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Mini review

Wearable Electrochemical Sensors for the Detection of Organic Metabolites and Drugs in Sweat

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As a kind of human body fluid, sweat contains a large number of substances closely related to human metabolism. Analysis of the sweat components can offer important information for medical diagnosis and health management. Traditional methods for sweat analysis often require large-scale biochemical analysis equipment, which are not conducive to the timely and in-situ monitoring of sweat components. Wearable sensors can be used to detect metabolites in sweat, saliva and tears and avoid the damage caused by blood detection. Electrochemical sensors can convert the target concentration into electrical signals. In recent years, the breakthrough of wearable auxiliary technology has helped the development of electrical sensors for the real-time analysis of sweat components. In this work, we summarized the wearable electrical devices for analysis of organic metabolites and drugs in sweat.

Keywords: Wearable electrochemical biosensor; sweat analysis; metabolites

1. INTRODUCTION

Human sweat includes kinds of small organic metabolites, such as glucose, lactic acid, cortisol, uric acid and so on. Monitoring of the metabolites in sweat is helpful for understanding human metabolism, health management and disease diagnosis [1, 2]. In addition, the drug molecules in sweat can be monitored to adjust the drug dose and improve the treatment plan in time [3]. Thus, analysis of organic metabolites and drugs in sweat plays an important role in medical diagnosis and health management. However, the previous methods for sweat analysis usually require large-scale medical equipment, complex sampling and analysis process and a lot of manpower and time [4, 5]. Wearable

sensors become new medical devices for dynamic monitoring of sweat components, which can avoid the damage caused by blood detection [6].

Wearable sweat sensing devices can be mainly divided into two types: optical and electrical sensors [7, 8]. Optical sensor are designed based on the reaction between the substances to be tested in sweat and the corresponding chromogenic reagents to produce color changes, which are conducted as semi-quantitative analysis through naked-eye observation or imaging technology. Electrochemical sensors with high sensitivity and fast response time have become the main development direction of wearable devices for monitoring of small molecular substances in sweat, including enzymatic and enzyme-free sensors [9]. Usually, the enzymatic sensors have the advantages of high selectivity and re-used characteristics although they require the use and immobilization of high-cost enzymes [10]. In this article, we summarized the progress in the development of wearable electrical devices for analysis of small metabolic substances and drugs in sweat, including glucose, lactic acid, cortisol, ascorbic acid, uric acid, drug molecules and so on.

2. WEARABLE ELECTROCHEMICAL SENSORS

2.1 Glucose detection

Diabetes is a highly concerned health problem all over the world. At present, there are about 520 million diabetics in the world, which brings heavy medical burden to the society. Blood glucose meters are regularly used for monitoring of glucose in the blood of diabetic patients [11]. However, the commercial blood glucose meters are unable to achieve real-time monitoring. Therefore, development of real-time monitoring and non-invasive wearable devices is of great significance [12]. In 2001, Tierney et al. developed a glucose monitoring wearable device similar to a small wristwatch, which can extract glucose from sweat through reverse iontophoresis technology [13]. Abellan-Llobregat et al. used stretchable screen printed electrochemical sensors for glucose detection, including enzymatic and enzyme-free sensors. The enzymatic sensor exhibited high selectivity and sensitivity by the use of Pt electrode functionalized with glucose oxidase as the working electrode [14]. Because the concentration of glucose in sweat is far lower than that in blood, the key requirement is to improving the sensitivity of the wearable sensor. Xuan et al. prepared a wearable glucose sensor by depositing gold and platinum alloy nanoparticles on the reduced graphene oxide electrode and integrating chitosan glucose oxidase composite material on the electrode [15]. This electrode has high sensitivity and selectivity for glucose detection. The linear range of the sensor was 0 – 2.4 mM with a detection limit of 5 μM. The paper-based sensor has good biocompatibility and dense fiber matrix, which is convenient for enzyme modification with good flexibility and suitable for the manufacture of wearable devices. Cao et al. used screen-printing technology and lithography technology to prepare three-dimensional paper microfluidic screen-printing electrode [16]. After functionalization of glucose oxidase, the detection dynamic range of the sensor for glucose was 0.1 ~ 25 mM and the detection limit was 25 μM.

Wearable devices based on sweat analysis have the advantages of noninvasive, easy collection of sweat and rich physiological information, but there are still some challenges, such as irregular or low sweat, easy to carry pollutants on the skin, and lacking of sweat evaporation and transportation protection measure [4, 5]. Recently, Martín et al. proposed an epidermal microfluidic platform which can realize

rapid and continuous sweat sampling and detect both glucose and lactic acid with oxidase and Prussian blue-modified sensor electrode [17]. As shown in Figure 1, the device consists of two polydimethylsiloxane (PDMS) layers and a double-sided adhesive layer. The two PDMS layers integrate the electrode system and include the inlet and outlet channels and detection reservoir, respectively. Therefore, the flexible device can readily adhere to the epidermis and provide conformal contact with the sweat pores .This facilitates the flowing of sweat to the sensing reservoir quickly and withstand the repeated mechanical deformation experienced by the wearer. The device can be integrated with a flexible electronic board for wireless real-time data transmission.

