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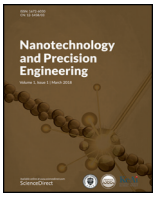

Sweat detection theory and fluid driven methods: A review

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ABSTRACT

In recent years, analyses of sweat have become more popular since it doesn't require invasive sampling procedures. Although blood still remains the golden standards in clinical, analyses of other common body fluids, such as sweat, have become increasingly important. Because the compositions of sweat and blood are osmotically related, the content of certain metabolites in sweat can directly reflect the disease. Sweat detection can be used as an alternative to blood detection and allows continuous monitoring. Increased development of wearable sensors makes it possible for continuous sweat detection. Here, this paper gave a review about the sweat detection methods, such as fluorescence sensing, electrochemical sensing and colorimetric sensing. The advantages and disadvantages of each method and their developing trend in sweat detection were summarized. Then, for the problem of continuous sweat sampling, three methods (capillary force, hydrogel osmotic pump, evaporation-driven micropump) were introduced through different structures of microfluidic chip, and the level of sweat collection and transport achieved by related research was demonstrated. This review aims to provide guidance for future research in sweat detection and stimulate further interest in continuous monitoring of sweat using microfluidic chip.

1. Introduction

Sweating is a physiological function for the body to detoxify and regulate body temperature. Sweat is a fluid secreted by sweat glands and the sweating area is widely distributed through the whole body skin. Normal people evaporate about 500 to 700 mL of water per day. If exercise strenuously, the sweating rate can be as high as 2–4 L/h.[1] Therefore, sweat is a common and easily accessible biological fluid.

Human sweat is rich in chemicals and can reflect the physiological state of the human body. Generally speaking, sweat contains metabolites (lactate,[2] glucose,[3] etc.), electrolytes, trace elements, and small macromolecular components. These biomarkers can be used for non-invasive detection of physiological health status as well as disease diagnosis and treatment. In the process of health examination, blood drawing is often unavoidable, and many people are unwilling to go for blood drawing because of the pain of needle sticking. In addition, blood tests are unlikely to provide continuous information. The correlations of chemical molecular levels in blood and sweat have been reported, such as glucose,[4] lactate,[5] ethanol,[6] ammonia and urea.[7] To some extent, sweat analysis can replace blood analysis. However, the chemical composition of sweat samples is complex, and the collected amount is usually small. How to distinguish the components of sweat and improve the sensitivity of sweat detection is very important. The use of wearable sweat sensors provides an attractive method of dynamic health assessment.[8]

The wearable sweat sensors are in direct contact with the skin, which can simultaneously collect and detect sweat. The wearable sweat sensors are not only small and convenient, but also can detect multiple biomarkers at the same time. The University of California, Berkeley research team has made progress in developing a fully integrated non-invasive patch of wearable sensor array. The multi-sensor array on the patch performs detection of four biomarkers and skin temperature simultaneously.[9] Another sensor patch could even simultaneously detect six biomarkers.[10] Due to sweat pollution, these patch-type in situ detection can't achieve high accuracy in long-term sweat detection. The microfluidic chip could be used to solve the problem of continuous sweat detection. However, only a few sensors are truly wearable by using a microfluidic chip to capture and sample sweat. Sweat detection in wearable electronics remains many difficulties and challenges. There is a long way to develop high-selectivity, high-sensitivity and low-cost detection materials. At present, the research work on sweat collection, transportation and real-time detection at home and abroad is still in its infancy, and the key technologies are still immature, which can't meet the demand for efficient sweat transport and continuous sweat detection. In addition, microfluidic chips and electrodes require stretchability, and the development of self-powered wearable sensors is urgently needed.

This paper gave a review about the sweat detection methods, such as biosensors, fluorescence sensing, electrochemical sensing and colorimetric sensing. Moreover, the advantages, disadvantages and their

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developing trend in sweat detection were summarized. In terms of biosensors, select excellent biometric materials to achieve specific detection of sweat components; reasonably design sensors, so as to achieve effective sensing and sufficient reactant contact to improve detection sensitivity. On the other hand, the use of a microfluidic chip is also crucial for improving the sensitivity of sweat detection. Microfluidic chip can transport the sweat in time after the detection and reduce pollution. For the detection of multiple analytes, several independent chambers can be set up to avoid cross-reactivity. Then, this review focused on the design of sweat analysis microchips. For continuous sweat sampling, three methods (capillary force, hydrogel osmotic pump, evaporation-driven micropump) were introduced and lots of the microfluid driven devices for sweat detection have been described. In addition, this paper appropriately reviewed some of the challenges faced by wearable sweat sensors and their future development prospects.

2. Sweat sensing principles

2.1. Biosensors

Biosensors are designed for the detection of biological components in sweat. A biosensor is essentially a chemical sensor, except that its identification system uses biological components (e.g. enzyme, ionophores).[11] Fig. 1 displays a schematic of the different components in a biosensor. The target analyte in sweat interacts with a specific biological receptor, and then the biotransducer converts the biological signal into a processable electrical signal or optical signal, and finally the electronic device further processes the signal (e.g. amplification and filtering) and outputs it.[12]

The principles for sweat sensing can be roughly divided into two types, electrochemical sensing and optical sensing. Optical sensing includes colorimetry, fluorescence and luminescence, etc.[13] Here we introduce three kinds of common sweat sensing methods, fluorescent sensing, electrochemical sensing, and colorimetric sensing. Table 1 lists these sensing principles and the analytes that can be detected in sweat by these methods.

2.2. Fluorescence sensing

Fluorescence method is an optical sensing technology. This method relies on the relationship between analyte concentration and fluorescence intensity. When the fluorescent material is exposed to specific excitation light, it generates fluorescence. When the fluorescent material undergoes a specific reaction with the target analyte, the fluorescent signal will change. The advantages of fluorescence sensing include high sensitivity, strong selectivity and ease of use.[14] Fluorescence sensing has been reported to detect metabolites (such as lactate and urea)[15] and electrolytes (such as Cl^-, Na^+, Cu^{2+}) in sweat.

In the sweat detection, the fluorescence method is often used to measure Cl^- whose content is the gold standard for diagnosing cystic fibrosis (CF). The Cl^- concentration in the patient's sweat can be abnormally high (> 60 mmol/L).[16] Zhang et al.[17] reported a smartphone operated chloridometer for the first time. Fig. 2 shows a schematic of the system. The fluorescent reagent in the processed sweat sample is irradiated by ultraviolet light. Then the fluorescent signal is captured by the mobile phone camera. Their team proposed and synthesized the fluorescent sensing material CA cysteine, which has the advantages of low cost, high Cl^- selectivity, and wide linear range.[18] The detection limit of the system for Cl^- is 0.8 mmol/L, and the linear range is 0.8–200 mmol/L. The device can be used as a reliable method to diagnose CF, but the sweat needs to be collected from the patient through iontophoresis and pretreated before test (add sulfuric acid and CA cysteine). So the device is not suitable for wearable sweat detection.

The sweat detection method of Zhang et al.[17] needs to collect and transfer sweat to the sample pool to realize the detection of Cl^-. Vallejos et al.[19] presented a new film-shaped sensory polymer which can detect Cl^- in sweat directly on the body skin without pretreatment of sweat samples. The device uses a smartphone to take a photo of the patch on the patient's skin to obtain fluorescent information. They used pendant 6-methoxyquinoline as fluorescent material which has a high water swelling rate and can quickly detect Cl^-. Detection range is 0–100 mmol/L, and response time is less than 40 s. Other methods for the detection of Cl^- take minutes or even 1 h. In addition, the material is inexpensive, simple to prepare, and can be reused many times, providing hope for the development of simple point-of-care testing (POCT) equipment.

In order to achieve a highly sensitive detection, Xu et al.[20] used two fluorescent materials (Ag^+/Eu^{3+} @ UiO-67 and DUT-101) to manufacture a ratiometric fluorescent sensor (Fig. 3). The sensor is integrated on a patch, which can be easily adhered to multiple positions on the human skin. Sweat is generated by physical exercise without any stimulation of the skin. The two fluorescent materials belong to lanthanide metal–organic frameworks (MOFs) and have excellent fluorescent properties for Cl^-. Coupled with the ratiometric design, one material is used as the working fluorescence center and the other is used as the reference fluorescence center, which will greatly improve the detection sensitivity. The fluorescence response shows a high sensitivity (limit of detection = 0.1 mmol/L), wide linear range (0–200 mmol/L) and selectivity in a short time (35 s). This band-aid design supplies a way to develop more fluorescent methods in wearable medical devices. In addition, the researchers have developed a set of codec devices for smartphones that can provide health information by monitoring changes in Cl^- levels.

Table 1
Sensing principles and the corresponding analytes of sweat.

Sensing principle	Suitable analytes	Reference
Fluorescent technology	Cl^-, Na^+, Cu^{2+}, Hg^+	21–23
Electrochemical method	Glucose, lactate, Na^+, K^+, pH, Cl^-	9,28,31,34,35
Colorimetric method	Glucose, lactate, pH, Cl^-	38,49

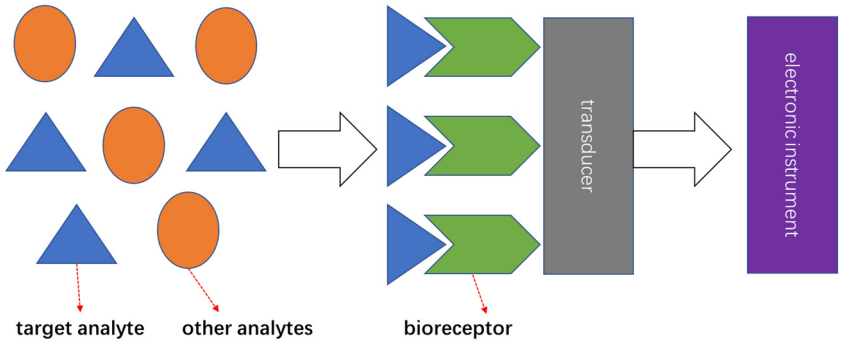

Fig. 1. Schematic of the main components in a biosensor.

