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Wound Healing: From Passive to Smart Dressings

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The universal increase in the number of patients with nonhealing skin wounds imposes a huge social and economic burden on the patients and healthcare systems. Although, the application of traditional wound dressings contributes to an effective wound healing outcome, yet, the complexity of the healing process remains a major health challenge. Recent advances in materials and fabrication technologies have led to the fabrication of dressings that provide proper conditions for effective wound healing. The 3D-printed wound dressings, biomolecule-loaded dressings, as well as smart and flexible bandages are among the recent alternatives that have been developed to accelerate wound healing. Additionally, the new generation of wound dressings contains a variety of microelectronic sensors for real-time monitoring of the wound environment and is able to apply required actions to support the healing progress. Moreover, advances in manufacturing flexible microelectronic sensors enable the development of the next generation of wound dressing substrates, known as electronic skin, for real-time monitoring of the whole physiochemical markers in the wound environment in a single platform. The current study reviews the importance of smart wound dressings as an emerging strategy for wound care management and highlights different types of smart dressings for promoting the wound healing process.

1. Introduction

A skin wound is a pathological condition caused by disease, injury, or physiochemical damages. Based on the origin of the damage and the duration of healing, the wounds are classified as acute and chronic wounds. Traumatic physical/chemical damages or surgical procedures cause acute wounds, while diseases such as infection, diabetes/vascular disease, and cancer contribute to the wound that cannot be healed over time and defines as hard to heal or chronic wounds.[1] Based on the wound size, depth, and level of damage in the epidermis and dermis layer, the healing process would be different. Moreover, some other factors, including systematic nutritional or immunological weakness, age, chronic stress, and other comorbidities, are involved in the poor or prolonged healing process.[2]

The poor healing process in patients with traumatic skin disorders contributes to the immense physical and emotional stress and pain in the wound site.[1] Due to the hard healing process and inefficient therapeutic intervention, diabetic foot ulcers are known as the most chronic wound, precede over 70% of the wound site which may lead to lower limb amputation.[3] As the world population ages, the potential of chronic diseases is expanding which brings about a huge economic burden. Thus, a universal effort is needed to increase the global awareness about the prospective clinical challenges of chronic wounds and practices that need to be developed to address them. Furthermore, the annual management of chronic wounds allocates 6% of total healthcare expenditure in the developed countries. Statistical reports from NIH demonstrated that for the U.S.A., an annual cost of US$20 billion has been imposed on the economy of the state only for the case of chronic wound management.[4]

More than 70% of all lower-limb amputations resulted from chronic diabetic foot ulcers. In some cases, the level of amputation defines the mortality rate. Depending on the percentage of amputation, the rate of mortality for the patients varied. Five years is the average year for the patients with amputations between 40% and 70% and resulting adverse impact on the economy. Clinical studies have reported that every 30 s in the world an amputation happens as the result of chronic nonhealing wounds.[5] Moreover, social isolation, psychological issues, and immense pain compel drastic financial burden to the society through a reduction in productivity.[6,7]

Consequently, the development of novel technologies and practices into the best practice clinical management of chronic wounds is imperative to diminish the possible burdens for the health and economy of the society and optimize the healthcare management for this prospective silent pandemic.[8,9]

Over the past decade, new classes of wound dressings with the potential to analyze the wound healing progress status in a real-time manner apply the appropriate treatment and report the overall status of the healing process to the patients in a smart manner have been developed. Moreover, versatile types of wearable sensor-integrated skin bandages are fabricated by mounting multiple optical (fluorescence, colorimetry, etc.) and/or electrical

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(impedance, potentiometry, amperometry, etc.) mechanisms into conventional wound dressing substrates to form smart wound dressings to detect and convert the data from biomarkers at the wound site into visualized electrical signals for applying subsequent actions.[10]

In this manuscript, we reviewed the recent development of skin wound dressing and highlighted the latest progress in manufacturing novel wound dressing for better wound care management.

2. Wound Dressings

Based on the founded manuscripts in the clay tablets from an ancient civilization, the bandaging of the wound is dated to 2000 BC. Archaeological remains demonstrated that the first kind of wound dressing was developed by the ancient Egyptians. The ancient wound management system consisted of three steps, including washing the wounds, making the plasters, and bandaging. They were the first people who applied honey to the wounds and invented the adhesive wound dressing. In the present day, plasters are known as wound dressing. A mixture of substances, including oil, mud, or clay, and medical herbs formed the plaster basis.[2]

Nowadays, smart wound dressing emerged as a promising strategy for improving wound care management thanks to the advances in material science and technology. From long ago until now, wound dressing has been implemented to provide an environment for accelerating the healing process. For chronic wounds that cannot be healed in an orderly and timely manner, wound dressing plays a cardinal role in returning the healing progress to the normal state.[9] Imposed financial and psychological burdens of the wounds have provoked scholars to develop new strategies for improving biomaterials characteristics and fabrication technologies into designing advanced wound dressings to achieve better healing outcomes.[11]

The current review article will focus on the various types of wound dressings, from the early traditional bandages to the most recent smart dressing with integrated microsensors prototypes, and discuss the advantages of smart wound dressings in skin wound management.

2.1. Traditional versus Advanced Wound Dressings

The wound dressing is designed as a substrate to be in direct contact with the wounds, while bandaging is used as a supporting bed for the dressing. Along with the advances in the textile industry, a wide range of woven and nonwoven gauze dressing based on natural and synthetic fibers was developed as wound dressers.[9]

Fabricated bandages out of natural fibers like cotton wool or cellulose tended to be used as short stretch compression bandages.[2] Thanks to the fibrillar structure of the traditional dressing, sterile gauze pads are used for absorbing secreted exudates from the wounds. Still, the need for frequently changing the dressing to prevent infection and adhering to the wound as a result of wound exudates absorption are the major complications related to the traditional dressing, which have turned this type of dressing less desirable at present.[12]

Moreover, the traditional wound dressings are limited in providing a proper moist environment for the wounds. Generally, traditional dressings are effective for clean and dry wounds and unable to provide essential conditions for accelerating the wound healing process. Therefore, modern dressings with advanced properties have been developed.[9]

Composite of natural and synthetic polymers in different forms of fabrication, including films, foam, hydrogel, and hydrocolloids, were developed to enhance the limitations related to the traditional dressing and create a moist environment around the wound and potentially augment the healing process.[13,14] Chronic wounds contain a high level of proinflammatory cytokines in the wound's environment. Thus, fabricating a dressing that can alleviate the wound conditions is essential.[14,15]

Recent developments in the field of smart wound dressings have enabled the generation of a new class of dressings that can actively monitor the wound conditions and help with understanding or the interference of the wound healing stage (**Figure 1**).

2.2. The Requirements of Ideal Wound Dressings

As one of the most complicated pathological healing processes in the human body, several factors are contributing to the wound healing process. Based on the diverse types of wounds, the healing process would proceed in three different phases, including inflammation, proliferation, and remodeling. As a supportive structure, a correct wound dressing not only protects the wounds from infection but also provides vital conditions and amplifies the healing process.[16]

The major characteristics of a proper dressing are absorption of secreted exudate, proper mechanical strength, prevent wound dehydration by maintaining a moist environment, gas exchange permeability, nontoxic and biocompatible, nonadherent, comfortless and remove easily, and antibacterial/fungi properties. Besides amplifying the healing process, many of these criteria for an ideal wound dressing are considered for diminishing the cicatrix of the wounds.[17]

One of the most reported complaints about traditional dressing was the immense pain resulted from removing the intertwined sections of dressing from wounds, which worsen the wound condition and increase inflammation.[17,18]

The resulted inflammation disturbed the process of healing. Thus, the new generation of dressings is aimed at monitoring the healing process smartly and reducing the limitations associated with traditional dressings.[19]

This section aims to investigate the requirements considered for creating an ideal wound dressing. The moist managing as a critical feature of wound dressers has been investigated by several scholars. Thomas highlighted the importance of wound environment moisture as a critical feature in the generation of wound dressers for preventing wound maceration. In this study, the characteristics of an ideal wound dressing for protecting highly vulnerable periwound tissue from secondary damage caused by dressing replacement as a result of weak moisture management and prospective infection were compared. They concluded that advancements in modern dressings, including permeable foam/film and hydrogels with enhanced fluid handling properties, can substantially diminish the risk of

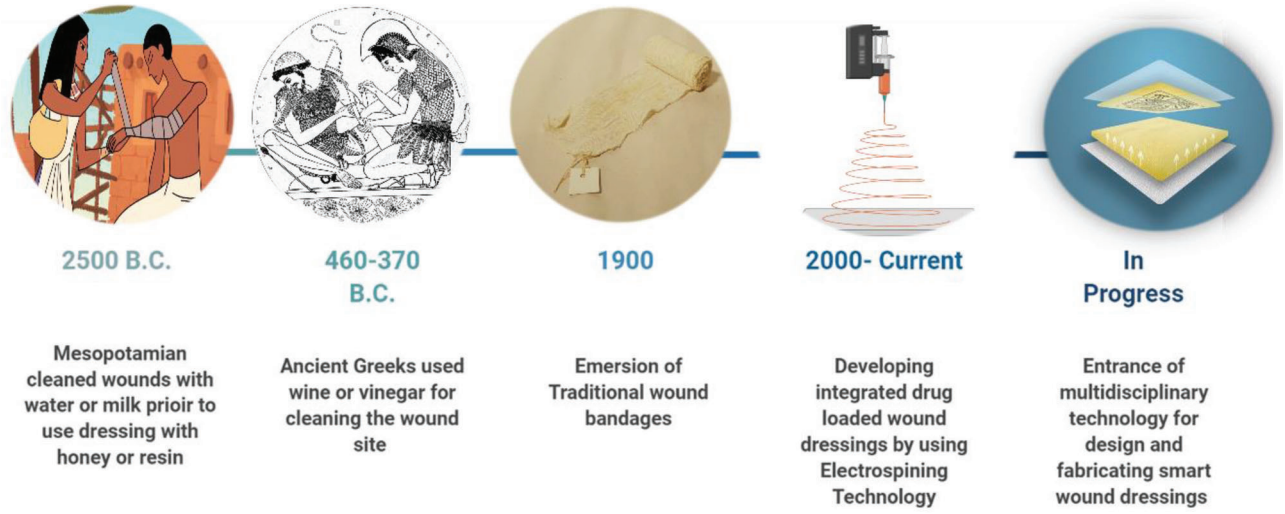

Figure 1. Historical timeline of wound dressing evolution. Created with BioRender.com.

wound maceration formation in comparison to traditionally used dressings.[20]

The wound healing process is highly affected by the level of moisture at the wound interface. Coloumbe compared the pace of re-epithelialization and wound closure between an open-air exposed wound and moisture level-controlled wounds with a proper dressing. They concluded that the wounds with a moisture-controlling dressing promote the pace of epithelialization.[21] In another study, Sweeney et al. demonstrated that excessive moisture, specifically secreted from chronic wounds, could damage the macerated peri-wound epidermis and hinder the regeneration process.[22]

Wound exudate management is another cardinal performance parameter for an ideal dressing. Based on the type of wound, the exudate composition would be different. In the acute wounds, secreted exudate appeared to promote wounds remodeling and repair, while in the chronic wounds, due to the presence of a high level of denaturing proteins such as protease and proinflammatory cytokines, the proliferation of wound reconstructing cells slowed or completely barricaded. In this regard, some wounds are categorized as highly exuding.[23]

In the case of chronic wounds, the selection of an ideal dressing is based on the size, type, volume, and viscosity of the secreted exudate.[24] The dressing for the highly exudating wounds should have proper liquid absorption concerning its physical dimensions; otherwise, fluid leaks through or around the dressing. The highly exuding wound provides an ideal environment for bacterial growth and spread and slows down the healing process.[25]

Besides of high liquid absorption capability for a proper wound dressing, the ability to retain the absorbed fluid is an important characteristic of an ideal dressing. Overhydration or maceration are other major features that a proper dressing must be able to tackle by making a balance in wound's-environment moisture.[26]

Developing artificial structures capable of providing characteristics like natural skin tissue such as hindering bacterial penetration and balancing the wound environment moisture level is of importance in wound care management. Recently, asymmetrical polymeric membranes, membranes consist of different layers, each with a unique structure and function have been introduced as promising wound dressings. Different fabrication approaches, including electrospinning, bioprinting, dry/wet, have been implemented for developing these practical wound dressings.[27]

In a study by Alves et al., a photocrosslinkable multilayer asymmetric electrospun nanofibrous meshes were constructed using polycaprolactone (PCL)/gelatin methacryloyl (GelMA), PLA/GelMA at the top layer, and GelMA/chitosan methacrylamide (chMA) at the bottom layer for skin regeneration. In vitro studies confirmed the advantageous characteristics of this prototype in providing a protective/healing environment for wounds.[28] Morgado et al. used the supercritical carbon dioxide ($scCO_2$)-assisted phase inversion method to prepare interconnected microporous structure poly(vinyl alcohol)/chitosan (PVA/CS) asymmetrical membranes with drug-releasing capability. The interconnected structure of membranes facilitated the adsorption of the wound exudates and simultaneously released the encapsulated ibuprofen to the wound site.[29]

Despite significant efforts in developing dressings that are compatible with the dynamic nature of chronic wounds, but still, reaching the ideal dressing is a critical challenge to the healthcare systems. An ideal wound dressing substrate should be capable of real-time monitoring the progression/deterioration status of the wound, which requires advanced types of equipment amalgamated in the dressing structure. Thanks to the breakthroughs in real-time monitoring equipment, promising progress in manufacturing ideal smart wound dressings have been made in the last few years and will be discussed in the next sections.[25]

3. Evolutionary Trend of Wound Dressings

Over the past decade, the advances in microfabrication technologies have contributed to the development of numerous types of cutting-edge wound dressings and devices that able to mimic the native skin tissue environment and monitor the healing process.[30,31] A wide range of materials has been considered for the fabrication of a wound dressing using natural or synthetic polymers.[32] Advanced wound dressings are developed not only

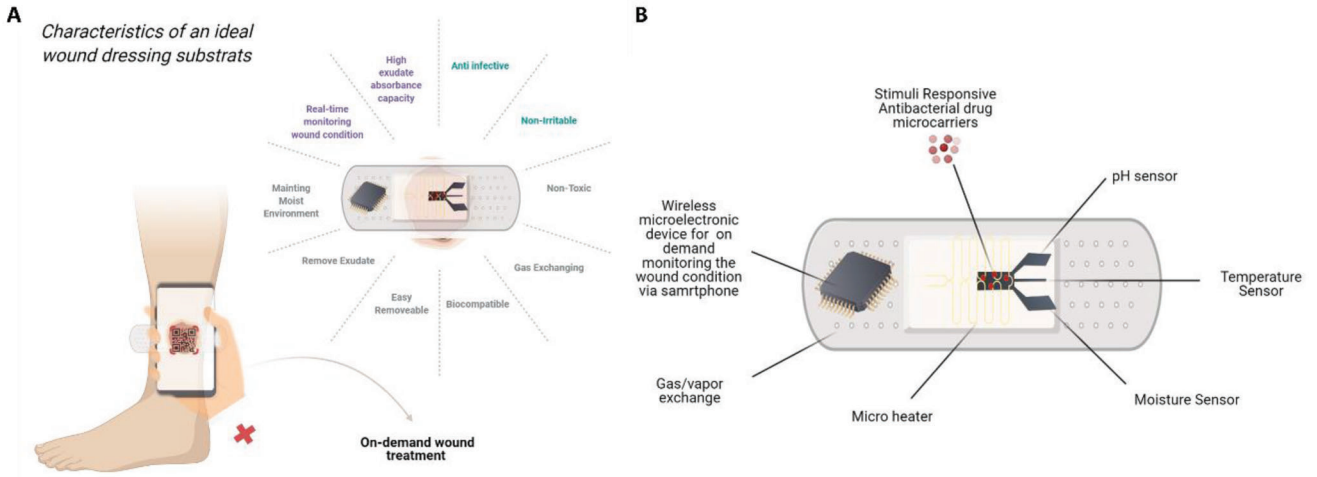

Figure 2. A,B) Required characteristics of an ideal wound dressing. Created with BioRender.com.

to perform as a protective covering but also to act as a diagnosis sensor, monitor the wound conditions, and apply proper treatment to promote the healing process. Based on the interactions between dressing and the wound environment, the dressings are categorized into three groups, including passive, interactive, and bioactive products.[33]

The traditional dressing, including gauze and tulle products, are considered passive or nonocclusive dressing.[33] In the nonocclusive dressings, the material transfer is facilitated; therefore, gases and moisture molecules can easily pass through the dressing. On the other hand, in interactive or occlusive dressings, a sealed environment covered the wound, and no molecules would transfer through the dressing.[34]

It has been proposed that passive dressings are suitable for dry wounds. Due to the materials transport capability of passive dressings, in chronic wounds where the level of secreted exudate is high, dressing adheres to the wound and may cause severe pain and damage during detachment; therefore, in recent clinical practices, passive dressings are less favorable to use for such wounds.[35]

In the other two classes of dressing, interactive and bioactive dressings, the dynamic interactions between the wound environment and dressing enhance the healing progress.[36] Several studies have indicated that the induced hypoxic conditions in the occlusive dressing lead to an enhanced angiogenesis process, which amplifies the re-epithelialization, granulation tissue formation, and collagen synthesis.[232,233] D'Alessandro et al. study showed that the occlusive environment created by the interactive dressing not only decreases the risk of bacterial infection but also provides a moist environment that increases regeneration.[37]

In another indicative study by Helfman et al., the healing mechanism of some types of clinically used occlusive wound dressings (including polymeric films, hydrocolloids, transparent films) was investigated. The results demonstrated that epithelial cell movement was achieved by providing a moist environment and increasing the oxygen tension that ultimately prevents the wound desiccation in animal models.[38]

Bioactive or smart dressings are a class of dressings that are able to deliver bioactive compounds in the wound site when the level of disruptive cytokines increases in the wound environment and create an active and dynamic interaction with the wound's environment.[39] Numerous bioactive substrates have been developed that are sensitive to the specific molecules or environmental conditions to be activated. Recently, the advent of the wearable smart wound dressing captured growing interest among scholars as a new concept of smart bioactive dressing.[40] The main characteristics of an ideal smart wound dressing are demonstrated in (**Figure 2**).

3.1. Smart Materials for Smart Wound Dressings

The applications of temperature, pH, and enzymatic responsive materials in fabricating smart wound dressings were addressed in the previous sections. In this section, the use of smart materials, including shape memory and reactive oxygen species (ROS)-responsive materials, is highlighted.[41] Due to the convoluted nature of wound healing mechanisms, numerous studies are in progress to find a comprehensive optimal solution for interacting with these highly dynamic microenvironments to modulate the healing process based on the status of wounds. A class of biomaterials, known as smart materials, can alter their structure/physiochemical properties in response to environmental change.[234]

Smart materials have been used to integrate self-adjust treatments into the complicated process of wound healing.[42–44] In this regard, a variety of smart materials, as well as ROS-responsive, temperature-responsive, pH-responsive, and enzyme-responsive, and shape-memory materials, have been explored for interacting with altering parameters involved in the wound healing process.[45,46]

ROS such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), and peroxynitrite ($ONOO^-$) have been considered as mediators of a variety of biological and pathological events.[47] The patients with chronic wounds usually remain in a constant pathological inflammatory state and are susceptible to oxidative stresses due to the excessive amount of ROS at the wound site. Therefore, several classes of ROS-responsive materials have been

developed to alleviate excessive oxidative stress conditions at the wound site. To improve wound healing by promoting vascularization, Tang et al. developed ROS-responsive nanoparticles based on poly-(1,4-phenyleneacetone dimethylene thioketal) (PPADT) to encapsulate stromal cell-derived factor-1α (SDF-1α). According to the excessive levels of inflammation in the wound environment, thioketal bonds cleaved, leading to the depolymerization of PPADT and the release of SDF-1α. The ROS-responsive SDF-1α-loaded PPADT nanoparticles were implemented by intravenous infusion to mice with full-thickness skin wounds. The responsive release of SDF-1α promoted the migration of MSCs toward the wound and its periphery, enhancing wound vascularization and healing.[48]

Shape memory polymers (SMPs) are a class of smart materials with the potential of keeping their temporarily programmed shape and recover their original formation upon exposure to specific external stimuli. Versatile types of SMPs, responsive to stimuli such as thermal, light, pH, or moisture, have been used to fabricate smart controlled drug release and wound monitoring dressings. Polyurethane, polyester, poly-hydroxyproline, polysilamine, poly(*N*-isopropylacrylamide) (PNIPAAm), and polythiophene hydrogels are among the most common SMPs that have been employed for fabricating such smart wound dressings.[49]

Li et al. fabricated a copolymerized novel zwitterionic shape memory polymer composed of sulfobetaine methacrylate (SBMA) and diol acrylate monomer (dihydroxypropyl methacrylate, DHMA) for wound healing applications.[50] In this report, boric acid was added as crosslinkers to the polymeric complex. Shape memory behavior for this hydrogel dressing was created from electrostatic interactions of PSBMA chains with dynamically bonded boron esters, which are triggered by either temperature or absorbing moisture. Then and to examine the shape memory properties of this synthesized zwitterionic polymer, sodium chloride was incorporated into the polymer to investigate the antielectrolyte effect of salt content on mechanical, shape memory, and self-healing properties of this hydrogel dressing. Incorporation of salt into the hydrogel lowered the glass transition temperature from 70 °C to the room temperature and increased the strain at the failure state of the healed sample.[52] Moreover, PSBMA chains have high hydrophilic property, therefore the shape recovery process can be achieved by absorbing the moisture in the wound site. Therefore, the SMP could be used as potent materials for wound dressing purposes.[51–53]

3.2. Smart Bandages for Monitoring the Skin Wounds Status

The hard healing process of chronic wounds has made them susceptible to infection.[54] Being aware of the chronic wound's status is an essential factor for the management of the healing process. The existing chronic dressing at the best condition could passively deliver the therapeutic agents and mostly act as a wound coverage. The current dressings can decelerate the rising statistics of this silent pandemic by providing proper primary conditions for the wound environment, but due to the dynamic essence of chronic wounds, these types of dressing cannot cover all the required features for augmenting the healing process.[55] Thus, the current dressing inefficiency in the treatment of hard-to-heal wounds has revealed the urgent need for a new class of wound dressing for better management of chronic wounds.[56]

Initial efforts for developing smart wound dressings with the capacity of active monitoring the wound conditions were allocated to dressings responsive to the wound's environment stimulus.[57] Developing dressings for the early detection of wound bacterial infection was the prototype of smart wound dressings. Numerous types of wound dressings sensitive to the expressed prevalent bacterial infection markers including (pH, temperature, secreted enzymes, and toxins) in the format of electrospun nanofiber meshes, hydrogels, or a composite of them were developed as the next generation of wound dressings known as smart dressings. In the next step, researchers integrated the drug delivery systems to these stimuli-responsive dressings for the controlled release of drugs and effective wound managing.[58]

In the last few years, integration of microelectronic technology with wound dressing substrates has led to the emersion of a new type of wound dressing known as "the smart skin bandages" capable of real-time monitoring of the markers expressed in the wound site and on-demand release of encapsulated therapeutic molecules to the wound site. Microelectronic sensors, microprocessors, and wireless communication are the major parts of smart bandages.[7,59]

The integration of sensors and actuator technologies within the dressing introduces new approaches for monitoring the wound status in a real-time manner without the need for dressing replacement. Thanks to the embedded flexible microsensors within the dressing, various wound parameters such as pH, temperature, moisture level, and oxygen concentration, which cannot be measured with the former dressing, now become measurable.[7]

The advent of smart bandages capable of simultaneously analyzing and delivering therapeutic molecules to the wound site in an automatic/semiautomatic fashion would significantly promote the outcomes of wound management. The following section will discuss the specific wound parameters being diagnosed with dressing biosensors and delineate their role in the wound healing process.[58]

3.2.1. Smart Bandages with the Ability of Sensing

Infected acute wounds, full-thickness skin burns, and chronic ulcers all have different environments, and each requires a specific dressing. The dynamic environment of chronic wounds is expressing specific molecules that influence the healing process.[59] Clinical studies have recognized several determinative factors that provide information about the wound healing status. These parameters include pH, temperature, moisture, and oxygen levels in the wound environment.[60] By measuring the wound exudate, the stage of the wound healing process could be determined. Implemented microsensors within the smart bandages can sense and process the expressed markers in the wound environment and provide important information about the wound conditions.[61] Tamayol and co-workers aimed at developing an automated, integrated drug-loaded hydrogel—smart, flexible wound dressing with different incorporated microsensors encapsulating drug molecules for real-time monitoring the chronic status. In one of their recent studies,[62] an antibacterial

drug, cefazolin, was encapsulated within a temperature-sensitive poly(*N*-isopropylacrylamide) (pNIPAM) carrier and embedded in an alginate (ALG) hydrogel. Then, the hydrogel complex was integrated into the parylene-based pH and temperature microsensor substrate, and the whole substrate was applied to the wound. The fabricated small substrate can monitor the pH of the wound. Once the pH of the wound reached 6.5, the heater was automatically activated and intrigued by the release of cefazolin from thermoresponsive pNIPAM carriers (**Figure 3**).[60]

pH Sensing Smart Bandages: It has been reported that, depending on the type of wound, the required pH for initiating the healing process is different.[63,64] For acute wounds, the wound repair mechanism tends to be in the range of (pH ≈ 5–6), while, for nonhealing wounds, the pH of the wound environment is in the range of (pH ≈ 7–9).[65] Importantly, the changes in the wound pH indicate the risk of bacterial infection in the wound site. Bacterial biofilm colonization on the wound site is a vital pathogenic state of wound infection where clinical intervention becomes necessary and as a result, the wound is transforming into a chronic and nonhealing state. Clinical reports indicated that bacterial biofilm formation also plays a dominant role in chronic wounds as a healing interrupter.[66]

Various types of electrochemical and optical pH sensors have been developed for the continuous monitoring of pH levels in the wound environment.[16,67] Integration of these sensors with wound dressings has been introduced as a promising type of smart wound dressing Kassal et al. have engineered a novel wireless smart Hydromed D4 polyurethane pH-sensitive hydrogel-based wound bandage containing cellulose particles covalently modified with a pH indicator dye (GJM-534). The bandage is integrated with (optical chemical sensors and radio-frequency identification (RFID)-based contact-less readout platform for real-time measurement of wound's pH. The information of the wound is collected and transmitted wirelessly to a computer by RFID. Any changes to the pH of the wound contribute to a change in the color of the pH-sensitive indicator. The integrated photodiode in the dressing senses the color change and by converting the received data to digital format (ADC code), and then transmit the converted data wirelessly to the patient.[65] Together, manufacturing a wound bandage capable of analyzing the pH level of the wound could provide important insight on possible infection or the healing stage, specifically on diabetic wound ulcers (**Figure 4**).

