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# Construction of Redox-Active Multilayer Film for Electrochemically Controlled Release

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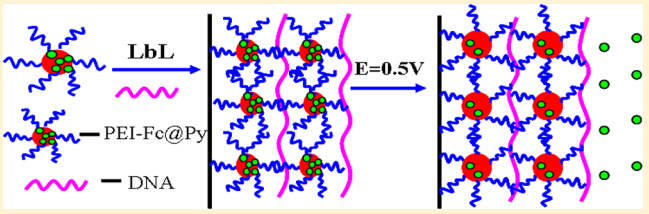
**ABSTRACT:** An electrochemically controlled drug release from a redox-active multilayer film is reported. The multilayer film is fabricated by alternate assembly of the electrochemical redox-active micelles and DNA. The buildup of multilayer films is monitored by spectroscopic ellipsometry, UV−vis spectroscopy, and fluorescence spectroscopy. A ferrocene-modified poly (ethyleneimine) (PEI-Fc) is used to form a hydrophobic ferrocene core and hydrophilic PEI shell micelle, showing the electrochemical redox-active properties. Hydrophobic pyrene (Py) molecules are then incorporated into the micelles. The PEI-Fc@Py micelles are assembled into the (PEI-Fc@Py/DNA) multilayer film by layer-by-layer assembly. Thanks to ferrocene groups with the properties of the hydrophilic-to-hydrophobic switch based on the electrical potential trigger, pyrene molecules can be control released from the multilayer film. The electrochemically controlled release of pyrene is investigated and confirmed by electrochemical quartz crystal microbalance and electrochemistry workstation. The (PEI-Fc@drug/DNA) multilayer film may have potential applications in the field of biomedical and nanoscale devices.




## INTRODUCTION

Controlled release in drug delivery systems offers many advantages over conventional therapies, such as enhancing the effectiveness of drugs, reducing the adverse reactions, and preventing systemic toxicity.[1] Many methods to control release of drugs based on pH,[2−6] light,[7,8] magnetic field,[9] redox,[10] and temperature,[11,12] have been reported. However, precisely controlled drug release from the thin films under mild conditions is still a challenge. A stimulus to control release of drugs based on electrical potential could offer unique advantages, because it can easily be controlled with local, continuous, precise, and reversible features.[13] Miller et al. reported an electro-controlled release of biomolecules from an intrinsically conducting polymer, in which the molecules were incorporated into the "holes" of the films before releasing.[14,15] Drugs and functional molecules could also be loaded into the electrically erodible polymer gel[16] or hydrogels.[17] The release of drugs can be thus controlled through deswelling or erosion of the gel based on an electrochemical treatment. However, a relatively high voltage and a long-time electrical potential treatment as well as gel fatigue generally limit their applications.

Layer-by-layer (LbL) assembly is a universal method for preparing functionalized polyelectrolyte multilayer films.[18,19] This technique is simple and versatile, and typically involves alternate deposition of oppositely charged components. The multilayer films are general nano and micrometer thickness and can be deposited onto almost any kind and shape of substrates. It is thus a good candidate for studying of controlled drug delivery. Specific, the multilayer films with controlled release of drugs based on the electrochemical treatments have been reported. For example, Vörös et al. studied the electro-dissolution of poly (L-lysine)/heparin multilayer films and the controlled release of heparin. They demonstrated that the release of heparin can be regulated by the electrical potential.[20] Recently, the same group reported a new electrochemical stimuli release of drugs from a liposome embedded polyelectrolyte multilayer film.[21]

Ferrocene is an electroactive organic molecule. It will undergo reversible oxidation and reduction reaction when applying electrochemical means.[22] The interconversion between Fe(II) and Fe(III) states results in electrical transition of ferrocene, leading to a hydrophobic-to-hydrophilic switch.[23] Recently, we have reported a ferrocene-modified poly (ethyleneimine) (PEI-Fc). This macromolecules with redox-active properties was used to form micelles[24] or hydrogel.[25] The ferrocene groups on the side chain of PEI-Fc not only act as a redox responsive trigger, but also as the hydrophobic tails. We envision that these features of ferrocene could be employed as a new strategy to loading and release of the hydrophobic drugs. More importantly, this release could be controlled by electrochemical treatment because of the electrical redox properties of ferrocene.

