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Abstract: The wearable revolution is already present in our society through numerous gadgets. However, the contest remains in the fully deployable wearable (bio)chemical sensing. Its use is constrained by the energy consumption which is provided by miniaturized batteries, limiting the autonomy of the device. Hence, the combination of materials and engineering efforts to develop sustainable energy management is paramount in the next generation of wearable self-powered electrochemical devices (WeSPEDs). In this direction, this review highlights for the first time the incorporation of innovative energy harvesting technologies with top-notch wearable self-powered sensors and low-powered electrochemical sensors toward battery-free and self-sustainable devices for health and wellbeing management. First, current elements such as wearable designs, electrochemical sensors, energy harvesters and storage, and user interfaces that conform WeSPEDs are depicted. Importantly, the bottlenecks in the development of WeSPEDs from an analytical perspective, product side, and power needs are carefully addressed. Subsequently, energy harvesting opportunities to power wearable electrochemical sensors are discussed. Finally, key findings that will enable the next generation of wearable

devices are proposed. Overall, this review aims to bring new strategies for an energy-balanced deployment of WeSPEDs for successful monitoring of (bio)chemical parameters of the body toward personalized, predictive, and importantly, preventive healthcare.

1. Introduction

Wearable (bio)chemical sensing is an innovative research field that is bringing valuable outcomes for health and wellbeing management.[1,2] Among the numerous type of wearable devices up to date, wearable chemical sensors are on the rise due to the easiness of monitoring (bio)chemical parameters through body biofluids.[3–5] Particularly, wearable electrochemical devices (WEDs) are attractive due to the direct conversion of (bio)chemical information into the digital domain for easy data interpretation.[6,7] In this way, WEDs are mainly employed for monitoring the physiological status of the wearer to: (i) properly manage diseases;[8] (ii) provide accurate diagnostics;[9] (iii) determine the wellbeing level of an athlete during sports practice;[10] (iv) determine illicit drug consumption;[11] or for personalized nutrition.[12] The ability of WEDs to be embedded on the body through conformal materials allows for autonomous monitoring of physiological parameters.[13–15] Therefore, the attractiveness of such devices comes from gathering relevant data for decision-making processes, without the wearer noticing the action.[16] This autonomous data collection will allow full-body computing in the near future with unprecedented progress in health management.[17] Importantly, the integration with wireless transmission systems permits the data to be sent to the cloud and be accordingly treated by machine learning algorithms or directly by a specialized doctor.[14] Thereafter, a user-friendly interface announced the required action (e.g. alert, drink water, take therapeutic drugs) or even provide an automatic dosage in the case of closed-loop systems for personalized medicine.[11] Overall, WEDs perform as interfaces between the human physiological status and the digital domain, contributing to improve personalized, predictive and lastly, preventive healthcare.

The noninvasive nature of WEDs is providing a new way of data collection that can be used for health and wellbeing decisions.[6] In fact, the noninvasive sampling is gaining significance in certain circumstances: (i) while performing sport to avoid the extraction and collection of biofluids which can be painful and hardly practical; (ii) when there is no availability of trained personnel to obtain the biofluid; (iii) for continuous and real-time monitoring; (iv) in children or people with loss of cognitive functioning where WEDs can autonomously gather information while avoiding painful extraction. Following these use cases, common targets of WEDs are glucose for Diabetes management or to monitor the energetic status of the sports practitioner,[18] ions such as sodium, potassium, and pH to determine the dehydration degree of the body,[10] sweat-rate or sweat loss,[19] and lactate as a biomarker of muscle fatigue.[20] Other targets such as alcohol,[21] drugs (e.g. nicotine[22] or levodopa[23]), and vitamin C[24] are being employed in WEDs for abuse-, therapeutic- or nutrition-controlled purposes. Recently, multiplexed analysis of several analytes by WEDs is showing promises towards massive data collection to empower the control of body health.[25] Interestingly, WEDs have been recently employed to simultaneously detect glucose for Diabetes management in interstitial fluid (ISF), and lactate, caffeine, and alcohol in sweat in combination with other physical sensors for tracking the metabolic and hemodynamic parameters of the wearer.[26]

What is exactly a wearable electrochemical device? A WED is based on an electrochemical device made up of conformal materials that permits the seamless integration on any part of the body (e.g. skin, mouth, eyes, etc.) by any type of design (e.g. epidermal patch, textiles, mouthguard, etc.) allowing for autonomous sample analysis and data collection.[27] A WED might consist of five different modules: (i) an electrochemical sensor, which provides the (bio)chemical analysis of the relevant target; (ii) a wireless transmission system, which allows the analytical output to be sent for its proper treatment and display; (iii) a user interface, which shows an accessible interpretation of the results either in the WED (e.g. electronic display or electrochromic display) or by other electronic platforms (e.g. cell phone); (iv) an energy supply,

which provides enough power to all the modules; and last but not least (v) the flexible printed circuit board (FPCB) which mechanically supports and electrically connects all the electronic components and modules that enable the functioning of the WED. Overall, a WED system provides a noninvasive, comfortable, and autonomous analysis of relevant biomarkers through a physical platform that is integrated with a user-friendly display for an easy decision-making process.

Recently, the energy management module is gaining relevance as it is essential to ensure continuous operation of the whole device during long-time data collection. Until now, the miniaturization of WEDs into epidermal patches does not allow the integration of long-lasting batteries which hinders the data acquisition during the entire life of the device. Therefore, the challenge lays in recharging the battery of the WED which is an inconvenient step when dealing with wearable applications. In an attempt to overcome the frequency of charging or even provide a self-powering capacity, a new set of energy harvesting and storage modules is being developed.[28–31] From stretchable supercapacitors to hybrid energy harvesting systems, innovative energy systems are converted into wearable and conformal modules that are integrated with wearable electrochemical sensors.[32,33] Moreover, the development of wearable self-powered (bio)sensors allows for an autonomous sensing application including the production of energy[28,34] and storage[35] to power the entire device. For these reasons, the rise of wearable self-powered electrochemical devices (WeSPEDs) will lead the new generation of WEDs into sustainable and self-sufficient tools for health and wellbeing monitoring. All in all, innovations in materials and engineering fields are bringing wearable electrochemical sensing into a flawless device for massive data acquisition.

While numerous reviews on WEDs have been recently published,[7,13,16,27,36–42] none of them are focused on the integration of self-powered functionality. Therefore, in this review, recent advances in WeSPEDs are critically discussed as the next generation tool for health and wellbeing management. First, a general description of the elements that compose a WeSPED

including the types of wearable designs, electrochemical sensors, analytical demands, energy harvesting, energy storage, and user interface used is depicted (**Figure 1**, **Section 2**). Thereafter, current challenges that WeSPED still need to tackle for accurate and continuous monitoring are described (**Section 3**). From the analytical perspective, sensing parameters are essential to characterize a device that can be used to provide accurate levels of key biomarkers for a proper decision, especially in the health domain. Besides, power management is carefully discussed as it is a current bottleneck in WeSPEDs to unravel the full monitoring capability. User-friendliness is included as a key parameter to engage end-users (e.g. patients or sports practitioners) in using this type of device. Parameters such as attractive interface and easy-to-interpret results are imperative to bring WeSPEDs into successful products. Subsequently, energy harvesting strategies are deeply described, as power management is the next critical technology to be integrated into wearable devices to fulfill completely autonomous monitoring (**Section 4**). Afterward, progress in existing WeSPEDs is exemplified by showing feasible devices for health and wellbeing management (**Section 5**). Finally, key findings and coming challenges are identified and described in **Section 6** to motivate the research community on addressing the next technological challenges.

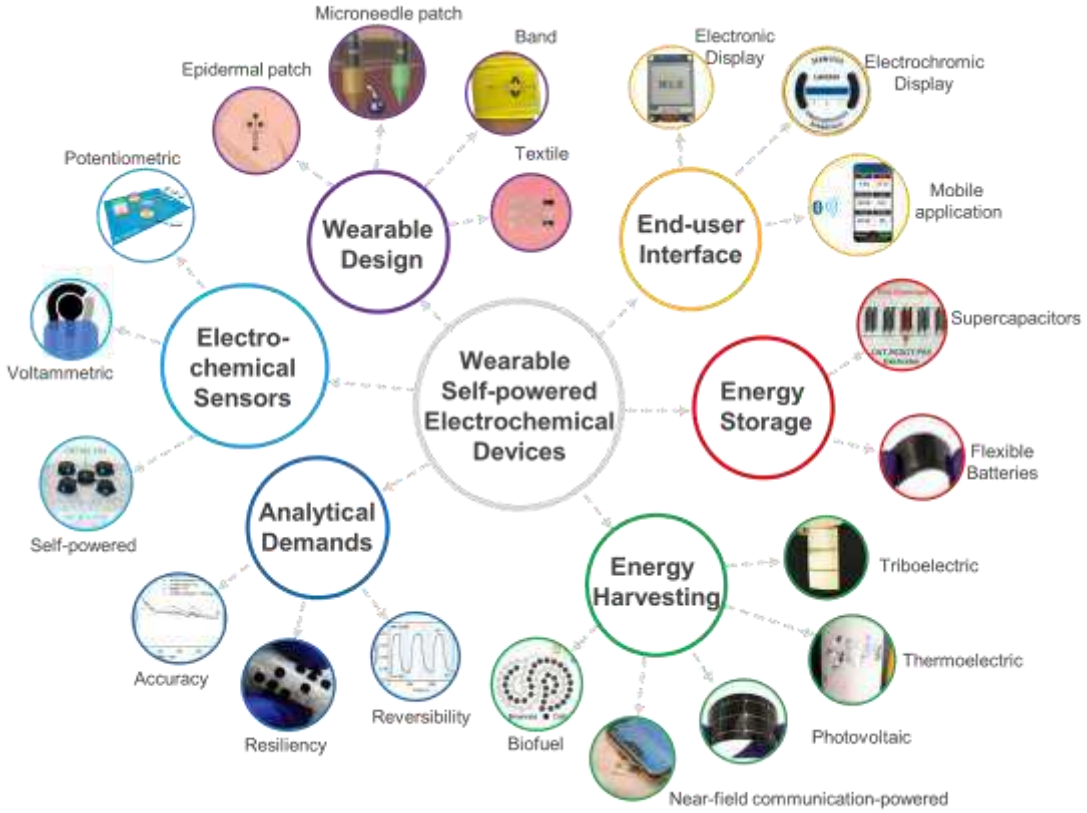

Figure 1. *Schematic overview of the elements involved in the development of wearable self-powered electrochemical devices. Reproduced with permission.*[43,44] *Copyright 2021 Elsevier. Reproduced with permission.*[45] *Copyright 2016 Elsevier. Reproduced with permission.*[46] *Copyright 2018 Royal Society of Chemistry. Reproduced with permission.*[47] *Copyright 2021 Springer Nature. Reproduced with permission.*[10,48,49] *Copyright 2019 American Chemical Society. Reproduced with permission.*[34,50] *Copyright 2020 American Academy for the Advancement of Science. Reproduced with permission.*[51] *Copyright 2016 John Wiley & Sons.*

2. Current elements in wearable self-powered electrochemical devices

A WeSPED is built upon six essential elements: (i) the wearable design which is essential for a reliable sampling of the biofluids through seamless integration on the body; (ii) the electrochemical sensor using the suitable technique toward the analyte of interest; (iii) the fulfillment of strict analytical demands (e.g. resiliency, reversibility) which can differ from the regular point of care tests and are required to gather reliable data; (iv) the end-user interface

that provides an easy interpretation of the (bio)chemical information, and includes the miniaturized electronics such as an FPCB and wireless transmitter, preferably using a low-power consumption mode (e.g. Bluetooth or near-field communication); and the power unit, which includes (v) the energy harvesting and (vi) energy storage elements, thus rising more complexity in WeSPEDs than in regular WEDs. Following this approach, **Figure 1** displays the elements and key aspects that encompass the successful fabrication and utilization of WeSPEDs. In the following subsections, these elements are linked and discussed for a fruitful understanding of the complexity in WeSPEDs.

