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Internet of things (IoT) in nano-integrated wearable biosensor devices for healthcare applications

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A R T I C L E I N F O

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A B S T R A C T

An individual's health is one of the essential aspects of life, but due to the limited technology at health care centers, many people face various restrictions during their treatment. These days, Internet-of-Things (IoT) is the most fascinating topic that provides solutions to these limitations in various ways. The IoT is utilized in various healthcare conducts that include detection, treatment, and monitoring of diseases. Wearable devices are a part of IoT that is proposed for helping patients to get the correct treatment. The conventional communication networks developed for humans-based applications face many issues like stringent latency, restricted computing capability, and short battery life. On the other hand, the onset of 5G has developed a new set of technologies that offer the vital "backbone" for connecting to the billions of devices for the upcoming IoT that would completely modify our professional and private lives. Due to the data capabilities, intelligent management, and superfast connectivity of 5G, this network has enabled new health care opportunities that include treatment, data analytics, diagnostics, and imaging. In the current review, a systematic literature survey of IoT, IoT-based wearable devices, and the role of 5G in IoT for healthcare is described in detail. Furthermore, we have explained the usage of wearable devices in detecting the issue in terms of healthcare, such as curing, monitoring, and detection of disease. Nevertheless, this review article also emphasizes the employment of IoT architecture and its wearable devices in addition to the upcoming research challenges related to this area.

1. Introduction

With the increase in the advancement of technology, the demand for comfort and accessibility is also increasing, leading to an increase in the development of funding programs. Usually, it has been observed that many city hospitals lack to fulfil certain medical requirements of the patients, and therefore, patients have to search in other cities/move to other countries' hospitals to complete their desired medical needs (Surantha et al., 2021). These days, the Internet-of-Things (IoT) in healthcare has become one of the latest trending subjects and has been found as a promising characteristic to improve the current technologies that lower its cost in each aspect of healthcare. Moreover, the IoT in biomedical is considered as the need of an hour that is required to provide medical aid to humans for monitoring, managing, detecting, and taking action from the system after receiving data, thereby effectively reducing the cost of health expenses (Khan et al., 2018). IoT is the sub-category of a computer having sensors, microcontrollers, and transceivers that are interconnected to provide information to aid the user with detailed information. It is applied in various healthcare means, including detection of disease as a precaution, monitoring disease as a self-healing route, and treating disease as the healing solution (YIN et al., 2016). Wearable devices are a part of IoT that have been developed for helping people to get the correct treatment. The IoT-based wearables are smart devices that could be worn with external

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accessories, tattooed or even adhered on the skin, implanted in the body, or embedded in garments and clothing. These smart devices are linked with the internet for collecting, sending data, and receiving information for making smart decisions. These wearable have now become a vital fragment of IoT technology, and their growth is shifting towards more specialized and practical utility from simple accessories (Singh et al., 2021b). Also, these smart wearables can interact with other groups of devices, like smartphones for communication and computing purposes. Fig. 1 shows a schematic illustration of development of different biosensors that detect analytes from biofluids under an ambient environment.

Biosensors are suitable, low-cost, portable instruments for detecting infections, proteins, and other analytes quickly. These sensors were created to replace traditional testing techniques, which are technical in nature and need specialized knowledge and time, resulting in a major expense in their respective sectors (Alocilja and Radke, 2003; Andreescu and Sadik, 2004; Luong et al., n.d.). Biosensors are a booming field of multidisciplinary study that has been heralded as a possible revolution in consumer, healthcare, and industrial testing. The worldwide biosensor business is presently worth over 10 billion dollars yearly. However, the expense of biosensors is a major impediment to their broad use. The present high prices are usually attributed to the specialized nature of the needed apparatus and the reliance on high-grade analytical reagents and materials. A variety of initiatives are now being tried to reduce the cost of biosensors. One option to minimize the cost of some systems is to allow them to be reused, lowering the cost per test. Biosensor regeneration is a technology that may be used in conjunction with current systems to save costs and speed up the commercialization process. When it comes to designing biosensors that suit the demands of the poor world, cost reduction is very crucial. Another critical need to enhance biosensor technology in this rapidly developing world is for healthcare and diagnostic tools for illnesses that are now causing high mortality and morbidity rates (RODRIGUEZMOZAZ et al., 2005).

The benefits of smart wearables have provided expansion of wearable technology, reduced the size of electronic sensors and devices, and progressions of low-power mobile networks at a fast speed (John Dian et al., 2020). There is evidence of the fast advancement of smart wearable devices reformed for different usage during the last few years, as illustrated in Fig. 2. Some examples of wearable products developed for different uses are smart jewellery, hand and worn devices, body straps, earbuds, headsets, eye wears, wristbands, and smartwatches (Hwang et al., 2018; Yao et al., 2011). However, the vital life-changing applications are mostly found in medical and health monitoring cases of wearable technology.

As wearable devices become more entrenched in everyday life, conventional communication networks mainly designed for human-oriented applications face remarkable problems like stringent latency, limited computing capability, and short battery life. However, the upcoming fifth-generation, i.e., the 5G wireless systems, are the next step for evolving mobile communications that seem to support massive connectivity, low latency, and unprecedented high capacity. The 5G would completely change our professional and private lives, especially for novel services applications like connected homes, remote healthcare, wireless robots, and driverless cars. Moreover, 5G would provide a 'backbone' to link with billions of products for the upcoming IoT, supporting thousands of products per square kilometer. The 5G network would support all the IoT devices with varying data demands and capabilities (Boric-Lubecke et al., 2015). It has enabled new health care prospects, including treatment, data analytics, diagnostics, and imaging due to the superfast data capabilities, intelligent management, and 5G connectivity. As it is the portion of the so-called 'internet of medical things' (IoMT), it comprises devices like remote sensors and clinical wearables in addition to other devices which screen and transfer medical data electronically, for example, medication adherence, personal safety, physical activity and vital signs (Miorandi et al., 2012). These devices would offer high-quality video conferencing, treatment services, and telemedicine diagnosis, thereby providing quality care at economical prices.

Previous reviews have presented detailed discussions on various roles of different kinds of wearable sensors in personalized health monitoring, smart wearables and prosthetics using assistive technologies to enable disabled people to operate the surrounding through motorised equipment using their active organs, sensors, actuators, and system-packaging technologies to develop wearable sensing devices and sensory feedback devices (Choi et al., 2011; Demolder et al., 2021; Khoshmanesh et al., 2021). But, this review aims to describe the trending IoT-enabled wearable techniques that are utilized in the current years for creating a better understanding of how IoT and its

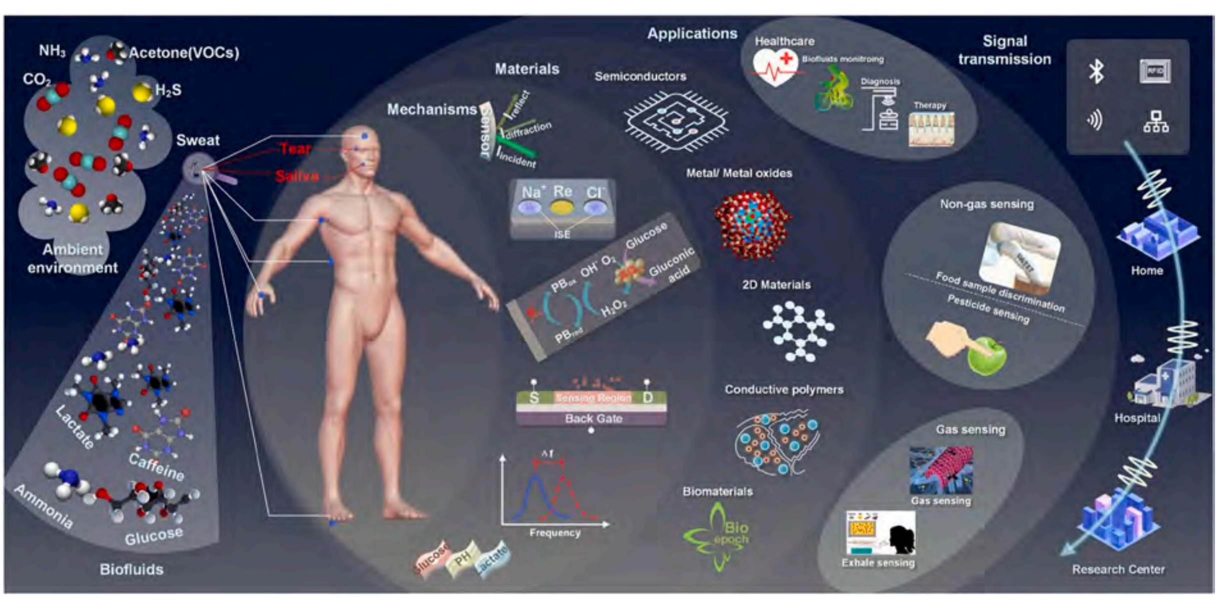

Fig. 1. The development of wearable biosensors for detection of different analytes present in biofluids under ambient environment enabled by several mechanisms, using different materials like metal and semiconductor materials to flexible/stretchable 2D material, polymer and biomaterials, these wearable biosensors have shown great potential in healthcare and environmental monitoring by interfacing with different signal transmission technologies, such as Bluetooth, WiFi, RF (reproduced with permission from (Wen et al., 2020)).

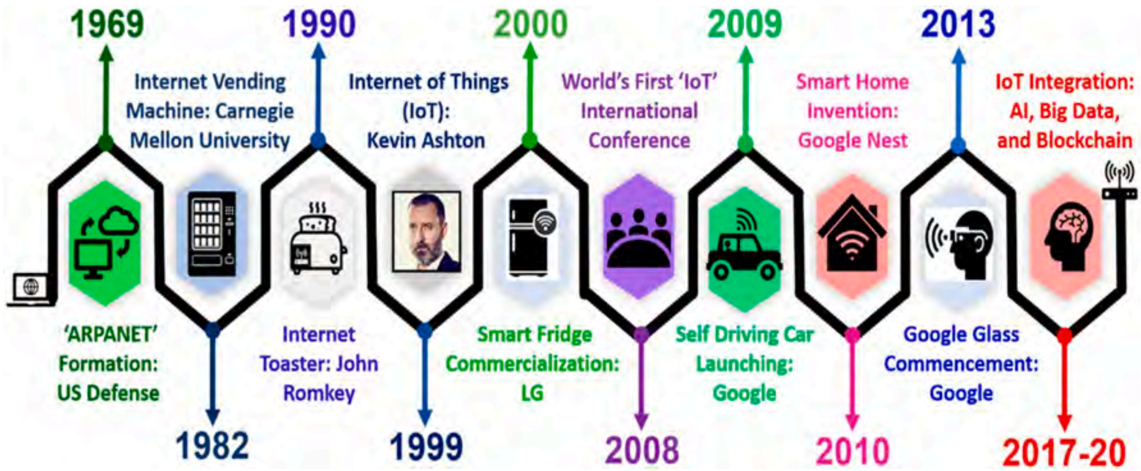

Fig. 2. Infographics of the timeline of the Internet of things (IoT) (1969–2020) (reproduced with permission from (Mishu et al., 2020), distributed under attribution 4.0 international (CC BY 4.0)).

