

Hydrogen-Bonding Induced Alternating Thin Films of Dendrimer and Block Copolymer Micelle

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Abstract. The hydrogen-bonding induced alternating multilayer thin films of dendrimers and block copolymer micelles were demonstrated. The block copolymer micelles derived from amphiphilic poly(2-ethyl-2-oxazoline)-*block*-poly(ϵ -caprolactone) (PEtOz-PCL) in aqueous phase have a core-shell structure with a mean hydrodynamic diameter of 26 nm. The hydrogen bonding between the PEtOz outer shell of micelle and the carboxyl unit of poly(amidoamine) dendrimer of generation 4.5 (PAMAM-4.5G) at pH 3 was utilized as a driving force for the layer-by-layer alternating deposition. The multilayer thin film was fabricated on the poly(methyl methacrylate) (PMMA) thin film spin-coated on silicon wafer or glass substrate by the alternate dipping of PEtOz-PCL micelles and PAMAM dendrimers in aqueous solution at pH 3. The formation of multilayer thin film was characterized by using ellipsometry, UV-vis spectroscopy, and atomic force microscopy. The PEtOz outer shell of PEtOz-PCL micelle provided the pH-responsive hydrogen bonding sites with peripheral carboxylic acids of PAMAM dendrimer. The multilayer thin film was reversibly removed after dipping in aqueous solution at pH ≥ 5.6 due to dissociation of the hydrogen bonding between PEtOz shell of PEtOz-PCL micelle and peripheral carboxyl units of PAMAM dendrimer.

Keywords: micelle, dendrimer, thin film, hydrogen bond.

Introduction

Recently, the research efforts on layer-by-layer (LBL) assembly techniques have been of great interest due to their unique characteristics and technological significance.¹⁻³ Well-organized layer systems of nanostructures through LBL deposition techniques could be useful not only for photonic, optical, and electronic devices, but also for a drug delivery formulation.⁴⁻⁹ Moreover, the integration of stimuli-responsive properties into LBL system takes an advantage in the development of smart nanodevices with functional specificity. The multilayer thin film system combined with storage capability and stimuli-responsive characteristics would open a possibility for the construction of multilayer thin film for time-scheduled and multiagent delivery.^{10,11}

The supramolecular architectures based on block copolymers have been used in numerous scientific fields due to their stability and functionality.¹² Dendrimers are interesting nanomaterial due to unique characteristics such as well-defined globular shape, monodisperse molecular weight, and tailorable surface functionalities.¹³⁻¹⁶ Therefore, the utilization of nanocarriers such as polymeric micelles and den-

drimers as building blocks for thin film fabrication has been of great interest due to potential application for nanodevice applications.¹⁷⁻²⁷ Recently, we have reported on a block copolymer micelle system based on poly(2-ethyl-2-oxazoline) (PEtOz) as a hydrophilic block and poly(ϵ -caprolactone) (PCL) as a hydrophobic block.²⁸⁻³² The PEtOz-PCL micelle with a narrow size distribution was highly stable in aqueous conditions without any precipitation for several months and could be used as an efficient nanocarrier for delivery of hydrophobic anti-cancer drug, paclitaxel.³² In addition, we showed that PEtOz-PCL block copolymer micelle can undergo reversible complexation with multifunctional carboxylic acids in aqueous phase via pH-responsive hydrogen bonding.²⁸⁻³¹ The PEtOz outer shell of the micelle undergoes pH-responsive hydrogen bonding with poly(acrylic acid) or poly(methacrylic acid) in acidic aqueous solution. These complexes could be reversibly dispersed as micelles in basic aqueous solution due to breakage of hydrogen bonding between the PEtOz outer shell and the carboxyl group of poly(carboxylic acid)s.

In this work, we report on the construction of novel multilayer thin film with stimuli-responsive characteristics and storage capability by alternate deposition of PEtOz-PCL micelle and poly(amidoamine) (PAMAM) dendrimer

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with peripheral carboxyl groups. We demonstrated that the pH-responsive hydrogen bonding motif between the PEtOz outer shell of PEtOz-PCL micelle and the surface carboxyl group of PAMAM dendrimer can be effectively utilized for the construction of multilayer thin film via interlayer hydrogen bonding in an appropriate pH condition. In addition, these building blocks can be reversibly released from the multilayer thin film in a basic pH condition. This work would provide an efficient method for the fabrication of thin films with micelles and dendrimers which are unique nanocontainers.