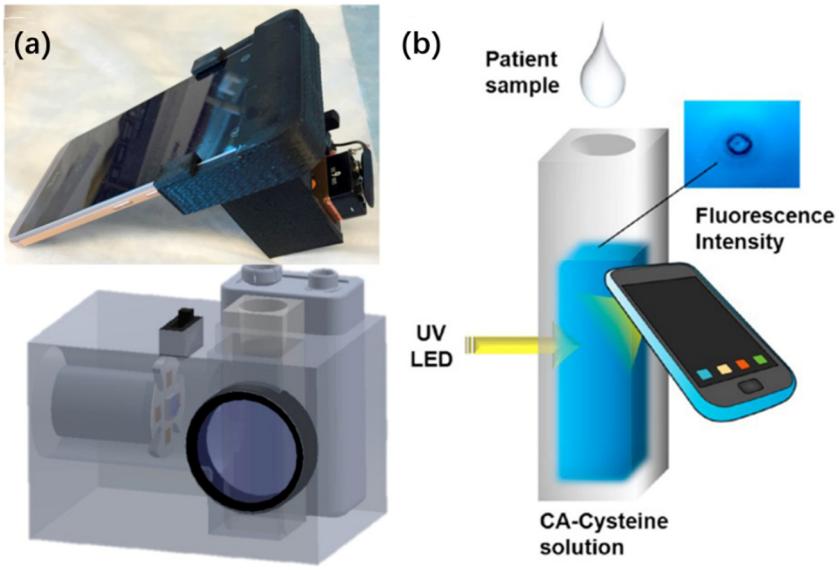

Fig. 2. (a-b). Photo and schematic diagram of the chloridometer system.
Reproduced from [Zhang et al.[17]].

In addition to detecting Cl^-, fluorescence sensors can also be used to monitor metabolites (lactate, urea, etc.)[15] and other electrolytes (Na^+,[21] Cu^{2+},[22] Hg^+,[23] etc.) in sweat. However, compared to electrochemical sensors, the sensitivity of fluorescence sensors is low in the detection of these substances. Furthermore, it is also necessary to select appropriate fluorescent materials. At present, a variety of fluorescent materials for the detection of Cl^- have been developed, while there are few fluorescent materials for detecting other analytes. The trend of miniaturization of analysis equipment has prompted researchers to integrate the optical sensing elements and detection elements into one chip. Instead of using large circuit boards, fluorescent sensing devices don't require complex designs and can more easily evolve toward wearables.

In summary, for fluorescence sensing, the development of new fluorescent materials with low synthesis cost and high selectivity is the key. On the other hand, efforts should be made to reduce the measurement error of the fluorescence method. For example, the fluctuation of the excitation light source can be reduced by using a photodiode. The use of a miniaturized spectrometer can better resolve the fluorescence spectrum.[24] The miniaturized spectrometer has a highly sensitive detector and a high efficiency filter, which can distinguish the weak signal light excited by the sample from the high intensity excitation light. Further, in sensor design, ratiometric measurement can be used. Compared to a single emission, the ratiometric measurement can amplify the fluorescent signal and reduce signal changes caused by concentration

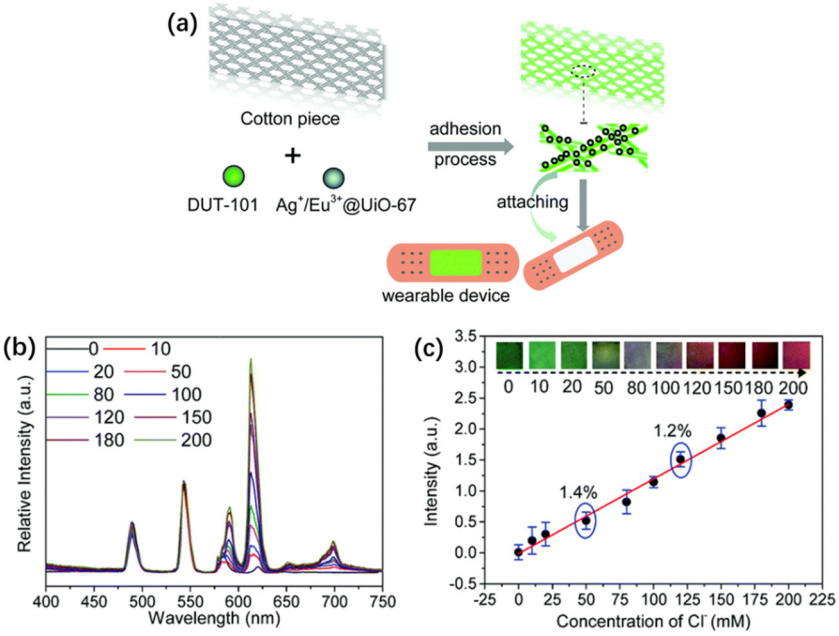

Fig. 3. (a) Manufacturing process of wearable sweat monitoring device. (b) Relationship between emission spectrum and Cl^- concentration (0–200 mmol/L). (c) The linear relationship between fluorescence intensity and Cl^- concentration.
Reprinted from [Xu et al.[20]].

fluctuations or heterogeneity by correlating the working fluorescence with the reference fluorescence signal.[25]

2.3. Electrochemical sensing

Electrochemical sensing is to fix bio-sensitive substances (such as antigen, antibody, enzyme, hormone, et al.) on the electrode, and then conduct specific reaction with target molecules and generate electrical signals to achieve the qualitative or quantitative detection of target analytes.[26] Electrochemical sensing is a common and mature sweat analysis method, which is widely used in wearable sensors.

Electrochemical biosensors can be used to detect a variety of chemical substances, while the most widely used is electrochemical glucose sensors. Diabetes is a group of metabolic diseases characterized by high blood sugar. There is currently no cure for diabetes, but diabetes can be controlled through a variety of treatments. Among them, insulin treatment is usually the most effective way. If the patient can adjust the dosage of the drug at any time according to the blood glucose level, self-monitoring of blood glucose can be achieved. However, it is difficult to monitor glucose in blood continuously. Sweat-based glucose measurement is a potential solution. The normal glucose concentration in human sweat is 50–120 μmol/L,[3] and the normal glucose concentration in blood is 4.9–6.9 mmol/L.[27] In order to improve the electrochemical performance (such as sensitivity, stability, response time) and realize the detection of low-concentration substances, the electrode surface needs to be chemically modified (such as gold nanoparticles, graphene,[28] carbon nanotubes[29] and metal oxides[30]).

Recently, Xuan et al.[28] successfully developed a flexible electrochemical glucose biosensor (Fig. 4). The sensor is integrated on a patch and can be easily attached to the wrist. In order to fabricate electrodes with high sensitivity and selectivity, MEMS manufacturing technology was first used to deposit reduced graphene oxide (rGO) onto the Ag/AgCl electrode surface. Then gold and platinum alloy nanoparticles were electrochemically deposited on the surface of rGO, and finally a specific glucose oxidase was integrated on the electrode surface. The electrochemical response shows high sensitivity (48 μA/(mmol·L^{-1})), wide linear range (0–2.4 mmol/L) and selectivity in short time (20 s). By testing human sweat samples, the sensor has a good detection ability for low concentrations of glucose in human sweat. In electrochemical sensors, the manufacture and surface modification of electrodes is very complex. Pu et al.[31] proposed an inkjet printing technology, which makes the production of electrodes easier. Through inkjet printing, gold nanoparticles, graphene, and platinum nanoparticles were deposited on the surface of the working electrode.[32]

Due to the high sensitivity of electrochemical sensing, in addition to glucose, it can detect a variety of metabolites, such as lactate, ethanol,[33] ascorbic acid, uric acid,[10] et al. Ion-selective electrodes (ISE) are also electrochemical sensors in nature and can be used to detect pH,[34] Na^+, K^+, Cl^-,[35] etc. Gao et al.[9] proposed a mechanically flexible and fully integrated sensor array (FISA) for multiplexed in situ sweat analysis (Fig. 5). The device integrated five different sensors that can simultaneously and selectively measure glucose, lactate, Na^+, K^+, and skin temperature. Na^+ and K^+ were measured by ISE. Temperature measurement was performed through a thermistor sensor. Temperature greatly affects the activity of enzymes, and temperature compensation can ensure the accuracy of glucose and lactate concentration readings. The sensitivity of the glucose sensor is 2.35 nA/(μmol·L^{-1}) and the linear range is 0–200 μmol/L. The sensitivity of the lactate sensor is 220 nA/(mmol·L^{-1}) and the linear range is 0–30 mmol/L. Rather than improving the sensitivity and detection range of the sensor, they focused on

