Self-Powered Drug-Delivery Systems Based on Triboelectric Nanogenerator

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1. Introduction

Personalized healthcare is a customized medical model that designs a suitable treatment plan for patients based on personal information and big-data analysis. Compared with traditional therapeutic modes, it could maximize the therapeutic outcome and minimize the unwanted side effects.¹ So far, it is urgently needed for real-time monitoring of the patients’ health and realizing corresponding adjustment of the treatment plan to form a closed-loop diagnosis and treatment system.² On-demand drug release and delivery can control dosage, duration, and rate of drug release, as well as drug-delivery efficiency during disease development or healing progresses, promising substantial improvements in the treatment of local diseases. Compared with those traditional drug-administration routes such as oral or intravenous administration of conventional drugs, on-demand drug release and delivery could control the drug concentration at the disease sites more precisely, thus avoiding peripheral and off-target side effects.³ In addition, it can also release drugs over a long period of time (from weeks to months), avoiding repeated administration and improving patient compliance. Most drug-releasing systems rely either on the exogenous physical stimuli, such as light, ultrasound, electric and magnetic fields, or on responses to endogenous local microenvironment factors, such as pH, enzymatic cleavage, hydrolysis, etc.⁴ Among them, electrical-stimulation-regulated drug release has advantages of repetitively and spatiotemporally controlled drug release (ON/OFF drug-release kinetics), allowing drug delivery at the ideal time and dose, thus showing great potential in improving therapeutic outcomes. Furthermore, drug delivery based on electroporation or iontophoresis can further improve the utilization of released therapeutics. However, bulky electrical stimulators or implantable ones needing frequent battery replacement are inconvenient with poor patient compliance, and even might increase the risk of surgical infection, which impose significant limitations to clinical transformation of the drug-delivery systems. There is an urgent demand for technology to harvest energy in daily life to sustainably power drug-delivery systems.

Recently, a series of energy harvesters have been proposed to power wearable or implantable medical devices, which can convert energy from organisms or surrounding environment into electricity to realize self-powered system. According to the different energy sources, they can be divided into three categories: 1) mechanical energy harvester, including triboelectric nanogenerator (TENG), piezoelectric nanogenerator (PENG), and oscillation generator (OG);² 2) biochemical energy harvester, including biofuel cells and endocochlear potential (EP) collector;³ and 3) environment energy harvester, including photovoltaic cell (PVC) and pyroelectric nanogenerators (PYENG).⁵ Among the aforementioned energy sources, mechanical energy is more abundant and flexible in organisms, such as limb movement, heartbeat, respiration, blood and biofluid flow, and is not limited by the environment and spatial disturbances. As a mechanical-energy harvester, TENG can convert these biomechanical energy into electricity based on the combination of triboelectrification and electrostatic induction.⁶ Compared with other mechanical-energy harvesters (i.e., PENG and OG), TENG has a higher electrical conversion efficiency and has developed four fundamental working modes to adapt to different

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DOI: 10.1002/aesr.202100013
scenarios, including vertical contact-separation mode, lateral sliding mode, single electrode mode, and freestanding triboelectric layer mode. Furthermore, it has advantages of flexibility, lightness, adjustable output and shape-adaptive ability, thus showing great potential in biomedical field for self-powered sensing and therapy. From these points of view, TENG stands out among the aforementioned energy harvesters. In 2016, Wang et al.\textsuperscript{[9]} first integrated a TENG and microneedle arrays on a thin flexible skin patch. Although the electricity generated by the TENG is not used to promote microneedle transdermal drug delivery, this experiment is meaningful for the design of future self-powered drug delivery system. Since then, a wave of self-powered drug release and delivery systems based on TENG technology have been designed, which eliminate the need for any external power sources, and promise to address the challenges of miniaturized on-demand drug delivery for clinical applications.