In this work, we report that a redox multilayer film based on LbL assembly of PEI-Fc@drug and DNA for electrochemically controlled release of hydrophobic drugs (see Scheme 1). Pyrene (Py) is used as a hydrophobic model drug.[26,27] Transmission electron microscopy (TEM) and dynamic light scattering (DLS) are used to characterize the micelles that formed by PEI-Fc and pyrene (PEI-Fc@Py). The PEI-Fc@Py micelles are then used to fabricate multilayer film. The buildup

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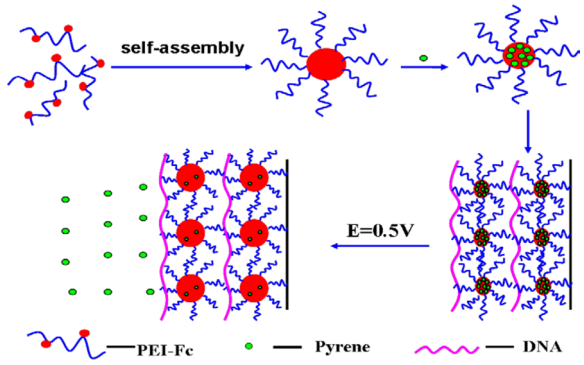
**Scheme 1. Illustration of the LbL Assembly of PEI-Fc@Py Micelles and DNA and Electrochemical Stimuli Release of Model Drug**




of the multilayer film is followed by using spectroscopic ellipsometry, UV−vis, and fluorescence spectroscopy. Finally, an electrochemical-stimulus-dependent controlled release of pyrene was investigated by electrochemical quartz crystal microbalance (E-QCM), fluorescence spectroscopy, and scanning electron microscopy (SEM).

## MATERIALS AND METHODS

**Materials.** Poly (ethyleneimine) (PEI, branched, $M_w$ 25000), pyrene, and ferrocene-carboxaldehyde were purchased from Sigma-Aldrich. Ferrocene-grafted Poly (ethyleneimine) (PEI-Fc, 11 mol % grafting density of Fc) was synthesized as previously reported in our group.[24,25] Deoxyribonucleic acid (DNA, fish sperm, sodium salt) was purchased from AMRESCO (U.S.). Ethidium bromide (EtBr) was purchased from BBI Biotech (U.S.). Phosphate buffered saline (PBS) was purchased from Sangon (P.R. China). Ultrapure water was obtained from a Millipore water purification system (Milli-Q, >18 MΩ, Millipore S. A., Molsheim, France).

**Formation and Characterization of the PEI-Fc@Py Micelles.** A 10-mg portion of PEI-Fc was first dissolved in PBS (10 mL) to form micelles. A 2-mL portion of pyrene in acetone solution (1 mg/mL) was then added dropwise into the micelle solution. Acetone was totally removed through a sonication process for 1 h in dark at room temperature. The solution was then centrifuged for 10 min at 3500 rpm to eliminate the precipitated pyrene. The intensity-average diameter and size distribution of the PEI-Fc@Py micelles were measured by a laser particle size analyzing system (DLS, Brookhaven 90 plus, U.S.) at the scattering angle of 90°, and the wavelength was set as 658 nm throughout the entire experiment. The PEI-Fc@Py micelles were also observed by TEM. Briefly, a drop of the micelles solution was placed onto a carbon-coated copper grid. The specimens were observed (TEM, at an accelerating voltage 80 kV, Jem-1230, JEOL, Japan).

**Clean and Pretreatment of Substrates.** Quartz, silicon wafers, Au-coated resonator, and Indium tin oxide (ITO) glass were used as the substrates for preparation of the multilayer films. Except for ITO glass, the substrates were first cleaned by immersing them in hot piranha solution ($H_2O_2$:$H_2SO_4$ = 3:7 V/V) for 30 min (*Caution: piranha solution is extremely corrosive*) and then washed with Milli-Q water thoroughly. After that, the substrates were cleaned by a solution containing 1 vol% $NH_4OH$ (29 wt % aqueous solution), 1 vol% $H_2O_2$ (30 wt % aqueous solution), and 5 vol% $H_2O$ at 75 °C for 30 min, and then washed with a copious amount of Milli-Q water. ITO glass (10 × 20 $mm^2$) was successively cleaned in acetone, ethanol, and Milli-Q water for 10 min, respectively, and then dried with $N_2$.

