Mini review

Wearable electrochemical sensors for monitoring of inorganic ions and pH in sweat

Kai Zhao[1,2,], Bingbing Kang[1] and Binbin Zhou[3,*]*

[1] Henan Engineering Laboratory of Intelligent Medical Internet of Things Technology, Pingdingshan University, Pingdingshan 467000, Henan, China
[2] College of Information Engineering, Pingdingshan University, Pingdingshan 467000, Henan, China
[3] College of Chemistry and Chemical Engineering, Hunan Institute of Science and Technology, Yueyang, Hunan 414006, China
[*]E-mail: zhaokai@pdsu.edu.cn (K.Z.); bbzhou1985@163.com (B.Z.)

Sweat is a metabolite of human body. Traditional sweat analysis often relies on large-scale instruments and equipment, thus limiting the timely and in-situ analysis of sweat and increasing the detection cost. Electrochemical sensors have the advantages of portable equipment, simple operation and high sensitivity. They are widely used in the fields of medical health and environmental monitoring. In recent years, the construction of wearable electrochemical sensors based on human body fluids including sweat has become a hot topic for scientific researchers. In this work, we reviewed the research progress of wearable electrochemical sensors for monitoring the change of inorganic ions and pH in sweat.

1. INTRODUCTION

With the increasing popularity of wearable devices, wearable sensors make the monitoring of human health more and more convenient [1]. Typically, the emergence of blood glucose meter has stimulated the researchers' interest in developing more versatile wearable sensors for monitoring disease indicators. Compared with traditional medical diagnosis methods, wearable sensors obviates the need of expensive investment and large medical devices [2]. They can not only monitor disease indicators in real time, but also save social resources to the greatest extent. At present, most wearable devices on the market are related to monitoring heart rate and physical exercise indicators, which cannot reflect the relevant information of human health from the molecular or ionic level [3, 4]. Therefore, it is urgent to develop more versatile wearable devices by promoting the use of chemical sensors. Electrochemical

sensors can dynamically monitor the physiological state of human body in real time. The sensors can realize the selective identification and detection of biomarkers in sweat by the use of conductive materials and selective electrodes [5]. The signal change can be monitored by the difference of current, potential or resistance [6, 7]. Thus, the electrochemical detection methods include potentiometry, chronoamperometry, voltammetry and electrochemical impedance spectroscopy. Among them, potentiometry and chronoamperometry are the most commonly used methods of electrochemical sensors due to their simple detection procedure and good selectivity.

It is easy to obtain body fluid samples such as sweat, tears, blood, saliva and urine. However, in addition to sweat, the applications of wearable devices for monitoring other body fluids have certain limitations. For example, blood monitoring is mostly embedded, which is difficult to be analyzed with non-invasive wearable sensors and not friendly to the elderly and children. The wearable sensors based on sweat monitoring can be perfectly realized in a non-invasive way. Health information could be attained by the analysis of human sweat since many substances are included in sweat, such as inorganic salt ions, organic molecules, proteins, hormones and peptides [8-10]. Through measuring the content of various substances in sweat, the dynamic monitoring of human health can be realized. Thus, it shows the great prospect of wearable sensors in sweat analysis [11, 12]. This paper summarizes the research progress of wearable electrochemical sensors for monitoring the change of inorganic ions and pH in sweat. The shortcomings and future development trends of the wearable sensors were further discussed.

2. WEARABLE ELECTROCHEMICAL SENSORS

Sweat glands are widely distributed in the human body. Sweat contains a variety of biomarkers, making sweat a feasible and ideal non-invasive biological liquid of disease diagnosis. For example, sweat contains a large number of inorganic ions and metabolic molecules. The inorganic salt ions in sweat include sodium, potassium, magnesium, ammonium and chloride [8, 13, 14]. It is of great significance to analyze the content of these inorganic ions in sweat. Particularly, sodium ion is the main positively charged species in human extracellular fluid, which can participate in water metabolism and maintain acid-base balance in the body. The loss of a large amount of sodium ions in human body will lead to hyponatremia and seriously affect physiological conditions. Moreover, the loss of chloride ion is closely related to cystic fibrosis. Therefore, the development of wearable ion-selective sensors for monitoring inorganic ions in sweat has become a research hotspot of wearable sensors in recent years.

