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Conjugated Polymer for Voltage-Controlled Release of Molecules

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Conjugated polymers are attractive in numerous biological applications because they are flexible, biocompatible, cost-effective, solution-processable, and electronic/ionic conductive. One interesting application is for controllable drug release, and this has been realized previously using organic electronic ion pumps. However, organic electronic ion pumps show high operating voltages and limited transportation efficiency. Here, the first report of low-voltage-controlled molecular release with a novel organic device based on a conjugated polymer poly(3-hexylthiophene) is presented. The releasing rate of molecules can be accurately controlled by the duration of the voltage applied on the device. The use of a handy mobile phone to remotely control the releasing process and its application in delivering an anticancer drug to treat cancer cells are also successfully demonstrated. The working mechanism of the device is attributed to the unique switchable permeability of poly(3-hexylthiophene) in aqueous solutions under a bias voltage that can tune the wettability of poly(3-hexylthiophene) via oxidation or reduction processes. The organic devices are expected to find many promising applications for controllable drug delivery in biological systems.

Conjugated polymers have been extensively investigated for biological applications in recent years due to many advantages, including solution-based preparation, excellent mechanical flexibility, good biocompatibility, low cost, and being ionic and electronic conductive.[1–4] Besides their applications as high-performance organic transistors for biosensing and neural interfacing,[5–9] conjugated polymers have been employed in organic electronic ion pumps (OEIP) to deliver not only small ions but also large-sized biomolecules and drugs under bias voltages.[10–14] For example, Simon et al. demonstrated precise transport of neurotransmitters to neuron cells using OEIPs and monitored the response of the cells in vitro.[13] Tybrandt et al. designed an OEIP with a 10 μm size transfer channel and used it to efficiently stimulate single neuron cells by delivering a neurotransmitter acetycholine.[14] These results indicate that the electroactive OEIPs are a promising platform for cell stimulation, drug delivery, and microenvironment regulation in biological systems. In comparison with other approaches for controllable release triggered by either individual external stimuli of light, pH, temperature, or combination of multisignals,[14–17] voltage-controlled release can be more precise and convenient in many applications especially for implantable devices. Previously reported OEIPs are normally based on a lateral structure with a small cross-sectional area and a relatively long organic transfer channel. Consequently, they require complicated patterning procedure and high operating voltages (tens of volts) for pumping ions and demonstrate limited transportation efficiency of ions and biomolecules.[13,14]

Here, we report a novel organic device for molecular release, which has a simpler structure and a much lower operating voltage than OEIPs. The device has a vertical multilayer structure and the key is to contain a layer of conjugated polymer poly(3-hexyltthiophene) (P3HT) for controlling the molecule release. The working mechanism is attributed to the fact that the P3HT layer in the device can be tuned between hydrophobic and hydrophilic states by a bias voltage due to electrochemical oxidation and reduction processes.[18,19] This unique property leads to switchable permeability for aqueous solutions across the P3HT layer and thus controllable release of molecules from the source layer beneath it. We find that the operating voltage of the devices is only ≈1.0 V and the releasing rates of several different molecules in the devices are estimated to be several ng s^{-1}, which are several orders of magnitude higher than that of a typical OEIP. Thanks to the low operating voltage, the drug release devices can be handily controlled via a mobile phone. As an example, we demonstrate their use in

