Vol. 13, No. 1 (2025), pp.1–19

CHITKARA UNIVERSITY

Journal of Pharmaceutical Technology Research and Management

Hydrogels in Chronic Wound Care: A Multifaceted Approach to Healing and Regeneration

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REVIEW ARTICLE **Open Access**

ARTICLE INFORMATION

Received: 04 February, 2025
Accepted: 23 July, 2025
Published Online: 25 August, 2025

Keywords:
Hydrogels, Polymers, Wound dressings, Chronic wounds, Wound healing

DOI: 10.15415/jptrm.2025.131001

ABSTRACT

Background: In wealthy nations, 1-2% of people suffer from serious chronic wounds. In India, chronic wounds have a prevalence rate of approximately 4.5 per 1000 individuals, with diabetic foot ulcers and pressure ulcers being the most common.

Purpose: Chronic wound treatment is necessary to maintain patients' physical and emotional well-being and improve quality of life. Numerous methods, including hydrogel dressings, skin grafts, debridement, ultrasound, electromagnetic, and negative pressure wound treatment, may be used to treat chronic wounds.

Methods: Recent literature has been surveyed from PUBMED, GOOGLE SCHOLAR, etc., like search engines, for summarizing detailed ongoing developments in the field of hydrogels in chronic wound care.

Conclusions: Due to their functional qualities that may be adjusted, hydrogel dressings are a viable and promising solution for accelerating the healing of chronic wounds. These characteristics include biodegradability, adhesion, and bioactivities that are pre-antigenic, antibacterial, and anti-inflammatory. This overview summarizes the various types of chronic wounds, stages of the healing process, and important treatment modalities. The advantages of hydrogel-based dressings for treating chronic wounds are discussed, along with their multifunctional qualities, illustrating their superiority over other dressing types for long-term wound healing.

1. Introduction

The human skin, being the biggest organ, serves as an essential barrier against external factors. Severe burns or wounds on the skin set off a regulated series of phases that include remodeling, proliferation, inflammation, & hemostasis (Mamun *et al.*, 2024). Each of these phases has a set time and occurs in a particular order throughout the typical wound-healing process. Depending on the kind of damage, healing phases take varied amounts of time (Strodtbeck, 2001). The four closely monitored phases of wound healing are homeostasis, proliferation, remodeling, and inflammation. The right steps must be taken in the right order and within the allotted time for a wound to heal properly. Adult wound healing involves several processes, such as homeostasis, an inflammatory response, mesenchymal cell migration, differentiation, and multiplication, angiogenesis, transient re-epithelialization, & collagen synthesis, cross-linking, and organization, to give the healing tissue structural integrity (Oliveira *et al.*, 2022; Rodrigues *et al.*, 2018). In the immediate aftermath of trauma, blood vessels constrict to prevent further blood loss. Following that, fibrin and platelets are released to form a thrombus, or blood clot, which seals injured blood vessels & stops blood loss. The moment equilibrium is reached, inflammation begins. By facilitating the transportation of leukocytes and exudates near the wound site, local capillary dilatation lowers the risk of infection throughout the healing process. Meanwhile, neutrophils release reactive oxygen species (ROS) and toxic proteases to clear the wound area of cellular debris and destroy invasive infections. Macrophages are necessary to promote the regeneration of skin tissue. In early phases of immune

response, macrophages generate cytokines to draw and activate more leukocytes, which strengthens the response (Delavary *et al.*, 2011). Additionally, macrophages trigger apoptosis and eliminate apoptotic cells, such as neutrophils. At this stage, redness and pain are frequently seen surrounding the wound bed. The third stage in the process of wound healing is termed proliferation. In this phase, there is the formation of granulated tissue along with an extracellular matrix containing newly formed blood vessels and connective tissue. This development occurs under suitable levels of moisture and oxygen. Granulated tissue development is significantly influenced by T-cell migration into the wound bed. At this point, the injured tissue's extracellular matrix is rebuilt to resemble healthy tissue (Jiang & Scharffetter-Kochanek, 2020). Differentiated myofibroblasts are primarily responsible for controlling this phase. In this phase, the wound's vascular density is restored & a large number of recently formed capillaries recede. Wound repair is greatly aided by activities of different cell types, and biomolecules are involved in various phases of wound healing. Based on the stage at which a particular wound is healing, the best course of action may be selected. Understanding the intricate mechanisms underlying these wound healing phases is crucial for developing advanced therapeutic strategies. This review article explores the key cellular and molecular events involved in wound healing, highlighting recent advancements in targeted interventions and biomaterial-based approaches to enhance the repair process (Figure 1).

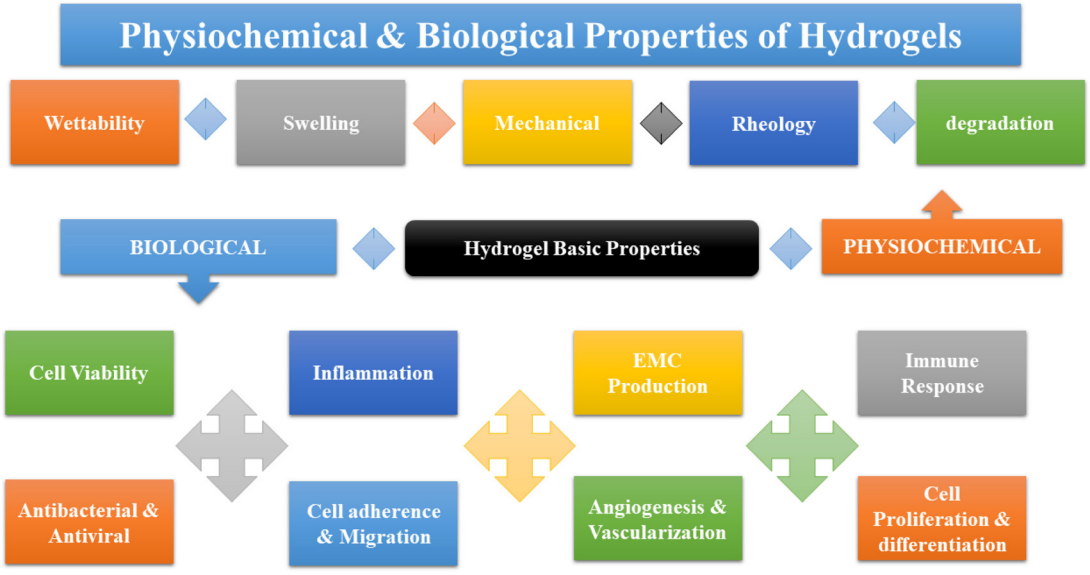

Figure 1: Physiochemical & Biological Properties of Hydrogels

This figure illustrates the key physiochemical and biological properties of hydrogels, including their composition, structure, and functionality. It highlights essential factors such as swelling behavior, mechanical strength, biocompatibility, and biodegradability, which contribute to their application in biomedical fields.

