

Novel Drug Delivery Systems for Scarless Wound Healing

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Abstract:

Wound healing is a complex biological process that often results in pathological scarring with major functional and cosmetic impact. Effective scarless wound healing remains a big concern despite advances in pharmacological therapy. This study reviews the recent progress of biomaterial-based drug delivery methods for scarless wound healing. The design methodology, mechanisms of action and therapeutic benefits of five main platforms (hydrogels, microspheres, nanofibers, microneedles, and exosomes) are described. New combinatorial approaches that combine several platforms like hydrogel-nanofiber composites and microneedle-assisted exosome delivery are explored too, emphasizing their complementary benefits in attaining improved therapeutic efficacy and spatiotemporal control over drug release. However, clinical translation of these promising preclinical findings is impeded by fundamental challenges including industrial scalability, long-term biosafety, regulatory ambiguity, and differences between animal models and human wound biology. The review closes with a potential roadmap to overcome the gap towards scarless wound healing.

Keywords: drug delivery; scarless; wound healing; microneedles; hydrogels; microspheres; nanofibers; exosomes

1. Introduction

A wound is characterized by a disruption of the skin's structure or function caused by several stressors¹. Fibrotic lesions, which are known as pathological scars, arise from abnormal wound healing after tissue injury, including burns. Scars are often linked to deformity and dysfunction, significantly diminishing life quality for affected individuals^{2,3}. Globally, around 100 million individuals are impacted by scar-related disorders, with expenses beyond \$20 billion^{2,4}. Increased wound size results in elevated expression of fibrotic and pro-inflammatory genes that lead to inflammatory responses and fibrous hyperplasia, ultimately culminating in scar formation. Moreover, under mechanical tension, reticular dermis fibroblasts are more liable to differentiate into myofibroblasts, thus increasing fibrosis⁵. Wound healing is a multi-phase dynamic process that encompasses hemostasis, tissue regeneration, cellular proliferation, and matrix remodeling^{1,6}. Pathologically, a scar is not the end of the healing process, and is an imbalance because of interrelated inflammation, proliferation, and remodeling phases. In this process, the transforming growth factor-beta (TGF-β)/Smad

axis plays a critical role in early healing, but then leads to fibrosis via myofibroblast differentiation and excessive accumulation of collagen⁷.

In addition to the TGF-β pathway, scar development has been associated with several signaling pathways such as integrin, PI3K/AKT and Wnt pathways⁸.

As a master regulator of mechanotransduction, YAP/TAZ (Yes-associated protein/Transcriptional coactivator with PDZ-binding motif) is essential for transmitting extracellular mechanical signals to the nucleus in order to start downstream biochemical signaling⁹. According to reports, the mechanism of scar development is the ongoing activation of YAP, which causes excessive ECM deposition and fibrosis¹⁰.

Despite the widespread use of traditional wound healing formulations in clinical practice, such as gauze, cotton cloth, and surgical sutures, there are drawbacks, including inadequate adhesiveness and the need for foreign objects for additional fixation around the wound¹¹. Traditional wound care procedures and conventional dressings simply cover up the wound defect and must be changed frequently. Such techniques often encounter challenges such as slow recovery and infection. This has led to the development of new therapeutic strategies. Because of

their potential to enhance tissue repair and drug delivery, nanomaterial-based devices offer significant advantages in this regard^{1,6}.

Laser therapy, surgical procedures, and corticosteroid injections are examples of current treatments that frequently have high recurrence rates, poor efficacy, and unfavorable side effects, such as dermal atrophy. Besides that, the dense structure and extensive extracellular matrix deposits in scar tissue constitute a considerable obstacle to efficient drug penetration, thereby restricting therapeutic effectiveness.²

A paradigm shift in scar treatment technique is currently underway, moving from a corrective method that targets mature scars to a preventive approach that promotes scarless wound healing¹². Conventional passive coverage products have given way to sophisticated dressing systems that include multimodal therapies in modern wound care techniques.¹³ This review summarizes the latest applications of novel drug delivery systems combined with biomaterials in the field of scarless wound healing. This review focuses on five key biomaterial platforms—hydrogels, microspheres, nanofibers, microneedles, and exosomes—and their engineering methodologies for facilitating scarless wound healing. During the dynamic phases of inflammation, proliferation, and remodeling, these platforms precisely control immune and growth signals on demand, enabling multi-targeted, sequential intervention in pathological conditions¹².