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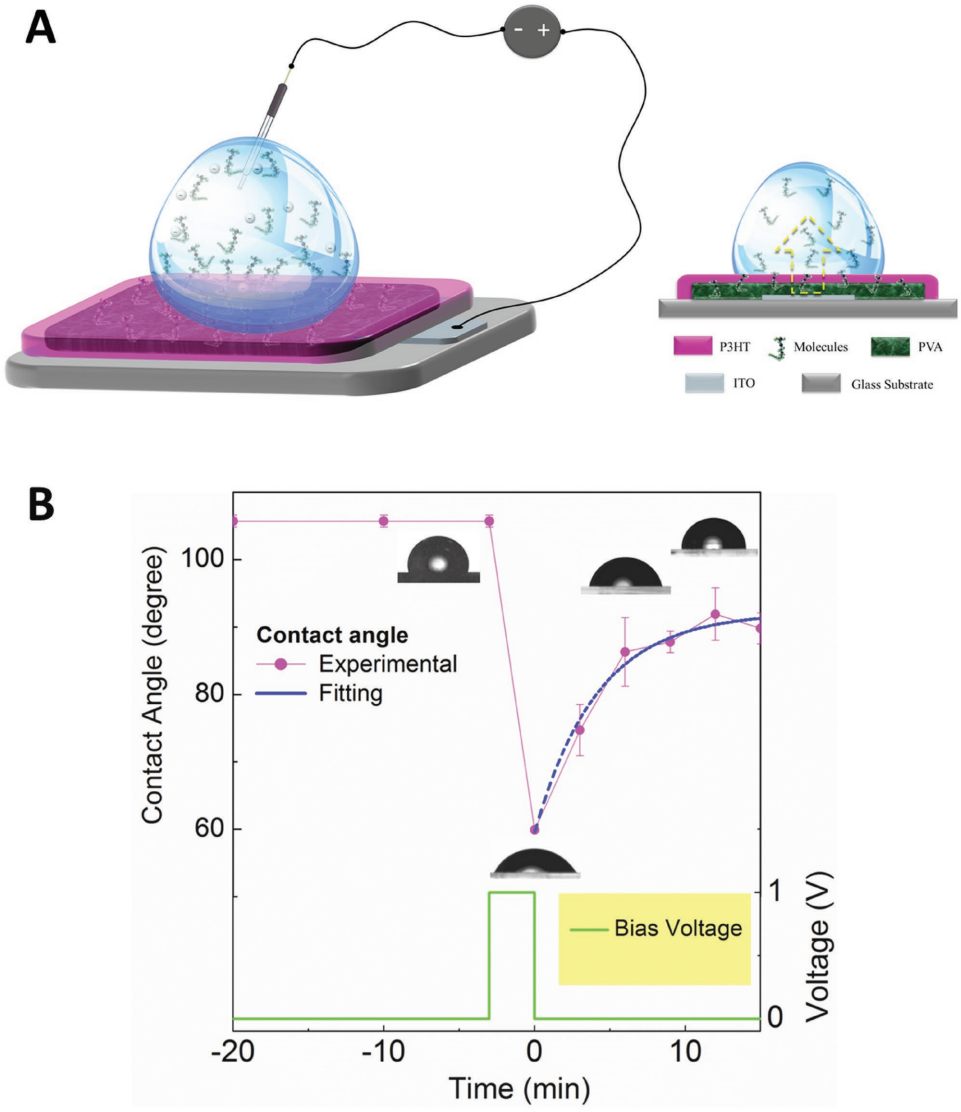

Figure 1. Design of a drug release device. A) Schematic diagram (left) and the cross-sectional view (right) of the device based on a P3HT/PVA/ITO multilayer and operated in an aqueous solution. The Ag/AgCl electrode was placed in the electrolyte. B) Water contact angles on the P3HT film of a device before and after the electrochemical oxidation by a bias voltage applied on the bottom ITO electrode. The recovered contact angle after the removal of the bias voltage was fitted with the equation: $\theta = \theta_0 + \Delta\theta(1 - e^{-t/\tau})$.

remotely controlled release of an anticancer drug to efficiently inhibit cancer cell growth. All of the results provide solid evidences that the organic drug-release devices are promising for numerous biological applications in the future.

Figure 1A shows the schematic diagram of the device for voltage-controlled molecular release. The device contains a solid source electrolyte layer (polyvinylalcohol (PVA)), a P3HT layer, and a target electrolyte. In the device fabrication, PVA and P3HT thin films were sequentially coated on a patterned ITO electrode on a glass substrate and the molecules to be released were incorporated in the PVA layer. PVA is an ideal carrier for molecule storage because it is soluble in water and can be easily mixed with different molecules to act as a molecule reservoir.[20] The release of the stored molecules in the source layer can be controlled via applying a voltage between the bottom electrode (ITO) beneath the PVA layer and the Ag/AgCl electrode in the target electrolyte.

The purpose of coating a P3HT layer on the device is to control the release of the molecules contained in the PVA layer. It has been reported that the wettability of P3HT can be tuned by electrochemical oxidation under a bias voltage.[19] To confirm this property, we characterized the contact angles of water on the P3HT thin film of a device before and after the application of a bias voltage of +1.0 V. The bias voltage was applied for 3 min on the ITO electrode relative to an Ag/AgCl electrode placed in a phosphate buffered saline (PBS) solution. As shown in Figure 1B, the contact angle of deionized (DI) water on the neutral P3HT film (before voltage application) is 105.3° and it is decreased to 59.9° after the oxidation (after voltage application). The change of the surface energy of the P3HT thin film is related to the charge and density of doped anions, which is similar to the case of many other conjugated polymers like polypyrrole and polyaniline reported before.[18,19,21–23] When a