Experimental

Materials. PAMAM dendrimer with peripheral carboxyl groups (Generation 4.5, $M_w = 26,258$, PAMAM-4.5), poly (methyl methacrylate) (PMMA, $M_w = 75,000$) and disperse red 1 were purchased from Aldrich and used without further purification. Tetrahydrofuran (THF) was used after distillation under sodium and benzophenone. The PMMA coated substrate was prepared by spin coating (at $\sim 2,200$ rpm) pre-cleaned silicon wafer (MEMC Electronic Materials, Inc.) or glass slide with a solution of PMMA (0.3 wt%) in toluene. The roughness of the PMMA surface observed by atomic force microscopy (AFM) was about 1 nm.

Preparation of Micellar Solution. To prepare micellar solutions, triply distilled water (10 mL) was added dropwise to a THF solution of PEtOz-PCL block copolymer. Then, THF was evaporated at 30 °C under reduced pressure. The concentration of the micellar solution was 0.5 g/L. For the preparation of dye-loaded micelle, disperse red 1 (1.0×10^{-3} g/L) was added into a THF solution of PEtOz-PCL block copolymer (0.1 g/L) and then THF was evaporated at 30 °C under reduced pressure. The micellar characterization was performed by using transmission electron microscope (TEM) and dynamic light scattering (DLS) techniques.³⁰

Preparation of Thin Films. The thin films were fabricated by alternate dipping of a PMMA coated substrate into the aqueous solutions of PEtOz-PCL micelle and PAMAM-4.5 at pH 3 for 12 h.

Atomic Force Microscopy. The AFM images were recorded under ambient condition using a tapping mode of a multimode imaging unit, SPA-400 (Seiko Instruments Inc., Japan) equipped with a controller, SPI 4000 (Seiko Instruments Inc., Japan). The AFM image was obtained with a thin film on PMMA-Si wafer substrate.

Ellipsometry. Ellipsometric measurement were performed on a Plasmon ellipsometer ($\lambda = 632.8$ nm) (Plas Mos SD 2302).

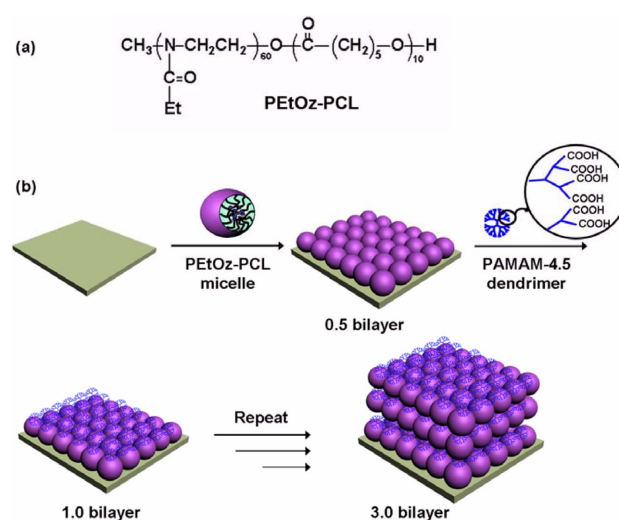
Ultraviolet-visible Spectroscopy. Ultraviolet-visible (UV/vis) spectra were obtained with a Hewlett-Packard 8452A spectrophotometer. The absorption spectra of the thin film with dye-encapsulated micelles were obtained with a PMMA-glass slide substrate.

Results and Discussion

For the construction of stimuli-responsive thin films with alternating multilayer of polymer micelle and dendrimer, PEtOz-PCL block copolymer and PAMAM-4.5 with peripheral carboxyl groups were selected as building blocks. The synthesis and micellar characterization of the PEtOz-PCL block copolymer in Scheme I were carried out by following reference procedures.²⁸⁻³² The M_n value of the block copolymer was 8,200 ($M_w/M_n = 1.17$), and the mean hydrodynamic diameter of the block copolymer micelles in aqueous solution, measured by DLS experiment was 26 nm (polydispersity factor, $\mu_2/\Gamma^2 = 0.12$) at 25 °C. For the dendritic building block, the PAMAM-4.5 with carboxyl surface was used to utilize the pH-responsive hydrogen bonding between the PEtOz shell of micelle and the carboxyl surface of the dendrimer.

The multilayer thin film was fabricated by alternate dipping of the PMMA coated substrate into the aqueous solution of PEtOz-PCL micelle and PAMAM-4.5 at pH 3 (Scheme I). The formation of multilayer thin film could be achieved by the motif of hydrogen bonding between PEtOz outer shell of PEtOz-PCL micelle and the carboxyl surface of PAMAM-4.5.

