Light-controlled drug releasing polymer films combining LbL self-assembly and host-guest interactions

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Abstract. By combining LbL (layer-by-layer) self-assembly approach and host-guest interactions, a unique multilayer film was constructed and employed for a light-controlled drug release system. The drug molecules can be loaded and released into the resulting polyelectrolyte multilayers containing azobenzene (Azo) function groups by using the irradiation of visible light and UV light alternately. The photo-sensitivity of the multilayer films was studied through UV-vis spectrum, fluorescence spectrum and confocal microscopy. The target molecules could be rapidly released from the multilayers after 300 W UV light irradiation for 20 minutes. Moreover, they could be readsorbed into the multilayers uniformly when illuminated under the 300 W visible light for 10 minutes confirmed by the observation of confocal microscopy, and the readsorption ratio exceeds 100% evidenced from UV–vis spectroscopy. After several cycles of the above-mentioned process, the multilayer films show good fatigue resistance. All these results indicate the photo-sensitivity and high-efficiency of the multilayer films, which have great potential in controlled drug delivery platform and biomedical applications.

Keywords: coatings, layer-by-layer, host-guest interactions, light response, drug delivery

1. Introduction

In the past decade, supramolecular chemistry has attracted more and more attention and gradually penetrated into various areas of material and biomedical science [1–3]. The supramolecular system based on host-guest interactions have seen a significant breakthrough, which was shown to be partially successful for drug release [4], biological sensors [5], optically controlled catalytic system [6], molecular shuttles [7], hydrogels [8], and micelles and vesicles [9]. Particularly, photo-controlled molecular recognition of cyclodextrin (CD) with Azobenzenes (Azo) has been widely used for host-guest inclusion compound. Cyclodextrin, a typical host molecule, is a kind of polysaccharides with good

biocompatibility and water-solubility. As one of the most widely used guest molecule to cyclodextrin, Azo constitute a class of light-responsive compounds that can undergo *trans-cis* photoisomerization in response to UV and visible (Vis) light [10, 11]. It is well-known that the apolar and rodlike *trans*-Azo can form a stable inclusion complex with CD, while the bent and polar *cis*-Azo cannot. This process is fully reversible under irradiation with UV and Vis light alternately. Reports about the reversible and photo-responsive supramolecular system have come to the fore [6, 12–14]. For example, Zou *et al.* [15] first put forward supramolecular type amphiphilic molecule concept and prepared a series of rotaxane-like supramolecular amphiphiles. Alter-

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nating irradiation with UV and Vis light allows for reversible sliding of α-CD along the surfactant, leading to the formation of rotaxane-like vesicles. Based on this principle, light-responsive host–guest assembly and disassembly between Azo and CD hold great potential to design a reversible drug delivery profile [16, 17].

Layer-by-layer (LbL) self-assembly approach is particularly well-suited for fabricating functional multilayer thin films with ultrafine nanometer-scale structure for use as drug delivery vehicles [18–21]. The traditional means of loading drugs on layers of LbL platform always uses physical adsorption or chemical bonding. However, these methods of loading drugs have a common drawback: drug loading and release is irreversible. This is a critical problem in LbL multilayers for drug delivery. Therefore, it's desired to devise a reversible LbL-based system to manipulate the drug release in a more controllable manner. In the past decade, the pioneering work on LbL assembly with supramolecular interaction has been established by Ikeda *et al.* [22]. Subsequently, Smith *et al.* [23] have reported that loading small-molecule drugs on the layers of LbL-based system using supramolecular interaction. On another front, the light-induced drug release from a LbL-based system is the most elegant way to combine reversibly and efficiency, because light as an attractive stimulus can be applied rapidly, remotely, and locally [24, 25]. While numerous well-established photoresponsive LbL-based systems are available [26, 27], their applications in drug release based on polyelectrolyte multilayers or coatings is scarce and little progress.

Thus, all mentioned above inspires us to develop a reversible light-controlled drug releasing thin film by combining polyelectrolyte LbL technique and host-guest interactions, which is capable of addressing the demand for small-molecule delivery with highly controlled release kinetics. Our basic approach is to conjugate drugs with α-CD through chemical bonding due to the availability of functional groups on their surface. Meanwhile, by introducing the Azo to the layers of LbL system, multiple drugs or functional groups can be loaded into the Azo polymers directly and mildly *via* host-guest interactions. Thus, α-CD–drug complexes will be released and loading from the polyelectrolyte multilayers under alternating irradiation with UV and Vis light. Moreover, the usefulness of cyclodextrin conjugated with drugs offers a simple method to increase drugs solubility, bioavailability, stability. Herein, α-CD modified rhodamine B (α-CD-RhB) was selected as a drug model. We believe that the ability of α-CD to complex with multiple drugs gives these LbL films available versatility to many traditional drug delivery systems [28].