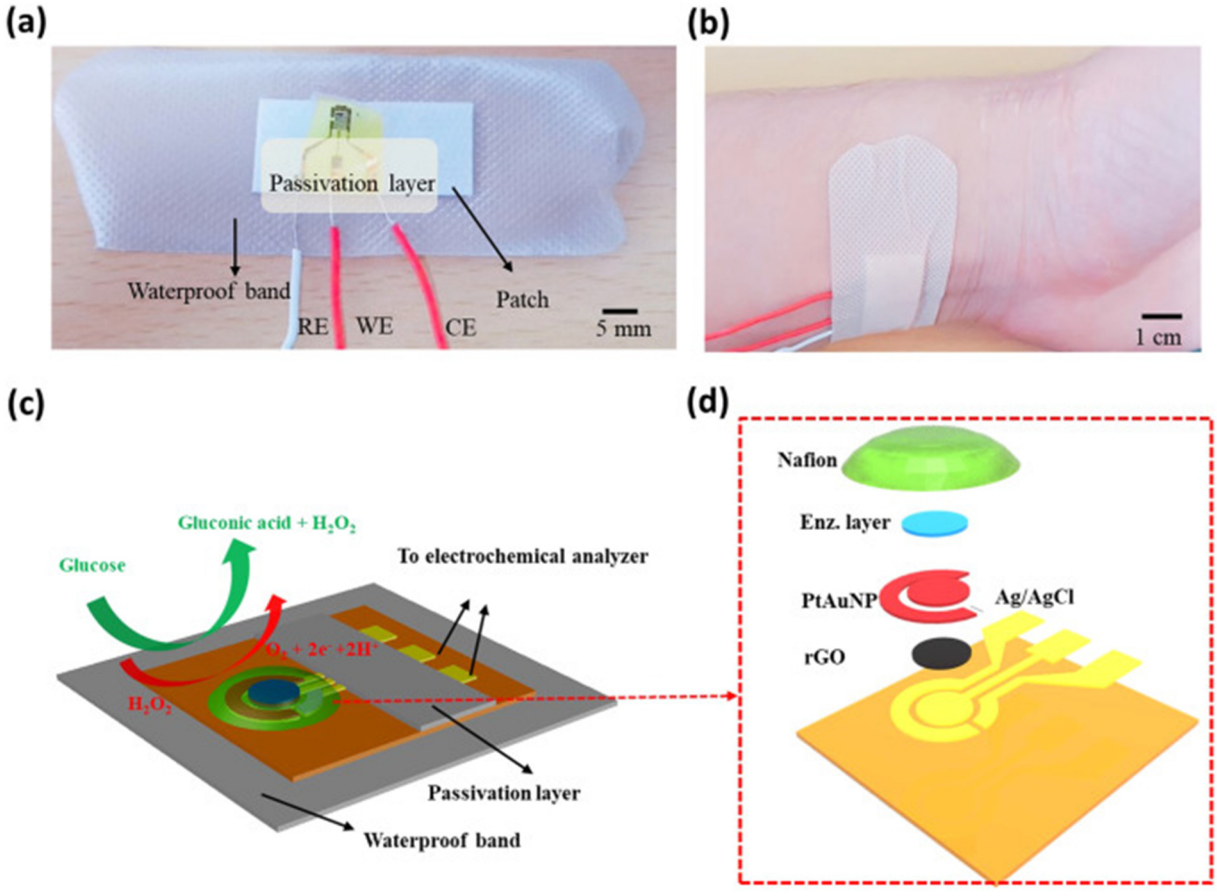

Fig. 4. (a-b) Photograph of the fabricated wearable glucose biosensor. (c-d) Schematic and exploded view of the biosensor. Reproduced from [Xuan et al.[28]].

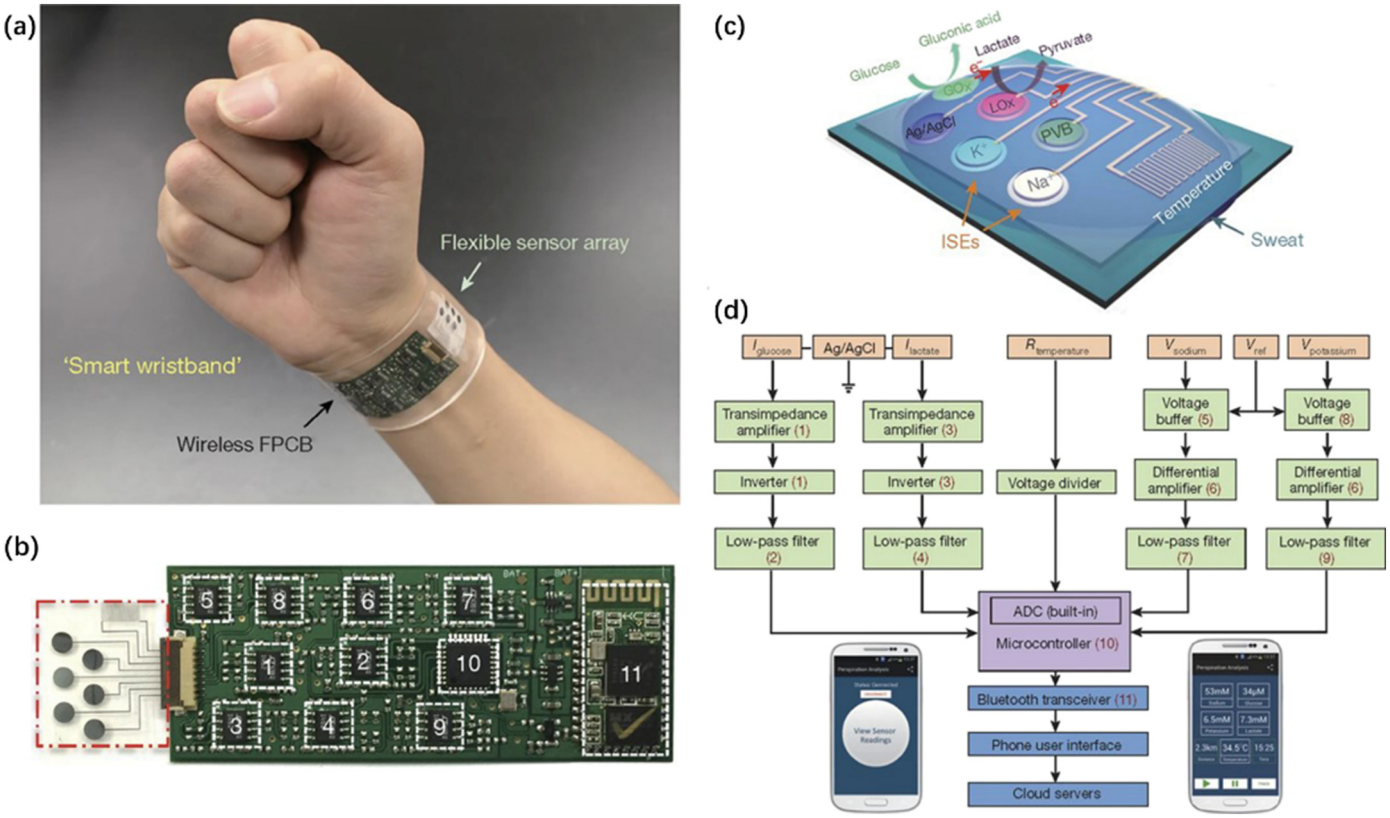

Fig. 5. (a) Photograph of a wearable FISA on a wrist. (b) Physical picture of the FISA including the sensor array and the integrated circuit components. (c) Schematic of the sensor array for multiplexed perspiration analysis. (d) System-level block diagram of the FISA.
Reproduced from [Gao, et al.[9]].

fabricating a wearable device. The sensor is manufactured on the flexible material, polyethylene terephthalate (PET). Integrated circuits manufactured using flexible printed circuit board (FPCB) technology realize the transmission and processing of signals. The whole system is flexible and wearable, and can be used for prolonged physical exercise. In addition, the platform can be utilized or reconfigured to perform in situ analysis of other biomarkers in sweat.

Optical measurement methods need to acquire image or spectral information, which is not conducive to miniaturization of equipment. Electrochemical sensing is based on the detection of electrical signals, which is easy to be miniaturized and achieve through integrated circuits. So the real wearable sweat sensor is mainly an electrochemical sensor. In addition, among these three measurement methods, the sensitivity of electrochemical sensing is the highest and the accuracy is the best. In the evaluation of physical exercise activities and the healthcare applications, electrochemical sensors show great development potential. Especially in the management of diabetes, its ability of continuous glucose monitoring in sweat shows a huge market prospect. However, wearable electrochemical sweat sensors still face some challenges. The manufacturing process of the electrode is complicated. Enzymes for high selectivity are sensitive to environmental conditions, and have poor stability and high cost.[36] In addition, the immobilization process of enzymes also needs continuous improvement.

2.4. Colorimetric sensing

Colorimetric sensing is an optical sensing technology that is widely used in sweat detection. This method relies on the relationship between analyte concentration and color intensities. When the sensing material reacts with the target analyte in a specific chemical reaction, the color changes. By quantifying this color change, detection of biomarkers in sweat is achieved. Therefore, colorimetric sensing also requires optical detection equipment. Today, colorimetric measurement has attracted more and more attention. It is reported that metabolites (such as glucose and lactate) and electrolytes (such as H^+ and Cl^-)[37] in sweat can be detected through colorimetric sensing.

Colorimetry is more commonly used to measure lactate in sweat. Lactate is an important metabolite in sweat, and muscles usually produce large amounts of lactate during hypoxia or vigorous exercise. The normal human lactate concentration is in the range of 0.5–1.5 mmol/L, which can reach 12 mmol/L during exercise, and may increase to 25 mmol/L during high intensity physical exercise.[2] Lactate monitoring is of great significance in diagnosing diseases, assessing human athletic ability, and guiding athlete training. Zhang et al.[38] introduced a flexible and wearable biomarker patch that can simultaneously and sensitively measure lactate, glucose and sweat pH (Fig. 6). They used screen printing technology to create sweat flow channels on the paper. In addition, an area was designed to collect sweat. For lactate detection, they cast L-lactate oxidase solution, horseradish peroxidase, and *o*-phenylenediamine dihydrochloride (OPD) on the lactate detection zone successively. The sensing enzymes and color substrates were loaded on the center of the detection zone. The glucose detection was similarly achieved using glucose oxidase, horseradish peroxidase, and AAP/DHBS solution. The pH was detected by pH indicator. Photos of the wetted patches were taken by a smartphone and analyzed by computer software to calculate the color intensities. By testing 0–20 mmol/L artificial sweat, the device showed a good linear relationship between color intensity and lactic acid concentration, and the sensitivity is 0.2009 a.u./(mmol·L^{-1}). The color change can be clearly seen by naked eye, and the patch can be used as a convenient method for monitoring the concentration of lactate in athlete sweat.

