International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	ADVANCED BIOMATERIAL PLATFORMS FOR CHRONIC WOUND CARE: SMART DRESSINGS, 3D BIOPRINTING, AND 4D RESPONSIVE TECHNOLOGIES
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6090
RECEIVED	21 April 2026
ACCEPTED	27 July 2026
PUBLISHED	06 August 2026
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ADVANCED BIOMATERIAL PLATFORMS FOR CHRONIC WOUND CARE: SMART DRESSINGS, 3D BIOPRINTING, AND 4D RESPONSIVE TECHNOLOGIES

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ABSTRACT

Chronic non-healing wounds constitute a significant health concern and impose a substantial financial burden on healthcare systems. This creates a pressing need for advanced solutions capable of improving therapeutic efficacy. The aim of this review article is to analyze the current state of knowledge regarding the application of smart dressings and 3D and 4D bioprinting technologies in the treatment of chronic wounds. The methodology was based on a critical review and synthesis of scientific literature in the fields of biomaterials engineering and regenerative medicine. Contemporary hydrogel-based matrices integrated with biosensors and machine learning algorithms effectively transform passive mechanical wound protection into an automated system for monitoring the wound microenvironment and actively responding to its changes. Concurrently, 3D bioprinting techniques enable precise architectural reconstruction of tissues and the fabrication of grafts tailored to the unique size, shape, and depth of individual injuries. Although smart dressing technologies, 3D and 4D bioprinting are undergoing intensive development, additional preclinical and clinical studies are required to establish their safety and efficacy profiles, which is a prerequisite for the development of national regulatory standards.

KEYWORDS

3D Bioprinting, Chronic Wounds, Smart Dressings, 4D Printing

CITATION

Nadzieja Krasucka, Aleksandra Zynkowska, Aleksandra Magdalena Skrzyniarz, Maria Kiełbus, Julia Oziębło, Magdalena Kijowska, Karolina Klusek, Michał Batory, Jakub Jakubowski, Karol Kraska. (2026) Advanced Biomaterial Platforms for Chronic Wound Care: Smart Dressings, 3D Bioprinting, and 4D Responsive Technologies. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6090

Chapter 1. Introduction

1.1. Scale of the Problem and Economic Burden of Chronic Wound Management

Chronic skin injuries represent a major clinical and economic challenge for contemporary healthcare systems. Wounds that fail to heal within 12 weeks are classified as chronic wounds. In clinical practice, these wounds most commonly manifest as three major disease entities: diabetic foot ulcers, venous leg ulcers, and pressure ulcers [1]. On a global scale, chronic wounds constitute a substantial economic burden. In Spain, the annual cost of chronic wound management has been estimated at €587 million [2]. In Australia, leg ulcers are among the wound types associated with the highest healthcare expenditures due to prolonged healing times, the projected increase in the elderly population, and high recurrence rates reaching 78% [3]. Chronic wounds are frequently associated with multimorbidity and significantly reduce patients' quality of life because of pain, malodor, and impaired mobility. Furthermore, these symptoms often lead to patient dependence on caregivers and necessitate continuous interaction with healthcare services [4–6].

1.2. Molecular and Cellular Pathomechanisms of Impaired Wound Healing

The physiological process of wound healing comprises a complex sequence of biological events, including the phases of hemostasis, inflammation, proliferation, and tissue remodeling [7]. The pathophysiology of chronic wounds is associated with disruption of progression through these successive healing stages due to factors such as persistent inflammation, hypoxia, infection, vascular insufficiency, and cellular dysfunction (Table 1) [8,9].

Table 1. Characteristics of the major pathological factors impairing tissue regeneration.

Pathological factor	Molecular and cellular mechanism	Consequences for wound healing
Excessive inflammation	Massive infiltration of Langerhans cells, neutrophils, pro-inflammatory macrophages, and proteases, accompanied by impaired cellular function (e.g., formation of cytotoxic neutrophil extracellular traps [NETs], defective bacterial phagocytosis, and impaired efferocytosis).	Continuous active destruction of wound tissue preventing transition to the resolution phase; increased susceptibility to infection; the severity of these abnormalities correlates directly with the clinical stage of ulcer progression.
Cellular senescence	Mitotically active cells enter a senescent state and acquire a senescence-associated secretory phenotype (SASP), characterized by hypersecretion of pro-inflammatory cytokines and proteases.	Loss of cellular proliferative capacity, inhibition of new extracellular matrix (ECM) deposition, and degradation of healthy tissue.
Hyperglycemia and advanced glycation end products (AGEs)	Non-enzymatic glycation of structural skin proteins (ECM); AGEs trigger inflammation and reactive oxygen species (ROS) generation; inhibition of HIF-1α transactivation and subsequent dysregulation of vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1 (SDF-1) expression.	Altered biomechanical architecture of the skin (loss of elasticity and increased susceptibility to friction), impaired neovascularization, microcirculatory damage resulting in local tissue hypoxia, and increased susceptibility to microbial colonization.
Impaired re-epithelialization	Hyperkeratotic and parakeratotic transformation of wound edges; aberrant localization of β-catenin and elevated nuclear c-Myc expression in keratinocytes; dysregulated expression of cell-cycle markers.	Apparent uncontrolled proliferation of cells at the wound margin accompanied by inhibition of their migratory capacity and inability to achieve wound closure.
Dysbiosis and bacterial biofilm formation	Reduced skin microbiome alpha diversity; colonization by pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* and formation of multispecies aggregates embedded within a protective extracellular polymeric substance (EPS) matrix.	Development of resistance to conventional antibiotics and host defense mechanisms, perpetuating a vicious cycle of infection and inflammation.

