

Stimuli-Responsive Hydrogels for Precision Wound Therapeutic: Potential, Applications Challenge's, and Future Perspectives

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www.jrasb.com || Vol. 5 No. 2 (2026): April Issue

Received: 20-03-2026

Revised: 23-03-2026

Accepted: 28-03-2026

ABSTRACT

Wound healing is a complex biological process that involves a sequence of overlapping phases including hemostasis, inflammation, proliferation, and remodeling. Delayed or improper healing can lead to chronic wounds, infections, and increased healthcare burden. Conventional wound treatment methods such as gauze dressings, ointments, and surgical interventions often fail to provide an ideal healing environment. In recent years, hydrogels have emerged as promising wound dressing materials due to their high-water content, biocompatibility, flexibility, and ability to maintain a moist environment at the wound site. These properties support cell migration, tissue regeneration, and protection against microbial invasion. Hydrogel-based dressings can also be designed to absorb excess exudate, deliver therapeutic agents, and promote faster healing of both acute and chronic wounds. This review summarizes the basic concepts of wound healing, existing treatment approaches, and the role of hydrogels as advanced wound dressing systems. Additionally, the applications, advantages, current challenges, and future prospects of hydrogel-based wound dressings are discussed to provide a comprehensive understanding of their potential in modern wound care.

Keywords- hydrogels; polymers; wound dressing; tissue regenerations.

I. INTRODUCTION

The skin is the human body's biggest organ and the primary barrier that protects internal tissues from mechanical injury, microbial invasion, and excessive fluid loss. Wound healing is a highly controlled biological process that occurs when skin integrity is disrupted by trauma, burns, surgical intervention, or pathological conditions. This process proceeds through the overlapping phases of hemostasis, inflammation, proliferation, and remodeling, involving coordinated interactions among cells, signaling molecules, and extracellular matrix components [Guo and DiPietro, 2010; Velnar *et al.*, 2009]. Any disruption in these events may result in delayed healing or chronic wound formation [Frykberg and Banks, 2015]. Based on healing duration and physiological progression, wounds are broadly classified as acute or chronic. Acute wounds, such as surgical incisions and minor injuries, usually

heal in a predictable time frame, whereas chronic wounds, including diabetic foot ulcers and pressure ulcers, fail to progress through normal healing phases and remain in persistent inflammatory states [Frykberg and Banks, 2015]. The growing prevalence of chronic wounds due to aging populations and metabolic disorders presents a significant clinical challenge and highlights the need for advanced wound care solutions [Boateng *et al.*, 2008].

Conventional wound management involves the use of cotton gauze, bandages, and topical antiseptics to protect wounds and absorb exudate. However, these traditional dressings often provide only passive protection and may adhere to the wound bed, causing secondary injury during removal [Boateng *et al.*, 2008]. The recognition that moist environments accelerate wound repair led to the development of modern interactive wound dressings designed to regulate hydration and promote cellular activities essential for tissue regeneration [Winter, 1962].

Hydrogels have emerged as one of the most promising classes of biomaterials for wound care due to their three-dimensional hydrophilic polymer networks capable of retaining large volumes of water. Their high-water content mimics native tissue conditions, providing a non-adherent and biocompatible interface that supports epithelial migration and granulation tissue formation [Ahmed, 2015]. Owing to these advantages, hydrogel-based systems have been widely investigated for biomedical and tissue engineering applications [Shen *et al.*, 2023; Zheng *et al.*, 2024].

Recent developments in hydrogel technology have expanded their functional capabilities beyond conventional moisture-retentive dressings. Self-healing hydrogel systems capable of restoring structural integrity after mechanical disruption have been explored to improve dressing durability and long-term wound coverage [Abd-ElSalam *et al.*, 2024;omidian *et al.*, 2024]. In addition, multifunctional hydrogels incorporating antibacterial agents or bioactive molecules have been developed to prevent infection and manage complex wound environments [Hu *et al.*, 2024; Hosseini *et al.*, 2025]. Emerging research has also focused on stimuli-responsive and smart hydrogel platforms that can modulate drug release or biological responses according to wound conditions [Wang *et al.*, 2024].

Furthermore, advanced hydrogel-based delivery systems are being designed to regulate inflammatory responses and enhance healing in chronic and diabetic wound models [Fan *et al.*, 2024; Du *et al.*, 2026]. These innovations highlight the rapidly evolving landscape of hydrogel biomaterials and their growing significance in next-generation wound care strategies. Accordingly, understanding wound physiology and current treatment approaches is essential to appreciating the role of hydrogel-based dressings, which is explored in detail in the following sections.

II. HYDROGEL

The term hydrogel describes 3D network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water. Hydrogels are swollen 3D viscoelastic polymeric networks which have similar physical properties to natural tissue. The network is formed by crosslinking polymers with covalent bonds or noncovalent interactions and their structure can be then designed to suit the final application [Calvo Catoira *et al.*, 2019].

Based on their source and composition, hydrogels can be broadly classified into natural, synthetic, and composite hydrogels.

Table 1: Categories of hydrogels: natural, synthetic and composite.

CATEGORIES	Natural	Synthetic	Composite
EXAMPLES	- Chitosan - Alginate - Collagen - Gelatin - Hyaluronic acid - Agarose - Cellulose - Fibrin	- Poly-Vinyl alcohol - Poly ethylene glycol - Polyacrylamide - Poly(lactic-co-glycolic) acid - Poly Urethane - Poly caprolactone - Poly methylmethacrylate - Poly acrylic acid	- Chitosan-PVA - Chitosan-HPMC - Alginate-PVA - Collagen-PCL - Chitosan-PEG - Hyaluronic acid-PEG

2.1 Natural Hydrogels

Natural hydrogels, derived from biopolymers of plant, animal, and microbial origin, have emerged as versatile and indispensable materials in modern biomedical science. Each category brings distinct physicochemical characteristics that define their functionality across therapeutic platforms. Natural hydrogels, as hydrophilic 3D polymeric networks, exhibit key attributes such as biocompatibility, biodegradability, and structural similarity to the native Extra cellular matrix [Segneanu *et al.*, 2025].

