

Emerging Smart Patch Technologies for Healthcare from Nano Biosensing to AI-Enabled Therapeutic Systems

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ABSTRACT

"Smart patches" is the buzzword that is changing the paradigm in healthcare industry. Though rooted from the conventional patch sensors, smart sensors are equipped with advanced features powered by nano-biosensors, artificial intelligence and wireless communication. Smart patches demonstrate capabilities equivalent to an intelligent care-taker capable of monitoring vital signs, trans-receiving real-time diagnostic data with the physician as well as delivering precise medicine to the patient wearing it. Inspired by the fascinating capabilities of smart patches, this review strives to unveil the recent advancements, technologies used, challenges faced and opportunities available for development of smart patches. The article starts with a brief review of the conventional point-of-care patch sensors which are potential candidates for enhanced smart sensors in near future. Following which the review delves into the recent researches with respect to the design and development of smart patches, highlighting the rise of nano materials and nano science that act as backbone for smart patches along with AI and IoT. In spite of their significance, challenges exist in the design as well as commercialisation of such smart patches and the challenges that need to be addressed to facilitate the design, acceptance and use of smart patches in healthcare applications is reviewed and presented. Thus, this review acts as a resource hub that identifies and highlights the potential areas of research that requires research intervention for the development and use of smart patches in biomedical/healthcare applications.

Keywords: patch sensors, nano-biosensors, IoMT, Machine learning, precise drug delivery, patient-physician communication

How to cite this article: Umapathi K, Krishnaraj S. Emerging Smart Patch Technologies for Healthcare from Nano Biosensing to AI-Enabled Therapeutic Systems. *Int J Drug Deliv Technol.* 2026;16(37s): 440-455. DOI: 10.25258/ijddt.16.37s.56

Source of support: Nil.

Conflict of interest: None

1. Introduction

Smart and non-invasive patch type sensing devices are transforming the healthcare services by enabling real-time health monitoring, proactive alerting and precise drug delivery. The functionality of smart patches has gained attention in various fields, including biomedical diagnosis, advanced therapies, patient monitoring and tailored drug delivery systems. Smart patches are designed to be multifunctional, providing more than one function at a time. For instance, smart patches have the capabilities to monitor multiple parameters like temperature, heart rate, pulse rate, SpO₂, glucose, patient movement etc., [1]. Additionally, they have been utilized to prevent wound infections and promote tissue remodelling, in healing surgical wounds [2][3][4][5]. Furthermore, microneedle attached smart patches are used for drug delivery. Such smart patches are thus capable of providing controlled drug release based on measured vital signs [6][7].

Objective of the review

Aimed to identify the areas that demand research intervention for advancing smart patch technologies, this review,

1. Categorise smart patches based on their healthcare usage into point-of-care (PoC) and remote monitoring devices and to study the constituents of a fully integrated smart patch device say (i) nanotechnology, (ii) artificial intelligence and (iii) internet-of-medical-things (IoMT) and their sub categories.
2. Identified two innovative solutions that can be integrated into smart patches in addition to providing a digital caretaker function.
3. Discuss the challenges that hurdle advancing smart patch technologies along with feasible solutions and opportunities. Highlighted some of the emerging techniques that can be integrated to smart patches in near future.

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Being identified the research importance in the field of smart patches, the review is organised as follows: (i) Section 2 categorises smart patches based on their functions, section 3 details the underlying technologies that enable the realization of smart patches followed by section 4 that details the innovative solutions/applications that are provided by smart patches and section 5 addresses the challenges that need to be addressed and the opportunities that await research intervention in order to advance the capabilities of smart patches.

2. Smart Patches – Providing Revolutionary Healthcare Solutions

Smart patches have been the research focus in recent years due to their inherent patient friendly design and capabilities of providing healthcare solutions ranging from simple biological measurements to remote health monitoring and precise drug delivery. Though initially developed with the objective of providing non-invasive and PoC healthcare solutions to patients, recent advancements are enabling smart patches to provide complete healthcare solutions, that in near future could replace care takers [8]. Advancements in electronics, communication, medical diagnosis and engineering remain the driving forces behind smart patches research.

2.1. Types

Intrinsic to their multi-functional nature, in addition to monitoring vital signs, smart patches could provide diagnostic advice too based on the present health condition. The classification of smart patches based on their application is shown in figure 1. However, in some cases like wound healing, post-surgery rehabilitation, smart patches are capable of ingesting the required amount of medication based on measured vital signs [2][3][4]. These devices were similar to the conventional patch sensors with added patient specific advice or patient health condition specific drug release capabilities and thus, smart enough to provide PoC solutions to patients. Such devices are intelligent than conventional diagnostic patches and can be categorised as AI powered PoC smart patches and they demand periodical tuning based on a physician's advice. These devices could be integrated with trans-receiving capabilities in order to make them a complete monitoring device that could replace a care taker.