Temperature Sensor Integrated Dressings: Recent advancements in the field of bioelectronics have resulted in the emersion of smart, flexible electronics-integrated substrates as a potent prototype of wound dressings. Pang et al. developed an antibacterial drug-loaded double-layered smart, flexible wound dressing with multiple light and temperature embedded microsensors for early detection of bacterial infection with an on-demand treatment capacity. In this study, a full-thickness wound, 3 cm in diameter, was created on the dorsal surface of Bama minipig (female, 7–9 kg) to assimilate wound infection. To prevent wound shrinkage, a polypropylene ring of the same size was placed over the created wound area. After two weeks of pressure therapy, a UR-integrated system wrapped in gauze was used to cover the whole area. Thanks to the integrated multiple microelectronic sensors in the bandage, the temperature of the wound environment were monitored, and the obtained data transmitted continuously via Bluetooth. At the onset of infection, the integrated UV-responsive antibacterial hydrogel and UV-LEDs were activated and triggered the in-situ release of the loaded antibiotic into the wound site (**Figure 5**).[66]

In another report, Oh et al. demonstrated the fabrication process of a highly sensitive and flexible bioinspired octopus-mimicking adhesive behavior skin-attachable temperature sensor for wound dressing applications. They combined the resistor type temperature sensor poly(N-isopropylacrylamide)/poly (3,4-ethylenedioxythiophene:polystyrene sulfonate (pNIPAM/PEDOT:PSS/carbon nanotube (CNT)) with polydimethylsiloxane (PDMS)-pNIPAM-based adhesive hydrogel dressing for precise measurement of skin temperature, a range of 25 and 40 °C, which can be reused multiple times without any degradation signs.[67]

Oxygen Sensing Dressings: Acute hypoxia as one of the detrimental symptoms of chronic wounds interrupts the neovascularization process in the wound environment leading to insufficient wound oxygenation. Therefore, real-time monitoring of the oxygen concentration in the wound environment is critical. In this regard, Mostafalu et al. developed a 3D-printed smart, flexible skin bandage for the continuous monitoring of wound oxygenation along with a wireless data transmission system in a single package. The oxygen concentration was measured by a customized microsensor constructed in an electrochemical galvanic cell on a flexible parylene C substrate.[68] Ochoa et al. developed a low-cost paper-based smart, flexible wound bandage for continuous sensing and delivering of oxygen to the wound site. In this study, parchment paper was used as a basement layer of the dressing and provided structural flexibility, selective molecules and fluid filtering, and adhesive property. These paper-based dressings have a functionality similar to the natural skin tissue by allowing/preventing viral or pathogenic molecules pass through the wound while preventing the entrance of wound surrounding aqueous solutions to the wound site. In this study, agarose-based H_2O_2 releasing gel with phosphorescent oxygen-sensitive ink ruthenium compound has been printed on the paper dressings for the simultaneous sensing and delivery of oxygen molecules. In vitro study revealed the potential of this substrate for sensing oxygen in a range of 5–26 ppm, which made it a promising type of smart wound dressing for clinical applications (**Figure 6**).[33]

Moisture Controlling Dressings: Providing a moist condition in the wound microenvironment has been indicated as the cardinal parameter for promoting the wound healing process.[73,74] Although current dressings provide appropriate control on the absorbance of the wound exudate alongside keeping the wound environment moist, in order to evaluate the moisture level in the wound site, disturbing the wound dressing was the only left invasive assessment approach for the patients. Milne et al. have developed a Hydrofiber-based wearable wound dressing integrated with a commercialized moisture sensor by Ohmedics (Ohmedics Ltd, Glasgow, UK) for real-time monitoring of wound moisture for developing a dressing suitable for clinical applications. This study suggested the potency of small electronic sensing systems for further in vivo studies as a noninvasive approach of monitoring the moisture level of the wound environment without causing irritation or further damage to the healed area.[69]

Smart Bandage with Integrated Multifunctional Sensors: Recently, multifunctional smart wound dressings capable of monitoring different parameters in the wounds simultaneously

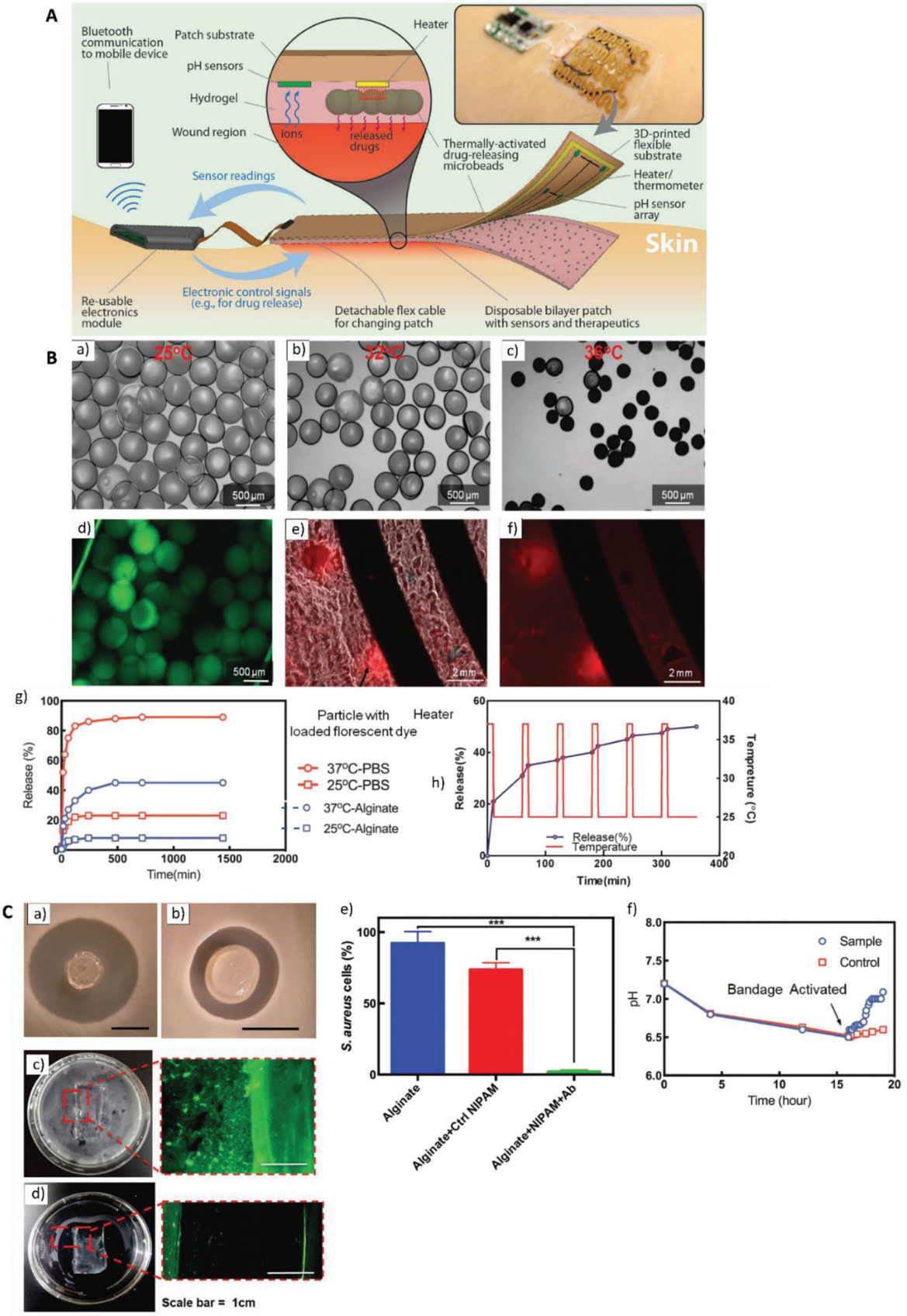

Figure 3. A–C) Schematic of the smart wound bandages with wound markers sensing capabilities and on-demand delivery of therapeutic molecules for the treatment of chronic wounds. A) Conceptual view of the automated smart bandage. The bandage comprised a multilayer flexible pH sensor and a flexible heater for on-demand release triggering thermoresponsive drug carriers containing antibiotics in the wound site with wireless communication capabilities to smartphones. B) Schematic view of integrated drug-releasing microparticles within the dressing. a–c) Optical image of the temperature-responsive microparticles at different temperatures. d–f) Fluorescence images of embedded drug microcarriers inside the smart microheater attached hydrogel dressing. Rhodamine B was used for better visualization of drug carriers inside the dressings. g) Release profile of cefazolin as a model antibiotic drug in different temperatures. h) Controlled release profile of cefazolin. C) In vitro assessment of the antibacterial activity of the smart bandage. a,b) Demonstration of antibacterial releasing diffusion test for cefazolin containing hydrogel and without cefazolin. c) Live–dead staining for formed bacterial biofilm on control patch. d) Live–dead staining for formed bacterial biofilm on a patch containing an antibacterial drug. Live bacteria have appeared as green moieties. e) Colony-forming unit counting test for *S. aureus* using cefazolin. f) Schematics of in vitro model for evaluating antibacterial activity of cefazolin-loaded patch against cultured *S. aureus* bacteria in a bioreactor monitored with pH sensor. Reproduced with permission.[60] Copyright 2018, Wiley-VCH GmbH.

have captured much attention.[76] While many current smart wound dressings are capable of measuring one or two wound parameters, the next generation of smart wound dressing can simultaneously monitor essential chemical and physical parameters involved in the wound healing, including pH, moisture, temperature, and uric acid (UA), in a single flexible device.[77–79]

Khatib et al. engineered a smart multifunctional dressing by integrating self-healing capabilities into soft electronic devices and sensors for high sensing performance toward temperature, pressure, and pH levels. This electronic platform provided the foundation for the development of a new class of smart wound dressing for multifunctional self-monitoring, treating and, healing function.[80] In another study, Sharifuzzaman et al. fabricated a flexible smart bandage integrated with multifunctional sensors detecting UA, pH, and temperature to accurately monitor chronic wound conditions. To do this, 2D MXene nanosheets were utilized to functionalize 3D porous laser-guided graphene (LGG) sheets via C–O–Ti covalent crosslinks to obtain LGG–MXene hybrid scaffolds. Then, the LGG–MXene hybrid scaffolds were successfully transferred onto PDMS to engineer a high-performance smart stretchable and flexible multifunctional integrated sensor wound bandage capable of detecting the UA, pH, and temperature at the wound site. Functional assays for the performance of the mounted sensors on the dressings exhibited accurate repeatability, sensitivity, and stability responses for detecting UA, pH, and temperature both in analytical and real samples; therefore, can be implemented as a potent candidate for smart wound dressing applications.[71]

Hereupon, the need for developing a kind of dressing with the ability to monitor the multiple chemical and physical parameters

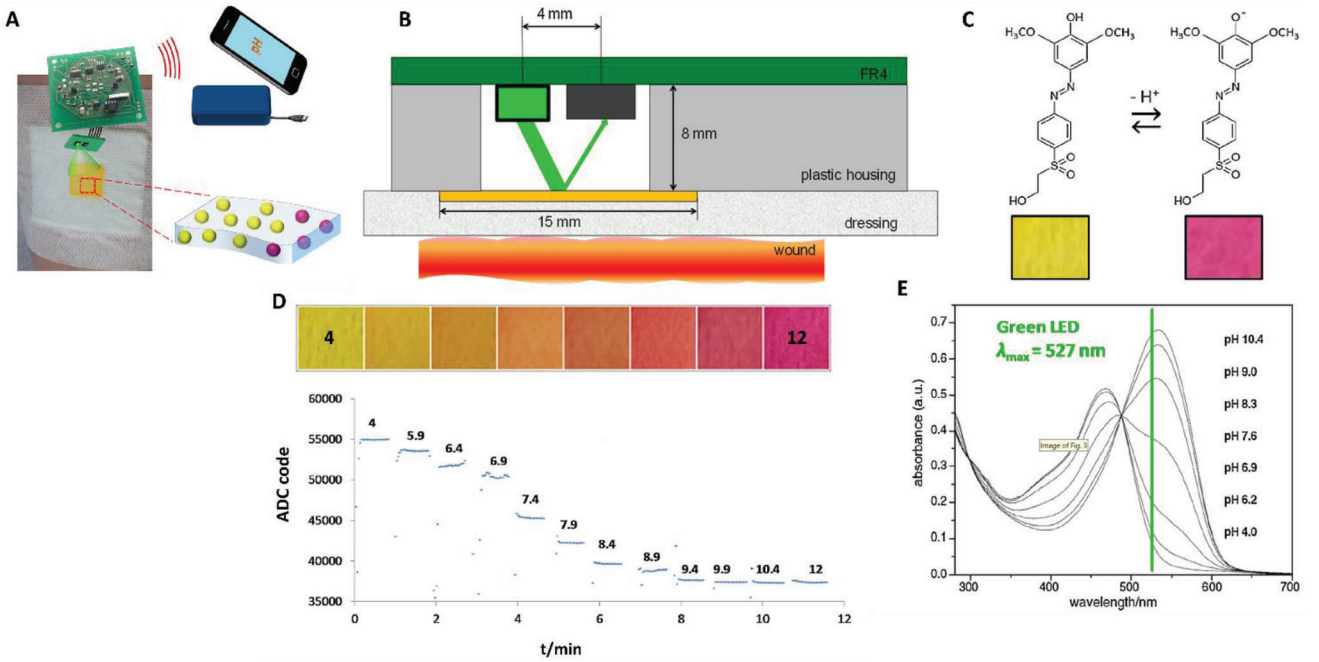

Figure 4. A–E) Schematic view of pH sensing smart wireless smart bandage. A) The pH-induced color change of cellulose particles with covalently linked GJM 534 is precisely measured via a miniaturized optoelectronic probe and sent by using radio-frequency identification (RFID) contactless readout to a remote unit. B) Cross-section of the optoelectronic probe with the pH-sensitive film, illustrating the optical component configuration. C) Chemical structures of the protonated and deprotonated forms of GJM534 and their respective colors. D) Schematic of smart bandage indicator color changing upon increasing in pH of the medium into the basic state. The conversion of readout electronics of the smart bandage response to the changes in pH values of standard buffer solutions (pH 4–12). E) Absorbance spectra of immobilized GJM 534 on cellulose substrate, exposed to buffers solution with different pHs. The green line peak demonstrates the maximum absorbance spectra of immobilized GJM 534 wavelength of the LED used in the smart bandage. Reproduced with permission.[65] Copyright 2017, Elsevier.

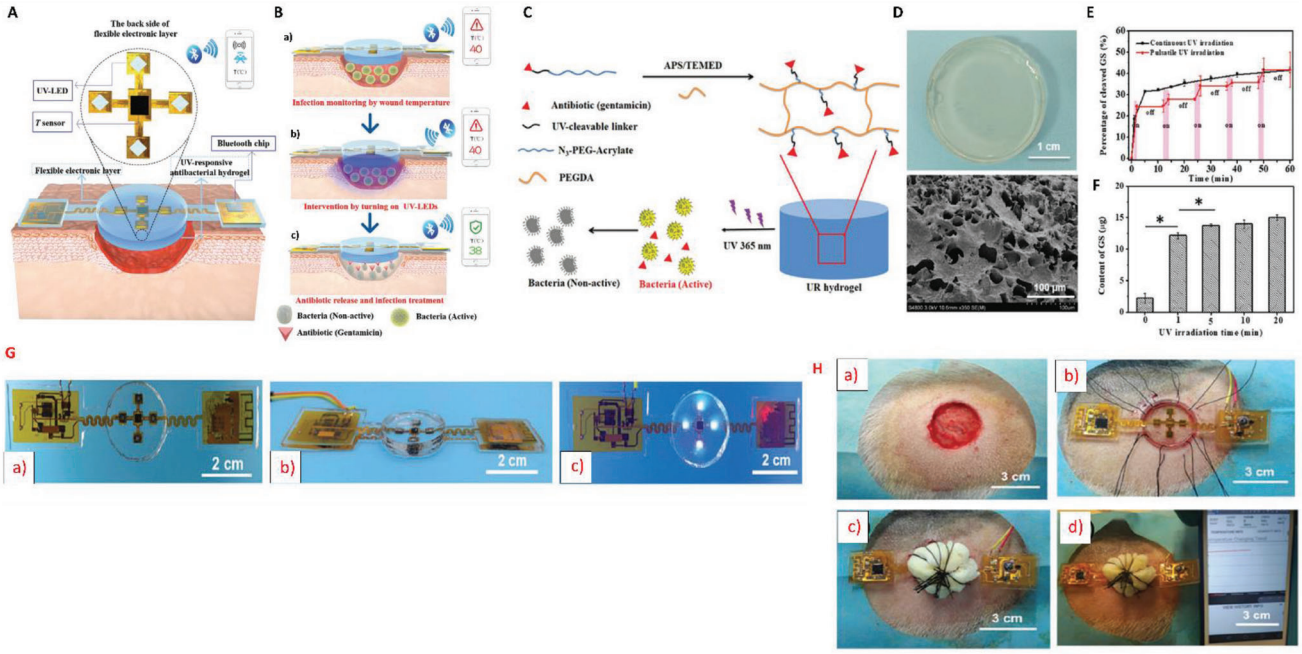

Figure 5. A–H) Schematics illustration of the function of smart, flexible temperature-sensing antibacterial wound dressing. A) An integrated, flexible electronic system was fabricated using a polydimethylsiloxane-encapsulated layer and a UV-responsive antibacterial hydrogel. A temperature monitoring sensor and four UV-LEDs, for emitting UV light (365 nm), were integrated within the dressing to trigger the release of encapsulated antibiotics from the UV-responsive antibacterial hydrogel when the temperature is increased at the wound site. A Bluetooth chip is also immobilized for real-time wireless data transmission. B) Theoretical illustration of the function of smart wound dressing for real-time monitoring of infected-wound with on-demand treatment capability: a) real-time monitoring of the wound temperature for reporting an alert of bacterial infection as a result of hyperthermia at the wound site; b) triggering the release of antibiotic drug from UV-responsive hydrogel to the wound site by turning on the UV-LEDs; c) inhibition of wound bacterial infection by on-demand releasing of antibiotics. C) Schematic of the UV-responsive antibacterial hydrogel synthesizing process, gentamicin (GS) as the model antibiotic drug, were covalently bounded to the PEG-based hydrogel using a UV-cleavable linker, which facilitated the drug release under UV irradiation at a certain wavelength (365 nm, 110 W cm^{-2}). D) Macrostructure and SEM image of the UV-responsive hydrogels (UR hydrogel). E) Release profile of cleavageable GS from the UV-responsive (GS-linker-PEG-acrylate) complex under continuous UV irradiation (black line) and pulsatile UV irradiation (red line) at different times and cycles. F) Comparison of the amounts of released GS from UV-responsive hydrogel for different time points. G) Different optical views of the flexible electronic compartment of smart dressing: a) the top view, b) the side view, and c) the top view of the system under working conditions. H) Surgical operational procedure on Bama minipigs: a) wound creation, b) implantation of the integrated wound dressing system, c) pressure dressing, and d) real-time wound-temperature monitoring. Reproduced with permission.[66] Copyright 2020, Wiley-VCH GmbH.

of the wound would be highly practical for better wound management (**Figure 7**).

Therefore, manufacturing a wound bandage capable of real-time monitoring the physiochemical markers in the wound environment (**Table 1**) could provide important data on possible infection or healing stages.

3.3. Dressings with Drug Delivery Potential

During the healing process of wounds, the properties of the wound environment dynamically change and result in a complex healing condition.[70] Recently, significant effort has been devoted to comprehending the biological factors or drugs that can modulate one or multiple physiological processes involved in skin regeneration. Integration of therapeutic molecules within the wound dressing is a practical strategy for improving the wound healing process by introducing regulating bioactive molecules to the wound site. Different strategies, known as active, passive, and semipassive approaches, have been employed for the effective delivery of therapeutic molecules from dressings to the wound site.[69,72]

A passive delivery system is the most common drug delivery method when a predesigned dosage of drug or molecules is integrated within the wound dressing or in a structure, i.e., drug carriers embedded within the dressings. Such a delivery method cannot address the complex dynamic nature of chronic wounds; thus, a semipassive approach has been introduced to release the therapeutic molecules based on the wound healing progress status. In this type of delivery method, different types of responsive materials to the different wound environment stimuli are utilized in the dressings structures to adjust the drug release rate based on the properties of the wound environment. pH, temperature, and secreted enzymes and toxins are among the typical stimuli that semipassive systems are responsive to them to trigger the drug release.[88]

Nonetheless, lack of external control over the release profile of the integrated drug molecules has revealed the need for developing a dressing capable of an on-demand delivery system. Recent advancements in wearable bioelectronic technology and

Table 1. Summary of the developed smart skin bandages with multiple integrated sensors and wireless communication module for real-time monitoring of the wound conditions.