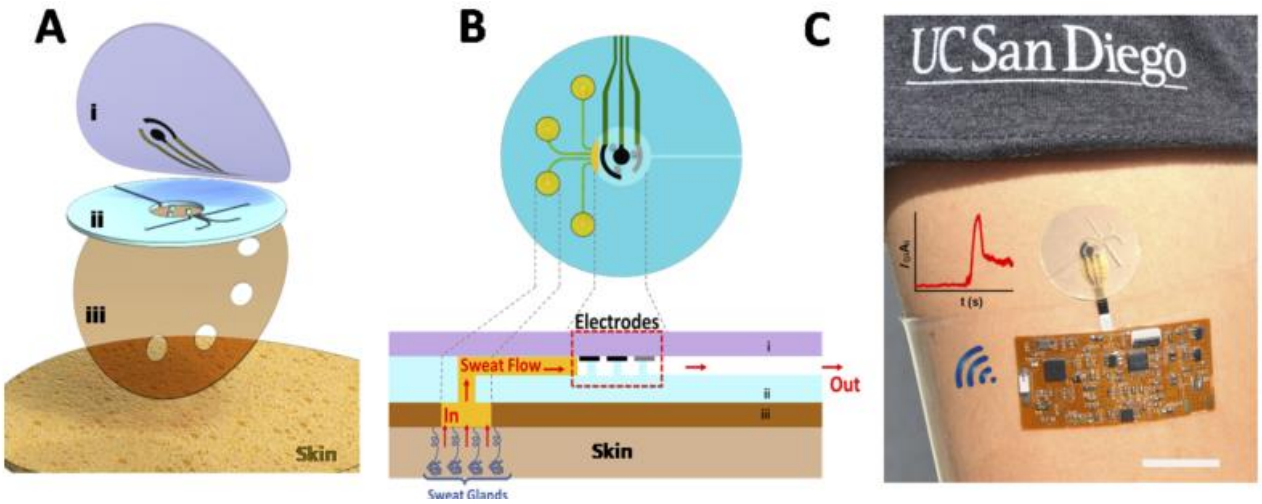

Figure 1. Microfluidic device design and operation. The soft epidermal microchip device conforms to the skin and routes the sampled sweat toward the electrochemical detector. (A) Schematic representation of layered microfluidic device configuration on skin composed of: (i) top PDMS layer with incorporated sensor electrodes, (ii) PDMS microfluidic device, and (iii) adhesive layer on the skin. (B) Schematic representation of microfluidic device sweat collection and operation on skin in top-down and cross-sectional views. (C) Photograph of microfluidic device integrated with wireless conformal electronics on skin with lithography-based gold current collectors and screen-printed silver−silver chloride (RE) and Prussian blue (WE and CE). Inset: Electrochemical temporal response to sweat metabolites. Scale bar, 5 mm. Copyright 2017 American Chemical Society [17].

Metal nanomaterials can effectively increase the electrode surface area and surface conductivity [18]. They have been widely used to modify the electrode for improving the sensing performance. Paul et al. encapsulated gold nanoparticles and glucose oxidase into the zeolitic imidazole framework (ZIF-8) for amperometric sensing of glucose [19]. They confirmed that gold nanoparticles can be evenly distributed in the cavity and enhance the activity of glucose oxidase. This sensing strategy had a detection limit of 50 nM for glucose. After that, Bae et al. integrated the non-enzymatic nanoporous gold (NPG) with a stretchable capillary microfluidic device. The wearable sensor can accurately transport sweat from the skin surface to the electrode, achieving highly sensitive detection of glucose [20]. Kang et al. prepared a single-walled carbon nanotube wearable device based on the functionalization of glucose oxidase-nanoparticle composites [21]. Zhao et al. prepared a working electrode by depositing Prussian blue on the stretchable gold fiber for further modification of glucose oxidase. The reference electrode

was made by depositing Ag/AgCl on the gold fiber, and the unmodified gold fiber was used as the counter electrode [22]. The linear range of the sensor for glucose detection in sweat is $0 - 500$ μM. Moreover, Lin et al. synthesized a porous membrane for the effective immobilization of enzyme and then prepared a glucose sensor with significantly enhancing the sensing performances [23]. In this work, the porous membrane was integrated with the nano-textured electrode after the immobilization of glucose oxidase.

2.2 Lactic acid detection

Lactic acid in sweat is the product of glycolysis and anaerobic glucose metabolism. It was produced in the process of anaerobic activities such as high-intensity exercise. Clinically, the determination of lactic acid plays a very important role in guiding the treatment of some severe patients, especially those with myocardial infarction and insufficient blood supply to tissues [24]. Therefore, monitoring of the lactic acid content in sweat is of great significance for the analysis of physical fitness indexes of endurance athletes. It has been demonstrated that there is a certain relationship between the content of lactic acid in sweat and that in blood. However, blood testing is carried out in an invasive way. Wearable sweat sensors can realize real-time monitoring of lactic acid in a non-invasive and painless way. In recent years, wearable electrochemical devices for monitoring of lactic acid in sweat have aroused great interest of researchers. At present, most strategies for determining lactic acid in sweat require the use of lactic acid oxidase that can decompose lactic acid into pyruvate and hydrogen peroxide. The current signal was generated by the oxidation of hydrogen peroxide on the electrode surface. Jia et al. first proposed an electrochemical tattoo sensor to monitor the change of lactic acid content in sweat with exercise intensity in real time (Figure 2) [25]. The tattoo-based sensor can fit with the skin to facilitate sweat collection. The working electrode of the sensor was prepared by coating lactic acid oxidase and chitosan on a printed tattoo electrode functionalized with tetrapentene disulfide (TTF) and multi-wall carbon nanotube (MWCNT). Besides, Abrar et al. developed an amperometric lactic acid sensor using silver nanoparticles-modified electrode [26]. The sensor was prepared by the use of bovine serum albumin to immobilize lactate oxidase on the serpentine-crossing silver electrode. The electrode can effectively reduce the impedance with skin and has excellent stretchability and bending abilities. Higson's group developed a sensing strategy with two highly porous polycarbonate membranes to immobilize lactate oxidase through covalent crosslinking [27]. Hydrogen peroxide produced from the oxidation of lactic acid was measured by electrochemical method. The detection range of the sensor is 0 ~ 70 mM. The biosensor relying on lactic acid oxidase has the problems of poor stability and complex procedure for enzyme immobilization. For this view, Zaryanov et al. developed an enzyme-free sensor for lactic acid detection based on boric acid-functionalized polyaniline [28]. 3-Aminophenylboronic acid (3-APBA) was electropolymerized on the surface of working electrode imprinted with lactic acid. This enzyme-free sensor exhibited high sensitivity and stability after being stored at room temperature for six months.

