

Recent Progress of Nanogenerators Acting as Self-Powered Drug Delivery Devices

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Self-powered technology based on nanogenerators (NGs) has developed rapidly since the invention of NGs. This technology can transform mechanical energy into electrical energy and be applied to self-powered healthcare systems. Meanwhile, after the development of five generations, drug dosage forms have entered the era of pulsed drug delivery system (DDS), which promotes the application of NGs in self-powered DDS. This review first reviews the type, working principle, materials, and structure strategy of NGs. Next, frontier applications of NGs as drug delivery devices (DDD), in combination with membrane, microneedle, electrochemistry, microfluidics, and electroporation techniques, are introduced. Then the challenges of NG technology applied for clinical treatment and research are discussed. In the future, NG may become the key technology for drug controlled release, which can realize precise drug delivery and clinical disease therapy.

dosage forms have undergone five generations. The first generation is the paste or pill containing active pharmaceutical ingredient, which can be used externally or orally. The expansion of clinical demand and the way of administration promote the second generation of agents, namely currently used aerosol, capsule, tablet, and injection. The controlled drug delivery system (DDS), named the third-generation product, can achieve long-term maintenance of effective drug concentration in vivo after one or several doses of administration, which can circumvent the limitation of administration time and number of times.^[2] The fourth generation of targeted DDS can achieve drug enrichment in specific organs, tissues, and cells,

1. Introduction

When drugs are used in disease prevention, diagnosis and therapy, they all need to be prepared into appropriate dosage forms. Drug effect is usually valued by the rationality, precision, safety, and effectiveness of the dosage forms.^[1] The drug

which can not only reduce the toxic and side effects of drugs to the body, but also improve the therapeutic effect. The targeted DDS is most widely applied in the field of tumor therapy.^[3] Based on the synchronization of chronobiological technology and physiological rhythm, the pulsed DDS that automatically releases drugs in vivo during the period of disease, can be considered as the fifth generation (Figure 1).^[4]

Since the 1990s, as the interdisciplinary fusion of material science, bionics and modern biomedical makes great progress in the studies of drug release, the research of drug dosage forms has entered the era of DDS, mainly including controlled DDS,^[5] targeted DDS^[6] and intelligent pulsed DDS.^[7] Recently, Trani et al. demonstrated a silicon carbide-coated nanofluidic membrane to tunably control drug release. By applying a low-intensity voltage to an encapsulated electrode, a large polymer poly(sodium 4-styrenesulfonate), a small fluorophore (Alexa Fluor 647) and a medically relevant DNA were achieved to reproducible and repeatable release.^[8] In 2020, Shadman et al. employed biodegradable poly(D,L-lactic-co-glycolic acid) (PLGA) fibers formed by thermal drawing process for sustainable release of FITC-labeled dextran.^[9] In the same year, Zhong et al. presented a biodegradable *spirulina platensis* (*S.plantensis*) based target DDS, which had been used to deliver doxorubicin (DOX) for breast cancer therapy and imaging in vivo.^[10] Also in 2020, An et al. developed an iontophoretic transdermal DDS utilizing polypyrrole incorporated poly(vinyl alcohol) (PYP) and disposable reverse electro dialysis battery, which could electrically mobile Fluconazole and Rosiglitazone for the treatment of diet-induced obese mice.^[11]

DDS makes a great contribution to the modern medicine, but its further development still faces many challenges, such as how to reduce dose-dumping release due to weak ability of

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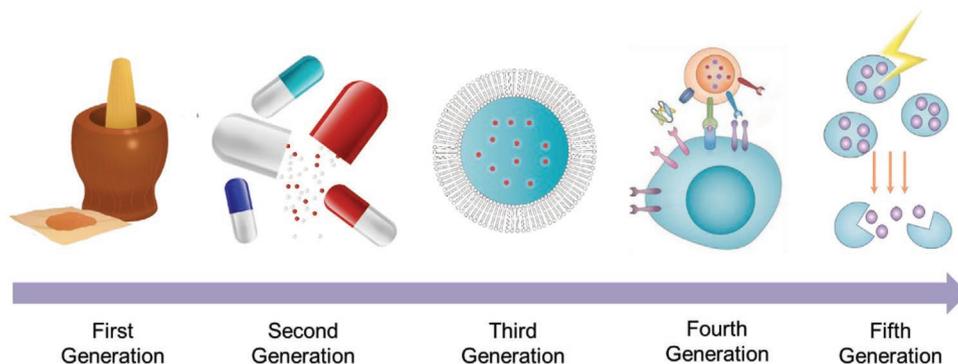


Figure 1. The development of dosage forms. The 1st dosage form of paste, the 2nd dosage of capsule, the 3rd dosage form of controlled DDS, the 4th dosage form of targeted DDS and the 5th dosage form of pulsed DDS.

controlled release, degradation of active pharmaceutical ingredients, toxicity of the materials, high production costs and patient discomfort caused by large size. Another burning problem is power supply of implantable pulsed DDSs. As the battery life is limited, they need to be removed by a secondary surgery, which undoubtedly increases the risk of infection or death as well as the economic burden to the patients.

The self-powered technology based on nanogenerator (NG) provides practical solutions to the above problems. Self-powered system is a system that can function and work without an external power supply. In intelligent controlled DDS, self-powered devices can generate electric power to fundamentally solve the energy problems of controlling drug release, and the output can be regulated by the structure and function design of NGs. In addition, biodegradable NG can not only effectively avoid the surgical risk, but effectively reduce the volume and quality of the entire drug delivery device (DDD). Professor Zhong Lin Wang first proposed and developed the NG in 2006, realizing the conversion of mechanical energy into electrical energy.^[12] In the past decade, a series of NG technologies, including piezoelectric nanogenerators (PENG),^[13] triboelectric nanogenerators (TENG),^[14] and pyroelectric nanogenerators (PYENG),^[15] have been invented to make a great progress in self-powered systems. There are a variety of mechanical energy, chemical energy and heat energy in human body, among which mechanical energy is the most common and abundant. For example, human walking, running, contraction/diastole of heart, muscles, lung and blood vessel will produce mechanical energy, which can be collected and converted into electrical energy by the self-powered technology.^[16]

The NG can not only collect biomechanical energy, but also combine with modern biological, chemical, medical and other technologies to be integrated into the new intelligent DDSs. This review first briefly introduces the type, principle, materials and structure strategy of the NG. In addition, we focus on the research progress of self-powered DDDs combined with the microneedle technology, membrane technology, electroporation technology, microfluidic technology and electrochemistry technology for the intelligent DDSs (Figure 2). Finally, we discussed the challenge and future research direction of self-powered DDDs for the clinical application. This review could promote the future evolution of NGs for DDDs in daily life and in clinic.

2. Working Principle of NG

The theoretical origin of NG is based on Maxwell displacement current.^[17] For example, TENG is generally made up of two triboelectric layers and two electrodes. When the triboelectric layers independently move vertically/horizontally to each other, this will introduce opposite charges on the surfaces. Under periodic external force, these charges can generate electric field varied over time. Then the change of magnetic flux induced by time-varying electric field leads to the generation of displacement current between the two electrodes.^[18]

2.1. TENG

The principle of TENG is based on coupling triboelectrification effect and electrostatic induction effect. When the two triboelectric layers of TENG rub each other in the process of vertical or horizontal contact, charging effect will be produced. The basic principle is that the electrons is transferred from one material's

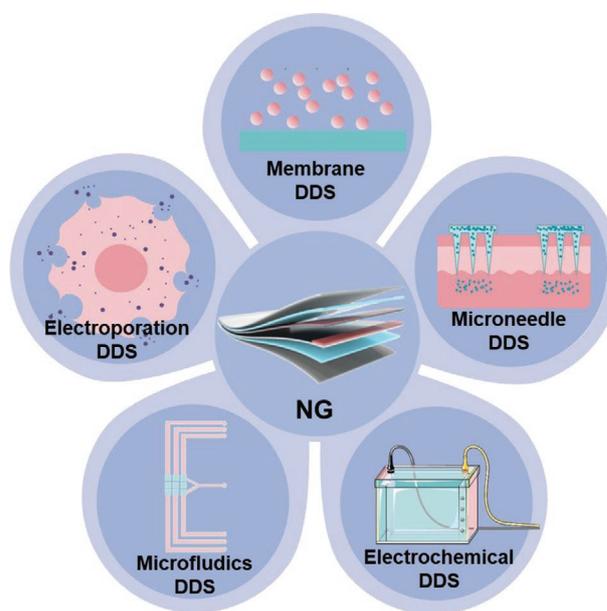


Figure 2. Several major applications of NG as the DDD.

