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Review

An Overview on Gelatin-Based Biofilm for Chronic Diabetic Wound Healing

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Abstract: Millions of people worldwide suffer from diabetes, and many develop chronic wounds like diabetic foot ulcers that struggle to heal. Traditional wound dressings often fall short. They cannot effectively control infections or create the ideal conditions for healing. This is where gelatin-based biofilms come in. Made from collagen, gelatin is naturally compatible with the human body and can be tailored to meet the specific needs of diabetic wounds. This overview explores how gelatin-based biofilms are revolutionising wound care. Recent advances in gelatin-based biomaterials demonstrate significant promise for improving wound healing outcomes. Studies show these materials achieve 50–100% wound closure within 12–18 days, with gelatin-QAS/PCL/bioglass nanofibers and GelMA/graphene oxide composites showing remarkably rapid healing. The materials exhibit strong antibacterial properties against common pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. coli*, while maintaining excellent cell viability above 80%. Mechanical testing reveals favourable properties, including compressive strength of up to 412 kPa and porous structures that are ideal for tissue regeneration. Key findings include enhanced granulation tissue formation (reaching a thickness of 1.6 mm), reduced wound areas (remaining at just 4.9% after treatment), and promotion of neurovascular regeneration. The evidence suggests gelatin-based biomaterials are ready for more extensive clinical validation, with future research needed to optimise degradation rates and transition these promising results into clinical practice. They are paving the way for real-world solutions that could transform the lives of people with diabetes. By combining nature's building blocks with cutting-edge science, these advanced dressings offer hope for faster, safer, and more effective wound healing.

Keywords: Gelatin; Biofilm; Chronic Diabetic; Wound Healing; Wound Care; Wound Dressing

1. Introduction

Nearly 422 million people worldwide are affected by diabetes, with most of them living in low- and middle-income countries [1]. In 2014, the global prevalence of diabetes among adults aged 18 years and older was 8.5%. Diabetes was directly responsible for 1.5 million deaths in 2019, with 48% of these deaths occurring before the age of 70. Additionally, diabetes contributed to another 460,000 deaths from kidney disease and was linked to approximately 20% of cardiovascular deaths due to elevated blood glucose levels. The report also highlights a 3% increase in age-standardised mortality rates attributed to diabetes for the past two decades.

Diabetes is a chronic metabolic disease characterised by elevated blood glucose levels resulting from either insufficient insulin production by the pancreas or the body's inability to utilise the insulin produced effectively. This condition can lead to severe complications over time, including damage to the heart, blood vessels, eyes, kidneys,

and nerves. The two most common types of diabetes are Type 1 and Type 2 [2]. Type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes, is usually diagnosed in childhood or adolescence and is characterised by the pancreas producing little or no insulin [3]. In contrast, Type 2 diabetes, the most common form, typically occurs in adults and arises when the body becomes resistant to insulin or does not produce enough insulin [4].

Many individuals with diabetes, particularly those with Type 2 diabetes in the early stages, may not experience any symptoms. Without proper treatment, uncontrolled diabetes can lead to various complications, such as peripheral arterial disease, neuropathy, limited joint mobility, abnormal foot pressures, minor trauma, and foot deformities. Diabetic patients have a 15–25% risk of developing chronic wounds, including foot, venous, and pressure ulcers. Chronic diabetic foot ulcers (DFUs) are non-healing wounds that prolong and complicate the healing process [5]. Due to its susceptibility to infection and chronic nature, DFUs have a significant public health impact on treatment and recovery. Most chronic DFUs lead to leg amputation or permanent removal of infected legs, especially those with diabetes mellitus. Besides that, this disease also causes a reduction in the quality of life for the patients as they need constant and careful attention for dressing the wound. Diabetes mellitus patients who received conventional wound dressings for their wounds require a longer treatment time, which will prolong their recovery times. As a result, exposure to other complications also increases. In addition, the growing prevalence of antibiotic-resistant bacteria and improper diet further escalates the wound treatment durations. Due to the chronic nature of DFUs, there is a need for better and innovative wound dressing materials that can effectively address the aforementioned challenges while promoting healing effectiveness, shortening recovery times, reducing or even minimizing the risk of complications, and improving the quality of life for patients with DFUs [6].

Currently, several clinical methods are practiced to treat diabetic wounds, including skin grafting, negative pressure wound therapy, hyperbaric oxygen therapy, debridement, and various wound dressings [7]. The most popular option is wound dressings, as this method can safeguard the wound area and promote cell adhesion, proliferation, and tissue regeneration. To promote ideal and practical wound dressings, the materials should be biocompatible, non-inflammatory, non-toxic, support angiogenesis, and possess inherent antibacterial properties. Furthermore, an excellent moisture retention property will enable the wound to remain hydrated, absorb exudate, and have sufficient strength to ensure the material remains intact during treatment. Generally, there are four stages of wound healing, namely remodelling, proliferation, inflammation, and haemostasis [8]. Therefore, wound dressing materials should consider these stages of the wound healing process. Poor attention to wound treatment may lead to several complications, such as keloidal scarring, hypertrophic scarring, infections, discomfort, and, in chronic cases, can lead to leg amputation and reduced movement ability of the patients. Continuous treatment due to prolonged recovery treatment will directly impact the patient's emotions and cause significant financial hardship.

