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Self-Powerbility in Electrical Stimulation Drug Delivery System

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On-demand drug delivery is one of the main research directions of the drug delivery system (DDS). At present, with the development of various stimulus-responsive materials and technology, it is possible to regulate drug release through various external or internal stimuli. Among them, electrical stimulation DDS has great potential due to its easy combination with sensor or microchip and precise time and space controlled-release ability. At the same time, with the rapid growth of research in self-powered devices, the self-powerbility of electrical stimulation DDS has also received a lot of attention. In this review, the current biomaterials used in electrical stimulation DDS, such as conducting polymers, electroconductive hydrogels, carbon-based nanomaterials, metal, and semiconductors are first introduced. Further the route of administration and recent advances of electrical stimulation DDS is summarized. The development and classification of self-powered devices used in DDS are highlighted. In the end, the major challenges and future perspectives of electric stimuli-responsive DDS are discussed.

1. Introduction

With the development of precision medicine, higher requirements are put forward for drug delivery system (DDS). The traditional DDS has some shortcomings, such as low bioavailability, the fluctuation of blood concentration of the drug, first-pass effect and tolerance of constant rate administration, which will increase the side effects and reduce the clinical efficacy. In particular, for some diseases requiring long-term administration, controlled drug delivery systems on demand that increase safety, therapeutic effect and patient compliance are the key point. The development of materials, electronics, and micromechanical technology has promoted the extensive research and rapid development of DDS for time and space-specific release.

External stimulating signals, such as temperature,[1,2] magnetic,[3] electrical,[4–6] optical,[7] and ultrasound[8] and internal stimulating signals, such as glucose[9] and pH[10] can be used to trigger or control drug release and achieve the purpose of drug administration on demand. Among them, the electrical stimulation system has attracted much attention because electrical signals are easily controlled and can allow repeatable and reliable drug release for clinical needs. At the same time, it can be easily combined with sensors or microchips to control drug delivery and information feedback. It lays the foundation for remote diagnosis and treatment, as well as on-demand precision medicine.[11]

Electrical stimulation DDS is to load the drug into the electric-responsive carrier and use the electric field or current in vitro or in vivo to promote or control drug release. Drug release can be simply divided into pulsed drug delivery and continuous constant speed drug delivery, the drug release can last several days or years. The main research of electrical stimulation DDS can be divided into three parts, including electroactive biomaterials, electrical supply system, and the route of administration. Electroactive biomaterials including conductive polymers, conductive hydrogels, etc. Which have been chemically modified and physically doped to obtain more materials with excellent performance and good electrical responsiveness for drug delivery. The route of administration ranges from transdermal administration to injectable, implantable, and ingestible DDS. In addition to wireless microchips, electrodes are usually placed on the skin or placed subcutaneously, and the electrical stimulation system works by placing them on the skin or by injection or implantation into the body. It is suitable for different needs and administration scenarios. Various commercial power sources are still the most commonly used sources for stimulation, but with the rise of mobile medical care, more attention has been paid to various self-powered medical devices. Self-powered wearable and implanted generators based on triboelectric, piezoelectric, photovoltaic, hydrovoltaic, biofuel, galvanic, and pyroelectric have been extensively studied (**Figure 1**).

In this review, we will briefly summarize the current electroactive biomaterials and recent advances in the development of drug delivery by electrical stimulation, the self-powered harvesters used in DDS at present will be highlighted. Finally, we will present the challenges and opportunities of electrical stimulation DDS.

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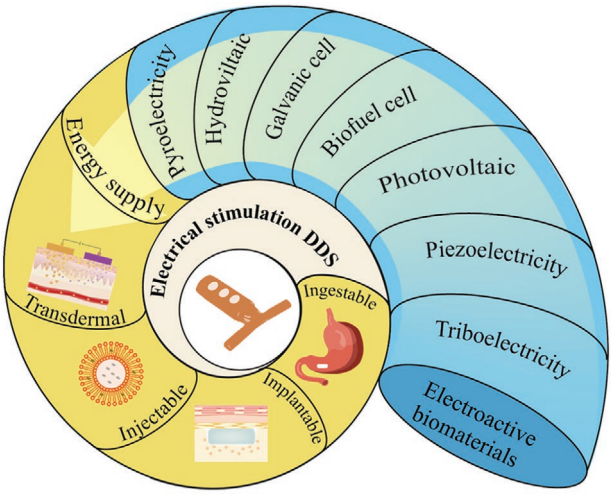

Figure 1. An overview of the main research contents of electrical stimulation DDS. Reproduced with permission.[12] Copyright 2018, John Wiley and Sons.

2. Electroactive Biomaterials

Electroactive biomaterials are considered a new generation of smart materials that can change their physical and chemical properties under the action of electrical signals (electric-response) or generate electrical signals under the action of external stimulation (generate electricity), which can meet different drug release needs. Electric-response biomaterials for drug delivery mainly include conductive polymers (CPs), conductive hydrogels, carbon-based materials, and some metal/semiconductors materials, etc. There are many kinds of biomaterials for electricity generation, according to different external stimuli, including triboelectric, piezoelectric, pyroelectric, photovoltaic, hydrovoltaic, et al. Electret is a special type of electroactive material, it is a kind of dielectric material with its charge, and the charge is almost permanent.[13] The electrets used for drug delivery mainly appear in the form of patches for wound healing and transdermal drug delivery.[14,15] **Figure 2** shows the developing roadmap of some electroactive biomaterials. By the 19th century, most of the electrical stimulation materials were found. Subsequently, various polymers, semiconductors, and piezoelectric materials are used in drug delivery systems. At present, researchers mainly modify and process various materials to prepare better and more suitable composite materials. In addition to good electrical reactivity, good biocompatibility is also required. The development of electroactive materials provides a good solution for drug-controlled release.

2.1. CPs

Conducting polymer is a kind of polymer whose conductivity can be extended from insulator to conductor by chemical or electrochemical doping of polymer with conjugated π bond. As a new generation of organic materials, CPs exhibit properties similar to metal and inorganic semiconductors, such as good electrical properties.[25] At the same time, it is easy to synthesize, flexible to process, small in density and has good mechanical compatibility like polymer. Since the first conductive polymer polyacetylene was discovered in the 1970s, a series of new conductive polymers have been exploited.[26] So far, there are about 25 conductive polymers has been reported, CPs such as polypyrrole (PPy), polyaniline, polythiophene, poly(3,4-ethyelenedioxythiophene) (PEDOT), and their derivatives have been widely studied because of their good biocompatibility,[27,28] electrical conductivity, and excellent physical and chemical properties.

There are two kinds of synthesis methods of conducting polymers: electrochemical synthesis and chemical synthesis. Compared with electrochemical synthesis, chemical synthesis usually produces powder, which is more complex, but easier to be produced on a large scale. Electrochemical synthesis of thin films, polymerization and doping process is more controllable, with better electrical and chemical properties, but not sui for large-scale production. Different synthesis methods can be selected according to different requirements.

Drugs can be encapsulated into the polymer by using the doping characteristics of conductive polymers during or after polymerization, besides, drugs can also be loaded by physical embedding. When the polymer is electrically stimulated, the redox state of the polymer changes, it is accompanied by ions

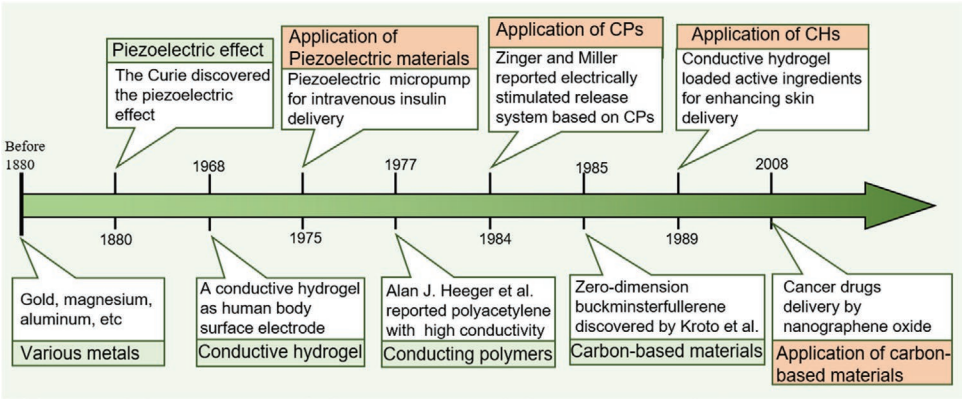

Figure 2. Developing roadmap of electroactive biomaterials. Piezoelectric effect,[16] conductive polymer hydrogel first proposed,[17] conductive hydrogel skin patch,[18] the first piezoelectric micropump,[19] the introduction of conductive polymer,[20] the first report of the controlled release system based on CPs,[21] 0D carbon-based materials,[22] conductive hydrogel for drug delivery,[23] carbon-based materials for cancer treatment.[24]

and solvents migration, the length, volume, color, mechanical properties, and hydrophobicity of CPS will have a reversible transformation, which can release loaded drugs under electrostatic actuation or deformation actuation.[29] Drug release caused by redox of PPy as an example, when negative voltage is applied to PPy and the total amount of positive charge on the molecular chains is reduced, anionic drugs will release from the polymer system due to the weakening of electrostatic effect. When positive voltage is applied to PPy, the cationic drugs are released under the electrostatic repulsion. The release of neutral drugs is mostly driven by deformation, but some studies have also shown that the release of neutral molecules can be achieved by combining with electric molecules.