2.1 Analysis of sodium ion

Sodium ion is an inorganic metal ion with the largest proportion in sweat. It can promote sweat secretion through the osmotic pressure of gland lumen. Its concentration in the body surface can often predict the emission rate of sweat [15-17]. It is one of the important ions in sweat health analysis. Roy et al. developed a wearable sweat sensor using carbon nanotube electrode array (Figure 1) [18]. The solid ion-selective electrode to sodium ion was prepared by coating plasticized poly(vinyl chloride) (PVC) doped with ion carrier and exchanger on the carbon nanotube electrode. In this work, the problems of sensor stability and reliability caused by the poor adhesion of ion-selective membrane conductor was

resolved. The performance of the solid-state reference electrode was improved by using porous carbon nanotube electrode. The sensitivity of the ion-selective wearable sensor to sodium ion is 56 ± 3 mV/decade, and the detection limit is 1.12×10^{-6} M. Moreover, Schazmann et al. developed a device for real-time monitoring of sodium content in athlete's sweat by integrating sweat collection and analysis on the same platform [19]. The device was composed of sodium sensor band and selective electrode. The atomic absorption spectrometry result further verified the feasibility of this method for continuous monitoring.
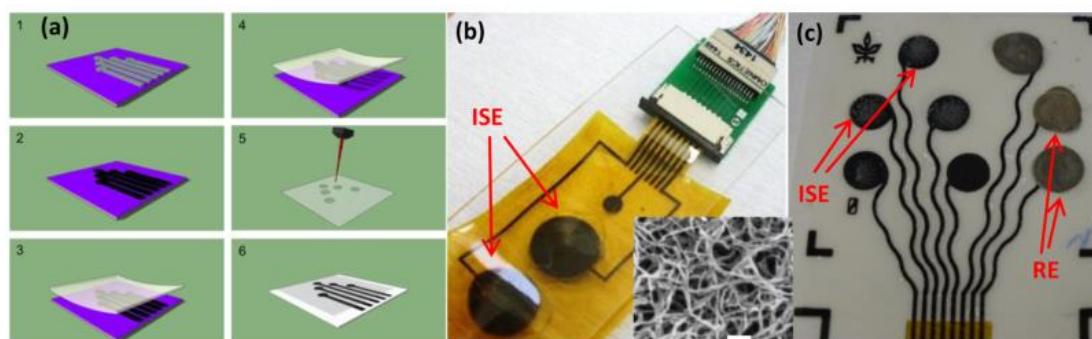

Figure 1. CNT-based flexible ISEs. (b) ISEs on polyimide (Kapton) substrate. (inset) SEM image of the surface of the CNT electrodes. Scale bar is 200 nm. (c) ISEs on temporary tattoo paper. Reprinted with permission from reference [18]. Copyright 2017 American Chemical Society.

In wearable electronic products, flexibility, strength and durability must be considered. Wang et al. reported a detection platform for sweat sodium ion using gold nanodendrite (AuND) as the all-solid ion-selective electrode and PVA/KCl membrane-coated Ag/AgCl as the reference electrode (Figure 2) [20]. The influence of the surface area of ion-selective electrode on the sensing performance was explored. It was found that the electrode with smaller surface area showed stronger stability. In addition, Rose et al. reported an adhesive radio-frequency identification sensor patch that could completely fit with human skin [21]. This patch device provides convenience for sweat collection and ion monitoring. By combining the solid contact ion-selective electrode and liquid-junction-free reference electrode on a double screen printed substrate, Matzeu et al. prepared a wearable sensor for real-time monitoring of sodium ion in sweat [22]. Wang's team prepared a temporary skin transfer tattoo potential sensor with screen-printing technology for the first time [23]. The insulation layer was firstly printed on the tattoo paper by screen-printing, then two electrodes and contact points were printed, and finally the sensor and wireless transceiver were coupled together. As a feasible device for monitoring the content of sodium ion in sweat, tattoo sensor system has considerable application prospects, and opens up a new way in the field of wearable wireless non-invasive sensor and body sensing network.