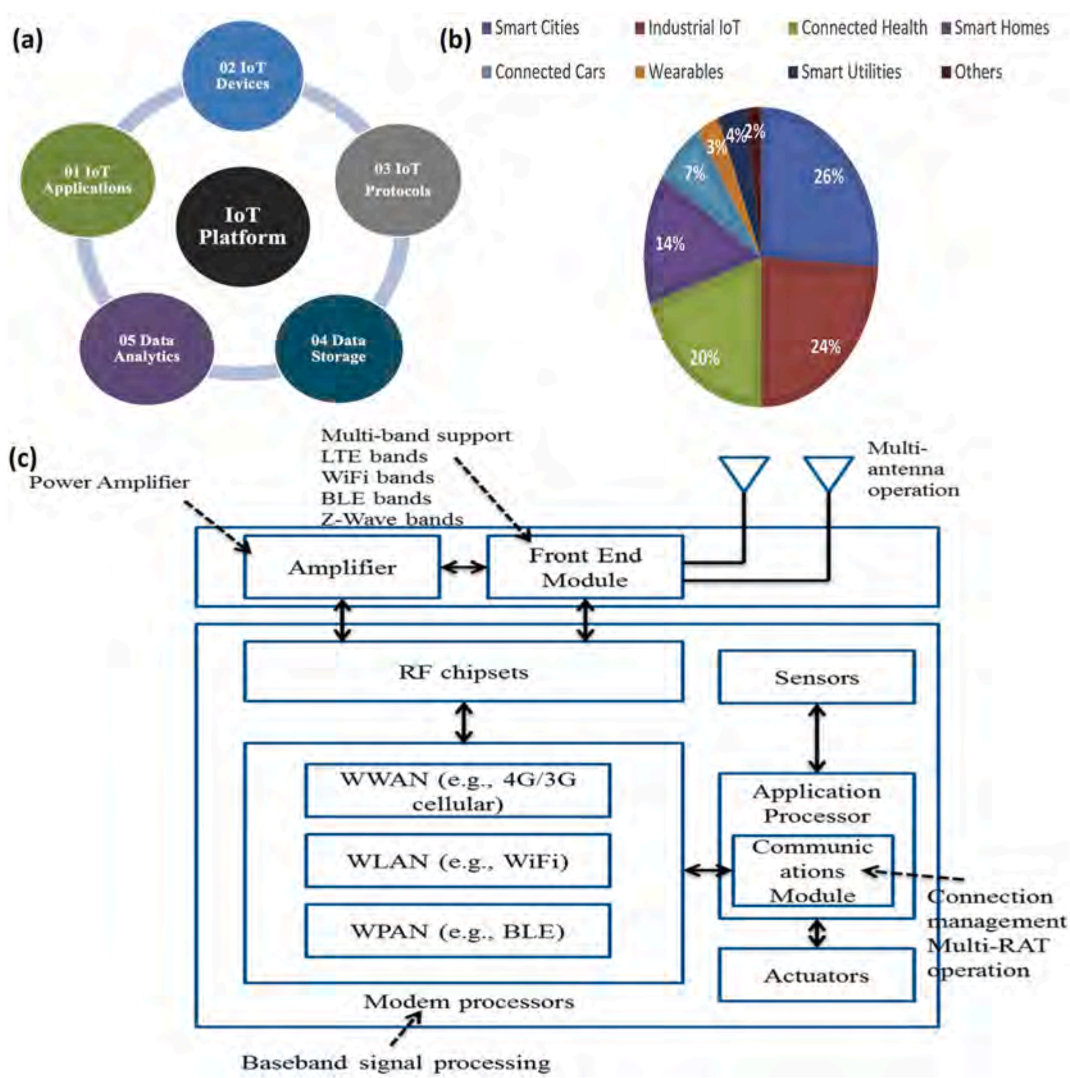

Fig. 3. *(a) Schematic illustration relating the components of an IoT platform (reproduced with permission from* (Hossein Motlagh et al., 2020), distributed under attribution 4.0 international (CC BY 4.0))*; (b) General market structure of IoT technologies (reproduced with permission from* (Nižetić et al., 2019))*; and (c) General structure of IoT network and connectivity (reproduced with permission from* (Abbas and Yoon, 2015), distributed under attribution 4.0 international (CC BY 4.0))*.*

wearable devices create an impact on the healthcare aspect, as well as its device working that includes infrastructure and sensors. Further, this review also highlights the importance and impact of 5G in IoMT, IoT, and IoT-based wearables and explains the persisting weaknesses of some wearable products that would be future challenges for other researchers. This might be a help for them to fabricate IoT-based wearables devices in healthcare. To the best of our knowledge, this review article is the first survey regarding the 5G impact in IoT and IoT-enabled wearables opportunities, applications, and challenges, where we have discussed different groups of smart wearables. The authors anticipate that 5G will revolutionize the area of IoT and IoT-based wearable technology.

2. Internet of things (IoT)

The fast advancement and applications of smart IoT-based technologies have opened up many new possibilities in technical developments in all areas of life (Zheng et al., 2020). Digitalization has endorsed 'smart' as the core center of existing technological developments. Nowadays, IoT technologies are widely regarded as one of the fundamental pillars of the fourth industrial revolution, owing to their great potential for innovation and societal benefits. The IoT is a new internet-based technology that promises to connect physical devices like industrial equipment and home appliances or 'things' (Haseeb et al., 2019). By utilizing suitable communication networks and sensors, these devices could offer people various services and valuable data. The growth in IoT technologies is gaining power, and according to forecasts, over 125×10^9 IoT devices are likely to be linked in the next 10 years (Darren Anstee, 2019). Also, the estimated funds for IoT technologies are high, having over 120×10^9 USD by the year 2021, in addition to the compound annual growth rate of almost 7.3% (Nižetić et al., 2020). Fig. 3 shows the current market structure for IoT technologies, representing that the bulk of the market is concentrated on industrial and smart city IoT. The selection of IoT components like computing, data storage, communication protocols, and sensor devices must be suitable for the intended use when creating an IoT application i.e., the initial stage in designing IoT systems. For example, an IoT platform designed for operating a building's air conditioning, cooling, and heating (HVAC) involves the use of relevant communication technology and appropriate environmental sensors (Ramamurthy and Jain, 2017). Fig. 4 depicts the various modules of the IoT platform and the common IoT connection and network structure, respectively (Jia et al., 2019).

According to reports of the World Bank, the population is continuously rising at a pace of 1.1% per year and the present population of approximately 7.7×10^9 (The World Bank, 2020). As previously said, cities have a high population density, and UN forecasts predict that by 2050, 68% of the world's population will be living in cities (Population

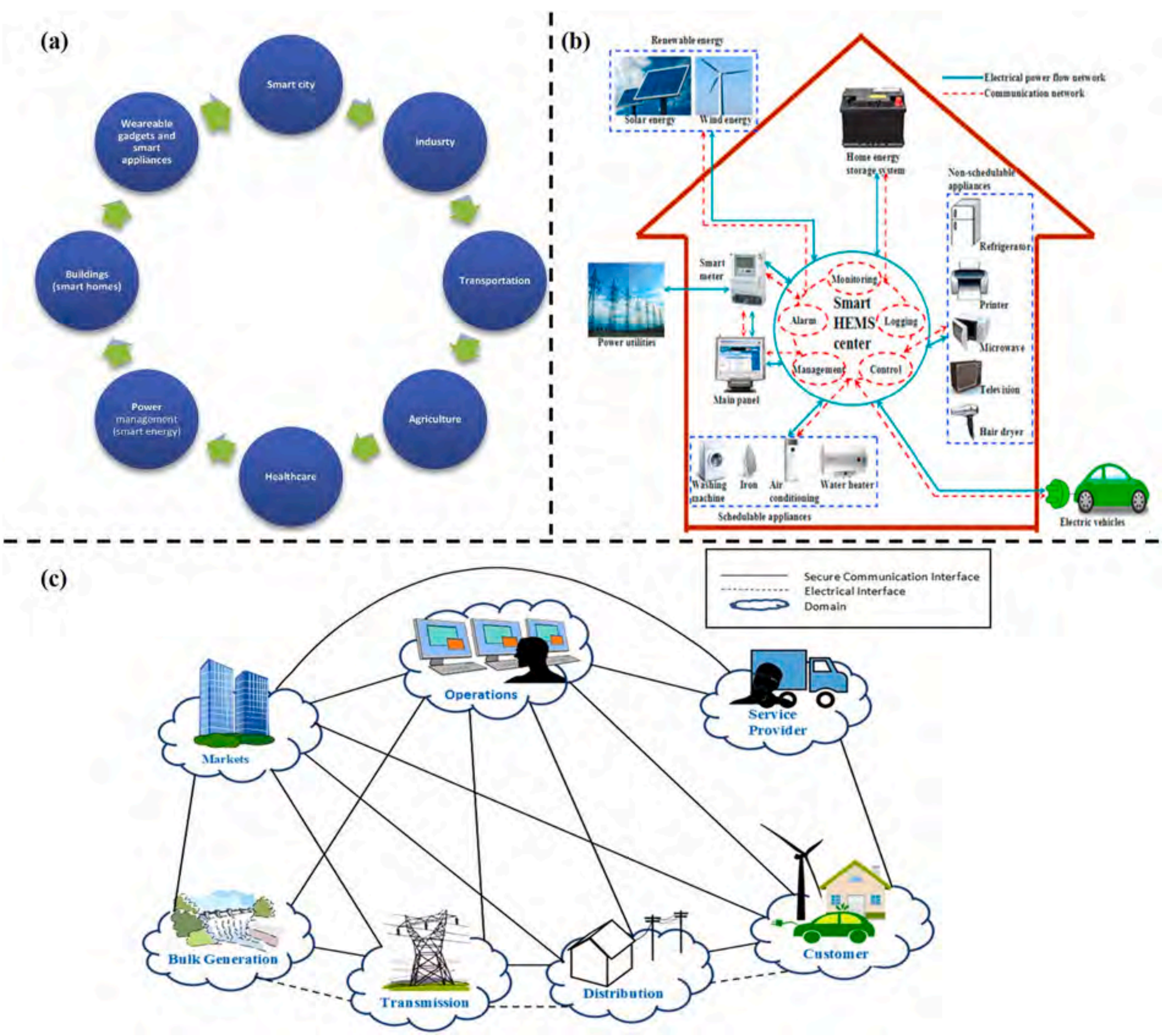

Fig. 4. *(a) Application areas of IoT technologies (reproduced with permission from (Nižetić et al., 2020)); (b) Schematic representation of a smart home system using smart home management system (HEMS) (reproduced with permission from (Zhou et al., 2016)); (c) Smart grids (reproduced with permission from (Tuballa and Abundo, 2016)).*

