Recent advances in intelligent wearable medical devices integrating biosensing and drug delivery

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Abstract

The primary roles of precision medicine are to perform real-time examination, administer on-demand medication, and apply instruments continuously. However, most current therapeutic systems implement these processes separately, leading to treatment interruption and limited recovery in patients. Personalized healthcare and smart medical treatment have greatly promoted research on and development of biosensing and drug delivery integrated systems, with intelligent wearable medical devices (IWMDs) as typical systems, which have received increasing attention because of their non-invasive and customizable nature. This review focuses on the latest progress in research on IWMDs, including their mechanisms of integrating biosensing and on-demand drug delivery. The current challenges and future development directions of IWMDs are also discussed.

Keywords: Wearable device, smart material, biosensing, drug delivery, integrated system

1. Introduction

To satisfy the increasing personal healthcare requirements and overcome the obstacles of passive therapy, the field of intelligent wearable medical devices (IWMDs) has advanced rapidly, with research emphasis on physiological/pathological factors inducing biosensing and active delivery of therapeutic agents in an on-demand manner[1]. IWMDs constitute a vast array of wearable types, such as wrist bands, smart contact lenses, smart patches, and electronic textiles, which are used to measure biophysical or biochemical signals and, most recently, to achieve therapeutic interference by establishing microenvironmental detection-delivery feedback cycles. Accordingly, IWMDs have become critical components in achieving personalized healthcare and precision medicine[2]. Such devices can provide predictive bio-analysis and offer timely treatment intervention, improving drug efficacy,

overcoming the potential dangers due to delayed treatment, and expanding the flexibility of drug use in time and space.

For biodetection and monitoring, wearable biosensing devices (WBDs) have been developed to detect many physiological features such as mechanical deformations, electrocardiogram (ECG) signals, body temperature[3-5], and biochemical components such as glucose, calcium ions, and lactate[6-8]. For a long time, efforts have been made to advance WBDs by tracking single analytes to multiple analytes. Previous reviews have described several types of representative wearable sensors for healthcare monitoring[9].

For drug delivery, transdermal/topical wearable delivery devices (WDDs) are advantageous over oral and injection delivery modalities in terms of flexibility and scalability and have been utilized to deliver therapeutic agents such as polypeptides[10-12], polysaccharides[13], small molecules[14], and growth factors[15] continuously and responsively. Recent studies indicate that wearable transdermal patches that constructed from responsive materials show great advantages and attractive prospects in application of WDDs[16].

Despite the considerable development of WBDs and WDDs, efforts are being made to combine them into a single system to provide both sensing and delivery services, for which IWMDs are expected to realize two core functions: identification of physiological/pathological markers and delivery of therapeutic agents.[17] As **Figure 1** shows, IWMDs are defined as composite pieces of equipment that contain multiple subsystems, including embedded sensors, drug repositories, and their connecting attachments. In addition, some other components, such as power supplies, communication modules, and electronic interfaces, are co-integrated by electronic circuits. To provide active medical services, IWMDs can be activated by physiological signals and deliver drugs to target areas in a smart and on-demand manner. Compared with single therapeutic administration modalities, IWMDs exhibit greater removability, wearability, sustainability, simple operability, and interactivity. Meanwhile, IWMDs have several advantages, such as low pain, strong controllability, convenient management, and high bioavailability[18]. It is worth mentioning

that, compared to their rigid counterparts, flexible substrate-based IWMDs can conform to soft bio-interfaces for long periods with minimal pain and irritation[19,20].

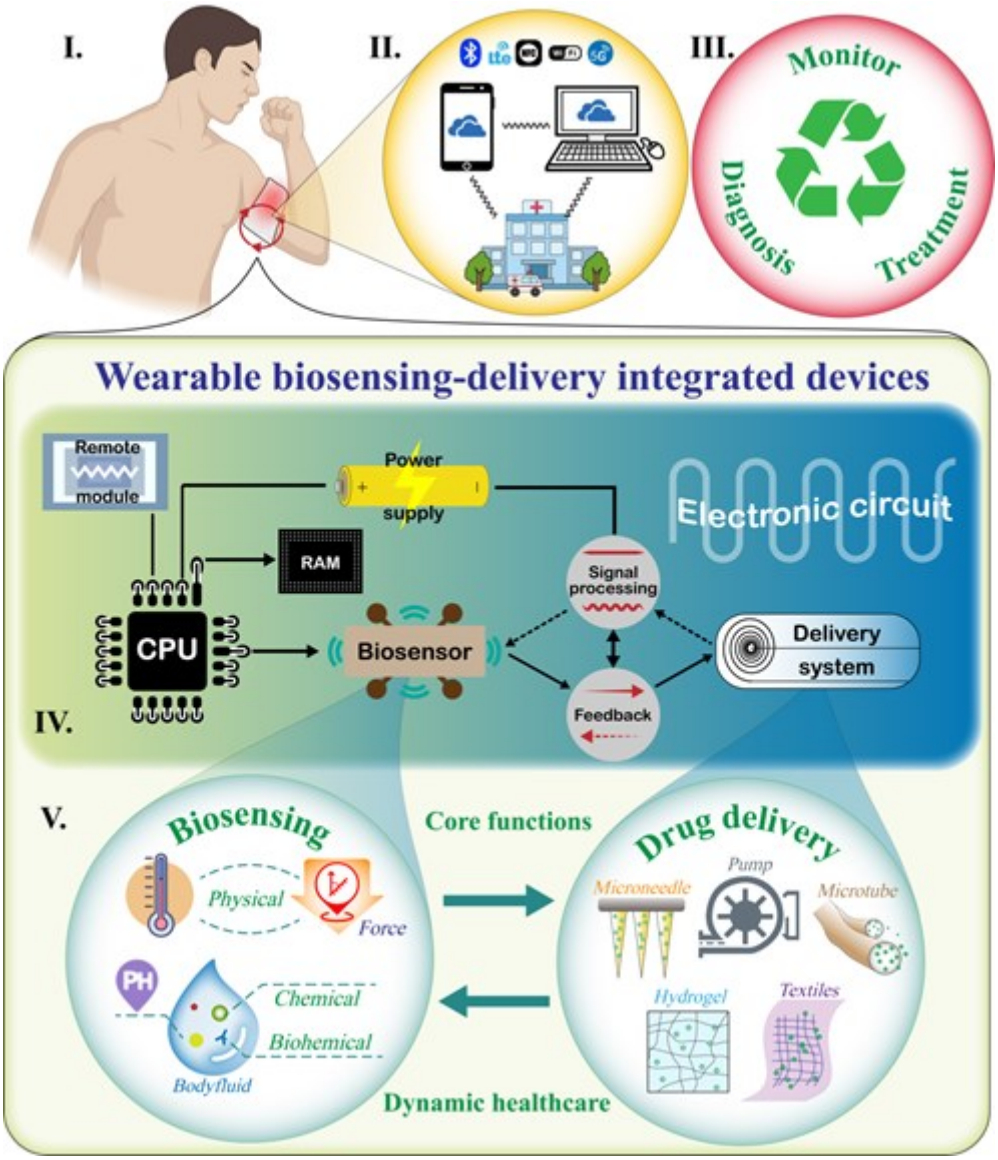

Figure 1. Schematic illustration of IWMDs. Overall, when IWMDs are applied to disease areas (I.), they can provide visual health status information and customizable medical care with the help of communication technology (II.), realizing the functions of monitoring, diagnosis, and treatment (III). In terms of structure, biosensors, delivery systems, and other components such as power supplies, remote modules, and feedback and signal processing units are integrated into single wearable devices (IV.), providing biosensing and drug delivery services for dynamic healthcare (V.)

This article highlights the latest progress in WBDs, WDDs, and IWMDs, with the developments shown in **Figure 2**. We aim to provide insights into the attractive areas of wearable and personalized medical devices for emphasizing the new paradigm in the management of diseases. Herein, WBDs for physiological/pathological detection through biophysical and biochemical signal monitoring are introduced first. Second, several advanced WDDs and their fabrication methods are discussed. Third, we detail IWMDs with novel responsiveness for biosensing-delivery integration. Next, the frequently used functional materials, manufacturing technologies, and working mechanisms of reported IWMDs are reviewed. The last section describes the current challenges hindering the practical application of IWMD platforms and the prospective utilization of many more multifunctional electronic systems to construct next-generation biosensors and controlled delivery systems integrated with IWMDs.

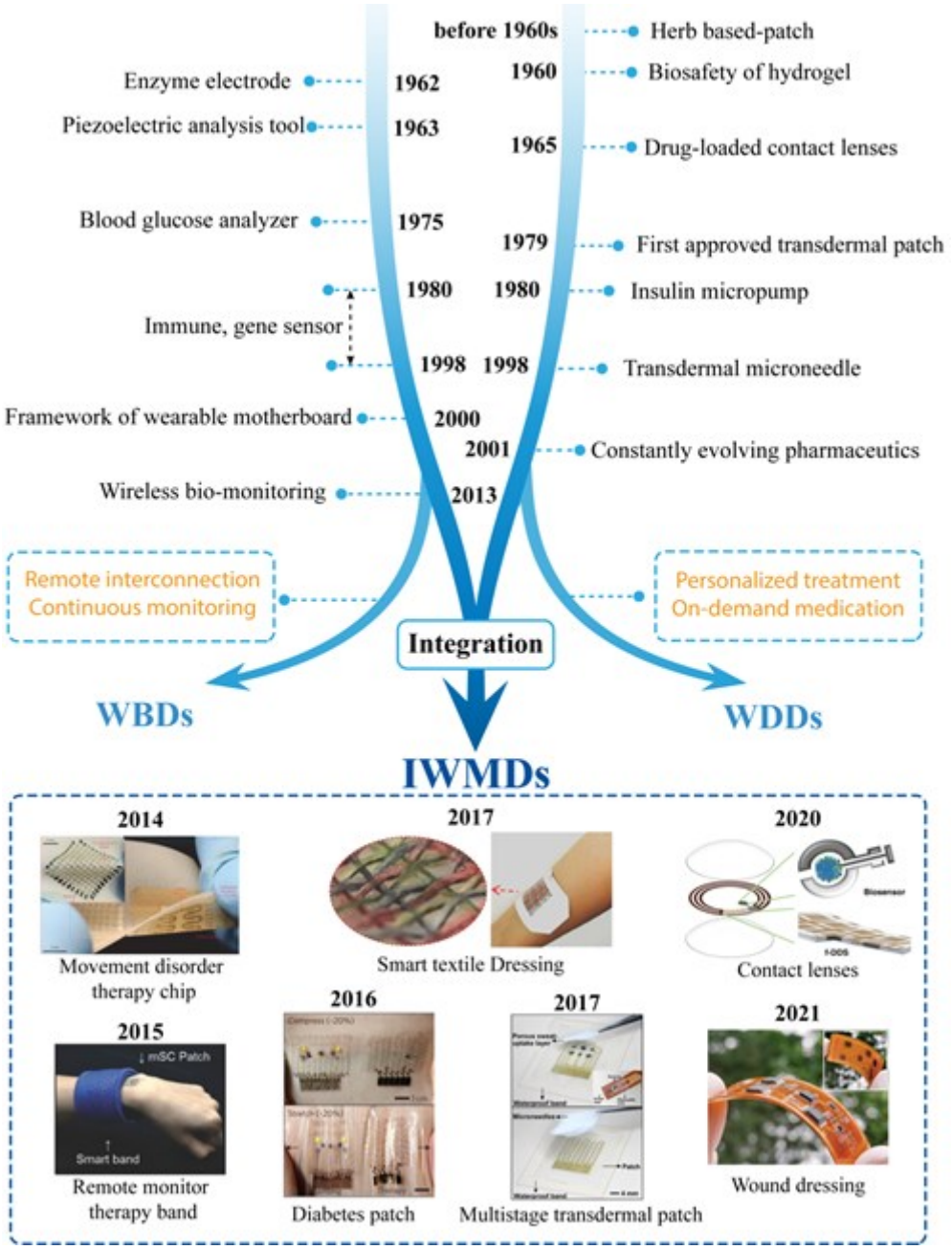

Figure 2. Development of biosensing, drug delivery, and IWMDs. WBDs research has been focused on the continuous development of different principles to realize accurate detection. For WDDs, extensive studies have been conducted on personalized treatment devices. Nowadays, multiplexed WBDs combined with portable WDDs, called the new generation of IWMDs, are receiving substantial attention in healthcare. The development of IWMDs is gradually reforming the disease care model as well as contributing to future clinical treatment. 2014-movement disorders therapy chip. Reproduced with permission.[21] Copyright

2014, Springer Nature. 2015-remote monitor therapy band. Reproduced with permission.[22] Copyright 2015, Wiley VCH. 2016-diabetes patch. Reproduced with permission.[23] Copyright 2016, Springer Nature. 2017-smart textile dressing. Reproduced with permission.[24] Copyright 2017, Wiley VCH. 2017-multistage transdermal patch. Reproduced with permission.[25] Copyright 2017, AAAS. 2020-contact lenses. Reproduced with permission.[26] Copyright 2020, AAAS. 2021-wound dressing. Reproduced with permission.[27] Copyright 2021, Wiley VCH.

