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Chemically Engineered Devices for Skin Analysis: A Comprehensive Mini-Review

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Abstract:
Among all organs in humans, the skin is considered the largest organ and is covered on the surface of the human body. It is continuously exposed to and affected by many harsh conditions, like natural, chemical, and anthropogenic nanomaterials, from external and internal contributions. This phenomenon may cause irreversible health effects, from skin corrosion to cancer. Thus, there is an increasing demand for minimal monitoring of everything that may jeopardize skin conditions, especially human facials. These include noninvasive in situ analysis of body fluids that may contribute to unhealthy skin in the human body. This adaptation urges the researchers to develop many types of electrochemically active materials and wearable biosensors. This attempt with mechanically soft and flexible materials enables them to suit the geometric nonlinearity of the human skin. For each device's design, its purpose is different. Therefore, this mini-review will summarize the developments of skin analyzers with chemical engineering design. In short, this review will cover five type of skin conditions with different analyzers: (i) normal skin conditions; (ii) sweat skin analysis; (iii) skin hydration; (iv) skin wounds; and (v) the secretion of organic chemicals through the skin. For each criterion, the reaction of each analyte to the sensor performance was also discussed. Special attention is also included regarding the safety, usage, and reusability of the devices. In certain cases, there is also data security, which the authors may consider elaborate. From here, the authors hope that this review can benefit those interested in developing future commercialized sensors for skin analysis.

Keywords: Skin analyzer; Flexible; Sweat; Sensors; Chemical engineering

1. INTRODUCTION

The skin, which covers the entirety of the human body, is said to be the largest organ among all the organs in humans (1, 2). It has several functions, particularly regulating heat, conducting physical sensations, and acting as a mechanical barrier to protect the body from microorganisms, radiation, mechanical damage, heat, and chemical burns. Due to these, it is constantly subjected to and impacted by a variety of hostile environments, including internal and externally-sourced nanoparticles that are natural (volcano, earthquake, rainfall, etc.), chemical (pollutants, construction, hairdressers), and man-made chemicals (cosmetics, textiles, tattoos, and drug delivery systems) (1, 2). Even though the aforementioned mechanisms are still scarce, these conditions may result in cancer and other irreversible health problems, such as skin erosion, as there is strong evidence that being continuously exposed to such conditions may lead to chronic toxicity, resulting in severe skin pathologies. As a result, there is a growing need for minimal monitoring of everything that could endanger skin problems, particularly facials performed on humans (1, 2).

Among these are noninvasive in situ analyses of bodily fluids that may be linked to a person's unhealthy skin. Researchers are compelled by this adaptation to create a wide range of wearable biosensors and electrochemically active materials. They can accommodate the geometric nonlinearity of human skin thanks to this attempt with mechanically soft and flexible materials. Every device has a distinct purpose based on its design. It is the best choice of device that may provide the consumer with a high-performance device, low cost, miniaturization, and wide applicability (3, 4).

During the predicted period of 2022–2028, the global market for skin analysis devices is expected to experience significant expansion and reach a significant valuation. Skin analysis tools are used to assess the general health of the skin, identify skin conditions, and recommend suitable courses of action. These tools provide objective, precise measurements that support customized skincare and treatment regimens. The global market for skin analysis devices is expected to grow at a compound annual growth rate (CAGR) of 7% over the course of the forecast period. Their worth would rise dramatically to USD 700 million by 2028 from its estimated USD 400 million in 2020 (5).

Thus, the advancements in chemical engineering design for skin analyzers will be summed up in this mini-review. Five types of skin conditions with a separate analyzer will be covered: (i) normal skin conditions; (ii) sweat skin analysis; (iii)

