Wet Interface Technologies for Wearable Sweat Sensors

Kuniaki Nagamine and Shizuo Tokito

1 Introduction

The recent key issue is the development of chemical sensors to support the realization of personalized healthcare that can track the daily physiological conditions of individuals and provide personalized advice to encourage behavioral changes. Portable biosensors that can easily detect chemical substances with a signal converter equipped with biological receptors have been developed for point-of-care-testing applications, especially for self-management of blood glucose in diabetic patients [1]. Recent dramatic improvements in the sensitivity of biosensors have enabled the detection of ultra-trace amounts of chemical components in tears, saliva, sweat, breath, and skin gas. Besides, comprehensive omics analysis of the chemical compounds has uncovered useful biomarkers in these biological samples [2, 3]. The more important point is that these fluids and gases can be noninvasively and easily collected from the human body, enabling daily self-health monitoring based on the possible biomarkers in these bodily fluids and gases avoiding an invasive blood sampling process. Among these bodily fluids and gases, sweat is one of the most favorable fluids because it is easily accessible from the skin. Sweat is made up of 99% water, with the remaining 1% containing chemicals that contain useful biomarkers [4, 5]. Therefore, biosensors capable of multi-sensing possible biomarkers are essential for highly reliable sweat-based healthcare. In this chapter, we describe the basic physiology of perspiration

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and its components and then summarize the current methods of sweat collection. In particular, the promising non-invasive sweat collection method, wet-interfacing method, and sweat sensor that implements this method are summarized to introduce and discuss recent advances and issues of this type of sensor for non-invasive at-rest sweat-based healthcare.

2 Sweat Components

Sweat, which has a similar composition to serum, contains various biomarkers. These biomarkers are related to some diseases listed in Table 1. For example, sweat glucose is a typical biomarker that many researchers have found to be correlated with blood glucose levels [13]. On the other hand, the origin of sweat components is still under research, and the correlation between blood components has not been sufficiently proven [4]. In order to realize highly reliable healthcare using sweat components as biomarkers, the study of the correlation between blood components should be continued.

3 Sweat Collection Methods

3.1 Passive Collection

Sweat is excreted from sweat glands under some circumstances including exercise, bathing, hot weather, or the skin under the occluded environment. Visible sweat can be easily sampled by absorbing it with filter paper, cotton, gauze, or towels (Fig. 1a). PharmChek, a semi-occlusive dressing consisting of a cellulose-based collection pad, is a commercially available passive sweat collection system that has been utilized for sweat analysis [33]. The passive processes for sweat collection are straightforward and useful for disposable use. However, it takes a relatively long term to collect enough amount of sweat for biosensing purposes. In addition, the method of analyzing accumulated sweat makes it difficult to track continuous changes in sweat composition.

The on-skin microfluidic system is a promising device for continuous sampling and monitoring of sweat components (Figs. 1a, 2a) [34]. Poly(dimethylsiloxane) (PDMS)-based microfluidic channel is generally flexible and conformable to human skin. Therefore, its inlet can be tightly faced to the skin surface containing sweat glands in order to directly introduce the secreted sweat into the microchannel. This device configuration suppresses the volatilization of the collected subtle sweat (typical perspiration rate is a few nL min^{-1} $gland^{-1}$) [35]. The sweat collected into the microchannel is continuously discharged from the outlet of the microchannel to keep the sweat in the channel fresh. However, owing to the slow perspiration rate, the sweat