1.1. History of Biodegradable Hydrogel Formulations

Whichterler and Lim developed and characterized the first hydrogel poly (2-hydroxethyl methacrylate) (PHEMA) in 1960. After that, it was included in contact lenses, which were able to absorb moisture (Almawash *et al.*, 2022). It features a three-dimensional binding structure and is similar to current hydrogels. Its findings sparked excitement and attention from the scientific community. Lim and Sun synthesized calcium-alginate gel composites for cell embedding in the 1980s using islet-droplet microcapsules, showcasing the hydrogels' physical characteristics with biological soft tissues (Almawash *et al.*, 2022). After this, as the production and study of natural, synthetic, and mixed polymer hydrogels increased, hydrogels emerged as a key field of research for biomaterial scientists. Since these polymeric materials were non-invasive therapeutic agents that offered a controlled/sustained delivery depot at the site of interest, their sol–gel phase transition properties, muco-adhesiveness, and biodegradation through physiological stimuli (temperature, pH, and enzyme) revolutionized the field.

1.2. Classification of Skin Wounds

Skin wounds are divided into several categories based on how long the healing stages take (Abazari *et al.*, 2022). Three months after the original harm, wounds will entirely heal both physically and functionally if all steps in the wound healing process are completed on schedule & methodically. We refer to these kinds of injuries as non-chronic wounds (Muire *et al.*, 2022). However, wounds become chronic when any of the healing phases are skipped. This may result in changes to the anatomical or functional characteristics of the skin, which may cause wounds to either not heal at all or heal slowly. Delays often occur while a wound is healing from inflammation. The three most common forms of chronic wounds are diabetic, pressure, and vascular ulcers. The impact of the particular kind of chronic wound on the healing process is covered in the section that follows.

Patients with peripheral neuropathy are typically the ones who develop diabetic ulcers. As a result, the patients are blind to repeated, minor injuries to their feet or legs. In this scenario, elevated glucose levels cause ischemia, increased ROS, DNA modification, & inflammation surrounding the wound (Yousif *et al.*, 2024). Patients' wounds may heal at different rates depending on how severe they are. Differences in angiogenesis, growth factor production, collagen deposition, cell migration & proliferation, & protease-modified extracellular matrix (ECM) are the reasons for the different wound healing timeframes. Another kind of persistent wound is a pressure ulcer. The majority of people who have neuropathies and restricted mobility also have pressure ulcers. Injury-related hypoxia and ischemia can result from a physical stress that is brought on by extended direct pressure & shear forces on skin. Adipose cells react by inducing inflammation. Consequently, individuals with pressure ulcers typically have increased neutrophil concentrations. Since these individuals have higher interstitial fluid levels, necrotic tissue is also seen in them (Vathulya *et al.*, 2023). When vascular insufficiencies are present, this kind of chronic wound may worsen, leading to complications such as venous ulcers (Zhao *et al.*, 2016). An insufficiency of veins is the hallmark of venous ulcers, which is why edema, varicose veins, and hyperpigmented areas are often observed with these ulcers.

2. Advanced Strategies for Chronic Wound Treatment: The Role of Hydrogels

Recent developments in hydrogel technology have led to the creation of "smart" hydrogels, which can react to different stimuli. Because of their lengthy healing periods and vulnerability to infection, chronic wounds, such as pressure ulcers, diabetic foot ulcers, and venous leg ulcers, are challenging to treat (Abarca-Cabrera *et al.*, 2021). When these wounds do not undergo the typical healing processes of hemostasis, inflammation, proliferation, and remodeling, tissue damage endures, and problems such as biofilm formation and bacterial growth are more likely to occur (Sankar & Muthukaliannan, 2024). Among the things that impede wound healing are chronic inflammation, poor blood flow, and high levels of toxic stress. Hydrogels are one of the most promising methods for treating chronic wounds because they promote tissue healing by giving cells the perfect moist environment in which to work. It's great because hydrogels can retain a lot of water, are biocompatible, and control the release of bioactive compounds (Liang *et al.*, 2021).

These might include substances that change in response to the environment around the wound, such as those that are sensitive to pH or temperature (Farahani & Shafiee, 2021). These cutting-edge hydrogels may fight diseases, encourage tissue repair, and administer drugs in controlled ways. Additionally, bioengineered hydrogels that include extracellular matrix components and biopolymers like collagen, chitosan, or alginate provide enhanced cellular adhesion and mobility, which speeds up wound healing (Saberian *et al.*, 2024). With greater research and development, hydrogel-based bandages are expected to transform the way chronic wounds are treated by providing patients with more effective and pleasant treatment alternatives. Hydrogels are important in the realm of regenerative medicine because of their various benefits. Their tendency to be biocompatible allows for the creation of an environment that encourages tissue regeneration and cellular proliferation by simulating the extracellular matrix seen in nature (Olteanu *et al.*, 2024).

The various characteristics of hydrogels, including their stiffness, porosity, and breakdown rates, allow them to be tailored to specific tissue needs and improve the healing process for a range of applications (Revete *et al.*, 2022). Certain items' anti-inflammatory qualities alter immune responses to enhance tissue healing conditions. Targeted therapeutic treatments are enhanced by their topical, implantable, or injectable forms of minimally invasive medicine, which provide exact localization at tissue defects or damaged regions (Ashammakhi *et al.*, 2019). Hydrogels may provide short-term structural support during tissue healing since they decompose at controlled rates. Over time, they will integrate with newly formed tissue and eliminate the need for removal treatments (Zhang *et al.*, 2021). Hydrogels are clearly positioned as versatile and promising tools in the area of regenerative medicine because of the combination of these characteristics. Their use offers appealing possibilities for tissue repair, organ regeneration, and enhancing treatment results in a range of diseases and wounds.

2.1. Challenges in Chronic Wound Healing

Managing complicated wounds presents a variety of issues for medical practitioners and wound care specialists (Malone & Schultz, 2022). Even with all of the recent advancements in wound care therapies & our understanding of the pathophysiology underlying chronic wounds, nothing can override the importance of adhering to fundamental principles of wound care, which include proper wound bed preparation, debridement (including surgery), offloading (or compression), management of ischemia, management of infection, and thorough evaluation with medical and nutritional optimization (Al-Mutairi *et al.*, 2024). Following established wound care guidelines and these concepts should often result in positive results. It's also critical to employ sophisticated wound care treatments with caution if wounds do not heal with basic care after four weeks, or sooner if needed. Generally speaking, the data should guide the treatment selection to optimize the efficacy of novel medications. Chronic wound management might be difficult at times, but it doesn't have to be if basic care instructions are regularly followed. Future treatment will be guided by a comprehensive assessment of the patient & wound, which will reveal underlying problems that need special attention. Consequently, a methodical approach to evaluation and treatment ought to provide positive results most of the time. A mixed approach to treatment has been shown to be very beneficial and is often advised since scars and patients are frequently complex. The patient's medical/holistic care and wound care must begin simultaneously. Diabetes patients often need better food control, as well as treatment for hyperglycemia, renal failure, and other related conditions that may impede the healing of their wound or wounds (Bowling *et al.*, 2015; Burgess *et al.*, 2021). Patients with a VLU may often have circulatory changes that need greater medical care, while PU patients, who are typically immobile due to coexisting conditions, may have serious nutritional deficits that need to be addressed to promote tissue recovery. Although they are mostly determined by the patient's circumstances, the extent of the wound, and the artery anatomy, the exact roles of open bypass and endovascular treatments are still being determined (Mills Sr, 2008). Hyperbaric oxygen treatment (HBOT) is sometimes recommended when angioplasty has not worked or is not practical. Topical oxygen treatment, which was long disregarded as having no role in this sector, is currently being used once again to improve tissue oxygenation. When compression treatment is ineffective or severe venous illness results in repeated VLUs, surgery to correct the shallow, deep, and/or weak perforators is recommended (Franks *et al.*, 2016). Once again, in these situations, it is critical to recognize combined arterial and venous sickness because the resulting arterial weakness complicates the conventional treatment for venous ulcers.