Presently, several types of polymer-based biofilms have been extensively studied, including gelatin-based, cellulose-based, collagen-based, chitosan-based, and alginate-based biofilms, as well as their mixtures, such as chitosan–gelatin, chitosan–alginate, and collagen–gelatin. Among these, chitosan–gelatin-based biofilms have received considerable attention due to their excellent biocompatibility, biodegradability, and cost-effectiveness, as presented in **Table 1** [9–11]. In contrast, cellulose-based and collagen-based biofilms have attracted relatively limited interest from researchers, primarily due to their structural complexity and lower biocompatibility compared to chitosan–gelatin-based biofilms [12,13], which makes them less suitable for biomedical applications. However, despite the advantages of chitosan–gelatin-based biofilms, they still suffer from poor antibacterial activity and low mechanical strength. As a result, numerous studies have been conducted to address these limitations through various modification strategies [14–16].

Gelatin-based biofilms have sparked interest among researchers and industries to explore the promising potential of this material for use in wound dressing applications [17]. As gelatin is derived from collagen (renewable resources and environmentally friendly materials), it possesses unique properties such as being biocompatible, biodegradable, non-toxic, cost-effective materials, and easy to fabricate without neglecting the functional properties of this material as wound dressing materials. These characterisations of gelatin-based biofilms make them a convincing option for various applications. Other than that, studies also reported that gelatin-based biofilms exhibit other characteristics that are suitable to addressing irregular wound surfaces, such as high-water content to keep the wound hydrated, permeability to oxygen and moisture, which is pivotal in ensuring the wound area recovery and promotes cell adhesion as well as proliferation for wound healing [18–21]. Since gelatin-based biofilms are easy to process and modify to further enhance their wound dressing functionality and therapeutic ability by incor-

porating bioactive agents, such as antibacterial properties to effectively combat a wide range of pathogens in the wound area, growth factor agents, and extracellular matrix components, which boost tissue regeneration potential. The preclinical studies show that these bioactive-loaded gelatin-based biofilms have promising results, especially in promoting wound healing, reducing inflammation, and preventing pathogens colonisation [22–24]. Despite the preferable properties and characteristics of gelatin-based biofilms, there are other disadvantages of this material that require special attention to make them clinically viable, such as poor mechanical strength [25], poor stability [26], and potential immunogenicity [27]. Moreover, rigorous clinical tests are required to assess the efficacy and safety of this material as a DFU wound treatment. These tests are necessary to establish and validate its therapeutic effects prior to clinical viability, either through *in vitro* or *ex vivo* tests.

Table 1. Comparison between different biofilm-based approaches.

Type	Advantages	Disadvantages	Ref.
Gelatin-based	• Biocompatible. • Biodegradable. • Promoting cell adhesion and proliferation. • Supports angiogenesis and has haemostatic properties. • Cost-effective. • Easy to process into films or scaffolds.	• Poor mechanical strength. • Poor stability. • Limited antibacterial properties.	[28,29]
Cellulose-Based	• Excellent mechanical properties and structural integrity. • Promotes tissue regeneration. • Biodegradable and derived from renewable resources. • Can support inter-kingdom biofilms, enhancing treatment efficacy.	• Complex structure can hinder penetration of topical treatments. • Potential for high water absorption, which may lead to maceration of surrounding tissue.	[4,30,31]
Collagen-Based	• Naturally occurring protein that promotes cell migration and tissue repair. • Supports angiogenesis and has inherent antibacterial properties. • Mimics the extracellular matrix that enhances biocompatibility.	• Higher cost compared to synthetic alternatives. • May require cross-linking to improve mechanical properties (complicate processing).	[32–34]
Chitosan-Based	• Antimicrobial properties effective against a wide range of pathogens. • Biodegradable and promotes wound healing through moisture retention. • Supports cell adhesion and proliferation. • Promotes tissue regeneration.	• Limited mechanical strength and flexibility. • Cationic nature may cause irritation.	[35–37]
Alginate-Based	• Excellent moisture-retentive properties, creating a favourable environment for healing. • Biocompatible. • Biodegradable. • Forms hydrogels that can encapsulate growth factors and drugs for localised delivery.	• Hydrophilic - can be less effective in dry wounds. • Limited mechanical strength. • In certain conditions, the gel stability can be affected due to the potential for ion exchange with calcium.	[38]

Hence, this article provides an overview of gelatin-based biofilms, particularly their role, properties, and future research that can further enhance their functionality as a method for chronic DFUs wound healing. This overview aims to provide comprehensive and insightful information to guide future research and development in this area from the perspective of gelatin-based biofilm preparation, fabrication, and characterisation tests.

2. Gelatin-Based Biofilm

2.1. Role

Biofilms are made from biopolymers such as polylactic acid (PLA), polyhydroxyalkanoates (PHA), poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), starch, cellulose, proteins, gluten, and polyether ether ketone (PEEK). Studies have reported that these biopolymers possess excellent film-forming capacity and can be used in various applications, including food packaging, pragmatic industry, implants, food industries, drug delivery, food

coatings, wound therapy, and other industrial uses [39–41].

