Autonomous Microcapillary Drug Delivery System Self-Powered by a Flexible Energy Harvester

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1. Introduction

During the past decades, several organic electronic drug delivery materials and devices have been suggested and demonstrated that provide electronic addressing and control over the on/off dynamics of release and delivery rate of drugs and biochemicals. In conducting polymer electrodes,[1–4] and in their composites,[5] the coupling between electronic charges and (charged) compounds serves as a versatile functionality to control the affinity and diffusion of biomolecules. As the charge accumulation varies in these electrodes, upon doping the electrostatic interaction, volume expansion, and overall morphology change and thus impact the uptake and release of biomedical compounds. In addition, polyelectrolytes are efficient ion exchange systems and have been explored for both passive and active drug release applications,[6] in the form of fibers,[7] ultra-thin shells,[8] and spheres.[9] In a device structure where conjugated polymers are combined with a polyelectrolyte structure, electrophoretic-controlled delivery of drugs can be achieved. The organic electronic ion pump[10] (OEIP) is just such an iontronic[11,12] drug delivery device that has been repeatedly demonstrated to be suitable for implantable therapeutics. The OEIP uses a micrometer-scale selective ionic conductor to electrophoretically transport charged biomolecules from a source reservoir to a target reservoir or tissue. OEIPs have been used in vivo to modulate hearing in guinea pigs by local delivery of the neurotransmitter glutamate,[13] to suppress chronic pain in awake rats by delivery of γ-aminobutyric acid directly to the spinal cord,[14] and to stop epileptic seizures in rats.[15] Further efforts are however needed to enable fully- or semi-autonomous implantable organic drug delivery devices, to enable smart decision making, wireless communication, and self-powering. Here, we report on the feasibility and, to the best of our knowledge, the first demonstration of combining an iontronic drug delivery device, in the form of a microcapillary-based OEIP, with a piezoelectric energy harvester, as a step towards self-powered and highly localized biochemical therapeutic technologies.

In recent years, flexible energy harvesters have been considered as an alternative energy source for several distributed and autonomous emerging technologies.[16–21] In particular, flexible energy harvesters represent a promising energy source for powering various types of wearable and implantable devices through regularly occurring motions or displacements from the surrounding environment or by human movements and activity.[22,23] Their feasibility and biocompatibility for practical use have been demonstrated through numerous experiments
reported in previous papers, including self-powered deep brain stimulation,[24] a self-powered cardiac pacemaker,[25] in vivo self-powered wireless transmission,[26] etc.[27] Therefore, flexible energy harvesters can be used to realize fully flexible bioelectronic systems which can operate a wide array of bioelectronic devices and that exclude the need for regular replacements of bulky batteries.

2. Results and Discussion

In order to supply electrical power for the microcapillary-OEIP (see Figure 1 for an overview of the system and Figure S1, Supporting Information, for a photograph), we implemented a high-performance flexible piezoelectric energy harvester consisting of a large-area lead zirconate titanate (Pb\([\text{Zr}_{x}\text{Ti}_{1-x}]\)O\(_3\), or simply PZT) thin film on a plastic substrate, as previously reported.[19] A 2 µm-thick crystalline PZT film on a rigid sapphire substrate was annealed at 650 °C in air for 45 min and then transferred onto a flexible polyethylene terephthalate (PET) substrate via inorganic laser lift-off (ILLO).[28–30] This ILLO process resulted in no structural damage or material degradation of the active PZT layer. Additionally, we confirmed the proper piezoelectric properties of the PZT film through several material analyses and characterizations. Using scanning electron microscopy (SEM, Figure S2, Supporting Information), we verified a resulting high-quality crystallization of the 2 µm-thick PZT film, which was manufactured through 20 cycles of film deposition. Further, the surface of the PZT thin film was analyzed by X-ray photoelectron spectroscopy, which showed major spectral peaks of the PZT material composed of Pb, Zr, Ti, and O (Figure S3, Supporting Information). From X-ray diffraction and Raman spectroscopy (Figures S4, S5, Supporting Information), we also verified that spectral peaks, before and after the ILLO process, remained constant. From this set of material analyses, we conclude that a high-quality PZT thin film was successfully transferred from the sapphire substrate onto the flexible PET substrate without any significant material deterioration. In Figure 1b, a simplified diagram for the entire self-powered drug delivery system is shown. A microscopic image and a photographic image of two core elements in this system (a microcapillary-OEIP and a flexible PZT energy harvester) are shown in Figure 1c,d, respectively.