Previously, we have demonstrated that an intelligent 'PnP' (Plug and play) polyanionic template driven by the photo-switchable host-guest interactions was first prepared for the light controlled loading/unloading of small molecule drugs. We have shown that the antineoplastic drug and other functional moieties such as target ligand can be simultaneously released and loaded into the template by using UV and Vis light irradiation alternately [29]. Herein, we describe polyelectrolyte LbL multilayers based on Poly(diallydimethylammonium chloride) (PDAC) and azo-modified polyacrylic acid (PAA-C_6-Azo) loaded α-CD-RhB *via* host-guest interactions as a drug carrier that can reversibly capture and release small drugs. From the investigation, α-CD-RhB could be rapidly released from the multilayers after 300 W UV light (365 nm) irradiation for 20 minutes and they could be adsorbed into the substrate uniformly when illuminated under 300 W Vis lamp (455 nm) for 10 minutes. Moreover, a 'forever'-pattern was presented onto this LbL film surface *via* area-selective release and the obtained results may be of great potential for applications in biomedical device based on well-defined nano-sized materials surface of arbitrary topography. Light-responsivity of the host-guest interactions based on Azo and α-CD-RhB and schematic illustration of α-CD-RhB-loading polyelectrolyte multilayers are illustrated in Figure 1. Multilayers are denoted as (PAA-C_6-Azo/PDAC)n where *n* is the number of deposited bilayers.

2. Experimental details
2.1. Materials and characterization
Acryloyl chloride (AC), rhodamine B (RhB) and 3-aminopropyltriethoxysilane (APTES), PDAC (poly (diallydimethylammonium chloride) solution, M_v = 20 000–35 000, 20%) were obtained from Shanghai Aladin Co., Ltd. (China) and used directly. N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC.HCl, 98.5%), 1-azobiscyclo-hexanecarbonitrile (ABCN), N,N′-dimethylformamide (DMF), 1,4-dioxane and dimethyl sulfoxide (DMSO)
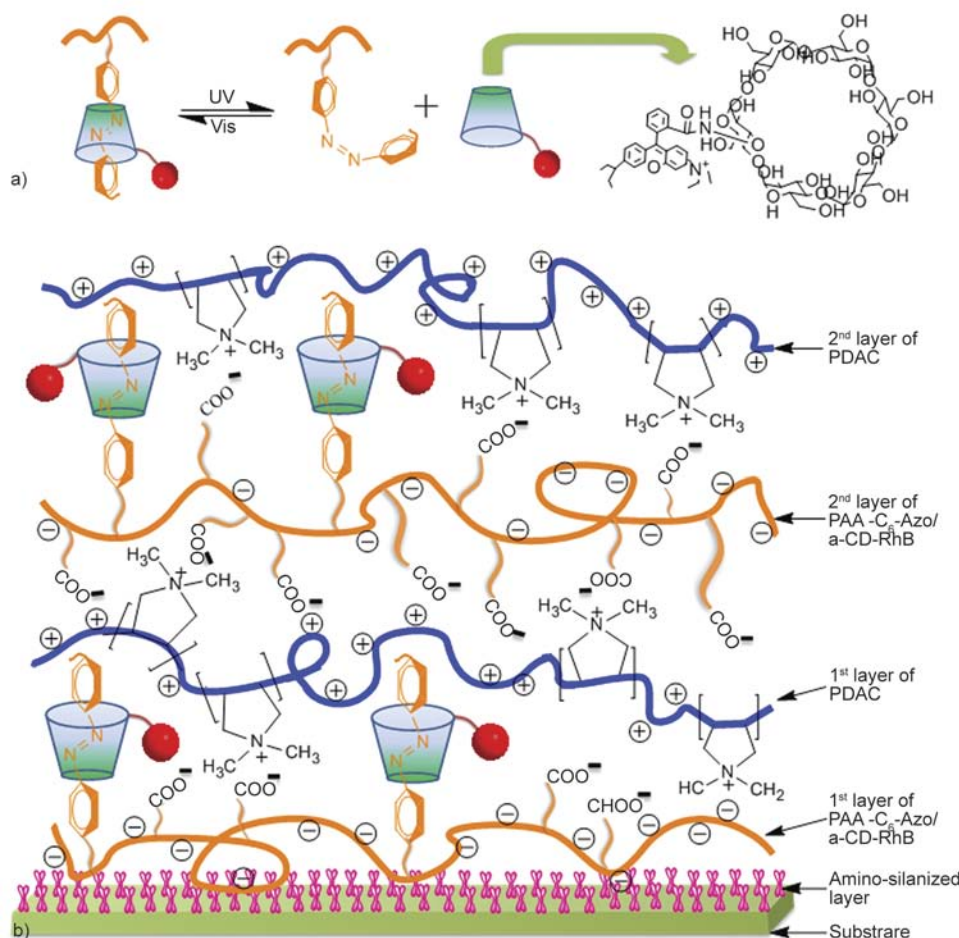
Figure 1. (a) Photoresponse of the host-guest system of Azo group and α-CD-RhB. (b) Schmatic representation of polyelectrolyte multilayers loaded with α-CD-RhB.

were purchased from Aldrich. DMF was azeotropically distilled with benzene for dehydration and then distilled under vacuum. DMSO and 1,4-dioxane were previously dried with molecular sieves. ABCN was recrystallized from methanol before use. All other chemicals were used without further purification. All absorption and fluorescence measurements were performed on solutions in 1 cm² quartz cuvettes. Absorption spectra were measured on a Shimadzu UV-2550 spectrometer. Fluorescence spectra were measured on a Photon Technologies International LS-55 luminescence spectrometer. Solutions were made into 1 mg/mL aqueous. The fluorescence images of multilayer films before and after UV light irradiation were viewed using confocal laser scanning microscopy with BD Laser at 543 nm.