Table 1 A list of sweat biomarkers

Diseases	Sweat biomarkers	References
Active tuberculosis	Proteins	[6]
Atopic dermatitis	Dermcidin, Amino acids	[7, 8]
Cardiovascular diseases	Na^+, Ascorbic acid, Neuropeptide Y	[9]
Chronic anxiety disorders, Major depressive disorder	Neuropeptide Y	[10]
Chronic hepatitis C	Hepatitis C virus	[11]
Cystic fibrosis	Cl^-	[12]
Diabetes	Glucose	[13]
Fatigue	Lactate	[14]
Fatigue	NH_4^+	[15]
Gout	Uric acid, Tyrosine	[16]
Hand surface infection barrier	Lactic acid	[17]
Heart failure	Lactate	[18]
Hepatic encephalopathy Diagnosis	NH_4^+	[19]
Heat stroke	Na^+	[20]
Hypoxia	Lactate	[21]
Inflammatory Bowel Disease	IL-1β, CRP	[22]
Inflammatory/infectious diseases	IL-6, IL-8, IL-10, TNFα	[23]
Kidney disorder	Creatinine, Urea	[24]
Lung cancer	Monogluceride, Muconic acid, Suberic acid, Tetrahexose, Nonanedioic acid, Urocanic acid	[25]
Major depressive disorder	Cytokines, Neuropeptide Y, Substance P, Calcitonin-gene-related peptide, Vasoactive intestinal peptide	[26]
Mental stress	Cortisol	[27]
Nutritional imbalance	Vitamin C	[28]
Ocular Behcet's disease	l-Citrulline, l-Pyroglutamic acid, Urocanic acid, 2-Oxoadipic acid, Cholesterol 3-sulfate, Pentadecanoic acid	[29]
Psoriasis	Choline, Glutamic acid, Phenylalanine, Lactic acid, Urocanic acid, Citrulline	[30]
Schizophrenia	Proteins	[31]
Vogt-Koyanagi-Harada diseases	Amino acids	[32]

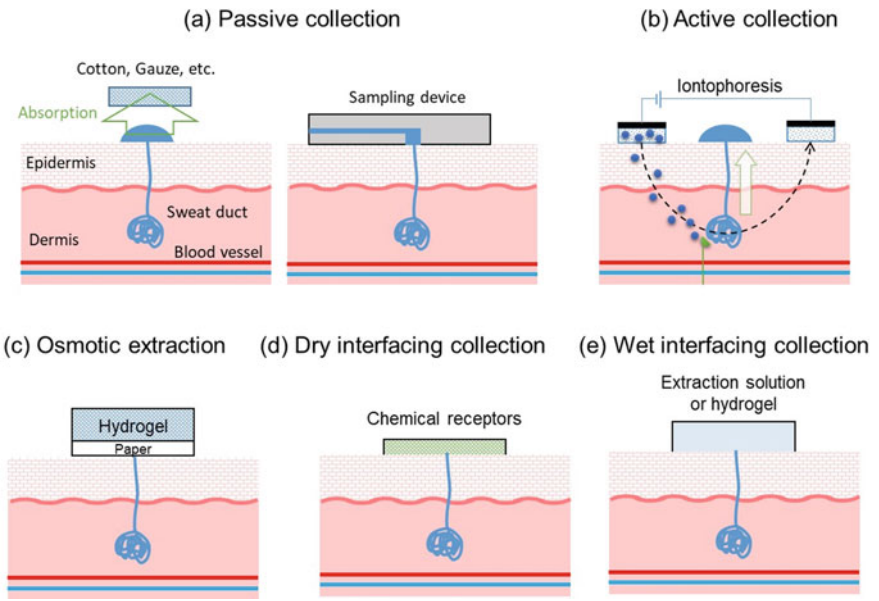

Fig. 1 Summary of the sweat collection methods. **a** Passive collection, **b** active collection, **c** osmotic collection, **d** dry-interfacing collection, and **e** wet-interfacing collection

collected earlier is more likely to be mixed with the sweat collected later, resulting in the concentration of the sweat components averaging. To solve this issue, the active transport of passively collected sweat was achieved using digital microfluidic technology. Electrowetting on dielectrics is a typical digital microfluidic technology that employs the electric field generated by a high voltage to transport droplets of sweat collected at different times in real time [36]. The other strategy developed by Kim et al. was an open, truncated cone-shaped vertical sweat microchannel (height: 1 mm, bottom diameter: 1.5 mm, top diameter: 0.5 mm) and a sweat-clearing structure composed of a hydrophilic carbon nanotube-PDMS sponge at the top of the channel (Fig. 2b) [37]. When the sweat excreted from the sweat gland fills this vertical microchannel, the sponge-based top layer quickly wicks the sweat to clear the channel. This process was repeated for the continuous collection of fresh sweat into the channel.

