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Unveiling the power of smart patches- A revolutionizing wound care

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Abstract

Chronic wounds impose a substantial healthcare impact. This may not heal as quickly as they should, which can lead to additional wound complications like infection and even amputation. This review manifests, how smart upgrades are perhaps a good solution to address conventional wound dressing problems.A brief discussion regarding wound biology as well as the procedure for rebuilding is provided in this overview, with an emphasis on the key elements affecting a good closure. This context addresses the emerging risks of resistance to bacteria in wound care and go over antibacterial tactics. The discussion then turns to stimuli-responsive antibacterial nanomaterials, which are a vital element of smart patches that plays a key role in both improved antibacterial activity and tailored drug delivery. In addition to this it explores the idea of "all-in-one" smart patches, combining multiple features for all-encompassing wound care. A critical analysis of several smart patches that researchers have designed, each with a variety of features are included. Conclusion infused with the current constraints of smart patches and delineate fascinating prospects for this emerging domain. This review also sets the stage for the development of smart patches in clinical wound healing by providing an up-to-date and thorough analysis of the technology.

Keywords

Intelligent patches, Smart patches, Wound healing,Stimuli responsive nanomaterials, Sensors, Chronic wounds, biosensors, wound care.

Introduction

Recent data released by Trusted Market Research projects, the worldwide wound care market to develop at an average yearly rate of 4.61% from 2023 to 2030 (Sen CK, 2023). In Europe, there are over 1.5–2 million people with chronic wounds, while in the US, there are over 6.5 million. These individuals place a heavy financial strain on the healthcare sector, having annual treatment costs up to 250 million USD (Zimlichman E *etal*.,2013;and Phillips CJ *etal*.,2016). Chronic wound occurrences amongst senior citizens are rising exponentially as diabetes and obesity become increasingly prevalent in this demographic (Clayton Jr W*etal*.,2009),(Sen CK*etal*.,2009), (Standl E*etal*.,2019).

Approximately $15 billion is spent on things related to wound closure, and an additional $12 billion is spent on skin scar management. Together, these wound healing treatments represent a significant economical activity (Han G *etal*.,2017).The whole external layer of the human physique is wrapped by skin, that is in regular contact with the outside world. It senses stimuli from outside the body, controls the internal temperature, and shields the body from harm (Dąbrowska AK *etal*.,2018).

The body of an individual might become considerably more susceptible to infections as a result of skin damage (Bayram Y *etal*.,2013). Skin has exceptional rejuvenation qualities that enable it to mend from damages quickly(Singer AJ *etal*.,1999).But some deep wounds that result in substantial skin damage, like burns, or deeper medical conditions like diabetes, may exceed the skin's ability to regenerate itself (Bjarnsholt T *etal*.,2008).The typical healing processes of inflammation, proliferation, and maturation do not take place in these kinds of wounds. One of the main problems with chronic wounds is infection; patients should be monitored for symptoms of infection by medical specialists either regularly or in a hospital. This will increase the expense of therapy (James GA *etal*.,2008),(Edwards R *etal*.,2004).It is quite helpful to have smart solutions that can keep an eye on the condition of wounds without requiring dressing changes or visit to the hospital (Saghazadeh S *etal*.,2018). The latest advances in wearable intelligent medical devices for disease detection and management are getting better with the advent of modular electronics (Jin Y *etal*.,2020). It is possible to put together several sensors and actuators within one unit that can keep skin in an uniform proximity (Najafabadi AH *etal*.,2014). A good way to keep an eye on bacterial infections is by tracking the acidity of the wound area (Lu N *etal*.,2012),(Schneider LA*etal*.,2007).Standard wounds that heal have a pH around 5.5 and 6.5 while they are healing. The pH will be higher than 6.5 in infected wounds that are not healing (Rahimi R*etal*.,2017).This review mainly focuses on the different types of stimuli responsive antibacterial nanomaterials, where the bactericides can be exposed or precisely release on demand. Indeed, This strategy has a lot of potential to notice theproblem of overusing bactericides and mitigating the emergence of drug-resistant bacteria. And focuses on ALL IN ONE type of patches that combine biosensors and responsive drug release systems which have become a novel strategy to accelerate wound healing.