Chitosan

Chitosan, derived from crustacean exoskeletons, offers innate antibacterial activity and excellent biocompatibility with hemostatic and antioxidant properties [Shahzad *et al.*, 2025]. Chitosan is a linear polysaccharide composed of β-(1–4) linked D-

glucosamine with randomly dispersed N-acetyl-D glucosamine groups, obtained by partially deacetylating chitin, the primary structure of arthropods exoskeletons. Structurally chitosan is similar to glycosaminoglycans contained in the ECM. Physical and mechanical properties are directly correlated with chitosan molecular weight and degree of deacetylation [Calvo Catoira *et al.*, 2019]. The advantages of using chitosan in hydrogel preparations are: antibacterial properties, easy to sterilize, a low cost, bioactive, biocompatible and its degradability can be controlled by changing the level of deacetylation [Huang *et al.*, 2005].

Alginate

Alginate is a polysaccharide component of brown algae cell walls and some bacteria capsule. Its structure is based on two different monomers: β-D-mannuronate (M) and α-L-guluronate (G) organized into

blocks. Since G blocks form ionic bridges, alginate mechanical properties are related with the amount and disposition of these blocks [Calvo Catoira *et al.*, 2019]. It provides biocompatibility, biodegradability, non-antigenicity, chelating ability as well as a good stability for a long time. Alginate can absorb large quantities of biological liquids and be purified to prevent immunogenicity, rendering alginate an ideal polymer for hydrogel preparation under mild conditions [Zhao *et al.*, 2023]. Alginate hydrogels can maintain a structural similarity to the ECM in tissues and from the biological point of view for medical applications alginate represents nontoxic and non-inflammatory properties [Calvo Catoira *et al.*, 2019].

Collagen

It is a widely used ECM protein to produce hydrogels for biomedical applications due to its widespread availability in nature (bovine, porcine and marine), biocompatibility, biodegradability, and recognition by cells. It can form gels by thermal condensation, although they show limited mechanical properties and stability, tending to degrade when cultured with cells [Gomez-Florit *et al.*, 2020]. It plays an important role in structural proteins for most tissues, i.e., skin, bones, muscles, blood vessels, and cartilages, and contains plenty of functional groups, i.e., hydroxyl, amino, carboxyl, guanidyl, and imidazoles, endowing collagen with many physical and chemical properties. Collagen is able to self-assemble into a triple-helical fibrous structure under physiological conditions, giving collagen a great tensile strength and durability [Zhao *et al.*, 2023].

Gelatin

It is a partially hydrolyzed form of collagen, which can be easily processed and modified using different procedures and chemistries [Gomez-Florit *et al.*, 2020]. As explained, the thermal condensation of gelatin derived from many animal sources has been widely explored to form hydrogels. Regarding the chemical crosslinking of gelatin to produce materials, a good example could be the modification of gelatin with methacryloyl residues (GelMA), which has been commonly used to produce hydrogels with well-defined architectures using bioprinting, photomasking, micromolding, self-assembly, and microfluidic techniques. The obtained hydrogels have been evaluated as potential tools to regenerate different tissues (e.g., bone, cartilage, cardiac, vascular) as well as for drug and gene delivery [Yue *et al.*, 2015].

Hyaluronic acid

Hyaluronic acid is a natural polysaccharide found in the ECM prominently throughout the body, comprising N-acetyl-glucosamine and D-glucuronic acid residues. Hyaluronic acid is well known for its bioactivity, which is the main nonsulfuric glycosaminoglycan that regulates many cellular responses in the ECM [Zhao *et al.*, 2023]. As a main component of the ECM, hyaluronic acid plays a significant role in many

physiological functions, including lubrication, water absorption, and retention for tissue and the ECM, and structural and space-filling functions, and interacts with various cell receptors to coordinate cell communication and behavior [Zhao *et al.*, 2023]. Because of its nontoxicity, nonallergy, biocompatibility, and biodegradability, hyaluronic acid has been widely used as biomedical materials including tissue engineering scaffolds, wound dressings, and drug carriers [Yang *et al.*, 2021].

Agarose

Agarose is a natural oxygen-rich polysaccharide extracted from sea weed, consist ingofalternating1,3-linked β -D-galactoseand1,4-linked3,6-anhydro- α -Lgalactoseunits [Wang *et al.*, 2023]. Agarose has good biodegradability, antibacterial properties and high hydrophilicity and is widely used in biomedicine and bioengineering. Agarose forms a porous three-dimensional network with defined pore size and permeability that enables the diffusion and transport of macromolecules through interconnected channels. In addition, agarose exhibits high biocompatibility and solute permeability, making them effective platforms for controlled drug release in biomedical applications (Pluen *et al.*, 1999; Jarosz *et al.*, 2023). A notable feature of agarose is its self-gelling behavior at low temperatures, where the polysaccharide forms a double-helix structure, creating a water-insoluble, gel-type structure, and the melting temperature of agarose gel ranges80–90°C [Zhao *et al.*, 2023].

Cellulose

Cellulose, the most abundant organic polymer on Earth, is a structural component of the cell walls in green plants, certain algae, and select bacteria. Composed of linear chains of β -D-glucose units connected via β -1,4-glycosidic bonds, cellulose exhibits notable properties such as biocompatibility, biodegradability, and non-toxicity. These attributes have driven substantial interest in its use for hydrogel development across biomedical, pharmaceutical, environmental, and food-related applications. Structurally, cellulose consists of repeating cellobiose units, each formed by two glucose molecules [Sepe *et al.*, 2025; Segneanu *et al.*, 2025]. Several cellulose derivatives have been developed to improve hydrogel performance. Carboxymethyl cellulose (CMC) is a water-soluble derivative known for its excellent thickening and stabilizing properties, especially in pharmaceuticals and food [Segneanu *et al.*, 2025]. Hydroxypropyl methylcellulose (HPMC), another widely used ether derivative, serves as a film-former and drug delivery vehicle. Cellulose-based hydrogels have the advantages of strong water retention, good biodegradability, good biocompatibility, highly modifiable, low cost, and good mechanical properties [Namara el al., 2015; Bao *et al.*, 2022].