Wound biomarker/marker	Method	Description	Refs.
pH	Potentiometric	Highly stretchable and flexible potentiometric pH sensor fabricated via laser carbonization and machining of carbon–polyaniline composite highly for wearable point-of-care applications	[16]
pH	Image processing	Epidermal pH-responsive hydrogel-fiber skin patches with the capabilities of continuous monitoring of wound pH level that can be employed as promising point-of-care systems for skin disorder such as skin wounds	[82]
pH, blood	Electrical (capacitance and resistance)	Continuous wireless monitoring system was fabricated by inkjet printing method to monitor wound healing parameters, including wound irregular bleeding, variations in the pH levels, and external pressure at the wound site	[73]
pH	Voltammetry	Incorporation of poly-L-tryptophan with a carbon fiber mesh was conducted for the formation of a conductive composite wound dressing. Carbon fiber has been used in countless sensors, specifically with applications in wound condition diagnostic capabilities	[74]
Uric acid	Electrochemical	A smart bandage for the measurement of uric acid (UA) level at the wound site was generated by direct printing of an amperometric biosensor on a wound dressing. The immobilized uricase, paired with a printed catalytic Prussian blue transducer, facilitates chronoamperometric detection of uric acid at a low working potential	[75]
Temperature	Thermoresponsive flexible heater on-demand drug release	A hydrogel-based dermal patch with a flexible heater for active, on-demand drug delivery applications was fabricated. Thermoresponsive NIPAM drug microparticles in the hydrogel are released upon changes in the temperature	[76]
Temperature	Photothermally triggered drug release	An rGO-nanosheet photothermal skin adhesive patch was with the capacity to release the drug by thermal increment at wound site upon exposure to NIR	[77]
pH	Colorimetric measurement of pH	A 3D-printed alginate-based pH-responsive and gentamicin-loaded hydrogel skin patch was fabricated. Colorimetric sensing of bacterial infection was confirmed	[83]
Temperature	Electrical	Adhesive skin patches for monitoring wound status	[79]
Blood glucose	Electrical	Skin-attachable microneedle patches responsive to the changes in blood glucose level and the smart delivery of insulin at different volumes	[80b]
Excessive biofluid	Self-pumping	Dressings with the capacity to balance the moisture at the wound site	[81]
pH	Electrical	pH-sensitive hydrogels and controlled electronic circuitry developed for precise electrical control over the temporal profile of pH-mediated drug release	[61]
Bacterial infection Temperature	UV irradiation	This UV-responsive antibacterial hydrogel dressing with an integrated temperature sensor capable of real-time monitoring of wound status markers to provide an early infection diagnosis strategy. Integrated temperature sensor controlled the release profile of antibiotics at the wound site, which was triggered by on-demand exposure of UV irradiation	[66]
pH, temperature	Thermoresponsive drug carriers	A smart and automated, flexible wound bandage constructed of embedded thermoresponsive pNIPAM drug carriers within a hydrogel dressing integrated with an electronically flexible heater	[60]
Full-thickness diabetic wounds	Miniaturized needle arrays/electrical micropump	Dressing for on-demand release of drugs with wireless data transiting compartment. The endothelial growth factor (VEGF) was delivered to a diabetic mouse to enhance re-epithelialization. A wide range of drug molecules with independent release profile can be delivered to deeper layers of the wound bed via miniaturized needles	[84]
pH, glucose	Image processing	A multifunctional antibiofouling and biocompatible zwitterionic poly-carboxy betaine (PCB) hydrogel matrix encapsulated pH indicator dye, two glucose-sensing enzymes, glucose oxidase (GOx), and horseradish peroxidase (HRP)	[85]
Temperature	Thermoresponsive drug carriers	Thread-based patch coated on a flexible thread-based heater for the transdermal delivery of encapsulated antibiotics and vascular endothelial growth factor (VEGF) in thermoresponsive particles embedded in a hydrogel layer	[86]
Temperature, humidity, glucose, and pH	Thermoresponsive flexible heater on-demand drug release	A multifunctional microneedle-based skin adhesive patch with drug delivery potential. By constant monitoring of the glucose level in the bloodstream, the microneedle patch can controllably release Metformin by an integrated microneedle array	[87]

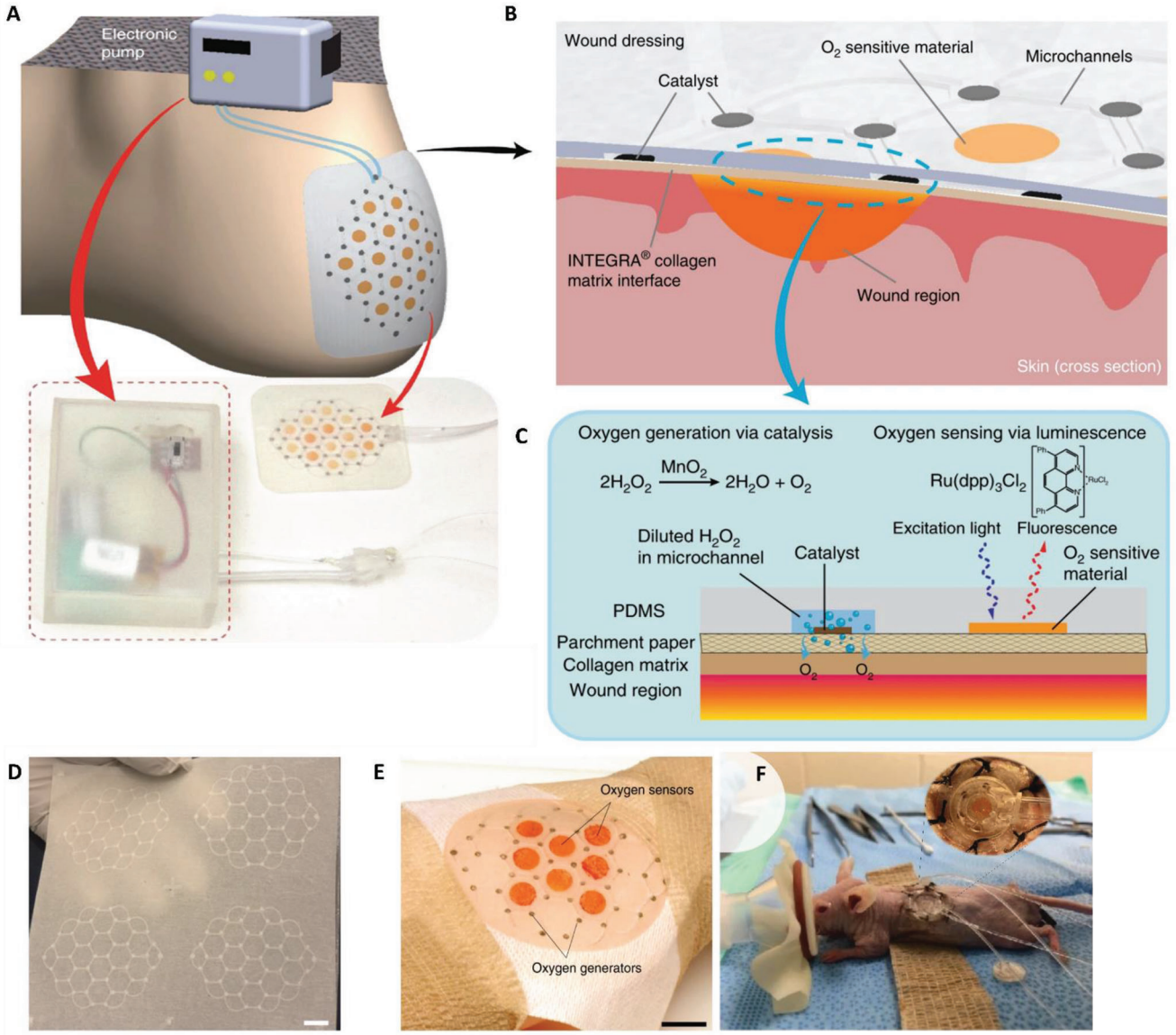

Figure 6. A–F) Design and function of oxygen sensing smart wound dressing. A) Overview illustration of the smart oxygen sensing patch for real-time oxygen-generating and sensing application. B) Cross-sectional view of the flexible smart oxygen-generating and sensing wound dressing applied on a created wound model on SKH1 mouse. C) Mechanisms for oxygen generating and sensing for flexible smart wound dressing. D) Demonstration of four smart oxygen patches. E) Close-up view of the oxygen generation and sensing sites on the smart dressing. F) In vivo testing of the device during H_2O_2 perfusion on O_2-treated mice. Reproduced with permission.[33] Copyright 2020, Nature Publishing Group.

microfabrication technologies have enabled the development of the next generation of wound dressings with the capacity to release drug molecules in response to external stimuli. The on-demand drug release strategy would promote the healing process of chronic wounds due to the controllability over the wound condition.[89]

A broad range of bioactive molecules, including antibacterial drugs, growth factors (GFs), and nucleic acids, have been incorporated within dressings to prohibit the wound environment from bacterial infection and amplified skin regeneration.[90] Recently, researchers have focused on the applications of drug-loaded nanofiber-based meshes as modern wound dressings for preventing bacterial infection. In a study by Fu et al., an innovative smart "ON–OFF" photocontrollable drug release system was fabricated from a surface-loaded R-cyclodextrin-5-fluorouracil (R-CD-5FU) prodrug on a PVBC-*b*-PGMA crosslinked nanofibers with azido groups. Photoresponsive host-guest interaction of 4-propargyloxyazobenzene (PAB)–vinyl benzyl chloride (VBC) and glycidyl methacrylate (GMA) (PVBC-*b*-PGMA) nanofiber mesh, provide a photocontrollable, on-demand, fast "ON–OFF" mechanism of release, which could be used in a situation where fast delivering of therapeutic molecules was vital.[91] In another example, Tamayol et al. developed a smart thermoresponsive, biodegradable, drug-loaded elastic nanofibrous prototype

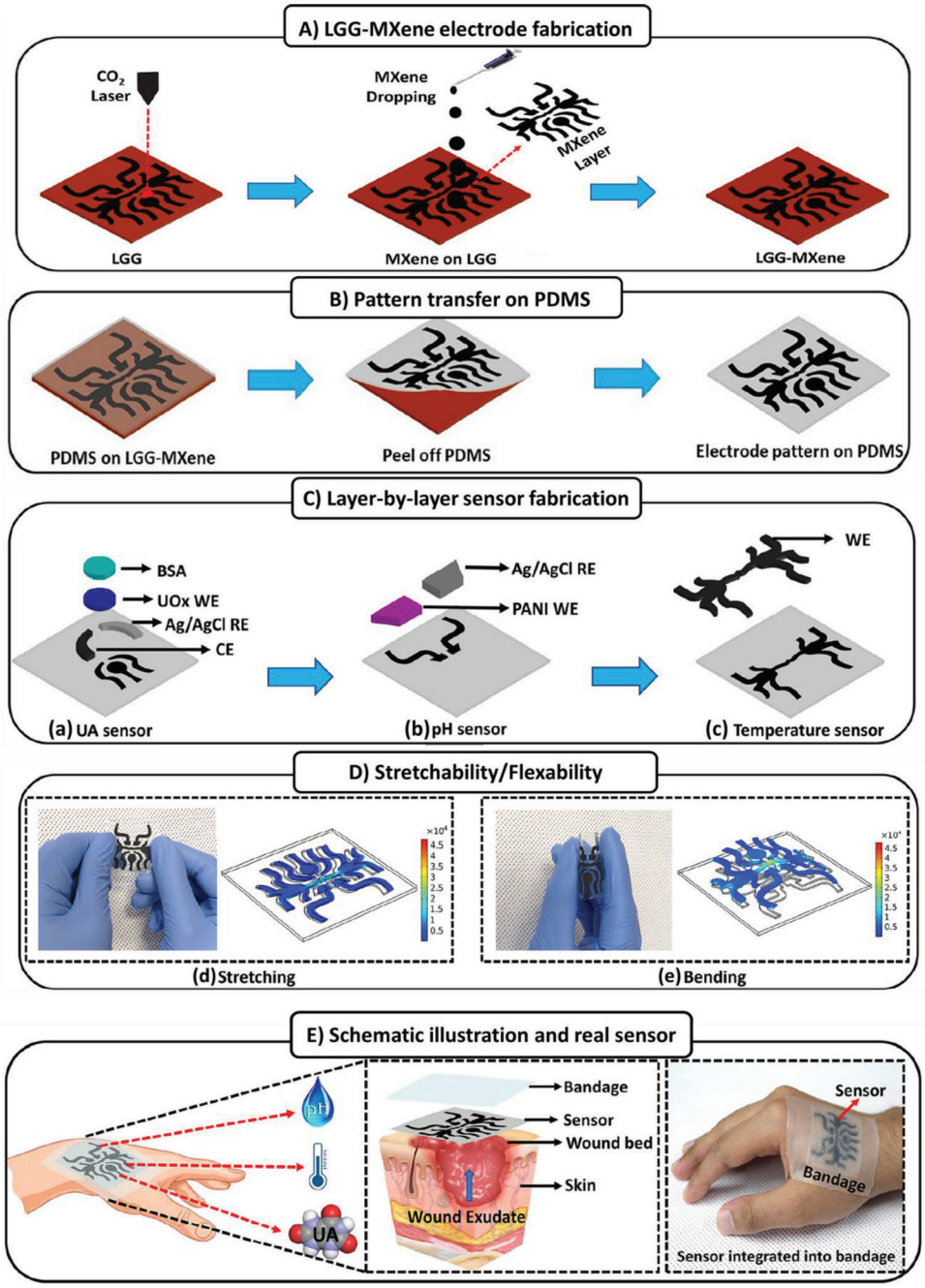

Figure 7. A–E) Stepwise fabrication illustration of a stretchable and flexible smart bandage with integrated multifunctional sensors. A) Schematic view of an LGG–MXene stretchable hybrid porous graphene bandage having multifunctional sensors with the capacity to monitoring uric acid, pH, and temperature at the wound site. B) Different steps of transferring integrated multifunctional stretchable LGG–MXene sensor pattern onto flexible PDMS layer using the peel-off process. C) The layer-by-layer fabrication of integrated multifunctional sensor: a) UA layer sensor, b) pH layer sensor, and c) temperature layer sensor. D) COMSOL simulation for demonstrating different stress distributions on electrode traces: d) stretching and e) bending. E) Schematic illustration and real image of the stretchable and flexible multifunctional smart bandage embedded on the patient's hand with the capacity to monitor moisture, pH, and uric acid. Reproduced with permission.[71] Copyright 2020, Elsevier.

composed of poly (glycerol sebacate)–poly(caprolactone) (PGS–PCL) blends. This platform was loaded with PEGylated CS-based thermoresponsive drug nanocarriers. To achieve an on-demand drug delivery to the wound, the sheet was surfaced patterned with a bioresorbable metallic heater for applying thermal stimulation for controllable release of antibiotic. At a certain range of temperature (38–40 °C), the integrated heater unit, triggered the release of antibiotics.[82]

Smart flexible skin patches constructed using hydrogels have allocated expanding attention in the last few years as the next

generation of wound dressing prototypes.[92] Self-healing hydrogels have demonstrated promising potential for developing a new class of materials for different biomedical applications. Meanwhile, polymeric hydrogel-based materials are known as the leading-edge alternative in the development of these smart self-healing biomaterials. The smartness of these substrates is referring to the capacity of emulating the biological systems to heal themselves.[93]

Chen et al. fabricated an injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties that can be used for diabetic ulcer treatment. This antibacterial Ag–SH-PEG dressing system was engineered using coordinative crosslinking of multiarm thiolated polyethylene glycol (SH-PEG) with silver nitrate ($AgNO_3$). Also, desferrioxamine (DFO), as an angiogenic drug, was integrated within the hydrogel to promote angiogenesis alongside antibacterial activity. The dynamic and reversible nature of the Ag–S coordination bond provides self-healing properties of the hydrogel after repeated injection through a medical needle. The self-healing characteristics of the fabricated hydrogel helped the system to diminish gel structure fragmentation and also integrate ruptured gels, even after external mechanical destruction at the target site. According to the heterogeneous structure of diabetic foot ulcers, this type of dressing is a promising candidate for promoting the diabetic wound healing process.[94]

For the last few years, microneedle (MN) patches with the capability of avoiding wounds from bacterial infection and promoting wound healing have been explored.[80b] In a study by Jamaledin et al., a biomass CS hydrogel was used as the most reported antibacterial biomaterial for manufacturing microneedle array patch encapsulating vascular endothelial growth factor (VEGF) for promoting skin regeneration alongside preventing bacterial infection.[95] Derakhshandeh et al. introduced a wirelessly controlled active microneedle array systems (MNAs). Accordingly, a 3D printing approach was implemented to fabricate a miniaturized array of hollow needles from a biocompatible resin (3-aminopropyl) triethoxysilane (APTES) and then loaded it on a flexible PDMS-based microfluidic layer to form a programmable minimally invasive wound drug delivery device. The whole module was then bounded to a wearable wireless control system with integrated miniaturized pumps to deliver different pharmaceutical bioactive molecules into the deeper layers of the wound bed. In comparison to the traditional topical administration of the drugs, this completely on-demand drug-releasing smart MNAs device could inject the encapsulated molecules to the targeted wound sites more efficiently.[96] In another study, the multifunctional microneedle skin patches with a hollow microneedles array were developed for the continuous infusion of a precise volume of morphine sulfate to the skin dermal layer.[97]

Recently, a large body of research has been devoted to generating highly efficient delivery systems to overcome the limitations of traditional drug delivery systems, and fundamental transformations on how drugs are delivered to patients are expected in the foreseeable future. Lack of control over the release of the encapsulated molecules was reported as a prevailing limitation of the current wound dressings. Recent smart wound dressers with the capacity of on-demand delivery of the therapeutic molecules to the wound site have turned these innovative dressings into a practical, cost-effective, and accurate solution for better wound management.[98]

3.3.1. Bandages with Antibacterial Capability for Wound Dressings Utilization

Maintaining the moisture in the wound environment and protecting the wounds from bacterial infection are the essential factors that an ideal wound dressing must provide. Bacterial biofilm formation following wound infection as the result of accumulation, embodiment, and growth of bacterial cells at the wound site, is known as one of the main reasons for delayed wound healing.[112] The existing dressings with antibacterial activities could provide a temporary condition for hindering the biofilm formation by passively releasing the antibacterial molecules.[113] Meanwhile, extensive researches are ongoing on fabricating a novel class of wound dressing with the potency of real-time monitoring of the wound conditions alongside with on-demand delivery of therapeutics.[96]

Developing a dressing that is smart enough to identify bacterial film colonization would be beneficial to healthcare providers. Recent studies have been focused on the development of smart wound dressing responsive to the physical (pH, light, and temperature) and biochemical (enzymes, toxins secreted by bacteria) as indicators of wound bacterial infections. These smart dressings, able to monitor and analyze the wound conditions in a real-time manner and release the encapsulated antibacterial drug molecules in a controlled fashion.[99] Thet et al. developed an innovative biosensor-based wound dressing which smartly diagnoses and indicates the bacterial (*Enterococcus faecalis*) biofilm formation by generating visible fluorescent color change on the bandage. They encapsulated self-quenching fluorescent dye inside an array of the lipid-based vesicle and integrated it within the agarose hydrogels as the basis precursor of the smart dressing. The dye would release by sensing the virulence factors of pathogenic wound biofilms, and the prospective risk of bacterial contamination could be diagnosed rapidly (**Figure 8**).[100]

Numerous studies have reported the potential of smart multifunctional antibacterial wound dressings. Mirani et al. developed a multifunctional wound dressing known as (GelDerm). The GelDerm has the potential of detecting bacterial infection by colorimetric measurement of wound's bed pH and releasing the antibiotic agents at the wound site at the onset of infection. Antibacterial resistance as the result of biofilm formation has caused life-threatening problems for patients with chronic wounds and burns.[89] To decrease antibacterial resistance, Zhou et al. have engineered a theranostic UV-photocrosslinable methacrylated gelatin (GelMA) hydrogel-based wound dressing encapsulating antimicrobial and fluorescent vesicles for early detection of bacterial infection and treatment. The dual-layer construction of the dressing's substrate was designed to detect the onset of the infection by releasing self-quenching carboxyfluorescein dye from the encapsulated vesicles embedded in the top layer and simultaneously releasing the antibacterial therapeutics to hinder the infection growth.[101]

To get a more controllable drug releasing system for delivering antibacterial therapeutics to the wound site, stimuli-responsive nanoparticle-based antimicrobial therapies were generated to overcome the limitations of previous drug delivery systems.[102] The high surface to volume ratio of nanoparticles has enabled them to provide multiple responsive, functional groups to the bacterial microenvironment in the wound site.

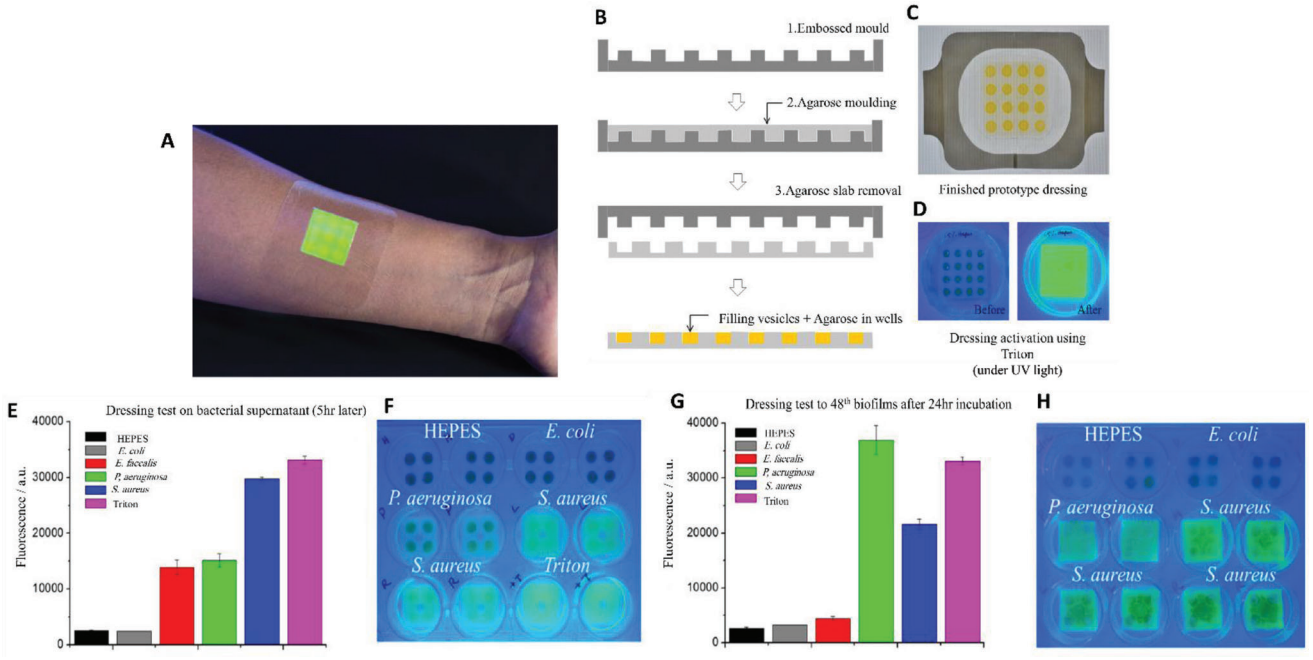

Figure 8. A–H) Schematic demonstration of a smart hydrogel-based wound dressing. A) An intelligent hydrogel wound dressing for the early detection of wound infection. B) Schematics of the stages of the smart wound dressing fabrication process. C) A close-up view of the final prototype of the smart wound dressing. D) Assessment of the function of treated dressing by using Triton under UV light exposure. E) Responses of dressing to bacterial supernatants and colony wound biofilm models of the supernatants. F) Wound dressings after 5 h incubation with supernatants. G) Colorimetric evaluation of dressing response to colony biofilm models of SPE pathogenic bacteria under UV light exposure. H) The response of dressings to biofilm formation after 24 h incubation. Reproduced with permission.[100] Copyright 2015, American Chemical Society.