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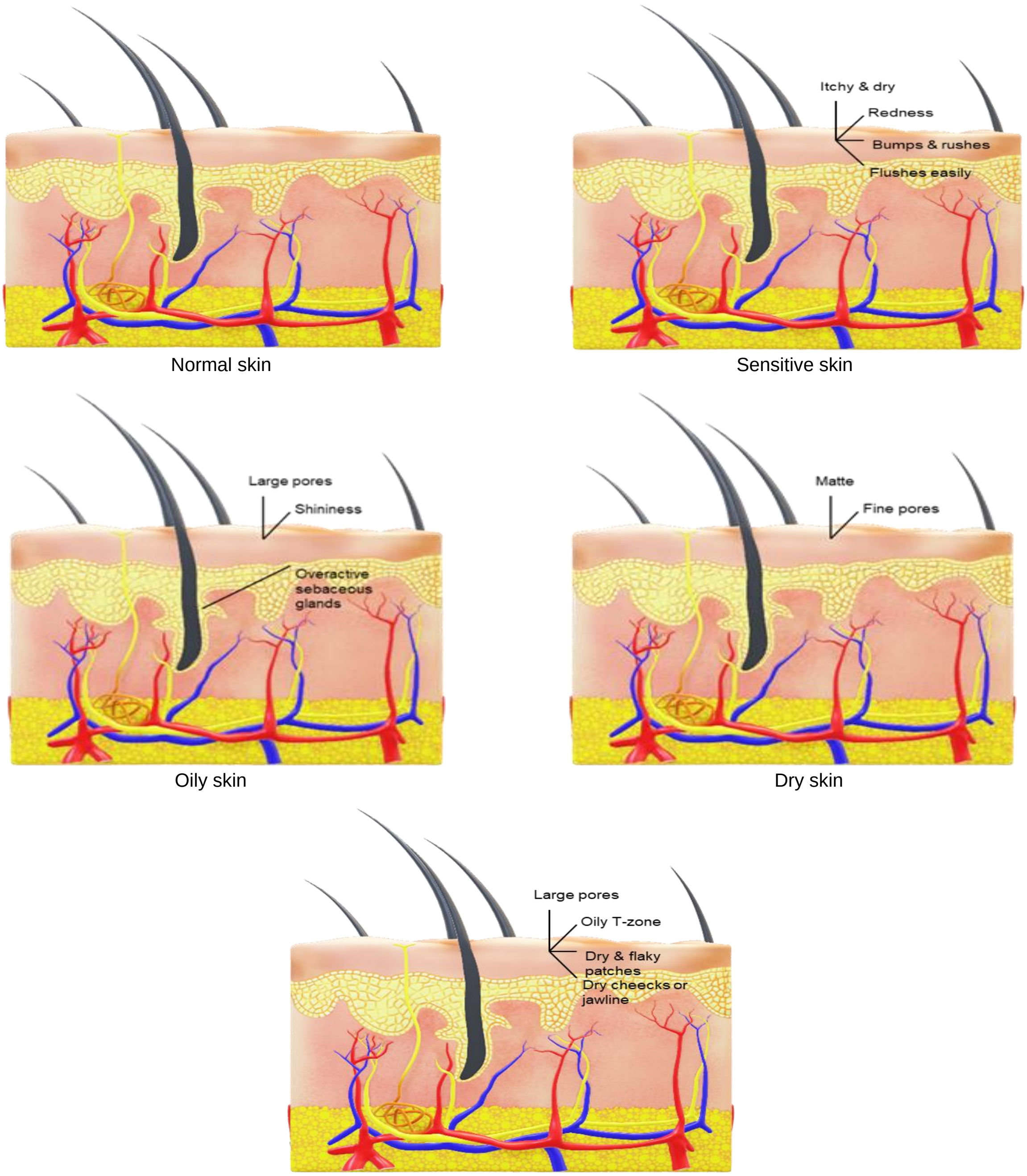
skin hydration; (iv) skin wounds; and (v) the secretion of organic compounds through the skin. The response of each analyte to the sensor performance was also covered for each criterion. A special focus is also placed on the gadgets' use, safety, and reusability. Data security is another issue that the authors may think is more complex in some circumstances.

2. DIFFERENT SKIN CONDITIONS

Although the face is a vital aspect of the body, the skin of the face is in close contact with the atmosphere. Therefore, compared to other locations, the skin on the face is more susceptible to damage. Normal skin, oily skin, dry skin, sensitive skin, and combination skin are the five varieties of skin. Normal skin typically contains an ideal ratio of water to oil. They are smooth and soft, blood circulation is steady, their pores are fine, and they are not sensitive. On the other hand, excessive sebum production causes oily skin, which makes a person's skin look greasy, glossy, or oily. People who have oily skin often produce too much oil on their faces. Conversely, dry skin produces less sebum. Dry skin is typically more prone to infection from detergents, soap, or inappropriate cosmetics. Skin that is sensitive is more likely to become inflamed. Combination skin is defined as having both oily and dry or oily and sensitive skin types. Because there are more oil glands and drier cheeks on the forehead and nose, areas with combination skin tend to be oilier (6) (Figure 1).



