APPLICATION OF HYDROGEL POLYMERS FOR SKIN REGENERATION: A REVIEW

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ABSTRACT

The skin is the largest organ of the human body that plays a pivotal role in shielding organs and tissues from damage by external conditions. Sources of skin wounds include severe injury, infection, or underlying conditions such as diabetes. While conventional treatments have relied on drugs and wound dressings, hydrophilic gels crafted from three-dimensional cross-linked polymeric networks offer an alternative to traditional invasive treatments. Recent research has shown the increasing demand for both natural and synthetic hydrogel polymers due to their ability to simulate the extracellular matrix and mechanical properties of natural tissues. This potential is further enhanced by their ideal biocompatibility and biodegradability characteristics. Tissue engineering is a discipline of biomedical engineering dedicated to the restoration of functional tissues and organs outside of the body. This multidisciplinary field of research is responsible for the development and experimentation of biomaterials aimed at revolutionizing regenerative medicine. Among the diverse range of biomaterials utilized for this purpose, hydrogel polymers have gained attention as a result of their unique physical and chemical properties. This paper provides a comprehensive review of existing literature on six types of natural and synthetic hydrogels utilized in tissue regeneration: collagen, hyaluronic acid (HA), silk, polyvinyl alcohol (PVA), polyethylene glycol (PEG), and carboxymethyl cellulose (CMC). Through a comparative analysis of each type's characteristics, hybrid hydrogels composed of collagen and polyethylene glycol (PEG) can be recommended for use in therapeutic treatment for skin regeneration. Due to the advantages and potential future advancements in utilizing hybrid hydrogel dressings for skin regeneration, patients suffering from skin wounds could benefit from effective treatments, thus improving their overall quality of life.

Keywords: Skin regeneration, hydrophilic gels, three-dimensional cross-linked polymeric networks, extracellular matrix, biocompatibility, biodegradability, tissue engineering, regenerative

medicine, collagen, hyaluronic acid (HA), silk, polyvinyl alcohol (PVA), polyethylene glycol (PEG), carboxymethyl cellulose (CMC), therapeutic treatment

1 INTRODUCTION

The integration of materials science and regenerative medicine has initiated a groundbreaking period for therapeutic interventions, particularly in the field of skin regeneration. The skin serves several vital functions in the human body, acting primarily as the immune system's first line of defense against pathogens and antigens. It defends the body by detecting changes in pressure, temperature, and pain, and conveying these signals to the brain (Abdallah et al., 2017). Despite its critical role, skin is not as strong as is often believed. Skin tissue is susceptible to significant damage that it is incapable of repairing on its own, particularly under conditions of intense heat or pressure (Jeong et al., 2017). While first- or second-degree burns may only cause temporary discomfort and potentially leave lasting scars, third-degree burns inflict severe damage to the skin. In serious burn cases, immediate skin grafting is necessary to prevent secondary infections due to the shortage of suitable donor skin (Markiewicz-Gospodarek et al., 2022). Thus, the urgent need for skin-regenerative tissue engineering has become apparent, prompting advancements in the field.

Among the wide array of materials under exploration, hydrogel polymers stand out due to their unique properties, which include softness, high adaptability, water retention, and superior bioactivity (Sánchez-Cid et al., 2022). Furthermore, their porous structure not only facilitates cell movement and growth but also ensures the effective transportation of nutrients and healing compounds to the affected area (Uppuluri et al., 2022). These remarkable properties, including their high water content, give hydrogels exceptional oxygen permeability and the ability to absorb wound discharge. Additionally, because of their adaptable physical and chemical properties, hydrogels can simulate the composition and mechanical properties of natural tissues, providing ample space and structural support for cell movement and the regeneration of tissues (Arabpour et al., 2024).

This report begins by providing an overview of the challenges encountered in skin regeneration, emphasizing key parameters such as biocompatibility, the skin healing process, swelling ratio, and biodegradability. It then transitions into a detailed exploration of hydrogel polymers, covering both their composition and synthesis. Through a critical review of recent studies, this report assesses the formation of hydrogels from a variety of polymeric materials. Furthermore, it explores the advantages and limitations of both natural and synthetic hydrogels to determine the ideal polymeric material for hydrogel applications.

2 PARAMETER CONSIDERATION

To comprehensively explore the range of polymers suitable for hydrogel applications in skin regeneration, it is imperative to analyze the following parameters. These parameters are vital for material design and selection, ensuring biocompatibility, optimizing functionality, mitigating risks, tailoring properties to specific applications, and adhering to regulatory standards (Revete et al., 2022). Through systematic consideration of these factors, researchers can develop hydrogel materials that are safe, effective, and suitable for clinical use in tissue engineering and regenerative medicine.

2.1 Biocompatibility

Comprehending biocompatibility involves understanding the diverse chemical, biochemical, physiological, and physical mechanisms that occur when biomaterials interact with cells in the body, as well as grasping the resulting outcomes of these interactions. When assessing the biocompatibility of hydrogel polymers, overlooking crucial factors such as cytotoxicity, carcinogenicity, mutagenicity, pyrogenicity, allergenicity, and thrombogenicity can lead to significant repercussions. Instances abound where the absence of cytotoxicity evaluations resulted in cell death and inflammation upon hydrogel implantation, emphasizing the necessity of comprehensive biocompatibility testing. Similarly, overlooking cytotoxicity and carcinogenicity assessments could result in adverse outcomes like inflammation and tumor formation (Revete et al., 2022).