The biology and healing of wounds

Systematic and meticulously timed biological processes that are abnormal in chronic wounds lead to wound repair. Proper wound healing can be adversely affected by a number of both local and systemic variables, such as infection, chronic inflammation, insufficient dietary content, elevated local pressure, and inadequate perfusion (Guo SA *etal*.,2010). Evidently have endured numerous investigations on the a part of extremely controlled aspects engaged in wound healing, like inflammatory tissues, cytokines, and chemical messengers in wound healing. There are four major stages in wound healing. Namely, Hemostasis, Inflammation, Proliferation and Remodeling which are depicted in figure.1

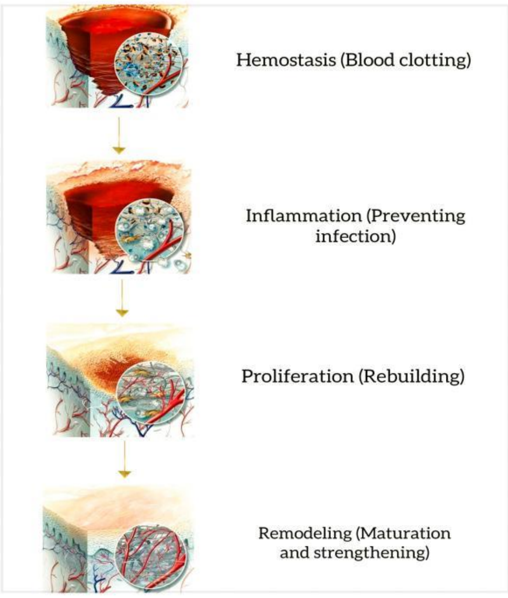

Figure 1. Stages of wound healing

Formation of resistance to bacteria and antibacterial techniques

The term "bacterial resistance" describes a bacteria's capacity to tolerate the adverse reactions of antibiotics, either by becoming susceptible to them or by decreasing its sensibility to them with continued administration, which eventually results in ineffectual therapy (Clatworthy AE *etal*.,2007). Most scientists agree that the main ways that bacteria develop resistance to antibiotics are by changing the shape of their cell walls to prevent drug entry (Darby EM *etal*.,2023) and by elevating eliminating enzymes that break down medicines, making them futile (Gupta A *etal*.,2019) decreasing the likelihood of binding of antibiotics and their intended targets by changing the number and shape of antibiotic binding sites (Schaenzer AJ *etal*.,2020). Excessive expression of efflux pumps that work to remove medicines, hence lowering intrinsic level of drugs to ineffectual levels (Walsh C *etal*.,2000). Furthermore, bacteria are able to create biofilms, which constitute communal defensive survivability . As a form of protection, biofilms help bacteria fend off the entry to immunological chemicals or antibiotics. They can therefore cause bacterial resistance and show reduced responsiveness to antibiotics (Makabenta JM *etal*.,2021).

Antibacterial nanomaterials attuned to stimuli

In the war over bacteria, specifically those that are resistant to conventional antibiotics, Antibacterial Nanomaterials attuned to Stimuli offer immense potential as a novel and effective weaponry. These nanomaterials fall into two categories: those that respond to exogenous stimuli and those that respond to endogenous stimuli. These are depicted in figure.2. Personalised therapy and self-adjusting antibacterial systems were enabled by nanomaterials that respond to cues derived from bacterial byproducts (Zhang J *etal*.,2023).

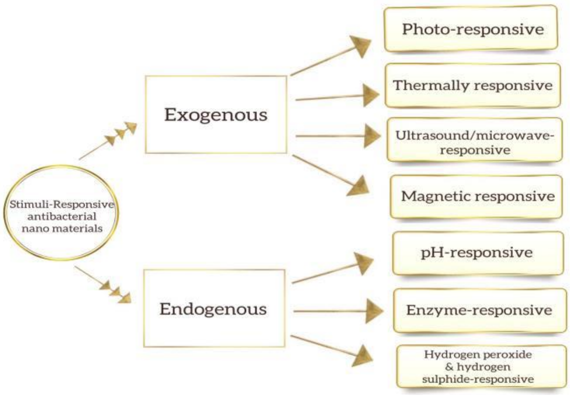

Figure 2. Stimuli-Responsive Antibacterial Nanomaterials

Antibacterial nanomaterials attuned to endogenous stimuli

It is well established that the microenvironment of biofilms constructed by bacteria and diseased tissues is distinct from that of healthy tissues. Numerous characteristics, including low pH, elevated Reactive oxygen species (ROS), and activated enzymes, define this microenvironment which is depicted in figure.3. Theoretically, nanoparticles' stimuli-responsive nature provides an advantage since it can be selectively triggered upon arrival at the site of infection, greatly increasing medication bioavailability.

