Smart 3D-Printed Drug-Loaded Scaffolds for Skin Tissue Regeneration: Biomaterials, Fabrication Strategies, Therapeutic Applications, and Future Perspectives

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***Abstract*—Three-dimensional (3D) printing has become an advanced biofabrication approach for designing personalized scaffolds that combine structural support with controlled drug delivery for skin tissue regeneration. Traditional wound dressings mainly provide protection but have limited ability to overcome challenges such as inflammation, infection, poor vascularization, and delayed tissue repair. This review highlights recent progress (2021–2026) in smart 3D-printed drug-loaded scaffolds, focusing on biomaterials, printing technologies, therapeutic incorporation, and responsive drug delivery systems. Different fabrication methods, including extrusion printing, stereolithography, and fused deposition modeling, are discussed with emphasis on their advantages and applications in regenerative medicine. The role of natural, synthetic, and composite biomaterials in improving scaffold strength, biodegradation, and cellular interaction is explored. Emerging smart scaffolds responsive to biological stimuli, along with the integration of antibiotics, growth factors, and nanotherapeutics, are evaluated for enhanced wound healing. Future perspectives include AI-based design, 4D printing, biosensor integration, and personalized regenerative therapies.**

***Index Terms*—3D printing; Smart scaffolds; Drug delivery; Skin tissue regeneration; Wound healing; Biomaterials; Bioprinting; Regenerative medicine.**

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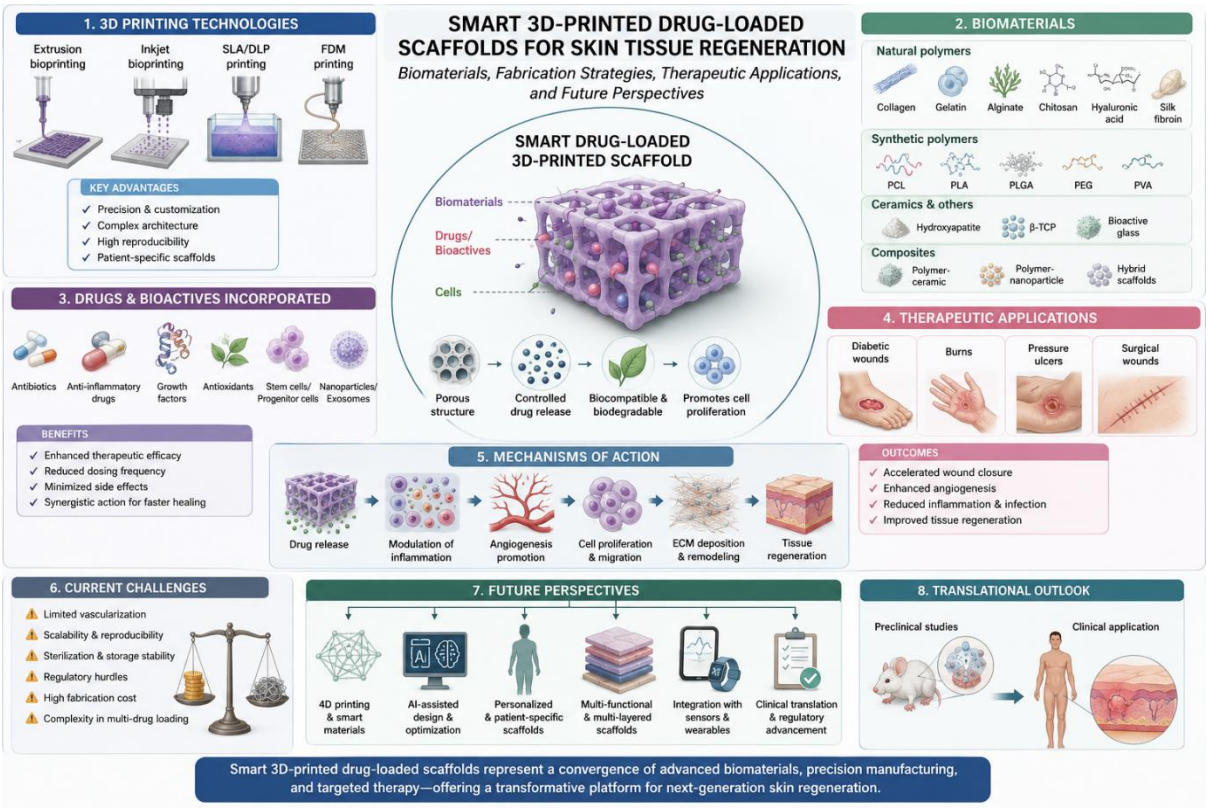

Graphical abstract illustrating the design and therapeutic concept of smart 3D-printed drug-loaded scaffolds for skin tissue regeneration. The schematic summarizes major 3D-printing technologies, biomaterial selection, incorporation of bioactive therapeutics, mechanisms of action, clinical applications, current challenges, and future perspectives, highlighting the integration of advanced biofabrication and controlled drug delivery for personalized wound healing.

