Flexible Substrate-Based Sensors in Health Care and Biosensing Applications

Paramita Karfa, Kartick Chandra Majhi, and Rashmi Madhuri

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Abbreviations

CNT	Carbon nanotube
CP	Conducting polymers
CVD	Chemical vapor deposition
ECGs	Electrocardiograms
EEG	Electroencephalography
EMG	Electromyography
FET	Field-effect transistor
ITO	Indium tin oxide
LOx	Lactate oxidase
MWCNT	Multi-walled carbon nanotube
NTC	Negative temperature coefficient
PANI	Polyaniline
PC	Polycarbonate

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PCO	Polymers of cyclic olefin
PDMS	Poly(dimethylsiloxane)
PEDOT:PSS	(3,4-Ethylenedioxythiophene) poly(styrene sulfonate)
PEN	Poly(ethylene naphthalate)
PEO	Polyethelene oxide
PET	Polyethylene terephthalate
PI	Polyimide
PMMA	Poly(methyl methacrylate)
POC	Point of care diagnostic
POE	Polyolefin elastomer
PP	Polypropylene
PPY	Polypyrrole
PS	Polystyrene
PTC	Positive temperature coefficient
PVDF	Polyvinylidene fluoride
Rgo	Reduced graphene oxide
SAALD	Spatial atmospheric atomic layer deposition
SWCNT	Single-walled carbon nanotube
TENG	Triboelectric nanogenerator
TTF	Tetrathiafulvalene

1 Introduction

Sensor word can be defined as a device, which can produce measurable signal because of the biological, physical, and/or chemical stimuli responses. On a similar basis, they may be categorized as biological, physical, or chemical sensor depending on the analyte they are detecting or quantifying (Akyildiz et al. 2002). Sensor is actually a combination of receptor and transducer (Chong and Kumar 2003). In a sensor, the analyte gets engrossed to the receptor site, which produces an electrical energy as a result of interaction between them. After that, the transducer does the next work by transducing the electrical signal to the readable format, which will further analyze. Sensors are highly useful nowadays in a variety of applications like environmental monitoring, healthcare application, food adulterant determination, water examination, fabrication of drugs, forensic examination, and many more. However, to fulfill the recent demand and match with recent scenario, upgradation in sensor technology is happening in a day-to-day manner. Researchers are working in this field to develop the sensors with increased specificity, better sensitivity toward the analyte, low-cost fabrication process, and easy availability (Guth et al. 2009; Windmiller et al. 2013).

Recently, a new term i.e. flexible sensor came in limelight. Flexible sensor is made up of malleable material, which can be molded in any kind of design or modified with any kind of substrate (Nambiar and Yeow 2011). Before the flexible sensors, non-flexible or rigid sensors are more popular, which are mainly synthesized of silicon compounds.

Rigid sensors are not appropriate for monitoring human physiological factors because of its stiffness, which causes damage to the sensor with little stress (Castillejo et al. 2013). Therefore, flexible substrate-based sensor has gained interest of the researchers, owing to their numerous properties like lightweight, easy to stretch/fold/bend, effortlessly portable, biocompatible, high chemical stability and transparency. Other than monitoring human physiological factors, this type of sensors is also very popular in batteries, display in electronics, soft robotics, wearable electronics, mobile phones, solar cells, light-emitting diodes, robotics, and aerospace, owing to their high economical design/manufacture, biocompatibility, and multifunctional nature (Xu et al. 2003). On the commercial front, flexible sensors are designed or classified as chemical sensor, optical sensor, biosensor, strain and pressure sensor, temperature sensor, pH sensor, electronic sensor, etc. Flexible and wearable sensors have various biomedical applications also such as in point of care diagnosis of human health, electronic skin, smart medical prosthetics, etc. as shown in Fig. 1 (Xu et al. 2018a).

There are several reasons or advantages of increasing popularity of flexible sensors over rigid sensors, some of them are briefed below (Yang 2006):

1. Sensibilities of soft flexible sensor are comparable to that of rigid substrate sensor, even at very low temperatures.
2. Selectivity of the flexible sensor toward the analyte is more as compared to that of the rigid sensor. They can easily capture the analyte molecule, which is hindered in the conventional sensor due to its rigid surface.

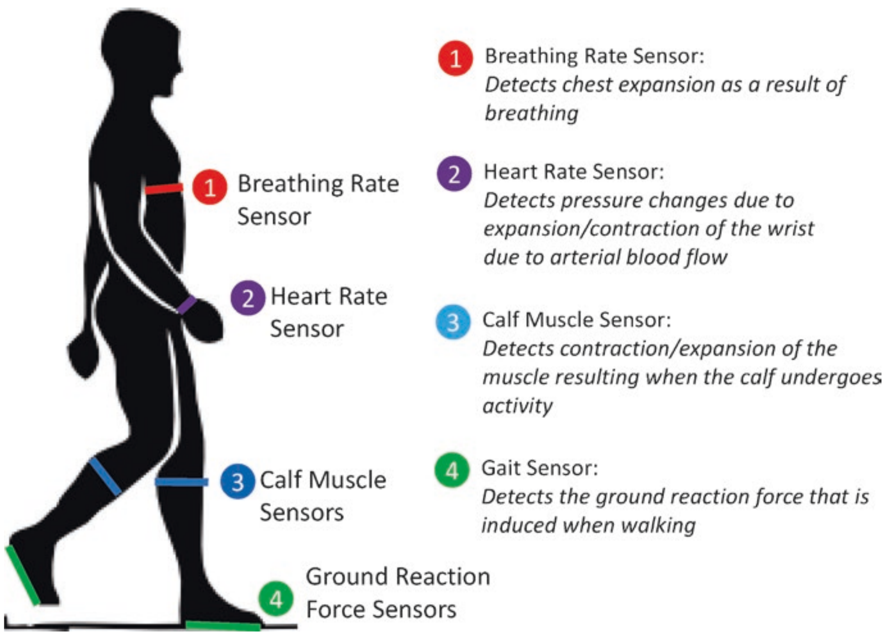

Fig. 1 Schematic diagram showing different types of wearable sensor used for human health monitoring (Taken with permission from (Xu et al. 2018a)

3. Flexible sensor possesses good stability and repeatability because of its stretchable/bendable nature.
4. With the use of flexible sensor, different devices can be designed, which can be folded, stretched, bended without any loss of performances, whereas, on the other hand, rigid substrate-based sensor, when thinned gets deformed and lose their activity.
5. Signal transduction of high quality is generated by the flexible sensor than the conventional rigid sensors.