2.1. Wearable design tailored to the target biofluid

The design of the device is essential to fulfilling a complete wearable and conformal configuration that leads to a comfortable integration with the body. The most popular wearable design is the epidermal patch or skin-interfaced patch, either for sweat analysis[52] which usually includes a microfluidic sampling device for accurate sampling,[53] or for ISF monitoring when using microneedle-based devices[49,54] or reverse iontophoresis.[55] The epidermal patch is usually attached to the skin of the wearer through a biomedical grade adhesive which provides a completely sealed environment for the microfluidic chamber with an only open area for sweat collection. This type of material along with the conformal shape of the patch allows an accurate flow towards the sensing area while avoiding contamination of sweat from surroundings, and evaporation which would preconcentrate the analyte and provide an error in the readout.[10,18]

Textiles embrace wide types of design. From an entire t-shirt to a wristband, textiles are considered any piece of cloth that can be regularly worn, thus several materials can be used (e.g. polyurethane bands,[51] cotton yarns,[56] fibrous textile threads,[57] or conductive threads[58]). Besides, smart t-shirts are developed by the functionalization of a regular t-shirt with several modules. For example, a lactate sensor and a heart-rate sensor were integrated into a t-shirt as a wearable chemical-electrophysiological hybrid biosensing system.[59] Wearable bands that can be worn in different parts of the body (e.g. head, arm, leg) are also a usually

selected design. Bands are made of a flexible or stretchable textile or polymer that allows them to perfectly fit with the part of the body.[60] The common configurations embed the electrochemical sensor in the inner part of the band which is connected to an FPCB. This type of design can be easily adjusted to the body facilitating the usability of the device. In contrast, a precise fixation of the device onto the skin is difficult and potential changes in the position might occur during the monitoring, especially during sports practice leading to errors in the readout. Therefore, bands might be useful for static application coupled to an iontophoretic module for passive sweating.[61] Concerning smart cloth, an accurate sampling design is mandatory to avoid cross-contamination of sweat from other parts of the body as well as evaporation. Interestingly, the microfluidic capability of yarns and threads on the textiles can be used to tailor the sampling towards the electrochemical sensor.[62]

Other designs include any portable device that can be worn on the body. For example (i) mouthguards for the detection of salivary glucose;[63] (ii) a miniaturized electrochemical glucose sensor in lenses for diabetic diagnosis;[64] (iii) the integration of eyeglasses for monitoring of lactate and potassium in sweat[65] or by adding a tear-based fluidic module for the analysis of alcohol, vitamins or glucose;[66] (iv) the direct printing of electrochemical sensors on gloves which have been used for the detection of multiple targets such as illicit drugs,[67] ethanol, vitamin C or pH,[68] pesticides,[69] among others analytes.

Considering the limited miniaturization of some of the WeSPEDs' modules to be worn in a comfortable manner, textiles embedded with all types of modules or elements might be the most feasible option to accomplish functional WeSPEDs. Hence, all elements can be distributed along the e-textile and connected through conductive yarns. In contrast, an epidermal patch that can be worn in any part of the body would be the ideal platform for wearable monitoring to gather localized data. However, still, some miniaturization issues must be addressed to integrate enough power generation modules for full self-sufficiency.

Wearable devices aim to analyze key biomarkers in noninvasive biofluids. Therefore, easy accessibility of these biofluids is essential for its continuous analysis.[70] The majority of WEDs employ sweat as a noninvasive matrix due to its easy availability all over the skin. Interestingly, sweat can be generated by active action as, a thermoregulation event during sport practicing,[71] or through passive perspiration which is usually induced by iontophoretic systems coupled to the WED.[72] Despite the promising use of sweat for noninvasive diagnostics and monitoring, still, the correlation with blood concentrations is the key parameter to truly enable sweat in the medical field.[73,74]

ISF is considered a minimally invasive biofluid as accessing such biofluid do not demand painful methods. Interestingly, ISF is gaining relevance in the field of wearable devices due to the glucose correlation with blood levels.[75] Although a delay might be observed, machine learning algorithms can potentially correct the data and provide a reliable measurement. Besides glucose, other target molecules such as antibiotics have been tested in ISF,[76,77] thus showing promises toward using ISF as a clinically relevant biofluid.[78,79] Normally, ISF can be: (i) extracted by a microneedle to be further analyzed by an electrochemical sensor;[80] (ii) directly analyzed by microneedle-based sensors on the dermis layer of the skin;[49] or (iii) extracted by reverse iontophoresis for analysis by the WED similar to sweat sensing.[81]

Saliva has been traditionally considered as an alternative biofluid for health monitoring.[82] Regardless of its availability in the mouth and easy collection, the variability of its physical properties and the changing composition depending on the status of the body might hinder its use in wearable devices.[83] Besides, the high loading of proteins and unknown flow rate hamper the direct electrochemical quantification of key biomarkers. In contrast, the detection of drugs in saliva can be an encouraging application due to the high levels of the illicit drug which fall between the linear ranges of conventional electrochemical sensors. Wearable saliva analysis has been traditionally performed by the embodiment of electrochemical sensors in mouthguards.[63]

Tear analysis has been pursued as the holy grail for noninvasive monitoring.[84] In fact, huge efforts have been performed by pharmaceutical and medical device companies to provide contact lenses able to monitor glucose in tear biofluid. However, a commercial contact lens has not still brought to market. In this way, the challenge still remains in the miniaturization of all the elements of a WED in a contact lens for continuous noninvasive monitoring. Fortunately, the WeSPED might be a promising approach for contact lens in the coming future. Another challenge for tear-based sensing is the unknown secretion rate which can alter the reliable detection of the analyte. Therefore, other strategies to collect and externally analyze tears, which can integrate a flow rate sensor, could have a meaningful application.

2.2. Electrochemical sensors toward the analytical excellence

Electrochemical sensing has historically demonstrated its usefulness in a high number of cases.[7] Importantly, the demanding versatility of wearable devices has led to the use of several types of electrochemical sensors including substrates from different nature with different properties that allows its suitable application (**Figure 2**) (the reader is referred to these reviews on materials for wearable applications [13–15,85–87]). From chemically modified electrodes and solid-contact ion-selective electrodes (SC-ISEs) to printed disposable electrodes and paper- and yarn-based devices, an immense variety of electrochemical sensors has been applied for wearable purposes.[7] Therefore, material science and nanotechnology have boosted the emergence of resilient and enduring electrochemical sensors that withstand regular movement (e.g. stretching, bending, crumpling) from the wearer without altering the analytical performance of the sensor.[51,88]

Electrochemistry also enables to tailor the electrochemical technique to the analyte of interest. For example, the detection of ions is preferable by the use of potentiometry with SC-ISEs, the employment of chronoamperometry for the monitoring of glucose through an enzymatic sensor, or the utilization of square-wave voltammetry (SWV) with nanomaterials-modified electrodes for the analysis of redox analytes. In this direction, wearable

electrochemical sensors have been reported for the detection and/or monitoring of ions,[89] drugs,[11] biomolecules,[90,91] nutrients,[12] explosives,[92,93], nerve agents,[94] or gunshot residues.[95] Therefore, a broad range of analytes can be measured by means of electrochemical sensors.

Wearable potentiometric ion sensors (WPIS) mainly based on SC-ISEs have been widely used since their first appearance for wearable missions more than a decade ago.[96] WPIS allows continuous monitoring of biomarkers through a simple configuration (working and reference electrode, **Figure 2A**),[10] and with almost no-power consumption as it only measures the difference of potential between the electrodes.[89] Indeed, the low-power consumption of potentiometric sensors is currently a feature of interest for WeSPEDs for self-sufficient monitoring while providing relevant physiological information. WPIS has already proved its validity in several medical applications,[97] traditionally for the diagnosis of cystic fibrosis.[72]

Voltammetry includes a wide range of electroanalytical techniques in which a potential is applied and a current is monitored as the readout for sensing intentions. Depending on how this potential is applied, each technique offers certain benefits than others toward a sensitive detection of the analyte in the suitable physiological range. Hence, chronoamperometry has been used in enzymatic sensors as it can provide continuous monitoring of the oxidation or reduction process taking place, therefore a real-time profile of the concentration of the analyte (**Figure 2B**) (for further information on the type and mechanism of action of enzymatic sensors, the reader is referred to [90]). For example, wearable enzymatic sensors have been used for monitoring glucose[18] and vitamin C.[98] Other voltammetric techniques used in WEDs are differential pulse voltammetry (DPV) which has been used for methylxanthine monitoring,[99] simultaneous detection of uric acid and tyrosine,[91] or SWV for the detection of fentanyl[100] and levodopa (**Figure 2C**).[23] These techniques unravel the electrochemical profile of redox-active compounds at a certain potential window suitable in most conventional printed electrodes.

Electrical resistance and electrical impedance have been also employed for measuring the sweat-rate in a wearable chemiresistor configuration,[19] and a microfluidic patch,[74] respectively. It is worth mentioning that sweat-rate is a key parameter for counting the electrolytes lost during sports practice. For example, knowing the concentration through SC-ISEs and the volume of sweat loss, the wearer can calculate how much beverage intake should perform to be at the optimal level, and thus maximize the body performance.