I. INTRODUCATION

Smart three-dimensional (3D)-printed, drug-loaded scaffolds are emerging as transformative wound dressings that combine biomimetic architecture with controlled therapeutic delivery. This review critically examines recent advances (2021–2026) in smart 3D-printed skin scaffolds, encompassing skin anatomy and wound healing, scaffold design criteria, fabrication technologies, biomaterials, drug loading strategies, stimuli-responsive systems, quality control, biological evaluation, and clinical translation. Skin consists of the avascular epidermis, vascular dermis, and subcutaneous hypodermis, whose coordinated physiological functions regulate tissue repair. Wound healing progresses through four overlapping phases—hemostasis, inflammation, proliferation, and remodeling—whereas chronic wounds such as diabetic ulcers remain arrested in the inflammatory phase, resulting in delayed healing. **(1–5)** Key scaffold requirements include excellent biocompatibility, controlled biodegradation, interconnected porous architecture, and mechanical properties that closely resemble native skin tissue. These scaffolds should facilitate vascularization while providing sustained and programmable drug release according to the wound healing stage. Various additive manufacturing technologies—including fused deposition modeling (FDM), stereolithography (SLA), digital light processing (DLP), selective laser sintering (SLS), inkjet printing, extrusion-based bioprinting, and laser-assisted bioprinting—have been successfully employed to fabricate customized scaffolds. Natural polymers such as collagen, gelatin, fibrin, chitosan, alginate, silk fibroin, and hyaluronic acid exhibit excellent bioactivity, whereas synthetic polymers including polycaprolactone (PCL), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polyvinyl alcohol (PVA) provide superior mechanical stability. Composite scaffolds integrating these materials have demonstrated enhanced structural integrity and

improved wound healing performance compared with single-component scaffolds. (6–12)

Therapeutic agents are incorporated into scaffolds through blending, encapsulation, or surface immobilization. Antibiotics such as tetracycline, gentamicin, and silver nanoparticles prevent bacterial infection, whereas growth factors (VEGF, EGF, PDGF), stem cell-derived exosomes, and anti-inflammatory agents such as dexamethasone and curcumin promote angiogenesis, tissue regeneration, and immune modulation. Drug release may occur through diffusion, scaffold degradation, or externally triggered mechanisms. Ahangar et al. demonstrated prolonged tetracycline release from a porous polyurethane scaffold for up to 72 hours, highlighting the capability of 3D-printed scaffolds for sustained drug delivery. (13–17) Smart scaffolds further enhance therapeutic efficacy by responding to wound-specific physiological stimuli. pH-responsive systems selectively release antimicrobials within acidic wound environments, whereas reactive oxygen species (ROS)-responsive polymers scavenge excessive free radicals while simultaneously releasing therapeutic agents. Du et al. developed a multifunctional polydopamine-coated chitosan/collagen scaffold capable of sequentially releasing antimicrobial peptides, antioxidant enzymes, exosomes, and epidermal growth factor in diabetic wounds, significantly accelerating wound closure and appendage regeneration. Additional smart systems include thermo-responsive, enzyme-responsive, electrically conductive, and four-dimensional (4D)-printed scaffolds capable of dynamic adaptation during tissue repair. (18–22)

The fabrication process generally involves computer-aided design (CAD), additive manufacturing, crosslinking, sterilization, and quality assessment. Critical quality attributes include dimensional accuracy, pore architecture, mechanical strength, and drug loading efficiency, evaluated using microscopy, micro-computed tomography, mechanical testing, and analytical techniques. Compliance with regulatory requirements, including FDA medical device pathways and ISO standards, remains essential for clinical translation. However, large-scale manufacturing continues to face challenges related to sterilization, process reproducibility, equipment costs, and regulatory complexity. (23–27) Biological performance is assessed through comprehensive in vitro and in vivo investigations. Cytocompatibility, cell proliferation, migration assays, antimicrobial activity, and controlled drug release are commonly evaluated in vitro, whereas rodent wound models assess wound closure, collagen deposition, angiogenesis, and re-epithelialization. Recent studies have consistently demonstrated accelerated healing, improved collagen organization, reduced inflammation, and enhanced neovascularization following treatment with drug-loaded smart scaffolds. (18,28–31)

Clinical translation of 3D-printed skin scaffolds is rapidly progressing. A landmark first-in-human clinical study conducted at Concord Hospital (Sydney, Australia) evaluated the LIGŌ bioprinting platform for direct deposition of autologous skin cells and biomaterials onto burn wounds, representing a major advance toward personalized regenerative therapy. Although currently available commercial skin substitutes such as Integra® and Apligraf® remain conventionally manufactured, emerging bioprinting technologies are expected to enable fully patient-specific tissue-engineered constructs. (32–35) Despite significant progress, major challenges remain, including Good Manufacturing Practice (GMP) compliance, sterilization, manufacturing costs, ethical considerations, and regulatory approval. Future developments are expected to integrate artificial intelligence-driven scaffold design, digital twin technology, biosensors, real-time monitoring, advanced vascularization strategies, and personalized regenerative medicine. Collectively, smart 3D-printed drug-loaded scaffolds represent one of the most promising technologies for next-generation wound management by combining biomaterials science, drug delivery, biofabrication, and regenerative medicine. (36–40)