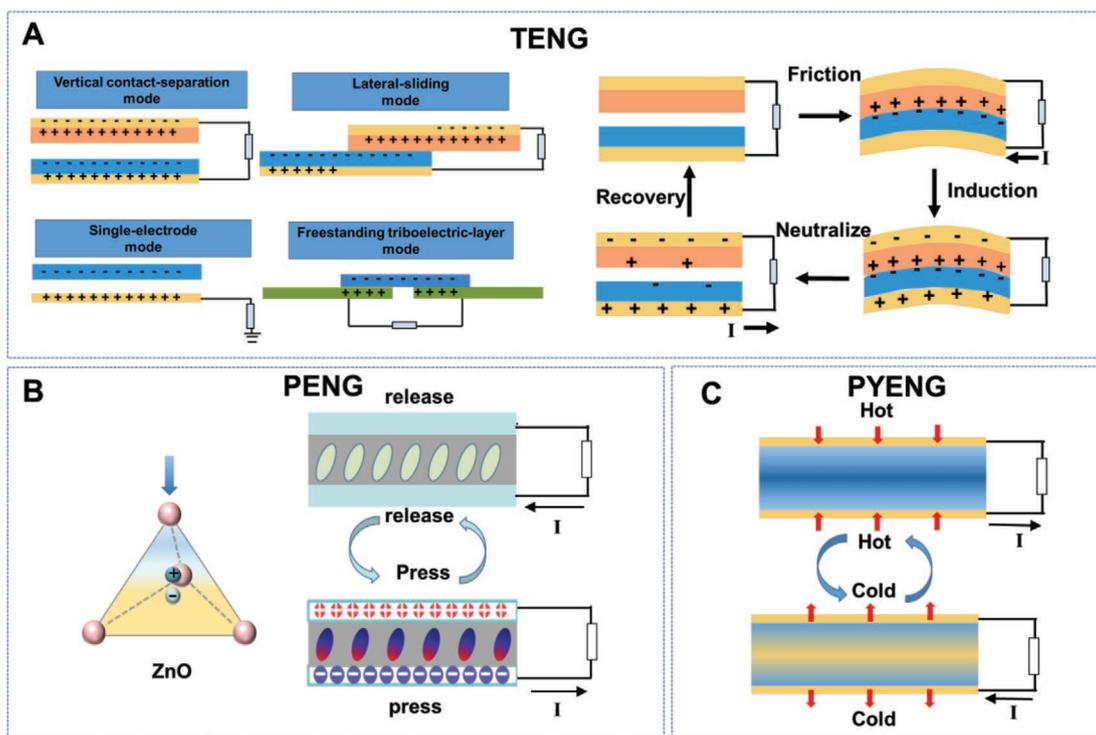


Figure 3. Structure and working mechanism of A) TENG, B) PENG, and C) PYENG.

surface to another due to their different electron binding ability, meanwhile, opposite charges are generated at the back electrodes of the two materials because of electrostatic induction. As the two materials are separated by external force, electric potential difference caused by opposite charges will drive the electrons flow to balance it. Thus, the electricity current is generated.^[19] Based on this mechanism, TENG can be divided into four basic working modes: lateral sliding mode, vertical contact-separation mode, single-electrode mode and freestanding triboelectric-layer mode (Figure 3A). The TENG of lateral sliding mode consists of two electrode layers, two triboelectric layers, and the connecting wires, which has the advantage of efficient charge transfer. The vertical contact-separation mode is made up of two triboelectric layers stacked face to face with metal electrode layer on the back and employs the vertical polarization. This type of TENG has the advantage of simple fabrication, easy packaging and low triboelectric layer material loss, thus playing an important role in implantable devices. The single electrode mode is invented for collecting energy from a moving object getting rid of connecting lead.^[20] The TENG with freestanding triboelectric-layer mode includes a free-moving frictional object and two abreast electrode layers. As the bottom electrodes are not in complete contact with the free-moving frictional object, this working mode can significantly extend the service life of the device.^[21]

2.2. PENG

PENG is composed of two electrodes and one piezoelectric material in the middle. As the center of negative and positive ions in the piezoelectric materials is no longer overlapped

under the action of external forces, a dipole moment will generate, thus generating the piezoelectric potential. At this time, when the external electrode of the piezoelectric material forms a circuit by the leading wires, the electrons will flow between the external electrocircuit to eliminate the potential difference. The materials of PENG can be divided into N-type and P-type. Take zinc oxide of wurtzite structure as an example. Under normal conditions, Zn^{2+} and O^{2-} are stacked and arranged in tetrahedron structure along the direction of c-axis and the centers are overlapped. When ZnO nanowire was deformed by outer stress, piezoelectric potential is generated. Electrical energy can be temporarily stored in the Schottky barrier at the tip of the ZnO nanowires and the metal electrode. If the electrodes at the ends of deformed ZnO are connected by lead wire, the charges will move to an equilibrium state (Figure 3B).^[22] Since the mechanical-to-electrical energy conversion principle of PENG was first described by Zhong Lin Wang,^[12] a series of flexible PENGs and applications have been developed successively.

2.3. PYENG

PYENG is a device that employs pyroelectric effects to convert thermal energy of the environment into electrical energy. Pyroelectric effect is the phenomenon that when some crystals are heated, their polarity changes with the change of temperature, resulting in the change of surface bound charge of crystals.^[23] Once the temperature of the material increases with time, the internal spontaneous polarization strength will also increase. Then electron can flow through the external circuit. When the temperature rises to the highest point, the temperature

and material polarization will not change, and the current will disappear. As the crystal temperature is lowered, the polarization of the crystal increases and the current is generated again (Figure 3C). PYENG is sensitive to the temperature and has great potential in temperature controlled closed loop DDS.

3. Materials and Structure Strategy for NG-Based DDDs

3.1. Materials

3.1.1. Triboelectric Materials

TENG has many advantages, such as high voltage, lightness, low cost and simple preparation. Almost all the materials have triboelectric effect, which include silk, polymer, metal and wood, thus resulting in a wide selection range of materials for TENGs (Figure 4). The triboelectric materials can be divided into four kinds, namely polymer-polymer,^[24] metal-polymer,^[25] semiconductor-polymer^[26] and others.^[27] In actual self-powered DDDs, the high output performance, low cost, good biocompatibility and sensitivity of materials should be priority. In 2012, the first TENG was proposed by Zhong Lin Wang et al. to collect irregular mechanical energy, which was made by polyester (PET) and Kapton.^[28] For bigger voltage output, metal and polymer was widely used in preparing TENGs. In 2014, Zheng et al. prepared an implantable TENG using Al and PDMS, then implanted it into the chest skin of a rat to harvest respiratory energy.^[29] In 2016, Zhao et al. used Al and Kapton to make a TENG with the voltage up to 1500 V.^[30] In the same year, polytetrafluoroethylene (PTFE) film and Al foil were utilized by Li et al. and the prepared TENG was implanted to a large animal Dutch pig.^[31] Lately, poly(vinyl alcohol) (PVA), poly(caprolactone) (PCL), poly(lactic acid) (PLA), and PLGA were used for biodegradable TENG.^[32] These works provide huge potential for developing self-powered TENGs as implanted DDDs.