Moreover, the oversight of mutagenicity assessment can pose long-term risks due to genetic mutations in exposed cells. Similarly, disregarding evaluations for pyrogenicity, allergenicity, and thrombogenicity can result in severe inflammatory reactions, allergic responses, or thrombotic events post-implantation. These examples underscore the critical importance of thorough biocompatibility evaluations to ensure the safety and efficacy of hydrogel polymers in biomedical applications (Revete et al., 2022).

Furthermore, the tailoring of hydrogel properties to meet specific requirements can be achieved through the selection of appropriate polymer combinations. For instance, blending different polymers can improve biocompatibility, mechanical strength, stability, and permeability. The sequential polymerization method involves initiating one polymer network first, followed by introducing the second polymer system, which permeates the gaps between the chains of the initial network (Chyzy & Plonska-Brzezinska, 2020). Alternatively, in simultaneous polymerization, various monomers or pre-polymers are polymerized together to create interpenetrating networks. The crosslinking of polymer networks further reinforces the structure of the interpenetrating polymer network hydrogel (Zohreh Arabpour et al., 2024). In summary, emphasizing the significance of considering biocompatibility as a critical parameter when evaluating various polymers.

2.2 Skin Healing Process

In the context of skin wound healing, the hemostatic properties of hydrogel materials play a pivotal role in facilitating rapid control of bleeding, a critical initial stage in the healing process depicted through part C in *Figure 1*.

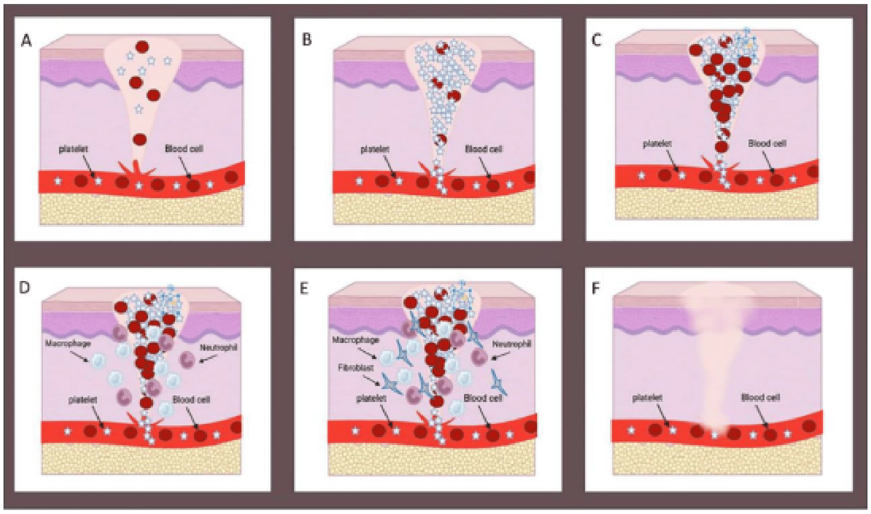

Figure 1: Wound healing Process: A) Blood vessel injury; B) Platelet activation for hemostasis; C) Formation of fibrin clot for hemostasis; D) Initiation of the inflammatory phase; E) Commencement of the proliferation phase; F) Onset of the remodeling phase. (Zohreh Arabpour et al., 2024).

The efficacy of these properties, however, is intricately tied to the specific polymer composition and structural characteristics of the hydrogel. Hydrogels are characterized by hydrophobic acrylate groups within a hydrophilic backbone, and possess the ability to retain water, thereby creating an optimal moist environment essential for skin cell regeneration (Revete et al., 2022). Certain hydrogel structures and polymers exhibit enhanced water retention capabilities, contributing to the maintenance of ideal moisture levels crucial for promoting tissue regeneration. Additionally, the polymer composition and structure influence the hydrogel's adherence to tissues, facilitating efficient sealing for achieving hemostasis. Furthermore, hydrogel materials with the capacity to attract negatively charged platelets contribute to the coagulation process, further aiding in the cessation of bleeding and promoting wound healing (Zohreh Arabpour et al., 2024).

The incorporation of one or more polymers lead hydrogel materials to exhibit fluid-retentive and activated structures that actively interact with clotting components, fostering efficient blood coagulation to arrest bleeding promptly. Beyond hemostasis, hydrogels promote tissue regeneration through granulation and re-epithelialization, which are essential processes in the wound healing cascade (Naahidi et al., 2017). The provision of an optimal moist environment by hydrogels not only accelerates re-epithelialization but also facilitates wound healing by supporting cellular proliferation and migration. By maintaining moisture levels conducive to tissue regeneration, hydrogel materials contribute significantly to the overall efficiency and efficacy of the skin healing process. Thus, the analysis of hydrogel parameters, including polymer composition and structural attributes, offers valuable insights into their potential applications and effectiveness in promoting skin wound healing (Jurak et al., 2021). In conclusion, underscoring the importance of ensuring the effective hemostatic properties when assessing various polymers.