2. Biomaterial-based Platforms for Drug Delivery

Sustained release, targeted transport, and improved medication stability are made possible by biomaterial-based delivery systems.² Recent developments in biomaterials provide a promising solution to the challenge of scar-free wound healing.¹⁴ Hydrogels, with their 3D hydrophilic networks, are best suited for creating a moist wound environment and delivering drugs in a sustained manner.^{15,16} Microspheres, due to their spherical geometry and injectability, enable minimally invasive delivery of multiple therapeutics^{17–19}. Nanofibers, by mimicking the native ECM architecture, provide topographical cues for cell migration.²⁰ Here, the most recently developed biomaterial-based drug delivery platforms will be discussed.

2.1. Hydrogels

Hydrogels have garnered significant attention among biomaterials because of their excellent biodegradability, biocompatibility, and tunable properties.¹⁴ Hydrogels are highly hydrated, biocompatible, three-dimensional polymer networks with mechanical adaptability, which accurately replicate the native tissue environment, making them suitable for wound-healing applications.⁴ The inherent porous structure of hydrogels renders them ideally suited for the efficient loading of various substances and their progressive release at designated places.^{21,22}

Their nanoporous nature, which can restrict cell migration and invasion when applied as dressings, is one significant problem. Furthermore, the healing process may be hampered by the limited diffusion through these nanopores. Regeneration is further delayed by inadequate porosity, which frequently leads to inadequate vascularization and a slow release of integrated medications. This problem has led to research into microgels, a novel type of hydrogel material, as a possible substitute for conventional nanoporous hydrogel systems. Microgels are attractive because of their microporosity, injectability, high surface area-to-volume ratio, and ability to create appropriate microenvironments for revascularization and cell invasion, thereby promoting expedited and efficient regeneration. Microgels - small microparticles created from hydrogel materials - have recently been studied as a potential substitute.^{23,24}

Hydrogels naturally exhibit a high water content, which is beneficial for the hydration of wounds.²¹ Beyond this inherent property, hydrogels for wound-dressing applications must meet several essential characteristics. An optimal wound dressing must provide a moist environment, facilitate gaseous exchange, absorb exudates, encourage cellular proliferation, and prevent the growth of bacteria.²⁵ The superior swelling capacity of hydrogels facilitates the efficient absorption of wound exudates.¹⁴

Hydrogels can function as delivery vehicles for bioactive compounds, allowing for regulated and sustained release of stem cell-derived vesicles, growth factors, and pharmaceuticals.¹⁴

Hydrogel-based dressings are moving from passive wound dressing to controlled therapeutic systems that can actively regulate the wound microenvironment.⁴

Functionalized hydrogels with specific anti-scarring peptides, such as LA-peptide, actively absorb excessive TGF- β in the wound environment, thereby suppressing

the TGF- β /Smad2/3 and PI3K/AKT signaling pathways in fibroblasts and macrophages. This inhibits fibroblast activation and proliferation and attenuates M2 macrophage polarization, reducing extracellular matrix accumulation while not delaying wound epithelialization^{26,27}.

Verteporfin (VP) was incorporated into hydrogels as a YAP inhibitor for wound-healing treatment. This approach was efficient in inhibiting YAP expression and nuclear localization, blocking activation of Engrailed-1 (En1), reducing fibrotic progression, and ultimately leading to scar-prevention results^{10,12}. YAP signaling inhibition affects mechanotransduction-related signaling, shifting the fibroblast identity from a proscarring fibroblast (EPF) to a proregenerative fibroblast (ENF) phenotype, therefore promoting tissue regeneration¹². YAP/TAZ signaling is responsive to the degradability and stiffness of hydrogels, although the response depends on the dimensionality of cell-biomaterial interactions⁹.

Lin et al. designed a dual-network hydrogel that enables the controlled release of bioactive compounds, thereby dramatically increasing macrophage polarization toward the M2 phenotype and downregulating inflammatory markers such as IL-6 and TNF- α . This double process may decrease the inflammatory phase duration for wound healing and, hence, decrease the likelihood of scar formation²⁸.

