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A Review on Pullulan-Based Formulations for Wound Healing Therapies

Shreya Nanavare[1] and Dr. Vasanti Suvarna[2]
[1]*Department of Pharmaceutical Chemistry & Quality Assurance, SVKM'S Dr. Bhanuben Nanavati College Of Pharmacy, Mumbai, India*
[2]*Department of Pharmaceutical Chemistry & Quality Assurance, SVKM'S Dr. Bhanuben Nanavati College Of Pharmacy, Mumbai, India*

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ABSTRACT:
In recent years, researchers have focused on biopolymeric drug delivery systems for wound management due to their biocompatibility and safety. Pullulan, a carbohydrate-based biopolymer, has emerged as a valuable component in wound care management. It plays a crucial role in skin regeneration, involving processes like skin proliferation and tissue remodelling. Various pullulan-based drug delivery methods, including nanobiocomposites, hydrogels, and nanofibers, have been developed for pharmaceutical and biomedical applications. This review article summarizes, various pullulan-based drug delivery systems, specifically focusing on their role in accelerating wound healing

KEYWORDS: Pullulan, chronic wounds, drug delivery, wound healing

I. INTRODUCTION

Wounds are a major healthcare concern worldwide, impacting millions of people. The complex wound-healing process makes it challenging to effectively treat wounds. Infections, burns, surgical procedures, trauma, and other factors may result in wounds.Numerous distinct forms of wounds exist. including: Abrasions, Lacerations, Incisions, Ulcers, Burns, and Avulsions. Clinically, wounds can also be divided into acute and chronic categories. Normal wounds generally take 2-3 weeks to heal while the chronic wounds can take up to a month in order to heal, this could be because of inflammation, chronic infections or physical agents. Wounds heal in various ways, according to the extent and type of tissue injury. These include natural healing, secondary wound healing, primary wound closure, and third-layer delayed wound closure.Haemostasis is the initial response to an injury, which involves controlling blood loss at the wound site. Following this, the inflammatory phase begins, lasting from 24 hours to 4-6 days following the injury. (1)During this phase, immune cells at the wound site develop proteolytic enzymes and pro-inflammatory cytokines. These cells also produce reactive oxygen species. The amount of ROS varies with the kind of wound, with higher levels observed in burns and chronic wounds.

The third phase is proliferation, which leads to epithelialization. Alongside the wound, new granulation tissue grows and develops, contributing to the formation of a new extracellular matrix. The final stage of healing is remodelling, which occurs when the matrix structure alters. Type III collagen is replaced by type I collagen, which increases the tensile strength of the new tissue.(2)A non-ionic biopolymer called pullulan is produced by fermenting black yeast, namely Aureobasidium pullulans. The non-toxicity, non-immunogenicity, non-carcinogenicity, and non-mutagenicity of this agent render it advantageous for a range of biological applications. Gene delivery, targeted medication therapy, tissue engineering, and wound healing are a few of these uses. Furthermore, pullulan has been employed in diagnostic applications including vascular microscopy, receptor, lymph node target-specific imaging, and perfusion.(3)Pullulan serves as an excellent wound dressing due to its diverse properties, it has a high absorption capacity, effectively removing excess fluid and exudate from wounds. This promotes a healing environment and helps prevent inflammation. Additionally, pullulan exhibits antibacterial properties, which can aid in preventing bacterial growth on wound surfaces. Due to its biocompatibility, biodegradability, absorbency, and antibacterial characteristics, pullulan holds promising value as polymer for wound dressings(4)Pullulan possesses properties such as adhesion, film generation, and fiber formation,

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which stems from its unique structure. This structure consists of linkages between successive (1→4)-α-d-glucosides that are (1→6)-linked, forming maltotriose. The reactive sites within pullulan's structure allow for various chemical modifications, expanding its potential applications. (3)