Nanoparticles, hydrogels, films, solids, and other drug carriers prepared from a variety of conductive polymers and their derivatives combined with metal, semiconductors have been used in the study of DDS. To control the release of nerve growth factor,[30] dexamethasone,[5,31,32] chlorpromazine,[33] heparin,[34] dopamine,[35] streptavidin,[36] and other substances.

In general, the potential difference between polymer and electrolyte is less than 1 V to release or capture ions. For drugs with electrical activity, high voltage may cause drug deactivation. Samanta et al. has investigated the drug release properties of polypyrrole nanoparticles synthesized under different oxidants and found that when ferric chloride was used as oxidant, the electric field as low as −0.05 V could also promote drug release.[37] These materials make it possible to use endogenous electricity to control drug release. Some typical electro-reactive materials used in DDS are summarized in **Table 1**.

2.2. Electroconductive Hydrogels (EHs)

Hydrogels are polymeric 3D networks that can fill with plenty of water and have certain mechanical strength and physical integrity. EHs combine the superior properties of conductive materials and hydrogels, have good electrical conductivity, stability, and mechanical properties, which makes it more practical. Some of these polymer networks are dexterous, the properties of hydrogels, such as phase, volume, shape, optics, mechanics, surface area, reaction rate, and recognition performance will be changed by electrical stimulation.

Currently, EHs are widely used in biomedical fields, including tissue engineering, drug delivery carrier, electronic skin etc.[69,70] Drug-loaded EHs are commonly used in transdermal systems or implanted devices to regulate the amount of drug required by adjusting the strength and duration of electrical stimulation. Subcutaneous crosslinked hydrogels are repeatedly deformed by the percutaneous application of a constant 1.0 mA current, resulting in the pulsed release of insulin.[71]

According to the composition structure of hydrogel, EHs mainly include several types: polyelectrolyte EHs, an inorganic substance added EHs and conductive polymer-based EHs. Polyelectrolyte EHs are usually hydrogels formed by chemical or physical crosslinking of hydrophilic monomers containing ionic groups. The ionic groups in these hydrogels are the key to the higher conductivity of hydrogels. Common inorganic fillers are graphite powder, carbon fiber, carbon nanotubes, metal particles, and so on. The inorganic conductive hydrogel is not only

Table 1. Electrical responsive material used as drug delivery systems in vitro/in vivo.

Classification[a)]	Materials	Active Ingredient	Mechanism	Application	Ref.
Conducting polymers	Biotin-doped conductive PPy	Nerve growth factor	Redox reaction and electrostatic interactions	Drug release in vitro	2006[38]
	PPy and temperature-sensitive hydrogel	Fluorescein	Redox reaction and iontophoresis	Subcutaneously release in vivo	2012[39]
	Modified silica nanoparticles doped PEDOT	Melatonin/doxorubicin /DNQX	Redox reaction and electrostatic interactions	Modulate neural activity	2019[40]
	P3HT/PVA	Fluorescent dyes/cisplatin	Hydrophobic to hydrophilic transition under a bias voltage	Remote-controlled drug release	2017[41]
Hydrogel	Calcium alginate hydrogels	Benzoic acid and tannic acid, and folic acid	Electrostatic interactions	Electric field-controlled drug release in vitro	2012[42]
	Chitosan-graft-polyaniline copolymer and oxidized dextran injec hydrogel	Amoxicillin and ibuprofen	Iontophoresis	Local sustained release in response to electric field and pH	2018[43]
	PEGDGE composited with rGO	Model drug methyl orange	Electrostatic interactions	Electrostimulated drug delivery	2015[44]
	PEDOT/PDMAAp Photocrosslinked hydrogel	Dexamethasone	Electrostatic interactions	Electrostimulated drug delivery	2019[45]
Metal and semiconductor materials	Carbon nanotube membranes	Nicotine	Electrophoretically	Treatments of drug abuse and addiction	2010[46]
	Multireservoir with metal sealing membrane	Two types of neurotracers	Electrically-stimulated ablation/degradation	Targeted administration on cerebral cortex	2018[47]
Electrets	Polypropylene film	Superoxide dismutase (SOD)	Improving skin permeability and promoting transdermal drug delivery	Transdermal drug delivery	2016[14]

[a)] P3HT, Poly(3-hexylthiophene); PVA, polyvinyl alcohol; PEGDGE, polyethylene glycol diglycidyl ether; rGO, reduced graphene oxide; PDMAAp, poly(dimethylacrylamideco-4-methacryloyloxy benzophenone-*co*-4-styrenesulfonate.

easy to prepare, but also has high and stable electrical conductivity. The conductive polymer-based conductive hydrogel is a mixture of polymers, have been widely reported and studied since they were firstly reported in 1994, it has not only high conductivity but also excellent hydrogel properties.[17]

Some of them have pH responsiveness because of the high concentrations ionic group. To improve the electrical responsiveness, drug release behavior or improve the tissue gel interface, various multicomponent and network interpenetrating hydrogels were developed. Qu et al. by combining the electroactive aniline trimer and dextran, and using six methylene diisocyanate as the crosslinking agent, the hydrogel was prepared to obtain good conductivity and ideal electrical stimulation drug release ability.[72]

Previously reported hydrogel matrices incorporating conductive nanomaterials such as carbon nanotubes and graphene and graphene derivatives can improve the mechanical properties, electrical conductivity of hydrogels, and exhibit excellent delivery properties.[6,73–76] Servant et al. incorporated pristine multiwalled carbon nanotubes (pMWNTs) into polymethacrylic acid (PMAA)-based hydrogel matrix in situ for polymerization. The electrical properties of the hydrogel hybrids were improved. At high pMWNT concentrations, drug release in the gel was significantly enhanced, reaching 70% of the loading dose after two electrical stimulations.[77] Liu et al. demonstrated that an rGO/PVA hydrogel can serve as an electrically responsive drug release system. The application of periodic electrical stimulation to the hydrogel resulted in highly controllable and repeatedly pulsatile lidocaine release.[78]

2.3. Carbon-Based Nanomaterials

With the development of nanotechnology, buckminsterfullerene was discovered in 1985 by Kroto et al.[22] Since then, carbon-based materials have developed rapidly in the field of drug release. Carbon-based materials have excellent electrical conductivity, mechanical strength, large specific surface area, and high drug loading. The researchers combined carbon nanotubes, graphene, graphene oxide (GO) and rGO with hydrogels or conductive polymers to obtain materials with better electrical responsiveness and mechanical property.[76,79]

2.4. Metal and Semiconductor

Metal materials such as magnesium and gold have been used in DDS due to their good biocompatibility and easy processing. The rate of metal electrochemical dissolution or electrothermal activation can be controlled by applying a voltage to the metal. Thus, a controlled release reservoir or a degradable drug release electronic can be used to control the rate of drug release.[47,80]

Semiconductor is a material whose conductivity is between metal and insulator at room temperature, with controllable conductivity. The photovoltaic effect of semiconductor materials is the mechanism of the operation of solar cells. As a semiconductor, silicon is also widely used in the preparation of DDS due to its rich content, good biological safety, and stability.[81]

3. Current Methods of Electrical Stimulation Administration

According to the route of administration, the electrical stimulation DDs can be divided into four types briefly: transdermal DDS, injec DDS, implan DDS, and ingestible DDS.

3.1. Transdermal Drug Delivery System (TDDS)

For the transdermal or mucosal DDS, the 1970s was the period of experiment and invention, and the 1980s was the period of commercialization. since the 1990s, transdermal technology has been developed with the help of new materials, microelectronics and new compounds. It is considered to be a promising DDS with the following advantages: 1) Bypass the first-pass effect of hepatic and the effect of gastrointestinal. 2) Easy to use and termination at any time. 3) Improvement of patient compliance. 4) Maintain stabilization and durable blood concentration.

However, the common TDDS is difficult to deliver biotechnology drugs such as proteins, peptides, and oligonucleotides due to their high molecular weight, charged, and/or polar. Therefore, many penetration enhancement methods have been developed in recent years, including chemical enhancers and physical enhancement methods and pharmaceutical methods. Physical methods, such as iontophoresis and electroporation by electrical regulation not only have the advantages of transdermal drug delivery but also meet the treatment requirements at different times by adjusting the electrical parameters.[82] Hasan et al. have reviewed the recent studies of iontophoresis-binding liposomes, reported that iontophoresis using weak electric current can induce cell-specific endocytosis and improves transdermal penetration compare with individual agents or another route of drug administration.[83] According to the form of administration, transdermal DDS can be divided into various noninvasive patches and minimally invasive microneedles.

3.1.1. Transdermal Patches

Electrically regulated transdermal patches include a variety of drug-loaded conductive hydrogel, film integrated with power supply and power management system and can control of drug delivery through iontophoresis, electroporation, and electrothermal patch.