**Fabrication and Characterization of the (PEI-Fc@Py/DNA) Multilayer Film.** The (PEI-Fc@Py/DNA) multilayer film was assembled on quartz substrate for UV−vis and fluorescence spectrometry, silicon wafer for ellipsometry, Au-coated resonator for EQCM, and indium tin oxide (ITO) glass (10 ×20 $mm^2$) for electro-stimulation drug release and SEM. The substrate was alternately immersed in PEI-Fc@Py micelles and DNA solution (both solutions were 1 mg/mL in PBS) for 10 min each and rinsing between steps for 2 min, followed by drying under a stream of $N_2$. The process was repeated until a desired number of bilayers had been deposited.

The buildup of the (PEI-Fc@Py/DNA) multilayer film was followed by UV−vis spectrometry on a UV−vis spectrophotometer (UV-2505, Shimadzu) through measuring DNA absorbance at 260 nm. Ellipsometry (M-2000, J.A. Wollam, Japan) was used to measure thickness of the multilayer film. Spectra were obtained in the wavelength region 124−1700 nm at two different incident angles (65 and 70°). Δ and Ψ values were chosen for data analysis. The buildup of the multilayer film was also followed by fluorescence spectrophotometer (LS 55, Perkin-Elmer, U.S.) at room temperature, in which the emission spectra were recorded over the range of 350−550 nm with an excitation wavelength of 336 nm. The electrochemical redox properties of the (PEI-Fc@Py/DNA) multilayer film were characterized by cyclic voltammetry (CV, CHI 660D electrochemistry workstation, Shanghai Chenhua, P.R. China). For CV measurement, it was carried out by using a three electrode cell. The working electrode was an ITO substrate coated with the $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film. The counter electrode was a platinum foil and the reference was a saturation calomel electrode (SCE). PBS was used as the electrolyte solution. The scan rate was 50 mV/s, and the potential range of the CV was 0−600 mV versus SCE.

**Electrochemically Controlled Release of Pyrene from the Multilayer Film.** The electrochemically triggered release of pyrene from the (PEI-Fc@Py/DNA) multilayer film was first performed using EQCM-D [QEM 401, Sweden]. The QCM chamber worked as a three-electrode electrochemical cell with an Ag/AgCl reference and a platinum counter electrode, and an Au/quartz crystal sensor that deposited with the $(PEI\text{-}Fc@Py/DNA)_3$ multilayer film as the working electrode. The fundamental resonant frequency of the crystal was 5 MHz. An electrical potential (0.5 V) was applied for 5 s to the multilayer film and then stopped. This process was repeated for several times. The change of frequencies was recorded by QCM equipment. The flow solution that contained released pyrene was measured by fluorescence spectrophotometer (LS 55, Perkin-Elmer, U.S.).

The controlled release of pyrene was further investigated by using a $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film. This multilayer film has greater thickness and contains more pyrene. The multilayer film was fabricated on an ITO-glass substrate as the working electrode. The reference electrode was SCE, and the counter electrode was a piece of platinum foil (2.5 $cm^2$). An electrochemistry workstation was used to carry out amperometric i-t curve measurement in a PBS buffer. Briefly, an electrical potential (0.5 V) was applied for 10 min to the multilayer film and then stopped for 10 min. This process was repeated several times. The incubated PBS buffer was sampled for fluorescence measurement (F-4500, Japan) every 2 min at room temperature, and the emission spectra were recorded over the range of 360−420 nm with an excitation wavelength of 336 nm.

To directly visualize DNA that was still incorporated in the multilayer films after the electrochemical treatment, ITO substrates coated the multilayer films were oxidized for 30 min at 0.5 V, and the PBS buffer was then added (100:1, vol %) EtBr solution (5 μg/mL). The fluorescence image of multilayer film was taken by fluorescence microscopy (IX81, Zeiss, Germany) with 4× objectives.

The $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film was also observed by SEM (JSM 5600 LV, JEOL, Tokyo, Japan). The $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film were prepared on the ITO glass, after applying a 0.5 V potential for 5 and 30 min, followed by vacuum drying overnight. The cross-section of the multilayer film was measured by using SEM at operation voltage of 3.0 kV.