2.3 Swelling Ratio

As briefly discussed earlier, the ability of hydrogels to absorb and retain water is essential for creating a moist environment critical for cell regeneration. This capacity for water absorption and retention is a physical process referred to as swelling and represents one of the fundamental properties of most hydrogels. The formula for calculating the swelling ratio of a hydrogel remains as follows (Uppuluri et al., 2021):

$$Swelling\ Ratio\ =\ \frac{m_{swollen} - m_{dried}}{m_{dried}}$$

Where $m_{swollen}$ represents the weight of the hydrogel after water absorption and m_{dried} represents the initial/dried weight of the hydrogel.

Depending on the polymer matrix utilized in the gel's creation, it can absorb several times more water than its dry mass. Increasing the hydrogel's mass allows for greater water absorption, thereby enhancing its absorption capacity (Firlar et al., 2022). The swelling process is significantly influenced by the presence of hydrophilic groups within the gel structure, with hydroxyl and carboxylic groups being particularly desirable. In the presence of water, these groups hydrate first, facilitating the penetration of solvent molecules into the gel matrix until an equilibrium state is reached. Hydrogen bonds formed between water molecules and the functional groups of the polymeric chain stabilize the hydrogel structure (Zohreh Arabpour et al., 2024).

In modern pharmacy and regenerative medicine, the swelling process offers opportunities to utilize hydrogels as carriers for therapeutic substances. In infected wound treatment, for instance, modifying polymer structures to enhance the swelling ratio enables the delivery of antibacterial agents, including antibiotics and silver particles more effectively (Hoc Thang Nguyen et al., 2023). Overall, underscoring the importance of the swelling ratio parameter as a crucial aspect to consider when assessing different polymers.

2.4 Biodegradability

Biodegradability stands as a pivotal consideration in assessing the ideal polymer structures within hydrogels for skin regeneration (Barba et al., 2016). Biodegradable polymers offer the advantage of temporary functionality, followed by controlled degradation into less complex materials that are metabolized and eliminated by the body (Kim et al., 2019). This characteristic mitigates the risks associated with the prolonged presence of foreign materials, potentially preventing the need for surgical removal. These polymers undergo in vivo degradation, either enzymatically or non-enzymatically, transforming into biocompatible and non-toxic by-products (Boominathan & Ferreira, 2012). Therefore, the selection of biodegradable polymers necessitates the capacity for controlled degradation rates while upholding mechanical integrity, particularly crucial for applications like controlled drug delivery. Key factors influencing biodegradation include molecular weight, percentage of crystallinity, and hydrophobicity of the polymer, along with environmental factors such as pH, enzyme concentration, and water content (Das, 2018).

In the pursuit of optimal polymer structures for skin regeneration, careful consideration of factors contributing to biodegradation is imperative. Selecting polymers that exhibit suitable degradation rates while maintaining mechanical integrity ensures the harmonization of degradation kinetics with tissue regeneration processes (Rousselle et al., 2019). Moreover, understanding the interplay between polymer properties and environmental factors of an open wound allows for the optimal selection of hydrogel structures and materials that are tailored to specific application requirements (*Promoting Wound Reepithelialization | WoundSource*, 2020). By integrating biodegradability as a guiding criterion in polymer selection, researchers can develop hydrogel-based materials that effectively support tissue regeneration while minimizing long-term complications associated with foreign body response.

3 HYDROGEL POLYMERS

A scaffold serves as a structure manufactured from either natural or synthetic materials, designed to support the growth of tissue for the replacement of diseased or damaged tissue inside the body. (Qizhi et al., 2016). Clinical interventions, such as hydrogel polymer scaffolds, play a pivotal role in the treatment of critical skin wounds, as these materials facilitate the typical wound healing process by fostering natural and rapid healing of tissue. Hydrogels are preferred for this role due to their capacity to regulate moisture levels, defend against infections, reduce tissue necrosis, and overall mechanical support (Arabpour et al., 2024). This section aims to evaluate the composition and manufacturing procedures of hydrogel polymers.

3.1 Composition

Callister and colleagues (Callister et al., 2010) described how polymers comprise one of the four primary categories of biomaterials. These hydrocarbon-based macromolecules are composed of individual repeating units of monomers. Their molecular structure labels hydrogels as network polymers, which contain multitudes of cross-links due to covalent bonding between monomers within their molecular structure. The incorporation of hydrophilic functional groups into the polymeric backbone of carbon atoms provides an explanation for the materials capacity to absorb and retain water (Ahmed et al., 2013). Polymerization of cross-linking within the three-dimensional network allows for water to fill interstitial spaces between macromolecules, thus simultaneously resisting dissolution and maintaining structural integrity.