Fibrin

Fibrin, a natural, insoluble fibrous protein that plays a fundamental role in hemostasis. Fibrin originates from fibrinogen, a soluble plasma glycoprotein produced by the liver. Upon vascular injury, thrombin, a serine protease activated in the coagulation cascade, cleaves fibrinogen, releasing fibrinopeptides A and B. This cleavage triggers the polymerization of fibrin monomers into a crosslinked, 3D fibrous network, forming a provisional ECM. This scaffold stabilizes the clot and facilitates cellular adhesion, migration, and proliferation, critical for effective wound healing and tissue regeneration [Segneanu *et al.*, 2025; Sanchez *et al.*, 2025].

2.2 Synthetic hydrogels

Synthetic hydrogels are 3D, hydrophilic polymeric networks capable of retaining large amounts of water while maintaining their structural integrity. Due to their tunable mechanical, chemical, and degradation properties, they have attracted substantial interest in biomedical applications such as Drug Delivery System, wound healing, diagnostics, and Tissue Engineering. Unlike natural hydrogels, synthetic hydrogels offer precise control over stiffness, porosity, and bio-inertness, making them more suitable for engineered therapeutic systems [Thang *et al.*, 2023; Segneanu *et al.*, 2025].

Poly-vinyl alcohol (PVA)

Polyvinyl alcohol is a synthetic hydrophilic biocompatible polymer with a high affinity for water, process-ability, and minimal cell and protein adhesion. It is used in various pharmaceutical applications, such as drug delivery, scaffolding, contact lenses, dialysis membranes, and artificial cartilage [Cuéllar Gaona *et al.*, 2023]. PVA can form hydrogels through repeated freeze-thaw cycles (physical cross-linking via crystallization) or chemical cross-linkers. Known for its high mechanical strength and elasticity [Gupta *et al.*, 2025]. PVA hydrogels exhibit high water uptake (>90 wt %), yielding large swelling ratios that facilitate nutrient diffusion and sustained release of payloads [Segneanu *et al.*, 2025].

Poly-ethylene glycol

PEG is a synthetic polyether of the general formula $H-(O-CH_2-CH_2)_n-OH$, prized in biomedicine for its chemical inertness, hydrophilicity, and biocompatibility [Segneanu *et al.*, 2025]. PEG hydrogels have been applied to the formation of multicellular tumor spheroids by 3D cell cultures for anticancer drug screening. PEG hydrogels are also used for 3D cultures with stem cells to evaluate their efficacy in hiPSCs differentiation and the behavior of mMSCs at similar stiffness of myocardial infarction microenvironments in vivo [Ho *et al.*, 2022].

Poly-acrylamide

PAAm is a linear synthetic polymer formed by the free radical polymerization of acrylamide monomers, yielding repeating $-[CH_2-CH(CONH_2)]-$ units. In aqueous solution, PAAm chains can be crosslinked into

3D hydrogels through covalent bifunctional agents such as MBAm, divinylbenzene, or GAD, which bridge polymer chains at multiple points to create network junctions. Chemically inert under physiological conditions, PAAm exhibits excellent chemical stability and minimal protein adsorption, reducing nonspecific fouling. While native PAAm is non-degradable, copolymerization with hydrolyzable segments or incorporation of enzymatically cleavable linkers can endow controlled biodegradability [Vera *et al.*, 2022; Segneanu *et al.*, 2025].

Poly (lactic-Co-Glycolic) Acid

The hydrophilicity and water uptake of PLA/PLGA hydrogels can be effectively tuned by adjusting the LA-to-glycolic acid (GA) ratio. Higher GA content enhances the hydrophilicity of the hydrogels, resulting in increased water absorption and accelerated degradation rates. PLGA hydrogels are formed by creating 3D networks through physical gelation (e.g., hydrogen bonding or hydrophobic interactions in aqueous media), chemical crosslinking (using di isocyanates, carbodiimides, or multifunctional acrylates), solvent casting with particulate leaching, or electrospinning to yield fibrous mats. These techniques produce tunable pore structures, swelling behavior, and mechanical properties suited to specific biomedical uses. [Choi *et al.*, 2024; Segneanu *et al.*, 2025].

Poly-urethane

PU are segmented copolymers featuring alternating soft (polyol derived, hydrophilic) and hard (di- or poly-isocyanate derived, hydrophobic) domains linked by urethane ($-NH-COO-$) bonds. By selecting the type and molecular weight of the polyol, the functionality (di-, tri-, or higher) of the isocyanate, and the soft/hard segment ratio, PU networks can be finely tuned in terms of hydrophilicity, elasticity, mechanical strength, and degradation behavior. In hydrogel form, PU assemble into 3D, water-swallowable networks whose elastic, tear-resistant character arises from the reversible association of soft segments interspersed with rigid, hydrogen bonding hard segments. PU hydrogels swell to high water contents (often >80 wt %), yet maintain resilience and elasticity even under large deformations. Their mechanical modulus can span from tens of kPa (soft tissue mimics) to MPa (load-bearing constructs) by adjusting crosslink density and segment composition. The interplay between hydrophilic soft segments and hydrophobic, hydrogen-bonding hard segments confers rapid shape recovery, tunable permeability, and minimal creep. Many PU formulations incorporate biodegradable ester or carbonate linkages in the soft blocks to permit hydrolytic erosion and control mass loss [Mandru *et al.*, 2019; Segneanu *et al.*, 2025; Martino *et al.*, 2025].

Poly-caprolactone

Polycaprolactone (PCL) is a semicrystalline, biodegradable synthetic aliphatic polyester widely explored for biomedical and wound healing applications due to its excellent mechanical strength,

biocompatibility, and slow degradation rate. PCL-based hydrogels exhibit good flexibility and structural stability, which makes them suitable for long-term wound dressing and tissue engineering scaffolds. The degradation of PCL occurs primarily through hydrolytic cleavage of ester bonds, resulting in a controlled and predictable degradation profile that is particularly advantageous for chronic and non-healing wounds [Dias *et al.*, 2022; Shah *et al.*, 2025].