3.1.2. Piezoelectric Materials

After years of development, the materials of PENG are in continuous improvement. In 2006, Zhong Lin Wang invented the first zinc oxide nanowires based PENG, the output voltage of which was 6–9 mV only.^[12] In 2012, Park et al. made a PENG employing BaTiO₃ nanoparticles doped PDMS membrane, and a commercial light-emitting diodes (LED) was enabled to work by the output.^[33] In 2014, Jeong et al. proposed a PENG using PbZr_{0.52}Ti_{0.48}O₃ (PZT) to generate a voltage of 140 V.^[34] In 2016, Cheng et al. invented a PENG based on polyvinylidene fluoride (PVDF) as a sensor for blood pressure, and the sensitivity reached 173 mV/mmHg.^[35] In 2017, plumbum (Pb)-free LiNbO₃-doped (K, Na) NbO₃ thin-film was used by Jeong et al. to fabricate a PENG.^[36] These improvements increase the output performance, biosafety, flexibility and stability of PENG, which provides new chances for the application of PENG as self-powered DDDs.

3.1.3. Pyroelectric Materials

The materials for PYENG can be subdivided into crystals such as potassium tantalum niobate (KTN), triglyceride sulfate (TGS), ZnO, BaTiO₃, LiTaO₃, etc., and pyroelectric ceramics such as PZT, PVDF, etc. In 2012, Yang et al. demonstrated ZnO nanowires based PYENG for harvest thermoelectricity with the characteristic pyroelectric coefficient of $\approx 0.05\text{--}0.08\text{ V m}^2\text{ W}^{-1}$.^[37] In the same year, Yang et al. reported the KNbO₃/polydimethylsilane (PDMS) based PYENG for harvest heat from the sunlight.^[38] In 2014, Lee et al. invented a PYENG based on poly(vinylidene fluoride-co-trifluoroethylene) [P(VDF-TrFE)], which has the pyroelectric coefficient up to $\approx 200\text{ }\mu\text{C m}^{-2}\text{ K}^{-1}$.^[39] In 2016, Ko et al. demonstrated a PZT based PENG for collect heat energy and mechanical energy in harsh environment.^[40] Therefore, these materials which have both piezoelectric and pyroelectric effect can be designed for both PENG and PYENG.

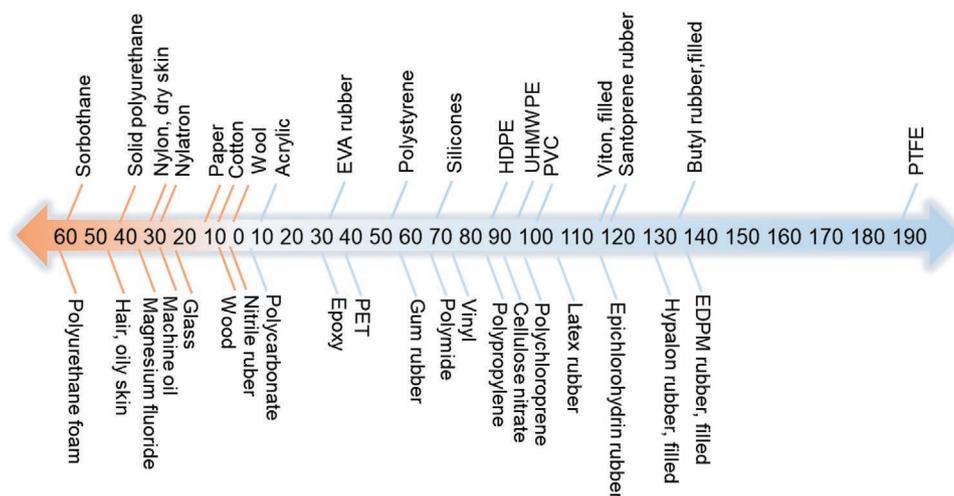


Figure 4. Triboelectric series chart of common materials.

3.2. Structure

3.2.1. Structure of TENG

For in vitro application, the TENGs with freestanding mode, lateral sliding mode and vertical contact-separation mode were mostly used. Based on freestanding mode, TENG designed with disk,^[41] drum and cylindrical structures^[42] are more likely to achieve higher voltage and current output, which are widely applied in DDDs. For implantable TENG, vertical contact-separation mode was most widely used because of the motion style of internal body.^[43] In this structure, a spacer like shim, spring or sponge is commonly unutilized to separate the two triboelectric layers at the initial state.^[44] To improve the outputs and guarantee the stability of the TENG, a highly resilient metal strip based keel structure was fixed on one triboelectric layers to replace the traditional spacers.^[45] Besides, Zhao et al. introduced a pair of magnets to reduce the substrate support of triboelectric layers and spacers, which simplified the structure of implantable DDD.^[46] To further improve the output performances of TENG, various modification approaches of the surface structure were developed. In 2016, Zhao et al. used sandpaper to make various microgrooves on the surface of triboelectric layers to enhance the contact area.^[30] In 2017, Ouyang et al. demonstrated a TENG with surface modification by ICP etching, resulting in nanostructures such as pillars, which were also helpful to enhance the outputs of the TENG.^[47]

3.2.2. Structure of PENG and PYENG

Biomechanical and thermal energy are randomness, multidirectional and small scale. Therefore, PENG and PYENG with thin membraned structure can maximally collect energy and transform it into electric output.^[48] Besides, excellent flexibility and shape-adaptation can also be maintained. Membraned PENG and PYENG are usually fixed on the support materials such as PET and polyimide (PI) film, which also need materials with excellent biocompatibility such as PDMS as encapsulation layer to guarantee the biosafety and stability.

4. Application of Self-Powered Technology in DDSs

As present, most pulsed DDSs employ commercial power sources. However, their finite energy, ultrahigh weigh and rigid structure limit the application in wearable and remote medicine. Especially when the DDDs need to be implanted into the human body for a long time, the energy exhaustion could be a big problem. NGs including TENG, PENG, and PYENG can collect the body movement and environment mechanical energy to provide electric energy without external power source, which can reduce the costs and weigh of DDDs. The manufacturing process can also be simplified. In this regard, these systems could broaden the application of DDDs. Besides, most commercial power sources are not proper for electric stimulation in the DDSs at present. The NG based DDDs can be fabricated with soft and flexible structure for implantable DDSs.

4.1. Self-Powered Membrane DDS

Membrane-controlled DDS are prepared by drug particle, tablet, or powder loaded into polymer films of good mechanical properties and film-forming properties. Based on diffusion driving force generated by the concentration difference between two sides of the film, the drug release behavior and release rate are controlled by the properties of the film.^[49] Traditional membrane DDS can realize the timing and positioning drug release to a certain extent, but just like the microneedle transdermal technology, the drug release cannot be precisely controlled.

In 2018, Zhang et al. proposed a new strategy based on PENG to promote drug release by combining a drug-containing polymer matrix with a piezoelectric substrate (Figure 5A).^[50] The DDD consisted of two parts, one was the substrate formed by vinylidene-hexafluoroethylene copolymer (PVDF-HFP) and modified reduced graphene (rGO), and the other was a drug-loading and releasing matrix formed by a dendrimer of polyam (PAMAM) through lay-by-lay (LBL) self-assembly technology. The piezoelectric membrane could generate a piezoelectric potential of 8.5 V after deformation, which could be maintained above 2 V for more than 10 s. At the same time, the self-assembled matrix membrane had good stability even under the piezoelectric potential and high ionic strength, and was well connected to the piezoelectric substrate after plasma treatment. The positive, negative and amphoteric ions of methylene blue (MB), luciferin sodium (SF), Rhodamine B (RhB) all responded well to the piezoelectric potential by finger pressing. Finally, the author simulated the swallowing process of human by combining with disposable gastric tube in vitro, achieving 200% drug release within 60 min.

In 2019, Zhang et al. prepared a self-powered active enzyme DDD based on piezoelectric effect, including an energy conversion unit with piezoelectric effect, a drug storage and a release unit (Figure 5B).^[51] The piezoelectric energy conversion unit was prepared by PVDF-HFP and modified rGO. Compared with PVDF-HFP alone, the composite film after rGO doped could maintain the piezoelectric potential for a longer time. While the rGO doping rate of 2.5% could produce an open circuit voltage of 5.4 V and a short circuit current output of 100 nA under a force of 5 N. In this study, mesoporous silicon nanoparticles (MSNP) were used as the carrier of the enzyme and assembled into the drug storage unit with polyallyl ammonium chloride (PAH) and DAS through LBL technology, which could keep bioactivity of the enzyme. By pressing the piezoelectric film with finger, accelerated release of drug molecules, such as MB, SF, polypeptides and catalase (CAT), were observed. The device materials have high biocompatibility and can be used as a self-powered implantable DDD, which has high application value in wound healing and antibacterial field.