1.1 Skin Structure and Wound Healing

Human skin is the largest organ of the body and serves as the first line of defense against physical, chemical, microbial, and environmental insults. Structurally, it consists of three major layers: the epidermis, dermis, and hypodermis (subcutaneous tissue), each possessing distinct anatomical and physiological functions. The epidermis is an avascular, stratified squamous epithelium primarily composed of keratinocytes, along with melanocytes, Langerhans cells, and Merkel cells. It provides an effective barrier

against pathogens, ultraviolet (UV) radiation, and excessive water loss. Beneath the epidermis lies the vascular dermis, a connective tissue-rich layer composed predominantly of collagen types I and III, elastin fibers, fibroblasts, blood vessels, lymphatics, nerves, sweat glands, sebaceous glands, and hair follicles. The deepest layer, the hypodermis, consists mainly of adipose tissue that provides thermal insulation, mechanical cushioning, and energy storage while anchoring the skin to underlying tissues (41–45). Wound healing is a highly coordinated biological process involving complex interactions among inflammatory cells, extracellular matrix (ECM) components, cytokines, growth factors, and resident skin cells. The repair process is classically divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Immediately after injury, hemostasis is initiated through platelet aggregation and fibrin clot formation, which prevent blood loss and establish a provisional matrix for subsequent cellular migration. During the inflammatory phase, neutrophils rapidly infiltrate the wound to eliminate microorganisms and cellular debris, followed by macrophages that regulate inflammation through cytokine secretion and orchestrate tissue repair. The proliferative phase is characterized by fibroblast proliferation, collagen synthesis, angiogenesis, granulation tissue formation, and keratinocyte-mediated re-epithelialization. Finally, the remodeling phase involves extracellular matrix maturation, collagen fiber reorganization, and increased tensile strength of the repaired tissue over several months**.** (42,43,46–48). In contrast to acute wounds, chronic wounds—including diabetic foot ulcers, venous leg ulcers, and pressure ulcers—remain trapped in a prolonged inflammatory state because of persistent infection, ischemia, oxidative stress, impaired angiogenesis, and excessive protease activity. These pathological conditions disrupt normal extracellular matrix remodeling and significantly delay tissue regeneration. Consequently, advanced biomaterial-based therapeutic approaches, including drug-loaded smart 3D-printed scaffolds, have emerged as promising strategies to restore an appropriate wound microenvironment and accelerate tissue regeneration (4,5,29,49,50).

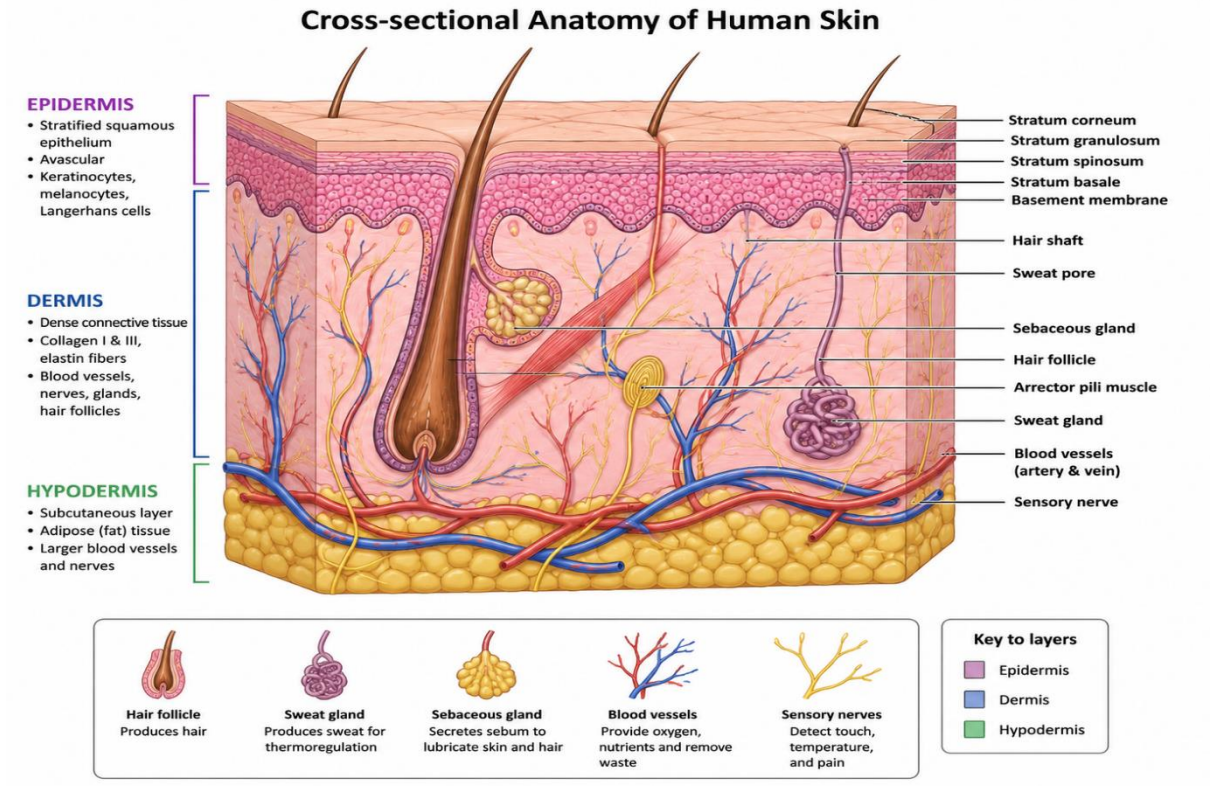

Figure 1. Cross-sectional anatomy of human skin illustrating the epidermis, dermis, and hypodermis, together with associated appendages including hair follicles, sweat glands, sebaceous glands, blood vessels, and sensory nerves. *Adapted from StatPearls and modified for review purposes.*