The design of hydrogel systems can be customized to achieve specific therapeutic outcomes. One method is to design hydrogels with distinct mechanical properties and degradation rates in each layer, enabling sequential drug release in alignment with the stages of wound healing. Zhang et al. developed a double-layer hydrogel technology for sequential drug release, tailored to the stage-specific requirements of wound healing.¹⁴ The lower layer, comprising chitosan nanoparticles loaded with curcumin, exhibits initial antioxidant and anti-inflammatory benefits, whilst the upper layer, containing gelatin microspheres encapsulated with pirfenidone, demonstrates late-stage anti-fibrotic action. Swelling trials demonstrated that the rate of swelling was significantly higher in the lower layer than in the upper layer. The degradation characteristics of this system were evaluated in PBS to replicate in vivo circumstances. The lower hydrogel layer exhibited faster disintegration, with roughly 75% breakdown by day 3, whereas at the same time point, the upper layer maintained approximately 50% of its mass. This different degradation corresponded with the design objective, facilitating sequential medication release to fit with the healing processes.¹⁴

Thermosensitive hydrogels represent an alternative approach for wound-healing applications. Researchers

created a simple injectable hybrid hydrogel (PF-127@ERD) infused with eriodictyol, demonstrating effective, continuous release of the scar-inhibiting agent across multiple phases of wound healing, promoting swift, scarless closure. Their results indicated that PF-127@ERD not only halts hemorrhage and mitigates local oxidative stress in cutaneous wounds but also modulates the inflammatory microenvironment through inhibiting pertinent inflammatory marker expression while facilitating the migration of fibroblasts. Moreover, PF-127@ERD inhibits excess collagen accumulation and modulates the expression of genes involved in scar formation, therefore facilitating scar-free wound healing. This simple hydrogel, depending on the skin regeneration phase, has significant potential for achieving scarless wound healing.²⁹

The physicochemical characteristics of hydrogels can be altered to improve their efficacy. In Yan et al.'s work, a Gallic acid nanocrystal hydrogel (GC-NCs-Gel) exhibiting anti-inflammatory, antibacterial, and antioxidant properties and wound tissue adhesion was synthesized. This versatile hydrogel offers significant benefits for wound healing and is anticipated to serve as a novel, effective method for wound therapy in clinical settings. GC-NCs-Gels show remarkable swelling characteristics of 963%, tensile stress of 28,000 Pa, adhesive strength of 9.6 kPa, and water vapor transmission rate of 2400 g/m²/h. In vivo tests demonstrated that GC-NCs-Gel expedited wound healing by enhancing epidermal regeneration, neovascularization, and deposition of collagen.³⁰

2.2 Microspheres

Another versatile biomaterial platform for wound healing is microspheres. Microspheres are useful for many dosage forms and product applications, and they are especially advantageous for wound-healing formulations, due to their small size (1–1000 μ m) and features such as environmental responsiveness, swelling, and bioadhesion. The flexibility of microspheres, along with their capacity to regulate drug release rates, has proven particularly beneficial in the management of chronic wounds.³¹ By controlling the encapsulation locations and binding configurations of various pharmaceuticals inside the carrier, microsphere-based delivery systems can facilitate the sequential release of several medications.³² Besides, microspheres can be created to encapsulate numerous medications for simultaneous administration.³¹ Micro- and nanoparticle systems that contain particulate matter in their formulations can pro-

vide the skin with an additional occlusive effect that is advantageous for wound healing.³¹

Regarding epidermal regeneration, wound contraction, and recovery during the inflammatory phase, rhEGF-loaded PLGA-Alginate microspheres show significant promise for accelerating and improving wound healing.³¹

