Advanced drug delivery systems for wound healing and tissue regeneration: Current progress and translational perspectives (Review)

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Abstract. Wound healing is a multifaceted and tightly regulated process involving four sequential, yet overlapping phases: Hemostasis, inflammation, proliferation and remodeling. Chronic wounds and extensive tissue injuries often remain unresolved due to the limitations of conventional therapies, including poor drug bioavailability, inadequate targeting and the lack of sustained release. Recent advances in drug delivery technologies have significantly improved therapeutic outcomes by enabling the precise, localized and temporally controlled delivery of regenerative agents. The present review explores the latest innovations in drug delivery systems, including nanoparticles, hydrogels, microneedles, exosomes and 3D-printed scaffolds, that facilitate enhanced tissue regeneration. These systems improve the delivery of bioactive molecules, including growth factors, stem cells and small-molecule drugs, thereby promoting angiogenesis, cellular proliferation and extracellular matrix remodeling, while reducing inflammation and the risk of infection. Furthermore, stimuli-responsive delivery platforms that react to pH, enzymatic activity, or oxidative stress provide dynamic regulation of the wound microenvironment. The integration of innovative biomaterials with biologics and engineering solutions marks a transformative step in regenerative wound care. The present review provides a comprehensive discussion of emerging drug delivery strategies that hold promise for accelerating and managing wound healing.

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Contents

1. Introduction

A wound is defined as a disruption in the normal anatomical structure of the skin or underlying tissues, typically caused by external forces such as trauma, surgery or accidents (1). The skin is a protective covering and a sound barrier that separates the body from the various environmental factors and wards off the invasion of harmful microbes. If the skin is injured, it also creates openings through which germs can invade the body, thereby significantly increasing the risk of disease or infection (2). In particular, extensive damage to the skin results in a massive loss of vital fluids, electrolytes and nutrients, which may eventually become a grave risk to life and could lead to fatal outcomes if handled with negligence (1,3). Millions of individuals worldwide suffer from both acute and chronic wounds annually; thus, this is not only serious health issue, but also poses a heavy economic burden. The numbers of patients with chronic wounds, representing ~2-6% of the global population, exhibit a steadily increasing incidence. In the USA, the average annual treatment cost surpasses 20 billion dollars, rendering these cutaneous wounds a significant clinical challenge necessitating urgent resolution (4).

The primary goal of successful wound care and treatment is to facilitate the healing of the skin at the earliest possible time, with the added assurance that the resulting outcome

is the best possible in terms of function and appearance (5). Over the past few years, a substantial increase in severe wound infections and chronic wounds has been observed (6). Chronic wounds usually exhibit necrotic tissue, a high pH level and an exceptionally high concentration of metalloprotease. These, in unison, disable the normal process of physiological healing events necessary for healing. Contrary to this, normal acute wounds heal very readily without the need for any therapeutic intervention or further medical treatment. The peculiar characteristics of these chronic wounds provide an exceptionally favorable environment for the invasion and growth of pathogens, which is the main reason for wound infections being so common in these wounds (7).

Contemporary interventions, including debridement, off-loading, antibiotics and negative pressure wound therapy, are extensively utilized in clinical settings. Nevertheless, these interventions only seek to decelerate the course of diabetic foot ulcers and mitigate discomfort, without completely restoring the complex and extended healing process, frequently rendering wounds susceptible to recurrence (8,9). Chronic and acute wounds pose significant healthcare challenges, particularly in patients with diabetes and in those who are immunocompromised. Conventional treatments often fail to achieve complete healing, necessitating advanced drug delivery strategies to optimize therapeutic outcomes (10). The scientific community is increasingly interested in areas related to skin regeneration. It is well established that nano-drug delivery systems significantly enhance and improve the process of wound healing and the quality of healing in general through a variety of apparent and substantial advantages (11). Research has demonstrated that nano-drug delivery systems are non-toxic and do not produce any adverse effects, rendering them completely compatible with the skin and allowing for safe utilization without any reaction. Furthermore, they provide a good moist environment, which is essential in initiating and enhancing the process of wound healing at a high rate. Aside from decreasing the number of administrations, extending the period during which a therapeutic dose of the medication is effective, and improving compliance, sustained-release also leads to a reduction in the economic burden (12).

The present review discusses several novel drug delivery technologies aimed at improving wound healing. The present review aimed to discuss the potential of novel therapies for the management of tissue regeneration, given the limitations of current treatments and the incidence of chronic wounds. The objective of the present review was to emphasize the transformative potential of innovative pharmacological strategies in chronic wound management by showcasing current advancements and clinical data. This may improve patient outcomes worldwide. The present review was conducted through an extensive literature search using electronic databases such as PubMed, Scopus, Web of Science and Google Scholar. Articles published from 2018 to 2025 were gathered using key words such as 'wound healing', 'drug delivery systems', 'nanoparticles', 'hydrogels', 'microneedles', '3D printed scaffolds', 'exosomes' and 'tissue regeneration'. Only peer-reviewed articles in the English language on advanced drug delivery strategies for wound healing and tissue regeneration were included. Following screening, duplicates, conference abstracts and unrelated studies were excluded.

2. Phases of wound healing

Chronic wounds, such as diabetic foot ulcers and venous leg ulcers remain in the inflammatory phase for a long period of time as opposed to acute wounds, due to excess reactive oxygen species (ROS) generation, increased protease activity, bacterial biofilms, alkaline pH, the prolonged release of inflammatory cytokines and impaired angiogenesis. This hostile microenvironment delays tissue regeneration and reduces the efficacy of conventional treatments. The knowledge of these pathological features explains the design of stimuli-responsive systems, such as pH-responsive and ROS-scavenging hydrogels. The various phases of wound healing, i.e., hemostasis, inflammation, proliferative and remodeling are discussed below and are illustrated in Fig. 1. In contrast to acute wounds, chronic wounds, such as venous leg ulcers and diabetic foot ulcers are stalled in the inflammatory phase due to excessive ROS generation, increased protease activity, hypoxia, bacterial biofilms, alkaline pH, impaired angiogenesis and the prolonged release of inflammatory cytokines. This hostile microenvironment severely hinders tissue regeneration and diminishes the efficacy of traditional therapies. The knowledge of these pathological conditions gives a rationale for the development of stimuli-responsive drug delivery systems, such as pH-responsive and ROS-scavenging hydrogels (13).

Hemostasis. Hemostasis is considered the first phase in terminating bleeding and initiating wound healing in the event of vascular injury. Initially, vasoconstriction occurs to reduce blood flow, followed by the aggregation and activation of platelets at the site of damage to form a temporary plug. These platelets release various chemical signals that amplify the hemostatic response. The subsequent formation of a stable fibrin clot reinforces the platelet plug, thereby sealing the wound. During this process, cytokines and growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), are released, preparing the tissue for the subsequent phases of wound healing (14).