The thin film was characterized by ellipsometry, UV-vis spectroscopy, and atomic force microscopy (AFM). To verify the integration of polymeric micelle with guest molecules into LBL thin film, a hydrophobic dye, disperse red 1, was encapsulated into a hydrophobic core of PEtOz-PCL micelle. The adsorption kinetics of the micelle for the formation of the thin film was investigated by using UV-vis absorption spectra for the thin film of the dye encapsulated PEtOz-PCL micelle. As shown in Figure 1(a), the adsorption of micelles onto the substrate was increased over time. Under the



Scheme I. (a) PEtOz-PCL block copolymer and (b) schematic description for the construction of the multilayer thin film of PEtOz-PCL micelle and PAMAM dendrimer.

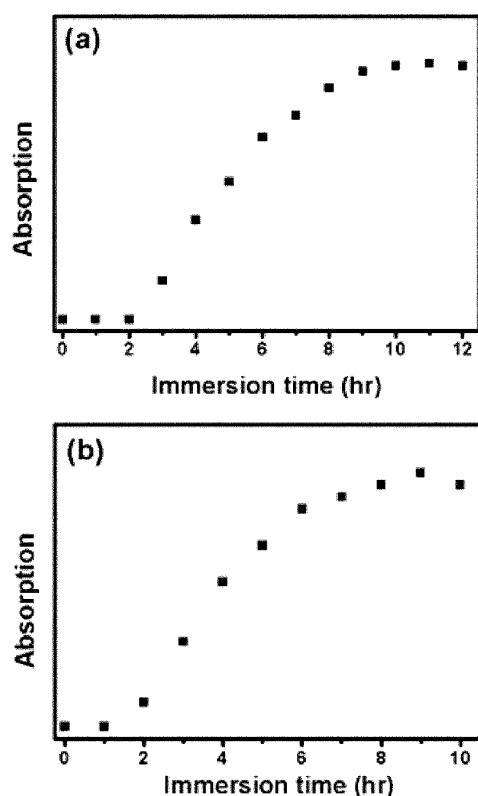


Figure 1. UV-vis absorbance at 512 nm as a function of immersion time for deposition of (a) the first PETOz-PCL micelle layer (0.5 bilayer) and (b) the second PETOz-PCL micelle layer on 1.0 bilayer thin film of PETOz-PCL micelle and PAMAM-4.5 (1.5 bilayer).

condition of dipping solution at pH 3, the deposition of a dye-loaded micelle layer became saturated within 9 h. After completion of deposition of the first micelle layer (0.5 bilayer), the thin film was dipped into the PAMAM-4.5 solution at pH 3 to produce 1.0 bilayer. Then, the micelle-dendrimer thin film was again dipped into the PETOz-PCL micellar solution to yield 1.5 bilayer. The adsorption result of the second micellar layer onto the 1.0 bilayer film of PETOz-PCL micelle and PAMAM-4.5 is shown in Figure 1(b), which is similar to that of the formation of the first micellar layer. However, alternate dipping into two different micellar solutions did not increase the film thickness, which indicates that PAMAM-4.5 takes a role of mortar to construct a micelle-dendrimer thin film.

Figure 2(a) shows a plot of UV-vis absorption spectra for the thin films with the dye encapsulated PETOz-PCL micelle and PAMAM-4.5. The absorbance of multilayer thin films at 512 nm was linearly increased with increasing the number of micellar layers. As shown in Figure 2(b), the ellipsometric thickness of the micelle-dendrimer multilayer film was proportionally increased upto 6 bilayers with a 12 nm-thickness increase every bilayer, which indicates that the alternating thin film of PETOz-PCL micelle and PAMAM-

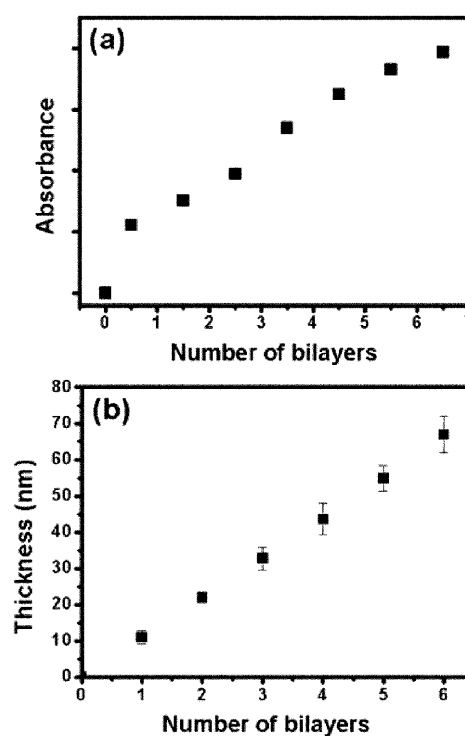


Figure 2. (a) Absorbance at 512 nm depending on the number of bilayers of the thin film and (b) ellipsometric thickness depending on the number of bilayers.