In 2019, Ouyang et al. proposed a portable TENG driven controlled transdermal DDD to precisely control release of drug on demand.^[52] The DDD consisted of a transdermal patch including a drug patch, a TENG in freestanding triboelectric-layer mode and power management circuit (Figure 5C). The TENG adopted rotary structure and the triboelectric layers were PTFE and Cu. TENG collected mechanical energy from human movement and converted it to alternating current (AC), which was in turn converted to the required direct current (DC) by power management

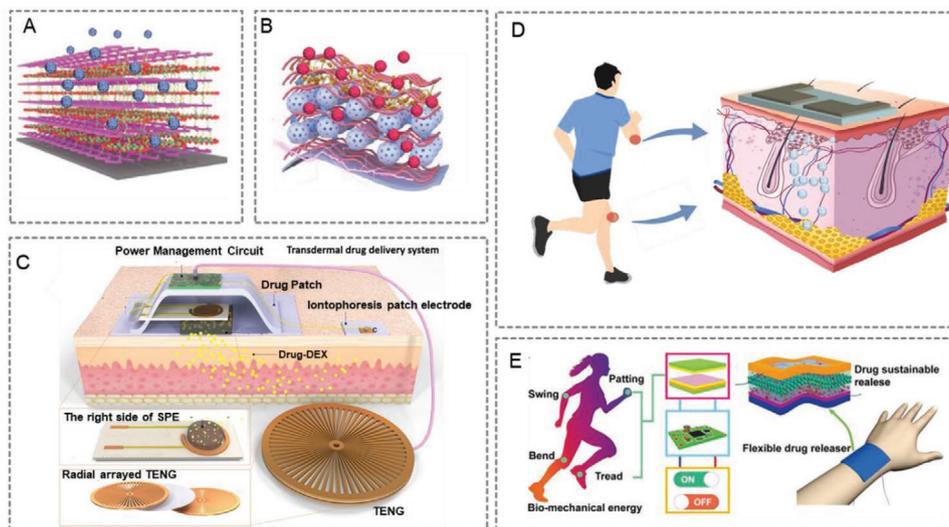


Figure 5. NGs have been applied in membrane DDS. A) The PVDF-HFP based PENG achieved 200% drug release in 60 min. Reproduced with permission.^[50] Copyright 2018, John Wiley & Sons. B) The PVDF-HFP and rGO based PENG could accelerate the release of active enzyme. Reproduced with permission.^[51] Copyright 2019, Royal Society of Chemistry. C) The portable TENG based transdermal DDS precisely controlled release of drug on demand. Reproduced with permission.^[52] Copyright 2019, Elsevier. D) A wearable TENG and iontophoresis hydrogel-based patches were integrated to a membrane controlled transdermal DDS.^[53] E) A flexible DDS based on TENG precisely controlled the delivery of drug with small molecule. Reproduced with permission.^[54] Copyright 2020, John Wiley & Sons.

circuits. Within the drug patch, a screen-printed electrode covered by a polypyrrole (PPy) film acted as a drug carrier for Dexamethasone Sodium Phosphate (DEX-P) and 6-carboxyfluorescein (FLU). After the drug was released under the stimulation of certain electric field, it passed through sponge soaked with phosphate-buffered saline (PBS) and speeded up its penetration into the skin under the action of iontophoresis treatment. The results indicated that TENG could be used for drug release on demand. Manual rotation of TENG (30–40 rpm) for 1.5 min resulted in drug release rate of 3 g cm^{-2} . In addition, the release rate could be accurately controlled in the range of $0.05\text{--}0.25 \text{ g cm}^{-2}$ by varying the charging time of TENG or the resistance of the power management circuit. In addition, an experiment on porcine skin *in vitro* had demonstrated that the drug release rate of the DDS was explicitly governed by TENG operation.

In 2019 Wu et al. proposed a membrane controlled transdermal DDS based on wearable TENG and iontophoresis hydrogel-based patches. Biomechanical energy collected by TENG could be used to drive and regulate drug release behavior for closed-loop exercise and disease surveillance therapy (Figure 5D).^[53] Wearable TENG adopted vertical contact-separation mode, triboelectric layers of which were PTFE and Al foil with the size of $10 \text{ cm} \times 10 \text{ cm}$. PET and Kapton were used as support material and spacer structure, respectively. Three TENGs of the same structure are folded and integrated to produce a voltage output of 1200 V. The hydrogel-based drug patch consisted of two side-by-side hydrogel units and two carbon-cloth electrodes embedded in a PDMS framework. The shapes of TENG were specially designed in order to convert mechanical energy of different parts of the body into electrical energy. The self-powered DDS used iontophoresis to accelerate the release rate of drug patch without additional external power sources. The feasibility of the DDS was successfully demonstrated *in vitro* with the ionic dye Rhodamine 6G (R6G) and MB as the model drugs.

In 2020, Liu et al. introduced a self-powered flexible DDS based on TENG for precisely control the delivery of drug with small molecule (Figure 5E).^[54] The DDS consisted of three parts: a TENG of contact separation mode, a power management module (PMM) and a flexible drug release device (FDRD). The materials of the triboelectric layers were polarized fluorinated ethylene propylene (FEP) and Cu, and acrylic sheet was used as the back support layer. By stepping, arm swinging, leg bending, and clapping, the TENG with size of $10 \text{ mm} \times 50 \text{ mm}$ could produce a voltage output of 600 V, then a stable voltage source managed by PMM is provided for sustained drug release. The bias voltage could regulate the wettability of poly(3-hexylthiophene) (P3HT) films in Na_2SO_4 aqueous solution, which modulated the release behavior of small molecules. When the mechanical switch turned on, small molecules could penetrate P3HT membrane and enter Na_2SO_4 aqueous solution. However, as it was closed, the molecule could not pass through the membrane. By real-time UV-vis absorption spectra, the concentration variation of R6G, fluorescein sodium (FSA) and MB released from FDRD was recorded. In order to further verify the performance of FDRD, small molecule salicylic acid (SA) was successfully detected in Na_2SO_4 aqueous solution under constant voltage, indicating that flexible and self-powered FDRD could realize accurately controlled release of small molecules.

4.2. Self-Powered Microneedle Transdermal DDS

Microneedle arrays are sophisticated micron-grade acicular structure produced by microelectromechanical systems (MEMS) processing machinery. The microneedle technique belongs to one of the physical methods to promote drug release and penetration. According to the actual treatment of customization demand and position, the shape, size, length and materials

(metal, silicon, polymer, etc.) of the needle can be altered. Micron-grade tip can penetrate the skin of the cuticle and reach a certain depth of subcutaneous part. During the piercing process, tiny channels through skin are produced, then some macromolecular drugs such as antigen can reach to specified location in the subcutaneous through the channels, thus greatly improving the absorption and utilization of drugs.^[55] Besides, the transdermal DDS of microneedles can effectively avoid the first pass effect of gastrointestinal tract to significantly improve the therapeutic effect of drugs and improve the compliance of patients.^[56] In addition, microneedle DDS, which has the advantage of the stable treatment effect, weak pain and self-administration, is an effective alternative to traditional transdermal drug delivery. Currently, according to the types, microneedles can be divided into porous microneedles loaded with drugs, hollow microneedles with sustained drug supply, insoluble microneedles coated with drugs and soluble microneedles formed together with drugs. The microneedle DDS is easy to administrate autonomously and reduce the pain feeling of patients. But in order to achieve better personal medical monitoring in the family, accurate control of administration dosage is urgently needed, which is difficult to realize with current microneedle DDS.

