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Review Article

ELECTROSPUN NANOFIBROUS WOUND DRESSINGS: A REVIEW ON CHITOSAN COMPOSITE NANOFIBERS AS POTENTIAL WOUND DRESSINGS

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ABSTRACT

Advancements in topical wound dressings led to the development of products to protect the wound and facilitate addressing special issues in healing and non-healing wounds. Rapidly growing interest in nanofiber research is leading to the development of potential candidates for wound dressing applications. Electrospinning nanofibers have been considered one of the effective materials in the development of scaffolds for tissue engineering applications. Nanofibers mimic the extracellular matrix with their structural similarities, high surface area, and porosity, thereby enabling the effective delivery of antimicrobial agents in the wound milieu. Chitosan, an excellent biopolymer, is offering versatile applications as electrospun nanofibers due to the presence of its inherent properties like nontoxicity, biodegradability, biocompatibility, and antimicrobial nature, as well as its efficiency towards reepithelialization and regeneration of the granular layer of the wounds. The current revi ew discusses the design and strategies used in the development of electrospun chitosan nanofibers, as well as the limitations of these strategies. This article provides the most recent information on the fabrication of chitosan composite nanofibrous materials and their applications for wound healing.

Keywords: Wound dressings, Electrospinning, Nanofibers, Chitosan, Composite

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INTRODUCTION

Human skin is a primary defence mechanism of the body, protecting us from adverse environmental conditions and microbial invasion [1]. Any disturbance to the structural and functional integrity of the skin causes wounds, which may be the consequences of mechanical trauma and injury, surgeries, burns, thermal effects, or diabetes. Invasion of microorganisms and loss of electrolytes or body fluids through wounds might sometimes become life-threatening. A wound can be defined as a disruption in the defensive function and loss of the natural cohesiveness of the skin [2, 3]. Mechanical trauma, injury, surgeries, burns, thermal effects, or diabetes may cause disturbances to the structural and functional integrity of the skin and result in a wound. Invasion of microorganisms and loss of electrolytes or body fluids through wounds might sometimes become life-threatening. Wounds can be categorised into different varieties, and treatment approaches vary with each class of the wound [4]. Based on the process and duration of healing, wounds can be classified as acute or chronic. Healing of acute wounds is based on the level and extent of injury in various layers of the skin within a predictable time period of 8 to 12 w, whereas chronic wounds do not heal within a fixed timeframe [5-7]. The elimination of pathogenic bacteria at the wound interface also serves as a vital step, especially in the process of chronic wound healing. Various factors influence and may delay the process of wound healing, like hypothermia, infection, tissue oxygen tension, the extent of damage to the skin, poor nutrition, person-to-person variability, and age [8]. Choosing an appropriate wound care product is very important to overcome challenges in wound healing. Topical dressings are widely used as a vital therapy for wound healing. Although various wound healing products have emerged, the lack of standard protocols, heterogeneity, and high cost of existing care products limit their clinical applications. To achieve proper healing, specificity in selecting various materials for a specific type of wound is critical. Over the last decades, researchers have investigated the use of biocompatible polymers from natural or synthetic sources for tissue engineering applications because of their multifunctionality and flexibility. Wound dressings developed from biocompatible polymers have shown promising results in addressing the problems in tissue regeneration, making them an appropriate choice for treating a wide variety of wound types in different conditions. Chitosan, a naturally occurring biopolymer, is an excellent candidate for designing wound dressing materials owing to its antimicrobial and hemostatic properties. Electrospinning technology has recently gained much interest in wound healing because of its ability to manufacture biomimetic nanofibers from a wide variety of natural and synthetic polymers [9]. This review focuses on investigating the possibilities and limitations of designing a suitable wound dressing based on chitosan using an electrospinning process, effective ways to enhance the electrospinning ability of chitosan, and the efficacy of chitosan-based nanofibers in skin tissue regeneration. This review is compiled using references from databases such as Elsevier, PubMed, and Google Scholar from the year 1999 to 2023 with keywords like "chitosan electrospinning," "electrospun nanofibers," "chitosan blends," "composite nanofibers," and "modifications of chitosan for electrospinning." The inclusion criteria were studies on electrospun nanofibers based on chitosan alone, modified chitosan, cross-linked chitosan, and mixtures of chitosan with other synthetic polymers.

Wound dressings

Wound dressings serve as an important therapeutic tool for wound healing. A wound dressing applied over the affected area is meant for protection against further damage and microbial invasion as well as provides suitable conditions for wound healing with minimised scar formation. Various products came into existence, ranging from antibacterial gauge dressings to growth factor-releasing *in situ* gels [10]. The development of traditional gauge dressings began in 19th century which was later followed by the development of occlusive dressings in 20th century. These occlusive dressings provide moisture to the wound and aid in the formation of collagen synthesis, quicker re-epithelialization, decreasing pH of the affected area, thereby lessening the infection. In the later years, several types of wound dressings were developed, including tissue adhesives, hydrogels, films, foams, alginate products and silicone meshes (table 1). A dressing is generally selected based on the nature and extent of the wound, wound exudate formation, presence of any infection and adhesion of the dressing to the wound area [8].

Traditional wound dressings

Traditional wound dressings (e. g., cotton, lint, plasters, gauze cloth, etc.) may be made from natural or synthetic materials. These are dry

materials that can be used as primary/secondary dressings for absorbing exudates from the wound to keep the wound surface always dry. But, the major drawback of a dry environment is a decreased rate of healing and pain during dressing removal. Due to the failure of traditional dressings to maintain sufficient moisture near the wound bed, these dressings are replaced with modern wound dressings [11].