These properties enable hydrogels to have a remarkable degree of flexibility, thus rendering them versatile and applicable across various industries. In regards to skin regeneration, the elasticity of hydrogels simulates the mechanical characteristics of naturally occurring tissues in the human body. In addition to retaining moisture, the molecular structure of hydrogels also permits gas exchange to facilitate the delivery of oxygen and vital nutrients to damaged tissues (Arabpour et al., 2024).

3.2 Synthesis

According to Uppuluri et al. (Uppuluri et al., 2021), the synthesis of polymeric hydrogel scaffolds entails employing cross-linking techniques to enable desired properties. As illustrated in *Figure 2*, typical manufacturing processes encompass both physical and chemical cross-linking. The selection of a particular method significantly influences the gelation rate of the hydrogel and, consequently, the efficacy of treatment for specific types of skin wounds.

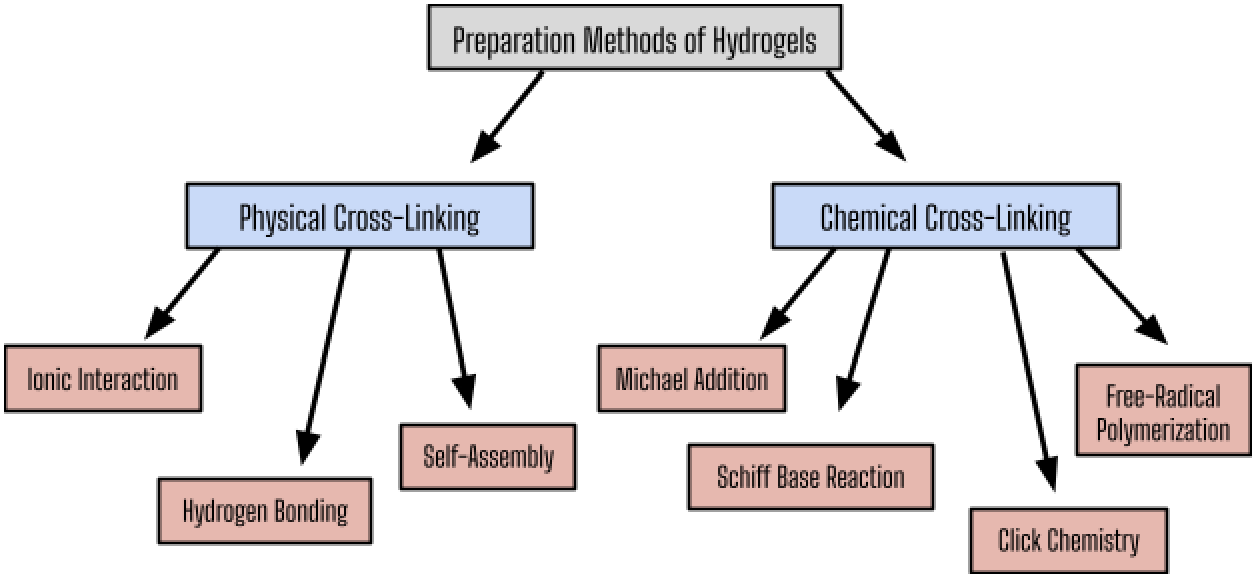

Figure 2: Schematic Diagram of Hydrogel Preparation Methods (Arabpour et al., 2024).

Physical cross-linking commonly involves reversible intermolecular interactions, including ionic interactions, hydrogen bonding, self-assembly, and similar mechanisms (Arabpour et al., 2024). Studies indicate the effectiveness of combining multiple physical cross-linking methods to enhance the overall mechanical strength of the material. The lack of chemical agents and capability of reversing the process highlights the biocompatible and biodegradable nature of physically cross-linked hydrogels. The distinctive attributes of each physical cross-linking method are displayed in *Table 1*.

Chemical cross-linking typically yields permanent linkages between polymer chains through chemical bonds. Various chemical reactions involved include Michael addition, Schiff base formation, free radical polymerization, click chemistry, and enzyme-mediated cross-linking. According to Arabpour et al. (Arabpour et. al, 2024), these processes are aided by factors such as light, heat, radiation, ultrasonic waves, and cross-linking agents. *Table 2* provides a summary of the characteristics of each chemical cross-linking method.

Table 1: Characteristics of Physical Cross-Linking Methods (Arabpour et al., 2024)

Method	**Characteristics**
Ionic Interaction	• weak mechanical properties • biotoxicity due to release of ions • thermal flexibility • polyelectrolytes
Hydrogen Bonding	• poor mechanical strength • prone to breakage • between hydrogen and electronegative atoms (N, O, F)
Self-Assembly	• spontaneous formation • non-covalent bonding • self-assembly in water or oil phases

Table 2: Characteristics of Chemical Cross-Linking Methods (Arabpour et al., 2024)

Method	**Characteristics**
Michael Addition	• injectable adhesive hydrogels • highly branched polymers • increased adhesive strength
Schiff Base Reaction	• reversible imine bond between amino and aldehyde groups • exhibit self-healing properties • antibacterial properties • tissue adhesion
Click Chemistry	• high reactivity and yield • mild conditions
Free-Radical Polymerization	• chain initiation, growth, termination • terminal olefinic bonds • health risks

4 POLYMER SELECTION FOR HYDROGELS

Skin tissue engineering has rapidly advanced in recent years, with a primary focus on the creation of hydrogels from a variety of polymeric materials (Oliveira et al., 2023). Having a high water content of up to 99%, they have properties that are similar to those of natural tissue, making them ideal for skin tissue regeneration. These polymeric materials can be divided into two general categories: natural and synthetic. This section will review several studies to assess how effective collagen, hyaluronic acid, silk, PVA, PEG, and CMC polymers are in creating hydrogels for skin regeneration.