Because the colorimetric method is difficult to measure biomarkers at low concentrations. Relative to the detection of lactate, Zhang et al.[38] focused more on the detection of glucose and conducted

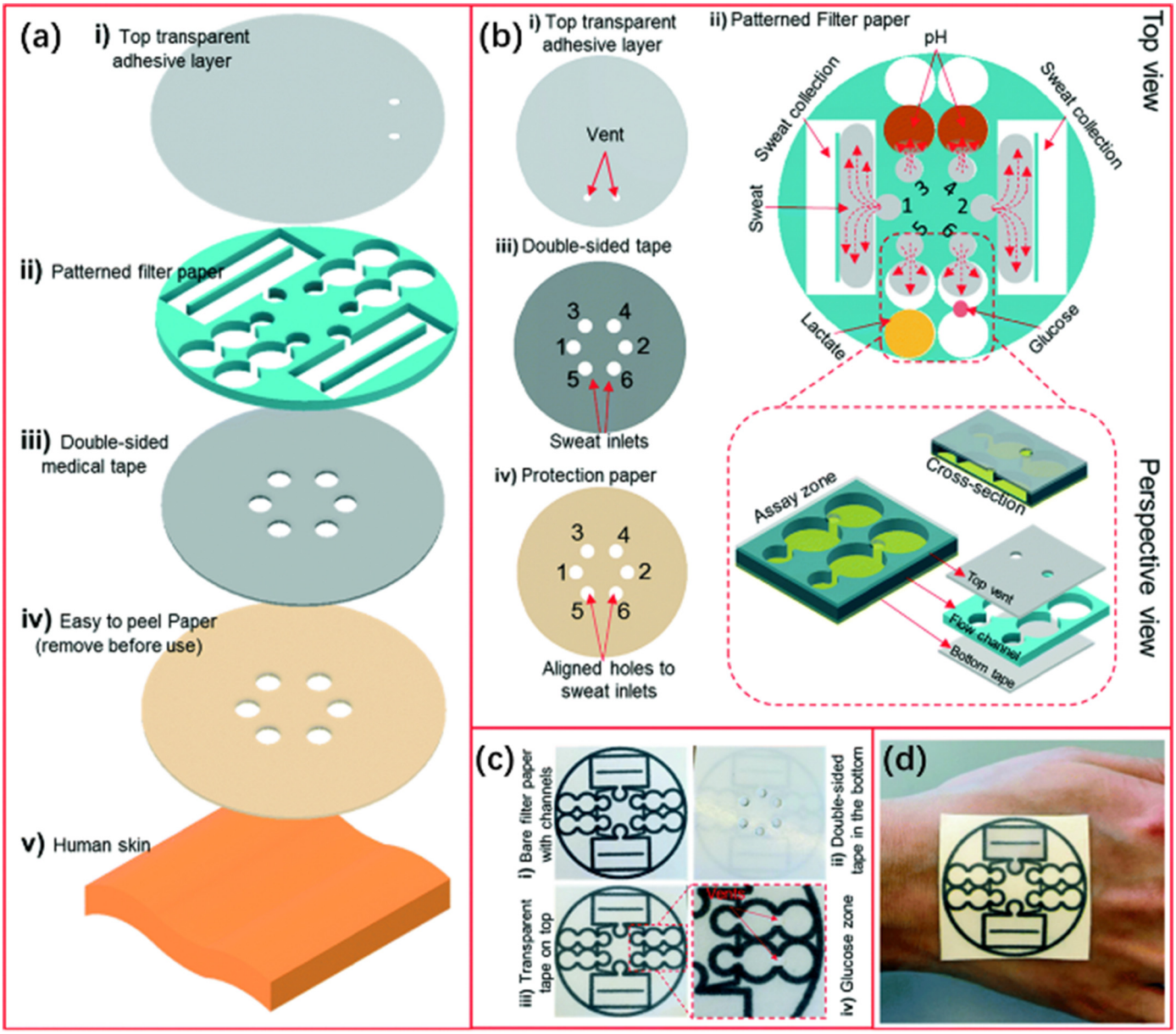

Fig. 6. (a) Layered schematic diagram of the wearable device. (b) More detailed device schematic diagram including perspective view of lactate and glucose detection zone. (c) Images of the device before and after the addition of the transparent and medical tape layers. (d) Photograph of the wearable device pasted on a human hand. Reproduced from [Zhang, et al.[38]].

human experiments. There is an vent above the glucose detection area (Fig. 6b), which can ensure the full progress of the enzymatic reaction and the concentrating of the colorant. In order to improve the accuracy of glucose detection, the data is corrected by the volume of sweat. The linear range of glucose is 50–300 μmol/L, and the sensitivity is 0.2009 a.u./(μmol·L^{-1}). The linear range can cover the physiological values of interest. Then in the same year, Xiao et al.[39] developed a microfluidic thread/paper-based analytical device (μTPAD) for sweat glucose detection (Fig. 7). The device was integrated on a hydrophobic cloth and an absorbent patch was placed under the cloth to collect sweat. The sweat was transported to the paper-based colorimetric detection area through a hydrophilic thread. For glucose testing, chitosan, glucose oxidase (GOD), horseradish peroxidase (HRP) and 3, 3, 5, 5-tetramethylbenzidine (TMB) were successively dropped on the filter paper. The image was taken by the smartphone. The unique feature is that a data processing system was built on the smartphone, which can obtain the glucose concentration directly by analyzing the R, G and B values of the color. The linear range is 50–250 μmol/L and the detection limit is 35 μmol/L.

Compared with the complex electrode manufacturing of electrochemical sensing, the colorimetric part is simple and requires no circuit design.[40] The presentation of biomarkers is intuitive and can even be obtained through naked eye observation.[41] However, the colorimetric patches are mostly disposable, which is not conducive to the realization of continuous detection. Taking photos with a smartphone requires consideration of ambient light and camera exposure.[42] Colorimetric sensor has low sensitivity and is more suitable for threshold measurement and warning indicators, such as lactate detection during exercise. In short, due to the simplicity of the entire device, the development prospect of colorimetric sensing is broad.

2.5. Challenge

We introduced three kinds of sweat sensing principles, fluorescent sensing, colorimetric sensing and electrochemical sensing. At present, these sweat sensing principles are widely used, and many wearable sweat biosensors have been developed, but there are still several issues

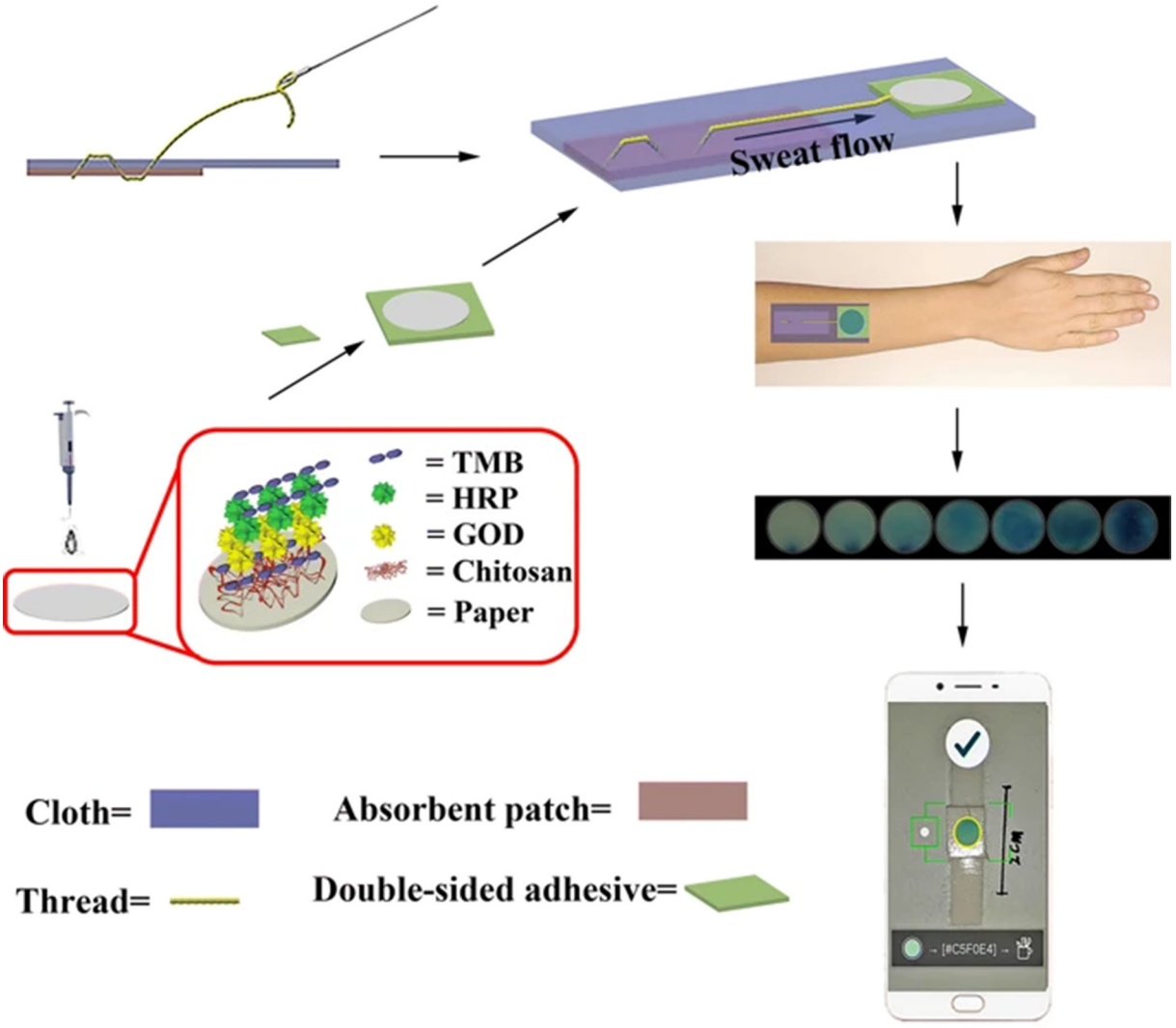

Fig. 7. Fabrication of a wearable μTPAD and its application for sweat glucose detection with a smartphone. Reproduced from [Xiao et al.[39]].