In 2015, Wang et al. proposed a stretchable and flexible microneedle skin patch including flexible microneedle array patch, triboelectric energy collector in single electrode mode, drug reservoir, micropump device and dry adhesive patch, which could adhere to the flat skin surface and joint site for drug delivery (Figure 6A).^[57] A single bendable microneedle was composed of a four-beam-pillar base made of polydimethylsilane (PDMS) with optimized stiffness and a rigid point formed by Su-8 photoresist, which ensured a high skin penetration rate as well as a certain volume deformation. This structure could effectively protect the microneedles from fractured during skin puncture. The liquid

reservoir and micropump device of the drug were arranged on the back of the microneedle patch to ensure the release and delivery of the drug after the microneedle acupuncture into the skin. Inspired by the hierarchical structure of Gecko foot hair, the acrylic dry adhesive with micropillar structure on the surface was prepared. The triboelectric energy collection device consisted of a micropatterned PDMS as the triboelectric contact surface, a Cu layer on the back as electrode layer, and a Kapton film covered the Cu layer to protect the metal from scratched. There were two working modes, namely bending and pressing the skin patch for electric generation. As the optimized load resistance of two modes were about 44.44 and 46.8 M Ω , it could generate maximal voltage output about 26 and 28 V, and power about 15.21 and 15.6 μ W, respectively. In the rat model, the microneedle patch could effectively release insulin in 5.5 h for lowering blood sugar level and keep stable for 3 h. Besides, the delivery volume of insulin could be accurately controlled by pressing force.

In 2016, Wang et al. proposed a self-powered DDD to precisely control insulin release and delivery by tapping the micropump device with a finger (Figure 6B).^[58] The triboelectric energy collection device with single electrode working mode included PDMS polymer and Kapton electrode on the back. The pyramid structure on the surface of PDMS could significantly increase output of the energy harvester, which was encapsulated with parylene by chemical deposition method to prolong the lifespan of the device. Finally, the energy collection device was assembled into a PDMS chamber with Al film fixed on the top. The triboelectric energy collection device was integrated into a Su-8 microneedle array to form a skin patch that monitored drug delivery by triboelectric liquid volume sensor. The DDD consisted of four parts: two check-valves, a pneumatic pump-chamber, several drug reservoirs in series and microcirculation channels. By tapping the pump chamber, the

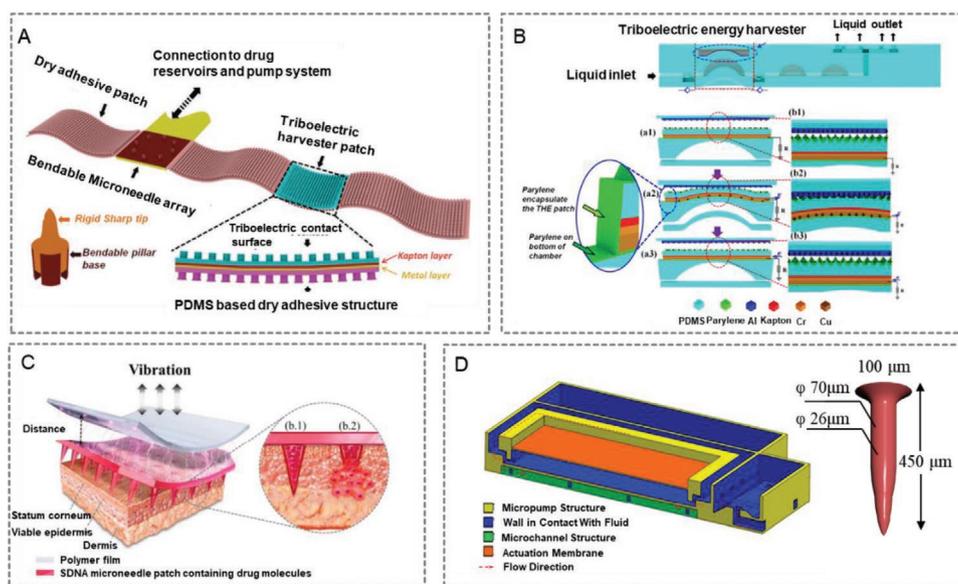


Figure 6. NGs have been applied in DDS integrated with microneedles. A) The single-electrode TENG based on PDMS generated a voltage of 26–28 V. Reproduced according to the terms of the CC-BY license.^[57] Copyright 2016, The Authors. B) The PDMS and Kapton based TENG generated a voltage of about 30 V, which could accelerate the release of insulin. Reproduced with permission.^[58] Copyright 2016, Elsevier. C) The SDNA and PTFE based TENG in a microneedle DDS generated a voltage about 100 V. Reproduced with permission.^[59] Copyright 2018, Royal Society of Chemistry. D) The PENG based on PZT could control the flow speed and direction of drugs. Reproduced according to the terms of the CC-BY license.^[60] Copyright 2019, The Authors.

drug liquid containing insulin in the reservoir could be drawn into the microchannels from the inlet and released through the outlet. After three macromolecular polymer films stacked, the triboelectric collect device was 2 cm × 2 cm in size. By flapping rate of 2 Hz, it generated a voltage of about 30 V and a power of 33 μW when the resistance was 16.67 MΩ. The rat experiment verified that the DDD could effectively reduce the blood glucose level within 5.5 h of insulin release and remain stable for 3 h. Moreover, the output of the triboelectric energy harvester accurately controlled the release of insulin and blood glucose level.

In 2018, Bok et al. combined TENG with deoxyribonucleic acid (SDNA) based soluble microneedles for drug delivery (Figure 6C).^[59] The SDNA-based film and polymer film formed a TENG in vertical contact separation mode, which could generate an electric field applied to the microneedle array and the skin, thus accelerating the transdermal delivery of drug molecules after the microneedle dissolved under the skin. The triboelectric voltage output of SDNA film and PTFE polymer was about 100 V, which was higher than that of SDNA film and polyimide (PI) polymer. Besides, the effects of drug concentration in SDNA films on the output characteristics of TENG were compared, and the result demonstrated that added drug affected the charge movement. When implanting the device into the skin tissue of pork, the voltage of TENG reached about 95 V. As external mechanical force of 2 Hz and 0.2 MPa was used, the release amount of a model drug RhB were about 225 and 50 ng within 60 s, respectively, which confirmed that the TENG effectively accelerated and controlled the release of drugs.

In 2019, Jennifer et al. developed a transdermal microneedle DDD based on piezoelectric effect and thermopneumatic effect through computer-aided design (CAD) technology (Figure 6D).^[60] The device consisted of an array of 38 microneedles, a microvalve formed by PZT and a micropump formed by a closed thermopneumatic film chamber. By changing the temperature, the gas in the top chamber expanded/contracted, resulting in volume and pressure change of the bottom chamber, so as to promote the flow of drug liquid. The flow speed and direction of drugs were controlled by the microvalve composed of a pyramid shaped PZT. The drugs left the bottom chamber and entered the microneedle array for drug release and delivery. The release system could deliver insulin without damaging activity and reduce feeling of pain in patients.

4.3. Self-Powered Electrochemical DDS

Electrochemistry focuses on the conversion of electrical energy and chemical energy. During the electrochemical reaction process, electrode reaction such as hydrogen, oxygen and chlorine can be generated on the electrode surface. The generated gas will be adsorbed on the electrode surface in the form of bubbles, thus resulting in the volume change of reactants in the closed reactor, which can be used to promote and regulate the release of drugs.

In 2017, Song et al. proposed the first implantable DDD based on self-powered technology and electrochemical reaction, which consisted of a TENG, a drug reservoir, a microtube and a pair of gold (Au) electrodes on a silicon substrate (Figure 7).^[61] The TENG adopted rotary structure, which consisted of two Cu layers with gridded structure and a middle PTFE layer. After voltage transformation and rectifying, the TENG could produce a DC

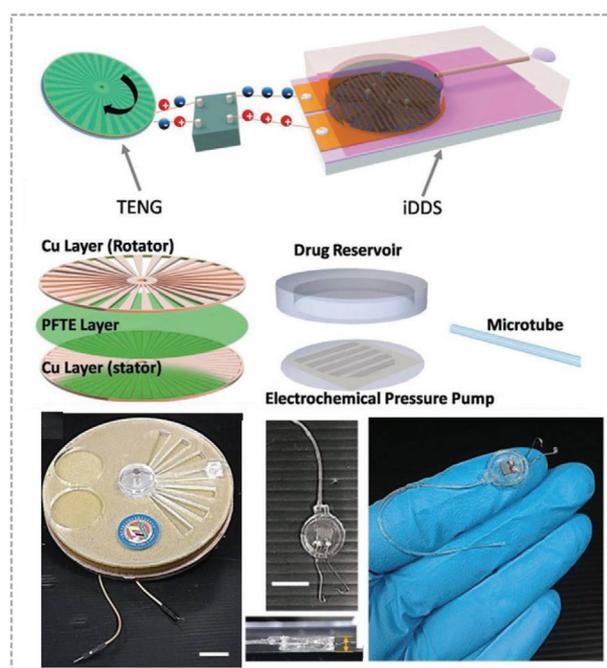


Figure 7. NGs have been applied in DDS using electrochemical reaction. Reproduced with permission.^[61] Copyright 2017, John Wiley & Sons.

voltage of 12–16 V. When TENG rotated, the Cu electrode rubbed the PTFE film, producing free-moving electrons that resulted in an electrochemical reaction between a pair of gold (Au) electrodes in the drug reservoir. The generated gas pressurized the drug storage device, then forced drugs to be released through microtubules. The release speed of drug was determined by the rotational speed of TENG. In the experiment, the release rates of luciferin ranged from 5.3 to 40 L min⁻¹ at different rotational speeds. Besides, in isolated porcine eyes, scleral administration was successfully achieved with the TENG based self-powered DDD.