Until now, the electrochemical sensors described in this section require energy to perform the analysis. In the last decade, self-powered electrochemical sensors are becoming a trend due to the ability to provide analytical outcomes without the need for a power supply.[101] Mainly, self-powered sensors are used under the biofuel cell (BFC) configuration. The BFC usually utilizes oxidoreductase enzymes to catalyze the conversion of chemical energy into electrical energy. Despite the need for the functionalization with an enzyme at the (bio)anode, the cathode can be chemically modified (for more information concerning materials, challenges for the construction of BFC, the author is referred to the literature[102–104]). Remarkably, a triboelectric-biosensing unit has been used as a self-powered sensor for the detection of several targets (i.e. urea, uric acid, lactate, glucose, sodium, and potassium in sweat).[105] The biosensing unit can be driven by body motion through efficiently converting mechanical energy into a triboelectric current, which in turn the triboelectric output of the biosensing unit is influenced by the target biomarkers concentration. Similarly, the modification of piezoelectric materials led to a self-powered sensor.[106] Hence, the piezo-enzymatic reaction coupling process on ZnO nanowire arrays can convert the mechanical energy of body movements into piezoelectric impulses. Accordingly, the output of the piezoelectric signal corresponds to the lactate concentration in sweat. Lastly, the coupling between sweat evaporation-biosensing effect was used for lactate monitoring utilizing the thermoelectric generation (**Figure 2D**).[107] Therefore, the enzymatic reaction can change the zeta potential at a porous carbon surface and influence the outputting voltage which is used as an analytical signal.

Among the different techniques to manufacture wearable devices, scalable techniques such as screen-printing[43] or roll-to-roll gravure[108] are desired to benefit from mass production and thus provide affordable solutions to high-demand health monitoring. Besides, the aforementioned techniques provide low consumption of reagents and an easy automation process. In contrast, the miniaturization of the patterns is limited to the submillimeter level. Lithography is also commonly used as it provides high-resolution patterning which allows for miniaturization of the sensors in stretchable substrates.[34,50] However, added processes, such as plasma etching, wet etching, and the high consumption of reagent limit its application to the laboratory scale. Besides, the appropriate level of expertise and expensive instrumentation increases the cost per electrode, hindering the translation to the industry.

Concerning the electrochemical techniques, potentiometry which has low-power consumption for continuous monitoring, and strategies that have zero power consumption (self-powered) are attractive to minimize the demand of power generation from the energy harvesting modules.

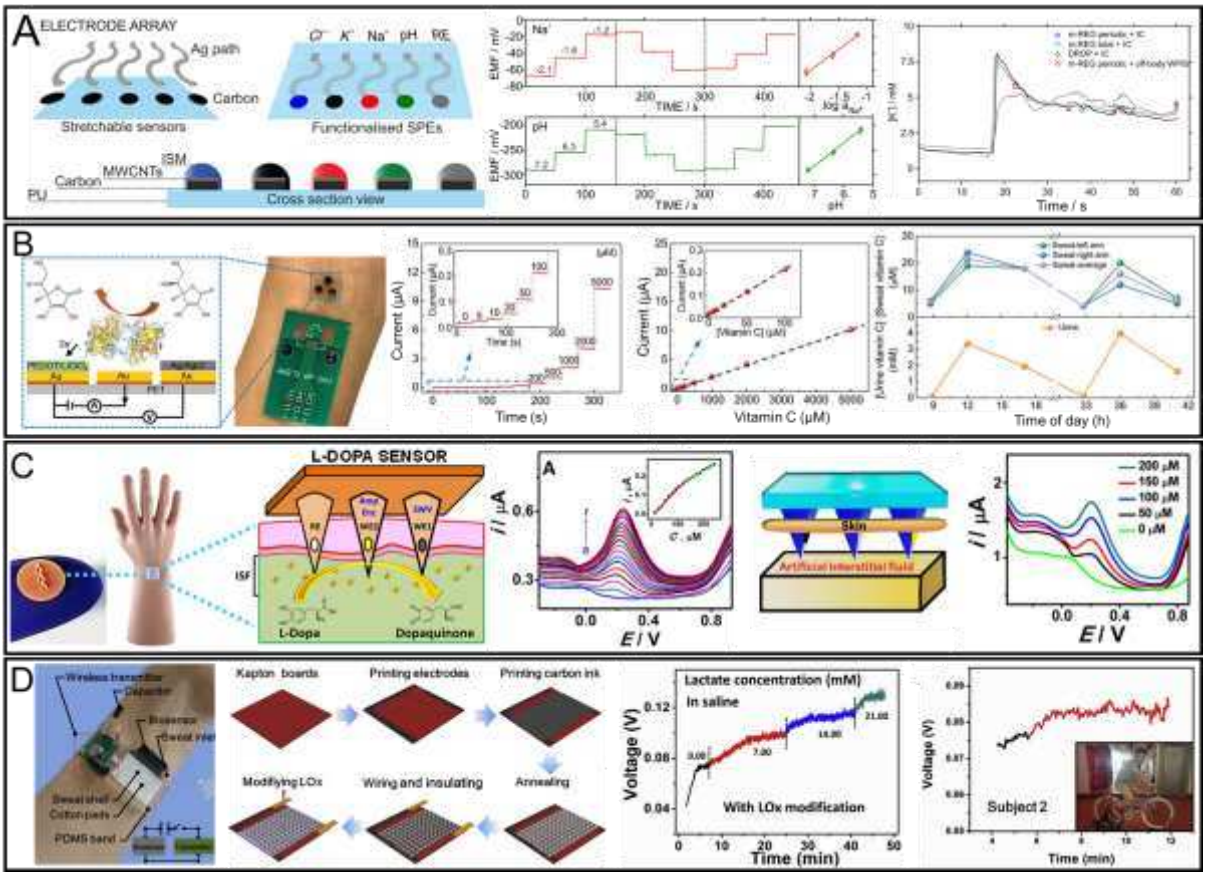

***Figure 2**. Types of wearable electrochemical sensors: A) Potentiometric sensors based on solid-contact ion-selective electrodes for chloride, potassium, sodium, and pH monitoring. Reproduced with permission.*[10] *Copyright 2019 American Chemical Society. Voltammetric sensors, including: B) amperometric enzymatic sensor for monitoring vitamin C in sweat. Reproduced with permission.*[98] *Copyright 2021 John Wiley & Sons; And C) microneedle-based electrochemical sensor using square-wave voltammetry for the monitoring of Levodopa. Reproduced with permission.*[23] *Copyright 2019 American Chemical Society. D) Self-powered sensor for the monitoring of lactate in sweat based on the difference between thermal energy. Reproduced with permission.*[107] *Copyright 2019 Elsevier.*

2.3. Wearable energy harvesting and storage

The energy harvesting module is the critical element in WeSPEDs. This module can harvest chemical, thermal, solar, or kinetic energy by BFC, thermoelectric generators, photovoltaic

cells, and triboelectric or piezoelectric generators, respectively, and use it to charge a battery or a capacitor.[30] In the case of the capacitor, once it charges to a certain voltage, it discharges the energy that is used to power the sensor analysis and performs the wireless transmission. In the case of the battery, the scavenged energy is stored and used when a measurement is necessary to be taken according to the suitable monitoring frequency. Therefore, the energy harvesting element should be accompanied by an energy storage component such as a flexible battery,[109] a bendable capacitor,[110] or a stretchable supercapacitor.[111] For further information on energy storage elements, the reader is referred to [29,112,113]. Interestingly, a wearable biosupercapacitor has recently shown the ability to harvest and store energy from sweat lactate in the same skin-mountable dual-functional device.[35] Overall, advances in wearable energy elements and the integration within wearable electrochemical sensors are paramount for the next generation of wearable devices. Further details on the most used energy harvesting strategies in WeSPEDs are described in **Section 4**.

2.4. End-user interface

The end-user interface is essential to cherish a user-friendly device able to engage potential customers (e.g. patients or sports practitioners). Currently, three kinds of interfaces display the output of the electrochemical analysis: (i) an electronic display is an affordable option, and it has been traditionally used in digital watches.[48] (ii) An electrochromic display, has recently gained importance as an intermediate solution between user interpretation and simplicity.[43,114] The difference of voltage generated by the analytical signal can be indicated by a change of color in the display, thus providing an easy interpretation by the user. Last but not least, (iii) the mobile application, is the most employed in wearable applications as the data is wirelessly transmitted to a mobile phone or smartwatch and displayed in a user-friendly manner. Considering that WeSPEDs aims to continuously monitor health parameters, the mobile application should be the most suitable interface as it allows to store the data in the external device or to send the data to the cloud for further analysis. In this way, all health information

can be treated by the physician or by machine learning activities which can trigger an alarm when certain levels of biomarkers are reached, or even provide preventive, and eventually, predictive healthcare.

3. Current challenges in wearable electrochemical devices

Wearable devices are experiencing exponential growth in the last decade, showing the tremendous potential for solving societal issues, and thus, with massive market opportunities. WEDs have been demonstrated to be a rising subject in wearable devices due to their unique ability to convert (bio)chemical data from the environment including the body to the digital domain. Still, few cases of WEDs have reached the market. Therefore, there are some challenges that WEDs must tackle to accomplish a trustworthy delivery of health data.

Figure 3 displays a diagram of the four main challenges that the authors have identified that need to be addressed to fulfill a complete deployment of WEDs. Before discussing the challenges of WEDs, it is assumed that the maturity of wearable electrochemical sensors allows to obtain a suitable analytical performance for the application of purpose: (i) linear range within the physiological levels of the analyte; (ii) limit of detection below the basal level of the biomarker for adequate diagnostic and avoid false negatives; (iii) excellent sensitivity for the proper discrimination of healthy and diseased conditions for accurate monitoring; (iv) reversibility of the electrochemical readout able to detect fluctuations of the analyte; (v) rapid response, essential to unravel a sudden variation on the target for a rapid decision on a patient treatment or health status; (vi) selectivity, the electrochemical sensor only respond to the target analyte to avoid false positives; and last but not least, (vii) reproducibility, upon manufacturing electrochemical devices, the analytical signal should be similar to allow a calibration-free approach and an easy on-body use.