Inflammation. The inflammatory phase represents the initial response of the body to tissue injury, lasting from several hours to a few days. Its primary role is to remove debris, pathogens and dead cells, thereby preparing the wound bed for tissue repair. This phase is marked by vasodilation and increased vascular permeability, which facilitates the recruitment of immune cells to the injury site. Neutrophils are the first responders and perform phagocytosis to eliminate microbes and cellular debris. As the phase progresses, macrophages become predominant, releasing pro-inflammatory cytokines, such as interleukin 1 and tumor necrosis factor-α, along with growth factors that initiate the next stage of healing. Clinically, this phase is characterized by the classic signs of inflammation: Redness, swelling, warmth and pain (15).

Proliferation. Following the inflammatory phase is the proliferative phase, which focuses on tissue regeneration and repair. Fibroblasts proliferate and deposit type III collagen, forming a temporary extracellular matrix for tissue repair. Concurrently, neoangiogenesis (the formation of new blood

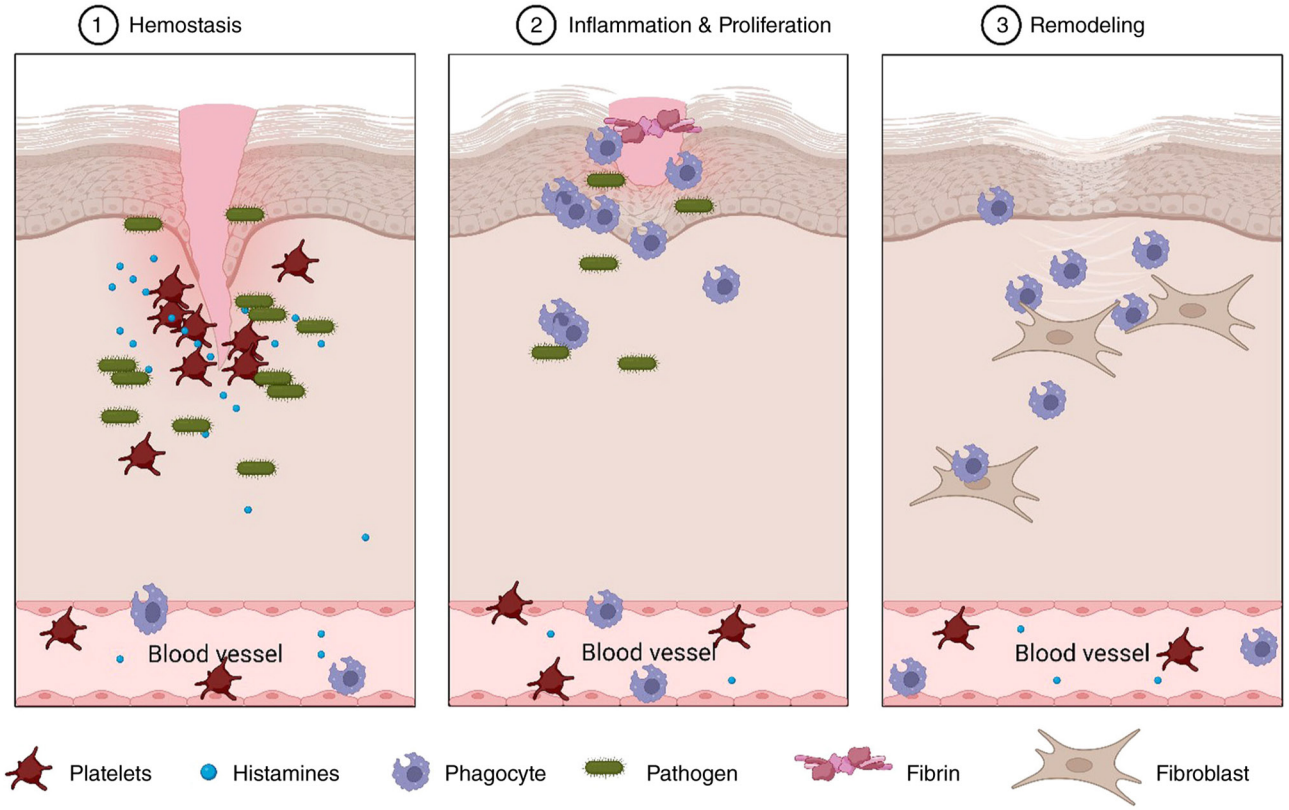

Figure 1. Schematic diagram illustrating the phases of wound healing.

vessels) occurs to restore oxygen and nutrient supply to the healing tissue (16).

Maturation or remodeling. Finally, the maturation or remodeling phase occurs, aiming to strengthen and reorganize the newly formed tissue. During this phase, the type III collagen initially deposited is gradually replaced by the stronger and more organized type I collagen. Simultaneously, vascular regression occurs, and a scar forms as excess blood vessels are removed. Over time, the tensile strength of the wound increases, eventually reaching ~80% of that of the original tissue (17).

3. Nanoparticle-based drug delivery systems

Nanoparticles have emerged as promising carriers for drug delivery due to their tunable physicochemical properties, controlled release capabilities and the ability to penetrate cellular barriers. Different types of nanoparticles, including lipid-based, polymeric and inorganic nanoparticles, have been utilized in wound healing applications (18). The different types of nanoparticles used in chronic wound healing are illustrated in Fig. 2.

Polymeric nanoparticles. In recent years, polymeric nanoparticles have received considerable attention in the promising and fast-evolving areas of biomedicine and bioengineering. These novel polymeric devices, when administered in the body or conjugated with target sites, effectively protect drugs from proteolytic attacks in wounds, allowing for controlled and regulated drug delivery, while significantly reducing dosage frequency (19). Nanoparticle applications provide a viable option to meet the growing need for the effective delivery of a wide variety of biomolecules, which may include critical components, such as DNA, growth factors that stimulate healing and highly effective antibacterial agents utilized to avoid infection (20). In the contemporary age, polylactic-co-glycolic acid (PLGA), is one of the most commonly used materials for synthesizing polymeric nanoparticles. Alginate, gelatin, chitosan and several other polymer mixtures are the most commonly used polymers in a vast variety of applications. The synthesis of polymeric nanoparticles capable of effectively encapsulating antimicrobial agents has been explored across a broad spectrum of scientific fields through numerous research studies (21). Antimicrobial peptide LL37-loaded PLGA nanoparticles (PLGA-LL37 NPs) are a biodegradable drug delivery system for healing. The nanoparticles inhibited *Escherichia coli* in antibacterial activity and caused cell migration, but did not affect the proliferation of keratinocytes. The PLGA-LL37 NPs-treated group exhibited enhanced formation of granulation tissue in the full-thickness excisional wound model, as reflected by significantly enhanced collagen deposition, re-epithelialized content, and neovascularization (21,22). Chitosan, a biopolymer derived from chitin in crustaceans, such as shrimp and crab, has also garnered considerable interest in drug delivery systems. The reason for this is largely due to its remarkable properties, including being mucoid, biodegradable, non-toxic, and biocompatible. Properties, such as this position chitosan in an immensely versatile