Whereas, in some applications like elderly patient monitoring, smart patches capable of alerting their guardians were developed [9]. Even advanced smart patches were developed with the objective of post-surgery monitoring, chronic disease monitoring. These patches aid in communicating the health condition

periodically with the physician and provide options for the physician to control the amount of drug being administered to the patient based on the present health condition. Such smart patches were equipped with trans-receiving capabilities and enable physician control over the device.

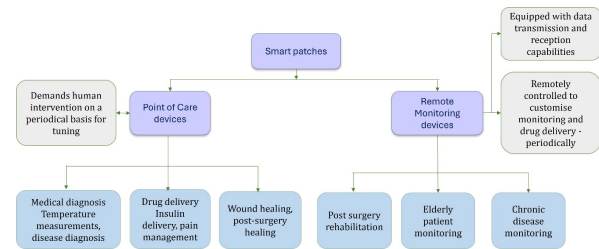


Figure 1. Smart patches and its types.

Smart patches have emerged as a revolutionary technology in healthcare, offering a non-invasive and convenient approach to patient care. These patches integrate various advanced materials and technologies, such as wearable sensors, wireless connectivity, and artificial intelligence, to enable real-time health care services [10][9]. The development of smart patches has significantly transformed healthcare delivery by providing precise and tailored healthcare solutions at reduced costs, enabling better diagnosis, and facilitating early prevention [11][12]. Furthermore, smart patches have been designed to cater to specific healthcare needs, such as vital signs measurement, wound management, pain management, drug delivery, and fitness tracking, thereby offering a multipurpose solution for patients requiring nursing and medication.

2.2. Point of Care - Smart patches

Smart patches were initially developed to provide non-invasive and minimal pain PoC healthcare solutions. Such patches were capable of measuring vital signs, diagnosing diseases and monitoring an individual health condition at the comfort of the patient. They are equipped with sensors capable of sensing and measuring physiological signals and detecting disease biomarkers efficiently in a painless, non-invasive way. The recent pandemic necessitated the search for PoC diagnostic systems. With the advent of nanoscale materials and nano fabrication techniques, electrochemical, optical and micro-fluidic biosensors have emerged as solutions to the necessity. Integration of such biosensing systems with smartphone devices and IoT could enable remote healthcare monitoring in addition to PoC diagnosis [13].

Diagnosis and Wound healing therapy

A colorimetric smart patch that exhibits colour shift between red and greyish violet based on sensed temperature is developed. The colorimetric smart patch was developed using depositing gold (Au)

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nanoparticles (NPs) on microgel substrates (poly(N-isopropylacrylamide) (PNIPAM)) [14]. Wounds, either surgical or accidental could be a life-threat for a diabetic. Conventional wound treatments demand regular monitoring along with tailored medications. Smart patch based wound healing bandages have changed the scenario of wound healing process. Such smart patches are capable of providing personalized health care, by preventing wound infections and promoting tissue remodelling [3]. The prima-facia requirement for an effective wound healing system is its ability to diagnose as well as facilitate treatment at the same time. This necessitates (i) a biosensor that could respond to wound-related biomarker, (ii) signal processing system to facilitate tailored drug delivery. From the materials perspective painless microneedles fabricated over good adhesive patches are required candidates. Use of biocompatible materials and drugs for wound healing is also a topic of concern and attempted by researchers [5]. Real-time biomarker monitoring and on-demand drug delivery facilitated by smart microneedle patches enable intelligent wound care solutions [2]. Temperature and pH values are good quantities that could reliably predict a wound status [4]. The above discussed examples were capable of providing smart bio-medical diagnosis and treatment. Such systems when embedded with AI and IoT facilities could emerge as monitoring devices. In addition, integration of multiple sensing units could result in development of a whole healthcare monitoring systems.

2.3. Advanced Medical treatment and therapy

Smart patches with remote monitoring facilities are equipped with sensors, electronics for signal processing, wireless communication features and are powered by flexible batteries. In addition to signal processing units, electronics in advanced devices may host intelligent decision-making algorithms for periodical tuning of the device. In such case, wireless communication will also be a full duplex communication facility that could aids physicians to receive health data and devices to receive periodical diagnosis automatically.

Monitoring and Drug Delivery

Experimental study to evaluate the robustness of a temperature measuring smart patch capable of transmitting the sensed data to cloud. The sensors was demonstrated to process and transmit analytics to an individual's smart phone [9][10]. The temperature sensing smart patch could reliably sense body temperature under non-feverish conditions in the range (32.53 to 38.2 degree C). A breathable and

conformable smart patch for continuous monitoring of biological signals, addressing the challenge of all-day monitoring was introduced. Two sensors one for temperature and one for humidity measurement were patterned lithographically on a polyimide substrate. The kirigami-serpentine shaped sensor developed was flexible, stretchable and can accommodate higher deformability and stretchability under harsh environments. The fabricated sensors were used along with a commercially available 3D accelerometer. The device so developed was able to monitor patient biological signals along with the condition when patient falls from bed and alert the care taker, hospital staff by transmitting data to smart phone [9]. With the developments in biosensors, stress cardiomyopathy biomarkers could be effectively identified even at earlier stages to introduce treatment plans [11]. A sweat analysing smart patch with an iontophoresis interface was demonstrated effective in diagnosing cystic fibrosis and blood/glucose correlation analysis by conducting human subject studies [12].