Normal skin

Sensitive skin

Oily skin

Dry skin

Combination skin

Figure 1. Different types of skin conditions.

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For this section, five common skin conditions - normal skin conditions, sweat skin analysis, skin hydration, skin wounds, and the production of organic compounds through the skin - will be discussed and each with its own analyzer.

2.1 Normal Skin Conditions

In general, human skin consist of three layers where epidermis, dermis, and hypodermis. The hypodermis is the lowest tissue formed by adipose and loose connective tissue that function to support dermis layer. The dermis layer is elastic connective tissues, highly vascularized, to support epidermis and skin appendages (Figure 2). Normal skin conditions are normally covered with some bacteria on the skin surface. However, attempts have been made to study bacteria changes as the change in the ratio of bacteria species within their population may result in pathologies like psoriasis, atopic dermatitis, or other skin diseases. Normally, the bacteria species found on the skin surface is *Staphylococcus aureus*. However, if the number of *Propionibacterium acnes (P. acnes)* goes below, the skin disease may develop. Other factors that may contribute to unhealthy skin is like Figure 2 (volcano, earthquake, rainfall, pollutants, construction, hairdressers, cosmetics, textiles, tattoos, and drug delivery systems etc.) and Table 1. The transport of these carcinogenic nanomaterials through the skin can be three pathways where (i) intracellularly (straight forwarded route), (ii) through keratinocytes, and (iii) trans-appendageal, across the hair follicles (HFs) and sweat glands. Due to these reasons, most researchers are developed variety of device to characterize skin porosity, skin enzymatic activity or bacterial activity (2, 7).