Infection is a major risk factor for later lower limb amputation in the case of DFUs, much like wound healing failure. Wound healing may be hampered by even excessive bioburden. Significant infections or abscesses may be hidden by neuropathy, although early infected wounds are easily seen (Cefalu *et al.*, 2017). As previously stated, clinically, no infected wounds should be treated or developed with systemic antibiotics. However, if osteomyelitis is found, bone culture is recommended for this persistent condition, followed by a specific antibiotic treatment (and maybe surgery) (Rao *et al.*, 2011). However, it often happens after infection management and the start of wound care procedures. As Leaper *et al.* have succinctly said, the term TIME has been used to promote a methodical approach to wound bed preparation throughout the last 10 or so years.

2.2. Role of Hydrogels in Chronic Wound Management

Three-dimensional networks of hydrophilic polymers make up hydrogel bandages. Through granulation and re-epithelialization, they provide a moist environment at the wound site, which promotes tissue repair (Ribeiro *et al.*, 2024). Hydrogel bandages have shown effectiveness in the management of long-term injuries. Hydrogel-based bandages' characteristics are readily adjustable, in contrast to other chronic wound treatment techniques (da Silva *et al.*, 2019). The flexibility and adaptability of hydrogel bandages allow for customization with proteins, growth factors, cells, antibiotics, antiviral medications, and antifungal medications to promote wound contraction and healing (Ferraz, 2025). Figure 2 shows the latest developments in the use in clinical research and tissue engineering. Hydrogels' vascularization potential, biocompatibility, biodegradability, adhesiveness, and antibacterial, anti-inflammatory, and pro-angiogenic qualities are only a few of their functional qualities that may aid in the healing of chronic wounds (Zhang *et al.*, 2024). The hydrogels' biodegradability and rate of biodegradation are crucial characteristics because they act as a temporary template for the production of fibroblasts, re-epithelialization and neovascularization, and chronic wound healing (Vinchhi *et al.*, 2021). Bioadhesivity, which also improves the balancing effect, keeps the wound wet and absorbs tissue exudates during healing and is essential for the long-term safety of the hydrogel patches around the wound region (Basit *et al.*, 2024). Antibiotic hydrogels may be helpful in preventing infections since chronic scars that take longer to heal may be more prone to infection, which might slow the healing process.

Chronic scars reduce quality of life and raise expenses because they need more care. Numerous factors, including

stress, inflammation, ischemia, and pressure, may cause delays in the healing process (DesJardins-Park *et al.*, 2022). Ultrasound and electromagnetic treatment may be used to heal surgical wounds, venous and pressure sores, and more. These treatments might, however, result in small burns or damage to the vascular cells if the proper parameters are not followed. The patient's range of motion is restricted when negative pressure is used to treat wounds. Additionally, the patient is harmed by excessive loudness during treatment. Skin patches are more expensive and need more complex processes than other approaches. All of the above-discussed methods need clinical doctors and well-equipped medical facilities.

Many individuals apply bandages to wounds that don't go away. They may be made as sheets, films, foams, hydrogels, and hydrocolloids. Their usage is limited by a number of challenges, even though they are successful in avoiding further injury or problems in the area (Kus & Ruiz, 2020). Film bandages allow exudates to build up and are difficult to remove from the wound. The wound may itch and hurt when covered with gauze. If the foam bandages stick to the wound, it might be difficult to remove them. Overgranulation may occur as a consequence of hydrocolloid dressings. Hydrogel bandages have the potential to hasten wound healing by moistening the wound bed and promoting autolytic debridement. Hydrogels are easy to remove from chronic wounds without damaging newly developed keratinocytes. Moreover, they may not need removal from the wound because of their biodegradability (Firlar *et al.*, 2022). Additionally, hydrogel-based bandages may be altered to enhance their vascularization capacity, antimicrobial properties, adhesiveness, anti-inflammatory properties, and antioxidant properties. It is expected that multifunctional hydrogel bandages would hasten the development of new goods for growing uses in the treatment of chronic wounds. Figure 2 shows the applications of hydrogels in tissue engineering, drug delivery, and wound healing.

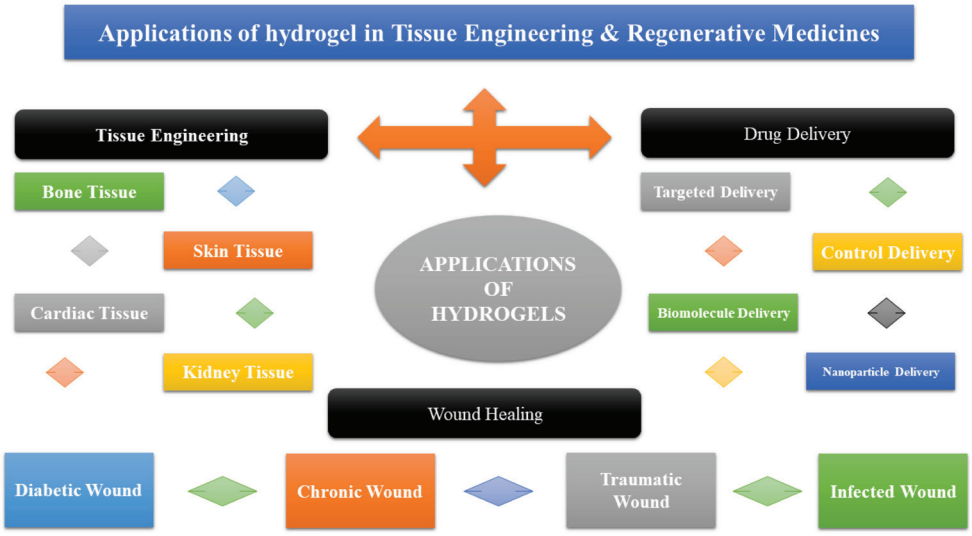

Figure 2: Applications of Hydrogels in Tissue Engineering, Drug Delivery, and Wound Healing

This figure illustrates the diverse applications of hydrogels in regenerative medicine, highlighting their role in tissue engineering (bone, skin, cardiac, and kidney tissue), drug delivery (targeted, controlled, biomolecule, and nanoparticle delivery), and wound healing (diabetic, chronic, traumatic, and infected wounds). The versatility of hydrogels makes them a promising material for biomedical applications, enhancing therapeutic outcomes in various clinical settings.