Young-Hyeon et al. have reported a por patch ion permeation DDS based on a reverse-electrodialysis battery. The conductive hydrogel patch was loaded with electrically mobile drug nanocarriers and has excellent skin permeability, percutaneous delivery of rosiglitazone can produce an obvious antiobesity effect in mice (**Figure 3**a).[73]

For transdermal patches, the firmly laminating and easy to peel off is important, Figure 3b presented an octopus tentacles-inspired adhesive, which can be used for wireless control of drug delivery with good adhesion and comfort. In particular, the device can be used again after cleaning and drug delivery can be promoted by iontophoresis.[84]

Heat can affect the volume and shape of the nanocarriers, resulting in drug release. Therefore, transdermal patches based

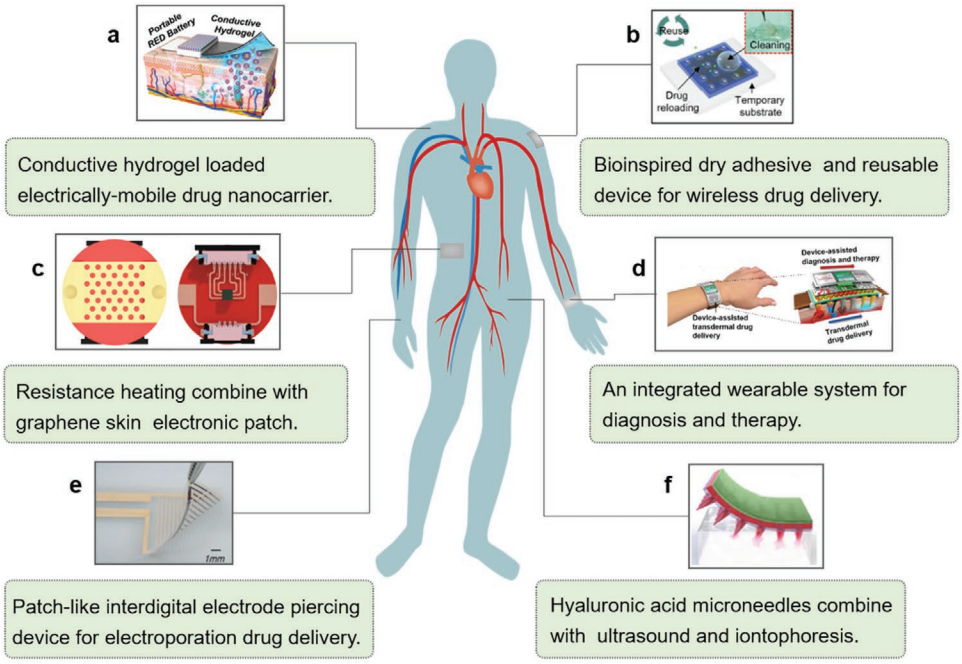

Figure 3. Electrical stimulation transdermal drug delivery systems. a) Schematics of reverse electrodialysis (RED) battery coupled with electroconductive hydrogel for iontophoresis. Reproduced with permission.[73] Copyright 2020, American Chemical Society. b) Schematics of cephalopod-inspired miniaturized dry adhesives integrated with drug-delivery actuators. Reproduced with permission.[84] Copyright 2015, John Wiley and Sons. c) Schematics of the active and passive backside of the electrothermal patch. Reproduced with permission.[85] Copyright 2018, Royal Society of Chemistry. d) Schematics of the diagnosis and therapy platform. Reproduced with permission.[86] Copyright 2018, Elsevier. e) Image of parallel electrodes pliable patch. Reproduced with permission.[87] Copyright 2015, Springer Nature. f) Schematic illustration of hyaluronic acid microneedles. Reproduced with permission.[88] Copyright 2020, Springer Nature.

on electrothermal generation combined with heat-responsive drug carriers have also been studied. Quentin et al. have developed an electrothermal patch to deliver drugs, such as insulin on-demand.[85] The nanoporous gold film was integrated on the surface of Kapton film as a resistance heating unit and graphene oxide film was deposited on the surface for the drug reservoir. The temperature can rise to 40 °C in 10 s with the voltage of 1 V, the higher the deflection voltage, the higher the s temperature (Figure 3c). Sara et al. have illustrated a hydrogel transdermal DDS to promote wound healing. The hydrogel was covered with a flexible metal heater and drugs were released from the nanocarriers during heating and then diffuse through the skin.[89]

Disease diagnosis and treatment integration is a major development direction of wearable medical devices. Percutaneous drug delivery combined with disease diagnosis can accurately control the drug dose and duration according to the physiological condition of patients, so as to maximize the therapeutic effect (Figure 3d).[86] Emaminejad et al. applied iontophoresis to the introduction of sweat stimulants, which can induce sweat secretion, and continuously and noninvasively monitor electrolytes and glucose in sweat through integrated biosensors.[90] Studies have shown that iontophoresis also promotes macromolecular drug delivery in diseases like psoriasis with thickened epidermis.[91]

Electroporation uses a high-voltage pulse to improve the permeability of the cell membrane and absorb the foreign molecules in the surrounding medium. The technology has been used as an effective method of drug delivery for human and animal in vivo drug delivery due to its efficient delivery strategy. Wei et al. presented a patch-like interdigital electrode piercing device with flexible parylene substrate, which was utilized to transfer siRNA and DNA by electroporation in vivo (Figure 3e).[87]

Most previous studies and application were focused on transdermal drug delivery[92,93] and in recent years its potential to delivery drug into the mucous, enamel,[94] and other tissues have been illustrated.

3.1.2. Microneedles

Microneedles as a very promising transdermal drug delivery method, combine the advantages of both transdermal patch and hypodermic syringe, microneedle delivery system has significant advantages: 1) A painless drug delivery system. 2) Drugs can be targeted to a specific depth of the skin, promoting the transdermal penetration rate of the drug. 3) It belongs to physical penetration promoting technology, with little damage to the skin. 4) Easy to use so that patients can take the drug anytime and anywhere, improving the compliance of the patient.

Microneedles have been widely used in combination with other electrical stimulation technologies to promote drug delivery. Microneedles-iontophoretic, microneedles-electroporation have shown synergistic effects, which can enhance the flux[95] and increase skin permeability.[96] Bok et al. combine ultrasound, iontophoresis with hyaluronic acid

microneedles, which have a synergistic effect on drug transdermal delivery(Figure 3f).[88] Jung et al. used microneedles to inject fluorescent nanoparticles into the suprachoroidal space of rabbit, and nanoparticles delivered to the back of the eye by iontophoresis were more than twice as noniontophoretic.

However, there are few studies on the DDS directly loading electrical stimulation onto the microneedles. To realize the drug-controlled release of microneedle system, conductive microneedles loaded drugs can be used to effectively adjust the drug release rate by electrical stimulation.

At present, the sensor system based on the microneedle system has been widely used in the research of body fluid detection.[97] If the interstitial fluid sampling from the skin and drug delivery can be realized at the same time, a closed-loop system combined diagnosis and treatment can be achieved, which could provide drugs according to the information given by the monitoring component. This integrated diagnosis and treatment system will be further developed in the future.

3.1.3. Injec Electrical Stimulation Drug Delivery System

Nanodrug delivery systems have been widely used in the treatment of a variety of diseases, promoting drug release through the action of local pH, temperature, magnetic field, and electric field.[98] Electrically responsive drug delivery carrier can also be designed to be dispersible, which can be injected directly into the local area or aggregated at the disease site through the circulation of the blood system, and the electric field can also drive the migration of drug carrier. Local nanocarriers are then electrically stimulated to release the loaded drug. Under the action of the electric field, the charge of nanocarrier changes during reduction or oxidation, resulting in the change of conformation and affinity, which ultimately leads to drug release. This section presents recent studies on electro-responsive nanocarriers such as particles, micelles, vesicle structures, and electrically driven nanorobotic, etc. (**Figure 4**).

3.1.4. Nanocarrier

Nanocarriers include various nanoscale particles, vesicular, micelles, etc. Ge et al. have described an electric field responsive PPy nanoparticles, through the oxidation or reduction produced by DC electric field (0.5 V), the release of daunorubicin with positive charge and fluorescein with a negative charge are realized respectively.[39]

Ying et al. have prepared brain-targeting angiopep-modified electro-responsive hydrogel nanoparticles (ANG-ERHNPs) that could penetrate the blood–brain barrier easily. Under the action of the electric field, the entrapped drugs can be released from ANG-ERHNPs quickly, so resulting in the release of drugs during seizures to inhibit abnormal neuronal discharges in time.[101] The nanoparticles can also combine with conductive materials to attain electric field responsive properties. Mohapatra et al. established an inkjet printing interdigitated electrodes with good biocompatible for electrical stimulation drug release of chitosan-based magnetic nanoparticles.[102]

Micelles are nanoassociations formed by the self-assembly of amphiphilic molecules. There are some studies on the micelles which can release drug in response to voltage. Noncovalent amphiphilic polymers fabricated by host–guest interaction with ferrocene can be controlled reversibly by external voltage and the drug release can be controlled by electricity.[99]

Some amphiphilic molecules, such as many naturally synthesized surfactants and phospholipids that cannot simply associate micelles, spontaneously form a class of ordered molecular assemblies with closed bilayer structures when dispersed in water, called vesicles, also known as liposomes. Caramazza et al. have applied nanosecond pulsed electric fields (nsPEFs) to enhance the membrane permeability of stimuli-sensitive liposomes for releasing the hydrophilic model drug.[103] Under the same condition, the drug release amount of the electrical stimulation group was 20% higher than the control group without stimulation.