2.2. Preparation of poly (acryloyl chloride) (PAC)

PAC was synthesized according to the literature [30]. Briefly, Acryloyl chloride (20 mL), dry 1,4-

dioxane (20 mL), and ABCN (0.668 g) were added into a flask under N_2 protection. The flask was sealed and then heated in an oil bath (50°C) for 14 h. The polymer was precipitated by adding petroleum ether (100 mL), collected by filtration, and washed twice with petroleum ether. The product was dried at 60°C under vacuum for 48 h.

2.3. Preparation of PAA-C₆-Azo

PAA-C₆-Azo was prepared as described elsewhere [31, 32]. PAC (0.3 g, 0.0033 mol), triethylamine (0.56 mL, 0.0040 mol), and 2-[4-(4-ethoxyphenylazo) phenoxy] ethanol (whose amount was determined by the required degree of functionalization) were dissolved in anhydrous DMF (33 mL). The mixture was stirred at room temperature for 12 h under N_2 protection. Then suitable amount of water was added into the mixture and stirred for 10 min. The product was precipitated from HCl water solution (0.01 mol/L), collected by filtration, washed several times with water, and dried under vacuum.
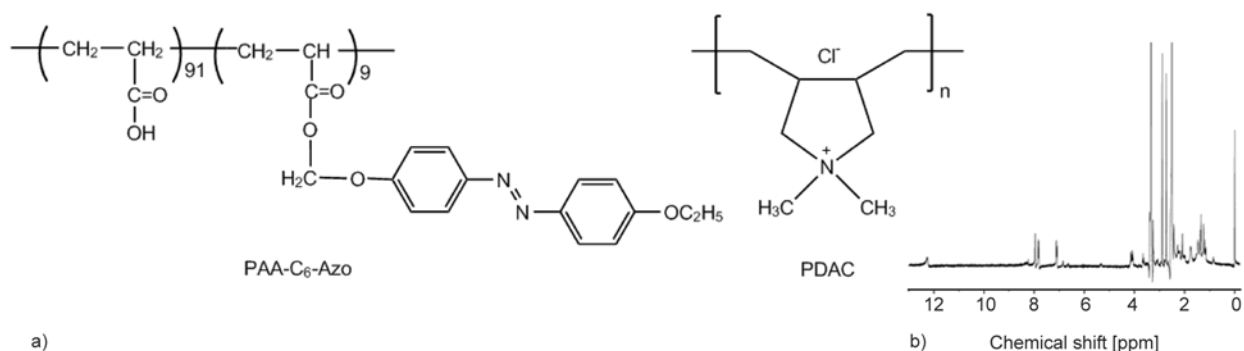
Figure 2. (a) The molecular structure of linear polymer PAA-C$_6$-Azo and polypositive charge polymer PDAC. (b) The ^{1}H NMR spectra of PAA-C$_6$-Azo.

The polymer was further purified by dissolving in THF and precipitated from petroleum ether, collected by filtration, and washed twice with petroleum ether. The final product was dried at 70°C under vacuum for 24 h. The molecular weight of PAA-C$_6$-Azo was determined by GPC measurement (M_n: ~28.6 kDa, PDI: 1.98), and the degree of modification (the number of Azo molecules to one acrylic acid unit of PAA) was calculated to be 9 mol% by ^{1}H NMR as shown in Figure 2b.

2.4. Synthesis of α-CD-rhodamine B (α-CD-RhB)

α-CD-RhB was synthesized according to our previous paper [29]. Briefly, 60 mg 3-NH$_2$-α-CD and 148 mg RhB were dissolved in 5 mL deionized water, after the solution's pH value was adjusted to 5, 80 mg EDC was added into this solution and stirred for 24 h at room temperature. The reaction mixture was poured into a large excess of acetone to recover the product. The residue was washed with acetone four times and dried for 2 days under vacuum drying.

2.5. Inclusion complex formation

The drug complex of PAA-C6-Azo/α-CD-RhB was prepared as follows: 32.2 mg (1.1·10^{-3} mmol) PAA-C$_6$-Azo was respectively dissolved in 40 mL H$_2$O (a suitable amount of sodium hydrogen carbonate was added into the solution to promote the solubility of PAA-C$_6$-Azo). After completely dissolving, the pH values of the solution were adjusted to be 7.0 by adding a few drops of HCl dilute solution. Then 40 mg (0.0286 mmol) α-CD-RhB was respectively added under ultrasonic condition at room temperature. The mixtures were stirred overnight at room temperature and then dialysis against uncomplexed α-CD-RhB for 48 h in a dialysis tube.