II. SCAFFOLD DESIGN CRITERIA

An ideal scaffold for skin tissue engineering should closely mimic the structural, biochemical, and mechanical characteristics of the native extracellular matrix while providing a temporary microenvironment that supports cellular attachment, proliferation, migration, and differentiation. The scaffold should exhibit excellent biocompatibility without inducing cytotoxicity, chronic inflammation, or adverse immune responses. Equally important is controlled biodegradability, allowing gradual scaffold degradation that corresponds with new tissue formation, thereby eliminating the need for surgical removal (9,12,17,51–53). Scaffold architecture plays a pivotal role in successful tissue regeneration. Highly interconnected porous structures facilitate oxygen diffusion, nutrient transport, waste removal, vascular infiltration, and cellular migration throughout the construct. Numerous studies suggest that pore size, porosity, and pore interconnectivity significantly influence angiogenesis, collagen deposition, and overall wound healing efficiency. Simultaneously, scaffolds must possess adequate tensile strength, elasticity, and flexibility to withstand physiological stresses while conforming to irregular wound geometries. Surface chemistry and topographical features should further promote protein adsorption, cell adhesion, and extracellular matrix deposition (11,17,29,52,54,55).

Beyond structural support, modern wound scaffolds are increasingly designed as multifunctional therapeutic platforms. Incorporation of antimicrobial agents effectively reduces bacterial colonization and biofilm formation, whereas sustained and programmable release of antibiotics, anti-inflammatory drugs, antioxidants, growth factors, stem cell-derived exosomes, or nucleic acids provides continuous therapeutic activity throughout the healing process. Drug release profiles may be engineered to achieve an initial burst release for infection control followed by prolonged delivery to stimulate angiogenesis and tissue remodeling **(13–22,56).** Recent advances in smart biomaterials have enabled scaffolds capable of responding dynamically to changes within the wound microenvironment. Stimuli-responsive scaffolds can sense alterations in pH, temperature, reactive oxygen species (ROS), enzyme concentration, electrical stimulation, or glucose levels and subsequently trigger controlled therapeutic release only when required. Such "on-demand" drug delivery minimizes systemic exposure while maximizing local therapeutic efficacy. Consequently, the next generation of wound scaffolds integrates biomimetic architecture, controlled biodegradation, mechanical robustness, bioactivity, antimicrobial functionality, and intelligent drug delivery into a single multifunctional platform for precision regenerative medicine (18–22,36–40,57–60).

III. 3D PRINTING TECHNOLOGIES

Additive manufacturing enables precise, patient-specific scaffold geometries. Table 1 compares major 3D printing modalities.

Technique	Principle	Materials	Resolution	Pros	Cons
FDM/FFF	Melted thermoplastic filament extrusion	Biodegradable polymers (PCL, PLA, PLGA)	~100–300 µm	Low-cost, simple, widely available, robust mechanical strength【48†L2-L9】	Heat may denature biomolecules/cells; coarser resolution; limited to thermoplastics
SLA (UV)	Laser photopolymerisation of resin	Photocurable resins (PEGDA, GelMA)	~20–100 µm	Very high resolution/detail; smooth surfaces; compatible with cell-laden	Resin toxicity, expensive, limited biomaterials, requires post-curing

				bioinks after UV-curing	
DLP	DLP projected light on resin	Photocurable hydrogels	~50–100 µm	Faster than SLA (whole layers at once); similar resolution	Same material limitations as SLA; light scattering
SLS	Laser sintering of powdered material	Thermoplastic/ceramic powders (PA12, PCL, ceramic)	~100–200 µm	No support structures needed (powder bed supports); can print complex 3D lattice	High temps; rough surface finish; expensive laser systems
Inkjet (Droplet)	Material jetting of micro-droplets	Low-viscosity hydrogels, cell inks	~50–100 µm	Can precisely dispense multiple materials/cells; non-contact	Drops can clog; limited viscosities; modest mechanical strength
Extrusion Bioprinting	Pneumatic/piston extrusion of viscous bioink	Cell-laden hydrogels (alginate, gelatin, ECM blends)	~100–200 µm	Direct cell printing; wide material viscosity range; multi-nozzle printing	Shear stress on cells; slower; lower resolution
Laser-Assisted (LIFT)	Laser-induced forward transfer	Protein/bio-ink droplets	~10–50 µm	No nozzle clogging; high resolution; gentle cell placement	Complex equipment; low throughput; high cost

Table 1. Comparison of 3D-printing techniques for scaffold fabrication. Resolution and capabilities vary; choice depends on material and cell/bioink compatibility. (Sources: general bioprinting literature.)