to consider. (1) Sweat detection requires sensors carefully modified with high selectivity and sensitivity, so costs will inevitably rise. For example, the electrochemical method requires the use of gold nanoparticles and graphene to modify the electrode. Lithography is also a time-consuming and expensive technology. Although sometimes the colorimetric method can be selected for which don't require high-precision measurement. However, the development of high-selectivity, high-sensitivity, and low-cost detection materials is still the direction of future efforts. (2) Data processing is essential for sweat measurement. The electrochemical method requires the measurement of electrical signals, which can be obtained directly by appropriate circuit design. The colorimetric method and the fluorescence method need to measure optical signals. Obviously, it is impossible to use a large-scale spectrometer in a wearable device. On the other hand, images could be captured by mobile phones. Then post-processing of images is very important for the accuracy of sweat detection and algorithms draw much attention in this field. (3) In continuous sweat detection, the reagents need to be replaced regularly, otherwise the measurement accuracy will be affected. The colorimetric patches are mostly disposable, and the electrochemical electrode also requires regular replacement. None of the existing sweat detection technologies can achieve long-term measurement, which is detrimental to the development of wearable sweat sensors. (4) Small changes of the environment (humidity, pressure, and temperature) can cause significant changes of the signal, which affects the sensor reading. For example, temperature can change the enzyme electrode's properties in real-time. On the other hand, the wearable sensor is close to the skin and affected by human body activity. The vibration or deformation of the electrode will also affect the sensor reading.

3. Chip design

3.1. The general idea of chip design

Sweat collection is required before sweat analysis. In fact, sweat collection is more difficult than sweat detection. How to collect sweat efficiently and then detect it in a specific area of the chip? It can not only detect sweat at a certain moment, but also achieve long-term continuous detection. The chip design is of great significance for the detection of low-concentration biomarkers in sweat. For example, if the colorimetric method is used to measure low concentrations of glucose, it is very necessary to design a good chip. Excellent chip design can ensure the efficient transmission of sweat, enhance the sensing ability, reduce the pollution of sweat and improve the accuracy of sweat detection.[43,44]

There are two types of sweat detection, in-situ detection and ex-situ detection. The in-situ sweat detection is to directly contact the sensor with the skin, and detect the sweat at the site. In ex-situ sweat detection, a microfluidic chip could be used to collect sweat first and then measure the biomarks in it. The epidermal microfluidic chip is able to

capture, process, and locally store sweat when sweat exudes from the skin surface. The ex-situ sweat detection can continuously and accurately quantify sweat loss, sweating rate and biomarker concentration.[45,46]

However, by using a microfluidic chip to capture and sample sweat, only a few sensors are truly wearable. In traditional chip technology, the control of microfluidic flow usually requires valves and complex external control modules, which is obviously not compatible with portable detection of sweat. In this case, novel driving force to ensure the continuity of sweat transport is required. In addition to using the sweat gland itself as a pressure source to drive the fluid, capillary force, osmotic pressure, evaporation pump, et al. can be used to activate the sweat transport without complicated external devices. Next, these three kinds of driving force were introduced to show their function in continuous sweat collection and transportation.

3.2. Capillary force

Capillarity is a common physical phenomenon in nature. Insert a very thin glass tube into the water, and the water surface inside the tube will rise. This phenomenon is called capillarity. Capillarity is basic and important in microfluidic chips. Almost all microfluidic structures utilize capillary action to realize the collection and transportation of sweat.

Nyein et al.[47] introduced a microfluidic patch driven entirely by capillary force, which can be used to detect Na^+ concentration and sweat rate (Fig. 8). The design of the chip is simple, consisting of a sweat collection chamber and a spiral microchannel. This microchannel generates capillary force. First, sweat is secreted by the sweat glands and has an initial motivation. However, without the help of capillary force, this power can only allow sweat to enter the chip across the entrance, which is not enough to support the continuous flow of sweat in the chip. Capillary force promotes the flow of sweat along microfluidic channels. The microfluidic channel has a depth of 200 μm and a width of 600 μm, and can hold 14 μL of sweat. Based on an average arm sweat secretion rate of 10 nL/min/gland,[48] it can last about 50 min. The microfluidic channel here was prepared with polydimethylsiloxane (PDMS) by photolithography, and then hydrophilically treated by O_2 plasma.

The microfluidic channel of the above device is simple, and sweat flows in a single manner. To further study the concentration of biomarkers changing over time, a valve structure can be added to the microfluidic chip. Choi et al.[37] reported a microfluidic device with a capillary blast valve (CBV) structure that can control the direction of sweat flow (Fig. 9). The device has 12 independent chambers, which can be filled sequentially with the flow of sweat. The specific valve structure is shown in Fig. 9d. The opening pressure value of the three valves is #1 < #2 < #3. When sweat reaches #1 and #2, #1 turns on first, and then sweat fills the chamber. Subsequently, #2 turns on and sweat reaches #1 of the next chamber. By analogy, sweat filled all 12 chambers. Finally, the detection of sweat is performed with a mass spectrometer. Before that, the sweat in the device need to be centrifugally extracted. At this time # 3 is turned on and the sweat is transferred to the extraction chamber. They tested the content of lactate, Na^+ and K^+ in different chambers, and evaluated the sweat rate and the pollution of sweat. The addition of valves is conducive to detailed analysis of sweat.

In addition to valve technology, chemical functionalization technology can be used on the channel surface to customize its hydrophobicity and hydrophilicity. Then the capillary force is adjusted to control the flow of liquid. Kim et al.[49] reported a colorimetric patch for detecting Cl^- in sweat. The microfluidic chip is composed of 5 identical units, and the sweat flow sequence is from T1 to T5 (Fig. 10a). Each unit contains three independent chambers, the specific structure is shown in Fig. 10b. Sweat enters from the entrance and follows path 1 to reach the junction of path 2 and path 3. The channel of path 2 is hydrophilic, and the channel of path 3 is hydrophobic, so sweat will first enter the hydrophilic side. The red part is the colorimetric detection area. When it is filled with sweat, the valve in the blue dotted line is activated. The valve is made of a super absorbent polymer (SAP) material that can expand to close path 2. So sweat can only flow into path 3 passively, and then go to the next unit. The microfluidic channel here is also made of PDMS, which is a hydrophobic material (water contact angle>100°).[50] Here, path 2 is hydrophilically treated by O_2 plasma, and path 3 is untreated. In addition to plasma treatment, other methods are developed to create hydrophilic PDMS surfaces, such as by depositing polyvinyl alcohol (PVA) or hydrophilic ultraviolet (UV) cured films.[51,52] PDMS is a polymer material with good biocompatibility, stable chemical properties, easy molding, and high light transmittance that make it become one of the most commonly used materials for microfluidic chips.[53]

Many microfluidic channels are made of paper and fabric, because there are many small channels in these objects, which function as capillaries. Anastasova et al.[54] used two kinds of papers with different absorption rates to achieve sweat flowing in the microfluidic device (Fig. 11). Fast-absorbing paper is used for the straight part of the microfluidic platform. The sensor is installed on this straight channel. There are four circular pads at the end of the channel. The pads are made of large-capacity absorbent paper and are used to collect and store sweat. Excess sweat can be discharged through the outlet on the top layer. The top and bottom layers are made of polymethylmethacrylate (PMMA) material and are connected by a pressure sensitive adhesive (PSA). Fabric can be used as the microfluidic

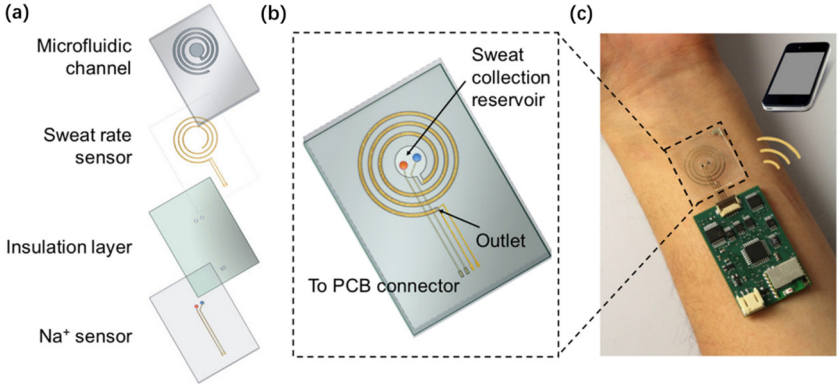

Fig. 8. (a) Layered schematic diagram of the microfluidic sweat sensor. (b) Photograph of the microfluidic device. (c) Photograph of the sweat sensing patch on the subject's wrist including wirelessly transmitting data to the phone via Bluetooth.
Reproduced from [Nyein et al.[47]].