4.1 Natural Polymers

Natural polymers consist of long monosaccharide chains linked together by glycosidic bonds. They are produced naturally and are derived from plants, animals, and microorganisms. They are ideal for skin repair and regeneration due to their similarity to the extracellular matrix (ECM), mechanical flexibility, biocompatibility, and water-retention ability. A few commonly used natural polymers include collagen, hyaluronic acid, and silk.

4.1.1 Collagen

Collagen is the most abundant protein in the mammalian body and a key component of the extracellular matrix. It possesses ideal qualities for wound healing, including biocompatibility, minimal antigenicity, and high mechanical strength. Additionally, it facilitates cell binding, proliferation, differentiation, and production of the ECM (Arabpour et al., 2024). Among collagen types, type 1 collagen is the most abundant protein in native dermal tissue, making it the most commonly used in skin scaffolds.

Ge et al. (2020) investigated the production of collagen hydrogels from tilapia fish skin, with a focus on pepsin-soluble collagen (PSC) and acid-soluble collagen (ASC). Animal experiments revealed that the use of collagen hydrogel dressings dramatically accelerated the wound healing of deep second-degree burn wounds. They displayed excellent mechanical qualities, water retention, and no cytotoxic effects. The increased development of epidermal layers and skin appendages surpassed commercial products, demonstrating the promising potential of collagen-based therapy in wound care.

4.1.2 Hyaluronic acid (HA)

Hyaluronic acid is a natural polysaccharide in the ECM, composed of alternating D-glucuronic acid and N-acetyl-D-glucosamine units linked via β-1,4 and β-1,3 glycosidic bonds (Xu et al., 2012). It governs a variety of cellular responses inside the ECM, which are critical for physiological processes including lubrication, water absorption, structural support, and cell communication. HA is commonly used for skin regeneration purposes due to its non-toxic, non-allergenic, biocompatible, and biodegradable nature. Three-dimensional HA systems have been utilized in experimental approaches, both in vivo and vitro, including disease modeling, tissue and organ repair, wound healing, and encapsulating stem cells for tissue regeneration (Zhao et al., 2023).

Dong et al. (2020) conducted a study that explored the use of a hyaluronic acid-based hydrogel as a delivery vehicle for adipose-derived stem cells (ASC) to treat burn wounds. By incorporating an RGD motif into the gel, cell attachment and proliferation were enhanced. The hydrogel effectively improved ASC survival, accelerated wound healing, reduced scar formation, and promoted blood vessel formation in animal models. Hong et al. (2018) demonstrated the efficacy of HA in the form of HA2 hydrogel by comparing its performance against other treatments in a full-thickness skin defect model. HA2 enhanced α-SMA expression for wound contraction and angiogenesis, which resulted in quicker wound closure compared to clinical cotton dressings. Furthermore, HA2 decreased inflammation and enhanced skin regeneration by boosting VEGF expression, leading to better wound repair and reduced scarring. These findings highlight the potential of HA-based hydrogels for enhancing skin regeneration and wound healing.

4.1.3 Silk

Silk is a naturally occurring macromolecular protein polymer, primarily produced by members of the Arachnida class and species of the order Lepidoptera. It is composed of two main proteins; fibroin, which originates in specific epithelial cells lining silk glands, and sericin, which binds the fibroin fibers together. Studies have shown that sericin-free fibroin fibers exhibit exceptional biocompatibility in both vivo and vitro (Arabpour et al., 2024). Silk fibroins (SFs) boast excellent biological properties, including high biocompatibility, adjustable degradation rates, low immunogenicity, and impressive mechanical properties when formed into various shapes. They have recently gained attention in tissue engineering for their ability to enhance cell activity at tissue defect sites and mitigate tissue damage-related factors.

Zhang et al. (2022) created a hybrid hydrogel consisting of SF, PGS, and chitson. The PGS hydrogel was tested with and without the addition of SF and Chitson polymers. Results showed that the PGS composite scaffold exhibited better attachment, proliferation, and deeper penetration of cells into the scaffolds with the modification of SF and chitosan. This highlights SFS's capabilities in enhancing cell activity.

4.2 Synthetic Polymers

Artificially produced in labs, synthetic polymers have emerged as prominent candidates for hydrogel formulations. Compared to natural polymers, synthetic polymers have superior mechanical strength and a customizable biodegradation rate. Their inherent adaptability enables them to be employed in various forms that promote the ideal development of tissues (Arabpour et al., 2024). For example, manipulating both the hydrophilic and hydrophobic regions during production allows for precise control, resulting in the creation of more uniform frameworks and an increased ability to retain water. Some synthetic polymers include PVA, PEG, and CMC.