Micro-needles, drug reservoir, sensors for measuring biological condition for drug delivery, sensor signal conditioning, drug control mechanism constitutes the major components of a smart drug delivery system. Certain systems include IoT facilities to alert caretakers.—An efficient pain management by precise/timely delivery of drugs is made feasible by microheaters printed over microneedle patches [6]. A hybrid cotton patch with fluorescent jute carbon dots and herbal neem-based drug is fabricated. The drug loaded patch exhibited a higher drug release at pH 5 as compared to that at pH 7 indicating its pH dependent drug release capabilities [7].

3. Understanding the Functionality of Smart Patches – Technologies that power smart patches Pillars behind Smart Patches

Development of smart skin-adhesive patches has been a focus of research in recent times as they have the potential to change bio-medical diagnosis and therapy. Flexible electronic devices could be designed to make conformal contact with skin, cornea, dental and intra-cochlear interfaces and they are able to collect physiological and bio-chemical signals from human body enabling real-time monitoring of vital signs, stimuli-response based drug delivery and theranostic systems [15]. Certain smart patches that collect health data from sweat, skin could offer non-invasive monitoring paving way towards comfortable healthcare monitoring for elderly and infant patients [16].

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The design and development of smart patches greatly depends on developments in nano technology that facilitated the realisation of hydrogel adhesives with tough and tuneable adhesion, transdermal drug delivering and patient vital sign monitoring [1]. These requirements could satisfy the development of PoC smart skin patches whereas remote monitoring with advanced features demand some wireless connectivity and smart electronics. With this said, it is clear that the pillars that hold the “Future of Smart Patches” includes (i) Nano materials with unique sensing properties and good adhesion, (ii) nano technology that helps realise miniaturisation of devices, (iii) Internet of Things (IoT) that could provide wireless connectivity and (iv) Artificial Intelligence that enables predicting anomalies, delivering health advices. A schematic representation of the pillars behind the realisation of smart patches is shown in figure 2. A review of nanostructures used for biosensing, highlighted the need for inclusion of AI, IoMT, cybersecurity for enhancing biosensing performance and marching towards smart patch realisations [17].

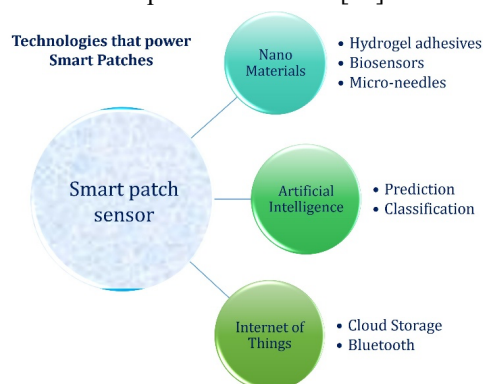


Figure 2. Constituents of a smart patch

1. Material Science – Nano materials and Nano science

Nanotechnology has impacted almost every field and the major shared holders being electronics and biomedicine. Nanotechnology powered bio-sensing has facilitated unique sensors and sensing techniques with excellent sensitivities. However, there are numerous challenges in commercializing such nano sensors due to highly sensitive nature and associated toxicities [17][18].

The selection of materials is significant in determining the characteristics of smart patches. The advent of nano materials and nano science occupies a major role in miniaturization and realisation of technologies with unique properties and the developments in smart patches is not an exception. Certain nano materials by themselves exhibit multi-functional properties and in some cases act as sensors as well as drugs in imparting

diagnosis and treatment to illness. For instance, a natural formulation based on neem extract loaded with cotton patches were found to release neem extract in different concentration based on pH variations [7]. Developments in chemical engineering have made possible the realization of light-weight, easy to control and nature-inspired adhesive systems [19]. 4D thermo-responsive structures that are capable of changing their structures fabricated by Fused Deposition Modelling (FDM) – based printing was demonstrated to excel as a tissue scaffold that can be used for repairing cardiac tissues [20].