3.2 Active Collection

For the daily use of the sweat sensors, it is necessary to develop a mechanism that can collect sufficient sweat at any time. To solve this issue, an iontophoretic device was developed to actively stimulate perspiration at any time (Figs. 1b, 2c) [38]. This device can enhance the transdermal administration of pilocarpine, a cholinergic

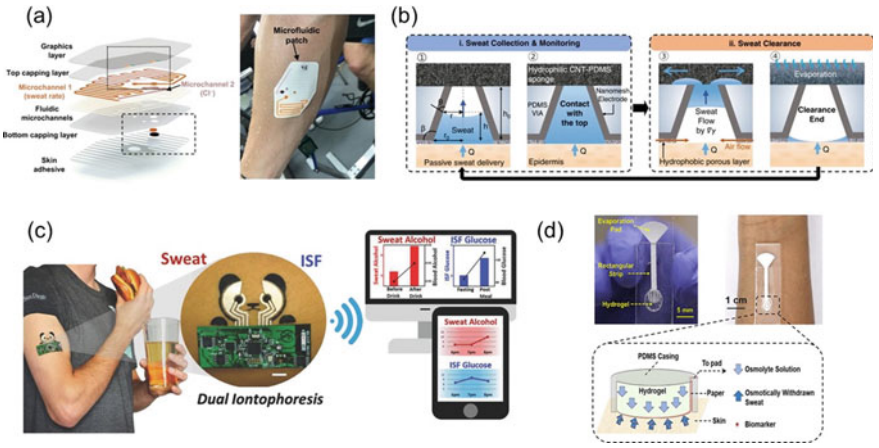

Fig. 2 Research examples of the sweat collection methods. **a** Passive collection using the on-skin microfluidic system (reproduced with permission from Ref. 34, http://creativecommons.org/licenses/by/4.0). **b** Passive collection using the open, truncated cone-shaped vertical sweat microchannel (reproduced with permission from Ref. 37, http://creativecommons.org/licenses/by/4.0). **c** Active collection using the iontophoretic technique (reproduced with permission from Ref. 38, http://creativecommons.org/licenses/by/4.0). **d** Osmotic pressure-driven paper-based microfluidics (reprinted with permission from Ref. 39. Copyright (2021) American Chemical Society)

agonist to activate eccrine sweat glands, through transcutaneous delivery of ionic current. However, some people may experience discomfort due to the application of ionic current. Besides, daily drug administration may also be unacceptable to the users.

3.3 Osmotic Extraction

Saha et al. developed osmotic pressure-driven paper-based microfluidics to achieve continuous collection and detection of the sweat biomarkers, even at rest (Figs. 1c, 2d) [39, 40]. The device is composed of a PDMS-based microfluidic channel filled with Whatman 542 paper, and its inlet contains a hydrogel disk with a high concentration of glucose or glycerin. The hydrogel disk contacts the human skin via paper. The difference in osmotic pressure between sweat and the hydrogel disk enables the effective collection of sweat into the paper. Continuous collection and detection of sweat lactate was achieved by utilizing a passive osmotic pressure-driven pump and the capillary action of the paper-based channel even under a resting state [40]. In this principle, the collected sweat is mixed with solutes in the hydrogel; therefore, it is necessary to adjust the composition of the hydrogel according to the target analytes.

3.4 Dry Interfacing Collection

Dry interfacing collection means that the receptors immobilized on the dry substrate are directly in contact with the human skin surface to capture the secreted compounds left on the skin (Fig. 1d). One of the representative devices is the ELIPatch (enzyme-linked immunospot array on a patch). The capture antibodies are arrayed on a substrate to detect multiple skin components [41]. A similar dry-interfacing collection device is the fingerprinting approach [42]. When human skin is brought into contact with the antibody-immobilized substrate, sweat components are captured by the antibody, followed by visualization by labeling detectable second antibodies. This assay process has been developed as a lateral flow device and is commercially available for sweat-based drug screening [43]. Antibody-based sweat sensors are potentially useful in healthcare using sweat protein-based biomarkers.

