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Mini review

Wearable Electrochemical Sensors for Monitoring of Glucose and Electroactive Drugs

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Wearable sensors have attracted extensive attention due to their flexibility, simplicity and portability. Electrochemical technology is considered to be an ideal method for fabricating point-of-care detection platforms. In recent years, wearable electrochemical sensors have attracted extensive attention in monitoring human health and measuring drug levels in body fluids. This work reviews the research progress of wearable electrochemical sensors for glucose detection and drug monitoring in sweat, tear, saliva and interstitial fluid. The current challenges and development trends are also discussed to promote the future technological innovation of personalized therapy.

Keywords: Wearable sensors; electrochemistry; glucose; drug monitoring

1. INTRODUCTION

Glucose can easily entry into the blood to provide a powerful and rapid energy supplement for patient, athletes and other people. The elevated concentration of glucose can lead to serious complications, such as kidney failure, blindness, heart attack, stroke and so on [1]. In addition, real-time monitoring of drug levels also has important reference value for understanding patients' physical condition, adjusting drug dose and improving therapeutic schedule [2, 3]. Thus, it is expected to monitor glucose and drug molecules in real-time, continuous and noninvasive ways, so as to make an important assessment of health status. With the rapid development of the internet of things, wearable sensors have attracted extensive attention in recent years because of their flexibility, simplicity and portability [4, 5]. Wearable devices for monitoring glucose and drug molecules in human sweat, tear, saliva and interstitial fluid are an important field of current research [6]. Due to their high sensitivity, rapid response and easy miniaturization, electrochemical sensors have considered to be the ideal tools for designing of point-of-care detection platforms to monitor the levels of glucose and drugs [7, 8]. Wearable electrochemical biosensors have attracted more and more attention because of their great prospect in real-time monitoring with soft and stretchable electrodes [9]. This work reviews the research progress of wearable electrochemical sensors for glucose detection and drug monitoring, with emphasis on the current challenges and future development trends.

2. WEARABLE ELECTROCHEMICAL SENSORS FOR GLUCOSE

2.1 Types of electrochemical glucose sensors

For the electrochemical detection of glucose, enzymes or nanomaterials are usually modified on the electrode surface to generate an electrochemical signal. According to difference in the electron transfer mechanism, enzyme-based electrochemical glucose sensors can be divided into three categories, while enzyme-free glucose sensor is called the fourth category [1]. In the first electrochemical glucose sensor, glucose can be oxidized by oxygen with the help of glucose oxidase (GOx). However, in the internal environment, the content of oxygen may be limited and related to the region. Additionally, some reducing substances and biological dirt may show a significant impact on the detection. In order to overcome these interferences, electrocatalysts and anti-biological fouling membranes have been introduced into the first type of sensor. The second type of glucose sensor shows excellent performances by using redox medium instead of oxygen to transfer the electrons between the active center of GOx and the electrode surface. The third type of electrochemical glucose sensor is based on the direct electron transfer (DET) between the redox center of GOx and the electrode, which does not require oxygen or other synthetic substances. However, $FADH_2$ is buried at a distance of about 1.3 to 1.5 nm below the apoenzyme [10], making the speed of DET much slow. In the fourth type, nanocatalysts are used instead of GOx to modify the electrode for direct electrocatalytic oxidation of glucose. Enzyme-free sensors overcome the shortcomings of enzyme sensors. However, due to the lack of selective recognition sites, its selectivity is poor. In addition, nanomaterials and their composites are inevitably affected by toxicity. In terms of the basic principle of glucose sensors, the first and second types of glucose sensors are relatively mature technologies for lab researches and practical applications. There is no doubt that novel materials are the basis for developing flexible and soft wearable devices with comfortable wearing experience and satisfactory accuracy [11]. Moreover, the practical applications of wearable sensors are challenged by power and communication system. Herein, we summarized the progress in the design of wearable electrochemical sensors for monitoring of glucose in sweat, tear, saliva and interstitial fluid.