3.1. The first challenge: continuous monitoring

After a successful *in vitro* evaluation of the analytical performance of the electrochemical sensor, the embodiment into a wearable configuration must still comply with the ability to continuously monitor the analyte of interest. Hence, the stability of the electrochemical readout to a certain concentration is essential to avoid inaccurate interpretation. Thus, the electrochemical sensor cannot exhibit any drift on the signal. Whether a drift occurs during long-term measurement (e.g. hours or days), a baseline subtraction can be integrated into the software (prior tests must be performed to simulate the drift correction). Calibration-free is another essential parameter to consider for accurate continuous monitoring. It is known that some commercial devices are calibrated from time to time to gather reliable output.[115] This need for a calibration step can be produced due to biofouling of the electrodes, change in the environmental conditions, or loss of performance of the selective or transduction layer. Ideally, the next generation of WEDs should be calibration-free, either during its use and also from the manufacturer, meaning that each WED does not need to be previously calibrated at the factory. In the end, the wearer should be able to easily replace the WED and continuously monitor her/his health status without any calibration step. Finally, wearable materials must withstand common motion and tensile stress at the same time that allows the electrochemical sensor to keep its analytical performance. For example, polymeric conductors such as poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) and silver/silver chloride (Ag/AgCl) inks containing silicone-based elastomeric polymers,[116] blends based on CNTs and polyurethane,[88] or the incorporation of styrene-block-polyisoprene-block-polystyrene in commercial carbon ink[117] permits a high degree of flexibility and stretchability without losing electrical performance. Moreover, the combination of thin- and thick-film fabrication technologies (e.g. photolithography for high-resolution serpentine patterns and screen-printing of stress-enduring inks, respectively) is able to design 'island-bridge' devices that offer an extra level of conformability essential in wearable devices.[118] Recently, an 'island bridge' electrochemical device employs a composite Ag ink based on eutectic gallium-indium particles

as dynamic electrical anchors within the inside percolated network.[119] The synergistic effect enables the printed microstructures to maintain mechanical and electrical properties under an extreme (~800%) strain. Overall, the mechanical resilience of these functional materials accommodates the kinetic forces and ensures continuous monitoring, especially during endurance sport practice where long-term monitoring and high mechanical demands are required to identify potential health emergencies.

3.2. The second challenge: validation

Electrochemical sensors have been effectively validated against laboratory standard methods proving their usefulness as point-of-care tests.[120,121] In contrast, when translated to WEDs, few works have validated the continuous analysis with standard methods. There are several reasons: (i) a method to analyze the noninvasive fluid needs to be standardized (e.g. sweat or ISF); (ii) a sampling method has to be designed and coupled with the standard method (e.g. regional sweat collection); and (iii) real-time analysis of the biofluid is challenging as the determination by the standard method cannot be performed *in situ*, thus several errors along the manipulation of the sample might rise inconsistent results. Therefore, a whole analytical method must be developed to compare the results with the WED analysis. Moreover, noninvasive biofluids are recently presented for diagnostics and health monitoring. Yet, the medical community does not completely agree with the use of such biofluids for therapeutic or diagnostic purposes. To increase awareness and proof the usefulness of noninvasive biofluids, a correlation with blood levels should be attained. In this way, physicians would be willing to accept such matrices in medical decisions. Therefore, extensive in-human testing needs to be performed while keeping the high standards in medical trials.[122] Unfortunately, few investigations are showing the clinical relevance of such biofluids which hinders the acceptance by the medical community. In consequence, it is time that high-performance WEDs correlate their values with blood levels and/or physiological status through new analytical methods to ensure the usefulness of WEDs for health applications.

3.3. Third challenge: User-friendliness

This challenge is essential for a complete deployment of WEDs in society and a full engagement of the early adopters. To fulfill user-friendliness, several features must be considered: (i) easiness of use, a plug-and-play system that is ready to use when placing the WED on the body in a way that it is connected/plug to the body; (ii) facilitated data interpretation through an interface (user interface has been previously discussed in **Section 2.5**), the results of the analysis must be comprehensively displayed either to the wearer or to the corresponding physician/nutritionist/coach; and (iii) enhanced user experience, not only the interface should exhibit the real-time results, but also a software should be integrated to enhance the interactive display, have access to medical records, permit direct connection to medical practitioners, and incorporate machine learning capabilities that predict health outcomes. Importantly, each WED has to be tailored to each application. In this way, the combination with algorithms can provide a customized diet or a personalized treatment in the case of using a wearable nutrition tracker or a wearable therapy monitor, respectively.

3.4. Fourth challenge: Power generation and management

WEDs demand certain power which depends on several factors: (i) type of electrochemical technique; (ii) frequency of the measurements; and (iii) type of wireless data transmission. In order to realize a feasible WED to be used in real scenarios, a suitable power generation unit and an autonomous power handling unit are necessary for long continuous measurements. Hence, the energy harvesting module is paramount to collect sufficient energy from the environment to power the sensor and electronics for continuous monitoring. Subsequently, the electronic module has to properly administrate the power generation from the harvesters or suppliers, and power consumption from the electrochemical sensor and wireless transmission or display, to maximize the life of the WED. A reliable WED would involve the use of low-power consumption sensors (e.g. potentiometric or self-powered sensors) and wireless transmission (e.g. near-field communication), the incorporation of energy harvesting modules

to attain a WeSPED and provide self-sufficiency to the system, and a supercapacitor or miniaturized battery to supply the device with the energy when necessary. Thus, the challenge is to engineer a device to provide sufficient energy with the ability to administrate the power at a suitable time. Finally, the power requirements must be tailored toward the application according to the frequency of data required for a meaningful decision (e.g. administrate the correct dose at a day, or identify dehydration during intense sports practice).

Overall, these features still pose a challenge in the development of WEDs. However, advances in materials, energy, and analytical sciences as well as in the engineering fields will enable the progress of WEDs into self-sufficient units. In this direction, the technology for energy scavenging is vital for the flourishing of self-powered applications. For this reason, the next section describes the recently used wearable energy harvesters to be integrated into WeSPEDs.

Figure 3. *Diagram of the current challenges in wearable electrochemical devices: continuous monitoring for health tracking; validation toward a trustworthy application; user-friendliness for a full engagement of the wearer; and power generation and management toward a long-lasting self-sustainable mission.*

4. Energy harvesting opportunities to power wearable electrochemical sensors

As previously mentioned, one current challenge of wearable (bio)chemical sensing is the lack of long-lasting monitoring due to the insufficiency of energy supply. This lack of power supply for daily applications can be attributed to the use of small batteries that are integrated into the wearable design and the high power consumption of some electrochemical sensors and wireless transmitters. Therefore, today, a battery replacement or frequent recharging is required. These operations might decrease the engagement of the consumer as it hinders the operability of, for example, an epidermal patch.

Two approaches can expand the working life of the device: (i) the use of high energy density batteries[123,124] which would increase the size and weight of the WED; or (ii) the integration of energy-generation modules with small energy-storage devices (batteries and supercapacitors) with rapid charge and discharge capabilities. According to the energy scavenging resource, the energy for wearable applications can mainly be provided from biochemical energy (i.e. biofuel cells, **Subsection 4.1**), mechanical energy (i.e. triboelectric and piezoelectric generators, **Subsection 4.2** and **4.3**), thermal energy (i.e. thermoelectric generator, **Subsection 4.4**) and solar energy (i.e. photovoltaic cell, **Subsection 4.5**). In the following subsections, the most commonly used energy harvesting technologies with the potential to be integrated into WeSPEDs are described. Further information on power generation modules for wearables systems is described elsewhere.[125] Interestingly, the review unravels a broad range of harvesting methods, summarizes and compares several energy generators with corresponding power outputs, as well as covers sensors, materials, and methods of interrogating the wearability of the devices. Finally, the authors describe perspectives in self-powered and self-awareness wearable systems for flexible and printable electronics which will cover the next generation of WeSPEDs.

4.1. Biofuel cells (BFCs)

BFCs became an attractive technology in wearable applications as they can remarkably provide two functionalities at the same time: (i) energy harvesting from biochemical reactions with body fluids, and (ii) self-powered sensing capability.[28,101,126,127] BFCs employ enzymes as biocatalysts at the bioanode and tailored (bio)cathode to generate power from biochemical reactions (**Figure 4A**). Considering the high concentration (i.e. millimolar) of some molecules in biofluids, BFCs are ideal for power harvesting. Lactate, a product of glycolysis especially during exertion, could be easily used to power WeSPEDs in sweat.[47] In contrast, glucose, which is at low levels in sweat, can be utilized as biofuel in ISF as it is found at similar levels than in blood/serum (i.e. millimolar).

From the early epidermal tattoo designed to harvest energy from lactate (ca. 13 $\mu W\ cm^{-2}$) following a bioanode configuration with lactate oxidase (LOx) as the enzymatic catalyst, tetrathiafulvalene (TTF) as an electronic mediator, and carbon nanotubes (CNTs) as surface-enhanced electrocatalytic nanomaterial coupled with a cathode based on platinum black, [128] many efforts have been put to increase the power output reaching ultimately 3.5 $mW\ cm^{-2}$.[34] This dramatic increase in the power performance is driven by the design and integration of new nanomaterials such as hybrid reduced graphene oxide/functionalized CNTs with mediators for the bioanode construction (immobilized with LOx), and platinum-cobalt nanoparticles decoration of mediator-CNTs at the cathode for efficient oxygen reduction and enhancement of the long-term stability. The use of such nanocomposites drastically increases the electroactive surface area which boosts the power performance of BFCs while keeping miniaturized patterns.

As seamless integration is essential in wearable applications, flexible and even stretchable BFCs have been developed.[88,129] Here, the materials are paramount to confer stretchability to the system while keeping high conductivity. The blending of CNTs with polyurethane allows the development of stretchable electrodes. Besides, the design of the electrodes and interconnections permits an extra degree of stretchability and conformability due to the folding and unfolding of serpentine interconnections. In this way, a high-density BFC was

accomplished by using stretchable materials with serpentine interconnectors either by using a densely-packed three-dimensional CNT-based bioanode and cathode[130] or CNT-based buckypaper as electrode material.[129]

Despite the attractiveness of BFCs, there are some bottlenecks to consider when integrating BFC into a WeSPED: (i) limited power density from the biofuel for full WeSPED functioning; (ii) dependence on the biofluid availability (e.g. limited sweat flow at certain conditions); (iii) high and constant concentration of the biofuel to avoid fluctuation on the target that can lead to power cuts during monitoring; and (iv) short lifetime due to the enzymatic reaction, and fouling of platinum catalyst.[131] Overall, the compromise between design, materials, and frequency of analysis can allow self-sufficient monitoring from biochemical energy in the biofluid.

4.2. Triboelectric nanogenerators (TENG)

Triboelectric nanogenerators (TENG) is a newly emerging technique for energy conversion from mechanical motions. The triboelectric effect is ubiquitous in our daily life and results from the electrostatic charges raised when two dissimilar material surfaces with different electron affinity become in contact.[132,133] Hence, TENG is based on the coupling of the triboelectric effect and electrostatic induction to harness regular body biomechanical motions. Specifically, triboelectrification/contact electrification provides static polarized charges on materials surfaces in contact, while electrostatic induction drives the transformation of mechanical energy to electricity through the change in electrical potential induced by mechanically agitating separation.[132] In TENG, there are four fundamental working modes: (i) vertical contact-separation mode; (ii) lateral-sliding mode; (iii) single-electrode mode; and (iv) freestanding triboelectric-layer mode. Remarkably, recent advances in TENG are already leading applications in biomedical sensing[134] and therapeutics.[135]

In wearable sensing, freestanding-mode TENG has been integrated into a WeSPED to monitor several ions in sweat (**Figure 4B**).[50] In this case, the TENG consists of an interdigital stator and a grating-patterned slider. Polytetrafluoroethylene (PTFE) and copper were used as

tribo-pairs. As copper is more triboelectrically positive than PTFE, electrons accumulate on PTFE during the sliding process. The unidirectional sliding process results in a charging flow between stator electrodes until the grating slider fully overlaps with the second stator electrode with reversed polarity. Another TENG mode based on lateral sliding has been also recently used to power another WeSPED for sodium monitoring within a hybrid system with BFCs.[47] Notably, the TENG modules were formulated into a screen-printable ink with an elastomeric binder to withstand the mechanical stress from regular movements.

