Zoology, Ecology and Pharma Advances
Content Available at www.uniquepubinternational.com
(An International online peer reviewed Journal) ISSN (O): 3139-2075

Review Article
OPEN ACCESS

EMERGING TRENDS IN HYDROGEL TECHNOLOGY FOR REGENERATIVE MEDICINE

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Article History: Received: 24 Feb 2026, Revised: 26 Apr 2026, Accepted: 24 May 2026

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Abstract
Hydrogels have revolutionized wound care with their unique properties, providing a moist environment that facilitates healing. These polymer-based dressings absorb wound exudates, exhibit shape adaptability, and can be modified to incorporate active compounds. Hydrogels promote wound healing by reducing inflammation, preventing infection, and enhancing tissue regeneration. They're effective for chronic wounds, burns, and surgical wounds. Advanced hydrogel technologies include smart hydrogels that respond to stimuli, injectable hydrogels for deep wounds, and antimicrobial hydrogels that prevent infection. Hydrogels can be designed to release therapeutic agents in controlled manner, promoting optimal healing. They're biocompatible, biodegradable, and non-toxic, reducing risk of adverse reactions. Hydrogels have high water content, similar to native tissues, making them ideal for dermal wound healing. Multifunctional hydrogels are a promising area of research, with potential to revolutionize wound care. They're being explored for various applications, including diabetic wounds, pressure sores, and traumatic injuries. Hydrogels can promote haemostasis, angiogenesis, and tissue regeneration, while reduce scarring and improve patient comfort. Research hydrogels are ongoing to improve their performance and expand their applications. Hydrogel-based dressings a crucial role in wound management due to unique properties. They're being used to develop advanced wound care products, including wound dressings, implantable devices, and tissue engineering scaffold.
Keywords: *Chronic wounds; wound dressings; hydrogels; wound healing; polymers.*

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INTRODUCTION

Hydrogels may be formed through physical or chemical crosslinking mechanisms. In physically crosslinked hydrogels, the polymer networks are held together by reversible interactions such as hydrogen bonding, ionic interactions, or hydrophobic forces. These reversible bonds allow the hydrogel to respond to environmental changes and, in some cases, return to a soluble state. In contrast, chemically crosslinked hydrogels are formed through irreversible covalent bonds between polymer chains. This results in a permanent and stable three-dimensional network structure. Chemically crosslinked hydrogels generally exhibit greater mechanical strength and structural integrity. They maintain their network architecture even under physiological conditions. Due to their stable framework, they provide sustained performance in biomedical applications. Additionally, their hydrophilic nature enables them to absorb and retain large amounts of water. This property makes them highly suitable for wound dressing and tissue engineering applications.

The Skin

The skin is the largest and a multifunctional organ of the human body, responsible for protection and maintenance of internal homeostasis [1]. It is composed of \three main layers: epidermis, dermis, and hypodermis. The epidermis, which forms the outer protective barrier, is primarily made up of keratinocytes and lacks blood vessels, relying on the dermis for nutrient diffusion [2]. It also contains melanocytes that produce melanin and Langerhans cells that provide immune defence [3]. The epidermis consists of five layers-stratum Basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The stratum Basale contains stem cells responsible for continuous keratinocyte production, while keratinization begins in the stratum spinosum [4]. The stratum granulosum contributes to keratin aggregation and lipid barrier formation, and the stratum lucidum is present in thick skin such as palms and soles [5]. The outermost stratum corneum forms a strong protective barrier, and complete epidermal turnover takes approximately 25–45 days. Beneath the epidermis lies the dermis, a connective tissue layer divided into papillary and reticular regions [6]. The deepest layer, the hypodermis, contains adipose tissue that provides cushioning, insulation, thermoregulation, and structural support.

WOUND HEALING PHASES.

The wound healing process is a coordinated physiological mechanism involving multiple cell types to restore skin integrity. It begins with haemostasis, where vasoconstriction reduces blood loss and a clot forms a temporary extracellular matrix [7]. Injured cells release chemokines that attract inflammatory cells, with neutrophils arriving first, followed by monocytes that differentiate into macrophages to remove pathogens and damaged tissue [8]. Macrophages stimulate fibroblast and epithelial cell proliferation, initiating the proliferative phase. During this phase, neovascularization occurs, and fibroblasts differentiate into myofibroblasts to aid wound contraction and extracellular matrix deposition [9]. The granulation tissue formed contains capillaries, fibroblasts, inflammatory cells, endothelial cells, and myofibroblasts. The transition from inflammation to proliferation is critical for wound healing, promoting angiogenesis, fibroplasia, and keratinocyte activation. These processes generally start within the first 48 hours and can continue for up to 14 days, depending on wound severity [10].