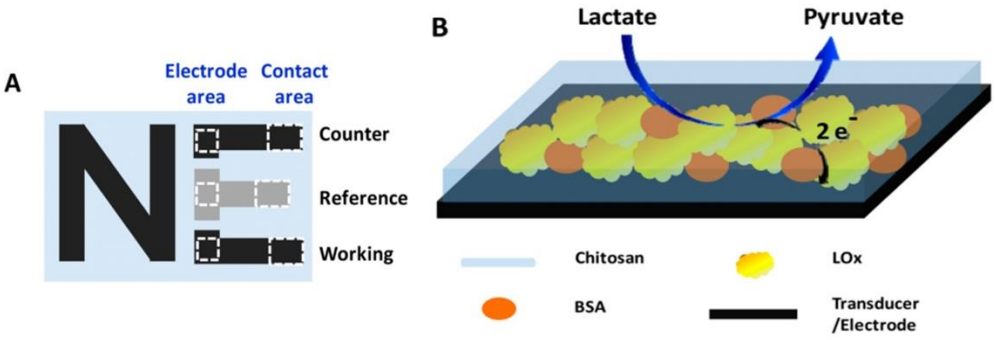

Figure 2. (A) Schematic illustration of a three-electrode "NE" tattoo biosensor for electrochemical epidermal monitoring of lactate. (B) Constituents of the reagent layer of the working electrode which is coated by biocompatible polymer (chitosan). See the text for further details [25]. Copyright 2013 American Chemical Society.

2.3 Cortisol detection

Cortisol is a glucocorticoid secreted by adrenal cortex, which plays an important role in maintaining the balance and stability of physiological function [29]. When stress reaction occurs, the body can quickly secrete cortisol into the blood to maintain the balance of glucose level and blood pressure. It has been confirmed that there is a certain relationship between the concentration of cortisol in blood, sweat and saliva. Therefore, noninvasive detection of cortisol in sweat or saliva has attracted much attention in recent years. For example, Kinnamon et al. prepared a cortisol biosensor by integrating cortisol antibody-functionalized molybdenum disulfide nanosheets into the electrode system [30]. The interfacial impedance of molybdenum disulfide nanosheets was changed with the increase of cortisol concentration, which can be measured by electrochemical impedance spectroscopy, thus achieving the detection of cortisol in sweat. The dynamic range of the sensor was 1 – 500 ng/mL and the detection limit was found to be 1 ng/mL. Stability and selectivity are the two keys to wearable devices. In order to overcome the limitation of unstable recognition of existing biomarkers, Parlak et al. prepared an artificial recognition membrane for stable recognition of cortisol based on molecular imprinting technology and then developed a wearable biosensor by integrating it with electrochemical transistor [31]. Moreover, organic electrochemical transistors (OCETs) can realize the combination of electronics and biology and have stepped into the limelight in the field of bioelectronics [32]. Gao's group developed a cortisol flexible device based on competitive electrochemical immunosensor and special properties of laser-induced graphene [33], which can continuously monitor sweat day and night. The materials used for wearable devices should be flexible, easy to handle and amorphous so that they can be easily transferred to the body or clothing. An et al. developed a strategy for the development of flexible and wearable devices by coating polyacrylonitrile (PAN) nanofiber (NF) and poly(3,4-ethylenedioxythiophene) (PEDOT) on the silk matrix (Figure 3) [34]. The aptasensor consists of a patterned gold electrode with the source and drain. The aptamer-modified PEDOT-PAN NF is displayed in the center to act as a sensor channel. The sensitivity of the sensor was found to be 10 pM with 10 s injection time and 5 s response time. The performance was basically maintained when the aptasensor was transplanted to the swab and human skin, or even to a sweating exercise person.