Modern wound dressings

Modern wound dressings provide a suitable moist environment for the wound healing process, enhancing the healing rates. These dressings are especially preferable in serious types of wounds like burns and chronic ulcers where moist wound bed maintenance will prevent cell death due to desiccation and also moist wound healing provides favourable conditions for fibroblast proliferation and reepithelialisation by the migration of keratinocytes along the newly formed surface of granulation tissue. It is important to optimise the moisture levels as excess wound exudates can cause colonisation of bacterial species and might adversely damage the surrounding healthy area. Hence, it is extremely important to select a suitable wound dressing in order to maintain favourable conditions for healing. Currently, there are numerous therapies for wound healing, such as hydrocolloids, hydrogels, fibers, foams, transparent films etc. [12].

Table 1: Types and examples of commercially available wound dressings

Type of dressing	Examples	References
Traditional dry gauze wound dressings	Medifin® paraffin gauze dressing, Xeroform® gauze dressing, Vaseline® petrolatum gauze	[2, 13]
Moist occlusive/semi-permeable films	Tegaderm® and Tegaderm® HP transparent film dressings, Bioclusive® transparent wound dressing, Cutifilm®	[2, 13-15]
Hydrocolloids	Aquacel® Ag, Granuflex® dressing, NU-DERM™ dressings	[2, 13, 14, 16]
Hydrogels	NU-GEL®, Vigilon®, Flexigel®, Aquamatrix®, DuoDerm® hydroactive gel and Restore™ hydrogel dressing	[13, 14, 17]
Alginate dressings	Curasorb calcium alginate dressing, SeaSorb Ag alginate dressing and Sorbsan silver alginate dressings	[11, 13, 14]
Foams	Kendall™ foam dressing, Med Vance ™Silicone-Bordered silicone adhesive foam dressing, Dynarex CuraFoam foam dressings	[13, 14]
Collagen products	Oasis™ collagen product, Medifil™collagen particles, Promogran Prisma™ matrix, a combination of collagen, oxidized-regenerated cellulose, and silver.	[13, 14, 18]

Nanofibers-development and applications

Nanofibers are exciting materials produced from a range of polymers and have shown outstanding properties in various biomedical and engineering applications. High porosity and surface area offered by the structural arrangement of nanofibers made them widely used in the medical field [19]. Nanofibers are known to be involved in promoting tissue formation, enhancing vascular regeneration, and fastening the wound-healing process. Various techniques, like electrospinning, template synthesis, centrifugal spinning, blow spinning, self-assembly, and microfluidic spinning techniques, are available to produce nanofibers. But electrospinning is considered the simplest and most practical technique for producing fibers of micron to nano size range [20, 21]. Nanofibers fabricated by the electrospinning method showed a promising approach in various areas like wound healing, tissue regeneration, and drug delivery applications [21-25].

Electrospinning technique for the fabrication of nanofibers

The electrospinning technique allows the formation of nanofibers from polymeric solutions under the influence of a high-voltage electric field [26]. A typical electrospinning apparatus shown in fig. 1 includes a high-voltage power supply system, a spinneret system (syringe with a metal needle), and a collecting system.

The polymeric solution in a suitable solvent, including drugs and additives at a predetermined concentration, will be loaded into the syringe and pushed towards the needle tip driven by the syringe pump. The high voltage power creates an electric field, thereby causing charge induction of the solution, which generates a taylor cone at the tip of the needle, causing a jet of the polymer solution to stretch into fibers while moving towards the collection plate [28]. Properties of nanofibers are determined by the selection of the type and concentration of polymer, the solvent system, flow rate, applied voltage, and collector distance from the tip of the needle. Necessary modifications can be done to match the structural and functional requirements of fibers. One such modification is the coaxial electrospinning technique, in which two spinnerets are used to co-electrospun different solutions, resulting in the formation of core/shealth nanofiber. Core/shealth nanofibers can combine different properties of the both the spun polymers within a single structure, and this technique is also useful to incorporate drugs intended for modified release in the core or create suitable surfaces for further functionalization [29]. A variety of structures of electrospun fibers are possible as shown in fig. 2, such as core-shell [30, 31], hollow [32], nanowire-in-microtube [33] and three-dimensional fiber scaffold [34] produced by modifying the basic setup of the spinning apparatus.

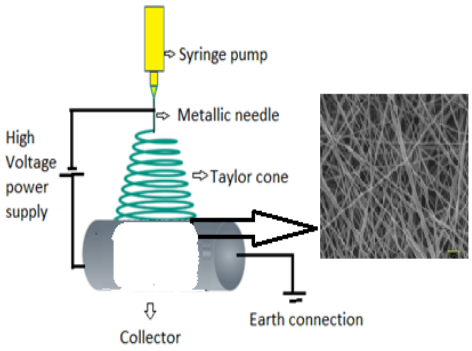

Fig. 1: A typical electrospinning unit [27]

Applications of electrospun nanofibers in tissue engineering

Electrospinning nanofibrous membranes have attracted a lot of attention from researchers and are considered an advanced development in the field of modern dressings for applications in tissue engineering and the delivery of bioactive agents to the site of damage [35]. The electrospinning process has high flexibility and versatility in the fabrication of uniform and continuous nanofibers with control over pore structure. These nanofibrous membranes can be developed into scaffolds or mats containing antibacterial agents [36], hemostatic dressings and wound healing dressings, drug delivery vehicles for incorporation and controlled release of drugs, medical implants, filtration devices, textiles for protection, etc. [37].