Gelatin is a versatile protein mixture made by breaking down collagen, a structural protein found in animal tissues like bones, tendons, and skin [42, 43]. While it primarily comes from collagen types I and III, traces of other collagen types may also be present [44–46]. There are two main types of gelatin, namely Type A and Type B, both produced through partial collagen hydrolysis [47]. Type A gelatin is made using an acid-based process and is typically sourced from pigs (porcine), fish (piscine), or birds (avian). In contrast, Type B gelatin is derived from cattle (bovine) using an alkaline treatment [48]. These two types differ in their chemical makeup. Type B has about 65% more aspartic and glutamic acids than Type A, giving it more negative charges and a lower isoelectric point (pH 5 vs. pH 8.5 for Type A) [49]. Because of these properties, porcine Type A and bovine Type B are widely used in biomedical research. Interestingly, fish-derived gelatin behaves differently from mammalian gelatin. It has fewer amino acids (molecules that contain both amine and carboxyl functional groups). But more serine and threonine. This results in weaker gel strength and a lower melting point, making it less firm than gelatin from land animals [50].

Gelatin-based biofilms have become a promising alternative in wound dressings due to their favourable characteristics, including biocompatibility, biodegradability, non-toxicity, and non-inflammation, as well as the capacity for functional modification or engineering, as this material can act as a crosslinking agent [51]. Gelatin is made through the irreversible denaturation of collagen proteins in animal bones, cartilage, and skin. This leads to gelatin-based biofilms that are capable of promoting cell adhesion and proliferation, supporting angiogenesis, and exhibiting haemostatic properties similar to those of collagen-based biofilms. As a result, they serve as an alternative material to replace collagen in biomaterial applications. Therefore, this material is particularly valuable for further advancements in wound dressings with enhanced therapeutic effects. Several studies have reported optimising the properties of gelatin-based systems to make them multifunctional materials that not only protect wounds but also actively promote wound healing effects [52–54]. As gelatin-based biofilms can act as a crosslinking agent, this widens the potential of this material in wound dressings and healing, which is the reason for continuous research being conducted to optimise this material, especially as a wound healing material.

One of the established advancements is the development of novel bilayer hydrogel biofilm. This advancement was made to address multiple wound healing needs simultaneously [55]. This novel bilayer hydrogel biofilm has an upper layer made of crosslinked lactose. This layer provides strong mechanical support, while the lower layer is made of modified chitosan with citric acid. This layer functions with excellent swelling properties and biocompatibility. The study reported on preclinical tests in *ex vivo* wound healing assays and displayed a promising, effective next-generation wound dressing.

Wound dressings can be classified into two main categories: traditional and modern wound dressings [56]. In traditional dressings, this approach primarily serves as a protective barrier to prevent further infection and control bleeding [57]. Meanwhile, modern dressing techniques are often produced from natural or synthetic polymers. These techniques enable the materials to enhance further the functionality of traditional dressings, which can extend beyond the passive protection barrier and actively promote angiogenesis, cell adhesion, and proliferation. This enhancement is a crucial step in the wound healing process [58]. These advanced dressings come in various forms, including foams [59], sponges [60], hydrocolloids [61], alginates [62], and hydrogels [63]. This is where gelatin-based materials play a crucial role, as they possess attractive properties, excellent biocompatibility, and biodegradability. However, to further advance the functionality of gelatin-based materials as therapeutic agents and enhance their mechanical strength, some modifications are required via the incorporation of nanoparticles and bioactive compounds or crosslinking with other polymers [64].

The establishment of gelatin-based materials in wound healing and dressing arises as it is made of collagen proteins present in animal bones, cartilage, and skin. The unique properties of collagen derivatives enable them to mimic the extracellular matrix, thereby enhancing biocompatibility and exhibiting self-assembly, gelling, and functional properties, while also promoting cell migration and tissue repair. Moreover, gelatin exhibits unique physicochemical properties that allow this material to penetrate lipid-free interfaces and preserve its stability under thermal and chemical stress [65]. Crosslinking gelatin with other polymers can address the drawback of gelatin, which is its poor mechanical strength, to achieve high tensile strength fibres. This promotes gelatin-based materials as an ideal scaffold for wound healing by extending their functionality to three phases of tissue regeneration [66]. In the initial injury phase, gelatin-based material acts as a haemostatic agent, capable of absorbing exudates

and creating a protective barrier from further inflammation. In the second phase (proliferation), the extracellular matrix and porous structure facilitate cell migration and tissue repair via new tissue formation. Lastly, in the maturation phase, gelatin-based materials help direct nutritional support to the wounds, minimising scarring and tissue remodelling. Thus, making gelatin-based materials a valuable material in tissue regeneration and healing.

2.2. Recent Findings

Recently, various research reports have been published on new approaches aimed at establishing ideal multifunctional gelatin-based biofilms, either to improve the existing advantageous properties of this material or to provide solutions to address its limitations. Several studies have reported on the enhancement of gelatin-based biofilms using gentle preparation conditions known as the physical crosslinking method. Through this method, gelatin-based biofilms become more appealing for use in biomedical applications, as they do not contain toxic chemicals [67]. For instance, an innovative approach was achieved by adding calcium-crosslinked alginate hydrogels to gelatin, resulting in chitosan-gelatin films formed via a hydrogen bonding method. Although this method can promote the hydrophobic properties of gelatin, it is unable to overcome the limitations of gelatin's mechanical strength and stability.