Matters, 2020). Therefore, cities are likely to face tremendous infrastructure pressure due to increased urbanization; thus, solutions from innovative technology would be vital in ensuring the regular functioning of cities in these demanding and complicated circumstances. In this scenario, the widespread use of smart technology and IoT could play a critical role in bridging some of the city's main infrastructure concerns. Further, IoT technologies have also enabled a wide range of smart applications, devices, or networking and efficient services that caused synergistic effects and were proved beneficial for day-to-day life. Further, IoT has many applications, from construction, logistics, and manufacturing (Jan Holler, V. Tsiatsis, C. Mulligan, n.d.) to drone-based services, energy proficient building management, healthcare services and systems, and environmental monitoring (Atzori et al., 2010; Evans, 2011; Hui et al., 2017; Motlagh et al., 2019).

In terms of several project outcomes, the most vital and fastest-growing applications in IoT fields are the idea of smart cities (G. Sivanageswara Rao, K. Raviteja G. Phanindra, 2020), the industrial sector (Osterrieder et al., 2020), agriculture sector (Villa-Henriksen et al., 2020), management of power network (Martín-Lopo et al., 2020), smart energy management (Nižetić et al., 2020), and the area of transportation (Porru et al., 2020). Moreover, IoT-based techniques provide a whole new vision for advancement in multiple areas like medicine (Salagare and Prasad, 2020), agriculture (Farooq et al., 2020), engineering (Zaidan and Zaidan, 2020), and so forth. Some potential fields in IoT technologies are still not clear or yet to know, which indicates that deep research investigation should be performed in this challenging area for new and vital potential profits to society. Therefore, the importance and relevance of IoT techniques should be clearer in future terms that would play a significant role.

3. IOTs in healthcare

IoT has efficiently revolutionized the world and created an influence on both living and working lifestyles (Myrka, 2020). The most important IoT field is medical and health care, which is poised to alter the healthcare industry over the next decade because of its vast potential for various applications, ranging from hospital-centric to patient-centric (Shayda Khudhur, 2017). Patients are getting more involved in their treatment due to the IoT technology, which would allow them to reach their doctors, organize appointments, and access their health records *via* a portal. The health workers and individuals could also monitor their health from home in real-time using the home monitoring systems, providing benefits for elderly people and patients with long-term diseases (Wickramasinghe and Bodendorf, 2020). The IoT in healthcare could improve patient care due to various smart devices like ultrasound, mobile X-ray machines, smart beds, glucose meters, blood-pressure analyzers, and thermometers units (Erin Lorelle Cook, 2020). The current categories of IoT-based portable devices include body clothes (pants, underwear, and coats), heads (helmets and glasses), wrists (gloves, bracelets, and watches), somatosensory modulators, like, body and feet sensory control devices.

Furthermore, the internet's functionality is evolving from the Internet of Computers (IoC) to the Industrial Internet of Things (IIoT) because most linked systems are made up of people and their surroundings involving smart items, embedded devices, and infrastructure. But security and ethical concerns possess the risk of harming the IoT, because when every piece of data and gadget is connected to the network, hackers may access it and use it for various frauds. Artificial intelligence (AI) is frequently employed in the healthcare business to improve the quality of life in various ways through wearables. In today's world, AI has become quite popular for transforming computers into logical human beings (Ramasamy et al., 2022). By aiding with medical picture analysis and diagnosis, AI in healthcare has the potential to enhance patient care and staff efficiency (Ibrahim, Ahmed Abdulkadir Muhamma, Yasin Zhuopeng, n.d.). Further, with the help of data collected in the Kaggle repository, doctors may now use an AI-enabled IoT in patients to detect a variety of illnesses, including diabetes, heart disease, and gait difficulties. The Google Brain initiative's AI-powered diabetic eye disease detection is a current example of AI-based IoT based on Deep Learning, which employs neural networks to learn and execute a specific job through repetition and self-correction. Another example is next-generation wearables for blind people that utilize ultrasounds to identify impediments in the user's path and alert them so they may safely navigate items around them. Furthermore, AI wearables can aid fitness professionals with their everyday training activities by allowing them to track their progress. The wearable gadget will count and show the steps if the user walks 12000 steps. Wearables with AI can not only measure data, but also recommend what the user should eat, how much sleep they should get, and how they should train to enhance their fitness, among other things. Bluetooth smart with AI biosensors measure heart rate, elevation, motion, proximity, and touch in headphones that also serve as fitness trackers. These headphones provide the best approach to attain your own exercise objectives based on your health criteria. To summarise, artificial intelligence in wearables pushes the boundaries by supporting patients and clinicians with remote tracking, precautions, remote diagnostics, and guiding patients in making progressive decisions. In the fitness business, artificial intelligence enables gadgets to act as personal assistants, assisting consumers in taking care of themselves. Further, this section of the review article covers the various wearables that are currently in use or are in progress of development.

3.1. *Wrist mounted wearables*

The wrist-wearables are usually meant for the wrist to monitor physiology, having the benefits of miniaturization along with an increase in battery life for converting the raw signals to real-time interpretable information (Guk et al., 2019). Screening of hypertension or high blood pressure is a major, crucial, and important variable risk cause for investigating the status of patient health having the cardiovascular diseases (Rastegar et al., 2020). Nevertheless, measuring arterial blood pressure appears to be a potential method for monitoring and controlling the prevalence of cardiovascular disease-affected patients. As a result, blood pressure monitoring has become one of the essential physiological measures in the ambulatory context for monitoring an individual's health condition (Meng et al., 2018). In this respect, wrist-based wearables can be a clinical tool with a high acceptance rate by the patient. Further, wrist-based devices are used to track daily activities such as patient monitoring, acceleration, rotation, gesture, and motion. Additionally, smartwatches or fitness bands (Seneviratne et al., 2017) are commercially available wrist-worn gadgets that are utilized as non-invasive human monitoring tools (Kamišalić et al., 2018; Seneviratne et al., 2017).

3.1.1. *Fitness bands*

The wristbands are specifically developed to measure fitness activities and human health and are commonly characterized as wrist-worn wearable gadgets among smartwatches and wristbands (Seneviratne et al., 2017). For instance, Huawei Talkband B3 (Seneviratne et al., 2017), Fitbit ("Fitbit"), and the UP4 band ("UP by Jawbone") are being designed to measure and monitor walking as well as to record the sleeping cycle. The various sensors on the inner surface of the band can also capture signs like galvanic skin reaction, body temperature, and heart rate. Measurement of blood pressure is one of the vital parameters for a person's health state (Khattar et al., 1999). For solving the conventional pulse wave sensors issue, Lee's group has developed a wearable sensor with a Hall device that could be worn on the wrist. This device helps detect the small variations in the permanent magnet's magnetic field and gives the data in the form of a pulse wave without using a cuff (Lee et al., 2011). Further, a skin surface integrated personal wearable prototype for monitoring the health system was designed to collect high-fidelity waveforms of blood pressure in real-time and connected through wireless devices such as laptops and smartphones (Hsu and Young, 2013). Different applications utilizing photoelectron imaging (PPG) cantered heart rate sensors for the wrist have been developed (Hwang and Lee, 2017). Moreover, Ishikawa et al. designed a bracelet-style PPG heart rate sensor that determines the variations of the noise-free heart rate, employing the noise reduction pulse signals for autocorrelation and peak detection methods (Hwang and Lee, 2017; Ishikawa et al., 2017). According to the latest market trends, the wristband market is rapidly rising, showing its growing interest in well-being and healthcare monitoring.

3.1.2. Smartwatches

Smartwatches have become the most vital wearable device that screens humans' biomechanics and physiological signals in modern-day life. As a result, it functions as a fitness tracking gadget, allowing users to automatically document their daily activities, such as calories burned, step counts, heart rate, and record workout times (Henriksen et al., 2018). Smartwatches collect data with sensors connected with a lithium-ion battery that sends it to a smartphone or a cloud server for readability and analytics. The Food and Drug Administration (FDA) has approved GlucoWatch® biographer [Cygnus Inc., Redwood City, CA, USA] for commercial use, the first smartwatch for non-invasive monitoring of glucose (Vashist, 2012). This device obtains information regarding the glucose concentration electrochemically from skin interstitial fluid collected by reverse iontophoresis. Moreover, Glennon et al. developed a watch that could continuously monitor the sodium levels in the body *via* perspiration (Glennon et al., 2016). For a patient suffering from Parkinson's disease, a smartwatch with an accelerometer/gyroscope feature could be helpful for monitoring and analyzing balance dysfunction and tremor (López-Blanco et al., 2019). Similarly, Roberto and his team have accessed the smartwatches for tremor measurement in Parkinson's patients, clinical connection, reliability, and acceptance as a screening tool. Besides, Tison et al. have developed smart devices and produced an algorithm to identify atrial fibrillation of heart rate from data collected using an accelerometer and a photoplethysmography (PPG) sensor (Tison et al., 2018). Thus, the smartwatch has the potential to get good approval from patients and could act as an effective clinical tool.