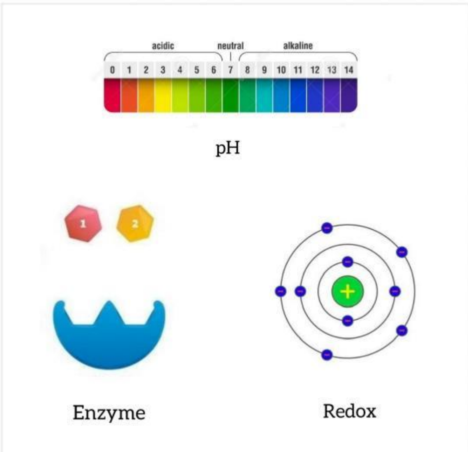

Figure 3. Types of Endogenous stimuli

pH-responsive antibacterial nanomaterials

Acidity is a common feature of the milieu of bacterial infections. fermentation that is anaerobic brought on by hypoxia may lead to bacteria that alter the ambient pH of tissue that is infected. Two main categories exist forthe underlying process of pH-responsiveness: (1) protonation/deprotonation of carboxylic and amine categories, and (2) breaking of bonds between molecules. Development of pH-responsive small platforms is frequently achieved through the protons from forming of groups of amines.As an outcome, many different pH-responsive antibacterial nanoparticles with greater efficacy in the management of infections caused by bacteria have been identified. pH responsive based nanomaterials were designed by various researchers (Wu S *etal*.,2021), (Shi Y *etal*.,2022), (Wang C *etal*.,2020), (Tan P *etal*.,2023), (Pal VK *etal*.,2022) presented in Table 1.

Enzyme-responsive antibacterial nanomaterials

Another feature of the infection with bacteria is the production of enzymes. The area of infection is given a distinct microenvironment by these enzymes. Because of their outstanding selection as well as effectiveness under mild physiological settings, enzymes are thought of being the most clever drug delivery technique (Hu Q *etal*.,2014). Smart nanomaterials can be designed with enzyme-labile links to enable on-demand and responsive release of drugs upon enzyme stimulation, therefore reducing the side effects of medicinal medications (Huang Y *etal*.,2024), (Zhang Y *etal*.,2022), (Gaut JP *etal*.,2001), (Long Y *etal*.,2021).Enzyme responsive based nanomaterials were developed by various researchers (Wu K *etal*.,2022), (Liu Y *etal*.,2019), (Cheng X *etal*.,2020), (Li Y *etal*.,2016) presented in Table 1.

High levels of H_2O_2, H_2S-responsive antibacterial nanomaterials

Higher H_2O_2 and H_2S concentrations are often found near bacterial infection sites and are important in the pathophysiology of infections (Shatalin K *etal*.,2021). Multiple investigations have proven that almost all bacteria have the enzymes that are necessary to create H_2S as a defence against oxidative stress One effective tactic to prevent bacterial resistance is to inhibit the formation of H_2S (Zhu J *etal*.,2021), (Fei Y *etal*.,2020), (Park D *etal*.,2016), (Gao Q *etal*.,2018), (Manoharan D *etal*.,2019),(Su Z *etal*.,2022).This type of nanomaterials were designed by various researchers (Yang N *etal*.,2021), (Guo G *etal*.,2020) which is presented in Table 1.

Antibacterial nanomaterials attuned to exogenous Stimuli

External stimulus-responsive nanoparticles are capable of being triggered by a variety of exogenous stimuli, including light, ultrasonic, magnetic, and electric fields. The term exogenous stimuli-responsive nanoplatforms, which hold considerable promise for attaining spatiotemporally regulated medication administration due to their ease of controllability over these external stimuli like light, temperature, electric, magnetic and ultrasound which is presented in figure. 4. (Ran B*etal*.,2021), (Huo J*etal*.,2021).