However, these limitations can be addressed by using chemical crosslinking methods, including gamma or UV light exposure, photoactivated polymer grafting for accurate 3D structure modification, or polymer grafting methods [68]. These chemical-crosslinking methods are capable of creating stronger mechanical strength with more stability than gelatin-based biofilms. However, delicate and special attention is required when formulating using these methods, as it could trigger the presence of toxins from the residual crosslinking agents. Recently, several studies have demonstrated the significant potential synergy effects of physical and chemical crosslinking approaches, primarily for creating ideal and balanced gelatin-based biofilms with good mechanical performance and therapeutic properties for wound treatment. These findings are crucial for gelatin-based biofilms that can withstand mechanical stress and enhance their potential for tissue regeneration [69–71].

Gelatin, derived from natural resources with good biocompatibility properties, can be formed into a hydrogel suitable for advanced wound dressing applications. Researchers continually develop ideas to enhance the properties of bare gelatin, either in terms of strength or biological activity. Through these innovations, significant progress was made in addressing wound treatment challenges, particularly for individuals with diabetes. These recent innovative strategies are summarised in **Table 2**. It demonstrates that creating clinically viable solutions for treating DFU wounds with complex and specialised formulations is possible.

Table 2 shows that diabetic wound healing has seen remarkable progress through the development of innovative gelatin-based biofilms. Researchers have engineered these materials to overcome the unique challenges of chronic wounds by combining the natural biocompatibility of gelatin with cutting-edge modifications. The latest formulations not only protect wounds but also actively promote healing through carefully designed structural and functional enhancements. A key focus has been on combating infections, with many of these advanced dressings demonstrating potent antimicrobial effects against common wound pathogens, such as *Staphylococcus aureus*, MRSA, and *Escherichia coli*. The materials showcase an impressive range of physical properties, from highly absorbent nanofibrous membranes capable of 400% water uptake to robust 3D hydrogels with tensile strengths suitable for various wound types. Several innovative approaches stand out in recent studies. Scientists have created oxygen-generating dressings by combining gelatin-alginate matrices with specialized nanoparticles and antimicrobial peptides.

Table 2. Summary of recent previous findings on gelatin-based materials for wound healing.

Material Composition	Fabrication Method	Result	Ref.
Gelatin/sodium alginate + Pt/peptide	Peptide - Precipitation and dispersed using water bath ultrasonication and then dried in vacuum	• Fragmented and chaotic hydrogel structure. • Honeycomb erosion cavity appeared after 4^{th} days. • Excellent cytocompatibility and antibacterial properties (Methicillin-resistant *S. aureus*). • Wound length reduces: 50% after 18 days. • Granulation tissue thickness increases to 1.6 mm after 18 days of treatment.	[72]

Table 2. *Cont.*

Material Composition	Fabrication Method	Result	Ref.
ILs/GelMA hydrogel + resveratrol	Simple photo-crosslinking	• Porous structure. • Fracture compressive strength: 412 kPa. • Compressive fracture strain: 81.5%. • Excellent cell viability and antibacterial properties (*Pseudomonas aeruginosa* and *E. coli*).	[73]
Gelatin-QAS/PCL/bioglass nanofibers	Electrospun	• Nano wire structure: average diameter 312 nm. • Water absorption: ~ 400%. • Modulus: 76 ± 5.2 MPa. • Ultimate stress: 5.5 ± 0.1 MPa. • Strain: 2.3 ± 0.3%. • Hydrophilic surface: 135°. • Excellent antibacterial properties (*S. aureus* and *E. coli*). • Wound healing rate: 100% after 14 days.	[74]
Gelatin/fucoidan + silver nanoparticles	Simple polymerization	• Sphere-like nanoparticles: 2–10 nm (diameter). • Excellent antibacterial properties (*S. aureus*, Methicillin-resistant *S. aureus* and *E. coli*). • Excellent cell viability: > 80% after 24 hours. • Excellent wound healing effect after 48 hours. • Migration ratio: ~ 50% after 36 hours.	[75]
GelMA + bio-ionic liquid (Choline-based)	Photopolymerization	• Superior angiogenic capacity. • Promoting and maintaining vascular networks. • Chronic wounds healing success - after 14 days.	[76]
Gelatin/PVA + piezoelectric crystals	Dual crosslinking + ultrasound-responsive	• Porous structure: ~ 100 um (internal pores). • Low degradation rate: 3% after 14 days. • Promotes neurovascular regeneration. • Excellent migrate rate: ~ 60%. • Excellent cell viability.	[77]
Gelatin/carrageenan + Chlorella	Physical cross-linking	• 3D porous structure. • Highest tensile strength: 12.3 kPa. • Adhesive strength: 9.84 ± 1.23 kPa. • Excellent antibacterial properties (*S. aureus* and *E. coli*). • Wounds completely healed after 14 days.	[78]
Gelatin-MAP hybrid scaffold	Encapsulated hydrogel	• 3D porous structure. • Pores size: ~ 100 nm. • Compressive modulus: ~ 8 kPa. • Wound repair rate: 91.791±3.306%. • Excellent antioxidative properties.	[79]
GelMA + graphene oxide/QEO	Encapsulated hydrogel	• 3D porous structure. • Particle size: < 200 nm. • Excellent antibacterial properties (*S. aureus* and *E. coli*). • Wound healing rate: ~ 90% healed after 12 days.	[80]
GelMA/HAMA + wormwood oil/BP	Physical extrusion technique	• 2D sheet-like morphology. • Average thickness: 5.58 ± 1.72 nm. • Diameter of particle: ~ 400 nm. • Excellent antibacterial properties (*S. aureus* and *E. coli*). • Excellent antioxidative properties. • Wound healing rate: 4.9 ± 2.1% of the wound area remaining after 14 days.	[81]
Gelatin/oxidized cellulose + FeNPs	Precipitation	• Average size of the hydrogel: 143.5 nm. • Zeta potential values: +29.5 mV. • Volume of hydrogel decreased and diminished within 2 days left on the wound. • The swelling index, pH responsiveness, viscous nature, and moisture, best suitable for transdermal drug delivery applications. • Maximum DLE and DEE (1:1 ratio of INS and MET): 93.2% and 98.8% and 90.2% and 95.1%. • Good antibacterial activity that prevents wound beds from pathogenic attack. • No skin irritation was observed within 4 hours.	[82]