In skin wound healing, a dynamic imbalance is a critical factor in the development of hypertrophic scars (HS). Conventional therapies often focus solely on a specific phase of the wound-healing process and do not adequately treat the dynamic imbalance, thereby complicating the attainment of scarless wound healing. Recent research has established a chronologically adaptive microsphere delivery system (G/E/T) based on gelatin methacrylate (GelMA). This system achieves extensive therapeutic intervention in wound healing by the precise orchestrating epigallocatechin gallate (EGCG) and triamcinolone acetonide (TA) sequential release. EGCG can adhere to the surfaces and shallow cavities of microspheres via hydrogen bonds due to its water-solubility. This binding mechanism enables rapid detachment from the carrier through surface diffusion, resulting in early release. Conversely, as TA is fat-soluble, it is securely trapped within the core of the 3-D GelMA scaffold via hydrophobic interactions, and its release mechanism is contingent upon the carrier material's degradation rate, resulting in slow release during the intermediate and later stages. The findings indicated that the encapsulation efficiency (EE) of TA and EGCG was $93.83 \pm 1.84\%$ and $80.05 \pm 0.50\%$ respectively, and their drug loading (DL) was $10.43 \pm 0.20\%$ and $8.89 \pm 0.06\%$, respectively.³²

Another method involved the development of gelatin-tannic acid (GelTA) microspheres that encapsulate zinc phosphate (AZP) and amorphous selenium (Se) nanoparticles for extensive wound healing. The findings indicated that the application of Se nanoparticles to H₂O₂-stimulated L929 cells reduced the reactive oxygen species (ROS) level by 59.7%. Moreover, AZP nanoparticles markedly improved migration in human umbilical vein endothelial cells (HUVECs). A quantitative investigation of a rat dorsal full-thickness injury model for wound healing demonstrated a higher healing rate than the control group at 4 days post-surgery. The findings validated that, within 14 days, the concurrent application of GelTA-AZP and GelTA-Se microspheres

reduced scarring, expedited wound healing, and facilitated hair follicle regeneration. The delivery of GelTA-Se/GelTA-AZP hybrid microspheres presents an excellent approach for the functional regeneration of extensive skin wounds, demonstrating considerable prospects for clinical applications.³³

Additionally, magnetic microspheres infused with therapeutic elements derived from the stem cell secretome were engineered to facilitate wound healing actively. These microspheres enable sustained release of bioactive agents and can be accurately controlled by external magnetic fields. In vitro, they show significant anti-inflammatory activity and slowly stimulate the proliferation and migration of skin cells. In contrast to traditional therapies, magnetic propulsion enables more effective penetration of dense wound barriers.³⁴

2.3. Nanofibers

Current research focuses on multifunctional bioactive wound dressings that use nanofibers as potential nanomaterials for skin tissue scaffolds and improved drug delivery systems (DDS). Nanofibers resemble the ECM, offering breathability, interconnected porosity, high water absorption, and moisture permeability.²¹ Electrospun nanofibers have attracted much interest as wound dressing materials due to their distinctive architectural characteristics, which create an optimal environment for promoting wound healing.³⁵ They have high porosity, gas permeability, and surface-to-volume ratio. These properties stimulate cellular respiration, moisture retention, skin regeneration, exudate removal, and hemostasis.^{36,37} In order to create nanofibrous patches with high porosity, biodegradability and biocompatibility, electrospinning technique has recently drawn interest. These patches are interesting platforms for the treatment of acne wounds because they can have antibacterial activity, absorb exudates, and give mechanical protection. The capability of electrospun nanofibers infused with exosomes or mesenchymal stem cells as advanced treatment methods for facilitating scarless acne recovery has been recognized.³⁷ Fibers with isotropic and anisotropic topologies have been shown to effectively alleviate M1 macrophage polarization, reduce inflammation and regulate M2 macrophage polarization. These polarization changes are necessary for wound healing and tissue restoration and these ECM-like micro/nanofibers have remarkable biocompatibility, which allows them to control inflammation

and immune responses and reduce the risk of infection²⁰.

In another study, a fibrous membrane from electrospun gelatin/poly(l-lactide-co-ε-caprolactone) nanofibers facilitated the transition from M1 to M2 phenotypes, which subsequently inhibited fibrosis-related genes such as α-SMA, CD36, and collagen, resulting in accelerated skin repair, reduced collagen accumulation and scar formation, and inhibited fibrosis.^{26,38}

In a study by Nazemoroaia et al., researchers developed an asymmetric wound dressing inspired by the skin's structure, comprising an alginate and chitosan hydrogel bottom layer and an electrospun PCL-silk sericin (PCL-SS) top layer. The upper layer's electrospun PCL-SS fiber offered both biocompatibility and mechanical strength. Gas exchange is facilitated and wound healing is encouraged by the porous, permeable outer layer produced by electrospinning. In order to protect against external threats, including chemical, physical, and bacterial agents and to regulate gaseous exchange (O₂, water vapor, and CO₂), asymmetric membranes usually include a denser outer layer that mimics the epidermal skin layer. Additionally, these membranes' inner layer has a porous shape that can assist cell adhesion and proliferation while absorbing exudates.²⁵