3.5 Wet Interfacing Collection

Here, we introduce a simple sweat collection method using 1% aqueous ethanol as an extraction solution [44]. Simply by contacting the skin with 1% aqueous ethanol, sweat components can be diffused from the sweat glands into the solution and collected (Fig. 1e). This method has also been utilized for the glucose analysis of sweat [45, 46]. Considering biological safety, the extraction solution has recently been replaced with phosphate-buffered saline (PBS) [18] or hydrogel patches in PBS [47–49]. A similar technique using PBS as an extraction solution has also been applied to the immunoassay of dermal biomarkers [50–52]. This immunoassay method evolved into a transdermal analysis patch, which is an antibody-immobilized flexible membrane in contact with the human skin surface for in-situ capture of sweat biomarkers [53]. Heavy metal ions dissolved in human sweat were detected using a similar technique called the “finger immersion method” [54]. The fingers of the subjects were immersed in high-purity water containing 0.1% nitric acid to extract nickel from the skin, followed by quantification using induced coupled plasma-optical emission spectrometry. The drawback of this method is that extremely small amounts of sweat components are diluted with the extraction solution. Therefore, a highly sensitive analysis with liquid chromatography and mass spectrometry, for example, is essential for quantifying the extracted components. Such expensive and large size of systems are unsuitable for daily use. The combination of at-rest sweat collection technology using the wet interface and portable biosensors is expected to create advanced sweat sensors for daily use.

4 Hydrogel-Based Wearable Touchpad Biosensors for Extracting and Detecting At-Rest Human Sweat Components

As described above, the most important issue in sweat biosensors is the development of an easy way of collecting at-rest sweat that can be performed anytime and anywhere. We proposed that one of the critical solutions to this issue is the use of a novel wet-interfacing collection-based biosensor, named the hydrogel touchpad-based sweat sensor for the first time (Fig. 3a) [55]. Our first model of this type of biosensor was a lactate oxidase (LOx)–based sweat lactate sensor. LOx and Prussian blue (PB)-modified working electrode and an Ag/AgCl reference electrode are covered by an agarose hydrogel in PBS as a sweat extraction pad. When the human skin is in contact with the hydrogel-based sweat extraction pad, the sweat lactate diffuses from the sweat glands into the gel and is extracted. The sweat lactate in the gel was electrochemically detected using the LOx-PB-modified electrode. Our subsequent sensor was equipped with a liquid-junction reference electrode that exhibits a stable reference potential to detect Cl^- ion in at-rest sweat [56].

Hydrogel touchpad-based sweat sensors have continued to evolve after our invention to this day as listed in Table 2. Lin et al. developed an agarose hydrogel touchpad embedding an electrochemical lactate sensor [57]. Their sensor had a sensitivity of 1.88 ± 0.24 μA/(mM cm^2) in the lactate concentration range of 0 to 4 mM. The