4.4. Self-Powered Microfluidic DDS

Microfluidic technology, which can accurately manipulate and control microscale liquids, covers a variety of interdisciplinary subjects such as chemistry, fluid physics, microelectronics, materials science, biology and biomedical engineering, etc. Since emerged in the 1980s, it has been widely applied in printing technology,^[62] drug delivery,^[63] chemical analysis,^[64] and so on. In order to control the movement and position of liquids in the microchannels accurately and effectively, it is extremely important to develop some effective liquid operation methods, one of which is electrowetting technique. Electrowetting technique has the advantages of good repeatability, fast response time and low energy consumption. The basic principle is that the contact angle between the substrate and droplets can be changed by applying different external voltages, so as to cause deformation and displacement of the microfluidics. However, in the electrowetting systems, an insulating dielectric film is essential to separate the electrode from the fluids, so a high voltage is required to drive the fluid in practical electrowetting applications. Moreover, the hydrophobic dielectric surfaces gradually degrade under the high voltage,

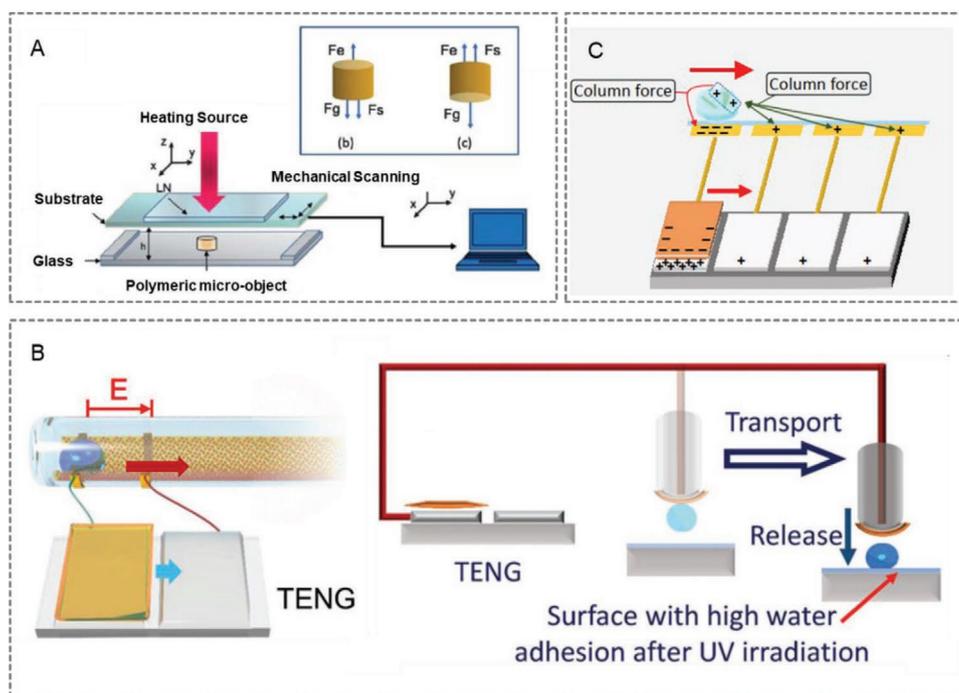


Figure 8. NGs have been applied in microfluidics-based DDS. A) The PYENG based DDS could manipulate small droplets as well as solid. Reproduced with permission.^[65] Copyright 2011, Royal Society of Chemistry. B) The TENG based microfluidic DDS could transport micro/nanodroplets for a long distance. Reproduced with permission.^[66] Copyright 2018, John Wiley & Sons. C) The TENG based on Kapton and Al generated a voltage up to 3000 V, which could drive liquid droplets to a targeted location. Reproduced with permission.^[67] Copyright 2018, American Chemical Society.

thus resulting in failure of the microfluidic system. Hence, it is urgent to develop an appropriate power supply with self-protection ability and safety. In this regards, self-powered technology can possibly solve these problems and further decrease the complexity by sparing external power source and control circuit, which enhance the feasibility of DDS for clinical use.

In 2011, Veronica Vespini et al. proposed a Pyroelectric-Adaptive-Nanodispenser microrobot (PYRANA), which could control the movement of solid or liquid nanometers on the surface of a solid dielectric (Figure 8A).^[65] The PYRANA contained a cover glass, a lithium niobate (LN) crystal, and a cylindrical dielectric between them. On the surface of the cover glass, PDMS was spinning coated to form hydrophobic substrate. At the same time, LN crystals are installed in a mechanical holder which could be controlled by a computer. The pyroelectric field generated when the heating tip is close to the LN could attract the captured dielectric moving. Also, the dielectric could carry droplets from the storage tank position to the target position. The PYRANA could not only manipulate the motion of solid PDMS, poly-methyl methacrylate (PMMA) and multi-walled carbon nanotubes (MWCNTs), but also grab and release droplets of different shapes and sizes.

In 2018, Nie et al. developed an intelligent microfluidic system using TENG and photocontrollable adhesion surface (PCAS), which could transport micro/nanodroplets for a long distance (Figure 8B).^[66] The TENG used freestanding layer mode with triboelectric layers of Al film and Kapton, respectively. The generated voltage of ≈ 3000 V could drive droplets to a distance up to 640 mm (a maximum distance/diameter ratio of 300). Besides, droplets movement under thicker dielectric layer up to 2 mm could also be manipulated. The TENG based

intelligent microfluidic systems show good applicability in both DDS and other fields.

In the same year, Nie et al. developed a microfluidic DDS using TENG in combination with electrowetting technology (Figure 8C).^[67] In this system, TENG adopted the freestanding layer model with free-moving Kapton film at the top and Al film at the bottom as the triboelectric layer. A single triboelectric layer with a size of $8\text{ cm} \times 10\text{ cm}$ could produce an open-circuit voltage up to ± 3000 V. TENG drove liquid droplets containing silver nanoparticles to a targeted location up to 16 mm away when the concentration of nanoparticle was 10 mg mL^{-1} . Besides, droplets could be driven both in horizontal and vertical direction. In addition, a mini vehicle fabricated by a pallet of $6\text{ mm} \times 8\text{ mm}$ and four droplets of minimum 70–80 nL could be used to transport tiny objects under the TENG driving. TENG displayed excellent ability to provide both power supply and control signals for pallet movement with a maximum load of 500 mg and a maximum speed of 1 m s^{-1} . The self-powered microfluidic technology not only has great application value in DDS, but also has broad application potential in microsolid/liquid manipulator, microrobot and human–computer interaction.

