Chapter

Introductory Chapter: Wearable Technologies for Healthcare Monitoring

Noushin Nasiri

1. Introduction

Wearable technologies are becoming increasingly popular as personal health system, enabling continuous real-time monitoring of human health on a daily basis and outside clinical environments [1–3]. The wearable device market is currently having a worldwide profit of around $34 billion and is expected to reach above $50 billion by 2022 owing to wearables' ease of use, flexibility, and convenience [4]. Real-time monitoring, operational efficiency, and fitness tracking are reported as main factors supporting the market growth of health wearable devices such as smart watches, smart glasses, and other wellness gadgets, with expected $12.1 billion world market by 2021 [5].

In the past decade, the recent progress in developing wearable devices was more focused on monitoring physical parameters, such as motion, respiration rate, etc. [3, 6, 7]. Today, there is a great interest in evolving wearable sensors capable of detecting chemical markers relevant to the status of health. Different approaches have been applied by researchers to design and fabricate wearable biosensors for remote monitoring of metabolites and electrolytes in body fluids including tear, sweat, and saliva [3, 8–10]. A great example would be the development of small and reliable sensors that would allow continuous glucose monitoring in diabetic patients [11, 12]. Diabetes is a chronic disease that can significantly impact on quality of life and reduce life expectancy. However, diabetics can stay one step ahead of the disease by monitoring their blood glucose level to minimize the complication of the disease by proper administration of insulin. Currently, blood analysis is the gold standard method for measuring the level of glucose in patient's blood. However, this technique cannot be applied without penetrating the skin, which can be painful and inconvenient, and requires user obedience. Therefore, current research focuses on the development of portable and wearable devices capable of continuous glucose sensing through noninvasive detection techniques.

2. Tear analysis

A majority of the recent studies in this field have targeted the area of personalized medicine, endeavoring to develop miniaturized wearable devices featuring real-time glucose monitoring in diabetic patients [12–15]. One great example is contact lens which is an ideal wearable device that can be worn for hours without any pain or discomfort [16]. Integration of glucose biosensors into contact lenses has recently been demonstrated by several research groups [9, 17, 18]. However, the level of glucose in tear fluid is very low (0.1–0.6 mM), requiring a high sensitivity of the sensor for picking up the signal from expected chemical reaction [3, 19]. Yao et al. [16] have fabricated a contact lens with integrated sensor for continuous tear glucose monitoring with wireless communication system over a distance of several centimeters. The sensor demonstrated a fast response of 20 s with a minimum detection of less than 0.01 mM glucose, which is 10–60 times lower than glucose level in human tear [16].

In addition to glucose, lactate is an important metabolite in the human body, which gets converted into L-lactate under hypoxic condition [20]. L-Lactate levels in tear fluid is about 1–5 mmol L^{-1}, which might increase significantly due to some heath conditions including ischemia, inadequate tissue oxygenation, stroke, and different types of cancer [21]. Thomas et al. [22] demonstrated an invasive detection of lactate in human tear by integrating an amperometric lactate sensor with Pt working (WE) and reference (RE) electrodes as well as a counter electrode (CE) as current drain, on a polymer-based contact lens, measuring lactate in situ in human tears without any need for physical sampling [22].

Very recently, Park et al. [17] reported a novel approach for fabricating fully transparent and stretchable smart contact lens capable of wirelessly monitoring the level of glucose in the tears of diabetic patients. **Figure 1** shows the layout of fabricated devices made of glucose sensors, wireless circuit, and display pixel on soft and transparent contact lens substrate (**Figure 1a** and **b**). The circuit diagram of the device is illustrated in Figure 1a, with radio frequency antenna receiving signals from a transmitter and a rectifier converting the signals to DC (**Figure 1a** and **c**). A continuous network of ultralong Ag nanofibers was used as stretchable electrodes for the antenna and interconnects (**Figure 1d**). In the case of any change in the concentration of glucose in tear, the sensor resistance changes resulting in the light-emitting diode (LED) pixel turning on or off. The device was tested in vitro using a live rabbit, providing substantial finding for smart contact lenses as one of the promising wearable devices in healthcare system [17].