In the past, wearable sweat sensors are usually used for active sweating people, such as athletes and workers. Such wearable sensors are not convenient for scientific research to obtain a large amount of data. Therefore, it is a feasible method to stimulate the human body to produce sweat by other ways. Sonner and co-workers used nicotine agonists to produce sweating reaction through iontophoresis into the skin [24]. This sweat stimulation technology exploited the use of an underutilized pharmacological phenomenon named as sudomotor axon reflex sweating, overcame the previous limitations on

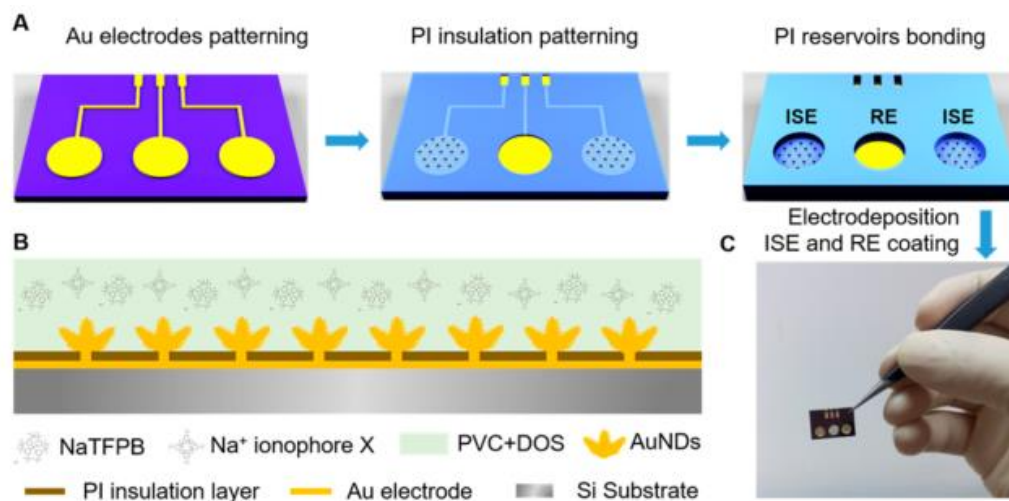continuous sweat stimulation, and made the wearable sweat sensor more widely applicable to the population.

Figure 2. Schematic of chip fabrication process and AuND solid-contact-based all-solid-state Na$^+$ sensor chip. (A) Photolithography (Pl)-based chip fabrication process. (B) Schematic profile of AuND-based all-solid-state ISE. (C) Optical image of Na$^+$ sensor chip. Reprinted with permission from reference [20]. Copyright 2017 American Chemical Society.

2.2 Analysis of chloride ion

Cystic fibrosis is a genetic exocrine gland disease. It mainly affects gastrointestinal tract and respiratory system. The disease is usually characterized by chronic obstructive pulmonary disease, poor exocrine function of pancreas and abnormal increase of sweat electrolyte [25, 26]. Wearable sensors have been used to monitor chloride ion in sweat for the diagnosis of cystic fibrosis. Usually, the concentration of chloride ion in sweat of cystic fibrosis patients is 60 – 150 mM, which is much higher than that of healthy control (10 – 40 mM). Therefore, monitoring of chloride ion in sweat is the most commonly used method for the diagnosis of cystic fibrosis. In 2017, Searson and co-workers reported a wearable chlorine sensor which innovatively integrated the salt bridge into the thin film [27]. The technique solved the test error caused by the balance between the reference and test solutions. The analytical model was used to evaluate the balance rate between the two solutions. Thus, the measurement error was predicted as a function of the geometry of the salt bridge. The sensor could be easily and comfortably worn on the body and had a good response for chloride ion in the range of 10 – 150 mM. They also proved that the geometry of the salt bridge is the key to minimize the balance between the two solutions (Figure 3) [28], so as to minimize the measurement error. The steady-state flux of chloride ion from the reference chamber to the test chamber could be minimized through appropriate geometric design of the salt bridge. In the salt bridge length and diameter variable sensor, the equilibrium of salt bridge followed the prediction via ion transport. Based on the study, a relatively simple and low cost wearable equipment for monitoring chloride in sweat was designed and manufactured by using polydimethylsiloxane shell, reference solution gel and two silver chloride electrodes. In addition, Searson's group also used pilocarpine iontophoresis to induce perspiration in patients with cystic fibrosis