Jiang and Loo have previously reviewed the potency of the antimicrobial stimuli-responsive nanoparticles as a promising alternative for smart wound dressing applications.[103]

The excellent potential of electrospinning technology in producing nanofibrous meshes has enabled the fabrication of wound dressings with the capacity of loading therapeutic molecules.[91] Extensive studies have implemented the drug-loaded nanofiber-based substrates for tissue engineering applications.[104] The antimicrobial stimuli-responsive nanofibrous wound dressings have captured widespread interest as a simple, effective, easy to fabricate type of wound dressings with environmental stimuli responsiveness properties. For this purpose, Rivero et al. have fabricated nitrofurazone-loaded pH-responsive Eudragit S100 (ES100) nanofibrous membranes as a smart nanofibrous-based antibacterial dressing for severe skin burns or chronic wounds.[105] In another similar approach of fabricating composite nanofiber-based wound dressings, Nudelman et al. informed the superb biomedical applications of jellyfish (JF) biomass as a promising biomaterial for regenerative medicine applications. They prepared JF–polycaprolactone nanofibers, incorporated with in situ generated biotemplated metallic silver nanoparticles as a smart anti-infection wound dressing.[106]

Fast detection and simultaneously applying the required treatments in a controlled manner are the main goals in the fabrication of antibacterial wound dressings. Therefore, various innovative wound dressings with antibacterial capacity, including paper-based dressings, microneedle patches, and flexible microelectronic integrated skin bandages for real-time monitoring and treating wound bacterial infection, have been developed.[106,108]

3.3.2. Dressings for Small Interfering RNA (siRNA) and MicroRNA Delivery Applications

Recently, the application of therapeutic nucleic acids (TNAs), including plasmid DNA, siRNA, and microRNA (miRNA) has emerged as a promising approach in wound healing and skin regeneration. TNAs can effectively modulate the healing process of nonhealing wounds by providing a prohealing condition in the wound microenvironment toward targeting the expression of targeted genes associated with inflammation, angiogenesis, and epithelialization.[31,109]

The utilization of siRNA and miRNA has been more reported in the literature as the most common approach for wound healing using TNAs[119] siRNA molecules play an important role in different stages of the wound healing/regeneration process by interfering with the translation of mRNA through the myriad of cellular pathways. Moreover, the capability of siRNA molecules in silencing the expression of genes that are involved in hard-to-heal wounds, including p53, matrix metalloproteinases (MMPs), transforming growth factor-beta receptor 1 (TGFBR1) has been reported.[110]

The effect of siRNA in downregulating the expression of connective tissue growth factor (CTGF) for scarless wound healing applications has been widely investigated.[111,114] Obtained

information about the involved genes in diabetic wounds through gene profiling using microarray techniques has indicated the prospective role of miRNA in hard-to-heal wound healing. Unlike the siRNA, miRNA molecules target multiple genes by repression and degradation of the target mRNA translation and ultimately modulate the healing process.[115]

The application of TNAs has major limitations, including limited bioavailability, rapid degradation, and transient expression mechanism; therefore, a broad range of scaffold-based delivery systems using natural and synthetic biomaterials for encapsulating them was implemented to maximize the impact of TNAs.[116-118] Nelson et al. developed a promising approach for protecting siRNA molecules from biodegradation and sustained intracellular (cytoplasmic) delivery for smart local silencing of detrimental genes in chronic wounds by using injectable, biodegradable endo-lysosomal pH-responsive diblock micelles encapsulated within polyurethane (PUR) nanoparticles. The high porosity structure of PUR nanoparticles facilitated the controlled intracellular release of the pH-responsive micelles containing siRNA. The diblock structure composed of dimethylaminoethyl acrylate (DMAEMA), polyacrylic acid (PAA), and butyl methacrylate protects the siRNA from serum nucleases. Upon acidification of wound environment, the composition of pH-responsive micelle alters and releases the encapsulated siRNA molecules.[119]

3.3.3. Dressings for Growth Factors Delivery Capacity

The exceptional role of GF in improving tissue repair and regeneration has been established in numerous studies.[120] Researchers have identified several effective GFs involved in the wound healing process including, recombinant human platelet-derived growth factor (rhPDGF-BB), vascular endothelial growth factor-A (VEGF-A), and fibroblast growth factors (FGFs), especially FGF-2. Sequestering of these important molecules from natural tissue extracellular matrix (ECM) regulates a cascade of vital cellular activities that are involved in the wound healing progression. For instance, platelet-derived growth factors have been clinically used for various tissue regeneration treatments, or VEGF-A was employed as a common angiogenic growth factor.[121] However, due to their high cost, GFs translation into the clinic is limited and significant effort has been made to develop an efficient delivery system. GF therapy is among the recent approaches in regulating the wound healing process by modulating the release of these molecules into the wound site. A variety of biomaterials (polymeric nanofibrous meshes and hydrogels) have been developed for the controlled delivery of GFs to the wound site.[122]

In a study reported by Lee and co-workers, a poly(lactic-*co*-glycolic acid) (PLGA)-based nanofibrous mat was fabricated for the controlled delivery of rhPDGF-BB, a potent GF for augmenting the wound closure in a diabetic rat model. The developed system provided a prolonged sustained release of rhPDGF for 21 days, which promoted the wound closure.[123] In another study, Liu and co-workers fabricated bFGF-loaded cocrosslinked hydrogel film composed of thiolated derivatives of chondroitin 6-sulfate and heparin (CS-HP ECM) as a potent wound dressing for full-thickness wounds in the db/db mice model. In vivo experiments confirmed the biodegradability and sustained release of bFGF. Moreover, the CS-HP ECM films promoted complete wound re-epithelialization after 4 weeks of treatment.[136]

Smart wound dressings responsive to various stimuli in wound environment such as proteolytic enzymes, pH, and temperature have gained increasing attention to be implemented for sustained low doses release of bioactive GFs to the wound site and preserve the bioactivity of these highly sensitive bioactive molecules against the proteolytic environment of the wound bed. For example, Kim et al. introduced a coextruded polymeric nanofiber patch encapsulated genetically engineered EGF covalently conjugated using an MMP-9 cleavage sequence for smart controlled delivery of GFs to the wound site. The presence of MMP in the early stages of wound healing triggered the release of EGF from the electrospun mesh and promoted the proliferation and migration of human keratinocytes into the wound site.[123]

Inspired by embryonic wound contraction, Blacklow et al. developed a tough, adhesive hydrogel containing a thermoresponsive component, pNIPAM as a substrate for the controlled delivery of GFs for skin regeneration applications.[124] Diverse approaches have been developed in the last few years for maximizing the therapeutic efficiency of GFs by incorporating them within a stimuli-responsive smart material for controlled delivery, but challenges still exist in the application of such "smart" materials for wound dressing application which need further investigations.[145]

3.4. Dressings for the Delivery of Cells or Cell Derivatives

The extracellular vesicles (EVs), also known as the exosomes, are bilayer lipid compartments secreted from cells with sizes ranging from 50 to 100 nm and containing various proteins and receptors, as well as DNA and RNAs.[126] Extensive studies have been indicated the vital regulatory role of exosomes in retaining the normal physiological state of the tissues. Also, recent discoveries have proposed the therapeutic role of EV as robust multifunctional signaling molecules in accelerating the tissue regeneration process through controlling cellular functions by transferring the vital biomolecules such as transcription factors, oncogenes, miRNA, and mRNA to the targeted cellular microenvironment.[87,127]

Exosomes regulate cellular homeostasis activities such as proliferating, apoptosis, migration, and differentiation. Yi et al. concluded that the secreted exosomes from osteocalcin expressing endothelial progenitor cells could stimulate angiogenesis and increase blood vessel formation.[128] The unique potential of EVs as a vigorous therapeutic and diagnostic tool for the treatment of several pathological conditions has attracted great attention among scientists.[129] Properties including i) the ability to encapsulate and releasing various therapeutic compounds as well as drug and nucleic acid-based molecules (miRNA, short hairpin RNA (shRNA), siRNA), ii) passing through the blood–brain barrier, and most importantly iii) their regenerative and anti-inflammatory capacity have turned them as robust alternatives for various biomedical applications.[130] For example, the potency of mesenchymal stem cell (MSC)-secreted exosomes for tissue regeneration purposes has been established.[131] The significant immunomodulation, immunosuppression, regeneration, and angiogenic activities of MSCs and MSC-derived EVs

have highlighted their potential for the treatment of chronic wounds.[132]

Referring to the promising clinical outcomes of the MSCs and MSC-derived exosomes for the treatment of chronic diseases, numerous efforts have been implemented to augment the therapeutic effectiveness of this approach. In particular, researchers have used various types of wound dressings for incorporating cells and exosomes to promote the wound healing processes.[133]

Shi et al. derived exosomes from gingival MSCs and embedded them into a CS/silk hydrogel sponge dressing for improving a 10 mm diameter full-thickness wound created on the upper back of 20 rat models. CS and silk are widely used for fabricating a biocompatible and biodegradable wound dressing with antimicrobial properties. The combination of these two biopolymers created a microenvironment that improved the ECM reconstruction alongside providing biomolecules transportation.[133] The desirable structural and physical properties of freeze-dried fabricated chitosan–silk dressings have revealed promising characteristics for implementing as a scaffold for delivering exosomes. This combinational therapy promoted the skin wound healing in a streptozotocin (STZ)-induced diabetic rat model by amplifying re-epithelialization, deposition, and remodeling of ECM.[134]

To maximize the possibility of exosome migration into the wound sites, Karahaliluglo et al. implemented a porous CS/silk dressing. They concluded that the porous structure of the wound dressing demonstrates significant delivery of various biomolecules to the wound site and promotes the healing and regeneration processes.[93] In one study reported by Ma et al., a collagen/PLGA blended nanofibrous wound dressing was fabricated to investigate the effect of bone-marrow-derived MSCs (BM-MSCs) migration on the full-thickness wounds. To enhance the MSC migration into the wound site, the collagen/PLGA scaffold was modified with CD29 antibody and promoted the attachment of MSCs to the surface of the scaffolds.[134]

In the last few years, polymeric nanofiber scaffolds have been widely implemented for fabricating tissue engineering matrices owing to their numerous desirable properties.[137,138] The polymeric nanofibrous scaffolds can be used to provide a temporary niche for the cells. Applications of these substrates for promoting the wound healing process have been highlighted before.[111]

3.5. Dressings for Immunomodulating the Wound Microenvironment

The immune system plays a central role in the regulation of tissue homeostatic and disease progress.[139] Alongside defending the body against pathogenic factors, it modulates the regeneration process of diseased tissues by orchestrating the innate and adaptive immune responses. In particular, the immune system regulates wound healing and skin regeneration as one of the complex dynamic processes in the body. Uncontrolled inflammation of chronic wounds indicated the modulating role of the immune system. By providing a complex inflammatory cascade in the wound microenvironment, damaged cells are cleared, tissue hemostasis is restored, and the regeneration process started.[140,141]

It has been reported that the excessive inflammation in the chronic wound microenvironment is hindering the healing process. Macrophages, as the special cell population of the immune system, had a cardinal role in the prevention or progress of the pathogenic conditions by orchestrating a diverse array of functions, including controlling the inflammation and tissue regeneration by attuning the immune responses.[142,143]

Platelets are the first cells that infiltrate into the wound site and initiate the coagulation cascade to prevent further blood loss. Platelets also provide a provisional ECM facilitating the infiltration of other cells. Then, neutrophils are recruited into wounded tissue and remain for about 24 h before undergoing apoptosis. Next, the proinflammatory macrophages (M1 macrophage) are activated and start removing the cellular debris, damaged matrix microbes, and neutrophils. M1 macrophages secrete proinflammatory cytokines and growth factors (including IL-1, FGF-2, PDGF, and VEGF, which mobilize more immune cells and promote the proliferation of keratinocytes fibroblasts, and epithelial cells during the inflammatory phase. At the end of the inflammation phase, macrophages undergo phenotypic changes from a proinflammatory to a proregenerative state. As the inflammation is resolved, the wound progresses into the wound healing process, matrix formation with angiogenesis and remodeling. Different cell types, including anti-inflammatory macrophages, regulatory T cells, and T helper-2 cells, and growth factors/cytokines including TGF-b, PDGF, FGF-2, IGF1, tumor necrosis factor (TNF)-a, and VEGF are involved in this step. During the final phase of wound healing, antifibrotic macrophages release numerous MMPs, including MMP-2, MMP-12, and MMP-19, and T lymphocytes are activated to trigger the production of ECM molecules essential for local tissue integrity.[144]

Studies of the influence of macrophage polarization on the wound healing process have demonstrated macrophage polarization in response to the wound microenvironment signals.[145] It has been reported that macrophages can be polarized into M1 (inflammatory phenotype in early stage) or M2 macrophages (anti-inflammatory phenotype in the mid-stage) based on the wound's status.[146] Previous studies have demonstrated that manipulating the polarization of macrophages into M2 macrophages able to accelerate the healing process by stabilizing angiogenesis, increasing the fibroblast and keratinocyte cell proliferation, and ECM remodeling (**Figure 9**).[147]

New studies aim to enhance the wound healing by promoting re-epithelialization, vascularization, recruitment of endogenous stem cells, directing macrophage polarization, or reducing the inflammatory responses.[148]

Using the fabrication technologies, we can generate biomaterials and recapitulate immune microenvironments that render the immune responses to pathogenic agents.[149] In recent years, the application of biomaterials with specific physicochemical properties has inspired researchers to engineer wound dressings with an immunomodulating capacity.[150,152]

3.6. Dressings for Postoperative Cutaneous Scar Management

Scar formation is a pathological condition caused by the overgrowth of the cells of an injured tissue after surgical incision, physical trauma, skin burn, or chronic disease. Scars impose huge psychological, emotional, and social burdens on the patients. Based on the exuberant granulation tissue on the wound

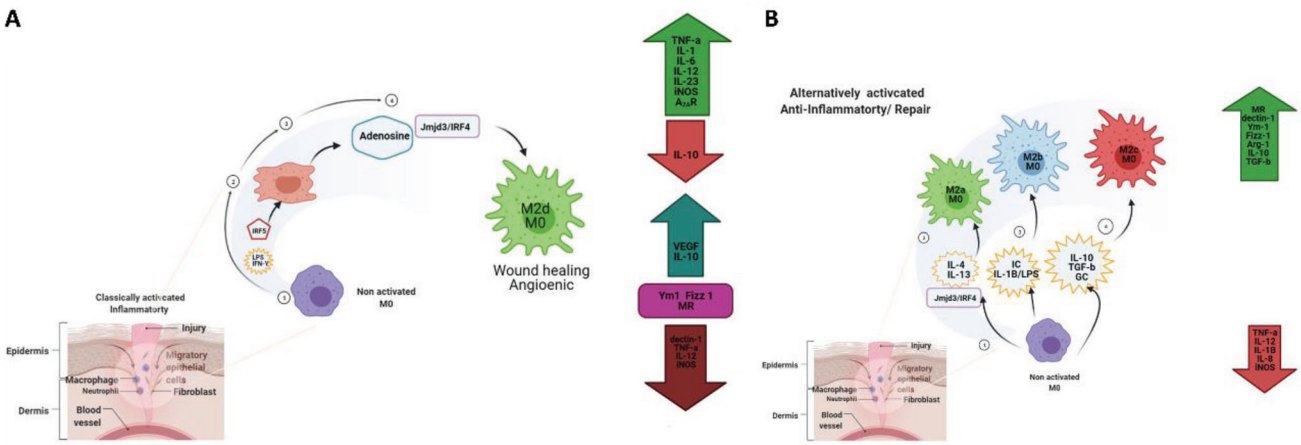

Figure 9. A,B) Macrophage polarization in the wound healing process. Created with BioRender.com.

site, scars are categorized into two types, hypertrophic and keloid. The main difference between these two types of scars is the scar tissue exterior appearance and wound border extension. Clinical evaluation has demonstrated that hypertrophic scars are more feasible in management due to the arranged collagen, thinner scar tissue, and scar regression over time, while, in the keloid scars, as a result of disarranged collagen construction, a thicker painful tissue with extended wound border is formed.[153–155]

Various approaches, including pharmaceutical products, laser/radiation therapy, special types of sutures, pressure therapy, and biomaterial-based dressings, have been developed for scar management.[156] Advanced polymeric biomaterial-based wound dressings incorporated with bioactive molecules have been used and contributed to the promoted wound healing with minimized scar formation.[157] Pressure therapy, also known as compression therapy, has also been utilized as a potent strategy in clinical applications for hypertrophic scar management. In this approach, an elastic bandage made of compression garments/elasticized fabrics is used to provide constant and equal pressure over the healed wound area to parallel the collagen bundles.[145,158]

Although applying automated, precise pressure on the wound site in a controllable manner is a challenging process, but in recent years, numerous pressure sensing tools have been developed to overcome such challenges.[159] Ghassemi et al. manufactured a smart polycarbonate-based wound dressing, equipped with a wireless communication device (XBee 2.4 GHz RF modem; Digi International, Inc, Minnetonka, MN), and a compression chamber with a force sensor was developed for the real-time monitoring and application of an on-demand amount of pressure. This automated pressure delivery system (APDS) was then attached to two 100 mm × 100 mm full-thickness wounds created on the flanks of two animals (Red Duroc pigs) with an electric dermatome (Zimmer, Inc., Warsaw, IN). The ex vivo studies expressed the capability of this medical device on promoting the quality of hypertrophic scars by constantly delivering 30 mmHg pressure on the wound scars for 2 weeks.[160]

Distinguished properties of electrospun nanofiber-based wound dressings, including ease of fabrication, degraded without causing any substantial immune-response, have turned these constructions into a favorable substance for direct delivery of therapeutic molecules to the wound site.[167] Jiang et al. fabricated a nanofiber-based wound dressing using gelatin/polycaprolactone conjugated with dopamine to eliminate the postsurgical defect of sutures after surgical incision.[103] In another study by Mahmoud et al., a collagen–CS was fabricated for encapsulating norfloxacin as a promising antiscarring wound dressing. Ex vivo study on newly born Albino mice skin demonstrated an accelerated wound healing process as a result of controlling wound infection, which led to lower inflammation and higher cell growth.[229]

The applications of biomaterials as wound dressings have captured significant attention for wound treatment and scar management. Recent studies have been indicated the potential of MSC-seeded dressing for efficient tissue regeneration during wound healing by augmenting the angiogenesis and regulating inflammatory responses.[144] Silicone gel has been extensively used in the clinic to reduce scarring. Silicone gels are the most common clinically used dressings for hypertrophic and keloids scars. Studies have shown that silicone gel sheeting provides an occlusion substrate for the wound and retains the environment moist, which are the key physical factors for reducing scarring.[145,146] In a recent report by Zhang et al., the prospective potential impact of the smart silicone-based scar care pad on the healing improvement of the severe hypertrophic scar by providing optimal pressure and occlusion effects were studied. The results of this study revealed that the combination of silicon stiffener layer with gradient studs and medical-grade silicone gel creates a tailor-made localized pressure and occlusion environment, which maximizes the treatment process.[147]

A wide range of hydrogel-based products, including amorphous gel, hydrogel sheets, hydrogel film, and hydrogel impregnated gauze, have been used in clinical practices for reducing post wound scars.[148] Catanzano et al. synthesized a composite hydrogel containing alginate and hyaluronan for promoting the wound healing process with minimum scar tissue formation. For in vivo studies, a full-thickness wound with a diameter of 2.5 cm was made in the back of male Wistar albino rats. The results demonstrated that the physically crosslinked alginate–hyaluronic composite creates a promising dressing capable of providing a

moist environment in addition to increasing the proliferation and migration of keratinocytes to the wound site and facilitating skin regeneration.[149]

Scars, as an unavoidable result of the wound repair procedure, impose considerable cosmetic appearance and functional impairment burdens on the patients. Although various approaches of wound scarring management from in vitro to clinical point of view were examined, due to the perplexing nature of wound healing and the mechanisms involved in scar formation, further researches must be conducted to identify the essential factors in accelerating the scar-less wound closure.[150]

4. Bioinspired Active Dressings

The search for finding novel approaches for addressing wound healing obstacles, as one of the remaining issues for the world health care system, indicated a continuous effort in finding a better alternative to promote wound healing and tissue regeneration. Sophisticated architectures of the evolved structures in nature have always been an exceptional source of inspiration to fabricate materials with different properties.[151] Therefore, numerous biomaterials with desired properties have been developed with special functions originated from nature for different biomedical applications. The naturally derived biopolymers have contributed to the fabrication of the next generation of substrates for wound healing purposes.[152]

In recent years, the application of bioadhesive substrates as the potential wound dressing has captured much interest.[153,154] The adhesiveness of gecko's footpads on the surface has inspired scholars to design and fabricate substrates for different applications.[155]

Moreover, the multilayered structure in marine mussels has inspired the researchers to fabricate a self-supportive freestanding multilayer membrane that could be applied as a skin wound dressing.[156] Sousa et al. developed a hyaluronic acid (HA)-containing dopamine multilayer film with appropriate mechanical adhesion and biocompatibility for wound dressing purposes. They reported that introducing catechol groups in the multilayer's construction have a supportive effect on cell adhesion and could be used as a potential wound dressing. For this purpose, a layer-by-layer (LbL) assembly technique was used to fabricate a bioinspired, adhesive multilayer membrane comprised of CS (CHT), ALG, and modified hyaluronic acid with dopamine (HA–DN). The presence of catechol groups in the dopamine amplified the adhesiveness, and bioinspired freestanding of the constructed multilayer membranes demonstrated proper support for wound healing.[157]

In a novel approach called active adhesive dressings, inspired by the contraction ability of embryonic wounds, Blacklow et al. introduced a dressing by inducing mechanical cues, which promoted wound healing. To create active adhesive dressings with temperature-triggered contraction and antibacterial function, alginate-loaded Ag nanoparticles were used as the basis of the hydrogel dressing, and *N*-isopropylacrylamide (NIPAM) polymers as thermoresponsive modulator were bonded to the hydrogel with CS and carbodiimide mediated reactions. The bioadhesive polymeric films containing an antimicrobial agent showed appropriate function as a wound dressing and inhibited the bacterial-film formation.[145]

The implementation of 3D printing of solvent-free, highly porous fibrous scaffolds using the melt electrowriting (MEW) technique has provided an unprecedented opportunity for researchers to develop a biomimetic architecture scaffold for different tissue engineering applications.[158,159] Recently, combining 3D-printed biomimetic wound dressings and stem cell therapy has emerged as a promising strategy for promoting wound healing with reduced scar tissue formation.[160]

A 3D-printed medical-grade polycaprolactone (mPCL) wound dressing with biomimetically designed architecture was developed by Shafiee et al. for accelerating wound closure with less scarring in a rat model over six weeks. The hierarchical design of fabricated MEW mPCL, assimilated the J-shaped strain stiffening, anisotropic behavior of natural skin tissue, and created a cellular environment similar to native stem cell niche that enhanced human gingival tissue multipotent MSC (hGMSC) attachment and proliferation.[167] In another study, Li et al. developed a novel transparent in situ forming hydrogels dressing with multiple properties including moist-retaining, self-healing, and bioadhesiveness to augment the wound healing process. A hydrogel was synthesized by combining oxidized hydroxyethyl starch (O-HES) and modified carboxymethyl chitosan (M-CMCS). This combination resulted in the preparation of hydrogel network structure with excellent self-recoverable extensibility–compressibility, biocompatibility, biodegradability, and transparency properties. This composite structure was able to reduce the wound fluid loss and consequently generated a moist environment, which resulted in accelerated wound healing.[169] To promote skin wound healing, Le et al. developed a smart in situ forming bioinspired pH and temperature-responsive injectable adhesive hydrogels for the delivery of DNA-bearing polyplexes. Body physiological condition (pH 7.4, 37 °C) transforms the sol nature of this dressing to a stable gel structure with acceptable physicochemical properties, which controlled the release profile of DNA-bearing polyplexes for 10 days. This smart bioinspired in situ-forming pH and temperature-sensitive characteristics of the fabricated gel provides a promising strategy for subcutaneous implantation of PEG–poly(sulfamethazine ester urethane copolymer sols to seal the ruptured skin defects effectively.[161]

Bioinspired strategies for designing substrates with adhesive performance have drawn significant attention in wound dressing applications. In the last few years and as a consequence of exclusive properties of naturally inspired biomaterials, many efforts have been made in the development of substrates with similarity to the natural materials in the body.[162] Researches are in progress to design and fabricate functional bioinspired substrates to control cell–matrix interactions at any length scale for effective wound healing.