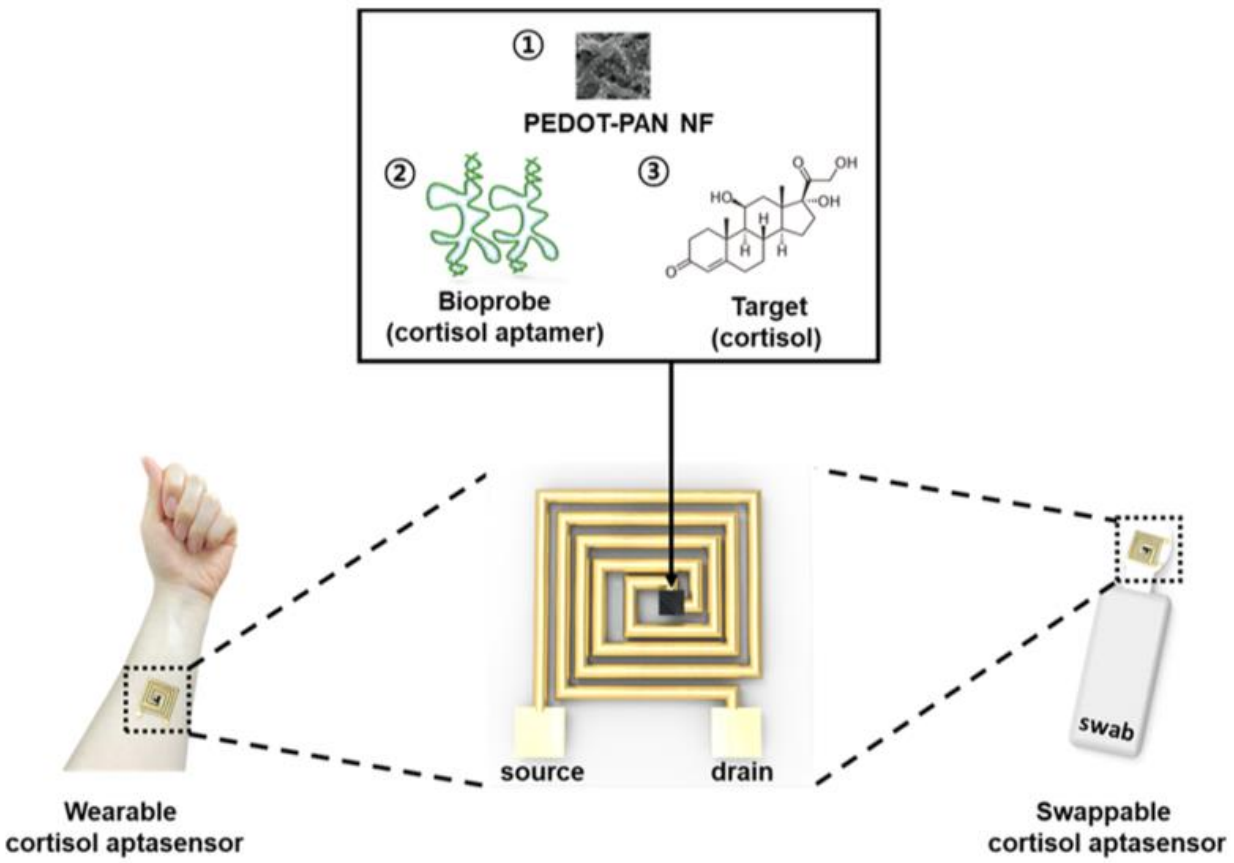

Figure 3. Schematic illustrations of the overall schematic illustration of the cortisol aptasensor. Copyright 2022 American Chemical Society [34].

2.4 Drug detection

Most of the wearable devices reported in the early stage are used for monitoring of human metabolites and electrolytes. Drug monitoring is of great significance in optimizing clinical treatment plans and drug abuse supervision. In recent years, the use of wearable devices for drug monitoring has aroused the interest of researchers [3]. For example, levodopa is a drug used to treat the patients with Parkinson's disease. Its dose has an impact on the physiological state and emotion of patients and there are some defects in the traditional optimum formula. For this consideration, Tai et al. reported a wearable sensing strategy for quantitative detection of levodopa in sweat (Figure 4) [35]. The quantitative analysis was realized by measuring the Faraday current generated by the oxidation of levodopa to dobraquinone by tyrosinase. The signal was enhanced by using the electrode with gold dendritic nanostructure. The detection limit of the sensor reached to 1 μM. In addition, Beitollahi et al. prepared an electrochemical sensor for the simultaneous determination of levodopa and tyrosine using graphene/ZnO nanorods-modified screen printed electrodes [36]. The nanocomposite-modified electrode shows a wide linear range and has the disadvantage of cumbersome processing steps. Kilic et al. designed a smart e-patch for monitoring of the drugs taken by the patients with schizophrenia. Despite the interference of electroactive substances in sweat, the detection limit of this sensor still reached to 0.82 μM.