2. Self-Powered Drug Release

Controlled release of drugs is the key to on-demand administration. Song et al.\textsuperscript{[9]} presented the first TENG-based self-powered controlled drug-release system, which comprised a TENG as the energy harvesting system and a drug pumping system (electrochemical pressure pump, a drug reservoir, and a long microtube). The output of the TENG was transformed and rectified to a direct current (15 V; 1.5 mA) for the electrochemical pressure pumping. The generated oxygen and hydrogen during water-splitting process pressurized the drug reservoir and pumped the drug out of the reservoir through the microtube for ocular drug delivery. The drug-releasing speed can be adjusted from 5.3 to 40 µL min\(^{-1}\), which was determined by the output of the TENG. Electroresponsive biomaterials are the most commonly used drug carriers that can release therapeutic agents on-demand, triggered by local chemical reactions or physical transformations such as redox processes, hydrophilic conversion, degradation, or swelling under an appropriate electrical stimulus. Doxorubicin (DOX)-loaded red blood cells (RBCs) were designed as the antitumoral drug-release system.\textsuperscript{[10]} Upon the electrical stimulation of TENG (70 V), the release of DOX increased remarkably due to the increased permeability of cell membranes caused by electroporation, and then fell back to normal level after the stimulation (Figure 1a). This self-powered controlled drug-release system obtained an outstanding antitumoral efficacy both in vitro and in vivo. In addition, switchable wettability of poly(3-hexylthiophene) films (under voltage of 1–2.48 V)\textsuperscript{[11]} and redox state of polypyrrole (PPy) porous films (0.8–1.2 V)\textsuperscript{[12]} were also used to realize a controlled drug release powered by TENG with a power management module.

3. Self-Powered Drug Delivery

The effective utilization of drugs after controlled release is another focus of on-demand administration. Electroporation uses a high electric field to form transient pores on the plasma membrane, thus introducing foreign molecules into cells. Bok et al.\textsuperscript{[13]} first proposed a self-powered in vitro electroporation system, which integrated a microneedle patch with TENG. Under electrical stimulation of the TENG (≈95 V), the system increased drug delivery to the gelatin hydrogel (model skin tissue) by about fourfold. Our group developed a TENG-powered electroporation system for intracellular drug delivery and transdermal delivery.\textsuperscript{[14]} In this system, a biomechanical-energy-driven TENG as a stable voltage pulse source triggered the increase in cytomembrane permeability. Cooperatively, the nanoneedle-array electrode was used to enhance the localized electrical field at the nanoneedle–cell interface. According to the electrical-field simulation, the local electric field could reach ≈2800 V cm\(^{-1}\) at an applied TENG voltage of 20 V. The integrated system realized an efficient delivery of exogenous species into different types of cells with delivery efficiency up to 90% and cell viability over 94%. Moreover, it successfully achieved a transdermal biomolecule delivery with an approximately fourfold depth enhancement in mice (Figure 1b,c). Other 1D nanostructures such as copper oxide nanowires\textsuperscript{[15]} and silver nanowires\textsuperscript{[16]} are also introduced into the self-powered electroporation systems. Our group designed a high-throughput and self-powered electroporation system assisted by microfoam electrode, and its handle throughput achieved as high as 10\(^5\) cells min\(^{-1}\) on the continuously flowed cells (Figure 1d).\textsuperscript{[16]}

In addition to electroporation, iontophoresis is also an effective physical permeation enhancement approach to deliver charged molecules into the tissues based on electrophoresis and electro-osmosis effects. Typically, the current should be <0.5 mA cm\(^{-2}\) to ensure human safety.\textsuperscript{[11]} Wu et al.\textsuperscript{[19]} designed a self-powered transdermal drug-delivery system based on iontophoresis. A wearable TENG is used to convert biomechanical motions into electricity (10–40 µA) for iontophoresis, and a pair of side-by-side electrodes on soft patch is designed to enable non-invasive iontophoretic drug delivery. This self-powered transdermal drug-delivery system significantly enhanced the delivery depth of model drug molecules to pig skin. Ouyang et al.\textsuperscript{[12]} proposed an integrated system for electricity-responsive drug release and subsequent activation of iontophoresis to improve drug-delivery efficiency (Figure 1e,f). A miniaturized TENG was used to power the system, and a home-built power management circuit was designed to store, adjust, and stabilize the electricity, as well as to switch the two modes of this system (drug release or delivery). This system had achieved a tunable drug release rate from 0.05 to 0.25 µg cm\(^{-2}\) per minute by changing the TENG charging time or the circuit resistance. Also the drug-delivery efficiency on porcine skin was enhanced by ≈50% compared with the conventional transdermal patches (Figure 1g).

4. Conclusion and Outlook

In summary, TENGs have shown promising applications in self-powered controlled drug release and on-demand drug delivery. Due to its advantages of flexible, lightweight and good biosafety, TENG has been widely used in biomedical research to power wearable and implantable devices. Self-powered drug-delivery systems based on TENG not only integrate the advantages of traditional electrical-regulated drug delivery with repetitively and spatiotemporally controlled release but also overcome its disadvantages of frequent battery replacement or charging. Furthermore, due to the flexible structural design and simple operation of TENG, this self-powered drug-delivery system is more comfortable and easier...
for patients to control, which is conducive to the advancement of personalized medicine (Table 1). However, the existing TENG used in drug-delivery system mainly consider the electrical output, while less consideration is given to their portability or wearability.