We proceeded to investigate the electrical properties of the flexible energy harvester to determine if they match the operational requirements of the OEIP. The flexible energy harvesting device generated an open circuit voltage of \(\approx 170\) V and a short circuit current of \(\approx 1.9\) µA upon transduction of small mechanical deformations (a curvature of 0.5 cm\(^{-1}\) and a strain rate of 2.3%), see Figure 2a,b. In addition, the voltage and current output from the full-wave bridge rectifier used to obtain the DC output of the flexible energy harvester are shown in Figure 2c,d, respectively. The output voltage of the flexible energy harvester routed through its corresponding rectifier circuit (Figure 2e,f, photograph shown in Figure S6, Supporting Information), was used to charge either a 110 µF or 330 µF load capacitor, as shown in Figure 2g. The charged voltage of the capacitors can be described by
Figure 2. Characterization of the flexible energy harvester (f-EH). a) Open-circuit voltage and b) short-circuit current of the f-EH. c) Open-circuit voltage and d) short-circuit current of the f-EH after passing through the full-wave bridge rectifier. e) Circuit diagram for capacitor loading by bending motions of the f-EH (see Figure S6 for photograph in Supporting Information). f) Photograph of the f-EH mounted in the bending machine. g) Voltage versus time plot of charging curves by repetitive bending cycles of the flexible energy harvester (330 μF: ≈3400 cycles; 110 μF: 1400 cycles). h) Magnified charging curve for the 330 μF capacitors over the first 60 s.
\[ V(t) = V_0 \left(1 - e^{-\frac{t}{\tau}}\right) \]  

(1)

where \( V_0 \) is about 78 V and \( \tau \) is RC time constant. The \( \tau \) values were calculated at 374 min (110 \( \mu \)F) and 52.8 min (330 \( \mu \)F) by exponential decay fitting of charging curves. For the operation of OEIPs, both capacitors were charged until they reached 5 V under a bending radius of 20 mm and frequency of 1 Hz. This charging process took approximately 23 min (equivalent to \( \approx \)1400 bending cycles) for the 110 \( \mu \)F capacitor and 57 min (\( \approx \)3400 bending cycles) for the 330 \( \mu \)F capacitor. Figure 2h shows the magnified charging curves of the 330 \( \mu \)F capacitor by continual bending of the flexible PZT harvester with rectifier circuit.

Even though OEIPs have been miniaturized down to planar strips 1.2 mm wide and 200 \( \mu \)m thick, \[41\] this two-dimensional form factor still limits their all-directional mechanical flexibility and would potentially take up too much volume inside the target tissue. In comparison, various fiber-based devices, including capillaries \[32,33\] and optical fibers, \[32,33\] have been studied and successfully used in numerous in vivo applications. Furthermore, multifunctional fibers have recently been shown to offer microfluidic drug delivery in combination with electrical and optical sensing. \[14\] One major drawback of microfluidic delivery systems relates to the fact that flow and dispensing of liquids may perturb the biological target and environment, and also add complexity when designing high-accuracy devices with optimal operational specifications (on/off, spatiotemporal resolution, dose accuracy, etc.). Here, the OEIP offers distinct advantages, as the electrophoretic drug delivery is essentially flow-free and can be driven and exactly controlled by two simple electrodes. \[35\] Furthermore, OEIPs have been repeatedly demonstrated to exhibit very high transport efficiency (ratio of intended drug delivered to electrical driving current, with 100% defined as 1 drug molecule per measured electronic charge) due to the high charge selectivity and effective pore size of the ion transport materials. \[10,13,36,37\] By integrating OEIPs into fibers, \[36–40\] new opportunities open up for implantable devices, as the form factor is more flexible, more easily miniaturized, and can incorporate additional elements (e.g., optical lumina in a multi-lumen fiber). In this work, semi-flexible (Figure 1c) and brittle uncoated silica capillaries were used due to the ease of processing and availability. Improved mechanical conformability, flexibility and/or mechanical stability could be obtained by the use of appropriate coatings or a change to plastic capillaries.