ACUTE AND CHRONIC WOUNDS

Acute and chronic wounds are differentiated by healing time and the presence of physiological damage. Acute wounds fully heal within 8–12 days, leaving minimal scarring, and are caused by mechanical trauma, surgical incisions, burns, or electrical injuries [11]. Chronic wounds occur when healing is disrupted, often due to bacterial infections and biofilm formation, which trigger excess neutrophils that release reactive oxygen species and enzymes, impairing cell migration and tissue repair [12]. Post-surgical nosocomial infections further increase the risk of chronic wounds. Common chronic wounds include vascular ulcers, such as diabetic, pressure, venous, and arterial ulcers.

MECHANISM OF WOUND HEALING

Wound healing is a highly regulated process that restores tissue integrity through the coordinated action of multiple cellular and molecular systems. It is generally divided into four stages: haemostasis, inflammation, proliferation, and remodelling. During haemostasis, blood clotting seals the wound, and a fibrin matrix provides a scaffold for cell migration. The inflammatory phase recruits' neutrophils and macrophages to remove debris, bacteria, and damaged tissue while releasing cytokines and chemokines that guide repair. In the proliferative phase, keratinocytes re-epithelialize the wound, endothelial cells promote angiogenesis, and fibroblasts generate extracellular matrix to rebuild tissue. Finally, the remodelling phase strengthens and matures the tissue through collagen fibre realignment and removal of excess cells, coordinated by growth factors and other molecular signals. This precise coordination ensures complete and effective tissue repair.

CURRENT TREATMENT METHOD

Wound dressings are chosen based on the wound's depth, size, location, exudate, inflammation, and adhesion. Moisture-retentive dressings like gels, films, and gauzes promote healing by protecting the wound, supporting granulation tissue, and reducing infection, whereas dry dressings can stick to the wound and cause tissue damage [14]. Negative Pressure Wound Therapy (NPWT) uses a controlled vacuum to remove fluid and debris, but is not suitable for wounds with osteomyelitis, malignancy, necrotic tissue, or eschar, and may limit mobility [15]. Hyperbaric Oxygen Therapy (HBOT) delivers 100% oxygen at higher-than-sea-level pressure, enhancing oxygen delivery, speeding tissue regeneration, and shortening healing time for non-healing wounds [16].

HYDROGELS FOR WOUND HEALING

Hydrogels are advanced wound dressings known for their ability to absorb and retain large amounts of water or biological fluids while maintaining structural integrity. Their soft and malleable nature mimics the extracellular matrix (ECM) of soft tissues. They can be prepared using radiation, freeze-thaw, or chemical crosslinking, and physical (reversible) gels maintain structure through ionic or molecular entanglements. Hydrogels are made from natural polymers (chitosan, gelatine, hyaluronic acid, alginate), synthetic polymers (polyethylene glycol, polyvinyl pyrrolidone, polyethylene oxide, polyvinyl alcohol), or multipolymer combinations to enhance mechanical strength and absorption. They create a moist wound environment, can be tailored for specific wound types, and have applications in sprayable, smart, nanogel, aerogel, cryogen, injectable, and wound dressing formulations, including modified versions like carboxymethyl chitosan (CMCS) for diabetic wounds.

NATURAL AND SYNTHETIC HYDROGELS.

1. Natural Hydrogels

Hydrogel wound dressings are made from natural, synthetic, or multipolymer combinations to enhance mechanical strength and absorption. Natural hydrogels such as chitosan, gelatin, hyaluronic acid, and alginate are biocompatible and mimic the extracellular matrix. Chitosan offers antibacterial activity, maintains a hydrated wound environment, and reduces scarring, though its mechanical strength is limited [17]. Gelatin promotes cell adhesion and tissue regeneration but lacks antibacterial properties, often requiring hybridization with antimicrobials. Hyaluronic acid (HA) supports elasticity and tissue regeneration and can be cross-linked for stable hydrogels, showing rapid healing and antimicrobial effects. Alginate forms gels with divalent cations, accelerates chronic wound healing by activating macrophages, and allows painless dressing removal [18].

2. Synthetic hydrogels.

Synthetic hydrogels such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) offer tenable mechanical properties, biocompatibility, and ease of fabrication [19]. PEG-based hydrogels support tissue repair and protein attachment, PVA hydrogels provide stiffness, adhesion, and rapid self-healing, and PVP hydrogels are non-toxic, adhesive, and film-forming, suitable for wound healing applications. Multipolymer and hybrid hydrogels combine the advantages of natural and synthetic polymers for advanced wound care.

MULTIFUNCTIONAL HYDROGELS WOUND DRESSINGS

- Hydrogels provide physical protection and maintain a moist wound environment.
- Modern hydrogel dressings are customizable for different wound types and complex shapes.
- Ideal dressings should have mechanical strength, oxygen permeability, self-healing, injectability, and biodegradability.