2.3. Advanced Hydrogel Technologies for Chronic Wound Healing

Regenerative hydrogels have enormous potential for the medical profession and provide notable benefits in wound healing. They mimic the process of natural healing by preserving moisture, which creates the perfect environment for cell migration, growth, and tissue regeneration (Fani *et al.*, 2024; Revete *et al.*, 2022). Furthermore, its appropriateness for less invasive delivery systems, such as oral or injectable forms, ensures accurate wound site targeting, reducing patient suffering and improving the accuracy of treatment. These hydrogels support tissue regeneration and help in the repair of various tissues, such as internal organs, cartilage, and skin, by functioning as scaffolds and mimicking components of the extracellular matrix (Yi *et al.*, 2017). Future advancements might include improving polymers to create hydrogels with increased sensitivity, bioactivity, and mechanical strength, all

of which would increase the effectiveness of drugs (Ahmed *et al.*, 2025). To further improve healing outcomes and encourage tissue regeneration, hydrogels may be utilized in synergistic combinations with other treatments like growth factors, stem cells, or bioactive substances.

By creating useful alternatives for severe burns or chronic wounds, research initiatives on hydrogel-based bioengineered skin replacements aim to revolutionize wound treatment (Olteanu *et al.*, 2024; Yi *et al.*, 2017). For example, pH-sensitive hydrogels may release antibiotics in response to an acidic wound environment caused by bacterial infections, improving therapeutic effectiveness and minimizing needless exposure to antimicrobials (Lv *et al.*, 2020). In a similar manner, thermoresponsive hydrogels experience phase changes upon exposure to body heat, ensuring enhanced binding and prolonged drug release at the wound site. Furthermore, bioengineered hydrogels' extracellular matrix (ECM) constituents, such as collagen, fibrin, or hyaluronic acid, replicate the natural wound environment, accelerating tissue healing, cellular adhesion, and mobility (Rana & De la Hoz Siegler, 2024). These hydrogel scaffolds that have been biologically printed provide a three-dimensional structure that encourages the growth of new tissue, which makes them a viable method for personalized wound healing (Kammona *et al.*, 2024).

2.4. Debridement

In order to remove non-viable tissue from a wound bed of any kind, debridement is a systematic, first-line therapeutic procedure. Surgery, traditional dressings, larvae, enzyme preparation, hydrogels, polysaccharide beads, and larvae can all be used for debridement (Ruke & Savai, 2019). Different techniques provide comparable results, and only clinical professionals should carry out the debridement procedure. The remaining non-viable tissue may harm surrounding tissues if insufficient non-viable tissue is removed. It could thus be necessary to repeat the debridement procedure. Nevertheless, removing an excessive amount of non-viable tissue may result in loss of some viable tissue & prolong the healing process (Cazander *et al.*, 2020). For the wound region to remain alive and aid in the reconstruction of skin tissue, a single debridement procedure that results in the loss of just a minimal number of viable cells is ideal. Furthermore, discomfort both during and after the debridement procedure may be experienced by the patient. Individual patient differences exist in the efficacy of debridement. The debridement procedure in its entirety may be an expensive course of therapy.

2.5. Hyperbaric Oxygen Therapy

The goal of hyperbaric oxygen treatment is to raise the oxygen concentration of blood in the wound region by using a specific oxygen chamber to expose the patient to high-pressurized oxygen (Gottrup *et al.*, 2017). In instances when revascularization of the injured tissue proved unsuccessful or impractical, hyperbaric oxygen treatment has been demonstrated to expedite & enhance the wound healing process. On the other hand, expensive specialist equipment is needed to administer hyperbaric oxygen treatment. Furthermore, it is often restricted to pressure ulcers and diabetic wounds.

2.6. Ultrasound and Electromagnetic Therapies

Sound waves are used in ultrasound therapy to warm the region around the wound, which reduces discomfort. Endothelial tissue damage or burns are among the side effects of ultrasound treatment (Rashidi, 2017). When procedure settings are not adjusted in accordance with a patient's unique demands, these outcomes frequently happen. Electromagnetic therapy is an additional method of treating wounds. Treatment of surgical incisions, pressure ulcers, and venous ulcers has been recommended with this approach. It has not been demonstrated in a clinical setting that electromagnetic or ultrasonic therapy significantly affects the wound healing process (Vodovnik & Karba, 1992).

2.7. Negative Pressure Wound Therapy

This treatment covers the wound with an airtight covering that draws fluid and air out of it using a tiny tube that is attached to a pump (Bayer, 2018). Blood flow surrounding the area may also be aided by the negative pressure. This method speeds up the healing process for big chronic wounds by increasing the amount of moisture and oxygen in the surrounding tissue. It is applicable to primary as well as secondary therapy approaches. In well-equipped medical institutions, VAC therapy is commonly employed. In addition to limiting the patient's range of motion, the treatment process may make them uncomfortable owing to the loudness.

2.8. Skin Grafts

In most cases, skin grafts are applied to wounds that might not heal naturally. With this technique, a graft is created from human or synthetic donor skin, or donor skin tissue is removed from another area of the patient's body (Valencia *et al.*, 2000). But this method needs the knowledge of medical specialists in well-equipped hospitals. Additionally, skin grafting procedures are usually not economical.

2.9. Wound Dressings

To achieve optimal therapeutic outcomes, the ideal wound dressing must include the following characteristics:

Some benefits include preserving moisture of the wound environment while removing or absorbing surplus fluids & exudates, aiding in gas exchange, thwarting microbial intrusion, shielding the wound from external injuries, and being easily removable or possessing biodegradable characteristics to prevent painful removal and harm to newly regenerated tissue (Nouri *et al.*, 2022). Additionally, they help sustain cell viability, minimize wound discomfort, & are cost-effective. Numerous wound dressing types have been studied; however, their usefulness varies according to the wound's features, such as its depth & exudate level. Common forms of wound dressings and their uses are covered in the section that follows (Dabiri *et al.*, 2016).

2.9.1. Films

A film dressing refers to a thin, transparent polymeric cover that acts as a protective barrier against external contaminants and injuries, maintaining moisture in the wound region (Stoica *et al.*, 2020). Furthermore, accumulating fluid may harm recently developed keratinocytes since the films are unable to gather and eliminate fluid from the wound environment. Dressings for chronic wounds that are simple to remove should be taken off to reduce the risk of harm to cells and tissues.

2.9.2. Gauze

Wet-to-dry dressings are another term for gauze dressings. A thin, elastic, gas-permeable, transparent, nontoxic, biocompatible, and biodegradable polymeric material is commonly used to fabricate gauze (Firlar *et al.*, 2022; Hosseini *et al.*, 2023). The weaving structure of gauges is open and free. Prior to and following each warp yarn, weft threads are arranged in pairs & crossed. The gauze is held in place firmly by this organization. Gauze dressings are used to remove superficial wound debris from the wound bed by adhering to necrotic tissues and drying them out (Devey *et al.*, 2016). Furthermore, gauze dressings guard against microbial infection of the wound. But leukocyte and phagocyte activity can be hindered by tissue cooling when the phase of proliferation replaces inflammation. Furthermore, gauze may stick to the tissue surface while it dries, which might prevent tissue healing by reducing oxygen to the injured region, constricting blood vessels, or inflicting further damage to it. When hydrogels, saline, or petrolatum are impregnated into the gauze, the functioning is enhanced.

2.9.3. Foam Dressings

Strong adsorbents and foam dressings can manage the huge volume of exudates found in chronic wounds. They create an atmosphere that is wet and insulate the fluid without sticking to the wound site (Romano *et al.*, 2023). To keep foam dressings on the wound, a second dressing may be necessary. If the incision is dry or has little exudate, foam may stick to it.