In addition, a group of scientists has developed light-activated gelatin methacryloyl (GelMA) hydrogels infused with enhanced therapeutic functionality thanks to a compound called resveratrol. This compound exhibits both structural integrity and biological properties to address the mechanical structural limitations of gelatin. It is noteworthy to emphasize that incorporation between a living hydrogel system and microorganisms called "chlorella" is capable of producing oxygen at the wound site continuously.

With a clinical trial showing positive outcomes, many tailored and engineered advanced dressing technologies can complete wound closure within two weeks while maintaining excellent tissue compatibility. This synergistic effect enables these materials to address multiple aspects of wound healing simultaneously. This is possible by combining the infection control agents, antioxidant protector, blood vessel regeneration, and collagen remodelling into a single dressing approach. This truly highlights the invaluable versatility and uniqueness of gelatin as a basis for wound dressing. Through a delicate and systematic blend of physical and chemical crosslink modification techniques, a new generation of innovative wound dressing technology is born. This new generation wound dressing technology successfully meets the complex requirements of DFU wound management. This was achieved mainly due to the meticulous and delicate tailoring of their optimised design, which offered both the required mechanical strength for wound protection and biological activity for the therapeutic process.

This thrilling evolution in gelatin-based technologies represents a pivotal step toward DFU wound care, offering the anticipation of improved results and a better quality of life for patients with DFU who struggle with acute or chronic wounds. The continuous efforts to transform this promising material into even more effective alternatives are forthcoming.

2.2.1. Gelatin and Crosslinking Agents

Gelatin is derived from natural resources found in animal bones, skin, and cartilage, making it a natural biopolymer. This makes gelatin a valuable material for wound dressings, as it possesses an inherent extracellular matrix that shares a very similar molecular structure and function to collagen, promoting biocompatibility and being beneficial for wounds that require special attention, especially those that are away from pathogens and inflammation. The lacking part of this material is only its mechanical and stability properties, which can be overcome by crosslinking it with other agents, as gelatin is among the best materials to be incorporated with other materials. This can be seen as gelation has been widely used in various applications, including food, cosmetics, and pharmaceuticals. Gelatin derives from natural resources and does not induce toxicity, antigenicity, or other adverse effects that could harm human cells. Nevertheless, toxicity can occur when it is improperly crosslinked with other reagents, as this material requires a chemical crosslinking process with another reagent to enhance its poor mechanical and stability properties, which are crucial in fulfilling wound care demands.

Several studies have proven the value of gelatin as a wound-healing material, with various research efforts focused on optimizing its properties and biological activities. For instance, a study successfully engineered a bilayer hydrogel system with lactose-mediated crosslinking, which enhances mechanical resistance [83]. This innovative approach creates a durable upper layer that retains the structural integrity of gelatin and protects the wound area. Meanwhile, another study demonstrates an effective modification strategy by crosslinking gelatin with citric acid, primarily to generate porous gelatin matrices with enhanced swelling capacity, which is crucial for facilitating wound bed formation, cell migration, and tissue regeneration [84]. This strategy exhibits optimal moisture retention, which is preferable in the wound healing process without maceration of surrounding tissue.

Furthermore, the enhancement of gelatin's functionality is possible due to the emergence of advanced composite systems. Recent studies have reported the incorporation of dialdehyde cellulose nanocrystals into chitosan-gelatin films, resulting in improved oxygen permeability and anti-inflammatory properties [85]. Through this, several critical variables for wound healing, such as modulation of gas exchange and control of inflammation, are solved simultaneously.

These findings further validate that the delicate and proper formulation of crosslinked gelatin with reagents produces gelatin with excellent biocompatibility, mechanical strength, and biological activity. The flexibility and tunable properties of gelatin make it easy to modify by incorporating specific reagents into gelatin formulations, thereby achieving the desired mechanical strength and its therapeutic potential. Above all, these advancements in modifying gelatin by incorporating it with other materials demonstrate the possibility of developing optimum biocompatible gelatin-based biofilms for DFU wound management without the presence of cytotoxicity and reduced

inflammation, as well as promoting tissue regeneration and repair.