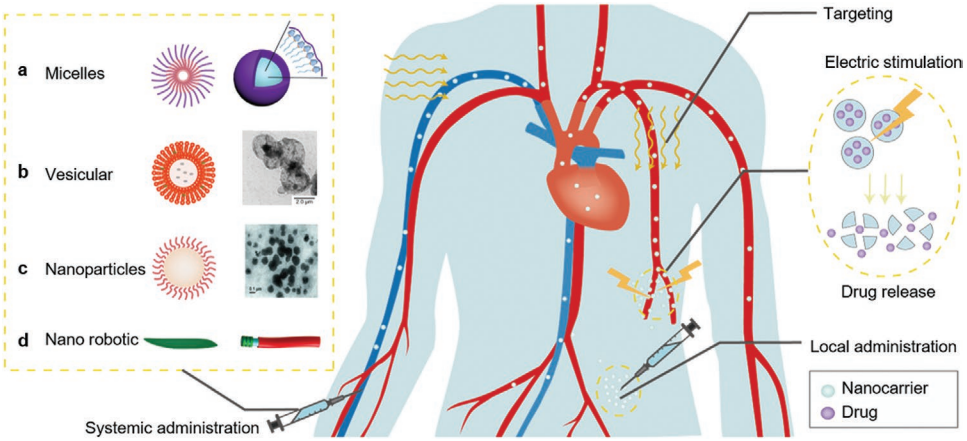

Figure 4. Dispersed electrical stimulation drug delivery systems. A variety of drug-containing nanocarriers, including micelles, vesicular, nanoparticles, and nano robotic can enter the human body by intravenous injection or local administration, reach the designated site under the action of physical and chemical targets and control the drug release through electrical stimulation. a) Reproduced with permission.[99] Copyright 2019, American Chemical Society. b) Reproduced with permission.[100] Copyright 2015, Royal Society of Chemistry. c) Reproduced with permission.[101] Copyright 2014, John Wiley and Sons. d) Reproduced with permission.[48] Copyright 2019, John Wiley and Sons.

Due to the rigidity and dielectric anisotropy of polymer chains, liquid crystalline polymers have a sensitive response to the electric field. Honda et al. synthesized linear and cyclized amphiphilic copolymers and studied the response of these polymers to an electric field.[100] They have shown that small vesicles turn into larger vesicles under the action of an electric field (1.5 V mm^{-1}), The polymers have a certain potential in the field of electrically responsive drug delivery.

3.1.5. Nanorobotic

Nanorobots have excellent flexibility and adaptability, compared with general nanocarriers, the biggest difference is that their movement or behavior can be controlled through external signals. Soto et al. have introduced the most recent development of nanorobots in precision medicine.[104] It has great potential in biomedical fields, such as targeted drug delivery and release, disease diagnosis, and therapy.

In the field of drug delivery, the research on electrically controlled micronanorobots is still in its infancy and there are a few related researches. Kopperger et al. using an electric field to power the DNA nanorobot arm and realized the precise movement of the nanoscale. They made a 400 nm long robot arm, which bonded one end of the manipulator to the DNA platform through a base-pair connection and attached a 25 nm gold particle to the end of the DNA manipulator that was free to move. When the external electric field is turned on, the DNA manipulator starts to rotate due to the negative charge of DNA, which can drive the nanoparticles at the top to move at the same time. It can be driven in milliseconds, much faster than using enzymes.[105]

Chen et al. designed wire-shaped nanorobotics with magnetostrictive FeGa core and piezoelectric P(VDF-TrFE) shell.[49] After that, a similar nanoeel was prepared by Mushtaq et al, the nanoeels include piezoelectric tail made of P(VDF-TrFE), attached to polypyrrole nanowires, and magnetically driven by nickel rings. The therapeutic agent was adsorbed on it after being treated with polydopamine. Under the action of rotating magnetic field, the deformation of piezoelectric polymer led to its polarization change and promoted drug release.[48] For PVDF-HFP without piezoelectric effect, the magnetic field did not promote drug release, while for piezoelectric PVDF-TrFE, the magnetic field can control the drug pulsed on-demand release. At the same time, there are different driving modes by different magnetic parameters. The drug release in the release mode was more than four times that in the static mode.

Through the combination of different drive control methods, DDS achieves better motion control and information feedback, meanwhile put forward higher requirements for technical integration and operation.

3.2. Implan Drug Delivery System

Implan drug delivery systems (IDDS) are a kind of controlled release systems by surgical implantation or needle introduction to subcutaneous or other target areas. IDDS mainly have the following advantages: 1) Realize local or systemic administration, reduce dosage and reduce side effects; 2) Avoid first-pass effect, improve bioavailability; 3) High drug loading capacity, extend drug action time, especially sui for long-term treatment of chronic and senile diseases, and improve patient compliance. It is a more simple and effective method for diseases with poor efficacy of systemic medication and transdermal patches.

The application scope of IDDS has been expanded from the original contraceptive treatment to multiple treatment fields. According to the difference between how the drug exists in the implant and how the implant is used, electrical stimulation IDDS can be divided into solid or injec drug-loaded implants and microelectromechanical systems.

3.2.1. Solid or Injec Drug-Loaded Implants

Solid drug-loaded implants refer to drug-loaded hydrogels and polymer scaffolds. The implant can be implanted into the designated site by needle puncture or surgery and can achieve a controlled release by surface-attached electrode or needle electrode with electrical stimulation.

Servant et al. have fabricated graphene-based polymeric implants for pulsatile drug delivery with good reproducibility and almost eliminated the resistive heating.[75] Xie et al. developed electro responsive polydopamine polypyrrole microcapsules that can precisely release drugs to a maximum of 90 μg cm^{-2} in 10 min.[106] Jeon et al. used porous anodized alumina as the substrate to prepare polypyrrole doped sodium dodecylbenzene sulfonate nanoporous membrane.[107] When the electrical stimulation is applied, the change of the redox state of PPy results in the change of the volume and pore size of PPy film. Therefore, when the drug is entrapped in the pore size, the pore size switch can be regulated by electrical stimulation to achieve the purpose of electrical stimulation of drug release. Because the system has a fast transition time (less than 10 s) and high-throughput drug release, so it can be applied to emergency treatment (**Figure 5**a).

Injec drug-loaded implants mainly refer to injec hydrogels. The liquid material is injected into the body, and the response of the material to stimulation is used to make the polymer disperse or change under physiological conditions and transform from liquid to gel which becomes a semisolid drug reservoir. When the drug-loaded conducting polymer nanocarriers are doped in the liquid solution, the drug release in the particles can be controlled by electrical stimulation.[43,111] As a minimally invasive local DDS, injec implants have shown promising application prospects.

Compared with other micromechanical systems, this kind of implant with a simple structure has greater flexibility and controllability, can adapt to different drug delivery sites and is easier to achieve biodegradable and bioabsorbable functions.

3.2.2. Microelectromechanical Implant System

With the continuous development of microfabrication technology and bioelectronics, microelectromechanical system (MEMS) has a more and more wide range of clinical applications and one of the important directions is controlled DDS.

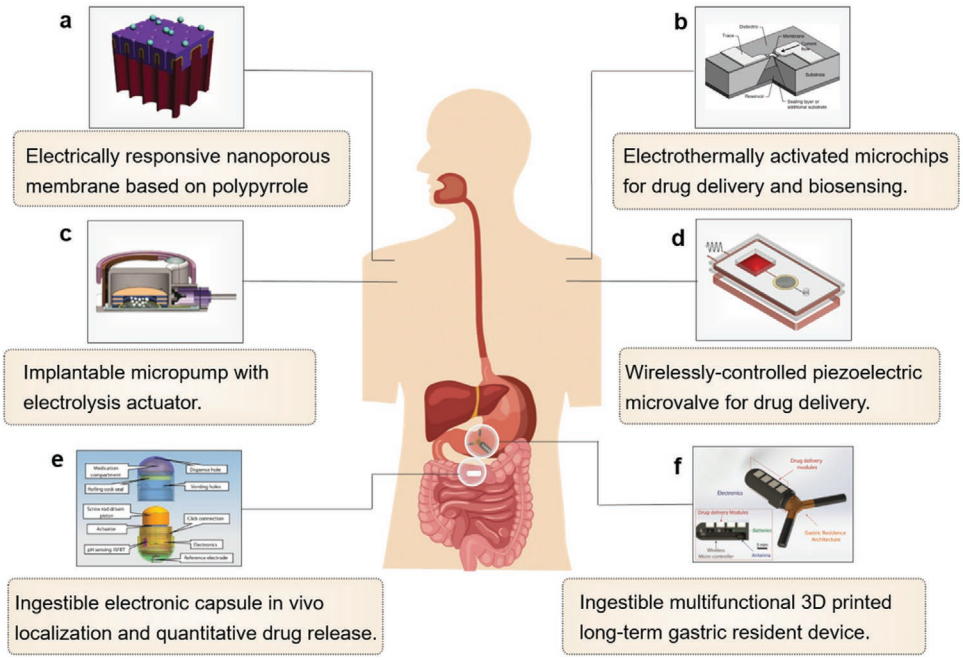

Figure 5. Implan and ingestible electric controlled drug delivery device. a) Polypyrrole was electropolymerized on gold layer and the pore size can be changed reversibly by electrical stimulation. Reproduced with permission.[107] Copyright 2011, American Chemical Society. b) A representative section of a reservoir-based microchip. Reproduced with permission.[80] Copyright 2005, Elsevier. c) Schematic diagram of electrolysis drug delivery system. Reproduced with permission.[37] Copyright 2016, Elsevier. d) 3D diagram of the wirelessly-controlled piezoelectric microvalve. Reproduced with permission.[108] Copyright 2018, Elsevier. e) Schematic diagram of the capsule showing the main components. Reproduced with permission.[109] Copyright 2013, Elsevier. f) Schematic diagram of the gastric-resident electronics device. Reproduced with permission.[110] Copyright 2018, John Wiley and Sons.