Synthesis of pullulan

Pullulan can be synthesized from various carbon sources, including sucrose, glucose, fructose, maltose, mannose, and even agricultural waste through the saccharification of plant fibers into glucose using multiple enzyme systems1. However, when the carbon source concentration exceeds 5%, it can inhibit pullulan production due to the suppressive effect of sugars on enzymes involved in pullulan synthesis. Pullulan yields up to 60.7% at optimal sucrose and nitrogen supply concentrations. (Bender et al., 1959; Sandford, 1979; Duan et al., 2008)Pullulan production can reach up to 60.7% yield when optimized concentrations of sucrose and nitrogen source are used. However, certain carbon sources, such as acetate, d-galactose, glycerol, lactose, and D-mannitol, do not support pullulan production. Ammonium ion (NH4+), a nitrogen source, plays a crucial role in promoting pullulan synthesis by influencing protein production. The depletion of nitrogen signals the start of pullulan formation. A 10:1 carbon/nitrogen ratio is considered optimal for highest pullulan production. Additionally, the concentration of mineral salts in the growth medium impacts pullulan production. An ideal medium for pullulan production includes 75 g/L of sucrose, 3 g/L of yeast extract, and 5 g/L of ammonium sulfate(5)

Properties of Pullulan

Pullulan is a highly soluble polymer with significant intermolecular hydrogen bonding and excellent hydrophilicity. It can form fibres and films, making it an ideal coating material. Pullulan is a translucent polymer often used in packaging. Its thin films are edible, odourless. Pullulan is a white, non-hygroscopic powder that is insoluble in organic solvents but dissolves quickly in both hot and cold water. It possesses anti-inflammatory, antithrombotic, and anticoagulant qualities. Pullulan decomposes at temperatures between 250°C and 280°C and is non-toxic, benign, and thermally stable. Furthermore, it is a biocompatible and biodegradable polymer that breaks down into non-toxic monomers.(6)

Applications of Pullulan

Pullulan is a versatile biopolymer that is used in many different industries. It is utilised as a food coating as well as for gene and drugs delivery. Pullulan has a significant role in the food and pharmaceutical industries. In addition, pullulan is utilized in the packaging of dietary supplements and in pharmaceutical applications for tissue engineering, targeting, surface modification, nanoparticles, cancer treatment, and bio-imaging. Aside from that, it has practical usage in dental care products, paper sizing, and as a non-caloric food component. Pullulan's usefulness is further increased by its ability to gel, bind, and play a part in improved oil recovery. Notably, pullulan films serve as functional components, especially in antibacterial treatments.

Fabrication strategies and characteristics of pullulan-based delivery systems

Pullulan-based delivery methods have been shown to enhance drug absorption via their distinct physicochemical characteristics. Pullulan, can produce nanoparticles that encapsulate medications and protect them from degradation, increase solubility and bioavailability, and provide targeted administration. Pullulan is an affordable biopolymer for drug delivery systems since it is simple to extract from renewable sources. Pullulan-based delivery systems ought to be stable under a range of circumstances, including pH, temperature, and storage duration. Overall, the fabrication strategies and characteristics of pullulan-based delivery systems are critical for developing effective and efficient drug delivery systems that can improve the efficacy and safety of drugs.

Grafts and scaffolds play a crucial role in wound dressing to facilitate healing and tissue regeneration. A graft is a piece of tissue surgically placed on or within a wound to cover and protect it. Common graft types include skin, bone, and cartilage. Grafts serve as a source of cells that promote healing. For instance, skin grafts provide skin cells that can migrate to the wound and aid in healing. Scaffolds are essential components in wound dressings, aiding in healing and tissue regeneration. Acting as a framework, they support the growth of new tissue, thereby promoting wound healing. These scaffold-based dressings are effective for various wound types, including burns, chronic wounds, and surgical wounds. Moreover, they can deliver growth factors and other bioactive molecules, further enhancing the healing process. There are several types of scaffold materials that can be used in wound dressings, such as collagen,