3.1.3. Wrist patches

Nyein et al. developed a microfluidic and flexible-based patch device to examine sweat samples in real-time. This sensor has the potential to monitor ion concentrations (Cl^-, K^+, Na^+, H^+) and sweat rate, which enables it to monitor clinical situations and human physiology through sweat parameters (Nyein et al., 2018). Similarly, Lee et al. designed a wearable lab-on-patch system for the detection of cortisol using an integrated microfluidic collecting device and polydimethylsiloxane. The patch has a linear range of 1.0 pg mL^{-1}, having a limit of detection of 1.0 pg mL^{-1} (Lee et al., 2020). In another study by Parlak et al., an artificial molecularly imprinted polymer (MIP) was prepared *via* copolymerization reaction for cortisol detection. The same group designed another " SKINTRONICS " system to measure stress levels through electrodermal sensing of galvanic skin reaction. This device is multilayer in nature with a 7-h wear time as well as has characteristics of flexible hybrid skin-conformant that enable it to collect data in real-time (Parlak et al., 2018). Recently, different skin-interfaced sensing systems or wearable-patch are under progress, displaying attention in the direction of flexible sensing (Kim et al., 2020).

3.2. Head-mounted devices

The head-mounted devices are the visual tools having hands-free abilities, generally fixed to the person's head such as caps, glasses, and helmets which are recently applied in education, simulation, imaging, surgery as well as in navigation tools (Iqbal et al., 2016; Peake et al., 2018). Wearable systems consist of smart glasses that also fall under the category of the head-mounted computer having a display. For instance, Constant et al. designed smart glasses, pulse-sensing glasses with a PPG sensor on the nose pad that can regularly detect heart rate (Constant et al., 2015). Wang et al. showed eyeglasses with nose pads that include a lactate biosensor and potassium ion-selective electrode to monitor lactate and detect potassium ions present in sweat, thereby proving the benefit of an interchangeable sensor (Sempionatto et al., 2019). The sensors like GPSs, magnetometers, barometers, altimeters, gyroscopes, and accelerometers could also be incorporated for fabricating the smart glasses. Recon Jet's smart glasses are more advanced smart glasses that aim to record their owners' health situation when riding a bicycle or running through the display (Barnwell, 2015). Based on the literature, numerous smart eyeglasses are being developed for different applications like biosensors for sweat lactate utilizing bienzymatic Gel-Membrane through eyeglasses (Zhang et al., 2020), EOG (electrooculography)-based human–wheelchair interface (Kuo et al., 2009), health monitoring and medical use (Yu et al., 2019), computational eyeglasses for sensing drowsiness and fatigue (Rostaminia et al., 2017), biosensing of tear for minerals and vitamin detection (Sempionatto et al., 2019). Cavitas wearable sensors are fitted to body cavities like mouth guards and contact lenses that deliver data from the biological fluid. Several cavitas' sensors are developed to detect biomolecules in transcutaneous gases at the mucosa of the eyelids and tear fluid. In addition, these mouth guard sensors have also been explored for real-time detection of substances in saliva. A mouth guard glucose sensor establishes on microelectrochemical system (MEMS) having enzyme membrane immobilized glucose oxidase was developed (Arakawa et al., 2016).

For monitoring important symptoms and signs in neonates, the progress in non-invasive and portable health devices is of tremendous interest as new born babies cannot express their health complaints or discomfort (Kumar et al., 2020). Carmona et al. developed a pacifier biosensor operating wirelessly for non-invasive monitoring of chemicals in the saliva of neonates to detect glucose (García-Carmona et al., 2019). Likewise, Kim et al. have presented an enzyme-based biosensor attached to the mouth guard for determining lactate and salivary uric showing high sensitivity and selectivity (Arakawa et al., 2016; Kim et al., 2015). Also, Danish and his collaborators developed a helmet for treating depression by transmitting weak electrical pulses to the brain and re-energizing the depressed body parts for fast patient recovery (Brabant, 2014). The FDA has approved the helmet to treat depression using weak electrical impulses transferred to the brain from depressed body parts (Kamentez, 2013). It has also been reported that the design of two heads-up display-based systems can reduce physiological disorders like body posture, seizures, and nausea. (Chi et al., 2011; Deleeuw, William C., Sedayo, 2015).

3.3. Smart clothing/e-textiles

Smart clothing, also known as e-textiles, is a growing interdisciplinary area of wearables having potent usage in fitness and healthcare (Ismar et al., 2020). It comprises clothing material and conductive devices connected to sensing various environmental situations and responding to mechanical, chemical, or thermal fluctuations. The textile-based analytical system includes sensors utilized for biofluids analysis (Liu and Lillehoj, 2016). A controlling unit, an actuator and a sensor is used for designing smart textiles ("E-textiles," n.d.) that are employed for monitoring human physical activity like pressure, body acceleration and motion, biomechanics and physiological signals (Pacelli et al., 2006; Seneviratne et al., 2017).

Further, Liu et al. designed a detection system of lactate and glucose by utilizing lactate oxidase and glucose oxidase-based electrodes embedded in a piece of fabric for measuring lactate and glucose with high precision (Liu and Lillehoj, 2016). Further, Liu and his group also fabricated a glove and living material connected with hydrogel-elastomer mixtures combined with genetically engineered bacteria, including genetic circuits for providing materials with desired functions (Liu et al., 2017). The bacterial sensor, i.e., IPTGRCV/GFP, RhamRCV/GFP in contact with inducer such as IPTG, Rham, results in activation of fluorescence response. e-textiles are also used to monitor physiological signals, like temperature, breathing rate, and heart rate (Paradiso et al., 2005; Sibinski et al., 2010). The breathing and heart rate screening during regular activity could be done using the Hexoskin wearable vest (Villar et al., 2015). An electronic shoe was designed to monitor walking ability like ground reaction forces, toe pressure, heel strike, and lateral plantar pressure (Jung et al., 2013; S. I. H. Lee et al., 2017), providing basic information for differentiating between the walk phases.

Mishra et al. designed a glove including an electrochemical biosensor having a flexible, printable enzyme-based electrode capable of detecting organophosphate (OP) nerve-agent composites. This glove-based device was used as a point-of-use monitoring technique and in food security and defense applications (Mishra et al., 2017). Similarly, Kundu et al. developed a conductive-clothing-based wearable biosensor to sense the breathing rate, which is established on a capacitive approach. This t-shirt is generally worn at the chest or abdomen position. The respiration cycle is monitored using the capacitance between the two electrodes located on the posterior and inner anterior sides of the t-shirt (Kundu et al., 2013). Hyland and his collaborators described the development of wearable thermoelectric generators (TEG) for harvesting the heat of the human body that advanced the power of wearable electronics (Hyland et al., 2016). Additionally, a smart shirt-based biosensor was designed to measure the acceleration signals and electrocardiogram for real-time and regular health tracking (Lee and Chung, 2009). These wearable sensors have been developed to fit comfortably into a shirt with low power consumption and tiny size to decrease the battery size. Because of its mechanical flexibility and low cost, the biosensor using artificial biology technology offers the potential to monitor the environment and healthcare.

3.4. Chest mounted devices

The checking of postural and falling disability of patients is a top concern for health workers or caregivers (Taj-Eldin et al., 2018). The two vigilant systems that are offered commercially for safety monitoring are the AlertOne medical alert system ("AlertOne: Medical Alert System, " n.d.) as well as the Life Alert Classic *via* Life Alert Emergency Response Inc ("LIFE ALERT CLASSIC," n.d.). A pendant is combined with a push button in these devices, and hitting the button sends the message wirelessly to a remote place. Similarly, the Wellcore system utilizes accelerator meter components and advanced microprocessors to monitor postural movement (Pannurat et al., 2014). This device helps in distinguishing between falls body and normal movements that further communicate to a remote center. Halo Monitoring TM invented the My Halo TM, a chest-worn device employed to monitor the temperature, sleep pattern and heart rate, etc. ("myHalo™ Personal Monitoring and Alert System," n.d.; Patel et al., 2012). In summary, a device with an integrated system on a smartphone and a balance sensor that prompts automated dialling on an emergency number in the fall incident would be extremely valuable.

4. Nano-integrated based wearable biosensors

With the current pace and advances, nanotechnology has efficiently surpassed various conventional techniques and has made its way in leading futuristic technologies. This high success rate of nanotechnology purely belongs to its distinctive size that helps them exhibit unique properties that the bulk matter cannot exhibit. Moreover, the introduction of nanotechnology in the biomedical field has elevated its popularity among researchers worldwide. The nanoparticles act as a theragnostic agent in the biomedical field, which means they can be used as both therapeutic and diagnostic methods (Nayak et al., 2021; Ukhurebor et al., 2021). Further, the advancements in the development of biosensors are one of the commendable achievements in the science and technology domain as these biosensors have seen tremendous growth from traditional electrochemical biosensors to the point of care, lab-on-a-chip, wearable nanobiosensors, etc. (Singh et al., 2021a; Singh and Singh et al., 2021a; 2021b). Wearable biosensors have become futuristic devices as they are widely used to monitor personal and public health and are widely recommended by health experts and physicians. Today, various types of biosensors are available in the market which is used to monitor heart rate, sleep time, temperature, stress management, oxygen level, steps, voice, breath, motion, humidity, pressure, force, voice, etc. (Bariya et al., 2018; Heikenfeld et al., 2018, 2019; Lou et al., 2017; Xue et al., 2020). However, its potentiality and affordability for every person is still a challenge to achieve, but an increase in the research is bringing us near towards future revolution in the biomedical field, practices, and healthcare facilities. Biosensors aim to monitor an individual's physical state by efficiently detecting specific biomarkers and giving regular information to the individual (Heikenfeld et al., 2018). Moreover, the continuous utilization of smart wearable nanobiosensors has been highly advanced and will reach $97.8 billion in the upcoming five years (Yao et al., 2018). The advancement in designing sensors and functionalizing materials has been observed over the past few years, which has ultimately resulted in the development of flexible, stretchable, non-invasive, and high-performance biosensors. Various advantages and challenges of different wearable biosensors are combined in Table 1.