1.3. Classification of Conventional Wound Dressings

The complex and multifactorial pathophysiology of chronic wounds involves the need to use individualized local treatment strategies. Dressing selection should consider the stage of wound healing, exudate intensity, microbiological status, presence of cavities, sinus tracts or fistulas, and the condition of the periwound skin. Consequently, an ideal dressing should maintain appropriate moisture levels, temperature, and gas exchange within the wound bed, absorb excess exudate and contaminants, provide an effective microbiological barrier, possess a non-adherent structure, be easy to apply, available in multiple size configurations, and remain cost-effective [10].

To address diverse clinical needs, numerous categories of specialized wound dressings have been developed, differing in their mechanisms of action, physicochemical properties, and clinical indications (Table 2).

Table 2. Comparative characteristics of dressings used in chronic wound management [10–15].

Dressing type	Mechanism of action	Advantages	Limitations
Gauze and traditional dressings	Passive protection and exudate absorption	Low cost and wide availability	No active support of healing; potential damage to newly formed tissue during dressing changes; inability to maintain a moist wound environment
Hydrogel dressings	Water absorption and maintenance of optimal wound hydration	Absorption of excess exudate; maintenance of hemostasis and gas exchange; strong adherence to the wound bed; facilitation of autolytic debridement	Susceptible to cracking and mechanical failure under tension or patient movement, potentially leading to bacterial contamination; risk of maceration; difficult removal without tissue damage
Hydrocolloid dressings (adhesive plates and pastes)	Gel formation upon contact with wound exudate, creating a moist environment	Occlusive barrier providing complete isolation from the external environment; maintenance of an optimal wound microclimate; stimulation of proliferation and epithelialization	Unsuitable for infected wounds; potential epidermal damage during removal, particularly in elderly patients with fragile skin
Alginate dressings (calcium and calcium-sodium alginates)	Exudate absorption and gel formation	High absorbency and hemostatic properties	Require a secondary dressing; unsuitable for dry wounds; low stability and poor mechanical and barrier properties
Polyurethane foam dressings	Capillary absorption of exudate, cellular recruitment, stimulation of fibrinolysis, and promotion of angiogenesis	High absorbency and non-adherent properties	Reparative processes depend on the presence of exudate; require frequent replacement; unsuitable for dry wounds
Silver-containing dressings	Antimicrobial activity	Suppression of inflammatory responses; broad-spectrum antibacterial activity; reduction in wound infection risk	No significant effect on wound area reduction; no demonstrated benefit in diabetic foot ulcer management

Despite the wide variety of available dressing materials, none of the currently used products fulfills all the requirements of an ideal dressing for chronic wound treatment. Consequently, contemporary research is focused on the development of advanced wound dressings capable of actively supporting regenerative processes. Particular attention has been directed toward smart dressings, which integrate advanced biomaterials, biosensors, and controlled drug-delivery systems to monitor the wound microenvironment and dynamically adapt therapy to the patient's current clinical condition [16,17].

In parallel, advances in tissue engineering and three-dimensional (3D) printing technologies have opened new avenues for the treatment of hard-to-heal chronic wounds. Three-dimensional bioprinting enables the fabrication of personalized tissue scaffolds and skin substitutes incorporating bioactive biomaterials, living cells, and growth factors [18]. An emerging direction in this field is four-dimensional (4D) printing technology, which employs stimuli-responsive materials capable of undergoing dynamic, time-dependent architectural transformations directly at the wound site [19].

The aim of this review is to present the current state of knowledge regarding the application of smart dressings and 3D bioprinting technologies, as well as the future prospects of 4D systems in chronic wound management, with particular emphasis on their effects on the wound-healing process, clinical applicability, and potential benefits for patient health and quality of life.

Chapter 2. Methodology

This study was conducted as a narrative literature review in accordance with the principles of evidence-based medicine (EBM). A structured literature search was performed between January 2020 and May 2026 using two databases: PubMed/MEDLINE and Google Scholar. Search terms were combined using Boolean operators (AND, OR) and included the following keywords: "smart dressings," "3D bioprinting," "4D printing," "chronic wounds," "diabetic foot ulcers," "venous leg ulcers," and "hydrogels."

The inclusion criteria comprised original research articles (including *in vitro* studies, *in vivo* studies, and clinical case reports), systematic reviews, meta-analyses, and peer-reviewed narrative reviews; publications written in English or Polish; and studies directly evaluating smart, stimuli-responsive wound dressings or 3D and 4D printing technologies in the context of chronic or hard-to-heal wound management.

The exclusion criteria included studies focusing exclusively on the general characteristics of biomaterials without direct relevance to chronic wound treatment, as well as conference abstracts, editorials, and non-peer-reviewed commercial reports.

Following the initial database search, studies were screened based on title and abstract relevance, after which full-text analyses of selected articles were performed. To complement the electronic search strategy, the "Similar Articles" function in PubMed was utilized, and the reference lists of eligible studies were manually screened using a snowballing approach to identify additional relevant publications. The final analysis included a total of 72 publications. The extracted data were organized thematically and synthesized using a narrative approach.

Chapter 3. Smart Dressings in Modern Chronic Wound Therapy

3.1. Fundamentals of Materials Engineering: Hydrogel Matrices and Functional Fillers

A smart dressing is defined as an advanced system composed of biosensors and stimuli-responsive materials capable of continuously and dynamically responding to changes in the wound microenvironment in real time. Furthermore, upon external stimulation, these systems can provide controlled drug delivery on demand [16,20].