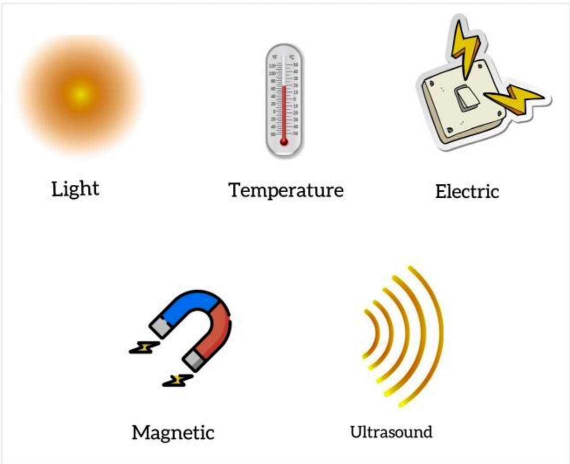

Figure 4. Types of Exogenous stimuli

Photo-responsive antibacterial nanomaterials

As chromophores with the ability to transform stimuli from light to chemical-based or the energy outputs, photo-responsive antibacterial nanomaterials are frequently employed in light-mediated therapies. This is due to their inherent optical characteristics, as well as when they work in tandem with photosensitive substances and photothermal agents for therapeutic purposes (RenY*etal*.,2020).These tactics comprise a variety of methods, such as photodynamic therapy (PDT) and photothermal therapy (PTT) (Wei G*etal*.,2020). PTT is a type of thermal treatment that works by converting light energy to heat energy by means of nanomaterials that have a significant photothermal transformation rate upon exposure to an external illumination source.PDT's ability to be repeated without causing unwanted drug resistance is a noteworthy benefit over traditional antibiotic-based therapy. (Xu X*etal*.,2018), (Zhang H*etal*.,2021), (Li R*etal*.,2021), (Aksoy I*etal*.,2020). Photo-responsive based nanomaterials were designed by various researchers (Li Z*etal*.,2021), (Xu Q*etal*.,2020), (Dai X*etal*.,2018). which is presented in Table 1.

Thermally responsive antibacterial nanomaterials

Unlike light-thermal nanomaterials, that are considered as another kind of "smart" nanomaterial, these have the capacity to alter their physical characteristics (e.g., shape, size, etc.) in accordance with slight variations in temperature, leading to a controlled release of drug(Wang L*etal*.,2017), (Dutta K*etal*.,2020). Poly(N-isopropylacrylamide) (pNIPAM) is the thermoresponsive polymer which is utilised most extensively amongst other materials. it can reversibly change from a hydrophilic spiral form into a hydrophobic globule form. This change in state is easily controlled by modifying the level of concentration of the polymer and by introducing surfactants and copolymers (Cui J*etal*.,2021). These nanomaterials were developed by various researchers (ZhanJ*etal*.,2018), (Yan X*etal*.,2019)which is presented in the Table 1.

Ultrasound/microwave-responsive antibacterial nanomaterials

During ultrasonic or microwave stimulation, nanomaterials that are particularly susceptible to these stimuli typically produce reactive oxygen species (ROS) or heat, both of which are extremely deadly to a variety of bacteria that are drug-resistant (Xiang Y*etal*.,2023), (Pang X*etal*.,2019), (Guan W*etal*.,2019), (Li G*etal*.,2021), (Yu Y*etal*.,2021), (Wang R*etal*.,2022). because of its benefits of non-invasiveness, superior tissue penetration, and restricted ultrasonic site irradiation, which produces antibacterial effects, this indicates enormous possibilities in the management of deep infections (Ma L*etal*.,2023), (Wei S*etal*.,2021). This type of nanomaterials were developed by various researchers (Yang SR*etal*.,2023), (Sun X*etal*.,2023), (Wei S*etal*.,2021) presented in Table 1.

Magnetic-responsive antibacterial nanomaterials

Magnetically triggered antibacterial techniques are being developed as a result for the ability of magnetically sensitive nanomaterials that can be triggered by magnetic fields. Because tissue from humans is transparent to magnetic fields, magnetic stimulation has the benefit of deep tissue absorption and stimulation over light-based methods. Research has focused on two fundamental pathways:

(1) Localised variations in temperature brought about by magnetic stimulation are known as hyperthermia caused by magnetic fields. (2) Magnetophysical action: upon exposure to an induced magnetic field, nanoparticles demonstrate antibacterial activity prompted by kinematic pressures (Rabbi MA*etal*.,2021), (Wang P*etal*.,2022), (Hou X*etal*.,2021).Magnetic- responsive based nanomaterials were designed by various researchers (Elbourne A*etal*.,2020), (Liu G*etal*.,2022)which is presented in Table 1.