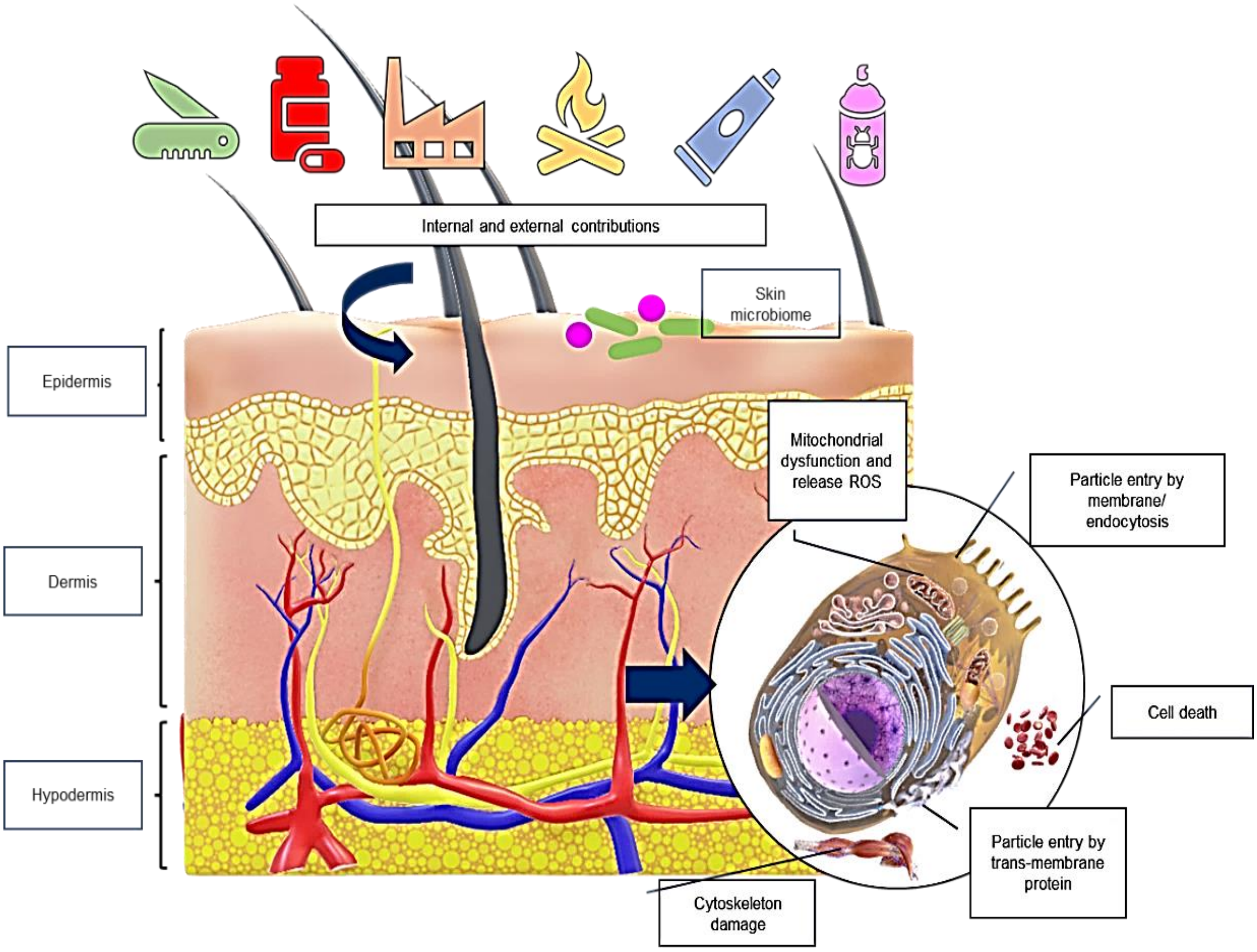

Figure 2. Skin structure and factors contribute to skin damage.

There is a study that described a thin, flexible sensing platform based on silver electrodes screen-printed on a thin elastomeric substrate for skin monitoring. The mechanical properties of the patch resistant against degradation by electrical applied once using an acrylate porous adhesive layer. To measure, a conventional table-top impedance setup was utilized. It consists of Argentum (Ag) and plastic materials make it a promising disposable sensor with low -toxicity materials (7).

Because they are generally made of metal and semi-conducting materials, most traditional sensors are large and heavy. Their extreme mobility and flexibility render them unsuitable for use with wearable electronics. The plastic and elastomeric substrates used by modern sensors have various advantages over traditional ones, including improved biocompatibility, stretchability, transparency, wearability, and continuous detecting capabilities (8).

Table 1. Factor affecting skin surface.

	Factors	Skin conditions (9)
1	Drying temperature	Inflammatory reactions
2	Aging and skin type	Allergic reactions
3	Environment/climate change/lifestyle/occupation	Inflammatory reactions/ Pilosebaceous reactions/ Pigmentary disturbances
4	Nutrient and hydration	Inflammatory reactions
5	Peripheral circulation/oedema	Allergic reactions
6	Immobilisation	Pilosebaceous reactions
7	Level of consciousness	Pigmentary disturbances
8	Trauma	Benign epidermal reactions
9	Activity	Inflammatory reactions
10	Faecal/urinary incontinence	Allergic reactions
11	Fever/infection	Inflammatory reactions/ Allergic reactions/ Pigmentary disturbances
12	Metabolic state	Inflammatory reactions
13	Immune system	Allergic reactions
14	Sensation	Inflammatory reactions

For each device, there is a validation test to validate the non-invasive device before planning to next plan. Below is the equation on how to measure the results from validation (Figure 3).

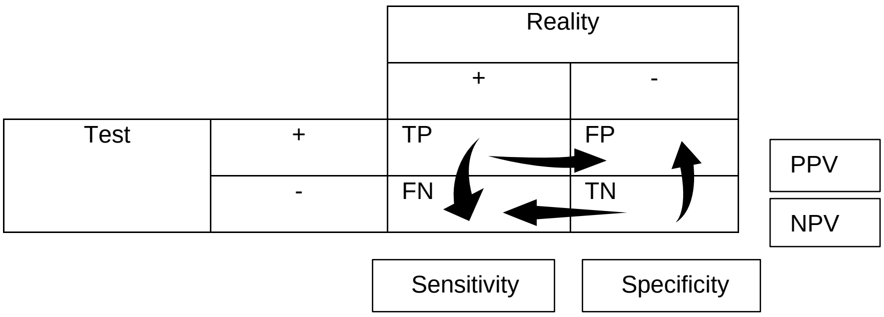

Figure 3. Validation test to validate non-invasive device. Legend; TP (true positive), FP (false positive), FN (false negative), TN (true negative), PPV (positive predictive value), NPV (negative predictive value) (10).