2.2 Monitoring of glucose in sweat, tear, saliva and interstitial fluid

Sweat mainly comes from the gland in the epidermis. The collection of sweat is very simple, which makes the wearable sensor for sweat assay become the focus of research [12, 13]. Gao et al. reported a wearable sensor for in-situ analysis of multiple analytes in sweat (e.g. glucose, lactic acid, potassium, and sodium) and monitoring of the body temperature [14]. The sensor shows excellent sensitivity, stability and selectivity. Gold fibers exhibit excellent stretchability, conductivity and strain insensitivity. Zhao et al. reported a wearable electrochemical device for determining glucose in sweat using gold fiber [15]. This highly stretchable glucose sensor offers considerable potential for the development of wearable diagnostic device. Wang et al. developed a wearable sweat sensor with wear-resistant fabric (Figure 1) [16]. The active materials were coated on carbon nanotube fiber to enhance the detection performances. The fibers are further woven into clothing for in-situ analysis of targets in sweat such as glucose and other analytes. Lin et al. developed a non-invasive sensor for real-time monitoring of glucose in natural sweat without actively stimulating perspiration [17]. The sensing devices include a hydrogel patch to collect sweat and an electrochemical sensor to detect glucose. In addition, Promphet et al. reported a wristwatch sensor for real-time monitoring of glucose and lactic acid in sweat based on a cotton thread electrode [18]. The cotton wire electrode modified with cellulose nanofibers/carbon nanotube ink-prussian blue/chitosan greatly improved the perspiration collection, enzyme fixation and electrode conductivity. Flexible substrate materials are of great significance for the development of wearable devices. Polydimethylsiloxane (PDMS) films are suitable materials for the construction of flexible sensing devices due to their simple preparation, stable chemical properties and good mechanical properties. Therefore, Shu et al. prepared flexible Au/PDMS thin film electrode by depositing Au on PDMS thin film [19]. Singh et al. prepared sweat glucose sensors by depositing a copper-manganese metal layer on a pyrrole treated fabric [20]. The concentration of glucose in sweat is very low (0.02 ~ 0.6 mM) [21]. Thus, sweat-based glucose sensors require high sensitivity. Additionally, some researches have suggested that the correlation between sweat and blood glucose concentration is limited [22]. Meanwhile, the accurate detection of glucose in sweat is challenged by the change in skin temperature, pH, and pollution from the surroundings and possible interferences.

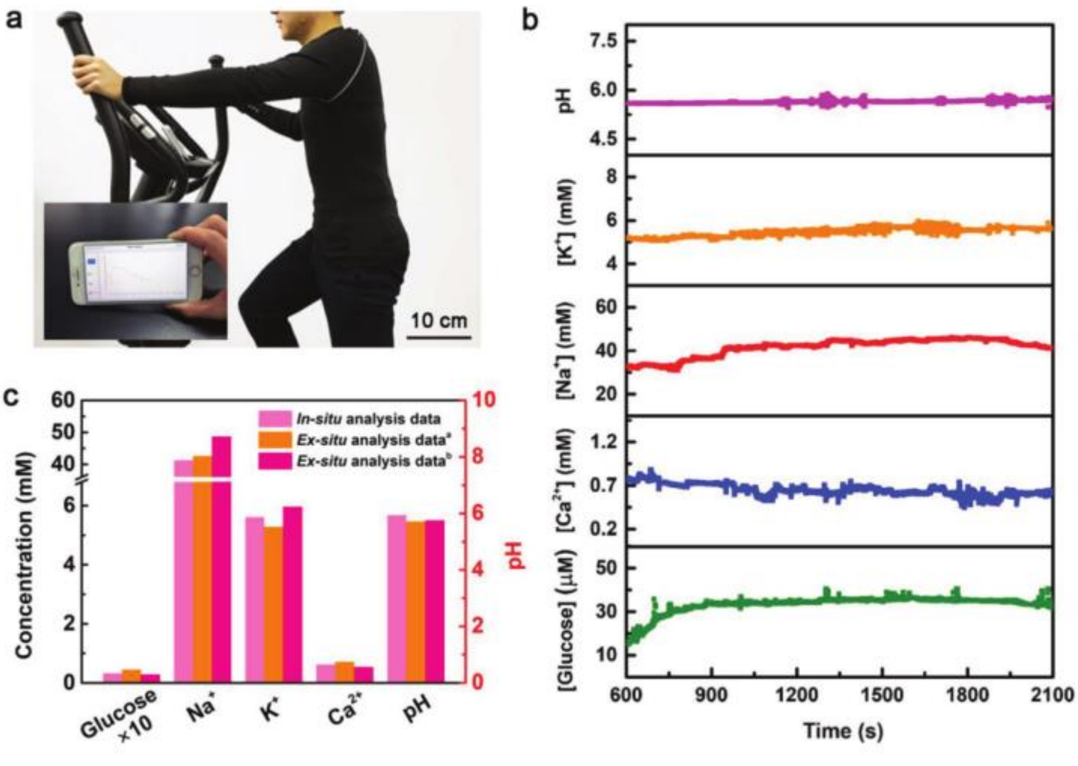

Figure 1. Application and demonstration of the integrated electrochemical fabric. a) Photograph of a subject wearing the garment device while running. The inset shows a smartphone that wirelessly receives data with a custom-developed application. b) Real-time sweat analysis using the garment device. c) Comparison of ex situ data from the collected sweat samples with that of the in situ [16]. Copyright 2018 John Wiley and Sons.