2. WBDs for biophysical and biochemical signals detection

WBDs have received considerable attention since the advent of smartphones and other mobile terminals because of their ability to provide useful insights into personal health status. Currently, WBDs are defined as biometric elements that can meet the monitoring requirements of long-term sustainable or mutated signals, perform real-time visualization in sports healthcare, and provide guidance for personalized healthcare and precision treatment. The working mechanisms and manufacturing technologies of the reported WBDs are shown in **Figure 3**. Topical WBDs generally include two functional units: biotarget analytes (such as antibodies and enzymes) and physico-chemical transducer (such as optical and electrochemical) recognition units.

The reported WBDs enable long-term monitoring of humoral physiological aspects such as deformation pressure[28,29], ECG signals[30], body temperature[31], and the biomarkers such as the components of sweat, tears and saliva[32]. These time series of bio-data are sent to mobile phones or hospitals for long-term health monitoring. Ideally, WBDs are expected to permit close skin contact, non-invasive extraction of biological fluids, and acquisition of physiological status[33]. Due to the unprecedented expansion of human health issues, the current activities of WBDs are mainly focused on the minimally invasive monitoring of target signals such as glucose, with the translation potential to be enhanced. As shown in the

representative examples in **Table 1**, some devices still require large-scale verification studies and equipment regulation approval to realize final marketing paths.

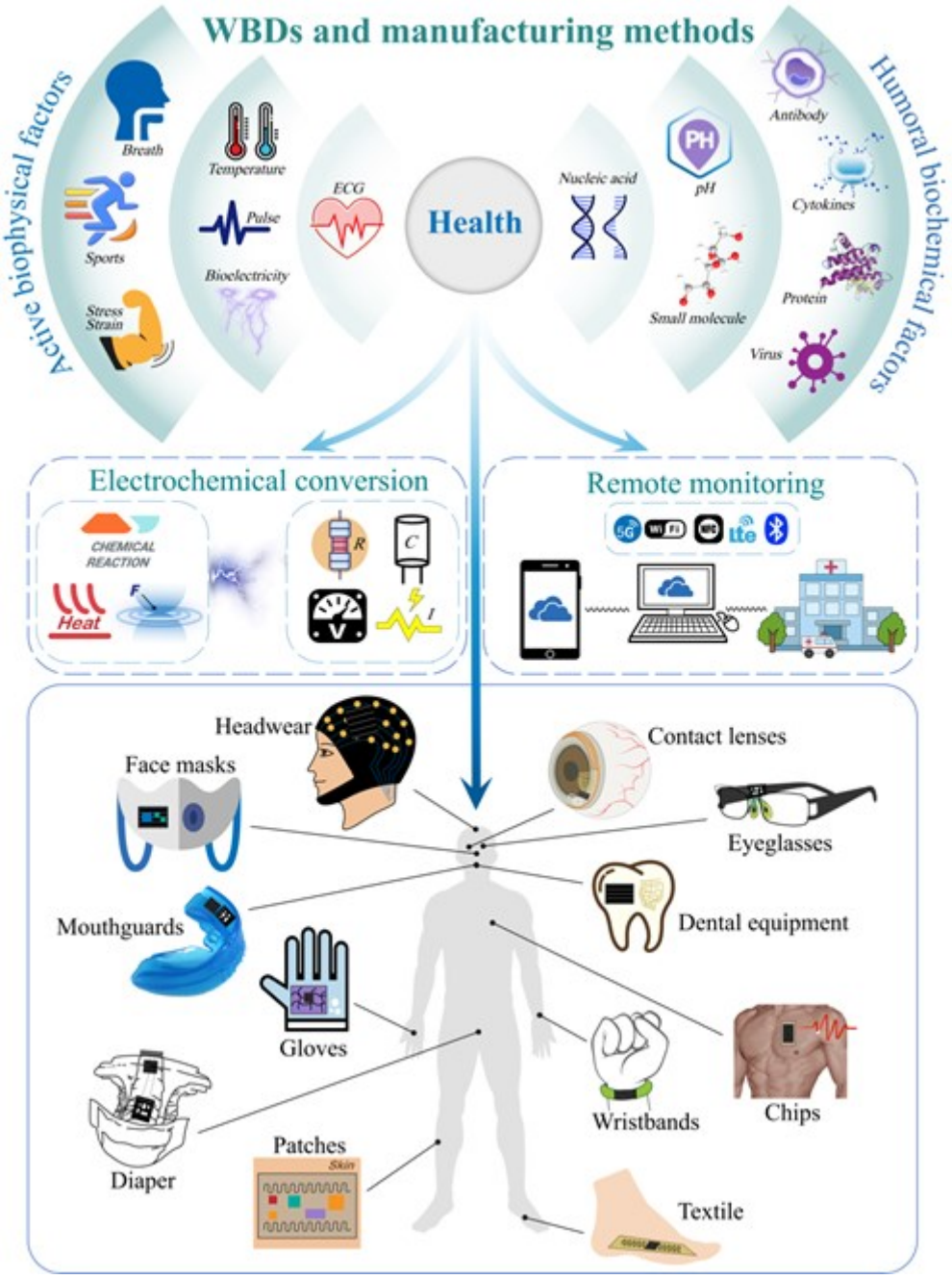

Figure 3. Principles and representative examples of WBDs. The humoral biochemical and biophysical factors are detected and quantified by electrochemical conversion, and the signals indicating health level are sent to terminals and hospitals by remote monitoring. All these

functions are embedded in different types of wearable devices, such as contact lenses, mouthguards, eyeglasses, wristbands, smart masks, gloves, and patches.

Table 1. Several smart WBDs for diseases diagnosis and healthcare applications

Treatment or monitor	Detection object	Detection target	Sensing material	Manufacturing technology	Biosensing mode	Wearing mode	Reference
Diabetes	Intravascular blood	Glucose	Prussian blue film	Bionic ROSE transfer printing	Enzymatic reaction amperometric technique	Patch	[34]
	Tears	Glucose	functionalized hydrogel	Photopolymerization	Photonic structure response	Contact Lenses	[35]
Hypertension	Food intake	Na^+	Ion-selective electron	Double transfer printing	Electrochemical	Oral cavity	[36]
Acute infectious diseases / Immune diseases	Body fluid	Cytokine (IFN-γ)	Graphene–Nafion	Chemical vapor deposition	Molecular specific binding	Patch	[37]
	Aqueous phase	Interleukin-1β	AuNPs, MoS_2	micro printing method	LSPR shifts	Patch	[38]

Respiratory related diseases	Inhaled gas	NO_2	NaOH treated WO_3	Spray-deposited, laser etching	Chemical adsorption	Portable device	[39]
	Respiratory rate	Respiratory parameters	Mini Venturi tube	Electronic components integration	Flow velocity and pressure difference sensing	Mask device	[40]
Cardiovascular disease	Pulse	Pulse parameters	Conductive and nylon yarns	Full cardigan stitch knitting	Electrostatic induced external force stimulation	Artery positions	[41]
	Heartbeat	Heart rate	Nickel-Chrome	Roll-to-roll method	Resistive strain sensing	Wrist radial artery	[42]
Ca^{2+} related diseases	Body fluid	Ca^{2+}, pH	Calcium ionophore II (ETH 129)	Electrochemical deposition	Open circuit voltage measurement	Patch	[43]
Cushing's syndrome or Addison's	Sweat	Cortisol	3D-nanostructured Au working	3D-printed	Electrochemical sensing	Patch	[44]

disease			electrode				
Gout etc.	Saliva	Salivary uric acid	Uricase enzyme, o-phenylene diamine	Chemical modification, screen-printing	Electrochemical measurement	Mouth guard	[45]
Microalbuminuria	Urine	Albumin	Single-walled carbon nanotubes	Chemical synthesis	Photoluminescence responses	Portable device	[46]
COVID-19	Nasopharyngeal swab specimens	SARS-CoV-2	Graphene	Reactive ion-etching	Field-effect transistor	Portable device	[47]

2.1 Active biophysical WBDs

2.1.1 Strain WBDs

The human body is rich in mechanical energy and deformation, and the measured Young's modulus of human skin varies greatly, ranging from 5 kPa to 140 MPa[48]. Strain WBDs transduce deformation-induced external mechanical stimuli into electrical signals and have received extensive research interest owing to their potential uses in human motion detection, human–machine interfaces, and so on[49].

Resistive-type strain sensors have been widely used in engineering, and the type of WBDs demanded has changed from brittle to stretchable. For example, flexible varistors

containing single-walled C nanotubes, Ge/Si nanowires, and vertical ZnO nanowire arrays can accurately monitor deformation changes[50,51]. In addition, some transduction mechanisms, including capacitive[52], electromagnetic[53] and optical[54] mechanisms, can realize strain sensing. In the past decade, piezoelectric materials with electromechanical coupling properties have been employed to generate electrical signals under deformation and are among the main materials used to fabricate stretchable strain WBDs. Some flexible polymer materials, such as poly(vinylidene fluoride-trifluoroethylene)[55], $Pb[Zr_xTi_{1-x}]O_3$[56], and polyvinylidene fluoride (Young's modulus of 2 GPa[57]) are commonly utilized to achieve good biocompatibility, flexibility, and chemical stability.

Strain WBDs are widely used in sports healthcare, including in sensing large deformations such as upper limb bending, lower limb movement, and mechanophysiological signs such as pulse or respiration rates. Despite the good sensing performance in some aspects, measuring decoupled strains in multidirectional and multiplane deformations remains challenging[58]. In addition, strain WBDs have considerable room for improvement in continuous signal transmission and conformal contact.

2.1.2 Pressure WBDs

Pressure WBDs have working principles very similar to those of strain WBDs, and the occurrence of strain is often accompanied by local pressure, so that the use of material technologies is similar to that of strain WBDs. The perception mechanisms of flexible pressure sensors can be divided into piezoresistivity, capacitance, and piezoelectricity. Although pressure WBDs can sometimes be employed for strain detection, there are some different applications in practice. For example, pressure WBDs are often used to monitor the forces generated by trace deformations such as those caused by the heart rate, blood pressure, and pulse[59,60]. Moreover, owing to the development of pressure WBDs, developing epidermal tactile sensors with high resolution, high sensitivity, and rapid response for various applications has become the key research goal, and soft electronic skin is a typical example. However, the current main problem is that local stress may include pressure, tension, shear, and other forms that can be difficult to distinguish using the current devices; thus, more

accurate and precise results are expected to be achieved by the next generation of wearable pressure sensing systems.

2.1.3 Flexible ECG WBDs

Cardiovascular disease is one of the leading causes of death in adults[61]. Real-time ECG monitoring is an effective means of predicting sudden heart disease[62]. C nanotube[63], elastomers[64], and soft polymers[65] are often constructed as electrodes in common wearable ECG devices, and the output of the Abe current and open circuit potential are detected by the Ag/Pt/C electrode[66]. For example, Lee et al. constructed an epidermal sensor using electroless Ni-impregnated electrodes and conductive hydrogels to construct ECG WBDs.[67] The polyurethane packaged ultra-thin sensor patches with sufficient electrode space could capture complete PQRST waveforms. In addition to simple instantaneous current detection devices, accelerometers, acoustic devices, and other technologies can be used to fabricate wearable ECG monitoring equipment. Some smart watches are at the forefront of this field. For example, the ECG sensing function has been added to the Apple watch, which can be used as an auxiliary means of health monitoring and has achieved positive results in large-scale population assessment[68].