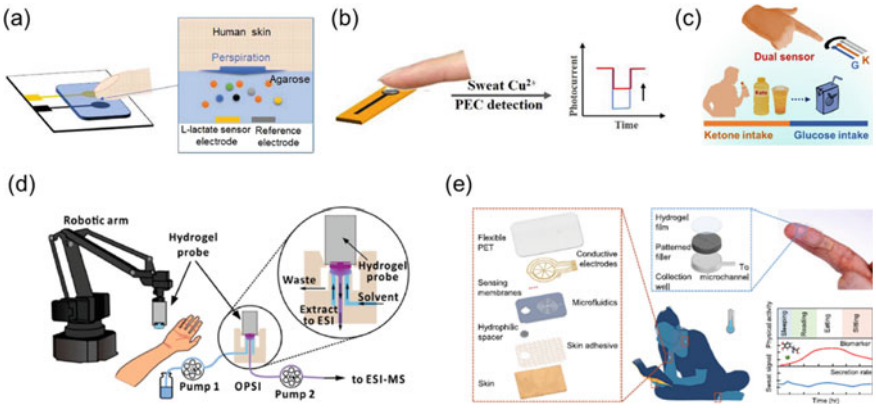

Fig. 3 Representative examples of the hydrogel-based touchpad sweat biosensors. **a** Electrochemical sweat lactate sensor using an agarose hydrogel-based touchpad (reproduced with permission from Ref. 55, http://creativecommons.org/licenses/by/4.0/). **b** Photoelectrochemical sweat Cu^{2+} sensor (reproduced with permission from Ref. 64, http://creativecommons.org/licenses/by/4.0/). **c** Sweat β-hydroxybutyrate (HB) sensor (reprinted with permission from Ref. 65. Copyright (2022) American Chemical Society). **d** Agarose hydrogel touchpad equipped with an electrospray ion source (reprinted with permission from Ref. 68. Copyright (2023) American Chemical Society). **e** Combination of a hydrogel touchpad inlet with a microfluidic channel (reproduced from Ref. 70, http://creativecommons.org/licenses/by/4.0/)

data collected by this sensor was wirelessly transferred to a cloud system for further analysis. Yin et al. developed a hydrogel touchpad-based self-powered biosensor for sweat lactate detection [58]. They used a porous polyvinyl alcohol (PVA) hydrogel as a touchpad due to its softness, mechanical strength, and the diffusibility of the sweat components. The concentration of sweat lactate was visually understood as a change in color of poly(3,4-ethylenedioxy)thiophene:poly(styrene sulfonate) (PEDOT:PSS) used as an electrochromic display, which was driven by the self-powered sensor depending on the sweat lactate concentration. Sempionatto et al. developed a thin porous PVA hydrogel touchpad-based electrochemical biosensor for sweat glucose [59]. Sweat glucose is expected to be an important biomarker that can reflect blood glucose levels. They determined a parameter that takes into account individual differences in the correlation between sweat glucose concentration and blood glucose level and demonstrated the possibility of indirect blood glucose level prediction using their sensor. Lin et al. developed a sweat glucose sensor using a PB-doped PEDOT nanocomposite as a mediator between glucose oxidase and the electrode [60]. The quantitative range of this sensor was 6.25 μM to 0.8 mM, and the limit of detection was 4 μM, which is high sensitivity enough to detect low concentrations of sweat glucose extracted in the agarose hydrogel. They demonstrated that there is a correlation between diurnal fluctuations in sweat glucose and of blood sugar levels. Tang et al. developed an electrochemical sensor using a molecularly imprinted polymer (MIP)/PB composite membrane for the detection of sweat cortisol [61]. The quantitative range of this sensor was 10 nM to 1 μM with a sensitivity of 60.31 nA/log [nM] in artificial sweat, which is enough sensitivity to detect sweat cortisol extracted in the hydrogel. They successfully monitored diurnal fluctuations in sweat cortisol using this sensor. Moon et al. developed an electrochemical L-dopa sensor to monitor its sweat concentrations after oral administration of the L-dopa/carbidopa drug [62]. The sensor was composed of a tyrosinase-modified electrode covered by a thin porous PVA hydrogel. The concentration range of linear amperometric response to L-dopa was 1–30 μM with a limit of detection of 300 nM. They demonstrated intermittent monitoring of sweat L-dopa while measuring blood L-dopa concentrations. They claimed that continuous monitoring data of sweat L-dopa can be helpful in establishing guidelines for individualized treatment of Parkinson's disease patients. Wang et al. fabricated a colorimetric sweat sensor composed of a hydrogel touchpad composed of arrayed chemical probes for pH, glucose, Cl^-, and Ca^{2+} [63]. The hydrogel was adhesive to the human skin surface in order to stably monitor the color change attributed to the change in the concentration of the extracted sweat components. Zhang et al. developed a highly sensitive photoelectrochemical sensor for the detection of natural sweat Cu^{2+}, which is a possible marker for diseases such as Wilson's disease, Menkes disease, hematological abnormalities, and kidney and cardiovascular diseases (Fig. 3b) [64]. Laser-induced graphene and In-doped CdS (LIG-In-CdS) were fabricated by laser engraving of a chitosan/Cd^{2+}/In^{3+}/ cysteine composite membrane coated on a polyimide film. The active area was covered with a PVA hydrogel. The photocurrent of the LIG-In-CdS electrode changed depending on the concentration of sweat Cu^{2+} in the range of 1.28 ng/mL to 5.12 g/mL. Moon et al. developed a natural sweat β-hydroxybutyrate (HB) sensor