Electrospinning nanofibers are exhibiting tremendous potential in the field of tissue engineering due to their structural and functional similarities to the natural extracellular matrix. They can act as cellular support for the adherence, growth, migration, and differentiation of cells during wound repair [38]. High porosity and specific surface area of nanofibers become advantageous, especially to allow the exchange of gases at the wound site and control the loss

of blood, thereby minimising wound drying and dehydration. Nanofibers have the ability to block the entry of external microorganisms due to their ideal interconnected network and nanopores [39]. Furthermore, the higher specific surface area offered by nanofibers is also favourable for good absorption of wound exudates and loading of several drugs, antimicrobial agents, metal nanoparticles, or growth factors [40, 41]. The release pattern of the loaded drugs/agents can be controlled by adjustment of fiber structure and morphological characteristics to achieve desirable therapeutic activity [42].

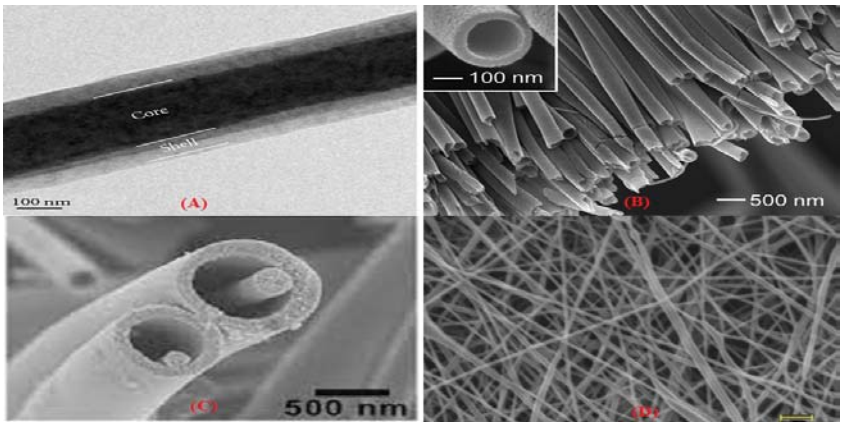

Fig. 2: Various structures of electrospun fibers (A) core-shell fibers prepared by coaxial electrospinning [31] (B) Hollow nanofibers with walls [32] (C) Nanowire-in-microtube structures [33] (D) 3D fibrous scaffold [34]

Materials used in the fabrication of nanofibers

Nanomaterials alone or in blends used in the fabrication of electrospun nanofibers can be natural, synthetic, or a combination of both natural and synthetic polymers [43]. Natural materials derived from plants or animals, including chitosan [44], collagen [45], gelatin [46], cellulose [47] and silk fibroin [48] are biocompatible and have the ability to promote tissue regeneration and reconstruction. Synthetic polymers that are nontoxic, biodegradable, and have suitable physicochemical and mechanical properties with proven applications in the biomedical field are generally selected for electrospinning nanofibers. Some of these polymers include polycaprolactone (PCL) [49], polyethylene glycol (PEG) [50], polyethylene oxide (PEO) [51], polylactide (PLA) [52], poly-L-lactic acid (PLLA) [53], poly (lactic-co-glycolic acid) (PLGA) [54], polyvinyl alcohol (PVA) [55].

Strategies in electrospinning of chitosan-based nanofibers

Chitosan

Chitosan, the second most abundant natural polysaccharide obtained from the shells of crustaceans, is a partially deacetylated derivative of chitin and a mixture of β-(1–4)-linked d-glucosamine and N-acetyl-d-glucosamine [56]. Chitosan has an advantage over other polysaccharides because of the ease with which precise alterations can be made at the C-2 position due to its chemical structure [57]. Chitosan has been found to inhibit the growth of microbes in most of the research works [58]. Its nontoxicity, biodegradability, and biocompatibility, along with its inherent antibacterial and anti-inflammatory ability, facilitate numerous applications of chitosan in various fields like pharmaceuticals, tissue engineering, textiles, food packaging, and agricultural products [59, 60]. These promising characteristics of chitosan make it possible to produce nanofibers mainly for drug delivery or tissue engineering applications. Hence, there is a need to develop wound dressings based on chitosan with great biocompatibility for accelerated wound healing.

Chitosan alone nanofibers

Chitosan is polycationic with a rigid chemical structure, ability to form hydrogen bonds, and fewer chain entanglements. Hence, fabrication of chitosan into nanofibers by electrospinning is challenging to the researchers [61, 62]. However, few researchers have fabricated electrospun chitosan nanofibers using trifluoroacetic acid or acetic acid (90%) and co-solvents like dichloromethane.

Ohkawa *et al.* (2004) successfully prepared the finest chitosan nanofibers (8% wt) of diameter 330 nm when a mixture of trifluoroacetic acid (TFA) and dichloro methane (DCM) at a ratio of 70:30 was used as a solvent. The researchers also observed that morphology improved from spherical beads to interconnected fibers with a rise in chitosan concentration [63]. Another study by Sangsanoh *et al.* (2010) also used 70:30 v/v trifluoroacetic acid/dichloromethane solvent systems to fabricate 7% w/v chitosan nanofibers with a mean diameter of 126±20 nm. Chitosan nanofibers fabricated in this study were also found to promote the attachment and viability of cultured keratinocytes [64].

