Non-Invasive Wearable Biosensors for Detection of Sweat and ISF in Daily Life

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Abstract. The potential of wearable sensors to non-invasively continuously monitor single or multiple objects within biological fluids such as sweat, saliva, interstitial fluid, and tears has been widely recognized. There have been recent breakthroughs in optical, electrical, piezoelectric and iontophoresis-based sensors. Targeted monitoring of glucose, alcohol, cortisol and lactic acid can be achieved. There are also some works devoted to multi-source sensor integration and the construction of multi-analyte sensors. Various research efforts are devoted to sensor miniaturization, the development of flexible materials, and the improvement of reliability. Although the current non-invasive wearable sensors for sweat and interstitial fluid have proven to have high potential, the relationship between the chemical components in sweat and interstitial fluid and the components in blood still needs more experimental verification, and their application in daily life The stability and accuracy of live tense has not been proven. It is necessary to conduct a detailed and in-depth exploration of the connection between various monitoring indicators and human health to promote the credibility and recognition of sensors in daily society. Non-invasive wearable sensors for sweat and interstitial fluid will have a profound impact on people's daily lives and health monitoring.

Keywords: Non-invasive, wearable sensors, health monitoring.

1. Introduction

Early sensors focused on detecting some simple reactions and some obvious activities of the human body. With the development of integrated circuits and smart devices, sensors have gradually become miniaturized and intelligent. In recent years, the focus of research has shifted to using biosensors to help solve major human health problems. Sweat is a biological fluid of low consumption but high significance, containing metabolites, electrolytes, trace elements, as well as minimal amounts of macromolecules. Because some of the components in sweat diffuse from the blood, some of them have been proven to reflect the health of the human body by reflecting the physiological state of the blood. Sweat has become a non-invasive monitoring medium that has received considerable attention. And ensures sustainable detection of sweat through methods such as long-term exercise, heat additive, pressure and iontophoresis. Interstitial fluid diffuses directly from blood vessels through the endothelium, lies beneath the skin surface and centers at the spaces between tissue cells. Many interstitial fluid components show a good correlation with blood components [1]. Noninvasive interstitial fluid specimens can be easily carried out on the epidermis, often through iontophoresis and phonophoresis. The current level of research can only achieve single monitoring of sweat or interstitial fluid using non-invasive wearable sensors, and the joint monitoring of interstitial fluid and sweat has not yet been specifically studied. When sweat or interstitial fluid monitoring is used alone, monitoring accuracy has not been guaranteed.

This article will report on the current progress of non-invasive wearable sensors in different sensor types and sensors that detect different detection indicators. The research on optical and electrochemical sensors is relatively mature, and emerging research mainly focuses on piezoelectric, iontophoresis, and multi-analyte integrated sensors. There are also many emerging monitoring sensors for detecting components such as glucose, alcohol, lactic acid, cortisol, pH, and electrolytes in sweat and interstitial fluid [2, 3].

The purpose of this study is to discuss the current progress of non-invasive wearable sensors based on different sensor types and different detection components and to find problems that need to be improved from existing research to guide the direction of subsequent development. To help develop non-invasive wearable sensors with high accuracy, durability, and affinity that can be used for health monitoring in daily life and to aid clinical practice.

2. Equipment and Testing Technology

2.1. Optical Wearable Sensors

An optical sensor consists of a substrate, a sensing unit, and a signal conversion and processing unit. Like other components, optical sensors measure chemical or biological reactions such as absorbance, fluorescence, scattering, and color changes. Optical sensors primarily encompass sensors based on surface-enhanced Raman scattering, colorimetry, fluorescence, plasma, photoplethysmography, and interference. Various optical techniques including fluorescence, colorimetry, photoplethysmography, and SERS were investigated for wearable detection. Colorimetric sensors focus on wavelength changes in the absorption spectrum, while fluorescent sensors use fluorophores to monitor the absorption and emission of light energy. Optical sensors currently monitor blood, breathing, body activity, and more. SPR-based optical sensors, optical fiber-based biosensors, and stretchable skin-like wearable optical sensors based on PDMS films all have good potential.

2.2. Electrochemical Wearable Sensors

An electrochemical sensor consists of a substrate, a bioreceptor, electrodes, amplifier circuitry, software, and a display. Electrochemical sensors primarily use screen-printed electrodes and imprint transfer electrodes to form a durable and flexible thick film that can be used to measure pH, sodium, copper, chlorine, cadmium, ammonium, lead, calcium, glucose, lactic acid, uric acid, mercury, ethanol, ascorbic acid, and cortisol in a sample. Electrochemical sensors have a higher potential for miniaturization and automation [4-7].