Despite its favourable mechanical properties, PCL is inherently hydrophobic and lacks intrinsic bioactivity, which can limit cell adhesion and proliferation when used alone. To overcome these limitations, PCL is frequently blended or combined with natural polymers such as collagen, gelatin, chitosan, or alginate to form composite or hybrid hydrogel systems. These modifications enhance hydrophilicity, improve cellular interactions, and promote tissue regeneration while maintaining the mechanical robustness of the polymer. PCL-based hydrogels and composites have demonstrated significant potential in promoting angiogenesis, supporting fibroblast growth, and providing sustained release of therapeutic agents, thereby improving overall wound healing outcomes [Woodruff and Hutmacher, 2010; Dash and Konkimalla, 2012].

Poly-methyl methacrylate

PMMA is the most well-known polymer in the methacrylate family, obtained through the in-chain polymerisation of methyl methacrylate. It is a low-density, stable and durable polymer that offers excellent biocompatibility, hemocompatibility and high transparency, making it suitable for various biomedical applications. Currently, PMMA is the most commonly used denture base material due to its low cost, lightweight nature, insolubility in oral fluids, excellent aesthetic properties and ease of repair [Pascual, 2022; Banthia *et al.*, 2025].

Poly-acrylic Acid

PAA is a water-soluble, anionic polymer obtained by free radical polymerization of acrylic acid monomers. Its backbone comprises repeating $-\text{[CH}_2-\text{C(=O)-C(OH)-]}_n-$ units, each bearing a $-\text{COOH}$ moiety whose ionization state varies with pH. In alkaline environments, deprotonated carboxylates impart strong electrostatic repulsion and chain expansion, whereas in acidic media, protonated groups favour coil formation. Crosslinking, either covalent (e.g., MBAm) or ionic (via multivalent cations like Ca^{2+}), converts soluble PAA into 3D hydrogels capable of dramatic, reversible swelling. PAA hydrogels stand out for their pronounced pH sensitivity: swelling ratios can exceed $100\times$ in basic media yet collapse under acidic conditions. This tunable expansion is ideal for on demand release of encapsulated agents. Mechanical strength and elasticity are governed by crosslink density: increasing MBAm or ionic crosslinker content produces stiffer gels, while low

crosslinking yields softer, highly deformable matrices. The abundant $-\text{COOH}$ groups confer high water uptake and excellent biocompatibility, although unmodified PAA may require purification or copolymerization to attenuate any cytotoxicity associated with residual monomers [Qiu *et al.*, 2001; Segneanu *et al.*, 2025].

2.3 Composite hydrogels

Composite hydrogels represent an advanced class of materials synthesized by combining natural and synthetic polymers to create multifunctional systems with superior biocompatibility and mechanical strength. Natural polymers such as chitosan, alginate, and collagen impart biological recognition, degradability, and low immunogenicity, whereas synthetic polymers like PVA, PEG, and PAAm offer tunable mechanical and physicochemical properties. The integration of these polymers within a single hydrogel matrix leads to a 3D, hydrophilic polymer network that exhibits desirable features from both components. These materials are tailored for biomedical applications, including wound healing, controlled drug delivery, biosensing, and RM, due to their customizable structure and multifunctionality [Segneanu *et al.*, 2025].

Chitosan-PVA

Chitosan/PVA hydrogels are a preferable choice for wound dressings because they provide a stable and moist healing environment by combining the mechanical strength, flexibility, and hydrophilicity of PVA with the biocompatibility, biodegradability, and antibacterial qualities of chitosan. The chitosan/PVA blend presents an optimum equilibrium between antibacterial efficacy and structural integrity, particularly advantageous for wound care applications [Shahzad *et al.*, 2025].

Chitosan-HPMC

Chitosan has limited stability and low mechanical strength, which could hinder its application for topical gels. To overcome these potential drawbacks, chitosan can be blended with other polysaccharides such as hydroxypropyl methylcellulose (HPMC). HPMC belongs to the group of cellulose ethers, as a semisynthetic nonionic water-soluble polymer. HPMC forms a gelatinous layer, which regulates water transport in the system, contributing to the controlled release of substances from the hydrogel. Additionally, incorporating HPMC into chitosan might be a beneficial approach to enhance the mechanical strength of the hydrogel to provide greater therapeutic efficiency [Zanchetta *et al.*, 2024].

Alginate-PVA

PVA hydrogels may form undesirable elastic and stiff membranes, which restricts their use as wound dressings. SA, as a blended material, has been utilized to modify the clinical properties of PVA hydrogels for wound dressing applications. This polymer presents high protein absorption ability, fast biodegradability, high hydrophilicity, antibacterial activity, and pleasant

hemostatic and biological properties. As a result, PVA/SA hydrogels benefit from the desirable features of both polymers; PVA provides sufficient mechanical properties, whereas SA improves the physical and biological characteristics of the samples [Bahadoran *et al.*, 2020].

Collagen-PCL

The mechanical and morphological stability of collagen can be improved by combining the protein with different synthetic biodegradable polymers such as poly- ϵ -caprolactone (PCL) or PVA in the electrospun solution. On the other hand, the presence of collagen improves wettability, biocompatibility and cell recognition of the fibers. Different wound dressings based on collagen have been for this reason proposed to cover burns and wounds, as they help in promoting cell growth and activating inflammatory phase of wound healing. PCL has shown non optimal cell adhesion, proliferation, and migration when utilized as cell growth support. Therefore, a synergistic effect is achieved, and this combination not only allows to significantly decrease PCL hydrophobicity, but also has a favorable influence on cellular response of the scaffold [Miele *et al.*, 2020; Fonseca *et al.*, 2023].

Chitosan-PEG

When chitosan is combined with PEG, the resulting chitosan-PEG composite hydrogel benefits from the bioactivity of chitosan and the mechanical robustness of PEG. These hydrogels exhibit high swelling capacity, maintain a moist wound environment, permit oxygen diffusion, and absorb excess wound exudate. At the same time, the presence of chitosan provides antibacterial protection, reducing the risk of wound infection. Such synergistic properties make chitosan-PEG hydrogels particularly suitable for treating both acute and chronic wounds [Shiekh *et al.*, 2019].

Hyaluronic acid-PEG

Due to its good cytocompatibility, the HA/PEG hydrogel has great potential for biomedical hydrogel systems [Wang *et al.*, 2018]. Hyaluronic acid (HA)-polyethylene glycol (PEG) hydrogels are composite biomaterials extensively studied for various biomedical applications, particularly in cell delivery and soft tissue regeneration [Jeong *et al.*, 2014]. These hydrogels combine the natural polymer HA with synthetic PEG to create materials with tunable properties and enhanced biocompatibility [Thangprasert *et al.*, 2010].