4.1. Epidermal based wearable biosensors

The epidermis covers most parts of our body, and therefore skin-based wearable biosensors have successfully paved their way in the world of sensors. The epidermal wearable biosensor gained much attention as they can easily detect the biomarkers present in the epidermal fluids like sweat, interstitial fluid (ISF), blood, etc., which facilitates real-time analysis of an individual's fitness and health monitoring. Basically, the epidermal-based biosensor works by detecting the biomarkers present in the sweat and ISF from the skin surface and transports it to the transducer surface, as shown in Fig. 5. The transducer can be electrochemical, optical or mechanical, combined with either bio-catalytic or ion-recognition receptors, that convert the chemical signals into detectable signals and process the obtained data into a readable format (Bandodkar et al., 2015a; Jeerapan et al., 2016; Jolles and Harrison, 1970; Lee et al., 2016; Matzeu et al., 2015; Xue et al., 2016). Currently, various types of biosensors are available in the market, which are either directly transferred onto the skin in temporary tattoos, as printed e-skin, or in the form of patches and wristbands.

Additionally, nowadays, these epidermal-based wearable biosensors are also integrated into smartwatches that are in direct contact with the epidermis and allow the sensor to detect the physical activities and mechanical stress that occurs due to the physical movements. The epidermis-based wearable biosensors have already started to rule the market by exceeding their value of USD 1 billion (Heikenfeld et al., 2019). For instance, Glucotrack, a non-invasive glucose monitoring biosensor designed in-ear clip, detected glucose levels and was approved by the European Union (EU) in 2016. The biosensor measured the glucose levels present in the earlobe tissue with a life of six months and showed a working range from 3.9 to 27.8 mM. There are several other devices approved by the FDA, in which Dexcom G6CGM and FreeStyle Libre (Abbott) are the two biggest examples of transdermal patches used for the detection of ISF glucose. The Dexcom patch worked for almost ten days and showed a working range from 2.22 to 22.2 mM, whereas the Abbott patch showed a 14 days life, with a working range from 2 to 27.8 mM. However, Dexcom patches frequently require self-calibration two times a day. Moreover, in June 2019, the FDA granted approval to Eversense (Senseonics), which also measures the ISF glucose levels for 90 days by using fluorescence mechanisms, therefore becoming the first

Table 1
Advantages and disadvantages of different wearable biosensors.

S. No.	Wearable biosensors	Advantages	Challenges	Ref.
1.	Epidermal-based sensors	• Eliminates the use of unnecessary needles. • Cost-effective. • Control of non-invasive body fluids.	• Causes skin irritation. • Do not provide long-term stability. • Requires fresh sweat sample. • Juvenile studies on accuracy and reliability. • Readings are hindered from other glucose sources.	Kim et al. (2018)
2.	Tear-based sensor	• Shows minimum invasiveness. • Continuously monitors biomarkers. • Easy to use. • Portable.	• Dependent on the enzymatic reaction. • Does not show repeatability or stability. • Frequent sterilization is required. • Does not provide comfort to the user.	Tseng et al. (2018)
3.	Exercise-based sensor	• Real-time analysis. • Non-invasive measurements.	• Limitations in the sample volume. • Not compatible for monitoring glucose in daily life without exercise.	Kim et al. (2019)
4.	Saliva-based sensor	• Portable. • Sensitive. • Compatible. • Easy to handle.	• The viscosity of fluids interferes with the results. • Difficult to maintain hygiene and requires proper washing.	Zheng et al. (2021)
5.	Iontophoresis-based sensors	• Do not harm the skin. • Flexible. • Easy to use.	• Cannot be miniaturized. • Does not provide long-term stability. • It is not user-dependent.	Bandodkar and Wang (2014)
6.	Microfluidic-based sensor	• Miniaturized. • Low detection of limit. • Easy to develop.	• Cannot precisely detect target molecules at lower concentrations like ng/mL. • Chances of getting false results are high.	Choi et al. (2011)

glucose monitoring sensor using an optical technique. The device is available in a small stick implant and costs up to USD 99, and gives a working range of 2.22–22.2 mM (Kim et al., 2019). Moreover, large-scale manufacturing and cost-effective wearable nanobiosensors are still in progress.

Currently, the microwave biochemical wearable biosensors have attracted good attention as their principle of working relies on the change of electromagnetic properties of the sensing materials as they exhibit strong resonance behavior in the presence of electromagnetic properties (Porter et al., 2016). These resonant frequency changes according to the concentration and content of the sample, which means the resonant frequency highly depends on the sample's concentration and constituents; therefore, these microwave biochemical wearable biosensors are highly used for developing wireless sensors for monitoring

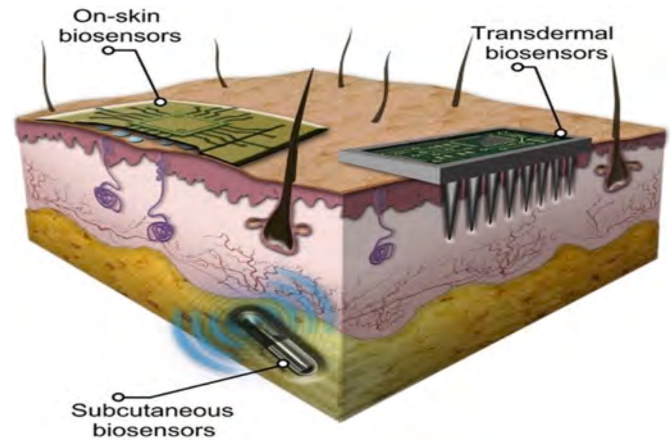

Fig. 5. Schematic illustration of different skin-based biosensors embedded in skin layers (reproduced with permission from (Dervisevic et al., 2020)).

humidity (Wang et al., 2012), temperature (Girbau et al., 2012), etc. because they show passive conduction and high frequency. Moreover, with the help of a low-cost screening technique, these micro-strip microwave sensors can be fabricated with substrates as planar electrodes that exhibit compactness (Kang et al., 2019). The first flexible microwave-based wearable biosensor was designed by Mason and Korostynska et al. that monitored lactic acid. Although, the sensor exhibited certain limitations like the size of the sensor hindered the limit of detection, response time, and trace detection capability of the designed microwave-based wearable biosensors (Mason et al., 2018). Therefore, research on improving response signals and trace detection is still required. However, it has been observed that by increasing the roughness of the metal surface, the electromagnetic mechanism will be enhanced, leading to an increase in the electric field intensity. Therefore, for this purpose, the metamaterial is used, which is an electromagnetic material that is periodically arranged according to the size smaller than the wavelength of the incident electromagnetic wave (Chen et al., 2012). The major advantage of using metamaterials in sensing is that it allows the maneuvering of the electromagnetic waves, and studies on them are also increasing continuously (Jakšić et al., 2010).

Furthermore, a nanostrip type of metamaterial to enhance microwave biosensing was designed using a 100 nm ordered conductive polymer nanowire array. These nanostrips were fabricated on the plastic substrate with the help of a nanoscale soft printing approach featuring facile fabrication (Xue et al., 2019). Moreover, it was also used to detect glucose by using glucose oxidase enzyme directly doped on the nanostrips with biotin-streptavidin conjugation. This flexible wearable biosensor efficiently detects the levels of glucose from the skin and can also be used for the detection of various others biomolecules by using different biomarkers and holds futuristic prospects in the biomedical field (Dalirirad and Steckl, 2019). Moreover, the increase in technology has led to the development of various wearable nanobiosensors that utilize the internet of things (IoT). These biosensors are now available in smartwatches, skin patches, skin tattoos, implantable healthcare wearable devices, and wearable vests.

4.2. *Tear based wearable devices*

Another important bio-fluid that plays an important role in diagnosing and analyzing various kinds of diseases is tears. Diabetes is one of the diseases which can be detected by using tears. Although multiple approaches have been developed to instantly diagnose blood glucose levels through blood, urine, or sweat, but, using tears to diagnose diabetes was considered an innovative, rapid and advanced technique. A comparative study was performed in which the concentration of glucose from tear samples and the blood and urine samples of diabetic patients were analyzed. The study showed that the tears contained a high glucose level compared to the blood and urine samples of both diabetic patients and healthy individuals (Sen and Sarin, 1980). With the basis of this experiment, various wearable biosensors have been developed which detect glucose from tears of the individual, in which one of the famous commercialized products is the Triggerfish that keeps track of intraocular pressure of glaucoma patients, and similarly, Novartis with collaboration with Google lens helps in detection of diabetes by using features of Google. These smart contact lenses that utilized hydroxyethyl methacrylate (HEMA) and phenylboronic acid (PBA) were designed to detect and monitor diabetes using tears. Moreover, these lenses show reversible covalent interactions between PBA-HEMA with glucose, which helped increase the size of these PBA-HEMA-based lenses in the presence of glucose. The lens length linearly increased concerning the increased glucose concentration from 0 to 20 mM within 15 min, as illustrated in Fig. 6 (Keum et al., 2020). However, in November 16, 2018, Novartis and Google announced that they would discontinue the project because of the lack of correlation between tear glucose and blood glucose (Otis, 2018).

Additionally, this device did not utilize any embedded power circuits and photosensors but utilized the software of smartphones. The smartphones had an inbuilt software to analyze the glucose level by detecting the light reflected by the smart lens's light-emitting diode (LED) (Lin et al., 2018). Hence, a low-cost, portable, innovative and smart technique was developed to easily detect the blood glucose level without blood and urine samples at home. The designed lens was flexible, transparent, airy, and did not hamper the normal vision. However, there are certain limitations like leakage of fluids, microbial contamination, and collection of debris that limits their wide application utilities, but by overcoming these limitations, this technique can also help in the early detection of various diseases, and researchers still need to explore and develop the tear based biosensors (Halldorsson et al., 2015; Iqbal et al., 2021).

4.3. Exercise-based wearable sweat biosensors

Wearable biosensors have been termed a non-invasive alternative to traditional diagnostic methods requiring blood and urine samples, which increases the chances of generating several infections and physical traumas (Pirovano et al., 2020). Early researches were majorly focused on developing sweat based biosensors that can detect a single bio-analyte from the sweat generated during exercises or any other physical activities by using tattoos or microfluidics, but as the research advanced, the sweat based biosensing platform increased by the introduction of various substrates, nanotechnology, detection mechanisms, transduction technology (optical, mechanical, electrochemical), etc. (Gao et al., 2016a, 2016b; H. S.I. Lee et al., 2017; Oh et al., 2018). Since sweat consists of numerous biomolecules, metabolites, ions, etc., among these, glucose is widely researched (Bhide et al., 2018; Han et al., 2017; Mishra et al., 2018). An integrated mobile, non-invasive, and multi-functional wearable smart band biosensor was designed that consisted of a disposable sweat-based glucose-sensing strip, which was used to monitor pre and post-exercise glucose levels as well as determining different physiological signals like heart rate, physical activity and blood oxygen saturation levels by combining the sweat and physiological monitoring data. Moreover, this data also helped evaluate and provide important information that can prevent hypoglycemic shocks during exercise. The early detection of hypoglycemic shock is necessary as diabetic patients are most vulnerable to it as it can also lead to the death of the affected individual.