Therefore, continuous efforts are needed to improve further the properties and biological performance of gelatin-based biofilms, specifically for wound dressing and healing, as these materials demonstrate efficacy in addressing the complex and varied conditions of wounds.

2.2.2. Incorporation of Additional Materials

The performance of both mechanical and therapeutic effects of gelatin-based biofilms can be remarkably enhanced by the delicate and systematic incorporation of various functional materials tailored to achieve the desired targeted outcomes. For instance, chitosan has been widely used as a composite material due to its good wound-healing properties and ability to enhance mechanical strength [83–85]. Recent advancements have demonstrated that the improved structural integrity and water vapour transmission properties of films can be achieved by incorporating tannic acid and bacterial nanocellulose into gelatin [86]. Meanwhile, antimicrobial functionality in wound healing has been successfully reported by integrating silver nanoparticles [87].

Recent studies have demonstrated an improvement in the therapeutic potential of gelatin-based biofilms. This advancement is made possible by incorporating gelatin-based biofilms with various bioactive compounds that exhibit good antimicrobial properties, reduce inflammation, promote cell adhesion, enhance moisture retention, facilitate proliferation, and support tissue regeneration. For instance, some bioactive compounds, such as aloe vera and epidermal growth factor, have demonstrated efficacy in shortening the wound healing process by modulating inflammatory responses as well as promoting fibroblast migration. Both bioactive compounds are invaluable for treating chronic wounds [84]. In addition, encapsulated gelatin methacryloyl (GelMA) with thymol has demonstrated synergy in its functionality as an anti-pathogen and anti-biofilm agent. This finding addresses a critical challenge in the treatment of non-healing wounds [88]. Incorporating additional materials into gelatin-based biofilms not only enhances their therapeutic properties but also complements the inherent properties of gelatin, such as biocompatibility, biodegradability, supporting angiogenesis, haemostatic properties, and cell adhesion.

2.3. Characteristics of Gelatin-Based for Wound Healing Application

2.3.1. Antibacterial and Healing Properties

Gelatin-based biofilms have demonstrated considerable potential in wound treatment, especially when combined with other compounds to enhance their mechanical strength and therapeutic properties. Various efforts have been reported to enhance these properties by incorporating gelatin-based biofilms with metallic nanoparticles, bioactive compounds, chemical reagents, and many more. For instance, a study tailored the gelatin-based biofilms by adding silver nanoparticles and copper-doped polydopamine nanoparticles. These metallic nanoparticles significantly contributed to enhancing the antimicrobial activity of gelatin-based biofilms that are commonly present during the wound healing process [87,89]. Enhancing its antimicrobial properties expands the functionality of gelatin-based biofilm towards combating pathogens while retaining its biocompatibility with host tissues.

Additionally, the addition of bioactive compounds contributed to promoting better healing properties by facilitating enhanced cell adhesion and proliferation around the wound area, which is crucial for tissue repair and regeneration. Meanwhile, the addition of bioactive compounds, such as aloe vera and EFG, has demonstrated efficacy in improving keratinocyte and fibroblast migration, which are also crucial components during wound treatment [84]. This effort demonstrates the flexibility of gelatin-based biofilms as a foundation for reinforcing other bioactive compounds in addressing their limitations.

In another study, the introduction of novel synergy effects of gelatin-based wound dressings with antimicrobials as a solution to antimicrobial resistance. Incorporation of gelatin-polyacrylamide films with silver nanoclusters that are paired with ursodeoxycholic acid has proven broad-potential antimicrobial activity against both gram-positive and gram-negative bacteria [90]. This strategy has enhanced the healing properties of gelatin-based biofilms by reducing the tendency towards bacterial resistance.

Similarly, enriched gelatin hydrogels with dual components, known as silver nanoparticles and lactoferrin, have demonstrated synergistic antimicrobial effects [91]. The study reported that embedding dual-component systems into gelatin hydrogels resulted in significantly better penetration and bacterial clearance compared to single-component system formulations. The synergistic antimicrobial effects were enhanced thanks to lactoferrin, which

adds another layer of protection against biological activity by leveraging the natural immune components. This layer complements the inherent antimicrobial properties of bio-nanosilver.

Overall, several efforts were made, primarily to enhance the antibacterial and healing properties of gelatin-based biofilms. These advancements were achieved by manipulating the flexibility of gelatin-based biofilms, which serve as reinforcement for other compounds. Advanced formulations can produce synergistic effects between multifunctional wound dressings, providing enriched antimicrobial control and supporting tissue repair requirements. The flexibility of gelatin-based biofilms as matrices for antimicrobial agents, as well as the bioactive components, promotes this method as a potential solution to current limitations in wound treatment.

2.3.2. Structural Characteristics

The therapeutic efficacy of gelatin-based biofilms in the wound healing process is significantly influenced by their physical, mechanical, and chemical properties. Current research often focuses more on the fabrication of bilayer structure biofilms, which offer distinct functional zones within a single substrate. This structure typically incorporates a dense and mechanically robust upper layer, which serves as a protective barrier against contamination, such as bacteria and viruses. On the other hand, the lower layer of biofilms remains a porous structure, facilitating wound healing interactions and thereby reducing treatment time for patients [83,89].