Smart dressings are based on the integration of a hydrogel matrix with functional fillers, achieved through physical blending, cross-linking, or the fabrication of dual-network systems. The combination of matrix and filler enhances the mechanical strength and adhesive properties of the dressing while enabling the conversion of physicochemical stimuli into measurable optical or electrical signals [21]. A particularly promising strategy for optimizing these systems involves the incorporation of composites based on conducting polymers (CPs), such as polypyrrole (PPy), polyaniline (PANI), and poly(3,4-ethylenedioxythiophene) (PEDOT). Their molecular structures contain delocalized π-electrons subjected to oxidative p-type doping, conferring high electrical conductivity, and enabling bioelectrical stimulation (ES). Such stimulation mimics endogenous bioelectrical signals, thereby actively promoting cell migration, tissue repair, and wound regeneration [22].

Smart dressings may also incorporate a wide range of antimicrobial agents, including conventional antibiotics, medical-grade honey, plant-derived essential oils, iodine and iodine complexes, chlorhexidine gluconate, and silver nanoparticles [23]. Currently, various categories of smart dressings are being developed, including biomechanically active, stimuli-responsive, self-healing, self-detaching, and monitoring dressings [22].

3.2. Classification of Stimuli-Responsive Systems and Biosensors for Monitoring Wound Microenvironment Parameters

Depending on the materials employed, smart dressing systems may respond to different physiological or external stimuli and monitor specific wound microenvironment biomarkers that provide objective information regarding wound status (Table 3).

Table 3. Characteristics of advanced hydrogel systems responsive to chronic wound microenvironmental stimuli [23–34].

Wound microenvironment parameter	Stimuli-responsive dressings: mechanism of action and clinical/biological effect		Monitoring dressings: detection method and diagnostic purpose
Temperature	Thermoresponsive systems are based on the lower critical solution temperature (LCST) phenomenon. Synthetic polymers (e.g., PNIPAm, poloxamers) and natural polymers (e.g., chitosan, gelatin) undergo reversible sol–gel transitions in response to temperature changes.	Elevated local wound temperature, potentially indicating infection, triggers enhanced release of therapeutic agents; enables injectable application and conformity to irregular wound geometries; maintains a moist healing environment and prevents drug loss.	Colorimetric detection via temperature-sensitive polyacrylamide hydrogel (PAAM) membranes. Electrochemical sensing based on resistance changes in multilayer systems integrated with skin-mimicking constructs or Kapton-based gold electrode sensors.
pH	pH-responsive polymers alter their charge density in response to alkaline shifts typical of chronic wounds, resulting in hydrogel swelling and structural modification.	Improved wound cushioning and exudate absorption; enhanced conformity to wound surface; controlled release of antimicrobial agents, metal ions, and anti-inflammatory compounds proportional to pathological severity.	Colorimetric detection uses phenol red, brilliant yellow, or curcumin; fluorometric detection uses 5(6)-carboxynaphthofluorescein and pyranine; electrochemical detection via potential shifts between PANI (polyaniline)-based electrodes; ion-sensitive field-effect transistor (ISFET) systems.
Proteolytic enzymes	Matrix metalloproteinases (MMPs), elastases, and collagenases cleave peptide sequences or labile chemical bonds incorporated into hydrogel networks, triggering degradation.	Enables localized, self-regulated drug delivery with release rates proportional to enzymatic activity; progressive matrix degradation supports cell infiltration, extracellular matrix deposition, and angiogenesis during tissue repair.	Graphene field-effect transistor (GFET) biosensors functionalized with aptamers for selective detection of MMP-9.
Ultraviolet (UV) radiation	Photoreactive compounds undergo rapid chemical crosslinking upon exposure to specific UV wavelengths.	Rapid *in situ* gelation within seconds, enabling adaptation to complex wound geometries; provides immediate hemostatic sealing and an occlusive barrier; may eliminate the need for sutures or mechanical fixation.	
Electrical stimulation	Conductive biomaterials such as graphene, PPy, PANI, and carbon nanotubes respond to external electric fields or endogenous bioelectric signals.	Enhances fibroblast and keratinocyte proliferation, promotes angiogenesis, exerts antimicrobial effects, and enables electrically controlled drug release via modulation of hydrogel swelling and conductivity.	