Compared with the traditional polymer-based DDS, MEMS with digital capabilities has greater temporal control ability, better repeatability, and uniformity in industrial production. Drug release can be divided into two ways: passive drug release and active drug release. The passive drug release is mainly sustained and controlled release preparations of which the drug release rate is constant. According to the changes of physiological signals in vivo, the needs of biological rhythm or the changes of external stimulation signals, active drug release can adjust the drug release rate-to realize pulse drug delivery. At present, many kinds of triggered drug delivery devices, including micropumps, microreservoirs, and microchips, have been developed to prepare an electrical responsive integrated drug delivery MEMS.[112]

Implan microreservoirs or microchips for drug-controlled release are typical examples of MEMS in drug delivery. The microreservoirs system can contain one or more drug reservoirs and has adaptive flexibility with various delivery options including zero-order, pulsation, and on-demand release (Figure 5b).[80,113,114] In 1999, langer's group has reported a solid-state microchip with thin metal film covering microreservoirs filled with drugs. The film will melt and the drug is released when a current is applied.[81] The device contains 34 reservoirs and can load different drugs or be controlled individually to satisfy the demand. It has the advantages of small size, fast response, and low power consumption. Afterward, a large number of microdevices based on this principle were reported. In 2012, the first-in-human testing of implanting a controlled-release microchip in long-term operation is reported.[115] Chung et al. has fabricated a silicon microreservoir that can deliver 15 μL dose by two kinds of electrolytic reactions which can dissolution gold and release gas to propel well contents out.[116] Most of these devices are complex in structure, rigid, and difficult to conformally match with the tissue in vivo, so some flexible and smaller-size devices have been developed gradually. Sung et al. have fabricated a flexible wireless energy-driven DDS in the cerebral cortex.[47] The drug delivery microdevice can be well attached to the surface of curved organs and release the chemicals precisely. The flexibility and miniaturization of the whole device including the energy system and the time and dose accuracy of drug delivery are still the important directions of development.

Micropump is an important component of the micromechanical system. As the heart of the whole system, micropump pumps drugs from the reservoirs to the administration site through microfluidic channels. The micropump for drug delivery does not need a high flow rate, but high precision and high reliability. Electrically activated micropumps for drug delivery can divide into two categories, called mechanical and nonmechanical pumps. Mechanical pumps exert oscillatory or rotational forces on the fluid (electrostatic micropumps, electroactive polymer composite micropumps, electrohydrodynamic (EHD) micropumps etc.), while nonmechanical pumps directly convert electrical energy into the fluid flow (electroosmotic micropump, electrowetting and electrochemical micropump, bubble-type and evaporation-type micropumps, etc.).[117,118]

The micropump was first used for drug delivery in 1978 when a piezoelectric micropump with electronic was used

to release insulin.[119] Cobo et al. present a wireless micropump with a low power electrolysis actuator.[37] The bottom of the actuator is a pair of interdigital platinum (PT) electrodes, when the electric current is applied on the electrode which will decompose the water, increase the pressure of the chamber, and displace the surrounding fluid to the designated location. It has been proved that the flow rate change in a single pump is less than 6% when 30 μL dose is provided every day (Figure 5c). Bruno et al. have reported an implan nanofluidic system. The surface charge of the nanochannel can be changed according to the polarization of the buried gate electrode, and the transport of ionic drugs can be controlled. Compared with other electrokinetic phenomena, the power consumption is reduced by 2–3 orders of magnitude.[120]

Piezoelectric micropump is a kind of equipment that uses the reverse piezoelectric effect to make the piezoelectric membrane deform and change the volume of the chamber to push the micropump to work. It contains basic components including piezoelectric layer, inlet and outlet valve and chamber (Figure 5d). The progress of micropumps in the biomedical application is summarized by Wang et al.[112]

Absorbability or degradability can avoid the inconvenience and risk of secondary operation, which is the development trend of implan equipment. Koo et al. have introduced a wirelessly controlled and completely bioresorbable drug delivery device. The coil of the device can transfer energy to accelerate the electrochemical corrosion of the metal grid structure, and the device can achieve the release of a variety of drugs by using different frequencies.[121]

In addition to drugs, micromechanical systems can also load cells for cell-based therapy. Cell therapy is a very promising therapy, encapsulate cells in implan devices that are engineered to fine-tune in situ production and delivery of proteins for specific therapeutic purposes in response to changing microenvironments in vivo. A cofactor-free bioelectronic interface is proposed by Krawczyk et al., which can regulate the gene expression process of loaded therapeutic cells by receiving signals from mobile app, to control the treatment of patients (Figure 5d). The electrical stimulation of human β-cells in the customized bioelectronic device can control the release of vesicular insulin in real-time, and the insulin level can reach the peak within 10 min. When implanted subcutaneously, this electrically triggered vesicle release system successfully restored normal blood glucose levels in type I diabetic mice.[122]

At present, microprocessing DDS is still in the early stage of research, but it can be predicted that with the continuous maturity of microprocessing technology and its combination with biotechnology, people will be able to develop an intelligent biofeedback system with the functions of detection, response, and release, which integrates microsensors, micropumps, microswitches, and microrepositories and have a strong ability to develop in various chronic diseases, such as osteoporosis, infertility, Parkinson's disease, Alzheimer's disease, multiple sclerosis, etc.

3.3. Ingestible Drug Delivery Electronics

Oral administration is the most commonly used, simplest and safest method of administration in the clinic. To achieve a better therapeutic effect, many sustained and controlled-release formulations have been developed through drug diffusion or polymer degradation. However, due to the limitations of dosage forms and the influence of gastric emptying, there are some limitations, such as unable to release on-demand and short maintenance time. The ingestible electrical stimulation drug delivery device can provide some solutions.

Intellicap is an intelligent electronic capsule that integrates precise in vivo localization and quantitative drug release, the capsule including a drug reservoir, temperature sensor, stepper motor, and electronics, a por unit for wireless transmission. The capsule is about 27×11 mm^2 in size and can be programmed in advance to control the location and release behavior. The real-time position can be obtained by the pH sensor, and any drug release profile can be controlled by a computer in real-time (Figure 5e). After the drug is released, it can be directly discharged from the body.[109,123]

The capsule is small in size and convenient for oral administration, but it has the problem of short residence time in the body and cannot adapt to long-term administration. Kong and the co-workers have described a multifunctional 3D printed long-term gastric resident electronic device.[124] After swallowing, the capsule-sized robot will dissolve the outer gelatin, expands the capsule in the stomach and becomes larger to prevent it from passing through the pylorus for up to 36 days, and can control drug release through Bluetooth for up to 15 days (Figure 5f). This research provides more options for wireless gastric resident electronic devices.

4. Self-Powered Electrical Stimulation Drug Delivery System

At present, most of the power supply systems used as electrical stimulation are still various commercial power supplies. However, their rigid structure, temporal-, and spatial-constraints limit the application in the future remote and wearable medicine, making the self-powered system more and more widely concerned. Especially for the long-term or multiple drug delivery devices that need to be implanted into the human body, the energy demand is in the range of μW with mW range. The self-powered supply can meet the demand without the problem of energy exhaustion. The parameters of electrical stimulation DDS include intensity, DC or AC signal, frequency, etc. According to different electrical stimulation performance needs, different energy harvesting devices can be used for drug delivery. It should be able to improve the efficiency of drug delivery without reducing the efficacy and convenience to use. In recent years, a variety of energy collectors, have been used in the research of drug delivery. According to the energy source classification, it can be divided into mechanical energy harvester, including piezoelectric nanogenerators (PENG), triboelectric nanogenerators (TENG), oscillation generators; thermal energy harvester, including thermoelectricity, pyroelectric, chemical energy harvester, including galvanic cell, biofuel cell, and environment energy harvester, including photovoltaic, hydrovoltaic, etc.

Self-powered DDS can stimulate drug release without the need for an external power source. This simplifies the manufacturing process and may reduce production costs. Also, these

systems may do not need power wiring to broaden the application of DDS, especially for implant systems. However, due to the limitations of energy collection form, output efficiency, and materials, some harvesters have not been used in the study of electrical stimulation drug release at present. The following is a discussion on the electrical stimulation DDS which are widely studied at present and summarized the main energy collection methods for self-powered DDS (**Table 2**).

Table 2. Summary of energy classification methods for self-powered drug delivery systems.