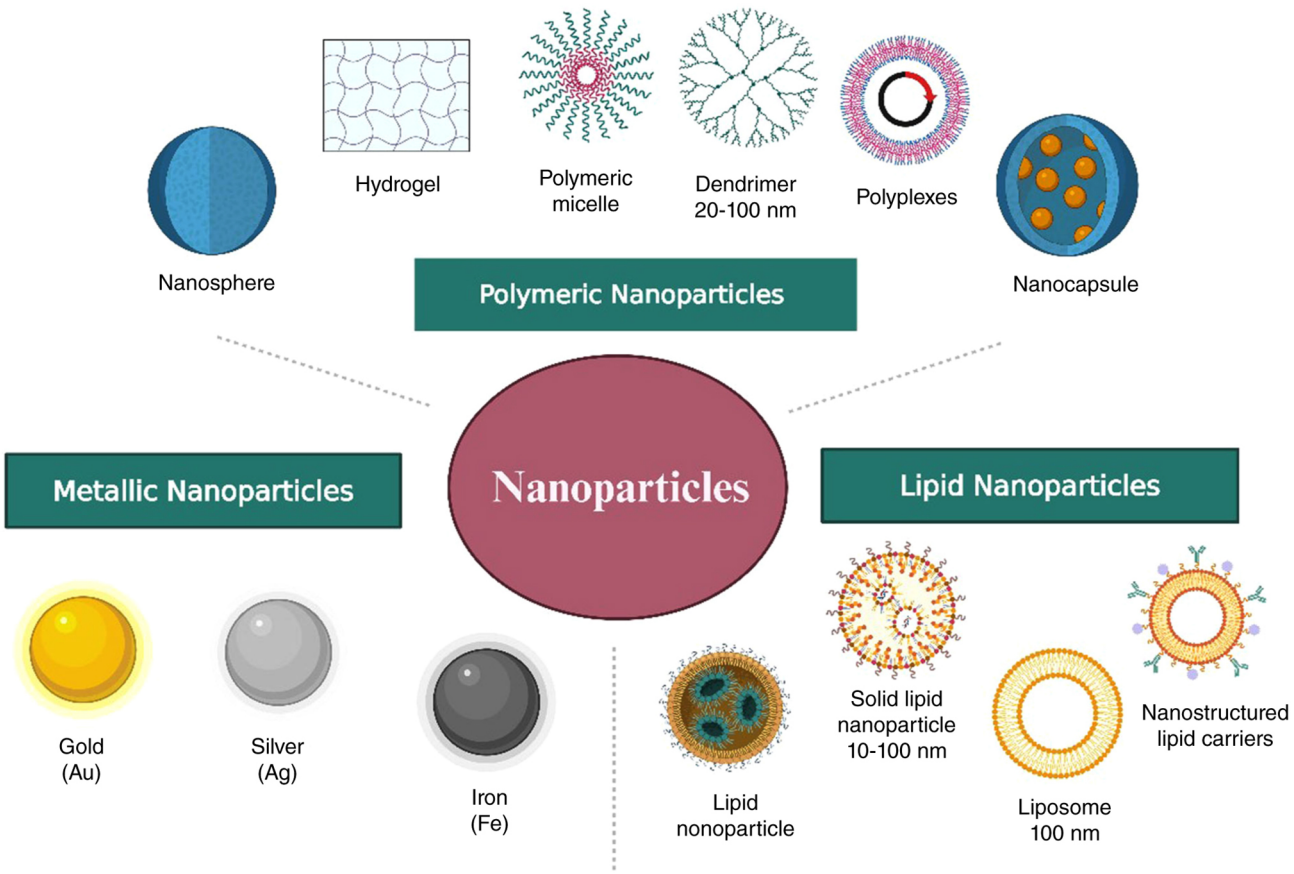

Figure 2. Schematic diagram illustrating the various nanoparticles used in chronic wound management.

manner for applications across a wide range of drugs, from lipophilic to hydrophilic drugs (22). Chitosan particles are between 10 and 500 nanometers in diameter, a size that significantly increases their uptake by cells. The presence of amino groups also signifies a positive zeta potential, which increases interaction with mucosal surfaces and negatively charged cell membranes. Chitosan also has the capability of slowing the rate of drug administration through the provision of the potential to regulate how rapidly the drugs are delivered into the system (23). Chitosan-based topical systems have gained attention in chronic wound management due to their film-forming ability, biocompatibility and intrinsic wound-healing potential. In this context, in a previous study, a chitosan–polyvinyl alcohol film-forming solution loaded with doxycycline demonstrated rapid film formation, sustained drug release, and effective matrix metalloproteinase inhibition, highlighting the utility of chitosan in improving healing outcomes in diabetic foot ulcers (24). The different types of polymeric nanoparticles with their distinct features, advantages and disadvantages as drug delivery systems in chronic wound management are summarized Table I (25-30). All the nanoparticle systems have their own merits and demerits; however, they have exhibited promising therapeutic outcomes. Polymeric nanoparticles provide controlled drug release and biodegradability, while lipid nanoparticles provide increased skin penetration and drug retention. Although metallic nanoparticles have an improved antimicrobial activity, there are concerns regarding the long-term toxicity and bioaccumulation. Thus, balancing efficacy, biosafety, scalability and cost is key for successful clinical translation (31).

Lipid nanoparticles. Solid lipid nanoparticles and nanostructured lipid carriers facilitate skin penetration and drug retention. An intriguing and important class of nanomaterials, known as lipid nanoparticles, finds widespread application in the areas of gene therapy, drug delivery systems and vaccine production. These novel particles consist of several lipids that come together to form nanoscale structures, which have the unique property of encapsulating and delivering drugs or other biological molecules with efficiency and specificity (32). A summary of various lipid nanoparticles utilized in chronic wound management is presented in Table II (21,33-35). All the nanoparticle systems have their own merits and demerits; however, they have shown promising therapeutic outcomes. lipid nanoparticles provide increased skin penetration and drug retention.

Metallic nanoparticles. Silver and gold nanoparticles exhibit antimicrobial properties, which reduce wound infections and accelerate tissue regeneration. Generally, metallic nanoparticles are tiny particles with dimensions ranging from 1 nanometer to 100 nanometers. These tiny particles are primarily composed of a sequence of metals (36). Unlike bulk metals of larger dimensions, metallic nanoparticles possess exceptional physical, chemical and

Table I. Different types of polymeric nanoparticles with their distinct features as drug carriers in chronic wound management.