2.9.4. Wound Fillers

Non-adherent biomaterials known as wound fillers, which come to hydrate the wound bed and absorb exudates, in the form of pastes, granules, or powders (Bianchera *et al.*, 2020). The absorption capability is determined by the filler makeup.

2.9.5. Hydrocolloid Dressings

When applied to non-infected wounds, hydrocolloid dressings primarily provide a moist, insulated environment that enhances the development and quality of granulation tissue by activating the body's endogenous enzymes (Moura *et al.*, 2013). Hydrocolloid dressings do have certain restrictions, though. They might encourage the production of granulation tissue excessively and let a foul-smelling, gel-like substance drain. Similarly, it might be challenging to use hydrocolloid dressings to heal wounds surrounding cavities. Even though this approach has many benefits for wound healing, new, more convenient, and effective techniques can be utilized to treat chronic wounds.

2.10. Hydrogel Dressings

Hydrophilic polymer networks are arranged in three dimensions to form hydrogel dressings. There are hydrogel dressings that make treating chronic wounds simple. By adding cells, growth hormones, antibacterial, antiviral, and antifungal agents (Kłapcia & Domalik-Pyzik, 2025), as well as biomolecules, hydrogel dressings, which are flexible and adjustable, can acquire new functional qualities that can accelerate wound healing and contraction. Certain wounds can have hydrogel dressings made for them depending on the size, location, & severity of the wound.

2.11. Bioadhesive Hydrogels for Chronic Wound Healing

Bioadhesive hydrogels can offer long-term stability and help hydrogel dressings adhere to moist wounds more readily. When a hydrogel is present on the wound, the patient feels more comfortable because of its stretchability and elasticity (Zhang *et al.*, 2020). The improved hydrogel dressings' bioadhesivity and antioxidant activity were credited for the more effective wound closure in this study when CS-GA dressings were used instead of pristine CS dressings (Sun *et al.*, 2022).

2.12. Pro-Angiogenic Hydrogels for Chronic Wound Healing

A chronic wound's insufficient oxygen and nutrition delivery might be the reason for its delayed healing. To provide the wound with the necessary quantity of nutrients and oxygen, stimulation of angiogenesis is essential (Song *et al.*, 2024). Certain hydrogels may be naturally pro-angiogenic, or they may be made so by adding substances that stimulate angiogenesis to the hydrogels. Angiogenesis can be induced or activated by bioactive ions. Heat stimulation stimulates angiogenesis; hot spring baths, for example, are a good source of minerals with medicinal qualities. Hot spring bath treatments served as the model for the development of N, O-carboxymethyl chitosan (NOCS) and fayalite, two bioceramics made of ferrous and silicate ions (Sheng *et al.*, 2021). Bioactive ions were released from the NOCS hydrogel into the wound bed with little heat stimulation using the photothermal effect. The various biomimetics of hydrogels that promote wound healing are shown in Figure 3.

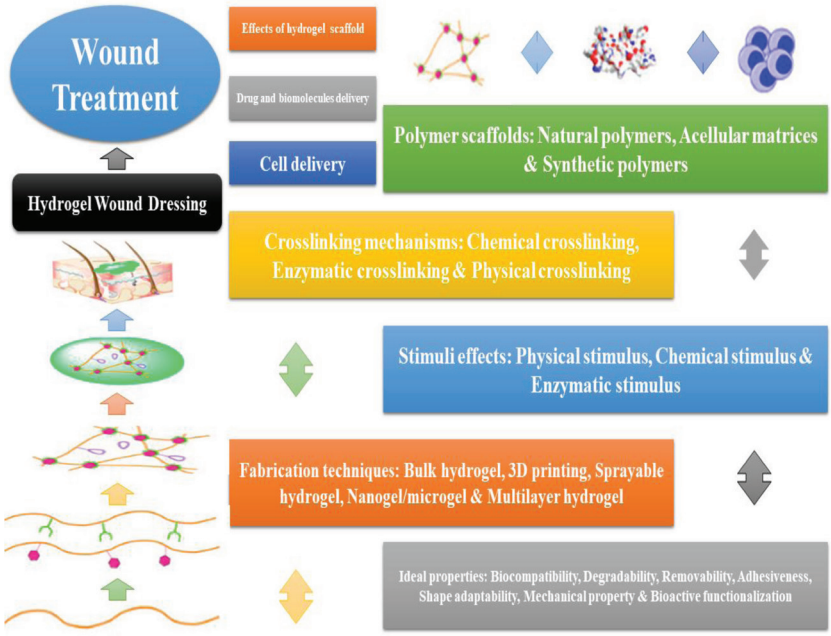

Figure 3: Biomimetic Hydrogels to Promote Wound Healing

This figure showcases biomimetic hydrogel systems designed to enhance wound healing. It outlines the structural and functional properties that mimic natural extracellular matrices, fostering cell proliferation, tissue regeneration, and accelerated wound closure while minimizing scarring.

2.13. Hydrogel Dressings for Chronic Wounds that are Sold Commercially

HydroDerm™, as mentioned by Xue and Jackson (2015), is a sheet-form hydrogel dressing, while DermaSyn® is a hydrogel gauze dressing. Both these dressings operate similarly to Suprasorb® G. They apply to both recent and old wounds. Similar to this, an amorphous gel called ActivHeal® (Winsford, Cheshire, UK) works well for debriding necrotic tissue from dry wounds. Since it works so well, ActivHeal® is frequently used to treat chronic wounds that pose a serious risk to life.

Gauze that has been impregnated with hydrogel is called DermaGauze™ (North Bergen, NJ, USA). It improves autolytic debridement and offers sufficient moisture to dry up slightly exuding lesions. It's not as popular as other options for managing and treating chronic wounds because of the additional dressing required. The Neoheal® dressing (Ujazd, Poland) is made of hydrogels with agar, polyethylene glycol, and polyvinylpyrrolidone that are mechanically robust, in contrast to the earlier examples. 90% of Neoheal® is water, and it debrides necrotic tissue and enhances angiogenesis and autolytic debridement to promote granulation & re-epithelialization of the wound surface. Granulation & re-epithelialization are encouraged, and autolytic debridement is facilitated.

3. Patented Hydrogel Innovations for Chronic Wound Management

This section explores various patented hydrogel formulations designed to enhance chronic wound healing. It includes a discussion on bioactive substances such as growth factors,

antimicrobial agents, & stem cell-derived exosomes that promote tissue regeneration and infection control. Additionally, it highlights emerging trends in smart hydrogels with self-healing capabilities, improved mechanical strength, and stimuli-responsive drug release for optimized wound healing.

The discovery of hydrogel-based wound dressings has generated significant interest in the field of chronic wound care, leading to a number of patents and clinical studies aiming at enhancing healing results (Yadav *et al.*, 2024). Patented hydrogel formulations include a range of bioactive substances, including growth factors, antibacterial agents, and stem cell-derived exosomes, to improve tissue healing and infection control (Saberian & Abak, 2024). Some of the main problems with chronic wound healing that these developments address include increased inflammation, bacterial infection, and decreased angiogenesis. New patents also explore smart hydrogels with self-healing capabilities, increased mechanical strength, and stimuli-responsive drug release mechanisms to optimize wound healing.