Microneedles

Microneedle fabrications mark a significant milestone development of drug delivery patches and a review of the types of micro-needles, different materials used for micro-needle fabrication, methods used for manufacturing, different applications of micro-needles were discussed in literatures [21]. The review emphasized the versatility and potential of microneedles, which could be integrated into smart patches for various biomedical applications. Microneedle patches find immense applications in wound healing and drug delivery systems [2]. Microneedle patches with printed micro-heat sensors have shown promising results in precisely controlling drug delivery for pain management [6]

Nano Biosensor

Biosensors, capable of quantifying biological signals in real-time are well-known for higher sensitivity and compatible design. A classification of the biosensors based on their transduction principle is shown in figure 3. In addition, figure 3 shows the feasible types of inputs and output in each case. Inherent to their excellent properties, biosensors are used across various domains in addition to healthcare. Some examples include, (i) food industry – in order to check food safety by identifying food-borne pathogens, (ii) environmental monitoring – for detecting contaminants in water bodies, air pollutants etc, (iii) medical field – disease diagnosis, providing healthcare monitoring and personalised medicine [22] [23]. Because of their reduced size, biocompatibility and flexibility, biosensors have been used as wearable healthcare monitoring devices [24][25]. Interdisciplinary advancements in material chemistry, healthcare management systems, micro/nanoelectronics, nanofabrication techniques and computing science are acting as driving force in reshaping wearable biosensors as even miniaturised smart patch devices. In contrast to the traditional flexible electronic sensors, present day chemical sensors enable the detection and

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identification of bio-markers and which help in monitoring health information at molecular levels [26].

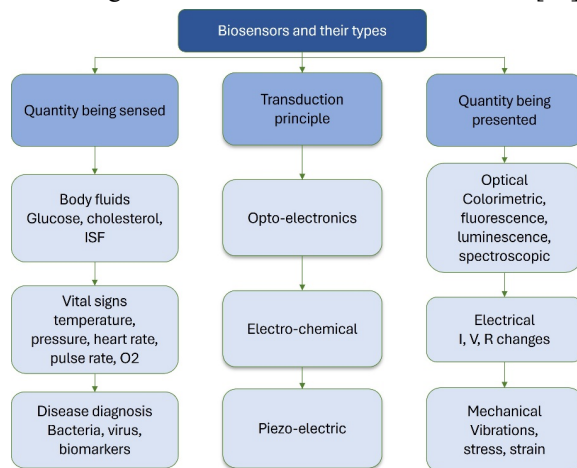


Figure 3. Types of biosensors

Discovery of novel materials with unique properties is the driving force behind the rise of biosensor developments [27] – [33]. For instance: The dependency of dielectric properties of polymer composites on polarization is studied and utilized for the preparation of polymer composites with high permittivity and low losses. Such polymer composites are recommended for realising small storage capacitors and biosensors [27]. A curable conductive ink was developed from Ag nanoparticle decorated CNTs prepared by wet chemical method. Conductive traces could be fabricated by screen printing this ink. Prototype strain sensors with good stretchability, smart gloves that can mimic human finger's gestures, piezo-resistive vibration sensors, wearable masks to monitor human respirations, patch sensor to detect pulmonary cycles, energy- efficient flexible heaters are fabricated using this ink and demonstrated to produce excellent performance [28].

Electro-chemical

Whole blood assay is considered as the reliable and important biological fluid in determining health care diagnosis and management and in recent days electrochemical biosensors have emerged as a reliable tool for whole blood assays [29]. Advancements in chemical sensors have opened up new avenues for detection of health information from various analytes say tear, saliva, interstitial fluid (ISF), blood and breath enabling retrieval of health care information at molecular levels which is not achievable with conventional biosensors [26]. Such biosensors are effective in quantifying chemical constituents from a variety of chemical analytes under study [30].

Soft dendrimers nano materials were effectively used as sensing, transduction, signal amplifiers in electrochemical immunosensors [31]. A wearable

capacitance sensor was fabricated using multiwalled carbon nanotube (MWCNT), a composite dielectric and porous Polydimethylsiloxane (PDMS) polymer. It demonstrated a high sensitivity of 2.42 kPa^{-1} with a limit of detection of 1.46 Pa and withstood 9000 cyclic loadings [32]. Antimicrobial peptides are effective elements to sense bacterial pathogens at an early stage and prevent the formation of bio-films [33]. Hybrid biotic conductive electrodes were fabricated from leaf skeleton using depositing Au to improve interlayer adhesion and Ag deposition to fabricate nanowires. The electrode fabricated has exhibited good mechanical properties with excellent optical transparency and hydrophobicity. The so fabricated electrode is capable of obtaining ECG and EMG signals successfully even without electrode gel or electrolyte [34]. Biosensors were developed from aggregation induced emission (AIE) gold nanoclusters encapsulated in zeolite imidazolate framework (ZIF)-8 nanocrystals enabled high sensitivity glucose detections [35]. Chemical sensing by organic transistors can detect chemicals from human body enabling the monitoring of various physiological signals and thus aid in health care monitoring [36]. Liquid metal-based biosensing devices that exhibits unique characteristics resembling both metals and liquids are capable of providing good conductivities. Such biosensing devices are found to be excellent candidates for wearable and implantable medical sensing devices [37].