Another technique involves the development of poly [octanediol-co-(citric acid)] (POCA)/gelatin nanofibrous mats loaded with curcumin (CUR/POCA-Glt NM) that respond to inflammatory microenvironments. The synthesized nanofibers exhibit sensitivity to MMP-2. Amorphous curcumin is generated in response to elevated levels of MMP in inflammatory wounds. The CUR/POCA-Glt NM system signifies a notable progression in wound healing treatment, especially for difficult wounds such as hypertrophic scars and diabetic ulcers. This technology utilizes curcumin-loaded nanofibers responsive to MMP-2, providing a targeted medication release mechanism that successfully mitigates localized inflammation and fosters scarless regeneration.

Research indicated that CUR/POCA-Glt NM stimulates fibroblasts at the wound site, aiding the reestablishment of local immunological homeostasis and thus enhancing regenerative healing while efficiently directing the process toward scar-free repair rather than fibrotic healing.³⁹

Microneedles (MNs) can penetrate wounds, delivering active substances to deeper layers in a painless, least-invasive approach by circumventing the stratum corneum, thereby facilitating targeted local drug delivery and attracting the attention of numerous researchers in the wound-healing field. The typical MN length is under 1 mm, and their tips are sharper than those of hypodermic needles. This geometrical configuration allows MNs to infiltrate biofilm or necrotic tissue, facilitating the effective delivery of active substances while avoiding contact with nerve terminals and blood vessels in the dermis or epidermis. Microneedles, as an innovative transdermal drug delivery technology, have garnered significant attention due to their straightforward drug administration, controlled release, and multifunctionality.^{1,2} Microneedles have emerged as essential elements of sophisticated DDS owing to their unique benefits and are developing as a smart alternative to conventional methods.^{2,40,41}

Polymeric microneedles have attracted significant interest due to their straightforward, cost-effective production methods, abundant availability of materials, superior biocompatibility, and customizable mechanical properties. Polymeric microneedles (primarily comprising dissolving and hydrogel MNs) exhibit greater flexibility and biocompatibility than microneedles fabricated from alternative solid substances, such as ceramics, metals, silicon, and glass.¹

The integration of nanomaterials into polymeric microneedles may exert a dual effect on their functional and physicochemical properties; thus, it is essential to optimize material ratios to mitigate adverse effects on performance. Mass manufacture and effective composite MNs storage are essential for practical applications.¹

Hydrogel microneedles (HMNs) are distinguished from other microneedle types by their superior biocompatibility, adjustable drug release characteristics, and substantial drug-loading capacity. The HMNs' swelling capacity is governed by the crosslinking density of the polymer's 3D network structure, enabling fine regulation of drug-release rates and loading capacity.⁴⁰

Dissolving microneedles (DMNs) can be applied through the skin to deliver medicine to a deep wound site efficiently and, when combined with nanomaterials, provide prolonged and accurate drug delivery and gene regulation.^{42,43}

3. Novel Drug Delivery Platforms

3.1. Microneedles

Simvastatin (SIM) may enhance wound healing; however, its water-insolubility restricts its use. Yang et al. developed a DMN-based DDS (SIM-NC@DMNs) comprising SIM nanocrystals (SIM-NC) and assessed its effectiveness in wound treatment. The dissolution efficacy of insoluble SIM is markedly enhanced upon formulation into SIM-NC. The SIM-NC's saturation solubility in PBS and deionized water rose by 320.14-fold and 150.57-fold, respectively. Upon the profound insertion of the SIM-NC@DMNs in the wound, the insertion needle segment, comprised of hyaluronic acid (HA), swiftly dissolves, facilitating the efficient release of the SIM-NC into the deeper wound region for maximal treatment effectiveness. The integration of DMNs and NC enhances the efficacy of this system for wound healing. Their collective research indicates that the recently formulated SIM-NC@DMNs have significant potential to expedite wound healing. The residual wound area was 21.34% in the control group, whereas in the SIM-NC@DMNs group, it was merely 2.36% on day 12 post-treatment. The results also provide proof of its effectiveness in wound-healing therapy. The SIM-NC@DMNs DDS could serve as an effective therapeutic approach that enhances wound healing, demonstrating significant potential in wound-healing research.⁴³