Classification[a)]	Administration	Typical materials	Output	Size	Application	Ref.
PENG	Injec	P(VDF-TrFE)/Ni nanoring-PPy nanowires	300 nV	200 nm × 8 μm	Magnetoelectrically assisted drug release ≈35% cancer cell death invitro	2019[48]
	Injec	FeGa@P(VDF-TrFE) core–shell nanowires	NA	≈300 nm	Magnetoelectrically assisted drug release ≈40% Cancer cell death	2017[49]
	Wearable	rGO-PEI/PVDF-HFP composite film	2.7 V ≈ nA	≈1 cm^2	Antiemetic release under pressure	2018[50]
	Wearable	(PAH/MS)n(PAH/DAS) n@ rGO-TFB/PVDF-HFP composite film	NA	NA	Stimulated drug releases from film preserved its activities	2019[51]
TENG	Wearable	PTFE and Al as the triboelectric material	≈4 V ≈320 nC ≈12 μA	NA	Percutaneous iontophoresis	2019[52]
	Implan	PTFE and titanium film	70 V 0.55 μA 25 nC	≈12 cm^2	Drug loaded red blood cell electroporation, ≈80% cancer cell death	2019[53]
	Implan	Silk and magnesium	≈60 V ≈1 μA	2 × 4 cm^2	Epilepsy-triggered antiepileptic drug release in SD mouse	2018[54]
	Implan	PTFE and Cu film	≈15 V ≈1.5 mA	≈30 cm^2	Ex vivo ocular drug-delivery by driving electrochemical micropump	2017[55]
	Wearable	PTFE and Cu film	19 mW cm^{-2}	NA	Transdermal iontophoretic delivery improve by ≈50%	2019[56]
	Wearable	PTFE and Cu film	≈20 V	4 × 4.5 cm^2	Intracellular electroporation drug delivery	2019[57]
	Wearable	FEP and Cu film	647.6 V 165.6 μA	NA	The drug controllable released from flexible devices powered by TENG	2020[58]
	Wearable	SDNA film and PTFE film	≈95 V	NA	Drug loaded SDNA as microneedle and one friction layer	2018[59]
Biofuel cell	Implan	Fe^{3+}cross-linked alginate-modified and PQQ-GDH modified electrode	≈150 mV	NA	Glucose stimulated drug release	2013[60]
	Implan	Immobilized FADGDH and immobilized BOD	510 mV 245 μW cm^{-2}	NA	Liquid-pumping system powered by a glucose fuel cell	2014[61]
	Wearable	FDH-modified anode and BOD modified carbon fabrics cathode	0.75 V ≈300 μA cm^{-2}	1 cm^2	Iontophoretic transdermal delivery of molecules	2015[62]
	Implan	$(Os(bpy)_2PVI)$-GO_x anode and $Os(bpy)_2PVI$-Box/PEDOT cathode	0.387 V 2.05 μW cm^{-2}	NA	All contents are immobilized, controlled release of three model compound	2020[63]
Solar cell	Wearable	H_2Pc/PTCDI organic OPV cells	100 μA cm^{-2}	2 × 1 cm^2	Light-stimulated transport of cations	2019[64]
Galvanic cell	Ingestible	Zinc–Copper cell	1.14 μW mm^{-2} 2.2–3.3 V	3 × 1 cm^2	Prolonged energy harvesting microreservoir device	2017[65]
	Ingestible	Zinc core and $PEDOT^+$ shell	NA	20 × 5 μm^2	Micromotors autonomous delivery and release therapeutic in mouse stomach	2015,[66] 2019[67]
Others	Wearable	Oxygen-containing groups between graphite electrodes	≈480 mV ≈8 μA	≈0.87 cm^2	Iontophoretic transdermal	2020[68]

[a)]NA, not available; P(VDF-TrFE), poly(vinylidene fluoride-trifluoroethylene); PPy, polypyrrole; rGO reduced graphene oxide; PEI, Polyetherimide; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene; PAH, Poly(allylamine hydrochloride); MS, mesoporous silica; DAS, 4,4'-Diazidostilbene-2,2'-disulfonate; PTFE, Polytetrafluoroethylene; SDNA, salmon deoxyribonucleic acid; PQQ, Pyrroloquinoline quinone; GDH, glucose dehydrogenase; FAD, flavin adenine dinucleotide; FDH, fructose dehydrogenese; BOD, bilirubin oxidase; H_2Pc, phthalocyanine; PTCDI, N,N'-dimethylperylene-3,4,9,10-tetracarboxylic diimide; OPV, photovoltaic; PEDOT, Poly(3,4-ethylenedioxythiophene); ZnO, zinc oxide.

4.1. PENG

PENG is a device that converts mechanical energy into electrical energy, which is mainly composed of nanomaterial or bulk material with a piezoelectric effect. Flexible substrates and connected conductors are also required in practical applications. The working principle of a PENG is illustrated in **Figure 6**a. When the force is applied at the insulating piezoelectric material, the charge is accumulated at the two ends of the material, the polarization charge density increases with the increase of applied force.[125] PENG has many applications in the biomedical field, such as arterial pulse sensor[126] and nerve stimulation[127] and cancer therapy,[128] etc. There are also some studies in the field of drug delivery.

Zhang et al. constructed a piezoelectric dielectric composite membrane, on which a drug-loaded polyelectrolyte matrix was self-assembled. The piezoelectric membrane was mechanically stimulated to release drugs, the drug release could be doubled within 60 min after swallowing.[50] This type of composite membrane can be loaded with a variety of electrical drug molecules to accelerate the release under pressure without side effects on the activity of sensitive drugs.[51] This kind of electrical stimulation method without wire and power supply has great potential in the field of drug delivery.

4.2. TENG

TENG has the advantages of simple and controllable shape, long service life, which can convert different forms of mechanical energy into electrical energy. When two kinds of materials with different tribological properties are subjected to mechanical force, the electric potential difference is caused by contact electrification and electrostatic induction (Figure 6b).[125,129] According to the different driving modes and configuration structures, TENG can be divided into four working modes to adapt to the energy collection in different scenarios.[130] As the power supply device of wearable and implan electronic medical equipment, it has been widely studied in the circulatory system,[131] nervous system, cell regulated microbial disinfection,[132] biodegradation electronics, and DDS.[133,134]

The first TENG-based self-powered implan drug-delivery system (iDDS) was reported in 2017.[55] Through the electric energy provided by the nanogenerator, the aqueous solution containing the drug is electrolyzed to generate gas and drive the solution out of the reservoir. The porcine eyes ex vivo drug delivery experiments show that 50 μL solution can be delivered into the anterior chamber by hands operation on TENG, which can be satisfied with the treatment of eye diseases, such as glaucoma. However, the TENG can not realize the full implantation and needs to be studied in miniaturization, lightweight, and flexibility to meet the needs of the implantation.

After that, Ouyang et al. used a similar rotary TENG to explore transdermal drug systems, using PPy film loaded with drugs as a drug reservoir, which can release DEX on-demand ex vivo. Compared with the conventional transdermal patch, the drug delivery rate was increased by half.[56] Other groups reported a hydrogel iontophoretic TDD system based on a variety of wearable TENG, which could promote transdermal drug delivery.[52] Liu et al. reported a flexible drug releaser, which can regulate the release of drug rate flexibly precisely by changing the hydrophobicity of the membrane by applying voltage.[58]

As the power supply of electroporation system, TENG has the advantages of high delivery efficiency and high cell survival rate because of its high voltage and low current characteristics. Liu and the co-authors reported a TENG-driven electroporation system for intracellular drug delivery. High-voltage pulses generated by TENG act on cells through nanoneedles, producing electroporation and introducing drugs into cells.[57] Subsequently, they fabricated a self-powered electroporation system based on Ag NW-modified PPy microfoam and TENG, it has an efficiency with throughput achieved as high as 10^5 cells min^{-1} on continuously flowed cells.[135] Yang et al. have fabricated a TENG-driving platform for efficient intracellular siRNA delivery on various cell lines and successfully regulate the activity of transfected cells.[136]

For wearable or implan medical devices, the flexibility and miniaturization of the system are very important for practical applications. Therefore, more flexible TENG has been used in drug delivery research with better application scenarios. For example,

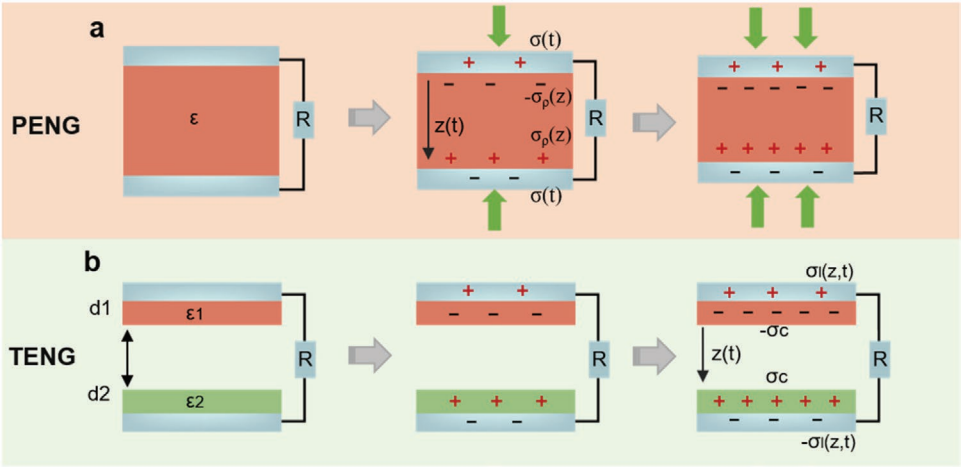

Figure 6. The working mechanism of a) PENG with the increase of the applied stress, and b) TENG with the increase of contact cycles.