## RESULTS AND DISCUSSION

**Formation and Characterization of the PEI-Fc@Py Micelles.** We have previously reported that PEI-Fc can self-assemble in aqueous media to form micelles with hydrophobic ferrocene core and hydrophilic PEI shell.[24] Hydrophobic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pyrene can be thus entrapped into the PEI-Fc micelles by driving the hydrophobic interactions. Figure 1a shows the size

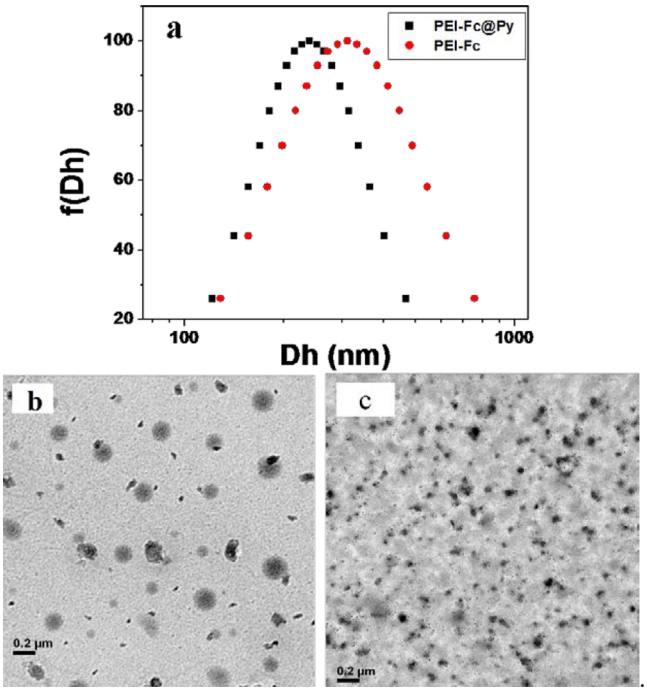


**Figure 1.** DLS results of PEI-Fc (●) and PEI-Fc@Py (■) micelles (a) and TEM images of PEI-Fc (b) and PEI-Fc@Py micelles (c) in PBS buffer solution at 1 mg/mL.

distributions of PEI-Fc and PEI-Fc@Py micelles in PBS as measured by DLS. PEI-Fc micelles have an average diameter at 311 nm. After loading of pyrene, the size of the micelles decreased to 238 nm. This decrease of size could be ascribed to the strong interactions between ferrocene and pyrene, resulting in a more compact core. Shuai et al[27] and Licciardi et al[28] have reported a similar phenomenon. TEM was employed to directly observe the micelles, showing a similar observation. As can be seen in Figure 1b,c, the PEI-Fc micelles showed spherical shape with a diameter of 161 ± 20 nm (Figure 1b). However, after loading of pyrene, the size of the micelles significantly decreased to 117 ± 15 nm (Figure 1c). Obviously, the size measured by TEM is much smaller than that of DLS, which could be ascribed to the hydration of micelles in DLS measurement. The positively charged PEI-Fc@Py micelles can serve as a nanocontainer for the following LbL assembly.

**Fabrication and Characterization of the (PEI-Fc@Py/DNA)$_n$ Multilayer Film.** The multilayer film was fabricated through the alternate deposition of the PEI-Fc@Py micelles and DNA. We chose DNA as anionic polyelectrolyte because of its good biocompatibility and commercially availability. Figure 2 shows an exponential growth of the (PEI-Fc@Py/DNA)$_n$ multilayer film as measured by ellipsometry. The thickness of the (PEI-Fc@Py/DNA)$_6$ multilayer film was 444 ± 18 nm. Such thickness is a little bit higher than that of the (PEI/DNA)$_{6.5}$ (~400 nm).[29] Although the size of the PEI-Fc@Py micelles is about 238 nm (DLS measurement), the micelles in the multilayer films are in a compact shape, which means that the thickness of one layer of the micelles is not as large as 238 nm. The thickness should be much thinner. Furthermore, during the fabrication of the multilayer films, one deposition would not ensure a full coverage of the micelles, which means a