The inside wall of fused silica capillaries (25/125 \( \mu \)m inner/outer diameter) was treated to improve adhesion to acrylates. \[42\] Ion conductive channels were fabricated by filling and polymerizing the negatively charged acrylate monomer 2-acrylamido-2-methylpropane sulfonic acid (AMPS) inside the microcapillaries \[42\] (Figure 3a). After hydration, the polymer (pAMPS, Figure 3b) formed a continuous, homogenous, and stable channel “plug” inside the microcapillary. One end of the microcapillary was fixed to a source solution reservoir (heat-shrink tubing), while the other was free to be placed in the desired target system (Figure 3c). To determine the ion conductive properties of the microcapillary channels, the source reservoir was filled with KCl electrolytes of varying concentration (1 \( \mu \)M – 1 M) and the delivery tip was immersed into a KCl electrolyte of the same concentration (Figure 3d, Table S1, Supporting Information). The conductivity of the channel was then estimated from the electrical current upon application of 5 V between electrodes immersed in the two electrolytes (i.e., using the capillary ion channel as a “salt bridge”). The selectivity towards cations or anions for an ion conductive material is dependent on the concentration of fixed charges in the conductor versus the surrounding electrolyte concentration \[43\] and the specific ion conductive materials used for OEIPs are chosen (or designed) with optimal selectivity in mind. \[32,33\] At low electrolyte concentration the fixed charges in the material can, to a high degree, repel similarly-charged ions (co-ions). The mobile ions in the material are thus primarily oppositely charged ions (counter-ions), resulting in selective ion transport. At increased electrolyte concentration the ability of the fixed charges to repel co-ions is reduced, leading to an increased amount of both co- and counter-ions in the material. The additional ions result in increased conductivity and decreased selectivity. The conductivity versus electrolyte concentration is thus an indicator of the material’s ion selectivity.
where a good ion selectivity results in minimal conductivity increase.

For the pAMPS-loaded microcapillary-OEIPs, the estimated conductivity (Figure 3d) increases only marginally with electrolyte concentration, and significantly less than would be expected if the capillary was filled with the external electrolyte (which should give an approximately linear relationship between conductivity and electrolyte concentration), showing that the pAMPS polymer channel “plug” is fairly cation selective. Furthermore, as expected from a cation selective material, exchanging the cation in the source electrolyte to acetylcholine (ACh, a molecule with a lower diffusion coefficient, and thus expected lower mobility than potassium) significantly reduced the conductivity.

Charge generated by the flexible energy harvester was then used to drive the delivery of the neurotransmitter ACh through flexible microcapillary-OEIPs, by connecting the positive and negative terminals of the charged capacitors to the OEIP source and target electrode, respectively. Additionally, the current through, and the voltage over, the OEIP was continuously measured (Figure 4a). The charged capacitor and the OEIP together form a typical RC circuit where the capacitor is discharged through the OEIP (playing the role of a resistor). In such a circuit, the (discharge) current is expected to decay exponentially according to

$$I = \frac{V_0}{R} e^{-t/RC}$$

where $V_0$ is the initial capacitor voltage, $R$ the resistance of the OEIP, $t$ the time, and $C$ the time constant, which is equal to the product of $R \times C$. After $t = 1$, the current is thus reduced by ~63%. As $R$ is approximately 250 MΩ (Figure 3d), $t$ is on the order of 23 h. The dynamic and accumulated transport of ACh using the flexible ion pump/energy harvester combination was assessed by sampling the target solutions and analyzing the ACh concentration (Figure 4b). The amount of ACh increased linearly with the amount of charge drained from the capacitor, showing a fitted ratio of 10.11 ± 0.25 pmol ACh delivered per 1 µC of charge, or an equivalent delivery efficiency of about 98%. As 3400 bending cycles were needed to charge 330 µF capacitors to 5 V, i.e., to 1.65 mC, each bend of the flexible energy harvester produced enough energy to deliver a 4.9 pmol “dose” of ACh. The 98% efficiency means that the electrical current driving the OEIP corresponds almost exactly to the delivery of ACh

$$ACh\, delivery\, rate = 0.98 \times \frac{I}{F}$$

where 0.98 corresponds to the 98% efficiency, $I$ is the electrical current in ampere (A), and $F$ is the Faraday constant 96 485 C mol⁻¹.

3. Conclusion

We have demonstrated a miniaturized drug delivery/chemical stimulation system powered entirely by a flexible energy harvester. The amalgamation of the microcapillary-OEIP and the flexible energy harvester provide an autonomous solution for self-powering of the highly localized delivery of small-sized drug molecules, ions, and neurotransmitters, especially those of interest for neurological applications.[13–15] Furthermore, since there is a linear correlation of the repeated displacements/bends applied to the flexible energy harvester and the charge/voltage accumulated in the connected capacitor—which in turn drives the OEIP and the release of drugs—one can also foresee auto-suppression of some symptoms of neurodegenerative disorders, such as tremors.[44] Further, with a proper decoding and processing of the flexible energy harvester output signal, one can extend the functionality of the flexible energy harvester beyond just self-powering and auto-regulation of the microcapillary-OEIP to also encompassing communication interfacing and sensing. With such additional features, one can envisage that specific repeated or large displacements/bends could produce a signal beyond a pre-defined threshold which then initiates release of drugs. Such functionality could be of interest, e.g., to initiate immediate therapy protocols or responses due to trauma and accidents.