Additionally, the sweat-analysis strip displayed the collected sweat, and pre-stabilized film reduced the time of signal saturation and enhanced the robustness of glucose sensing. Therefore, the designed exercise sweat-based wearable smart band biosensor can be efficiently used to detect the blood glucose level through sweat and can be utilized for creating new and innovative opportunities for broad diagnosis and health management (Hong et al., 2018). Another commercially available electrochemical biosensor based on conductive threads decorated with zinc-oxide nanowires (ZnO-NWs) that tracks sweat's physical activity was designed. The designed biosensor was an e-textile based sensor that showed high flexibility, elasticity, sensitivity, selectivity, wearability, good electronic integration, low cost, and unobtrusiveness. Moreover, the sensor detected the lactate and sodium in perspiration during physical exercise, as shown in Fig. 7 (Zhao et al., 2021).

Similarly, another miniaturized simple sweat sodium monitoring wearable biosensor was designed that used gold nanorods (AuNDs). The solid-state ion-selective electrode (ISE) and reference electrode (RE) were coated with AuNDs and polyvinyl acetate/inorganic salt (PVA/KCl), respectively, as they are easy to use and show high stability. The AuNDs-ISE showed enhanced potential stability because the AuNDs exhibited high surface area and double layer capacitance, providing stable all-solid-state ISE. Additionally, the AuNDs-ISE also showed a

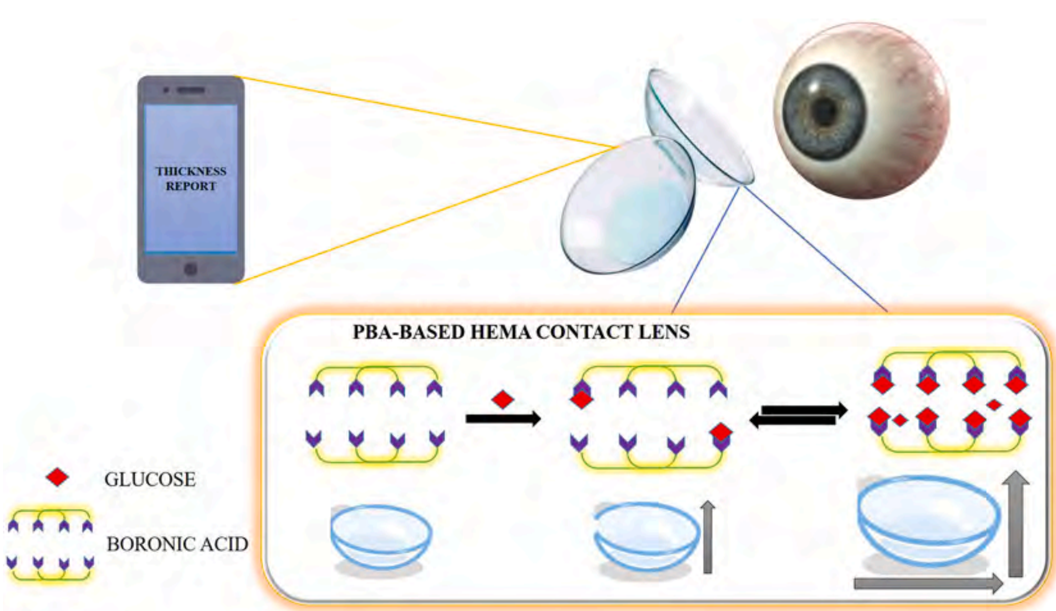

Fig. 6. Design of a smart IoT-based contact lens with integrated biosensor used to detect blood glucose level, indicated by increasing lens thickness.

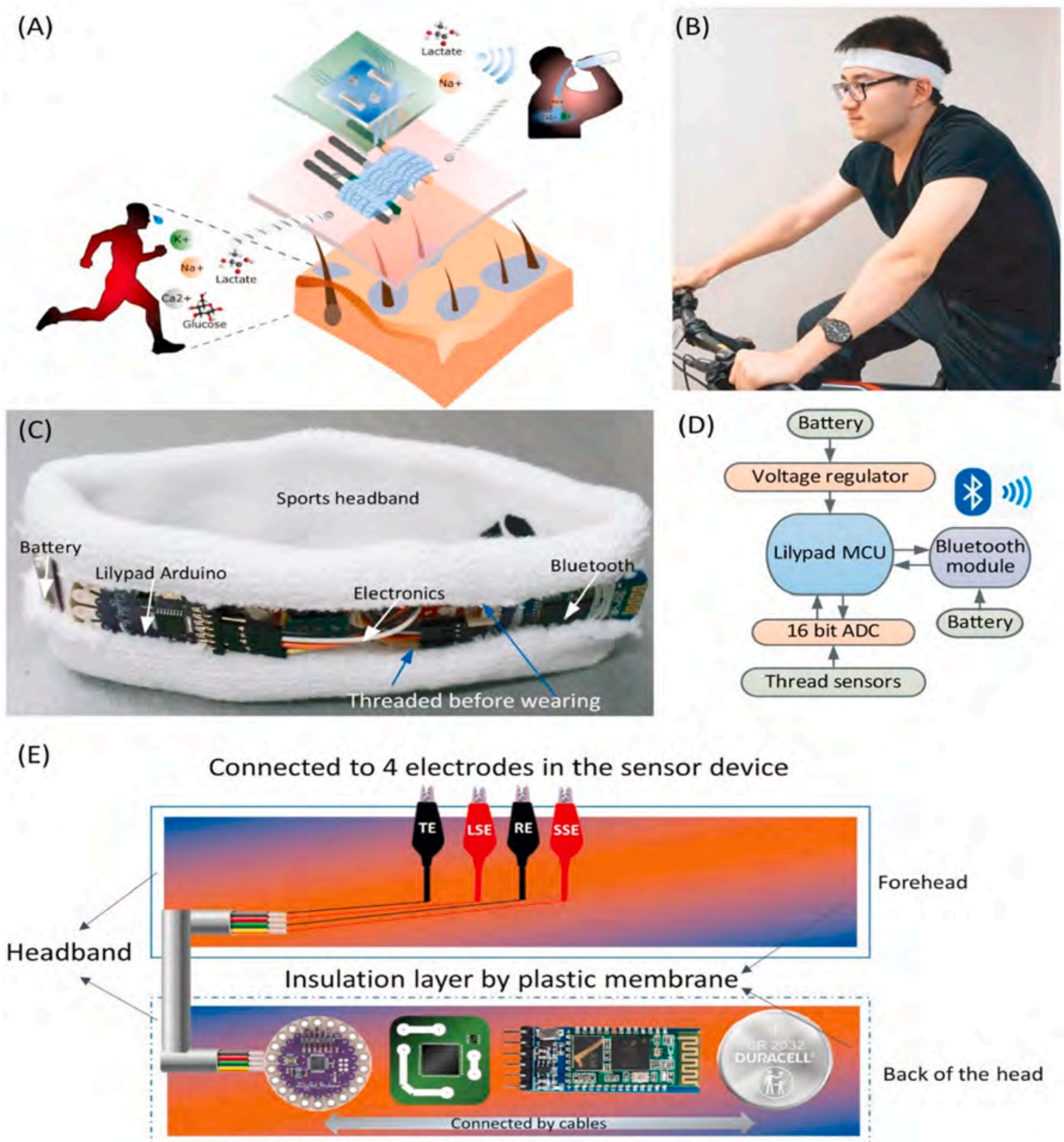

Fig. 7. Design of the wearable biosensor and its 'smart' headband for signal readout. (A) Schematic illustration of the wearable biosensor for on-body sweat sensing during physical activities. (B) A user is wearing the headband. (C) Photograph of the signal readout headband. (D) The schematic architecture of the signal readout circuit. (E) A sectional view of the headband. TE: Trigger electrode (control electrode); LSE: lactate sensing electrode; RE: reference electrode; SSE: sodium sensing electrode (reproduced with permission from (Zhao et al., 2021)).

good near-Nernstian response of 56.58 ± 1.02mV/dec to Na^+, a limit of detection of 0.8×10^{-6} M, and a very stable short-term and long-term stability. Similarly, PVA/KCl membrane was also coated with Ag/AgCl RE, which showed the PVA/KCl-Ag/AgCl RE was highly stable and had a short condition time towards electrolytes. Further, to develop sodium monitoring devices, the AuNDs-ISE and the PVA/KCl-Ag/AgCl RE were integrated on a miniaturized chip, used for designing wearable sweat-band. This sweatband can be worn on the forehead of a human and provides real-time monitoring by collecting sweat and analyzing the sodium level during exercise. The proposed platform showed a promising application in portable and wearable sensor devices (Wang et al., 2017).

4.4. Saliva sensing wearable biosensors

One of the frequently used biofluids, other than blood, sweat, tears, urine, is the saliva as it consists of various non-invasive bio-markers like DNA, RNA, enzymes, proteins, microbiota, amino-acids, etc. as many bio-markers are directly diffused into viscous saliva from the blood through salivary glands (Mishra et al., 2020). Compared to traditional diagnosis methods that utilize blood or urine as samples, saliva-based sensors for detecting diseases are preferred as there are no chances of contamination, physical piercing, or traumas. However, developing a device that can be inserted in the oral cavity should be compatible, breathable, and should have minimum thermal and mechanical loading to the tissue; therefore, microporous materials of low-modulus are generally used to fabricate and optimize the core properties like permeability, porosity and rigidity of the material (Nemiroski et al., 2014; Sharma et al., 2015). Keeping these in mind, an electrochemical saliva sensor was designed that consisted of a platinum-nanocluster decorated electrode, and it was used for the monitoring of cholesterol. The developed sensor showed a sensitivity of 132 μA mM^{-1} cm^{-2}, linear range from 2 to 486 μM, and a low detection limit of 2 μM (Eom et al., 2020).