2.6. Substrate preparation

Quartz slides were used as substrates for the UV-vis absorption. A quartz substrate was immersed into a fresh piranha solution (30% H$_2$O$_2$:98% H$_2$SO$_4$ (v/v) =1:3; CAUTION: Piranha solution is a very aggressive, corrosive solution, and appropriate safety precautions should be utilized, including the use of acid-resistant gloves and adequate shielding) and heated until no bubbles were released. The substrate was rinsed carefully with deionized water and dried with nitrogen. The cleaned quartz slide was treated in 2% (v/v) APTES/95% ethanol solution for 20 min, and then was dehydrated at 110°C for 1 h to obtain the amino-silanized quartz slide.

2.7. PAA-C$_6$-Azo/PDAC multilayer fabrication and characterization

Linear polymers we used in the experiments are shown in Figure 2a. First, 32.2 mg (1.1·10^{-3} mmol) PAA-C$_6$-Azo and 80 mg (4.0·10^{-4} mmol) PDAC were respectively dissolved in 40 mL H$_2$O (a suitable amount of sodium hydrogen carbonate was added into the solution to promote the solubility of PAA-C$_6$-Azo). After completely dissolving, the pH values of the solution were adjusted to be 7.0 by adding a few drops of HCl dilute solution. Next, a freshly treated quartz wafer was alternately dipped in the PAA-C$_6$-Azo solution and the PDAC solution each for 10 min. After each dipping, the wafer was washed with enough Milli-Q water for 30 s.

2.8. The extraction of α-CD-RhB from multilayers

It has been reported [33] that the release of small molecules from the LbL film through pH sensitive, ion strength, thermo-sensitive and so on. Here we use the UV light to control the release and uptake of

the model molecule. The UV irradiating light was from a high-intensity 365 nm UV lamp equipped with 5 in. diameter filter. The intensity of the lamp was 8000 µW/cm^2 at distance of 15 in. A 300 W xenon lamp equipped with a filter (λ = 455 nm) was used as visible light source. The sample was placed 15 cm away from the lamp. The surrounding temperature of the samples was controlled at 25°C using a cold plate.

2.9. The reversibility of unloading/loading behavior

To examine the reversibility of unloading/loading behavior, a quartz substrate with 12 assemble monolayers was transferred into a 20.0 mL water and then irradiated by UV light. After 20 minutes of UV light irradiation, the sample was placed into a cuvette with 20.0 mL of α-CD-RhB aqueous solution (0.38 mmol) and then irradiated by visible light for another 10 minutes. The unloading/loading curve of α-CD-RhB at λ = 566 nm was monitored for more than 8 cycles of UV/visible light irradiation.

3. Results and discussion
3.1. The characterization of the host-guest interactions

UV-vis spectroscopy is a widely applicable means for charactering the formation or dissociation of a host-guest system [34, 35]. We firstly carried UV-vis studies in aqueous solution to understand the inclusion complex of Azo with α-CD-RhB, as shown in Figure 3a. Distinct inclusion complex effects on absorption were encountered for dye molecules exhibiting host-guest stoichiometry-dependent shifts in their spectra. In the same concentration (7.8·10^{-6} M), the maximum absorbance of the

RhB, α-CD-RhB and host-guest system (Azo/CD-RhB) are located in 552, 563 and 565 nm respectively, which means that the three solutions tagged by RhB happen red shift gradually. We can observe the difference by comparing the molecular structure of RhB with α-CD-RhB. For α-CD-RhB, the carboxyl group in RhB turns into amido linkage, and chromophores are unchanged but the auxochromes vary, leading to the obvious decrease for the energy of the electronic transition. Therefore, the maximum absorbance undergoes red shift. It has been established that the formation of the host-guest system would affect the maximum absorbance as well as the characteristic absorption [36]. With the addition of the guest molecule, the maximum absorption wavelength of the guest molecule (Azo function molecule) is red shifted and its absorbance increases, reflecting that the Azo functional groups have dropped from hydrophilic conditions into the hydrophobic environment. These data provide enough evidence for the formation of supramolecular system based on Azo and α-CD [37]. In case of the formation of the host-guest interactions, the environment of the chromophoric group has changed and the polarity becomes weaker. As a result, the hydrophobic environment leads to the maximum absorbance red shift as well [38].