Providers need to understand the chance of a patient having a condition by integrating knowledge of diagnostic evaluations and pretest probability in order to make therapeutic decisions and direct patient care. In healthcare settings, diagnostic tools are frequently used to establish treatment protocols; nevertheless, a number of these technologies have error-proneness. Sensitivity and specificity are crucial markers of test accuracy that help medical professionals decide whether a diagnostic instrument is appropriate. With the appropriate degree of confidence in the findings resulting from known sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios, and negative likelihood ratios, providers should employ diagnostic tests. Sensitivity is the capacity of a device or test to produce a positive result for a patient with that illness, while specificity is the test's or the instrument's capacity to produce normal range or negative findings for a healthy individual. PPVs identify the proportion of real positives among all positive findings, while NPVs identify the proportion of true negatives among all negative findings (10).

$$\text{Sensitivity}=\frac{TP}{(TP+FN)} \qquad (1)$$

$$\text{Specificity}=\frac{TN}{(TN+FP)} \qquad (2)$$

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$$\text{PPV} = \frac{TP}{(TP + FP)} \qquad (3)$$

$$\text{NPV} = \frac{TN}{(TN + FN)} \qquad (4)$$

The primary hypotheses for sensitivity and specificity are as follows;

H01: $\Pi_{Sen} = 0.90$
vs.
HA1: $\Pi_{Sen} > 0.90$

H02: $\Pi_{Spec} = 0.92$
vs.
HA2: $\Pi_{Spec} > 0.92$

The need for minimal monitoring of everything that could endanger skin disorders is growing, particularly regarding facials. Among these are noninvasive in situ analyses of bodily fluids that may be linked to a person's unhealthy skin. Researchers are compelled by this adaption to create a wide range of wearable biosensors and electrochemically active materials. These devices were designed with chemically engineered for skin analysis. They can accommodate the geometric nonlinearity of human skin thanks to this attempt with mechanically soft and flexible materials. Every device has a distinct purpose based on its design (3, 4).

2.2 Sweat Skin Analysis

Sweat is colorless liquid found in the skin and emitted on the epithelial surface by way of ducts. Sweat consists of mostly water (up to 99%) but also with small number of solutes like sodium, potassium, calcium, magnesium, and chloride ions, lactic acid and urea, iron, zinc, copper and sometimes also chromium, nickel, and lead ions as well as small amount of glucose, and exogenic organic materials. Due to this reason, most sweat device is often based on electrochemical transduction. There are two main approaches when the transduction principle was mentioned: electrical or colorimetric. For electrical, the design normally resists stretching, bending or any other deformation of the device. For colorimetric, the results are normally visual by eyes or camera as it can be referred to from color sensor changing (acidic to alkaline color). No electric needed for this kind of device. However, it also has drawbacks where the possible of poorly interpret quantitatively. Sweat analyzers are normally designed by considering the reaction of pH, chloride (Cl), and sodium (Na) compounds that are present in human sweat. The detection of these compounds from biomarkers will appear on the screen, and the recognition of images or pH ranges in smartphones or computer storage will tell the skin conditions. The sensor can work to detect the pH in the range of 4 - 7. Higher normal pH for women is 5.6 ± 0.4 and for men 4.3 ± 0.4, $p < 0.05$. These pH skin values are varied to different skin regions (11, 12). Example is electrochemical patch made of polyimide (PI) and silicone. This device has the ability to mass transfer gas and fluids from skin to sensing material. As a result, its conductive layer is highly curved to be stretchable to every direction. Another study proposed on colorimetric assays where it includes multi-instrumented Poly(methyl methacrylate) (PMMA) patch to measure sweat rate, pH, temperature, concentrations of ions and metabolites and it does not require electric but using smartphones to capture the picture. The transformation of the color patch will determine the skin conditions (7, 13-15) (Figure 4).

Figure 4. Example of electrochemical patch for sweat analysis.

2.3 Skin Hydration Analysis

Skin hydration is very important in skin analysis as the hydration will influence the skin function. Therefore, it is important for chemical skin sensor. Skin hydration is always measured using impedance based on capacitance or conductance and also concentration of electrolytes in sweat (7). There is a study propose on fast-response and flexible conductance humidity sensor for real time monitoring. Silicon-nanocrystal film was deposited on a PI substrate. The humidity is range from 8-

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83% with time response 40 ms (7). Another study proposed on stretchable and conformal sensor for continuous monitoring the moisture skin. The sensing layer is made of the blend of reduced graphene oxide, and polyurethane, deposited onto poly(3,4-ethylenedioxythiophene) (PEDOT): polystyrene sulfonate (PSS) electrodes and supported on a Polydimethylsiloxane (PDMS) substrate (Figure 5). The response time is 3.5 s (7).