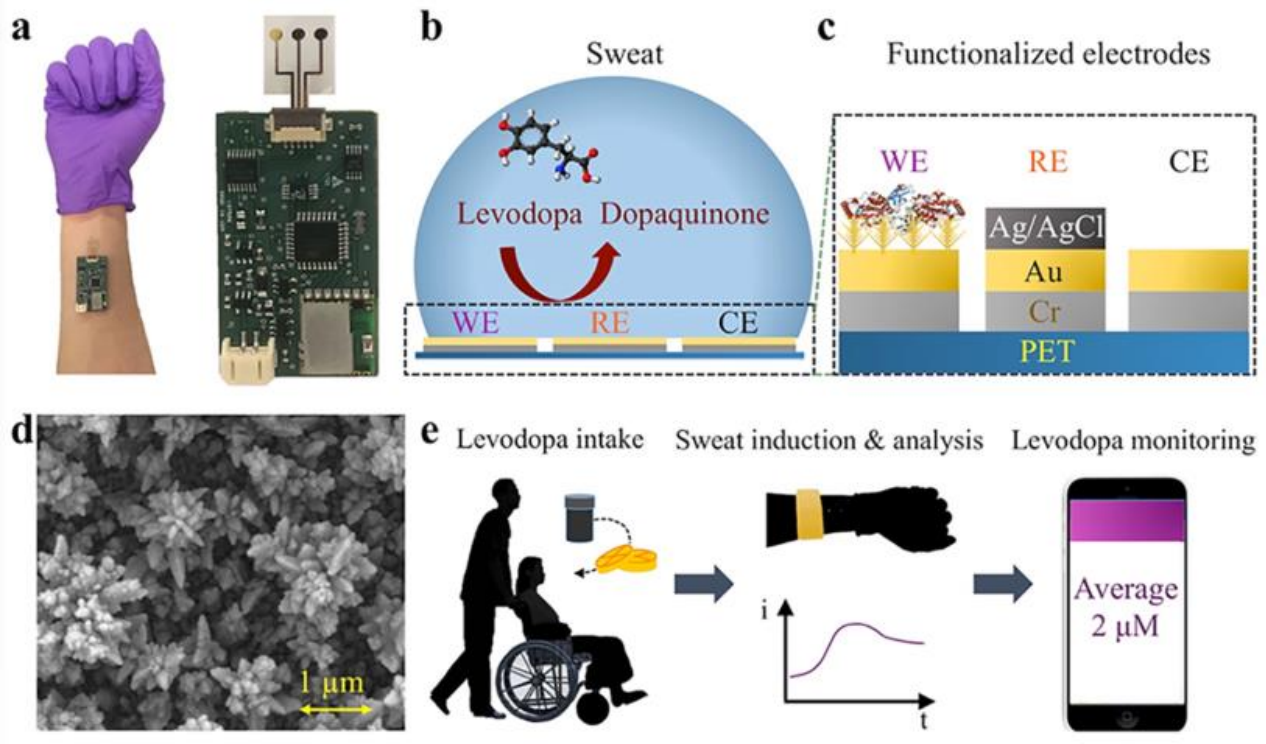

Figure 4. Schematic of the s-band and drug sensing mechanism. (a) Optical image of the s-band worn on a subject's wrist. (b) Sensing mechanism of the levodopa sensor. WE, RE, and CE are working electrode, reference electrode, and counter electrode, respectively. (c) Cross-section view of the gold electrodes on a flexible sensor patch. (d) Scanning electron microscope image of the gold dendritic structures. (e) Real-time sweat levodopa monitoring using the s-band after levodopa intake. Copyright 2019 American Chemical Society [35].

Detection of analeptic is very important in sports events. For example, caffeine, a methylxanthine drug, is an energy drug that is banned in sports events. Tai et al. reported a sensing platform for the detection of caffeine in sweat based on differential pulse voltammetry (DPV) [37]. As shown in Figure 5, the triple-electrode array was patterned on the poly(ethylene terephthalate) (PET) substrate and interfaced with the printed circuit board (PCB). The DPV signal from the oxidation of caffeine at 1.4 V was implemented with the PCB. The current value allowed for the quantitative assay of caffeine in sweat with a detection limit down to 3 μM. The value is lower than that (11 μM) in the sweat after caffeine intake. The detection technology for caffeine is similar to that for other drugs. Thus, the strategy is expected to be used for the detection of other drugs. Moreover, Emaminejad's group developed a noninvasive wearable sensing platform for the detection of electroactive drugs, such as dipyridamole, acetaminophen and caffeine [38]. Javey's group reported a wearable sweat band to determine nicotine by integration of a flexible electrode array with a compact PCB [39]. The working electrode was modified with dendrite nanogold and then coated with 11-mercaptoundecanoic acid (MUA) for the immobilization of nicotine oxidase.