5. Soft Electronic Materials in Fabricating Smart Wound Dressings

Skin is the largest human organ that acts as an ideal signal source to generate and transmit vital biological signals from inner organs. Unique elastic characteristics of human skin have inspired researchers to develop a class of materials to mimic the function of this organ. In the last recent years, soft, flexible, and stretchable electronic devices are commonly known as "Lab-on-skin" have

been engineered to provide a novel interface platform with soft tissues to control biological responses.[173,163]

Electronic skin, epidermal electronics, or electronic tattoos, are the common terminology for the smart substrates that are fabricated from versatile skin-mounted biosensors as a diagnostic tool for real-time monitoring of the different health-related physiological status of the human body, including electrocardiology, hydration, blood oxygen, wound-healing rate, sweat content, skin surface temperature, blood pressure, electromyography, and electroencephalography.[164] For example, a microelectromechanical accelerometer has been utilized as an innovative alternative approach for collecting acoustic signals from inner organs for clinical diagnostic purposes.[175] Xu et al. developed a noninvasive, skin-mounted mechanoacoustic sensor from a miniature accelerometer for continuous, simultaneous record of electrocardiography and seismocardiograms (SCG) information created by local vibration of the chest in response to heartbeats. This epidermal device utilizes a thin, small, flexible, and low-power acceleration transducer with a bandwidth of 0.5–550 Hz and is placed in the dorso-ventral perpendicular axis to the chest surface with a sensitivity of 300 mV g^{-1} of the signal-conditioned voltage output.[165]

Real-time monitoring enables the early detection of diseases by the patient. Moreover, lab-on-skin devices have been used to detect biomarkers in human sweat. The human sweat provides an ideal source to access many biomarkers accurately and unobtrusively.[166] Therefore, flexible, and stretchable electronics have been converged with the microfluidic devices to collect and store the data from sweat. These type of thin-film skin bandages can be employed for multiple purposes, including analyzing the drug abuse, athletic performance, or disease diagnosis at the early stages.[167–169] The utilized electrodes and biosensors in these sweat analyzing skin bandages are capable of detecting a broad class of biomarkers including ions (Na+, Cl−, K+, NH4+), molecules (cortisol, urea, lactate, glucose), or small proteins and peptides.[170] Koh et al. fabricated a soft, flexible, and stretchable epidermal microfluidic sensor patch that allows for collection and storage of sweat during exercise for analyzing overall health conditions. The lab-on-skin devices have reservoirs with embedded assays that can respond and interact with the biomarkers such as chloride and hydronium ions, glucose, lactate, pH, and creatinine. Also, wireless communication modulus and image capture hardware enable wireless data transfer and analysis through a smartphone.[171] In a series of studies Wang and co-workers, printed various electrochemical sensors on flexible substrates or garments for the real-time monitoring of different molecules such as ammonium, dopamine, UA, acetaminophen, and lactate.[172–174]

6. Advanced Hydrogels for Wound Monitoring and Treatment

Wound dressings are generally designed to act as a temporary protecting layer for the wounds and also to accelerate the healing and skin regeneration process by providing a moist and antibacterial condition. Although different types of wound dressings have been developed in recent years to provide an ideal condition for this purpose, due to the dynamic and complex nature of chronic wounds, there is an urgent need for developing a new class of wound dressing that not only act as a protective layer for the wounds but also able to actively monitor the condition of wound progress.[175] Advancements in the field of polymer science and materials fabrication technology have proposed hydrogel materials as a promising innovative class of wound dressing substrates. According to the exclusive characteristics including high water content, which provides a proper moist environment for the wound site, and the capacity of loading and on-demand releasing of a wide range of bioactive molecules (drugs, proteins, nucleic acids, growth factors, etc.) to the wound site, turned the hydrogels as potent wound dressings for the treatment of chronic/nonhealing wounds.[176–177]

The presence of a high number of functional groups in the structure of the hydrogel's polymeric network has enabled these substrates to actively interact with their surrounding microenvironment. The smartness of these dressings is achieved by the integration of several physiochemical stimuli-responsive moieties with the backbone of the polymeric network of smart hydrogels to interact actively with the dynamic environment of the wound site. Hydrogel properties such as swelling/deswelling alteration and changes in the gelation behavior by modulating mechanical stiffness are among the most important characteristics of the smart hydrogels in response to environmental stimuli.[178-180] In this regard, a broad range of studies have been performed to engineer stimuli-responsive/smart hydrogels for wound dressing applications. Early detection of wound bacterial infection is a highly important feature for improving the healing process of chronic wounds.[181,182] Developing smart wound dressing with the ability of early detection of bacterial biofilm formation and providing an on-demand treatment have gained engrossing from research communities.[183]

Qiao et al. developed a bacterial infection sensitive smart nanocomposite hydrogel-based dressing composed of PVA, a UV-cleavable linker (gentamicin sulfate (GS)-Linker-poly(ethylene glycol) methyl ether (MPEG)), GS (an aminoglycoside antibiotic), silica nanoparticles modified with Cy3 and Cy5(SNP-Cy3/Cy5), and upconversion nanoparticles (UCNPs). The modified Cy3 and Cy5-silica nanoparticles (SNP-Cy3/Cy5) act as a pH-responsive fluorescent probe to detect and reveal bacterial infection in the wound site based on the florescence resonance energy transfer (FRET) effect principle, also it can enhance the mechanical properties of the dressings after absorbing the wound exudates. By the time of increasing bacterial activity in the wound environment, the pH-responsive probe would be activated by irradiating the dressing under the near-infrared (NIR) light. Then the encapsulated antibacterial drug in the UCNPs will be released.[184]

Bagherifard et al. engineered a thermoresponsive smart Ca-alginate hydrogel-based skin patch with the ability to release the dual biomolecules in a controlled fashion. The integrated flexible heating elements in this patch, provide the required heat for the controllable delivery of encapsulated biomolecules (dug and growth factor) from the embedded NIPAM thermoresponsive microparticles.[76]

More recently, the integration of microelectronic sensors with the convenient hydrogel-based wound dressings structure has gained tremendous attention among researchers as a novel smart wound bandaging for remote monitoring of chronic wounds. Ajovalasit et al. developed a prototype model of

xyloglucan–poly(vinyl alcohol) hydrogel membrane for wireless smart wound monitoring and investigating the performance of this prospective new class of wound dressings after contacting with simulated biological fluids. Under a wide range of frequencies (100–106 and 108–1011 Hz), they analyzed the changes that occurred in the structural properties of the dressings. The body fluid absorbance of the xyloglucan–poly(vinyl alcohol) hydrogel membrane increased the swelling degree of the hydrogel substrate which resulted in an escalation in the membrane conductivity in different frequency regions (kHz and UHF) ranges.[185] Thanks to the advantages of this type of smart dressings, the moisture level in the wounds can be wirelessly monitored and reported to the patients/clinicians for applying the proper treatment.[76,185]

Exclusive characteristics of hydrogel materials including high water content, adjustable composition, and transparent structure alongside precise recapitulating the biological properties of natural tissues, including skin, have turned these biomaterials into a robust alternative among the different types of scaffolds for wound dressing applications. Also, the capacity of microsensor integration within the hydrogels, not only amplified the inherent limitations of these substrates but also added monitoring features to these practical substances for better wound healing (**Figure 10**).[186,187]

7. Fibrillar Networks as Wound Dressings Materials

One of the most primary efforts in the development of a new generation of wound dressing was related to the advent of electrospinning technology. High similarity to the natural ECM structure, capacity of continuous and uniform producing nanofibers, form almost any synthetic and many natural polymers with porous structures, capable of loading and delivering bioactive molecules (drugs, proteins, growth factors, etc.) to the wound site, and large surface to volume ratio, are among the main characteristics of nanofibers for the wound healing purposes. Nanofibers can retain the wound site moisture and enhance angiogenesis and collagen synthesis as the vital factors of wound healing and skin regeneration. Over the last decade, considerable efforts have been made in the fabrication of smart electrospun nanofibers to be used as biosensors, biomembrane, wound dressings, etc., with the ability to respond to the physical and chemical environmental stimuli such as pH, temperature, light, electric or magnetic fields, or a combination of them.[189,188] Moreover, nanofibers are potent carriers for the local delivery of bioactive molecules due to the ease of encapsulation of molecules during the electrospinning process.[190,191]

The responsiveness to the external triggers has encouraged the researchers to develop activation-modulated systems for regulating the release behavior of the encapsulated biomolecules using nanofiber for promoting the wound healing process. Based on the reported studies about the different embedded stimuli-responsive moieties within the electrospun nanofiber-based wound dressings, pH has been the most studied stimulus.[192,193]

The mechanism of drug release from these wound dressings is based on the pH alteration in the wound site. Yuan et al. fabricated an ibuprofen-loaded pH-responsive poly(L-lactide) (PLLA) smart anti scar nanofibrous dressing[194] by incorporating a pH-sensitive sodium bicarbonate ($NaHCO_3$) moiety into the dressing structure, which triggers the release of ibuprofen when the pH of the wound microenvironment becomes acidic, as a result of bacterial activities in the wound site. The fabricated dressing was tested in a full-thickness (2 cm in diameter skin wound) on the dorsum skin of 8-week old Sprague-Dawley rats. Immunohistochemical examination showed that the acid-responsive ibuprofen-loaded electrospun fibrous dressing could prevent excessive inflammation in the early stage of wound healing. Also, the electrospun nanofiber structures provide a natural skin tissue ECM for cells to contribute to the regeneration of complete and scarless skin tissues.[195]

Li et al. fabricated a thermoresponsive nanofibrous-based wound dressing by blending poly di(ethylene glycol) methyl ether methacrylate (PDEGMA) with poly(L-lactic acid-*co*-ε-caprolactone) (P(LLA-CL) to provide a thermotensile biocompatible substrate for on-demand release of ciprofloxacin (CIF) into the wound site. In vivo animal study on male Sprague-Dawley rats with 3 cm × 3 cm open excision wounds indicated that the PDEGMA/P(LLA-CL) composite fibers loaded with CIF improved wound healing progress by promoting the adhesion and proliferation of L929 fibroblasts and inhibiting the growth of *Escherichia coli* and *Staphylococcus aureus* compared to commercial gauze and CIF-loaded PLLA-CL fibers.[196]

In another study, and for on-demand release of the encapsulated drug molecules in the absence of any chemical toxic moieties, as stimuli, sensitive parts of current dressings, Huang et al. engineered hybrid levofloxacin-loaded wound dressing composed of electrospun PVA nanofibrous mesh. The mesh was embedded with upconverting nanoparticles and NIR light cleavable conjugates for on-demand drug release to the wound site. In this light-responsive wound dressing substrate, patients can completely control the release of antibacterial drug molecules by irradiating NIR light to the dressing which led to the excitement of encapsulated UCNPs to cleavage the *o*-nitro benzyl (ONB) linkage of the levofloxacin conjugates in the PVA mesh and emits UV light at 365 nm.[197] Although, different strategies have been considered for enhancing the therapeutic properties of nanofiber-based wound dressings further investigation is needed to evolve this highly efficient substrate as a smart wound dressing (**Figure 11**).[198,199]

8. Microneedle/Nanoneedle Skin Patches for Drug Delivery Applications in Wound Healing

Microneedle/nanoneedle arrays (M/NAs) are new types of minimally invasive, painless, mediated drug delivery systems with the ability to bypass the stratum corneum and overcome the potential drawbacks of current transdermal drug delivery methods such as subcutaneous injections, chemical enhancers, nano, and microparticles, or physical treatments. M/NAs contain micro/nanoscopic needle-like projections that can perforate the stratum corneum layer of the epidermis, creating ducts that facilitate the transport of large molecules (>500 Da) containing proteins and nanoparticles through the skin.[200]

Different types of materials have been utilized for fabricating M/NA skin patches including solid, coated, hollow, dissolving, and hydrogel-forming micro/nanoneedles. Recent studies have

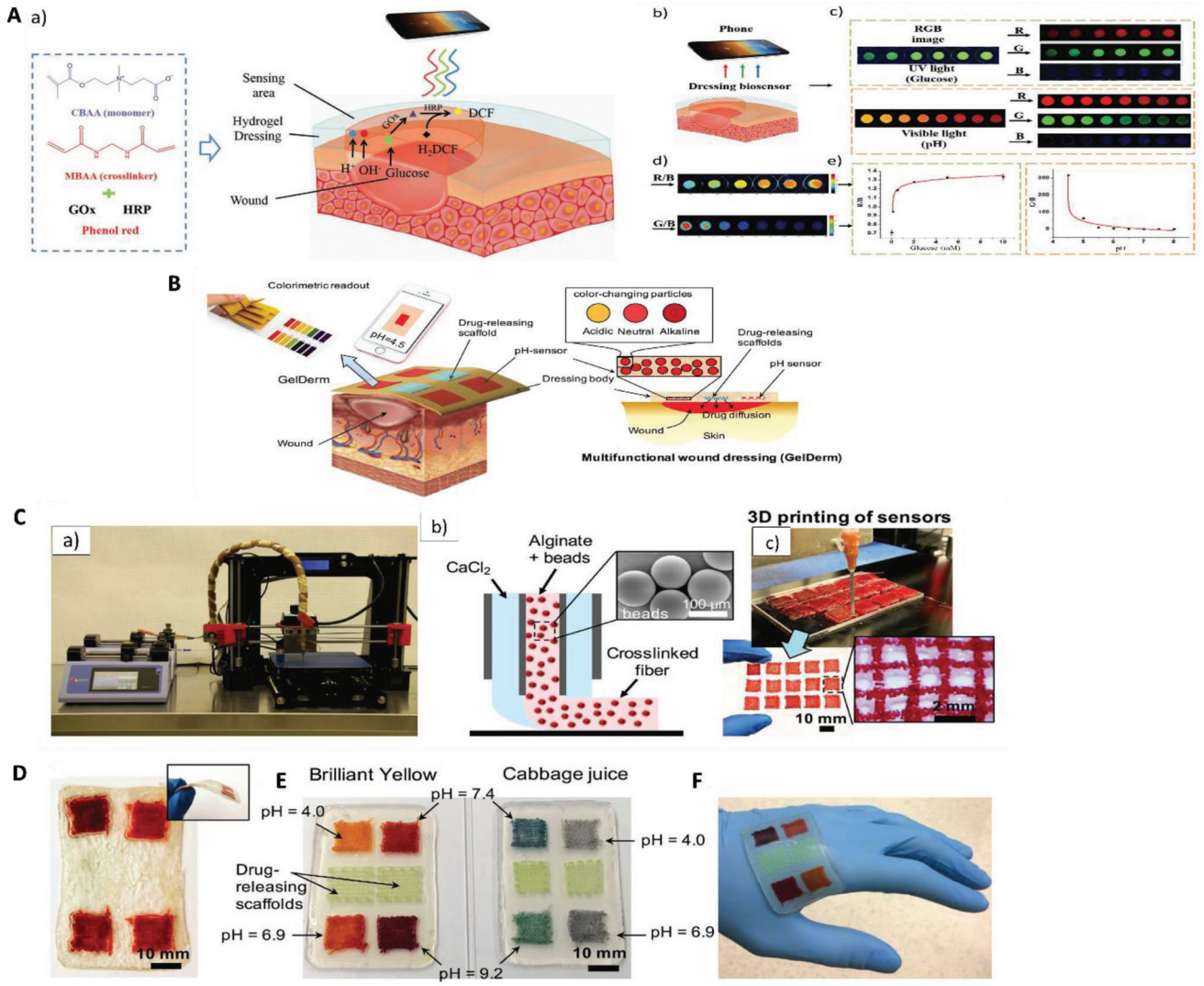

Figure 10. Intelligent hydrogel wound dressings for monitoring chronic wound conditions. A-a) Schematic presentation of a smart biocompatible zwitterionic poly-carboxy betaine (PCB) hydrogel dressing for simultaneous detection of pH values (under visible light) and glucose concentrations (under UV light) from wound exudate. b) Smartphone-assisted real-time monitoring of wound status. c) RGB images of the functions of PCB-PE-E hydrogel sensor under different glucose concentrations or pH values. d) R/B image colors section demonstrate glucose-sensing, and G/B image represents the pH sensing. e) The fitted curves for glucose concentrations and pH values under testing conditions. Reproduced with permission.[85] Copyright 2020, Wiley-VCH GmbH. B) A 3D printing fabricated multifunctional hydrogel-based alginate-loaded gentamicin with a pH-responsive dye skin patch (GelDerm) with functions of wound monitoring and delivery of antibiotic agents. C) Schematic representation of GelDerm for monitoring and treatment of epidermal bacterial wounds, with pH-sensitive colorimetric sensing of bacterial infection and drug-releasing compartments. C-a) A coaxial flow microfluidic nozzle 3D bioprinter was utilized to fabricate sensor structure. b) Fiber deposition step using coaxial flow system. c) Arrays of 3D-printed porous sensors for large-scale fabrication of smart dressings. D) View of lyophilized, sterilized smart dressing. E) Demonstration of used model pH indicators (Brilliant Yellow and naturally derived cabbage juice) for implementing as a pH-responsive sensor in dressing. These sensor arrays are capable of detecting the spatial variations of pH level and releasing encapsulated drugs at the wound site. F) Proper placement of GelDerm dressing on irregular surfaces. Reproduced with permission.[83] Copyright 2017, Wiley-VCH GmbH.

investigated the potential of M/NA skin patches for different biomedical/pharmaceutical applications, such as vaccinations, gene therapy, cancer therapy, and obesity treatment.[201] The potential of M/NA for the delivery of bioactive molecules, proteins, antibodies, antigens, and other biotechnological active ingredients has been shown in previous literature.[202,203] Chi et al. investigated the potential of M/NA in developing smart wound dressing that not only avoids wound infection also promotes tissue remolding simultaneously. For this purpose, biomass-derived CS microneedle array (CSMNA) patch integrated with smart temperature-responsive NIPAM microgels were fabricated for the delivery of VEGF in the wound.[230] To investigate the dual function of this smart patch, an infectious wound was created on the back of the Sprague-Dawley rat. In vivo studies demonstrated the robust impact of this smart patch in preventing bacterial biofilm at the wound site, due to the potent antibacterial

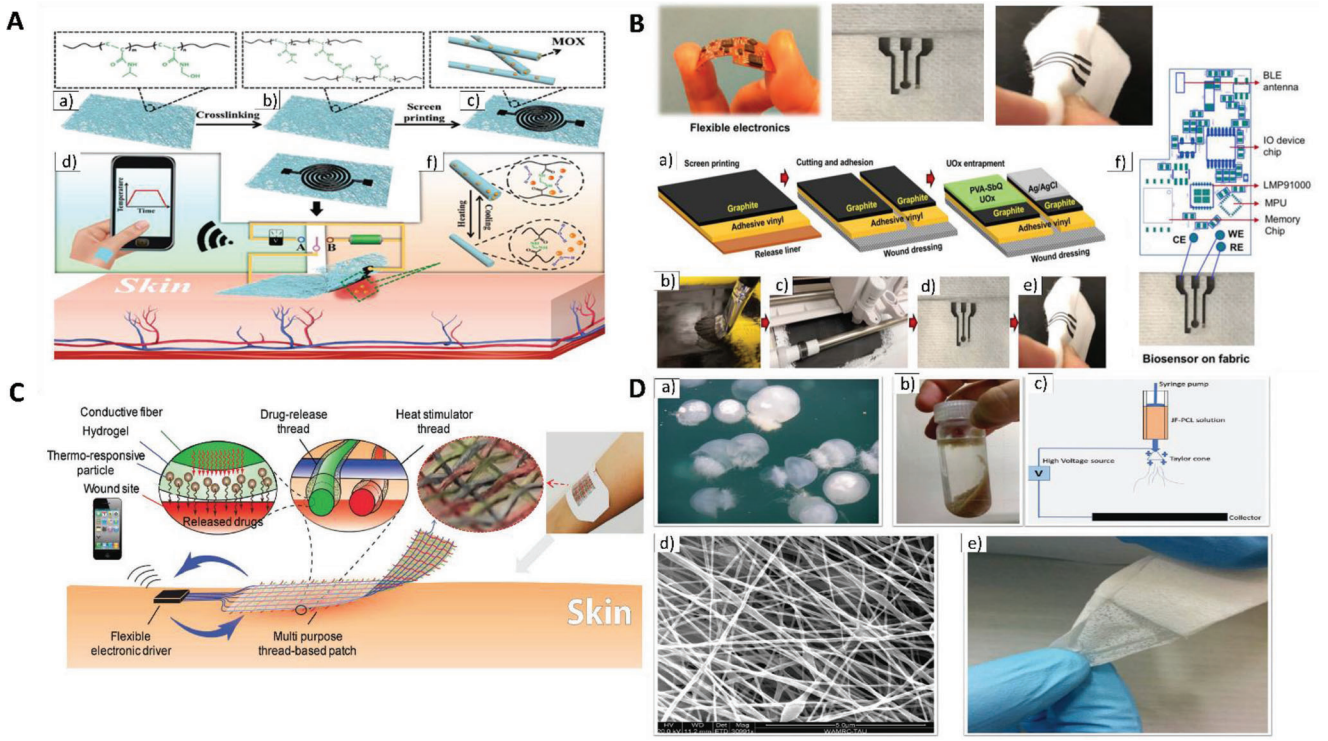

Figure 11. A–D) Different types of electrospun nanomesh-based wound dressings for smart wound care management. A) Schematic view of flexible, breathable electronic skin devices with a mounted conductive pattern with the capability of wound bed temperature-sensing for controlled drug delivery. a) Chemical structure of the thermoresponsive poly(*N*-isopropyl acrylamide-*co*-*N*-methylol acrylamide) (PNHM)-loaded MOX nanomesh. b) Crosslinking process of C-PNHM nanomesh. c) Mounting screen-printed crosslinked SC-PNHM on C-PNHM nanomesh. d) Illustration of the performance of smart integrated temperature sensor on a flexible and breathable on-skin electronic nanomesh for on-demand drug-releasing applications. Reproduced with permission.[92] Copyright 2017, Wiley-VCH GmbH. B) Printed circuit board interfaced with the flexible wound sensor circuit designed for the continuous monitoring of wound healing using a wearable enzymatic uric acid biosensor. a) Different steps in preparation of IOT electrode, b) illustration of the screen-printing method using conductive graphite paste, c) precise electrode design process, d) mounting of a flexible electrode on dressing, e) flexibility of mounted electrode, and f) circuit design of components embedded on the PCB interfaced with the flexible wound sensor. Reproduced with permission.[177] Copyright 2018, Electrochemical Society. C) A schematic view of a smart wound dressing using substrate constructed of the knitted fibers with core electrical heater, covered with a layer of hydrogel encapsulating thermoresponsive drug carriers. Different antibiotics and vascular endothelial growth factors (VEGF) are embedded within the fibers for in vitro elimination of bacterial infection and inducing angiogenesis. Reproduced with permission.[82] Copyright 2020, Wiley-VCH GmbH. D) Jellyfish–PCL nanofibers decorated with in situ generated biotemplated metallic silver nanoparticles (AgNPs) provided a fast and complete wound tissue recovery with potent antibacterial properties on a porcine model. a) Image of the group of jellyfish near the Israeli shores (photo by Amit Lotan). b) Processing jellyfish to biomass. c) Schematic view of jellyfish biomass–PCL electrospinning process. d) ESEM image of JF–PCL nanofibers. e) Optical image of jellyfish–PCL electrospun nanofibers. Reproduced with permission.[106] Copyright 2019, Wiley-VCH GmbH.