Table 1. Work done by various researchers using different types of stimulus responsive nanomaterials

S.No	Type of work done	Type of stimulus	References
1	Photodynamic nanoparticles	pH, Photo responsive stimulus	(Wu S *etal*.,2021)
2	Self activated nano reactors	pH responsive stimulus	(Shi Y *etal*.,2022)

3	Cage like polymeric nanoparticles	pH responsive stimulus	(Wang C *etal*.,2020)
4	Chimeric peptide nano assemblies	pH responsive stimulus	(Tan P *etal*.,2023)
5	Bioactive peptide nano assemblies	pH responsive stimulus	(Pal VK *etal*.,2022)
6	Cage like frame nano spheres	Enzyme responsive stimulus	(Wu K *etal*.,2022)
7	Mesoporous ruthenium nanocarriers	Enzyme responsive stimulus	(Liu Y *etal*.,2019)
8	Metal-organic framework nanoparticles	Enzyme responsive stimulus	(Cheng X *etal*.,2020)
9	Polymeric vesicles	Enzyme responsive stimulus	(Li Y *etal*.,2016)
10	Copper oxide nanoparticles	H2O2, H2S-Responsive stimulus	(Yang N *etal*.,2021)
11	$CuFe_5O_8$ nanocubes	pH, H2O2 stimulus	(Guo G *etal*.,2020)
12	Methylene blue (MB) and lysozyme (LYZ)-loaded upconversion nanoparticles	Photo responsive stimulus	(Li Z*etal*.,2021)
13	Multifunctional composite hydrogel	Photo responsive stimulus	(Xu Q*etal*.,2020)
14	water-soluble galactose-based on BODIPY	Photo responsive stimulus	(Dai X*etal*.,2018)
17	Reversible Exposure and Hiding of Antimicrobial Peptides on an Implant	Thermal responsive stimulus	(ZhanJ*etal*.,2018)
18	*In Situ* forming hydrogel	Thermal responsive stimulus	(Yan X*etal*.,2019)
23	Engineering-based microneedle	Ultrasound responsive stimulus	(Yang SR*etal*.,2023)
24	Sono-Immunotherapeutic Nanocapturer	Ultrasound responsive stimulus	(Sun X*etal*.,2023)
25	Engineering of Red Phosphorous–Metal	Ultrasound responsive stimulus	(Wei S*etal*.,2021)
26	Levofloxacin-Loaded Nanosonosensitizer	Ultrasound responsive stimulus	(Li G*etal*.,2021)
27	Single-Atom Catalysis	Ultrasound responsive stimulus	(Yu Y*etal*.,2021)
28	Sonodynamic therapy in antibacterial application	Ultrasound responsive stimulus	(Wang R*etal*.,2022)

29	Nanocomposite hydrogels	Ultrasound responsive stimulus	(Yang SR*etal*.,2023)
30	Sonodynamic Bacterial Inactivation	Ultrasound responsive stimulus	(Sun X*etal*.,2023)
31	Nanocrystalline jute cellulose nanocomposites	Magnetic responsive stimulus	(RabbiMA*etal*.,2021)
32	Multifunctional hydrogel	Magnetic responsive stimulus	(Wang P*etal*.,2022)
33	Biofilm treatment	Magnetic responsive stimulus	(Elbourne A*etal*.,2020)
34	Nanosheets	Magnetic responsive stimulus	(Liu G*etal*.,2022)

All-in-one patches

Wound patches which integrate biological sensors along with responsive medication release mechanisms have come about as a unique approach for speeding up healing of wounds, owing to the development of adaptable electronics. The patch itself has the ability to give medication locally while also doing real-time monitoring. Wireless device included within the patch can be utilised to facilitate wound healing as well as fulfil the goals of prompt diagnosis and controlled therapy (Wang Y*etal*.,2021).

Table 2. Fabrication of smart patches by different researchers for wound healing activity

Sl.no	Title	Stimulus	Sensors	Stimulus used	Sensors Incorporated	Author
1.	Polymer Hydrogel-Based Multifunctional Theranostics for Managing Diabetic Wounds	✓	✓	pH responsive stimulus, Redox responsive stimulus	Electrochemical sensor	(Gong X*etal*.,2024)
2.	Design and fabrication of the paper fluidic–based wound sensor patch	✗	✓	---	PETAL Paper sensor	(Zheng XT*etal*.,2023)
3.	Design of the fully integrated stretchable wearable bioelectronic system	✓	✓	Electrical responsive stimulus	Electrochemical sensor, Glucose sensor, pH and Temperature sensors.	(Shirzaei Sani E*etal*.,2023)