positive voltage is applied, small polarons (holes) with positive charges are induced in the backbone of polymer chains due to the doping of anions from the PBS solution. Consequently, dipoles formed by holes and anions can increase the surface energy of the P3HT film, leading to the wettability switching from hydrophobicity to hydrophilicity.[19] After the removal of the bias voltage, the contact angle was then recovered to about 90° in ≈10 min in the PBS solution, which can be attributed to the diffusion of the doped anions back to PBS solution (reduction process) because no chemical bonds were formed between the anions and the P3HT polymer chains. The contact angle θ was fitted with the equation: $\theta = \theta_0 + \Delta\theta(1 - e^{-t/\tau})$, where θ_0 is the initial contact angle for the oxidized P3HT film, $\Delta\theta$ the recovery value of the contact angle, t time, and τ is the time constant for the recovery process. The best-fitting curve in Figure 1B shows that the time constant $\tau = 4.09$ min, which reflects the average diffusion time of anions from P3HT back to the PBS solution.

Next, we demonstrate that this hydrophilicity-hydrophobicity switching behavior can be readily used for controlling the penetration of aqueous solutions across the P3HT film and thus the releasing of molecules from the underlying PVA layer to the target electrolyte. For this purpose, a device was enclosed in a poly(dimethylsiloxane) (PDMS) well where PBS solution was filled as an electrolyte. In the device, we added fluorescein sodium salt (FSA) $C_{20}H_{10}Na_2O_5$ in the PVA layer. The molecular weight (M_w) of FSA is 376.28 g mol^{-1} and the structural formula is illustrated in the inset of **Figure 2**A. The concentration of the released FSA in the PBS solution can be conveniently determined by measuring its UV–Vis absorption spectrum. The experiments were then carried out in the following steps. PBS solution with the volume of 1.5 mL was first added to the PDMS well and then an aliquot of PBS solution (80 µL) was taken out after every 10 min by a pipette for measurement. Next, a bias voltage of +1.0 V was applied between the ITO electrode and the Ag/AgCl electrode in the PBS solution for 3 min. The same amount of PBS solution (80 µL) was taken out and tested each time to check the concentrations of the released FSA when the voltage was applied for 1.5 and 3.0 min. The same analysis was also done at 5, 10, 18, and 30 min after the removal of the bias voltage.

Each solution sample taken out by a pipette was diluted to the volume of 800 µL and characterized under a UV–vis absorption spectrophotometer. As shown in Figure 2A, negligible light absorbance of FSA can be detected in the PBS solution before the application of a bias voltage, indicating that FSA in PVA is protected very well by the hydrophobic P3HT layer on the top. After the application of the bias voltage for 1.5 min, an absorbance peak at ≈490 nm is observed in the solution, suggesting that FSA molecules are released across the P3HT film to the PBS solution. When the bias voltage is applied for 3 min, the absorbance peak intensity is increased by about 106%. Since the absorbance peak intensity is proportional to the concentration of FSA in PBS, the amount of the released FSA molecules is thus doubled when the bias period is extended from 1.5 to 3 min.