Tear is mainly secreted by the lacrimal gland. It plays an important role in protecting the ocular surface from the influence of external environment. Contact lenses have become an important platform for integrating micro glucose sensors. As shown in Figure 2, wearable smart contact lens platforms have been integrated with flexible power transfer systems to wirelessly monitor physiological signals (e.g. intraocular pressure, corneal temperature, and pH), biomarkers (e.g. glucose, proteins, ions, and virus), and controlled drug release in diagnostic and therapeutic applications [23]. Yao et al. designed a contact lens with current-type glucose sensor [24], in which a polydimethylsiloxane (PDMS) eye model was used to simulate the experiment. Keum et al. proposed a wireless smart contact lens for diabetes diagnosis and treatment [25]. The sensor shows good sensitivity and stability after storage for more than 63 days. The level of glucose in the tears measured by the contact lenses is exactly matched with that in blood. Although a few companies are committed to overcoming the natural obstacles of blood glucose monitoring with smart contact lenses, people are cautiously optimistic about the practical application of tear sensor in the short term [21]. Convenience and comfort are the two biggest obstacles for the contact lenses. For tear assay, wireless power supply systems are highly desired. The stimulation and potential heat caused by the sensors might be the major reason for the consumers to refuse to use them.

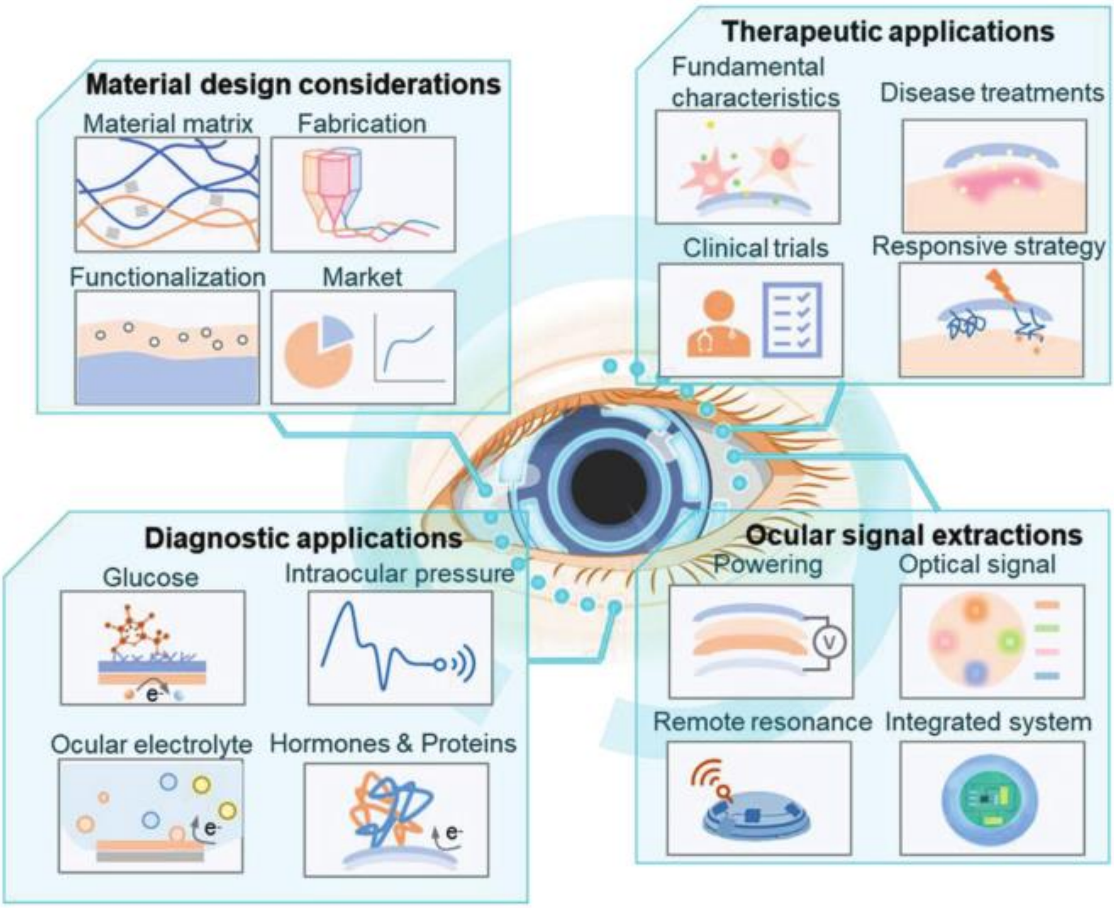

Figure 2. Lab-on-a-contact lens [23]. Copyright 2022 John Wiley and Sons.

Saliva is mainly produced from the capillaries of salivary gland. Usually, saliva contains a variety of biomarkers, including glucose, lactate, phosphate, α-amylase, hormones, antibodies and so on [26, 27]. The concentration of glucose in saliva is in the range of 0.23 ~ 0.38 mM [21]. Zhang et al. have developed a disposable sensor for continuous monitoring of glucose in saliva [28]. In contrast to the UV-Vis assay, the accuracy of the method is more satisfactory. In recent years, wearable sensors for saliva assay have made great advances in integrating mouthguard, pacifier or other platforms. For example, Garcia-Carmona et al. proposed a pacifier biosensor for monitoring of glucose in saliva (Figure 3) [29]. Saliva flows from mouth into the electrochemical chamber was facilitated by natural oral movement, and a channel was designed to ensure one-way saliva flow. A functional screen-printed electrode was inserted into the chamber for glucose detection. Wearable sensors for saliva analysis are usually suitable for specific target groups. They cannot be used to monitor glucose in patients with diabetes. In addition, the development of wearable sensors based on saliva also faces some major challenges. First, the glucose content in saliva is very low, thus requiring a highly sensitive sensor electrode. Second, considering the physiological safety, all components in the sensing system have to be biocompatible and nontoxic. Third, food or beverage residues and other redox-active compounds in saliva may seriously affect the performances of the sensor.