2.1.4 Temperature WBDs

Temperature is an important physiological aspect of the human body, indicating infection or fever to some extent[69]. To ensure sensitivity, response time, and temperature resolution, WBDs are mainly constructed by measuring the resistances of thermistors, which are often composed of polymers[70], metal nanowires[71], graphene[72-74] , Ni oxide[75], or their copolymers. Recently, 2D-MXene nanosheets, known as second-generation graphene materials, were utilized to design scalable WBDs and could detect physiological indices such as pH and temperature at specific sites after functionalization by covalent cross-linking, dip-coating, and spray-coatin[76,77]. However, the inaccurate measurement caused by the influence of strain bending on the resistance of the thermistor materials remains to be solved[78]. On the other hand, as a single indicator, the local temperature has some uncertainty

in disease diagnosis; thus, many more sensing channels are proposed to be used to assist this process.

2.1.5 Respiration WBDs

Respiration is a complex physiological process in which various breathing parameters such as temperature, tidal volume, respiratory rate, exhalation peak flow rate, and respiratory waveforms can reflect comprehensive respiratory health state[79]. At present, most wearable breathing temperature and humidity sensors are mainly based on resistance or capacitive platforms, of which MXene[80], graphene-based materials[81], silver nanomaterials[82] and polymers[83,84] are widely used. In addition, the high sensitivity of the stretchable strain sensor is desirable for accurate measurement of the physical signals of exhalation and inhalation, and the working mechanism and manufacture of the strain WBDs have been mentioned above. In recent years, various self-supply schemes such as piezoelectric and frictional nano-generators have shown great potential in building respiration WBDs[85]. The challenge remains to integrate breath-based multimodal sensing miniaturization devices, which place higher demands on sensitivity, wear resistance, and stretchability.

2.2 Humoral biochemical WBDs

Body fluids are rich in chemicals and contain extensive physiological and metabolic information[86-88]. Abnormal health status can significantly affect the composition of body fluids by changing the concentrations of the analysis[89-91]. However, to date, most body fluids still require exploration to be utilized for the manufacturing of practical WBDs. Considering the full integration of multiple detection functions and components, electrochemical testing has become the most advantageous method because of its short response time, high sensitivity, and selectivity. For example, square-wave anodic stripping voltammetry can trace metal[92]. Cyclic voltammetry is suitable for the detection of substances with redox states, such as glucose and uric acid[32,93]. Differential pulse voltammetry is widely used for nucleic acid or protein detection because of its ability to capture biomolecules from small molecules

to large proteins[94]. Electrochemical impedance spectroscopy uses the relationship between the biological affinity signal and electrical impedance to achieve quantification[92]. In fact, current intensity or voltage quantification is sufficiently accurate that screen-printed electrode sensors can monitor micro-current signals based on smartphone systems. Trace detection of various biomolecules can be performed simultaneously[95]. Consequently, based on the specific recognition of receptors to biomarkers, WBDs can achieve flexible detection of most body fluids, such as sweat, tears, and saliva, utilizing electrochemical methods. The applicability and challenges associated with manufacturing WBDs with different body fluids are explained below.

2.2.1 Epidermal WBDs

As the epidermis covers most of our body, sweat is the most readily obtainable biofluid. The ion content in sweat may cause or react to the occurrence of diseases such as hypokalemia[96] and cystic pulmonary fibrosis[97]. Abnormal electrolytes in sweat can also be used to diagnose hypocalcemia, liver disease, etc. Thus, sweat is especially suitable for in situ analysis[98]. Recent research has been focused on constructing soft epidermal WBDs for analyzing epidermal biofluids (sweat and ISF) produced by motion or extracted by iontophoresis to evaluate the health state[99].

Epidermal WBDs are subject to mechanical stress and deformation encountered during physical movement; thus, various flexible substrates, such as wires, soft polymers, flexible plastics, and traditional silicon integrated circuit hybrid systems have been explored to achieve satisfactory ductility by lithography or printing manufacturing technology[100-103]. Because electrochemical methods constitute the main means of detection, the electrode materials for sensing must meet the requirements of chemical inertness, stability, conductivity, and good electronic transport performance. In addition to graphene-based materials, which have attracted long-term attention, other sensing materials have made great progress in achieving selective detection using bioreceptor-free sensors, such as transition metal dichalcogenides, monoelemental Xenes (silicene, germanene, etc.), C nitrides, B nitrides, transition metal carbides, and nitrides (MXenes)[104]. The doping or de-doping of

conjugated polymers such as polypyrrole (PPy), polyaniline (PANI), and poly(3,4-ethylene dioxythiophene) (PEDOT) also shows great potential for applications in biosensing[105]. Future research will concentrate on systematic studies to evaluate the scalability and miniaturization of developed wearable devices, as well as whether sensing-based materials can replace a wide range of biological receptors, which will take a long time to verify.

In recent years, epidermal WBDs combined with different factors, concentrations, substrates and detection mechanisms have been reported[33,106]. The complexity of sweat secretion makes accurate measurement challenging. Different biomarkers must be simultaneously screened for multivariate analysis. An integrated sensor system can solve these problems[7]. For example, a hybrid wearable sensing system consisting of chronometric microfluidic platforms and embedded colorimetric assays was recently presented[107]. This system integrated real-time sensing of the concentrations of chloride, lactate, and glucose, simultaneously with pH, sweat rate, and total sweat loss sensing. Electrochemical sensing draws on the idea of biofuel batteries, enabling significant device simplification using a multipath sensing function.

However, despite the rapid progress in sensing technologies in recent years, many challenges remain in humoral multivariable analysis using wearable devices, which mainly occur in the process of body fluid acquisition, selection, and sensing. For example, blood, cerebrospinal fluid, and interstitial fluid are extracted invasively, which can cause pain and infection. Some variable environments, such as the oral cavity, can easily lead to inaccurate saliva detection. Furthermore, the methods of extracting seminal fluid, stool, and nipple aspirate fluid cause difficulties in real-time monitoring. In contrast, sweat may be a relatively ideal detection object for non-invasive extraction and in situ detection of WBDs[108]. It is worth emphasizing that sweat biosensors can be compatible with body fluids of other types of diseases to a large extent, such as the blood of diabetic patients and wound exudate.

2.2.2 Ocular WBDs

Tears are another potential biological fluid that can be used to monitor physiological conditions, and contact lens-based systems represent an attractive solution for tear collection. Because the eyeballs are very fragile, the material used to make contact lenses must be highly flexible and soft to minimize eye irritation and avoid discomfort in the wearer. Simultaneously, these materials need to ensure oxygen permeability to avoid changes in metabolite content caused by hypoxia, reducing the monitoring accuracy. Thus, hydrogel-based materials are the only candidates.

In particular, there is a good correlation between tears glucose and blood glucose concentration[109,110]. Tear proteome analysis is often performed to identify eye diseases[111]. Contact lens WBDs show great potential for the monitoring and treatment of diabetes and eye diseases[112]. In fact, glucose in surrounding tears can be detected in a non-invasive manner by embedding wireless control chips, miniature electrochemical sensors and glucose sensors into contact lenses[113]. In the construction of ocular WBDs, the miniaturization of power transmission and data communication remains a long-term challenge. Recent studies have involved photon microsensors based on hydrogel matrices for continuous monitoring of glucose. Independent sensors can be installed directly on the surfaces of commercial contact lenses, and smartphones record the reflected power. This approach provides an attractive alternative method for eye-use WBDs based on electrochemistry.

2.2.3 Oral-cavity WBDs

It has been reported that the concentration of uric acid in saliva may be associated with a various of diseases (hyperuricemia, ventilation, and renal syndrome)[114]; therefore, dynamic chemical data can be obtained by installing a sensor on a dental appliance or tooth surface[45]. Other studies have shown that there is a close relationship between blood glucose and saliva glucose level in diabetes.[115] Therefore, oral-cavity WBDs have great potential in diabetes care, as well as food intake analysis, oral bacterium detection, etc.

To solve the problem of equipment miniaturization, the use of technology based on impedance changes or the use of modified screen printing electrodes is still the main approach in oral-cavity WBDs. Furthermore, microfabrication techniques such as transfer printing, electroplating deposition, and photoetching are necessary. However, these aspects present challenges to operational stability and the proficiency of the operator, as well as high costs. In addition, problems such as the easy contamination of the oral environment and saliva by external factors and bleeding gums seriously hinder the large-scale study of oral sensors, and considerable effort should be made to realize successful conversion in commercial markets.

3. WDDs for transdermal/topical drug delivery

The new field of WDDs has attracted considerable attention for drug delivery because of the superior accuracy and convenience of drug dose management using these devices as well as their avoidance of systemic side effects. Representative WDDs are listed in **Table 2**. For WDD manufacturing, micro-sized devices are designed to implement effective drug treatment, and template forming is a common method of achieving this objective. With the development of micromachining technology, laser cutting, and etching (mainly used in metal materials), lithography technology has solved the problem of precision manufacturing of components[116]. Three-dimensional printing also introduces flexible programmable steps into the manufacturing of WDDs to solve the problems of complex processes and high costs. This approach has contributed to the development of most current WDDs, such as microscale platforms, hydrogels, and textile-based WDDs. The scheme for the design of several widely investigated WDDs is presented in **Figure 4**.

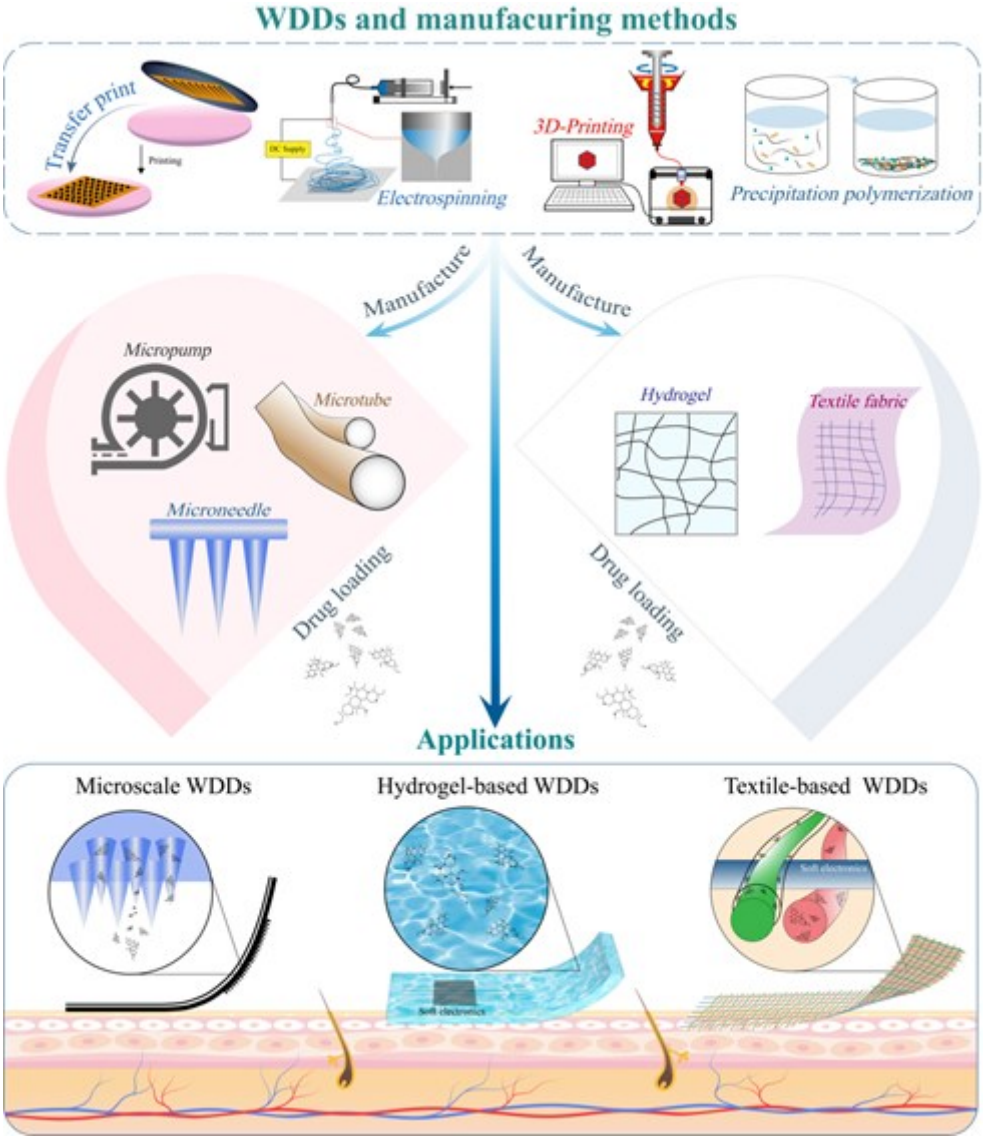

Figure 4. Manufacturing of representative WDDs. The drug release components, including microneedles, micropumps, microtubes, hydrogels, and textile fabric units are manufactured using several advanced manufacture technologies. With drug loading, microscale WDDs and soft electronics implanted hydrogel/textile-based WDDs have been developed for the precise treatment of many diseases