(Fig. 3c) [65]. β-hydroxybutyrate is a promising biomarker for diabetic ketoacidosis diagnosis. A dual HB/glucose sensor was composed of an Au nanoparticle-modified screen-printed carbon electrode. The surface of the electrode was modified by a chitosan polymer containing toluidine blue O (as a mediator), β-hydroxybutyrate dehydrogenase, and nicotinamide adenine dinucleotide (as a cofactor), followed by entirely covering with a PVA hydrogel. The sensitivity of the sensor was 3.15 nA mM^{-1} cm^{-2} in the HB concentration range from 0.1 to 2.0 mM. The limit of detection was 14.43 μM. The glucose sensor also showed a current response depending on the glucose concentration in the concentration range from 0.1 to 2 mM. They demonstrated non-invasive dual monitoring of sweat HB and glucose during two kinds of drinks, the ketone beverage and the sweetened fruit beverage, by comparing blood ketone and glucose levels. Hu et al. developed a physical/chemical multisensing device composed of a reduced graphene oxide-modified hydrogel-based strain sensor and a hydrogel touchpad-based sweat sensor [66]. A sweat sensor based on a closed bipolar electrode was composed of a reduced graphene oxide-modified hydrogel as the cathode and a luminol-modified hydrogel as the anode. The self-healing ability of these hydrogels allows them to adhere to each other to construct a closed bipolar cell. Chemical reactions between sweat components and the reaction reagents at the cathode were coupled with the electrochemiluminescence (ECL) reaction at the anode to give a highly sensitive ECL signal. In vivo measurements were conducted by attaching the reduced graphene oxide-modified hydrogel containing reaction reagents to the subject's skin during exercise to collect sweat components into the gel. This was followed by the peeling off of the skin and wrapping one end of the luminol-modified hydrogel to measure the ECL signal correlated with the analyte concentration. Lin et al. fabricated a hydrogel touchpad-based sensor combined with photoplethysmography (to detect the subject's heart rate and oxygen saturation level) and a finger scanner to translate the touch-based input into encrypted bioinformation [67]. Two types of biosensors, an alcohol oxidase-based ethanol sensor, and a hydrogen-terminated boron-doped diamond-based acetaminophen sensor, were developed. They demonstrated the integration of a sensing system on a car handle to check the ethanol level in the driver's sweat. Another application was a pill case integrated with an acetaminophen sensor to monitor medication intake and record personal health. This multimodal sensing system will open a new era in bio-human–machine interfacing engineering. Yu et al. developed an agarose hydrogel touchpad equipped with a time-of-flight mass spectrometer (Fig. 3d) [68]. The hydrogel touchpad was held using a robotic arm for automatic sampling and highly sensitive analysis of arginine, citrulline, and histidine extracted in the agarose hydrogel. Various metabolites extracted from human skin were quantified using this system.

It is also possible to integrate the wet interface into commercially available chemical sensors (Fig. 4) [69]. For example, a filter paper impregnated with PBS as a touchpad was put on the sensing part of the commercially available sodium ion sensor (LAQUAtwin Na-11, Horiba) to establish the touchpad-based sweat sodium sensor. We hope that the practical use of the touchpad-based sweat sensor will be accelerated by actively using commercially available chemical sensors.