Zhang and the co-authors report on a silk-based, implan, biodegradable transient electronic device for real-time in vivo monitoring and treatment of seizures. Transient triboelectric nanogenerators (T^2ENG) can transform mechanical energy into an electrical signal, when an epileptic attack, the detected signal will increase above the threshold value. Subsequently, T^2ENG-based system can automatically trigger the thermal unit and promote the release of antiepileptic drugs in the silk film. The integration of diagnosis and treatment is based on mobile-device readouts and has the potential to be applied to more types of diseases.[54]

An electronic controlled DDS which is developed by integrating microneedle and TENG was fabricated by Bok et al. It mainly includes two parts: Salmon deoxyfibronic acid (SDNA) microneedle and Teflon film. In vitro experiments indicate that the drug release rate is more than 4 times higher than only the needle was attached at 60 s. When the friction was applied, making the microneedle with positive charge, promoting the ion electric penetration of the positive charge medicine in the skin, accelerating the release of the drug.[59] The overall structure is simple, different materials can be selected according to different drugs, so that TENG can be effectively applied in transdermal drug delivery by electrical stimulation.

Self-powered electrostimulation drug delivery has also been applied to the field of tumor therapy. Zhao and the co-authors design an encapsulated magnet-TENG (MTENG) to control the drug release from doxorubicin-loaded red blood cells, When the drug-loaded red blood cells gathered in the tumor site, the high-voltage electric field can promote the electroporation of the red blood cell and release the anticancer drug, which can significantly improve the killing efficiency of cancer cells in vitro and in vivo.[53]

Since its invention in 2012, TENG has experienced great progress and technical improvement. With the gradual improvement of energy collection efficiency and output performance, as well as the continuous optimization of the power management system, the application field of TENG has gradually expanded and is gradually moving towards commercialization. In the field of drug release, many reports have shown that it has the potential of commercialization, but before that, the effect of the whole system in the actual work scenario, the stability of TENG under the actual work, the size, flexibility, and long-term biosafety of TENG still need further study.

4.3. Biofuel Cell

Biofuel cell is a special fuel cell that directly or indirectly uses organic matter as a substrate to generate electrical energy through chemical transformation and generate electrons and protons at the anode. Electrons are transferred to the cathode through an external circuit to form a current, while protons are directly transferred to the cathode. The oxidant gets electrons reduced at the cathode and combines with protons to form water (**Figure 7**a). It can be divided into microbial biofuel cells (microorganism as the catalyst, *E. coli*, actinobacteria, et al.),[137] abiotic biofuel cells (the catalyst is inorganic species, Pt, Au, et al.)[138] and enzymatic biofuel cells (the catalyst is an enzyme, glucose oxidase, D-glucose dehydrogenase, et al.) depending on the catalyst.[139] Most of the designed biofuel cells are the production of microscale power,[140] which can be used as wearable and implan energy collection devices for blood, sweat, saliva, and other human biofluids to convert lactic acid[141] or glucose into electrical energy.[60,142]

In the field of electrical stimulation DDS, biofuel cells have many application scenarios. Microbial biofuel cells have obvious limitations for drug delivery due to the need for microorganisms but can be used for the bacterial-induced release of antibacterial agents.[143] The bacterial affinity electrode is used to sense the presence of bacteria and promote the release of antimicrobial agents to the electrode after generating electrical signals, to achieve the theranostic applications.

Enzymatic biofuel cells (EFCs) have good biocompatibility and selectivity to reaction substrate, while abiotic biofuel cell has better stability, but poor selectivity. Both of them were successfully applied to electronic medical devices.[138,144] Zhou et al. demonstrated a self-powered "sense-act-treat" system based on EFCs.[145] The abdominal injury was used as a model of injury, and lactate and lactate dehydrogenase biomarkers were used as inputs, the boolean logic anode will switch the biofuel cell to the ON state, which results in the release of the therapeutic agent from the cathode.

Ogawa et al. established the EFCs-built organic iontophoresis patch, including fructose dehydrogenase-modified carbon fiber (CF) anode and bilirubin oxidase (BOD)-modified O_2-diffusion CF cathode connected with an internal resistance based on a conductive polymer.[62] Hydrogel film containing fructose and

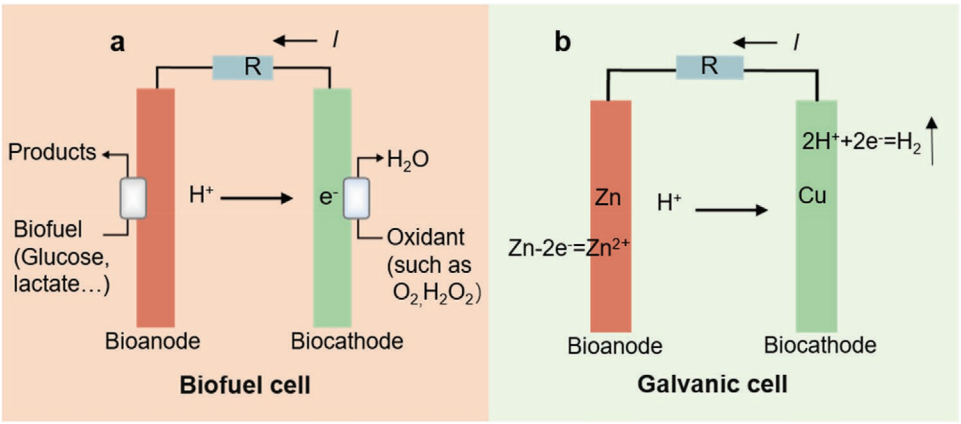

Figure 7. The working mechanism of a) biofuel cell and b) galvanic cell.

drugs are placed directly below the anode and cathode. When mounted on the skin, the patch can generate a transdermal ionic current to generate an osmotic flow from the anode to the cathode, thereby administrating drug into the skin.

Mailloux et al. reported a drug-mimicking release process was triggered by a glucose signal.[60] The electrode modified by PQQ-dependent glucose dehydrogenase formed a negative potential on the electrode triggered by glucose. The other electrode is iron alginate polymer Fe^{3+} cation, which is electrochemically reduced to Fe^{2+} by negative potential and cannot crosslink alginate polymer, followed by gel dissolves and releases the encapsulated drug. Using the same principle, Katz et al. realized the release of nanoparticles functionalized enzyme, antibody-enzyme conjugates, antibacterial drug, etc.[143,146] Alginate substrates with a different signal trigger release different kind of biomolecules and nano-objects, which can be used in many different biomedical and biotechnology applications.[147]

The inherent low power consumption of biofuel cells limits their application as power sources for implan devices.[61] Hanashi et al. develop an autonomous self-powered biosensing actuator that is powered by a glucose enzyme fuel cell. At the same time, it can be converted into a s power supply by using a biocapacitor to operate the liquid-pumping system.

In recent years, biofuel cells have been widely studied and a variety of flexible and wearable devices come into people's view. They can produce high output voltage and power, which is helpful to the development of a wearable DDS.[148,149]

4.4. Galvanic Cell

The galvanic cell can also convert chemical energy into electrical energy through chemical transformation. However, unlike the biofuel cell, it uses two different active metals or metal and other conductive materials and does not need a catalyst. Copper zinc cell is the typical galvanic cell when the copper and zinc electrodes are immersed in the electrolyte together, zinc is easy to lose electrons and the electrons flow from the zinc electrodes to the copper electrodes through the external electrical circuit, the hydrogen ion obtains electrons from the copper electrode and is reduced to hydrogen (Figure 7b).

In 2008, Wallace et al. made a simple galvanic cell composed of active metal, polypyrrole film doped with anionic drugs and electrolyte solution. The metal negative electrode loses electrons and is oxidized, and the electrons of polypyrrole are reduced and the anionic drugs are released.[150] However, this type of device needs an external circuit, which is not easy to be used in vivo. Subsequently, a lot of researches have prepared DDS without external circuit by coupling cathode and anode for in vivo research. For example, Gao et al. demonstrated an acid-powered zinc-based micromotor for intragastric administration. PEDOT coated zinc galvanic cell was prepared by using a porous polycarbonate membrane containing micropores as a template. In an acidic environment, hydrogen ions are reduced to produce hydrogen, which is essential to drive zinc batterie as a micromotor to achieve high-speed propulsion of ≈60m s^{-1}. When the micromotor is pushed into the gastric mucosa, the reduction reaction of the cathode polymer material occurs due to the pH close to neutral, and the drug is released After drug release, the micromotor gradually dissolved in gastric acid without any toxicity.[66] Cui et al. prepared a similar structure, as shown in Figure 7e, compared with the inert copper electrode, the galvanic cell composed of zinc electrode tends to be neutral with pH, and the drug release amount increases. Strong fluorescence was detected in the gastric mucosa of mice, studies have shown that gastric acid-driven propulsion can effectively improve gastric mucosal drug retention.[67]

Based on the same principle, a self-powered device has been developed that can continuously detect temperature and wireless communication for an average of 6.1 days in the gastrointestinal tract of pigs.[65] It has been demonstrated that energy-harvesting devices can also be used to stimulate drug release by corrosion gold film. To be eventually applied in the clinic, further miniaturization of the devices, improving the energy output of cells, prolongation of working time and the dosage and accuracy of the drug need to be further studied.

4.5. Solar Cell

Ambient light is ubiquitous and solar cells have been commercialized for a long time with well-known performance. The basic principle is shown in **Figure 8**a, under the action of the built-in electric field in *p*–*n* junction, the hole flows from *n* area to *p* area, and the electron flows from *p* area to *n* area. After the circuit is connected, the current is formed. With the rapid development of photovoltaic technology, it has been proved that photovoltaic (PV) devices can provide power for various wearable and implan device. Rigid monocrystalline silicon photovoltaic modules have been used to power pacemakers in pig models.[151]

The use of PV devices for electrical stimulation has not been widely reported, probably because it can only be used as subcutaneous implants or wearable drug delivery devices, and the environmental light irradiation, implant coverage by clothing will seriously affect the power output. At the same time, most of the photovoltaic cell materials are rigid crystalline silicon materials, and the preparation technology is expensive. Therefore, there are a few examples found in the literature.