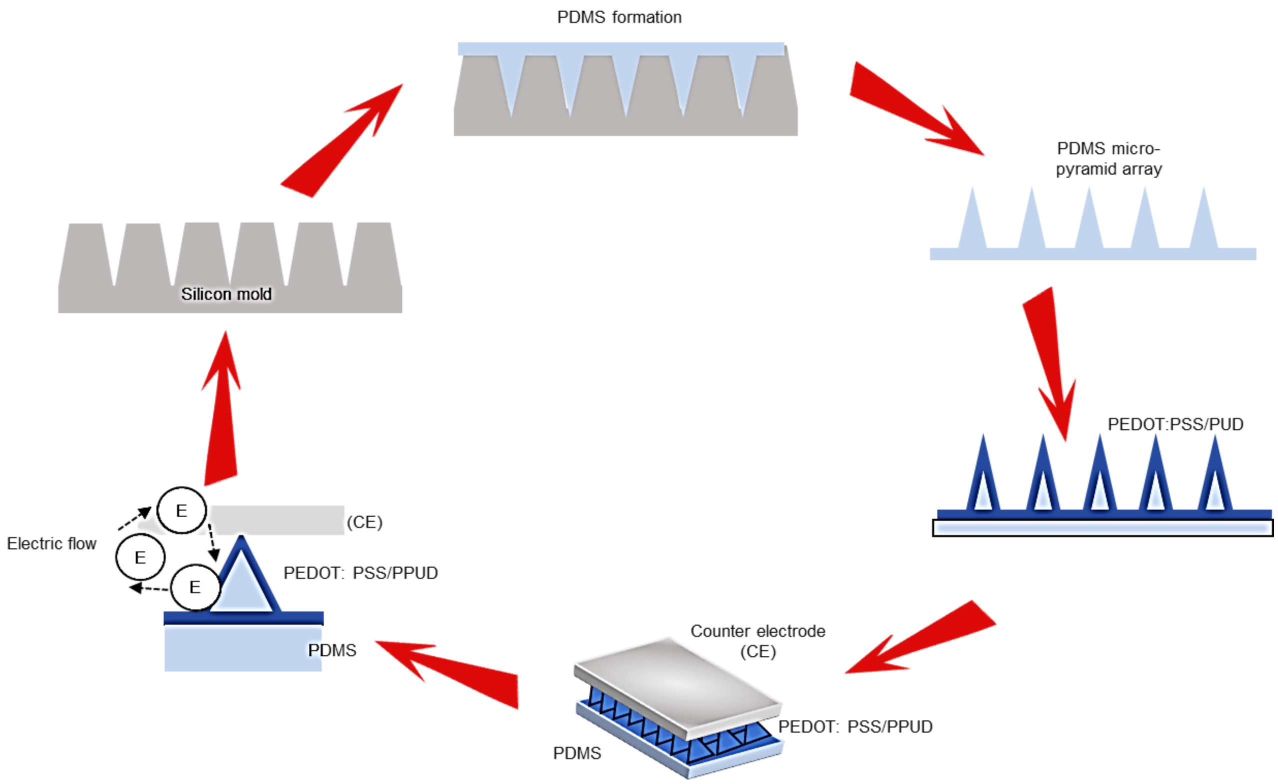

Figure 5. Example of skin hydration measurement.

2.4 Skin Wounds

Monitoring skin wounds condition is very complex due to time healing, reduce scars, restore skin function, bacterial infection, and many others. Because of this challenge, the sensor device for this kind of treat is always with two options; (i) physical parameters of the wounds (pressure applied, wound depth, temperature), (ii) biochemical parameters of the wounds (enzyme activity, pH etc.). Example given a wearable wireless sensor system to monitor skin pressure, temperature, and humidity. The sensor consists of a thin waterproof adhesive patch (<1 mm) with silicon-based sensor, microcontroller, wireless transmission antenna and polymer battery. The patch can attach to human skin up to 7 days.