Wound microenvironment parameter	Stimuli-responsive dressings: mechanism of action and clinical/biological effect		Monitoring dressings: detection method and diagnostic purpose
ROS	ROS-sensitive linkers (e.g., phenylboronic acid derivatives) or polymeric micelles are cleaved under oxidative conditions, leading to controlled degradation of the hydrogel network.	Reduction of oxidative stress shortens the inflammatory phase; ROS-triggered degradation enables targeted or accelerated release of therapeutics such as copper ions, diclofenac, or mangiferin.	
Glucose	Glucose binds to phenylboronic acid (PBA) moieties, increasing hydrogel hydrophilicity and inducing swelling; alternatively, glucose oxidase (GOx) or lectin-based systems may be incorporated.	Enable closed-loop regulation in diabetic wounds; increased swelling triggers-controlled release of antidiabetic agents (e.g., metformin) and insulin, reducing local glucose concentration and improving healing.	Optical systems based on photonic crystals and fluorescence (GOx/peroxidase systems); electrochemical biosensors measuring current, voltage, or impedance changes linked to glucose oxidation.
Ultrasound	Ultrasound waves induce reversible de-crosslinking and re-crosslinking of hydrogel networks.	Allows on-demand, spatially controlled drug release.	
Oxygen	Embedded hydrogen peroxide systems are catalytically decomposed into oxygen; some platforms include integrated oxygen sensors.	Local oxygen supplementation enhances cell proliferation, angiogenesis, and collagen synthesis.	Colorimetric phosphorescence quenching assays using oxygen-sensitive dyes (e.g., metalloporphyrins); electrochemical detection via Clark-type amperometric sensors.
Magnetic field	Magnetic nanoparticles (MNPs) convert magnetic energy into mechanical deformation of hydrogel networks, inducing swelling or relaxation of polymer chains.	Promotes pro-angiogenic gene expression, enhances fibroblast activity, directs cell migration, and enables remote-controlled drug release.	
Moisture / exudate			Sensors integrated at the wound–dressing interface or within electronic skin systems (CNTs/graphene/GelMA) enable continuous monitoring and closed-loop management, including exudate removal systems.
Bacterial infection			Colorimetric biosensors detecting bacterial enzymes (e.g., lipase activity), enabling early infection diagnosis.
Uric acid			Electrochemical sensors used as biomarkers of wound severity and oxidative stress.
Mechanical pressure			Sensors measuring pressure magnitude, gradients, and temporal fluctuations to guide offloading strategies and prevent pressure-induced tissue damage.

Smart bandages integrated with triboelectric nanogenerators (TENGs), forming PZ-TENG systems, have also demonstrated considerable potential for wound management. These platforms provide a simple, efficient, and cost-effective means of continuously monitoring residual therapeutic agent concentrations *in situ*. Real-time assessment enables precise determination of dressing replacement intervals, thereby minimizing drug waste, reducing cross-infection associated with frequent dressing changes, and preventing secondary damage to regenerating tissue caused by premature wound exposure [35]. Another promising and relatively inexpensive approach involves autonomous battery-free textile bandages capable of measuring electrochemical parameters through a three-electrode configuration using frequency modulation or enzyme-free sensors based on organic electrochemical transistors (OECTs). Such systems enable continuous monitoring of pH and uric acid levels within the chronic wound environment [36,37].

3.3. Integration of Wearable Platforms with Mobile Technologies and Artificial Intelligence (AI)

To optimize wound-healing surveillance, advanced wound dressings are being developed that combine non-contact sensing technologies with artificial intelligence (AI), machine learning (ML), and mobile platforms. These algorithms can classify wound types, estimate wound area and depth, detect signs of infection, and predict healing trajectories [38].

Key requirements for intelligent wound-monitoring systems include non-invasiveness, rapid detection, low manufacturing costs, user-friendly operation, and highly reliable outputs with minimal error rates [31]. The effectiveness of these systems is further enhanced through the integration of Internet of Things (IoT)-enabled biosensors embedded within modern dressing architectures. Such sensors allow immediate wireless transmission of biological parameters to healthcare databases. Furthermore, the convergence of wearable devices, AI algorithms, and cloud-based connectivity creates automated closed-loop systems capable of predictive and highly personalized therapeutic management [38].

Several technologies employ smartphone cameras, where RGB image analysis enables accurate monitoring of wound pH. Other systems integrate hydrogel dressings, wearable electronic devices, and mobile applications into a single platform. These solutions allow real-time monitoring of wound glucose and pH levels while enabling on-demand drug delivery through smartphone-generated feedback signals [39]. To eliminate the need for active patient involvement in image acquisition, alternative systems based on immobilized pH indicators attached to cellulose particles have been developed. In these devices, colorimetric measurements are performed by a microchip integrated into the dressing, which wirelessly transmits quantitative data to smartphones and clinical databases via radio-frequency identification (RFID) technology. Additional systems support wireless monitoring and analysis of wound temperature, enabling real-time assessment of local blood flow, leukocyte extravasation, and infection risk [27].

Mobile applications also facilitate controlled compression therapy, which requires maintenance of approximately 40 mmHg of pressure, by processing signals from capacitive sensors and notifying patients when pressure redistribution is required. Smartphone-based software additionally supports wireless acquisition of uric acid concentration data and bidirectional control of therapeutic closed-loop systems through feedback commands that trigger drug release [31].

3.4. Smart Dressings in the Treatment of Chronic Wounds

Owing to their multifunctional properties, modern hydrogel-based smart dressings enable simultaneous monitoring of multiple biological parameters and precise therapeutic delivery, making them particularly attractive for the treatment of chronic wounds. One example is a dressing specifically developed for venous ulcer therapy, consisting of a perforated wound-contact layer, a microfluidic exudate collector, an integrated immunosensor, and a breathable barrier. The transparent substrate allows convenient, completely non-contact visualization of the wound bed throughout treatment. In addition, the perforated contact layer protects fragile granulation tissue from mechanical damage, while the outer membrane ensures adequate oxygen and water vapor exchange [27].