1. Antibacterial Hydrogel

- Protects wounds from bacterial invasion after trauma.
- Chitosan and CT/EPL hydrogels disrupt bacterial membranes and eradicate bacteria.
- Effective against MRSA in animal burn wound models.

2. Antioxidant Hydrogel

- Controls excessive reactive oxygen species (ROS) that damage fibroblasts and endothelial cells.
- Supports angiogenesis and extracellular matrix (ECM) regeneration.
- Antioxidants can be chemically coupled to the hydrogel or directly incorporated into the matrix.

3. Anti-inflammatory Hydrogel

- Reduces inflammation and supports tissue regeneration.
- Incorporation of EGF in GelMA hydrogels enhances epithelial repair.
- Bilayer EDC-crosslinked gelatine hydrogels reduce biofilm formation and improve wound closure.

PREPARATION TECHNOLOGIES OF HYDROGEL WOUND DRESSINGS

Hydrogel wound dressings can now be functionalized with active compounds through chemical grafting or physical deposition, enabling improved wound healing. Advances in technology allow for precise control over the hydrogel's structure, composition, and bioactivity, making them more effective and customizable for different wound types.

BioprintingTechnology

3D bioprinting uses cell-laden bioinks to build layered hydrogel structures that closely mimic natural tissue architecture. Bioactive compounds, such as growth factors or anti-inflammatory drugs, can be integrated during printing. This technology promotes cell proliferation, tissue regeneration, and patient-specific hydrogel dressings, accelerating the wound healing process.

MicrofluidicTechnology

Microfluidics employs microscale channels and chambers to fabricate hydrogel microfibres with controlled morphology. Using techniques like one-step microfluidic spinning, these porous hydrogel fibres provide enhanced angiogenesis and antibacterial properties, which help speed up wound healing.

Microneedle(MN)Technology

Microneedles are tiny arrays that allow minimally invasive transdermal drug delivery. Hydrogel-based MNs swell after absorbing water in the skin, gradually releasing therapeutic agents. GelMA/PEGDA hydrogel MNs can stimulate angiogenesis, promote cell migration, and are particularly useful for diabetic and chronic wounds.

APPLICATION OF HYDROGEL-BASED DRESSINGS

Hydrogels are tailored to specific wound types; no single formulation works for all wounds.

1. Acute Wounds

- Treat surgical cuts, burns, abrasions, bites, lacerations.
- Maintain moisture, support cell migration, and accelerate healing.

2. Chronic Wounds

- Include diabetic ulcers, pressure ulcers, vascular wounds.
- Hydrogels provide antibacterial, antioxidant, ROS/glucose-responsive, and angiogenesis-promoting properties, plus sustained drug release.

3. Infected Wounds

- Require simultaneous bacterial control and tissue regeneration.
- Antimicrobial hydrogels with metal ions, antibiotics, conductive polymers, or photothermal agents reduce infection and inflammation.

4. Pressure Ulcers

- Common in immobile patients, may cause secondary injuries.
- Dressings offer mechanical strength, conductivity, antimicrobial properties, and pressure sensitivity, some with real-time monitoring.

5. Wound Monitoring Applications

- Smart hydrogels track pH, temperature, glucose, infection, and pressure.
- Enable personalized treatment, early infection detection, and intelligent wound care.

FUTURE PERSPECTIVE

The future of wound management relies on overcoming the complexity of the wound-healing process, especially in chronic and diabetic wounds, where no single hydrogel-based dressing can address all healing challenges. Although multifunctional hydrogels show strong potential, their clinical translation is limited due to insufficient human trials, differences between animal models and human skin, and incomplete understanding of their underlying healing mechanisms. Future research must focus on mechanistic insights, personalised hydrogel design, and large-scale clinical validation. Integrating hydrogels with advanced technologies such as nanomaterials, exosomes, stem cells, 3D bioprinting, and cold atmospheric plasma, along with optimised, cost-effective manufacturing, will be crucial for developing safe, effective, and next-generation wound-healing therapies.

CONCLUSION

Hydrogel-based wound dressings have revolutionized modern wound care by offering multifunctional properties that actively support all stages of the wound-healing process. Their ability to maintain a moist environment, deliver bioactive agents, and promote tissue regeneration makes them especially effective for difficult-to-heal wounds such as burns, diabetic ulcers, chronic inflammatory wounds, and wounds in sensitive areas. Future wound dressings are expected to become more advanced and multifunctional through the integration of emerging technologies like 3D printing, electrospinning, microfluidics, and microneedle systems, along with deeper insights into wound-healing mechanisms, enabling more effective, targeted, and innovative wound-management strategies.

ACKNOWLEDGEMENT

The authors would like to acknowledge all individuals and institutions that supported this work directly or indirectly.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the preparation and completion of this manuscript.

FINANCIAL SUPPORT

The authors received no financial support for this study.

DECLARATION OF COMPETING INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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