III. WOUNDS

A wound is a flaw or a breach in the skin that occurs as a consequence of physical or thermal damage, or as a result of an underlying medical or physiological condition. Wounds are classified into three main categories based on: the causes, clinical appearance,

nature of the repair process, skin layers affected along with contamination happening in the wound [Ghanizadeh Tabriz and Douroumis, 2022]. Infection is among the major causes of wound complication and occurs due to the favorable environment for the growth of microorganism [Yazarlu *et al.*, 2021]. Wounds should be treated as soon as possible to avoid them deteriorating and causing more tissue damage and hypertrophic scarring [Ghanizadeh Tabriz and Douroumis, 2022].

3.1 Duration of healing process

Based on the duration of healing process, wounds are classified into acute wounds and chronic wounds.

Acute wounds:

An acute wound is an injury to the skin that happens suddenly rather than over time and heals at a predictable and expected rate, normally within 8–12 weeks according to the normal wound healing process. Acute wounds can happen anywhere in the body and vary from superficial scratches to deep wounds damaging blood vessels, nerves, muscles or other body parts. Acute wounds are often precipitated by trauma, such as burns, lacerations, or abrasions. The main causes of acute wounds are mechanical injuries which are caused by external factors such as incision, laceration, abrasion and ulceration [Ghanizadeh Tabriz and Douroumis, 2022].

Chronic wounds:

Wounds that do not heal within three months are often considered chronic and chronic wounds do not heal in an orderly set of stages and in a predictable amount of time as in acute wounds [Ghanizadeh Tabriz and Douroumis, 2022]. The principal risk factors associated with the development of chronic wounds include age, immunological status, malnutrition, infection, low oxygen levels or perfusion, tobacco use, underlying disorders, drugs, exposure to radiation, and chemotherapy [Gounden and Singh, 2024]. Bacterial infection is a significant factor in the development of chronic wounds. Chronic wounds are frequently infested by bacteria that create complex communities known as polymicrobial biofilms. Biofilms, when present on a wound, induce a surplus of neutrophils that are unable to engulf the bacteria bound to the biofilm. However, these neutrophils continue to release enzymes (cytokines and proteases) and reactive oxygen species (ROS), which disrupt the migration of cells, hinder wound healing, and compromise the nearby tissue. In cases of long-lasting infections, there is a harmful cycle of continual inflammation induced by ongoing biofilms, resulting in excessive and continuous NETosis, which leads to tissue damage [Zhao *et al.*, 2016]. Chronic wounds are commonly classified as vascular ulcers, including venous or arterial ulcers, diabetic ulcers, and pressure ulcers [Gounden and Singh, 2024].

CLASSIFICATION AND CHARACTERISTICS OF WOUNDS

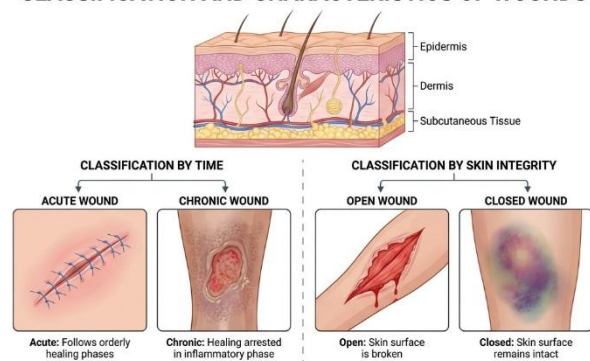


Fig 1: Classification of wounds based on healing time – Acute and chronic wounds and based on skin integrity – Open and closed wound.

3.2 Skin integrity

Based on the skin integrity, wounds are classified as open wounds and closed wounds.

Open Wounds:

An open wound involves a break in the skin that leaves the internal tissue exposed. They may result from falls, blunt trauma, and surgery [Varma and Eske, 2025].

Generally open wounds can be divided to:

- Abraded wound which damages the superficial part of the dermis and has a good healing rate.
- Punctured wound which is caused via sharp-pointed objects and seems negligible but can lead to anaerobic infection along with damage to blood vessels and nerves.
- Incised wound which is caused by sharp objects, such as knives or shard of glass, slicing into the skin. This means that the size and shape of the wound are usually regular and the wound itself is smooth, neat and has best healing.
- Cut wound which is caused by sharp objects and blunt additional force. Patient might end up having uneven edges after the healing process.
- Crush wound which is caused by blunt force and pressure and can lead to bleeding as well as uneven and torn edges that are usually deeper than abrasions and cause more pain and bleeding.
- Torn wound which is caused by great tearing or pulling and can end up with an incomplete amputation [Ghanizadeh Tabriz and Douroumis, 2022].

Closed wounds:

A wound that does not have a break in the skin and occurs under the skin's surface is a closed wound. Nevertheless, there may be bleeding, tissue damage, and internal injury under the skin's surface. These wounds result from a force or blow like from a fall, being hit by an object, or a collision with a person or inanimate object. Examples include contusions and hematomas. A closed wound results from a contusion brought on by blunt force trauma. Closed wounds allow blood to leave

the circulatory system but remain inside the body. Sometimes the term *closed wound* may relate to how wound edges are brought together. An example is when nurses say the wound is closed with sutures or staples [Chhabra *et al.*, 2016; Borges *et al.*, 2024].

Closed wounds can be divided into:

- Contusions (Bruises):** Contusions, commonly known as bruises, are a type of wound caused by trauma that damages small blood vessels beneath the skin without breaking its surface, resulting in discoloration and tenderness. Bruises usually appear reddish at first, but over time, the color changes to purple, blue, green, yellow, or brown as the body breaks down and reabsorbs the blood.
- Blisters:** Blisters are small, fluid-filled pockets that form on the skin, typically as a result of friction, burns, and irritation. Blisters are usually in the form of raised, bubble-like formation on the skin with a clear fluid inside. In some cases, blisters may contain blood (if capillaries are damaged) or pus (if the blister is infected).
- Seroma:** A seroma is a clear, yellowish fluid that builds up in a tissue or body cavity, often after surgery or trauma. It commonly occurs after procedures like breast surgery, liposuction, or abdominal surgery.
- Hematoma:** A hematoma is a localized collection of blood outside of large blood vessels, typically caused by trauma or injury that damages blood vessels.
- Crush injuries:** A crush injury happens when a body part is enduring intense pressure or force, often being trapped under a heavy object. The skin typically remains intact, but the underlying issues, like muscles, blood vessels, and bones, may be damaged [Kazzam and Ng, 2023; Buljbasich and De Cicco, 2024].