Similarly, for remote monitoring of bacterial population in the tooth enamel, a highly sensitive battery-free graphene-based nanobiosensor was developed that was inserted in the tooth's enamel. The designed nanobiosensor was the first-order sensor and provided an in-situ point-of-care diagnosis of the bacterial population present in the tooth's enamel, although AMP exhibited semi-selective nature with pathogenic bacteria, and therefore, multiple species of bacteria were not detected. However, work is still going on for designing various multi-ligand-based biosensors that help miniaturized design point of care diagnostic tools (Mannoor et al., 2012). Further, to regularly monitor salivary uric acid from the saliva, a mouthguard-basic uric acid biosensor integrated with a microcontroller, potentiostat, and a Bluetooth low energy (BLE) transceiver was designed. The proposed biosensor exhibited rapid response time, high sensitivity, selectivity, and stability, which helped obtain dynamic chemical data of the oral cavity containing uric acid. Further, this detection method was found to be a suitable alternative for detecting uric acid through blood and urine. It can also help diagnose various diseases like renal syndrome, hyperuricemia, etc. Furthermore, various reports are reported on mouthguard-based biosensors that are used to detect various biomolecules and monitor an individual's health and fitness (Kim et al., 2015).

4.5. Iontophoresis-based biosensors

Many factors like age, temperature, physical activity, hydration level, oxygen level, etc., play a role in sweat secretion. It also varies according to an individual's health. To develop sweat-based biosensing devices, sweat secretion should be maintained for regular health monitoring, but in elderly people, sweat secretion decreases, and it causes a limitation to develop sweat-based biosensors for them. To resolve this issue, iontophoresis was facilitated, in which a mild electric current is passed across the skin, and iontophoresis generates the release of small sweat-inducing drugs like methacholine, acetylcholine, and pilocarpine in the dermis near the sweat glands. Additionally, two hydrogel-modified electrodes are required. The current flows from anode to cathode, inducing the transfer of drug molecules from hydrogel to the skin, followed by the flow of current into the dermis layer from the epidermal layer, where the sweat glands are activated. Therefore, sweat is secreted without any physical activity (Bariya et al., 2018). Whereas on the other hand, when a mild current is induced between the anode and cathode, it generates migration of ions between skin epidermal and dermal layers towards the cathode; this process is known as reversal iontophoresis and is majorly used to enhance the biomarker's content present in the sweat (Bandodkar et al., 2015b). The negative charge of the skin causes the electrophoretic transport of neutral molecules to the skin surface during neutral pH, which creates an electro-osmotic flow of ISF from the dermis to the epidermal layer that causes the electrophoretic movement of neutral molecules. Further, the electrochemical sensor combined with the iontophoresis technique has helped monitor various biomolecules like lactate, glucose, urea, etc. and diseases like cystic fibrosis (Emaminejad et al., 2017).

An integrated iontophore based wearable biosensor was discovered that was used to collect sweat and further detected the sodium (Na^+), chlorine (Cl^-) ions, and glucose levels of healthy and cystic fibrosis patients. The Na^+ and Cl^- levels in healthy individuals were reported as 26.7 and 21.2 mM, whereas the cystic fibrosis patient showed 82.3 and 95.7 mM, indicating a high level of Na^+ and Cl^- level in the patient's body. Moreover, the designed sensor was found to be stable and sensitive towards glucose as well, but it does not exhibit a good working range; therefore, it is very necessary to enhance the working range, which can be further used to detect the glucose in the diabetic patients (Emaminejad et al., 2017). One of the commercially available reverse iontophoresis-based wearable biosensors was GlucoWatch by Cygnus Inc., but unfortunately, its commercialization was stopped as the complaint of skin burns was reported (Tierney et al., 2000, 2001). Therefore, to overcome this problem, an electrochemical glucose biosensor was developed with increased consistency of analyte that consisted of graphene oxide hydrogel reservoir made up of graphene-based film decorated with platinum nanoparticles (PtNPs), which was used to analyze glucose levels through sweat. The proposed biosensor showed increased sensitivity, conductivity, and surface area. Additionally, through microfabrication techniques, this sensor could be used for developing high-resolution patterns on wearable sensors. However, with few optimizations and fabrication, the product can be enhanced and ready for commercialization.

4.6. Microfluidic biosensor

A wearable microfluidic biosensor was designed to capture, store, and sense pH, lactate, chlorine (Cl^-), and glucose. The device was composed of multilayer three subsystems: a skin-compatible adhesive layer that was integrated with micro-machined opening for sweat collection, a sealed collection of the microfluidic channel and four reservoirs with integrated color-responsive chemicals for colorimetric detection, a near field communication (NFC) electronics that were used for wireless communication with an external device. The design of the channel prevents the backpressure, which allows the free flow of fluid. This biosensor was then made commercially available as colorimetric d-lactate, and Cl^- kits and pH indicator solutions were used for colorimetric sensing (Koh et al., 2016).

Moreover, the flexible properties of thread were used to develop thread-based microfluidic circuits to analyze physical and chemical markers in an integrated thread-based diagnostic device (TDD) platform as threads are cost-effective and are widely utilized in textile industries. The thread transports fluid through capillary action by modifying their surface and electrical properties. Further, with the help of inexpensive dipping technique, these modified threads were mixed with nanomaterials to perform electrochemical sensing and were used for sensing pH and strain *in vitro* and *in vivo*. The results of the study revealed that this microfluidic thread-based sensor can be efficiently utilized as a part of clothing or can be implanted on human skin. Further, the designed TDD was also stitched into a tissue or organ in three dimensions, making it a novel diagnosis platform. This novel platform can be applicable in developing smart bandages, surgical implants, point-of-care diagnostics, organ-on-a-chip platforms, etc. However, more studies are still needed for the long-term use of thread-based microfluidic devices, therefore, this creates a bigger room for exploration and discussion for their potentialities in the biomedical domain (Mostafalu et al., 2016).

Similarly, a soft microfluidic platform for epidermal-based electrochemical sensor consisted of a detection reservoir and two PDMS layers: a three-electrode system (counter, working and Ag/AgCl) and a microfluidic channel. The device attaches itself to the skin, and sweat is filled in the microfluidic device to detect glucose and lactate is present in the sweat. Moreover, a photo-lithography technique was used to develop a pattern sensor and also interconnect different layers. Further, with the help of an e-beam evaporator, these coatings were coated by depositing nanolayers of titanium (Ti), copper (Cu), and gold (Au). Additionally, the Prussian blue-modified carbon ink was used to screenprint Au nanolayer-based connector for counter and working electrodes, and similarly, Ag/AgCl was used for the reference electrode. The lactate oxidase and glucose oxidase were used to modify the working electrode for sensing lactate and glucose, respectively. The proposed device was also tested on human subjects, and the sensor efficiently detected the on-body electrochemical flow of lactate and glucose. Further, it was concluded that combining nanotechnology with micro-technology can be efficiently used to develop and fabricate printed electronics (Martín et al., 2017).

4.7. Implantable biosensors

Measuring and monitoring the activities happening inside the body becomes an interesting and innovative approach in developing various biosensors. These types of biosensors are known as implantable biosensors that are either partially or fully inserted into the human body for a long time and are biocompatible and less invasive. Moreover, the implantable biosensors are a viable alternative for regular monitoring of individual health, and additionally, they are painless and comfortable. Also, it has been predicted that implantable biosensors hold a potential future in the biomedicine domain as it provides clear data of events happening inside the body, which helps in maintaining the level of biological metabolites, nerve impulses, electric signals, etc., especially after operation or transfusion, and they can also help in tracking of chronic diseases (Qin et al., 2014). However, the human body produces a negative response against the implantable devices as it is a foreign body and result in biofouling, which can damage the functionality of the sensor and can also cause harm to the individual. However, many reports and reviews have discussed various possible ways to dodge these impulsive biological responses by majorly focussing on the development of biocompatible material, surface modification of the chemical surface, covering the outer of the device with steroidal or non-steroidal anti--inflammatory drugs, etc. Recently, it has been reported that covering the device with nano- or micro-patterns can help surface modification of the biosensor as they can mimic the natural topography of the extra-cellular matrix (ECM) (Rodrigues et al., 2020).

A paper-based immunochromatographic assay for detecting bovine serum albumin (BSA) was reported that utilized nanoconjugates. This vertical flow assay exhibited short response time, minimal consumption of sample, high selectivity and sensitivity, and zero line interference and Hook Effect, cost-effective and simple. Functionalized AuNP/multi-walled carbon nanotubes (MWCNT) nanobioconjugate was used as a probe, and when compared to the ELISA kit, the proposed biosensor showed a total time assay of 10 min, whereas ELISA takes 3–4 h; therefore, the method was found to be promising for the rapid detection of various diseases (Weng et al., 2018).

5. 4G, the IoT and wearable devices

The 3GPP (3rd Generation Partnership Project) established the fourth generation (4G) of mobile phone standards, LTE (Long Term Evolution), which delivers seven times higher upload speeds of up to 50mbps. The advantages of 4G LTE include much-decreased latency times and increased capacity. These are essential for the seamless retrieval of real-time data from IoT applications, such as data from production systems or traffic information. Since 5G baseband modems were designed for the consumer mobile broadband market when they were first released, they were not suitable for many IoT applications outside the automobile area and fixed wireless terminals. 4G, unlike 2G and 3G, was not threatened by network sunset. 60% of the module types cataloged were 4G, which covered both high and low bandwidths. Mobile carriers are able to address a larger portion of the wireless IoT market with 4G networks. Power Saving Mode (PSM), extended Discontinuous Reception (eDRX) cycles, and Coverage Enhancement (CE) are all features that may let IoT applications tailor their wireless interfaces to their demands. The major growth engine of 4G cellular connection, LTE Advanced technology, and its growing new upgrades provide the required characteristics to enable a range of high and low performance and cost-optimized IoT applications. While 4G is still extensively available, 5G is still in its early stages. The majority of IoT devices will use wireless machine-to-machine connections. For fleet management, ATM banking services, and personal health monitoring, over 60% of today's cellular IoT devices employ 4G technology, which usually creates little data traffic. IoT applications produced low demand for LTE during the previous several years since 4G LTE is optimized for mobile broadband. 3G and 4G technologies now dominate the cellular IoT industry, but 5G is the way of the future.