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[29]. The chlorine content determined with wearable sensor was compared with that monitored by standard medical means. The difference between the two methods is 6.2 ± 9.5 mEq/L and the Pearson correlation coefficient is 0.97, indicating that the result of wearable sensor is in good agreement with that of the standard method.
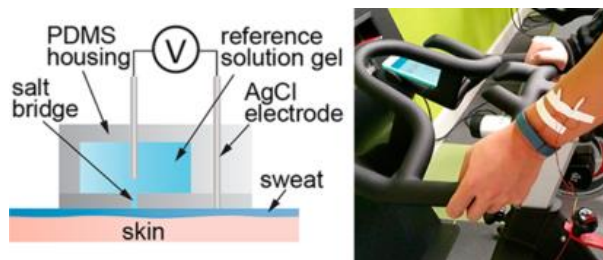

Figure 3. Schematic illustration of the sensor with an optimized salt bridge (left). Sensor worn by subject during exercise (right). Reprinted with permission from reference [28]. Copyright 2017 American Chemical Society.

2.3 Analysis of pH

pH value is a key index for disease diagnosis. The occurrence and progress of some diseases may be accompanied by abnormal change of pH in sweat [30]. For example, the pH value of patient with type 2 diabetes mellitus is lower than that of normal control. In addition, the change of pH value in sweat may lead to skin diseases such as atopic dermatitis, ichthyosis and fungal infection [31, 32]. Rahimi et al. reported a scalable electrochemical pH sensor, which is composed of a pH-sensitive working electrode and a liquid-junction-free reference electrode [33]. This stretchable conductive interconnection structure was formed by laser carbonization and micromachining of polyimide sheets bonded to the elastic ecoflex substrate. This work, for the first time, demonstrated that direct laser carbonization technology can be used to manufacture high-performance stretchable electrochemical sensors, especially stretchable pH sensors for wearable care point applications. In this study, the response of the sensor to pH value of sweat was detected by electrochemical method. It was found that the sensor had high sensitivity and stability. The electrical signal had a linear relationship with pH value in the range of pH 4 ~ 10, and the sensitivity was found to be −53mV/pH, which can be used for the sensitive detection of pH value of sweat. Moreover, Takei's group developed a wearable flexible sweat sensor to monitor the change of pH value (Figure 4) [34]. The device was composed of ion sensitive field effect transistor and temperature sensor. The real-time measurement of pH value and skin temperature was realized through skin contact. The work provided an idea for the subsequent development of sensors for the detection of multiple markers. In addition, Dahiya et al. prepared a retractable pH sensor with graphite polyurethane composite [35]. After in-depth electrochemical test, the sensitivity of the pH sensor patch is 11.13 ± 5.8 mV/pH. The interference from other ions and analytes (e.g. sodium, potassium and glucose) on the performance of the sensor was negligible.

The ideal wearable devices require a suitable geometry and an ability to withstand repeated mechanical stress. Only in this way can the interference to the wearer's daily life be minimized. For this view, Wang et al. prepared a tattoo-based solid-contact ion-selective electrode [36]. The polyaniline-

modified working electrode and reference electrode were prepared by screen-printing technology. The tattoo sensor can withstand the mechanical stress during movement, providing an objective prospect for wearable potential sensors for various applications. Madrid's group introduced a potential textile pH sensor composed of conductive textile materials and electrodeposited iridium oxide film [37]. The sensitivity to pH and the effect of temperature on the three used conductive fabrics (argenmesh, ristop silver and stainless steel mesh) were examined. The result indicated that stainless steel mesh had the best response with an error of 4%, which is comparable to that of the commercial pH test strip. Cheng et al. developed a stretchable electrochemical pH sensor through elastomer-bonded gold nanowire-coating technology [38]. The dry-spun elastic gold fiber coated with polyaniline was used as the working electrode and the gold fiber plated with Ag/AgCl was used as the reference electrode. The stretchable gold fiber with large specific surface area and excellent conductivity can be well stitched with textiles. It is a good choice to use textile as the electrode material of sensors, bringing new ideas to the development of wearable devices.
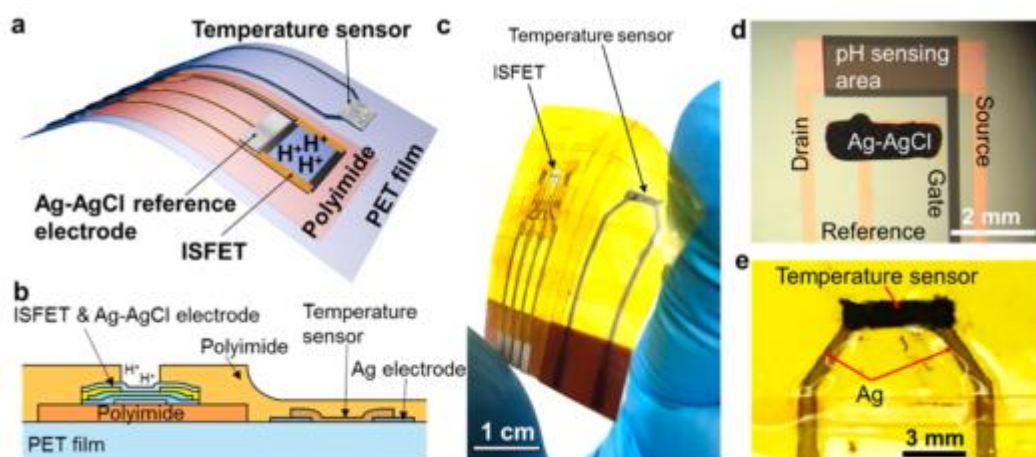