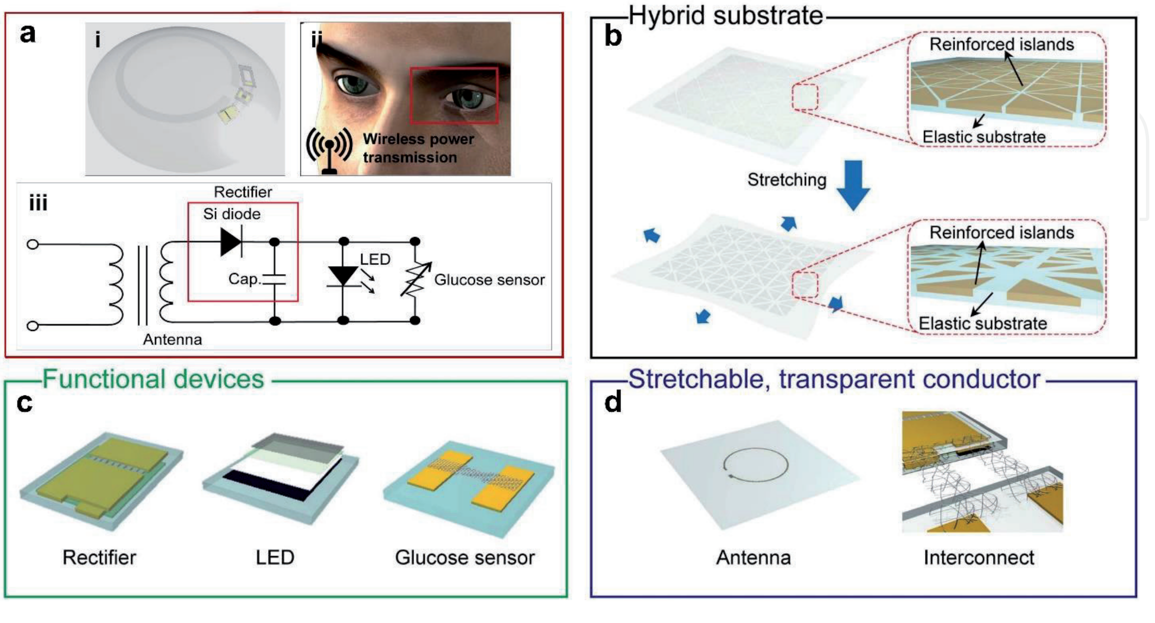

Figure 1.
(a) (i) Schematic illustration and (ii) operation of the soft, smart contact lens and (iii) the circuit diagram of the smart contact lens system. The soft, smart contact lens is composed of (b) a hybrid substrate; (c) functional devices including rectifier, LED, and glucose sensor; and (d) a transparent, stretchable conductor for antenna and interconnects [17].

3. Sweat analysis

In addition to tear, sweat electrolyte concentrations and blood serum are related [2, 8]. As one of the most readily accessible human biofluids, a great deal of information about the human body and its physical performance could be obtained via monitoring sweat electrolyte concentrations [23, 24]. Several groups have reported the key biomarkers in human sweat (e.g., sodium level, pH change, lactate concentration) relevant to human health and well-being, for monitoring athletic performance during sporting activities [25]. Jia et al. fabricated a skin-worn tattoo-based sensor for real-time monitoring of lactate in human sweat, offering substantial benefits for biomedical as well as sport applications [25]. In another approach, Curto et al. [26] fabricated a wearable and flexible microfluidic platform capable of monitoring changes in the sweat pH in real time. Anastasova et al. [27] developed a flexible microfluidic device for real-time monitoring of metabolite such as lactate as well as electrolytes such as pH and sodium in human sweat. Recently, Gao et al. [28] developed a flexible and wearable device (**Figure 2**) made of arrays of sensors for real-time monitoring of heavy metals, such as Zn, Cu, and Hg in human sweat. The device fabrication method is presented in **Figure 2a**, showing the deposition and stripping steps on microelectrodes. The sensing mechanism was based on an electrochemical detection of targeted heavy metals through four microelectrodes, including Au and Bi working electrodes, Ag reference electrode, and an Au counter electrode (**Figure 2b** and **c**). The fabricated device demonstrated high stability and selectivity toward heavy metals, providing a great platform to advancing the field of wearable biosensors for healthcare application, via monitoring the level of some heavy metals in human sweat [28]. A balanced level of Zn is necessary in the human body as a low and high Zn concentration can lead to pneumonia and liver damages, respectively [29, 30]. High level of Cu in the human body can lead to several diseases including Wilson's disease and heart, kidney, and liver failures as well as brain diseases [31, 32]. The fabricated device demonstrated high stability and selectivity toward heavy metals, providing a great platform to advancing the field of wearable biosensors for healthcare application [28].