Current challenges of TENGs such as high power scavenging to meet WeSPED energy consumption, wearability and conformability of the modules, and the increment of the longevity of TENGs will be attained by employing nanostructured surface patterns and/or modification with nanomaterials.[136] Interestingly, the functionalization of current textiles and fabrics with nanomaterials has led to a direct wearable flexible TENG with high mechanical durability and excellent voltage/current outputs.[137] Both a silver (Ag)-coated textile and polydimethylsiloxane (PDMS) nanopatterns based on zinc oxide (ZnO) nanorod arrays on an Ag-coated textile template were used as active triboelectric materials. Another example is the use of nanowrinkle-patterned TENG based on PDMS and polyvinylidene fluoride (PVDF) composite films showing a maximum power density of 832 mW m^{-2}.[138] Besides, highly stable V_{oc} output was demonstrated after continuous operation over 2200 cycles, showing promising resilience for wearable configurations. Finally, a highly stretchable and transparent TENG with a peak power density of 35 mW m^{-2} enables seamless integration in soft skin-like electronics.[139] Overall, functionalized materials regularly used in wearable applications, following fiber and yarn configurations,[140] supporting high biomechanical resilience for sports practice, make TENG an ideal platform for energy harvesting toward intelligent training.[141]

4.3. Piezoelectric generators (PEG)

Another type of energy scavenging technology from mechanical energy is the piezoelectric generator (PEG).[142] PEG is based on the piezoelectric effect which generates an internal

potential when mechanical stress is applied to certain materials.[143] Specifically, the generation of spatially separated electrical charges with an opposite sign during an external force, and subsequently, the accumulation of electrical charges at two ends of the material body allows the formation of an electric dipole.[140] Lastly, the relative displacement of the cations with respect to the anions results in the formation of a piezoelectric potential. Metal-insulator-metal structure is traditionally used in PEGs.[144] There are several types of materials for the construction of PEG such as crystals, ceramics (e.g. GaN, InN, CdS, ZnO), or polymers (e.g. PDVF).[145] Concerning wearable applications, composite materials using polymers and ceramics are the most suitable combination to obtain a synergistic effect for maximal power output while allowing for flexibility and conformability.[145]

Figure 4C illustrates the fabrication of a flexible PEG employing chemically stable and biocompatible group-III-nitride thin film, corresponding short-circuit current plots upon maximum compressions, and at different compressing times. The small PEG could generate an open-circuit voltage of 50 V, a short-circuit current of 15 μA and a maximum power of 167 μW at a load resistance of 5MΩ. Another PEG based on a heterostructure of a ferroelectric polymer, poly(vinylidene fluoride-co-trifluoroethylene) [P(VDF-TrFE)], and two conductive fabrics has been directly integrated via simple fabrication of tape casting and hot pressing following a similar method as regular graphic patches attached to the garments by heat press.[146] Interestingly, a promising hybrid energy harvester module comprising a top piezoelectric layer, a bottom piezoelectric layer, and a middle triboelectric layer was fabricated based on flexible piezoceramic nanofibers to generate a maximum voltage (power) of 253 V (3.8 mW), with a short time of 40 s required to charge a 0.1 μF capacitor to 25 V.[147]

PEG is an encouraging energy harvesting module for wearable applications due to its varied selection of materials available and geometric variations.[140,148] However, to improve the piezoelectric outputs and overcome common obstacles such as poor efficiency at the low-

frequency regimes, surface nanostructures, and hybrid piezoelectric materials have to be further developed.

4.4. Thermoelectric generators (TEG)

A thermoelectric generator (TEG) is a device that converts thermal energy into electrical energy through thermal gradients. The thermoelectric effect has its fundaments in the Seebeck, Peltier, and Thomson effects. Mainly, the Seebeck effect demonstrates the generation of a difference of potential when two semiconductor materials are connected at their edges and subjected to a temperature gradient.[149,150] A TEG consists of p-type and n-type semiconductors where the p-type has surplus holes and the n-type has surplus electrons to carry the electrical current. When a gradient of temperature rises from the hot surface to the cold surface through the thermoelectric material, free charges move which subsequently converts thermal into electrical energy.[150] Materials for the development of TEG require low thermal conductivity, high zT, and a high Seebeck coefficient, being bismuth telluride-based alloys a commonly used material.[151]

By taking advantage of the localized thermal gradients on the skin, wearable TEGs are becoming an increasingly viable power source for energy harvesting.[152,153] **Figure 4D** shows a wristband-based TEG utilizing bismuth telluride grains assembled on a flexible polyimide substrate.[154] The device exhibited a power density of 3.5 μW cm^{-2} and 12.3 μW g^{-1} and a boosted output voltage of 2.8–3.3 V at body temperature in motionless and windless conditions. The TEG was able to continuously supply energy for simultaneously monitoring temperature, humidity, and activity of the human body. Another high-performance wearable TEG with self-healing capabilities was designed on a soft motherboard-rigid plugin module.[155] The TEG produced an outstanding open-circuit potential (OCP) density of 1 V cm^{-2} at a temperature difference of 95 K. However, previous TEG were fabricated by using bismuth, telluride, and selenium alloys which are resource-limited materials. Recently, CNTs have been used to built TEG with promising energy outcomes. In that direction, washable CNT-based fibers have been

manufactured by a simple electrostatic spray technique.[156] The CNT fibers were easily converted into n-type via polyethyleneimine doping process and therefore used with p-type CNT fibers. As a result, maximum power of 26.2 nW with an output voltage of 6.46 mV is achieved at a temperature difference of 33.4 K. Similarly, the direct printing of CNT-hydroxypropyl cellulose composite film allowed the fabrication of a TEG with no additional doping or sorting processes, reporting a power factor of 208 $\mu W\ m^{-1}\ K^{-2}$.[157]

In contrast to TENG and PEG, TEG clearly shows the advantage of continuously harvesting energy from body heat under any physical condition. Hence, this feature exhibits a promising use in healthcare and therapeutic applications. Nevertheless, higher power outputs are still demanded to supply enough energy to a WeSPED. Hence, progress in advanced materials to maximize power output (e.g. nanostructured alloys and nanomaterials) with flexible and stretchable capabilities are paramount for the complete utilization of TEG in WeSPEDs.

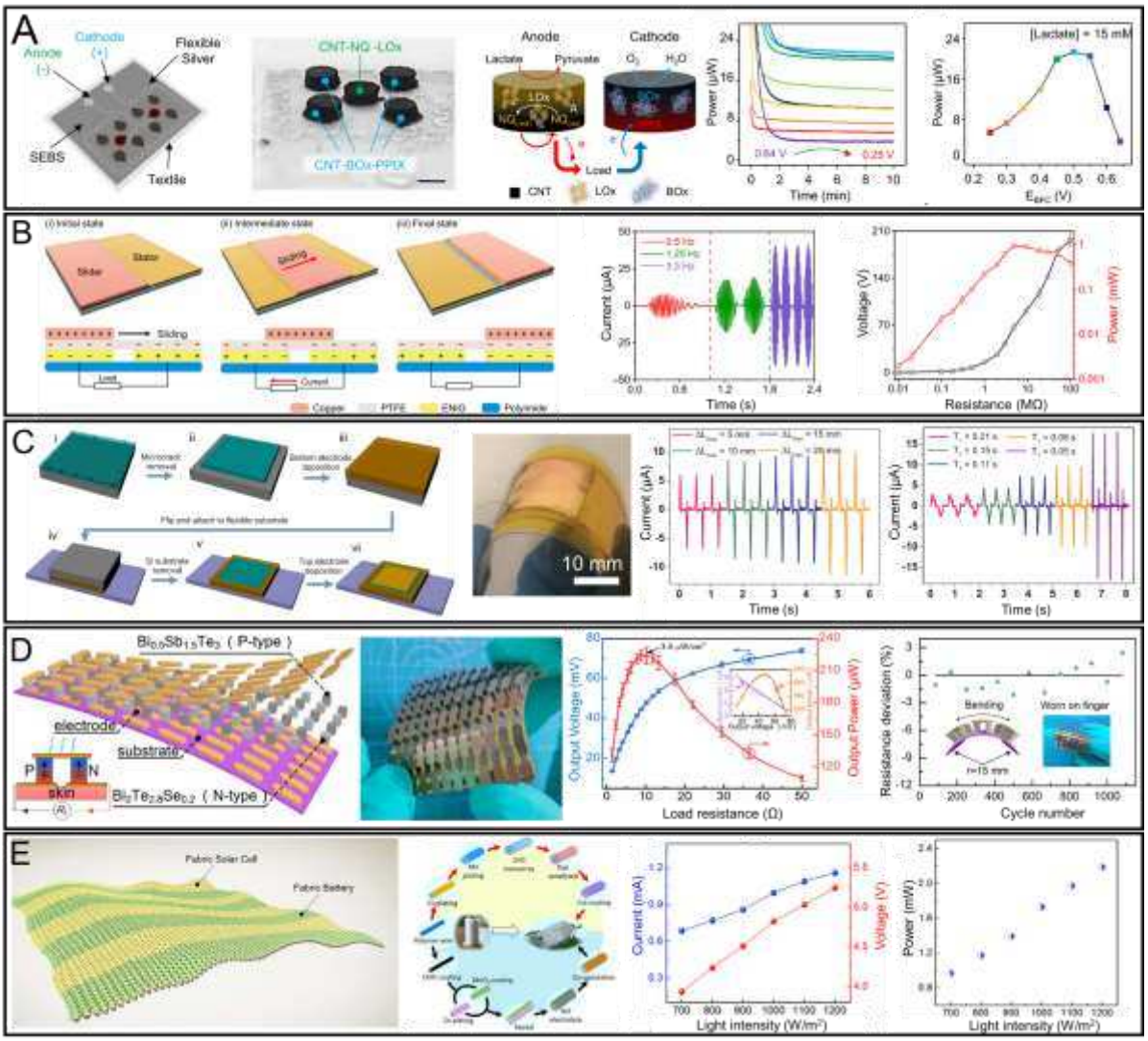

Figure 4. *Wearable energy harvesting systems. A) Flexible biofuel cells based on enzymatic bioanode and biocathode for chemical power generation from lactate in sweat. Reproduced with permission.*[47] *Copyright 2021 Springer Nature. B) Triboelectric nanogenerator for harvesting kinetic energy from movement during sports practice. Reproduced with permission.*[50] *Copyright 2020 American Academy for the Advancement of Science. C) Flexible piezoelectric generator for biomechanical energy harvesting through body activity. Reproduced with permission.*[158] *Copyright 2019 Elsevier. D) Flexible thermoelectric generator for the conversion of body heat into usable energy. Reproduced with permission.*[154] *Copyright 2020 Elsevier. E) A photovoltaic fabric for solar energy conversion. Reproduced with permission.*[159] *Copyright 2020 Cell Press.*

4.5. Photovoltaic device (PV)

Solar power-related technologies have attracted considerable attention due to their easy harvestable energy source. Photovoltaic devices (PVs) are thus emerging tools to harness renewable energy in an easy and convenient manner. A PV consists of an anode, a cathode, and a photoactive layer, where an electron/hole transport layer is used in perovskite and organic solar cells to decline the charge recombination, while dye-sensitized solar cells containing electrolyte for their charge transport and redox reaction.[160] PV are mainly categorized into three groups: (i) perovskite solar cell;[161] (ii) dye-sensitized solar cell;[162] (iii) and organic solar cell.[163] Recent solar cells are made with flexible and stretchable materials that allow being combined on any garment or fabric, thus enabling its wearability in regular cloth.[163] Therefore, flexible PVs can be integrated within wearable configurations as potential energy harvesters for WeSPEDs.