Figure 4. (a) Schematic of a wearable device integrating flexible pH and temperature sensors, (b) cross-sectional diagram of the device, and (c) photograph of the fabricated device. (d) Optical micrograph of the ISFET component prior to covering with polyimide, and (e) magnified picture showing the temperature sensor. Reprinted with permission from reference [34]. Copyright 2017 American Chemical Society.

2.4 Analysis of other metal ions

At present, most of wearable sensors used for monitoring of inorganic ions in sweat are sodium and chloride. Herein, we also introduced the relevant works for the detection of other inorganic ions in sweat. For example, Wang's group reported a wearable potentiometric tattoo sensor for monitoring the content of ammonium ion in sweat [39]. A screen-printed temporary transfer tattoo paper was prepared by using ammonia-selective polymer film and solid-state reference electrode. Polyvinyl butyral (PVB) was applied to the wearable device as a solid-state reference film for the first time. The combination of screen-printing technology and temporary transfer tattoo facilitated the sensitive detection of ammonium ion in sweat. The linear range of the sensor is $10^{-4} \sim 0.1$ M, which is comparable to the traditional potential electrode. In addition, Wang's group developed a tattoo sensor for real-time monitoring of zinc

ion in sweat [40]. The sensor made of bismuth/Nafion film electrode on temporary tattoo paper could withstand the repeated mechanical stress fatigue and showed a stable response for zinc ion in human sweat.