capability of CSMNA hydrogels. During the wound healing process, inflammatory reaction at the wound site leads to local skin temperature increment, which induced the temperature-sensitive pNIPAM hydrogel to shrink in the cores of the CSMNA and release VEGF into the wound sites in a sustained manner and promote wound healing and skin regeneration.[205]

9. 3D Printing Technologies for the Development of Wound Dressings

Recently, 3D bioprinting technology has received significant attention as a new area of research in medicine. Diverse applications of this technology in the fabrication of native tissue mimicking structures or biosensing substrates have promised a bright future for the treatment of different types of diseases,[167,197] including skin burns, and chronic wounds.[198] Thanks to the superiority of bioprinting technology in the precise deposition of cells and biomaterials in a 3D orientation fashion, clinical applications of this approach in fabricating appropriate wound dressings promise an auspicious skin regeneration alternative for large skin size defects compared to previous conventional approaches.[199]

Pressure ulcers are identified by infection and frequent bleeding in wound sites in patients with limited mobility. Thus, the development of a system capable of monitoring the wound conditions and continuous reporting the analyzed data to the patients could be essential for preventing the formation of this painful and hard to heal wounds.[200] In a practical strategy, Farooqui and Shamim investigated the potential of injecting printing technology for fabricating a low-cost smart bandage for wireless monitoring wound parameters like irregular bleeding, variations in pH levels, and external pressure at the wound site. This low-cost, disposable, inject printed smart bandage prototype with wireless electronics compartments, can provide long-term data

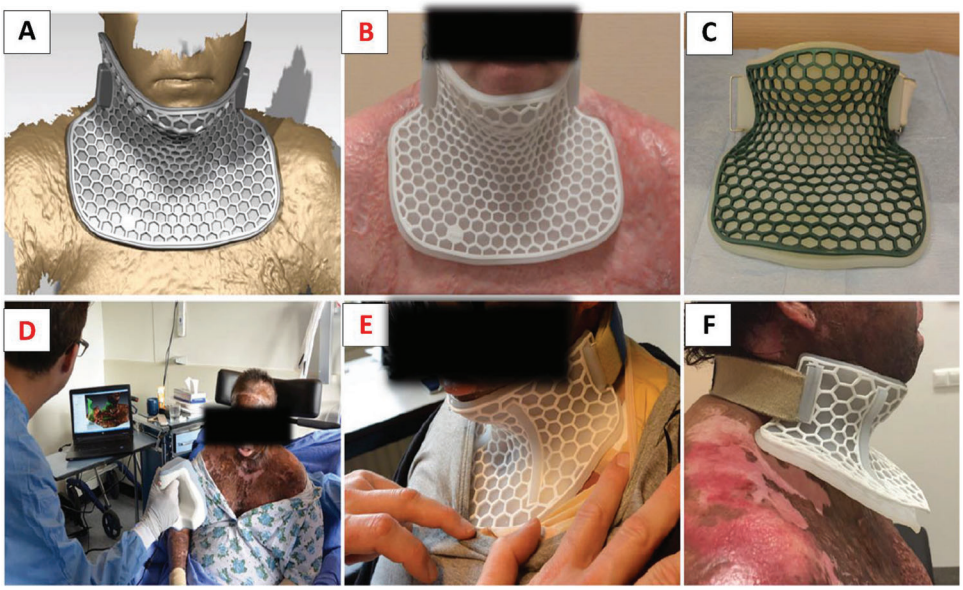

Figure 12. A–F) Schematic view of a patient-specific splint for neck burns. A) Patient-specific computer-aided design (CAD) of neck splint. B) 3D printing of patient-specific neck splints for the treatment of postburn neck contractures. C) 3D-printed prototype of neck splint. D) Contactless optical 3D scanning process for mapping the burned area. E) 3D-printed neck splint on the same patient. F) Healing process after wearing neck splint. Adapted with permission.[173] Copyright 2018, Burn and Trauma.

transition about the healing progression of any type of chronic wounds regardless of size to patients and health care providers with reusable capability. The obtained results from this study revealed the robust potential of this bandage concept to be implemented in daily life and provide an attractive solution for remote monitoring of the wound conditions and consequently reduces the prospect burden on patients and health care services.[201]

The 3D-printed wound dressings have demonstrated a huge potential for facilitating skin defects in the last few years.[201,73] Full-thickness burns are among the skin defects that are difficult to heal, especially for the sensitive parts of the body such as the head and neck. Visscher et al. developed patient-specific 3D printing neck splints for the treatment of postburn neck contractures and demonstrated successful clinical outcomes for improving the treatment process of this hard-to-heal area (**Figure 12**).[173]

In another study, Long et al. fabricated a 3D-printed drug-loaded CS–pectin hydrogel wound dressing. The dressing was loaded with lidocaine hydrochloride to provide antibacterial and pain-relieving activity. This dressing demonstrated an appropriate drug-releasing profile, biodegradability alongside proper biocompatibility.[174]

Molecules, therapeutics, and cells could be encapsulated within the hydrogel to promote the wound healing processes.[204,205] In a study reported by Si et al., a Nafcillin-loaded double-crosslinked network of HA)–methacrylic anhydride (MA) and 3,30-dithiobis (propionyl hydrazide) (DTP)(SH) hydrogels were synthesized as a bioink for the 3D bioprinting of an antibacterial wound dressing. The rheological performance, drug release profile, and cytocompatibility (Live/Dead and CCK-8 assays) of this novel 3D-printed, double-crosslinked HA–SH/HA–MA loaded with Nafcillin, revealed the potential of this hydrogel-based wound dressing for prospective treatment of diabetic foot ulcers.[207]

The limited proper area for harvesting split-thickness skin autografts for substituting in full-thickness skin defects has revealed the urgent need for developing a solution that provides rapid on-site management of wounds with extensive size such as third-degree skin burn. In situ bioprinting also known as ''in vivo" bioprinting is the direct implementation of bioinks to create functional living tissues or organs at a defect site.[10a,207] For this purpose, Albanna et al. proposed an accelerated approach of wound dressing preparation by in situ bioprinting of autologous skin cells for extensive excisional full-thickness wounds. The proposed mobile skin bioprinting system in this study created functional layered dermal fibroblast and epidermal keratinocytes structures like healthy skin tissues.[210]

3D printing enables the fabrication of customized structures like native skin tissues. As a consequence of potential applications of these substrates for skin defects treatment, additional researches are taken in part for developing standardized clinical-grade 3D bioprinters and biocompatible bioinks to enable wider use of this technology in clinical practices (**Table 2**; **Figure 13**).[10a,212]

10. Current Clinical Trial in the Application of the Smart Dressings

Despite the extensive understanding of the wound healing mechanism and development of various wound care products, still, reaching the so-called ''ideal dressing'' with effective clinical outcomes remains an area of intense research. Notwithstanding the recent advances in wearable smart wound bandages and dressings, the bench to bedside transition of these products is challenging.[220]

In traditional dressings, owing to the limited knowledge about wounds and the ruling parameters in the regeneration process,

Table 2. Application of 3D printing technology for fabricating wound dressings, according to the method of printing and used biomaterials.

Printing ink	Cells/organisms	Printing method	Outcomes	Refs.
PhycoTrix sulfated marine-derived polysaccharide	Mouse (L929) fibroblast and human adipose-derived stem cells (hASCs)	3D-Bioplotter (EnvisionTEC, Gladbeck, Germany)	PhycoTrix demonstrated relatively high cell binding affinity and proliferation that could be used as a potent wound dressing	[199]
Antimicrobial metals (zinc, copper, and silver) incorporation with FDA-approved polymer (polycaprolactone: PCL)	Antibacterial efficiency evaluated on *S. aureus*	Hot-melt extrusion	The silver and copper wound dressings showed appropriate bactericidal properties	[213]
Medical-grade polycaprolactone (mPCL)	Human gingival tissue multipotent mesenchymal stem/stromal cells	Melt electrowriting	The regenerative potential of fresh or frozen cell-seeded mPCL-based wound dressing was investigated in a splinted full-thickness excisional wound model in a rat model over six weeks. MSC-seeded 3D-printed biomimetic wound dressings enhanced wound closure with reduced scarring	[167]
Carboxymethylated-periodate oxidized nanocellulose	*Pseudomonas aeruginosa* PAO1	3D-Bioplotter (EnvisionTEC GmbH)	The 3D porous transparent film created a moist wound healing environment with bioresponsive antibacterial properties	[214]
Chitosan dressing crosslinked with genipin and plasticized with glycerol (GLY) and polyethylene glycol (PEG)	Skin fibroblast cell lines	Jet dispenser	Cytotoxicity (MTT) assay on human skin fibroblast cell lines demonstrated acceptable cell viability (more than 90%) after 48 h of treatment, which confirmed the nontoxic origin of the 3D-printed CH-GE-PEG600 films as a promising type of wound dressing to be used for chronic wound healing applications	[208]
Chitosan, alginate, collagen	Human fibroblasts (Nhdf) and keratinocytes (HaCaT)	Hybrid 3D bioprinter by incorporating a 3D home-made low-temperature module into a fused deposition manufacturing (FDM) 3D printer	The 3D-printed chitosan biopolymeric scaffolds showed a faster healing rate in an excisional wound model in rat	[209]
Carboxymethyl cellulose (CMC), alginate	Human skin cells: keratinocyte, fibroblast	3D-Bioplotter (EnvisionTEC GmbH)	Two different dressing fabrication techniques including a 3D bioprinting and electrospinning approaches were implemented to fabricate combined dual drug delivery of nonsteroidal anti-inflammatory drug (NSAID) diclofenac sodium (DCS) and the local anesthetic lidocaine (LID) to the wound site, respectively, based on the wound healing progress	[210]
Chitosan-pectin hydrogel	Epithelial cells	Extrusion-based 3D printer	3D-printed CS-PEC hydrogel incorporating the local anesthetic drug lidocaine hydrochloride (LDC) showed good printability, dimensional integrity, and self-adhesion as a potential wound dressing candidate for wound healing applications	[205]
Satureja cuneifolia-loaded sodium alginate/polyethylene glycol	Fibroblast (L929) cells	Extrusion 3D printer (Hyrel 3D, SDS-5 Extruder, GA, USA)	The 3D-printed scaffolds showed excellent cytocompatibility and antibacterial activities, especially against Gram-positive bacteria	[218]
Silk-sericin-based (SS-based) transparent hydrogel and methacrylic-anhydride-modified gelatin (GelMA)	L929 cells, HaCaT, and HSF	Extrusion-based 3D printing	The 3D constructs showed antimicrobial activities against *Escherichia coli* and *Staphylococcus aureus* strains	[78]
Polydimethylsiloxane with antibacterial nanosilver (iPDMS/AgNPs)	*Staphylococcus aureus* and *Escherichia coli*	3D bioprinter (HKable 3D)	The 3D-printed iPDMS/AgNPs demonstrated biocompatibility and antibacterial activity and also promoted the growth of neoepithelial and granulation tissue in a murine wound model	[187]
Polyacrylamide (PAM)/hydroxypropyl methylcellulose (HPMC) hydrogel	L929 cells/Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213) and Gram-negative bacteria *Escherichia coli* (ATCC 25922)	Fused deposition modeling (FDM)	The AgNP crosslinked superporous hydrogel dressings promoted the healing of the infected wounds and restrained the scarring	[212]

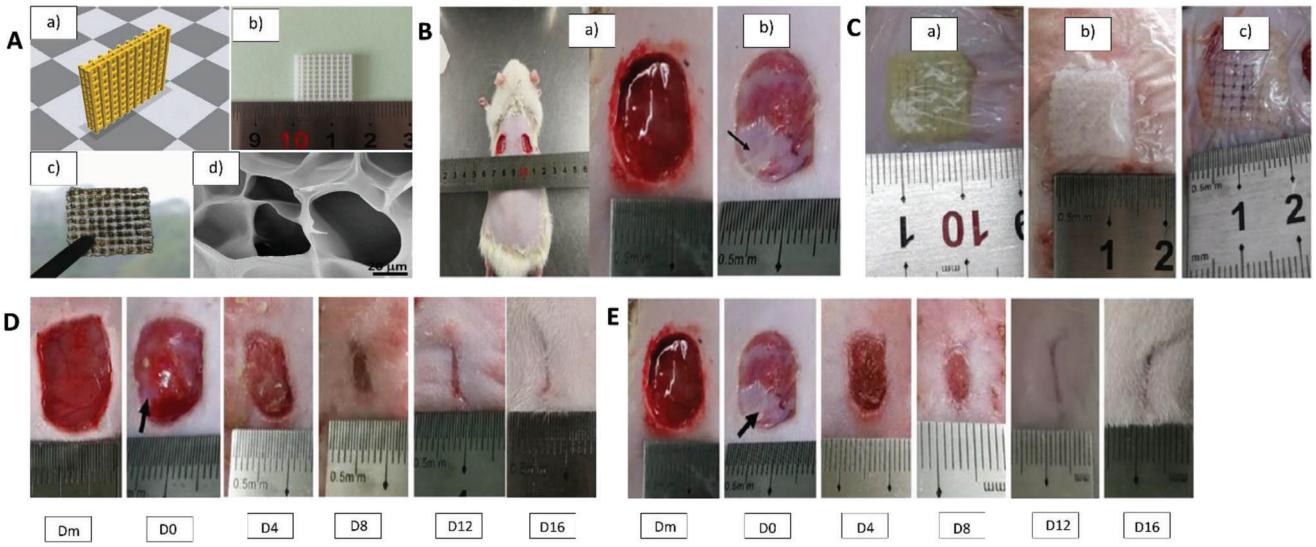

Figure 13. A–E) In vivo applications of 3D-printed superporous hydrogel wound dressing prototype. A-a) Computer-aided design prototype of dressing, b) 3D-printed PLA template (15 × 15 × 3 mm; pore diameter: 1.2 × 1.2 × 0.8 mm), c) 3D-printed superporous AgNP–PAM/HPMC hydrogel dressings prototype, and d) SEM image of the as-prepared superporous hydrogel dressing (scale bar: 20 μm). B) Animal study for the *S. aureus*-infected wounds on SD rats. a) Established fresh wounds on the dorsal side of SD rats, and b) *S. aureus* wound infection 24 h after wound establishment. C-a–c) Applying different superporous hydrogel dressings AgNP–PAM/HPMC, PAM/HPMC, and PAM/CS for covering the infected wounds. Panels (D) and (E) demonstrate the healing process of a bacterially infected wound treated by different types of superporous hydrogel-based wound dressings over time. Reproduced with permission.[181] Copyright 2019, American Chemical Society.

dressing material composition was the main factor for clinical trial evaluation. In the early 19th century, sterilized gauze was extensively used as a surgical dressing. Although the clinical usage of these types of dressing proved at that time as the only option for covering the wounds to prevent further infection, the damages created after removing these dressing hindered the usage of these products in the late 20th century.[221]

Moisture retentive capability is one of the most important characteristics of an ideal dressing. The healing process will be amplified if the applied dressing maintained the wound environment moist. Among the variety of modern dressing with the potential of moisture-retentive, FDA-approved dressing types include films, hydrogels, hydrocolloids, foams, alginates, and hydrofibers were developed for clinical trial practices.[211]

Films are transparent, the self-adhesive thin layer of polyurethane with characteristics including, elastic structure, easily shape conforming, water/gas permeability, proper for wounds with complex shape and angle with the close area and low-level exudate superficial lacerations. TegadermTM (3M) is one of the film-based wound dressings in the market for first-degree burns or superficial lacerations for clinical practices.[24] Changeable physiochemical properties of hydrogel-based wound dressing have created a dynamically responsive environment that is ideal for partial-thickness burns and chronic wounds. According to the high-water content, hydrogels are considered the best option for dry wounds to rehydrate and maintain a moist environment. Painful, nonexudative wounds are a class of wounds that hydrogel dressing can successfully improve the pathologic conditions. Silver hydrogels including SilvaSorb (Medline), Elasto-GelTM (SW Technologies), FlexiGelTM (Smith & Nephew), and KendallTM CurafilTM (Covidien), and (Repithel) are commercially available hydrogel dressing with effective results for dry wounds.[212,222]

In a randomized observer-blinded, phase III clinical study, Vogt and co-workers investigated the effect of poly(*N*-vinylpyrrolidone) (PVP)–iodine-containing a 3% iodine concentration (Repithel) skin mesh on promoting epithelialization in comparison to typical wound gauze (Jelonet) in 167 patients. The results demonstrated that the targeted defect site which received Repithel dressing, healed significantly faster (9.4 vs 12.4 days; $p < 0.0001$), compared to the gauze (Jelonet).[224] In another report, Homann et al. investigated the skin burn healing potency of a novel PVP–I-loaded liposome hydrogel in comparison to a market medical-approved product (silver sulfadiazine cream) in a randomized controlled trial. This study demonstrated that the novel hydrogel dressing was capable of promoting wound healing because of the controlled release system integrated into the dressing construction.[192]

The negative pressure wound therapy (NPWT) was developed in the early 20th century as a robust approach for the treatment of pressure ulcers. In this method, the rate of granulation and epithelialization for draining wounds was promoted by applying subatmospheric pressure.[222] With the advances in material science and fabrication technologies, the more sophisticated dressing was developed, and various practices were considered to evaluate their clinical applications. For over 20 years, negative pressure wound therapy has played a key role in the treatment of skin tissue wounds caused by diseases or surgical incisions.[225] The efficacy of this type of wound dressing in decreasing wound size and scarring, and amplifying the healing process have been clinically proven through numerous clinical trial studies.[213] In an extensive comparative clinical trial report over forty patients with

a diabetic foot ulcer, the effect of two different negative pressure therapy, a low-pressure silicone-covered dressing (75 mmHg) and a high-pressure polyurethane foam (125 mmHg) negative-pressure wound dressing were examined for up to 4 weeks. Results showed both types of dressings can successfully reduce the wound size which demonstrated the potency of the negative pressure wound dressing in the treatment of chronic wounds.[227]

In a comparative study, Cetinkalp et al. evaluated the clinical efficiency and safety of a composite drug-loaded bilayered dermal matrix (Dermalix) with a standard wound care product in a randomized trial. In this study, wound healing was investigated in 48 patients with diabetic foot ulcers in 4-week and 2-month follow-up. The fabricated dressings were composed of collagen–laminin containing resveratrol-loaded HA and dipalmitoyl phosphatidylcholine-based microparticles for promoting the healing process. The results of this clinical study demonstrated that "Dermalix" can increase chronic wound healing rate two times faster than the standard dressing.[215]

The importance of providing a moist environment by a wound dressing has been investigated through numerous studies.[215] The "TheraGauze" is a new polymer-dressing designed to regulate the moisture level of the entire surface of a wound. This smart selective moist retaining dressing, balance the moisture level of the entire wound surface by absorbing/delivering moisture only where it is needed.[198] Although smart dressings have been scientifically demonstrated as the potential next generation of wound dressings under real-time monitoring and reporting the wound healing status, no significant clinical trials have been reported. By regulating an appropriate preclinical testing regulatory principle for these automated (feedback-controlled) types of wound bandages, extensive preclinical models are mandatory to facilitate the process of getting approval from the wound management systems.[96]

11. Regulatory Aspects of Wound Dressings

According to the World Health Organization definition of medical devices, any materials, instrument, apparatus, appliance/software, whether used alone or in combination, to monitor the human health condition is considered as a medical device. A medical device is a product that is used for various medical purposes including diagnosis or therapy. Compared to the biochemical effects of pharmaceutical molecules, the effect of the medical device on patients is primarily physical. Based on the defined characteristics related to a medical device, wound dressings are classified as medical devices. Moreover, based on the different types of wounds, they are categorized into different classes.[199]

Wound care management systems have a specific policy for wound dressing. In most of the countries, the proposed guidelines are similar, nonetheless, there are still differences in dossier content submission, for example in the evaluation procedures. Thanks to the harmonization law in dossier submission format of licenses for a medical device, due to the mutual agreement and similarities in regulatory factors for a specific product, if a medical device is approved in one country, that product could be approved and marketed more rapidly in another country. For example, in Australia, dressings with a CE mark are acceptable for import/export. What causes these differences in guidelines is the inability of manufacturing the device similar to the guidelines. The following introduces the challenges for manufacturers in different countries for regulating a medical device such as wound dressing.[216]

According to the US FDA guidelines, simple and minimally invasive bandages that are utilized in general hospitals and personal daily applications including fibrillar, hydrophilic, occlusive, and nonresorbable gauze/sponge are designated as Class I of wound dressings. Other types of dressing products that contain drugs/bioactive molecules, biomaterials, and human or animal cellular moieties are considered as the Class II and III of wound dressings.

In the Canada health organization guideline, Class I of wound dressings are defined as mechanical barriers to the wound's external environment or for compression or absorption of wound exudates. Also, noninvasive dressings that come into the contact with the injured skin are considered in the Class I category. Furthermore, all noninvasive devices that are intended to be in close contact with the injured skin, to promote the healing process by providing a moist environment along with relief of pain, are classified as Class II of wound dressings.

In European Medical Device Directive (MDD) organization, factors including the degree of risk associated with the device usage, the amount of time the device is in contact with the human body, and the degree of invasiveness of the device determine the classification of medical devices. In the European MDD guideline, wound dressings are classified as medical devices. According to the European MDD provisions, all-noninvasive devices, which come into contact with the injured skin are in Class I. Additionally, dressings that are implemented to enhance the healing process by controlling the level of moisture, pH, and temperature at the wound site, are classified as Class II a and b dressings. The European MDD classifies all the manufactured devices that utilizing animal tissues as Class III.