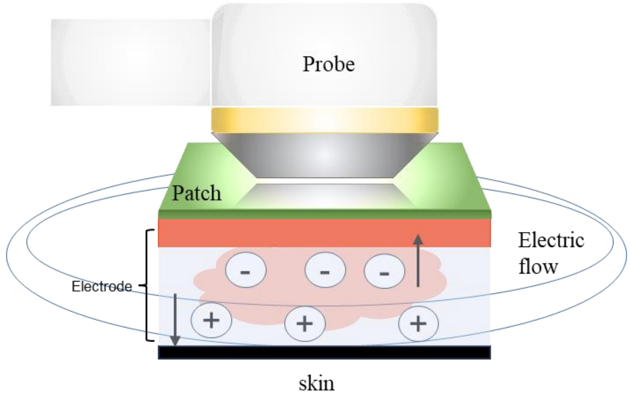

Figure 6. Example of probe function.

Another study even more complex. The device consists of probe with light source (Figure 6), optical RGB (red, green and blue) camera, depth camera, thermal camera, and an array of chemical sensors. This probe will transfer the data to a computer (7). Through to these systems, it can analyze tissue segmentation and classification, three-dimensional (3D) modeling for wound measurement, thermal analysis, multi-spectral analysis as well as chemical sensing. The detection of sensor on the probe will transform the data to the computer. The image processing will take place and the model appeared on the screen will recognize the type of skin conditions. There are many ways to monitor this wound analysis; pH skin, color changing of sensor, through direct visual, through the drug change on bandage for instance, direct analysis of skin cells and many others (7, 16).

2.5 The Secretion of Organic Chemicals

Alcohol and drug abuse is the most common serious health problem with violent behaviors and immoral act. The most common method use is breath analyzer. There is a study proposed on stannic oxide (SnO_2) sensor for monitoring ethanol on the skin. This device is using sweat as analyte vector to measure alcohol level in human. On the other hand, to measure drug using skin sensor is very difficult as not many studies published on the device. However, not long ago, there is study proposed on electronic nose as to which to detect body odor for example cannabis consumption. Two data processing were used: principal component analysis (PCA), and pattern recognition with subsequent support vector machines (SVM). Technically, this device consists of non-specific gas sensors like combustible gases, hydrocarbons and NO_2. The color change on the stannic oxide sensor and the stretching of the patch will show the result of the ethanol influencer and the secretion of the chemicals through the skin and this will determine the skin conditions (7) (Figure 7).

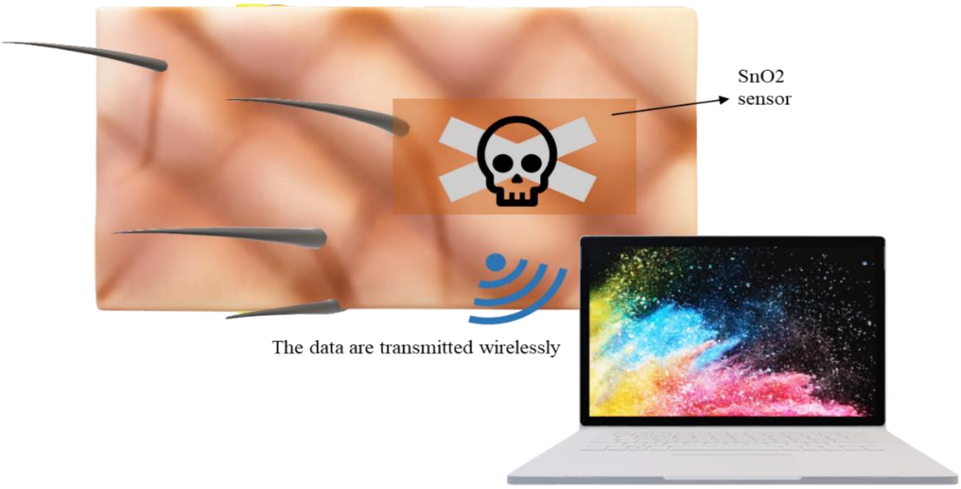

Figure 7. Skin analyzer for drug abuse.

3. SAFETY ISSUES AND DATA SECURITY

Considering that the US Food and Drug Administration (FDA) is now the principal regulatory body for these devices, it is critical to take note of their criteria. Devices that "health care providers can reprocess and reuse on multiple patients" are classified as reusable medical devices and “Intended for use on one patient during a single procedure... and is not intended to be reprocessed (cleaned, disinfected, or sterilized) and used on another patient,” is how the FDA describes a single-use device, also referred to as a disposable device (17).