1.1 Materials Used for Manufacturing of Flexible Sensors

Designing of flexible sensors totally depends upon the expenses of manufacturing and availability of materials used for their preparation. Most commonly, flexible synthetic polymers like polystyrene (PS), poly(dimethylsiloxane) (PDMS), polypropylene (PP), poly(ethylene naphthalate) (PEN), polycarbonate (PC), poly(methyl methacrylate) (PMMA), polymers of cyclic olefin (PCO), poly(3,4-ethylenedioxythiophene) polyimide (PI), polyethylene terephthalate (PET) were used for preparation of base of the sensor that can be converted into thin films also, if needed (Han et al. 2017). Among them, the widely used soft polymer material, as a substrate, is polydimethylsiloxane (PDMS), which is a silicone-based elastomer and commercially popular with the name of Ecoflex, Dragon skin, or Silbione. PDMS has several advantageous properties like low elastic modulus, good stretching ability, durability, flexibility, optical transparency and can be synthesized by simple steps. Soft elastomers-based flexible sensors like PDMS-based sensor is more convenient to synthesize than the other thermoplastics like PEN because of the less easy stretching and conformability of the later. PDMS can be synthesized through formation of resin mixture and curing in a respective mold. Pu et al. have synthesized flexible substrate-based glucose sensor with five polydimethylsiloxane (PDMS) layers and were fabricated using the technique of micro-molding (Pu et al. 2016). Luo et al. have synthesized resistive electronic skin for pressure sensing using graphene platelet and multiwalled carbon nanotube on PDMS substrate. The prepared sensor showed high-pressure sensitivities and outstanding stability (Luo et al. 2019).

PET is another popular polymer, which is a synthetic polymer of esters and used as an electric insulator, has mechanical properties like inertness, optical transparency, and thermal stability. Similarly, Teonex the commercial name of PEN is also popular polymer, which is better than PET in their intrinsic properties like durability and chemical resistance. In addition, PEN also has better optical transparency and very popular in optical devices. Chun et al. have synthesized flexible pressure sensor using PEN as the flexible substrate and successfully transferred CNT film of high electrical conductivity on it through chemical-free process (Chun et al. 2018). The prepared sensor shows piezoresistive responses which can be used for various healthcare application like to detect the motion of hands, wrist, etc. Another polymer, which is popular in flexible sensor, is PI with commercial name Kepton, which can be easily stretched, molded, and folded, have low cost, high biocompatibility, easy to manipulate, and therefore used in fabrication of biosensors, bioelectronics, fuel cells, etc.

Metals and ceramics are nowadays avoided for preparation of flexible substrate material in spite of their outstanding electrical properties, which is good for efficient signal transduction but due to their rigidness, low elasticity they are vulnerable to mechanical damage. Textile, paper, silk are ecofriendly flexible materials, which are easily available and very much economical. Decreasing the size of the paper from micrometer to nanometer increases the optical transparency of the paper, which can be further used in different sensing modalities. Different nanocelluloses are also used as a substrate for biosensors nowdays such as bacterial nanocellulose, cellulose nanocrystal, nano-fibrillated cellulose (Lee et al. 2015).

Flexible sensor has two parts stretchable and flexible substrate and the active sensing material, which can be in solid or liquid forms. To prepare the flexible sensor device, the active materials were coated or attached to the flexible materials, which can be able to convert the sensing stimuli in information transducing or sense the stimuli, which later on send to the signal generating readable electronic devices. The popular active sensing material in solid form, which can be used in flexible sensor, can be conducting polymers, metals, metal nanowires, semiconductor material, carbon-based material, nanoparticles like graphene, CNT, or nanofibers of polymer. The popular liquid form of active sensing material is ionic liquids (Barlow et al. 2002).

Conducting polymers (CP) which are included in the flexible material are (3,4-ethylenedioxythiophene) poly(styrene sulfonate) (PEDOT:PSS), polyaniline (PANI), polypyrrole (PPY), which have conjugated π systems with organic backbone. CP has a great affinity toward biological analytes through functional group modification for biosensing application. Nanoparticles of metal, carbon-based nanomaterial like carbon nanotube (CNT), graphene-like 2D nanomaterial having good electronic properties, mechanical properties, flexibility, wear-resistance are used for the formation of electrode material for sensors and are also sometimes used to form the core of the sensor (Yamada et al. 2011).

1.2 Fabrication of Flexible Sensor

The different method for the synthesis of flexible sensors is always a point of research because they demand innovation in material and new cost-effective synthesis process for better commercialization. Till date the process through, which the flexible sensors can be fabricated are as follows:

- Screen printing.
- Inkjet printing.
- Gravure printing.
- Photolithography.

- Direct writing.
- Roll to roll printing.
- Spin coating.
- In-situ polymerization.
- Drop casting.
- Weaving method.

Among them, ink-printing process and weaving method are very popular for fabrication of flexible sensors. In ink-printing process, conductive ink is prepared from the metallic or inorganic particles suspension, which is deposited on to the polymer substrate with curing at high temperature. Whereas, in weaving method, conductive fibers are weaved on the textile to form fresh wearable known as e-textile. They can sustain high pressure, have high robustness, versatility and can be used in biomedical engineering and healthcare application.

Some of the synthesis processes commonly used for fabrication of flexible sensor are discussed below. For example, Dubourg et al. synthesized flexible humidity sensor using laser ablation method on PET (poly-ethylene terephthalate) and used screen printed TiO_2 as the active material which is shown in Fig. 2 (WDubourg et al. 2017).

Lou et al. have synthesized electronic skin based on piezo-resistive pressure sensor using polyaniline hollow nanospheres as the active component. The sensor was fabricated using PDMS substrate through conventional photolithography method (Luo et al., 2017). Romeo et al. have synthesized nonenzymatic electrochemical

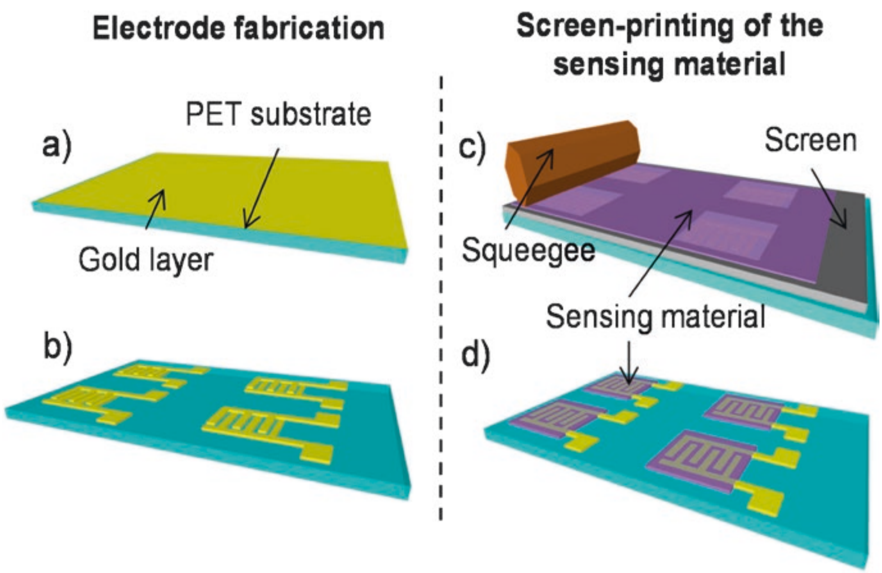

Fig. 2 Schematic representation showing different steps for the synthesis of humidity sensor (**a**) substrate deposited with gold layer, (**b**) laser ablation of the deposited gold layer, (**c**) incorporation of the TiO_2 material through screen printing, and (**d**) the whole prepared sensor. Adapted from Ref. (WDubourg et al. 2017)