Table 2. Different types of WDDs for diseases treatment

Wearing mode	Drug carrier	Drug release	Manufacturing technology	Auxiliary technology	Drug	Treatment	Reference
Bandage type	Alginate-based hydrogel	Heat-activated drug microcarrier	Heater electronic integration	3D-printed	Rhodamine isocyanate	Chronic wound healing	[117]
	Alg-PEGDA hydrogel	Thermal response	Textile processes	Microfluidic flow-focusing	Cefazolin, VEGF	Antimicrobial and angiogenesis in chronic wound	[24]
	Nanofiber network	Thermal response drug nano-carrier	Electrospinning	Screen printing	Cefazolin, Ceftriaxone	Bacterial infection	[118]
	Miniaturized Needle Arrays	Deep percutaneous drug delivery	3D-printed	Micropump	VEGF	Chronic diabetic wounds	[15]

	Graphene electrode	Ion electroosmosis and thermal stimulation	Thermally controlled transfer printing	Ion electroosmosis therapy	Doxorubicin	Customized wristband for TDD	[119]
	Intradermal microneedle	Insert self-release	Microneedle transdermal targeting	Near-infrared therapy	B16F10 melanoma vaccine	Antitumor effects	[120]
	Molecularly Imprinted Polymers	Local sustained release	Precipitation polymerization	Synergistic adsorption	Diclofenac	Localized painful and inflammatory conditions	[121]
Eye type	Poly(hydroxyethyl methacrylate)	Contact sustained release	The free radical polymerization	Modified cast molding	Moxifloxacin HCl	Bacterial conjunctivitis	[122]
	Embedded Microtubes	Diffusion or stretch release	PDMS	Soft lithography process	Timolol	Glaucoma	[123]
	PDMS drug	Triboelec	Standard printed	PDMS soft	Fluorescent	Ophthalmic	[124]

	reservoir	tric- Nanogenerator	circuit board technology	lithography	polystyrene microparticles	disease	
	Commercial contact lenses	Diffusion	Vitamin E modified	Combination therapy	Timolol, dorzolamide	Glaucoma therapy	[125]
Ear type (Headwear)	Micropump	Cochlear administration	Reciprocating micropump	Cochleostomy	Glutamate receptor antagonist, DNQX	Auditory disorders	[126]
	Scalable peristaltic micropump	Thermally phase-change material	3D-printed	Bullaostomy surgery	Salicylate solution	Auditory and vestibular disorders	[127]
Intraoral type	PLA，PVA filament	Sustained release	3D-printed mouthguard	Hot Melt Extrusion	CDS, VA	Alleviating oral inflammation	[128]

3.1 Microscale WDDs

An ideal drug delivery system is expected to be able to deliver drug molecules intelligently to exact targets at precise time points. While research is being conducted to achieve this goal, the search for a microscopic-scale solution based on a “top-down” approach to deliver drugs maybe an unavoidable research avenue due to the fast measurement

and high sensitivity of microscale drug carriers[129,130]. Furthermore, microscale WDDs ensure miniaturization and measurement accuracy and can be integrated with electronic modules to achieve multiple functions in a relatively simple manner[131]. These excellent performance aspects make microscale WDDs ideal carriers for drug loading. It has been reported that the drugs that can be delivered by microscale WDDs include various chemical drugs[132,133], peptides[134,135], and vaccines[136,137] and so on. It is expected that the restrictions on WDDs will be greatly reduced with the advances in microscale fabrication platforms. Thus far, representative microfluidic devices in wearable fields have been developed in the form of microtubes (MTs), micropumps (MPs), and microneedles (MNs)[138,139], and some combinations have been applied to these microscale devices to overcome the limitations of individual use[140,141].

MTs are especially suitable for in situ extended drug delivery for ocular disease treatment, because device invasion into the fragile eye structure needs to be avoided. MT-embedded contact lenses have two types of free diffusion and pressure adaptive drug delivery. Studies have shown that MTs-based WDDs can ensure non-invasive drug release for up to seven weeks[123]. MPs usually serve as drug repositories or actuators and have been integrated with MNs into labs-on-a-chip[127]. Switch mode and precise flow control make MPs especially suitable for WDDs. Silicone, ethylene vinyl acetate, polyurethane, and polymethylmethacrylate[142] have been used to fabricate wearable MPs. As early as 2016, the Food and Drug Administration approved MinimedG670[143], the first wearable medical MP produced by Medtronic for blood glucose monitoring and long-acting insulin delivery. In recent years, based on the development of micro-manufacturing technologies such as lithography, molded embossing, plasma etching, and laser-assisted methods, MPs with various power types have been developed for wearable applications including subcutaneous, transdermal, and inner ear delivery[127,144].

Precisely engineered MNs can easily penetrate the stratum corneum and deliver drugs into the dermis without damaging nerve cells to induce pain. Therefore, patches including MNs have been widely explored for transdermal delivery and are highly accepted in wearable

device development fields. MNs with different properties are manufactured using silicon[145], metal[146], polymer[147], ceramic[148], hydrogel[149], and sugar-based[150]. To solve the problem of a broken needle staying inside the skin due to lateral relative movement, soft polydimethylsiloxane (PDMS) is often used as the bases of MNs so that their tips can be pulled out without breaking[151]. Furthermore, a biodegradable MN array releases the drug when it dissolves, so that the patch can be removed directly after treatment, which greatly simplifies the application of WDDs.

3.2 Hydrogel-based WDDs

Hydrogels have been widely used as dressings to provide local treatment owing to their structural similarity and excellent biocompatibility with the natural extracellular matrix. However, a simple gel system is unable to meet the requirements of complex disease treatment, although combining bioelectronics and conductive materials with gel systems may be a means of overcoming this issue. Recently, conductive hydrogels coated with flexible electronics or embedded ion components have attracted tremendous interest in the construction of hydrogel-based WDDs with multiple functions of signal transmission and drug delivery. To increase the conductivity of hydrogels, doping conductive materials such as carbon-based materials[152,153] or directly introduced free ion-generating substances such as acids, metal salts, and ionic liquids are commonly used[154,155]. However, physical doping reduces the drug delivery ability of the hydrogel; thus, conductive polymer-based hydrogels such as PEDOT[156] PANI[157] have been investigated to maintain drug efficacy. Conductive hydrogels have therefore been widely studied as alternatives to inorganic materials for constructing soft WDDs owing to their suitable mechanical, electrical, and chemical properties.

Soft electronic hydrogels composed of WDDs have been studied to achieve on-demand drug delivery[117]. A common design involves directly embedding the flexible heater inside the conductive gel, which then triggers the release of drugs from the thermally responsive hydrogel[158]. Conductive hydrogels can also be used as nano-drug reservoirs by physical doping and directly connected to the battery system to construct transdermal WDDs with

iontophoresis, which improves the skin barrier penetration of drugs[159]. However, some problems remain to be solved. For example, simple connection can easily cause the separation of components, which is a fatal defect for the preparation and long-term maintenance of therapeutic electronic skins. The method of self-assembly surface modification and UV-induced polymerization has been studied to connect tough gels with non-porous solids[160,161], and the dispersion adhesive was synthesized by Daniela et al. to connect hydrogels with soft or hard devices.[162]

3.3 Textile-based WDDs

Traditional textile fabrics incorporate drugs into silk or cotton-based fabric, and therapeutic applications have been realized by directly applying WDDs to damaged tissue[163]. However, the single functions, limited drug loading capacities, and modification potentials of these conventional WDDs have been considered as limitations. Later, textile fibers, including polyester[164], polyurethane[165], and poly(lactic-co-glycolic acid)[166] were developed with controllable mechanical and thermal properties; however, the biosafety of the chemical residues of the polymers must be addressed. Recently, smart textiles or nanofibers have attracted new exploration owing to the multiple functions of drug loading and responsive delivery with good biocompatibility. In addition, flexible bioelectronic implants endow them with properties of wireless transfer and connection, which is of great significance in the field of telecare. Consequently, Pooria et al. developed temporal and dosage-controlled textile-based WDDs, which are almost the first WDDs that doped soft wire-based heaters into drug-loaded textile dressings and performed a wireless controllable strategy.[24] Although the concept of textile-based nano-fabrics is of great significance to WDDs, most studies still focus on energy storage, sensors, or fiber-optic applications. Current textiles can release drugs, perform biometric identification, and provide simple treatment; however, the method of utilizing drug delivery dressings combined with flexible electronic devices is just the beginning of textile-based WDDs. Numerous optimizations on the structure and characteristics will facilitate the realization of multiple functions of smart textile-based WDDs.

4. IWMDs integrating biosensing and drug delivery

At present, radiology[167], medical assay[87], pathology and clinical microbiology examinations[168] are still the most reliable diagnostic methods for diseases. However, considerable clinical skills are required, and for most people, long-term monitoring in a fixed place is unrealistic. In contrast, IWMDs can indicate the occurrence of diseases and guide the delivery of therapeutic agents or reflect the status of injured sites dynamically and thus possess great potential to achieve the long-term goal of building closed-loop feedback therapy systems[169,170].

IWMDs are based on controller algorithms and self-regulating equipment and are highly integrated into single devices and directly connected to drug reservoirs to achieve on-demand treatment and controlled release. Generally speaking, IWMDs commonly contain multiple cooperating elements, where complex signals of WBDs are transmitted to WDDs and drugs are delivered by relatively regular and controllable signals, which is called "responsive release." The types of IWMDs with different responsiveness are summarized in **Figure 5**. With the integration of WBDs and WDDs, many more drugs will have the potential to be delivered by IWMDs, including insulin[171-172], adriamycin[10], tannicacid[14], sodium salicylate[151], lidocaine[173], and dexamethasone[174]. These IWMDs are especially suitable for diseases that require on-demand delivery of drugs[172], immediate response[175,176], or targeted treatment[177], or involve acute pain.

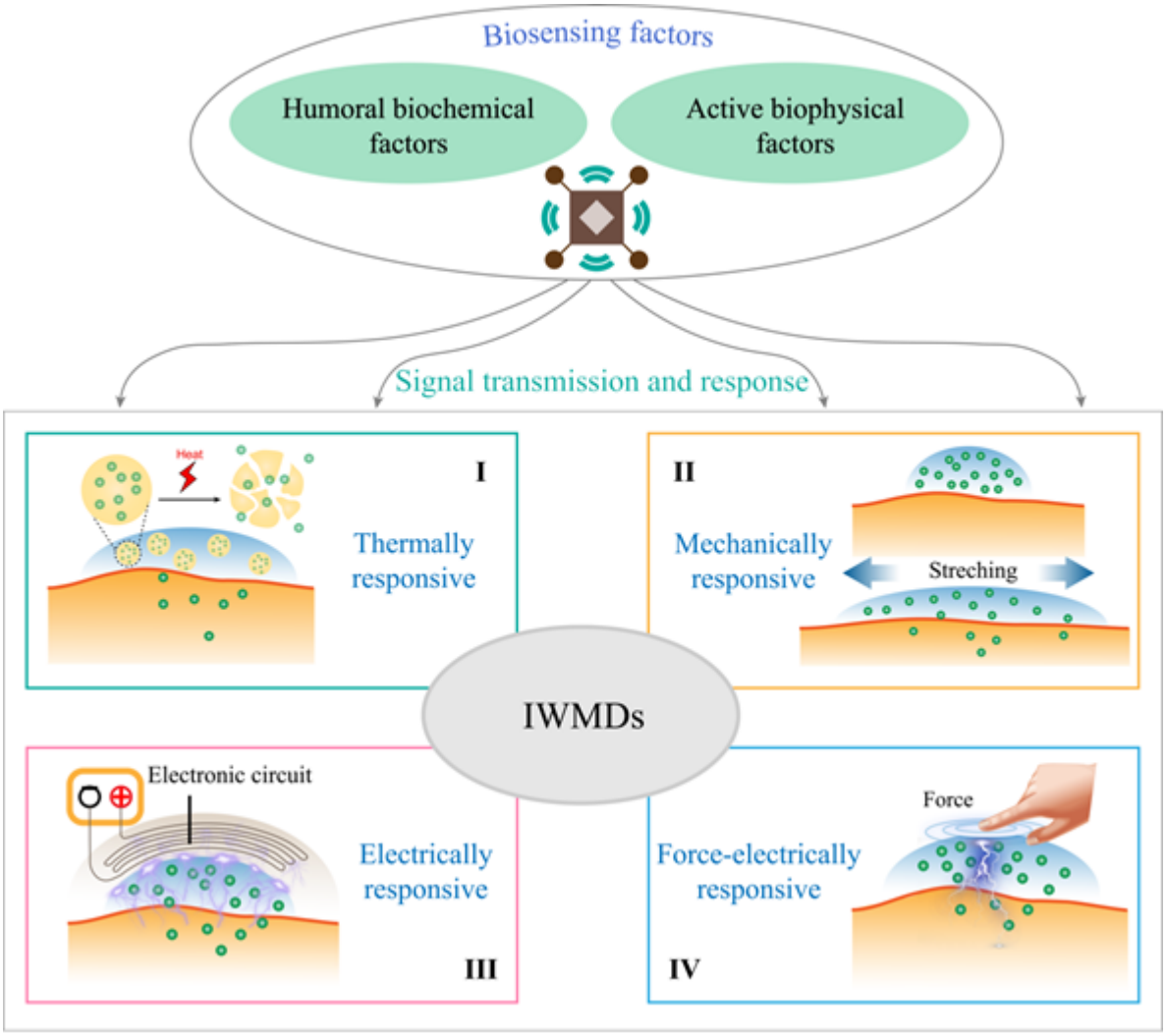

Figure 5. Categories of IWMDs. Responsive devices triggered by mechanical, thermal, electric, and force-electric signals.