Optical biosensors

Optical biosensing techniques aid in the effective identification of biomarker and thus disease diagnosis. In addition, optical biosensing could achieve such results non-invasive thus at the comfort of the patient. Progresses in optical biosensing demands interdisciplinary research from various fields such as biology, electro-chemistry and nano material science [38]. Biosensors fabricated using novel nano materials such as photonic crystals [39], colorimetric hydrogels [4], fluorescent materials [40] were found to hold immense promise in developing cost effective, reliable and compact patient friendly biosensing systems as compared to conventional biosensing systems [39][4][40].

A pH-responsive hydrogel patch is developed by copolymerisation of methacrylate (MA) modified phenol red with alginate/polyacrylamide (PAAm) hydrogel matrix. Such a hydrogel patch produces a colorimetric response to changes in pH values say when pH of the wound is near normal skin (5) the patch remains yellow while a pH increase (7.4 to 8) results in color change to orange and a higher pH (9) makes the

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patch red indicating an infected wound [4]. Thus, such a hydrogel could be a good candidate as a substrate for smart wound dressings.

Fluorescent biosensors were effective in the detection of neurotransmitters and neuromodulators, by producing difference in their intensity of fluorescence when attached to neurotransmitters allowing for the monitoring of chemical transmission in vivo with high precision. Such fluorescent biosensors could also detect neurotransmitter-binding proteins from bacteria, plants, and eukaryotes [40]. optical biosensors were effective in detecting viruses. Whereas, studying their multi-photon interactions and non-linearities and utilizing artificial intelligence methods could aid in improving their sensitivity towards identifying complex low dimensional agents and dynamic objects [41]. The importance and the capabilities of biosensors being in the limelight, fast developments and discovery of novel biosensors and materials are in demand. And in order to identify and rectify design gaps and accelerate bio sensor design computational methods have been suggested as a promising tool [42].

2. Machine Learning – Artificial Intelligence

Recent advances in biosensors have been reinforced by machine learning, leading to the development of non-invasive biosensors for healthcare applications AI-powered biosensors have created a new revolution in healthcare monitoring. With the help of AI algorithms, data collected from biosensors are processed and used for predicting and thus diagnosing healthcare conditions using which an abnormality could be addressed earlier. When integrated with wireless data transmission systems such systems could alert caretakers and physicians about the anomaly in order to prevent them [43]. Integration of AI algorithms in diagnosing multi-photon interactions and non-linearities of optical biosensors could open up new avenues for studying low dimensional agents and dynamic objects [41]. Computer aided drug discovery or drug suggestion for precise personalised drug suggestion based on patient specific information [44]. Multiplexed array of biosensors powered by AI and IoT facilities were demonstrated to be effective in detecting mutations of SARS-CoV-2 virus [45]. Smart patch devices integrated with IoT facility and AI-based healthcare prediction was demonstrated to monitor vital signs and transmit health data to care takers and hospital staff effectively [46].

3. IoT

a. Integrating Smart Patches into Everyday Life

The integration of IoT and wearable devices has played a pivotal role in revolutionizing conventional healthcare services, allowing for remote health monitoring and personalized care. Internet of Healthcare Things offers facilities for storing healthcare diagnosis, monitoring data to be stored in cloud and remote access, monitoring of data [76]. Wearable devices facilitated by IoT services help take proactive and preventive healthcare actions [47]. IoT technologies have emerged as a boon to senior citizens who rely on some healthcare monitoring on a regular basis.

A Smart ECG patch is fabricated using Amorphous Indium Gallium Zinc Oxide (a-IGZO) Thin Film Transistors (TFTs) over a flexible substrate. the smart patch is included with electronics for conversion of sensed ECG signals to bit-streams and are transmitted wirelessly using Near Field Communication to a smart phone [48]. Biosensors for glucose detections were equipped with wireless transmission capabilities for receiving an update on glucose value in smart phone [35]. Efficient encoding is proposed as a means to enhance data security [49]. The integration of advanced materials, wearable sensors, and IoT technologies has propelled the development of smart patches, enabling personalized and precise healthcare delivery. A schematic representing the conceptual framework of connected smart patch device is shown in figure 4.

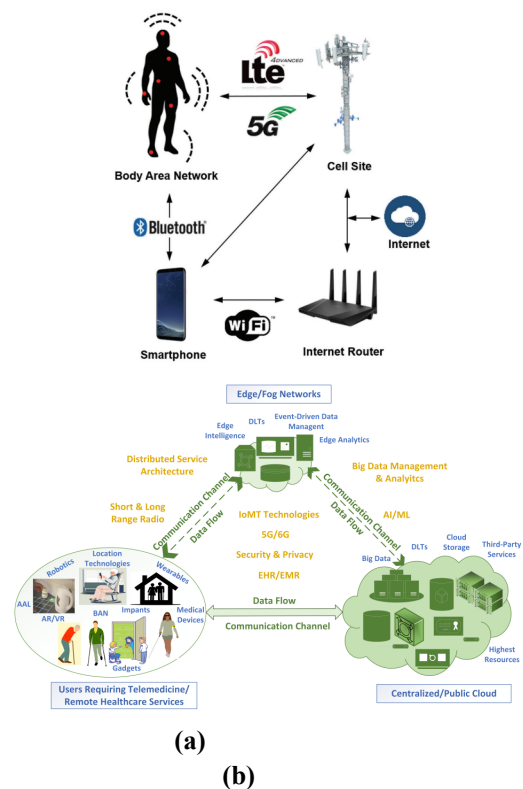


Figure 4. An overview of future healthcare industry. (a) Schematic representation of smart patches and