Table 1. Summary of self-powered drug-delivery systems based on TENG.

| Application               | Mode                        | Size            | Output          | Mechanism                                    | Effect                                      | Ref.       |
|---------------------------|-----------------------------|-----------------|-----------------|----------------------------------------------|---------------------------------------------|-----------|
| Drug release              | Implantable, vertical       | ≈12 cm²         | 70 V, 0.55 µA   | Red blood cell electroporation               | On–off drug release                         | [10]      |
|                           | contact-separation mode     |                 |                 |                                              |                                             |           |
|                           | Wearable, vertical          | 3 × 4 cm²       | ≈600 V          | Switchable wettability of poly(3-hexylthiophene) films | On–off drug release                         | [11]      |
| Drug delivery             | contact-separation mode     |                 |                 |                                              |                                             |           |
|                           | Wearable                    | 2 × 3 cm²       | ≈95 V           | Tissue electroporation                       | Drug delivery increased by 4.4 times        | [13]      |
|                           | Wearable, lateral sliding   | 4 × 5.5 cm²     | ≈20 V           | Tissue electroporation                       | ≈ fourfold depth enhanced transdermal delivery | [14]      |
|                           | Wearable, vertical          | 10 × 10 cm²     | 10–40 µA        | Iontophoresis                               | Enhanced the delivery depth to pig skin     | [18]      |
| Drug release +            |分离模式的盘形TENG            | ≈35 cm²         | ≈15 V, 1.5 mA   | Electrochemical pressure pump; injection    | Pumping flow rates from 5.3 to 40 µL min⁻¹  | [9]       |
| drug delivery             | Wearable, disk TENG         |                 |                 |                                              |                                             |           |
|                           | Wearable, disk TENG         |                 | 19 mW cm⁻²      | Redox state of PPy porous films; iontophoresis | Tunable drug release rate from 0.05 to 0.25 µg cm⁻² per minute; drug delivery to dermis improved by ≈50% | [12]      |

Figure 1. Self-powered drug-delivery systems based on TENG. a) Schematic illustration to show the loading of DOX into RBCs, and the subsequent controlled DOX release by TENG. Reproduced with permission. Copyright 2019, WILEY-VCH. b) Illustrations of TENG-driven in vivo electroporation system for transdermal drug delivery. c) Fluorescent images showing tissue sections for dextran-FITC delivery after nanoneedle-array (left) and nanoneedle array + TENG (right) treatment. Reproduced with permission. Copyright 2019, WILEY-VCH. d) Schematic illustration of the TENG-driven high-throughput electroporation system. Reproduced with permission. Copyright 2020, American Chemical Society. e) Schematic illustration of the self-powered, on-demand drug release and transdermal delivery system. The system consisted of transdermal patches (drug patch and iontophoresis patch electrode), TENG, and power management circuit. f) Drug release curve in the 20 min electricity-stimulated duration and 60 min pause period. g) The fluorescent images show the drug delivery on porcine skin ex vivo after drug release and iontophoresis. Reproduced with permission. Copyright 2019, ELSEVIER.
Also it is still a challenge to collect the weak and disordered mechanical energy of human bodies and directly apply it to the application circuit. Therefore, it is urgent to design a flexible structure to efficiently collect human mechanical energy, and design a suitable circuit management module to transform the electrical output to match the application circuit. In addition, TENG can also be designed as a mechanical sensor with excellent performance and high sensitivity. A large number of implantable and wearable TENG-based sensors have been reported for monitoring cardiac, pulse and respiration activities, as well as joint and muscle movement. Moreover, the monitoring signal can be wirelessly transmitted and big data can be established to judge whether various physiological indicators are normal, which is of great significance for the diagnosis of many diseases. Thus, a closed-loop drug-delivery system is expected to be realized by combining real-time disease diagnosis and on-demand drug delivery. With the contribution of worldwide researchers, the self-powered drug-delivery systems show great prospects for self-tuning drug delivery as well as wearable and implantable medicine for personalized healthcare.

Acknowledgements
The work was supported by the National Key R&D project from Minister of Science and Technology, China (2016YFA0202703), the National Nature Science Foundation (No. 82072065, 81471784), and the National Youth Talent Support Program.

Conflict of Interest
The authors declare no conflict of interest.

Keywords
controlled drug release, drug delivery, self-powered, triboelectric nanogenerators

Received: January 15, 2021
Revised: February 2, 2021
Published online: March 8, 2021

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