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synthetic,electrospun, and biodegradable scaffolds.Grafts and scaffold have been extensively studied for their potential application in wound healing when incorporated into wound dressing materials.Hydrogels, which mimic the natural extracellular matrix (ECM), offer an advantageous biological scaffold for wound healing

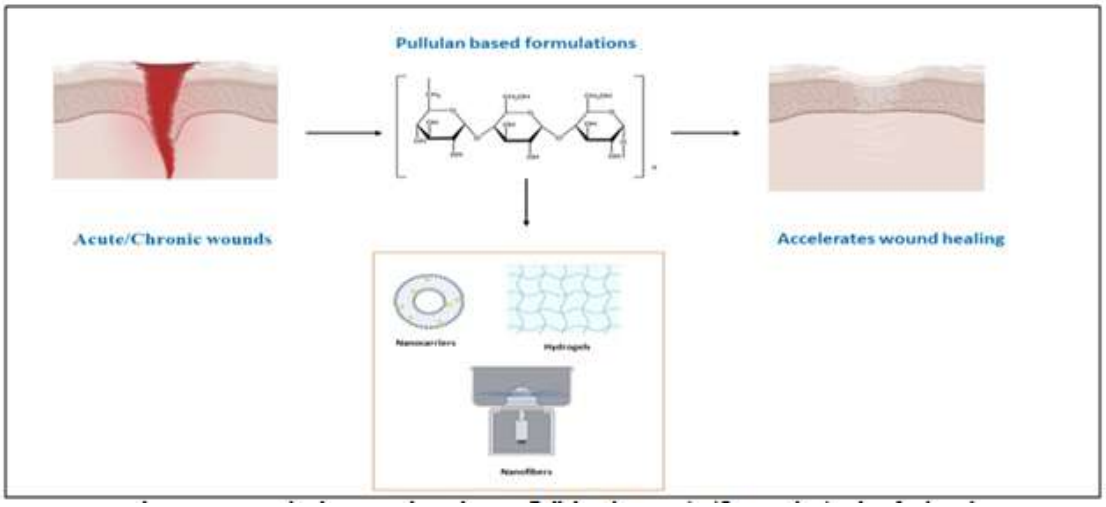

Figure 1: Pullulan Based Formulations in wound healing

Hydrogels

There is limited statistics that overtly compares the compositions of different hydrogel components, even though the majority of research has concentrated on the advantages of hydrogels in accelerating wound healing. In one reseach, the formulation was examined using histopathologic studies of the explanted scar tissues to evaluate variations in collagen structure and alignment as well as tissue response. This research was done on a splinted excisional wound model that mimics human-like wound healing in mice. The results showed that hydrogel dressings can greatly affect healing time and cellular response, resulting in faster wound healing.(7)Oxidized pullulan, a modified polysaccharide with carboxyl groups, is used to crosslink the polymer and fabricate cryogels, Cryogels, a type of hydrogel formed by freezing a polymer-solvent solution followed by lyophilization, have been studied by researchers.These multifunctional cryogels, produced using (hemi)acetal and Schiff base bonds, are suitable for hemostatic wound dressings(8)AWound healing formulation, such asHydrogel-immobilized bacterial cellulose (HBC), combineswith the unique properties of bacterial cellulose (BC). BC's high water-holding capacity keeps wounds moist and supports cell growth. It is biocompatible and serves as a scaffold for cell attachment. Immobilizing BC in a hydrogel matrix protects it and controls drug release. Compared to traditional dressings, HBC promotes faster wound closure and reduces scarring. Additionally, HBC has antimicrobial effects. A bilayer wound dressing with vitamin C and E (VtC and VtE) was formulated using pullulan and BC. The BC/PUL-VtC layer remained intact, and the BC side provided strength, while the PUL side was flexible. VtC&VtE synergistically enhanced collagen synthesis, wound healing, and antioxidant activity. (9)Another Research indicated that compound having anti-inflammatory, antibacterial, and antioxidant qualities may be found in the root bark of Ulmus davidiana var. Japonica (UDJ), a traditional medicinal plant used for wound treatment in Asia. Research comparing pullulan and UDJ root bark suggested that the combination promotes faster wound healing thanUlmus davidiana var. Japonica alone. The mixture lowers inflammation, stimulates the formation of new blood vessels, and supports cell division. For more serious lesions like diabetic ulcers and pressure sores, UD root bark powders work great for creating gel films. When UD gel films with certain particle sizes are compared to pullulan films, the former show better mechanical qualities and superior thermal stability. (10)In recent advances, the healing efficiency of pullulan hydrogel on suture-less wounds in rats were investigated on the Male Wistar rats. Pullulan hydrogel (10%) was tested for wound healing efficiency in suture-less rat wounds. The hydrogel was applied to incisions, and healing rates were compared to control and positive control groups. Pullulan-treated wounds