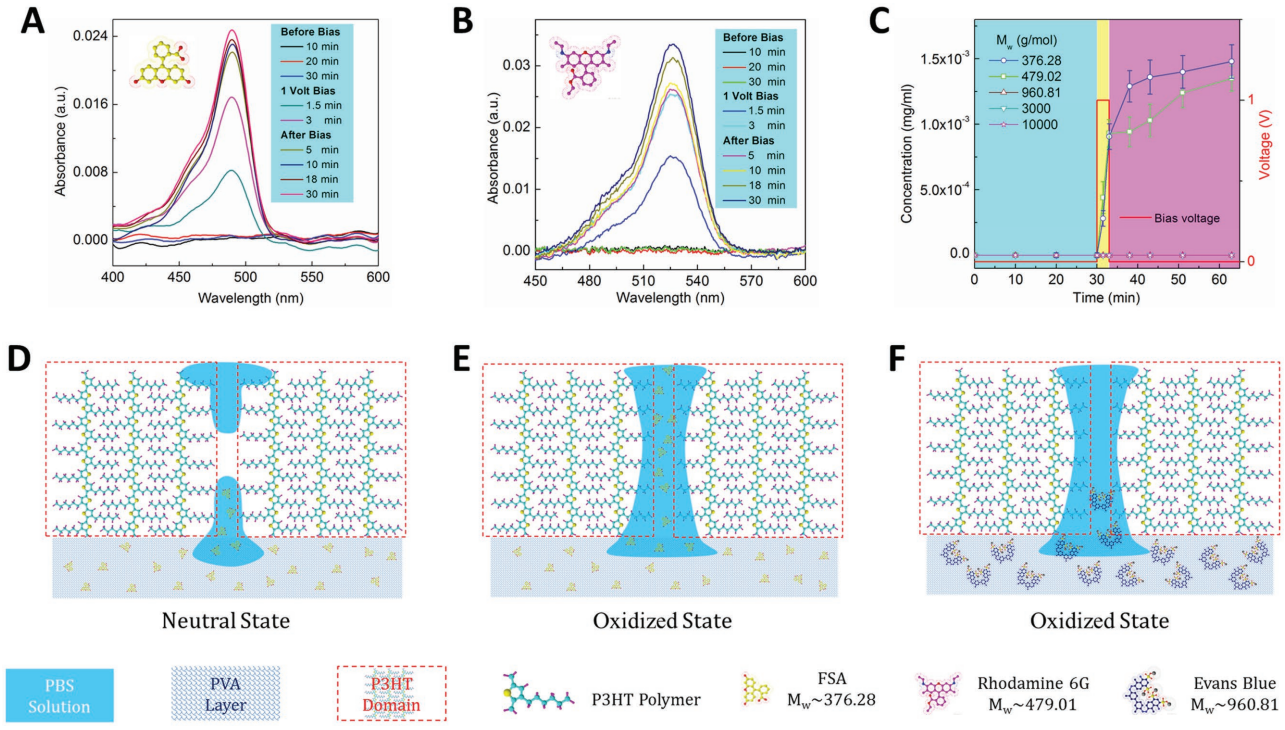

Figure 2. Molecular release of organic devices controlled by a bias voltage. UV–vis absorption spectra of A) FSA ($C_{20}H_{10}Na_2O_5$, $M_w \approx 376.28$ g mol^{-1}) and B) Rhodamine 6G ($C_{28}H_{30}N_2O_3$•HCl, $M_w \approx 479.02$ g mol^{-1}) in PBS solutions at different time. A bias voltage of 1.0 V is applied on the devices for 3 min. Inset: structural formula of the corresponding molecules. C) The time-dependent concentrations of released molecules for different molecular weights before and after the application of bias voltages. The error bars represent the standard errors for at least three identical devices. D) Schematic diagram for a neutral P3HT film that is hydrophobic and impermeable to an aqueous solution. E) Small molecules (FSA) can while (F) big molecules (Evans Blue) cannot penetrate an oxidized P3HT film.

After the removal of the bias voltage, the peak intensities of the absorbance spectra at 5, 10, 18, and 30 min increase with the increase of time, indicating that slow molecular release still occurs even without a bias voltage. It is worth noting that the releasing rate dramatically decreases with the extension of time and the peak intensity tends to saturate after a relatively long period (see Figure S1, Supporting Information). The time-dependent peak intensity of FSA in the PBS solution $I(t)$ after the removal of the bias voltage can be fitted with the equation $I(t) = I_0 + \Delta I(1 - e^{-t/\delta})$, where I_0 is the initial peak intensity, ΔI the increased value to the saturation state, and δ the time constant. The least-square fitting of the data shows that the time constant δ is about 28.3 min, which is much longer than the recovery time τ for the water contact angle on the P3HT film in PBS solution. This result indicates that the releasing rate has a nonlinear relationship with the water contact angle on the polymer film. To accurately control the releasing amount in practical applications, the releasing process should be switched off more quickly. Novel conjugated polymers are thus needed, which should have a broader tunable range of wettability and quicker reduction of the oxidation state after the removal of a bias voltage.

It is notable that FSA has negative charge in a PBS solution.[24,25] So the release of FSA in the device is not directly driven by the positive bias voltage applied on the ITO electrode because the electrical driving force is opposite to the moving direction of the molecules. To further confirm this effect, we also applied a negative bias voltage (–0.5 V) on the ITO of a device while no molecular release could be observed because negative bias cannot lead to the oxidation of the P3HT film (see Figure S2, Supporting Information). In comparison, when a positive bias (+0.5 V) was applied on the same device, we found that molecular release occurred immediately, as evidenced by the increased light absorption peak of FSA in the PBS solution. These results indicate that the release mechanism is different from that of OEIPs reported before.[13]