Among the material properties of biofilms, porosity and swelling are the most crucial properties for enhancing the efficacy of the wound-healing process. To maintain wound hydration, a three-dimensional network is strongly recommended to strike a balance between structural integrity and fluid absorption capacity. Ultimately, this microenvironment promotes the deposition of the extracellular matrix and cellular proliferation. It is noteworthy to mention that a recent study has successfully developed a gelatin polyacrylamide biofilm composite, which exhibits excellent water absorption kinetics (more than 400% weight gain). Interestingly, this biofilm composite also possesses autonomous self-healing capabilities, which significantly prolong functional integrity, enhance wound protection, and exhibit biomimicry and responsive behaviour [90]. This biofilm composite addresses two persistent challenges in wound healing treatment: maintaining a moist wound and ensuring durability during treatment.

After reviewing numerous previous studies, it can be concluded that the optimal characteristics of gelatin-based biofilm for enhancing biological function are as follows: pore size distribution (50–200 μm), swelling ratios (300–500%), and tensile strength (0.5–1.2 MPa). These characteristics have been proven effective in supporting gas exchange through interconnected porosity, managing exudate through regulated fluid absorption, and promoting cellular infiltration.

2.3.3. Mechanical and Physical Properties

To ensure that gelatin-based biofilms are suitable for use in wound healing applications, they must possess good mechanical and physical properties. Previous studies on producing films with crosslinked gelatin, citric acid, and agar have reported tensile strengths ranging from 1.5 to 2.5 MPa. These findings almost mimic the properties of human skin [84]. These crosslinked formulations additionally exhibit controlled degradation kinetics, maintaining structural integrity for extended periods while gradually releasing therapeutic agents.

Material reinforcement strategies have been successfully employed to enhance the mechanical characteristics of gelatin composites. The incorporation of bacterial nanocellulose and tannic acid into chitosan-gelatin matrices has yielded notable improvements in both mechanical strength and functional properties [86]. The resulting composites exhibit increased tensile modulus (150–200%), enhanced water vapour transmission rates (2000–2500 $g/m^2/day$), and maintain flexibility (elongation at break > 50%).

These engineered properties address the dual requirements of wound dressings, which must have sufficient mechanical support to withstand physiological stresses while maintaining appropriate permeability to maintain an optimal wound moisture balance. The structural modifications achieved through these composite approaches have expanded the potential applications of gelatin-based films to include both high-exudate wound management and areas subject to frequent movement.

The relationship between material composition and mechanical performance has been quantitatively characterized through standardized testing protocols, including dynamic mechanical analysis and tensile testing. These studies confirm that the reinforcement mechanisms operate through both the physical entanglement of polymer networks and chemical crosslinking interactions. Current research continues to optimize these formulations to

achieve site-specific mechanical properties while preserving the essential biocompatibility of gelatin-based systems.

2.3.4. Biocompatibility and Cytotoxicity

The biocompatibility of gelatin-based biofilms represents a fundamental requirement for their successful application in wound care. Extensive research has demonstrated that these biomaterials typically exhibit excellent cellular compatibility, showing minimal cytotoxic effects on human cell lines. This favourable biological response stems from gelatin's natural derivation from collagen, a significant component of the extracellular matrix, which promotes cellular recognition and integration.

Recent studies have provided empirical evidence supporting the biocompatibility of modified gelatin formulations. For example, gelatin hydrogels incorporating lactoferrin-functionalized bio-nanosilver maintained regular cellular metabolic activity and proliferation rates, with cell viability consistently exceeding 90% in standardized cytotoxicity assays [91]. These findings confirm that the antimicrobial functionality of such composites can be achieved without compromising their biological safety profile.

Advanced crosslinking strategies have further enhanced the biocompatibility of gelatin-based systems. Chitosan-gelatin films crosslinked with dialdehyde cellulose nanocrystals demonstrated improved protein interactions, particularly with human serum albumin [85]. This modification resulted in an enhanced protein adsorption capacity (up to 35–40%), reduced expression of inflammatory markers, and improved cellular attachment and spreading.

3. Future Perspectives

Gelatin-based biomaterials have emerged as a promising platform for developing hydrogels and scaffolds in various biomedical applications. While these materials have shown considerable potential, a comprehensive analysis of their specific applications in specialised tissues, including hepatic, periodontal, intervertebral disc, and vascular systems, remains notably absent from the literature. This gap in research highlights significant unexplored opportunities for gelatin-based solutions in targeted tissue engineering and regenerative medicine.

The integration of nanobiotechnology has revolutionised chronic wound treatment strategies, with gelatin-based systems playing a pivotal role. Cutting-edge nanotechnologies, particularly electrospinning techniques, have enabled the fabrication of biomimetic scaffolds that precisely replicate native extracellular matrix architecture, provide practical barriers against microbial infection, and enable targeted therapeutic delivery.

These nanoengineered scaffolds have demonstrated exceptional capabilities in promoting cellular adhesion and migration, critical factors in wound healing processes. However, the field faces substantial challenges in establishing comprehensive toxicological profiles and standardised regulatory frameworks for these novel nanomaterials, which are essential for clinical translation.