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showed two-fold improvement in tensile strength (3.63 MPa). Additionally, histological analysis revealed increased fibroblast proliferation and faster epithelialization. The antioxidant properties of pullulan hydrogel contributed to accelerated wound healing.(11). In rat wound experiments, pullulan-treated wounds healed faster than control gel-treated wounds, with increased collagen deposition and angiogenesis. Additionally, pullulan gel enhances the proliferation and differentiation of human epidermal keratinocytes. Biochemical and biophysical investigations confirm its effectiveness in wound treatment. (12). Another type of hydrogel can also be studied for the understanding. Injectable hydrogels, composed of hydrophilic polymers, are biomaterials used for wound healing. They can be injected in liquid form and solidify into a gel at the wound site. These minimally invasive hydrogels conform to the wound, providing a moist environment for cell proliferation and migration, accelerating healing. They can also deliver drugs or growth factors directly to the wound. Examples include hyaluronic acid, alginate, and chitosan hydrogel. An injectable hyaluronic acid-pullulan-curcumin hydrogel has shown promise in promoting wound closure, reepithelialisation, angiogenesis, and collagen deposition in diabetic rat models. (13)In a different study, chitosan-grafted dihydrocaffeic acid (CS-DA) and oxidized pullulan (OP) were used to construct injectable pH-responsive hydrogels with multifunctional qualities. These hydrogels adhere to tissues, respond to pH changes, and are challenging to fabricate. In wound healing, they mimic the natural wound pH, promoting cell growth and faster healing these pH-sensitive hydrogels, loaded with the anti-cancer drug doxorubicin (DOX), demonstrated efficient drug release in vitro. These hydrogels effectively eliminated colon cancer cells and exhibited good antibacterial activity against E. coli and S. aureus when encapsulated with the antibacterialdrug.(14)Fabricating Pullulan with another biopolymer can enhance the wound healing process. Pullulan-collagen hydrogel, resembling the skin's extracellular matrix, promotes cell proliferation and migration. Wounds including diabetic foot ulcers, venous leg ulcers, and pressure ulcers can potentially be safely treated with it. A keratin-pullulan-based hydrogel membrane dressing loaded with cefotaxime sodium (CTX) ensures controlled drug release, preventing wound infection. In vivo results show faster wound closure, angiogenesis, and collagen deposition(15)A newly crosslinked hydrogel membrane demonstrated thermal stability. In vitro tests revealed optimal water vapor transmission rate (WVTR) and oxygen permeability for wound dressing. The membrane released cefepime effectively (88% drug release) due to swelling and surface porosity. It exhibited strong antibacterial activity against Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli. In an excisional rat model, the cefepime-loaded hydrogel promoted rapid wound healing. This promising topical treatment utilizes cefepime nanoparticles for expedited wound recovery(16)Furthermore, Pullulan dialdehyde crosslinked gelatin hydrogels, fabricated by crosslinking pullulan and gelatin using dialdehyde, exhibit improved mechanical strength and stability compared to hydrogels made from either pullulan or gelatin alone. Because they can replicate the extracellular matrix and offer a favourable environment for cell growth and regeneration, these biocompatible and biodegradable hydrogels are used in wound healing, tissue engineering, and drug delivery.Pullulan dialdehyde (PDA) is used as a macromolecular crosslinker to create robust gelatin hydrogels.(17)Pullulan and polydopamine (PDA) fibers are combined in the biocompatible hydrogel reservoir system (PHG-PDA), which is intended for medication delivery. This system offers flexibility and efficient fabrication, utilizing naturally resourced polymers. It hasvarious biomedical applications due to its ability to mimic the extracellular matrix and support cell growth and regeneration(18)