Smart microneedle systems facilitate real-time assessment of wound conditions and adapt drug delivery accordingly, hence allowing for more accurate treatment approaches for chronic wounds. These devices incorporate many stimulus-responsive processes, including oxidative stress, pH, and photothermal reactions, to facilitate on-demand medication release.⁴²

Zhang et al. created a core-shell-shaped microneedle array patch with programmable capabilities (PF-MNs) in order to dynamically regulate the wound immunological microenvironment in accordance with the different phases of healing. The MN with PF-MN consisted of a ROS-degradable poly(vinyl alcohol) (VP@PVA) shell containing the therapeutic drug verteporfin for wound remodeling and bacterial inhibition, and a core component of crosslinked heparin (cHP) for immune regulation.⁴⁴ In particular, PF-MNs produce ROS under laser irradiation to fight multidrug-resistant bacterial biofilm early on. The ROS-sensitive MN shell then progressively breaks down to reveal the MN core component, which promotes the phase shift from inflammation to proliferation and mitigates a number of inflammatory mediators. Verteporfin is released into the deep dermis after shell erosion and

prevents mechanotransduction. The released verteporfin impedes scar formation by obstructing the activation of Engrailed-1 (En1) in fibroblasts. Their results indicate that PF-MNs can facilitate scarless wound healing in mouse models of both acute and chronic wounds and prevent hypertrophic scar development in rabbit ear models.^{2,44}

Another study created a biocompatible, detachable hydrogel microneedle device for scarless wound healing. Bismuth nanosheets (Bi), a photosensitizing agent, and verteporfin, which is an inhibitor of the YAP signaling pathway, were included in the pyramidal MN array. The MN system possesses the mechanical strength to breach the skin; once the detachable connection deteriorates, the tips may remain within the tissue for ongoing active release, while the substrate can be removed safely. The research indicates that suppressing YAP signaling facilitates scarless wound healing devoid of fibrosis, accompanied by the regeneration of secondary skin structures, such as hair follicles and sebaceous glands. Consequently, MN can function as an exceptional DDS and provide various practical advantages for scar-free wound healing.⁴⁵

3.2. Exosomes

Exosomes, extracellular vesicles, cellular lysates, secretomes, and conditioned media have evolved worldwide as cell-free therapies. Although ultimately cell-free in application, it is essential to acknowledge that from a production standpoint, they are significantly more intricate due to their reliance on live cell sources as raw materials.⁴⁶ Exosomes, secreted by various cells, are nanoscale extracellular vesicles with diameters of 30-150 nm that serve as mediators of intercellular communication.⁴⁷

Mesenchymal stem cell-derived exosomes (MSCs-Exos) share structural and physical features with other exosomes and are increasingly preferred to help prevent scar formation during wound healing due to their regenerative and immunomodulatory properties. The primary mechanism of MSC-derived exosomes on recipient cells in cell-free therapies is through their payload containing nucleic acids, lipids, and proteins. MSCs-Exos may facilitate wound healing by modulating one or more variables. Engineered MSC-derived exosomes are potential exosomes that have been edited, loaded, or modified to reduce scar formation and enhance wound healing by diminishing the production of inflammatory factors.⁴⁷

In addition to controlling cell differentiation, stem cell exosomes also have homing effects and are less likely to be rejected by the immune system, which makes them a useful treatment strategy for wound healing.⁴⁸ Exosomes produced from adipose-derived mesenchymal stem cells (ADSCs) mitigate scarring by inhibiting the PI3K/AKT/mTOR and TGF- β 1/Smad signaling pathways.²

Wgealla et al. reported that human amniotic fluid derived stem cells (hAFS) enhanced wound healing. hAFS eased scar formation by stimulating ECM remodeling, upregulating immune response molecules, boosting anti-fibrotic action, and lowering the release of inflammation-associated cytokines via exosomal miRNA-146a-5p targeting CXCR4.⁴⁹