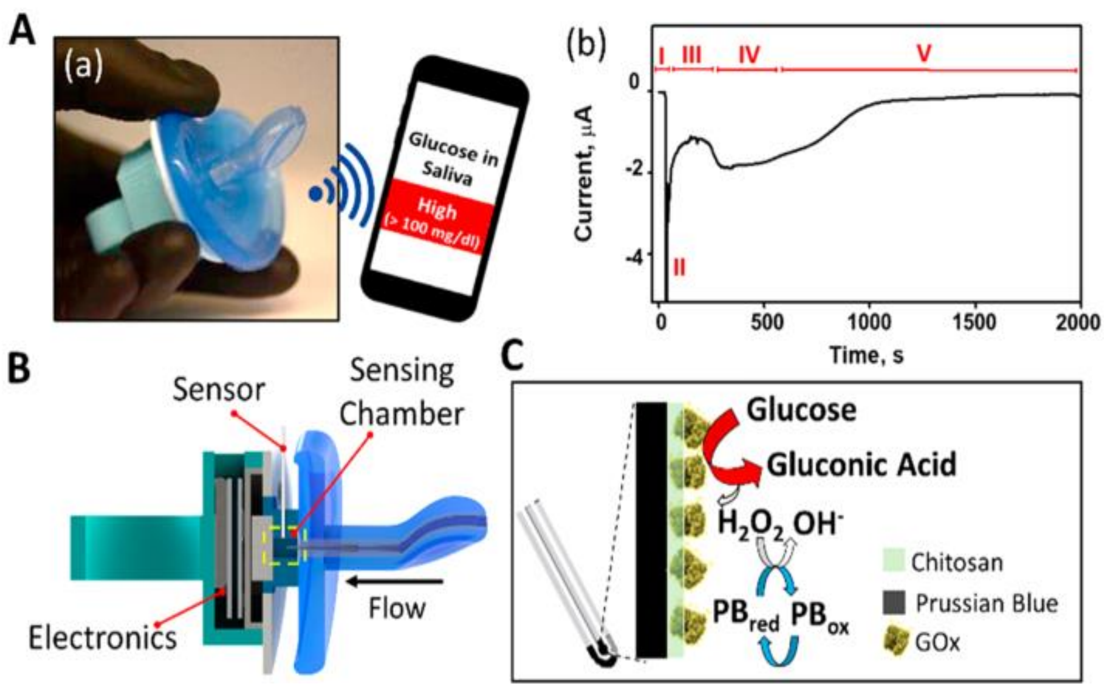

Figure 3. Glucose pacifier sensing concept. (A) Glucose pacifier working-principle. (a) Real picture and use of pacifier-biosensor. (b) On-body saliva monitoring for a healthy individual. Signal interpretation: a dry device (I), saliva reaches and starts to fill the electrochemical chamber (II), stabilization of the signal (III), glucose signal (IV), and saliva elimination from the pacifier (V). (B) Schematic of the assembled wireless pacifier-biosensor. (C) Schematic of the glucose enzymatic biosensing approach on the PB electrode [29]. Copyright 2019 American Chemical Society.

Interstitial fluid (ISF) accounts for about 75% of extracellular fluids. The substance can be exchanged between ISF and blood through diffusion from capillaries [30]. The low capillary density and slow metabolism lead to a lag time (5 ~ 15 minutes) in the concentration balance between ISF and blood

[31]. Reverse ion electrophoresis (RI) is a well-known method for extracting ISF without penetrating the skin. The Glucowatch, produced by Cygnus, is the first device to use RI technology. The Glucowatch can be worn on the wrist and extracts ISF with a current of 300 μA. Glucose is collected by a GOx-contained hydrogel dish. The device could achieve 12 h of continuous measurement of blood glucose. The accuracy is comparable to the commercial glucose meter. However, the sensing device has a few disadvantages, such as long lag time, long warm-up stage and the need for calibration through a glucose meter [31]. Some users experienced pain and irritation after using the device. Pu et al. reported a continuous strategy for glucose detection with flexible biological microfluidic technology [32]. In order to improve the extraction efficiency of ISF, the combination of thermal excitation and RI realizes the extraction of ISF at a low current. This effectively reduces skin irritation during extraction. The 3D nanostructure composed of graphene and platinum nanoparticles improves the sensitivity of the sensor. The biosensor can maintain high accuracy in dynamic and continuous glucose monitoring.

In addition to blood, glucose can be found in sweat, saliva, tears and tissue fluid. Due to the low testing cost and instant detection, wearable glucose sensors are showing increasing appeal to many normal people or patients. It is believed that it will lead to new developments in health care, exercise monitoring and disease management. With the popularity of smartphones and the extensive demand for real-time monitoring, wearable non-invasive devices will become the mainstream of real-time monitoring of glucose. Although wearable sensors have made some exciting progress, they still face with many basic challenges on material innovation, power devices and communication systems. Measurement accuracy, stability, utilization in sports and service life are urgent problems to be solved.