Rhodamine B emits strong fluorescence in the specific excitation wavelength (λ_{Ex} = 550 nm). This directly provides us with the opportunity of detecting the characteristic emission wavelength of RhB, α-CD-RhB and Azo/α-CD-RB solution in the same concentration using fluorescence spectrum. Figure 3b shows their maximum characteristic emission wavelengths are located in 575, 579 and 582 nm,
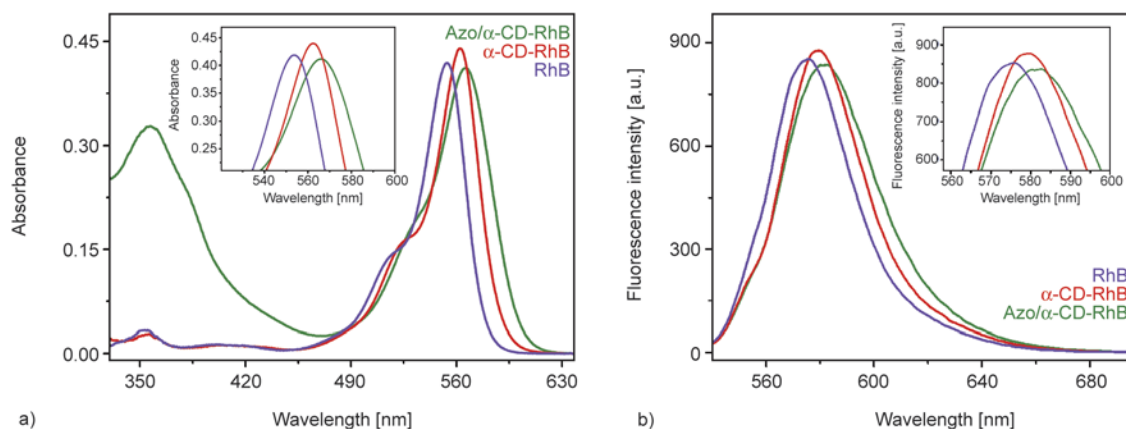
Figure 3. The host-guest interaction characterized by UV-vis spectroscopy (a) and fluorescence spectrophotometer (b).The inset shows the magnification of the characteristic absorption. The violet line is the absorption curve of RhB; the red line is the adsorption of α-CD-RhB and the olive one stands for the supramolecular Azo/α-CD-RhB.

indicating gradual red shift for the three solutions. Obviously, the fluorescence spectrum result is consistent well with that of UV-vis spectroscopy. In addition, the result can confirm our conclusion above that the formation of the amido bond change the electronic environment. As described by Wagner, the cause of further red shift for the host-guest system and LbL film should be attributed to the surrounding from aqueous solution state to dry LbL film after nitrogen blow [39]. Overall, although there is no direct proof for formation of a true host-guest inclusion complex, the data observed by fluorescence spectrum, as well as the results from UV-vis spectroscopy, does provide compelling indirect evidence that such inclusion complex based Azo and α-CD-RB is indeed formed.

3.2. Fabrication of multilayer films *via* electrostatic interaction

As well-known, electrostatic interaction is the most common driving force to build self-assembly multilayer films [40]. Water-soluble and multiple charge are required for the components to construct the electrostatic LbL multilayers. However, strict matching in position between the charges is not necessary, so it is unavoidable to introduce more than one building components into multilayer film with specific sequence [41]. In our work, photosensitive multilayers were prepared by alternately deposition of polyanion PAA-C6-Azo and polycation PDAC in aqueous. The stepwise self-assembly of the multilayers is characterized by UV-vis spectroscopy, as shown in Figure 4a. The absorbance maximum of

α-CD-RhB in the film at 566 nm is taken as the reference for monitoring the film growth. A linear increase with the number of layers is observed, which indicates this is a regular deposition process. Additionally, the absorption bands between 300 and 370 nm is mainly attributed to the π-π^* transition of the Azo groups in PAA-C_6-Azo. Moreover, we observe a similar linear relationship between the peak intensity of Azo at 355 nm and number of bilayers. It should be noted that the α-CD-RhB-loading multilayer desorbs abundantly during the deposition of the PDAC layer. After further deposition of an additional PAA-C_6-Azo/α-CD-RhB layer, the characteristic absorbance of α-CD-RhB increase again. A possible explanation for this phenomenon could be related to the ionic strength of the PDAC solution [28, 42].