flexible glucose sensor using inkjet printing for tear fluid analysis. For the synthesis of the flexible sensor CuO microparticles were used as the active sensing material and polyethylene terephthalate as the substrate for electrode preparation (Romeo et al. 2018). Kim et al. have synthesized piezo-resistive electronic skin of high flexibility, low resistivity of bimodal nature that is both temperature and pressure sensor using inkjet process for the synthesis of core of the sensor. They have used organic conductive elastomer PEDOT:PSS/polyurethane dispersion as the substrate and silver nanoparticle as the active sensing material for flexible sensor fabrication (Kim et al. 2017).

1.3 Signal Transduction

In the designing of sensor, role of transducers is very important. Depending on the sensing principle, the stress induced on the material causes electrical parameter variation, which can be detected and produced in the form of signal. The signal will be detected or read by the transducer and it will provide us the information in understandable format. The transducer can be of various types (Takei et al. 2015). The most commonly used signal transducers are as follows:

- Piezoelectricity.
- Resistivity.
- Capacitive.
- Triboelectricity.
- Field-effect transistor (FET).
- Optical.
- Electrical.
- Amperometry.

Among these transduction methods, the most famous is the piezoelectric transduction method, where voltage is generated in accordance to the applied pressure. In resistivity transduction method, variation of pressure and strain causes change in resistance, which is caused by structural deformation of the flexible sensor material. Capacitive transduction depends on the change in the dielectric constant between distances of the electrode caused by the stress induced on the material. Electrochemical sensing technique is also very popular, owing to their high sensitive and selective, which is generated as a result of electron transfer reaction between the analyte and the receptors.

1.4 Salient Features of Flexible or Wearable Sensor

For large-scale commercialization of flexible sensor, some important features must be considered:

- Gauge factor or sensitivity.
- Linearity.
- Self-powering.
- Self-healing.
- Self-cleaning.
- Transparency.

More stretchable the conductor more is their use as an interconnecting material and electrode material, while high piezoresistive material shows potential application in electrochemical and mechanical sensor (Zhao et al. 2017). Linearity refers to the relative change of the signal with respect to the stress applied, which is represented in the form of straight line. Mostly the strain shows linearity in less strain conditions and nonlinearity in large strain conditions. Nonlinearity of sensor occurs due to morphology deformation, possible occurred due to stress. So, highly stretchable sensor must have high linearity with challenging sensing property.

Electronic devices may get damaged after working for several times, therefore, the self-healing property of the electronic devices both electrically and mechanically is a powerful restoration phenomenon. The incorporation of thermally sensitive ionic liquids, self-healing property of the sensors can be improved. Patchable pressure sensor with incorporated storage and power generation devices enhances the self-powering system in the sensor. Supercapacitor and triboelectric nanogenerator (TENG) is incorporated to the sensor to increase their self-powering property. Li et al. have synthesized a triboelectric transducer-based sensor using nanowire arrays deposited on Kapton substrate through ion etching. This sensor has contact angle of 152°, which allows easy removal of water along with dirt and other contaminants enabling their self-cleaning property (Li et al. 2015). In addition, to all these properties, the sensor must be optically transparent so that it must be invisible during daily activities. Roh et al. have synthesized highly transparent, 100% stretchable, with 62.3 gauge factor strain sensor using PU-PEDOT:PSS/SWCNT/PU-PEDOT:PSS hybrid (Roh et al. 2015).

2 Flexible Substrate for Healthcare Application

People nowadays are very much fretful about their longevity and lifestyle, which made them progressively more interested in healthcare and daily life care. With the increase in the population age, numerous unwanted diseases captured our life, which needs to be diagnosed as early as possible, so the facility of daily rapid diagnosis of the disease through detection of human bio-signals at every given location and time is very important at the present time. Personal health monitoring devices not only facilitates the elderly human beings but also help in real-time checkup to professional athletes and detection of early damages caused in various people suffering from chronic ailment (Christodouleas et al. 2018). The discovery of sensor has transformed human life to the next level by sensing or monitoring a disease in few seconds or minutes. Fast diagnosis has broad spectrum of function in various disciplines like food safety, clinical medicine, monitoring of environmental pollution, immunoassays, clinical medicine, etc. Development of quick, inexpensive, portable, stable, accurate, point-of-care diagnostic (POC)assay for timely detection of disease to solve health care problem is of great demand in current time, because of the absence of laboratory facilities, trained personnel, adequate financial support in the field of clinic and health care (Shafiee et al. 2015). POC diagnoses provide us with rapid and timely detection, monitoring, and counseling of disease for better clinical management. POC is better than conventional detection technique because they do not require heavy instruments, trained personnel, and the patient does not need to travel to the hospital, have high accuracy, and cost-effectiveness.

Flexible and wearable sensor with high-quality signal transduction is nowadays used for POC diagnosis based on the detection of various parameters in human beings. These sensors are used for healthcare applications of human beings in the form of several wearable devices like bands, watches, sunglasses, clothes, etc. (Nayak et al. 2016). However, these types of wearable sensors are still underdeveloped because of bulky circuit system, complicated power supply, poor sensitivity and little skin contact, and limited detection toward multiple bio-signals. The main advantages of flexible sensors with respect to conventional sensors are that they are thin, flexible, devoid of mechanical deformation, easy to fabricate, inexpensive, made up from easily available material, disposable, easy to use, have easy interaction with the analyte, have wearable design, multifunctional sensing application, and most importantly can be miniaturized through various nanoscale morphologies, which keep them closer contact to body (Ha et al. 2018). The flexible sensor can easily detect three types of human bio-signals:

1. Physical.
2. Biochemical.
3. Electrophysiological.

Physical health indicator comprises of blood pressure, pulse rate, motion of limb, walking, respiratory rate, temperature, humidity, etc. Biochemical indicator comprises of body fluids, metabolites, proteins, glucose, cholesterol, ascorbic acid, uric acid, pH, and blood oxygen. Electrophysiological signals include electromyography (EMG), electrocardiograms (ECGs), and electroencephalography (EEG). Based on detection of these bio-signals, different flexible sensors are designed for healthcare applications (Segev-Bar and Haick 2013). Some of the recent flexible sensors like pressure, temperature, pH-based sensors are discussed in the next sections:

2.1 Pressure or Strain Sensor

One of the standardized applications of flexible sensor is pressure or strain sensor. These types of pressure sensor are mainly based on piezoelectric, piezocapacitive, and piezoresistive transducers, used for detection of various human motions for older disable long-suffering patient, monitoring sports and healthcare performances, rehabilitation, as well as physical therapy (Segev-Bar and Haick 2013). Pressure sensor mainly detects the physiological change which is caused by bending and stretching motion of the body like bending of the hand, legs, arms, motion of chest, face, movements, due to emotional expression, speaking, breathing, tremor caused due to Parkinson disease. From the pressure sensor, we can also detect various cardiovascular diseases through monitoring, blood pressure, pulse rate, etc. Using pressure and strain sensor of high sensitivity in the form of personal devices, which can regularly and periodically monitor heart rate and blood pressure, one can eliminate various diseases like arrhythmia and hypertension. Pressure miniaturized sensor can also detect health abnormalities like chronic lung diseases e.g. asthma, apnea, and respiration rate problem, with the measurement of movement caused in trachea, movements caused due to expiratory and inspiratory breathing, thoracic cavity expansion and contraction (Zang et al. 2015).

Yeh et al. have synthesized implantable wireless pressure sensor for long period monitoring of cardiovascular pressure. This type of sensor is inserted into the stent inside the blood vessel. They have used Parylene-C as the biocompatible polymer and PDMS as the substrate. The sensitivity of sensor was approximately 6.19×10^{-2} $kPa^{-1}$and the linearity of the sensor over the ranges of 0–6 kPa and 6–33 kPa, which is 91.5% and 87.6%, respectively (Yeh et al. 2019). Xu et al. have synthesized flexible pressure sensor using silver-plated polyester (PET) and polyaniline (PANI) as the conductive polymers, which is polymerized in situ on the PET fabric for the detection of various body movements. The use of silver imposed the sensor with antibacterial and antimicrobial properties. The response time of the sensor is 0.2–0.3 s (Xu et al. 2019). Pignanelli et al. have synthesized PDMS substrate rooted flexible pressure sensor based on capacitive sensing for rehabilitation and health monitoring which is shown in Fig. 3. The pressure sensor was prepared through four different patterning methods i.e. photolithography, replica model, inverse mold, and nonuniform microstructure. The sensitivity of the pressure sensor is found to be 0.7298 kPa^{-1} (Pignanelli et al. 2019). Kou et al. have synthesized micro-patterned sandwiched PDMS/graphene composite-based pressure sensor for wireless detection of movements of human facial and muscle movement shown in Fig. 4. Gold pattern was used as the active electrode material, the sensitivity of the sensor was found to be 0.24 kPa^{-1} in the low-pressure regime and in the high-pressure regime it is of 0.0078 kPa^{-1} (Kou et al. 2018). Jang and his coworkers have fabricated piezoresistive flexible pulse sensor which can detect the human pulse. In this sensor, the PEDOT:PSS was used as sensing flexible film and copper tape was used as the two counter electrode and on the other side the silver paste electrode was used at the edge of the sensor. The sensitivity of the sensor was measured to be 62.56 kPa^{-1} in low-pressure range and 8.32 kPa^{-1} in the high-pressure range (Jang et al. 2019).

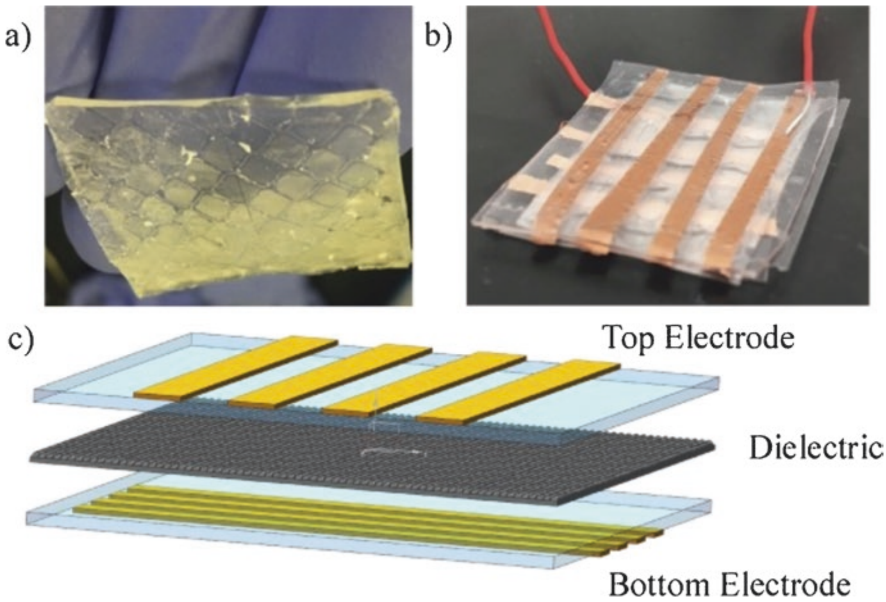

Fig. 3 Illustration showing (**a**) different layers of the flexible electrode (**b**) camera image of the fabricated electrode (b) full set up of the sensor. Taken permission from (Pignanelli et al. 2019)

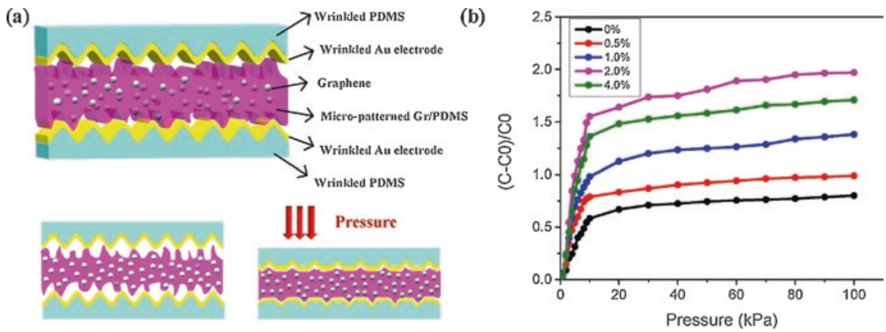

Fig. 4 Diagrammatic representation of (**a**) the whole pressure sensor (**b**) change in capacitance with different concentration of graphene. Taken permission from (Kou et al. 2018)

2.2 Temperature Sensor

Human body temperature does not vary much, but certain activities or situation leads to change in the body temperature like emotions, illness, and certain activity. The normal body temperature of healthy human beings is found in the range of 35–37.5 °C (Moser and Gijis, 2007). A person suffering from several illnesses like hypothermia, hyperthermia, cardiovascular diseases, healing of wound causes certain variation in temperature and needs effective detection devices for better treatment (Sibinski et al. 2010). Till date, point temperature measurement of a particular area through paste on sensor, spatial imaging through complex digital cameras are used but they are not the point-of-care diagnosis, so flexible highly sensitive temperature sensor is required for monitoring of temperature of our body both externally and internally because the inside and outside temperature varies from each other.