Numerous completed and ongoing clinical studies assess the safety, effectiveness, and clinical performance of hydrogel-based treatments in the treatment of chronic injuries. These studies assess factors including wound healing rate, infection rate reduction, pain management, and patient comfort in relation to traditional bandages (Solanki *et al.*, 2023). The results of these studies are crucial for moving hydrogel formulations closer to regulatory approval and broad clinical acceptance. Tables 1 and 2 provide a summary of important findings and clinical studies in hydrogel-based chronic wound care, emphasizing new developments and their beneficial uses. Table 1 summarizes various patented hydrogel formulations designed to enhance chronic wound healing. It highlights key features such as bioactive components, antimicrobial properties, and advanced drug delivery mechanisms aimed at improving tissue regeneration, reducing infections, and optimizing patient outcomes.

Table 1: Overview of Patented Hydrogel-Based Innovations for Chronic Wound Management

Patent No.	Title	Key Features	Functionality	Application	Filing Date	Status
US10500123B2	Injectable Hydrogels for Wound Healing	Biodegradable, temperature-sensitive hydrogels	Supports tissue regeneration, enhances drug delivery	Chronic wound healing (diabetic ulcers, burns)	May 21, 2019	Granted
US10842762B2	Hydrogel Compositions for Controlled Release of Bioagents	Cross-linked hydrogel with embedded growth factors	Controlled release of growth factors to promote angiogenesis	Diabetic foot ulcers, pressure sores	December 1, 2020	Granted
US11090213B2	Antimicrobial Hydrogel for Infection Control in Chronic Wounds	Silver nanoparticle-embedded hydrogels	Provides sustained antimicrobial action, reduces infection	Venous leg ulcers, chronic wound infections	August 17, 2021	Granted
WO2021012345A1	Conductive Hydrogel for Wound Monitoring	Hydrogel with conductive polymer network	Monitors wound healing via electrical signals	Monitoring chronic wound recovery	January 14, 2021	Applied
EP3815678A1	pH-Sensitive Hydrogels for Chronic Wound Care	Hydrogel responsive to pH changes in the wound microenvironment	Real-time detection of wound condition and controlled drug release	Non-healing ulcers	April 21, 2021	Applied
CN112345678A	Thermo-Responsive Hydrogel for Skin Regeneration	Hydrogel with collagen and hyaluronic acid	Temperature-triggered gelation, promotes cell migration and tissue repair	Chronic skin injuries (e.g., burns)	February 15, 2021	Applied
US11116485B2	Oxygen-Releasing Hydrogel System	Hydrogel integrated with oxygen carriers	Provides localized oxygen supply to hypoxic chronic wounds	Treating ischemic and diabetic ulcers	September 14, 2021	Granted

WO2022045678A1	Hydrogel Dressing with Growth Factor Releasing Properties	Biopolymer-based hydrogel loaded with platelet-derived growth factors	Controlled release of bioactive molecules to stimulate tissue regeneration	Complex chronic wounds	March 15, 2022	Applied
JP2021501234A	Hydrogel for Scarless Wound Healing	Hydrogel with bioactive peptides	Promotes scar-free healing by modulating inflammatory and repair phases	Chronic injury management (e.g., surgical wounds)	January 25, 2021	Applied
KR20230054321A	Hydrogel for Dual Drug Delivery in Chronic Wounds	Multilayered hydrogel with separate compartments for anti-inflammatory and antimicrobial agents	Simultaneous delivery of multiple drugs to manage inflammation and infection	Chronic wound infections	March 20, 2023	Applied
US4909244A	Hydrogel Wound Dressing	Provides a moist environment conducive to wound healing and granulation tissue formation; absorbs wound exudate.	Maintains optimal moisture levels to promote healing.	Chronic wounds, ulcers, burns.	March 20, 1990	Granted
US7910135B2	Hydrogel Wound Dressing and Biomaterials	Shape-retentive and shape-conforming aggregate wound dressings composed of gel.	Conforms to wound site, providing a moist environment for healing.	Various chronic wounds.	March 22, 2011	Granted
US6238691B1	Hydrogel Wound Dressing and Method	Highly absorptive hydrogel that contours to a wound site and maintains moisture.	Promotes healing by keeping the wound moist and absorbing exudate.	Chronic wounds, ulcers.	May 29, 2001	Granted

4. Clinical Trials on Hydrogel-Based Treatments for Chronic Wounds

This section presents an overview of completed and ongoing clinical trials evaluating the safety, efficacy, and performance of hydrogel-based treatments for chronic wounds. It discusses key factors such as wound healing rates, infection control, pain management, and patient comfort compared to traditional wound dressings. The findings from these trials are crucial for regulatory approval and widespread clinical application of hydrogel-based therapies. Table 2 provides a comprehensive overview of clinical trials assessing the safety, efficacy, and clinical performance of hydrogel-based treatments. It includes information on hydrogel types, applications, trial objectives, and study outcomes, showcasing their potential in improving chronic wound healing and patient care.

Table 2: Summary of Clinical Trials Investigating Hydrogel Applications in Chronic Wound Care

Clinical Trial Identifier	Title	Objective	Hydrogel Type	Application	Status	Phase Completed
NCT04123093	Safety and Efficacy of the Noxsano Wound Care Bandage	Evaluate the safety and efficacy of a local drug delivery dressing in wound treatment.	Hydrogel-based drug delivery dressing	Chronic wounds	Completed	Phase I Completed

NCT04058054	Skin Prick Test of KeraStat® Cream	Assess the safety of KeraStat® Cream, a hydrogel wound dressing, in managing partial thickness dermal wounds.	Hydrogel cream with keratin protein	Partial thickness dermal wounds	Completed	Phase I Completed
NCT04908748	Esflurbiprofen Hydrogel Patch in the Treatment of Blunt Injuries	Test the efficacy and safety of Esflurbiprofen Hydrogel Patch for blunt injuries.	Esflurbiprofen hydrogel patch	Blunt injuries	Completed	Phase II Completed
NCT04238728	Safety of Silverlon® in the Management of Infected Wounds	Evaluate the safety of Silverlon® dressings, which incorporate a hydrogel component, in managing infected wounds.	Silver-infused hydrogel dressing	Infected chronic wounds	Completed	Phase II Completed
NCT04819945	A Prospective, Multicenter, Single-arm, Clinical Investigation	Investigate the performance of a POx-hydrogel patch designed to adhere to tissue and form a seal across damaged tissue.	POx-hydrogel patch	Chronic wounds	Completed	Phase I Completed

5. Advances in Hydrogel Functions for the Management of Chronic Injuries

The treatment of chronic injuries has been completely transformed by recent advancements in hydrogel technology, which provide reactive, intelligent, and multifunctional wound care therapies (Fang *et al.*, 2025; Olteanu *et al.*, 2024). Modern hydrogels are made to combine restorative qualities that promote angiogenesis, fight infections, and speed up tissue regeneration in addition to preserving a moist wound-healing environment. The pH-sensitive, temperature-sensitive, and enzyme-responsive hydrogels are examples of stimuli-responsive hydrogels that allow the exact administration of antimicrobial medications, growth hormones, or anti-inflammatory substances as needed (Roy *et al.*, 2022). This involves adding liposomes, nanoparticles, and nanofibers to hydrogel structures to boost their antibacterial and healing qualities (Jacob *et al.*, 2021). These mixed hydrogels allow for the prolonged release of bioactive chemicals, encourage cellular mobility, and prevent the formation of bacterial biofilms—all of which are essential for wound healing (Duarte *et al.*, 2024). Furthermore, the incorporation of hydrogel-based biosensors into wound dressings is opening the door to a new level of customized wound care management by enabling real-time monitoring of infection symptoms, pH levels, and moisture content (Naser *et al.*, 2024). Since these improved hydrogel systems not only speed up healing but also reduce problems and improve patient outcomes, they will be an essential tool for treating chronic injuries in the future.