The medical device industry, which includes Original Equipment Manufacturers (OEMs) and the associated sterilization sector, is subject to stringent regulations aimed at ensuring the provision of safe and efficacious goods for patient/consumer usage. The instructions for use (IFU) and accompanying labelling for reusable medical devices meant to be processed in a healthcare facility before patient/consumer use provide the necessary processing requirements to ensure consumer safety, such as cleaning, disinfection, and/or sterilization, which are normally carried out by specialized facility departments (18).

The lifetime of the device is varied, however medical devices that meet a standard are deemed to have complied with all applicable safety, efficacy, and/or labeling criteria. It will still be necessary to provide further proof for any safety and efficacy standards that are not addressed by the standard. The ISO 13485 standard is often used to demonstrate compliance with the implementation of a quality management system. Meanwhile, among the often-used sterilization standards are ISO11137 (radiation) and ISO11135 (ethylene oxide) (19).

However, in some cases of skin analyser, in regards to data security, due to concerns about data privacy, laws like the General Data Protection Regulation (GDPR), China Cyber Security Law, and California Consumer Privacy Act (CCPA) were created, giving people rights over the collection, disclosure, erasure, and protection of their data from automated decision-making. With a specific focus on for-profit companies doing business in California, the CCPA guarantees data processing openness. Addressing class imbalance and growing databases can benefit from utilizing data from other organizations. However, privacy, technological, and legal barriers make exchanging medical records difficult. Without explicitly sharing data, Google's federated learning technique trains machine learning algorithms on local datasets. In order to create a common global model that can handle a variety of datasets and unreliable clients, local nodes trade parameters. A central server manages algorithmic stages and participating nodes in centralized federated learning. Conversely, decentralized federated learning eliminates the possibility of a single point of failure by transferring model changes to networked nodes independently of a central server. By using this method, update transmission bottlenecks are avoided. Healthcare systems are better equipped to handle constraints and privacy issues when federated learning and AI are used in a hybrid approach that involves distributed model training (20).

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4. LIMITATION AND CHALLENGE AND FUTURE RESPECTIVE

Certain requirements for wearable sensors such as high sensitivity, biocompatibility, stability, autonomous operation, and wireless data transmission must be met for the technology to be successfully used for skin monitoring. Although the use of nanomaterials, such as metal- or carbon-based nanoparticles can assist improve sensor surface and sensitivity, their application is still debatable due to the lack of current knowledge on their long-term toxicity and biocompatibility. Research should concentrate on creating fully autonomous sensors in the future that can function without the need for non-portable components and guarantee wireless data transfer. This will guarantee improved compliance and the developed gadgets' viability. Though persistent efforts to address these problems, there are still various limits concerning the miniaturization of optic probes, potentiostats, or batteries that are necessary for sensor operation. Both autonomous sensors and sensors that can be enhanced to accomplish these objectives have already been demonstrated in the literature in encouraging ways.

5. CONCLUSION

Over the last few years, wearable electronics have gained a lot of attention due to their rapid growth. Researchers have worked hard to create wearable electronics with great sensitivity, flexibility, and stability, and they have seen some success in their efforts. This brief study highlights various equipment intended for skin analysis. The reader will comprehend that, in terms of current trends and technology, wearable skin analyzers are more in demand than conventional sensors. The fact that flexible sensing devices with excellent sensitivity, cheap cost, portability, and long-term stability have been successfully fabricated suggests that wearable and flexible electronics will undoubtedly become the norm in this industry. Throughout this study, numerous researchers created devices with potential sensor detection capabilities, such as pH, color changing, image recognition, chemical detection, stretchability of the patch, and many others, to measure or diagnose skin conditions. These measurements could also be used to label skin as normal, sweat, hydrate, wound, or even chemically determined as there is certain range to measure the skin of different regions. There are also recommendations that requirements for safety, security, and privacy of data collecting be met by designers before being made available to customers. Standard operating procedures (SOPs) include ISO 13485, ISO11137, and ISO11135. Global data privacy protection organizations include the General Data Protection Regulation (GDPR), China Cyber Security Law, and California Consumer Privacy Act (CCPA). Though the device has fantastic information, there are certain obstacles to overcome when using it. Among them are accuracy of pulse, muscle contraction, and external contact. Comparing biochemical sensors to conventional medical devices, they are still insufficient, and handling data that is challenging for several functional modules.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. All co-authors have reviewed and approved the manuscript, and there are no financial interests to disclose.

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