Several advanced dressings have been developed for chronic diabetic wounds. One example is a pH/ROS-responsive hydrogel composed of hyaluronic acid functionalized with phenylboronic acid (HA-PBA) and PEG-dopamine interconnected through dynamic boronate ester bonds. This system incorporates a dual drug-delivery barrier in which an antimicrobial peptide (AMP) and micellar quercetin (QC) are released within acidic and ROS-rich wound environments. Quercetin promotes regenerative macrophage polarization toward the M2 phenotype through activation of the AKT–STAT6 signaling pathway [40]. Another boronate ester-responsive platform is the injectable AuNCs@PBA-Sa hydrogel, in which catechol-functionalized gold

nanoclusters exhibit superoxide dismutase-mimetic activity, suppressing superoxide anion generation. The hydrogel conforms to wound geometry and promotes the formation of anti-inflammatory, pro-regenerative M2 macrophages [41]. A multifunctional three-layer fibrous membrane (PCSNP) has also been developed for diabetic wound treatment. Its architecture comprises an inner layer designed for rapid sterilization, an intermediate layer responsible for pH-responsive drug release and colorimetric pH monitoring, and an outer self-powered layer. In addition to stimulating cellular proliferation, migration, and revascularization, the dressing demonstrates potent antibacterial activity against *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), two pathogens commonly associated with diabetic wounds [42]. An important direction in diabetic foot ulcer management involves conductive polymer-based dressings capable of generating bioelectrical stimulation. Hydrogel matrices containing PPy or PANI have been shown to facilitate fibroblast migration, reduce inflammation, and increase expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α), thereby promoting angiogenesis [22]. A thermoresponsive hydrogel composed of sodium alginate (SA), *Antheraea pernyi* silk gland protein (ASGP), and poly(N-isopropylacrylamide) (PNIPAm) undergoes phase and volume transitions when exposed to temperatures above its LCST threshold. This process induces the release of water and therapeutic agents directly into the wound bed. The dressing additionally stimulates fibroblast proliferation and provides stable adhesion to damaged skin [43]. Another system consists of an injectable polyethylene glycol (PEG)-based hydrogel incorporating anthocyanidin as a visual pH probe and poly(L-lactic acid) (PLLA) microcapsules loaded with cefazolin. Drug release is triggered by ultrasound stimulation [44].

A particularly promising closed-loop platform is a multifunctional, flexible wireless smart bandage integrating both diagnostic and therapeutic components within a single system. Its architecture includes a flexible electrochemical pH sensor fabricated on a PET substrate for continuous monitoring of the ulcer microenvironment, an integrated microheater, a thermoresponsive PNIPAm hydrogel containing hydrophobic polycaprolactone (PCL) microparticles loaded with cefazolin, and a low-power Bluetooth communication module. The platform enables real-time wireless pH monitoring via smartphone and, upon detection of infection, permits remote activation of the microheater, thereby triggering controlled and gradual antibiotic release directly into the wound bed [45].

For the treatment of infected chronic wounds, a smart composite hydrogel based on methylcellulose (MC) crosslinked with citric acid and incorporating silver nanoparticles (AgNPs) has also been developed. Under alkaline conditions characteristic of infected wounds, ester bond hydrolysis results in expansion of the polymer network and subsequent release of silver nanoparticles, providing localized antibacterial activity [46].

Chapter 4. 3D Bioprinting Technology in Skin Tissue Engineering

4.1. Biophysical and Technical Aspects of Skin Substitute Printing

Three-dimensional skin bioprinting represents an innovative approach in regenerative medicine, involving the precise fabrication of functional tissue through the layer-by-layer deposition of biological materials, including living cells, biomaterials, pharmaceuticals, growth factors, and cellular DNA. The principal advantage of this technology lies in its precise spatial control over cell distribution within anatomically accurate tissue layers, as well as the ability to create grafts tailored to the unique size, shape, and depth of individual injuries. Autologous patient-derived cells may also be incorporated into these constructs. Owing to the complex pathophysiology of chronic wounds, skin substitutes frequently combine materials from multiple sources, including dermal and epidermal components as well as acellular structures. Collectively, these features ensure appropriate tissue functionality, long-term structural stability, and a substantial reduction in the risk of graft rejection. Depending on the required resolution and viscosity of the employed bioinks, tissue engineering applications utilize inkjet bioprinting, microextrusion bioprinting, and highly precise laser-assisted bioprinting techniques [47].

To function effectively, an engineered skin substitute should be capable of achieving hemostasis, absorbing wound exudate, protecting against external pathogens, facilitating the removal of necrotic tissue, and enabling efficient gas and water exchange. To accomplish these objectives, porous three-dimensional scaffolds or hydrogels are employed, allowing unrestricted migration of cells and molecules between the substitute and the wound site while simultaneously promoting the formation of natural collagen and elastin networks. The biomaterials used must also be biodegradable and non-immunogenic [48].

The therapeutic efficacy of advanced skin substitutes in ulcer treatment is directly influenced by the physical mechanisms underlying 3D printing technologies. Extrusion-based bioprinting, which relies on pneumatic or mechanical extrusion of material through a nozzle, offers versatility, cost-effectiveness, and

compatibility with highly viscous bioinks. This approach enables the layer-by-layer fabrication of constructs such as angiogenic alginate/chondroitin sulfate patches and PCL scaffolds loaded with levofloxacin. In diabetic wound models, these constructs promoted neovascularization, bacterial eradication, and extracellular matrix reconstruction. Inkjet bioprinting delivers materials in droplet form at high speed and with good resolution. However, it requires low viscosity bioinks and may expose cells to thermal or piezoelectric stress. Laser-assisted bioprinting (LAB) is a nozzle-free technique characterized by high resolution, exceptional precision, and excellent cell viability due to the absence of shear stress. Stereolithographic bioprinting (SLA), in turn, utilizes light energy to induce layer-by-layer polymerization of photosensitive bioinks. This technique minimizes the risk of phototoxicity while efficiently encapsulating living cells within hydrogels such as gelatin methacrylate (GelMA) and polyethylene glycol diacrylate (PEGDA). Digital light processing (DLP) bioprinting provides high-resolution fabrication of biomimetic microarchitectures capable of directing cellular behavior and tissue organization. Nevertheless, DLP remains limited by the restricted range of photocrosslinkable bioinks and the potential risk of phototoxicity [49].