Together, by comparing the guidelines in the regulatory aspects of wound dressing classification in different countries in global health managements, it can be concluded that all the mentioned countries' regulatory principles are following a similar guideline in determining the classification of wound dressings.[216]

Different wound care products require different sterilization strategies. It has been reported that there is no specific sterilization procedure for dressing microbial controlling. Recent advances in microelectronic sensors and wireless communications for manufacturing wound monitoring devices or dressings have become a promising strategy for better regulation of wound care systems. However, there is a certain limitation in some types of sensors for integration into the wireless wearable wound monitoring dressings. The capability of the sensors to become miniaturized within the dressing bed, biocompatibility, flexibility, moisture and biofouling resistance, and disposability are among the major challenges which should be considered in defining the regulatory outlines for these products.[217]

Nowadays, advancements in technology, and human knowledge in understanding the disease mechanism, have improved the fabrication of medical devices. Numerous generic medical devices are developed in the market for various types of diseases which have turned them into an important part of the health care system.[231] Wound size and type are among the major challenges for the global health organization for establishing a

universal guideline for a dressing. The dynamic characteristics of the chronic wounds and the lack of an ideal animal model for estimating the wound's condition progress revealed the absence of a suitable guideline for clinical trials.[218]

Wound dressings are the most common medical devices that play a critical role in the health care systems. Further investigations are required for the establishment of universal regulatory frameworks for the newly manufactured dressings. Therefore, developing a proper dressing must be in line with the wound progression or deterioration condition. Consequently, current regulatory principles must be updated regularly and implemented during the manufacturing process.[219]

12. Conclusions and Future Perspectives

Cutaneous wounds as complex and aggressive skin defects, still, remain a major health issue for the world healthcare systems. Universal increase in the number of patients with nonhealing skin defects such as diabetic ulcers, skin burns, bedsores, physical trauma, etc., notably in the elderly population, imposes a huge social and economic burden.[220]In the last few years, with the breakthroughs in the material fabrication technologies and increased knowledge in the formerly unknown cellular and molecular pathways involved in wound healing, a broad range of wound dressings with multiple functions have been developed to accelerate the healing process of these nonhealing disorders.[221]

Continuous efforts need to be considered in resolving challenges for the development of practical dressing with the capacity to monitor a variety of parameters involved the wound healing. A better understanding of the biochemical pathways involved in the wound healing process has promoted the development of advanced dressings. Recently, some of these critical molecules, immunomodulatory cytokines, growth factors, miRNA, siRNA, exosomes, or cells have been combined/integrated within the dressings to improve the regenerative processes. In the last recent years, the integration of flexible and wearable microelectronic sensors into the dressings has introduced the next generation of wound dressings with an automated function that not only can cover the wound but also can actively monitor the wound conditions and apply the required actions for wound's environment management by real-time analyzing physiological signals of wound's exudate. However, there are numerous challenges yet lie in front of these types of functional dressings to be used in clinical practices.[10a,207]

Recently, the development of smart wound dressing integrated with the wearable sensors have advanced, but there are many challenges that still need to be addressed. Due to the subtle changes in the biomarkers at the early phases of wound infection, the sensitivity of wearable sensors and their accuracy require further improvement.[222]

In addition, due to the breakthroughs in fabricating miniaturized electronic sensors and their promising functions in biomedical applications, some have implemented the smart dressing in developing the next generation of interactive textiles for different purposes, for example in developing smart clothing.[223] Integrating versatile sensors into textiles enables the capture, analyze and monitoring of the physiological signals of individuals. Such sensors also have been used to respond to the changes in physiological conditions in the human body as well as temperature, moisture, or movement.[224,225] Several sportswear producing companies have explored new technologies to utilize a dressing's intelligence to monitor athletics' abilities on the court.[226] Monitoring athletes performance during the competition or training has been difficult in the past, but thanks to the embedded microsensors in sportswear, these smart clothing can monitor the most important physiological parameters for athletes including breathing patterns, heartbeat, blood pressure, the composition of body fluids (sweat, urine, etc.)[227] For instance, to monitor the heartbeat of athletes during training, as an important parameter for evaluating athlete's physical readiness, Perego et al. developed one single lead electromyography that was fabricated by two knitted electrodes integrated into the vest and shirt at thorax level. This smart clothing has been engineered for identifying possible countermeasures to altitude sickness during skyrunning.[228]

In this review, we have critically reviewed various types of wound dressings from traditional types to smart multifunctional ones. Developments made in the automated wound dressings would play a determinative role in the wound care management system by improving the patient's comfort.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

A.S. conceptualized the paper and M.F. prepared the original draft. Formal analysis and investigation were carried out by both M.F. and A.S. Both the authors were involved in writing, review, and editing.

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biomaterials, burn, chronic wounds, drug delivery, immunomodulation, microelectronic sensors

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[1] S. A. Eming, P. Martin, M. Tomic-Canic, *Sci. Transl. Med.* **2014**, *6*, 265sr6.
[2] S. Dhivya, V. V. Padma, E. Santhini, *BioMedicine* **2015**, *5*, 22.
[3] C. Lindholm, R. Searle, *Int. Wound J.* **2016**, *13*, 5.
[4] J. G. Powers, C. Higham, K. Broussard, T. J. Phillips, *J. Am. Acad. Dermatol.* **2016**, *74*, 607.
[5] M. Olsson, K. Järbrink, U. Divakar, R. Bajpai, Z. Upton, A. Schmidtchen, J. Car, *Wound Repair Regener.* **2019**, *27*, 114.
[6] K. Järbrink, G. Ni, H. Sönnergren, A. Schmidtchen, C. Pang, R. Bajpai, J. Car, *Syst. Rev.* **2017**, *6*, 15.
[7] S. O'Callaghan, P. Galvin, Z. Moore, R. Derwin, C. O'Mahony, 'Smart Dressings' for Advanced Woundcare: A Review.
[8] M. E. Aljghami, S. Saboor, S. Amini-Nik, *Ann. Biomed. Eng.* **2019**, *47*, 659.
[9] J. S. Boateng, K. H. Matthews, H. N. E. Stevens, G. M. Eccleston, *J. Pharm. Sci.* **2008**, *97*, 2892.
[10] a) E. M. Tottoli, R. Dorati, I. Genta, E. Chiesa, S. Pisani, B. Conti, *Pharmaceutics* **2020**, *12*, 735; b) P. Vowden, K. Vowden, *Wounds Int.* **2016**, *7*, 10.

[11] L. J. Borda, F. E. Macquhae, R. S. Kirsner, *Curr. Dermatol. Rep.* **2016**, *5*, 287.
[12] Y. Qin, H.-J. Kwon, M. M. R. Howlader, M. J. Deen, *RSC Adv.* **2015**, *5*, 69086.
[13] Y. Qin, *J. Text. Inst.* **2001**, *92*, 127.
[14] A. Sood, M. S. Granick, N. L. Tomaselli, *Adv. Wound Care* **2014**, *3*, 511.
[15] P. Zarrintaj, A. S. Moghaddam, S. Manouchehri, Z. Atoufi, A. Amiri, M. A. Amirkhani, M. A. Nilforoushzadeh, M. R. Saeb, M. R. Hamblin, M. Mozafari, *Nanomedicine* **2017**, *12*, 2403.
[16] R. Rahimi, U. Brener, M. Ochoa, B. Ziaie, in *2017 IEEE 30th Int. Conf. on Micro Electro Mechanical Systems (MEMS)*, IEEE, Piscataway, NJ **2017**.
[17] K. F. Cutting, *J. Wound Care* **2010**, *19*, 4.
[18] S. Seaman, *J. Am. Podiatr. Med. Assoc.* **2002**, *92*, 24.
[19] J. G. Powers, L. M. Morton, T. J. Phillips, *Dermatol. Ther.* **2013**, *26*, 197.
[20] S. Thomas, *World Wide Wounds* **2008**. http://www.worldwidewounds.com/2008/march/Thomas/Maceration-and-the-role-of-dressings.html?newwindow=true.
[21] P. A. Coulombe, *J. Invest. Dermatol.* **2003**, *121*, 219.
[22] I. R. Sweeney, M. Miraftab, G. Collyer, *Int. Wound J.* **2012**, *9*, 601.
[23] Z. Obagi, G. Damiani, A. Grada, V. Falanga, *Surg. Technol. Int.* **2019**, *35*, 50.
[24] K. C. Broussard, J. G. Powers, *Am. J. Clin. Dermatol.* **2013**, *14*, 449.
[25] G. Dabiri, E. Damstetter, T. Phillips, *Adv. Wound Care* **2016**, *5*, 32.
[26] S. M. Bishop, M. Walker, A. A. Rogers, W. Y. J. Chen, *J. Wound Care* **2003**, *12*, 125.
[27] S. M. Mousavi, M. Zarei, S. A. Hashemi, S. Ramakrishna, W.-H. Chiang, C. W. Lai, A. Gholami, N. Omidifar, M. Shokripour, *Symmetry* **2020**, *12*, 1100.
[28] P. Alves, M. Santos, S. Mendes, S. P. Miguel, K. D. De Sá, C. S. D. Cabral, I. J. Correia, P. Ferreira, *Polymers* **2019**, *11*, 653.
[29] P. I. Morgado, P. F. Lisboa, M. P. Ribeiro, S. P. Miguel, P. C. Simões, I. J. Correia, A. Aguiar-Ricardo, *J. Membr. Sci.* **2014**, *469*, 262.
[30] H. Khalil, M. Cullen, H. Chambers, M. Carroll, J. Walker, *Wound Repair Regener.* **2015**, *23*, 550.
[31] D. Chouhan, N. Dey, N. Bhardwaj, B. B. Mandal, *Biomaterials* **2019**, *216*, 119267.
[32] A. Bianchera, O. Catanzano, J. Boateng, L. Elviri, *Therapeutic Dressings and Wound Healing Applications*, John Wiley & Sons Ltd, Hoboken, NJ **2020**, pp. 337–366.
[33] M. Ochoa, R. Rahimi, J. Zhou, H. Jiang, C. K. Yoon, D. Maddipatla, B. B. Narakathu, V. Jain, M. M. Oscai, T. J. Morken, R. H. Oliveira, G. L. Campana, O. W. Cummings, M. A. Zieger, R. Sood, M. Z. Atashbar, B. Ziaie, *Microsyst. Nanoeng.* **2020**, *6*, 46.
[34] S. T. Tan, N. Winarto, R. Dosan, P. B. Aisyah, *Open Dermatol. J.* **2019**, *13*, 27.
[35] B. Rogina-Car, J. Rogina, E. Govorčin Bajsić, A. Budimir, *J. Ind. Text.* **2020**, *49*, 1100.
[36] C. Weller, V. Team, *Advanced Textiles for Wound Care*, Elsevier, Amsterdam **2019**, pp. 105–134.
[37] S. D'Alessandro, A. Magnavacca, F. Perego, M. Fumagalli, E. Sangiovanni, M. Prato, M. Dell'Agli, N. Basilico, *BioMed Res. Int.* **2019**, *2019*, 2626374.
[38] T. Helfman, L. Ovington, V. Falanga, *Clin. Dermat.* **1994**, *12*, 121.
[39] Y. P. Afsharian, M. Rahimnejad, *Polym. Test.* **2020**, *93*, 106952.
[40] A. E. Stoica, C. Chircov, A. M. Grumezescu, *Molecules* **2020**, *25*, 2699.
[41] B. A. Badeau, C. A. Deforest, *Annu. Rev. Biomed. Eng.* **2019**, *21*, 241.
[42] F. Piraino, Š. Selimović, *BioMed Res. Int.* **2015**, *2015*, 403801.
[43] F. Khan, M. Tanaka, *Int. J. Mol. Sci.* **2018**, *19*, 17.
[44] R. Z. Murray, Z. E. West, A. J. Cowin, B. L. Farrugia, *Burns Trauma* **2019**, *7*, 2.
[45] J. Deng, P. Y. Li, H. Cheng, *Smart Materials for Tissue Engineering: Applications*, Royal Society of Chemistry, London **2017**, pp. 258–289.
[46] L. Tan, J. Hu, H. Huang, J. Han, H. Hu, *Int. J. Biol. Macromol.* **2015**, *79*, 469.
[47] A. Soneja, M. Drews, T. Malinski, *Pharmacol. Rep.* **2005**, *57*, 108.
[48] T. Tang, H. Jiang, Y. Yu, F. He, S.-z. Ji, Y.-y. Liu, Z.-s. Wang, S.-c. Xiao, C. Tang, G.-Y. Wang, Z.-F. Xia, *Int. J. Nanomed.* **2015**, *10*, 6571.
[49] A. Lendlein, M. Behl, B. Hiebl, C. Wischke, *Expert Rev. Med. Devices* **2010**, *7*, 357.
[50] G. Li, Y. Wang, S. Wang, Z. Liu, Z. Liu, J. Jiang, *Macromol. Mater. Eng.* **2019**, *304*, 1800603.
[51] J. J. Song, H. H. Chang, H. E. Naguib, *Polymer* **2015**, *56*, 82.
[52] L. K. Jang, G. K. Fletcher, M. B. B. Monroe, D. J. Maitland, *J. Biomed. Mater. Res., Part A* **2020**, *108*, 1281.
[53] T. L. Landsman, T. Touchet, S. M. Hasan, C. Smith, B. Russell, J. Rivera, D. J. Maitland, E. Cosgriff-Hernandez, *Acta Biomater.* **2017**, *47*, 91.
[54] R. G. Frykberg, J. Banks, *Adv. Wound Care* **2015**, *4*, 560.
[55] M. Bates, *IEEE Pulse* **2020**, *11*, 22.
[56] C. Murphy, L. Atkin, T. Swanson, M. Tachi, Y. K. Tan, M. V. De Ceniga, D. Weir, R. Wolcott, J. Černohorská, G. Ciprandi, J. Dissemond, G. A. James, J. Hurlow, J. L. Lázaro Martínez, B. Mrozikiewicz-Rakowska, P. Wilson, *J. Wound Care* **2020**, *29*, S1.
[57] H. B. Schultz, R. B. Vasani, A. M. Holmes, M. S. Roberts, N. H. Voelcker, *ACS Appl. Bio Mater.* **2019**, *2*, 704.
[58] A. M. Ribeiro, T. H. S. Flores-Sahagun, *Int. J. Polym. Mater. Polym. Biomater.* **2020**, *69*, 979.
[59] A. Scalamandré, K. M. Bogie, *Innovations and Emerging Technologies in Wound Care*, Elsevier, Amsterdam **2020**, pp. 225–244.
[60] P. Mostafalu, A. Tamayol, R. Rahimi, M. Ochoa, A. Khalilpour, G. Kiaee, I. K. Yazdi, S. Bagherifard, M. R. Dokmeci, B. Ziaie, S. R. Sonkusale, A. Khademhosseini, *Small* **2018**, *14*, 1703509.
[61] G. Kiaee, P. Mostafalu, M. Samandari, S. Sonkusale, *Adv. Healthcare Mater.* **2018**, *7*, 1800396.
[62] C. Shi, C. Wang, H. Liu, Q. Li, R. Li, Y. Zhang, Y. Liu, Y. Shao, J. Wang, *Front. Bioeng. Biotechnol.* **2020**, *8*, 182.
[63] F. Vivaldi, D. Santalucia, N. Poma, A. Bonini, P. Salvo, L. Del Noce, B. Melai, A. Kirchhain, V. Kolivoška, R. Sokolová, M. Hromadová, F. Di Francesco, *Sens. Actuators, B* **2020**, *322*, 128650.
[64] Y. Li, Y. Mao, C. Xiao, X. Xu, X. Li, *RSC Adv.* **2020**, *10*, 21.
[65] P. Kassal, M. Zubak, G. Scheipl, G. J. Mohr, M. D. Steinberg, I. Murković Steinberg, *Sens. Actuators, B* **2017**, *246*, 455.
[66] Q. Pang, D. Lou, S. Li, G. Wang, B. Qiao, S. Dong, L. Ma, C. Gao, Z. Wu, *Adv. Sci.* **2020**, *7*, 1902673.
[67] J. H. Oh, S. Y. Hong, H. Park, S. W. Jin, Y. R. Jeong, S. Y. Oh, J. Yun, H. Lee, J. W. Kim, J. S. Ha, *ACS Appl. Mater. Interfaces* **2018**, *10*, 7263.
[68] P. Mostafalu, S. Amugothu, A. Tamayol, S. Bagherifard, M. Akbari, M. R. Dokmeci, A. Khademhosseini, S. Sonkusale, in *2015 IEEE Biomedical Circuits and Systems Conf. (BioCAS)*, IEEE, Piscataway, NJ **2015**.
[69] S. D. Milne, I. Seoudi, H. Al Hamad, T. K. Talal, A. A. Anoop, N. Allahverdi, Z. Zakaria, R. Menzies, P. Connolly, *Int. Wound J.* **2016**, *13*, 1309.
[70] C. Scott, S. Cameron, J. Cundell, A. Mathur, J. Davis, *Curr. Opin. Electrochem.* **2020**, *23*, 31.
[71] M. Sharifuzzaman, A. Chhetry, M. A. Zahed, S. H. Yoon, C. I. Park, S. Zhang, S. Chandra Barman, S. Sharma, H. Yoon, J. Y. Park, *Biosens. Bioelectron.* **2020**, *169*, 112637.
[72] M. F. Farooqui, A. Shamim, *Sci. Rep.* **2016**, *6*, 28949.
[73] M. F. Farooqui, A. Shamim, *Sci. Rep.* **2016**, *6*, 28949.
[74] A. Mclister, J. Mchugh, J. Cundell, J. Davis, *Adv. Mater.* **2016**, *28*, 5732.
[75] S. Kapoor, S. C. Kundu, *Acta Biomater.* **2016**, *31*, 17.

[76] S. Bagherifard, A. Tamayol, P. Mostafalu, M. Akbari, M. Comotto, N. Annabi, M. Ghaderi, S. Sonkusale, M. R. Dokmeci, A. Khademhosseini, *Adv. Healthcare Mater.* **2016**, *5*, 175.
[77] L. Chengnan, Q. Pagneux, A. Voronova, A. Barras, A. Abderrahmani, V. Plaisance, V. Pawlowski, N. Hennuyer, B. Staels, L. Rosselle, N. Skandrani, M. Li, R. Boukherroub, S. Szunerits, *Nanoscale* **2019**, *11*, 15810.
[78] C.-S. Chen, F. Zeng, X. Xiao, Z. Wang, X.-L. Li, R.-W. Tan, W.-Q. Liu, Y.-S. Zhang, Z.-D. She, S.-J. Li, *ACS Appl. Mater. Interfaces* **2018**, *10*, 33879.
[79] Y. Hattori, L. Falgout, W. Lee, S.-Y. Jung, E. Poon, J. W. Lee, I. Na, A. Geisler, D. Sadhwani, Y. Zhang, Y. Su, X. Wang, Z. Liu, J. Xia, H. Cheng, R. C. Webb, A. P. Bonifas, P. Won, J.-W. Jeong, K.-I. Jang, Y. M. Song, B. Nardone, M. Nodzenski, J. A. Fan, Y. Huang, D. P. West, A. S. Paller, M. Alam, W.-H. Yeo, J. A. Rogers, *Adv. Healthcare Mater.* **2014**, *3*, 1597.
[80] a) M. Khatib, O. Zohar, W. Saliba, H. Haick, *Adv. Mater.* **2020**, *32*, 2000246; b) H. Wang, G. Pastorin, C. Lee, *Adv. Sci.* **2016**, *3*, 1500441.
[81] L. Shi, X. Liu, W. Wang, L. Jiang, S. Wang, *Adv. Mater.* **2019**, *31*, 1804187.
[82] A. Tamayol, A. Hassani Najafabadi, P. Mostafalu, A. K. Yetisen, M. Commotto, M. Aldhahri, M. S. Abdel-Wahab, Z. I. Najafabadi, S. Latifi, M. Akbari, N. Annabi, S. H. Yun, A. Memic, M. R. Dokmeci, A. Khademhosseini, *Sci. Rep.* **2017**, *7*, 9220.
[83] B. Mirani, E. Pagan, B. Currie, M. A. Siddiqui, R. Hosseinzadeh, P. Mostafalu, Y. S. Zhang, A. Ghahary, M. Akbari, *Adv. Healthcare Mater.* **2017**, *6*, 1700718.
[84] H. Derakhshandeh, S. S. Kashaf, F. Aghabaglou, I. O. Ghanavati, A. Tamayol, *Trends Biotechnol.* **2018**, *36*, 1259.
[85] Y. Zhu, J. Zhang, J. Song, J. Yang, Z. Du, W. Zhao, H. Guo, C. Wen, Q. Li, X. Sui, L. Zhang, *Adv. Funct. Mater.* **2020**, *30*, 1905493.
[86] P. Mostafalu, G. Kiaee, G. Giatsidis, A. Khalilpour, M. Nabavinia, M. R. Dokmeci, S. Sonkusale, D. P. Orgill, A. Tamayol, A. Khademhosseini, *Adv. Funct. Mater.* **2017**, *27*, 1702399.
[87] a) H. Lee, T. K. Choi, Y. B. Lee, H. R. Cho, R. Ghaffari, L. Wang, H. J. Choi, T. D. Chung, N. Lu, T. Hyeon, S. H. Choi, D.-H. Kim, *Nat. Nanotechnol.* **2016**, *11*, 566; b) E. J. Bunggulawa, W. Wang, T. Yin, N. Wang, C. Durkan, Y. Wang, G. Wang, *J. Nanobiotechnol.* **2018**, *16*, 81.
[88] S. Saghazadeh, C. Rinoldi, M. Schot, S. S. Kashaf, F. Sharifi, E. Jalilian, K. Nuutila, G. Giatsidis, P. Mostafalu, H. Derakhshandeh, K. Yue, W. Swieszkowski, A. Memic, A. Tamayol, A. Khademhosseini, *Adv. Drug Delivery Rev.* **2018**, *127*, 138.
[89] P. Mostafalu, W. Lenk, M. R. Dokmeci, B. Ziaie, A. Khademhosseini, S. R. Sonkusale, *IEEE Trans. Biomed. Circuits Syst.* **2015**, *9*, 670.
[90] C. Zheng, C. Liu, H. Chen, N. Wang, X. Liu, G. Sun, W. Qiao, *Int. J. Biol. Macromol.* **2019**, *132*, 1098.
[91] G.-D. Fu, L.-Q. Xu, F. Yao, G.-L. Li, E.-T. Kang, *ACS Appl. Mater. Interfaces* **2009**, *1*, 2424.
[92] M. Gong, P. Wan, D. Ma, M. Zhong, M. Liao, J. Ye, R. Shi, L. Zhang, *Adv. Funct. Mater.* **2019**, *29*, 1902127.
[93] Z. Karahaliloglu, E. Kilicay, E. B. Denkbas, *Artif. Cells, Nanomed., Biotechnol.* **2017**, *45*, 1172.
[94] H. Chen, R. Cheng, X. Zhao, Y. Zhang, A. Tam, Y. Yan, H. Shen, Y. S. Zhang, J. Qi, Y. Feng, L. Liu, G. Pan, W. Cui, L. Deng, *NPG Asia Mater.* **2019**, *11*, 3.
[95] R. Jamaledin, C. K. Y. Yiu, E. N. Zare, L.-N. Niu, R. Vecchione, G. Chen, Z. Gu, F. R. Tay, P. Makvandi, *Adv. Mater.* **2020**, *32*, 2002129.
[96] H. Derakhshandeh, F. Aghabaglou, A. Mccarthy, A. Mostafavi, C. Wiseman, Z. Bonick, I. Ghanavati, S. Harris, C. Kreikemeier-Bower, S. M. Moosavi Basri, J. Rosenbohm, R. Yang, P. Mostafalu, D. Orgill, A. Tamayol, *Adv. Funct. Mater.* **2020**, *30*, 1905544.
[97] R. S. Ambekar, B. Kandasubramanian, *Eur. Polym. J.* **2019**, *117*, 304.
[98] S. L. Percival, K. E. Hill, D. W. Williams, S. J. Hooper, D. W. Thomas, J. W. Costerton, *Wound Repair Regener.* **2012**, *20*, 647.
[99] A. Bal-Öztürk, B. Özkahraman, Z. Özbaş, G. Yaşayan, E. Tamahkar, E. Alarçin, *J. Biomed. Mater. Res., Part B* **2020**, *109*, 703.
[100] N. Thet, D. Alves, J. Bean, S. Booth, J. Nzakizwanayo, A. Young, B. V. Jones, A. T. A. Jenkins, *ACS Appl. Mater. Interfaces* **2016**, *8*, 14909.
[101] J. Zhou, D. Yao, Z. Qian, S. Hou, L. Li, A. T. A. Jenkins, Y. Fan, *Biomaterials* **2018**, *161*, 11.
[102] A. G. Berger, J. J. Chou, P. T. Hammond, *Adv. Wound Care* **2020**.
[103] L. Jiang, S. C. J. Loo, *ACS Appl. Bio Mater.* **2020**, *4*, 3849.
[104] S. P. Miguel, D. R. Figueira, D. Simões, M. P. Ribeiro, P. Coutinho, P. Ferreira, I. J. Correia, *Colloids Surf., B* **2018**, *169*, 60.
[105] G. Rivero, M. Meuter, A. Pepe, M. G. Guevara, A. R. Boccaccini, G. A. Abraham, *Colloids Surf., A* **2020**, *587*, 124313.
[106] R. Nudelman, H. Alhmoud, B. Delalat, S. Fleicher, E. Fine, T. Guliakhmedova, R. Elnathan, A. Nyska, N. H. Voelcker, M. Gozin, S. Richter, *Adv. Funct. Mater.* **2019**, *29*, 1902783.
[107] G. A. James, E. Swogger, R. Wolcott, E. D. Pulcini, P. Secor, J. Sestrich, J. W. Costerton, P. S. Stewart, *Wound Repair Regener.* **2008**, *16*, 37.
[108] F. Tabei, B. Askarian, J. W. Chong, *IEEE Sens. J.* **2020**, *21*, 878.
[109] C. E. Nelson, M. K. Gupta, E. J. Adolph, S. A. Guelcher, C. L. Duvall, *Adv. Wound Care* **2013**, *2*, 93.
[110] S. A. Castleberry, B. D. Almquist, W. Li, T. Reis, J. Chow, S. Mayner, P. T. Hammond, *Adv. Mater.* **2016**, *28*, 1809.
[111] J. Layliev, S. Wilson, S. M. Warren, P. B. Saadeh, *Adv. Wound Care* **2012**, *1*, 218.
[112] Y.-W. Wang, N.-H. Liou, J.-H. Cherng, S.-J. Chang, K.-H. Ma, E. Fu, J.-C. Liu, N.-T. Dai, *J. Invest. Dermatol.* **2014**, *134*, 2016.
[113] J. K. W. Lam, M. Y. T. Chow, Y. Zhang, S. W. S. Leung, *Mol. Ther.—Nucleic Acids* **2015**, *4*, e252.
[114] A.-R. C. Lee, I. Woo, *Tissue Eng. Regener. Med.* **2018**, *15*, 711.
[115] T. C. Roberts, R. Langer, M. J. A. Wood, *Nat. Rev. Drug Discovery* **2020**, *19*, 673.
[116] C. Chen, Y. Liu, H. Wang, G. Chen, X. Wu, J. Ren, H. Zhang, Y. Zhao, *ACS Nano* **2018**, *12*, 10493.
[117] M. Caldorera-Moore, N. A. Peppas, *Adv. Drug Delivery Rev.* **2009**, *61*, 1391.
[118] Z. Wang, Z. Wang, W. W. Lu, W. Zhen, D. Yang, S. Peng, *NPG Asia Mater.* **2017**, *9*, e435.
[119] C. E. Nelson, M. K. Gupta, E. J. Adolph, S. A. Guelcher, C. L. Duvall, *Adv. Wound Care* **2013**, *2*, 93.
[120] K. Y. Kulebyakin, P. P. Nimiritsky, P. I. Makarevich, *Front. Endocrinol.* **2020**, *11*, 384.
[121] M. Nardini, S. Perteghella, L. Mastracci, F. Grillo, G. Marrubini, E. Bari, M. Formica, C. Gentili, R. Cancedda, M. L. Torre, M. Mastrogiacomo, *Pharmaceutics* **2020**, *12*, 120.
[122] C.-H. Lee, K.-S. Liu, S.-H. Chang, W.-J. Chen, K.-C. Hung, S.-J. Liu, J.-H. S. Pang, J.-H. Juang, C.-C. Chou, P.-C. Chang, Y.-T. Chen, F.-S. Wang, *Medicine* **2015**, *94*, e1873.
[123] S.-E. Kim, P. W. Lee, J. K. Pokorski, *ACS Macro Lett.* **2017**, *6*, 593.
[124] S. O. Blacklow, J. Li, B. R. Freedman, M. Zeidi, C. Chen, D. J. Mooney, *Sci. Adv.* **2019**, *5*, eaaw3963.
[125] A. Vedadghavami, F. Minooei, M. H. Mohammadi, S. Khetani, A. Rezaei Kolahchi, S. Mashayekhan, A. Sanati-Nezhad, *Acta Biomater.* **2017**, *62*, 42.
[126] Y. S. Gho, C. Lee, *Mol. BioSyst.* **2017**, *13*, 1291.
[127] S. El Andaloussi, I. Mäger, X. O. Breakefield, M. J. A. Wood, *Nat. Rev. Drug Discovery* **2013**, *12*, 347.
[128] M. Yi, Y. Wu, J. Long, F. Liu, Z. Liu, Y.-H. Zhang, X.-P. Sun, Z.-X. Fan, J. Gao, J. Si, X.-B. Zuo, L.-M. Zhang, N. Shi, Z.-P. Miao, Z.-R. Bai, B.-Y. Liu, H.-R. Liu, J. Li, *Am. J. Physiol.: Cell Physiol.* **2019**, *317*, C932.