3.3 Wound Healing

Wound healing is a complex process involving several inter-related biological and molecular activities for achieving tissue regeneration. It may be considered as a specific biological process related to the general phenomenon of growth and regeneration of damaged tissue. It is a dynamic process in which a variety of cellular and matrix components act together to re-establish the integrity of damaged tissue and replacement of lost tissue. Wound healing can be divided into four major stages: Hemostasis, inflammation, proliferation, and remodelling [Ghanizadeh Tabriz and Douroumis, 2022].

- Hemostasis:** The first physiological response to injury is hemostasis which starts within the very first few moments of the injury, where platelets play a role by aggregating, as well as by releasing cytokines, chemokines and hormones. Hemostasis is characterized by vasoconstriction and blood clotting, which prevents blood loss and provides the provisional matrix for cell migration. Drying of the

clot forms a scab that provides a temporary protection to the damaged skin in addition to serving as a provisional matrix for cell migration and as a source for cytokines and growth factors [Rodrigues *et al.*, 2019; Ghanizadeh Tabriz and Douroumis, 2022].

- ii. **Inflammation:** The inflammatory phase occurs almost simultaneously with haemostasis, sometimes within a few minutes of injury to 24 h and lasts for about 3 days. Tissue damage and the activation of clotting factors during hemostasis triggers the release of inflammatory mediators including prostaglandins and histamine from cells such as mast cells. These mediators make blood vessels next to the damaged area to vasodilate and become more permeable. The classic signs of inflammation are due to increased blood flow to the area and the accumulation of fluid in the soft tissues. Wound exudate is produced during this stage of healing due to the increased permeability of the capillary membranes [Dylanet *et al.*, 2017; Ghanizadeh Tabriz and Douroumis, 2022].

In acute wounds, proteases are tightly regulated by their inhibitors, but in chronic wounds, protease levels exceed that of their respective inhibitors, leading to destruction of ECM and degradation of growth factors and their receptors [Ghanizadeh Tabriz and Douroumis, 2022].

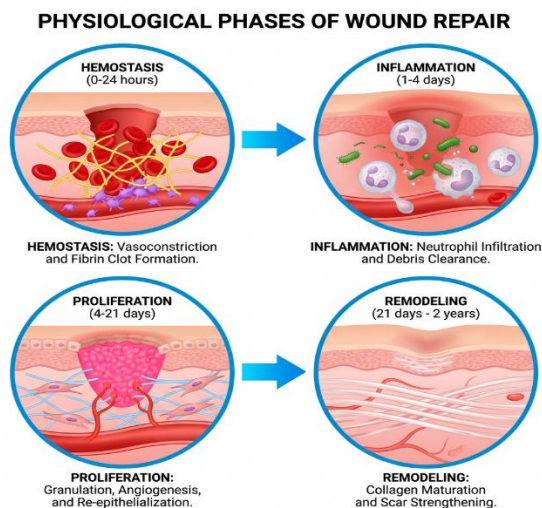


Fig 2: Wound healing phases showing hemostasis, inflammation, proliferation and remodeling.

- iii. **Proliferation:** The proliferation phase represents the third step in the wound healing phase, which is typically initiated on the third day following the injury and lasts for a few weeks. The primary goal of the proliferation phase is to repair and restore injured tissue by promoting the proliferation and migration of various cells essential for wound healing. It entails the coordinated interaction of

several cell types and their functions. In addition, crucial proliferative phase processes take place, including fibroblast migration, collagen synthesis, angiogenesis (the growth of new blood vessels), epithelialization, granulation tissue creation, wound contraction, and re-epithelialization [Ghanizadeh Tabriz and Douroumis, 2022; Borges *et al.*, 2024].

The proliferation stage of wound healing is an active and crucial phase. As new tissue grows and fills in the defect, the wound experiences substantial alterations throughout this stage. During this phase, it is essential to provide sufficient nourishment, oxygenation, and a moist wound environment to enable cell development and tissue repair [Borges *et al.*, 2024].

- iv. **Remodeling:** This phase is also called the 'maturation phase' and has an overlap with the proliferation phase [Ghanizadeh Tabriz and Douroumis, 2022]. Depending on the size and severity of the wound, this phase can extend anywhere from months to years following the initial damage. The newly created tissue goes through remodeling during this stage to increase its durability and functionality. It involves several crucial processes, including the reorganization of collagen, the development of scars, their remodeling and maturation, and the restoration of function [Borges *et al.*, 2024].

Collagen fibers that make up a scar are more arranged and less cellular than the tissue during the early phases of wound healing. The scar tissue continues to change, becoming more streamlined and compact. The purpose of scar remodeling is to improve the tissue's mechanical characteristics and bring it closer in consistency to the healthy tissue around it. The scar lessens in color and elevation with time and may eventually merge with the surrounding skin [Ghanizadeh Tabriz and Douroumis, 2022; Borges *et al.*, 2024].

- v. **Treatment Methods:** The treatment and management of a wound are essential in order to promote natural healing or to facilitate alternative methods to achieve healing such as dressings, surgery, negative pressure wound therapy, hyperbaric oxygen therapy, and so on. These methods for wound treatment are described below:

- a) **Dressings:** During the early years of wound management, traditional wound dressing products included gauze, lint, plasters, bandages (natural or synthetic) and cotton. They were used as primary or secondary dressings in order to secure the wound against contaminations. Gauze dressings are used as passive dressings in low exuding wounds. They are also used to absorb exudates in an open wound as they have fibres in their structure. However, they need to be changed frequently [Ghanizadeh Tabriz and Douroumis, 2022].