While antibacterial edible packaging currently dominates research interest, the next decade is expected to witness a paradigm shift toward nanoparticle-reinforced biofilms for advanced wound care. Several challenges, such as optimisation of loading efficiency, minimisation of adverse effects on patients, and precision control of drug release kinetics, should be paid more attention to in future research. All these challenges must be overcome to enhance the biocompatibility of gelatin-based films. Furthermore, it is also expected that future research will foster a deeper understanding of how to improve the low chemical stability and mechanical strength of this polymeric biofilm. It is generally acknowledged that treating DFUs is considered a complex and challenging process. Hence, integrating advanced systems, such as real-time monitoring and responsive therapeutics, is crucial for accelerating the healing process and alleviating the suffering of patients with the disease.

Additional clinical trials and toxicity tests must also be conducted to ensure the biocompatibility of gelatin-based biofilms. Recently, nanomaterials such as carbon nanotubes, halloysite nanotubes, and nanographene have attracted a great deal of attention due to their potential as drug delivery agents encapsulated in polymeric biofilms, thanks to their high surface area, excellent antibacterial properties, biocompatibility, and excellent mechanical strength. Extensive studies should be conducted to explore the optimum formulation of gelatin-based biofilm after mixing with nanomaterials. It is strongly believed that the addition of nanomaterials as drug delivery agents will facilitate the wound healing process and tissue regeneration during the treatment of diabetic foot ulcers.

Last but not least, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) should establish a clear guideline for the design, implementation, and preparation of clinical reports for gelatin-based biofilms. The guidelines from the prestigious authority guide all researchers in evaluating the biocompatibility of gelatin-based biofilms more systematically. The guideline should include advanced dressings, bioengineered tissues, and pharmacological interventions. A clear guideline enables the acceleration of the approval process and the pace of development, as well as reducing the number of unethical clinical trials. All these efforts will play a crucial role in transforming innovative ideas into practical solutions, thereby reducing the pain of patients suffering from DFUs.

Through continuous, hybrid, innovative, and systematically engineered modifications, the gelatin-based biofilm will make a significant contribution to DFUs wound dressing technologies. This could extend the functionality of the current limitations of this material, particularly its mechanical properties, while also further enhancing wound healing and tissue regenerative capabilities. Soon, with proper and guided research, these ideas will yield a promising alternative to gelatin-based biofilms, making it clinically viable as a treatment for DFU patients.

4. Conclusion

Recent advancements in gelatin-based wound dressings demonstrate significant potential for managing chronic diabetic wounds. A notable development involves a bioactive hydrogel system combining fish gelatin (FG) with oxidised hyaluronate (OHy), which has demonstrated remarkable efficacy in preclinical studies. This innovative formulation exhibited multiple therapeutic benefits, including excellent cytocompatibility, suppression of pro-inflammatory cytokines, and reduction of oxidative stress in cellular models. In diabetic mouse models, the hydrogel promoted accelerated wound closure, enhanced re-epithelialisation, and improved collagen organisation. Clinically viable treatment for DFUs can soon be achieved.

Although gelatin-based systems have shown promising potential in the field of DFU wound treatment, further research is needed to explore additional areas and provide a more comprehensive approach to treating DFU wounds. This can be achieved by further improving its therapeutic effect and accelerating the treatment period by exploring alternative strategies, such as omega-3-rich fish skin grafts, as this technique has been reported to be effective in managing acute post-operative DFU wounds. The diversity in treating DFU underscores the complexity of diabetic wound management. This required scientists to constantly find innovative ways to utilise emerging new materials in developing ideal, tailored therapeutic approaches tailored to the various characteristics and needs of patients' wounds.

The uniqueness of gelatin-based biofilms stems from the flexibility and versatility of gelatin, which can be tailored and engineered to achieve certain mechanical, antimicrobial, and other therapeutic functionalities. Through systematically tuneable and modifiable processes, including crosslinking optimisation as well as the incorporation of bioactive materials and enzyme-mediated bonding, these materials can be precisely engineered to meet specific wound healing requirements. According to the current formulation reported by researchers, gelatin-based biofilms can retain the moisture levels of the wound, prevent further inflammation, support the wound bed structure, and protect against pathogen attacks in the wound area.

The continuous exploration and development of gelatin-based wound dressings show promising potential as a clinically viable solution to address DFUs. Future work should focus on tailoring the therapeutic functionalities and further strengthening the mechanical and stability properties of this material by conducting rigorous tests, especially in light of the emergence of new materials and technologies in biomedical fields. This effort should also involve transitioning to other clinical tests by translating preclinical findings through larger-scale human trials.

Although gelatin-based biofilms offer numerous advantages in wound dressing applications, scientists should continually seek to evolve these materials with improved therapeutic effects as other innovative wound care technologies advance. The ultimate goal remains the development of safe, effective, and accessible solutions for managing diabetic wounds. This challenge will likely require a combination of material science innovation, biological understanding, and clinical validation. As research progresses, gelatin-based biomaterials are poised to play an increasingly important role in advanced wound care strategies.

Author Contributions

Conceptualization, M.A.S.; methodology, data curation, M.A.S. and T.C.L.; Both authors contribute to original draft preparation, review and editing; project administration, M.A.S.; funding acquisition, M.A.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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