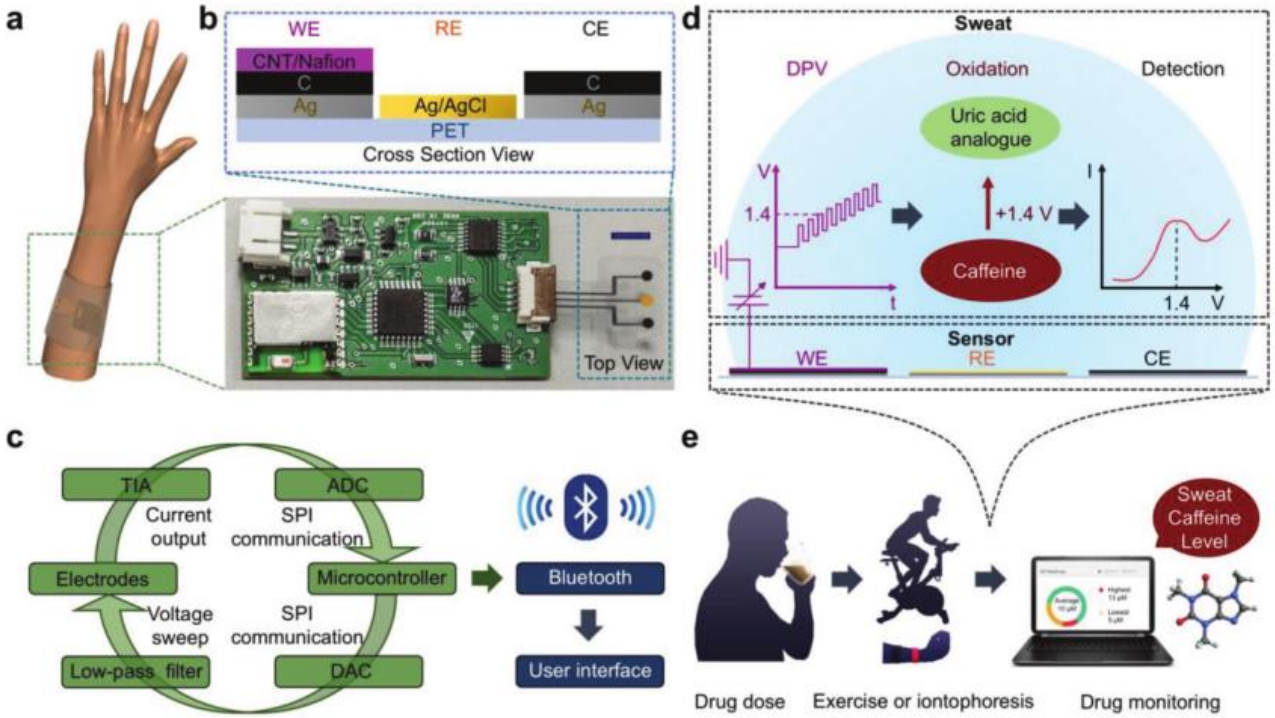

Figure 5. Schematic of the s-band and drug sensing mechanism. a) Schematic of the s-band worn on a subject's wrist. b) Optical image of the s-band and the cross-section view of a roll-to-roll printed flexible sensor patch. Scale bar, 5 mm. WE, RE, and CE are working electrode, reference electrode, and counter electrode. c) System-level diagram of the s-band platform for real-time sensing, data processing, and wireless transmission. d) Electrochemical detection of caffeine through differential pulse voltammetry (DPV). Oxidation of caffeine leads to an observable oxidation peak around 1.4 V. e) Real-time sweat caffeine monitoring using the s-band after caffeine intake. Copyright 2018 John Wiley and Sons [37].

2.5 Others

In addition to the detection of glucose, lactic acid, cortisol and drug molecules in sweat, wearable devices have also been used for the determination of other substances [40]. For example, Wang and co-workers, for the first time, developed a tattoo-based wearable alcohol detection system by integration of a drug-loaded iontophoresis and amperometric sensing of metabolites (Figure 6) [41]. The detection of alcohol was achieved by using alcohol oxidase and Prussian blue-modified sensor electrode. The flexible supporting electronic readout module was featured with wireless telemetry function. Since alcohol detection is very important for traffic law enforcement, the wireless sensing technology provides a great prospect for alcohol detection in the actual environment. Moreover, Semponatto et al. reported a wearable device for monitoring the dynamics of ascorbic acid (vitamin C) in sweat, as shown in Figure 7 [42]. The sensor was prepared by fixing ascorbic acid oxidase on the screen-printed electrode. This is the first noninvasive epidermal electrochemical sensor for enzymatic detection of sweat vitamin C. The device can track the dynamic trend of vitamin intake, thus providing a new idea for guiding individual nutritional solutions. The power supply system and wearable sensing device are two important functional units. Conductive polyaniline (PANI) with high capacitance and stable electron transfer characteristics can be used to prepare enzyme-free sensor for ascorbic acid detection. Ma et al. prepared a dual-function

self-powered sensing device for the detection of ascorbic acid in sweat by crosslinking polyaniline into graphene [43].

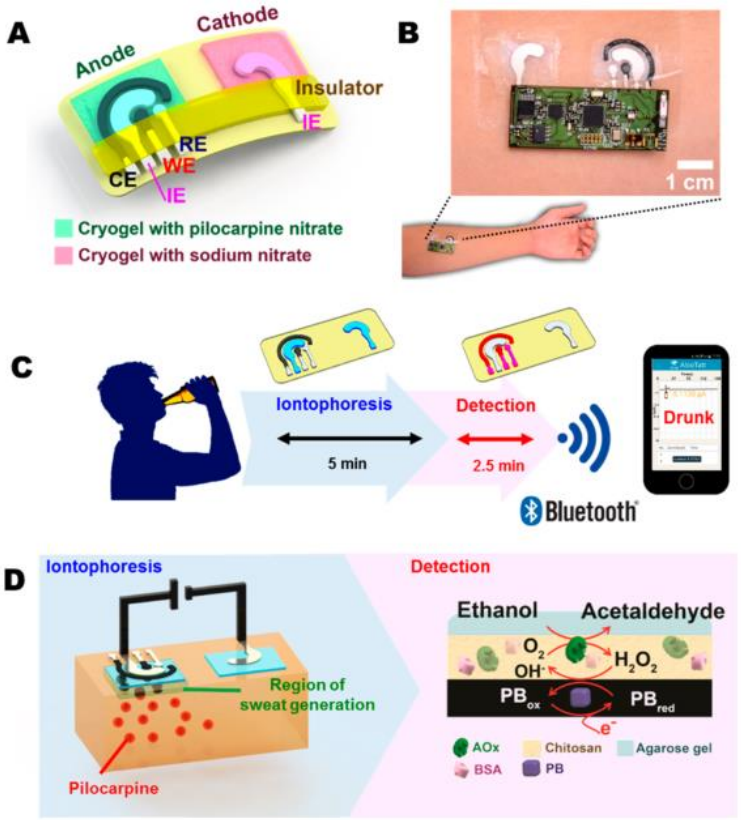

Figure 6. Tattoo-based transdermal alcohol sensor. (A) Schematic diagram of an iontophoretic-sensing tattoo device, containing the iontophoretic electrodes (IEs; anode and cathode) and the three sensing electrodes (working, reference, and counter electrodes: WE, RE, and CE, respectively). (B) Photograph of an alcohol iontophoretic-sensing tattoo device with integrated flexible electronics applied to a human subject. (C) Schematic diagram of a wireless operation of the iontophoretic-sensing tattoo device for transdermal alcohol sensing. In the diagrams of the tattoo-base device, blue and red highlights show the active zones during iontophoresis and amperometric detection, respectively. (D) Schematic diagram of constituents in the iontophoretic system (left) and of the reagent layer and processes involved in the amperometric sensing of ethanol on the working electrode (right). Copyright 2016 American Chemical Society [41].