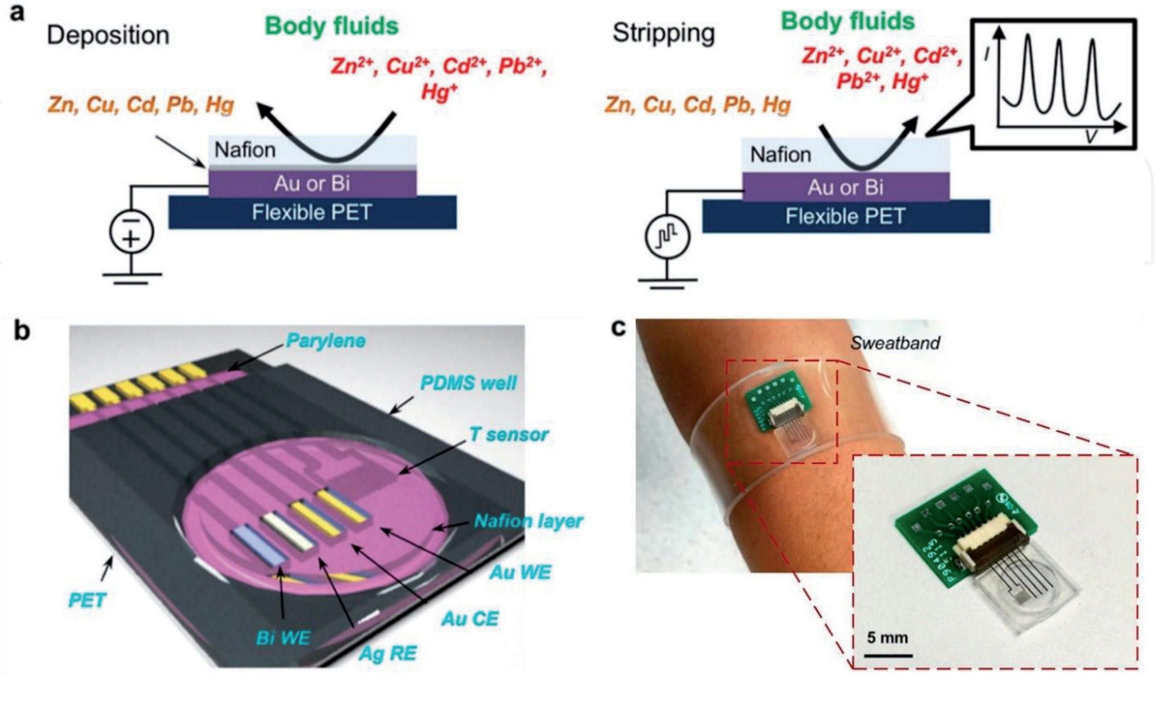

Figure 2.
(a) A schematic showing the concept of deposition and stripping on microelectrodes. (b) A schematic showing the composition of the microsensor array. (c) Optical image of a flexible sensor array interfacing with a flexible printed circuit connector [28].

4. Saliva analysis

Saliva, as a great diagnostic fluid, can be used in personal health devices for real-time monitoring of chemical markers including salivary lactate analysis [33]. Chai et al. developed a saliva nanosensor with a radio-frequency identification tag, integrated into dental implants for detecting cardiac biomarkers in saliva and predicting close heart attack in patients suffering from cardiovascular diseases [34]. In another approach, an instrumented mouthguard was designed and fabricated by Kim et al. [35] for measuring salivary uric acid levels which could be a biomarker for several diseases including hyperuricemia, gout, physical stress, and renal syndrome. The fabricated device showed high selectivity and sensitivity to low level of uric acid as well as great stability during a 4-h operation period [35]. Mannoor et al. [36] developed a hybrid biosensor made of graphene layers printed onto water-soluble silk, for noninvasive detection of bacteria through body fluids including sweat and saliva. This graphene/silk hybrid device illustrated an extremely high sensitivity to bacteria in body fluid with detection limits down to a single bacterium [36]. In addition, the fabricated device provided the potential users with battery-free operation and wireless communication system via radio frequency [36]. Arakawa et al. [37] designed and fabricated a salivary sensor equipped with a wireless measurement system, embedded onto a mouthguard support, featuring a high sensitivity toward detection of glucose over a range of 5–1000 μmol L^{-1}. The device demonstrated a great stability during a 5-h real-time glucose monitoring period in an artificial saliva with a phantom jaw [37]. In a similar approach, de Castro et al. [38] developed a microfluidic paper-based device integrated into a mouthguard, for continues monitoring of glucose and nitrite in human saliva. The saliva samples were collected from periodontitis and/or diabetes patients as well as healthy individuals. The fabricated device featured a low detection limit of 27 and 7 μmol L^{-1} for glucose and nitrite, respectively [38].

