NP1.

Acknowledgment. The authors gratefully acknowledge support from NSF Materials Research Science and Engineering Center (DMR 0213695) at the University of Massachusetts—Amherst. We thank John Harner and Professor David Hoagland for DLS assistance and Lou Raboin for assistance on FESEM. The authors also thank the 3M Corporation for generous support through a nontenured faculty award.

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MA071750X