The abnormal content of uric acid in sweat is indicative of some human diseases. For example, hyperuricemia, gout, renal syndrome and Lesch Nyhan syndrome will lead to the abnormality of uric acid content in the human body. Studies have also shown that there is a certain relationship between the content of uric acid in wound secretion and the severity of wound. In the past decade, wearable sensors for uric acid detection have also attracted the attention of researchers. For example, Kassal et al. prepared an intelligent bandage sensing system for the detection of uric acid in wound secretion [44]. Prussian blue-modified carbon electrode was printed on the bandage by screen-printing technology, and uricase was fixed on the working electrode by crosslinking of glutaraldehyde with BSA. Prussian blue can selectively reduce hydrogen peroxide generated by uric acid oxidase, thus producing a reduction current.

The content of uric acid can be calculated according to the generated current through potentiometer. In addition, Kim et al. developed a tooth guard sensor for the detection of uric acid in oral saliva [45]. The feasibility of the equipment was proved by the comparison between artificial saliva and human saliva. Yang et al. prepared a wearable sensing device for uric acid detection in sweat using carbon dioxide laser engraving technology [46]. This laser engraving technology does not require complex manufacturing processes and instruments, complying with the flexible structure worn on human body.

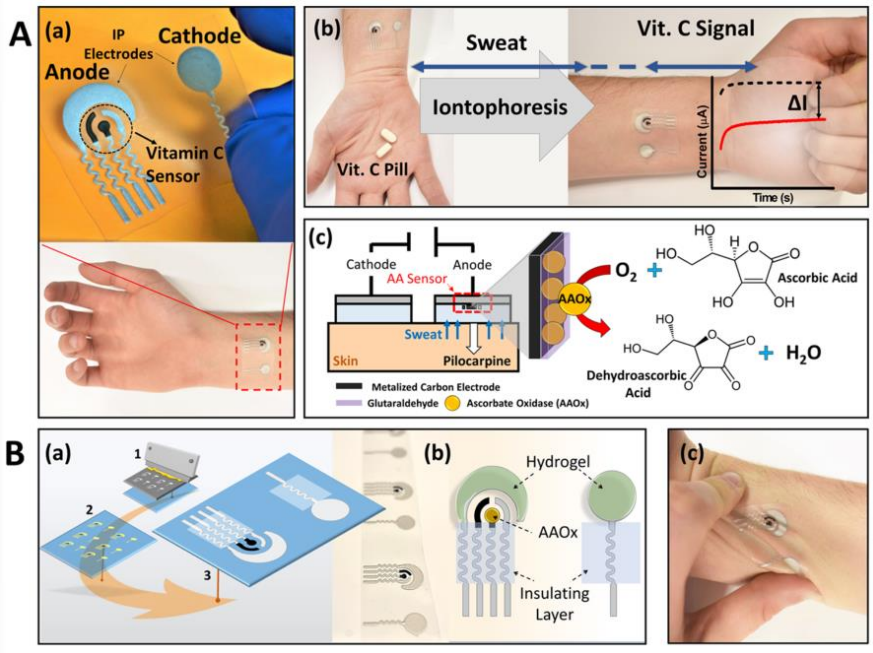

Figure 7. Ascorbic acid (vitamin C) determination in stimulated sweat. (A) (a) Electrode design for simultaneous sweat stimulation and detection. Sweat is stimulated by IP delivery of pilocarpine (located in the anode compartment) using the cathode and anode electrodes. Amperometric vitamin C detection is performed by using a three-electrode system located on the anode compartment. (b) Protocol used for the biosensing of ascorbic acid. Sweat is stimulated before (black dotted line) and after (red solid line) taking vitamin C pills; the vitamin C response is based on the difference in the current beforeand aftertaking thepill. (c) Schematic ofthe localized sweat stimulation using IP pilocarpine delivery and of the enzymatic reaction for detecting ascorbic acid on a metalized Rh-carbon printed electrode. Pilocarpine is delivered on the anode, where the AAOx-immobilized sensor using glutaraldehyde is located; the amount of oxygen consumed by the enzymatic reaction and hence the vitamin concentration is measured from the reduction current of oxygen. (B) (a) Fabrication of the vitamin C biosensor. 1-Screen printing using Ag/AgCl for the IP electrodes, reference and current collectors, and Rh-carbon ink for the counter and working electrodes. 2-printed and cured electrodes. 3-printing an insulating layer to define the electrode area. (b) Schematic showing the location of the hydrogel and the enzyme layer. On the anode, agarose (loaded with 2% pilocarpine) was used, and on the cathode, agarose in 0.1 M PBS was used. (c) Image of the epidermal sensor under mechanical (twisting) strain. Copyright 2020 American Chemical Society [42].