Nanofibers

Nanofibers, composed of biocompatible and biodegradable polymers like poly (lactic acid) (PLA), poly (ethylene oxide) (PEO), and collagen, hold promise for wound healing. Their small size provides a large surface area, promoting cell attachment and migration. Mimicking the body's extracellular matrix, nanofibers accelerate tissue formation. They can also deliver drugs or growth factors directly to wounds, enhancing healing. Techniques like electrospinning and melt blowing produce functionalized fibers of varying sizes and structures. In summary, nanofibers offer great potential for wound healing applications. The production of ultrafine drug-eluting fibers for use in therapeutic wound therapy is a useful application of electrospinning technology. Researchers incorporated an antimicrobial peptide derived from LfcinB into Pullulan nanofibers. The synthesized palindromic peptide, LfcinB (21–25) Pal: RWQWRWQWR, demonstrated significant

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antibacterial activity against E. coli ATCC 25922. Nanofibers were produced by electrospinning a solution of Pullulan or Pullulan-LfcinB (21–25)Pal.AFM and SEM imaging, along with RP-HPLC chromatography, were used to characterize these nanofibers. Peptide incorporation efficiency was 31 percent. The soluble Pullulan-LfcinB (21–25)Pal nanofibers immediately released the peptide and exhibited the same antibacterial activity against the E. coli strain as the free peptide. These findings suggest that Pullulan-LfcinB (21–25) Pal nanofibers hold promise for designing and developing antibacterial wound dressings(19). In further applications, the Researchers developed a bilayer electrospun scaffold using pullulan (PUL) and poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV) biopolymers. The scaffold aimed to address chronic wounds that don't heal naturally. The hydrophilic In addition to permitting the interchange of oxygen and water vapor, the PUL layer act as a barrier against the spread of microorganisms. In the meantime, a regenerative three-dimensional structure was formed by the PHBV layer, which maintained cell survival, proliferation, and migration. Overall, this natural-origin PUL/PHBV bilayer scaffold aids in for wound healing application.(20)Scientists also investigated antibiotic-loaded nanofiber substrates for topical skin delivery. Using Amoxicillin (AMX), a poorly water-soluble model drug, they created Pullulan (Pull) nanofibers that maintained antibacterial efficacy post-electrospinning. This novel approach could improve wound healing and skin treatments. (21)Some other approaches researched by scientist were,electro-wet-spinning to create continuous nonwoven fibers from pullulan. The rheological characteristics of pullulan dispersions were examined through the use of DMSO:water combinations as solvents. To achieve well-formed pullulan fibers, the dispersion concentration needed to be 1.88e2.25 times the entanglement concentration, depending on the DMSO:water ratio. Shear viscosity also played a crucial role. Electrospinnable pullulan dispersions exhibited shear viscosities between 0.06 and 2.2 Pa s at 100 s^-1, regardless of solvent composition. Other factors may influence fiber size as DMSO concentration varies. The resulting pullulan fibers ranged from hundreds of nanometers to tens of microns, with increased DMSO concentration leading to larger fiber and pore sizes in theelectrospun pullulan mat. (22)