Types of polymeric nanoparticles	Common polymers	Key features	Application	Advantages	Disadvantages	(Refs.)
Nanospheres	PLGA, PLA, PCI, Chitosan	The drug is uniformly dispersed in the polymer matrix	SR, vaccine delivery	Easy to produce, controlled release, high stability	Limited targeting ability, lower drug loading efficiency	(25)
Nanocapsules	PLGA, Eudragit	Drug confined to the inner core, surrounded by a polymer shell	Target drug delivery, gene therapy	Protection of sensitive drugs, controlled and target released	Complex synthesis, risk of burst release	(15)
Dendrimers	PAMAM, PPI	High surface functionality, precise control over release	Gene delivery, imaging, anticancer drugs	High surface functionality	Toxicity concerns, expensive and complex synthesis	(26)
Poly micelles	PEG-PLA, PEG-PCL	Amphiphilic block co-polymers, hydrophobic core for drugs	Solubilizing hydrophilic drugs, cancer therapy	Improved stability, long circulation time	Low drug loading	(27)
Hydrogels	PVA, chitosan, PEG	Swell in water, biocompatible	Wound healing, controlled release, tissue engineering	High drug loading capacity	Mechanical weakness, degradation rate may vary	(28)
Polyplexes	PEI, PLL, chitosan	Electrostatic complexation with DNA, RNA	Gene therapy, RNA delivery	Protects genetic materials	Cytotoxicity	(29)
Nanogels	PEG, PVA, chitosan	High drug loading, responsive to stimuli	Intracellular drug delivery, cancer therapy	Biocompatible	Complex formulation	(30)

PLGA, polylactic-co-glycolic acid; PLA, polylactic acid; PCI, photo-chemical internalization; SR, sustained release; PAMAM, poly (amidoamine) PPI, poly(propylene imine); PEG, polyethylene glycol; PCL, polycaprolactone; PVA, polyvinyl alcohol ; PEI, polyethyleneimine; PLL, poly-L-lysine.

biological properties, a characteristic attributed to their significantly smaller dimensions and the large surface area they exhibit (37). Surface plasmon resonance and related phenomena are feasible due to their notable capacity to absorb and scatter light in a highly concentrated form. This property renders them extremely effective catalysts for most chemical reactions due to their enormous surface area, which allows for maximum interaction with other reactants (38). Moreover, some metal nanoparticles, such as iron oxide, possess magnetic properties, which can be extremely useful for a wide range of applications, including medical applications and data storage devices. Moreover, electronic devices can improve their performance with higher conductivity, a property that can be achieved with these materials (39). The different types of metallic nanoparticles along with their applications, advantages and disadvantages are presented in Table III (40-47). All the nanoparticle systems have their own merits and demerits; however, they have shown promising therapeutic outcomes. Metallic nanoparticles exhibit an improved antimicrobial activity; however, there are concerns regarding the long-term toxicity and bioaccumulation. Thus, balancing efficacy, biosafety, scalability and cost is key for successful clinical translation. Metallic nanoparticles exhibit strong antimicrobial activity, but their long-term biosafety remains a matter of concern. However, clinical translation is still hampered by challenges, such as bioaccumulation, oxidative stress, inflammatory responses, delayed biodegradation and organ toxicity. Further research is required to focus on detailed *in vivo* safety evaluation and the development of biodegradable metallic nanoplatforms.

Table II. Lipid nanoparticles: Description, advantages and disadvantages.

Types	Description	Advantages	Disadvantages	(Refs.)
Solid lipid nanoparticles	Solid lipid matrix for drug encapsulation	High loading for lipophilic drugs, sustained release, good storage Stability	Limited for hydrophilic drugs, drug expulsion issues	(21)
Nanostructured lipid carriers	Blend of solid and liquid lipids for improved stability and drug loading	High drug loading, stability, good for both hydrophilic and lipophilic drugs	Complex preparation, surfactant dependency	(33)
Liposomes	Phospholipid bilayer vesicles for drug encapsulation	High encapsulation efficiency, biodegradable, suitable for both drug types	Stability issues, short circulation time, surfactant toxicity	(34)
Lipid core micelles	Micelles formed from amphiphilic lipids for encapsulating lipophilic drugs	Excellent solubilization, small size, non-toxic	Limited drug loading, instability under physiological conditions	(35)

Table III. Different types of metallic nanoparticles: Applications, advantages and disadvantages.

Metallic nanoparticles	Applications	Advantages	Disadvantages	(Refs.)
Gold (Au)	Drug delivery, diagnostic, cancer therapy	High stability, biocompatible, strong optical properties	Expensive, cytotoxic at high concentration	(40)
Silver (Ag)	Medical device, wound dressings, coating	Strong antimicrobial activity	Bioaccumulation leads to toxic effects (Argyria)	(41)
Iron (Fe)	MRI imaging, target drug delivery	Magnetic property for target delivery	Toxic effect on prolong exposure, risk of oxidation	(42)
Platinum (Pt)	Cancer treatment, catalytic converter	Durable, high stability	High cost, limited availability	(43)
Copper (Cu)	Antimicrobial coating, cancer therapy	Vigorous antimicrobial activity, cost-effective	Instability	(44)
Titanium (Ti)	Implants, bone regeneration, tissue engineering	Biocompatible, corrosion resistant	Limited solubility in biological systems	(45)
Zinc (Zn)	Antimicrobial, wound healing	Supports immune function, good antimicrobial	Toxic at high doses, unstable	(46)
Palladium (Pd)	Anti-cancer therapy, drug delivery	High efficiency in cancer therapy, effective in hydrogen-based therapy	Expensive, limited availability	(47)

4. Hydrogel-based drug delivery systems

The word ‘hydrogel’ was initially used in scientific publications by Van Bemmelen in 1884. Subsequently, moving forward to 1960, the and pioneering research by Wichterle and Lim led to marked advancements with the creation of a novel hydrophobic gel for different biological applications, which they named cross-linked hydroxyethyl methacrylate hydrogels (48). Hydrogels have been extensively researched and studied over the years, particularly in disciplines, such as tissue engineering, drug delivery and regenerative medicine, as well as in agriculture (49). Hydrogels are three-dimensional, hydrophilic polymer networks capable of absorbing large amounts of water, providing a moist environment for wound healing. Hydrogels can be loaded with growth factors, antimicrobial agents and anti-inflammatory drugs for enhanced therapeutic effects (2). Hydrogels play a crucial role in preventing undesired reactions during medical therapy since they are generally tissue biocompatible and non-toxic. Such a natural trait renders them ideal materials for use inside the human body. Additionally, these materials can release drugs with controlled and sustained release, with the advantage, not only of maximized drug effect, but also the reduced frequency of drug administration to significant levels, as a