5. Summary

In summary, there is a great potential for micro- and nanosensors' integration into healthcare monitoring devices, developing new technologies for noninvasive detection of diseases in the human body. Flexible wearable devices offer promising capabilities in real-time monitoring of body fluids including tear, sweat, and saliva. However, more research is required to expand the use of wearable platforms in continuous analysis of body fluids, providing reliable real-time detection of targeting ions and proteins, among other complex analytes.

Author details

Noushin Nasiri
School of Engineering, Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia

*Address all correspondence to: noushin.nasiri@mq.edu.au

References

[1] Trung TQ, Lee NE. Flexible and stretchable physical sensor integrated platforms for wearable human-activity monitoring and personal healthcare. Advanced Materials. 2016;**28**(22):4338-4372

[2] Nakata S, Arie T, Akita S, Takei K. Wearable, flexible, and multifunctional healthcare device with an ISFET chemical sensor for simultaneous sweat pH and skin temperature monitoring. ACS Sensors. 2017;**2**(3):443-448

[3] Tricoli A, Nasiri N, De S. Wearable and miniaturized sensor technologies for personalized and preventive medicine. Advanced Functional Materials. 2017;**27**(15):1605271

[4] Arnold JF, Sade RM. Wearable technologies in collegiate sports: The ethics of collecting biometric data from student-athletes. The American Journal of Bioethics. 2017;**17**(1):67-70

[5] Lymberis A, De Rossi DE. Wearable Ehealth Systems for Personalised Health Management: State of the Art and Future Challenges. Vol. 108. Netherlands: IOS Press; 2004

[6] Takei K, Honda W, Harada S, Arie T, Akita S. Toward flexible and wearable human-interactive health-monitoring devices. Advanced Healthcare Materials. 2015;**4**(4):487-500

[7] Honda W, Harada S, Arie T, Akita S, Takei K. Wearable, human-interactive, health-monitoring, wireless devices fabricated by macroscale printing techniques. Advanced Functional Materials. 2014;**24**(22):3299-3304

[8] Bariya M, Nyein HYY, Javey A. Wearable sweat sensors. Nature Electronics. 2018;**1**(3):160

[9] Kim J, Kim M, Lee M-S, Kim K, Ji S, Kim Y-T, et al. Wearable smart sensor systems integrated on soft contact lenses for wireless ocular diagnostics. Nature Communications. 2017;**8**:14997

[10] Malon RS, Sadir S, Balakrishnan M, Córcoles EP. Saliva-based biosensors: Noninvasive monitoring tool for clinical diagnostics. BioMed Research International. 2014;**2014**:962903

[11] Cappon G, Acciaroli G, Vettoretti M, Facchinetti A, Sparacino G. Wearable continuous glucose monitoring sensors: A revolution in diabetes treatment. Electronics. 2017;**6**(3):65

[12] Kim J, Campbell AS, Wang J. Wearable non-invasive epidermal glucose sensors: A review. Talanta. 2018;**177**:163-170

[13] Arakawa T, Kuroki Y, Nitta H, Toma K, Mitsubayashi K, Takeuchi S, et al. Mouth guard type biosensor "cavitous sensor" for monitoring of saliva glucose with telemetry system. In: 2015 9th International Conference on Sensing Technology (ICST), 2015. New Zealand: IEEE; 2015. pp. 46-49

[14] Blaikie TP, Edge JA, Hancock G, Lunn D, Megson C, Peverall R, et al. Comparison of breath gases, including acetone, with blood glucose and blood ketones in children and adolescents with type 1 diabetes. Journal of Breath Research. 2014;**8**(4):046010

[15] Chu MX, Miyajima K, Takahashi D, Arakawa T, Sano K, Sawada S-I, et al. Soft contact lens biosensor for in situ monitoring of tear glucose as non-invasive blood sugar assessment. Talanta. 2011;**83**(3):960-965

[16] Yao H, Liao Y, Lingley A, Afanasiev A, Lähdesmäki I, Otis B, et al. A contact lens with integrated telecommunication circuit and sensors for wireless and continuous tear glucose monitoring. Journal of

Micromechanics and Microengineering. 2012;**22**(7):075007

[17] Park J, Kim J, Kim S-Y, Cheong WH, Jang J, Park Y-G, et al. Soft, smart contact lenses with integrations of wireless circuits, glucose sensors, and displays. Science Advances. 2018;**4**(1):eaap9841