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healthcare monitoring. Reprinted from [15] under the terms of the Creative Commons CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>). (b) Remote health monitoring system powered by AI and IoT. Reprinted from [83] under the terms of a Creative Commons License (<https://creativecommons.org/licenses/by/4.0/>).

Innovative applications that can be integrated to Smart Patch health monitoring

1. Smart Patches: Bridging the Gap Between Patients and Physicians

An important category of people who demand periodical physiological monitoring and depend on caretakers are senior citizens and thus smart patches with monitoring facilities could be a boon that enhances their standard of living [50] [51]. Thus, smart patches could emerge as excellent candidates for continuous monitoring of biological signals and early detection of diseases revealing their potential in remote patient monitoring, treatment, and drug delivery systems [9]. The integration of smart patches with advanced technologies enhances physician-patient communication by periodical updates and anomaly alerts.

2. Personalized Medicine Through Advanced Biosensing Technology

Personalized medicine, also defined by the term precision medicine, is an emerging field that aims to more customised and precise medical treatment to the individual patient. It resides in taking into account genetic, environmental, and lifestyle factors of an individual together. Advanced biosensing technology remains the backbone behind precise personalised medicine developments. It provides real-time, accurate, and continuous monitoring of biomarkers and other relevant health indicators. This technology has the potential to revolutionize disease diagnosis, treatment, and management, ultimately leading to improved patient outcomes. Precise drug delivery characterised by on-demand drug release necessitates real-time examination and continuous monitoring [52]. The development of drug-loaded biosensing smart patches have made precise and patient specific medication a reality [53]. A smart bio-degradable and conductive patch loaded with drug is demonstrated to be effective in treating myocardial infarctions [54]. In the near future, the role of a pathologist will be to provide diagnostic, prognostic, and predictive answers by integrating morphologic and molecular information [55]. Such a statement emphasizes the prominence of biosensing technology in the personalized medicine scenario. Immune profiling of patients along with

continuous monitoring is demonstrated to be effective in determining drug dosage and treatment plan for Tuberculosis (TB) patients. A schematic representing this drug delivery system is shown in figure 5 below [56]. In spite of the fact that precise and patient-specific medication is possible with smart patches powered by biosensor, AI and IoT, there is lack of such closed-loop medication system development [57]. This underscores the necessity of removing the roadblocks that hinder advancements in the development and commercialisation of such devices.

Furthermore, the integration of biosensing technology with microfluidics has enabled the development of 3D models such as spheroids and organoids, which hold promise in personalized medicine and drug screening [58] [59] [60]. 3D cell models are analogous to natural 3D cell culture characterised by cell growth based on homeostasis. Spheroids and organoids are nature-inspired 3D models that are capable of differentiating cells, metabolism and drug resistance by patients [58]. 3D cell models for generation of tumour spheroids, stem cell spheroids were developed using microfluidics [59]. These models provide valuable tools for advancing personalized medicine and reducing the reliance on animal experimentation [60]. In conclusion, the integration of advanced biosensing technology with personalized medicine holds great promise for revolutionizing healthcare. The development of biosensing devices, wearable technology, and 3D models, coupled with the analysis of biomarkers and molecular information, is paving the way for more effective, precise, and patient-specific medical interventions.

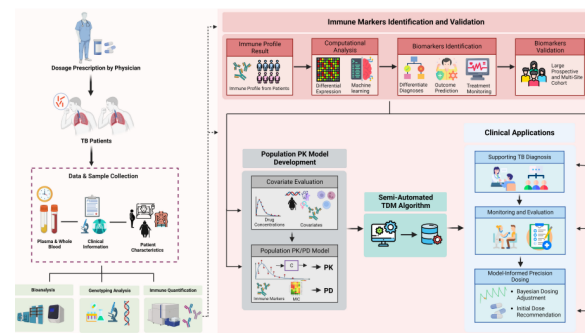


Figure 5. An example of automating the drug tailoring and delivery process. Reprinted from [56] under the terms of the Creative Commons Attribution License (CC BY)

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Challenges and Opportunities in Biosensor Integration

The integration of biosensors presents both challenges and opportunities across various fields [29].

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Addressing challenges such as miniaturization, biocompatibility, and stability while leveraging opportunities in nanotechnology and printing technology will be crucial for the future development of biosensor based smart patches.