3. WEARABLE ELECTROCHEMICAL SENSORS FOR DRUG MONITORING

Drugs are usually divided into therapeutic drugs and recreational drugs. Therapeutic drugs are commonly used by healthcare professional to treat diseases such as levodopa and theophylline. Recreational drugs often exists in a commercial product, including alcohol, nicotine and caffeine, and so on. After entering the human body, these drugs will cause excitement. The illegal drugs used for entertainment purposes such as psychoactive effects for athletes may strongly affect the central nervous system, therefore causing serious short-term and long-term health problems [33]. Although some of the categories are evolved primarily for medical purposes, the therapeutic utilization has been eclipsed by its potential abuse. With the continued increase in drug abuse, there is an urgent need for powerful and rapid tools to improve drug treatment and regulate drug abuse. At present, drug analysis mainly relies on liquid chromatography and gas chromatography-mass spectrometry to achieve quantitative analysis of multiple samples [33]. Although these methods provide highly reliable results, there is a huge demand for fast, simple and portable tools for real-time monitoring of therapeutic or recreational drugs.

Wearable sensors can provide real-time physiological information by measuring the dynamic changes of biomarker concentration in biological body fluids [34]. Wearable electrochemical devices are particularly attractive in drug monitoring because of their unique advantages, such as high selectivity for electroactive drug molecules, inherent miniaturization, low power consumption, low cost, and high scalability with the help of screen-printing technology [7]. Teymourian et al. proposed a wearable electrochemical sensor for monitoring therapeutic and abused drugs (ketone bodies). The wearable sensor devices can be easily worn for continuous monitoring of health in a noninvasive and non-emergent manner [35]. Screen-printed carbon electrodes modified with ionic liquids and plasticized polyvinyl chloride film have been used for the detection of fentanyl [36] and narcotic drug propofol [37], respectively. Some reports have combined electrochemical sensors with the ability to recognize biological receptors for antibodies, artificial receptors or molecularly imprinted polymers to enhance the specificity of electrochemical analysis [38]. In spite of the progress, further improvements are highly desired to transfer these sensors to wearable devices.