Limitations of chitosan alone nanofibers

The use of organic solvents in the preparation of chitosan nanofibers, especially trifluoroacetic acid, may result in toxic effects. However, pure chitosan nanofibers fabricated were shown to have poor mechanical and swelling properties. This strategy for the preparation of chitosan nanofibers is not considered acceptable for application in tissue engineering, and hence researchers have focused on alternative methods to fabricate chitosan-based nanofibers with suitable properties [65, 66].

Cross linked chitosan nanofibers

Various cross-linking methods used to improve the mechanical properties and stability of chitosan nanofibers were studied.

Chemical cross-linking

Chemical cross-linking can be used to modify the mechanical and swelling characteristics of chitosan nano fibers by interconnecting chitosan molecules [67-69]. Sarhan *et al.* (2015) fabricated chitosan/honey/polyvinyl alcohol nanofibers with high concentrations of honey (40% w/w) and chitosan (5.5% w/w) with 1% acetic acid as a solvent. The fabricated nanofibers were exposed to glutaraldehyde vapours for chemical cross-linking. They were further physically cross-linked by heating and freezing/thawing cycles. Cross-linked chitosan/honey/PVA nanofibers showed pronounced antibacterial activity against *Staphylococcus aureus* with no cytotoxic effects on cultured fibroblasts, and hence were found to have good biocompatibility and antimicrobial effects [70]. However, the limitation of this method is that chemical cross-linking might result in less availability of free functional groups with decreased biodegradability of the resulting membranes. It is evident that potential cytotoxicity might originate from chemical cross-linkers like glutaraldehyde [67, 68, 70].

Some researchers have studied genipin, a natural cross-linking agent, as an alternative for cytotoxic crosslinkers to cross-link

chitosan nanofibers. Zhenguang *et al.* (2018) used genipin to cross-link the electrospun chitosan-g-eugenol and the zwitterionic copolymer poly (sulfobetaine methylacrylate-co-2-aminoethyl methacrylate) on polycarbonate urethane substrate. It was observed that the prepared membranes exhibited antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* with lower hemolytic activity and good anticoagulant activity. The prepared membranes did not exert significant cytotoxicity on L929 fibroblasts, indicating the safety of genipin use as a cross-linker [71].

Photo cross-linking

Few researchers have used the photo cross-linking method using UV radiation along with photoinitiators like benzophenone for cross-linking chitosan-based nanofibers and achieved good wet and thermal resistance. Kianfar *et al.* (2019) fabricated photo-cross linked chitosan/poly (ethylene oxide) nanofiber mats by application of UV irradiation to improve the physico-chemical properties like stability and water resistance of the electrospun mats. Chitosan/PEO nanofibers were obtained with an average fiber diameter of 270 nm and good water resistance, thus demonstrating the application of photocrosslinking of chitosan membranes [72].

Ionic cross-linking

Chitosan nanofibers can be cross-linked by ionic cross-linking technique with non-covalent cross-linkers like sodium tripolyphosphate (TPP) [73], tannic acid (TA), and glycerol phosphate (GP) due to the ability of the cationic amino groups of chitosan to interact with negatively charged anions or molecules [74-79]. Compared with chemical cross-linkers, ionic cross-linkers have the merit of lower toxicity and fewer environmental concerns.

Sarkar *et al.* (2013) prepared chitosan-PEO electrospun nanofibers using 15 M acetic acid as a solvent. Ionotropic cross-linking of chitosan nanofibers was done using TPP. It was observed that cross linked nanofibers achieved bead-free morphology with an average diameter of 78 nm. TPP cross-linking was used to create a nanofiber mat with architectural stability in an aqueous medium. The cross-linked nanofiber mat exhibited good swelling characteristics with a longer degradation time. In this study, the prepared TPP cross-linked nanofiber mats resulted in good attachment, proliferation, and survival rates of 3T3 fibroblast cells. Hence, it can be stated that the non-toxic behaviour of TPP cross-linking can enhance the potential of chitosan based nanofibers in tissue engineering [80].

Physical cross-linking

Physical cross-linking is another method to improve the mechanical properties of chitosan nanofibers, which is mainly due to the attractive forces developed between chitosan molecular chains and other polymers. Hydrogen bonds, polar bonds, electrostatic interactions, or Vanderwaals forces may develop during the physical cross-linking of chitosan due to its polyelectrolyte nature. Chitosan forms composite hydrogels using alkaline solutions or oppositely charged polyelectrolytes like gelatin, collagen, and hyaluronic acid [81-83]. Research outcomes on physical cross linking indicated that physically cross linked chitosan fibrous materials possess great biocompatibility with less toxic effects [81].

Jeong *et al.* (2010) investigated the electrospinning ability of chitosan and alginate to form polyelectrolyte complex (PEC) nanofiber mats by *in situ* cross-linking. PEO is used to facilitate electrospinning and is later removed by incubating the nanofibers in water. The nanofibers obtained were uniform (≈10 0 nm) and exhibited good cell adhesion and proliferation. Hence, PEC nanofibrous scaffolds prepared without toxic cross linking agents have great potential in tissue regeneration applications [84]. In another study by Garcia *et al.* (2020) electrospinning technique was used to produce nanofibers from chitosan/hyaluron PEC. 4% w/w PEO solution was also added to improve the electro-spinnability of chitosan/hyaluron PEC. A 4-hour heat treatment at 120 °C is also done to control the level of swelling. The prepared fibers were stable in pH 7.4 buffer when formic acid/water (50/50) was used as a solvent for electrospinning [85].