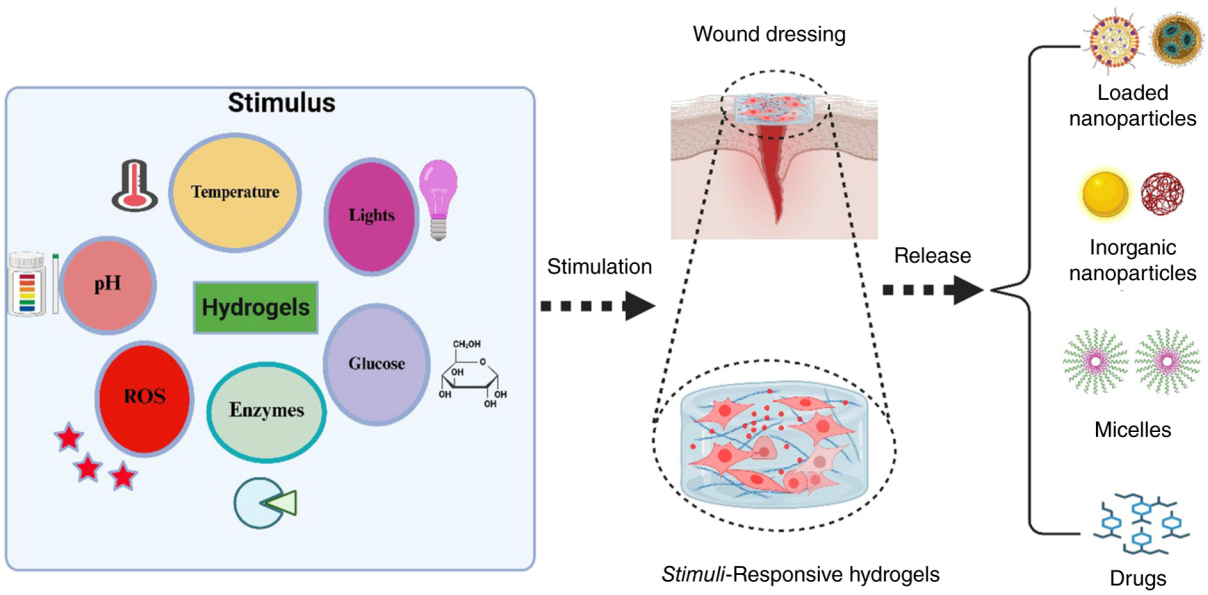

Figure 3. Schematic diagram illustrating smart hydrogel-based drug delivery systems for diabetic wounds.

result improving the compliancy and ease of the patient (50). Finally, some hydrogels carry intelligent properties. These hydrogels respond to different environmental cues, including changes in temperature, pH level, or the presence of specific enzymes in the environment. Such a property enables highly target-specific and sensitive drug release in the desired zone of action with maximum therapeutic yield (51). In addition, hydrogels can be efficiently engineered through various routes of administration, including, but not limited to, transdermal drug delivery, injectable devices, oral delivery systems, and drug delivery therapies via implanted systems, resulting in therapeutic flexibility (52). Smart hydrogels are responsive hydrogels that release drugs in response to environmental stimuli such as pH, temperature, or light (53). An illustration of the innovative hydrogel-based drug delivery system for diabetic wounds is depicted in Fig. 3. Hydrogel systems are good moisture retainers and drug release controllers; however, issues with sterilization, long-term stability, large-scale manufacturing and reproducibility remain unresolved. Although smart hydrogels combined with nanoparticles, stem cells, or exosomes exhibit promising multifunctional therapeutic potential, their regulatory approval and commercial scalability warrant further investigation (54).

Hydrogels responsive to pH. The environmental pH is of utmost relevance to the extent to which the hydrogels will swell. The performance of the materials is markedly effective under acidic conditions, particularly in situations where pH ranges are above what is commonly considered to be normal physiological ranges (55). Such a situation is common in a number of biological surroundings, such as tumor tissues or regions characterized by inflammation. For example, in the cancerous tumor microenvironment, the pH is likely slightly acidic, which allows for the targeted release of pH-sensitive drugs exactly where they are needed. Among all the various forms of stimuli-sensitive hydrogels that have been of interest to both scientists and researchers, one of the most prominent classes is thermosensitive hydrogels (56). This class of hydrogels possesses special characteristics as the hydrophobic groups in its composition undergo a phase transition when subjected to particular temperatures. As such, the structural organization of thermosensitive hydrogels can undergo a drastic change depending on the extent to which they swell upon being subjected to thermal stimuli. The most significant temperatures of relevance to such hydrogels are the lowest critical solution temperature (LCST) and the highest critical solution temperature (HCST), both of which play crucial roles in characterizing their behavior in solutions (57). LCST has become the most widely used form of thermosensitive hydrogel in a variety of applications. When the ambient temperature is below the LCST value, the hydrophobic interactions between the polymer chains decrease considerably, leading to a state where such interactions are considerably weaker. As such, this provides solubility of therapeutic drugs in the solution, thereby enabling direct injection into the target tumor while the drug remains in liquid form. Alternatively, when temperatures are above the LCST value, the polymer chains contained in the hydrogel undergo a drastic rise in hydrophobicity, which alters the manner in which they interact with the immediate environment (58).

Hydrogels responsive to temperature. Among the different types of stimuli-sensitive hydrogels that have gained the interest of scientists and researchers, thermosensitive hydrogels have been of particular interest. When temperature-sensitive hydrogels are exposed to certain temperature conditions, they undergo spectacular structural and physical property changes. Some hydrogels are better suited for use in injectable drug delivery systems, as they have been specifically engineered to gel at the natural temperature of the body. This feature enables them to set well after injection into the body (59). Furthermore, in the context of localized therapy, these advanced systems are extremely useful in the delivery of medication over a longer duration. This is due to the fact that this type of hydrogel is

Table IV. Classification of some common hydrogels.

Types of hydrogel	Examples	Properties	(Refs.)
Natural hydrogel	Alginate, chitosan, gelatin	Biocompatible, biodegradable, less mechanical strength	(65)
Synthetic hydrogel	PEG, PVA, polyacrylamide	High mechanical strength, tunable properties	(66)
Physically cross-linked gel	Gelatin, agar, pectin	Reversible, temperature and pH sensitive	(67)
Chemically cross-linked gel	Polyurethane, PVA, polyacrylate	Stable, strong, permanent cross link	(68)
pH responsive gel	Chitosan, polyacrylamide	Swell/contract with pH changes	(69)
Temperature responsive gel	Poly-N-isopropylacrylamide	Changes solubility with temperature	(70)
Ion responsive gel	Alginate, carrageenan	Sensitive to ionic strength	(71)

PEG, Polyethylene glycol; PVA, Polyvinyl alcohol.

essential owing to its sensitivity to physical structural transformations caused by temperature variations. This is owing to the fact that the thermosensitive hydrogels contain hydrophobic units that can achieve a high phase transition when they reach a specific temperature level. Such a temperature level is known as the HCST or the LCST. It acts as a decisive factor that determines the behavior exhibited by these hydrogels (60). Out of the two types, the LCST is the most widely used type of thermosensitive hydrogel in experimental and functional operations. When the ambient temperature drops below the LCST, the dominant hydrophobic interactions among the polymer chains are significantly decreased. Due to this decrease in hydrophobic bonding, the therapeutic drugs become easily soluble in the solution and can be delivered directly at the cancer site without being insoluble. When the temperature increases above the LCST, however, the polymer chains in the hydrogel become hydrophobic (61).