Electrochemical sensors work on four principles: amperometric method, potentiometric method, conductivity method, and field-effect crystal method. Chronoampering is a method in which the current response as a function of time is measured after a single or double potential step is applied to the working electrode of an electrochemical system. The rate of the redox reaction is strongly related to the concentration of the analyte, and the redox reaction determines the previous fixed potential value. Potentiometry is a technique for measuring the charge accumulation of a working electrode relative to a reference electrode in the absence of an electric current. In terms of how it works, potentiometric techniques are mainly used to detect different kinds of ions. The conductivity method is an approach to determining the conductivity between electrodes or the impedance of a solution, and it has a high sensitivity. Field-effect transistors (FETs) detect biomolecules by controlling the gate voltage of the input loop and measuring the source-drain current of the output circuit.

2.3. Piezoelectric Wearable Sensors

Piezoelectric wearable sensors harness the direct piezoelectric effect to transform mechanical energy into electrical energy via piezoelectric energy harvesters (PEH) or piezoelectric nanogenerators (PENG). These devices boast high sensitivity, power density, durability, scalability, mechanical stability, a straightforward design, and numerous other benefits. Piezoelectric wearable sensors consist of a flexible substrate, piezoelectric materials, and subsequent signal conversion and processing devices. Piezoelectric materials commonly used in piezoelectric wearable sensors include ceramics, quartz crystals, and inorganic semiconductors. Emerging piezoelectric materials include gallium nitride and bioelectronic skin. Piezoelectric wearable sensors are effective at monitoring subtle human activities, including facial activity, brain activity, and sleep. The high-voltage flexible and retractable piezoelectric energy harvester shows great potential in maintaining the sustainable operation of wearables, but there are still many problems with the biocompatibility of its materials [8, 9].

2.4. Iontophoresis-based Sensors

Most skin sweat sensors rely on large amounts of exercise to produce sweat, but the continuity of sweat produced by the human body under non-exercise conditions is less controllable. Choosing iontophoresis to induce sweat and interstitial fluid for monitoring has become a key research object. This method uses microcurrent to drive cholinergic agonists such as pilocarpine to influence nearby sweat glands to produce sweat or extract interstitial fluid. The use of iontophoresis to pass substances through the epidermis to the skin surface called reverse iontophoresis, enables non-invasive sampling of sweat and interstitial fluid components. Iontophoresis has the advantages of painless sampling and sufficient sample volume [10]. Some studies have combined iontophoresis, microfluidics and electrochemistry to simultaneously stimulate and monitor sweat. It is also pointed out that such integrated devices can be used for personalized medical care in the future. Another study also combined iontophoresis, microfluidics, and electrochemistry to specifically monitor β-hydroxybutyrate in sweat. This device can replace disposable enzymatic electrode blood electrochemical sensors that require frequent finger pricking. There is also research using the principle of dual iontophoresis that samples both interstitial fluid and sweat fluid, integrating a dual electrochemical biosensing system for the detection of glucose and sweat alcohol in interstitial fluid on a single disposable wearable tattoo platform [1, 10].

2.5. Multi-analyte Integrated Sensor

Early biosensors focused on a single detection of a certain physical property or chemical substance, but biological fluids are characterized by multiple analytes, mixtures, and complex components, hindering the usefulness of biosensors for comprehensive health assessment of organisms. Due to the need for long-term monitoring of complex environments or dynamics, a large number of recent studies have focused on integrated sensors for multi-analytes. Its stable detection over a long period of time can serve as a good alternative to complex invasive clinical testing. Hybrid multi-modal sensors can combine multiple single-modal sensors for different application scenarios and objects. Such devices play a role in early disease prevention, long-term monitoring and personalized treatment. Monitoring objects include brain and body activity, wound healing, blood and vital signs, etc. In addition to integrating multi-analyte sensors with energy modules, there are also studies involving the integration of artificial intelligence to face the complexity of processing objects and improve the accuracy of multi-analyte integrated sensors [11, 12].

3. Main Monitoring Objects

After the development of biosensors and the attention to personal health status and personal medicine, non-invasive wearable sensors have received great attention. Relying on its high accuracy, rapid detection, low cost, and energy consumption, and the characteristics of long-term monitoring, it can replace the invasive equipment in the hospital to complete painless, long-term and accurate monitoring of the use of objects. Non-invasive wearable sensors have been widely used in the monitoring of bodily fluids and even non-bodily fluids (sweat, tears, saliva). Its non-invasive nature keeps the collective protective tissue of the organism from being destroyed, ensuring that the health of the organism is not affected while monitoring. This long-term, real-time monitoring can help to understand the dynamic biochemical conditions in the user's body and can coexist well with the user's daily life because invasive physiological pain is avoided [1, 3, 4].