We have further investigated the self-assembly process from fluorescence spectrum (Figure 4b). It is clear seen that quartz/multilayers as well as solution of the host-guest system emit characteristic fluorescence, which are similar to RhB, whereas quartz without self-assembly are not fluorescent (λ_{Ex} = 550 nm). This confirms α-CD-RhB-loading linear polymers have been successfully assembled on the surface of quartz wafers. Further, as the number of layers increases, the fluorescence intensity for the quartz slide also grows (data not shown). These results are in good agreement with that of UV-vis spectroscopy. However, in comparison with the solution of the supramolecular system, the characteristic emission peak for Azo/α-CD-RB has moved from 580 to 587 nm. The reason for this red shift
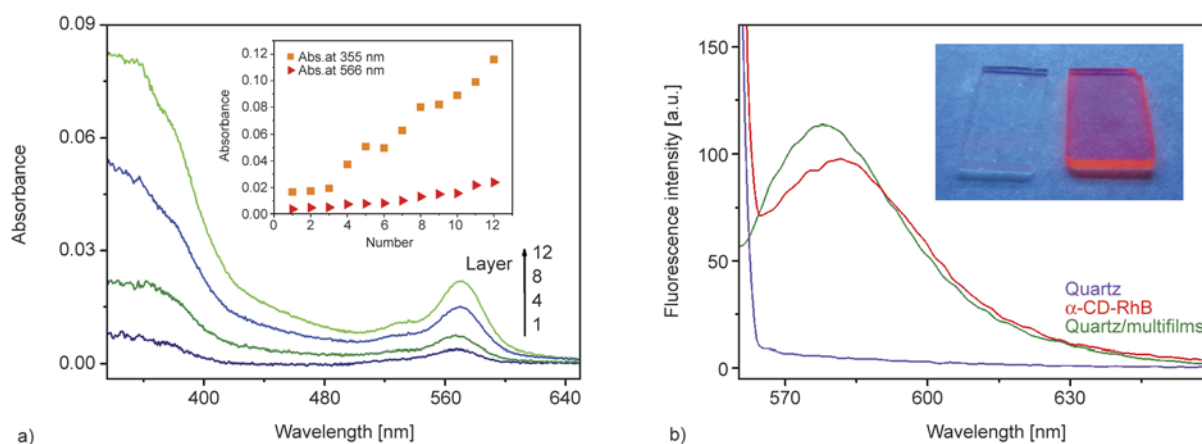
Figure 4. (a) The multilayers assembled on a quartz substrate and measured after each deposition treatment. The inset scatter diagram shows growth tendency of Azo (orange) and RhB (red), respectively. (b) Fluorescence spectra of Quartz, α-CD-RB solution and Quartz/multilayers (α-CD-RhB-loading 8-bilayer multilayers assembled on the quartz slide). The inset shows the photographs of a quartz slide before (left) and after (right) assembly treatment under a 28 W UV light (365 nm) in a dark environment.

may be the change of surrounding environment from dryness to aqueous, so does the polarity [43, 44].

3.3. Light-triggered release and loading

The multilayers were observed with confocal laser scanning microscopy (CLSM) (Nikon C1-si, BD Laser at 543 nm). It is clear seen that the red fluorescent surface of the (PAA-C$_6$-Azo/PDAC)$_8$ film confirmed α-CD-RhB is loaded on the layers before the irradiation of the UV light (Figure 5a). While the fluorescence almost disappears after irradiation with UV light (365 nm) for 20 minutes, indicating the release of α-CD-RhB from the films (Figure 5b). Before release, an average surface coverage of 0.91 drug molecules per nm^2 is calculated from the Beer–Lambert law, while the value drops below 0.05 after release. This reveals that the release process is com-

plete and obvious, which is attributed to disassemble of the specific host-guest interactions between Azo and α-CD-RhB upon UV irradiation.