4. Experimental Section

Manufacturing of Flexible Energy Harvesters: On a double-side polished sapphire substrate, PZT chemical solution (composition ratio of Zr/Ti of 52/48, excess PbO of 10% and a concentration of 0.4 mol L⁻¹) was spin-coated at 2000 rpm for 30 s. Immediately after the spin-coating process, the PZT layer was annealed at 650 °C for 10 min in air via rapid thermal annealing. This process was repeated 20 times to achieve the optimal thickness of 2 µm. After repeating the spin-coating
and annealing process 20 times, the PZT was annealed at 650 °C for 40 min to crystallize the amorphous film. This substrate was attached to a flexible polyethylene terephthalate (PET) substrate by using Norland Optical Adhesive. After attaching to the flexible PET film, a laser lift-off process (XeCl excimer laser, wavelength 308 nm) was conducted to detach the rigid sapphire substrate. Subsequently, interdigitated electrodes were deposited and were patterned in order to harvest energy. A UV-sensitive SU-8 epoxy was coated on top of the device, and finally the poling process was conducted at 80 °C at 800 V for 3 h.

**Electrical Characterization of Flexible Energy Harvesters:** A custom-designed linear bending stage (linear motor and controlling software) and a Keithley 2612A were used to measure the generated electrical signals from the periodic bending motion of the flexible PZT energy harvester and charging/discharging of capacitor. Manufacturing of Micro-OEIPs: 25 μm ID/125 μm OD fused silica capillaries (Molex TSP025150) were stripped of their polyimide coating by immersion in 120 °C concentrated sulfuric acid and rinsed in and flushed with deionized water. Approximately 20 cm of capillary was then flushed with H₂O by application of 5 bar nitrogen pressure at one end, followed by flushing and incubation with 2 M KOH (aq) for 2 h followed by 5 min drying with nitrogen. Next, 3-(trimethoxysilyl)propyl acrylate (10 wt% in toluene) was flushed and incubated for 2 h, again followed by 5 min drying in nitrogen. The polyelectrolyte plug was formed from a mixture containing 4 ml of 2-acrylamido-2-methylpropane sulfonic acid (AMPS, 50 wt% in water), 109 mg 2-hydroxy-4-(2-hydroxyethoxy)-2-methylpropiophenone (photoinitiator). The mixture was flushed through the capillary for 20 min, directly followed by exposure to ultraviolet light (254 nm) for 10 min. The capillary tube was then cut into 15 mm long pieces with a manual fiber cutter (Fujikura CT-02). The individual capillary pieces were mounted to adhesive lined shrink tubing, to form the source reservoir, by gently heating one side of the tube, inserting the capillary, and clamping the tube opening.

**Characterization of Micro-OEIPs:** The micro-OEIPs were soaked in water for at least 24 h before being used. The source reservoir was filled with 1 ml of 1 mM, 10 mM, 100 mM, or 1 M KCl (aq), and placed in an Eppendorf tube filled with the same electrolyte, serving as target. Two strips of poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) coated polyethylene terephthalate (AGFA-Gaevart Orgacon F-350), with silver painted contacts, were immersed in the electrolytes and used as electrodes. 5 V was applied over the electrodes (with negative bias on the electrode immersed in the target electrolyte) using a Keithley 2602A source measure unit, and the current was recorded over 10 min.

**Acetylcholine Assay:** The source reservoir was rinsed with dH₂O and replaced with 1 ml of 0.1 M acetylcholine chloride (aq). Acetylcholine was primed into the channel by applying 20 V until the change in channel resistance levelled and stabilized. The micro-OEIP was subsequently rinsed and placed in an Eppendorf tube with 400 μl 10 mM KCl (aq). Capacitors charged with flexible energy harvesters to approximately 5 V were used as a power source for the micro-OEIP to pump acetylcholine for between 10 and 120 min. The capacitor voltage and the OEIP current were measured using a Keithley 2602A source measuring unit. Evaporation of the source electrolyte was accounted for by measuring the tube’s weight before and after pumping. The acetylcholine level in the samples was determined using an Amplex Acetylcholine/Acetylcholinesterase assay kit (Thermo Fisher Scientific).

**Supporting Information**

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

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**Conflict of Interest**

E.O.G., M.B., and D.T.S. are shareholders in the small, researcher-controlled intellectual property company OBOE IPR AB (oboepi.com), which owns patents related to the ion pumps used in this research. The authors declare no additional competing financial interests.

**Data Availability Statement**

Research data are not shared.

**Keywords**

bioelectronics, drug delivery, flexible energy harvester, microcapillary, organic electronics, self-powered

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