The development of Organ-on-chip models that mimic natural organs aid in understanding and studying features of organs on their 3D structures. This minimises animal-based, human-based study trials to a great extent [61]. Such model designs are powered by computational methods. With the advent of biosensors and AI, such Organ-on-chip models could be developed with at most accuracy by incorporating data analysis studies based on biosensor data. Challenges such as miniaturization, biocompatibility, and flexibility hinder the successful integration of biosensors into Organ-on-a-Chip (OOC) platforms [61]. However, there is potential for miniaturization, nano-structuration, and integration with microfluidics and embedded electronics through nanotechnology and printing technologies, offering opportunities for electrochemical biosensors [62].

Effective sample collection for effective analysis, high sensitivity requirements in case of Saliva sensors and High-cost lithographic fabrication are highlighted as persisting challenges that hinder use of biosensors based smart patches. In addition, the requirement of temperature and humidity dependent adhesion is also a concern of fact and this requires development of nature-inspired adhesives [63]. The use of smart patches over a pertained duration may host bacterial growth resulting in harmful health conditions and this demands the development of antibacterial patches. A smart patch that exhibits adjustable adhesion and antibacterial performance is prepared using polydopamine (PDA)-modified Gallium liquid-metal nano droplet with polydimethylsiloxane (PDMS). Experimental results reveal that the smart patch expressed switchable adhesion and anti-bacterial performance [64].

Microbioreactors allow for miniaturisation of bio-processes and thus play a crucial role in pharmaceutical, food, biofuel industries. A novel biosensor that could monitor glucose is fabricated as an integrated chip with internal buffer flow for ensuring sterility, sensing range and stability which when surmounted on a bioreactor was able to monitor glucose in online and real-time. Such systems could be transferred to other applications too, thus providing opportunities for adaption [65]. The effectiveness of detecting viral infections demands proper selection of functionalised nanostructures [66]. Sweat analysis

based smart patch monitoring becomes ineffective for a sedentary patient and such a limitation could be addressed by introducing an iontophoresis interface to extract sweat. Such an interface could be programmed to extract sweat on a periodical basis for monitoring physiological conditions [12]. The use of nanoparticle loaded diagnosis chip were found effective in diagnosing early stages of cancer as such chips could effectively identify even low concentrations of extracellular vesicle EV – RNA [67]. Challenges associated with protein-based biosensing could be addressed by fabricating smart patches with Nucleic Acid (NA) and functionalized NA integration with them [68]. A thin-film CNT-FET fabricated from polymer-sorted CNT film is found to detect DNA sequences and microvesicles with high sensitivity and thus offering a good biosensing platform to be used with patch sensors for DNA detections [69]. Fabricating biosensors resistant to non-specific analytes, biofouling and bio-oxidation is a challenge in biosensor realization. A photoelectrochemical biosensor with such capability was fabricated by integrating branching peptide into synergetic dual-photoelectrode system. It was demonstrated that the so developed biosensor could detect cardiac troponin I with high sensitivity and specificity [70]. Challenges exist in developing point-of-care (POC) biosensors which includes (i) manipulating microbial interactions, infection mechanism, (ii) synthesis of nanomaterials for stable systems [13]. Smart flexible beams could be sources of multi-modal vibrations and suppressing such vibrations have been studied recently. Two piezoelectric actuators working on the principle of multi-variable minimum variance self-tuning is found to be suppress the vibrations from a smart flexible beam efficiently compared to conventional methods [71]. Though technological solutions to address the identified gaps are important, collaborative research between engineers and physicians is a prima facia requirement for the development, implementation and achieving desired results with smart patch medical devices [72]. Commercialisation of biosensor devices demands (i) diagnosis with very minimal quantity of samples, (ii) in-built sample preparation and (iii) use of devices for a long time in vivo without any inconvenience. These requirements are addressed by developing Lab-on-chip (LoC) devices [73]. In conclusion, the developments of smart biosensor patches present numerous challenges and opportunities for research and development in the field of smart patches is huge. Smart patch developments are powered by various fields, including nanotechnology,

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wearable technologies, and tissue engineering with the motto of developing miniaturised, comfortable devices that could diagnose and monitor every physiological sign of a patient.

Privacy Protection

The advent of the Internet of Things (IoT) and big data offers new opportunities as well as challenges for the realisation of smart patch medical devices. Adoption of wearable healthcare technology by consumers is greatly impacted by consumers' health beliefs and privacy protection on the perceived usefulness of such technologies. This sheds light on the factors influencing the acceptance and integration of smart patches into everyday life [74] [75]. Data security and privacy are the most required demands especially in healthcare applications and thus, numerous techniques were proposed for improving security of interconnected smart patch devices [76]. The introduction of Blockchain technologies resulted in using them for IoMT based smart health monitoring devices [77]. Bio-metric dependent data access is recommended for imparting security to IoMT based healthcare applications [78]. Methods to analyse security risks, efficient resource allocation, predicting smart grid advised ensuring cyber-security in the case of IoT applications [79]. A summary of the challenges faced, rectification methods and opportunities existing in the research and development of smart patches are depicted in table 1.