4.2.1 Polyvinyl Alcohol (PVA)

PVA is a water-soluble polymer with a repeating hydroxyl group in its backbone. These hydrogels are commonly used in wound dressings and tissue scaffolds because they keep the wound moist, which is extremely beneficial for healing. They act as a protective barrier against germs while still allowing oxygen and nutrients to reach the wound (Arabpour et al., 2024). PVA hydrogels can also carry bioactive substances like growth factors or antimicrobial agents. Additionally, combining them with natural polymers can further enhance their therapeutic effects and promote skin regeneration.

Zhou et al. (2023) demonstrated the utilization of PVA in hydrogels by fabricating scaffolds using a combination of fibrin and PVA. These scaffolds were evaluated in a full-thickness skin excision-defect model in mice. Assessment via immunofluorescence analysis revealed increased CD31 and α-smooth muscle cell expression, indicating improved blood vessel formation in the treated wounds. The results demonstrated a significant enhancement in wound healing compared to untreated wounds. Furthermore, the scaffolds facilitated the deposition of collagen fibers, which are crucial for enhancing skin strength and structure.

4.2.3 Polyethylene glycol (PEG)

PEG is a hydrophilic polymer that forms a backbone through extensive hydrogen bonding with water. They play a pivotal role in wound healing due to their exceptional properties. Its ability to retain moisture aids in maintaining an optimal healing environment, while its compatibility with growth factors and peptides enhances tissue regeneration (Arabpour et al., 2024). Similar to PVA, PEG hydrogels, when cross-linked with other polymers, can enhance functionality and efficacy. Moreover, blending PEG with specific amino acids enhances its ability to fight bacteria, making it more effective in advanced wound care.

4.2.3 Carboxymethyl cellulose (CMC)

CMC-based wound dressings are widely appreciated for their biocompatibility, biodegradability, tissue-like properties, affordability, and safety. Their hydrophilic nature allows them to blend and cross-link with other materials such as natural polymers, inorganic materials, and other synthetic polymers (Kanikireddy et al., 2020). Bilayered hydrogels, which consist of two different layers, are known for their important role in skin regeneration. CMC's outstanding swelling and mechanical qualities make it ideal for the production of bilayered hydrogel scaffolds for use in skin tissue engineering (Arabpour et al., 2024). For instance, Li et al. (2019) developed a bi-layer wound dressing using PVA/CMC/PEG hydrogels, controlling pore size through thawing-freezing. The dressing exhibited controlled pore sizes and good mechanical strength, effectively preventing bacterial penetration and accelerating wound closure in full-thickness skin defects.

5 ADVANTAGES AND DISADVANTAGES

The ideal system for skin regeneration should possess features that expedite and enhance the healing process, as shown in *Figure 3*. Fundamentally, these characteristics are crucial to promote a faster recovery with improved outcomes while minimizing complications (Gounden et al., 2024). Considering these essential qualities for the healing process, the utility of hydrogel systems for skin regeneration is meticulously analyzed to balance their advantages against any limitations.

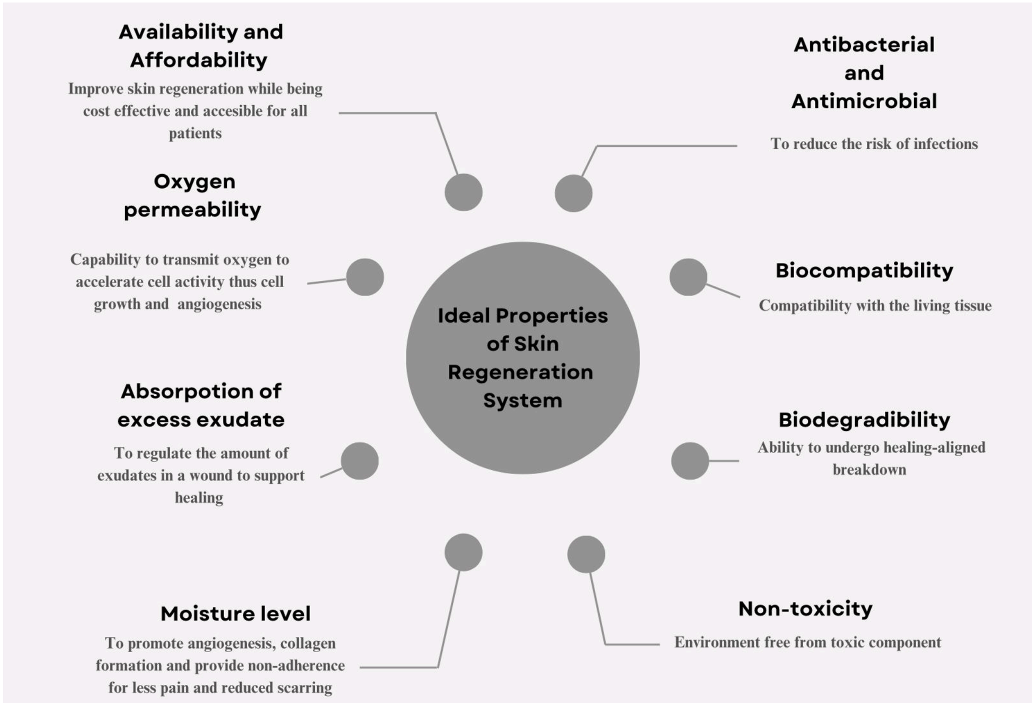

Figure 3: Properties required for skin regeneration system (Gounden, 2024).