4.5. Self-Powered Electroporation DDS

Electroporation is a phenomenon whereby an applied electric field leads to the formation of pores in cell membranes. Its mechanism is that when the width of electric pulse reaches microsecond or millisecond magnitude and the intensity of electric field reaches Kv cm^{-1} magnitude, massive micropores appear

on the membrane. Pore formation will drastically increase the permeabilization of cell membrane, which increases absorption of various drugs, liposomes, proteins and genetic materials and other macromolecules. Based on electroporation effect, electroporation technology combines high voltage equipment to provide voltage with specific pulse width, frequency and value with flat or needle electrode, which can cause breakdown to the cell membrane, thus increasing absorption or release of drugs. Typical electroporation apparatus in research or clinic can output high DC voltage from hundreds to thousands, and pulse frequency can be controlled by the high frequency switch. However, this equipment including generator, capacitor, electrode and corresponding electrode wire usually have large mass and volume,^[68] which limit its application as implantable pulsed DDS. Therefore, the design and arrangement of self-powered NGs and electrodes will contribute to the next-generation electroporation DDS.

In 2019, Liu et al. combined self-powered technology and electroporation technique to develop a DDS for intracellular drug delivery (Figure 9A).^[69] The experiment employed TENGs with lateral sliding model and vertical contact-separation mode, which was suitable for in vitro and in vivo, respectively. The

TENGs with PTFE and Cu as triboelectric materials could generate a voltage of 20 V. In the integrated DDS, self-powered TENG served as a stable voltage pulse source, and the silicon nanoneedle electrode could significantly enhance the local electric field to 400 V cm^{-1} at the interface of nanoneedle tip and cell membrane, which would reduce the mobility of plasma membrane and promote molecular influx with minimized cell damage during electroporation. The integrated DDS could effectively deliver external substances (propidium iodide, glucan, and siRNA) to human breast carcinoma cell line (MCF-7), human cervical cancer cell line (HeLa) and murine bone mesenchymal stem cell line (rBMSCs), with a transfer efficiency of up to 90% and cell viability of over 94%. By finger rubbing or hand slapping the TENG, transdermal delivery of glucan macromolecules into mice was successfully achieved.

In the same year, Zhao et al. designed an implantable magnet triboelectric nanogenerator (MTENG) to control drug release of doxorubicin (DOX) loaded red blood cell (RBC) at tumor sites (Figure 9B).^[46] The MTENG adopted vertical contact-separation mode with triboelectric layer materials of titanium (Ti) sheet and PTFE film. After packaged by PDMS, the

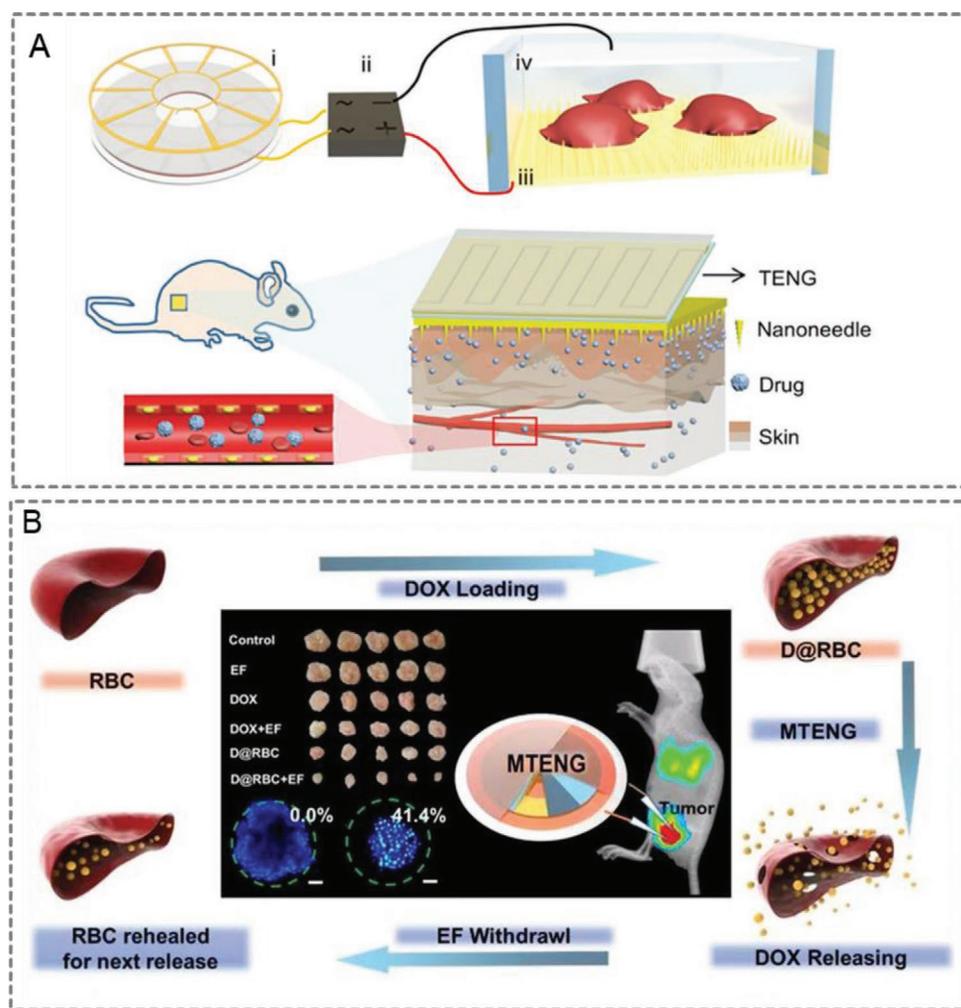


Figure 9. NGs have been applied in electroporation-based DDS. A) The TENG integrated DDS could effectively deliver external substances into cells. Reproduced with permission.^[69] Copyright 2019, John Wiley & Sons. B) The implantable TENG controlled drug release of DOX loaded RBC for tumor therapy. Reproduced with permission.^[46] Copyright 2019, John Wiley & Sons.

whole circular device was 2.5 cm in diameter and could produce a voltage of 70 V. The repulsion force of two magnets enabled MTENG to keep stable for a long time after encapsulation and implantation. Combined with microneedle electrodes or interdigital electrodes, the electric field generated by MTENG can reach above 4 Kv cm⁻¹, which could precisely control the release of drugs in the RBC. When MTENG was working, the drug release speed is 3–4 times of the background value. However, after the electric field was disappeared, the drug release speed quickly returned to the background value. Based on this principle, the DDS achieved excellent tumor cell killing effect under the administration of low concentration at 2D tumor cells and 3D tumor spheres. Moreover, combined with microneedle electrodes, the MTENG based DDS significantly extended the life span of tumor-bearing mice and had barely side effects on tumor-bearing mice in vivo.

5. Discussion

Since the 1990s, pharmaceutical preparations have developed into the era of DDS. In recent years, pulsed intelligent DDS and self-regulated closed loop DDS can control drug release through electricity, heat, ultrasound and other energy, which pay more attention to the demand of physiological rhythm. This progress greatly promotes the development and progress of modern medical treatment. Based on the triboelectrification effect, piezoelectric effect and pyroelectric effect, the NGs can transform the mechanical energy of the environment into electrical energy to provide energy for the DDS. At the same time, the NG devices can realize miniaturization, excellent flexibility and good portability. Combined with microneedle patch, polymer membrane materials, microelectrodes, microfluidic device or electrochemistry devices, NGs (TENG, PENG, and PYENG) can be integrated as the intelligent DDDs without external energy.

The PYENG was first used in microfluidics DDS in 2011, but the progress was slow in the following years. PENG first

appeared in membrane DDS in 2018 to delivery small molecules such as MB, SF and RhB. In the next year, PENGs based on organic PVDF-HFP and inorganic PZT, which had excellent piezoelectric properties, were emerged in the membrane DDS and microneedle DDS respectively. Moreover, piezoelectric film was more likely to realize no-wire DDD. Macromolecules such as polypeptide, CAT and insulin were successfully delivered, but the output of PENG kept nearly stable. The TENG with single-electrode mode first appeared in microneedle DDS in 2015, and the friction layers were PDMS and Cu respectively, which could only generate a voltage of 26–28 V. In the following years, TENG with freestanding triboelectric structure and vertical contact–separation structure could reach up to 3000 V. Because the TENG has the advantage of high voltage, it has widely been combined with microneedle, membrane, electroporation, microfluidic, and electrochemical techniques for self-powered DDSs. Materials play key role for the performance of NGs. The most commonly used TENG materials of frictional layer are PTFE and Al, which show significant electronegativity differences, as well as good biocompatibility and good flexibility. TENG can be used not only as an independent energy collection unit, but also as a friction layer for integrating microacupuncture or polymer film into the DDD. Besides, self-powered DDD have already been used to delivery small molecule drugs (DOX, MB, SF, Dex-P, FLU, R6G, etc.) and macromolecular bioactive protein drugs (insulin, CAT, etc.) (Table 1), which have been successfully applied in the treatment of tumor and diabetes animal models. The output and function principle of different NGs was summarized in Figure 10.