To better understand the releasing process, molecules with different molecular weights were then tested in the devices. Four fluorescent organic molecules, including Rhodamine 6G ($C_{28}H_{30}N_2O_3 \cdot HCl$, $M_w \approx 479.01$ g mol^{-1}), Evans Blue ($C_{34}H_{24}N_6Na_4O_{14}S_4$, $M_w \approx 960.81$ g mol^{-1}), fluorescein isothiocyanate dextran (FITC3000, $M_w \approx 3000$ g mol^{-1}), and fluorescein dextran D1821 (FITC10000, $M_w \approx 10\,000$ g mol^{-1}), were introduced in the PVA layer to further investigate the release kinetics. These molecules are surrogates for a large class of therapeutically useful and bioactive materials such as anticancer drugs, peptides, and RNAs. Therefore, the results establish a good indication of the device in biological and medical applications. As shown in Figure 2B, Rhodamine 6G molecules are able to diffuse through the P3HT film when a positive voltage is applied. Being similar to FSA, the absorbance peak intensity of Rhodamine 6G is dramatically increased when a bias voltage of 1.0 V is applied for 1.5 min and is further increased with the bias duration extended to 3 min. Similarly, the releasing rate decreases noticeably after the bias voltage is removed. Opposite to FSA, Rhodamine 6G ions are positively charged in the PBS solution,[26] which further confirms that the charge of ions is not the reason for the release. By calibrating the relationship between the absorption peak height and the concentrations of fluorescent molecules, we can estimate the time-dependent concentrations of both FSA and Rhodamine 6G released from the devices, as shown in Figure 2C. The average releasing rates for FSA and Rhodamine 6G are estimated to be 7.6 ± 0.8 and 7.8 ± 0.9 ng s^{-1}, respectively. So the releasing rates for the positive and negative ions are very similar, indicating that the electrostatic force induced by the bias voltage has little influence on the molecular release.

In a stark contrast to FSA and Rhodamine 6G, for the molecules, including Evans Blue, FITC3000, and FITC10000, with greater molecular weights (see Figure S3, Supporting Information), the P3HT film is impermeable even when a bias voltage is applied for the same period, as shown in Figure 2C. The size-selective property of our device can enable a defined transport and supply of particular drug molecules with a specific size range in certain applications. Many biological barriers like the stratum corneum of skin and cell membrane are essential to protect organisms from the invasion of environment.[27] Although these natural barriers have highly complicated selectivity and mechanisms, one common aspect is that they could allow very small molecules to diffuse through while block bigger ones.[28] For instance, stratum corneum allows molecules with a molecular weight of below 500 g mol^{-1} to permeate,[29,30] which is very similar to our device's molecular weight cutoff. Since the advantage of our technology is the controllable permeation, a potential utilization of this technology is to serve as an artificial biological barrier after further optimization to satisfy the complex needs of practical applications. For example, P3HT films can be deposited on soft substrates to make flexible devices for wound healing. Drugs can be controllably released to treat wounds. Meanwhile, the devices would allow water and air exchange between the wound and the atmosphere and protect the wound from the penetration of microorganisms, such as virus and bacteria, through the device.

After examining the voltage-controlled release of molecules in the devices, we next attempt to explain the mechanism. P3HT polymers are porous materials containing alternated nanosize crystalline domains and amorphous regions.[31] When P3HT films are hydrophobic in the neutral state, aqueous solutions cannot penetrate across the small pores in the films due to the opposite surface tension of liquid, as sketched in Figure 2D. However, once P3HT films are oxidized by a bias voltage and become hydrophilic, ions or small molecules will be able to diffuse through the small pores in the films, which is the case shown in Figure 2E. If the molecules or ions are over a certain size, the polymer films become impermeable because the pores inside them are smaller than the molecular size as shown in Figure 2F. This explains why the aforementioned big molecules cannot transport across P3HT films.

It is rather difficult to characterize the average size of the small pores in a P3HT film. The pore size should be related to the morphology of the film that is dependent on the processing conditions, the molecular weight, and the regioregularity of the material.[31,32] There are some evidences that ions with molecular weight higher than 100 g mol^{-1} can diffuse into P3HT films and induce changes in their conductivity.[33] A similar property can be found in poly(3,4-ethylenedioxythiophene):poly (styrene sulfonate) (PEDOT:PSS) films, in which molecules like glutamate, aspartate, and amino butyric acid with molecular