4.1 Thermally responsive IWMDs

In contrast to most chemical factors, physical factors such as temperature and pH may provide better information for treatment, avoiding variability and inhomogeneity. For example, thermally responsive carriers undergo sharp phase transitions caused by environmental temperature changes to release the encapsulated therapeutic agents[178]. Owing to the flexible treatment management mechanism, thermally responsive IWMDs are especially suitable for constructing closed-loop medical systems to treat chronic diseases such as wounds, burns, and diabetic ulcers **(Figure 6a)**.

Hydrogels have always been developed for wound treatment; however, current hydrogel-based wound dressings simply provide therapeutic agents to wound sites, leading to limited healing efficacy. Research on microelectromechanical systems and soft electronics has led to the development of smart bandages[179], where WBDs monitor the physiological contents of disease areas in real time and WDDs trigger the phase changes of responsive materials by thermal activation to release drugs[180-182]. Some studies have shown that temperature and pH are normal markers of wounds; by detecting these quantities at predetermined times, the corresponding IWMDs can be used for long-term monitoring and evaluation of wound status[183,184]. For example, some multifunctional dressings have been developed for pH remote detection and drug delivery to monitor and promote wound healing continuously **(Figures 6b and c)**. On the other hand, the release behavior of a drug can be visually observed through color change by the expansion or contraction of chromogenic factors such as photonic crystals based on Fe_3O_4@C nanoparticles[185] **(Figure 6d)**.

The connection between WBDs and WDDs has always been a challenge, and Lin et al. integrated temperature sensor elements, drug delivery channels, and repositories into a hydrogel matrix in a patterned manner.[186] When the local temperature rises to the threshold, the drug solution can be manually delivered to the corresponding drug reservoir through a non-diffusion channel and then diffuse to the hydrogel matrix and surrounding site in a continuous manner **(Figure 6e)**. The programmed process enables thermally responsive IWMDs to adapt to the characteristics of different drugs and implement procedures flexibly and controllably. In the thermal response phase, the drug carrier is usually cast directly on the top of the flexible heater to minimize the thermal contact resistance[186]. In this way, the electronic equipment can be reused to reduce the cost, and the entire dressing change process will be very simple, effectively avoiding drug abuse and treatment interruption.

For diabetes healthcare, IWMDs require extremely high sensitivity and low detection limits for biosensing. In contrast to the univariate response mode, the most responsive behaviors of carriers based on physiological stimulation are passive. It is difficult for a single signal to control the release rate accurately owing to the complex physiological environment.

Multiple-channel detection has great potential in this respect. Lee et al. constructed a hybrid sensing device to design a multifunctional diabetes care patch based on an electrochemical device for the thermally driven delivery of metformin.[23] The gold-doped graphene was patterned into a serpentine grid to achieve electrochemical activation, and the PEDOT, polyaniline, and polybutene electrodeposition electrodes were used as humidity, pH, and glucose sensors, respectively. When the humidity of the sweat collection layer reaches more than 80%, the in situ monitoring of glucose and pH using sweat starts, and the detection level is similar to that of a commercial blood glucose meter. Hyperglycemia then causes a warm boot of bioabsorbable MNs, which induces the phase change material to dissolve thermally and release metformin **(Figure 6f)**. As feedback, the skin temperature was monitored by a thermal stimulation device to prevent drug overdose and hypothermic burns. In the following years, another disposable diabetes care patch was developed, as shown in **Figure 6g**.[25] Based on previous research, this patch adopts a disposable-type design to enhance practical applicability; however, the long-term stability and uniformity of sensors and the relevance of biosensing and drug delivery modules need improvement.

On the one hand, thermally responsive IWMDs can detect local temperature changes of the body surface in real time with high sensitivity and have broad applications in wound treatment, fever warning, and other aspects. However, skin temperature is susceptible to environmental humidity, wind speed, clothing cover, air flow, etc., which interferes with the effectiveness of thermally responsive IWMDs and needs to be addressed. On the other hand, thermally responsive drug delivery modules based on flexible heaters associated with physiological signal detection and conversion can achieve precise controlled release of drugs and have good reusability. Meanwhile, the external environmental temperature interferes with the effectiveness of thermally responsive IWMDs; this interference needs to be solved and avoided.

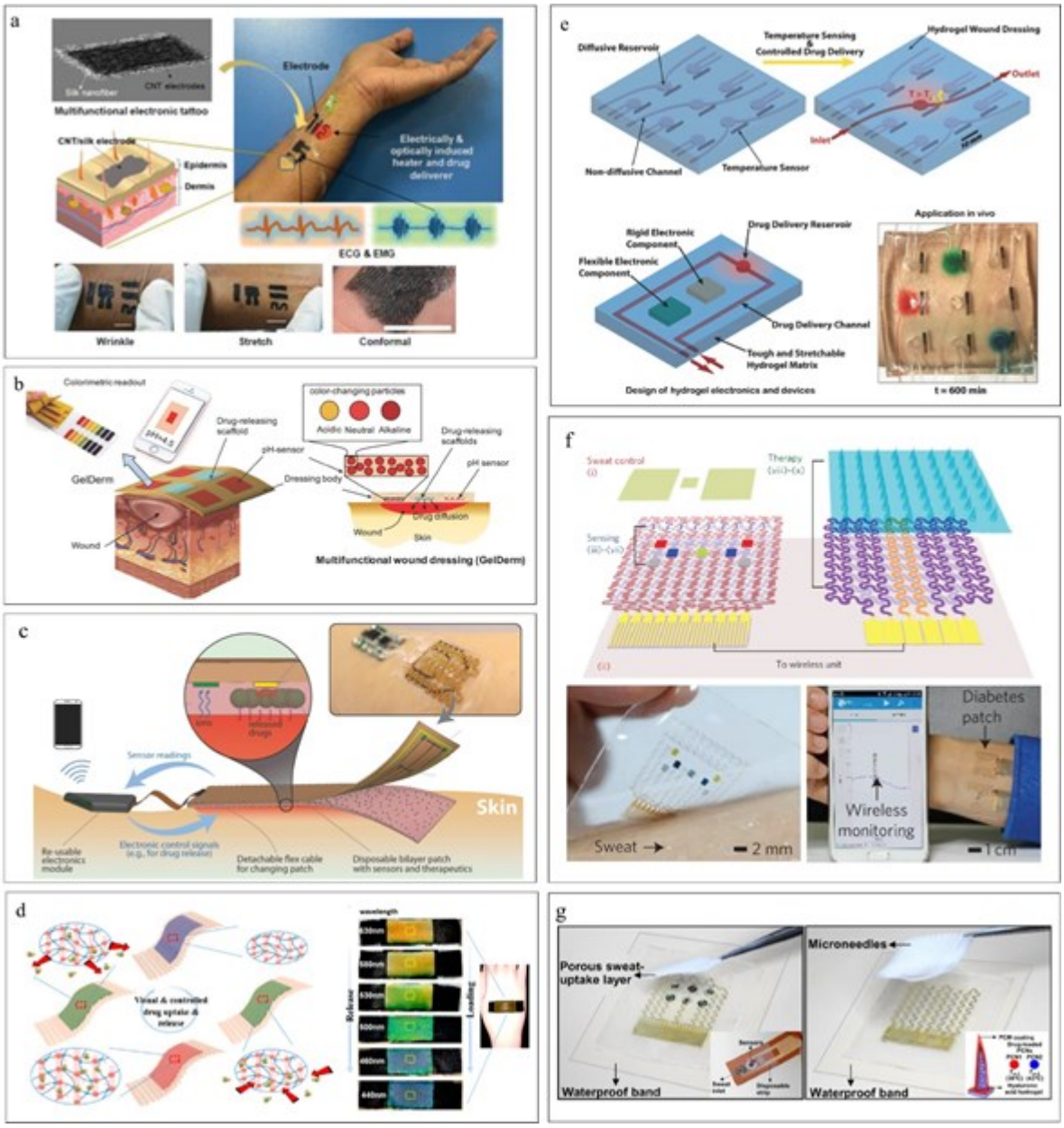

Figure 6. Thermally responsive IWMDs. a) Schematic and optical image of an electronic tattoo placed on a human forehand for multifunctional applications (electrically and optically active drug delivery, temperature sensing, ECG monitoring, and electromyography). Reproduced with permission.[187] Copyright 2021, Wiley VCH. b) The wearable composite fabric patch realizes on-demand drug release under gentle external heating and visualizes the results of real-time drug content detection by employing photonic crystals. Reproduced with permission.[188] Copyright 2017, Wiley VCH. c) Schematic representation of GelDerm treatment of epidermal wounds, with pH-sensitive and drug-eluting components. Reproduced

with permission.[179] Copyright 2018, Wiley VCH. d) The bandage is composed of an array of flexible pH sensors and a flexible heater that can trigger the release of antibiotics trapped in the thermally responsive drug carrier. Reproduced with permission.[185] Copyright 2020, American Chemical Society. e) Flexible stretchable hydrogel electronic equipment, which integrates stretchable conductors, functional chips, drug pipelines, and reservoirs, can achieve skin temperature sensing and sustained drug release functions simultaneously. Reproduced with permission.[186] Copyright 2015, Wiley VCH. f) Graphene-based electrochemical wearable device for diabetes detection and treatment. Multiple patch sensors simultaneously measure the pH, temperature, humidity caused by in situ sweat, and correct glucose concentration and record this information in remote mobile devices. The blood sugar is reduced by heat-driven MNs through transdermal drug delivery to achieve closed-loop immediate care of diabetes. Reproduced with permission.[23] Copyright 2016, Springer Nature. g) Wearable/disposable sweat monitoring device and MN-based transdermal drug delivery module, which contains thermal phase change MNs. Reproduced with permission.[25] Copyright 2017, AAAS.

4.2 Mechanically responsive IWMDs

Mechanical response refers to physical diffusion or mechanochemical activation caused by deformation and endogenous/external forces **(Figures 7a and b)**. The physiological force changes range from microscopic cellular force (10^{-9}–10^{-6}N)[189] to macroscopic force of tissue (up to 10^{3} N)[190], and external forces such as the active pressing of fingers cause considerable mechanical deformation. Consequently, mechanically triggered WDDs have aroused widespread research interest, where the drug particles are usually trapped in the pores of the material molecular network through electrostatic and hydrophobic interactions. Stretching and compression change the pore structure and trigger grid convection to achieve instantaneous pulse release[191]. The mechanical response release characteristics of the material itself seem promising for building closed-loop IWMDs; however, current research is focused on squeezing and pumping drugs, which may be due to the more precise and controllable microfluidic drug delivery.