Single-cell sequencing demonstrated that exosomes derived from human ADSCs facilitate scarless repair by targeting the 14-3-3 zeta-YAP-Hippo pathway to inhibit fibrosis, while concurrently reprogramming fibroblast interactions and keratinocyte plasticity to reduce scarring.¹² This issue is mechanistically significant as YAP facilitates scarring by enhancing En1 expression and inhibiting Trps1 expression. The activation of YAP specifically initiates a cascade of events that prompts fibroblasts to produce En1, transforming En1 lineage-negative fibroblasts (ENFs) at the site of the wound into EPFs.⁵ Targeting the YAP-En1 signaling axis to disrupt fibroblasts' fibrotic program is an essential tactic for guiding wound healing toward true scarless regeneration.¹²

3.3. Combinatorial and Synergistic Delivery Strategies

In earlier segments, each drug delivery system was reviewed individually. The possibility of synergistic integration of multiple platforms is discussed here. To address the constraints of single-platform strategies, improved wound care is transitioning to hybrid systems that integrate the advantages of various delivery systems to attain spatiotemporal accuracy in drug release kinetics.¹³

For example, it has been demonstrated that adding electrospun nanofibers to a hydrogel matrix enhances the scaffolds' mechanical characteristics and stability, allowing for sustained exosome release and contributing to tissue regeneration.^{50,51} Such a combination can enhance the consistent and organized framework of conventional hydrogels with the inclusion of nanofibers, thus more faithfully replicating the intricate architecture of native tissues.^{37,52} The hydrogel's physical integrity was greatly improved by the nanofibers' presence, which conferred mechanical strength and toughness too.^{37,53}

Microneedle-based hydrogels provide precise therapeutic control throughout the stages of wound healing by combin-

ing transdermal administration with localized microenvironment manipulation.⁴ As a representative example, a unique core-shell microneedle patch for scarless skin healing was created by Lyu et al. Mangiferin-laden GelMA hydrogel makes up the shell, and poly(lactic-co-glycolic acid)-dimethacrylate (PGLADMA) loaded with hMSC-derived exosomes makes up the core. This microneedle patch offers a novel method for sustained release of exosomes as a therapeutic approach in addition to showing potential to enhance wound healing and reduce scarring.^{40,54} Adverse responses resulting from mismatches between drug release and wound-healing phases can be minimized, and efficacy at the same dosage can be optimized by planned drug release at appropriate stages.²⁸

Through careful chemical and structural design, these combinatorial methods collectively integrate and synergize several crucial therapeutic actions across temporal and spatial dimensions.¹³

4. Clinical Translation Challenges

The clinical application of biomaterial-based drug delivery systems faces both general and platform-specific challenges that must be addressed to achieve scarless wound healing in practice. Numerous studies have focused on murine wound models, underscoring the need to evaluate the effectiveness of these nanomaterials and microneedle-based delivery methods in alternative animal models, including pigs, monkeys, and humans. There remains an insufficiency of robust preclinical models and empirical proof to substantiate the long-term consequences of nanoparticles and polymers that accumulate in the body following their therapeutic applications.¹

The diminutive dimensions, elevated surface-to-volume ratio, and modifiable surfaces of nanoparticles enable prolonged and precise drug delivery, potentially decreasing dosage frequency and improving therapeutic effectiveness. The long-term biological safety of inorganic nanoparticles remains a significant problem. Although they can improve drug delivery, thorough long-term tracking studies are lacking about their metabolic clearance pathways, in vivo distribution, and potential chronic toxicity risks from accumulating in organs like the spleen and liver.²

While dissolvable microneedles offer better biocompatibility and biosafety, non-dissolving microneedles must be handled aseptically and carry a residual risk.^{2,55,56} Despite the advanced design and fabrication procedures for microneedles established in a lab environment, the diminutive size of microneedles, the need for sterile conditions in the large-scale production of drug-loaded microneedle patches, and the high level of accuracy required for industrial production continue to pose considerable obstacles to large-scale manufacturing. Lastly, there is currently no policy support or quality standard for microneedle tech-

nologies, and the direct penetration of the skin's stratum corneum layer during microneedle treatment necessitates stringent regulation and approval.⁴⁰