Further, the surface morphology of multilayer films has been characterized by scanning electron microscopy (SEM). The SEM image of the α-CD-RhB-loading 8-bilayer film shown in Figure 5b illustrates a coarse surface morphology and some massive substance is observed, which may be the results of uniform assembly. After UV light irradiation, the α-CD-RhB-released multilayer shows a smooth and uniform surface coverage. We assume the irregular topography surface is a result of the fast assembly process. Therefore, the linear Azo polymers get behind in adjusting their configurations, but it definitely deserves further investigation, which is outside of the scope of this work. After illumination of
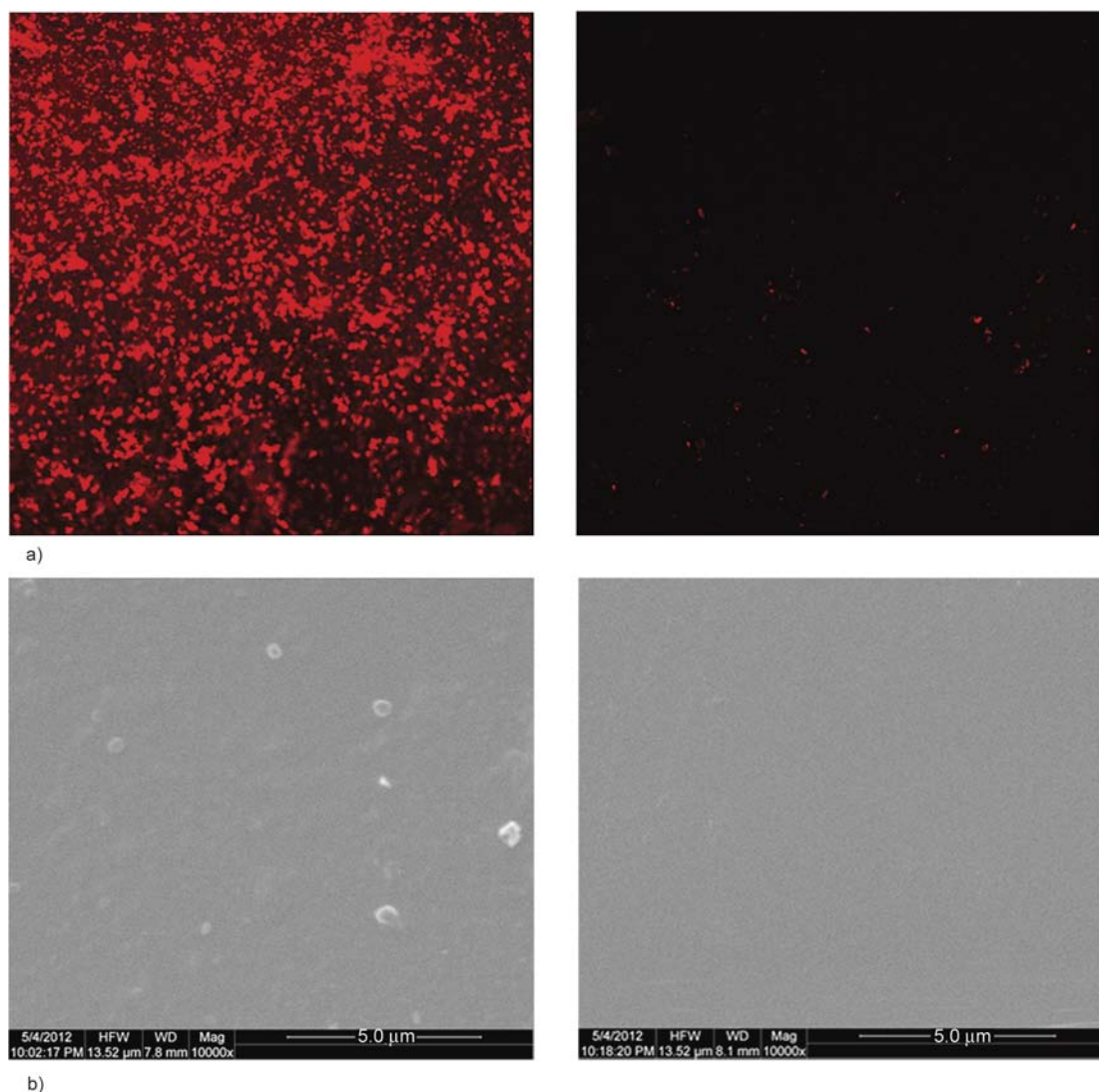
Figure 5. (a) CLSM images of multilayer films before (left) and after (rihgt) UV irradiation (the scale bar is 100 μm). (b) SEM images of multilayers before (left) and after (right) UV irradiation (the scale bar is 5 μm).
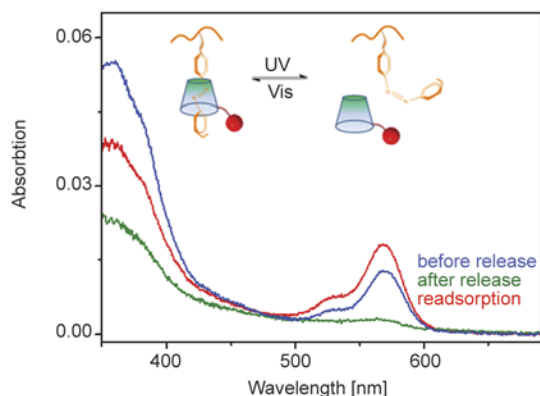
Figure 6. Absorption spectra of the α-CD-RhB loading multilayers before and after UV light irradiation for 20 minutes, then Vis light irradiation for 10 minutes in 40 mL α-CD-RhB aqueous solution for loading (1 mg/mL).

the UV light, the photoisomerization of the Azo resulted in the release of α-CD-RhB from the film, then the surface become smooth and even.

UV-vis spectrum was employed to monitor the release and reloading of multilayers (Figure 6). Application of 20 min UV irradiation induces a clear and rapid loss of dye from the 8-bilayer film. The absorbance of multilayer at 568 nm is about 0.026 before release, while the absorbance almost disappears after UV light treatment. It can be concluded that the loaded α-CD-RhB is almost completely washed out. For reloading studies, the film was immersed into 1 mg/mL of α-CD-RhB solutions for 10 min Vis light (455 nm) irradiation. Surprisingly, irradiation of Vis light for the multilayers after released introduces much more drug molecules move back into the multilayers. This is likely to be caused by a small number of free Azo molecules without assembling with α-CD-RhB during the fabrication of multilayers [32]. It should be mentioned that drugs release rate for PAA-C_6-Azo/PDAC film is rapid. 98 wt% of α-CD-RhB is released within 50 min for 20-bilayer film under UV irradiation, while 10-bilayer film takes 28 min to release of ca. 99% drugs. Hence, it is difficult to get detailed release rate, but the release trends can be attained. For 20-bilayer film, after 6 min of UV light irradiation, the release percentage starts to increase sharply, which raises to ca. 50% after 22 min. 88% of the loaded drugs is released in 40 min under UV irradiation and it reaches ca. 98% in 50 min. These results strongly demonstrate that the film exhibits a rapid response for light-triggered release.