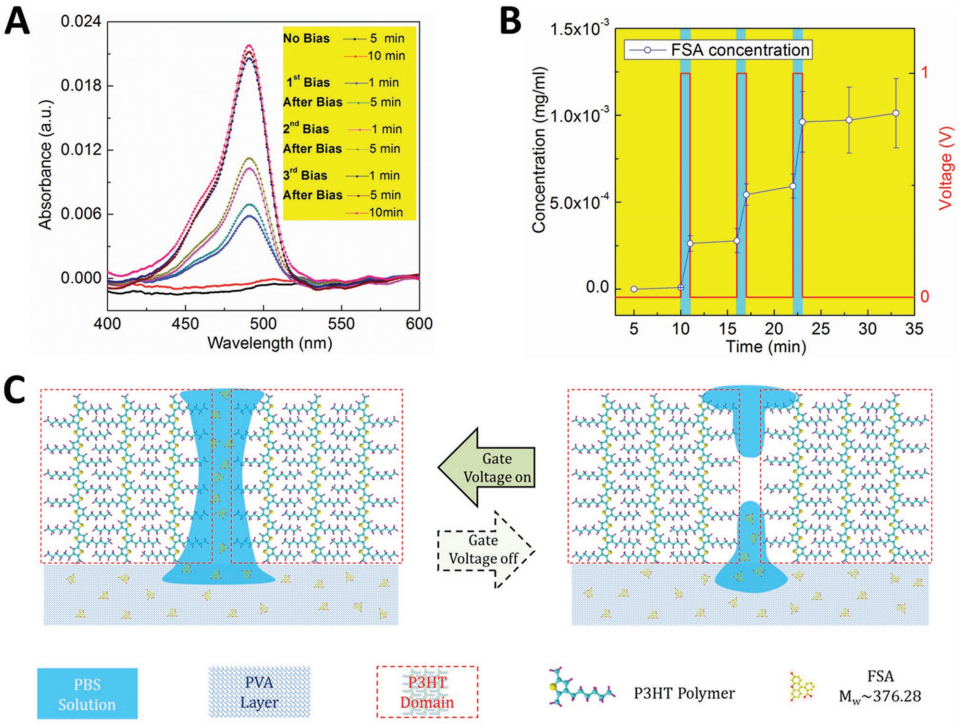

Figure 3. Switchable molecular release of organic devices. A) UV–vis absorption spectra of FSA in a PBS solution before and after the application of bias voltages. B) The concentration of released FSA (left axis) as a function of time under the application of bias voltage (right axis). The error bars were calculated from three devices. C) Schematic diagram for the voltage-controlled permeability and switchable molecule release of a P3HT film.

weights of above 100 g mol^{-1} can be transferred.[13] But the upper limit of the molecular weight for successful molecule transfer in conjugated polymers has not been systematically characterized yet.

In the above tests, an interesting phenomenon is the slowly stopped molecular release after the removal of the applied bias voltage, which can be ascribed to the recovery of the P3HT films to hydrophilic in water as shown in Figure 1B.[19] So the molecular release can be quantitatively controlled by the duration of the bias voltage. To further confirm this function, devices containing FSA were operated by applying a bias voltage of 1.0 V for three steps, and the duration of each step is 1 min, followed by a pause period of 5 min without the bias voltage. The concentration of the released molecules was characterized before and after each step and the results are presented in **Figure 3**A,B. It is notable that significant changes in FSA concentration can only be observed after the application of the bias voltage at each step, indicating that the releasing process can be switched on and off when the bias voltage is set to +1 and 0 V, respectively, as demonstrated in Figure 3C. Therefore, the concentration of the released molecules can be conveniently controlled by changing the duration of the bias voltage.

After knowing the effect of voltage application duration, the influence of the magnitude of the bias voltage on the releasing rate was then characterized. We found that the releasing rate increased with the increase of the applied bias voltage (see Figure S4, Supporting Information), which can be attributed to the improved oxidation level in the P3HT film. As reported in our previous work,[19] the P3HT layer can be oxidized to have a lower contact angle at a higher bias voltage. Therefore, it is reasonable to find that the releasing rate increased with the increase of the bias voltage. On the other hand, it is not necessary to apply too high bias voltage because we observed that a bias of 2.0 V could damage the P3HT film very quickly. Considering that the most sensitive tuning voltage is below 1.5 V as presented in our previous work,[19] the most suitable bias voltage is around 1.0 V. We also prepared devices with the different thicknesses of P3HT layers and found that the releasing rate decreased with the increase of P3HT thickness (see Figure S5, Supporting Information). This result is reasonable because the permeability of FSA molecules should be lower in a thicker P3HT film due to a longer diffusion distance.[34]

Since the devices could be conveniently operated by applying a low bias, we tried to realize remote control of the molecular release by a mobile phone, which will be very useful for many applications especially implantable devices in the future. As shown in **Figure 4**A, the device is connected to an Arduino UNO chip and the molecular release is switched on and off by the mobile phone, corresponding to the bias voltages of +1 and 0 V applied on the device, respectively. The device was first used for the release of FSA. We found that the concentration of the released FSA is proportional to the releasing duration (see Figure S6, Supporting Information), being consistent with the results obtained in previous experiments.