The recent efforts have made to combine a large number of wearable devices with different electrochemical technologies to develop wearable platforms for drug monitoring. For example, de Jong et al. reported a screening strategy for on-site fingerprinting of cocaine street samples [39]. To investigate the potential of the electrochemical device in practical applications, cocaine powders were measured and the result was validated by GC-MS. Moreover, Barfidokht et al. reported a glove-based sensor for fentanyl detection which relies on direct electrocatalytic oxidation of fentanyl at a fingerprint motor [40]. To improve the electrochemical performance of the electrode, the index finger working electrode was functionalized with carbon nanotubes and ionic liquid nanocomposites. Raymundo-pereira et al. suggested that a glove-based wearable sensor enabled the detection of four analytes, including analgesics, antidepressants, hormones, and uric acid [41]. The sensing layer is made of carbon material, ensuring the detection of analytes with high sensitivity and selectivity. Glove-based sensors can realize the accurate, rapid and real-time detection of a variety of compounds, which is of great significance for the rapid analysis of chemical components in pharmaceutical and food industries.

Sweat is a non-invasive biological liquid with rich physiological information. It can be easily obtained due to the abundant presence of sweat glands throughout the body. Sweat analysis has been widely used in disease diagnosis. In recent years, wearable devices have been introduced for immediate or continuous monitoring of precise medication and drug abuse such as cocaine and nicotine [42, 43]. Typically, different types of sweat sensors are integrated with commercial sweat patches. For example, Tai et al. reported a wearable platform to monitor drug with caffeine as the model analyte (Figure 4) [44]. The signal was measured by differential pulse voltammetry. After iontophoresis and removing of hydrogel, the produced sweat was collected by a commercial collector and then analyzed by the wearable sensor. After that, they fabricated an epidermal device for monitoring of levodopa in Parkinson's disease (Figure 5) [45]. An enzyme-based electrochemical sensor was prepared by using polyethylene terephthalate as the flexible substrate with a three-electrode system. Sweat was extracted by iontophoresis and physical exercise. The real-time pharmacokinetics curve of levodopa was obtained by monitoring its oxidation by tyrosinase to produce dopaquinone. Xiao et al. designed a wearable electrochemical sensor for the non-invasive detection of levodopa [46]. ZIF-8/graphene oxide nanocomposites loaded with tyrosinase were embedded in the flexible polyimide strip for highly sensitive detection of levodopa in the micromole range. These studies indicate that there is a great potential for non-invasive monitoring of drugs in sweat using skin-wearing devices. However, the development of reliable wearable sensors for monitoring drugs in sweat still requires large-scale validation investigations, especially for precise medication and closed-loop operation.

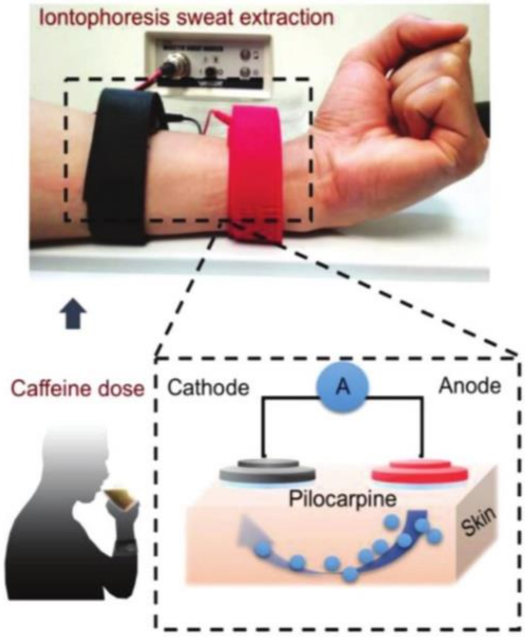

Figure 4. Caffeine monitoring through iontophoresis induced sweat. Schematic of iontophoresis-based sweat extraction [44]. Copyright 2018 John Wiley and Sons.