Pullulan (PULL), polyvinyl alcohol (PVA), and montmorillonite (MMT) clay combined to electrospin into nonwoven webs to create a novel super-absorbent substance, followed by heat treatment. Characterization revealed the coexistence of PULL, PVA, and MMT, with MMT layers in the composite of nanofibers exfoliated. In both distilled water and saline solution, the heat-treated PULL/PVA/MMT webs containing 5 weight% MMT electrospun nanofibers demonstrated remarkable water absorbency. Under extreme dry conditions, the webs retained significant water content. Heat treatment enhanced crystallinity and stability, while MMT addition improved thermal and mechanical properties. Overall, this composite shows promise for various application(23)

Researchers had a keen interest in investigating in green chemistry approach in electrospinning nanofibers. Green electrospinning minimizes its environmental hazard when compared to traditional methods. Using pea protein isolate (PPI) and the carbohydrate polymer pullulan (PUL), researchers used green electrospinning technology to create and analyze food-grade nanofiber films. The blend ratios influenced solution properties (viscosity, surface tension, and electrical conductivity) and nanofiber morphology. PUL addition reduced viscosity, maintained stable surface tension, and improved nanofiber formation. Rheological evaluation revealed pseudoplastic behavior. The nanofibers exhibited protein-polysaccharide entanglement. Thermal stability improved compared to pure PUL. Additionally, thermal crosslinking enhanced hydrophobic properties (24)Researchers aimed to create a greener dry-electrospinning process for food-grade modified starch by eliminating organic solvents. They investigated the rheological properties and electro spinnability of aqueous dispersions containing octenylsuccinylated (OS) starches with varying molecular weights. While high-Mw OS starches resulted in nanofibers with defects, adding pullulan (PUL) improved fibre morphology. PGU-PUL dispersions produced 147–250 nm long, smooth, bead-free nanofibers. Certain PUL additions were necessary for the electrospinning of 12%, 15%, and 20% aqueous PGU dispersions to be successful. This greenelectrospinning approach holds potential for producing starch-based nanofibers for applications like drug delivery, wound dressing, and tissue engineering.(25)

Films

Despite the development of various wound dressings, many limitations have occured such as rigidity, lack of porosity, weak mechanical strength, and reduced antibacterial effectiveness.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 657-666 www.ijprajournal.com ISSN: 2249-7781

By mixing chitosan/carboxymethyl pullulan polyelectrolyte complex (PEC) loaded with 45S5 bioglass (CCMPBG) and freeze-drying the mixture, researchers have now produced a novel 3D film for wound healing. The chemical composition, microstructure, and surface properties of these films were examined utilizing methods such as FTIR, XRD, EDS, and SEM. Overall, this innovative approach holds potential for addressing wound dressing challenge. (26) A temperature-sensitive topical film containing silver nanoparticles (Ag-NPs) was developed. This film demonstrates antibacterial activity and biocompatibility. It releases silver in a unique profile, comparable to a commercially available silver nano formulation. The antibacterial efficacy of the film was evaluated using S. aureus and E. coli as test subjects. Additionally, it shows potential as a new therapeutic approach for non-healing wounds due to its temperature-responsive properties. (27)