Temperature sensors of flexible nature are based on thermoelectric effect, thermocouples, thermistors, and various optical approaches. In many sensors, the temperature variation is detected through thermistor, which causes change in electrical resistance in two types: for increased temperature with increasing resistance it is positive temperature coefficient (PTC) and for increasing temperature with decreased resistance it is negative temperature coefficient (NTC) (Shih et al. 2010). Aliane et al. have developed temperature sensor through screen printing technique following thermistor effect using PET and PEN as substrate. The prepared sensor showed good sensitivity of 0.06 V/1C (Aliane et al. 2014). Huang et al. have fabricated flexible temperature sensor with polyvinylidene fluoride (PVDF) and polyethelene oxide (PEO) filled with graphite for monitoring of body temperature shown in Fig. 5. The prepared sensor showed high accuracy of about 0.1 °C and with temperature sensing ranging from about 25 to 42 °C (Huang et al. 2018). Hao et al. have synthesized thermochromic ink-based flexible temperature sensor, which can visualize the temperature change ranging from about 26 to 50 °C. The prepared sensor was synthesized using xanthan gum and pectin gum as the substrate. The prepared sensor has sensitivity of 53–130%$°C^{-1}$ in above-mentioned temperature range (Hao et al. 2018). Kim et al. have fabricated organic temperature sensor through spatial atmospheric atomic layer deposition (SAALD). The sensor was encapsulated with thin film of Al_2O_3 over PVA, which is used as a functional material to increase the linearity, endurance, and repeatability, in the sensor polyethylene naphthalate was used as the substrate. The sensor can detect temperature variation of about 25 °C–90 °C with high stability and reproducibility (Kim et al. 2019).

2.3 pH Sensor

The chemical state of the body can be easily determined by measuring the pH of different fluids present in the body. Body pH value in different area can be varied due to various factors like sweat pH can be changed by some skin diseases like

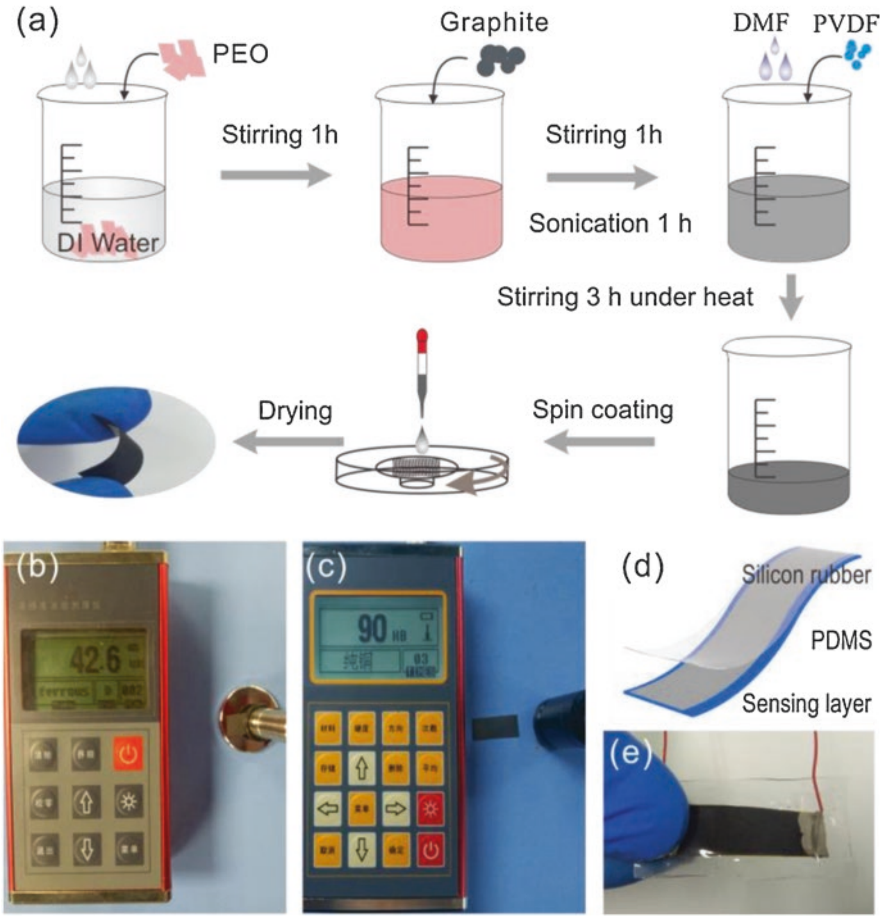

Fig. 5 Schematic representation showing (**a**) synthesis procedure of the prepared temperature sensor; temperature sensing layer thickness and hardness (**b**, **c**) (**d**) graphical representation of the temperature sensor (**e**) camera image of the fabricated sensor. Taken permission from (Huang et al. 2018)

fungal infection, dermatitis. Similarly, area of wound changes the pH with the increase in the amount of bacterial colonization inside it, which increases the difficulty of the wound by slow drying (Rahimi et al. 2016). Increase in gastric juice, whose pH is 1.0–3.5 gives alert of any gastrointestinal diseases. The pH of heart, brain, liver, skeletal muscle always remains neutral but any change in the pH indicates abnormal health. Conventional pH monitoring system includes glass probes, which is very much expensive, required removal after dressing, required trained personnel, cannot be detected at home, in short, such kind of point-of-care diagnosis is not available (Guinovart et al. 2014).