Table 2 A summary of representative hydrogel touchpad-based sweat biosensors

Biomarkers	Types of sensors	References
Lactate	Electrochemical sensor	[55]
Lactate	Electrochemical sensor	[57]
Lactate	Self-powered electrochemical sensor	[58]
D-glucose	Electrochemical sensor	[59]
D-glucose	Electrochemical sensor	[60]
Cl^-	Electrochemical sensor	[56]
Cortisol	Electrochemical sensor	[61]
L-Dopa	Electrochemical sensor	[62]
pH, D-glucose, Cl^-, Ca^{2+}	Colorimetric sensor	[63]
Cu^{2+}	Photoelectrochemical sensor	[64]
β-hydroxybutyrate D-glucose	Electrochemical sensor	[65]
Urea, Lactic acid, Cl^-	Electrochemiluminescence sensor	[66]
Ethanol, Acetaminophen	Electrochemical sensor	[67]
Arginine, Citrulline, Histidine, Caffeine	quadrupole-time-of-flight mass spectrometer	[68]
Sweat pH, Cl^-, D-glucose, L-Dopa, perspiration rate	Electrochemical sensor	[70]
Cortisol, Mg^{2+}, sweat pH	Electrochemical sensor	[71]

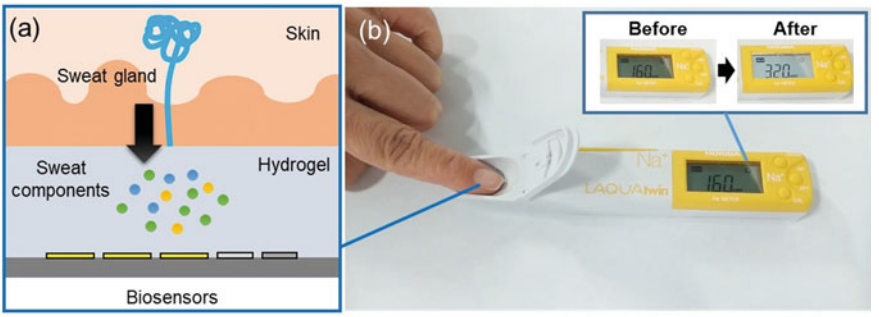

Fig. 4 **a** Illustration of the interface between human skin and a touchpad-based sweat biosensor. **b** Photograph of a touchpad-based sweat Na^+ sensor fabricated by using the commercially available sodium ion meter (reproduced with permission from Ref. 69, http://creativecommons.org/licenses/by/4.0/)

5 Limitations of the Hydrogel Touchpad-Based Sweat Sensors

Quantifying the amount of sweat extracted into hydrogels is still a major challenge. Therefore, it is difficult to distinguish whether the change in the concentration of sweat components detected by the hydrogel touchpad-based sensor is due to the amount of sweat extracted or the change in the concentration of sweat components. One straightforward strategy to solve this problem is to ignore the contribution of the perspiration volume over a relatively short sampling time compared to the volume of the hydrogel [67]. The other quantitative solution is the combination of a hydrogel touchpad inlet with a microfluidic channel (Fig. 3e) [70, 71]. In this configuration, the at-rest sweat extracted into the hydrogel touchpad was directly introduced into the microchannel to calculate the extracted sweat volume from the microchannel dimensions. Using this device, Nyein et al. calculated the rate of sweating in human fingers in contact with the hydrogel to be 0.1–1 $\mu L\ min^{-1}\ cm^{-2}$. However, because the rate of sweating at rest is so slow, the sweat previously introduced into the channel can be mixed with new sweat that has just been introduced, averaging the concentration detected by the sensor. Challenges remain in real time and simultaneous quantification of both the at-rest sweat volume and the concentration of at-rest sweat components in the hydrogel touchpad.

6 Conclusions and Future Perspectives

This chapter summarized the advances in sweat sensors and the relevant sweat collection methods. We consider that hydrogel touchpad-based sweat sensors are now among the best solutions for the quantitative collection and detection of at-rest sweat components because of their safety, and simple construction and use. On the other hand, detailed research is still required on the relationship between changes in the concentration of sweat components and diseases. By simultaneously analyzing sweat components and developing sensors for the required biomarkers, we hope to establish sweat component sensors that can contribute to the realization of individualized healthcare in the future.

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