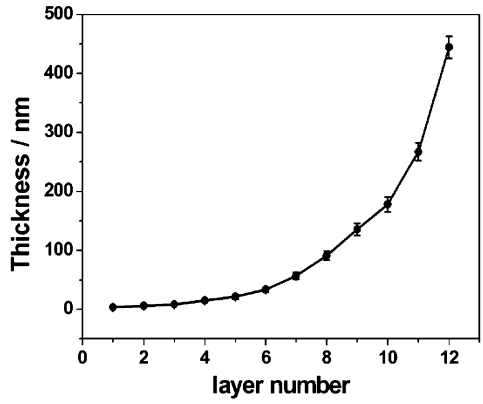


**Figure 2.** The thickness of (PEI-Fc@Py/DNA) versus layer numbers shows a successful fabrication of the multilayer film.

full coverage of the micelles could be obtained by after several deposition processes. We previously reported a similar phenomenon in the case of the (PEI-DNA nanocomplexes/PGA) multilayers.[30]

Because DNA has UV absorption at 260 nm, it is very convenient to follow the buildup of the multilayer film by UV−vis spectrometry. Figure 3a shows UV−vis absorption spectra of the (PEI-Fc@Py/DNA) multilayer film with 1−7 bilayers. An exponential increase was observed at 260 nm with the assembly number, which means that DNA has been successively incorporated into the multilayer film. To ensure that pyrene is still encapsulated in the PEI-Fc micelles during the LbL assembly process, fluorescence spectra were applied to trace the growth process of multilayer films, because we know that pyrene has the same characteristic UV absorption at 260 nm.[31] Fluorescence spectra of the multilayer films after the deposition of each layer of micelles were recorded, as shown in Figure 3b. The fluorescence intensity at 413 nm of pyrene in the multilayer films increased with respect to the increase of the number of layers, which means that pyrene has been successfully incorporated into the multilayer films. The amount of pyrene loaded in the multilayer films can be controlled by simply changing the cycles of films deposited.

To characterize the electrochemical redox properties, the (PEI-Fc@Py/DNA)$_{10}$ multilayer film was measured using CV, during which the oxidation and reduction peak of redox-active species could be observed.[32] Actually, ferrocene is a very common redox molecular probe.[33,34] In our multilayer films, PEI was modified with ferrocene groups to endow the multilayer films with redox properties. As shown in Figure 4, during the electrical potential treatment range from 0 to 0.6 V in PBS at a scan rate of 50 mV/s, ferrocene groups undergo oxidation and reduction processes. One can observe that the oxidation and reduction peak of ferrocene is 0.345 and 0.325 V, respectively, which suggests a good reversible electrochemical redox of ferrocene within the multilayer film. This CV measurement indicated that ferrocene groups were still electroactive. More important, the relative low oxidation potential value suggested that the electrochemically triggered release of pyrene could be carried out in a mild electrical potential.

**Electrochemically Controlled Release of Pyrene.** Due to the presence of the redox-active ferrocene groups, the alternation between hydrophobic ($[Fe(C_5H_5)_2]$) and hydrophilic ($[Fe(C_5H_5)_2]^+$) within the multilayer film could take place by a redox trigger.[35] This alternation could thereafter lead


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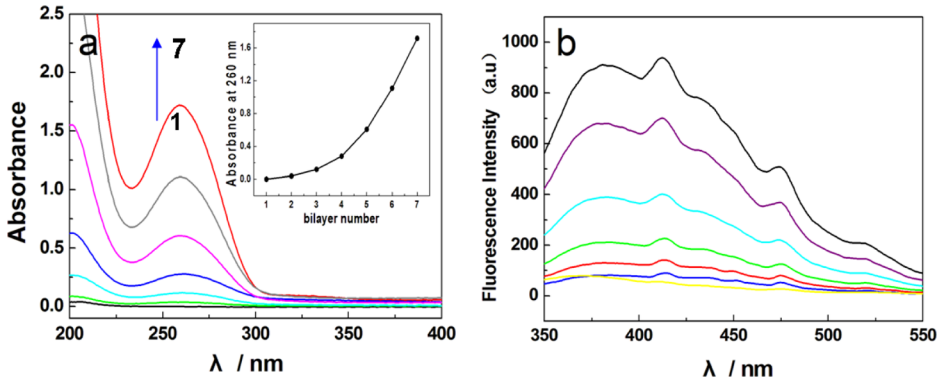


**Figure 3.** (a) UV−vis absorption spectra of the (PEI-Fc@Py/DNA) multilayer films with different numbers of bilayers. The inset shows the absorbance at 260 nm vs the number of bilayers. (b) Fluorescence spectra of the (PEI-Fc@Py/DNA) multilayer films from 1 to 7 bilayers.