4.	Flexible, Wearable and Fully-printed Smart Patch for pH and Hydration Sensing in Wounds	✘	✔	---	pH & hydration sensors.	(Iversen Metal.,2022)
5.	Intelligent Silk Fibroin Based Microneedle Dressing (i-SMD)	✔	✘	Thermo responsive stimulus	---	(Gao Betal.,2020)
6.	Smart Flexible Electronics-combined dresssings for wounds	✘	✔	---	Temperature Sensor	(Pang Qetal.,2020)
7.	A pH-regulated Drug Delivery transdermal Patch	✔	✘	pH responsive stimulus	---	(Jiang Hetal.,2019)
8.	A pH-Mediated Electronic Wound Dressing for Controlled Drug Delivery	✔	✔	Electrical responsive stimulus	pH Sensor	(Kiaee Getal.,2018)
9.	Smart Bandage for Monitoring and Treatment of Chronic Wounds	✔	✔	Thermo responsive stimulus	pH and Temperature Sensors	(Mostafalu Petal.,2018)
10.	Bacteria-responsive intelligent wound dressing	✔	✘	Photo responsive stimulus	---	(Zhou Jetal.,2018)
11.	An Advanced Hydrogel Dressing	✘	✔	---	pH Sensor	(Mirani Betal.,2017)
12.	Textile based dressing	✔	✘	Thermo responsive stimulus	---	(Mostafalu Petal.,2017)

Smart patches: limitations and future scopes

Eventhough many different formulations like emulgels (Sonule M *etal*.,2023), Nanoemulgels (Eman M.E. Dokla *etal*.,2023), Solid lipid nanoparticles (Kumar Kk *etal*.,2024). The improved intelligent patch produced by experts recently making a significant difference in the therapeutic treatment of wounds.

The implementation of novel innovations, such as 3D/4D printing along with the alteration of suitable natural resources, has led to the development of quicker and simpler ways to manufacture the ideal components for smart wound patches (Wang Y*etal*.,2021).

While these investigations have shown promising outcomes in lab studies, there are a very least amount of translation of these outcomes into healthcare settings (Saghazadeh S*etal*.,2018) and we cannot reliably determine the sort of pathogen or the level of infection via measurement of wound factors including pressure, temperature, and pH.

Although wearable technology has revolutionised therapy for managing the wounds, A lot of innovations are limited to only use in lab environments.Electronics and sensors ought to be suitable with the human body. This is particularly crucial for wounds that are visible. The associated electronics shouldn't cause harm to an already-existing wound. Human skin frequently interacts withelectronic parts connected to sensors and intelligent dressings, that could lead to biocompatibility issues. Clinical validation is a prerequisite for releasing sensors to end users.

The sensing capabilities of currently available wound-sensing gadgets are limited. Incorporating a diverse variety of sensors within wound dressings could allow the monitoring of many chemical and physical markers with great specificity and sensitivity in actual time, providing useful data for analysing the evolution of wounds (Lu SH*etal*.,2022).The integration of medication release and tracking has been included due to the advancement of exceptionally interconnected technology. While there is considerable potential for advancement in smart wound patches, This developing sector still has a lot of problems which have to be solved.

Conclusion

Individuals who have chronic wounds, experience great distress on both bodily and mental level, which places a heavy cost on medical systems around the globe. Though they work well, conventional wound dressings contain drawbacks. Eliminating them may result in more harm, and their inability to track in actual time may impede the best possible healing of wounds. A potential fix for these issues is the use of intelligent patches.

This review thoroughly examined how intelligent patches could transform the therapy for managing the persistent wounds. Hence the idea of "all-in-one" intelligent patches has developed as an intriguing potential route for complete wound care, which includes features like medicine administration, surveillance, and antibacterial action.

This review concludes by presenting a convincing image of intelligent patches as a game-changing innovation for treating the persistent wounds and research done on smart patches by different researchers are embodied. They hold the potential of quicker healing, lower infection rates, and better patient outcomes by combining the strength of cuttingedge materials, continuous surveillance, and targeted medicines. In order to drastically improve patient outcomes and lessen the strain on healthcare systems, intelligent patches have an opportunity to change the paradigm of chronic wound treatment with ongoing studies and advancements aimed at surpassing current constraints and preserving ethical standards.

Authors Contributions

All the authors have contributed equally.

Availability Of Supporting Data

The datasets of this study are available from the corresponding author on reasonable request.

Conflict Of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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