5.1 Hydrogel Behavior

Hydrogels have a high advantage in wound dressing, as their hydrophilic nature allows them to retain excess amounts of water while maintaining their form. Hydrogels are also known for their biocompatibility and biodegradability, which make them useful for skin regeneration treatments. Their elasticity is nearly identical to normal unaffected skin, allowing them to integrate with the body's natural structures. Hydrogels are designed to absorb exudates without becoming oversaturated, maintaining a moist environment necessary for wound healing. Their porous structure is a powerful barrier against bacterial infections while facilitating essential gas exchange such as oxygen. This encourages critical cellular processes like migration and proliferation that are crucial for skin tissue regeneration. Hydrogels also support the self-digestion of dead tissue by preserving wound hydration, thus presenting an ideal environment for tissue regeneration (Arabpour et al., 2024).

Even though hydrogels have several advantages in skin treatment, they also have some limitations. For instance, they have low absorption capacity, which means they need to be reapplied frequently. When used on extremely exudative wounds, their ability to absorb wound fluids can be quickly overwhelmed, leading to the need for regular dressing changes. This frequent replacement can strain healthcare resources and be uncomfortable for patients. Additionally, hydrogels can be very elastic, which gives them low mechanical strength. This makes them less durable and more likely to break down under stress or deformation. As a result, their use is limited in areas prone to mechanical forces or movement, which could compromise the protection and integrity of the wound dressing (Gounden et al., 2024).

5.2 Comparison of Natural & Synthetic Hydrogels

Natural hydrogel polymers are known for their biocompatibility, biodegradability, and biological activity. These attributes make them more favorable for skin regeneration as they can closely mimic the natural extracellular matrix to support cell adhesion, proliferation, and differentiation. However, natural hydrogels often have lower mechanical strength, limiting their durability and functionality. To address these limitations, natural hydrogels are often chemically modified to enhance their mechanical properties and stability. Synthetic polymers are engineered to address the limitations of natural polymers, but modifying the natural polymers' initial properties can introduce additional constraints (Arabpour et al., 2024).

Synthetic hydrogel polymers provide more precise control over their physical and chemical properties, including molecular weight, mechanical strength, and degradation rates. This control allows for the design of hydrogels with specific characteristics suitable for skin regeneration. Synthetic hydrogels can possess superior mechanical strength compared to their natural counterparts and their degradation rate can be finely tuned. However, the synthesis of these polymers can introduce potential limitations like the presence of residual monomers or cross-linkers, which could potentially lead to biological toxicity or immune reactions when implanted. Synthetic hydrogels cannot yet emulate the structure of natural polymers, so there is a need to incorporate functional elements to enhance their biocompatibility and performance in biological environments (Arabpour et al., 2024).

6 COMMERCIAL VIABILITY

The interdisciplinary field of research encapsulated by tissue engineering encompasses the array of products utilized in the treatment of skin wounds, as shown in *Figure 4*. Within the spectrum of wound care products available to consumers, products are commonly classified as either conventional or surgical wound care products. Conventional products include foam dressings, hydrocolloids, alginates, and hydrogels. Surgical products encompass concepts such as infection management, discharge management, active wound care, and medical equipment.

The healthcare industry has witnessed a rapid surge in demand for wound care treatments in response to an increase in the number of chronic diseases worldwide. The primary consumer market for hydrogel polymers comprises mainly hospitals and community health care centers, catering to surgical wound and burn patients who receive specialized treatment in hospital facilities. In 2019, hospitals were ranked as the predominant segment of the wound care market in North America, following a rise in advanced surgical procedures at the time (Arabour et al., 2024). The global market for polymer materials was valued at $533.6 billion in the year 2019, and is estimated to reach $838.5 billion by 2030 (Callister et al., 2010). This growing field of research aims to reduce costs of biomaterials in future advancements.

Figure 4: Hydrogel Wound Dressing Application.

7 SELECTION REASONING

Hybrid hydrogels for skin regeneration represent an innovative approach in the field of tissue engineering, formed by combining the advantages of natural and synthetic polymers. These hydrogels are engineered to provide a bioactive scaffold that mimics the natural extracellular matrix (ECM). Thereby, promoting cell attachment, proliferation, and differentiation (Arabour et al., 2024).

Collagen, constituting approximately 30% of all body proteins, serves as the primary protein in the ECM of mammalian tissues. In recent years, extracted and purified collagen has gained popularity in tissue engineering due to its excellent biocompatibility. However, as noted by Rafat et al. (2008), despite its resilience in vivo, extracted collagen undergoes rapid degradation and loses elasticity due to the disruption of natural cross-links during the isolation and purification processes.