Figure 4E displays a dye-sensitized PV fabric to harness solar energy.[159] The PV is based on a wire-type photoanode constructed by growing a layer of ZnO nanotubes on Mn-plated polybutylene terephthalate wires. After being dye-sensitized, a layer of copper(I) iodide (CuI) was deposited onto the ZnO nanoarrays as the all-solid hole-transfer material. Under solar irradiation, the photogenerated electron-hole pairs at the ZnO/CuI interface could be separated and then respectively transported to the counter electrodes, generating electricity in the external circuit. The energy fabric was able to constantly provide electric power under various scenarios at a discharge rate of 0.1 mA for 10 min after being charged for 1 min under the standard 1-sun condition. Another example of wearable PV is based on a stretchable elastomer-coated organic PV.[163] The double-coating with an elastomer simultaneously realizes stretchability and stability in water whilst maintaining high efficiency of 7.9%. Therefore, this type of device exhibits high promises for washable garments and the integration of wearable sweat sensors. Lately, a bioinspired flexible perovskite solar cell employs a conductive and glued polymer between indium tin oxide and perovskite layers, which simultaneously facilitates oriented

crystallization of perovskite. The PV achieves power conversion efficiencies of 19.87% and 17.55% at effective areas of 1.01 cm^2 and 31.20 cm^2, respectively. Interestingly, advances in solar cells and electronics miniaturization have permitted the development of flexible subdermal PV based on dual junction solar microcells with high-power generation (up to 9 mW cm^{-2}) for powering implantable devices.[164]

The integration of PV in WeSPEDs can be an optimal solution to harness energy from the environment, especially during the passive activity of the wearer. However, three characteristics are critical for the development of wearable PVs: (i) environmental stability to different changing conditions; (ii) sufficient energy efficiency to power the wearable device through all monitoring periods (including day and night); and (iii) mechanical robustness to withstand regular physical forces from the wearer. Lastly, semitransparent solar cells made by highly conductive nanomaterials on thin polymeric layers permit high transparency for an attractive integration in conventional products.[165]

4.6. Other energy harvesters and suppliers

Pyroelectric nanogenerators (PyNGs) are gaining attention due to their ability to convert thermal energy into electrical energy (similar to TEG). The difference with TEG is that PyNGs converts temperature change over time into electrical potential, in comparison to the thermoelectric effect that rises a permanent voltage when there is a temperature gradient.[166,167] Using the pyroelectric effect, a wearable PyNG based on a PVDF thin film integrated into an N95 face mask has been developed for scavenging energy from human respiration.[168] The PyNG could generate at the face mask output signals with an open-circuit voltage of 42 V and a short-circuit current of 2.5 μA, with a maximal power reaching 8.3 μW.

Sweat-activated biocompatible batteries have recently offered the ability to power advanced electronics for health monitoring.[169] Importantly, this sweat-activated cell (SAC) based on a Mg anode and a printed Ag/AgCl-based cathode is biocompatible which allows for seamless integration on the skin through an epidermal patch configuration in comparison to

other fluid-activated batteries that use hazardous materials. The SAC incorporates a hybrid silicone and paper-based microfluidic system to enable rapid sweat capture and storage. The SAC exhibited a specific capacity (~67 Ah kg^{-1}) comparable to a commercial cell (CR2032; specific capacity ~73 Ah kg^{-1}). Coupling the SAC with an electronic module allows active power management that addresses challenges in power fluctuations associated with the dynamic perspiration of each individual. Although the reported SAC is not integrated with electrochemical sensors, the potential integration with low-powered potentiometric sensors can enable the continuous monitoring of biomarkers for fitness and health purposes.

Near-field communication (NFC) is a wireless technology that can inductively power simple electronic devices and provide low-range data transmission.[170,171] By using these capabilities, NFC has been implemented in a microfluidic epidermal patch for noninvasive and *in situ* temperature monitoring.[172] Further wearable applications include the use of NFC to power electrochemical sensors for the detection of calcium and chloride[173] and cortisol in sweat.[44] A major bottleneck is that the sensors can only be powered within the near-field of the reader (e.g. few centimeters) when using a smartphone as a reader and for a limited time of analysis. Therefore, the NFC in WeSPEDs is limited to a low frequency of measurements, hindering its usefulness for continuous data analysis. Remarkably, a successful commercial wearable electrochemical device employs NFC for data transmission, although it still requires a battery to power the electrochemical sensor.[174]

4.7. The hybridization of power scavengers

Before the discussion on the hybridization of power strategies, it is essential to highlight the pros and cons of each type of energy scavenger that allow for comparison within technologies: (i) BFCs through miniaturized nanopatterned devices can provide high power outputs from inherent biofluids without the necessity of external stimulation. In contrast, power output depends on the physiological level of the fuel and the availability of the biofluid which might vary according to each individual. Interestingly, these BFCs can be manufactured in large

areas to maximize power generation. However, the cost and shelf life might be the main drawbacks. (ii) TENG can supply high power through regular biomechanical movements usually performed during the majority of sports practice. Despite the several configurations of TENG, the friction between stator and slider can damage the module during prolonged and/or intense exercise thus decreasing the harvesting performance. (iii) PEG faces similar advantages and drawbacks to TENG. Nevertheless, PEG usually uses small areas to harvest energy from mechanical stress. The limitation of pressing, bending, or stretching for power generation hinders the localization of PEG over certain garments (e.g. shoe insoles or close to body limbs). In general, it might decrease the overall power generation in comparison to a large area's TENG. (iv) Thermoelectrical conversion through TEG seems an interesting option for wearable configurations. Considering the ubiquitous localized thermal gradients from the skin to environmental temperature, TEG can continuously produce energy. Still, the power outputs can be lower than in TENG and BFC as well as the power output might also depend on environmental factors and motion factors. In contrast, large area TEG in CNT-based textile might provide a seamlessly integrated production of energy.[175] (v) PyNG rises a difference in potential when there is a temperature change, thus limiting the energy production in daily routines when the environmental conditions remain constant along the day. (vi) PV are attracting also interest in wearable devices due to their use in outside scenarios. Importantly, the realization of stretchable PV cells and PV textiles for large area wearable harvesters can overcome the current limitation of low energy conversion, therefore improving the feasibility of PV in wearable configurations. (vii) SAC is an interesting approach for disposable epidermal patches that can be used for fitness purposes as SACs are extremely low-cost and can provide sufficient power for 5 h which fits most of the sports practice goals. Finally, (viii) external power supply through NFC might be a straightforward approach to power WeSPEDs in static conditions, although being limited for certain applications. **Table 1** shows a potential match between the type of power generator and wearable application. The use of each power generator

should be tailored according to the application of interest (i.e. fitness or healthcare), and the frequency of analysis which is directly correlated with the power output of the generator and the ability to store sufficient energy.

***Table 1**. Common power generators for wearable applications.*

Energy generators	Conditions	Power output[125]	Wearable Area	Application	Frequency of analysis
BFC	Perspiration-dependent	0.01~3.5 mW cm^{-2}	0.1~10 cm^2	Fitness	min
TENG	Movement	0.002~8.3 mW cm^{-2}	10~40 cm^2	Fitness	min
PEG	Movement	1~300 μW	0.1~10 cm^2	Fitness/Healthcare	min ~ h
TEG	Thermal gradient	0.1~100 mW cm^{-2}	5~80 cm^2	Fitness/Healthcare	min ~ h
PV	Light source	0.3~20 mW cm^{-2}	10~80 cm^2	Fitness/Healthcare	min ~ h
NFC	Electromagnetic field	0.1~70 mW cm^{-2}	10~20 cm^2	Healthcare	h

BFC=biofuel cell; NFC=near-field communications; PEG=piezoelectric generator; PV=photovoltaics; TEG=thermoelectric generator; TENG=triboelectric nanogenerator.

For these reasons, the development of hybrid systems that includes several energy harvesting modules is postulating to be the solution for constant power supply through an efficient energy conversion.[176] Hence, weaknesses and strengths from certain energy-harvesting technologies can be overcome by a synergistic effect.[177] Besides, the specific application of the WeSPED demands certain energy generators. In this way, each energy harvesting technology will be selected whether the device is used (i) indoors or outdoors, (ii) in static or dynamic conditions, low or high frequency of measurements that along with the energy storage modules can allow for a prolonged charging and discharging capability. Therefore, whether the WeSPED aims for (bio)chemical monitoring in sports practice such as outdoor running (e.g. marathon), wearable PV, TENG can perform a preferable job than TEG and BFC that might be suited for indoor exercise where high perspiration should occur. Moreover, PV and PEG can be more interesting for daily measurements in health monitoring where energy can be harvested during the whole day or night, respectively. Specific examples of the synergistic effect are found in the literature. The low OCP from PV can be countered by the

high OCP from TENG. Tackling this energetic concern, a hybrid textile was designed to harness solar and mechanical energy.[178] The wearable device could continuously power an electronic watch, directly charge a mobile phone, and drive water-splitting reactions. Similarly, a fabric was functionalized with TENG and fiber-shape dye-sensitized solar cells.[179] Other energy harvesters were combined in a PEG and PyNG on non-woven nanofiber membranes for the integration in a shoe insole and epidermal patch.[180] BFCs and TENG have been combined to maximize the energy output and continuously power a WeSPED.[47] Last but not least, BFCs have been recently complemented with PEG for passive and active energy scavenging, respectively, to power an electrochromic display.[181] Overall, the progress in several energy harvesting technologies is broadening the possibilities for self-sufficiency wearable devices. The right selection of configurations will allow autonomous (bio)chemical monitoring toward massive WeSPEDs in body networks.