6. Future Prospects of Hydrogel Applications in Chronic Injury Management

The problem of acute and chronic wounds has impeded the social and economic environment, and in order to undo these detrimental effects, substantial healthcare reform is required (Hu *et al.*, 2024). The existing wound healing methods that reduce recovery durations have several issues. Therefore, a fresh and enhanced strategy is needed to address these shortcomings. Hydrogels have been suggested as appropriate wound treatments for both acute and chronic wounds due to their exceptional qualities, which include preserving a moist environment, absorbing exudates and dead tissue, and being flexible enough to cover wounds of different forms (Xu *et al.*, 2020). Hydrogels may be made from natural or synthetic polymers; mixed hydrogels with beneficial qualities for wound healing are best made from a mixture of the two. The next generation of wound dressings, sprayable hydrogels, can successfully cover wounds of any size or form. “Smart” hydrogels have gained popularity because they can utilize sensors to track the wound’s condition (Nandhini *et al.*, 2024). The creation of innovative hydrogels might provide a way to improve patient happiness and health overall, reduce the burden on the present healthcare system, and speed up the healing

process of wounds. The development of "smarter" hydrogels is conceivable.

- **Limitations and Outcomes/Overcomes:** Regarding their applicability, therapeutic processes, and endurance, hydrogel formulations have some limits as of right now and require further study. When heated to body temperature, or physiological temperature, many natural and synthetic hydrogel systems, including thermosensitive hydrogels, change from free-flowing sols at low temperatures to stable viscoelastic gel phases like poly(phosphazene), pluronic, and poly(N-isopropyl acrylamide) (Almawash *et al.*, 2022; Rana & De la Hoz Siegler, 2024). Poly(ester)-based copolymers offer a promising solution to circumvent these limitations, although they still need investigation. Moreover, poly(ester) and PEG-based hydrogels are ineffective for longer-term medication administration (Young *et al.*, 2019). Their oral and nasal routes are unsuitable, even though the FDA has authorized their usage in in vivo implants. Injectable hydrogels used for chemical interactions, proteins and peptide-controlled transport, burst release (when charged proteins are added to uncharged formulations), and structural compatibility are also facing future challenges (Gao *et al.*, 2021; Lee, 2018). Cross-linker monomers and hazardous catalysts are employed to break down or alter sensitive molecules, such as proteins, cells, and drugs, in response to enzymatic stimuli. Premature release, loading, and homogeneous packing are associated limitations and issues.
- **Injectable Formulation Challenges**: The capacity of self-assembled nanocarriers to specifically target receptors and the upregulation of antigens in tumor cells makes them intriguing therapeutic tools (Froimchuk *et al.*, 2020). IHs and their specific applications, which have already been studied, have certain important issues in common and need further study (Sanin *et al.*, 1994). Hydrogel cross-linkings must be compatible with weak molecules or cells, and growth must be controlled in a healthy environment in order to protect DNA, peptides, proteins, and oligonucleotides from enzymatic breakdown or denaturation (Chandra *et al.*, 2025; Denzer *et al.*, 2021). The degradation period, the release profile of bioactive factors, the gelation mechanism, rate kinetics, viscosity during the injection time, and mechanical sturdiness after gelation are among the factors that should be properly considered in the context of low reproducibility, poorly defined structures, and the use of systems (Ganji *et al.*, 2007; Ling *et al.*, 2022). It should be mentioned that the biological computability and chemical-physical bonding of these IHs need to be connected to application-specific design measures that are tailored to certain medical conditions or diseases.
- **Mechanical Robustness**: Maintaining a low viscosity and durability while preserving sufficient flexibility in situ for repeated load and volume is one of the primary design difficulties (Xu *et al.*, 2024). Since these hydrogels are delivered via a needle and syringe, repeated doses and in situ gelation are significant challenges. Currently used as skin fillers, shear-thinning polymers like hyaluronic acid are being replaced by injections for cartilage restoration. As a result, the elastic modulus and the polymer's molecular weight are negatively correlated, but the chains, crosslinking amount, crosslinking method, and viscosity are directly correlated with the molecular weight (Nielsen, 1969).
- **Loading and Release of Therapeutic Agents**: IH carriers, which have their own distinct physicochemical characteristics, may be used to load and release therapeutic agents such as biomolecules (proteins, peptides, nucleic acids, etc.), tiny drug molecules, or living cells into the environment (Pudlarz & Szemraj, 2018). These days, microparticle storage devices are among the IHs used in medical practice. Many hyaluronic acid hydrogel injectables have been approved for facial enhancements; the most popular depot formulations incorporate the anesthetic drug lidocaine (Jeong *et al.*, 2025). Hydrogel meshes hinder the release of lidocaine by causing rapid leakage. Similarly, it is crucial to exclude additional medicines from hydrogel formulations in order to prolong the release of proteins and medications in wound dressings. To maximize the liquid's binding and prolong its retention time, these recipes call for physical or chemical crosslinking to shrink the hydrogel mesh size.
- **Hydrogel Bioactivity**: The bulk hydrogel material has to enter, change, and break down in order to promote tissue repair. For hydrogel bioactivity to take place, cells or growth factors need to bind to sticky natural or artificial materials like gelatin, fibrin, or hyaluronic acid. Several recent clinical studies, including NCT04115345, NCT04115345, and NCT00981006, use the hydrogel bioactivity of gelatin in combination with cells and/or growth hormones. These bioactive hydrogels speed up the healing of damaged kidney or heart tissue by creating the right cell-adhesive environment. Certain non-adhesive polymers, including PEG and polyacrylamide, need chemical modification with sticky ligands to promote cell ingress and adhesion.
- **Immunological Compatibility**: One of the main areas of research in recent decades has been eliciting

immunological responses to IH biomaterials (Lock *et al.*, 2019). Therefore, limiting all types of immune responses during in situ gel changes is crucial for injected hydrogel compositions. The worst effects of injecting, inserting, and implanting biomaterials are thought to be immunological reactions, including fibrosis, hypersensitivity reactions, and inflammatory cascades (Anderson & Jiang, 2016). The performance, function, and future use of the hydrogel material may be impacted by these reactions, which are dangerous in and of themselves since they may result in associated physicochemical shifts and susceptibility.