Alternatively, the animal study performed by Chen et al. (2018) affirmed the effectiveness and ease of using PEG-based hydrogels for wound closure and bleeding control, showcasing their superior performance compared to commercial products. Furthermore, results demonstrated that the PEG polymer had strong tissue adhesion, controlled degradation, excellent biocompatibility, and elastic mechanical properties, highlighting the promise of the PEG-based hydrogel for skin regeneration.

Collagen and PEG together are a powerful combination for skin tissue engineering. PEG offers the engineering flexibility to create hydrogels with specific properties, while collagen offers a naturally conducive environment for cell growth and tissue regeneration. Together, they can create composite materials that combine their properties. The focused distribution capabilities of synthetic polymers integrated with the biocompatibility and healing qualities of natural polymers make them an excellent pair for advancing the field of skin regeneration.

8 SUMMARY

This review discusses the potential of hydrogel polymers for skin regeneration. It highlights the skin's susceptibility to damage and the limitations of traditional treatments used for wound healing. Hydrogels can mimic the properties of the extracellular matrix and natural tissue. They are also biocompatible and biodegradable. Critical parameters for hydrogel application in skin regeneration are investigated, which include biocompatibility, the healing process, swelling ratio, and biodegradability. The most proficient material is selected to ensure safety and efficacy in use for wound healing. The natural polymers, valued for their biocompatibility, are compared with synthetic polymers, which are known for their mechanical strength and customizable properties. While hydrogels have many advantages, there remain limitations, such as low absorption capacity and mechanical strength. Hybrid hydrogels that combine the assets of natural and synthetic polymers offer effective treatment by simulation of the extracellular matrix and support of cell growth for tissue repair. The collaboration of collagen and PEG combines the properties of both natural and synthetic hydrogels. The commercial viability of hydrogel polymers is driven by the increasing demand for advanced wound care. Hospitals and healthcare centers are expected as the primary consumers of these products, and the market for hydrogel polymers is projected to expand significantly.

9 CONCLUSIONS

1. Hydrogel polymers for skin regeneration present a promising avenue for advancing tissue engineering and regenerative medicine. When designing hydrogel materials suitable for clinical applications, it is crucial to evaluate parameters such as biocompatibility, skin healing process facilitation, swelling ratio, and biodegradability.
2. The combination of collagen and polyethylene glycol (PEG) as a hybrid hydrogel is optimal due to PEG’s flexibility to create hydrogels with specific properties, and

collagen’s ability to provide a naturally conducive environment for cell growth and tissue regeneration.

3. Biocompatibility is identified as a critical factor for effective hydrogels, emphasizing the importance of extensive testing to ensure the safety and efficacy of hydrogel polymers in biomedical applications. Additionally, tailoring hydrogel properties through appropriate polymer combinations and synthesis methods further enhances their suitability for skin regeneration.
4. In the skin healing process, hydrogel materials play a pivotal role in facilitating hemostasis, promoting tissue regeneration, and maintaining an optimal moist environment. This highlights their potential applications and effectiveness in wound care.
5. Synthetic hydrogel polymers offer precise control over their physical and chemical properties, making them ideal candidates for skin regeneration applications. However, the integration of natural polymers with synthetic polymers presents a promising approach to leveraging the advantages of both material types for enhanced therapeutic outcomes.
6. The commercial viability of hydrogel polymers in wound care is evident, with a growing demand for advanced wound care treatments worldwide. Further research and development efforts are warranted to optimize hydrogel formulations, improve manufacturing processes, and ensure scalability for widespread clinical adoption.

10 FUTURE RECOMMENDATIONS

When investigating the future of hydrogels regarding their treatment of skin injuries, future investigations into enhancing their properties while reducing costs, with a primary emphasis on addressing chronic wounds, would be of great benefit. To achieve this goal, further research must be conducted into the development and discovery of new natural, synthetic, and even hybrid hydrogels that possess advanced mechanical features capable of withstanding the dynamic nature of wound environments. The initial step towards this objective could involve modifying the molecular design of existing polymer structures within hydrogels and evaluating their performance based on the parameters outlined in this research paper (Zohreh Arabpour et al., 2024).

Additionally, the development of smart hydrogels is pursued to enable dynamic responses to changes in wound environments, adapting properties based on specific healing stages. Enhanced drug delivery capabilities, including controlled release of therapeutic agents, are sought after to promote healing and prevent infections effectively. Furthermore, the design of hydrogels with suitable degradation profiles addresses concerns regarding durability and potential removal methods. Lastly, the personalization and tailoring of hydrogel formulations to individual patient needs is an aspect of the application of hydrogels that needs to be studied. Considering factors such as skin type and wound characteristics is essential to maximize effectiveness and minimize side effects (Hama et al., 2023).

In conclusion, future advancements in hydrogel technology hold significant potential for revolutionizing the treatment of skin injuries. This involves developing advanced materials with improved mechanical properties, smart functionalities, and tailored drug delivery capabilities. The ultimate goal is to optimize healing outcomes while minimizing costs and side effects.

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