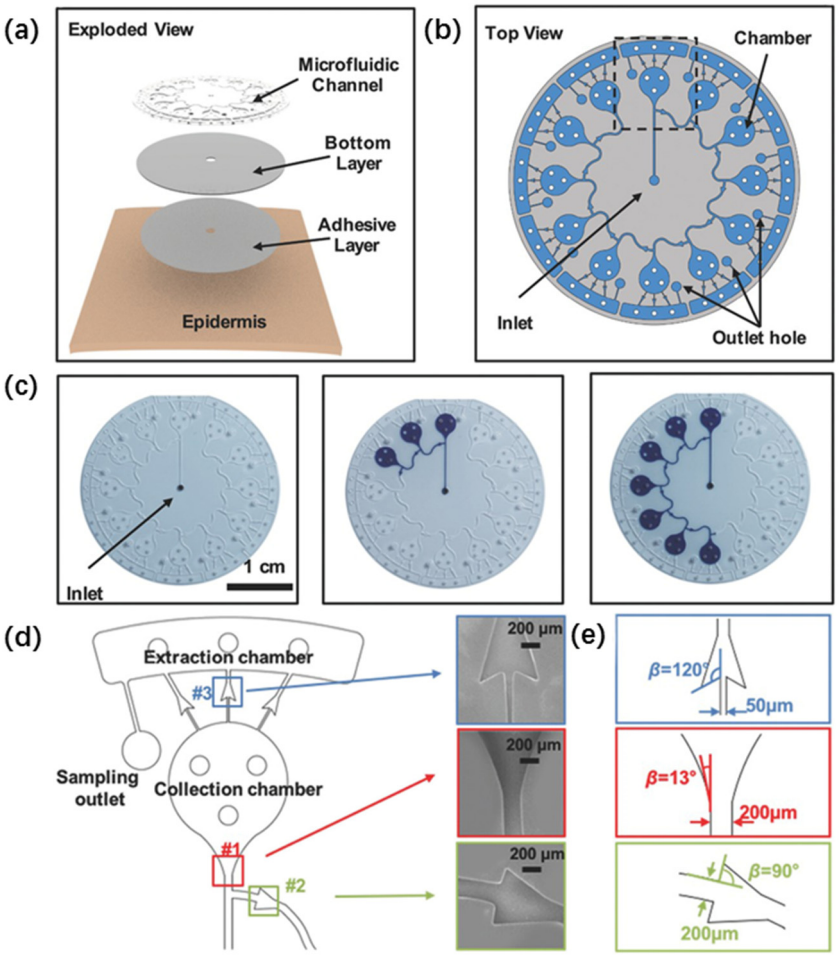

Fig. 9. (a) Schematic diagram of the device. (b) Top view of a microfluidic chip filled with blue dyed water. (c) The water with blue dye filled the microfluidic chamber in turn. (d) Detailed schematic of a single microfluidic chamber, including the SEM images of three capillary bursting valves (CBVs). (e) Schematic diagram of CBVs with specific channel width and divergence angle.
Reproduced from [Choi et al.[37]].

channel which has excellent sweat absorption and capillary flow capabilities as well.[55] Compared with paper microfluidic channels, fabric has higher elasticity and is suitable for use in sports scenes.

In summary, capillary forces promote the flow of sweat along microfluidic channels. The simple microchannel design can realize the collection and transportation of sweat, and the directional sweat path can improve sweat sampling and detection. The microfluidic devices can continuously replenish sweat on the sensing area during measurement. In slightly complex microfluidic systems, adding valve structures or hydrophilically treating the channel surface further controls the direction of sweat flow.

3.3. Hydrogel osmotic pump

Capillary force can be used as a passive microfluidic pump for sweat sampling, but it requires enough sweat accumulating at the entrance,

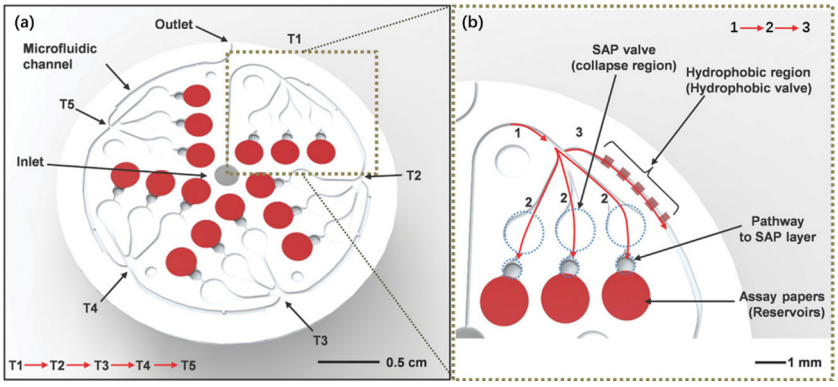

Fig. 10. (a) Top view of the microfluidic device. (b) Schematic diagram of microfluidic channels. Sweat flow tracks from route1 to route 2 (the SAP valves) followed by route 3 (the hydrophobic channel).
Reproduced from [Kim et al.[49]].

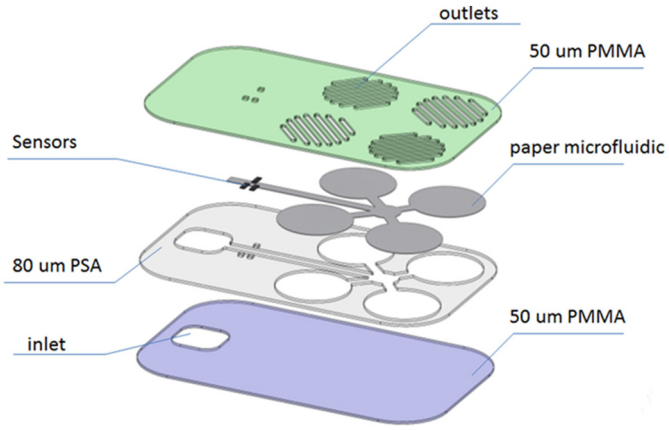

Fig. 11. Schematic representation of layered components of the microfluidic chip. Reproduced from [Anastasova et al.[54]].

which can only occur under high temperature or vigorous exercise. Collecting sweat directly on a dry interface (like unwetted filter paper or skin patches) usually takes a long time. The hydration interface (like wet filter paper or hydrogel) has shorter sampling time and improved sampling efficiency (greater analyte collection). Microfluidic chips typically have hydrogel placed at the entrance. There is an osmotic pressure difference between the hydrogel and the sweat. When human skin contacts the hydrogel, sweat is continuously extracted into the hydrogel, followed by pumping the fluid into a microchannel.

Hydrogels are a class of natural or artificially synthesized polymer materials. Microscopically, they are three-dimensional grid-like structures composed of hydrophilic polymer chains. The grid gap is usually a few nanometers to hundreds of nanometers. Artificial hydrogels include polyacrylamide (PAAM), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyhydroxyethyl methacrylate (PHEMA), et al. Natural hydrogels include agarose gels, Gelatin, sodium alginate gel, and hyaluronic acid. Part of the hydrogel can be synthesized in situ from its monomer solution by radical reaction initiated by ultraviolet or visible light.[56] Agarose hydrogel is often used in many reports and is a skin-compatible and highly hydrophilic natural polymer that promotes absorption of aqueous solutions and collects polar metabolites from the skin surface. To improve sampling efficiency, agarose also has been combined with other water-soluble polymers to prepare blended hydrogels.[57]

Biosensors can be directly integrated in the hydrogel to realize in-situ sweat detection. Nagamine et al.[58] reported a hydrogel-based touch pad for lactate detection (Fig. 12). In order to spread sweat evenly into the hydrogel, the Dulbecco's Phosphate Buffer Saline (DPBS) solution was dropped on the surface of the hydrogel. The osmotic pressure is controlled by changing the salt content in DPBS solution. Before the experiment, the subjects' fingers were cleaned with ethanol solution. When a finger is placed on the agarose gel pad, sweat is continuously extracted into the gel, and the lactate sensor responds immediately. Different concentrations of agarose gel have little effect on response time because agarose gel has a relatively large pore structure. As the thickness of the agarose gel increases, the time delay increases slightly. The device can easily obtain sweat from the human sweat glands without complicated sweating conditions (high temperature or vigorous exercise). However, the device is a proof of concept for hydrogel-based sensors, and the key performance indicators of the sensor have not been fully characterized.

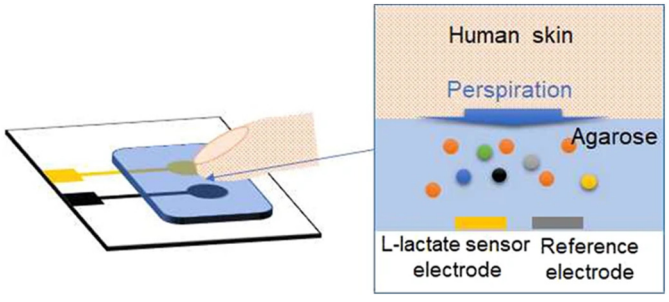

Fig. 12. Schematic view of the hydrogel-based touch pad for sweat analysis. Reproduced from [Nagamine et al.[58]].