Table 2: Treatment methods for wounds

Treatment methods	Description	Advantages	Limitations
Dressings	Traditional dressings include gauze, lint, plasters, bandages, and cotton to protect wounds from contamination. Gauze acts as a passive dressing for low-exuding wounds and absorbs exudates due to its fibrous structure [Ghanizadeh Tabriz and Douroumis, 2022].	Protect wound, absorb exudates, and support healing process [Ghanizadeh Tabriz and Douroumis, 2022].	Traditional dressings require frequent changing and may not actively promote healing [Ghanizadeh Tabriz and Douroumis, 2022].
Surgery	Includes direct wound closure, skin flaps, grafts, and musculocutaneous flaps. Selection depends on wound location, medical conditions, and desired outcomes. Requires specialized medical expertise and equipped healthcare facilities [Gounden and Singh, 2024].	Effective for severe wounds and tissue loss [Gounden and Singh, 2024].	Expensive, requires skilled professionals, long-term effects influenced by bed rest and preoperative risk factors [Gounden and Singh, 2024].
Negative pressure wound therapy	Applies continuous or intermittent sub-atmospheric pressure to the wound using a sealed dressing connected to a vacuum system. Removes debris and fluids, improves oxygen and moisture levels around the wound [Gounden and Singh, 2024; Riansrithongkham <i>et al.</i> , 2025].	Promotes faster healing, removes exudates, improves wound environment [Gounden and Singh, 2025; Riansrithongkham <i>et al.</i> , 2025].	Requires specialized equipment and clinical supervision [Gounden and Singh, 2025; Riansrithongkham <i>et al.</i> , 2025].
Hyperbaric oxygen therapy	Patients receive 100% oxygen in a pressurized chamber above sea-level pressure. Increases oxygen delivery to tissues, enhancing regeneration and reducing healing time. Commonly used for chronic non-healing wounds [Gounden and Singh, 2024; Riansrithongkham <i>et al.</i> , 2025].	Enhances oxygen supply, accelerates healing in chronic wounds [Gounden and Singh, 2024; Riansrithongkham <i>et al.</i> , 2025].	Expensive equipment, time-intensive procedure [Gounden and Singh, 2024; Riansrithongkham <i>et al.</i> , 2025].

Modern dressings have the capability to provide a moist environment for the wound and facilitate the wound healing process. New polymeric materials have been designed and created to support dressings with considerable technical and clinical benefits. Consequently, modern wound dressings are generally based on biocompatible natural or syn thetic polymers or their compositions [Ghanizadeh Tabriz and Douroumis, 2022; Gounden and Singh, 2024].

- b) **Surgery:** Surgery includes direct wound closure, skin flaps and grafts, and musculocutaneous flaps. The selection of the surgical intervention is contingent upon various factors, including the precise anatomical site, concurrent medical conditions, and the desired outcomes of the medical procedure. The long-term effects of surgical interventions exhibit variations determined by bed rest and preoperative risk factors. Implementing this procedure necessitates the involvement of medical specialists who possess the expertise required and have access to well-equipped healthcare facilities. In addition, surgery is not a

cost-effective method [Gounden and Singh, 2024].

- c) **Negative pressure wound therapy:** Negative pressure wound therapy (NPWT), also called vacuum-assisted wound therapy, is a wound-dressing concept used worldwide that continuously or intermittently applies sub-atmospheric pressure to the surface of a wound in order to promote healing [Riansrithongkham *et al.*, 2025]. This vacuum system facilitates the removal of debris and fluid from the site of injury by implementing a closed or foam covering connected to an extraction vessel. This methodology effectively improves the degree of oxygen and moisture in the vicinity of the lesion, thereby facilitating wound repair [Gounden and Singh, 2024].
- d) **Hyperbaric oxygen therapy:** Patients are administered 100% oxygen within a compression chamber with a maintenance pressure exceeding sea level. The improved degree of oxygen delivery to the wound increases regeneration efficiency, leading to a reduction in the duration required for the healing process [Gounden and Singh, 2024]. Hyperbaric oxygen therapy (HBOT) is currently

employed as a treatment modality for managing non-healing wounds. Implementing HBOT necessitates expensive, specialized equipment and is a time-intensive process. Hyperbaric oxygen therapy is often utilized to treat chronic wounds by boosting blood oxygen levels [Riansrithongkham *et al.*, 2025].

IV. HYDROGEL AS AN IDEAL SYSTEM FOR WOUND TREATMENT

Hydrogels are a category of substances that have extensive applications in the field of skin regeneration. Hydrogels are polymeric structures that exist in a three-dimensional structure, formed through physical or chemical cross-linking of hydrophilic polymer chains [Gounden and Singh, 2024]. Hydrogels were first developed in the 1950s and applied to wound therapy about 30 years later [Ghanizadeh Tabriz and Douroumis, 2022]. An ideal wound dressing should be biocompatible and biodegradable while being able to adapt to different shapes and depths of the wound, as well as to be removed without causing pain. Moreover, it should ensure good transpiration of the wound through the diffusion of oxygen and water vapor and remove the excess fluid for exuding wounds [Amante *et al.*, 2021].

Hydrogels show excellent biocompatibility, biodegradability, and ability to keep a moist wound environment make them perfect for speeding up healing and reducing inflammation.

Additionally, some natural hydrogels have inherent antimicrobial and hemostatic properties, which are especially useful for infected or chronic wounds.

Another critical feature is their tunable porosity and permeability; by adjusting polymer concentration, crosslinking density, and incorporating porogens or templating agents, the pore size and distribution can be precisely engineered. This interconnected porous architecture facilitates the diffusion of oxygen, nutrients, and therapeutic agents, while also promoting cell infiltration and tissue integration—crucial for both drug delivery and regenerative medicine [Pintilei *et al.*, 2025]



Fig 3: Hydrogel as an ideal system for wound healing.

V. APPLICATIONS

As the capabilities of hydrogels have dramatically increased over time, they have unsurprisingly become useful tools for a wide range of fields and disciplines. Important applications and a few instances of hydrogel use are recorded beneath [Kumary, 2022].