Conventional electrospinning, despite its extensive use, exhibits drawbacks such as inadequate mechanical strength, a wide diameter distribution of the resultant nanofibers, and difficulties in scaling the process.^{2,57}

Furthermore, rheological characteristics, reactor design, and application technology optimization are critical factors that must be precisely controlled for natural hydrogels to be scalable from laboratory to industrial-scale production.^{2,58}

In order to increase skin comfort and patient compliance, it is imperative to further optimize the material composition as well as processing techniques to make them adaptable to various wound types and locations while

maintaining adequate skin adhesion, mechanical strength, and biocompatibility.¹

Artificial intelligence (AI) can facilitate mass production; by machine learning (ML), researchers can swiftly discern superior hydrogel preparation techniques, thereby advancing the creation of a modular hydrogel platform.¹⁵

Future studies on HMNs must concentrate on structural design and enhancing material formulations to increase drug-loading capacity. Furthermore, the integration of smart devices with HMNs for continuous body monitoring and smart drug delivery should enhance the accuracy and efficacy of therapies.⁴⁰

The integration of wound care with real-time monitoring is an innovative approach to facilitate comfortable home care for chronic wounds.¹

Table 1 shows categorized clinical translation challenges and a future roadmap for scarless healing.

Table 1: Clinical Translation Challenges and Future Roadmap for Scarless Healing

Category	Current Clinical Challenges	Future Roadmap & Strategies	References
Manufacturing & Scale-up	Inconsistent quality, expensive, and varies from batch to batch.	Develop scalable, low-cost fabrication and deploy standardized quality control processes.	12,59,60
Safety & Biocompatibility	No monitoring of long-term toxicity and organ buildup (liver, spleen, etc.).	Improve biological safety via fluorescent tracking in porcine models.	2,61
Regulation & Ethics	Unclear regulatory classification of diagnostic-therapeutic integrated systems.	Enhance communication between industry, academics, and regulators on specific regulatory pathways.	12,62
Personalization & AI	Traditional therapies do not account for patient variability, which reduces efficacy and	Use AI/ML algorithms to develop tailored biomaterials rather than trial and error.	23,37,63
Clinical Modeling	Animal models (e.g., mice) do not accurately reproduce human wound biology.	Add humanized/ex vivo models. Validate in large animals.	4,12

5. Conclusion

Wound healing comprises a series of intricate biological processes meticulously regulated by the body. Current wound care methodologies have evolved from basic passive coverage solutions to sophisticated dressing systems that integrate multifunctional therapies.¹³ Rational design of biomaterial-based drug delivery systems has become a fundamental component of current wound healing research, providing precise control over the release kinetics of therapeutics, the spatiotemporal distribution, and the manipulation of the local microenvironment.⁶⁴

The microneedle, as a minimally invasive drug delivery system, has shown substantial promise in biotherapeutic applications. Even with this promise, there are obstacles in the fabrication of microneedles that adequately maintain the bioactivity of biotherapeutics.⁶⁵ The integration of MSCs and MSCs-Exos therapies with smart and responsive biomaterials that have antimicrobial properties and active monitoring could transform tissue regeneration and wound healing, making MSCs and MSCs-Exos an essential tool in the future of precision regenerative medicine.⁵⁰

Despite barriers in clinical translation of these therapies, continued advances in integrating stem cell therapies with sophisticated biomaterials, genetic modification methods, and nanotechnology offer intriguing opportunities to enhance wound-healing outcomes. As research advances, the objective of attaining scarless wound healing in adult tissues is approaching fruition, offering significant promise for enhancing patient outcomes across many wound-healing contexts.⁶⁶ In conclusion, while breakthroughs in wound healing have improved closure rates and cosmesis, a scarless approach to clinical treatment remains elusive. Current studies indicate a significant discrepancy between fetal-like microenvironments in animal experiments and the harsh biological realities of human healing. To advance the field, scientists must address scientific challenges, such as controlling immune system-fibroblast interactions to prevent En1-positive lineage activation and preserve wound healing inflammation. Most studies lack long-term evaluation of ECM designs and instead rely on superficial macro assessments. Future research should involve additional clinical trials and preclinical investigations using pig models, smart materials that can adapt to each wound-healing stage, and bio-functional regulations for combination products.²⁶

Conflict of Interest

The author declares no conflict of interest.

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