Next, we used devices for the release of a type of biologically functional molecule *cis*-diammineplatinum (II) dichloride $H_6Cl_2N_2Pt$ (cisplatin), which is an anticancer drug with a molecular weight ($M_w \approx 300.05$ g mol^{-1}) similar to that of FSA,[35,36] and show its effect on the cancer cells cultured on the device. The release of cisplatin through P3HT film from

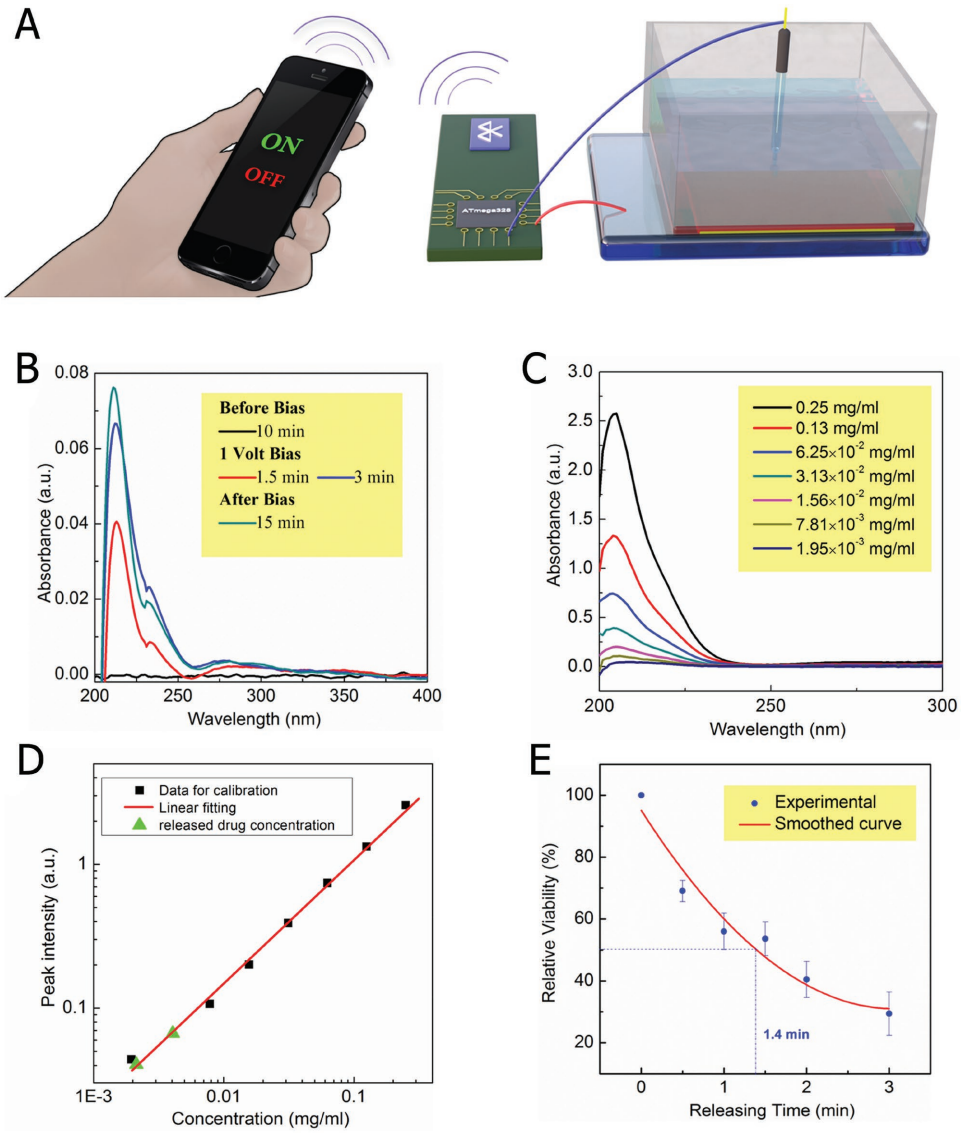

Figure 4. Remote control of drug release. A) Schematic for the molecular release of an organic device controlled by a mobile phone and bluetooth. B) UV–vis absorption spectra of cisplatin released in a PBS solution before and after the application of a bias voltage on a device. C) Light absorption spectra of cisplatin solution with different concentrations. D) The calibration curve for the peak intensity versus concentration. The green triangles are for the release drug concentrations decided from the peak intensity. E) Viability of cancer cells (MCF-7) in the culture media with released cisplatin as a function of bias duration (releasing time) controlled by a mobile phone. The releasing time for IC_{50} was determined to be 1.4 min from the polynomial fitting curve of the viability at different time points.