Hydrogels provide relatively mechanical and chemical environments for the loaded drugs. Applying external stimuli, such as pressure strain, can deform hydrogels, accelerate hydrogel dissolution, and thus control the nanocarrier release rate, which exhibits characteristics similar to those of mechanically sensitive drug carriers. Shi et al. conducted a preliminary study on creating a hydrogel-based wearable multifunctional device that can simultaneously administer drugs and record mechanical responses **(Figure 7c)**.[192] However, skin permeability barriers significantly restrict the delivery of macromolecular drugs and genes. Recently, scholars have combined MNs with IWMDs to overcome the skin barrier and enhance transdermal drug delivery efficiency. Kim et al. developed a pressure-regulating transdermal patch that included a strain sensor and MN array **(Figure 7d)**.[193] The MNs are composed of PLGA copolymers, and the strain sensor consists of metal NPs. The elastomers were selectively deposited and separated from the drug-storage chamber using a PDMS film. The MN array was used for painless puncture, the sensor chamber was pressed to release the drug, and the good linear relationship between the release amount and pressure could be utilized to control the drug delivery precisely. On the other hand, the highly sensitive sensor monitors the dynamic forces of the skin, and the drug release module added to the strain sensor can administer drugs and record physiological responses simultaneously.[194,195]

In the design of mechanically responsive IWMDs, recent work has been focused on the construction of series of smart bandages. The first proof of concept of wearable human-interactive devices was presented by Takei et al. in 2014, who demonstrated the first "smart bandage" that realizes wireless detection of touch and the skin temperature of the wearer as well as drug ejection.[196] In their study, a drug delivery pump with a microfluidic channel was fabricated using PDMS by soft lithography, and then the touch sensor, temperature sensor, and wireless coil were laminated together with the touch panel to form the bandage **(Figure 7e)**. The drug ejection rate and mechanical flexibility could be adjusted by applying pressure to the pump and bending radius, proving that the threshold pressure was within the range of gentle human touch and indicating that this DDP can be operated by anyone, including children. To solve the problem of power supply, a self-powered stretchable

skin patch was recently developed, which integrates pressure-regulating drug delivery MNs and a triboelectric energy harvester into a single wearable patch **(Figure 7f)**. Unique bendable MNs were also proposed to overcome the safety issues associated with MN breakage during application.

In recent years, increasingly many studies have shown that functionalized hydrogels and elastomers can release drugs via mechanical strain. For example, the delayed release of gel under mechanical stimulation can be achieved by introducing a special molecular structure network and residue into it[197], which is conducive to constructing long-term therapeutic IWMDs. Elastomers and hydrogels have similar mechanisms of drug loading and delivery.[198] Commonly, microencapsulated arrays are embedded into elastomer substrates[199,200], and the difference in Poisson's ratio between micelles and elastomers leads to drug release, which significantly slows down the natural diffusion of drugs and extends the duration of treatment.[10,201] All these results indicate that hydrogels and elastomers have great potential for constructing mechanically responsive IWMDs.

In summary, the drug release media of mechanically responsive IWMDs mainly focus on hydrogels, microflow pumps, materials with different compression properties, etc., and can be integrated with strain sensing functions to a large extent to achieve accurate and controllable release of drugs. The major challenge lies in the development of suitable materials with precise mechanically responsive properties and continuous durability. As flexible wearable devices, mechanically responsive IWMDs have high resolutions under low strain, which give them great application prospects. Sensitive and accurate pressure sensors are achieved by conformal contact with the surface of an object. However, the flexibility of the sensors also makes them sensitive to mechanical deformation. These sensors not only sense the normal force of the plane, but also produce interference signals when bending and twisting, which hinders the precise detection of the pressure and strain signals imposed on the flexible mechanical sensor. The ability to resist interference is a scientific problem that needs to be solved in the future application of flexible mechanically responsive IWMDs.

Furthermore, future developments in this field may focus on how to connect WBDs to WDDs amicably and work procedurally, which will be promising and challenging.

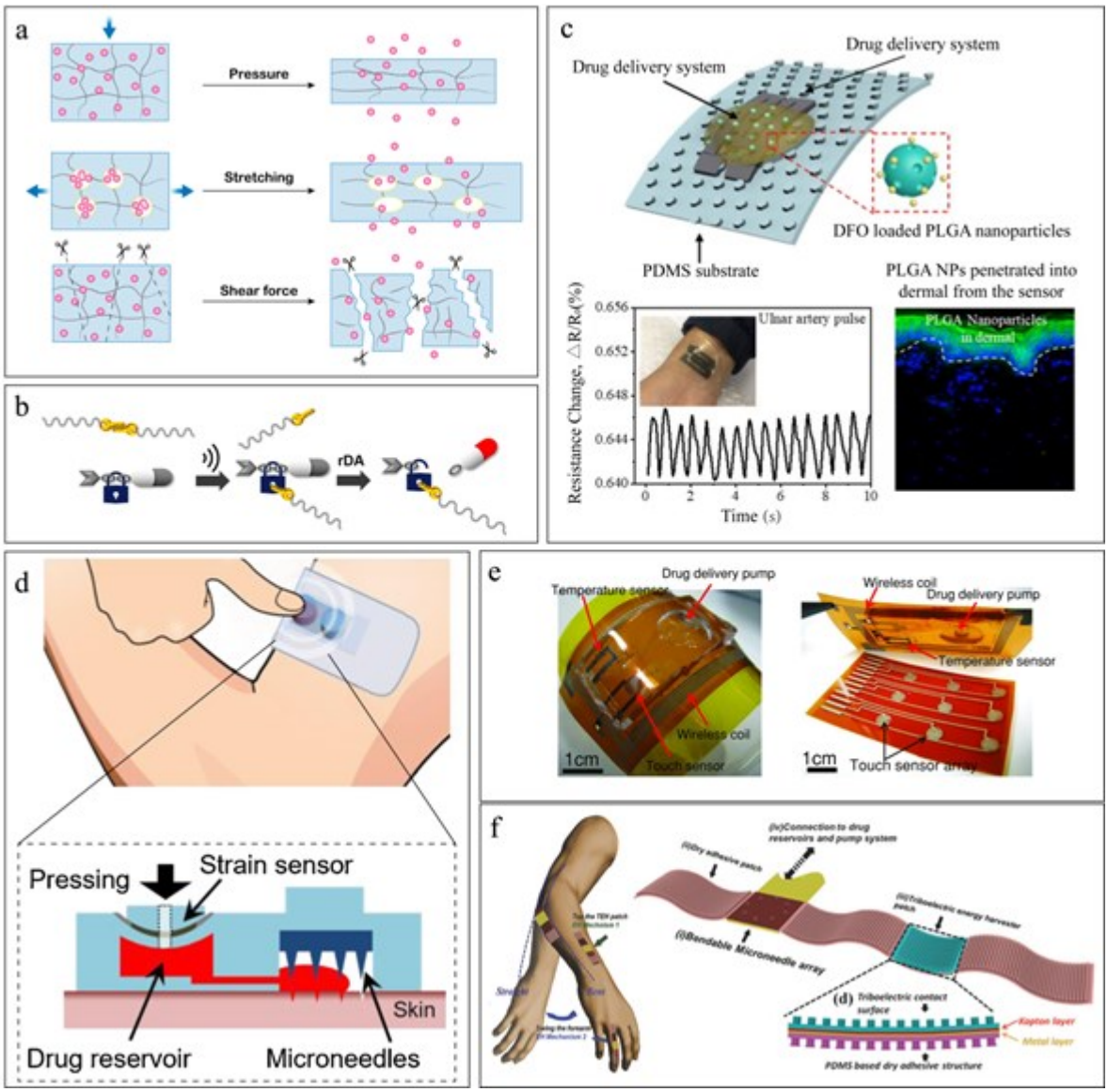

Figure 7. Mechanically responsive IWMDs. a,b) Physical (a), and chemical (b) drug release mechanisms of mechanoresponsive carriers. Reproduced with permission.[202]Copyright 2020, American Chemical Society. c) Multifunctional wearable device with graphene/silver nanowire based strain sensing and PLGA nanoparticles-based transdermal drug delivery. Reproduced with permission.[192]Copyright 2019, MDPI. d) The press-type quantitative penetration wearable patch adopts a double-chamber structure, and a chamber containing

MNs creates skin permeation channels; then, the drug storage chamber performs touch-actuated delivery. The dose is quantified by pressure sensing. Reproduced with permission.[193] Copyright 2018, Elsevier. e) Schematics of a smart bandage, integrated with touch and temperature sensors, a wireless coil, and a drug delivery pump (left) with and (right) without a capacitive touch panel. Reproduced with permission.[196] Copyright 2014, Wiley VCH. f) The flexible MN skin patch attached to the arm, elbow, and knuckle, composed of MN patch, dry adhesive patch, triboelectric energy harvester, and pump system. Reproduced with permission.[203] Copyright 2016, Wiley VCH.

4.3 Electrically responsive IWMDs

Recently, soft bioelectronics have been extensively studied to take advantage of their inherent polymer properties and organic electronics for constructing electrically responsive IWMDs with closed-loop features because of the controllable current. Electrically responsive IWMDs are delivery systems that utilize the frequency, time, and current/voltage output to receive the feedback sensing index of electrical signal intensity to achieve closed-loop connections and control drug release. In contrast to other IWMD systems, the electrical signal is the only one that runs through the entire system in electrically responsive IWMDs, so that the homogenous signal transmission will be easier to regulate.

Currently, electrically responsive IWMDs are based on the switching ability of polymers between oxidized and reduced states, and the charged molecules are absorbed or expelled during this morphological change **(Figure 8a)**.[204] Generally, charged drugs are loaded into electroactive materials by electrochemical methods, where anion and cation drugs can be released through reduction-negative or oxidation-positive potentials.[205,206] Among all conductive conjugated polymers, PPy[207,208], PEDOT[209-211] and PANI[212,213] are the most widely studied.[214] Ensuring adequate power supply of IWMDs to provide sufficient charge to support the entire system has always been a challenge. Many researchers have focused on the collection of free electric charges to fabricate self-powered miniature devices. For example, Ouyang et al. presented a WDD for precise and on-demand drug dosing, where the triboelectric nanogenerator converted mechanical energy into electrical energy and then

output it into alternating current to activate the release of drugs **(Figure 8b)**.[215] The entire process can be completed by manually rotating the portable triboelectric nanogenerator, ensuring good controllability of the drug dosage. Therefore, IWMDs have been highlighted as essential components for personalized healthcare systems.

Furthermore, a hybrid microelectronic tissue that integrates mechanical sensing and PPy-based drug delivery has been demonstrated, which has great potential for wearable use **(Figure 8c)**. In the past few years, smart medical skin frameworks **(Figure 8d)** has occurred, which describe bionic electronic patches that uses electrodes to trigger transdermal drug delivery during remote monitoring of vital signs. More specifically, a smart wound dressing for infection monitoring and controlled drug delivery has been developed **(Figure 8e)**, in which PPy film co-doped with cefazolin served as a WDD and delivered drugs under a small negative voltage. It was also proven in a previous study that the response time is much shorter than the thermal responsive drug delivery, supporting a strong promising solution for IWMDs. However, the complex mechanism of wound repair urgently requires specific diagnosis and comprehensive care.

Although various in situ treatment and biosensing strategies using either implantable or wearable devices have been developed, critical challenges for urgent medical situations, such as fatal seizures, remain. Innovative research has been conducted on the development of wearable semi-implantable devices. As shown in **Figure 8f**, a novel electric-responsive IWMD for rapid in situ treatment of fatal epileptic medical emergencies based on continuous electroencephalography monitoring was demonstrated. Controlled wireless power transmission from a wearable power transmitter to a drug delivery device is one of the key technologies for operating the entire system. It is worth mentioning that self-starting drug release behavior based on a wireless electroencephalography monitor provides a potential solution for tackling situations that cannot be treated easily by current methodologies, such as urgent situations that require rapid pharmaceutical treatment for rescue and also need to minimize invasiveness.

Wireless power transmission based on resonant inductive coupling provides another solution for self-powered electric-responsive IWMDs. Keum et al. developed integrated hydrogel-based contact lenses for non-invasive diagnosis and treatment of diabetic retinopathy **(Figure 8g)**.[26] The embedded receiver coil resonantly and inductively collects electric energy to maintain the basic operation of the contact lenses and RF remote communication. The sensor collects the tear glucose concentration information and sends it to the RF system as a current signal, then releases drugs after applying a constant voltage for a period of time. In contrast to normal electroactive drug carriers, defect-free Au covered the drug reservoir, which was melted in phosphate buffer under constant voltage in the form of $AuCl^{4-}$ and released the drug. This strategy avoids damaging fragile eyeballs by the heat generated by the electric current.