Nanoformulations

Nanoformulations have shown great potential in the field of wound healing and can be used as a potential wound dressing. These formulations are developed using various materials, such as polymers, metals, ceramics, and natural substances, and have unique properties that make them suitable for use in wound dressings. One of the main advantages of using nanoformulations as wound dressings is their ability to improve wound healing by promoting cell growth and tissue regeneration. Nanoformulations can also reduce inflammation and prevent bacterial infections, which are common complications in wound healing. Nanoformulations can be designed to have controlled release properties, which means they can release active ingredients such as growth factors, antibiotics, and anti-inflammatory agents at a controlled rate, thereby promoting faster healing and reducing the risk of infections. Furthermore, they can be designed to have properties such as high porosity, flexibility, and transparency, which make them suitable for different types of wounds and provide better comfort and mobility to patients. Overall, the use of nanoformulations as wound dressings shows great potential in improving wound healing and reducing complications associated with wound healing. Further research is needed to optimize their design and effectiveness, but they have the potential to improve patient outcomes in wound care. One of the key research being done on Bio-functional hydrogel membranes loaded with chitosan nanoparticles formulates hyaluronic acid, pullulan, and polyvinyl alcohol-based hydrogel membranes coated with chitosan-based cefepime nanoparticles for therapeutic use in healing cutaneous wounds. Infrared spectroscopy thermogravimetric analysis, scanning electron microscopy, dynamic light scattering, and proton nuclear magnetic resonance were all used to evaluate the developed membranes. The fabrication of the hydrogel membrane had new crosslinking, which also showed thermal stability. The in vitro investigation shows that the membrane exhibits oxygen permeability and a water vapour transmission rate (WVTR) of between 2000 and 2500 g/m2/day. An optimal dressing would have a permeability between 7 and 14 mg/L. Eighty-eight percent of the medication cefepime that was encapsulated was released due to the swelling capacity and surface porosity. Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli were more effectively inhibited by the cefepime-loaded hydrogel membrane, and the excisional rat model showed a rapid rate of recovery. A promising approach for topically applying the developed hydrogel membrane filled with cefepime nanoparticles has the potential to hasten the wound healing process.(28)

Nanosponges

Due to their unique properties, nanosponges, a novel type of nanomaterial, have drawn interest in the field of wound healing. Particles this small are often made of biocompatible materials such as polymers and have a highly porous structure capable of absorbing a wide range of compounds such as toxins, medicines, and other substances. Nanosponges have been investigated as a possibility for solutions to a number of problems, including wound healing. They can be used on wounds to get rid of toxic substances and dangerous microbes, which promotes healing and helps to prevent infections. Furthermore, therapeutic medications or growth factors can be loaded onto nanosponges and then slowly released into the wound site, resulting in a prolonged and localized distribution of these drugs. Traditional hemostatic medications on the market have significant limitations when it comes to controlling prolonged bleeding. A pullulan oxidation method was used for developing an injectable hemostatic sponge. Pullulan that has been oxidized at room temperature with NaIO4 supplies aldehyde groups for the hydroxyl groups to cross-link with through the acetal reaction, producing a hydrogel that can be lyophilized to yield a porous sponge with highly interconnected

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macro-pores that are 89.4–195.4 m in size. According to studies, the oxidized pullulan (OP) sponge has good hemocompatibility and biocompatibility. The Nanosponge,has a high fluid absorption ratio, outstanding shape memory property, and strong mechanical elasticity since it was produced using a 0.5:1 mass ratio of pullulan to NaIO4 Additionally, in vivo hemostatic data show that the OP@0.5 sponge can achieve fast hemostasis for injury models to the liver volume defect and the rat femoral artery (mean value of 40 s). (mean value of 33.8 s). The commercial gelatin sponges, in comparison, displayed 230 and 100 seconds under identical test conditions, respectively. Further studies demonstrate that the OP@0.5 sponge has effective antibacterial properties against Staphylococcus aureus and Escherichia coli (29)