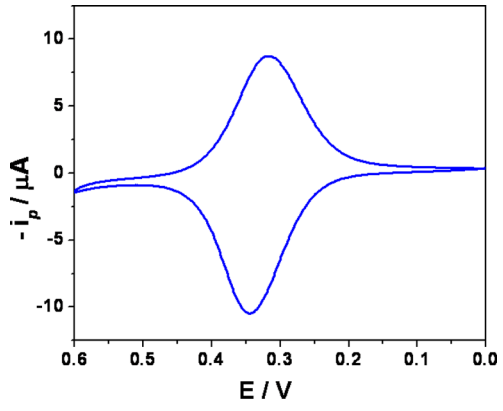


**Figure 4.** Cyclic voltammetry shows the electrochemical redox-active properties of the $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film.

to a change of the interaction between ferrocene and pyrene, resulting in the release of pyrene molecules.[36] In this study, we chose the electric potential to trigger such hydrophobic−hydrophilic alternation and the release of pyrene. We first used EQCM to investigate the electro-controlled release of pyrene in the $(PEI\text{-}Fc@Py/DNA)_3$ multilayer film. Herein, considering the sensitivity of QCM technique, a three-bilayer multilayer film was chosen to ensure the data had better precision. According to the above CV result, we chose 0.5 V as an oxidizing potential to ensure effective oxidation of ferrocene groups. As can be seen in Figure 5a, an increase of frequency from −845 to −815 Hz was observed when the multilayer film was subjected an electrical potential for 5 s, which suggested a release of molecules from the multilayer film. Whereas when the electrical potential was removed, the change of frequency was stopped. Such electro-dependent release was then repeated several times, showing a very good reproducibility (Figure 5a). To confirm the release of pyrene molecules, we measured the solution sampling from the QCM equipment after electrochemical treatment. As shown in Figure 5b, the fluorescence spectrum of pyrene was clearly detected. All these data indicated that pyrene can be electrochemical-dependently released from the (PEI-Fc@Py/DNA) multilayer film with a 0.5 V electrical potential stimulus, which is relatively lower than that of the traditional electro-controlled release studies.[21,37] Generally, a mildly low electrical potential could make the controlled release facile, easy to control, and avoid the occurrence of adverse reactions. We have further investigated the electro-stimulus controlled release in a thicker (PEI-Fc@Py/DNA) multilayer film. A 10 bilayer multilayer film was chosen. Figure 6 shows an increase of fluorescence density of pyrene in the incubation solution during the electrochemical treatment. With a treatment of only 0.5 V electrical potential, pyrene molecules were released into the incubation solution, showing a very clear electrical-potential-dependent type. This on/off process could quarantine a precisely controlled release of drugs.

To verify the integrity of the (PEI-Fc@Py/DNA) multilayer film during the electrochemical treatment, we characterized the multilayer film by SEM and fluorescence microscopy. Figure 7 shows cross-section images of the $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film before and after the electrochemical treatment. One can observe that the thickness of the as-prepared

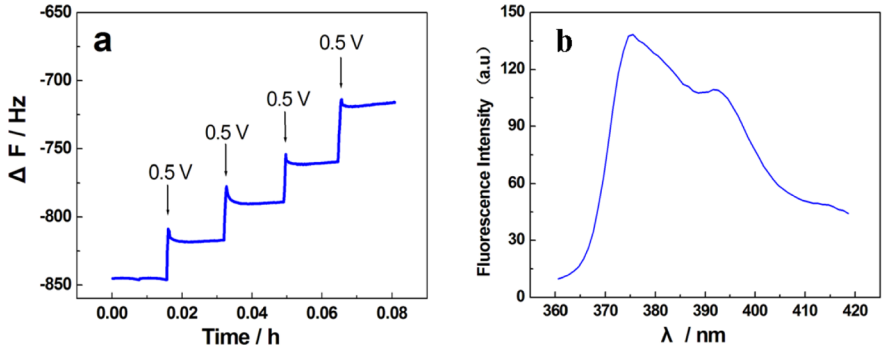


**Figure 5.** (a) The drug release from $(PEI\text{-}Fc@Py/DNA)_3$ film can be controlled by the electric potential of 0.5 V. EQCM is used to monitor the process. (b) The fluorescence spectrum of the PBS buffer suggests pyrene is released by electrochemical treatment.