4.5 was formed in each deposition cycle.

To investigate the process of thin film formation, the surface morphology of the thin film was monitored by using AFM after the alternate dipping of the substrate into the solution of PETOz-PCL micelle and PAMAM-4.5 at pH 3 (Figure 3). After first deposition of the PETOz-PCL micelle onto the substrate, the AFM image in Figure 3(b) showed the micelles densely packed on the substrate. After deposition of PAMAM-4.5 on the PETOz-PCL micelle layer in aqueous solution at pH 3, the first PETOz-PCL micelle/PAMAM-4.5 bilayer exhibited fairly smooth surface possibly because the small PAMAM-4.5 blocks (50 Å) would be packed on the surface of micelle layer to smooth the surface roughness (Figure 3(c)). The subsequent micellar deposition produced second micellar layer as shown in Figure 3(d). Repeatedly, the PETOz-PCL micelle and PAMAM-4.5 were adsorbed under the same condition.

The hydrogen bond between PETOz shell of PETOz-PCL micelle and the carboxyl group of PAMAM-4.5 in an acidic condition provided a motif for an alternating thin film structure. In addition, the hydrogen bonded complex could be reversibly dissociated in basic conditions. The pH-responsive dissociation behavior of the micelle and dendrimer from the multilayer thin film was investigated by monitoring the release kinetics of dye-loaded (disperse red 1) micelles from the multilayer thin film by using UV-vis spec-

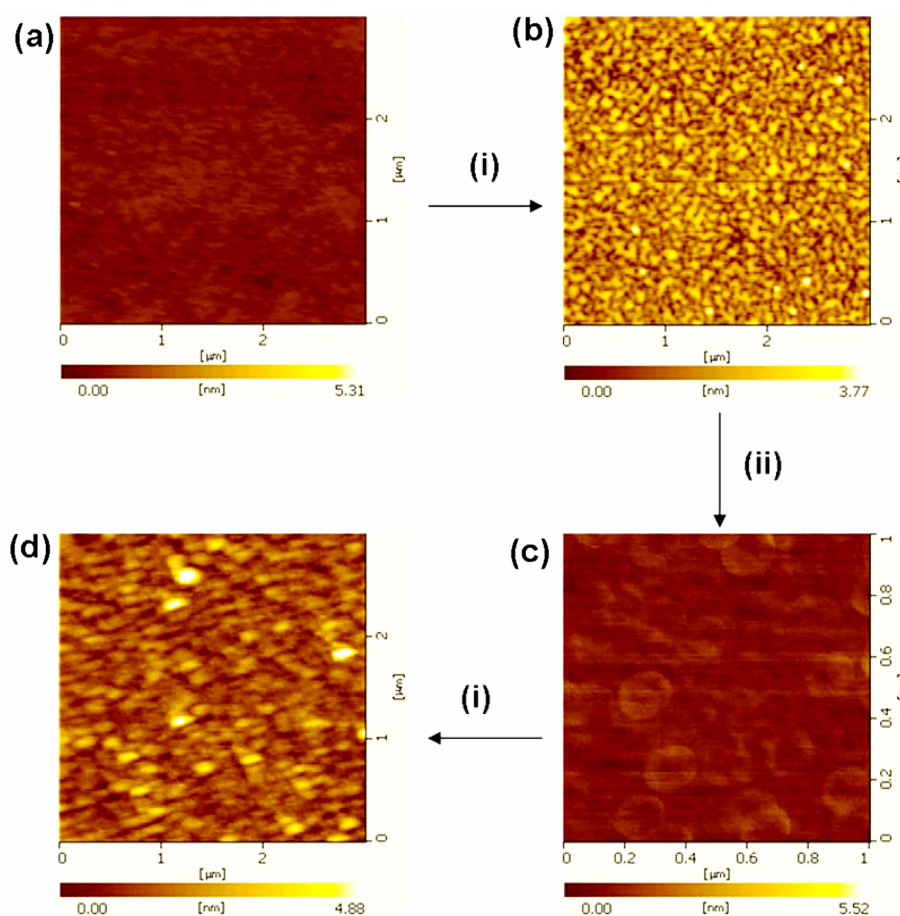


Figure 3. AFM images of (a) the surface of PMMA coated Si-wafer, (b) first PETOz-PCL micelle layer (0.5 bilayer), (c) first PAMAM dendrimer layer (1.0 bilayer), and (d) second PETOz-PCL micelle layer (1.5 bilayer). (i) Dipping into PETOz-PCL micelle solution at pH 3 for 12 h and (ii) Dipping into PAMAM dendrimer solution at pH 3 for 12 h.