3.4. Reversible loading and release

In order to investigate the potential of the α-CD-RhB-loading multilayers as a reversible light-triggered release platform, a quartz substrate with 8 assembled bilayers was transferred into 20.0 mL water and then irradiated by UV light. After 20 minutes of UV light irradiation, the sample was placed into a cuvette with 20.0 mL of α-CD-RhB aqueous solution (0.38 mM) and then irradiated by visible light for 10 minutes. The absorbance of (PAA-C_6-Azo/PDAC)$_6$ film was recorded, as shown in Figure 7. As expected, the multilayers exhibit good photo-responsive properties. It is shown that the absorption efficiency of the PAA-Azo/PDAC film is almost unchanged after 16 times of release and loading under irradiation with UV and Vis light alternately. This result demonstrates that the film is stable in these loading and release conditions, and can be used for a reversible drug delivery system.
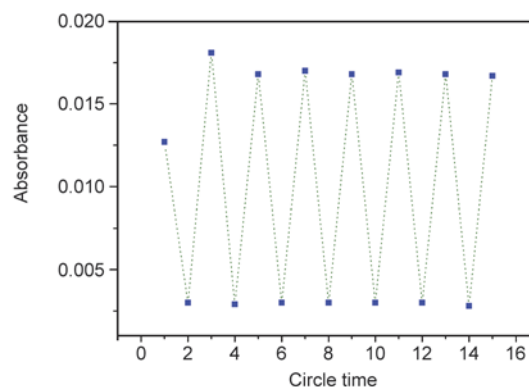

Figure 7. The cyclic absorbance features of (PAA-C_6-Azo/PDAC)$_6$ multilayer film at 566 nm as a result of the cyclic loading and release.

3.5. Surface patterning

Finally, to further verify the ability of light-sensitive of the LbL deliver platform, we presented a pattern onto the LbL film surface *via* area-selective release. Demonstration of the LbL film in area-selective release was conducted using a 'forever'-shaped mask (Figure 8b). The procedures of pattern formation are described as follows. Briefly, a quartz slide with as-prepared (PAA-C_6-Azo/PDAC)$_{20}$ film was transferred into a cuvette with 20.0 mL deionized water at room temperature. Next, a 'forever'-shaped mask was also immersed in water and positioned on the film. Then, they were irradiated by UV light for 40 minutes, followed by a brief wash-
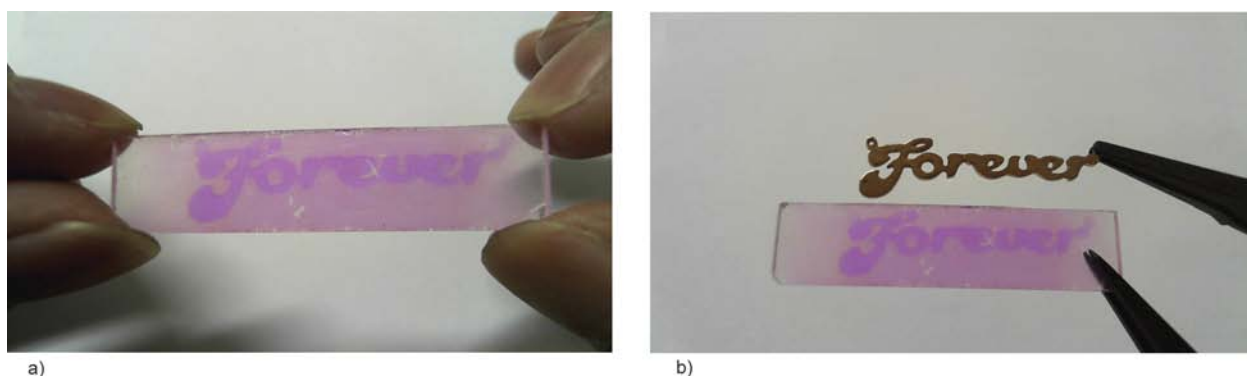
Figure 8. The patterned photograph of (PAA-C$_6$-Azo/PDAC)$_{20}$ multilayer film as a result of local release. (a) The well-patterned 'forever' on a quartz slide. (b) The contrast between the mask and the resulting pattern.

ing with neutral water and drying under a nitrogen stream. This process yielded a fluorescent display of 'forever'-shaped pattern. As seen clearly in Figure 8a, The UV irradiation areas are almost colourless, while the UV-free parts are red, indicating the area-selective release of α-CD-RhB from the LbL film. The well-patterned 'forever' is distinct with a clearly outline, which attributes to the photo-sensitivity of the multilayer film for release.

4. Conclusions

In summary, we have demonstrated a polyelectrolyte polymer film by combining LbL self-assembly and host-guest interactions for light-controlled drug release. The multilayer film based on electrostatic interactions between PDAC and PAA-C$_6$-Azo showed high stability under neutral conditions. Compared with traditional drug-loading methods of using physical uptake and chemical bonding, our supramolecular drug-loading approach of the LbL-based film exhibits convenient drug loading, ideal bonding strength, and light-controlled drug release. Moreover, the resulting film can catch and release multidrug, or other functional groups, as exemplified here by loading and release of α-CD-RhB. The process for loading and release is reversible for at least eight cycles investigated so far. Equipped with these smart features, this LbL-based film affords useful information for the development of intelligent drug delivery platforms and appropriate biological studies. Currently we are planning to apply this LbL-based system for the light-controlled release in biodegradable poly(lactic acid), which provides an ideal substrate for therapeutic delivery using surgical implantion.

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