Each three-dimensional (3D) printing technology possesses unique advantages and limitations that influence its suitability for skin tissue engineering applications. Fused deposition modeling (FDM), also referred to as fused filament fabrication (FFF), is widely employed for fabricating polycaprolactone (PCL)-based scaffolds because of its simplicity, affordability, and excellent mechanical stability. However, the elevated printing temperatures required during filament extrusion prevent direct incorporation of living cells or temperature-sensitive biomolecules. In contrast, stereolithography (SLA) and digital light processing (DLP) enable fabrication of highly complex and high-resolution scaffold architectures through photopolymerization of liquid resins, although their successful application depends on the availability of cytocompatible photopolymers and photoinitiators (7–10,23,27,61–63). Inkjet bioprinting and extrusion-based bioprinting permit precise deposition of cell-laden bioinks under relatively mild processing conditions, making them highly attractive for engineering living skin constructs. Nevertheless, these technologies generally produce scaffolds with lower printing resolution and reduced mechanical strength compared with laser-based approaches. Laser-induced forward transfer (LIFT) bioprinting offers exceptional printing precision and high cell viability without nozzle clogging, although its high equipment cost and limited scalability currently restrict widespread clinical implementation. Consequently, hybrid manufacturing strategies have emerged as promising alternatives. For example, mechanically robust PCL

frameworks fabricated by FDM can be combined with cell-laden hydrogel matrices produced by extrusion bioprinting, thereby integrating superior mechanical properties with enhanced biological performance and cellular functionality (6–10,20,61–64).

IV. BIOMATERIALS FOR SMART 3D-PRINTED SCAFFOLDS

The biological performance of three-dimensional printed scaffolds is largely governed by the physicochemical properties of the biomaterials used during fabrication. An ideal scaffold material should exhibit excellent biocompatibility, controlled biodegradability, suitable mechanical strength, and the capacity to support cell attachment, proliferation, migration, and extracellular matrix (ECM) deposition. Current biomaterials used in skin tissue engineering are broadly classified into natural polymers, synthetic polymers, bioactive ceramics, and composite materials (Table 2) (11,12,17,51,65).

4.1 Natural Polymers

Natural polymers closely resemble the native extracellular matrix and therefore possess excellent biological recognition and cell-interactive properties. Their intrinsic bioactivity makes them particularly attractive for wound healing applications despite their relatively poor mechanical stability.

- Collagen: Collagen is the most abundant structural protein within the extracellular matrix and represents one of the most extensively investigated biomaterials for skin tissue engineering. Owing to the presence of arginine-glycine-aspartic acid (RGD) sequences, collagen promotes cell adhesion, proliferation, and differentiation while exhibiting excellent biocompatibility and biodegradability. However, its limited mechanical strength and rapid enzymatic degradation often necessitate chemical crosslinking or combination with synthetic polymers (12,41,51,66,67).
- Gelatin: Gelatin, a denatured derivative of collagen, retains numerous cell-binding domains while exhibiting improved water solubility and processability. Methacrylated gelatin (GelMA) has become one of the most widely employed bioinks because it can be photocrosslinked during stereolithographic and extrusion bioprinting processes, enabling fabrication of highly cell-compatible hydrogel scaffolds. Nevertheless, gelatin alone possesses limited mechanical stability and relatively rapid degradation (8,12,67–69).
- Fibrin: Fibrin is a naturally occurring biopolymer generated during blood coagulation and plays a critical role in early wound healing. Its excellent biodegradability, angiogenic potential, and ability to support fibroblast migration make it an attractive material for acute wound dressings and bioinks. However, rapid enzymatic degradation and limited mechanical integrity restrict its application as a standalone scaffold material (41,46,67,70).
- Elastin: Elastin contributes to the elasticity and resilience of native skin tissues. Incorporation of elastin into collagen- or gelatin-based scaffolds improves elasticity, enhances cellular interactions, and better mimics the mechanical behavior of healthy dermal tissue. Consequently, elastin-containing composite scaffolds have demonstrated promising outcomes for soft tissue regeneration (65,71).
- Chitosan: Chitosan is a naturally derived polysaccharide obtained through deacetylation of chitin. Besides excellent biocompatibility, chitosan exhibits intrinsic antimicrobial activity, promotes hemostasis, stimulates fibroblast proliferation, and accelerates collagen deposition. Because chitosan is soluble under acidic conditions, its degradation profile can be precisely regulated through blending or chemical crosslinking with other polymers (11,15,17,65,72,73).
- Alginate: Alginate is an anionic polysaccharide extracted from brown seaweed that rapidly forms hydrogels in the presence of divalent calcium ions. Alginate hydrogels possess excellent biocompatibility and moisture-retention capacity, making them particularly suitable for wound dressings. However, because alginate lacks intrinsic cell-adhesion motifs, it is frequently combined with collagen, gelatin, or RGD peptides to improve cellular attachment and proliferation (12,65,74).
- Hyaluronic Acid: Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan widely

distributed throughout the extracellular matrix of skin. Owing to its remarkable hydrophilicity and involvement in cellular signaling pathways, HA promotes angiogenesis, cell migration, and tissue regeneration. Crosslinked HA hydrogels exhibit improved mechanical stability while remaining susceptible to enzymatic degradation by hyaluronidases during tissue remodeling (12,17,65,75).

- Silk Fibroin: Silk fibroin, derived primarily from *Bombyx mori* silkworm cocoons, possesses exceptional tensile strength, biocompatibility, and tunable degradation kinetics. Recent investigations have demonstrated that silk fibroin-based scaffolds significantly enhance collagen deposition, reduce inflammatory responses, and support long-term skin regeneration, making them promising candidates for chronic wound management (11,15,65,76).
- Keratin: Keratin, obtained from human hair or wool, contains abundant cell-binding peptides that facilitate cellular adhesion and proliferation. Keratin-based biomaterials have been successfully fabricated into films, hydrogels, sponges, and electrospun fibers for hemostatic dressings and skin regeneration applications because of their excellent biocompatibility and regenerative potential (65,77).