Crespo et al. proposed a wearable solid-state microneedle patch technology for monitoring potassium ion in interstitial fluid [41]. Potassium ion-selective electrode and reference electrode were prepared with solid microneedles by using different coatings and polymeric membranes. The microneedle electrodes were fixed to flexible and retractable polydimethylsiloxane substrates to prepare wearable devices. In vitro experiments with chicken and pig skin showed that the sensor can quantify the real-time change of potassium ion in skin. This work will contribute to the development of the next generation of wearable devices. However, further works are required to study various parameters, such as the adhesion strength of the membrane on the microneedle and the quantification of the insertion force in the human skin. Polsky and co-workers prepared a potassium ion-selective transdermal microneedle sensor by integrating hollow microneedle and microfluidic chip to extract the fluid through the channel toward the downstream solid-state ion-selective electrode [42]. The electrochemical performance, stability and selectivity of three-dimensional porous carbon and graphene electrodes were compared. As a result, the porous carbon electrode showed better performance and higher stability and could realize the selective measurement of potassium ion in the presence of interfering ions.
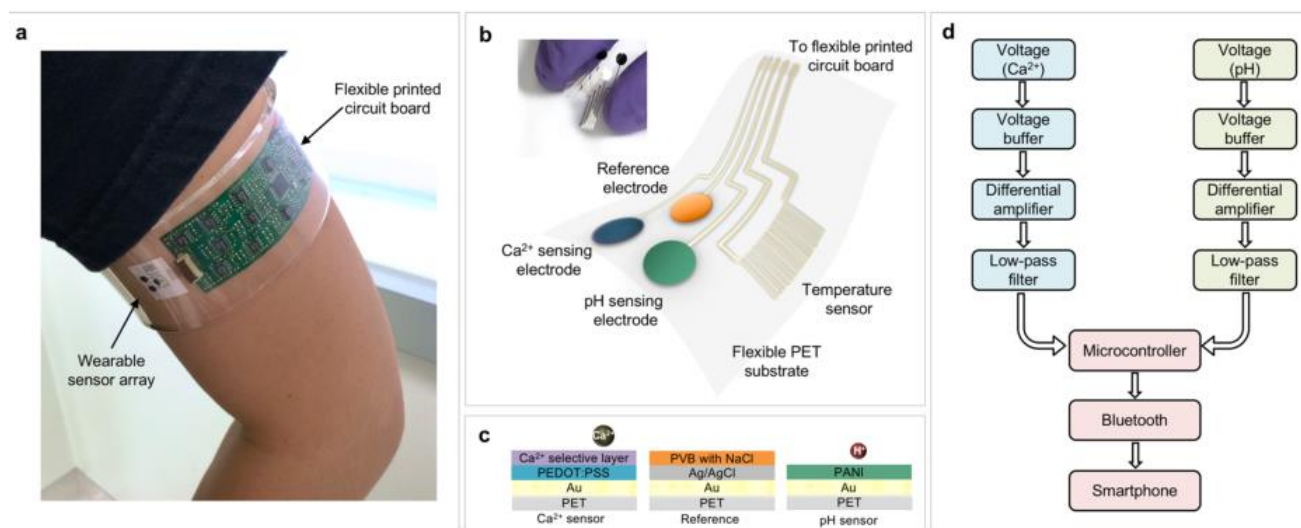

Figure 5. (a) A fully integrated wearable multiplexed sensing system on a subject's arm. (b) A schematic of a flexible sensor array containing Ca^{2+}, pH, and temperature sensors patterned on a flexible PET substrate. The inset shows a photograph of a flexible sensor array. (c) Surface membrane compositions of a Ca^{2+}, a reference, and a pH sensing electrodes. (d) A schematic of a FPCB system for signal conditioning of Ca^{2+} and pH sensors (blue and green respectively), data analysis via microcontroller (red), and data transmission to a mobile phone wirelessly via Bluetooth (red). Reprinted with permission from reference [43]. Copyright 2016 American Chemical Society.

Because of the critical relationship between different ion species in body fluids, it is necessary to simultaneously and selectively monitor detailed profiles of those species by a reliable wearable sensing platform. It has been reported that metabolic reactions and biological transport systems are

greatly dependent upon pH balance in body fluids. Concentrations of free metal ions are closely associated with pH values. Therefore, considerable attention has been focused on the accurate analysis of metal ions and pH value. Nyein et al. constructed a wearable electrochemical device for real-time determination of calcium ion and pH in body fluids [43]. As presented in Figure 5a and 5b, the platform was fabricated on the flexible polyethylene terephthalate substrate, which included a calcium ion sensor, a pH sensor, and a skin temperature sensor. The membrane composition of these sensors were shown in Figure 5c. Through real-time evaluation of sweat composition, it was found that the content of calcium ion increased with the decrease of pH, and the sensor was applied to real-time analysis of urine and tear.
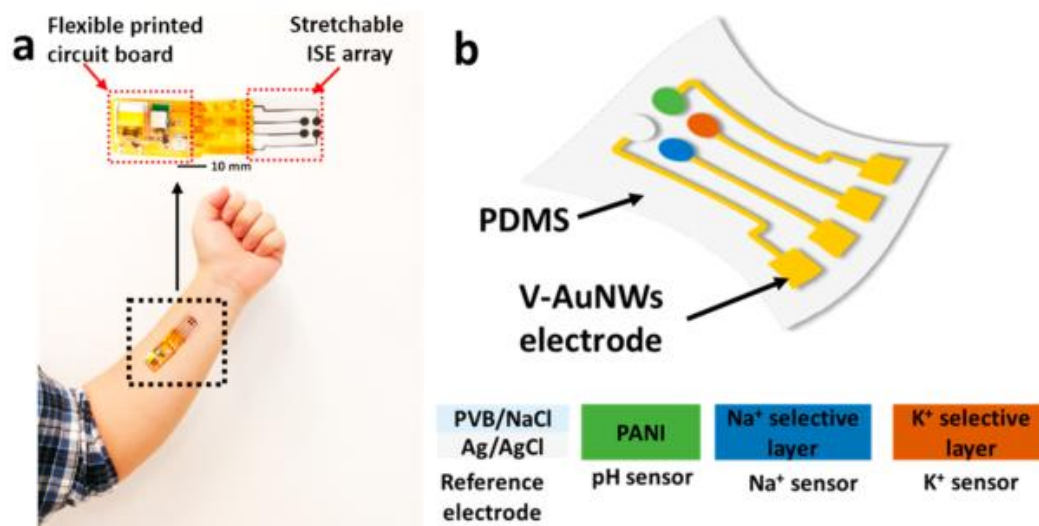