5.1. 5G: the future solution

Through the new uses of wireless technology like wearable gadgets, IoT, and 5G mobile technology, a greater mobile connection will reshape society, facilitating changes in our lifestyles. The 5G holds the promise to bring significant economic and social benefits resulting in a more connected society wherein mobile devices would become an enormously vital part of human lives (Akpakwu et al., 2018). The goal of 5G is to give connectivity to any application and type of device that includes mobile connection to people and other items for the operator location. Compared to conventional networks, 5G networks are more efficient, faster, and accommodate new users, services, devices, or other user cases without increasing carbon footprint or costs ("5G: What is it?," 2014). Fig. 8 depicts the predictable performance benefits of 5G that would serve as the "backbone" for connecting billions of devices for the upcoming wearable devices and IoT, providing support to plenty of devices (per square kilometer). Smartphones, sensors, wearables, automobiles, consumer electronics, and tablets are all part of IoT that enables data sharing and connectivity for intelligent services and applications. The IoT permits the items to be remotely managed to utilize the present network infrastructure, as well as offer new openings for direct integration of the digital and physical worlds, that lead to increased cost savings, accuracy, and efficiency ("Cellular Technologies Enabling the Internet of Things," 2015).

IoT communications would be facilitated through technologies like Bluetooth, Wi-Fi, cellular, in which 5G will act as the network to connect the devices. IoT devices would offer a wide range of data demands and capabilities wherein 5G network must accommodate them all. A fully developed IoT ecosystem requires a 5G network that links all the devices while considering the use of spectrum, data consumption, and power. The 5G network opens up new healthcare opportunities like treatment, data analytics, diagnostics, and imaging owing to its data capabilities, intelligent management, and speedy connectivity. As it is a part of the recognized 'IoMT', it comprises various devices like remote sensors, clinical wearable, and numerous other devices that electronically transmit and screen the medical data, for example, medication adherence, personal safety, and physical activity, and vital signs. These devices would deliver never seen before telemedicine treatment and diagnosis services along with high definition video conferencing, thereby providing quality products at economical prices. To improve medical care, 5G would also provide reliable and consistent experiences to users (West, 2016). Wearable health monitoring devices have grown in popularity due to significant developments in physiological sensing

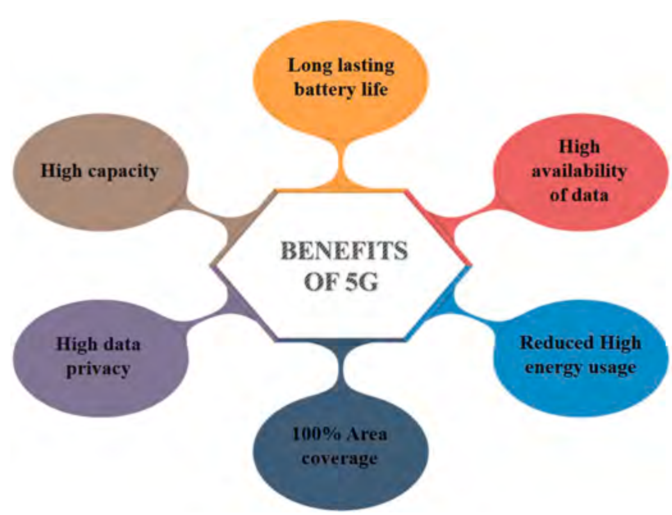

Fig. 8. A schematic illustration of various benefits of 5G technology.

and wireless communications technologies. With the fast evolution in user lifestyles, wearable devices, like smart fitness bands and watches, have gradually become the common articles of everyday life. These innovative techniques are quite promising for collecting physiological data without disturbing patients, including communication, sensors, software, and electronics, occasionally utilizing wireless technology. A wearable communication system using non-orthogonal multiple access (NOMA), multiple input multiple output (MIMO), and die-to-die physical layer medium access control (D2D PHY/MAC) schemes. These wearable devices offer a platform for communicating and collecting information regarding personalized wellness and health, including physical activity and physiological parameters, to monitor health remotely. IoTs might connect computing devices and peripheral sensing's like cloud computing devices, smartphones, and wearable sensors (Alkeem et al., 2017). Also, the stringent latency, restricted computing capability, and short battery life are the main challenges the wearable devices face for human-centered applications. The upcoming edge/-cloud architecture and 5G wireless technologies would considerably reduce these challenges.

6. Challenges for wearable biosensing

The daily use of wearable biosensors that give inclusive information about the individual's health and physical activity is still forthcoming. This foreseeable advancement is achievable through the brilliant accuracy and robustness of biomarkers present in the skin. However, various technological gaps and critical barriers like wearability, data acquisition, communications, power supply, security, etc., still need to be addressed. One of the important challenges in developing a wearable biosensor is the minimal disruption of the tissue and its microenvironment while fully functional, which is also connected to its biocompatibility and anti-fouling property. These properties play a major role in stabilizing the biosensor and deciding its long-term utilities. Apart from the degree of biocompatibility, anti-inflammatory, and flexible material, the long-term functionality is a very important factor for developing implantable biosensors. Dexcom G6 shows its functionality for a few weeks, whereas Eversense lasts for several months. Moreover, the attention should be focused on decreasing the use of calibration and typical operation of the biosensor, and therefore, biosensors with zero-baseline and one-point calibration should be designed (Bandodkar and Wang, 2014; Miyamoto et al., 2017).

These healthcare wearable devices using IoT still have plenty of room for advancement that needs to be addressed, like personal data privacy, data storage, power source, limited applications for physiological diseases, and noise and distortion reduction. Various reasons cause noise like constant body movements, the friction produced by the hair, reduced adhesion between skin and sensors due to hair, etc. Further, the use of AI algorithms and supervised learning regression algorithms can be utilized to monitor the behavior of various parameters for prognosis (Mohanta et al., 2019). Secure end-to-end communication is very important to secure the data of the user. Another limitation of wearable biosensors faces is the continuous supply of power because wearable devices have limited space, and efficient energy sources with good power management are highly required. Although, self-powered sensors such as triboelectric nanogenerator (TENG) and piezoelectric nanogenerator (PENG) are used as miniaturized energy harvesters (Li et al., 2020). The utilities of wearable biosensors in diagnosing psychological diseases are very limited compared to blood, glucose, cardiovascular diseases, etc., giving researchers room to explore more about the wearable sensors detecting various diseases.

The market demand for bio-multifunctional smart wearable sensors has increased with constant innovations in device designs and manufacturing methods. This increased market demand requires that sensors have the characteristics of biocompatibility, biodegradability, bioabsorbability, self-healing, and safe integrability with human and tissue surfaces. The bio-functionality of these devices is significant in terms of both practical applications and the accuracy/reliability of the resulting data. For example, from a medical perspective, the biocompatibility and biodegradability of devices significantly improve their intimacy and secure integration with the skin interface, whereas self-healing and water-proof wearable devices can reduce vulnerability and sensitivity to moisture, thereby enhancing the durability, reliability, and safety of devices. Moreover, body fluids like sweat, interstitial fluids, tears, etc. are rich in various biomarkers like small molecules, ions, proteins, etc. that are utilized for developing biosensors for the detection of various diseases (Broza et al., 2019; Lu et al., 2015). However, the presence of these multiple biomarkers in the body fluid act as interfering materials that cause limitations in designing highly selective and specific biosensors. Although, many commercially available biosensors have overcome this limitation, but research on this is still ongoing, and therefore, it provides a bigger room for exploration.

7. Conclusion and prospects

With the advancement in science and technology, the accessibility of healthcare has now become easy and affordable. But, many city hospitals lack the desired medical requirements, and therefore, the introduction of biosensors has eased these problems. Moreover, these days, the Internet-of-Things (IoT) in healthcare has become one of the latest trending subjects and a promising characteristic to improve the current technologies that lower its cost in each aspect of healthcare. IoT has become the need of the hour as it is useful for monitoring, managing, detecting, and taking action from the system after receiving data, thereby effectively reducing the excess cost of health expenses. Wearable devices are a part of IoT that have been developed to help patients get the correct treatment. These IoT-based wearables devices are considered smart devices that could be worn with external accessories tattooed or even adhered to on the skin, implanted in the body, or embedded in garments and clothing. These smart devices can link with the internet for collecting, sending data, and receiving information for making smart decisions. These wearables have become a vital fragment of IoT technology, and their growth is shifting towards more specialized and practical utility from simple accessories.

Additionally, these smart wearables can interact with devices like smartphones for communication and computing purposes. As these wearable devices become a part of our daily lives, certain limitations like stringent latency, limited computing capability, and short battery life remain unsolved. However, the next generation, the fifth-generation technology (5G), the wireless technology, is considered the next step for evolving mobile communications that seem to support huge connectivity, low latency, and unprecedented high capacity. It is believed that the 5G would completely revolutionize our professional and private lives, especially for novel services applications like connected homes, remote healthcare, wireless robots, and driverless cars.

Moreover, with the advancements in nanotechnology, these biosensors are suggested to be more efficient, sensitive, and stable, giving high performance. The unique properties of nanoparticles have made them distinctive from the bulk matter and have enabled their utilities in the medical domain and in other domains like agriculture, environment, robotics, etc. These nano-enabled biosensors are said to revolutionize the biomedical domain and efficiently be used in developing amputees for differently-abled people. However, the technique is costly and cannot be afforded by every person. The wearable sensors still face various challenges and limitations like the development of daily use sensors, covering the technological gaps, data acquisition, data privacy, long-term utilities, biocompatibility, continuous power supply, etc. However, these problems are said to be resolved by establishing strict regulatory rules and regulations with time. Hence, it is anticipated that 5G technology will revolutionize the area of IoMT, IoT and IoT-based wearable technology.

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CRediT authorship contribution statement

Damini Verma: Conceptualization, Data curation, Investigation, Resources, Validation, Visualization, Writing – original draft. **Kshitij RB Singh:** Conceptualization, Data curation, Investigation, Resources, Validation, Visualization, Writing – original draft. **Amit K. Yadav:** Data curation, Validation, Visualization, Writing – original draft. **Vanya Nayak:** Data curation, Validation, Visualization, Writing – original draft. **Jay Singh:** Conceptualization, Validation, Project administration, Supervision, Writing – review & editing. **Pratima R. Solanki:** Conceptualization, Validation, Project administration, Supervision, Writing – review & editing. **Ravindra Pratap Singh:** Conceptualization, Validation, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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