4.2. *In Vitro* and *In Situ* Bioprinting Strategies Employing Advanced Cellular Components

In vitro bioprinting technology enables the fabrication of skin substitutes with complex cellular compositions to improve graft integration and wound healing outcomes. In the context of diabetic foot ulcers (DFUs), skin substitutes typically incorporate keratinocytes and fibroblasts embedded within biocompatible scaffolds. Because diabetic wounds exhibit reduced levels of proangiogenic signaling, skin substitutes have been developed containing a layer of neonatal human dermal fibroblasts, epidermal keratinocytes, and human dermal microvascular endothelial cells (ECs) suspended in a fibrin–collagen bioink to enhance vascularization. *In situ* bioprinting, employing automated robotic systems or *drop-on-demand* inkjet devices enables the direct application of multilayered cellular bioinks adapted to the irregular topography of wounds. Studies have demonstrated that wounds treated with direct in situ bioprinting healed more rapidly than those in control groups [50].

Early preclinical studies in mice, as well as initial clinical investigations, indicate promising outcomes for wound treatment using 3D bioprinting technologies, demonstrating significant improvements in wound closure, vascularization, and tissue regeneration compared with control groups [49]. This technology was successfully applied clinically in a 78-year-old patient with DFUs and multiple comorbidities, for whom limb amputation had initially been recommended due to extensive tissue necrosis and osteomyelitis. Instead, treatment involved transplantation of autologous minimally manipulated homologous adipose tissue (AMHAT). This intervention resulted in a reduction of wound area exceeding 75% by postoperative week 12, stimulated the formation of healthy granulation tissue, and was not associated with complications such as autolysis or infection [51].

Chronic diabetic wounds are characterized by a hypoxic microenvironment resulting from vascular damage, which reduces adenosine triphosphate (ATP) production and impairs wound healing. To address this challenge, a coaxial three-dimensional construct composed of gelatin methacrylate (GelMA) and alginate was developed using biphasic bioinks containing calcium peroxide (CaO_2) nanoparticles for oxygen generation and ATP-releasing liposomes. This scaffold enhanced cell proliferation and viability, thereby significantly accelerating wound healing [52].

4.3. Integration of Secretomes and Liposomal Carriers in 3D Bioprinting

Secretomes represent advanced biological components that can be incorporated into 3D-printed constructs. These conditioned media consist of cell-secreted products, including metabolites, ions, peptides, growth factors, cytokines, chemokines, and extracellular matrix (ECM) proteins. Their incorporation into porous hydrogel scaffolds enables controlled and sustained release within the wound microenvironment while protecting them from rapid enzymatic degradation. This strategy provides essential biochemical signals that accelerate wound healing by simultaneously promoting neovascularization, suppressing inflammation, and stimulating extracellular matrix remodeling [53].

An alternative strategy for enhancing the functionality of 3D wound dressings involves integrating polymer matrices with liposomes, which serve as stable carriers protecting sensitive antimicrobial and anti-inflammatory compounds from premature physicochemical degradation. Through coaxial bioprinting, two distinct bioinks can be combined within a single filament. Consequently, the antimicrobial agent is released during the first 24 hours, while liposomes continue to be released for up to 10 days, providing sustained therapeutic support and ensuring continuity of treatment [54].

4.4. Characteristics of Advanced 3D Dressings

Contemporary biomaterials used for skin reconstruction are primarily based on structural scaffolds or hydrogels, each possessing distinct physicochemical properties. Combining these materials can generate composite structures that capitalize on the advantages of both components. Scaffolds are most commonly fabricated from synthetic hydrophobic materials such as polycaprolactone (PCL), polylactic acid (PLA), or dermal matrices (Integra), thereby providing stable mechanical support for tissue integrity and promoting the formation of the bilayered epidermal–dermal structure. Hydrogels, in contrast, are hydrophilic polymer networks composed of natural or synthetic polymers, including polysaccharides, peptides, and glycosaminoglycans. Owing to their porous architecture, they exhibit soft mechanical properties and function as carriers for physical or biological agents. The introduction of 3D-printing technologies has transformed these composites into intelligent multifunctional wound dressings that can be classified into several categories depending on their therapeutic objectives (Table 4) [55].

Table 4. Classification and Advanced Functions of 3D-Printed Hydrogels in Wound Therapy [55].