Figure 6. (a) An integrated wearable multiplexed sweat analysis device on a subject's wrist (inset: a photographic image of the integrated wearable device, including flexible PCB and stretchable ISE electrodes). (b) A schematic of a stretchable ISE electrodes based on v-AuNWs containing a Ag/AgCl reference electrode and pH, Na+, and K+ working electrodes. Reprinted with permission from reference [44]. Copyright 2020 American Chemical Society.

It is a big challenge for wearable analysis platform to accurately screen a variety of markers at the same time. Gao et al. proposed a fully integrated system based on flexible sensor array for real-time monitoring of multiple analytes in sweat. The wearable device worn by the tested person integrated a variety of marker-selective sensors, which can realize long-term real-time monitoring of metabolites, electrolytes and body surface temperature in sweat during exercise [45]. After that, Cheng's team reported an epidermal tattoo sensing strategy that can simultaneously monitor the pH and the content of sodium and potassium ions in sweat (Figure 6) [44]. They found that vertically aligned mushroom-like gold nanowires (v-AuNWs) could be used as the flexible electrode materials. The nanogold electrodes were modified by polyaniline, sodium ionophore X and a valinomycin-based selective membrane to achieve specific detection of pH, sodium and potassium. The sensitivity was 56.1 mV/pH for pH, 58.2 mV/decade for sodium ion, and 41.5 mV/decade for potassium ion. Mohan and co-workers proposed a wearable microfluidic sensor strategy for multi-channel sweat analysis, which integrated pH sensor, sodium ion sensor, potassium ion sensor and lactic acid sensor on the micro circuit board to monitor a

variety of markers in real time (Figure 7) [46]. The whole electrode array was printed on a flexible polyimide sheet, including four working electrodes and a Ag/AgCl reference electrode.
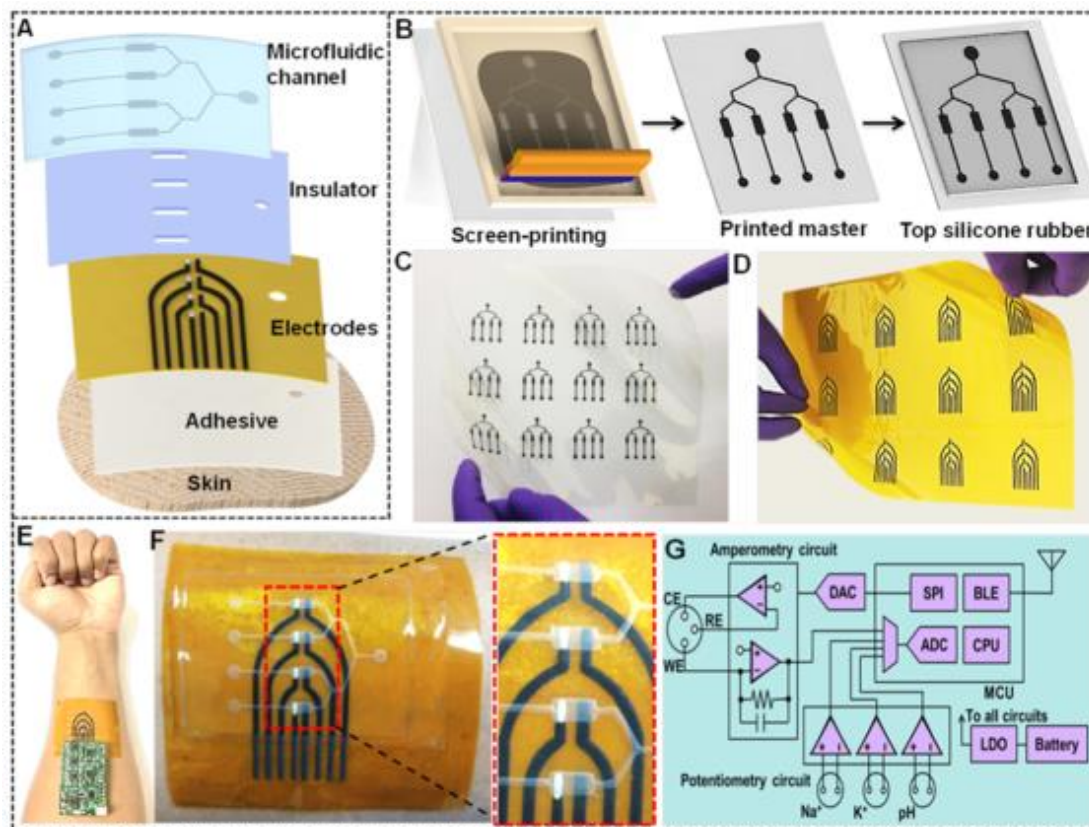