Response of hydrogels to light. Such hydrogels are designed to release drugs under specific conditions upon exposure to certain wavelengths of light. This characteristic renders them highly effective in treatments, such as photodynamic therapy, a well-established form of cancer therapy. The spatial and temporal accuracy provided by these hydrogels significantly improves the efficacy of the therapy by delivering drug release precisely at the correct location and time (62). The osmotic balance of the gel medium is grossly disturbed on ionization of the photosensitive radicals by light. The ionization leads to a permeability imbalance, and hence the entry or exit of ions and water into or out of the gel network. As a direct result of this imbalance, the gel swells or contracts in volume. The role of detecting light signals and transducing them into chemical signals is solely a function of the photosensitive part of the system. As a result of the light-induced reaction, the structure and properties of the hydrogel undergo a radical change, including processes such as isomerization, pyrolysis, and even dimerization, all of which contribute to the overall material alteration. The interference with chemical interactions between hydrogel polymer chains and photosensitive groups leads to the breaking of the photosensitive groups when exposed to ultraviolet or visible light (63). This effect increases the internal osmotic pressure of the hydrogel, allowing water molecules from the surrounding medium to penetrate the structure. The penetration of water enables the opening of pores in the hydrogel, thereby enhancing the release of drugs encapsulated within it. Furthermore, the inclusion of photothermal agents allows the hydrogel to generate heat locally through the effective absorption of light energy. It is also worth noting that the increase in temperature decreases the effect of hydrogen bonds. By contrast, the protophilic effect of hydrogels, which refers to the interactions between the segments of the polymer chain and the temperature-sensitive groups, increases (64). The classification of hydrogels is presented in Table IV (65-71).

Nanoparticle-impregnated hydrogels. Combining nanoparticles with hydrogels improves mechanical strength and drug delivery efficiency. In numerous applications and areas, such as drug delivery, tissue engineering, biomedical engineering, and environmental engineering, this new hybrid system is of immense interest to scientists and professionals alike. Hydrogels are water-friendly polymer networks that possess the unique ability to retain a high-water content. The addition of nanoparticles, such as carbon-based, ceramic, polymeric, or metallic, significantly improves parameters such as mechanical strength, conductivity and biological activity, thereby enhancing the application and efficiency of the materials in their respective fields (72). The different types of nanoparticle-impregnated hydrogels are presented in Table V (73-78).

Biopolymer-based hydrogels. Hydrogels prepared using biopolymers as formulators are gaining popularity and are increasingly sought after in applications as potential carriers for drug delivery systems. Most of the increase in popularity can be attributed to their superior properties, including biocompatibility, biodegradability and responsiveness to various environmental stresses. These hydrogels possess the unique property of being able to absorb large quantities of water or biological fluids, and they are composed of networks of natural or synthetic polymers (79). Notably, they possess the unique property of being capable of swelling or shrinking reversibly in response to changes in temperature, pH values,

Table V. Different types of nanoparticle impregnated hydrogels.

Types of nanoparticles	Examples	Properties	Applications	Key benefits	(Refs.)
Metallic nanoparticles	Ag, Au, Cu	Antimicrobial, conductive, catalytic	Would healing, drug delivery, biosensors	High biocompatibility, strong antimicrobial activity	(73)
Ceramic nanoparticles	Hydroxyapatite, alumina (Al_2O_3),	Biocompatible, osteoconductive, mechanical strength	Bone regeneration, dental implants, tissue scaffolds	Enhanced mechanical support, bone growth support	(74)
Carbo-based nanoparticles	Graphene oxide, carbon nanotubes	Large surface area, mechanical strength, high conductivity	Tissue engineering, sensors	Enhanced conductivity, enhanced mechanical support	(75)
Magnetic nanoparticles	Iron oxides, magnetite	Drug targeting	Cancer therapy, diagnostic	Target delivery	(76)
Silica nanoparticles	Mesoporous silica, nano-silica	Large surface area, stability	Drug delivery, imaging biosensing	High drug loading capacity, stable under various conditions	(77)
Lipid-based nanoparticles	Liposomes, solid-lipid nanoparticles	Biocompatible, controlled release	Cosmetic products, vaccine carriers, drug delivery	Enhanced skin penetration	(78)

ionic strengths, or other essential variables. The majority of naturally occurring polysaccharides used in hydrogel formulations include alginate, chitosan, pectin, hyaluronic acid and carboxymethyl cellulose. These biopolymers are particularly convenient for use in drug delivery due to their abundance in nature, primarily due to their high biocompatibility and biodegradability (80). Natural proteins, such as collagen, fibrin and gelatin, are also used to prepare hydrogels with enhanced mechanical and bioactive properties. These hydrogels are applied in areas where direct tissue contact and controlled release processes are required. In addition to natural polysaccharides and proteins, other biopolymers, including polylactic acid, polyglycolic acid and PLGA, are used in the composition of drug delivery hydrogels (81). This is due to the fact that the mentioned biopolymers are more biodegradable and undergo controlled degradation rates, making them the ideal choice for novel drug delivery systems. Biopolymer hydrogels, a platform for a vital drug delivery system, have numerous benefits, including controlled and targeted drug release, biocompatibility, and biodegradability. They are used more in medicine, and novel and improved formulations for different therapeutic applications are emerging as a result of continuous research into their limitations (82). A summary of biopolymer-based hydrogels, and their applications, properties and key benefits is presented in Table VI (83-91).

5. Microneedle-assisted drug delivery systems for advanced wound therapy

Microneedles are an innovative and minimally invasive technique for transdermal medication delivery, demonstrating significant potential for wound healing therapy. The technology involves the fabrication of micron-scale needle arrays, enabling the precise and effective delivery of bioactive chemicals into the epidermis and dermis while minimizing pain or discomfort (92). Microneedles, as an innovative drug delivery method, have garnered significant interest due to their non-invasive, pain-free and straightforward administration, regulated drug distribution and ability to load various cargos (5). Recent advancements in the design of microneedles have expanded their use in wound healing, particularly for diabetic and chronic lesions that necessitate regulated medication delivery and enhanced tissue regeneration (93).

Microneedles typically range from 50 to 900 μm in length, an optimal dimension that facilitates effective penetration of the stratum corneum (~15-20-μm-thick), while avoiding the deeper dermal layer, which houses nerve endings (94). This array of unique dimensions provides several significant advantages in transdermal medication administration. Microneedles provide painless delivery by circumventing skin nociceptors, significantly enhancing patient comfort compared to conventional hypodermic needles. Secondly, their ability to penetrate the outer skin barrier facilitates the administration of macromolecular therapies (5-100 kDa), which would otherwise be unable to access intact skin. The structural flexibility of microneedle systems facilitates customizable drug release kinetics, permitting both immediate and sustained delivery profiles tailored to specific therapeutic requirements. Collectively, these attributes promote improved patient adherence by integrating the efficacy of injectable medications with a minimally invasive, user-friendly platform (95).