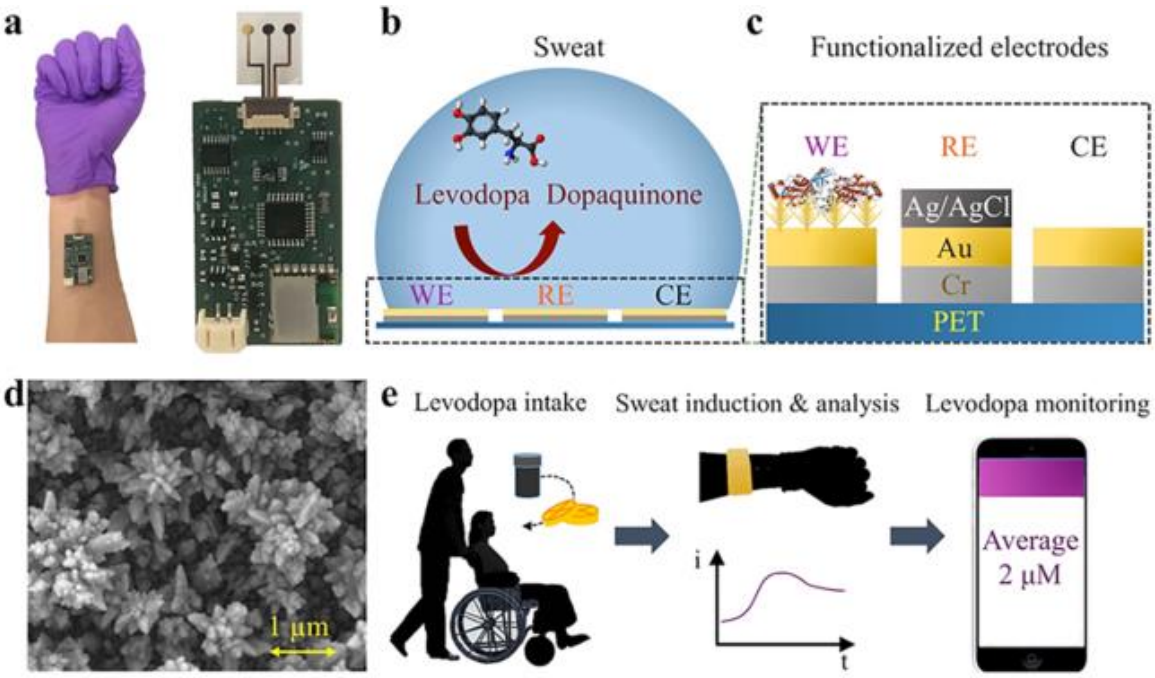

Figure 5. Schematic of the s-band and drug sensing mechanism. (a) Optical image of the s-band worn on a subject's wrist. (b) Sensing mechanism of the levodopa sensor. WE, RE, and CE are working electrode, reference electrode, and counter electrode, respectively. (c) Cross-section view of the gold electrodes 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 [45]. Copyright 2019 American Chemical Society.

Non-invasive or minimally invasive techniques have been developed to map tissue fluid (ISF), a biological fluid that is more difficult to obtain than sweat and saliva. Thanks to the advances in microfabrication, microneedles have become miniature replicas of hypodermic needles for ISF sampling, percutaneous administration, and diagnostic purposes. Electrochemical sensors based on microneedles have been reported to monitor various analytes [47]. The integration of multiple microneedle electrode arrays into tiny wearable patches has exhibited considerable promise for multiplex detection of analytes with different sensing modes to obtain more comprehensive information and improve therapeutic outcomes. For example, Mohan et al. reported the first microneedle-based drug monitoring system [48]. The selectivity of the microneedle sensor in an artificial ISF solution and the potential of this strategy for subcutaneous alcohol detection in ISF were investigated. At the same time, Sharma et al. reported a microneedle array platform for in-situ detection of glucose, lactate and theophylline [49]. In addition, Goud et al. reported a microneedle electrochemical sensor for continuous monitoring of levodopa (Figure 6) [50]. The nonenzymatic electrochemical signa was collected by square-wave voltammetry with microneedle electrode (WE1). Meanwhile, a tyrosinase (TYR)-based detection was carried out to measure the produced dopaquinone at the neighboring electrode WE2 by chronoamperometry. Recently, they designed a microneedle sensor patch for continuous monitoring of apomorphine (APO) [51]. Rhodium nanoparticles (Rh NPs)-modified carbon paste was used to fill the 3D-printed microneedles as the working electrode. APO was determined by monitoring two oxidation peaks from catechol and tertiary amine. Although the studies highlight the promise of microneedles as wearable analytical tools for drug monitoring, the long-term use of the microneedles may cause the surface contamination.