Figure 7. Overview of fully printed microfluidic device. (A) Schematic representation of different layers of the microfluidic patch. (B) Schematic illustration of the fabrication of silicone rubber-based microfluidic channels from the screen-printed carbon master. The optical images showing an array of printed (C) carbon master and (D) multiarray electrodes. Images showing (E) the skin-interfaced, fully integrated microfluidic sensor and (F) the close-up part of multiarray electrode having four sensing chambers. (G) Scheme representing the layout of miniature PCB capable of multiplexed analysis and wireless data transmission. Reprinted with permission from reference [46]. Copyright 2021 American Chemical Society.

Many wearable devices are fabricated based on textiles and screen-printing technology. Textiles can allow for the conformal contact between sensor and human body without losing the analysis ability under extreme mechanical stress. For example, by printing serpentine ion-selective electrode on textiles with screen-printing technology, including underwear, watch bands and elastic bands, Parrilla et al. reported the real-time monitoring of sodium and potassium ions [47]. Yoon et al. prepared a wearable sensor for simultaneous monitoring of sodium and potassium ions by integrating conductive fiber lines and self-healing bio-based polymer materials into textile sensors [48]. Although the strategy of making the sensing part into thin film has high sensitivity, it is easy to fracture and cannot adapt to high-strength mechanical stress. In order to solve this problem, the active material was covered on the carbon nanotube fiber as the sensing fiber weaved into the textile variety [49]. The prepared wearable fabric was successfully used to real-time monitor glucose, sodium ion, potassium ion, calcium ion and pH.

For wearable sweat sensors, the errors caused by sweat evaporation and secondary pollution should be avoided in the sampling process. Microfluidic technology can realize continuous analysis via sweat sampling in a controlled channel. To decrease the measurement errors, Nyein et al. integrated an electrochemical sensor and an electrical impedance-based sweat rate sensor in the microfluidic channel for effective sweat secretion analysis [50]. The integrated electrochemical sensor can detect a variety of sweat analytes including sodium ion, potassium ion, chloride ion and pH value. Moreover, Alizadeh et al. prepared a wearable sweat electrolyte analysis sensor by integrating sodium and potassium ion-selective electrodes with microfluidic components [51]. Semponatto et al. reported a flexible microfluidic potential sensor for the detection of sodium and potassium ions in sweat. The microfluidic network designed with four microchannel inlets was adopted to ensure that the generated sweat could flow effectively to a single detection channel and then be sampled repeatedly, thus improving the efficiency [52].

4. CONCLUSION

Wearable sweat sensors have broad application prospects in the fields of telemedicine, athlete training and so on. However, there are still some problems to be solved, such as the composition of sweat varies from person to person. Therefore, it is necessary to establish a unique personalized sweat data analysis system for individuals. The technologies related to the design of sweat sensors (e.g. novel material, high-performance ion-selective electrode, and array-integrated platform) should be further developed, so as to improve the sensitivity, selectivity and stability of wearable devices.

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