Chitosan composite nanofibers

The electrospinning capabilities of chitosan can be enhanced by simply blending it with other polymers having high electrospinning potential. To overcome issues with electrospinning of chitosan alone, chitosan has been blended with various synthetic polymers, natural polymers, nanoclays, mineral compounds, metal oxides, metal nanoparticles, zeolites, organic metal structures, etc. [86]. Chitosan is most commonly blended with synthetic polymers to produce composite nanofibers with excellent properties. These polymers include PLA [87], PCL [88, 89], PEO [90], PVA [91, 92]. Furthermore, research studies on chitosan electrospinning also showed that it can be blended with natural polymers like gelatin, silk fibroin, and collagen [93, 94].

Biranje *et al.* (2017) prepared chitosan/PVA nanofibrous membranes with varying blend compositions. Nanofibers obtained were uniform, with a mean fibre diameter of 80–300 nm with a blend of 2% w/v chitosan and 5% w/v PVA at 20–25 kV. From this study, it was found that strong intermolecular hydrogen bonding exists between the molecules of chitosan and PVA, whereas the morphology and fiber size were greatly influenced by the weight ratio of the polymers used [95].

A study on chitosan composite nanofibers was done by Dizaji *et al.* (2020) to fabricate paclitaxel loaded PLGA/chitosan nanofibers by incorporating various zeolites (hydrophilic Y zeolite and hydrophobic ZSM-5 zeolite) and metal-organic frameworks (MOFs) (MIL-101 and ZIF-8). All the fabricated nanofibers were within the diameter range of 340-410 nm. The fiber morphology became beaded when drug-loaded nanozeolites and NMOFs were incorporated into the PLGA/chitosan nanofibers. High drug loading efficiency and better-sustained release behaviour of paclitaxel were found with MOFs incorporated nanofibers when compared with those containing zeolites. Higher fibroblast cell viability and higher cell killing of LNCaP cancer cells within 72 h of incubation when tested with the prepared nanofibers indicate good biocompatibility and better performance of paclitaxel-loaded chitosan composite nanofibers [96].

Modified/Derivatized chitosan-based nanofibers

Chitosan has very low solubility in aqueous media; hence it is generally solubilized in organic solvents like acetic acid and trifluoroacetic acid for electrospinning. On a large scale, electrospinning of chitosan using organic solvents can present practical challenges. Hence, chitosan has been modified into various derivatives by most of the researchers. Due to the polycationic nature of chitosan, different functional groups are available for modification with different types of ligands. Some of the reactions involving the amide bond linkage of chitosan are schiff's base reactions, metal ion chelations, alkylations, carboxymethylation, sulfonation, grafting, quaternization, etc. The hydroxyl group of chitosan is also involved in chemical modifications such as phosphorylation, sulfonation, carboxymethylation, hydroxyethylation, etc. [97-99].

Wai Yan Cheah *et al.* (2019) modified chitosan to its quaternized derivative and fabricated a nanofiber membrane. The nanofiber membrane was hydrolyzed for covalent grafting of chitosan molecules, thus forming reaction sites from carboxylic groups. Quaternization of chitosan membranes is functionalized using a quaternary amine called glycidyl trimethyl ammonium chloride under differing pH conditions. It was observed that quaternization was better achieved in alkaline conditions. Quaternized chitosan has shown increased antibacterial activity against *Escherichia coli,* indicating the retention of inherent properties of chitosan even after modification [100].

Another study carried out by Jin E *et al.* (2022) included the modification of chitosan into a quaternized product, CS-*g*-polydimethylaminoethyl methacrylate (PDMAEMA), and fabrication of nanofiber membranes by modified CS/PVA. The characteristics of nanofibers were varied by the grafting ratio (*GR*) and degree of quaternization (*DQ*) of modified chitosan. The quaternized CS-*g*-PDMAEMA/PVA nanofibers were observed to be smooth with high tensile strength and moisture penetrability at optimised *GR (*21.5%) and *DQ* (12.3%). Nanofibers fabricated from modified chitosan exhibited greater antibacterial activity against *Staphylococcus aureus* in comparison with standard antibacterial membranes [101].

Chitosan composite nanofibres for wound dressing applications

Chitosan-polyvinyl alcohol (PVA) composites

PVA is a hydrophilic, nontoxic, biodegradable and biocompatible polymer having good mechanical strength and thermal characteristics. PVA forms excellent nanofibers through electrospinning which can be tailored to fit the required alignment and porosity [102, 103]. PVA is found to improve the electrospinnability of chitosan due to strong hydrogen bonding between both the polymers which was revealed by FT-IR and XRD studies in most of the research works. Many researchers successfully fabricated composite nanofibers scaffolds of chitosan and PVA at different ratios.

Alavarse *et al.* (2017) investigated the physicochemical, antibacterial and cytotoxic properties of Tetracycline hydrochloride (TCH) loaded chitosan/PVA electrospun mats. It was revealed that drug was incorporated uniformly along the nanofibers with an effective TCH release profile and antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus. epidermidis*. MTT assay followed by scratch assay confirmed that the developed drug-loaded nanofibrous scaffolds have good cytocompatibility. Hence, these membranes can be suggested for use as antibacterial wound dressing [104].