Recent years provide us with several sensing technologies, which can detect the pH of the body through several transduction methods like electrical, optical, and chemo-mechanical transduction method. Nowadays flexible pH test strip sensors are used for the detection of pH, which is fitted on optical fibers have high accuracy, sensitivity, and flexibility. Some of the pH sensors used for healthcare application are discussed here. Rahimi et al. have fabricated transparent and flexible potentiometric pH sensor for wound pH detection through cost-effective laser scribing method. The flexible substrate used here is indium tin oxide (ITO) coated on PET. The prepared pH sensor can detect physiological pH value of 4–10 having sensitivity of −55 mV/pH (Rahimi et al. 2018). Liu et al. have synthesized chemi-resistive flexible pH for wearable biomedical electronic devices, water quality maintaining for better environmental condition, and food safety monitoring. The sensor was prepared through growing single-walled carbon nanotube (SWCNT) on PET substrate. The sensor has great linearity, good performances, less power consumption, and high sensitivity in the pH range of 5–9 with a response time of 22.6 s (Liu et al. 2016). Smith et al. have fabricated well conductive flexible pH sensor using cotton yarn for monitoring pH of body sweat. They have used the dipping and drying method for the synthesis of the flexible substrate using multiwalled carbon nanotube (MWCNT), PEDOT:PSS, PANI, and cotton warn. The sensitivity of the sensor is around −61 ± 2 mV pH^{-1} in the pH range of 2–12 (Smith et al. 2019). Rahimi et al. have fabricated economical, biocompatible, flexible pH sensor for wound bed pH determination as shown in Fig. 6. The sensor was prepared by PANI-coated commercial paper as the flexible substrate with high stability, repeatability, and

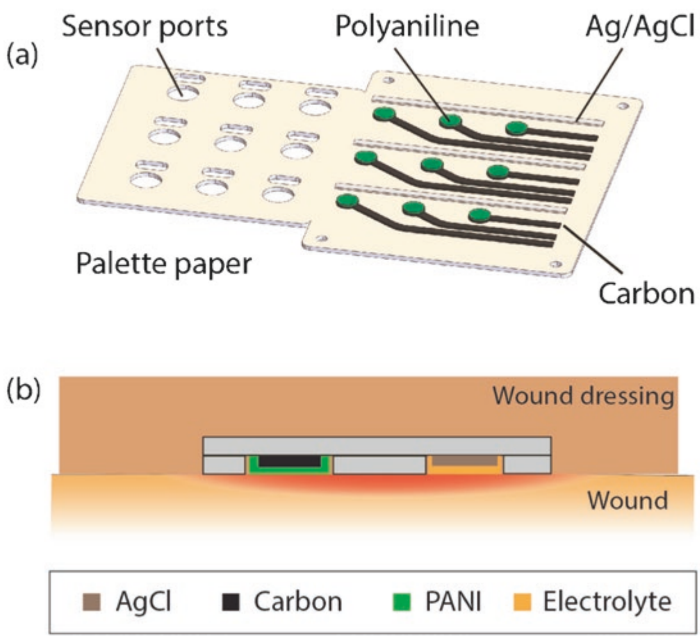

Fig. 6 (**a**) Graphical representation of the pH sensor (**b**) working principle of the sensor on the wound bed. Adapted from (Rahimi et al. 2016)

good linearity of $R^2 = 0.9734$. The sensitivity of the electrode is −50 mV/pH with detection range of pH 4–10 in different buffer solutions (Rahimi et al. 2016).

2.4 E-skin

In spite of the advancement of the wearable sensor, they still have certain demerits like lack of flexibility, brittleness, easy deformation, low stability, bulkiness, requirement of adhesives to settle on skin renders them unfavorable for healthcare monitoring (Hammock et al. 2013). Therefore, user-friendly, entirely flexible, miniaturized device for health monitoring is required, which can withstand extreme level of external strain. Electronic skin is the sensor, which has multimodal sensing property and ability to detect various bio-signals of human body. They have high flexibility, high accuracy, and mimics human skin in various activity. It is one of the great achievements of flexible sensor also known as e-skin, which can adhere to the human skin, made up flexible material and can detect various physiological parameters of body. They are formed of flexible pixel arrays where various external stimuli like temperature, pressure, strain are converted simultaneously into electrical signals (Núñez et al. 2017). E-skin devices have same water vapors permeability, thickness, elastic modulus, thermal mass, temperature as that of our skin. These types of soft sensors, which have mechanically invisible electronic interfaces with the human skin, get laminated at the epidermis of the skin with van der Waals forces and detect various bio-signals for health monitoring. Through e-skin we can detect various cardiovascular information, brain activity, movement of eyes, body temperature, body oxygen level, electrolytes present in epidermis, as well as pH of sweat (Chortos and Bao 2014). For such kind of versatility, the electronic skin must have self-healing, self-powering, self-cleaning properties with high flexibility. Researchers are studying to discover new materials, which have all above properties that can be incorporated into electronic skin for best possible health monitoring.

Some of the articles reported for the fabrication of electronic skin used in different healthcare applications are discussed here. Shi et al. have synthesized electronic skin for detection of pulse rate and movement of thumb by mounting it in the human body illustrated in Fig. 7. They prepared nanostructured Cu electrode through electrode-less deposition method and transferred it into adhesive flexible film of PET to form the sensor. The prepared sensor shows high sensitivity of 2.22 kPa^{-1} (Shi et al. 2019). Suen et al. have fabricated a flexible tactile electronic skin sensor with high flexibility, high force sensitivity for detection of multiple stimuli like bending, pressure, and torsion forces. The space between the two electrodes in the sensing platform is interlocked by zinc oxide nano rods, which increases the conductivity of the system. The substrate of the electrode is PDMS layer, which inputs great flexibility to the system. The proposed sensor has high sensitivity of −0.768 kPa^{-1}, high recovery time of 12 ms with great response time of 14 ms (Suen et al. 2018). He et al. have synthesized multifunctional electronic

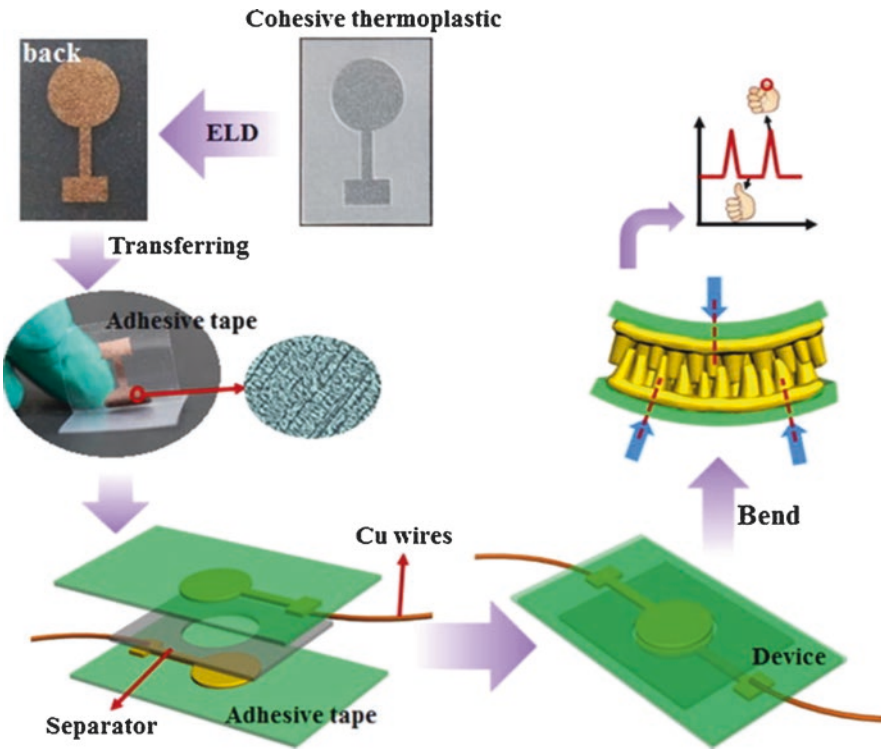

Fig. 7 Graphical illustration showing the working principle and set up of electronic skin-based sensor for movement of human body. Taken permission from (Shi et al. 2019)