[129] M. Di Trapani, G. Bassi, M. Midolo, A. Gatti, P. Takam Kamga, A. Cassaro, R. Carusone, A. Adamo, M. Krampera, *Sci. Rep.* **2016**, *6*, 24120.
[130] T. Yamashita, Y. Takahashi, Y. Takakura, *Biol. Pharm. Bull.* **2018**, *41*, 835.
[131] O. S. El-Tookhy, A. A. Shamaa, G. G. Shehab, A. N. Abdallah, O. M. Azzam, *Int. J. Stem Cells* **2017**, *10*, 144.
[132] R. Dalirfardouei, K. Jamialahmadi, A. H. Jafarian, E. Mahdipour, *J. Tissue Eng. Regener. Med.* **2019**, *13*, 555.
[133] Q. Shi, Z. Qian, D. Liu, J. Sun, X. Wang, H. Liu, J. Xu, X. Guo, *Front. Physiol.* **2017**, *8*, 904.
[134] K. Ma, S. Liao, L. He, J. Lu, S. Ramakrishna, C. K. Chan, *Tissue Eng., Part A* **2011**, *17*, 1413.
[135] M. Keshvardoostchokami, S. S. Majidi, P. Huo, R. Ramachandran, M. Chen, B. Liu, *Nanomaterials* **2021**, *11*, 21.
[136] S. Zhong, Y. Zhang, C. Lim, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* **2010**, *2*, 510.
[137] L.-C. Da, Y.-Z. Huang, H.-Q. Xie, *Regener. Biomater.* **2017**, *4*, 325.
[138] M. D. Bartlett, A. B. Croll, D. R. King, B. M. Paret, D. J. Irschick, A. J. Crosby, *Adv. Mater.* **2012**, *24*, 1078.
[139] A. Memic, T. Abudula, H. S. Mohammed, K. Joshi Navare, T. Colombani, S. A. Bencherif, *ACS Appl. Bio Mater.* **2019**, *2*, 952.
[140] M. Castilho, A. Van Mil, M. Maher, C. H. G. Metz, G. Hochleitner, J. Groll, P. A. Doevendans, K. Ito, J. P. G. Sluijter, J. Malda, *Adv. Funct. Mater.* **2018**, *28*, 1803151.
[141] A. Shafiee, A. S. Cavalcanti, N. T. Saidy, D. Schneidereit, O. Friedrich, A. Ravichandran, E. M. De-Juan-Pardo, D. W. Hutmacher, *Biomaterials* **2020**, *268*, 120558.
[142] J. Mcgovern, A. Shafiee, F. Wagner, C. Lahr, M. Landgraf, C. Meinert, E. Williams, P. Russell, J. Clements, D. Loessner, B. Holzapfel, G. Risbridger, D. Hutmacher, *Cancers* **2018**, *10*, 438.
[143] J. Li, F. Yu, G. Chen, J. Liu, X.-L. Li, B. Cheng, X.-M. Mo, C. Chen, J.-F. Pan, *ACS Appl. Mater. Interfaces* **2020**, *12*, 2023.
[144] J. Larouche, S. Sheoran, K. Maruyama, M. M. Martino, *Adv. Wound Care* **2018**, *7*, 209.
[145] X. Liu, Q. Zhang, G. Gao, *Adv. Funct. Mater.* **2017**, *27*, 1703132.
[146] A. Shafiee, J. A. Mcgovern, C. A. Lahr, C. Meinert, D. Moi, F. Wagner, M. Landgraf, E. De-Juan-Pardo, R. Mazzieri, D. W. Hutmacher, *Int. J. Cancer* **2018**, *143*, 1470.
[147] E. W. Zhang, C. W. P. Li-Tsang, T. M. H. Li, L. Huang, K.-K. Cheung, *Adv. Wound Care* **2020**, *9*, 564.
[148] J. R. Nakkala, Z. Li, W. Ahmad, K. Wang, C. Gao, *Acta Biomater.* **2021**, *123*, 1.
[149] O. Catanzano, V. D'esposito, S. Acierno, M. R. Ambrosio, C. De Caro, C. Avagliano, P. Russo, R. Russo, A. Miro, F. Ungaro, A. Calignano, P. Formisano, F. Quaglia, *Carbohydr. Polym.* **2015**, *131*, 407.
[150] M. P. Rodero, K. Khosrotehrani, *Int. J. Clin. Exp. Pathol.* **2010**, *3*, 643.
[151] J. L. Dziki, L. Huleihel, M. E. Scarritt, S. F. Badylak, *Tissue Eng., Part A* **2017**, *23*, 1152.
[152] M. O. Dellacherie, B. R. Seo, D. J. Mooney, *Nat. Rev. Mater.* **2019**, *4*, 379.
[153] J. J. Rice, M. M. Martino, L. De Laporte, F. Tortelli, P. S. Briquez, J. A. Hubbell, *Adv. Healthcare Mater.* **2013**, *2*, 57.
[154] C. J. Ferrante, S. J. Leibovich, *Adv. Wound Care* **2012**, *1*, 10.
[155] G. Grieb, G. Steffens, N. Pallua, J. Bernhagen, R. Bucala, *Int. Rev. Cell Mol. Biol.* **2011**, *291*, 1.
[156] M. Xue, C. J. Jackson, *Adv. Wound Care* **2015**, *4*, 119.
[157] M. P. Sousa, A. I. Neto, T. R. Correia, S. P. Miguel, M. Matsusaki, I. J. Correia, J. F. Mano, *Biomater. Sci.* **2018**, *6*, 1962.
[158] M. Rahimnejad, S. Derakhshanfar, W. Zhong, *Burns Trauma* **2017**, *5*, 4.
[159] M. L. Costa, J. Achten, R. Knight, J. Bruce, S. J. Dutton, J. Madan, M. Dritsaki, N. Parsons, M. Fernandez, R. Grant, J. Nanchahal, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 519.
[160] P. Ghassemi, J. W. Shupp, T. E. Travis, A. J. Gravunder, L. T. Moffatt, J. C. Ramella-Roman, *Rev. Sci. Instrum.* **2015**, *86*, 015101.
[161] T. M. D. Le, H. T. T. Duong, T. Thambi, V. H. Giang Phan, J. H. Jeong, D. S. Lee, *Biomacromolecules* **2018**, *19*, 3536.
[162] C. Dieckmann, R. Renner, L. Milkova, J. C. Simon, *Exp. Dermatol.* **2010**, *19*, 697.
[163] B. Bleasdale, S. Finnegan, K. Murray, S. Kelly, S. L. Percival, *Adv. Wound Care* **2015**, *4*, 422.
[164] S. H. Aswathy, U. Narendrakumar, I. Manjubala, *Heliyon* **2020**, *6*, e03719.
[165] K. Xu, Y. Lu, K. Takei, *Adv. Mater. Technol.* **2019**, *4*, 1800628.
[166] M. A. Heinrich, W. Liu, A. Jimenez, J. Yang, A. Akpek, X. Liu, Q. Pi, X. Mu, N. Hu, R. M. Schiffelers, J. Prakash, J. Xie, Y. S. Zhang, *Small* **2019**, *15*, 1805510.
[167] F. Fayyazbakhsh, M. C. Leu, *Proc. Manuf.* **2020**, *48*, 790.
[168] J. N. Dinoro, 3D printing PhycoTrix™ for wound healing, **2016**.
[169] S. Liu, C.-Z. He, Y.-T. Cai, Q.-P. Xing, Y.-Z. Guo, Z.-L. Chen, J.-L. Su, L.-P. Yang, *Ther. Clin. Risk Manage.* **2017**, *13*, 533.
[170] G. Chinga-Carrasco, *Biomacromolecules* **2018**, *19*, 701.
[171] A. Koh, D. Kang, Y. Xue, S. Lee, R. M. Pielak, J. Kim, T. Hwang, S. Min, A. Banks, P. Bastien, M. C. Manco, L. Wang, K. R. Ammann, K.-I. Jang, P. Won, S. Han, R. Ghaffari, U. Paik, M. J. Slepian, G. Balooch, Y. Huang, J. A. Rogers, *Sci. Transl. Med.* **2016**, *8*, 366ra165.
[172] M. Puertas-Bartolomé, M. K. Włodarczyk-Biegun, A. Del Campo, B. Vázquez-Lasa, J. San Román, *Polymers* **2020**, *12*, 1986.
[173] D. O. Visscher, S. te Slaa, M. E. Jaspers, M. van de Hulsbeek, J. Borst, J. Wolff, T. Forouzanfar, P. P. van Zuijlen, *Burns Trauma* **2018**, *6*, 15.
[174] J. Long, A. E. Etxeberria, A. V. Nand, C. R. Bunt, S. Ray, A. Seyfoddin, *Mater. Sci. Eng., C* **2019**, *104*, 109873.
[175] J. H. Y. Chung, S. Naficy, Z. Yue, R. Kapsa, A. Quigley, S. E. Moulton, G. G. Wallace, *Biomater. Sci.* **2013**, *1*, 763.
[176] H. Si, T. Xing, Y. Ding, H. Zhang, R. Yin, W. Zhang, *Polymers* **2019**, *11*, 1584.
[177] S. Singh, D. Choudhury, F. Yu, V. Mironov, M. W. Naing, *Acta Biomater.* **2020**, *101*, 14.
[178] P. He, J. Zhao, J. Zhang, B. Li, Z. Gou, M. Gou, X. Li, *Burns Trauma* **2018**, *6*, 5.
[179] M. Albanna, K. W. Binder, S. V. Murphy, J. Kim, S. A. Qasem, W. Zhao, J. Tan, I. B. El-Amin, D. D. Dice, J. Marco, J. Green, T. Xu, A. Skardal, J. H. Holmes, J. D. Jackson, A. Atala, J. J. Yoo, *Sci. Rep.* **2019**, *9*, 1856.
[180] A. G. Tabriz, D. Douroumis, J. Boateng, *Therapeutic Dressings and Wound Healing Applications*, John Wiley and Sons Ltd, Hoboken, NJ **2020**, pp. 385–398.
[181] Z. Wu, Y. Hong, *ACS Appl. Mater. Interfaces* **2019**, *11*, 33734.
[182] Z. Muwaffak, A. Goyanes, V. Clark, A. W. Basit, S. T. Hilton, S. Gaisford, *Int. J. Pharm.* **2017**, *527*, 161.
[183] A. Rees, L. C. Powell, G. Chinga-Carrasco, D. T. Gethin, K. Syverud, K. E. Hill, D. W. Thomas, *BioMed Res. Int.* **2015**, *2015*, 925757.
[184] B. Qiao, Q. Pang, P. Yuan, Y. Luo, L. Ma, *Biomater. Sci.* **2020**, *8*, 164957.
[185] A. Ajovalasit, M. C. Caccami, S. Amendola, M. A. Sabatino, G. Alotta, M. Zingales, D. Giacomazza, C. Occhiuzzi, G. Marrocco, C. Dispenza, *Eur. Polym. J.* **2018**, *106*, 214.
[186] E. Ilhan, S. Cesur, E. Guler, F. Topal, D. Albayrak, M. M. Guncu, M. E. Cam, T. Taskin, H. T. Sasmazel, B. Aksu, F. N. Oktar, O. Gunduz, *Int. J. Biol. Macromol.* **2020**, *161*, 1040.
[187] G. Shi, Y. Wang, S. Derakhshanfar, K. Xu, W. Zhong, G. Luo, T. Liu, Y. Wang, J. Wu, M. Xing, *Mater. Sci. Eng., C* **2019**, *100*, 915.
[188] H. F. Selig, D. B. Lumenta, M. Giretzlehner, M. G. Jeschke, D. Upton, L. P. Kamolz, *Burns* **2012**, *38*, 960.
[189] M. Szycher, S. J. Lee, *J. Biomater. Appl.* **1992**, *7*, 142.
[190] S. Finnegan, S. L. Percival, *Adv. Wound Care* **2015**, *4*, 398.

[191] S. Shahriar, J. Mondal, M. Hasan, V. Revuri, D. Lee, Y.-K. Lee, *Nanomaterials* **2019**, *9*, 532.
[192] H.-H. Homann, O. Rosbach, W. Moll, P. M. Vogt, G. Germann, M. Hopp, B. Langer-Brauburger, K. Reimer, H.-U. Steinau, *Ann. Plast. Surg.* **2007**, *59*, 423.
[193] M. Y. Hasan, R. Teo, A. Nather, *Diabetic Foot Ankle* **2015**, *6*, 27618.
[194] Z. Yuan, J. Zhao, Y. Chen, Z. Yang, W. Cui, Q. Zheng, *Mediators Inflammation* **2014**, *2014*, 858045.
[195] M. T. Eginton, K. R. Brown, G. R. Seabrook, J. B. Towne, R. A. Cambria, *Ann. Vasc. Surg.* **2003**, *17*, 645.
[196] H. Li, G. R. Williams, J. Wu, Y. Lv, X. Sun, H. Wu, L.-M. Zhu, *Int. J. Pharm.* **2017**, *517*, 135.
[197] H. Y. Huang, A. Skripka, L. Zaroubi, B. L. Findlay, F. Vetrone, C. Skinner, J. K. Oh, L. A. Cuccia, *ACS Appl. Bio Mater.* **2020**, *3*, 7219.
[198] A. Landsman, P. Agnew, L. Parish, R. Joseph, R. D. Galiano, *J. Am. Podiatr. Med. Assoc.* **2010**, *100*, 155.
[199] A. Ravizza, C. De Maria, L. Di Pietro, F. Sternini, A. L. Audenino, C. Bignardi, *Front. Bioeng. Biotechnol.* **2019**, *7*, 313.
[200] L. Barnum, M. Samandari, T. A. Schmidt, A. Tamayol, *Expert Opin. Drug Delivery* **2020**, *17*, 1767.
[201] M. Bilal, S. Mehmood, A. Raza, U. Hayat, T. Rasheed, H. M. N. Iqbal, *Adv. Wound Care* **2021**, *10*, 204.
[202] A. J. Guillot, A. S. Cordeiro, R. F. Donnelly, M. C. Montesinos, T. M. Garrigues, A. Melero, *Pharmaceutics* **2020**, *12*, 569.
[203] J. Yang, X. Liu, Y. Fu, Y. Song, *Acta Pharm. Sin. B* **2019**, *9*, 469.
[204] I. Menon, P. Bagwe, K. B. Gomes, L. Bajaj, R. Gala, M. N. Uddin, M. J. D'souza, S. M. Zughaier, *Micromachines* **2021**, *12*, 435.
[205] N.-W. Kang, S. Kim, J.-Y. Lee, K.-T. Kim, Y. Choi, Y. Oh, J. Kim, D.-D. Kim, J.-H. Park, *Expert Opin. Drug Delivery* **2021**.
[206] E. G. Andriotis, G. K. Eleftheriadis, C. Karavasili, D. G. Fatouros, *Pharmaceutics* **2020**, *12*, 56.
[207] M. S. Brown, B. Ashley, A. Koh, *Front. Bioeng. Biotechnol.* **2018**, *6*, 47.
[208] F. Hafezi, N. Scoutaris, D. Douroumis, J. Boateng, *Int. J. Pharm.* **2019**, *560*, 406.
[209] C. Intini, L. Elviri, J. Cabral, S. Mros, C. Bergonzi, A. Bianchera, L. Flammini, P. Govoni, E. Barocelli, R. Bettini, M. Mcconnell, *Carbohydr. Polym.* **2018**, *199*, 593.
[210] T. Maver, D. M. Smrke, M. Kurečič, L. Gradišnik, U. Maver, K. S. Kleinschek, *J. Sol-Gel Sci. Technol.* **2018**, *88*, 33.
[211] B. S. Atiyeh, *Aesthetic Plast. Surg.* **2007**, *31*, 468.
[212] P. M. Vogt, K. Reimer, J. Hauser, O. Roßbach, H. U. Steinau, B. Bosse, S. Muller, T. Schmidt, W. Fleischer, *Burns* **2006**, *32*, 698.
[213] R. E. Horch, *J. Wound Care* **2015**, *24*, 21.
[214] L. A. Lavery, J. La Fontaine, G. Thakral, P. J. Kim, K. Bhavan, K. E. Davis, *Plast. Reconstr. Surg.* **2014**, *133*, 722.
[215] Ş. Çetinkalp, E. H. Gökçe, I. Şimşir, S. Tuncay Tanrıverdi, F. Doğan, Ç. B. Avcı, İ. Eroğlu, T. Utku, C. Gündüz, Ö. Özer, *Int. J. Lower Extremity Wounds* **2020**, 1534734620907773.
[216] R. Rathinamoorthy, S. Rajendran, *Advanced Textiles for Wound Care*, Elsevier, Amsterdam **2019**, pp. 423–461.
[217] Y. Wang, P. K. M. Maitz, *Adv. Drug Delivery Rev.* **2018**, *123*, 1.
[218] R. Nunan, K. G. Harding, P. Martin, *Dis. Models Mech.* **2014**, *7*, 1205.
[219] V. Yadav, A. Mittal, P. Bansal, S. K. Singh, *J. Wound Care* **2019**, *28*, S32.
[220] M. Augustin, *Z. Evidenz, Fortbild. Qual. Gesundheitswes.* **2012**, *106*, 347.
[221] M. Mehrali, S. Bagherifard, M. Akbari, A. Thakur, B. Mirani, M. Mehrali, M. Hasany, G. Orive, P. Das, J. Emneus, T. L. Andresen, A. Dolatshahi-Pirouz, *Adv. Sci.* **2018**, *5*, 1700931.
[222] H. Derakhshandeh, S. S. Kashaf, F. Aghabaglou, I. O. Ghanavati, A. Tamayol, *Trends Biotechnol.* **2018**, *36*, 1259.
[223] S. Coyle, D. Diamond, *Advances in Smart Medical Textiles*, Elsevier, Amsterdam **2016**, pp. 215–237.
[224] S. Scataglini, A. Moorhead, F. Feletti, *Muscles, Ligaments Tendons J.* **2020**, *10*, 2314.
[225] A. Alzaidi, L. Zhang, H. Bajwa, in *IEEE Long Island Systems, Applications and Technology Conf. (LISAT)*, IEEE, Piscataway, NJ **2012**, p. 2317.
[226] J. M. Giménez-Egido, E. Ortega, I. Verdu-Conesa, A. Cejudo, G. Torres-Luque, *Int. J. Environ. Res. Public Health* **2020**, *17*, 1068.
[227] T. Chittenden, *Fash. Text.* **2017**, *4*, 22.
[228] P. Perego, A. Moltani, M. C. Fusca, R. Zanini, R. Bellù, G. Andreoni, in *PHealth 2012: Proc. of the 9th Int. Conf. on Wearable Micro and Nano Technologies for Personalized Health* (Eds: Bernd Blobel, Pharow Peter, Sousa Filipe) IOS Press, Amsterdam **2012**.
[229] A. A. Mahmoud, A. H. Salama, *Eur. J. Pharm. Sci.* **2016**, *83*, 155.
[230] J. Chi, X. Zhang, C. Chen, C. Shao, Y. Zhao, Y. Wang, *Bioact. Mater.* **2020**, *5*, 253.
[231] T. Sahu, Y. K. Ratre, S. Chauhan, L. V. K. S. Bhaskar, M. P. Nair, H. K. Verma, *J. Drug Delivery Sci. Technol.* **2021**, *63*, 102487.
[232] W. X. Hong, M. S. Hu, M. Esquivel, G. Y. Liang, R. C. Rennert, A. McArdle, K. J. Paik, D. Duscher, G. C. Gurtner, H. P. Lorenz, *Adv. Wound Care* **2014**, *3*, 390.
[233] S. Schrem, R. Szeimies, L. Prantl, S. Karrer, M. Landthaler, P. Babilas, *Br. J. Dermatol.* **2010**, *163*, 257.
[234] S. Matoori, A. Veves, D. J. Mooney, *Sci. Transl. Med.* **2021**, 13.

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