Sanaz *et al.* (2023) designed a nanofibrous structure composed of chitosan/PVA for the controlled release of colistin and meropenem. Three different concentrations of antibiotics (Colistin/Meropenem: 32/64 µg/ml, 64/128 µg/ml, and 128/256 µg/ml) were loaded into nanofibers and they were observed to have a beadless uniform fibrous structure. The membranes exhibited slow release of antibiotics for one week and synergistic antimicrobial activity against ATCC strains and clinical isolates of extensively drug-resistant *Acinetobacter baumannii*. Testing of membranes in *in vitro* cell lines and animal models suggested good cytocompatibility and biocompatibility. This study proved the efficacy of 128/256 µg/ml colistin/meropenem loaded CS/PVA nanofibrous scaffold for wound healing [105].

Chitosan-polyethylene oxide (PEO) composites

PEO is a crystalline, thermoplastic polymer with good biocompatibility, biodegradability, water solubility, and non-immunogenicity. PEO is a versatile polymer for various biomedical applications, mainly as scaffolds [106]. PEO can greatly improve chitosan spinnability as its incorporation results in additional hydrogen bond formation, breaking the self-association of chitosan chains. Improved chain entanglement and reduced repulsive forces lead to the fabrication of defect-free chitosan/PEO nanofibers [107]. As revealed from many of the research works, chitosan/PEO blend fibers are considered exciting materials in wound healing applications due to their uniform fiber morphology and size range, suitable mechanical and swelling properties.

Trinca *et al.* (2017) produced double-layer scaffolds composed of a primary layer containing chitosan/PEO nanofibers (diameters smaller than 200 nm) for the role of wound dressing, while the second layer provides mechanical support with polycaprolactone or polycaprolactone/cellulose acetate nanofibers (diameters of 1 to 4 µm). The addition of cellulose acetate addition enhanced the mechanical properties of the scaffold. The scaffolds exhibited good cytocompatibility towards L929 fibroblasts, indicating the suitability of the prepared scaffold as wound dressing [108].

Fereydouni *et al.* (2023) fabricated antibacterial nanofibers incorporating 1% w/w silver nanoparticles (SNPs) into chitosan/PEO blend nanofibers. It was observed that SNPs had little influence on the fiber morphology, and *in vitro* SNP release was rapid, reaching 36% in the first two hours. MTT assay confirmed the biocompatibility of prepared nanofibers with human dermal fibroblast cells and a normal fibroblast cell line (L929). A greater antibacterial effect was observed against various aerobic and anaerobic bacteria such as *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, *Streptococcus mutans, Streptococcus sobrinus,* and *Streptococcus sanguis*. Hence, SNP-loaded chitosan/PEO nanofibers can be considered suitable candidates for better healing of aerobic or anaerobic infection-related wounds [109].

Chitosan-poly (E-caprolactone) (PCL) composites

PCL is hydrophobic, non-toxic, biodegradable, and biocompatible, with suitable mechanical properties and longer biodegradation times. It is considered as one of the ideal materials for blending with chitosan for preparing nanofibers [110-112]. Mixing chitosan with PCL improves the electrospinnability of chitosan and also the drawback of hydrophobicity of PCL [113]. Hence, an electrospun nanofiber membrane composed of chitosan and PCL can exhibit the physicochemical properties of both polymers along with sufficient mechanical strength.

Yang S *et al.* (2020) designed chitosan/PCL scaffolds loaded with lidocaine hydrochloride and mupirocin for wound dressing applications using a dual spinneret electrospinning technique. Drug-loaded scaffolds exhibited enhanced interfacial interaction with blood cells and better blood coagulation capacity. Lidocaine was released rapidly, and mupirocin exhibited sustained release from the scaffolds. Drug-loaded scaffolds were observed to have greater antibacterial activity, and when tested in a full-thickness skin defect model, the scaffold exhibited enhanced wound healing ability with complete re-epithelialization and collagen deposition. These nanofibrous scaffolds may serve as promising candidates for wound dressings [114].

Ghazalian *et al.* (2022) prepared core-shell nanofibers of chitosan-PCL by the coaxial electrospinning method, embedding tetracycline hydrochloride in the chitosan core. Morphological investigations showed that CS-PCL nanofibers were beadless, with a mean diameter of 285±75 nm. Initial burst release followed by sustained release of drug from nanofibers was observed, and they exhibited good antibacterial activity. Hence, the prepared nanofibers can be suggested for use in biomedical applications [115].

Cui *et al.* (2022) prepared electrospun nanofibrous membranes of chitosan/PCL by coaxial-electrospinning to achieve a controlled release of ciprofloxacin. SEM, TEM, and FTIR characterizations confirmed the presence of the drug in core-shell structured fibers, which was released *in vitro* in a sustained manner for 15 d. 2% Ciprofloxacin loaded chitosan/PCL nanofibrous membrane exhibited better antibacterial efficacy against bacterial strains like *Escherichia coli* and *Staphylococcus aureus* and good cell proliferation with enhanced *in vivo* wound healing efficacy. The study recommended that the prepared electrospun membranes can direct the arrangement of skin fibroblasts with potential applications in wound healing [116].

Chitosan-polylactic acid (PLA) composites

PLA is a non-toxic, biodegradable, bioabsorbable, and biocompatible aliphatic polyester with good thermal and mechanical properties, thus making it one of the ideal materials for bioengineering applications [117-119]. Blends of chitosan and PLA can combine the superior properties of both polymers and electrospun nanofibers fabricated from these blends have found applications in wound-healing dressings.