the drug carrier PVA to a PBS solution was detected by UV–vis absorption measurements at different time and conditions, as shown in Figure 4B. It is apparent that the amount of cisplatin remained unchanged in the first 10 min in the PVA carrier due to the protection of the hydrophobic P3HT film. A pronounced change of the absorption spectra can be observed after applying a positive voltage (+1.0 V) on the device for 1.5 min. It is obvious that the P3HT film was oxidized and switched to be hydrophilic by the bias voltage, thereby leading to rapid diffusion of cisplatin molecules from the drug carrier to the PBS solution. When the voltage application period was extended to 3 min, a further increase in the absorption peak height can be observed, indicating that the continuous drug release occurred. Then drug release was gradually stopped when the bias voltage was switched off and only showed a little increase after 15 min. These findings are similar to the cases for FSA and Rhodamine 6G. To accurately assess the concentration of cisplatin released into PBS, a calibration curve for the relationship between the UV–vis absorption peak height and the cisplatin concentration was obtained as shown in Figure 4B,C. Then the released dosages of cisplatin into PBS solutions were estimated to be 2.13 and 4.06 μg mL^{-1} when the bias voltage was applied for 1.5 and 3 min, respectively. So the average releasing rate of the drug is estimated to be ≈34 ng s^{-1} (or 0.11 nmol s^{-1}), which is three orders of magnitude higher than that of acetylcholine release from an OEIP device at a bias at 5 V.[14]

A mobile phone was then used to remotely control the release of an anticancer drug to treat cancer cells. The solution filled in the devices was changed to cell culture medium. Michigan Cancer Foundation-7 (MCF-7) cell lines were cultured on the P3HT surface of two devices. One device contained cisplatin drug while the other did not possess any drug in the PVA layers. Before the application of a bias voltage, cells were able to grow well on both devices. Then we applied a voltage of +1 V on the ITO electrodes of the devices for 3 min and checked the morphology of the MCF-7 cells cultured on the device afterward. After 12 h, obvious difference of the morphology of the cells between the two samples can be observed (see Figure S7, Supporting Information). The MCF-7 cells possess irregular shape on the device without drug release, indicating that the cells can grow on P3HT film with a good condition. However, the cancer cells cultured on the device with released anticancer drug from the PVA carrier become round in shape, suggesting that the drug release in the device is very effective in influencing the growth of the MCF-7 cancer cells.

To quantitatively illustrate the drug-releasing effect of the devices, cell viability under a bias with different duration was determined to explore the release condition for the half maximal inhibitory concentration (IC50). As a widely used method for assessing cell metabolic activity, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay is a colorimetric test that is based on NAD(P)H-dependent cellular oxidoreductase enzymes to reflect the number of viable cells.[37] First, a bias of +1.0 V was applied on different devices with cell culture medium as an electrolyte for different durations, including 0, 0.5, 1, 1.5, 2, and 3 min. Then, the devices were kept at room temperature for 30 min to fully release the anticancer drug and the drug-released culture medium was collected. Next, MCF-7 cells at a concentration of 10^5 cells mL^{-1} were seeded in the culture medium (100 µL) containing the released drug in a 96-well plate, with six replicates for each time point. After 24 h incubation, the cell viability of cells was determined by the MTT assay. As shown in Figure 4E, the relative viability of the cells is 71.96% for the samples with 0.5 min bias application, which means that the concentration of the released cisplatin at this condition is not high enough. With the increase of the bias duration, the cell viability decreases accordingly due to the increased cisplatin concentration. When the bias duration is 3 min, the cell viability drops to the value of 36.44%, indicating an effective cell killing at this condition. By fitting the curve with a polynomial function, we can estimate the IC50 value of 1.4 min for the devices. In other words, with +1.0 V voltage application of 1.4 min, the liberated concentration of cisplatin is enough to realize 50% inhibition of the cells.

In summary, we observed that the permeability of P3HT films in aqueous solutions can be tuned by a low bias voltage for the first time. Based on this interesting effect, we designed and prepared novel organic devices for voltage-controlled release of different molecules. The device was successfully employed to release an anticancer drug cisplatin to inhibit the growth of cancer cells by a remote control. The releasing process can be conveniently switched on and off via a mobile phone by controlling the bias voltage. It is envisaged that the low-cost and disposable organic bioelectronics devices will be extensively used for controlled and size-selective drug delivery in biological systems.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

conjugated polymers, controlled release, organic bioelectronics, organic semiconductors, tunable wettability

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