- **Technological Challenges**: Successful clinical versions of hydrogel-based delivery systems face significant technological obstacles, such as chemistry, good manufacturing practices (GMP), well-defined & regulated regulatory requirements, practical adaptability, & high costs (Correa *et al.*, 2021). Research and manufacturing expenditures for hydrogel production systems to practical translation are estimated to range from USD 50 million to USD 800 million.
- **Scale-Up Strategies and GMP Processes**: As most hydrogel systems are made & produced at a small pilot-plant scale at preclinical stages, current good manufacturing practices (cGMP) for clinical translation & addition of biomaterial-based hydrogels in large-scale systems & their interaction are needed (Almawash *et al.*, 2022). Robustness, batch-to-batch variations, safety standards, predictability, & skill are required when performed at a big scale. Moreover, the high water content of hydrogels makes production, manufacturing, storage, longevity, cleaning, and all related improvement processes even more demanding.
- **Regulatory Approvals**: As we have said, regulatory affairs and FDA approval are drawn-out processes that take years, ranging from laboratory manufacture to market launch and monitoring. It is difficult to categorize and approve injectable hydrogel scaffolding by rules because of the variety of crosslinking polymers and nanoparticles that are utilized. In a variety of biological fields, such as tissue engineering, drug screening, cancer treatment, and cosmetic medicine, hydrogels have so far shown impressive outcomes (Catoira *et al.*, 2020; Song *et al.*, 2018). The thorough understanding of how cells act and how signaling transductions react to the hydrogel matrix's physical and structural properties supports the ongoing advancement of material techniques to better regulate cell biology and fate for acceptable needs. Generally speaking, the cell would absorb environmental information and transform it into internal chemical signals that might affect survival, gene expression, and cell lineage commitment. Crucially, in order to more accurately reproduce the intricate native matrix, researchers are concentrating on a broader variety of hydrogel attributes and dimensions, including three-dimensionality, hydrogel architecture, degradability, and dynamic properties. This will improve our comprehension of how hydrogels' physiochemical, mechanical, and structural signals regulate the phenotypic function and destiny of cells. Despite exciting and notable advancements in hydrogel design, unforeseen side effects, problems, and inappropriate delivery techniques have hampered the medical application of hydrogel products. These issues may be addressed by material augmentation once a material library has been created and screened. The long-term efficacy in vivo is yet unknown due to the complex cellular environment, despite the fact that the potential medicinal advantages of cell-loaded hydrogels for tissue regeneration and disease treatment have been successfully shown in vitro (Mancuso *et al.*, 2020). Therefore, a thorough and structured understanding of the interactions between cells and matrix is necessary to support their therapeutic uses in vivo. Furthermore, even though a number of dynamic hydrogel types have been developed, their use is mostly limited to the administration of medications (Hamidi *et al.*, 2008). Therefore, to increase their future applications, it will be helpful to comprehend the communication transductions and cell biology responses in smart hydrogel.

7. Conclusion

Chronic wounds have been treated with a variety of techniques, including skin transplants, etc. Every approach has its own pros and cons. Debridement speeds up the healing process and greatly enhances wound healing. Only diabetic foot ulcers can benefit from hyperbaric oxygen therapy, which is costly. Surgery incisions, pressure ulcers, and venous ulcers can all benefit from electromagnetic and ultrasound treatment. If the right parameters are not followed, these treatments might burn or cause superficial damage to the endothelium tissues. Patient movement is restricted by negative pressure wound treatment. Furthermore, loud noises during medical procedures hurt patients. Skin grafts are costlier and need more intricate processes than other techniques. All of the above-stated methods call for clinical experts and completely furnished medical facilities. Chronic wounds are frequently treated using dressings. Hydrocolloids, hydrogels, films, gauze, and foams are some of the forms in which they may be produced. They are useful in stopping more harm or complications from the wound, but their application is restricted by certain issues.

The problem of acute and chronic wounds has impeded the social and economic environment, and in order to undo these detrimental effects, substantial healthcare reform is required. The current wound healing techniques have some shortcomings when it comes to shortening recovery times. Therefore, a fresh and enhanced strategy is needed to address these shortcomings. Hydrogels have been suggested as appropriate wound treatments for both acute and chronic wounds due to their exceptional qualities, which include preserving a moist environment, absorbing exudates and dead tissue, and being flexible enough to cover wounds of different forms. Hydrogels may be made from natural or synthetic polymers; mixed hydrogels with beneficial qualities for wound healing are best made from a mixture of the two. The next generation of wound dressings, sprayable hydrogels, can successfully cover wounds of any size or form. "Smart" hydrogels have gained popularity because they can utilize sensors to track the wound's condition. The creation of innovative hydrogels might provide a way to improve patient happiness and health overall and reduce the burden on the present healthcare system. The development of "smarter" hydrogels is conceivable.

In summary, despite all of IH's traits, more investigation and analysis are still needed for their biological uses. It seems that their inventive potential may result in new discoveries and developments, especially in the fields of biomedical engineering, tissue regeneration, drug, protein & gene delivery, cancer chemotherapies, wound dressings, implants, superbug targeting, etc. Current prospective hydrogel research, FDA-approved formulations & clinical trials, biomedical applications, molecular-level studies, crosslinking modules, and natural, synthetic, & natural-synthetic hybrid synthesis have led to the use of hydrogels in a greater variety of medical conditions and complications. Outlining all of these limitations, the corresponding disadvantages, and the design challenges in injectable forms may help to enable and propose future research into more inventive and successful uses.

Abbreviations

TGF-β: Transforming Growth Factor Beta, **FGF**: Fibroblast Growth Factor, **PDGF**: Platelet-Derived Growth Factor, **EGF**: Epidermal Growth Factor, **ROS**: Reactive Oxygen Species, **ECM**: Extracellular Matrix, **IHs**: Injectable Hydrogels, **FDA**: Food and Drug Administration, **GMP**: Good Manufacturing Practices, **cGMP**: Current Good Manufacturing Practices, **MSCs**: Mesenchymal Stem Cells, **HSCs**: Hepatic Stellate Cells, **NASH**: Non-Alcoholic Steatohepatitis, **NAFLD**: Non-Alcoholic Fatty Liver Disease, **NAFL**: Non-Alcoholic Fatty Liver, **MRI**: Magnetic Resonance Imaging, **CT**: Computed Tomography, **HCC**: Hepatocellular Carcinoma, **AFLD**: Alcoholic Fatty Liver Disease, **DNL**: De Novo Lipogenesis, **T2DM**: Type 2 Diabetes Mellitus, **FFA**: Free Fatty Acids, **IL-6**: Interleukin-6, **TNF-alpha**: Tumor Necrosis Factor Alpha, **NNMT**: Nicotinamide N-Methyl Transferase, **DAMPs**: Damage-Associated Molecular Patterns, **PEG**: Polyethylene Glycol, **AST**: Aspartate Aminotransferase, **ALT**: Alanine Aminotransferase, **HSCs**: Hematopoietic Stem Cells.

Acknowledgement

The authors would like to express their gratitude to Chitkara College of Pharmacy for the continuous support in writing the review article.

Authorship Contribution

Himanshu Sharma and Sanchit Dhankhar: Conceived and designed the manuscript; Vishnu Mittal: Collected data on recent studies; Akashdeep Singhand Pooja Mittal:Drafted the manuscript; Balraj Saini: Critically reviewed and performed final approval of the version to be published.

Funding

There are no funding sources for this article.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of the article.

Declaration

It is an original article and has neither been sent elsewhere nor published anywhere.

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