Khazaeli *et al.* (2020) used the microwave-assisted electrospinning method to fabricate chitosan/PLA nanofibrous scaffolds encapsulated with different concentrations of cod liver oil. SEM and TEM images of the nano scaffold structures revealed that the fibers were defectless and uniform. Nanofibers loaded with 30% cod liver oil were rapidly absorbed in the wound area, with significant healing in 14 d. The researchers suggested that the prepared nanofibers can be a suitable candidate in designing wound dressing for diabetic foot ulcer syndrome [120].

Virijevic *et al.* (2022) prepared a scaffold of chitosan/PLA nanofibers. MTT assay confirmed the cytocompatibility of scaffolds by observing good proliferation and the viability of healthy fibroblast cells cultured over scaffolds. An *in vitro* scratch test done on a healthy lung fibroblast cell line to determine wound healing ability confirmed that treatment of a wound for a prolonged time promoted a greater proliferation rate and differentiation of cells. This study concluded that the prepared scaffolds have great potential in regeneration and restoration of damaged tissue, as proved under *in vitro* conditions [121].

Chitosan-gelatin composites

Gelatin is a naturally derived polymer having versatile applications as a drug carrier and substrate for cell cultures due to its properties like low antigenicity, biocompatibility, and biodegradability [122]. It can be combined with chitosan to form polyelectrolyte complexes due to the interaction of oppositely charged polyelectrolytes and facilitate electrospinning with superior antibacterial effects [123, 124].

Ferreira *et al.* (2021) developed chitosan/gelatin hybrid fibers incorporated with phlorotannin-enrich extract having antimicrobial and anti-inflammatory properties obtained from the seaweed *Undaria pinnatifida*. All the prepared samples had homogenous fiber morphology and high porosities which are very much needed to control the wound moist environment. Extract release from nanofibers was extended up to 160 d. The prepared nanofibers had shown antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* and cytoprotective nature towards hDNF cells. Thus electrospun phlorotannins-enriched extract-loaded gelatin/chitosan nanofibers can be explored for minimizing bacterial infections in the wound bed [125].

Ali *et al.* (2022) prepared electrospun chitosan/gelatin nanofiber scaffolds embedded with graphene nanosheets. Electron microscopic images confirmed the successful reinforcement of nanofibers with 0.15% graphene nanosheets with fine fiber diameter (106±30 nm) and high porosity. Prepared nanosheets showed greater antibacterial activity against *Escherichia coli* and *Staphylococcus aureus,* good biodegradability and swellability, and no cytotoxic behaviour on cultured human fibroblasts. Graphene nanosheets reinforced nanofibers were proven to be as effective antibacterial and wound-healing scaffolds [126].

Chitosan-silk fibroin composites

Silk fibroin (SF), a promising biomaterial extracted from cocoons of *Bombyx mori* silkworm, has excellent properties such as good biocompatibility, air permeability, biodegradability, and less potential to cause inflammatory reactions [127, 128]. SF-based fibers exhibit slow degradation, high tensile strength, and better flexibility. Few research studies have proven that SF promotes the binding and proliferation of fibroblasts and bone marrow cells [129, 130]. Hence, chitosan/silk fibroin blends can favour the electrospinning process with potential wound healing applications.

Khosravimelal *et al.* (2021) fabricated an antibacterial wound dressing composed of chitosan/silk fibroin nanofiber bilayer mats loaded with varying concentrations of cationic antimicrobial peptide (AMP). Nanofibers exhibited controlled release of AMP with significant antibacterial activity against standard and multi-drug resistant isolates of *Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa*. Prepared nanofibers have suitable mechanical and swelling properties, a high biodegradation rate and cytoprotective effect on human fibroblast cells. Peptide-loaded CS/SF bilayer containing can serve as an efficient candidate for the development of wound dressings, especially for MDR bacteria infected wounds [131].

Heydari *et al.* (2022) fabricated silver and curcumin-loaded chitosan/silk fibroin electrospun nanofibers, facilitating the pH-responsive release of loaded drugs. Curcumin loading and entrapment were enhanced after the incorporation of Ag nanoparticles in composite nanofibers. Nanofibers exhibited stronger microbial inhibitory effects and did not have considerable toxic effects on NIH 3T3 fibroblast cells [132].

Chitosan-collagen composites

Collagen, a natural biodegradable and biocompatible polymer, is widely used for tissue regeneration engineering applications [133]. Chitosan with collagen forms polyelectrolyte complexes, and electrospinning of these complexes together with other suitable polymers can form nanofibers with excellent physico-chemical properties, good biocompatibility, and mechanical strength [134].

Maria Rapa *et al.* (2021) used the coaxial electrospinning method to prepare nanofibers composed of chitosan and collagen hydroxylate incorporated with lemon balm and dill essential oils (EOs). The nanofibers obtained were in the diameter range of 471 nm to 580 nm. The antimicrobial activity of the prepared formulations was tested against bacterial strains such as *Enterococcus faecalis, Escherichia coli, Salmonella typhimurium, and Staphylococcus aureus,* as well as fungal strains such as *Aspergillus brasiliensis, Candida albicans, and Candida glabrata.* The formulations were found to have efficient antimicrobial activity in most of the tested reference strains. The presence of dill and lemon balm essential oils further improved the antimicrobial efficiency of the composite nanofibers. A good biocompatibility was observed when the electrospun materials were tested with a white swiss mouse model. Hence the prepared nanofibers could serve as potential candidates for biomedical applications [135].