5. Examples of wearable self-powered electrochemical devices for (bio)chemical analysis

Recently, several WeSPEDs have been reported to monitor biochemical parameters such as lactate, glucose, ions, or cortisol (**Table 2**). The integration of energy harvesting modules and sensing modules has successfully attained a self-sufficient (bio)chemical monitoring without the need for human interaction, apart from the first placement or attachment of the device onto the body. **Figure 5** displays several fully integrated cases which use energy harvesting and storage capabilities to power wearable electrochemical sensors for wellbeing applications.

***Table 2**. Wearable self-powered electrochemical devices for (bio)chemical analysis.*

Wearable design	Energy generators	Power output	Target	EC Sensor	EC technique	Human tests	Ref
Epidermal patch	TENG	~416 mW m^{-2}	Sodium pH	NaSE pHSE	Pot Pot	Sweat, upper back	[50]
Epidermal patch	BFCs	3.5 mW cm^{-2}	Urea, ammonium, pH, and glucose	Urease sensor NH_4^+SE pHSE GOx sensor	Pot Pot Pot Amp	Sweat, forehead	[34]

Textile	BFCs, TENG	21.5 μW BFC^{-1} 5.8 μA	Sodium	NaSE	Pot	Sweat, chest	[47]
Wristband	PVs	33% efficiency	Glucose	GOx sensor	Amp	Sweat, wrist	[48]
Epidermal patch	NFC	~2.65 V	Cortisol	Immunosensor	DPV	Sweat, arms	[44]
Epidermal patch	BFC, PEG	~400 mJ cm^{-2}	Sodium ascorbic acid	NaSE, AAOx sensor	Pot SP	Sweat, fingertip	[181]
Epidermal patch	BFC	270 μW cm^{-2}	Lactate	Lactate BFC	SP	Sweat, arm	[119]
Epidermal patch	SAC	~580 Wh kg^{-1}	Chloride pH	Colorimetric sensors	-	Sweat, chest	[169]
Epidermal patch	PEG	0.19 V	Lactate	Enzymatic sensor	SP	Sweat, chest	[182]

AAOx=ascorbic acid oxidase; BFC=biofuel cell; EC=electrochemical; GOx=glucose oxidase; DPV=differential pulse voltammetry; PEG=piezoelectric generator; NaSE=sodium selective electrode; NH_4^+ SE= ammonium selective electrode; pHSE=pH selective electrode; PVs=photovoltaics; SAC=sweat-activated cell; SP=self-powered; TENG=triboelectric nanogenerators.

WeSPEDs for monitor and control sports performance. Figure 5A represents the integration of an epidermal sensor powered by human motion. This battery-free platform uses an FPCB to connect an electrochemical multiplexed sensor based on ISEs for the detection of sodium and pH, a freestanding flexible TENG, and wireless transmission to display the results of the analysis in a cell phone.[50] The flexible TENG consists of an interdigital stator and a grating-patterned slider based on PTFE and copper as tribo-pairs. The copper films are patterned by photolithography to fabricate the interdigital electrode of the stator, and complementary grating structures of the slider. The stator is also patterned by photolithography with an electroless nickel/immersion gold surface finish and subsequently laminated by the PTFE. Interestingly, the scavenging system displayed a high power output of ~416 mW m^{-2}. This application would represent an advance in biomonitoring during sports practice in common cardiovascular exercises such as running, rowing, and elliptical training, in which the sliding motion on the TENG could supply enough power for data acquisition and transmission. Concerning the relevance of this WeSPED to provide information of the health status, the

continuous monitoring of sodium and pH allows the wearer to determine the hydration status and energy consumption of the body, respectively.[71,183]

A similar epidermal patch is described in **Figure 5B** which integrates electrochemical sensors based on ISEs for ammonium and pH monitoring and enzymatic sensors for glucose and urea monitoring.[34] Importantly, the pH and a temperature sensor enable the corrected glucose detection for accurate output even with a dynamic sweat pH composition and with environmentally changing conditions during the exercise. This wearable electrochemical sensor is integrated with a nanoengineered BFC array to maximize the power outcome from lactate in sweat, and thus accomplish self-sufficient monitoring of sweat biomarkers. The BFC array consists of LOx immobilized on the bioanodes to catalyze the lactic acid to pyruvate and Pt alloy nanoparticle-decorated cathodes that reduce oxygen to water. Moreover, the use of nanomaterials (i.e. CNTs, rGO) to increase the electrochemically active surface area and mediators (i.e. Meldola's Blue and TTF) to decrease the overpotential on the BFC, enhanced the energy harvesting performance. The assembled BFC module was able to reach a maximum power output of ~2.0 and ~3.5 mW cm^{-2} with 20 and 40 mM lactate solutions, respectively, with an OCP of ~0.6 V. The system is integrated with a FPCB that enables the conformational attachment on the skin, and a Bluetooth module for wireless broadcasting of the data.

The necessity of high power inputs to provide continuous monitoring of sweat biomarkers forces the creative strategy of combining different energy scavenging modules in the same WeSPED. For example, **Figure 5C** depicts a self-sustainable wearable E-textile based on a hybrid energy harvesting system for the continuous monitoring of sodium.[47] The microgrid is based on the combination of a BFC array and a flexible TENG. The BFC is built with CNT and mediators in a bioanode (LOx) and biocathode (bilirubin oxidase) to generate power from lactate oxidation. The testing of the BFC module resulted in a maximum power of 21.5 μW per module when discharging the BFC at 0.5 V. Concerning the TENG, the module generates charges by sliding motion from a poly-tetrafluoroethylene-based negative mover and an

ethylcellulose-polyurethane-based positive stator in interdigitated patterns which are deposited on the forearm and side of the lower back, respectively. The combination of both energy harvesting systems allows for the continuous supply of energy for biomarkers monitoring even during static and dynamic events. In this way, the flexible TENG can provide an immediate boost of energy to launch the sensing operation, and the BFC can provide the energy after the wearer start sweating. As the thermoregulation action of sweating is usually delayed, the WeSPED can continuously harvest energy even when the movement stops for data transmission, if needed. The synergistic effect between biomechanical and biochemical energy through TENG and BFC, respectively, and the ability to store the energy in a supercapacitor allow exhibiting the sodium level by using a wearable electrochromic display, thus facilitating the real-time data interpretation by the wearer. Overall, this innovative WeSPED brings a self-sustainable solution for health and wellbeing monitoring in sports that do not require continuous exercise, opening the application to a broader number of activities (e.g. tennis, football, soccer, etc.).

Figure 5. *Wearable self-powered electrochemical devices for wellbeing monitoring. A) Wireless battery-free wearable sweat sensor for the continuous monitoring of sodium and pH powered by human motion through a flexible TENG. Reproduced with permission.*[50] *Copyright 2020 American Academy for the Advancement of Science. B) BFC-powered soft electronic skin with multiplexed and wireless sensing of urea, ammonium, glucose, and pH. Reproduced with permission.*[34] *Copyright 2020 American Academy for the Advancement of Science. C) A self-sustainable wearable multi-modular E-textile bioenergy microgrid system powered by a flexible TENG and BFCs for the monitoring of lactate and sodium. Reproduced with*

permission.[47] *Copyright 2021 Springer Nature. D) A fully integrated and self-powered smartwatch from flexible PV for continuous sweat glucose monitoring. Reproduced with permission.*[48] *Copyright 2019 American Chemical Society. E) Battery-free, wireless, and flexible electrochemical patch powered by NFC for the analysis of sweat cortisol. Reproduced with permission.*[44] *Copyright 2021 Elsevier.*

WeSPEDs for monitor and control health status. Figure 5D displays a self-powered smartwatch for glucose management through its monitoring in sweat.[48] The fully integrated system included an energy harvesting module consisting of flexible PVs, flexible Zn-MnO_2 batteries for energy storage, an amperometric enzymatic glucose biosensor, and a FPCB. The power supply module of the smartwatch consists of two PV cells connected in parallel and three Zn-MnO_2 batteries connected in series. The integrated self-powered smartwatch can be charged up to 6.0 V within 1 h under outdoor sunlight. Upon charged batteries, the system achieves a cruising duration of up to 8 h. Under indoor activities with relatively low illuminance (around 7.5 W m^{-2}), the device requires around 2 h to charge the integrated batteries to 4.2 V, which can later support the system functions for around 1 h. In that sense, the PVs exhibit a 33% of energy transfer efficiency from the solar cell to the batteries. Regarding data interpretation, the smartwatch incorporates a simple electronic display showing low/mid/high labels corresponding to increasing concentrations of glucose. Hence, the wearer knows her/his energetic status in real-time and can take the proper action. The system is designed for passive sweat monitoring meaning that you need to perform sport to generate perspiration. However, an integration of an iontophoretic system in the smartwatch would allow for sweat induction, and consequently, broaden the application to healthcare (e.g. Diabetes management) or users that cannot perform sport regularly. Overall, the system has demonstrated an outstanding performance without external charging requirements that enables the monitoring of glucose in sweat for sport and therapeutic applications.

The use of NFC in self-powered devices is an interesting energy source for static applications, as the wearer does not need kinetic energy for a long time for powering the device. However, the wearer usually needs to take an extra step to launch the readout by approaching the NFC reader to the NFC antenna in the device. **Figure 5E** shows the coupling of an electrochemical immunosensor for cortisol detection with a NFC module for wireless power harvesting and data interaction with a NFC-enabled smartphone.[44] The NFC module in the wearable patch gathered energy when the NFC reader (i.e. smartphone) is in close contact, and subsequently supply power to the whole circuit to launch a DPV measurement through a miniaturized potentiostat. Later, the signal is transmitted under a 13.56 MHz electromagnetic field back to the smartphone. Using this configuration, the authors demonstrated the circadian rhythm of the body's sweat cortisol under a relaxed or stressed mood. Importantly, the results of the WeSPED during a week test were validated with an enzyme-linked immunosorbent assay test showing promises for successful monitoring of stress levels in sweat. In contrast, passive perspiration by sport practice is still needed to collect sweat samples which can hinder the easy monitor of stress levels for health applications. Therefore, the integration of an iontophoretic system would be desired to enable the passive collection of sweat, although it would require extra energy to power the whole system.

6. Key findings for the next generation of wearable self-powered electrochemical devices

To this point, several designs and strategies of WeSPEDs have been proposed showing the progress in the integration of self-powered modules with WEDs (**Figure 6**). From the careful analysis of the elements, challenges, and reported cases, this review highlights key findings that will enable advances in WeSPEDs for a successful deployment in real scenarios:

(i) Unlimited wearable configurations. The only limitation is that the device must be worn on the body. Therefore, endless designs can be used which are a result of scientific creativity. Sometimes, it is a matter of reusing conventional garments or wearable tools and turn into

WeSPEDs or by creating an attachable and conformable innovative device. Despite the variety of wearable designs, epidermal patches and e-textiles are mainly employed in WeSPEDs.