In another innovative work, Krawczyk et al. changed the common electroactive drug carriers using wireless electrical signals to stimulate engineered human β cells and trigger insulin-containing vesicle secretion.[216] The whole device was only the size of a coin and could be controlled through intelligent terminals wirelessly. Moreover, the current-derived thermal effect could be used as a stimulus signal. Many electrically activated transdermal patches for flexible resistance heaters have been developed, which are regulated by the electrothermal response.

The most significant feature of electrically responsive IWMDs is the redox state change of functionally conductive polymers induced by current/voltage, which results in drug release. The drug release rate and amount are strictly dependent on the current/voltage and time of action. Therefore, electrically responsive IWMDs have a highly precise drug release law and dose adjustability. At present, the initiators of electrically responsive IWMDs mainly focus on triboelectric nanogenerators, wireless detection, transmission, etc. It is worth mentioning that, for electrically responsive IWMDs, efforts should be made to realize the good attachment of electro-triggering devices with electro-sensitive drug delivery modules. Remote detection and drug delivery triggering are more feasible in the treatment of diseases such as epilepsy. In addition, the thermal effect of electric current can be coordinated for

disease intervention; thus, real-time detection and strict control of current should be considered in the application of electrically responsive IWMDs.

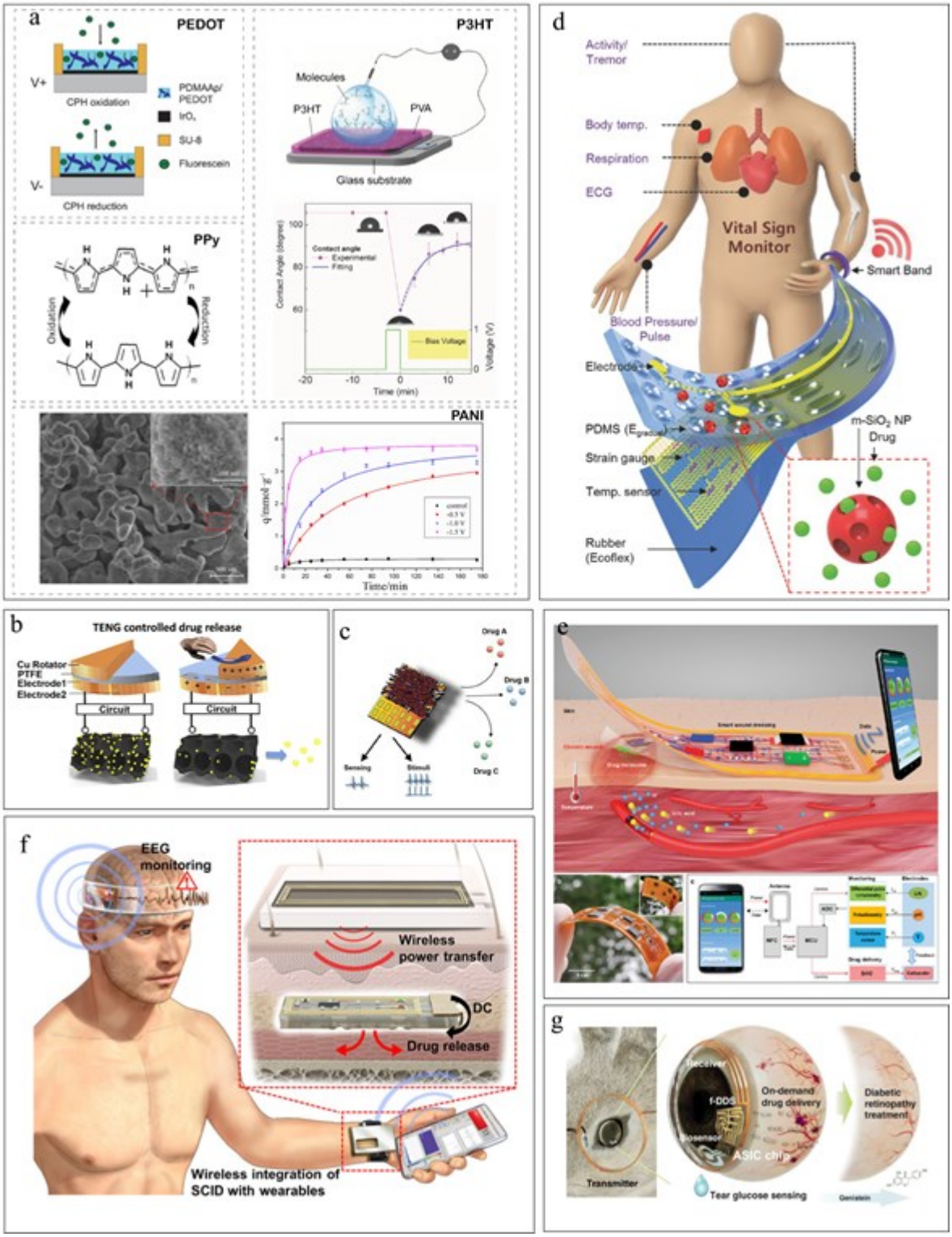

Figure 8. Electrically responsive IWMDs. a) Mechanism of electrically controlled release of conductive polymers PEDOT. Reproduced with permission.[217] Copyright 2019, Wiley VCH, PPy. Reproduced with permission.[218] Copyright 2010, Elsevier, P3HT. Reproduced with permission.[204] Copyright 2017, Wiley VCH. and PANI. Reproduced with permission.[219] Copyright 2020, Elsevier. b) Principle of a triboelectric nanogenerator provides power support for drug release in conductive polymers. Reproduced with permission.[215] Copyright 2019, Elsevier. c) The hybrid microelectronic tissue concept that can be used to monitor tissue functions, intervene through electrical stimulation, and control drug release. Reproduced with permission.[220] Copyright 2019, Wiley VCH. d) Schematic illustration of the multifunctional miniaturized suction cup electronic patch. The smart band provides transdermally drug delivery by iontophoresis, wireless functionalities, and a power source. Reproduced with permission.[22] Copyright 2015, Wiley VCH. e) Battery-free and wireless dressing for wound infection monitoring and electrically controlled drug delivery. Reproduced with permission.[27] Copyright 2021, Wiley VCH. f) Schematic illustration of implantable-wearable integrated drug delivery device, which is wirelessly integrated with a wearable power transmitter and a wearable EEG monitoring device. The wireless power is transferred through the skin, which induces the subcutaneous drug release. Reproduced with permission.[221] Copyright 2021, AAAS. g) Smart contact lenses that can monitor tear glucose and remotely apply electric potential to trigger the on-demand release of drugs to treat diabetic retinopathy. Reproduced with permission.[26] Copyright 2020, AAAS.

4.4 Force-electrically responsive IWMDs

Piezoelectric materials have attracted considerable attention owing to their unique electromechanical coupling characteristics. As early as the 1960s, piezoelectric materials were used to manufacture sensor tools, and the first study as a drug delivery pump appeared in 1988[222]. Currently, microfabrication and microelectronics further integrate piezoelectric materials into wearable medical devices, termed force–electrically responsive IWMDs, which show more initiative and intelligent response behavior. As a representative material for force-electricity conversion, piezoelectric materials can produce electric fields owing to

mechanical deformation or mechanical deformation under an electric field. This inherent electromechanical coupling effect is widely used in tissue regeneration and medical engineering[223-226]. Materials with high piezoelectric properties and electromechanical coupling coefficients are commonly utilized for manufacturing force–electric wearable devices. It has been reported that piezoelectric nanoparticles, single crystals, ceramics, and thin films such as $BaTiO_3$[227], lead zirconium titanate (PZT)[228], aluminum nitride[229], zinc oxide[230] and quartz crystals[231,232] can be used as smart materials for force–electric IWMD engineering. Consequently, the electromechanical coupling effect has been explored in several ways for drug loading and delivery, such as in mechanically driven pumps, manufacturing drug-loading electroactive stents[233-235], and promoting drug delivery using ultrasonic transducers.

Piezoelectric materials include thin films[236], nanoparticles[237], electrospun fibers[238], and nanotubes[239], which participate in most WDDs. Micro-electric voltage MPs integrated with the microfluidic systems packaged by PDMS have always been the main force–electric IWMDs because of their controllable driving mode[240]. To achieve the functions of actuators and sensors, piezoelectric materials with bidirectional conversion seem to provide an ideal solution[241], which can be used to manufacture flexible actuation-sensing integrated patches **(Figure 9a)**. Therefore, the concept of multifunctional electronic skin inspired by human skin is constantly being mentioned and studied.[242] The difficulty lies in the use of smart materials to design flexible electronic components to distinguish static/dynamic pressure sensing and temperature stimulation and to make friendly contact with the human body surface. The current research proves that this method is feasible **(Figure 9b)**.

Owing to sufficient power and unique triggering methods, force–electrically responsive IWMDs have been widely developed for chronic diabetes. One objective of controlling blood glucose is to create an “artificial pancreas”, a safe and durable wearable medical device. Closed-loop treatment systems require continuous monitoring of glucose levels[243], feedback systems and microscale devices for drug injection. As early as 2010, Liu et al. proposed an intelligent closed-loop insulin delivery system using algorithms to control PZT insulin pumps

automatically **(Figure 9c)**.[244] Unfortunately, early piezoelectric crystal pumps were not accurate. Debiotech demonstrated an insulin patch pump (JewelPump) driven by piezoelectric crystals at the American Diabetes Association Scientific meeting; the stroke of this device seems to be sufficiently accurate, but it has not yet been approved by the Food and Drug Administration. Large piezoelectric insulin pumps have now been replaced by pipeless, smaller insulin pump patches.[245] To realize transdermal drug delivery, it has been continuously sought to increase the pumping flow rate to achieve skin penetration.[246] The integration of MNs and piezoelectric MPs forms transdermal patches using wearable microscale platforms.[247] However, the difficulties in manufacturing integration have become the main obstacle to the development of force–electrically responsive IWMDs. On the other hand, Fernando et al. initially explored the use of an external piezoelectric probe to generate a high-intensity focused ultrasound pulse force to trigger transdermal delivery **(Figure 9d)** and achieved good results.[173] Recently, a closed-loop head-mounted IWMD based on piezoelectric-driven dual reservoirs was developed for automatic seizure detection and control[175], which includes multiple sub-modules for detection and drug delivery. The proposed framework includes the Internet of Things and helps enhance telemedicine monitoring and data recording **(Figure 9e)**.

As a self-powered intelligent wearable device, force–electrically responsive IWMDs solve the power supply disadvantages of large volume and poor rigidity of traditional wearable electronic devices and have good application prospects in disease treatment. The synthesis of new piezoelectric materials, the design of stretchable structures, and advanced manufacturing methods are key technologies for the development of force–electrically responsive IWMDs. The lack of output power when integrated in multi-mode sensors, effective combination of piezoelectric materials and stretchable structures, and performance problems of materials such as stability and durability, including debonding between adjacent layers, fatigue damage, and interface binding force failure, also need to be optimized to meet the growing demands of practical applications.

Currently, most piezoelectric medical devices provide single chemical or physical stimuli.[248,249] In fact, local micro-currents not only play a controlling role, but also have certain therapeutic effects on some diseases.[250] Previous studies have shown that the local electrical environment established by electroactive stents can ensure the effective delivery of drugs and enhance the repair process.[251,252] Thus, the synergistic effects of electrical stimulation and drugs that promote tissue regeneration have been widely studied.[253,254] However, the influences of piezoelectric responses on drug release in composite hybrid stents are yet to be elucidated. Therefore, we still have positive expectations for the future use of piezoelectric materials in manufacturing force–electrically responsive IWMDs for a wider range of medical applications, such as collaborative tissue regeneration.