skin, which is hybridized with tetrapod ZnO (T-ZnO) nanostructures and piezoelectric polyvinylidene fluoride (PVDF) anchored on PET fabric screen. The prepared electrode has self-powering, self-cleaning, and gas-sensing properties, thus used in health monitoring as well as atmospheric gas detection (He et al. 2017). Li et al. have synthesized electronic skin sensor for detection of vibration of vocal cord, pulse rate, elbow and finger movement with high stability and recyclability. They have used silver nanoparticle paste hybridized hydrophobic polyolefin elastomer (POE) membrane as the flexible substrate. The prepared sensor shows fast response time of 10 ms with gauge factor of 3953 and withstand 30% of strength (Li et al. 2019).

2.5 Flexible Substrate for Biosensing Application

Devices that have biological component to perform the body healthcare and disease management are known as biosensor (Malhotra and Chaubey 2003). Choice of the analyte mainly depends on the application of the biosensor in different fields. Due to

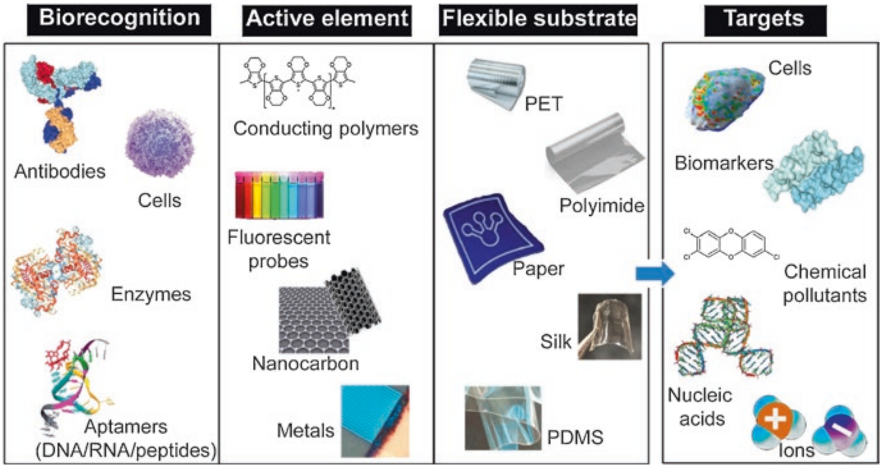

Fig. 8 Schematic representation of the components needed to prepare flexible biosensor. Adapted from (Xu et al. 2018b)

plethora of utilization, wearable biosensors have achieved great responses in the field of healthcare and ailment diagnosis. This type of sensor detects various biological components like different biomarkers, biomolecules like dopamine, lactate, glucose, ascorbic acid, DNA, RNA, whole cells for fatal diseases at very lower detection. Flexible biosensor usually consists of several components shown in Fig. 8 (Xu et al. 2018b):

1. Substrate which provides flexible support to the sensor system mainly made up of various synthetic polymers, papers, or textiles.
2. Bio-recognition sites like antibodies, aptamers, enzymes, oligonucleotide, which is specific and selective for particular analyte used.
3. An active material, which increases the conductivity and helps in signal transduction depending on detection mechanism from bioreceptor and analyte.
4. Specific analyte molecule depending upon the application.

Flexible substrate-based biosensors have high transparency, strechability, stability, biocompatibility, good portability, have light weight, inexpensive, and disposable. These types of sensors have inherent power unit, data acquisition mechanism, and signal transmission through wireless modules. Biosensors have mainly electrochemical method for detection like voltammetry, amperometry, field-effect transistor (FET), etc. because electrochemical methods possess high selectivity and sensitivity. Biosensors flexible electrodes are mainly fabricated through sputtering, lithography, drop casting, inkjet printing, stamping, electrodeposition, or chemical vapor deposition (CVD) methods (Shah et al. 2015). As this book chapter is based on healthcare application, we have discussed the use of flexible biosensors in physiological environment. Flexible biosensors in healthcare application can be used as external to the human body, internal to the body, or can be applied for the detection of analytes/biomarker taken from biological fluids.

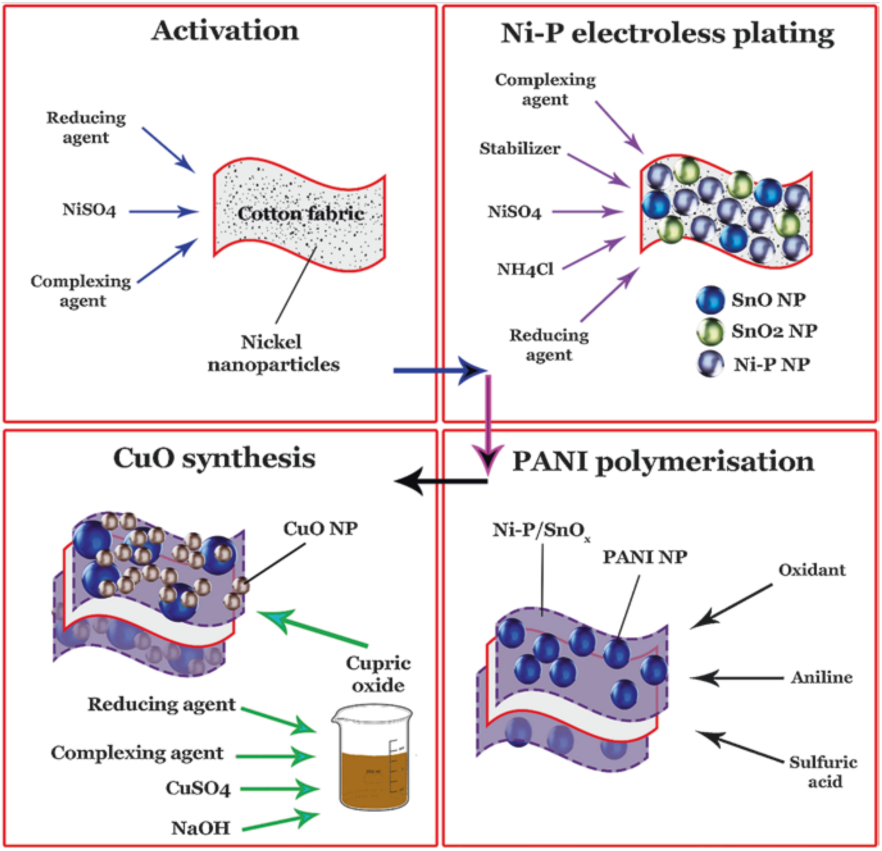

Fig. 9 Illustration showing the fabrication process of the flexible biosensor made up of $NiP_{0.1}$-SnO_x/PANI/CuO (NTPC) nanocomposite. Adapted from (Sedighi et al. 2019)