Emerging low-cost flexible materials are under constant research. Jakešová and the co-authors combine an organic electron-ion pump with a thin organic photovoltaic cell (OPV) to provide the voltage required to drive electrophoretic ion transport at low light intensities. OPV active material was selected because of its high absorption coefficient material, which provides flexibility for manufacturing devices with an active layer <300 nm. The device is pressed on the skin and can be easily driven by a red LED emitted through a 1.5 cm thick finger. This technology can realize the conveying operation of low-intensity red light.[64]

4.6. Other Energy Collection Strategies

In addition to the above energy collection devices which have been used in drug delivery, there are also some devices with potential applications in wearable and implan drug delivery devices. Such as pyroelectric nanogenerators (PyNGs) that

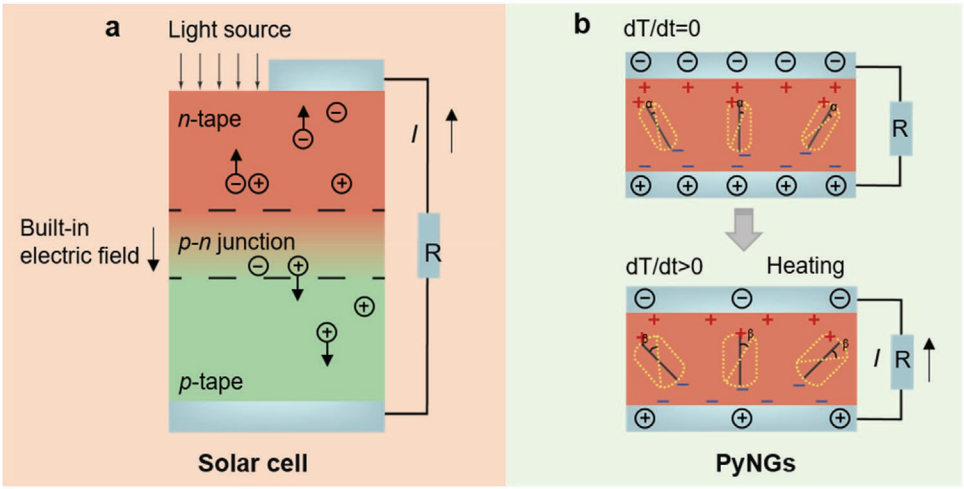

Figure 8. a) The working mechanism of the solar cell. b) The schematic diagram of the pyroelectric generating electricity under heated condition.

harvesting the thermal effect[152] and the biologic battery that collects the potential in the inner.[153] Oscillation generator that collects mechanical energy of the human body through electromagnetic effect. Hydrovoltaic that direct conversion of chemical energy into electrical energy in water. However, due to the limitation of energy output and application scenarios, there are few studies on the delivery of electrical stimulation drugs.

Some crystals can change the surface charge because of the temperature change, which is called pyroelectric effect. Pyroelectric has many applications and development in temperature sensing, thermal imaging, fire monitoring, gas detection, and other fields.[154,155] Figure 8b illustrated the pyroelectric generating mechanism, the direction of the molecule and the spontaneous dipole are affected by the thermal motion. At a certain temperature, the total average intensity formed by the spontaneous polarization of the electric dipole is constant with the wiggling angle α. As the temperature increases, the wiggling angle enlarges to β, as a result, the amount of charge induced on the electrode is reduced, resulting in a flow of electrons in the external circuit.[156] If the temperature drops, a reverse current will be generated. Therefore, the premise of pyroelectric generation is the existence of temperature fluctuation. There is abundant heat energy in the human body. Xue et al. illustrated a PVDF film integrated respirator, the peak current and voltage can reach 2.5 μA and 42 V with the breath.[157] It has potential application in drug release devices.

As new technology emerges in recent years, the hydrovoltaic effect is a general term for the phenomenon that water energy is directly converted into electric energy after the interaction between nanomaterials and water.[158] With the continuous progress of nanomaterials and technology, more and more nanomaterials and devices have been found to have hydrovoltaic characteristics.[159] [160] Xu et al. have fabricated an on-skin humidity energy harvester. The device was combined with eight parallel energy collection units to provide stimulating electricity for iontophoresis at a relative humidity of ≈95%. The iontophoresis has successfully transferred the model drug from hydrogels to pigskin in the direction of current flow.[68] At present, a variety of materials have been used as energy conversion materials, which can generate electricity through humidity and can be used as humidity sensing or self-powered source for other electronic devices. Increasing conversion efficiency and output is still the main research direction of moist electricity generation.[161]

5. Conclusion and Perspectives

The goal of DDS based on electrical stimulation is to deliver the accurate dose of drugs to the target in a specific time and specific space to reduce the side effects and increase the treatment efficiency of drugs. It can promote the development of precision medicine and telemedicine. At present, there are many devices in research, but considering that this is an emerging drug delivery method, especially for the self-powered system. Therefore, more extensive and in-depth research is needed in the future, mainly involving the following four aspects:

For the electroactive biomaterials, different materials have different characteristics. Electric-response biomaterials such as conducting polymers such as polypyrrole has been widely used due to its good biological, electrical, and physical properties. Electroconductive hydrogels have many similar properties with natural tissues, such as high water-content, wide range of Young's modulus, and adjus physical and chemical properties, have attracted wide attention in the field of electrical stimulation drug delivery. Some metal materials, such as magnesium, have good biodegradability. Generate electricity materials such as piezoelectric film can be used as the actuating part of micropump for drug delivery, or in the presence of force, it can be used for self-powered electrical stimulation. Characteristics of the above materials, including excellent biosafety, good conductivity, or electricity generation ability, degradability, stability, etc., are difficult to concentrate on one material. But with the development of materials science, and based on the actual medication scenarios and clinical requirements, a series of bioactive materials can be designed and an efficient and reasonable drug delivery device can be fabricated to achieve a better therapeutic effect.

For the power source, wireless technology and self-powered technology are the main development direction in the future. Wireless technology is of great significance for telemedicine. Doctors can obtain data in real-time and change the dosage according to the status of patients without patients going to the hospital. At present, due to the large power loss of wireless communication, it is difficult to guarantee the transmission distance and depth while miniaturizing, which limits its application. The optimization of wireless technology includes an internal circuit, antenna, transmitter, etc.

The self-powered system is meaningful for patients who need long-term administration at any time. In this review, we describe the progress of a variety of self-powered drug delivery systems, from various transdermal drug delivery patches, wearable systems, to injec, implan, and ingestible delivery systems, which can regulate the speed and dose of drug delivery precisely through electrical stimulation, and can better satisfied the actual treatment needs. Each progress shows that self-powered devices have great application prospects in the field of electrical stimulation drug delivery. However, if self-powered DDS wants to be applied in the clinical, it still faces great challenges. At present, most studies are still limited to the release of model drugs. For a variety of diseases, complex human environment, the effectiveness of drug regulation and treatment still need more research. Therefore, electrical stimulation drug delivery has the prospect and self-powerbility, but there is still a long way to go.

For drug delivery, closed-loop, precisely and targeted drug delivery is the main research direction. Such as hypertension and diabetes, the closed-loop DDS can adjust the dosage according to the physiological indexes to achieve a better therapeutic effect. The dosage can be controlled accurately, and the accurate dose of drugs can be released through one-time electrical stimulation or a certain amount of electricity; the targeted drug delivery can make the drug mainly in the treatment through direct administration at specific sites or through various active, passive, physical, and chemical targeting effects to achieve the best therapeutic effect.

For the drug delivery device, especially for the wearable and implanted device, there are also many challenges as follows:

1. Miniaturization and integration: At present, the research on electrical stimulation DDS is bulky and there are few researches on the integration of power supply, power management system, and drug storage devices. With the continuous development of microprocessing technology, drug delivery devices will become more and more miniaturized and integrated, which can increase the comfort of wearing or implantation and reduce the invasive type for solid implan devices surgical injury. Implan devices can integrate multiple functions to form an intelligent system integrating physiological function monitoring, disease diagnosis, data acquisition, storage, and analysis.
2. Flexibility: The human body and its tissues are mostly non-developable surfaces, and at the same time, they are flexible. For wearable devices, it can achieve a close fit between the device and the human body without affecting daily activities. For implan devices, reducing the mechanical mismatch between human tissues and organs and electronic devices can effectively reduce the immune response.[162]
3. Safety and stability evaluation: Safety assessment is particularly important for electronic devices entering the human body (implan, injec, and ingestible electronic devices), especially for devices that will exist in the body for a long time or biodegradable. It is necessary to establish a sui evaluation system to evaluate the biocompatibility and long-term durability of devices systematically.

The devices for the regulation of drug delivery by electrical stimulation are still under research, with more in-depth systematic research, it is hopeful that the new drug release device will be successfully applied in the clinic in the upcoming years.

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Conflict of Interest

The authors declare no conflict of interest.

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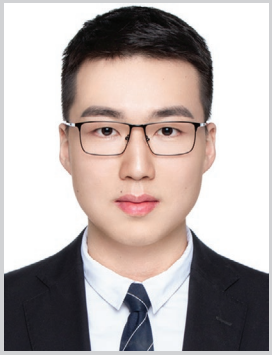

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