Table 2. Representative biomaterials for 3D-printed skin scaffolds. Natural ECM components (collagen, fibrin) provide cell cues, while synthetic polymers allow processability and strength.

Material Class	Examples	Biodegradation	Mechanical	Biofunction
Natural proteins	Collagen, gelatin, fibrin	Enzymatic (days–weeks)	Soft (Young's modulus ~1–10 MPa in gels)	Cell-adhesive (RGD), pro-healing
	Elastin, keratin	Slow enzymatic	Elastic (Elastin modulus ~1–2 MPa)	Elasticity (elastin); durable structure (keratin)
Polysaccharides	Chitosan, alginate, HA	Ionic/enzymatic	Hydrogel (modulus <1 MPa)	Hemostatic (chitosan); hydrating (HA)
Synthetic polymers	PCL, PLA/PLGA, PEG, PVA	Hydrolytic (weeks–years)	Tunable: PCL (∼10–100 MPa), PEG gel (~0.1–1 MPa)	Structural support (PCL/PLA); hydration (PEG)
Ceramics/glasses	Hydroxyapatite, β-TCP, bioactive glass	Dissolution/resorption (months–years)	Brittle; hard (∼1 GPa for HA)	Osteogenic (bone integration); ionic stimulation
Composites	PCL/collagen, gel/silica	Combined modes	Intermediate properties	Synergistic: combined strength and bioactivity

V. THERAPEUTIC LOADING AND DRUG RELEASE MECHANISMS

The incorporation of therapeutic agents into three-dimensional (3D)-printed scaffolds transforms passive structural matrices into multifunctional bioactive wound dressings capable of providing localized and sustained therapeutic effects. Drug-loaded scaffolds not only provide mechanical support for tissue regeneration but also create a favorable microenvironment by controlling infection, modulating inflammation, promoting angiogenesis, and stimulating cellular proliferation. Compared with conventional topical formulations, localized drug delivery minimizes systemic toxicity, improves drug bioavailability at the wound site, and reduces the frequency of dressing replacement (13–17,56,78–80). A wide variety of therapeutic molecules have been successfully incorporated into smart scaffolds depending on the desired biological response.

Antibacterial agents, including tetracycline, gentamicin, vancomycin, ciprofloxacin, and silver nanoparticles, are commonly employed to prevent bacterial colonization and biofilm formation, particularly in chronic diabetic wounds. Growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β) stimulate angiogenesis, fibroblast proliferation, extracellular matrix deposition, and re-epithelialization. Anti-inflammatory agents including dexamethasone, curcumin, and non-steroidal anti-inflammatory drugs regulate excessive inflammatory responses, whereas stem cells and mesenchymal stem cell-derived exosomes provide paracrine signaling molecules that accelerate tissue regeneration through immunomodulation and enhanced cellular communication (13–22,56,65,79–82). Various strategies have been developed to incorporate therapeutic agents into 3D-printed scaffolds. The simplest approach involves direct blending of drugs within the printing bioink, polymer solution, or thermoplastic filament prior to fabrication. Alternatively, therapeutic compounds may be immobilized onto scaffold surfaces through physical adsorption, covalent conjugation, or layer-by-layer coating following scaffold fabrication. More advanced delivery systems utilize drug-loaded nanoparticles, liposomes, microspheres, nanofibers, or hydrogel microcarriers dispersed throughout the scaffold matrix, enabling improved drug encapsulation efficiency and precisely controlled release kinetics while protecting sensitive biomolecules from degradation during the printing process (13,16,17,56,80,83–85).

Drug release from 3D-printed scaffolds is primarily governed by diffusion, polymer degradation, swelling behavior, and matrix erosion. Surface-associated therapeutic molecules typically produce an initial burst release that rapidly establishes therapeutic drug concentrations and suppresses microbial contamination during the early inflammatory phase. Subsequently, sustained drug release occurs through gradual diffusion and scaffold biodegradation, thereby maintaining therapeutic concentrations throughout tissue regeneration. The release profile can be precisely tailored by modifying scaffold porosity, polymer composition, crosslinking density, molecular weight, or incorporation of nanocarriers. Such programmable release systems ensure prolonged therapeutic efficacy while minimizing repeated drug administration (13–17,56,79,83,86). A representative example was reported by Ahangar et al., who fabricated porous polyurethane scaffolds using LAY-FOMM and LAY-FELT filaments containing tetracycline hydrochloride. Their study demonstrated sustained antibiotic release over a 72-hour period, with only approximately 30–40% of the incorporated drug released during the experimental timeframe, indicating effective prolonged drug delivery compared with conventional absorbent paper dressings. The porous architecture significantly influenced diffusion kinetics, highlighting the importance of scaffold microstructure in regulating therapeutic release (17,87).