Sha and his coworkers have synthesized flexible, low-cost, nonenzymatic uric acid sensor through electrochemical detection technique (Sha et al. 2019). They have hydrothermally synthesized MoS_2 grown on aluminum foil, which is then place on flexible cellophane tape. The prepared composite has sensitivity of 98.3 ± 1 nA μM^{-1} and detection limit of 10–400 μM. Sedighi et al. have synthesized glucose sensor of nonenzymatic type for the detection of glucose level of human blood for diabetic patients which is shown in Fig. 9. They have synthesized CuO, $NiP_{0.1}$-SnO_x, and PANI nanoparticle on flexible carbon fabrics to increase the conductivity of the sensor. The prepared sensor has sensitivity of 1625 μA mM^{-1} in the ranges of 0.001–1 mM and 1325 μAmM^{-1} cm^{-2} in the range of 1–10 mM (Sedighi et al. 2019). Munje et al. have synthesized flexible enzyme based biosensor for the detection of glucose in sweat through the electrochemical detection technique. Flexible polyamide substrate was used as the supporting material in which gold/zinc oxide thin film was grown as the electrode material. The sensor has detection limit of 0.01–200 mg/

dL with sensitivity of 19.5 μA mM^{-1} cm^{-2} (Munje et al. 2017). Xuan et al. have fabricated a wearable glucose sensor for the detection of glucose in human sweat through amperometry as detection technique. They have used flexible polyimide as the substrate where reduced graphene oxide (rGO) nanostructures are grown through microfabrication method and used as the electrode. The sensor has sensitivity of 48 μA mM^{-1} cm^{-2} with detection limit of 0–2.4 mM (Xuan et al. 2018). Kang et al. have synthesized wearable glucose biosensor for routine monitoring of glucose level in chronic diabetic suffering patients using thick polyimide (PI) flexible substrate. The substrate was grown with networks of single-walled carbon nanotube (SWCNT) films, which is further surface functionalized with glucose oxidase (GOD). The prepared sensor shows sensitivity of 41.397 μM^{-1} within the detection range of 50 μM to 1 mM (Kang et al. 2019). Jia et al. have synthesized flexible enzymatic tattoo-based wearable biosensor for lactate sensing from human perspiration. They have used carbon nanotube (CNT) and tetrathiafulvalene (TTF) functionalized with lactate oxidase (LOx) as the electrode and flexible GORE-TEX textile as the substrate. The sensitivity of the sensor is found10.31 μA/mM cm^2 with high linearity and stability (Jia et al. 2013). Some of the flexible substrate based biosensors are summarized in Table 1 [66–75].

Table 1 Summary of some of the flexible substrate-based biosensor for healthcare application

S. N.	Analyte	Flexible substrate	Detection mode	Detection range	References
1.	Lactate	PET	Potentiometric	0.2–3 mM	Chou et al. (2018)
2.	Glucose	R-go	Amperometric	2 μM to 13 mM	Wang et al. (2017)
3.	Urea	PANI	Amperometric	0.04 mM	Meibodi and Haghjoo (2014)
4.	Glucose	Bacterial cellulose	CV	0–50 mM	Lv et al. (2018)
5.	Glucose	CSF	Chronoamperometry	0–5 mM	Chao et al. (2018)
6.	Lactate	Tatoo-based paper	Amperometric	1–20	Jia et al. (2013)
7.	DNA	Polyimide	Low-temperature solution-processed IZO TFTs	–	Jung et al. (2014)
8.	Sodium	PET	Potentiometric	0.1–100	Bandodkar et al. (2014)
9.	Glutamate	PDMS	Chronoamperometry	1 μM to 1400 μM	Nguyen et al. (2019)
10.	Glucose	Polyurethan	Amperometric	0–20 mM	Fang et al. (2018)

PET polyethylene terephthate, *PDMS* polydimethyl siloxane, *R-go* reduced graphene oxide, *CSF* carbonized silk fabric, *PANI* polyaniline, *CV* cyclic voltammetry, *TFT* thin-film transistors(s), *IZO* In-Zn-O

3 Future Aspects and Conclusion

In the last few years, there is rapid growth in the landscape of flexible sensor for various applications with increase in the intrinsic searchability, engineering of sensor geometry, inclusion of active conductive material, incorporation of multimodal sensing platform, and use of new efficient signal transduction technique. This chapter includes versatile use of flexible sensor in biomedical and healthcare application. We have discussed here various types of sensors under different categories like pressure, temperature, and pH sensors. Large emphasis is nowadays given in multifunctional wearable human e-skin sensors, which have self-healing, self-powering, self-cleaning properties with great biocompatibility, elasticity, and flexibility, which can be easily attached to human skin for vital biological signal detection. Despite the emerging popularity of the flexible sensor, there are certain tribulations, which need great attention like:

1. The study of the sensing capabilities of the flexible sensors under harsh conditions like high humidity, high and very low temperature is rarely studied; they need certain super-hydrophobic or temperature resistive coating material for better performances.
2. The devoted attention toward increasing the sensitivity of the flexible sensor has surpassed other problems like packaging, integration of power, signal, and data processing unit in a small area. Thus, the sensor needs better packaging to survive in unfriendly environment.
3. Awareness must be increased about the use of this type of electronic skin-like wearable biosensor for quick detection and recovery of the diseases. People in spite of the great development of the wearable flexible sensor rely on conventional detection techniques, therefore, flexible sensor needs enhanced public promotion to enhance their popularity among common people.
4. Battery-free, self-powering human-friendly multiple sensor devices are also lacking in the market, which need to be studied more.
5. The fabrication method of the sensor with ultrafast laser-induced chemical technology should be carefully considered and explored greatly.

With the settlement of the above issues and combining unique effort of the multidisciplinary science fields like material science, nanotechnology, microelectronics, chemistry, and physics can amplify the rapid development of the flexible substrate in near future.

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