(ii) Fully wearable modules. The design of the end-product must accomplish a seamless integration of all wearable modules with the body. This permits the user to feel comfortable during all the analysis. For this purpose, flexible and even stretchable materials are needed to allocate the mechanical stress obtained from daily movements without draining any performance. From FPCBs, batteries, supercapacitors, energy harvesters, and electrochemical sensors, all must comply with high conformability to avoid any undesired friction with the body that can provoke skin irritation or rash. Last but not least, the wearable device in contact with the body must meet high biocompatibility standards (e.g. comply with medical device category for healthcare purposes) to avoid the toxicity of nanomaterials and potential allergies.

(iii) High analytical demands. The purpose of WeSPEDs is to continuously monitor key biomarkers for trustworthy decision-making processes, either in healthcare or in fitness. Hence, the analytical output from the device must be accurate and real-time. Besides, the linear range of the sensor must fit within the physiological and therapeutic levels of the target analyte, including trace detection in specific operations. Another critical aspect linked to the analytical output is that the biofluid target must be physiologically relevant for health and wellbeing decisions. For example, efforts in the correlation of sweat or ISF biomarkers to blood levels are considerably demanded. In this direction, proper human trials must be fulfilled by carrying out massive in-human testing while keeping the medical standards and operation protocols.[122] This information will gain the confidence of physicians and coaches to rely on the information of WeSPEDs and provide on-track meaningful decisions. If a correlation is not attained due to the regional use of the WeSPED, another possibility is to perform clinical studies showing the relationship between biomarkers levels in noninvasive biofluids with the physiological condition of the wearer.

(iv) Combination of energy modules. The hybridization of energy scavengers will be the next step in energy harvesting to circumvent the weaknesses of each type of generator. Ideally, a continuous power generation should be delivered to the WeSPEDs even during sedentary conditions or being independent of the external environment. Recently, a passive perspiration BFC coupled with a complementary PEG has been recently presented for bioenergy harvesting in the fingertips of a wearer.[181] Importantly, the scavengers can convert energy from passive perspiration (i.e. BFC from lactate at the fingertips) and active mechanical movement (i.e. PEG), thus maximizing the power generation. Besides, the use of the same module for energy harvesting and energy storage would simply the design and fabrication of the device toward optimal power management while maintaining high energy generation. For example, a dual-functional module called biosupercapacitor integrates a BFC configuration with the capabilities of a supercapacitor enabling a self-charging hybrid wearable device.[35] Overall, the integration of energy harvesting and storage features in the same device will boost the energetic delivery for future self-sufficient wearable systems.

(v) Data analysis and display. The output of the WeSPED must be analyzed and displayed in a user-friendly interface. Thus, complex data treatment which might involve machine learning algorithms can be performed in the cloud, and immediately shown as a simple result in the display (e.g. mobile phone or smartwatch). Certainly, the application of the WeSPED drives the need for further signal processing such as in the case of predictive and preventive medicine or in the evolution of the fitness status during athletic training where multiple parameters might be involved. Concerning data display, electronic or electrochromic displays directly integrated on the WeSPED might be useful for immediate data interpretation (e.g. during cardio exercise). In contrast, wireless transmission to a mobile phone or cloud is required for analyzing data and track the user performance or therapeutic treatment. Essentially, data analysis and display must be tailored to each application.

(vi) WeSPEDs for customized use-cases. Each WeSPED is designed to be used in certain situations. It is indeed challenging to use the same WeSPED for healthcare and fitness. Hence, the limitation of some WeSPEDs to be used under physical activity to allow active sweating and mechanical energy scavenging hinders its applicability in healthcare situations where patients cannot perform sports practice. For this reason, the composition of each WeSPED must be engineered according to the energetic demands of the electrochemical sensor and the application. For example, the realization of kinetic energy scavengers for sport applications and solar or thermoelectric harvesters for static therapeutic applications. Importantly, if hybrid energy harvesters can adapt WeSPED to different static or dynamic situations, they would open the door to universal WeSPED with multiple use cases.

Progress in multiple disciplines is allowing to separately tackle these key findings. Therefore, the combination of several core technologies in the next generation of WeSPEDs will pave the way to a full deployment of self-sufficient tools for gathering (bio)chemical information.

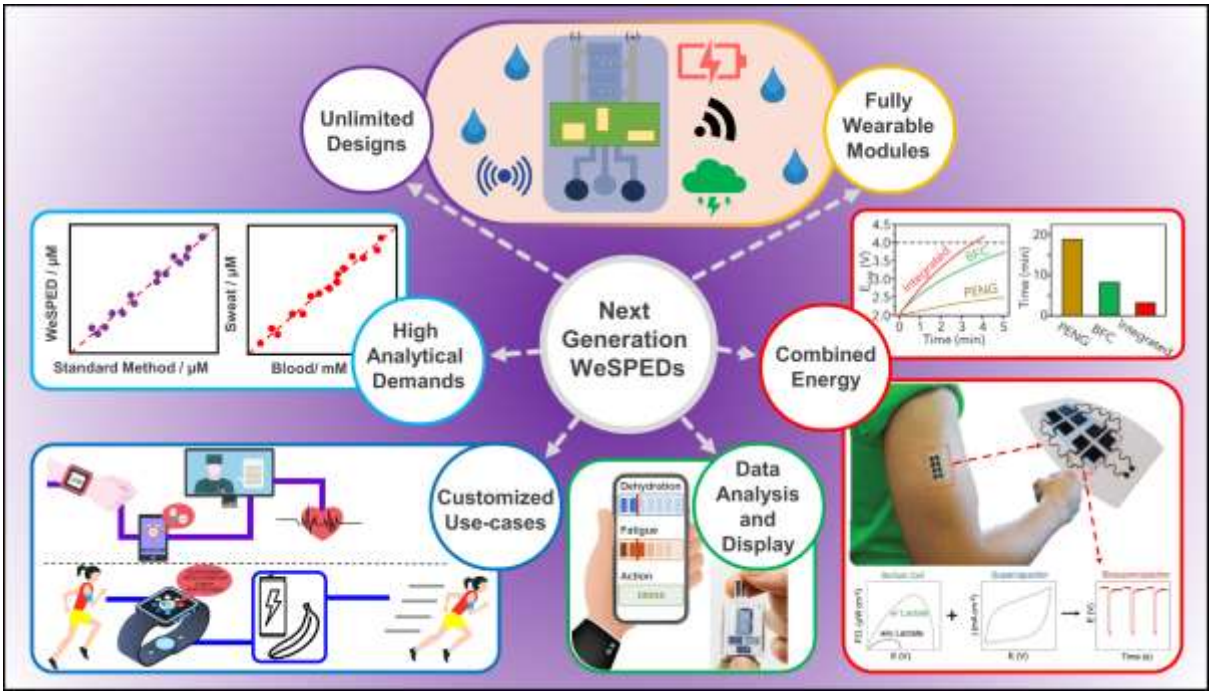

Figure 6. *Illustration of the key findings for the development of the next generation of wearable self-powered electrochemical devices. Reproduced with permission.*[181] *Copyright 2021 Cell Press. Reproduced with permission.*[35] *Copyright 2021 John Wiley & Sons.*

5. Conclusions and outlook

In this review, the new concept of wearable self-powered electrochemical devices has been featured. Since the recent integration of multiple energy harvesting and storage elements in the same wearable device, an unforeseen number of configurations are being realized. The key aspects are still to fulfill the analytical and power requirements to enable successful long-term monitoring during on-body missions. Hence, the alignment of (i) conductive and functional materials for electrode's design, (ii) flexible and conformable substrates, (iii) miniaturized and robust electronics, (iv) biocompatible system assemblies, (v) user-friendly interfaces, along with (vi) affordable and scalable manufacturing will attain a prosperous deployment of WeSPEDs.

Important challenges for wearable (bio)chemical sensing must be considered during the design of WeSPEDs: (i) continuous monitoring in the context of reliable analytical performance (e.g. stability, reproducibility, selectivity); (ii) validation either by analytical chemists with standard methods and correlation with blood levels by clinicians; (iii) power generation and distribution for the proper functioning of the device, including energy harvesting, storage, and supply, (iv) and last but not least, user-friendliness by integration of a display for easy data interpretation and transmission for further signal processing. Addressing these challenges will facilitate the application of multimodal WeSPEDs in real scenarios.

Advances in energy harvesting technologies show an easy way to harness energy from the environment during daily actions. Essentially, the hybridization of harvesters into the same device can enhance the energy conversion into power output to fuel WeSPEDs in different situations (e.g. dynamic or static analysis). Moreover, the integration of energy storage modules

(e.g. flexible batteries and stretchable supercapacitors) is critical to properly manage the energy generation toward a sustainable on-demand electrochemical analysis and data transmission. Low-powered (bio)chemical sensors such as potentiometric sensors and self-powered sensors such as BFCs play an important role when building WeSPED to accomplish the energetic requirement. Notably, the functionalization of current energy harvesters (e.g. TENG, TEG) with (bio)recognition elements has shown outstanding promises for self-powered sensing by blocking or enhancing the energy harvesting capability. This change in power output can be brilliantly used as an analytical outcome for the detection of biomarkers in biofluids.

The thriving realization of seamless integration of WeSPED on the body is an interdisciplinary effort that includes material science, analytical chemistry, and electric engineering for the development of the device. Besides, the incorporation of product development to design a user-friendly prototype, computer science to contribute with machine learning algorithms, and medicine for a trustworthy link between biomarkers to the physiological status of the body are essential for the accomplishment of meaningful devices. Notwithstanding the advances in each field, the combination of several core technologies is the main bottleneck in current WeSPEDs. Bridging modules by integrative collaborations will enlighten the progress of WeSPED for a self-sufficient and noninvasive (bio)chemical monitoring for personalized, predictive, and ultimately preventive training and medicine. Overall, the next generation of WeSPEDs will be nurtured by multifaceted technologies for accurate continuous management of health and wellbeing.

Conflict of Interest

The authors declare no conflict of interest.

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of sensor technologies that can be applied in different markets/sectors embracing the idea of responsible research and innovation.

This review features the novel concept of wearable self-powered electrochemical devices (WeSPEDs). Importantly, key challenges in the development of WeSPEDs with emphasis in the energy generation and management modules are carefully addressed. Overall, the rise of WeSPEDs will lead to the next generation of wearable devices for sustainable and self-sufficient management of health and wellbeing.

Marc Parrilla* and Karolien De Wael*

Wearable self-powered electrochemical devices for continuous health management

ToC figure