Lin et al.[59] also reported a thin hydrogel micro-patch (THMP) using fingertip sampling, which has a fingerprint recognition function (Fig. 13a). This study shows that hydrogel is excellent for natural sweat collection. Hydrogel can be used simultaneously as an interface for sweat sampling and as a medium for electrochemical sensing. To describe the enhanced sweat collection ability of hydrogel, they established a fluid model of the open-air interface and the hydrogel interface (Fig. 13b). And through the verification of caffeine and lactate sampling, the analyte sampled at the hydrogel interface is about three times that of the dry absorption pad (open-air sampling interface) (Fig. 13c-d), which is consistent with the established fluid model. However, for in situ detection, the reacted sweat will contaminate and dilute the fresh sweat, which results in inaccurate measurement. The hydrogel becomes dry or contaminated after several hours of use, and it needs to be replaced regularly.[60]

From the currently published literature on sweat detection, ex-situ detection is the majority. The combination of hydrogel and capillary action of microchannel is used to realize sweat extraction, transportation and ex-situ detection. Shay et al.[61] used the permeability of hydrogels to pump sweat to the microfluidic network for ex-situ detection (Fig. 14). A hydrogel disc is placed at the entrance of the microfluidic device. The high concentration of NaCl in the hydrogel will form a large osmotic pressure, which will drive sweat into the hydrogel disc. The hydrogel disc has a unique design. There is a small semi-circular gap in the place where it contacts the microfluidic channel, which is beneficial to pump sweat into the microchannel. The glucose sensor is installed on the straight channel. The detection of other biomarkers in sweat can be achieved in this kind of microfluidic devices. The hydrogel is synthesized from the acrylamide monomer solution by free radical reaction initiated by ultraviolet rays. Before the experiment, the hydrogel disc was soaked in saline. By changing the geometry or solute concentration of the hydrogel, the osmotic pressure in the hydrogel is adjusted, thereby changing the liquid flow rate. As the hydrogel continuously absorbs sweat, the solute is diluted, the osmotic pressure drops, and the flow rate gradually decreases with time.

In summary, compared to the other methods of sweat sampling and analysis, the sampling method with hydrogel is very convenient and has improved sampling efficiency (greater analyte collection). It can perform in-situ sweat detection directly in the hydrogel. Even with very few sweat droplets generated, hydrogels can still be used to collect analytes. In addition, hydrogel osmotic pump can drive sweat into the microfluidic device for ex-situ detection. On the other hand, many existing sweat sampling methods require active stimulation (such as iontophoresis, exercise, heating).[59] The use of hydrogels makes sweat sampling simpler with chemical stimulation. In addition to adding solutes to the hydrogel and using osmotic pressure to extract sweat, sweat-secreting chemicals can also be added to the hydrogel to increase the rate of sweat secretion.[3,62,63]

3.4. Evaporation-driven micropump

Inspired by the stomatal transpiration of plants, evaporation-driven force is used for continuous fluid flow pumping by designing micropores at the outlet of microfluidic chip. The diffusion rate at the edge of the macro surface is less than the diffusion rate at the center, and the diffusion law of micropores is just the opposite (Fig. 15). Therefore, the flow rate caused by the vaporation of the micropores array of the

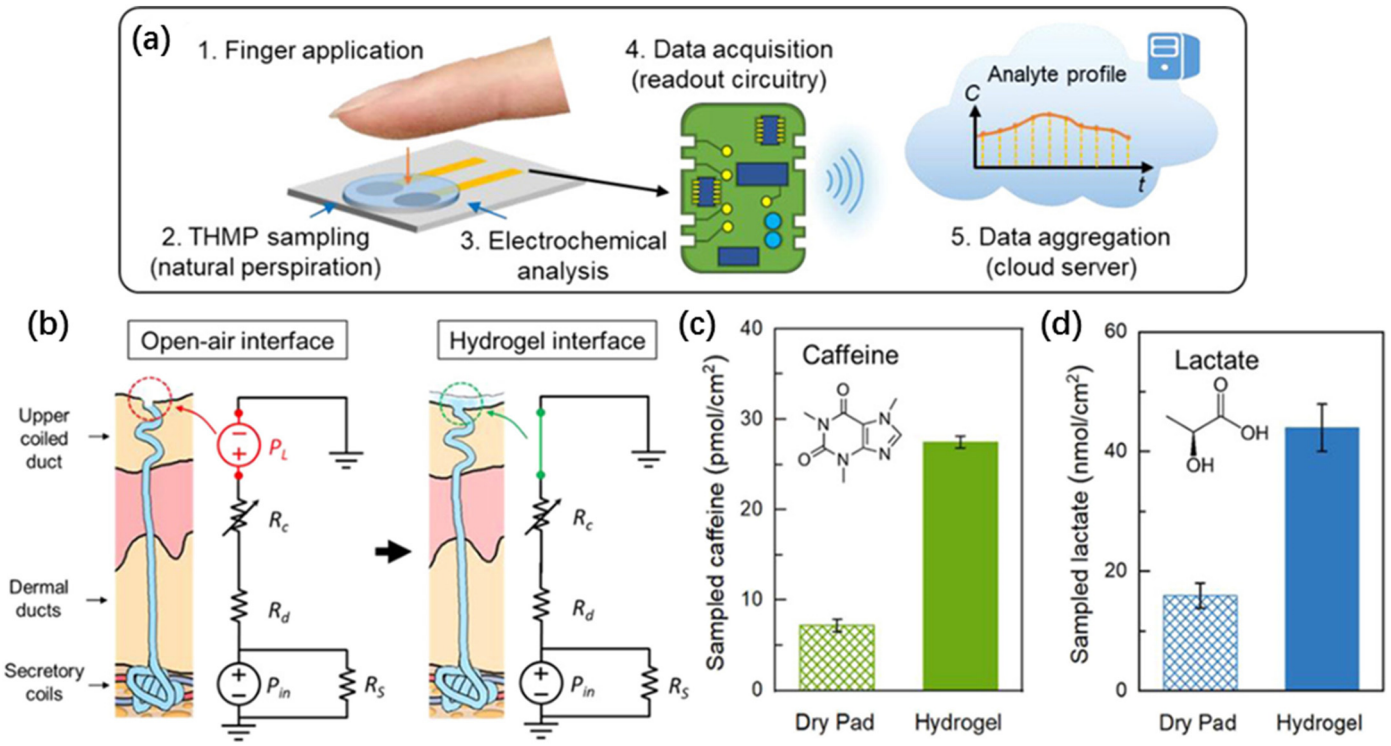

Fig. 13. (a) Schematic of the THMP including wireless in-situ electrochemical analysis. (b) Fluid model of the open-air interface and the hydrogel interface. (c-d) Amount of caffeine and lactate sampled per unit area on the fingertips with a dry absorbent pad and hydrogel interface.
Reproduced from [Lin et al.[59]].

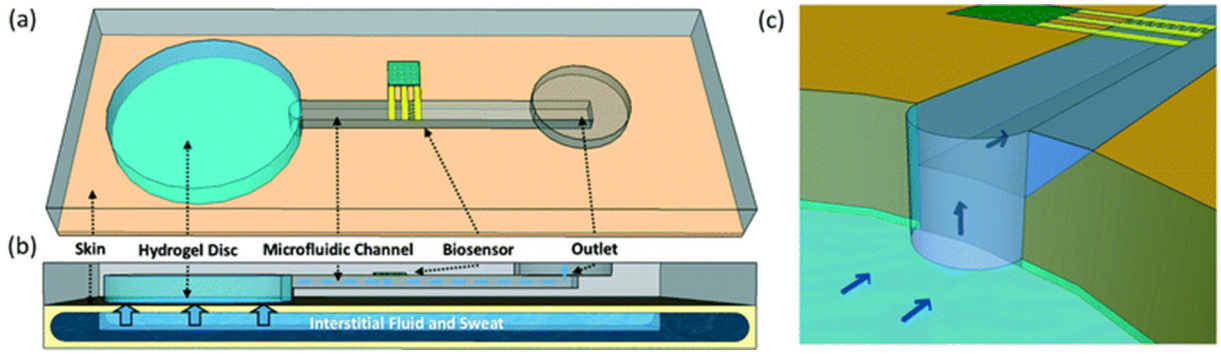

Fig. 14. (a-b) Schematic diagram of the microfluidic device. Hydrogel disc mixed with higher concentration of solute (NaCl) pumps sweat to the microfluidic channel for transportation. (c) The notch design of the hydrogel disc guides sweat to the adjacent microfluidic channel.
Reproduced from [Shay et al.[61]].

same area may be hundreds of times higher than that caused by the evaporation of the macro surface.[64] The evaporation-driven micropump is efficient for continuous sweat flow.

Nie et al.[65] introduced a microfluidic device based on evaporation-driven micropump (Fig. 16). The device is fabricated with PET. The microfluidic structure is simple with a straight channel connecting the inlet and the outlet. The sensing cavity is on the straight channel, but no sensor is installed, and this device is only used to study the transport of sweat. At the bottom of the device, there is a filter paper in the shape of a linear grid and a square filter paper is facing the entrance of the device. Above the square filter paper, there are two pieces of round filter paper to fill the inlet. Due to the capillary action of the filter paper, the sweat collected by the linear filter paper converges to the square filter paper portion, and then the sweat is transferred to the inlet of the

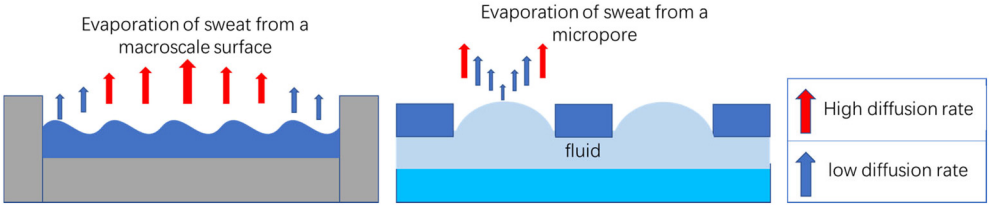

Fig. 15. Schematic diagram of macroscopic surface and micropore evaporation diffusion.