Recent advances have focused on stimuli-responsive or "smart" drug delivery systems capable of responding dynamically to changes within the wound microenvironment. Du et al. developed a multifunctional pH-responsive scaffold consisting of a polydopamine-coated chitosan/collagen matrix that selectively degraded under acidic inflammatory conditions. This intelligent scaffold exhibited sequential therapeutic release, initially delivering antimicrobial peptides and antioxidant enzymes to eradicate infection and reduce oxidative stress, followed by sustained release of epidermal growth factor (EGF) and mesenchymal stem cell-derived exosomes to promote angiogenesis, collagen deposition, and complete skin regeneration. Such hierarchical release profiles closely mimic the natural sequence of wound healing events and significantly improve therapeutic outcomes in diabetic wound models (18,20,57,88). In addition to pH-responsive systems, several other smart drug delivery mechanisms have been explored. Enzyme-responsive scaffolds utilize matrix metalloproteinase (MMP)-cleavable peptide linkers that selectively degrade in chronic wounds exhibiting elevated protease activity. Thermoresponsive hydrogels, particularly those based on poly(N-isopropylacrylamide) (PNIPAAm), undergo reversible phase transitions near physiological temperature, enabling controlled temperature-dependent drug release. Electrically conductive hydrogels fabricated using conductive polymers or carbon nanomaterials can release therapeutic agents upon external electrical stimulation,

offering opportunities for integration with wearable wound monitoring devices. Furthermore, reactive oxygen species (ROS)-responsive biomaterials containing thioether, thioketal, or boronic ester linkages simultaneously scavenge excessive free radicals while undergoing controlled degradation, thereby coupling antioxidant activity with site-specific therapeutic release. These intelligent delivery systems represent an important step toward personalized, adaptive wound management and next-generation precision regenerative medicine (20–22,36–40,57,58,89–92).

Table 3 summarizes drug-loading strategies. In practice, multiple agents (antibiotic + growth factor) are often co-delivered to address the wound's multifactorial needs.

Therapeutic Agent	Purpose	Delivery Strategy	Release Mechanism
Antibiotics (e.g. tetracycline, gentamicin, silver NPs)	Prevent/treat infection	Blended in polymer or in microspheres; surface adsorbed	Diffusion out or polymer erosion (possibly pH-responsive)
Growth Factors (VEGF, bFGF, EGF)	Stimulate angiogenesis, fibroblast/keratinocyte growth	Encapsulated in microspheres or covalently bound to matrix; layered scaffold designs	Enzymatic degradation of carrier (MMPs in wound) or hydrolytic release
Stem cells/Exosomes	Paracrine signalling for regeneration	Loaded in hydrogel core; protected by outer layer	Release after shell degradation (e.g. pH-trigger)
Anti-inflammatories (Dex, NSAIDs, curcumin)	Modulate excessive inflammation	Incorporated in scaffold matrix or nanocarriers	Sustained diffusion or degradation-mediated
Angiogenic peptides/GFs	Promote neovascularisation	Impregnated in ECM-like hydrogels	Gradual matrix breakdown releases factors
Nanoparticles (AgNP, AuNP)	Antimicrobial, imaging	Mixed into polymer or coated on scaffold fibers	Slow dissolution (Ag^+) or triggered by light/heat

Table 3. Drug-loading strategies for 3D-printed wound scaffolds. Co-delivery of multiple drugs (e.g. antibiotic+growth factor) is common. Triggers (pH, enzymes, light) can be built in for on-6. Smart (Stimuli-Responsive) Scaffolds

"Smart" scaffolds incorporate biomaterials capable of sensing changes within the wound microenvironment and responding through controlled therapeutic release. pH-responsive systems exploit the acidic environment commonly observed in chronic wounds (pH 6.0–6.5), where acid-cleavable polymers or coatings, such as polydopamine (PDA)-modified chitosan, release therapeutic payloads under inflammatory conditions. Reactive oxygen species (ROS)-responsive scaffolds contain ROS-cleavable bonds, including thioketal or boronic ester linkages, enabling simultaneous scavenging of excessive oxidative radicals and controlled drug release. Likewise, enzyme-responsive scaffolds utilize matrix metalloproteinase (MMP)-sensitive peptide linkers that selectively degrade in protease-rich chronic wounds. Thermoresponsive hydrogels based on Pluronic F127 or poly(N-isopropylacrylamide) (PNIPAAm) undergo sol-gel transition at physiological temperature, whereas electroactive scaffolds fabricated with conductive polymers such as polypyrrole or graphene facilitate electrically stimulated drug release and enhanced cell migration. Four-dimensional (4D) printing further extends scaffold functionality by employing shape-memory polymers capable of changing shape or stiffness after implantation, thereby mimicking the dynamic extracellular matrix during wound healing (18–22,57,58,89–92,93–98).

VII. FABRICATION WORKFLOW AND QUALITY CONTROL

The fabrication of smart 3D-printed scaffolds generally begins with computer-aided design (CAD) or patient-specific imaging data to define scaffold geometry and pore architecture. Following biomaterial and bioink preparation, printing parameters such as extrusion pressure, nozzle temperature, printing speed, and ultraviolet exposure are carefully optimized to ensure structural fidelity. Subsequent post-processing includes crosslinking, curing, sterilization, and dimensional finishing before biological evaluation.

Quality control encompasses dimensional accuracy, pore size analysis, porosity measurements, mechanical characterization, physicochemical analysis, drug content uniformity, sterility testing, and cell viability assessment for cell-laden constructs. Compliance with ISO 10993 standards, Good Manufacturing Practice (GMP), batch traceability, and process validation is essential for regulatory approval. Sterilization remains particularly challenging because highly porous scaffolds may be damaged by heat or radiation while residual sterilants may compromise biocompatibility (23–27,61–65,99–105).