As a biological fluid produced by the human body, the components in sweat, such as electrolytes, biological macromolecules, metabolites, etc., have been proven to have high scientific research value and can reflect the physiological and biochemical state of the human body. And in some cases, the independent concentration of the components in sweat can directly reflect the state of health. The extraction of blood is difficult due to the use of non-invasive devices to extract biological fluids. However, many of the physicochemical components of the interstitial fluid, which are present under the surface of the skin and fill the interstitial spaces between tissue cells, have been shown to have a very high degree of similarity to those found in blood. GlucoWatch company's ISF glucose sensing device is approved by the United States Food and Drug Administration for high reliability and potential to use ISF to monitor human health [13-18].

3.1. Glucose

Since glucose-related diseases such as diabetes have a great impact on the human body, the amount of glucose in the human body has been greatly valued. Since the 1970s, electrochemical blood glucose analyzers, enzyme electrode self-test blood glucose test strips, subcutaneously implanted needle blood glucose monitors, nanotechnology blood glucose monitors, and other devices have been developed one after another. Most of these electrochemical sensors rely on invasive blood sampling techniques and are enzyme-based. Scientific research focuses on creating non-invasive blood glucose monitoring techniques, such as through sweat. Non-invasive wearable blood glucose testing devices can achieve painless long-term dynamic monitoring of patients' blood glucose. Wang et al. proposed a highly stretchable platinum decorative graphitic-based non-enzymatic glucose sensor that records glucose oxidation microcurrents by chronoampering to achieve enzyme-free detection. In this study, it is also mentioned that glucose oxidase is immobilized on a platinum-decorated graphite-based biosensor for enzyme detection [19]. The sensitivity level of the enzyme-free sensor is greatly improved by the combination of the two methods. Studies have shown that non-invasive wearable biosensors have great potential as an alternative adhesive for glucose concentrations in long-term dynamic human sweat samples [13].

3.2. Alcohol

Due to the impact of alcohol on human physiological functions and social security and stability, society has a very high demand for alcohol testing, and a large amount of human and material resources have been invested. Blood alcohol concentration is currently the most commonly used indicator of alcohol intoxication and cannot be obtained without damaging the skin. This indicator is usually achieved by pricking the finger or earlobe with a lancet, which is painful and inconvenient and requires the cooperation of the user. Breathalyzers, which indirectly estimate blood alcohol concentration, are now widely used. Device results are susceptible to interference from humidity, temperature, and chemicals associated with consumer products such as mouthwash and breath fresheners, as well as environmental factors such as paint fumes, varnishes and alcohol vapors. Kim et al. presents an integrated, tattoo-based wearable system for effective non-invasive ethanol monitoring. This system utilizes sweat-induced iontophoresis and amperoenzymatic biosensing, along with a flexible electronic readout module that supports wireless telemetry capabilities. The device uses constant current iontophoresis to induce sweating followed by electrobiosensing of sweat ethanol without the need to change electrodes. And all electrodes are manufactured on wearable temporary tattoo paper using screen printing technology, with good cost control and easy to wear [14].

3.3. Cortisol

Cortisol is a neuroendocrine product of the regulation of the hypothalamic-pituitary-adrenal (HPA) axis caused by psychosocial and physiological stress, and long-term dynamic changes in the HPA axis are thought to be related to the body's adaptive response to stress and pathological processes. The quantification of stress levels is considered to be informative and of high diagnostic value. Previous research has linked cortisol circadian rhythm disruption to post-traumatic stress disorder and major depressive disorder and plays a key role in human performance under stress. Currently, the mainstream method of detecting stress hormones is blood testing, but its invasiveness and inability to monitor for long periods of time create uncontrollable factors for results. Tu et al. exhibited an integrated wireless mHealth device, known as the graphene-based sweat pressure sensing system (GS 4), capable of analyzing stress hormones in sweat. By uniquely combining laser-induced graphene and immunosensing, the device attains exceptional sensitivity, selectivity, and efficiency in stress hormone detection. The significance of this study is that for the first time, a dynamic stress response curve constructed from cortisol diurnal cycle and human sweat was constructed and presented. The characteristic circadian cortisol rhythm can be monitored over time, and the stress response triggered by acute external stimuli can be analyzed over time. Sweat has great potential to help monitor the long-term circadian rhythm of cortisol to better cope with stress and improve clinical detection and treatment [15].