Although self-powered DDD develops rapidly, it still has some shortcomings. First of all, previous research on NGs is limited to only providing energy. Second, the NG and the DDD are relatively independent in the electroporation, microfluidic and electrochemistry DDS. Third, the material selection for the preparation of the NG is restricted. Although the NG materials (PTFE/Kapton/Al, etc.) with voltage output above 100 V are flexible, rigid structure fixation such as acrylic sheet is often required as the support, which greatly affects the wearability

Table 1. Summarization of NG as self-powered DDD.

Technique	Type of NG	Materials	Output [V]	Drug	Literature
Membrane	PENG	PVDF-HFP	8.5	MB/ SF/ RhB	[50]
	PENG	PVDF-HFP	5.4	MB/SF/polypeptide/CAT	[51]
	Freestanding triboelectric-layer TENG	PTFE/Cu	250	DEX-P/FLU	[52]
	Vertical contact-separation TENG	PTFE/Al	1200	R6G	[53]
	Vertical contact-separation TENG	FEP/Cu	600	MB/FSA/R6G/SA	[54]
Microneedle	Single-electrode TENG	PDMS/Cu/Kapton	26–28	insulin	[57]
	Single-electrode TENG	PDMS/Al/Kapton	30	insulin	[58]
	Vertical contact-separation TENG	SDNA/PI/PTFE	100	RhB	[59]
	PENG	PZT	≈2	insulin	[60]
Electrochemistry	Lateral sliding TENG	PTFE	12–16	luciferin	[61]
Microfluidics	PYENG	LN		PDMS/PMMA/MWCNTs	[65]
	Freestanding triboelectric-layer TENG	Kapton/Al	3000		[66]
	Freestanding triboelectric-layer TENG	Kapton/Al	3000	Ag	[67]
Electroporation	Vertical contact-separation/lateral sliding TENG	PTFE/Cu	20	PI/dextran/siRNA	[67]
	Vertical contact-separation TENG	PTFE/Ti	70	DOX	[46]

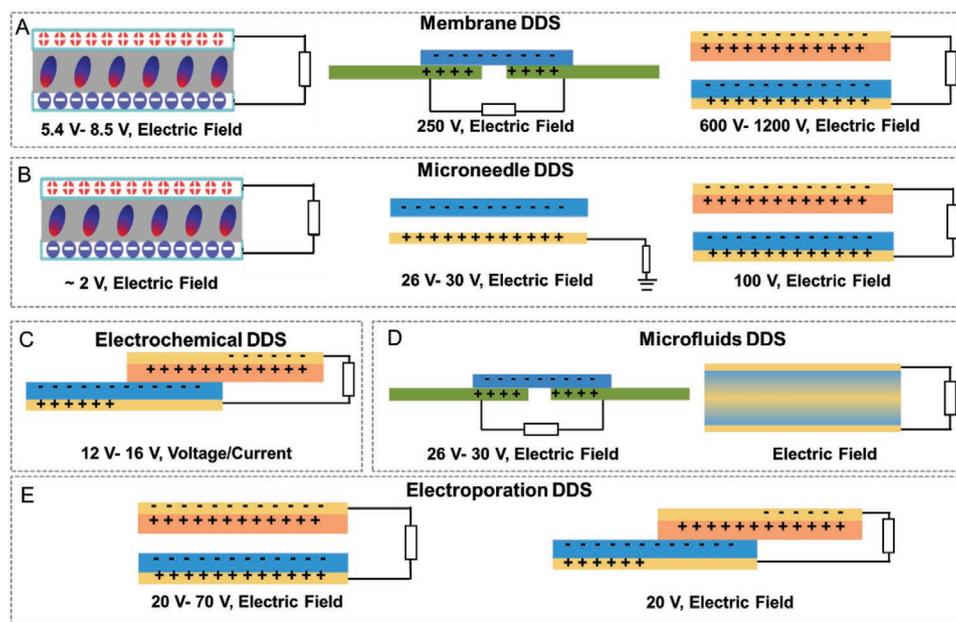


Figure 10. The output and function principle of NGs in A) membrane DDS, B) microneedle DDS, C) electrochemical DDS, D) microfluidic DDS and E) electroporation DDS.

and implantability of the DDS. Finally, the self-powered DDS mostly selects drug models to do the feasibility release research, so the systematic work such as the actual treatment effect of the disease model is still lacking.

In the future, on one hand, the NG can collect mechanical energy and convert it into electrical energy, which can be used for drug release. The electrical output provided by the NG coupled with electricity, light, sound and other related technologies will be integrated into the self-powered DDS. On the other hand, TENG is sensitive to low pressure, and triboelectric potential of the triboelectric layers can be changed by chemical substances such as catechin acid, phenol, heavy metal ions etc. While sensor based on PENG can work under high pressure and PYENG has the advantage of temperature sensitive. Above characters proved that the NGs can act as pressure, concentration of chemical substrate and temperature sensor, which can be used in closed-loop self-feedback DDS. Besides, self-feedback intelligent wireless transmission, display system and electrode equipment are also important research directions in the future. What is more, the successful development of implantable and biodegradable NGs also presents a new development direction for implantable and biodegradable DDS.^[70]

The NG has already been used to monitor the pressure and frequency of heart, pulse, gastrointestinal and bladder physiology, indicating that the NG can act as the self-powered DDS for the diagnosis and treatment of heart and gastrointestinal diseases.^[71] The unique temperature sensitivity of the PYENG can be used as self-powered DDS for fever, inflammation and bacterial infections relative diseases. The voltage and current of the NG can affect the activity of nerve cells^[32] and osteoblasts cells,^[72] which can be used to study the model of nerve injury and bone diseases. Besides, NGs can not only promote the release of drugs such as photosensitizers, but also drive light-emitting devices,^[73] which can be used in the photodynamic therapy of tumor and skin diseases. Moreover, ultrasound can deform piezoelectric

materials, thus generate a piezoelectric potential that can open the blood-brain barrier,^[74] proving that the self-powered DDS can be used in the study of brain relative diseases.

6. Conclusion

There are many kinds of energy in human body and other animals, including chemical energy, thermal energy and mechanical energy. The researchers have proposed various strategies for collecting different forms of energy to build self-powered DDSs, which are significant for the development of wearable and implantable medical devices. A series of self-powered systems based on NGs, including PENG, TENG, and PYENG, have been used to effectively collect the above energy and applied in DDS, biosense, speech recognition, biological monitoring and other fields. By further expansion and exploration, these self-powered biomedical applications will have an important impact on the future healthcare industry. This paper focuses on the NG based DDS, including membrane DDS, microneedle DDS, electrochemical DDS, microfluidic DDS and electroporation DDS. As an emerging research field, these applications are just the beginning of the self-powered DDSs. However, in order to make full use of the self-powered technology and achieve the standard of clinical application, more and more in-depth research is needed. First of all, for implantable scenes, NGs should be more miniaturized, flexible and self-adaptive, so as to reduce the sensation of foreign body and adverse effects caused by deformation of life activities in specific position of the body. As the implantable devices need to be removed by secondary surgery, the biodegradability, absorbability and durability of the materials also need to be studied. For wearable NGs, miniaturization, durability, packaging and electrical output will always be the research focus in the future. Second, the optimization of output performance, the design of

power management module and the study of supporting facilities such as electrodes need to be further optimized to meet the actual clinical requirements. Finally, in view of the future intelligent DDS, the sensing feedback and self-regulating drug release of temperature, humidity, blood oxygen saturation, and blood drug concentration should be together, so the development of hybrid self-powered DDS based on TENG, PENG, and temperature sensitive PYENG is of great significance.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioelectronics, drug delivery, nanogenerators, precise therapy, self-powered

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