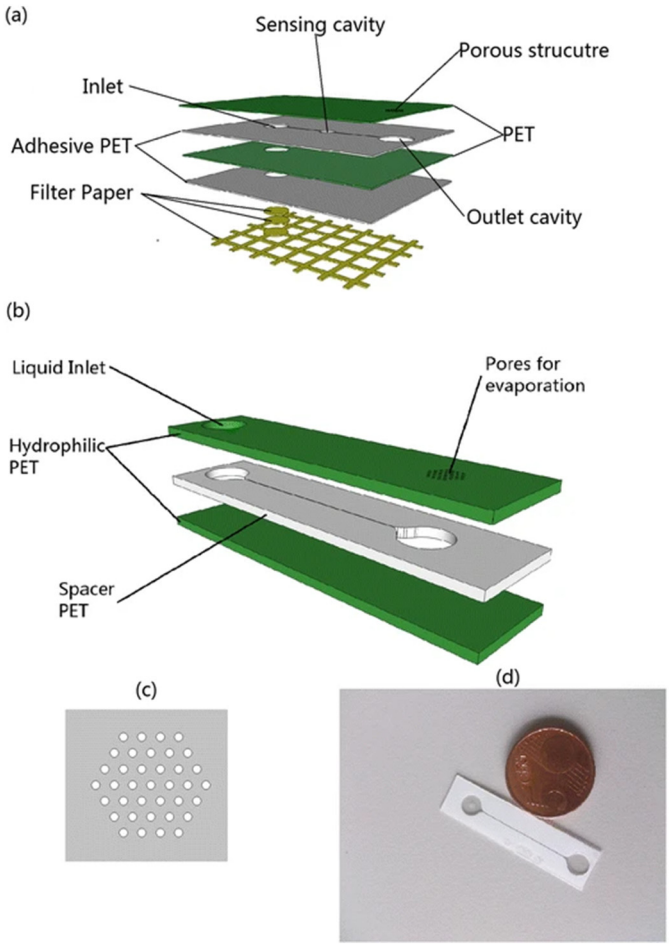

Fig. 16. (a) Schematic of the device based on evaporation-driven micropump. (b) Simplified device, without filter paper and sensing cavity. (c) the micropore array at the evaporation end. (d) Real device compared with a 5 Eurocent coin. Reproduced from [Nie et al.[65]].

microfluidic channel through the circular filter paper. At the outlet of the top PET, there are many micropores with regular hexagonal arrangement (Fig. 16c). The microfluidic channel and micropore array are fabricated by laser engraving machine. Sweat evaporates through this micropore array, thereby continuously driving the flow of sweat in the channel. In addition to the higher flow rate, the biggest advantage of micropore evaporation is that it is convenient to control the flow rate. By changing the number or shape of micropores, the flow rate can be easily controlled. The pumping performance calculated according to evaporation theory is in good agreement with the results using two-dimensional Particle Tracking Velocimetry (2D-PTV). At a temperature of 20 °C and a relative humidity of 40%, the micropore array with 61 pores (diameter = 250 μm, pitch = 500 μm) has a maximum flow rate of 0.145 μL/min.

Chen et al.[66] integrated an electrochemical sensor in a microfluidic chip based on evaporation-driven micropump for real-time monitoring of flow rate (Fig. 17). The device is fabricated with polymethyl methacrylate (PMMA) with three-layer structure. The inlet and three micropore arrays are on the top layer. Each hexagonal micropore array contains 37 small holes, each with a diameter of 250 μm and a fixed pitch of 500 μm. Three small detecting electrodes are located on the microfluidic channel of the middle layer, and the three exposed large electrodes are used to connect an external detection device. Since the entrance of this device and the evaporation pores are on the same layer, the design only carried out laboratory measurements. The sweat sample is injected into the inlet, and the sweat flows toward the outlet due to capillary action. The sweat then evaporates through the three micropore arrays, thereby continuously driving the flow of sweat in the channel. The entrance here is bare, and evaporation at the entrance may be greater than that of the micropores. But even so, there will be no backflow of sweat. Because the micropore itself has large capillary force, each liquid meniscus is nailed to the edge of the micropore and the liquid flowing to the outlet must be carried out to obtain a mass balance.[65] The maximum flow rate generated by this device is 0.235 μL/min.

By combining capillary action and evaporation action, the evaporation micropump can passively generate a continuous sweat collection flow for a long time. First, the driving force for evaporation is high. The evaporation of micropores can be two orders of magnitude higher than the evaporation caused by the macroscopic surface.[64] The evaporation micropump can generate enough pump speed to drive the continuous flow of sweat in the channel. Secondly, the micropump can match the average sweating rate of the human skin by a proper design.[66] It can change the evaporation rate and adjust the flow by changing the size, number and shape of the micropores. In addition, a heating element

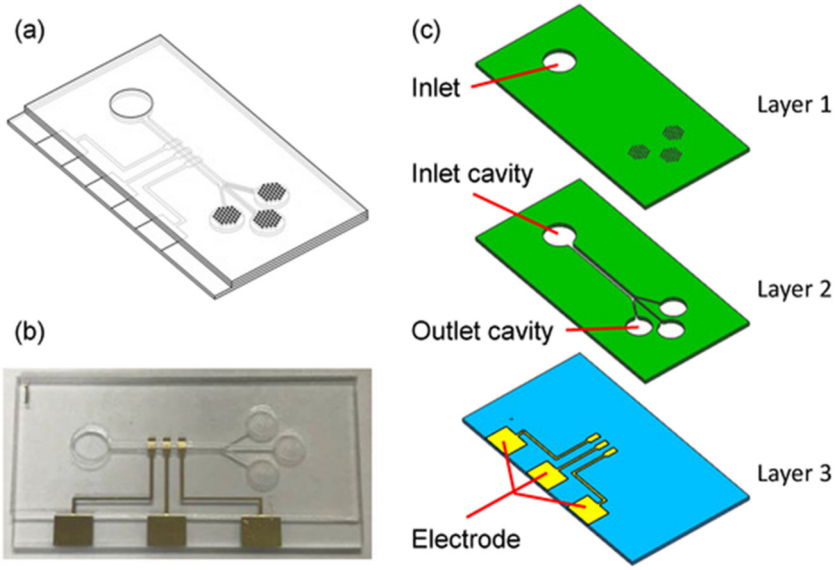

Fig. 17. (a) Schematic of the microfluidic device. (b) An image of the real device. (c) The layered structure diagram of the device. Reproduced from [Chen et al.[66]].

can be integrated to control the flow rate. The evaporation micropump shows the potential for sweat collection and real-time monitoring of sweat rate. However, the evaporation micropump is only used to monitor the sweat flow, and there is no integrated biosensor currently.

3.5. Challenge

Three kinds of driving force have been used to activate continuous sweat collection and transportation in microfluidic chip. However, several issues still need to be considered in wearable sweat detection devices based on microfluidic chips. (1) Without perspiration-promoting stimulation or exercise, the secretion of sweat is small, much lower than tears and saliva.[67] How to collect sweat and make good use of sweat is a very worthy issue. (2) The sweat detection chip is close to the skin, so the chip materials must be biocompatible.[68] Considering the leakage of detection reagents, the reagents should also be nontoxic. In addition, if using perspiration-promoting stimulation, it must also ensure that the chemicals and the applied current have little side effects on the human body.[69] (3) Because of the softness of human skin and the deformation during exercise, the microfluidic chip must be stretchable. And during the stretching process, the performance of the sensor cannot be affected. (4) In order to truly achieve real-time wearable detection, it is necessary to develop self-powered detection systems and wireless wearable electronic devices. For example, the near field communication (NFC) chip can convert the magnetic field energy generated by the mobile phone into an analog voltage output[70]; the electronic skin converts the tiny mechanical energy of human motion into triboelectric output.[71,72] Without power source, they can power external electronic devices. (5) Try to explore the relationship of the concentration of biomarkers between sweat and blood. Some analyte concentrations only represent the skin or endocrine sweat glands themselves, not the body.[44] For example, the lactate content in sweat is a byproduct of the local metabolism needed to support sweat production.[48]

4. Discussion

In recent years, analyses of sweat have become more popular since it doesn't require invasive sampling procedures. The principle of sweat detection is very mature and some analytical methods have been utilized, such as fluorescence technology, colorimetry and electrochemistry method. The development of wearable sensors makes continuous sweat detection possible. The chemical composition of sweat samples is complex. Efforts were underway to enhance the selectivity and sensitivity of sweat detection. In terms of sensors, select excellent biometric materials, such as specific enzymes, and highly selective fluorescent materials to achieve specific detection of sweat components. Reasonably design working electrode materials, such as precious metals (Au),[28] metal oxides[30] and grapheme,[31] so as to achieve effective electron transmission and sufficient reactant contact to improve detection sensitivity. The use of a microfluidic chip can transport the sweat in time after the detection and reduce pollution. The design of the microfluidic chip includes the extraction, transportation, storage, and detection of sweat. The difficulty lies in the controlled transport of sweat and realizing a long-term continuous flow of sweat. Capillary forces were widely applied to drive and collect sweat with well-designed configuration of microchannels. Passive valves can also be designed carefully to direct the flow of sweat for providing a precise sampling capability. Hydrogel osmotic pumping can noninvasively collect fluids into microfluidic channel without any external power. The evaporation-driven micropump can passively generate a continuous and stable sweat collection flow for a long time, and allow for active control of the pumping rate. With the help of capillary force, hydrogel osmotic pump and evaporation-driven micropump, continuous sweat collection and transportation can be realized. A microfluidic chip with proper design makes sweat detection convenient and fast, which is a key step for wearable devices. The combination of biofuel cells that obtain usable energy from the metabolites present in sweat and wearable technology has greatly promoted the further development of wearable devices. Self-powered wearable biosensors have shown broad prospects in epidermal detection for personal medical care and disease diagnosis, especially enzyme-based bioelectronic products have obvious advantages.[73] With the fusion of biomaterials, electronics and wearable devices, key challenges can be addressed through continuous multidisciplinary efforts and innovative solutions. Wearable electronic devices are expected to provide exciting opportunities for monitoring human physiology and will have a huge impact on various healthcare, sports training and national defense fields.

Declaration of competing interests

There are no competing interests to declare.

Acknowledgments

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