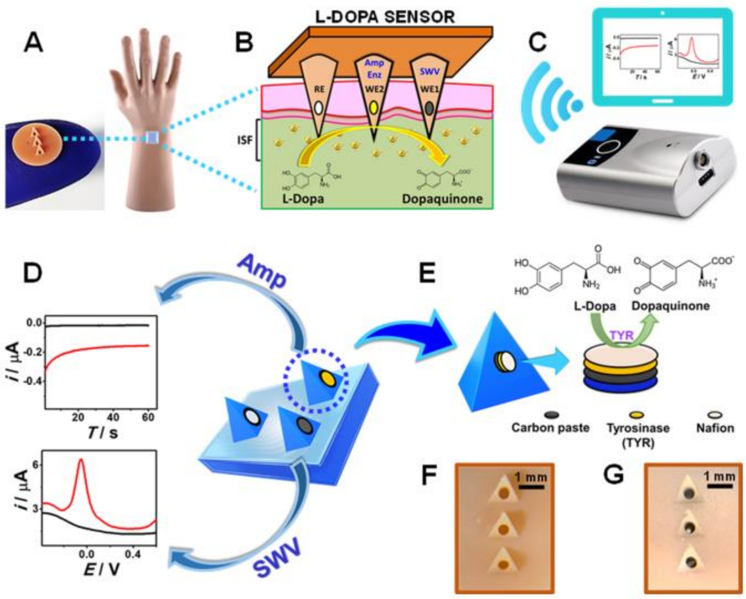

Figure 6. Microneedle sensor for L-Dopa detection; schematic representation of (A) mannequin hand wearing the microneedle sensor and (B) the microneedle sensor for L-Dopa monitoring in ISF. (C) Portable wireless electroanalyzer enabled with wireless data transmission to the smart device; (D) schematics of the microneedle sensor platform, illustrating three electrodes used for L-dopa sensing using SWV and amperometry; (E) microneedle sensor with the corresponding reagent layers, including the CP, tyrosinase, and Nafion layer. (F, G) Actual optical images of microneedles before and after packing with CP (scale bar, 1 mm) [50]. Copyright 2019 American Chemical Society.

Saliva-based sensors have been used for the detection of many analytes, including therapeutic drugs (e.g. antibiotics and psychiatry), antiepileptic drugs as well as abused drugs [52]. Although salivary diagnosis usually relies on disposable in vitro sensors, it is challenged to develop a wearable oral platform for real-time and continuous drug monitoring. It reflects the biological pollution influence, possible pollution caused by food, and potential safety [53]. In addition, it has been found that the route of drug administration greatly affects its salivary composition.

A variety of drugs have also been determined through tear analysis, including acetaminophen, lithium, methotrexate and minocycline [54]. Moreover, tear is more suitable than saliva as the matrix of antihistamines, antibiotics and antibacterial drugs for the treatment of conjunctivitis and eye diseases. The use of wearable device for ocular pharmacokinetic studies and improving the treatment of some eye-related diseases is attractive. Glasses-based sensing platforms have aroused interest in the consecutive monitoring of eye biomarkers. However, there are no examples of contact lenses for therapeutic drug monitoring.

In the case of wearable drug monitoring devices, there is an urgent need for reliable closed-loop systems to avoid insufficient drugs or toxic overdose events. However, such systems are still in the early stages of development, mainly due to the lack of reliable sensors that can continuously and accurately monitor therapeutic drugs in the body. Moreover, high stability is the key to obtaining reliable signals over long periods of time. Although the stability of the sensor is dependent upon the specific biological fluid, the drug target and the biological receptor, attention should be paid to the stability of surface biological contaminants and enzymes during long periods of operation. Another challenge is that many target drugs have low concentrations and narrow therapeutic ranges. The integration of nanomaterials to wearable sensors require can improve the sensitivity by providing specific electrocatalytic ability and increasing the sensor surface area. However, considering the possible toxicity of nanomaterials, the biocompatibility of them must be carefully examined for practical applications.

4. CONCLUSION

Wearable electrochemical sensors hold great promise for real-time, continuous and non-invasive monitoring of glucose, thus providing a comprehensive assessment of health. Recent efforts have also demonstrated the potential of the wearable devices for the detection of some therapeutic drugs and monitoring of abused drugs. Although there have been some exciting advances in wearable electrochemical sensors, the field still faces fundamental challenges related to the sensitivity, stability and selectivity. Moreover, the wearable electrochemical sensors should have good mechanical properties and maintain efficient and stable sensing performances under major deformation such as bending, tension or torsion.

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