Classification and functional properties of microneedle-based drug delivery systems. Along with current technological advancements in microneedle-based drug delivery systems, this section addresses several forms of microneedles, including dissolvable microneedles (DMNs) and hydrogel-forming microneedles (HFMNs). Based on its composition, mode of action and therapeutic uses, each type is investigated with an

Table VI. Biopolymers-based hydrogel with applications, properties and key benefits.

Types of biopolymers	Examples	Properties	Applications	Key benefits	(Refs.)
Polysaccharides	Starch, cellulose, chitosan, alginate	Biodegradable, hydrophilic, film-forming, good mechanical strength	Food packaging, drug delivery, wound healing, tissue engineering	Renewable, cost-effective, biocompatible	(83)
Proteins	Collagen, gelatin, silk fibroin, keratin	Biocompatible, good film-forming, water-soluble or insoluble	Biomedical scaffolds, drug carriers, cosmetics, tissue regeneration	High bioactivity, natural origin	(84)
Nucleic Acids	DNA, RNA	Programmable, highly specific binding, biodegradable	Nanomedicine, biosensors, gene therapy	Precision targeting, information-rich	(85)
Polyesters	Polylactic acid (PLA), polyhydroxyalkanoates (PHAs), PGA	Thermoplastic, biodegradable, tunable degradation rate	Implants, sutures, packaging, agricultural films	Mechanical strength, renewable sources	(86,87)
Polyamides	Poly(aspartic acid), Poly(glutamic acid)	Water-soluble, biodegradable, polyelectrolytic behavior	Biomedical applications, water treatment, agriculture	Environmentally friendly, biodegradable	(88)
Lignin-based	Lignosulfonates, Kraft lignin	Aromatic structure, UV absorbance, antioxidant properties	Packaging, adhesives, drug delivery, coatings	Waste utilization, natural antioxidant	(89)
Biosynthetic polymers	Bacterial cellulose, xanthan gum	Strong, highly pure, customizable structure	Biomedical devices, tissue engineering, food thickeners	Microbial origin, reproducible quality	(90,91)

PGA, polyglycolic acid; UV, ultraviolet.

eye towards developments that improve transdermal delivery efficiency, patient compliance and formulation stability.

DMNs. DMNs are a cutting-edge and therapeutically feasible microneedle technology, composed entirely of water-soluble polymers infused with medicinal compounds. Microneedles are often composed of biodegradable and biocompatible materials, such as hyaluronic acid, polyvinylpyrrolidone and PLGA, which facilitates safe administration and prolonged drug release (96). One of the primary advantages of DMNs is their substantial drug-loading capacity, allowing for the incorporation of up to 30% w/w of active pharmaceutical ingredients. Upon application to the skin, DMNs rapidly dissolve, typically within 5 to 15 min, facilitating the prompt and efficient medication delivery, while preventing the generation of biohazardous sharp debris (97). Their rapid dissolution characteristics and excellent biocompatibility make DMNs highly promising for various clinical applications, including the administration of antibiotics (e.g., vancomycin for wound infections), growth factors (e.g., VEGF to promote angiogenesis), and anti-inflammatory medications (e.g., dexamethasone) (98). The combination of rapid onset, substantial payload and user-friendly, minimally invasive administration underscores the potential of DMNs as an innovative technique for transdermal drug delivery.

HFMNs. HFMNs are a second-generation microneedle device designed for extended drug administration and enhanced wound care. HFMNs consist of cross-linked hydrophilic polymers such as poly(methyl vinyl ether-co-maleic acid), which rapidly absorb interstitial fluid upon implantation into the skin. The swelling results in the formation of a hydrogel matrix that serves as a drug reservoir, enabling regulated and prolonged drug release (99). Unlike dissolving microneedles, HFMNs have extended drug release patterns ranging from 24 h to 7 days, significantly reducing the necessity for frequent dosing. The hydrogel matrix creates an optimal moisture microenvironment (often 60-70% relative humidity) at the wound site, facilitating improved tissue regeneration, while preventing desiccation and excessive exudate accumulation (100). In addition to regulated medication delivery, HFMNs provide multimodal therapeutic capabilities, including serving as a

physical barrier against bacterial infiltration and facilitating autolytic debridement, benefits which are particularly critical in the treatment of chronic and non-healing wounds. The incorporation of prolonged medication release, hydration and infection prevention highlights the utility of HFMNs as a versatile and therapeutically relevant platform for advanced transdermal and wound care (101).

Recent technological innovations. Innovative smart microneedle devices are transforming personalised medicine through the integration of stimulus-responsive drug administration and real-time monitoring capabilities. Notable advancements encompass glucose-responsive microneedles for diabetic wound treatment, pH-sensitive microneedles that activate drug release in infected wounds, and photothermal microneedles that enable on-demand drug release via light stimulation (101,102). These intelligent solutions enhance therapy precision by dynamically responding to pathological variations in the wound microenvironment. Further advancements include sensor microneedle patches that are incorporated into diagnostic and therapeutic functions by continually monitoring wound parameters, such as temperature, pH and exudate biomarkers, in real-time (103). Some of the next-generation devices even incorporate closed-loop feedback systems in which data from sensors automatically drive drug release, maximizing therapeutic effectiveness, while decreasing the need for manual intervention. Collectively, these technologies signify a paradigm change towards intelligent, adaptive wound therapy that integrates diagnostics and treatment: clinical translation and its obstacles (104). However, the practical limitations of microneedle systems in chronic wound treatment are limited due to their advantages. Chronic wounds typically present with large amounts of exudate, necrotic tissue, irregular wound shapes and fragile tissue structures, rendering it difficult to uniformly insert microneedles. Improper application can increase patient discomfort and secondary tissue trauma, limiting clinical applicability.

6. Scaffold-based drug delivery systems for regenerative wound healing

Scaffold-based drug delivery systems have emerged as a transformative approach in regenerative medicine, providing biomimetic platforms that integrate structural support with temporally regulated therapeutic release to enhance wound healing. Engineered matrices are designed to mimic the native extracellular matrix (ECM) milieu, providing mechanical stability while promoting cellular adhesion, proliferation and differentiation. Among the various scaffold systems, 3D-printed scaffolds, electrospun nanofibers, and bioactive scaffolds, focusing on their design principles, drug delivery mechanisms, and clinical applicability (105).