Type of 3D-Printed Hydrogel	Mechanism of Action and Biochemical Characteristics
Hemostatic	Locally concentrate coagulation factors and exhibit strong adhesion to the wound surface, thereby isolating the wound from the external environment.
Anti-inflammatory	Through the incorporation of natural antioxidants (tea polyphenols, aloe vera gel, curcumin, ferulic acid, or clove oil), catechol-rich polymers, bioactive compounds and drugs (quercetin, doxycycline hydrochloride), or cerium metal–organic framework (MOF)-based nanozymes, these hydrogels reduce ROS levels and promote macrophage polarization toward the M2 phenotype.
Antibacterial	Eliminate bacteria through the release of antimicrobial agents (e.g., levofloxacin, lidocaine hydrochloride), natural compounds such as Manuka honey, photothermal therapy, or near-infrared (NIR)-responsive materials.
Self-healing	Prevent loss of structural integrity under mechanical stress through autonomous restoration of the polymer network via physical interactions (hydrogen bonding, electrostatic attraction, hydrophobic interactions) or dynamic covalent bonds.
Stimulus-responsive	Their porous network structure responds to physical, chemical, or biological stimuli, enabling precise and prolonged drug release.
Skin appendage-regenerating	Reduce scarring and fibrosis in deep wounds by promoting full-thickness skin regeneration, including hair follicles (HFs), sweat glands, and sebaceous glands.
Smart monitoring hydrogels	Monitor wound status in real time and present information visually through integrated sensing units equipped with biochemical sensors and data-transmission systems.

3D bioprinting enables the design of acellular hydrogel matrices containing bioactive compounds. Using this approach, hydrogels composed of calcium alginate and *Curcuma longa* L. (CR) have been developed, demonstrating promising potential as bioactive wound dressings [56]. Skin substitutes based on porcine skin-derived decellularized extracellular matrix (psECM) integrated with lithium octa-*n*-butoxynaphthalocyanine (LiNC-BuO) microsensors have also been engineered. In addition to promoting tissue repair, these constructs enable non-invasive monitoring of oxygen levels within the wound microenvironment through electron paramagnetic resonance spectroscopy (EPR/ESR), thereby facilitating optimization of decisions regarding adjunctive hyperbaric oxygen therapy. However, homogeneous dispersion of microsensors within the psECM bioink induced a localized immune response due to direct contact with host tissue. Therefore, future designs should ensure that the surface facing the wound bed remains entirely free of sensors [57].

A promising strategy for diabetic wound treatment involves dressings fabricated through the combination of electrospinning and 3D printing. A bilayer composite skin scaffold demonstrated efficacy both *in vitro* and *in vivo* for the repair of full-thickness skin defects. The outer epidermis-mimicking layer consists of a PCL membrane loaded with amoxicillin (AMX), whereas the inner dermis-mimicking layer comprises a sodium alginate–gelatin hydrogel incorporating recombinant human epidermal growth factor (rhEGF). This system exhibited excellent biocompatibility and enhanced cell adhesion and proliferation [58]. Phytotherapeutic hybrid scaffolds have also been developed to overcome the limitations of conventional antibiotic therapies. These constructs combine PCL fabricated using fused deposition modeling (FDM) with electrospun polycaprolactone–gelatin nanofibers containing peppermint or clove essential oil. Such scaffolds

demonstrated antibacterial activity, promoted cellular adhesion and proliferation, and reduced nitric oxide (NO) concentrations [59]. Another example of a bilayer wound dressing incorporates nanomicelles. Its outer nanofibrous layer consists of PCL, cellulose acetate (CA), and antibacterial chitosan–selenium nanoparticles (CS/SeNPs). The lower hydrogel layer is composed of sodium alginate, gelatin, and polyvinyl alcohol (SGPH), into which Pluronics@ nanomicelles loaded with the antioxidant rutin and the anti-inflammatory agent simvastatin have been incorporated. This bilayer system (PCL/CA2/LSGPH) inhibits *Escherichia coli* and *Staphylococcus aureus* growth, stimulates cell migration, and accelerates wound closure in vivo [60]. Auxetic hydrogel dressings have also been developed. Their matrix consists of polyvinyl alcohol, boric acid, gelatin, and citrate (PBGC), providing enhanced mechanical strength, self-healing capability, and the ability to expand under tensile loading while maintaining stable adhesion to mobile joints. This biocomposite incorporates $Ti_3C_2T_x$ MXene nanoparticles (MX) with antioxidant and anti-inflammatory properties, as well as carbonized polymer dots (CPDs), which exhibit antibacterial and pro-regenerative activities [61].

A promising future direction for 3D-printing technology is the integration of machine learning (ML), which may enable the fabrication of personalized hydrogel dressings tailored to wounds of varying geometries and depths. Furthermore, the implementation of multiplex sensors or convolutional neural networks (CNNs) supported by artificial intelligence (AI) could facilitate precise monitoring and assessment of wound healing processes [55].

Chapter 5. Discussion

5.1. Limitations and Clinical Challenges of Smart Dressings

Despite rapid advances in biomaterials engineering, contemporary smart wound dressing systems continue to face numerous technological, biological, and application-related limitations. Examples include inadequate adaptation to the changing stages of wound healing and the occurrence of burst release phenomena, both of which may compromise therapeutic efficacy [62].

Thermoresponsive hydrogels based on poly(N-isopropylacrylamide) (PNIPAM) and poloxamers often exhibit insufficient mechanical strength, brittleness, and rapid dissolution in wound exudate, making them susceptible to premature degradation and disruption of sustained drug-release profiles. Moreover, alterations in the wound microenvironment, including the acidic pH characteristic of infected tissues, may affect gelation behavior, increasing the risk of incomplete in situ gel formation and uncontrolled release of therapeutic agents. In addition, slowly degrading synthetic polymers may accumulate within tissues as foreign bodies, while residual catalysts or nanoparticles may induce cytotoxicity, oxidative stress, or chronic inflammatory responses [24].