Since the measurement of a single analyte can not achieve a comprehensive analysis of human physiological information, the wearable devices that can detect multiple markers simultaneously are highly desired [47-52]. Han et al. reported a self-powered multifunctional sensing strategy based on

enzyme/ZnO nanoarrays (Figure 8) [53]. Glucose, lactic acid, uric acid and urea in sweat were simultaneously detected by modifying glucose oxidase, lactic acid oxidase, uricase and urease on the surface of zinc oxide nanowires. The power of the sensor came from the coupling effect of enzyme/ZnO nanowires in piezoelectric-enzyme reaction. Bhide et al. prepared a dual-function sensor by integration of glucose oxidase and alcohol oxidase-functionalized zinc oxide sheets into the nanoporous flexible electrode [54]. This strategy achieved the detection of glucose and alcohol by measuring the impedance change. Moreover, Wang et al. proposed a new method to prepare MOF electrode based on flexible amino-functional fossil graphene paper. They found that $Cu_3(BTC)_2$ nanoparticle array can be transferred to the amino-functionalized fossil graphene paper. This paper electrode realized the enzyme-free detection of lactic acid and glucose in sweat [55]. Recently, Shen et al. developed an [aminotrimethylene phosphonic acid-assisted poly(vinyl alcohol)] hydrogel sensor and proposed an elastic electric coefficient sensitivity model as a new strategy to monitoring of various glucose, lactic acid and various ions [56].

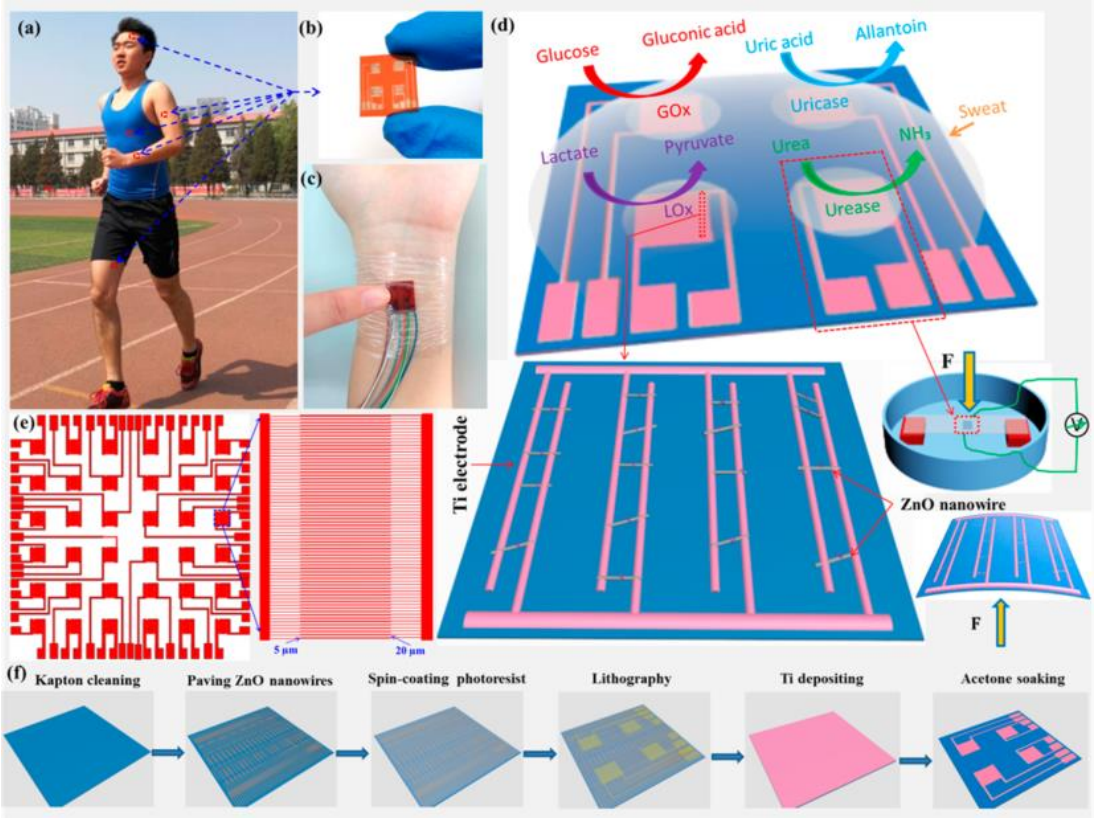

Figure 8. Experimental design, device architecture and fabrication procedure of the self-powered wearable noninvasive electronic-skin. (a) The electronic-skin attached on the surface of a runner at different body parts for monitoring the physiological status by analyzing perspiration components. (b, c) Optical images of the electronic-skin (on human wrist). (d) The experimental design of the electronic-skin for detecting lactate, glucose, uric acid, and urea. (e) The whole pattern of the electronic-skin. (f) The fabrication process of the electronic-skin. Copyright 2017 American Chemical Society [53].

3. CONCLUSION

Wearable electrochemical devices have solved a series of problems of the traditional sensors for sweat analysis. However, efforts are still required to realize the commercialization of wearable electrochemical sensors since various experiments and technologies must be carefully examined and continuously improved, such as sweat sample collection, power consumption and selectivity as well as anti-interference ability. Some of the problems may be solved by the development of self-powered and low-cost flexible sensors and the use of conductive materials and selective electrodes.

ACKOWLEDGMENTS
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