3D-printed scaffolds for precision medicine. Contemporary 3D printing techniques enable exceptional control over scaffold architecture, facilitating precise adjustments of pore dimensions (50-500 μm), mechanical characteristics (Young's modulus 1-20 MPa) and drug release kinetics (106). Digital light processing is an intriguing technique that achieves print resolutions of 50 μm using photocrosslinkable hydrogels such as gelatin methacryloyl (107). Recent research has demonstrated that thermoresponsive polymers, such as Pluronic F127, can be utilized in extrusion-based printing, facilitating temperature-regulated drug release kinetics (108). Polycaprolactone scaffolds infused with the dual agents VEGF and ciprofloxacin demonstrate enhanced wound healing efficacy, exhibiting a prolonged release over 14 days that accelerates wound closure by 40% in diabetic mouse models ($P<0.01$) (109). pH-sensitive hydrogels that preferentially release doxycycline in acidic wound environments (pH <6.5) have demonstrated a 99% reduction in bacterial load ($P<0.001$) (110). Chou *et al* (111) demonstrated that lipoic acid-modified gold nanoclusters (AuNCs) incorporated into a silk fibroin scaffold significantly accelerated burn wound healing by enhancing fibroblast proliferation through PI3K/Akt-mediated cell cycle activation, while simultaneously promoting collagen deposition, angiogenesis, and suppressing inflammation and apoptosis. These findings highlight the therapeutic potential of AuNC-based biomaterial scaffolds for regenerative wound healing (111). Silk fibroin/collagen composite scaffolds demonstrate significant efficacy in burn treatment, attaining complete re-epithelialization in full-thickness burns after 21 days, compared to 35 days for conventional dressings (112).

Electrospun nanofibrous scaffolds. Electrospinning technology has significantly advanced, enabling the fabrication of nanofibers with diameters ranging from 100 to 1,000 nm and exceptionally high surface-area-to-volume ratios, facilitating drug loading efficiencies of 90-100% (113). Recent advancements, such as coaxial electrospinning, enable the creation of core-shell nanofiber structures designed for sequential or sustained drug release (114). Functionalized electrospun systems, such as polyvinyl alcohol/chitosan nanofibers integrated with silver nanoparticles, have demonstrated exceptional efficacy as antimicrobial agents, achieving a 99% inhibition of biofilm formation by *Staphylococcus aureus* and *Pseudomonas aeruginosa* ($P<0.001$), while maintaining cytocompatibility (115). Furthermore, gelatin nanofibers infused with PDGF significantly boosted wound healing in severely diabetic conditions, achieving a 2.5-fold acceleration ($P<0.01$) in wound closure through improved fibroblast migration and collagen production. This indicates the effectiveness of electrospun nanofiber platforms as multifunctional carriers for targeted medication administration and advanced wound treatment (116).

Bioactive scaffolds. Collagen scaffolds incorporating fibroblast growth factor-2 and TGF-β3 have exhibited marked scar reduction potential, increasing the collagen III/I ratio by 3-fold ($P<0.01$) (117). VEGF-encapsulated alginate microspheres embedded in scaffolds have exhibited an enhanced capillary density by 80% ($P<0.001$) in ischemic wounds (118). Another study demonstrated that mesenchymal stem cell-laden decellularized ECM scaffolds promoted angiogenesis through the 80% upregulation of VEGF secretion in full-thickness burn models (11). It was also previously demonstrated that exosome-loaded hyaluronic acid scaffolds significantly improved fibroblast migration and collagen organization in chronic wounds ($P<0.01$) (8).

Exosome-based therapeutic systems. Exosomes are nanosized extracellular vesicles that can deliver proteins, nucleic acids, cytokines and growth factors to target tissues. Exosome-loaded hydrogels and scaffold systems have emerged as promising regenerative platforms for chronic wound healing due to their immunomodulatory, angiogenic and anti-inflammatory properties. Exosomes derived from mesenchymal stem cells significantly enhance fibroblast proliferation, collagen deposition, and neovascularization, while decreasing scar formation and the risk of immune rejection (119).

7. Translational perspectives and clinical translation challenges

The considerable breakthrough in the development of advanced drug delivery systems for wound healing has exhibited immense promise for further clinical application; however, it has yet to be successfully implemented in clinical trials. Although there have been promising results from the use of nanoparticles, hydrogels, microneedles, exosomes and bioengineered wound dressings, only a fraction of these technologies have reached the final stages of clinical trials and commercialization. Several obstacles remain that need to be overcome for the wider application of drug delivery systems for wound healing in clinical practice.

Firstly, it is difficult to scale-up the technology due to complex multifunctionality. In this case, one needs to use quite complex processes to produce a drug delivery system, which makes it harder to ensure the reproducibility of the physicochemical, drug-loading and biological properties of the product. Additionally, sterilization methods, such as gamma irradiation, ethylene oxide sterilization and autoclaving may compromise the structural stability of biomaterials, such as hydrogels and exosomes, thereby reducing the efficacy of the therapy. Recent studies emphasize the need to develop good manufacturing practice (GMP) and quality by design (QbD) approaches to overcome this issue.

Another issue lies in obtaining regulatory approval. Wound healing systems are relativley complex, as they may include drugs, biologics, biomaterials and medical devices. Moreover, exosome-loaded systems and stem cell-based scaffolds need to undergo additional regulatory approval due to factors, such as donor variability, immunogenicity, stability and safety concerns. Therefore, further research and clinical evidence should be provided in order to obtain approval from regulatory agencies. The third obstacle relates to the economics of the problem. Advanced biomaterials, personalized scaffold design and intelligent wound monitoring systems may lead to higher production costs, rendering them less available in resource-limited healthcare environments. Thus, further research is required to focus on cost-effective technologies and on scaling up the process without compromising product efficiency.

There are some innovations that may help accelerate the translation process. The integration of biosensors, wearable wound monitoring systems, artificial intelligence image analysis, and closed-loop drug delivery systems might improve personalized wound healing by allowing real-time assessment of wound status and the provision of an adequate response.

8. Conclusion and future perspectives

Advanced drug delivery systems have revolutionized wound management by providing controlled drug release, enhanced tissue targeting and regenerative modulation. The next generation of multifunctional wound therapeutics is the hybrid systems of nanoparticle, hydrogel, exosome, microneedle and scaffold-based biomaterial. However, there are still a number of translational barriers to overcome, including large-scale manufacturing, sterilization, regulatory approval, GMP compliance, storage stability and high production costs. Stringent quality control and reproducibility are necessary before clinical translation for complex systems, such as stem cell- or exosome-loaded smart hydrogels and 3D-printed scaffolds. Current clinical translation efforts should prioritize standardized manufacturing protocols, harmonized regulatory frameworks, large-scale multicenter clinical trials, and health-economic evaluations to facilitate commercialization and routine clinical adoption of advanced wound-healing technologies. Future research is warranted directed towards the development of patient-specific, cost-effective and clinically translatable biomaterial systems integrated with biosensors, artificial intelligence-assisted wound monitoring and personalized regenerative therapies.

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Authors' contributions

AKD and DPK prepared the original draft of the manuscript. OM and VKS were involved in the literature search, KS, RP, RS and HB reviewed and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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