Nanobiocomposite

A nanobiocomposite of pullulan refers to a material that is composed of pullulan and nanoparticles with dimensions in the nanoscale range. The addition of nanoparticles to pullulan can enhance its mechanical properties, increase its surface area, and improve its biocompatibility. Nanoparticles can also provide additional functionality to the nanobiocomposite, such as drug delivery or imaging capabilities. Nanobiocomposites of pullulan have been prepared by incorporating various types of nanoparticles, including metallic, magnetic, and polymeric nanoparticles. These nanobiocomposites have shown promisingproperties for applications in the biomedical field. For example, pullulan-based nanobiocomposites have been used as drug delivery systems for cancer therapy, wound healing, and bone tissue engineering. By casting pullulan and nanofibrillated cellulose suspensions in water, new bionanocomposite films with enhanced thermal and mechanical properties were developed. Glycerol was used as a plasticizer, and its effect on the materials' characteristics was also assessed. The nanocomposites underwent morphological, thermal, crystallographic, and mechanical characterization. All of the bionanocomposites' mechanical and thermal properties had greatly improved, with increases in strength and heat stability of up to 8000% and 20 C, respectively. When compared to pullulan films without filler, films plasticized with glycerol had higher Young's modulus and tensile strength, respectively. Also, because they were made from renewable resources and using environmentally friendly methods, these unique bionanocomposite might be referred to as sustainable materials. (30)The combination of chitosan, silver nanoparticles, and moxifloxacin creates a material with excellent antimicrobial properties. The chitosan provides a biocompatible and biodegradable matrix, while the silver nanoparticles add antimicrobial activity. The addition of moxifloxacin enhances the antimicrobial activity of the nanobiocomposite by adding a specific antibiotic action against bacteria. Chitosan-pullulan-silver-nanocomposite (CSPN) films loaded with novel moxifloxacin (Mox) showed antibacterial efficacy and were quickly synthesized for in vitro testing. Utilizing an aqueous mixture of both polymers, chitosan and pullulan have been widely employed as stabilisers along with sodium borohydride (NaBH4) as a facilitator for the environmentally benign synthesis of in-situ silver nanoparticles (AgNPs). The nanocomposite films worked as a promising delivery mechanism for the Mox model antibacterial. The films were formed by casting an aqueous composite solution incorporating Mox with standard solvents. The nanocomposites were screened for surface plasmon resonance (SPR) peak and AgNP nanometric size using UV-Vis spectroscopy and a zeta sizer. SEM, EDX, FT-IR, TGA, and DSC investigations were used to assess the surface morphology, elemental composition, functional group interactions, structural/crystallinity changes, and thermal stability of the synthesized nanocomposites. Pharmaceutical researchers looked into the properties of the nanocomposites' mechanical, swelling, water content, and water solubility, as well as their ability to release and permeate drugs and combat microorganisms. The synthesised AgNPs showed SPR peaks at 409–425 nm and had particle sizes less than 165 nm. The composite contains both AgNPs and Mox in a fully integrated and uniform manner. Efficient fabrication of the ternary nanocomposites, that provide sustained drug release and permeability and controlled swelling and increased water solubility. P. aeruginosa and MRSA were effectively combated by the synthetic Mox-loaded CSPN films (clinical strains). Due to pullulan's ability to prolong the release of Mox and silver, the composite's bactericidal activity against P. aeruginosa and MRSA was enhanced. According to research, the synthesised ternary nanocomposites are a promising biomaterial for drug delivery.(31)

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II. CONCLUSION

Pullulan-based drug delivery systems have demonstrated significant promise for use in wound healing projects due to their biocompatibility, biodegradability, and low toxicity. Pullulan can be modified to generate nanoparticles, hydrogels, or films that can encapsulate growth factors, cytokines, or other wound healing agents, providing controlled release and enhanced efficacy. For pullulan-based drug delivery systems for wound healing include developing new methods for optimizing the release rate and duration of wound healing agents, improving the stability and biocompatibility of nanoparticles or hydrogels, and enhancing their targeting abilities. Additionally, pullulan-based wound dressings could be combined with other technologies, such as regenerative medicine or gene therapy, to further enhance their effectiveness. In conclusion, the fabrication of pullulan-based drug delivery systems for wound healing has shown promising results. Pullulan hydrogels have been demonstrated to have excellent biocompatibility, biodegradability, and low toxicity, making them a promising candidate for wound healing applications. The stability and mechanical properties of pullulan hydrogels to better mimic the natural extracellular matrix of skin. Additionally, the incorporation of bioactive molecules, such as growth factors and cytokines, could further enhance the healing process. Overall, pullulan-based drug delivery systems have great potential for wound healing applications, and further research in the fabrication and optimization of these systems is needed to fully realize their benefits.

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