- **Drug Delivery:** Hydrogels provide localized and controlled release of therapeutics (drugs, proteins, genes), protecting them from degradation and reducing systemic side effects. Stimuli-responsive systems enable on-demand release [Gupta *et al.*, 2025].
- **Tissue Engineering and Regenerative Medicine:** Hydrogels serve as 3D scaffolds that mimic the native extracellular matrix (ECM), supporting cell adhesion, proliferation, and differentiation. They are used for engineering cartilage, bone, skin, blood vessels, and neural tissues. Bioprinting often uses hydrogel-based bioinks [Gupta *et al.*, 2025].
- **Wound Healing:** Hydrogel dressings create a moist wound environment, manage exudate, provide a cooling sensation, and can be loaded with antimicrobials or growth factors to accelerate healing (e.g., for burn wounds) [Gupta *et al.*, 2025].
- **Contact Lenses and Ophthalmology:** Silicone hydrogels are the standard material for modern soft contact lenses due to their high oxygen permeability and comfort [Gupta *et al.*, 2025].
- **Biosensors:** Hydrogels functionalized with enzymes or antibodies can be used in diagnostic sensors. Swelling or optical changes in the gel can be correlated to analyte concentration [Gupta *et al.*, 2025].
- **Smart hydrogels:** These hydrogels can present significant insights into the state of a wound, encompassing factors such as the concentration of bacteria, oxygen levels, inflammatory intensity, pH, and temperature. Many sensors have been created to quantify the pH level, moisture, temperature, oxygen supply, and mechanical and enzymatic activity [Gounden and Singh, 2024].
- **Sprayable hydrogels:** These hydrogels provide many benefits, including ease of use without needing specialized assistance, patient approval, and manufacturing cost-effectiveness. Furthermore, applying a spray can enhance the permeation of the hydrogel into the injured region, improving the administration of medicinal formulations or active substances. An ideal viscosity is thus needed to allow the sprayability of these hydrogels [Gounden and Singh, 2024].
- **Cosmetic:** Due to specific criteria, hydrogels are frequently used in different formulations of cosmetic. Usually, hydrogels that are widely used in cosmetic products are based on proteins or polysaccharides such as collagen, gelatin, starch,

hyaluronic acid, xanthan gum, alginate, chitosan, pectin, cellulose, and its derivatives. Among them, collagen, gelatin, chitosan, and hyaluronic acid are commonly used biomaterials in cosmetics due to their physicochemical properties and compatibility with the body [Shariati *et al.*, 2025].

- **Environmental applications:** Hydrogels can be used for water pollution removal. They can act as either a holder for purifier microorganisms or a pollutant absorber. Moreover, polyacrylamide or potassium poly acrylate hydrogels are applied as long-term reservoirs of water for plant growth in gardening, domestic and sometimes industrial horticulture Super Crystals®, Plant-Gel®, and Water-Gel Crystals®). The best working hydrogels for this purpose are composed of alginate, carrageenan, and agar [Shariati *et al.*, 2025].

VI. CHALLENGES

Hydrogel hydration-dependent properties, while beneficial for biocompatibility, pose challenges in real-world applications, particularly in maintaining durability and stability.

- **Mechanical Performance:** Many highly swollen hydrogels are inherently weak and brittle. Developing robust, tough, and fatigue-resistant hydrogels that do not compromise swelling or biocompatibility is a major focus [Gupta *et al.*, 2025].
- **Translation to Clinic:** Scaling hydrogel-based devices from laboratory research to commercial products introduces additional hurdles. High production costs stem from the use of specialized monomers, cross-linking agents, and conductive nanomaterials. For example, carbon nanotube-reinforced hydrogels remain prohibitively expensive for large-scale use [Ullah *et al.*, 2025].
- **Sterilization:** Sterilization methods also present obstacles as traditional techniques such as autoclaving or ethylene oxide treatment can degrade hydrogel networks. Although gamma irradiation has been effective for certain hydrogel formulation, it can alter the mechanical properties of synthetic polymers such as polyacrylamide [Ullah *et al.*, 2025].

Despite these challenges, progress has been made in enhancing the durability, signal reliability, and scalability of hydrogel-based sensors. Self-healing hydrogels and hybrid composites have improved structural resilience, although this in vivo healing kinetics require further optimization.

VII. FUTURE PERSPECTIVES

The current strategies in wound healing have multiple shortcomings in reducing recovery duration. Hence, a new and improved system is needed to

overcome these incompetencies. Hydrogels have been presented as adequate wound dressings for chronic and acute wounds through their ideal properties, such as maintaining a moist environment, absorption of exudates and necrotic tissue, and flexibility in shape to cover wounds with different morphologies [Gounden and Singh, 2024].

Biohybrid systems incorporating living cells within hydrogels could enhance biocompatibility and functionality in applications such as tissue engineering, biosensing, and neural interfacing [Ullah *et al.*, 2025].

Smart hydrogels have gained prominence due to their ability to monitor the state of the wound using sensors. The development of innovative hydrogels can be a solution for reducing the wound healing period, improving overall patient health and satisfaction, and reducing the load borne by the current healthcare system. The advent of “smarter” hydrogels is a possibility [Gounden and Singh, 2024].

VIII. CONCLUSION

Healthy skin is important for more than just its appearance; it also influences emotional well-being and general quality of life. Skin injuries, particularly those that leave scars, can have long-term psychological and social consequences. As a result, improving the skin's capacity to heal spontaneously and reducing scarring are critical goals in wound care. Present review study showing Polymer-based biomaterials used as wound dressings and regenerative scaffolds are critical in encouraging faster and more. Traditional wound care methods such as gauze dressings and surgical interventions provide basic protection but often fail to create an ideal environment for rapid and effective healing. In recent years, hydrogels have emerged as advanced wound dressing materials due to their high-water content, biocompatibility, flexibility, and ability to maintain a moist wound environment. These properties support cell growth, tissue regeneration, and patient comfort while reducing trauma during dressing removal. The ability of hydrogels to incorporate antimicrobial agents, drugs, and growth factors further enhances their therapeutic potential, especially in chronic and infected wounds. Although challenges such as mechanical weakness, high production costs, and sterilization difficulties remain, continuous research is addressing these limitations. Overall, hydrogel-based wound dressings represent a promising and evolving approach in modern wound care, with strong potential to improve healing outcomes and quality of life for patients in the future.

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