3.4. Lactic Acid

Lactic acid is a product of human body's anaerobic respiration, and real-time monitoring of its dynamic changes can help understand human health. Lactic acid is also associated with conditions such as hypoxia, metabolic disorders, kidney failure, heart failure, and respiratory failure. Traditional lactate testing equipment usually detects lactate content in blood, and long-term monitoring often requires repeated blood collection, which is inconvenient. Wearable non-invasive body fluid lactate sensors can solve this problem and achieve non-invasive long-term dynamic monitoring of lactate. Komkova et al. introduced two sensors for lactate detection: an enzyme-nanozyme biosensor designed for continuous, flow-independent monitoring of sweat lactate, and a high-precision, low-power wearable controller known as UMKA (Universal Monitoring Kit - Ammeter). In this study, it is proposed to integrate two sensors to control the effect of sweat secretion flow on lactate monitoring. Integrated equipment allows for fast, accurate long-term monitoring [16, 17].

3.5. pH and Electrolytes

The electrolytes and pH conditions in biological fluids have a great impact on the homeostasis of the biological internal environment, and some special electrolytes are closely related to the normal physiological functions of the human body. The physiological mechanism of the human body determines electrolytes and pH, and there is a mutual influence between different electrolytes. Therefore, there are some studies using one or more electrolytes together with pH as analytes. Gao et al. developed a fully integrated wearable electrochemical platform that enables simultaneous, in-situ analysis of Ca^{2+} and pH in body fluids, offering comprehensive insights into Ca^{2+} and pH homeostasis in the human body. Bandodkar et al. introduced a novel tattoo-based solid contact ion selective electrode (ISE) for non-invasive monitoring of epidermal pH levels, as well as direct and continuous non-invasive tracking of sweat sodium concentration on the human epidermis [18-20].

4. Challenges and Future Developments

Wearable, non-invasive sensors have been shown to be useful for long-term accurate monitoring of a wide range of sweat and interstitial fluid substances. For example, it is possible to detect body movements, electrocardiograms, heavy metals, metabolites, etc. Although non-invasive wearable sensors have come a long way, they still face many problems, especially in actual clinical trials and daily use. Whether the flexibility of the material can be adapted to human activities. Whether the sensor is manufactured to allow the user to adapt. Whether the sensor can cope with the mechanical stresses of everyday life. Whether the deformed circuits and biometric components can work stably. Whether the process of detecting biomarkers and the principles for drawing conclusions about health problems are universally effective. Whether it can successfully detect low concentrations and difficult to measure objects. Can multi-analyte integrated sensors ensure fast detection results? Whether the complex living environment will affect the operation of the sensor. There are many issues that need to be addressed urgently.

Wearable, noninvasive sensors for monitoring sweat and interstitial fluid are mostly in the early experimental stages and have a long way to go before they can be put into daily use on a large scale. However, there is a clear direction of work in this field. It is expected that in the future, wearable non-invasive sensors for sweat and interstitial fluid monitoring will be highly integrated, small in size, widely monitored, long in operation, and stable. It allows for a proper and comprehensive medical diagnosis and health assessment.

5. Conclusion

In this review, we focus on the main types of non-invasive sensors and the targets of monitoring, and present the studies that have demonstrated outstanding performance and potential. At present, a large number of non-invasive wearable sensors have been basically studied, but there is still a long way to go before they are widely used in clinical practice and put into the market. Existing studies have demonstrated the potential of non-invasive wearable sensors for long-term accurate detection in a variety of situations, but have also found that sensor strength and flexibility are not compatible. It also has the problems of small battery capacity, difficult to work for a long time, and the monitoring data and body condition are not strongly oriented.

However, the practical advantages of non-invasive wearable sensors are obvious, and they can be a perfect replacement for the current invasive, large-scale, difficult-to-move, and expensive detection instruments. Achieve non-invasive, long-term, and accurate monitoring. Achieve user-friendly, long-term dynamic monitoring and contribute to a more complete and accurate health care system.

In the future, the main direction of research is to develop hardware with affinity, durability and practicality, in-depth research on the reliable connection between sweat and interstitial fluid composition and body health, and improve the scope and monitoring ability of sensors. It is important to note that since the current research only focuses on the development of a single sensor, how to connect the sensor to the health network so that the information obtained can be used correctly and timely in the health system is an important topic. In addition, it should be noted that the society has not yet formed a specific concept of non-invasive wearable sensors, and it needs to be moderately promoted in the research and development process to help the society form awareness and recognition of non-invasive wearable sensors. This review argues that after the above problems are solved, non-invasive wearable sensors will greatly improve the ability of social health monitoring and can further help clinical treatment.

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