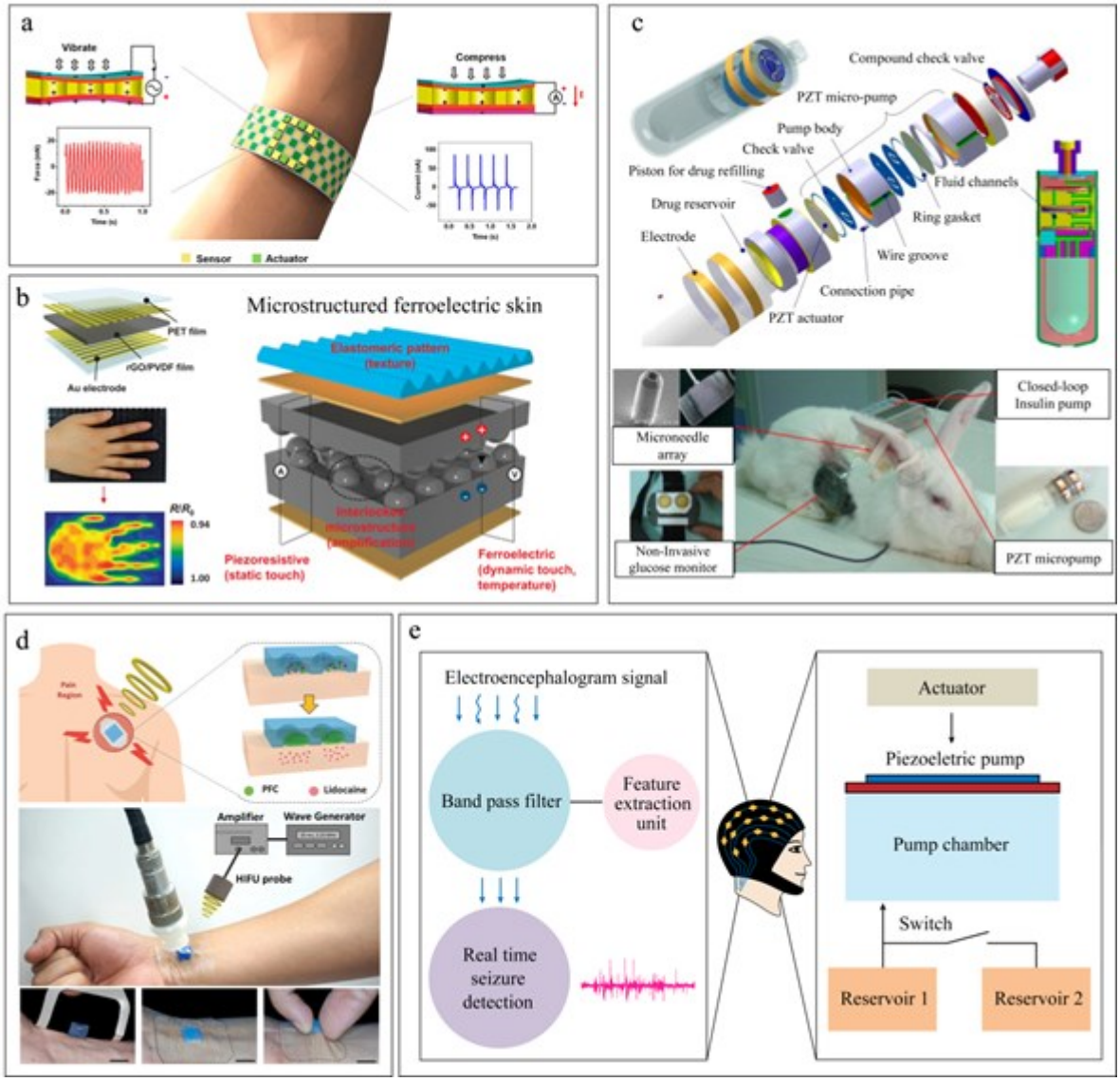

Figure 9. Force-electrically responsive IWMDs. a) A flexible sandwich device based on piezoelectric electret to realize the integration of sensors and actuators. Reproduced with permission.[241] Copyright 2019, American Chemical Society. b) Microstructure schematic diagram of electronic skin manufactured by smart materials, which can detect the temperature distribution on human palms. Reproduced with permission.[242] Copyright 2015, AAAS. c) High-performance disposable MPs for diabetes treatment. The non-invasive detection module wirelessly sends blood glucose information to the closed-loop control system, and then the PZT MP transdermally delivers insulin through the silicon MN array. The process is terminated when the sensor detects that the blood sugar returns to normal. Reproduced with permission.[244] Copyright 2010, Elsevier. d) Wearable patch delivering Lidocaine via acoustic droplet vaporization, and photos of triggering mechanism involving an external piezoelectric probe generating high-intensity focused ultrasound pulse force. Reproduced with permission.[173] Copyright 2018, Wiley VCH. e) Diagnostic detection head-mounted device, including an epilepsy detection unit and a PZT MP-based drug delivery unit, used for automatic control of epileptic seizures.

5. Current challenges and perspectives

Given that various types of IWMDs, including mechanically, thermally, electrically, and force–electrically activated IWMDs have been developed, there is great potential for application of these devices in modern clinical treatment and personal healthcare. However, several issues related to integration and security remain challenging. The realization of high resolution, high sensitivity, rapid response, low-cost manufacturing, and complex signal detection of flexible wearable electronic sensors is a significant challenge; however, it is only a small step in the field of IWMDs. Electrochemical sensors based on enzymatic or non-enzymatic reactions seem to have high precision under laboratory conditions, but avoiding noise pollution caused by biomarkers is a long-term problem. WDD construction also entails challenges pertaining to drug dose management, as most drug carriers such as

hydrogels or textiles have difficulty avoiding drug loss caused by natural diffusion, and microscale device manufacturing technology involves complex processes and high costs. Hence, a closed-loop diagnosis and treatment system for IWMDs remains to be built. The main types of challenges can be summarized as follows.

First, there are material design challenges. Both the biosensing part and drug delivery module require the contributions of material science. Although several external field-responsive smart materials have been used to develop various types of IWMDs, as mentioned in this review, some limitations may still prevent them from entering the commercial market. For example, materials with response characteristics have difficulty avoiding interference from external or other non-specific factors, resulting in instability and unreliability. In addition, some materials should overcome the shortcommings of delayed response, low drug-loading capacity, or even biocompatibility.

Second, there are manufacturing challenges. The separate developments in the fields of WBDs and WDDs are obvious and predictable, and the current difficulty is to combine these technologies into a single device without losing flexibility or portability. Manufacturing challenges arise from the fabrication of separate components and the integration of entire IWMDs. Some refined engineering techniques such as 3D printing and some microelectronics manufacturing technologies have been explored to construct IWMDs, as discussed; however, the obstacles of information interaction and intelligent tuning that occur in closed loop IWMDs themselves, or between humans and devices, require new types of technical support, such as programming languages and artificial intelligence.

Third, there are power challenges. The power consumption of most IWMDs comes from the following three aspects: the working process of the sensor module, the data filtering and signal transmission of the CPU, and the wireless communication module. Currently, there are several means of achieving self-power, such as solar cells, biofuel cells, piezoelectricity, and triboelectricity, where piezoelectric nanogenerators and friction nano-generators have been developed as power supply devices.[255,256] In addition, the recent progress in wearable

stretchable batteries such as spring-based silver-zinc batteries has opened up new opportunities for IWMDs because of their high energy density and good long-term stability.[257,258] With the advantages of flexible structures, controllability, and sustainable release, self-powered devices are expected to find great potential in IWMDs in the future.

Fourth, there are security challenges in IWMDs. The first of these is that the treatment loads of most wearable systems are limited, and frequent replacement of treatment devices easily leads to bacterial infection and human discomfort. In addition, the stability of current electronic elements requires short-term recalibration, which poses hidden dangers to drug delivery. The second issue is that the main benefits of IWMDs are remote and continuous monitoring of patient signals; however, the lack of advanced features of data security and privacy considerations may cause users to face intrusive hazards due to attacks or false health information. Therefore, it is essential to establish data processing protocols for IWMDs as soon as possible and to predict potential hazards.

Fifth, there are communication challenges. Low-power Bluetooth and near-field communication are commonly used in wireless communication modules.[259,260] However, the distance between the device and mobile terminal cannot be more than 100 m, or sometimes less, which is a problem for some elderly people and those who have lost their mobile phones. The most fundamental solution is to upgrade wireless modules to achieve long-distance signal transmission in high-density wearable networks, which depends on the communication technology innovation.

Sixth, there are practical challenges that hinder the applicability of IWMDs. These obstacles are mainly related to the compatibility, effectiveness, and comfort of IWMDs. Personal healthcare aims to realize precision medicine; however, individual or local differences require precise personalization, resulting in compatibility problems. In addition, the low drug loading capacities of IWMDs have prompted researchers to consider the infection or discomfort that may be caused by frequent device replacement. One of the recent studies on breathable bioelectronics was focused on patient comfort, where the risk of

inflammation could be significantly reduced by designing ultrathin and gas-permeable nanomesh sensors[261], highlighting the necessity of constructing flexible electronics-based IWMDs.[262]

Seventh, there is an economic cost challenge. Currently, most wearable sensing and therapeutic multi-functional electronic devices require expensive materials and equipment, as well as complex and time-consuming manufacturing technology, which will be borne by consumers and patients at a high cost. Therefore, there is an urgent need to develop simple, time- and labor-saving manufacturing technology. Three-dimensional printing, lithography, and other technologies can promote the transfer of complex computer-aided design to low-cost and powerful treatment systems, which will play a greater role in the next generation of wearable treatment systems.

Significant advances in closed-loop therapy foreshadow the huge market for the next generation of wearable devices. The development of artificial intelligence and machine learning will significantly advance the Internet of Everything, so it’s reasonable to expect that future closed-loop feedback on biosensor and drug controlled release will be based on the sophisticated and accurate digital or programmatic regulation, which requires surprising development in materials science and micro-electromechanical fields and further integration of interdisciplinary knowledge. In addition, the patient's condition will also be monitored and recorded in detail after drug delivery, so that the concept of feedback therapy will be continuously strengthened and deepened, which places higher demands on multi-dimensional biosensors. Last but not least, the ideal closed-loop system can combine all the functions in one wearable device to accomplish whose mission, for example, the IWMDs.

Ideal IWMDs are expected to overcome all the obstacles arising from power supply, security, system integration, and hardware and are presented as a completely self-regulative protectors for humans. Major health and safety incidents around the world, such as COVID-19, will promote further innovation of IWMDs in terms of infectious disease prediction, comprehensive medical diagnosis, and remote nursing. Future IWMDs will have

the ability to track health indicators in real time and provide targeted feedback on treatment. Thus, future IWMDs will be able to detect nearly all physiological markers (nucleic acids, proteins, ions, molecules, and so on) non-invasively, and, as immediate responses, to deliver various therapeutic drugs unrestrictedly, perform comprehensive diagnosis, and implement treatment procedures. Moreover, the relevant data produced by IWMDs will be sent to and stored at hospitals and other treatment institutions in the form of databases to realize meticulous nursing beyond time and space. In structure, IWMDs will become more streamlined, miniaturized, and blended into the daily lives of patients in the form of headwear, wristbands, textiles, or patches. However, the acceptance of these novel IWMDs by the medical community will require extensive and successful validation in human testing and an improved understanding of the clinical relevance of closed-loop treatment and precise medicine. Considering the huge market and unprecedented competition for wearable smart devices, exciting new developments in IWMDs are expected.

6. Conclusion

We summarized the technological advances in the development of IWMDs for physiological biosensing and self-starting therapeutic delivery. Active biophysical factors and humoral biochemical factors were collected and analyzed to provide guidance for drug delivery. To perform closed-loop medical treatment, thermal stimulation, mechanical forces, electrical signals, and physiological parameters have been successfully utilized to trigger and control the drug-release behavior of IWMD platforms. Even though surprising success has been achieved, challenges associated with accuracy, reliability, long-term use, and other aspects must be overcome. More clinical studies are urgently needed to evaluate the biosafety, curative effects, and possible side effects of IWMDs. In addition, research progress in materials science and manufacturing technology is essential to enable the improvement and development of self-powered, wireless, low-cost, and miniaturized IWMDs for long-term monitoring and feedback-controlled therapy. We envision that the impacts of IWMDs on

daily life will be expanded, acting as health consultants, caregivers, or even private doctors in a form distinct from traditional medicine in the future.

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Conflict of interest：

The authors declare no conflict of interest.

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Biographies

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ToC text

The intelligent wearable medical devices (IWMDs) are now intensively investigated for personalized healthcare and smart therapy. Recent advances in wearable biosensing-delivery integrated therapeutic systems are overviewed and summarized, with an emphasis on the functional materials, responsiveness models, working mechanisms and practices, to provide deep insights into the design, fabrication and bio-application of IWMDs.