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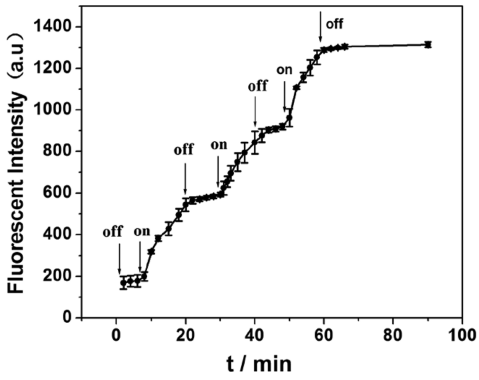


**Figure 6.** Control release of pyrene from $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer film by applying an electric potential of 0.5 V.

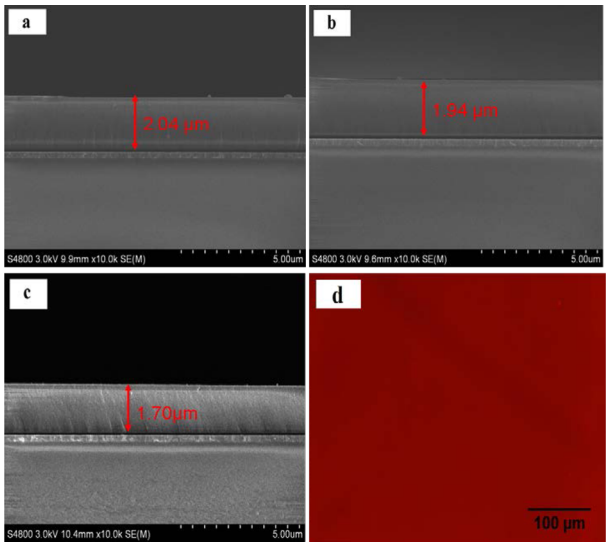


**Figure 7.** SEM images of the $(PEI\text{-}Fc@Py/DNA)_{10}$ multilayer films. The multilayer films were as-prepared (a), electrochemically treated (0.5 V) for 5 (b) and 30 min (c). (d) The fluorescence image of the multilayer film after an electrochemical treatment showing a EtBr-DNA interaction. Scale bar is 100 $\mu$m.

multilayer film was 2.04 $\mu$m (Figure 7a). Thickness was then decreased to 1.94 and 1.7 $\mu$m after a 0.5 V electrochemical treatment for 5 and 30 min (Figure 7b,c), respectively. This decrease of the thickness could be ascribed to the release of pyrene molecules. However, after a treatment of electrical potential, the micelles in the multilayer films could have structural change because of hydrophobic−hydrophilic switch of ferrocene. It could thus further lead to a structural rearrangement of the multilayer films, resulting in a decrease of thickness. However, the multilayer film was still uniform and kept in the original shape, and no destruction was observed. We then stained DNA within the multilayer film with EtBr to confirm that DNA molecules were not released (Figure 7d). All these data suggest that the (PEI-Fc@Py/DNA) multilayer film can be served as an electrochemically controlled drug delivery system under mild conditions.

## CONCLUSIONS

We have fabricated the (PEI-Fc@Py/DNA) multilayer film as an electro-controlled drug release system. The model drug pyrene was incorporated into the PEI-Fc micelles because of the hydrophobic ferrocene core. The PEI-Fc@Py micelle was then successfully assembled to form a thin multilayer film. Thanks to the electrical redox properties of ferrocene, there was a hydrophobic−hydrophilic interconversion within the multilayer film. Pyrene was thus control released by a 0.5 V electrical potential treatment. The (PEI-Fc@Py/DNA) multilayer film with the properties of electro-controlled drug release could be applied to active surfaces for tissue engineering and biomedical devices.

## AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

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