VIII. IN VITRO AND IN VIVO EVALUATION

Comprehensive biological evaluation is essential before clinical translation of smart scaffolds. In vitro studies commonly include cytocompatibility assays, Live/Dead staining, cell proliferation analysis, scratch migration assays, antibacterial testing, and controlled drug release studies under simulated wound conditions. In vivo investigations primarily utilize rodent excisional wound models, diabetic wound models, and occasionally porcine models owing to their closer resemblance to human skin. Therapeutic efficacy is evaluated through wound closure rate, collagen deposition, angiogenesis, granulation tissue formation, re-epithelialization, inflammatory cytokine expression, macrophage polarization, and biomechanical strength of regenerated tissue. Numerous studies, including those by Du et al. and Qi et al., have demonstrated significantly accelerated wound healing, enhanced collagen organization, increased vascularization, and reduced inflammatory responses using drug-loaded smart scaffolds compared with conventional dressings or blank scaffolds (18,28–31,56,87,88,106–111).

IX. CLINICAL APPLICATIONS AND CLINICAL TRANSLATION

The primary clinical applications of smart 3D-printed scaffolds include burn injuries, diabetic foot ulcers, pressure ulcers, venous leg ulcers, traumatic wounds, and postoperative soft-tissue defects. Composite scaffolds incorporating antimicrobial and angiogenic therapeutics have demonstrated promising outcomes in chronic wound management. A major milestone in clinical translation is the first-in-human clinical evaluation of the LIGŌ bioprinting platform developed by Inventia Life Science in collaboration with Concord Hospital (Sydney, Australia), where autologous skin cells suspended within biomaterial bioinks are directly printed onto burn wounds to eliminate the need for conventional skin graft harvesting. Existing commercial skin substitutes such as Apligraf® and Dermagraft® remain conventionally manufactured; however, three-dimensional bioprinting offers unprecedented opportunities for personalized, patient-specific regenerative therapies. Although multicenter randomized clinical trials remain limited, several pilot studies have demonstrated encouraging safety and efficacy outcomes, highlighting the growing translational potential of smart biofabricated wound dressings (32–35,112–116).

X. REGULATORY CHALLENGES, STERILIZATION, SCALE-UP AND ETHICAL CONSIDERATIONS

Successful commercialization of smart 3D-printed scaffolds requires compliance with stringent regulatory frameworks governing medical devices and tissue-engineered products. In the United States, additive-manufactured scaffolds are regulated by the Food and Drug Administration (FDA) under either the 510(k) or Premarket Approval (PMA) pathways depending on device classification. Comprehensive biocompatibility testing according to ISO 10993 standards, Good Manufacturing Practice (GMP), aseptic processing, and validated manufacturing protocols are mandatory. Sterilization remains one of the greatest technical challenges because porous constructs are susceptible to structural damage during thermal or radiation sterilization, while ethylene oxide treatment requires prolonged aeration to eliminate toxic residues. Furthermore, large-scale manufacturing is limited by expensive bioprinting equipment, specialized cleanroom facilities, lengthy fabrication times, and skilled personnel requirements. Ethical considerations include donor cell sourcing, animal experimentation, equitable access to advanced therapies, and the cost-effectiveness of personalized regenerative medicine (23–27,99–105,117–123).

XI. FUTURE PERSPECTIVES

Future developments in smart wound scaffolds are expected to integrate artificial intelligence (AI), machine learning (ML), digital twin technology, biosensors, robotics, and precision medicine into next-generation regenerative platforms. AI-driven computational models can optimize scaffold geometry, pore distribution, mechanical properties, and drug release profiles using patient-specific clinical data. Integration of biosensors capable of continuously monitoring wound pH, oxygen concentration, glucose, temperature, or bacterial infection may enable closed-loop therapeutic systems that automatically adjust drug release in real time. Emerging four-dimensional (4D) biomaterials, self-healing hydrogels, vascularized bioinks, and robotic bioprinting technologies are anticipated to further enhance scaffold performance and clinical translation. Collectively, these innovations are expected to transform personalized wound management by combining intelligent biomaterials with digital healthcare technologies (36–40,57–60,91,92,124–130).

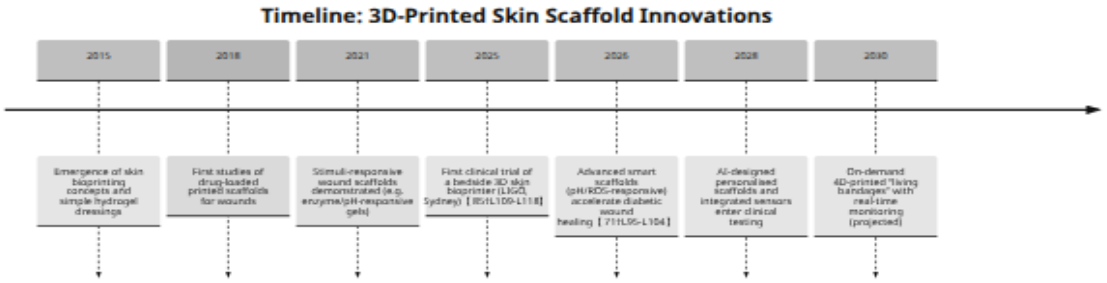

Figure 2. Roadmap of milestones in 3D-printed wound scaffolds (5-year periods). Notable events are highlighted with references. (After 2030, developments are speculative.)

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