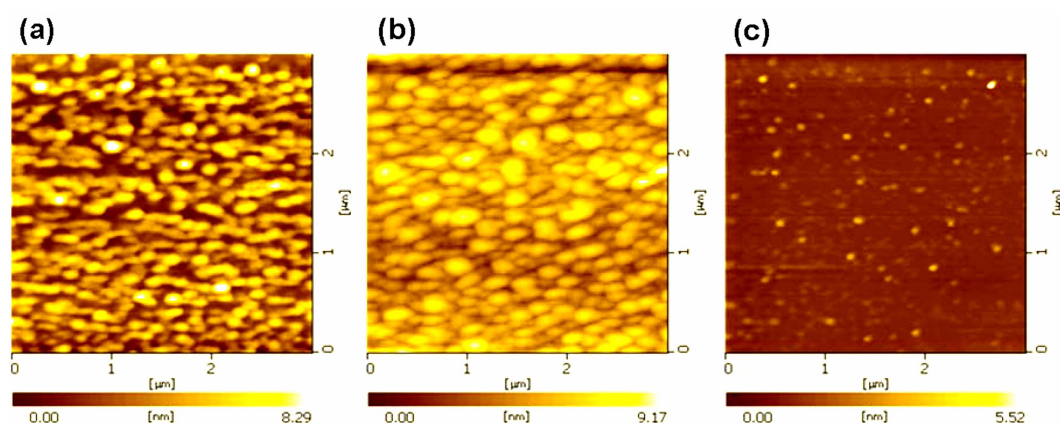


Figure 4. AFM images of (a) 6.5 bilayer thin film, (b) 6.5 bilayer thin film after immersion in aqueous solution at pH 3, and (c) pH 5.6 for 10 min, respectively.

troscopy and AFM. For this purpose, the thin film with 6.5 bilayers was immersed in aqueous solutions at different pH, then the thickness and the surface morphology were characterized. After dipping the thin film in an aqueous solution at pH 3, we observed a similar surface topology of the multi-

layer thin film. The AFM image in Figure 4 shows the densely packed micelles on the surface. However, at $\text{pH} \geq 5.6$, the thin film with 6.5 bilayers gradually degraded with increasing immersion time. Figure 5 shows the release kinetics of the dye-loaded micelle from the film at pH 5.6. Most of

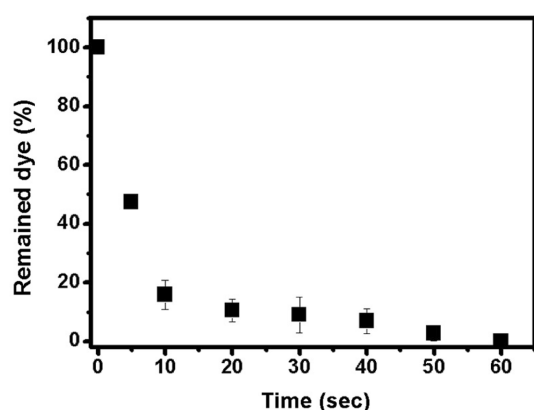


Figure 5. Release profile of dye-loaded PEOz-PCL micelle from 6.5 bilayer thin film after dipping in aqueous solution at pH 5.6.

micelles were released from the film within 1 min after immersion. The AFM image in Figure 4(c) also shows that the 6.5 bilayer film was degraded after dipping in aqueous solution at pH 5.6. This result indicates that the PEOz-PCL micelle and PAMAM-4.5 were reversibly released from the multilayer thin film by dissociation of hydrogen bonding between PEOz shell of the micelle and the surface carboxyl groups of PAMAM-4.5.

Conclusions

We have prepared pH-responsive multilayer thin films consisting of PEOz-PCL micelles and PAMAM dendrimers. The multilayer thin film could be efficiently fabricated by dipping the substrate alternately into the PEOz-PCL micelle and PAMAM-4.5 solutions at pH 3. The PEOz outer shell of the micelle provided a pH-responsive hydrogen bonding motif with the surface carboxyl groups of PAMAM-4.5. The reversible complexation characteristics of PEOz-PCL micelles and PAMAM-4.5 provided an efficient route not only to the fabrication of LBL thin film and but also to controlled release of the building blocks in different pH conditions. The multilayer thin film based on the alternate block copolymer micelles and dendrimers could offer a facile approach for unique thin film devices due to the nano-encapsulation and pH-responsive characteristics of the building blocks.

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