Jirofti *et al.* (2021) developed curcumin-loaded chitosan/PEO/collagen nanofibers by the blend–electrospinning process. Curcumin was loaded successfully in concentrations of 5%-15% in nanofibers without any beads, but there is a significant increase in the fiber diameter after drug loading (430 nm-514 nm) when compared to plain composite nanofibers (371±46 nm). Curcuminrelease was extended up to 3 d without any significant cytotoxicity of the prepared nanofibers in human dermal fibroblasts. *In vivo* studies on full-thickness wounds in the rat model indicated an efficient mean wound closure rate. The 15% curcumin-loaded chitosan composite nanofibers were considered an optimum formulation with excellent properties and could be considered a promising type of wound dressing [136].

Modified chitosan composites

Many researchers have developed quaternized derivatives of chitosan with increased solubility and antibacterial efficacy. Chitosan derivatives such as *N,N,N*-trimethylchitosan iodide [137], *N*-butyl-*N,N*-dimethylchitosan iodide [138], *N*-[(2-hydroxy-3-trimethylammonium)propyl] chitosan chloride [139], etc. were electrospun using water or less toxic solvents like DMF, DMSO to form composite nanofibers with synthetic polymers.

Ren *et al.* (2020) developed electrospun nanofiber mats from a stereo complex crystallite membrane composed of poly (lactic acid)/chitosan derivatives. The quaternized chitosan (QCS) was prepared by a reaction with glycidyl-tri-methyl ammonium chloride. The quaternized chitosan was further modified by ring-opening polymerization using D-lactic acid to form poly (D-lactic acid) grafted quaternized chitosan (QCS-PDLA). Further PLA/QCS-PDLA/QCS composite membranes were electrospun and exposed to thermal treatment for 1 h at 80 °C to restrict the mobility of lactide chains, thus forming a stereo-complex crystallite membrane. This heat treatment strengthened the mechanical and thermal properties of electrospun fiber mats. The prepared membranes have shown excellent wound healing ability within 15 d, providing a versatile platform for designing as a wound dressing [140].

Gao *et al.* (2021) fabricated a bilayered electrospun nanofibrous membrane composed of quaternized silicone/PCL as the outer layer and quaternized chitosan/PVA/collagen as the inner layer. PCL might provide suitable mechanical support, whereas quaternized silicone with antibacterial properties can suppress scar formation and provide a suitable environment for enhanced wound healing. The inner layer is shown to have good hydrophilicity and biocompatibility. Due to the hemostatic and antibacterial properties of the materials used, this layer can also promote wound healing. A rabbit ear full-thickness wound defect model was used to estimate the wound healing potential of the bilayer membrane in comparison with a commercial ointment. The prepared membranes exhibited excellent antibacterial activity, cell proliferation, hemostatic property, wound healing ability, and scar hyperplasia inhibition, making them an appropriate material for wound dressings [141].

Challenges and future perspectives

One of the biggest challenges in wound care is the development of novel smart wound dressings using smart nanomaterials, which have the ability to interact with the wounds and effectively facilitate wound healing. With the ability to fabricate scaffolds that mimic 3D

and other physiological characteristics of tissues and organs, electrospun nanofiber materials can play a critical role in overcoming many challenges in the regeneration of tissues and organs. Chitosan has demonstrated a satisfactory outcome for applications involving tissue regeneration. However, due to complications in the electrospinning of chitosan, strategies like cross-linking, modification, or co-spinning with synthetic polymers are generally employed to overcome the challenges faced in electrospinning chitosan. Although there are several studies reporting on chitosan nanofibers for different applications, there is still a dearth of information about the challenges that must be overcome in order to get desired fiber qualities. Even though researchers have been able to change the instrumentation and solution parameters to mimic natural tissue structure and morphology, further characterization and clinical trials in human models are required for their predictable use in tissue engineering. However, further work still needs to be done to obtain more promising results on electrospun nanofibrous materials by using advanced electrospinning techniques and scaling up the fabrication of nanofibers from the laboratory to commercial scales, especially for biomedical applications. In the future, manufacturers should focus on assembling nanofibers into several shapes of three-dimensional (3D) structures and combining them with other nanomaterials. Additionally, by utilizing the fiber diameter, size, morphology, and orientations in accordance with the intended clinical applications, researchers might develop unproven regenerative therapies.

CONCLUSION

Electrospun nanofibers possess several ideal properties to meet the requirements of biomedicine and tissue engineering. These materials can incorporate various types of active substances that can improve the overall performance of wound dressings in supporting the healing process. Chitosan and its derivatives have been exploited in various fields for several applications. In this context, research on chitosan-based materials has been focused on biomedical applications such as tissue engineering, gene delivery, wound healing scaffolds, hydrogels, and drug delivery vehicles. This review provides a detailed overview of various modifications and strategies involved in the fabrication of chitosan-based nanofibers by electrospinning technique. Research outcomes from various studies on chitosan-based nanofibers have demonstrated the antimicrobial and cytocompatible properties of chitosan and their suitability for application as wound dressings. Even though several types of chitosan products exist on the market, in the future, there will be a greater need to explore innovative nanofibrous materials of chitosan composites for large-scale production of commercial products.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

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