A major challenge associated with wound-monitoring dressings is their frequent limitation to the detection of a single biomarker, thereby hindering comprehensive wound assessment. Consequently, there is a need for technological solutions capable of simultaneously measuring multiple parameters with high precision [32]. One potential solution involves the development of multizone sensor matrices. These systems comprise distinct, independent sensing regions within the dressing that can detect specific wound biomarkers either through direct contact with wound exudate or via microfluidic transport mechanisms. An alternative strategy that may circumvent the labor-intensive and multistep design process of multizone matrices involves the development of multiplex sandwich-structured dressings utilizing conductive zwitterionic hydrogels [63].

Additional challenges include limited battery life, the susceptibility of electronic circuits to damage when applied to mobile body regions, and the leakage or depletion of drug reservoirs [64]. Another limitation is the relatively small number of studies investigating smart dressings integrated with mobile technologies. Existing platforms have not yet been tested in human subjects and remain unavailable commercially. Consequently, the field of digitally assisted wound care remains at an early stage of development, underscoring the need for further research [31].

It is also important to note that most studies on smart dressings rely on short-term rodent models, which fail to adequately replicate human wound size, biomechanics, microbiological diversity, patient comorbidities, ischemia, and recurrent contamination (factors that are particularly relevant in diabetic wounds) [65]. Beyond engineering challenges, compliance with national and regional regulations governing medical devices, including their manufacturing, registration, distribution, and clinical use, represents a substantial barrier. The complexity and duration of these regulatory processes hinder market implementation. Therefore, comprehensive clinical trials and assessments of interindividual variability in therapeutic response remain essential [28].

5.2. Limitations and Clinical Challenges of 3D Bioprinting

The primary technological barrier in 3D bioprinting is the recreation of functional vascular networks, particularly in large-scale tissue constructs. Another persistent challenge is the trade-off between printing resolution and cell viability, as cells passing through narrow nozzles may be damaged by shear stress. Currently, the technology is also associated with high equipment and bioink costs, time-consuming manufacturing processes, and limited production throughput. As with smart dressings, 3D-bioprinted constructs require extensive long-term preclinical and clinical validation to comprehensively evaluate their efficacy and safety before market approval [50]. A further limitation involves host immune responses to implanted foreign materials, emphasizing the importance of employing highly biocompatible materials to minimize this risk. The degradation behavior of biomaterials also represents a critical consideration, as degradation rates directly influence construct functionality and wound-healing outcomes [66].

The incorporation of induced pluripotent stem cells (iPSCs) into 3D bioprinting procedures introduces complex ethical challenges resulting from their unlimited self-renewal capacity and broad differentiation potential. The use of iPSCs necessitates the establishment of standards governing long-term storage, provenance traceability (cell lineage tracking), informed consent procedures, strict oversight of cell distribution, and rigorous adherence to international bioethical regulations [67].

5.3. The Role of 4D Printing Technology in the Development of Dynamic Biomaterials

Another example of innovative solutions for chronic wound management is 4D printing technology. Its principal advantage over conventional 3D printing lies in the ability to undergo dynamic, controlled structural transformations in response to external stimuli. Through the incorporation of responsive materials such as shape-memory polymers (SMPs), hydrogels, and liquid-crystal polymers (LCPs), the resulting biocomposites exhibit autonomous shape morphing, self-assembly, and self-healing capabilities in response to specific environmental cues [19].

Four-dimensional printing technologies enable dynamic activation of structures through diverse physicochemical stimuli. The most widely employed triggers include thermal stimulation, achieved through either direct heating or remote thermal activation, as well as hydration-induced responses, both of which can induce shape transformation. Equally precise control may be achieved through light-based activation, in which exposure to specific wavelengths induces chemical or physical changes. Furthermore, transformation can be triggered by biochemical and chemical stimuli, including pH fluctuations, changes in ion concentrations, and enzymatic activity within the environment. Endogenous contractile forces generated by cells themselves may also induce structural transformation, thereby enabling accurate replication of dynamic biological processes. Magnetic stimulation can additionally induce mechanical actuation through the alignment of magnetic particles [68].

Biomaterials fabricated using 4D-printing technologies may offer an effective therapeutic approach for chronic wounds by actively mimicking biological healing mechanisms. Through programmed contraction, stimulus-responsive drug release, and self-repair capabilities, these materials may significantly enhance wound-healing efficiency. However, optimization of response kinetics and the ability to respond simultaneously to multiple stimuli remain major design challenges. Therefore, future research should focus on the development of highly sensitive and programmable materials [69].

Chapter 6. Conclusions

The development of responsive biomaterials and 3D bioprinting technologies is establishing new paradigms in the treatment of chronic wounds, particularly chronic diabetic wounds. The integration of hydrogel matrices with biosensors, closed-loop therapeutic systems, and artificial intelligence algorithms enables a transition from passive mechanical protection toward automated, personalized monitoring and real-time modulation of the wound microenvironment. Concurrently, 3D bioprinting techniques facilitate the precise reconstruction of the anatomical architecture of skin tissue using autologous cellular components, thereby reducing the risk of skin substitute rejection.

Despite the high *in vitro* efficacy demonstrated by these systems, their translation into clinical practice requires overcoming key limitations of both technologies, including insufficient mechanical stability, premature degradation of responsive hydrogels, and inadequate vascularization of skin substitutes. In parallel, 4D bioprinting technology is being developed to enable dynamic alterations in construct geometry and replication of the natural contractile processes of healing skin through the incorporation of responsive materials. However, commercialization of these platforms will require intensified long-term preclinical and clinical investigations, as well as the establishment of international regulatory standards for hybrid medical devices operating at the interface between wearable electronics and cell-based therapies.

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