Table 1. Challenges that hurdle smart patches technology transfer and along with rectification methods

Si. No.	Device of concern	Challenges	Rectification options / Opportunities
1	Flexible and Stretchable Electrochemical Biosensors [63]	High-cost Lithographic fabrication	Printing technologies
		Temperature and humidity dependent adhesion	Nature-inspired adhesive materials
2	Smart patch adhesive [64]	Bacterial growth at the skin, patch interface	Nature-inspired flexible adhesion

3	Biosensors [65]	Ensuring stability, sterility, sensing range, controlling matrix effects	By using internal, 1. actuated buffer flow with a biosensor downstream 2. a diffusion limiting membrane to the sample upstream.
4	Biosensors [66]	Biosensor effectiveness in detecting viruses	Proper selection of functionalized nanomaterials
5	Sweat biosensor-based patches [12]	Sedentary patients	devising an iontophoresis interface
6	Biosensors in Tissue Engineering [67]	Detection of circulating RNA for early stage cancer diagnosis	Use of nano-biosensors with relevant binding target
7	Biosensors for Nucleic Acid Integrated Wearable Biosensors [68][69]	Identifying protein-based analytes	NA and Functionalized NA integration with smart patch sensors and thin-film CNT-FET
8	Biosensors [70]	Biosensors resistant to non-specific analytes, biofouling and bio-oxidation	-
9	Acceptance of smart health monitoring devices [75]	Privacy protection	Use of blockchain technologies

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10	Remote healthcare monitoring [76],[77]	Security and data privacy	Ensuring privacy protection
11	Security of IoMT [78]	Security and data privacy	Bio-metric based data access
12	Cyber security [79]	Security and data privacy	Methods to analyse security risks, efficient resource allocation, predicting smart grid compromises by Bayesian Attack Graph for Smart Grid (BAGS) tool
13	Biosensors [66]	Translation of research to commercial product	
		Materials	Adherence to safety regulations and bio-compatibility
		Automation	Data privacy, security and safety

User-friendly

While smart patches offer numerous benefits, challenges such as ensuring their adhesion properties, biocompatibility, and resistance to environmental factors need to be addressed. They have been designed to be breathable, flexible, and biocompatible, allowing for continuous monitoring and absorption of moisture from the skin without causing irritation. The development of patient-specific wearable devices and along with stringent clinical trials will facilitate the design of safe and effective approaches [10] [15]. Providing patient comfort at the same time achieving efficient physiological signal monitoring remains the primary goal in designing smart patches and thus development of patient friendly adhesives was recommended [64]. The right combination of treatment and monitoring policies results in minimising the cost

of any medical treatment [80]. The continuous advancements in smart patch technologies have also led to the emergence of innovative solutions for chronic disease management, and non-invasive healthcare diagnosis, thereby addressing critical challenges in the healthcare industry at the same time reducing cost associated with healthcare monitoring.

Future Trends in Smart Health Monitoring Systems

Being reviewed the challenges associated with the different constituents of a smart patch healthcare device, some of the recent advancements that could be integrated with smart patches in near future are highlighted below:

- Wearable devices like wrist bands were demonstrated to excel as weight control devices in obesity patients. Wearables were capable of achieving this by continuous monitoring and introducing physical activity and weight control measures in obese patients [81].
- Multiphoton interactions were found to enhance the sensibility exhibited by biosensors, presenting opportunities for biosensors assisted by multiphoton effects [41].
- Furthermore, the development of smart patches can be extended to include 4D thermo-responsive structure which are initially developed as cardiac constructs for myocardial cell therapy, highlighting their potential in tissue engineering and regenerative medicine [20].
- Salivary biomarkers could revolution healthcare diagnosis and could emerge as a means of non-invasive diagnosis and monitoring in the near future. Potential integration with biodegradable patches salivary sensors could be integrated with smart patches too [82].
- Developments in IoMT with enhanced security is going to play a major role in future healthcare monitoring [83].

Conclusion

“Smart Patches” with their inherent capabilities of providing (i) healthcare monitoring, (ii) therapeutic care by tailored drug delivery and (iii) anomaly prevention by timely alerting, are changing the healthcare paradigm completely. There is no doubt the future of healthcare industry will be ruled by smart patches. However, there are a lot of challenges that hurdle the growth of smart patch research and

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development. Major challenges are (i) biocompatibility associated with biosensors and their associated materials, (ii) data security associated with IoT capabilities and (iii) Manipulation of AI. Solutions such as (i) developing nature inspired materials as sensing elements, (ii) improving data security by blockchain technologies were advised to tackle these challenges. In addition, certain emerging technologies such as 4D materials, saliva biomarkers, multi-photon interactions were proposed as potential candidates that can be integrated with smart patches in near future. Thus, the areas that demand research intervention in order to elevate the development of smart patches are highlighted and reviewed.

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