[18] Badugu R, Lakowicz JR, Geddes CD. Noninvasive continuous monitoring of physiological glucose using a monosaccharide-sensing contact lens. Analytical Chemistry. 2004;**76**(3):610-618

[19] Lin Y-R, Hung C-C, Chiu H-Y, Chang P-H, Li B-R, Cheng S-J, et al. Noninvasive glucose monitoring with a contact lens and smartphone. Sensors. 2018;**18**(10):3208

[20] Farandos NM, Yetisen AK, Monteiro MJ, Lowe CR, Yun SH. Contact lens sensors in ocular diagnostics. Advanced Healthcare Materials. 2015;**4**(6):792-810

[21] Pankratov D, González-Arribas E, Blum Z, Shleev S. Tear based bioelectronics. Electroanalysis. 2016;**28**(6):1250-1266

[22] Thomas N, Lähdesmäki I, Parviz BA. A contact lens with an integrated lactate sensor. Sensors & Actuators, B: Chemical. 2012;**162**(1):128-134

[23] Liu G, Ho C, Slappey N, Zhou Z, Snelgrove SE, Brown M, et al. A wearable conductivity sensor for wireless real-time sweat monitoring. Sensors & Actuators, B: Chemical. 2016;**227**:35-42

[24] Pribil MM, Laptev GU, Karyakina EE, Karyakin AA. Noninvasive hypoxia monitor based on gene-free engineering of lactate oxidase for analysis of undiluted sweat. Analytical Chemistry. 2014;**86**(11):5215-5219

[25] Jia W, Bandodkar AJ, Valdés-Ramírez G, Windmiller JR, Yang Z, Ramírez J, et al. Electrochemical tattoo biosensors for real-time noninvasive lactate monitoring in human perspiration. Analytical Chemistry. 2013;**85**(14):6553-6560

[26] Curto VF, Fay C, Coyle S, Byrne R, O'Toole C, Barry C, et al. Real-time sweat pH monitoring based on a wearable chemical barcode micro-fluidic platform incorporating ionic liquids. Sensors & Actuators, B: Chemical. 2012;**171-172**:1327-1334

[27] Anastasova S, Crewther B, Bembnowicz P, Curto V, Ip HM, Rosa B, et al. A wearable multisensing patch for continuous sweat monitoring. Biosensors & Bioelectronics. 2017;**93**:139-145

[28] Gao W, Nyein HY, Shahpar Z, Fahad HM, Chen K, Emaminejad S, et al. Wearable microsensor array for multiplexed heavy metal monitoring of body fluids. ACS Sensors. 2016;**1**(7):866-874

[29] Lassi ZS, Moin A, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. Cochrane Database of Systematic Reviews. 2016;**12**:CD005978

[30] Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. Nutrition in Clinical Practice. 2012;**27**(1):8-20

[31] Crisponi G, Nurchi VM, Fanni D, Gerosa C, Nemolato S, Faa G. Copper-related diseases: From chemistry to molecular pathology. Coordination Chemistry Reviews. 2010;**254**(7-8):876-889

[32] Huster D. Wilson disease. Best Practice & Research. Clinical Gastroenterology. 2010;**24**(5):531-539

[33] Lee J, Garon E, Wong D. Salivary diagnostics. Orthodontics & Craniofacial Research. 2009;**12**(3):206-211

[34] Chai PR, Castillo-Mancilla J, Buffkin E, Darling C, Rosen RK, Horvath KJ, et al. Utilizing an ingestible biosensor to assess real-time medication adherence. Journal of Medical Toxicology. 2015;**11**(4):439-444

[35] Kim J, Imani S, de Araujo WR, Warchall J, Valdés-Ramírez G, Paixão TRLC, et al. Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. Biosensors & Bioelectronics. 2015;**74**:1061-1068

[36] Mannoor MS, Tao H, Clayton JD, Sengupta A, Kaplan DL, Naik RR, et al. Graphene-based wireless bacteria detection on tooth enamel. Nature Communications. 2012;**3**:763

[37] Arakawa T, Kuroki Y, Nitta H, Chouhan P, Toma K, Sawada S-I, et al. Mouthguard biosensor with telemetry system for monitoring of saliva glucose: A novel cavitas sensor. Biosensors and Bioelectronics. 2016;**84**:106-111

[38] de Castro LF, de Freitas SV, Duarte LC, de Souza JAC, Paixão TR, Coltro WK. Salivary diagnostics on paper microfluidic devices and their use as wearable sensors for glucose monitoring. Analytical and Bioanalytical Chemistry. 2019:1-10